The Catalytic Intramolecular Friedel-Crafts Acylation of Meldrum's Acid Derivatives and The Total Synthesis of Taiwaniaquinol B

By

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I hereby declare that I am the sole author of this thesis. This is a true copy of the thesis, including any required final revisions, as accepted by my examiners.

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Abstract

The intramolecular Friedel-Crafts acylation of aromatics with Meldrum's acid derivatives catalyzed by metal trifluoromethanesulfonates and other Lewis acids is reported. Meldrum's acids are easily prepared, functionalized, handled, and purified. The synthesis of polysubstituted 1-indanones from benzyl Meldrum's acids was investigated thoroughly, and it was shown that a variety of catalysts were effective, whilst accommodating a diversity of functional groups under mild conditions. The scope, limitations, and functional group tolerance (terminal alkene and alkyne, ketal, dialkyl ether, dialkyl thioether, aryl methyl ether, aryl TIPS and TBDPS ethers, nitrile- and nitro-substituted aryls, alkyl and aryl halides) for a variety of 5-benzyl (enolizable Meldrum's acids) and 5-benzyl-5-substituted Meldrum's acids (quaternarized Meldrum's acids), forming 1-indanones and 2-substituted-1-indanones respectively, are delineated.

This method was further applied to the synthesis of 1-tetralones, 1-benzosuberones, and the potent acetylcholinesterase inhibitor donepezil.

Mechanistic investigations were undertaken to determine the rate-determining step in the acylation sequence using Meldrum's acid, as well as to examine the role of the Lewis acid catalyst. Enolizable Meldrum's acid derivatives can react via an acyl ketene intermediate under thermal conditions, while quaternarized Meldrum's acid derivatives are thermally stable and only act as effective Friedel-Crafts acylating agents in the presence of a Lewis acid catalyst.

The total synthesis of (±)-Taiwaniaquinol B was completed. This natural product was the first ever isolated containing an unusual 6-5-6 fused ring system, and it also contains a hexasubstituted aromatic ring, and two all-carbon quaternary centers. This synthesis was accomplished via an intramolecular Friedel-Crafts acylation/carbonyl α-*tert*-alkylation reaction that exploits the unique chemistry of Meldrum's acid. This novel methodology can be used to access a variety of highly substituted fused ring systems of various sizes.

Acknowledgements

The guidance, support and friendship that Professor Eric Fillion has provided over the past few years have made research in his laboratory a pleasurable and rewarding experience. Special thanks to my committee members: Professors Mike Chong, Scott Taylor, and William Tam.

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With the completion of this thesis, and having earned both my Bachelor's and Master's degrees at the University of Waterloo, there are few members of the organic department who have not in some way participated in my chemical education, and I thank them for it.

Finally, this thesis is for my wife Nora, whose patience, support and love have made this experience possible at all. Thank you.

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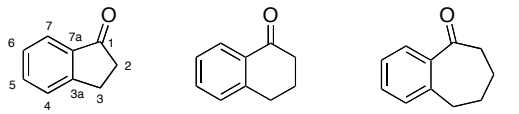
Chapter 1
Introduction and Background

Introduction

One of the major goals of modern synthetic organic chemical research is to provide new methodology and reagents that facilitate the synthesis of highly complex carbon-containing molecules, particularly those that might have biological activity or can be incorporated into materials with unique behaviour. The invention of new routes to access small molecule substrates for synthesis, and perhaps as targets themselves, is required to satisfy demands for high yields and to maximize molecular diversity. The ability to manipulate or modify substrates containing a variety of functional groups can simplify a synthetic sequence and improve overall product yields.

This thesis describes research into the catalytic formation of benzocyclic ketones. Benzocyclic ketones comprise 1-indanones, 1-tetralones, 1-benzosuberones, and related compounds (figure 1.1).[1]

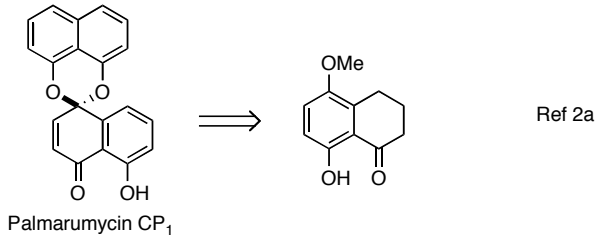
Figure 1.1: Common benzocyclic ketones



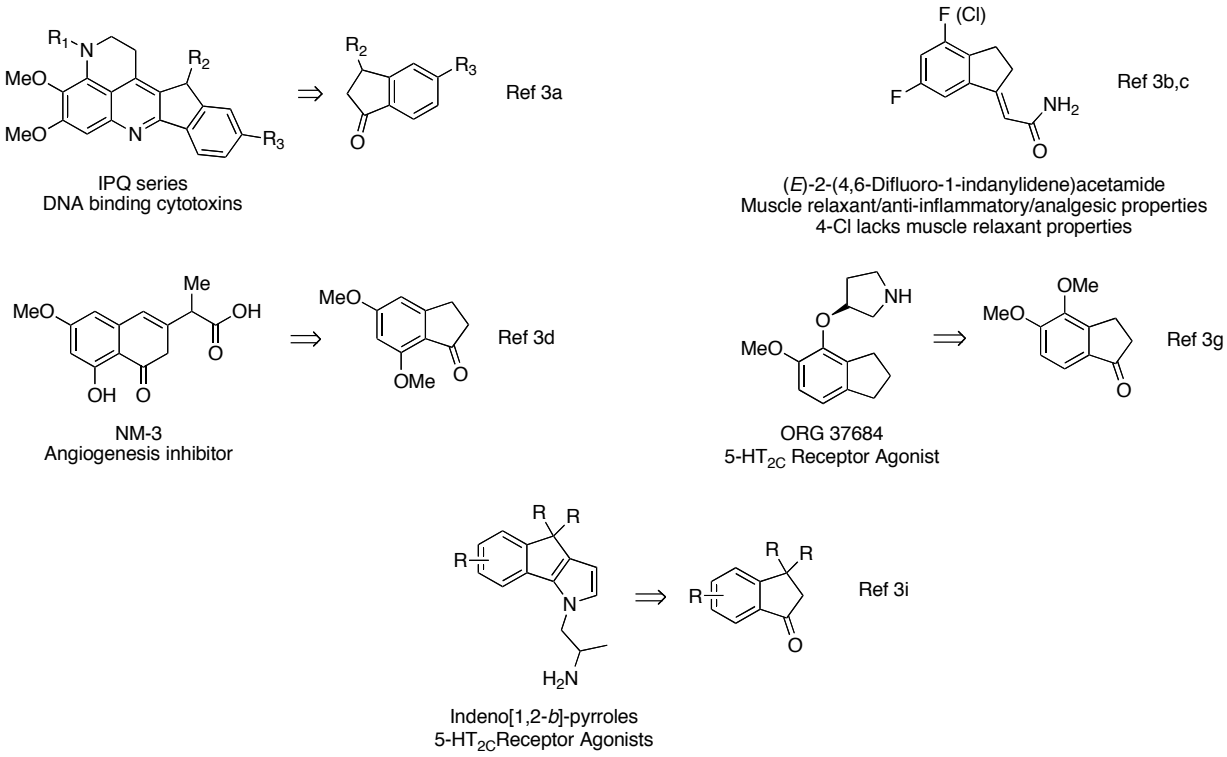
Both the aromatic ring and carbonyl functionalities of this diverse class of compounds can be readily exploited for synthetic manipulation. As a result, these structural motifs have proven utility in the synthesis of numerous biologically active natural products (scheme 1.1)[2] and play

a major role in medicinal chemistry and the development of pharmaceuticals (scheme 1.2).[3]

Scheme 1.1: Aryl ketones as synthetic precursors in natural product synthesis

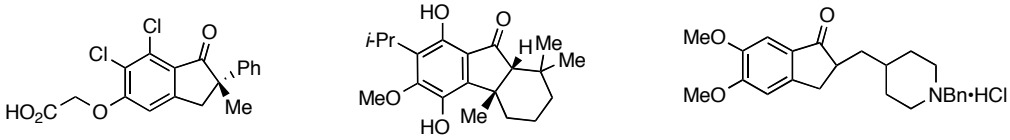


Scheme 1.2: Selected examples of aryl ketones as precursors to medicinal agents



As illustrated in Figure 1.2, the anti-hypertensive drug (+)-indacrinone[4], the sesquiditerpenoid natural product taiwaniaquinol B[5], and the acetylcholinesterase inhibitor donepezil hydrochloride (Aricept®)[6] used for the treatment of Alzheimer's disease, all contain a 1-indanone core.[7]

Figure 1.2: Bioactive 1-indanones



(+)-indacrinone taiwaniaquinol B donepezil hydrochloride (Aricept®)

The synthesis of benzocyclic ketones with varied substituents in both the aromatic and aliphatic rings of the bicycle remains a challenge, and no truly mild and general approach yet exists. 1-Indanones are a particular challenge and their formation is the main focus of the research presented in this thesis. If the synthesis of 1-indanones is examined specifically, a number of unique approaches have been explored and a cross-section of these will be briefly presented.

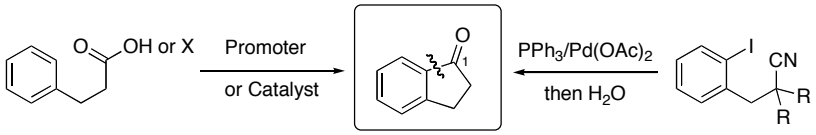
Synthetic Routes to 1-Indanones

Ar-C_1 Disconnections (scheme 1.3)**:**

The most commonly used synthetic disconnection utilized to access 1-indanones (and benzocyclic ketones in general) is the intramolecular Friedel-Crafts acylation of 3-arylpropionic acids or their derivatives. This class of reactions, using both stoichiometric and catalytic promoters, will be discussed in detail in the following section.

Larock's group has reported a palladium-catalyzed cyclization of 2-(2-iodoaryl)propionitriles.[8] This methodology works well for the formation of 2,2-disubstituted 1-indanones (and tetralones). Significantly lower yields were obtained for secondary and primary nitriles, largely giving dehalogenated starting materials, presumably due to difficulty in the carbopalladation step. As is common with organopalladium methodology development, extensive ligand optimization was required.

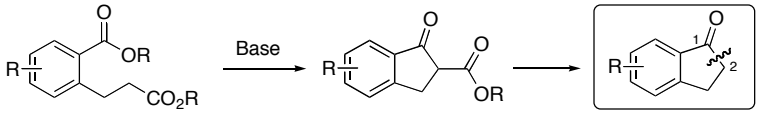
Scheme 1.3: Ar-C_1 1-indanone disconnections



C_1-C_2 Disconnections (scheme 1.4)**:**

The Dieckmann consensation has been utilized[9] to form a C_1-C_2 bond of 1-indanone with subsequent decarboxylation.

Scheme 1.4: C_1-C_2 1-indanone disconnection



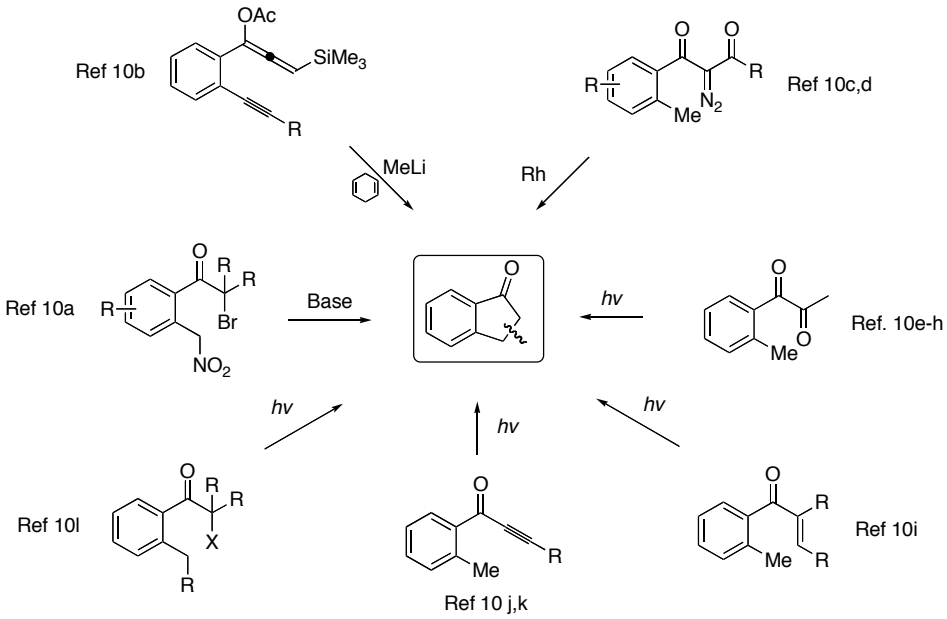
C_2-C_3 Disconnections (scheme 1.5)**:**

A variety of C_2-C_3 disconnections have been explored, including intramolecular nucleophilic substitution reactions[10a] and the cyclization of 2-(alkynylaryl)allenes.[10b] The insertion of rhodium ketocarbenes (generated by diazoketone decomposition) into the CH bonds of *ortho* alkyl groups has been accomplished.[10c,d]

Photochemical methods are well represented by the Norrish-Yang cyclization of 1,2-diketones,[10e-h] as well as photochemical cyclizations of enones[10i] and ynones.[10j,k] The generation and intramolecular reaction of diradicals to form 1-indanones has recently been reported.[10l]

The C_2-C_3 disconnection has produced some excellent methodology, but a limited variety of substrates have been utilized since their preparation can be tedious.

Scheme 1.5: C_2-C_3 1-indanone disconnections



Two Bond Disconnections (scheme 1.6)**:**

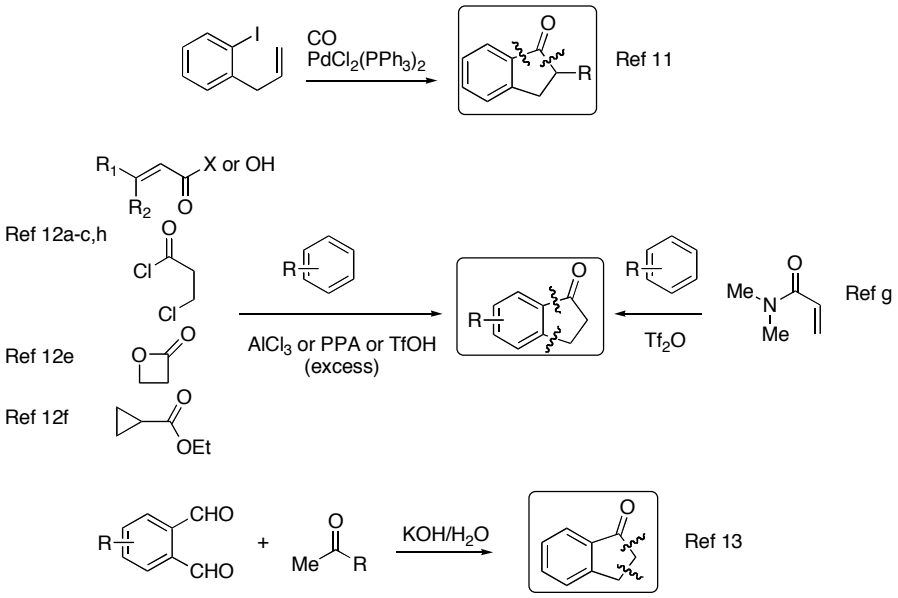
The palladium-catalyzed carbonylation of *ω*-vinyl-substituted *o*-iodoalkenylbenzenes has been studied comprehensively by Negishi.[11] High pressures of CO are required, the yields are modest to poor, and a number of side reactions are frequently observed.

The tandem Friedel-Crafts acylation/alkylation of benzene (and more electron rich aromatics) has been performed, although typically under harsh conditions and with poor to modest yields. Electrophiles include cinnamic acid, crotonic acid, β-chlorocrotonic acid[12a] and β-chloropropionyl chloride,[12b,c] all using excess $AlCl_3$, polyphosphoric acid or triflic acid as the promoter. 1-Tetralone and 1-indanone have been prepared from butyrolactone[12d] and propiolactone,[12e] respectively. Ethyl cyclopropanecarboxylate has been used in the Friedel-Crafts alkylation/acylation reaction, with $AlCl_3$ in refluxing benzene, to produce 2-methyl-1-indanone in very high yield.[12f] A complex of dimethylacrylamide and trifluoromethanesulfonic anhydride has produced 1-indanones in modest yield,[12g] but only for very electron rich and symmetrically substituted aromatic nucleophiles. Trifluoromethanesulfonic acid has been used (in excess amounts) as the promoter for the acylalkylation of a variety of aromatics in good yields, with a variety of alkenyl carboxylic acids.[12h]

The intramolecular Cannizzaro reaction with methyl ketones and phthalaldehydes has[13]

provided 2-acyl-1-indanones. The strongly basic (and nucleophilic) conditions and propensity for side reactions are limiting.

Scheme 1.6: Two bond disconnections to 1-indanones

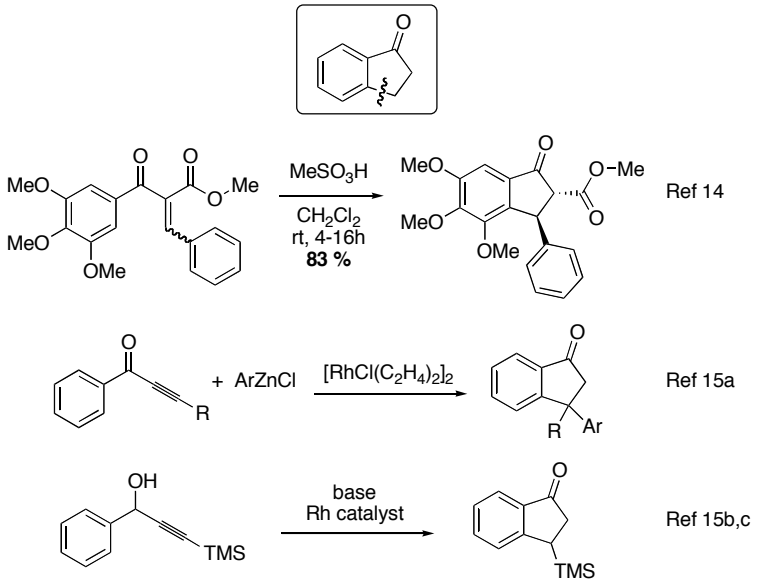


Ar-C_3 Disconnections (scheme 1.7)**:**

Very recently the aryl-C_3 disconnection has been tackled. The Nazarov cyclization of α-carbonyl dienones has produced a very small selection of 1-indanones using stoichiometric $MeSO_3H$ or $Cu(OTf)_2$.[14]

Rhodium catalyzed bond forming processes, both involving 1,4-rhodium migration followed by intramolecular 1,4-addition of aryl rhodium to enone, have been reported.[15] As with the palladium-catalyzed methods mentioned earlier, extensive optimization of ligand and reaction conditions was required, and substrate substitution patterns are limited.

Scheme 1.7: Ar-C_3 Disconnections to 1-indanone

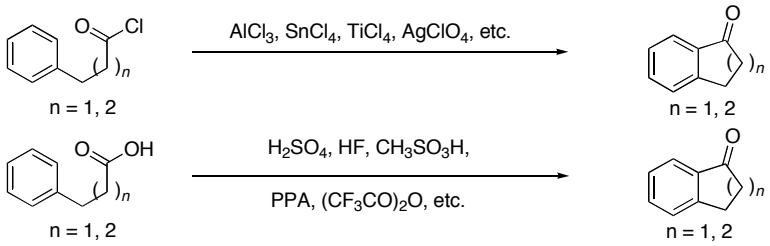


Intramolecular Friedel-Crafts Acylation:

The vast majority of research has been focused on the improvement of the Friedel-Crafts acylation reaction (scheme 1.3) – both new substrates, and reaction conditions. As the aryl-carbonyl (C_1) disconnection remains the most obvious from a retrosynthetic standpoint, conditions for the mild and catalytic acylation of aromatic compounds with broad functional group tolerance is desired. Existing procedures work well with simple substrates but are rarely applicable to functionalized precursors. The following section describes the current state-of-the-art of the intramolecular Friedel-Crafts acylation reaction.

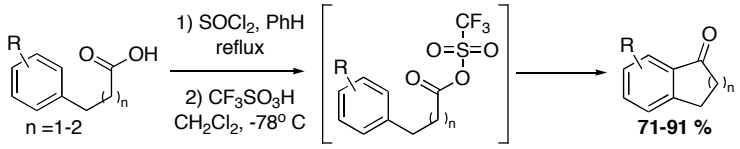
The classical intramolecular Friedel-Crafts acylation involves the reaction of an acyl halide or carboxylic acid with a tethered arene promoted by either Lewis or Brønsted acids (Scheme 1.8).[16]

Scheme 1.8: Intramolecular Friedel-Crafts acylation of carboxylic acid derivatives



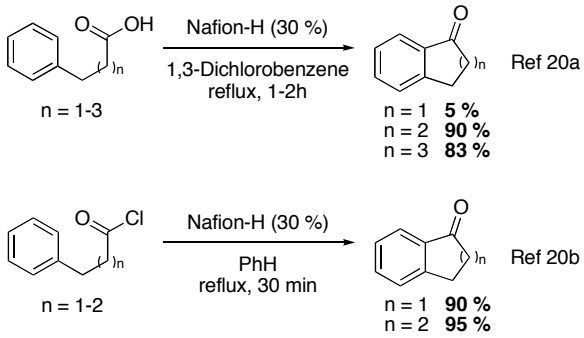
Reacting an aromatic with an acyl chloride in combination with a strong Lewis acid such as $AlCl_3$, $TiCl_4$, or $SnCl_4$ is one of the most common acylation procedures. However, due to catalyst inhibition by the product, via formation of a stable Lewis acid-aromatic ketone complex, stoichiometric or excess amounts of the oxophilic promoter are necessary. Furthermore, decomposition of this complex by aqueous work-up renders product isolation tedious. Additional drawbacks of this protocol include the moisture sensitivity of acyl chlorides and the generation of hydrogen chloride. Alternatively, the reaction of acyl chlorides with stoichiometric quantities of trifluoromethanesulfonic acid provides good yields of benzocyclic ketones via highly reactive sulfocarboxylic acid anhydride intermediates (scheme 1.9).[17] Lewis acid-catalyzed intramolecular Friedel-Crafts acylation procedures with acyl halides have not been reported.[18]

Scheme 1.9: Friedel-Crafts acylation of sulfocarboxylic acid anhydride



Complementary intramolecular acylation methods that directly use carboxylic acids as the electrophile suffer from the poor leaving group ability of the –OH moiety and thus require forcing conditions. Friedel-Crafts dehydrative acylation with carboxylic acids have been promoted by polyphosphoric acid[19], methanesulfonic acid, HF, or dehydrating agents like P_2O_5, trifluoroacetic anhydride, and trifluoromethanesulfonic anhydride.[16] Nafion-H, an immobilized perfluorinated sulfonic acid, does not form stable complexes with arylketones in the acylation with acyl chlorides or carboxylic acids.[20] Although Nafion-H has been reported to effectively promote intramolecular dehydrative Friedel-Crafts acylations to yield tetralones at moderate temperature, it was ineffective for preparing the synthetically more challenging indanones from aryl propionic acids (scheme 1.10).

Scheme 1.10: Friedel-Crafts acylation of carboxylic acids with Nafion-H



Generally, 1-tetralones are the easiest benzocyclic ketones to form by intramolecular Friedel-Crafts acylation. Difficulties are associated with 1-indanone synthesis and harsh conditions are typically required for their preparation, including high temperatures and long reaction times.[12h,21] As a result, the methodologies described above did not examine broad functional group compatibility, and only very simple substrates were considered.

Catalytic Intramolecular Friedel-Crafts Acylation Reaction:

The synthetic importance of the Friedel-Crafts acylation has generated interest in the development of a catalytic version under mild reaction conditions. Progress has been made toward intermolecular Lewis acid-catalyzed protocols using rare-earth metal triflates but cyclization precursors are still essentially limited to acid halides and anhydrides.[22] Kobayashi's group has reported the direct acylation of phenol and naphthol derivatives with carboxylic acids using a catalytic amount of metal triflate such as $Hf(OTf)_4$, $Zr(OTf)_4$ or $Sc(OTf)_3$.[22b] The intermolecular acylation of aromatics with carboxylic acids at moderate temperature by the combined use of excess perfluoroalkanoic acid anhydride and catalytic $Bi(OTf)_3$ or $Sc(OTf)_3$, via the *in situ* generation of an anhydride intermediate, was described.[23,24]

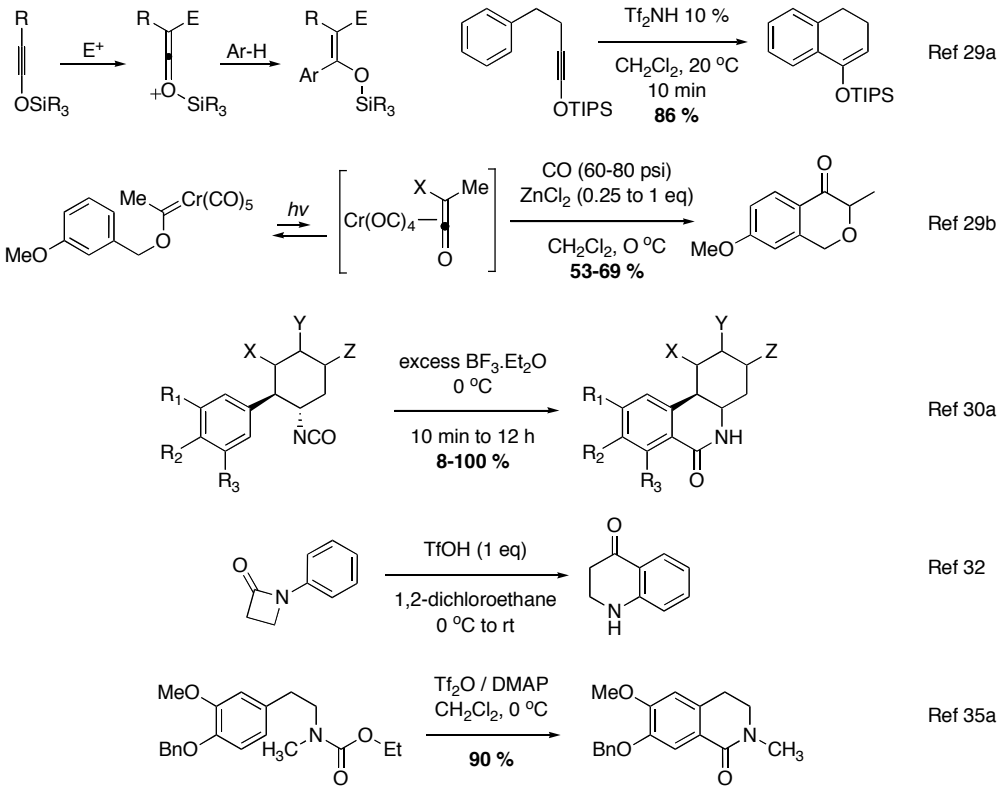
Dehydrative cyclization protocols catalyzed by $Bi(NTf_2)_3$ and $Tb(OTf)_3$ were reported, but elevated temperatures were required, between 180 °C and 200 °C for the synthesis of 1-tetralones[25], and 250 °C for the preparation of 1-indanones.[26,27]

Acylating Agents in the Friedel-Crafts Acylation:

Rather than examining reaction conditions, little attention has been paid to the elaboration of novel acylating agents. Operationally simple intramolecular Friedel-Crafts reactions would be facilitated by the availability of a moisture-stable, highly electrophilic precursor[28] that is easily prepared, functionalized and purified, preferably by recrystallization. Such a precursor should ideally provide aromatic ketones catalytically at moderate temperatures while generating only volatile and inert side-products. This acylating agent should be sufficiently flexible for the facile and expedient modification and assembly of diverse polycyclic ring systems.

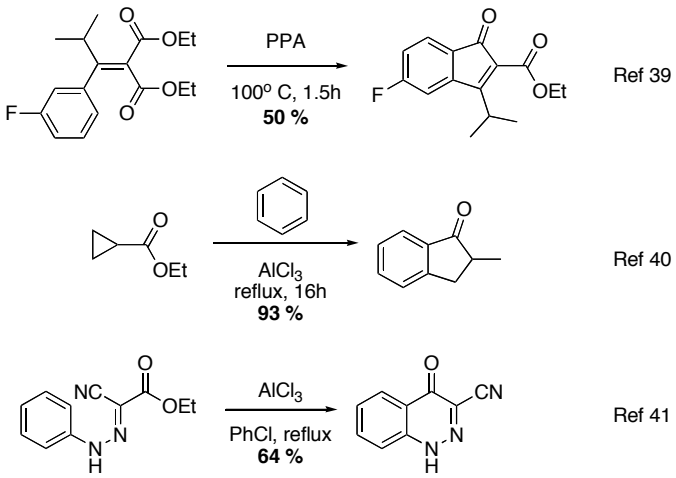
Ketenes[29], isocyanates[30], isothiocyanates[31], β-lactams[32], cyclic anhydrides[33], azalactones[34], carbamates[35], and nitriles[36] have been exploited as electrophiles in intramolecular Friedel-Crafts acylations but with limited success and/or lack of generality (scheme 1.11). Esters and lactones have attracted little attention as acylating agents due to the predominant Friedel-Crafts alkylation pathway[37]; the carboxylate being an excellent leaving group when activated by a Lewis acid.[38]

Scheme 1.11: 'Unconventional' electrophiles recently employed in F-C acylations



A survey of the literature on intramolecular Lewis acid-promoted Friedel-Crafts acylation with esters provided two examples (scheme 1.12).[39] Pinnick and coworkers reported a tandem Friedel-Crafts alkylation/acylation of benzene with ethyl cyclopropanecarboxylate promoted by excess $AlCl_3$ at 80 °C to yield 2-methyl-1-indanone in 93% yield.[40] Gewald's group described the formation of 4-oxo-1,4-dihydro-3-cinnolinecarbonitrile in 64% yield from ethyl 2-cyano-2-(2-phenylhydrazono)acetate and excess $AlCl_3$ at reflux in chlorobenzene.[41]

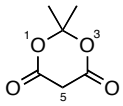
Scheme 1.12: Esters as electrophiles in the Friedel-Crafts acylation



Meldrum's Acid As An Acylating Agent:

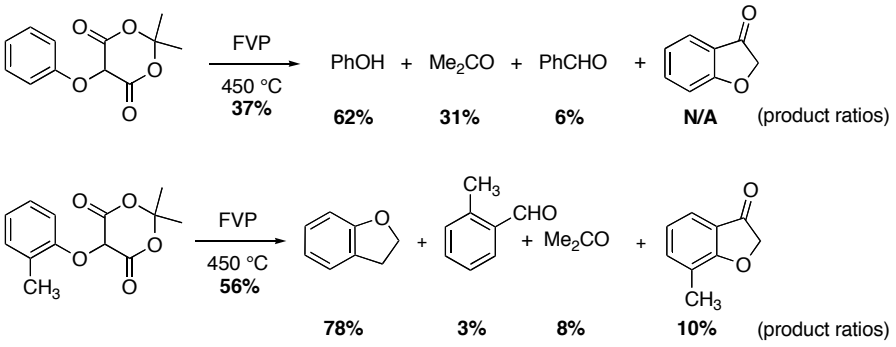
Crow and McNab reported that Meldrum's acid (2,2-dimethyl-1,3-dioxane-4,6-dione) (figure 1.3) could act as an electrophile in the Friedel-Crafts acylation.

Figure 1.3: Meldrum's Acid



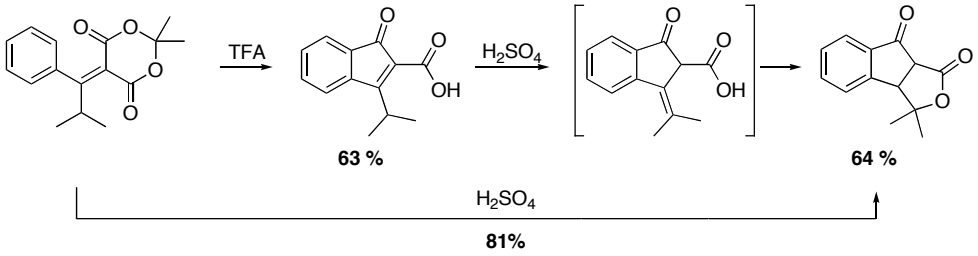
Flash vacuum pyrolysis (FVP) of 2,2-dimethyl-5-phenoxy-1,3-dioxan-4,6-dione at 450 °C yielded benzofuran-2(3H)-one in an undetermined (N/A) yield (Scheme 1.13).[42] Starting from the analogous toluyl derivative, a 10% yield of the Friedel-Crafts acylation product was obtained and the authors proposed that the acylation proceeded via the intermediacy of a phenoxyketene.

Scheme 1.13: FVP of Meldrum's acid derivatives



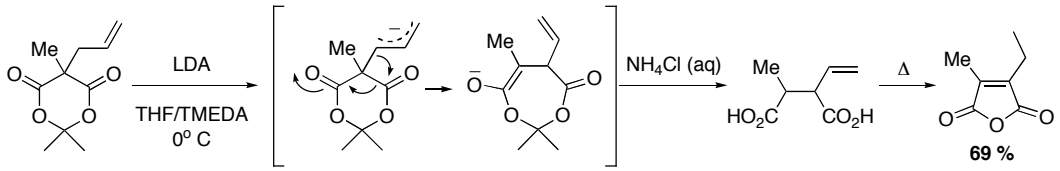
Campaigne and Frierson reported that isopropylidene phenyl Meldrum's acid could form 3-isopropylindenone-2-carbonylic acid after stirring in trifluoroacetic acid. Subsequent stirring in concentrated sulfuric acid provided an indanone-lactone (scheme 1.14).[43] The exclusive use of H_2SO_4 without using TFA provided the indanone-lactone directly.

Scheme 1.14: Friedel-Crafts acylation of Meldrum's acid with stoichiometric acid



Aside from the McNab and Campaigne examples forming aryl ketones, there has only been one occurrence of carbon nucleophiles adding to the carbonyls of Meldrum's acid derivatives.[44] Allylic anions of Meldrum's acid derivatives rearranged to form vinylsuccinates (Scheme 1.15).

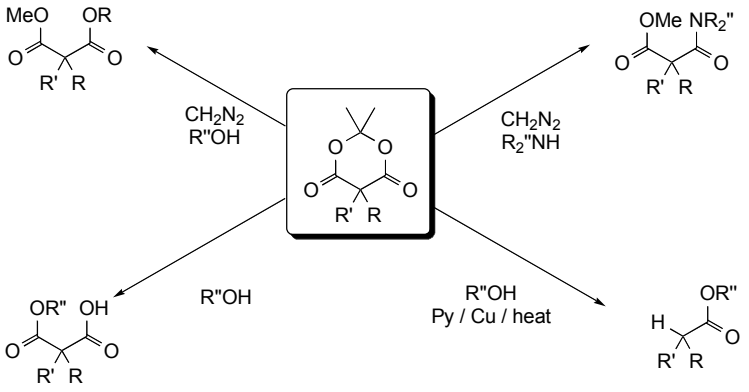
Scheme 1.15. 1,2-Carbonyl migration in 5-allyl Meldrum's acids



Meldrum's acid was discovered in 1908,[45a] yet its structure was not correctly identified until

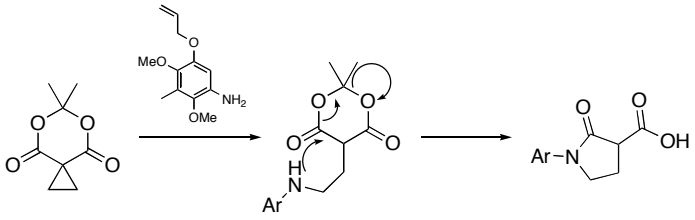
1948.[45b] The high acidity of Meldrum's acid (pKa 4.97)[46] and its propensity to enolize in the presence of weak Brønsted or Lewis bases complicate nucleophilic addition to its highly electrophilic carbonyl groups. Meldrum's acid is a versatile synthetic reagent that is readily mono- and difunctionalized at the 5-position.[47] Meldrum's acid derivatives are typically very easy to purify due to their highly crystalline nature, a property that makes them appealing alternatives to malonic esters in industrial processes. Their most common application is the acylation of heteroatomic nucleophiles via 1,2-carbonyl attack by water, alcohols or amines to provide mono- or diacids, mixed malonates or amides, respectively (scheme 1.16). The exceptional electrophilicity of Meldrum's acid also applies to the Meldrum's acid alkylidenes and arylidenes that readily undergo 1,4-addition to access tertiary and quaternary β-carbons.

Scheme 1.16. Common synthetic uses of Meldrum's acid derivatives



Danishefsky has investigated the ring opening of Meldrum's acid activated cyclopropanes.[48] With aliphatic primary amines, competition between ring cleavage and simple acylation was observed, but with aromatic amines, ring cleavage predominated. Subsequent intramolecular acylation afforded 3-acyl-1-arylpyrrolinones (scheme 1.17). This methodology was applied to the synthesis of a variety of heterocycles.

Scheme 1.17: Heterocycles from Meldrum's acid derivatives



The development of Meldrum's acid as an acylating agent in the Friedel-Crafts acylation reaction offers several advantages over the conventional electrophiles: the precursors are readily prepared by derivatization at carbon 5, and Meldrum's acids are highly stable with a long shelf life at room temperature. It was considered that neutral non-basic π-nucleophiles would add to Meldrum's acid derivatives in the presence of a Lewis acid to further activate the carbonyl groups.[49] In addition, volatile by-products, namely carbon dioxide and acetone, would be generated in the acylation process.

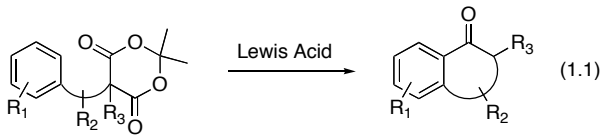
Summary:

Benzocyclic ketones are vital precursors to natural product synthesis and medicinal chemistry. While a number of routes are available for their synthesis, the intramolecular Friedel-Crafts acylation reaction is the most commonly used. Conventional Friedel-Crafts conditions are harsh, requiring more than stoichiometric quantities of Brønsted or Lewis acid promoters and high temperatures, particularly for 1-indanone formation. Some catalytic conditions have recently been reported but these still require high temperatures and rely on the availability of carboxylic acids or derivatives, which can be difficult to prepare, especially for more complex systems. A mild and catalytic intramolecular Friedel-Crafts acylation methodology with broad functional group compatibility and convenient substrate preparation is required.

The purpose of this research is the examination of Meldrum's acid derivatives as acylating agents in the catalytic intramolecular Friedel-Crafts acylation reaction. Meldrum's acids are established organic synthons, but the addition of π-nucleophiles has not been investigated at a practical synthetic level.

Chapter 2 of this thesis presents a full account of our findings on the intramolecular Friedel-Crafts acylation of aromatics with Meldrum's acid derivatives catalyzed by metal

trifluoromethanesulfonates (and other Lewis acids) under mild reaction conditions (Eq. 1.1). This method was further applied to the synthesis of 1-tetralones, 1-benzosuberones, and the acetylcholinesterase inhibitor donepezil.



Chapter 3 of this thesis discusses some investigations into the mechanism of this acylation reaction.

Chapter 4 presents the total synthesis of the natural sesquiditerpenoid Taiwaniaquinol B, which was completed using this methodology, and exploiting the unique reactivity of Meldrum's acids.

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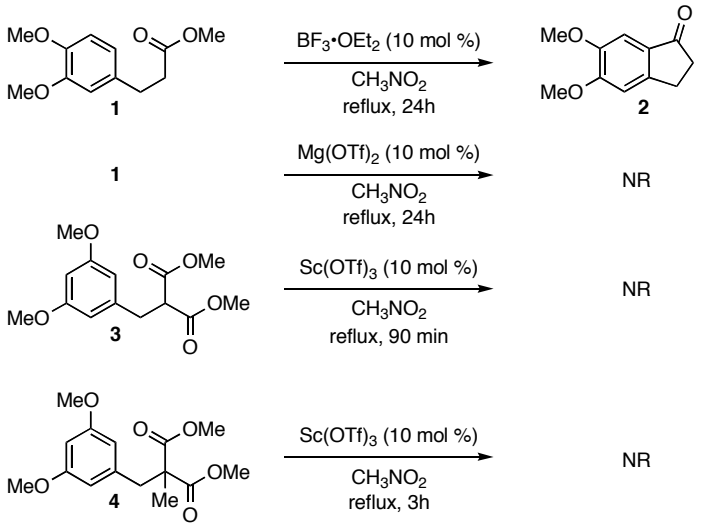
Chapter 2
The Catalytic Intramolecular Friedel-Crafts Acylation of Meldrum's Acid Derivatives

Introduction

Before studying Meldrum's acid as an acylating agent in the intramolecular Freidel-Crafts acylation, malonic esters were evaluated. As discussed in the preceeding chapter, esters have been used as acylating agents in the Friedel-Crafts acylation, but excessive amounts of promoter were required.

In our hands, the application of Pinnick's and Gewald's work to a catalytic Friedel-Crafts acylation protocol with esters for the preparation of 1-indanones was unfruitful. The methyl ester **1**[1], bearing an electron-rich π-nucleophile[2], was treated with a catalytic amount of BF_3•OEt_2. The formation of indanone **2** with only 10% conversion directly reflected the quantity of Lewis acid used and the stoichiometric nature of the process (Scheme 2.1). Since the primary objective was to devise a catalytic acylation reaction, metal trifluoromethanesulfonate catalysts were then examined. Ester **1** was treated with $Mg(OTf)_2$ but the starting material was quantitatively recovered after 24 h at reflux in CH_3NO_2. Mono- and dialkylated malonates **3**[3] and **4** were inert in the presence of $Sc(OTf)_3$, and it was therefore concluded that methyl esters held little promise in metal-catalyzed intramolecular Friedel-Crafts acylation reactions. Efforts were then focused on the development of a more potent electrophile for these reaction conditions, namely, Meldrum's acid.

Scheme 2.1: Intramolecular Friedel-Crafts acylation with esters and malonates



Results and Discussion

Substrate Preparation:

In order to examine the proposed methodology of catalytic Friedel-Crafts acylation with Meldrum's acid derivatives, a ready supply of substrates with appropriately tethered aromatics was required. Meldrum's acid is a poor nucleophile and has a high propensity to overalkylate at the 5-position due to the high acidity of the protons at this position. Because of this overalkyation problem, simple benzylation with a benzyl halide in the presence of a base was not a practical option. Simple 5-benzyl Meldrum's acids **5** (unsubstituted at the benzylic position) could be prepared conveniently on a large scale by reductive alkylation of Meldrum's acid with benzaldehydes (scheme 2.2).

Reductivealkylation methods, which proceed via a tandem Knoevenagel condensation/alkylidene reduction, were previously reported in the literature using sodium hydrogen telluride[4], borane•dimethyl amine complex[5], and triethylammonium formate[6] as the reducing agents.[7] 5-Alkyl Meldrum's acid have been prepared by reducing isopropylidene acylmalonates, via the intermediacy of an alkylidene, with either $NaBH_3CN$ or $NaBH_4$ in AcOH.[8,9] These methods all suffered from the use of rather exotic reagents (such as sodium hydrogen telluride) or a requirement for excess aldehyde. The two-step processes are at a disadvantage when the initial Knoevenagel condensation is poor, since an acceptable yield of the requisite alkylidene can be difficult to obtain cleanly. Based on analogy with the well

known reductive amination methods, it was believed that these reported protocols could be combined such that the condensation/reduction sequence could be conveniently executed in one-pot using $NaBH_3CN$ in a buffered medium.[10] Indeed, benzyl Meldrum's acids **5** were successfully prepared from substituted benzaldehydes and Meldrum's acid using $NaBH_3CN$ at room temperature in the presence of a catalytic amount of piperidinium acetate in EtOH. In most cases, the highly crystalline products were purified, for convenience and practicality, by recrystallization from MeOH or EtOH. $NaBH_3CN$ can easily reduce Meldrum's alkylidenes due to their high electrophilicity, and yet aldehydes remain unreduced. Isolation by crystallization was certainly the most convenient method, but flash chromatography is also an option.

5-Benzyl Meldrum's acid derivatives mono- and disubstituted at the benzylic position (scheme 2.2, **6**) were accessed via 1,4-conjugate addition of aryl Grignard's to Meldrum's alkylidenes following literature procedures.[11] Grignard additions to Meldrum's alkylidenes often result in inconsistent yields and literature yields are frequently difficult to reproduce, particularly with the use of copper salts. Ultimately, the direct, dropwise addition of Grignard reagent to the Meldrum's alkyidene at low temperature (-20° C to 0° C) provided consistent results.

Disubstituted Meldrum's alkylidenes were prepared by Knoevenagel condensation of Meldrum's acid with ketones (cyclohexanone, tetrahydro-4*H*-pyran-4-one, tetrahydrothiopyran-4-one, acetone) in pyridine in the presence of a catalytic amount of piperidine[12], molecular sieves[11a], or via dehydrative condensation using $TiCl_4$ in CH_2Cl_2.[13] The alkylidenes were initially believed to be unstable on silica gel and only purified by recrystallization from MeOH or EtOH. Ultimately it was found that the mother liquors of crystallization could be flashed to recover additional product. Mono-substituted Meldrum's alkylidenes were found to decompose readily on silica gel, however.

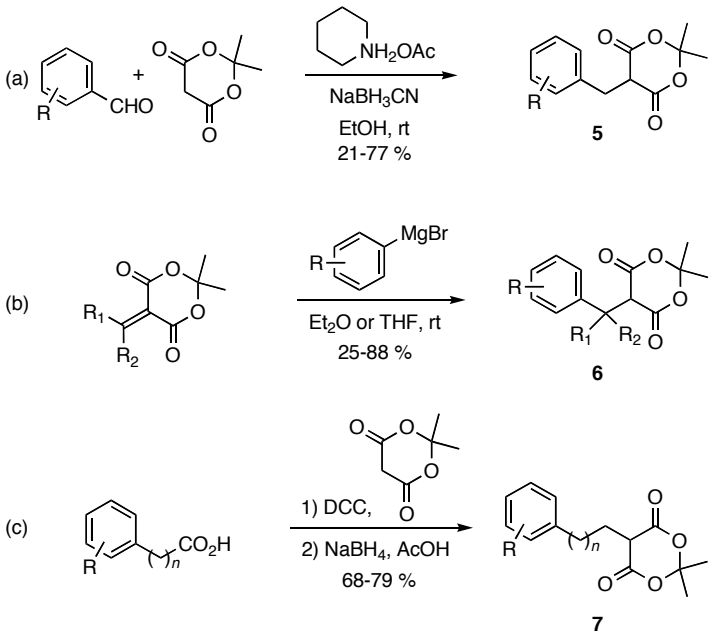
5-Benzyl Meldrum's acid derivatives monosubstituted at the benzylic position could also be obtained by conjugate addition of alkyl and aryl Grignard reagents or dialkylaluminum chloride[14] to Meldrum's acid arylidenes. The arylidenes were obtained by the condensation of Meldrum's acid with benzaldehydes in water[15], or by the addition of aryl Grignards to methoxymethylene Meldrum's acid. The Knoevenagel reaction in water is a particularly effective method for aryl aldehydes, and the desired Meldrum's arylidenes are obtained as

solids after stirring in warm water for only a few hours. It is notable that while the Meldrum's arylidenes are isolated as either white or yellow solids, they all form intense yellow solutions in organic solvents.

Substrates with longer tether length (5-ethylbenzyl and 5-propylbenzyl) (scheme 2.2, **7)** were synthesized using Tsukamoto's methodology.[16] Carboxylic acids were coupled to Meldrum's acid using DCC to form the isopropylidene acylmalonates that were subsequently reduced with $NaBH_4$ in AcOH to the corresponding 5-alkyl Meldrum's acids **7**.

Substrate classes **5** to **7** are termed enolizable Meldrum's acid derivatives since they all contain an acidic proton on carbon 5, and thus can tautomerize to the corresponding enol form (6-hydroxy dioxinone).

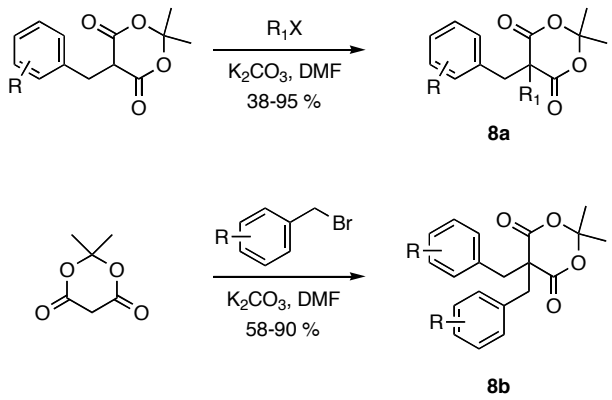
Scheme 2.2: 5-Monosubstituted Meldrum's acid synthesis



Symmetrical 5,5-dibenzyl substrates **8b** were prepared in one-step by reacting Medrum's acid with two equivalents of the appropriate benzyl bromide using K_2CO_3 in DMF (Scheme 2.3).[17] Unsymmetrical 5-benzyl-5-substituted Meldrum's acids **8a** were produced from mono-substituted substrates in an analogous manner, by alkylation with iodomethane, allyl bromide, propargyl bromide, and various benzyl bromides.[18] These quaternarized Meldrum's acids were easily isolated in an analytically pure form by extraction and further purified by

recrystallization from MeOH, or flash chromatography.

Scheme 2.3: 5,5-Disubstituted Meldrum's acid synthesis



Substrate preparation (of all types mentioned above) is facilitated by the exceptional crystallinity of Meldrum's acid derivatives, a property that makes them appealing in industrial applications. Meldrum's acids are often used in place of simple methyl or ethyl malonates because of their ease of functionalization and recovery.

More detailed discussion of specific substrates will be provided below along with the results of the Friedel-Crafts acylation studies.

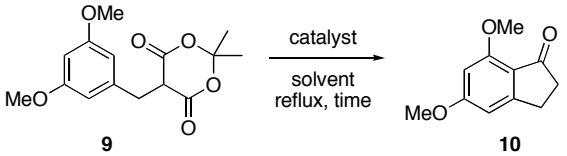
Friedel-Crafts Acylation with Enolizable Meldrum's Acids

Initial investigations focused on the screening of conditions that would promote the intramolecular Friedel-Crafts acylation of very electron rich benzyl Meldrum's acid derivatives. Using the one-pot reductive alkylation method described above, 3,5-dimethoxybenzaldehyde was condensed with Meldrum's acid in the presence of $NaBH_3CN$ to provide **9** in 61% yield after isolation by crystallization from methanol. This substrate is optimal since the aromatic nucleophile is activated at both the *ortho* and *para* positions, and both the 2 and 6 positions are equally available for attack. Furthermore, the desired indanone product **10** is a known compound, and the aromatic region of the NMR would provide very clean and characteristic signals.

Various conditions for the activation of Meldrum's acid were examined, including Lewis acids ($Sc(OTf)_3$, $Dy(OTf)_3$, $Yb(OTf)_3$, and TMSOTf), Brønsted acids (TfOH and TFA), and solvents. Optimal yields for the formation of 5,7-dimethoxy-1-indanone (**10**) were obtained when the acylation was catalyzed by $Sc(OTf)_3$ (table 2.1, entries 7-9). Refluxing nitromethane,

acetonitrile, and 1,2-dichloroethane provided comparable yields but with variable reaction times. Short reaction times motivated the use of nitromethane as the standard solvent. Nitromethane has been frequently used as a solvent for Friedel-Crafts chemistry due to its high polarity and boiling point of 101° C, and it is roughly equal in cost to acetonitrile. Acetonitrile was also found to be an effective solvent, and for many applications might be the solvent of choice due to its ready availability, though its lower boiling point (81° C) is the likely explanation for slightly lower yields and longer reaction times (table 2.1, entry 8).

Table 2.1: Condition screening for intramolecular acylation of Meldrum's derivatives



9 **10**

Entry	Catalyst	Solvent	Time (h)	Yield (%)
1	None	CH_3NO_2	6	55
2	TfOH (20 mol %)	$ClCH_2CH_2Cl$	2.75	38
3	TFA (20 mol %)	$ClCH_2CH_2Cl$	17	37
4	TMSOTf (20 mol %)	$ClCH_2CH_2Cl$	3	60
5	$Dy(OTf)_3$ (12 mol %)	CH_3NO_2	1	56
6	$Yb(OTf)_3$ (12 mol %)	CH_3NO_2	1	67
7	$Sc(OTf)_3$ (10 mol %)	$ClCH_2CH_2Cl$	4.5	72
8	$Sc(OTf)_3$ (8 mol %)	CH_3CN	2	68
9	$Sc(OTf)_3$ (12 mol %)	CH_3NO_2	1	73

$Yb(OTf)_3$ and $Dy(OTf)_3$ provided indanone **10** in lower yields (table 2.1, entries 5 and 6) compared to $Sc(OTf)_3$, even though TLC and ^1H NMR analysis of the crude reaction mixtures revealed clean material that could be easily purified by flash chromatography. When the acylation was conducted with 20 mol % of TMSOTf, TFA, or TfOH in refluxing 1,2-dichloroethane, a 60%, 37%, and 38% yield was obtained, respectively. Furthermore, complex mixtures of products were formed that made the indanone purification tedious.

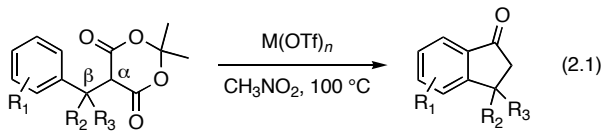
A control reaction conducted in the absence of any promoter revealed that the electrophilic substitution proceeded thermally within six hours in refluxing CH_3NO_2 to yield indanone **10** in 55% yield (table 2.1, entry 1), consistent with thermal decomposition of 5-monosubstituted Meldrum's acid derivatives. At temperatures above 100° C, Meldrum's acid derivatives tautomerize to the corresponding 6-hydroxydioxinones that further undergo a retro Diels-Alder reaction to furnish acylketenes[19] that underwent arylation. The product of the thermal reaction

was comparatively difficult to purify due to the formation of numerous by-products of similar polarity.

Considering the thermal instability of Meldrum's acids and the potential background reaction, it was speculated that the development of a protocol requiring short reaction times would minimize side reactions. Therefore, the typical acylation reaction was conducted by simple combination of the substrate, dried $Sc(OTf)_3$, and distilled nitromethane to a round-bottom flask equipped with a reflux condenser. The resulting suspension was immediately immersed in an oil bath preheated to 100-105° C. Consumption of the starting material was monitored by TLC. The scale of the reactions during methodology development was typically 100 to 300 mg, and so, for practicality, no aqueous workup was performed, and nitromethane was removed by rotary evaporation, and the resulting residue was purified by flash chromatography on silica gel.

Stoichiometric amounts of acetone and CO_2 are produced in the Friedel-Crafts acylation with Meldrum's acids. The volatility of carbon dioxide precludes side reactions with that by-product (particularly at these temperature), but to ascertain whether acylation yields were affected by side reactions between the 1-indanones and acetone, a control experiment was conducted with equimolar amounts of 1-indanone (**47**) and acetone with a catalytic quantity of $Sc(OTf)_3$ in refluxing nitromethane. GC-MS and ^{1}H NMR analysis of the crude reaction mixture showed no decomposition of the indanone, nor any formation of aldol products.

The scope of the intramolecular Friedel-Crafts acylation of 5-benzyl Meldrum's acids has been fully defined by varying the pattern of substitution and electron-donating ability of the π-nucleophile unit, as well as substitution at the β-position (in the tether) to generate a diversity of functionalized 1-indanones in yields ranging from 13 to 86% (Eq. 2.1). The results are compiled in table 2.2.

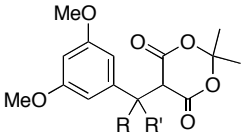
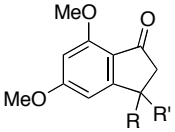
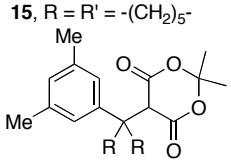
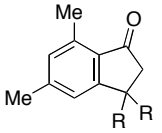
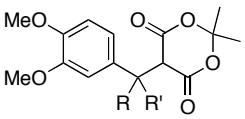
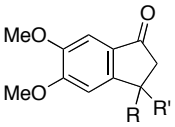
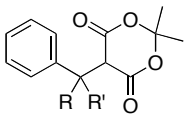
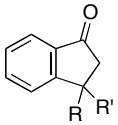


(2.1)

Mixed results were obtained for the acylation with enolizable Meldrum's acids. The electron-rich 3,5-dimethoxybenzyl Meldrum's acid substrates (entries 1-4) provided good yields (73-

83%) of 1-indanones, while yields were modestly lower (13-75%) with the less electron-rich π-nucleophiles (3,5-dimethylbenzyl, 3,4-dimethoxybenzyl, and benzyl).

Table 2.2: Enolizable Meldrum's acids as Friedel-Crafts acylating agents

entry	Meldrum's acid substrate	$M(OTf)_n$	loading (mol %)	time (min)	indanone	yield (%)
						
1	**9**, R = R' = H	$Sc(OTf)_3$	12	60	**10**, R = R' = H	73[a]
2	**11**, R = H; R' = Me	$Sc(OTf)_3$	12	120	**12**, R = H; R' = Me	77[b]
3	**13**, R = R' = Me	$Sc(OTf)_3$	12	120	**14**, R = R' = Me	82[b]
4	**15**, R = R' = $-(CH_2)_5-$	$Sc(OTf)_3$	12	120	**16**, R = R' = $-(CH_2)_5-$	83[b]
						
5	**23**, R = H	$Sc(OTf)_3$	12	560	**24**, R = H	52[c]
6	**25**, R = $-(CH_2)_5-$	$Sc(OTf)_3$	12	90	**26**, R = $-(CH_2)_5-$	75[d]
						
7	**27**, R = R' = H	$Sc(OTf)_3$	10	45	**2**, R = R' = H	59
8	**28**, R = H; R' = Me	$Sc(OTf)_3$	10	20	**29**, R = H; R' = Me	68
9	**30**, R = R' = Me	$Sc(OTf)_3$	9	20	**31**, R = R' = Me	69
						
10	**46**, R = R' = H	$Sc(OTf)_3$	12	540	**47**, R = R' = H	13[e]
11	**48**, R = R' = $-(CH_2)_5-$	$Sc(OTf)_3$	12	30	**49**, R = R' = $-(CH_2)_5-$	56[f]
12	**50**, R = Me; R' = $-(CH_2)_4Cl$	$Sc(OTf)_3$	10	15	**51**, R = Me; R' = $-(CH_2)_4Cl$	52

[a] A 68% yield was obtained in CH_3CN (2 h, 8 mol % catalyst), and a 72% yield in 1,2-dichloroethane (4.5 h, 12 mol % catalys [b] The reaction was run in CH_3CN. [c] The substrate was added by syringe pump, over approximately 8 h, to a refluxing solution of $Sc(OTf)_3$, followed by an additional ~1 h at reflux. The one-pot procedure yielded the indanone in 36% yield. [d] The slow addition protocol furnished the indanone in 73%. [e] The one-pot procedure failed to produce 1-indanone. [f] A yield of 57% was obtained when the slow addition procedure was used.

Referring back to table 2.1 it is apparent that the use of metal triflate catalysts accelerates the acylation reaction, but the yield increase is actually quite modest relative to catalyst loading. Nonetheless, the use of catalyst provided a qualitatively cleaner reaction and an apparent rate increase. For difficult cases (substrates providing a low yield of 1-indanone in the key step) a yield enhancement could be realized using slow addition of substrate into a stirring solution of

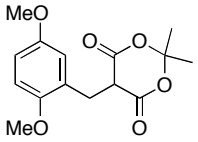
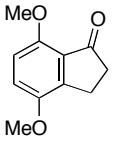
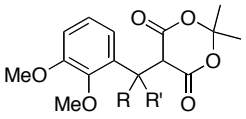
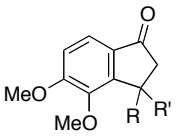
catalyst. 3,5-Dimethylbenzyl Meldrum's acid (**23**) afforded indanone **24** in a 36% yield using the standard protocol described above, yet the yield was increased to 52% via the slow addition technique (table 2.2, entry 5).

The introduction of substituents at the benzylic position (β-position) had a profound influence upon the ease of acylation. Increased substitution slightly improved the efficiency of the acylation reaction for the electron-rich 3,5-dimethoxybenzyl and 3,4-dimethoxybenzyl Meldrum's acid substrates (entries 1-4, and entries 7-9). Substantial yield enhancements were observed for cyclization precursors bearing a weak π-nucleophile like 3,5-dimethylbenzyl Meldrum's acid substrate **25** and benzyl Meldrum's acids **48** and **50** (table 2.2, entries 6, 10 and 11). For the latter, the acylations were reasonably efficient and, for comparison, Meldrum's acid **46** did not provide 1-indanone (**47**) under the same reaction conditions (entry 24). The slow addition procedure failed to increase the yield when the β-position was substituted. These observations may give some insight into the reaction mechanisms at work (discussed in chapter 3), but from a synthetic standpoint, unactivated aromatics could only be effectively acylated if benzylic substituents were present.

The acylation of the 3,4-dimethoxybenzyl substrates **27**, **28**, and **30** was regioselective (table 2.2, entries 7-9) and analysis of the crude mixtures by ^{1}H NMR and GC-MS showed the exclusive formation of 5,6-dimethoxy-1-indanones.

Some interesting results were observed with 2-methoxy containing substrates. A significant number of cases are described in the literature where intramolecular acylation of aryl ethers have proven difficult in the formation of 1-indanones.[20] Particularly challenging is the acylation of aromatics substituted with a methoxy group *meta* to the site of the electrophilic substitution, in which the methoxy inductively deactivates the π-nucleophile. Such a scenario is found in the 3,4-dimethoxybenzyl (table 2.2, entries 7-9), 2,5-dimethoxybenzyl, and 2,3-dimethoxybenzyl Meldrum's acids (table 2.3).

Table 2.3: Substrates containing *meta*- methoxy groups

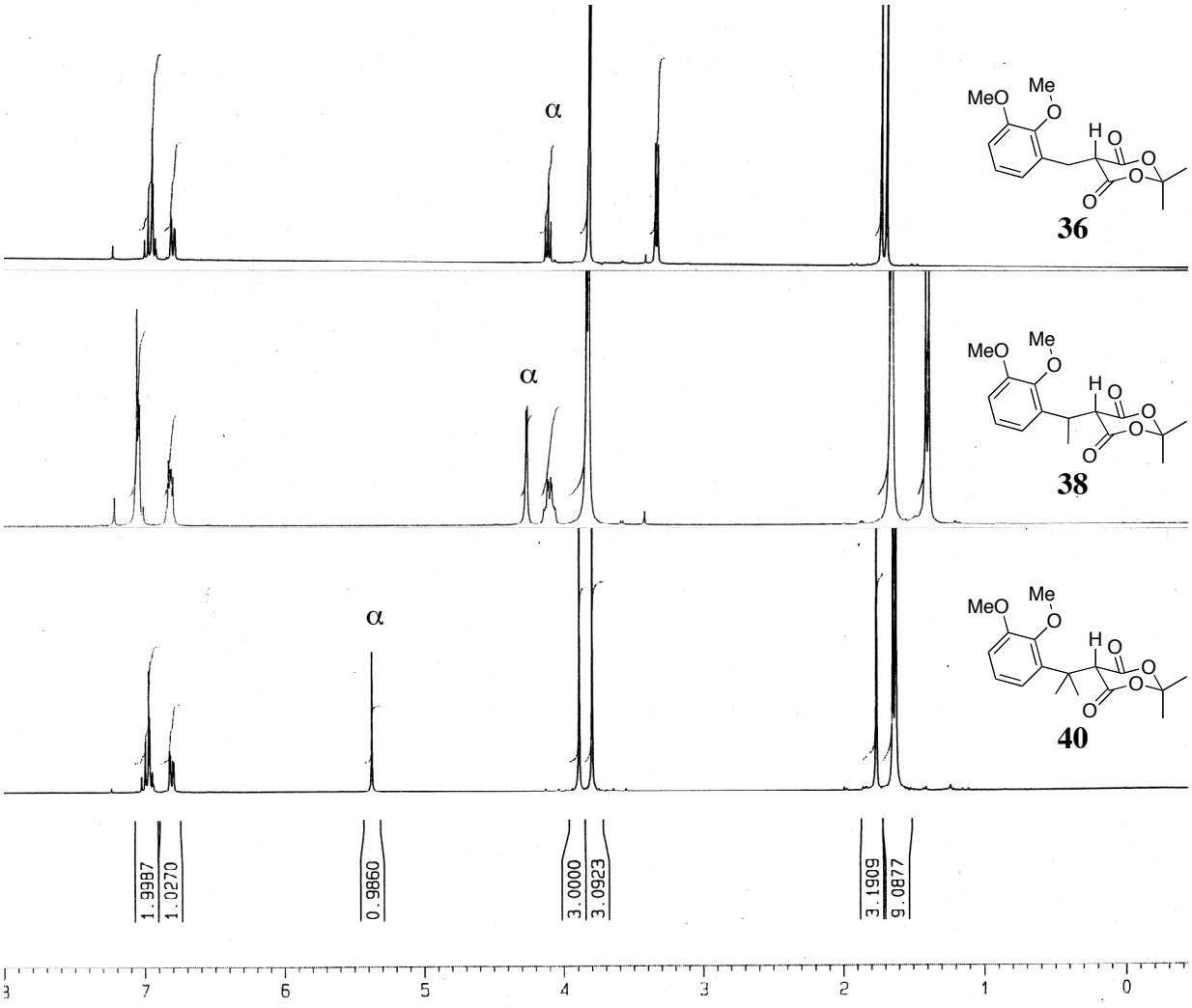
entry	Meldrum's acid substrate	$M(OTf)_n$	loading (mol %)	time (min)	indanone	yield (%)
1	**32** 	$Sc(OTf)_3$	10	20	**33** 	32
						
2	**36**, R = R' = H	$Sc(OTf)_3$	9	80	**37**, R = R' = H	64
3	**38**, R = H; R' = Me	$Sc(OTf)_3$	10	40	**39**, R = H; R' = Me	38
4	**40**, R = R' = Me	$Sc(OTf)_3$	10	35	**41**, R = R' = Me	N/A

Despite the presence of an *ortho* (table 2.3, entry 1) or *para* directing methoxy group (table 2.2, entries 7-9, table 2.3, entries 2-4), the overall π-nuclophilicity of the arene was reduced by the *meta* methoxy substituent and diminished the efficiency of the cyclization.

Substrate **36** underwent acylation providing indanone **37** in 64% yield. It had been expected that successive yield increases would be observed with each additional benzylic substituent as noted in the cases above (table 2.2), but quite a remarkable phenomenon was observed. Acylation of substrate **38**, with a methyl benzylic substitutent, provided a low yield of indanone **39** in 38%. The disubstituted substrate **40** produced only an intractable mixture of decomposition products. This surprising trend reversal may be attributable to the unusual conformation adopted by these substrates compared with the other series of β-substituted Meldrum's acids. That conformational difference is apparent from the unusual chemical shift of the acidic hydrogen of Meldrum's acid (the proton at the 5-position). The chemical shift is 5.38 ppm (singlet) for compound **40**, in comparison to 3.46 ppm and 3.59 ppm respectively for the analogous 3,4-dimethoxybenzyl and 3,5-dimethoxybenzyl Meldrum's acids **30** and **13**. Significant differences are evident within the 2,3-dimethoxy series as well. Figure 2.1 presents the proton NMR spectra with the chemical shifts of the α-protons indicated. Derivative **36** conforms to the trends observed for other Meldrum's derivatives mono-substituted at the 5 position, and little shift is observed for mono-methyl substrate **38**, despite the lower acylation yield (38%). These three compounds were also examined in DMSO-*d6* and the trend was

maintained. The *gem* dimethyl substrate **40** displayed a singlet at 5.19 ppm, compared with 4.64(t) and 4.45(d) for **36** and **38**, respectively. The C-5 ^{13}C chemical shift also reflects a change: **40** presents at 53.5 ppm, compared with 47.1 and 50.8 ppm for **36** and **38** respectively. The inability for **40** to undergo intramolecular acylation remains unclear but must have some relation to the unusual geometry imposed by the benzylic substituents in conjunction with the unusual interaction between the aromatic ring with the Meldrum's acid moiety.

Figure 2.1: NMR of 36, 38 and 40 - unusual chemical shift of α-protons

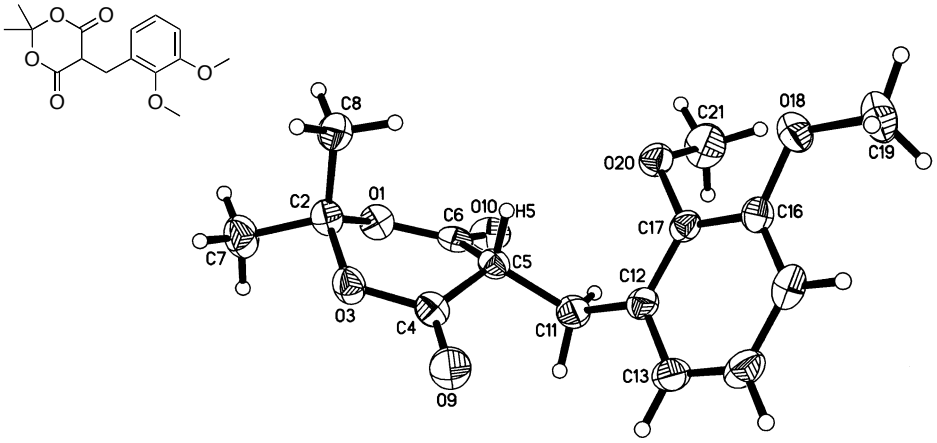


In order to determine the precise structural significance of the NMR data, crystals were grown for X-ray analysis. Once again, the high crystallinity of Meldrum's derivatives was found be very useful, and crystals were grown in methanol or benzene/petroleum ether at room temperature.

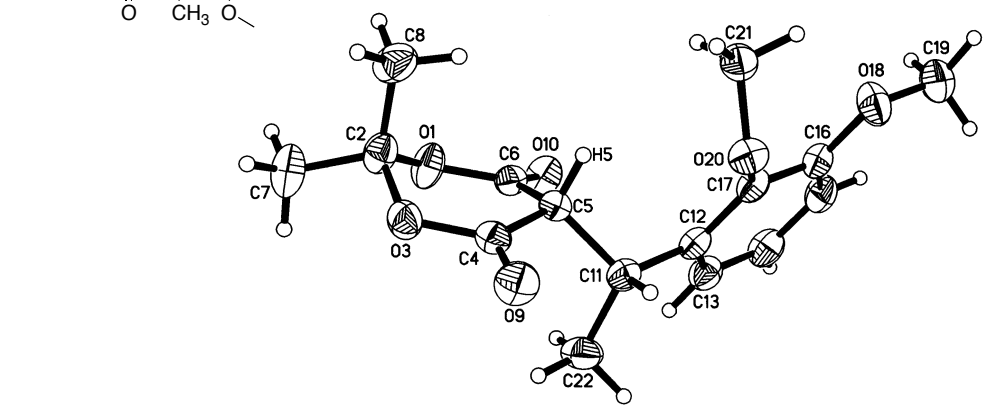
The X-ray structures obtained (figure 2.2) reveal that for the *gem* dimethyl substrate **40**, there is evidence for an intramolecular C-H•••O bond between the α-proton of Meldrum's acid with the oxygen of the *ortho* methyl ether of the aromatic portion.

Figure 2.2: X-ray structures of 36, 38 and 40

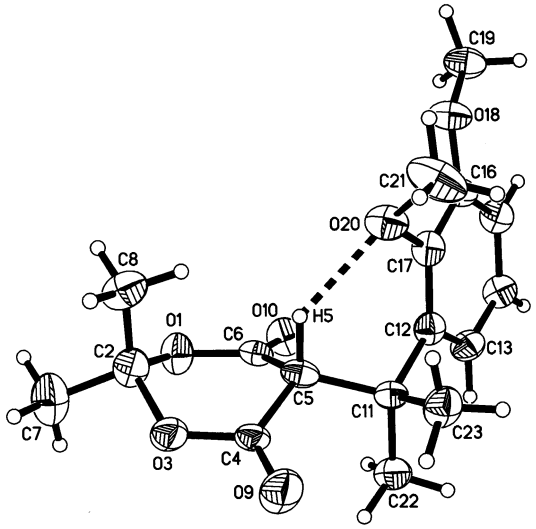
36



38



40

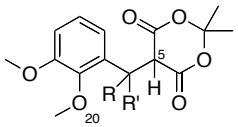


The existence of unusual hydrogen bonds has recently become an area of great interest in structural chemistry, supramolecular chemistry, and biochemistry.[21] The chemical properties of C-H•••X (where X = O, N, Cl) bonds and their persistence in solution have received much attention. The first experimental observations of such bonds in crystals were reported in the early 1960's,[22] and it was proposed that multiple electron withdrawing groups attached to an sp^3-hybridized carbon should be the necessary condition to make the carbon atom a proton donor in a C-H•••X interaction.[23] Despite that initial progress, the field went virtually untouched and few occurrences of such interactions were recognized. The recent reports of C-H•••O bonds that are persistent in solution[24] have rekindled investigations of the phenomenon with an eye to biological and pharmaceutical applications.

C-H•••O bonds are now considered to be involved with protein-protein recognition, enzyme-substrate interactions, biological and non-biological transition state stabilization, and in some cases have been useful in the construction of materials and supramolecular assemblies.[25]

Table 2.4 presents the observed solid-state atom distances for atoms involved in the proposed C-H•••O bond. For compound **40**, that presents the unusual NMR data and a H•••O bond length of about 2.15 Å, a crystal phase change was observed just below room temperature so data is reported for both phases. The low temperature crystal unit cell contains two molecules of **40** and is the reason for two sets of low temperature data.

Table 2.4: Atom distances for X-ray crystal structures



Solid Phase Structure	C5-H5 (Å)	H5-O20 (Å)
36 R = R' = H	0.95	2.55
38 R = H, R' = CH_3	0.97	2.57
40 R = R' = CH_3 room temp	0.94	2.15
40 R = R' = CH_3 (-93 ^oC)	0.97	2.16
40 R = R' = CH_3 (-93 ^oC)	1.01	2.13

Relatively acidic H-donors in the solid state produce short C-H•••O interactions with H•••O distances of ~2.1-2.5 Å.[21] In this series of compounds, an obvious H•••O contraction is observed (by about 0.4 Å). The C-H bond does not appear to change significantly however. C-H bonds in C-H•••O bonds have been reported to either lengthen (red shift) or contract (blue shift).[25]

Why this apparent hydrogen bonding with substrate **40** results in substrate decomposition during the catalytic Friedel-Crafts reaction is not clear. It could simply be a matter of the enforced geometry of the substrate due to benzylic substitents and/or intramolecular H bonding that prohibits appropriate orbital overlap for Friedel-Crafts acylation to occur. Unproductive side reactions via acylketene formed under the reaction conditions would predominate. Alternatively, the proximity of the *ortho* methoxy group to the activated carbonyls of Meldrum's acid may result in *O*-acylation to give an unstable oxonium species[26] that would further lead to decomposition.

Studies of the intramolecular C-H•••O bond are ongoing, and other substrates that display this phenomenon are being explored. Of particular interest is whether the steric limitations imposed by the *gem* dimethyl benzylic groups are necessary in all substrates.

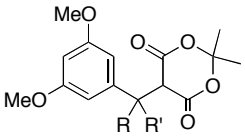
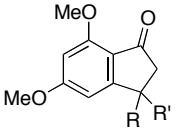
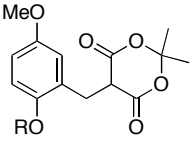
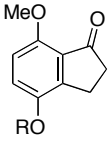
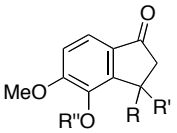
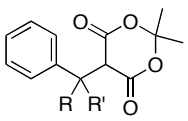
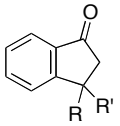
Functional Group Compatibility

A wide range of functional groups was compatible with this Friedel-Crafts acylation methodology. Accompanying aryl methyl ether cleavage by the Lewis acid catalyst has been observed previously in Friedel-Crafts acylation using the classical electrophiles and reaction conditions such as $AlCl_3$, $AlBr_3$[20] or PPA.[27] The Meldrum's based protocol was mild enough to not induce dealkylation of aryl methyl ether *ortho* and *para* to the newly introduced acyl group. Other functional groups were also explored, presented in table 2.5.

Dialkyl ethers (table 2.5, entry 8) and aryl TBDPS and TIPS ethers (table 2.5, entries 18, 22, 23) were accommodated, but the reaction conditions were fine-tuned in some cases. For instance, the Lewis basic cyclic ether **17**, when treated with $Sc(OTf)_3$, yielded a trace amount of indanone **18** but substantial decomposition was also observed. With the theory that $Sc(OTf)_3$ may be sequestered by the dialkyl ether oxygen and result in its cleavage (ultimately leading to further substrate decomposition), other Lewis acid catalysts were considered. The lanthanide triflate $Yb(OTf)_3$ gratifyingly produced the spiro-indanone **18** in 79% yield, but cleanly and quickly. The reaction was carefully monitored and worked-up immediately as the substrate was observed to be completely consumed. A similar result was obtained for the cyclization of dialkyl thioether **19** (table 2.5, entry 10).

The superior mildness of this Friedel-Crafts acylation protocol is illustrated by its compatibility with acid-labile 1,3-dioxolane. Submitting substrate **21** to the standard reaction conditions using $Sc(OTf)_3$ gave a 40% yield, after 20 minutes, of a 1.9:1 mixture of ketal:ketone. While complexation of the dioxolane oxygens with the catalyst is expected, hydrolysis to the ketone is not expected in the absence of water. Extreme efforts were made to exclude water, including fresh distillation of the solvent, additional high-vaccuum drying of the catalyst, and

Table 2.5: Functional group stability under the acylation conditions

entry	Meldrum's acid substrate	$M(OTf)_n$	loading (mol %)	time (min)	indanone	yield (%)
						
1	**17**, R = R' = -$(CH_2)_2O$	$Sc(OTf)_3$	10	15	**18**, R = R' = -$(CH_2)_2O$	N/A
2	**17**, R = R' = -$(CH_2)_2O$	$Yb(OTf)_3$	10	15	**18**, R = R' = -$(CH_2)_2O$	79
3	**19**, R = R' = -$(CH_2)_2S$	$Yb(OTf)_3$	8	20	**20**, R = R' = -$(CH_2)_2S$	86
4	**21**, R = R' = -$(CH_2)_2C(OCH_2)_2$	$Yb(OTf)_3$	7	1260 (21 h)	**22**, R = R' = -$(CH_2)_2C(OCH_2)_2$	78[a]
						
5	**32**, R = Me	$Sc(OTf)_3$	10	20	**33**, R = Me	32
6	**34**, R = TBDPS	$Sc(OTf)_3$	10	35	**35**, R = TBDPS	63
						
7	**36**, R = R' = H; R'' = Me	$Sc(OTf)_3$	9	80	**37**, R = R' = H; R'' = Me	64
8	**38**, R = H; R' = R'' = Me	$Sc(OTf)_3$	10	40	**39**, R = H; R' = R'' = Me	38
9	**40**, R = R' = R'' = Me	$Sc(OTf)_3$	10	35	**41**, R = R' = R'' = Me	N/A
10	**42**, R = R' = H; R'' = TBDPS	$Sc(OTf)_3$	10	40	**43**, R = R' = H; R'' = TBDPS	50
11	**44**, R = R' = H; R'' = TIPS	$Sc(OTf)_3$	13	40	**45**, R = R' = H; R'' = TIPS	45
						
12	**50**, R = Me; R' = -$(CH_2)_5Cl$	$Sc(OTf)_3$	10	15	**51**, R = Me; R' = -$(CH_2)_5Cl$	52

[a] Powdered 5Å MS (100 wt %) were added to the reaction mixture.

conducting the reaction in a sealable Schlenk tube, with all preparations performed in a dry nitrogen glove box. In spite of these efforts, deprotection was still observed. The use of other catalysts was attempted and the yields (and ketal:ketone ratios) improved substantially: $Dy(OTf)_3$ (77%, 2.5:1), $Yb(OTf)_3$ (75%, 1.7:1) and BF_3•OEt_2 (75%, 1.7:1). The proportion of deprotected material was still disappointing, however. Running the acylation with a protic acid scavenger, DTBMP (1 mol %), did not ameliorate the low ketal to ketone ratio and furthermore, a low conversion was obtained. $Mg(OTf)_2$ furnished promising results after 5 hours, giving an inseparable 5.5:1 mixture of 1,3-dioxolane:ketone, in 45% yield. Applying the vigorously anhydrous techniques noted above still failed to improved results with these promising conditions. It was finally found that addition of dried, powdered 5Å molecular sieves

(equal mass ratio), along with catalytic $Yb(OTf)_3$, gave a 78% yield of indanone **22** in 21 hours.[28] Analysis of the crude ^1H NMR showed a 28:1 ratio of 1,3-dioxolane:ketone.

In spite of the special conditions required for successful formation of the 1,3-dioxolane protected indanone, the use of such a protecting group would be incompatible with the conventional methodologies involving stoichiometric Lewis and Brønstead acids. Molecular sieves are metal aluminosilicates: for 5Å molecular sieves the composition is 0.8 CaO: 0.2 Na_2O: 1 Al_2O_3: 2 SiO_2. A control reaction eliminated the possibility that the molecular sieves were the effective catalyst in the transformation (no conversion was observed, and starting material was recovered).

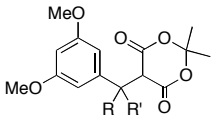
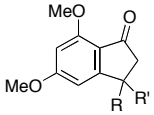
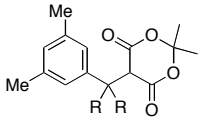
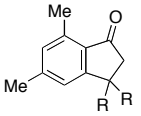
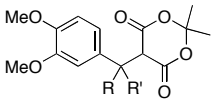
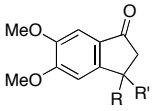
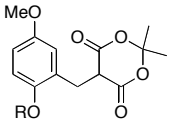
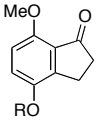
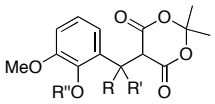
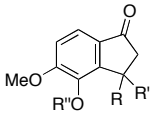
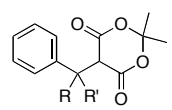
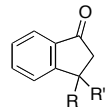
It was anticipated that acylation of 2-trialkylsilyloxy substrates **34**, **42**, and **44** (table 2.5) would be problematic and could lead to the formation of 2-chromanones. Aryltrimethylsilyl ethers have been shown to efficiently add to Meldrum's acid at room temperature to produce monofunctionalized malonic silyl esters.[29] In contrast to this reported reactivity of aryltrimethylsilyl ethers, aryl TIPS and TBDPS ethers were tolerated by the Friedel-Crafts protocol and lactonization not observed. These yields were modest, but once again, the use of these protecting groups would not likely be practical with traditional methods. Furthermore, the methyl ether analogues were not exceptional precursors themselves.

Alkyl chlorides were also compatible. Meldrum's acid **50** gave indanone **51** in 52% yield (table 2.5). This observed reactivity is consistent with that of other unsubstituted benzyl π-nucleophiles. Alkyl halides are useful for further functionalization of the benzocyclic ketones and cannot be directly obtained using classical Friedel-Crafts conditions. Note also that with this substrate and these catalytic conditions, the resulting indanone did not spontaneously undergo intramolecular alkylation with tethered alkylchloride to produce a 6-5-6 fused ring system, though this is an interesting possibility that should be pursued in the future (see also chapter 4 for an alternate approach to this ring system).

Summary For Intramolecular Acylation with Enolizable Benzyl Meldrum's Acids

Table 2.6 presents a master list of results discussed above for Meldrum's acid derivatives that were mono substituted at the 5-position. The yields are quite variable, but functional group tolerance is high, allowing for the formation of 1-indanones containing alkyl and silyl aryl ethers, as well as dialkyl ethers and thioethers, and alkyl chloride moieties.

Table 2.6: Intramolecular Friedel-Crafts acylation with enolizable benzyl Meldrum's acids

entry	Meldrum's acid substrate	$M(OTf)_n$	loading (mol %)	time (min)	indanone	yield (%)
						
1	**9**, R = R' = H	$Sc(OTf)_3$	12	60	**10**, R = R' = H	73[a]
2	**9**, R = R' = H	$Dy(OTf)_3$	12	60	**10**, R = R' = H	56
3	**9**, R = R' = H	$Yb(OTf)_3$	12	60	**10**, R = R' = H	67
4	**9**, R = R' = H	—	—	360	**10**, R = R' = H	55[b]
5	**11**, R = H; R' = Me	$Sc(OTf)_3$	12	120	**12**, R = H; R' = Me	77[c]
6	**13**, R = R' = Me	$Sc(OTf)_3$	12	120	**14**, R = R' = Me	82[c]
7	**15**, R = R' = $-(CH_2)_5-$	$Sc(OTf)_3$	12	120	**16**, R = R' = $-(CH_2)_5-$	83[c]
8	**17**, R = R' = $-(CH_2)_2O$	$Sc(OTf)_3$	10	15	**18**, R = R' = $-(CH_2)_2O$	N/A
9	**17**, R = R' = $-(CH_2)_2O$	$Yb(OTf)_3$	10	15	**18**, R = R' = $-(CH_2)_2O$	79
10	**19**, R = R' = $-(CH_2)_2S$	$Yb(OTf)_3$	8	20	**20**, R = R' = $-(CH_2)_2S$	86
11	**21**, R = R' = $-(CH_2)_2C(OCH_2)_2$	$Yb(OTf)_3$	7	1260 (21 h)	**22**, R = R' = $-(CH_2)_2C(OCH_2)_2$	78[d]
						
12	**23**, R = H	$Sc(OTf)_3$	12	560	**24**, R = H	52[e]
13	**25**, R = $-(CH_2)_5-$	$Sc(OTf)_3$	12	90	**26**, R = $-(CH_2)_5-$	75[f]
						
14	**27**, R = R' = H	$Sc(OTf)_3$	10	45	**2**, R = R' = H	59
15	**28**, R = H; R' = Me	$Sc(OTf)_3$	10	20	**29**, R = H; R' = Me	68
16	**30**, R = R' = Me	$Sc(OTf)_3$	9	20	**31**, R = R' = Me	69
						
17	**32**, R = Me	$Sc(OTf)_3$	10	20	**33**, R = Me	32
18	**34**, R = TBDPS	$Sc(OTf)_3$	10	35	**35**, R = TBDPS	63
						
19	**36**, R = R' = H; R'' = Me	$Sc(OTf)_3$	9	80	**37**, R = R' = H; R'' = Me	64
20	**38**, R = H; R' = R'' = Me	$Sc(OTf)_3$	10	40	**39**, R = H; R' = R'' = Me	38
21	**40**, R = R' = R'' = Me	$Sc(OTf)_3$	10	35	**41**, R = R' = R'' = Me	N/A
22	**42**, R = R' = H; R'' = TBDPS	$Sc(OTf)_3$	10	40	**43**, R = R' = H; R'' = TBDPS	50
23	**44**, R = R' = H; R'' = TIPS	$Sc(OTf)_3$	13	40	**45**, R = R' = H; R'' = TIPS	45
						
24	**46**, R = R' = H	$Sc(OTf)_3$	12	540	**47**, R = R' = H	13[g]
25	**48**, R = R' = $-(CH_2)_5-$	$Sc(OTf)_3$	12	30	**49**, R = R' = $-(CH_2)_5-$	56[h]
26	**50**, R = Me; R' = $-(CH_2)_4Cl$	$Sc(OTf)_3$	10	15	**51**, R = Me; R' = $-(CH_2)_4Cl$	52

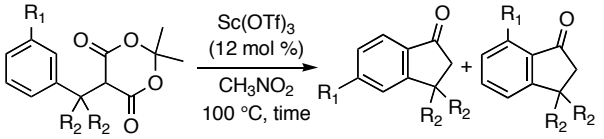
[a] A 68% yield was obtained in CH_3CN (2 h, 8 mol % catalyst), and a 72% yield in 1,2-dichloroethane (4.5 h, 12 mol % catalyst). [b] 90 % Conversion. [c] The reaction was run in CH_3CN. [d] Powdered 5Å MS (100 wt %) were added to the reaction mixture. [e] The substrate was added by syringe pump, over approximately 8 h, to a refluxing solution of $Sc(OTf)_3$, followed by an additional ~1 h at reflux. The one-pot procedure yielded the indanone in 36% yield. [f] The slow addition protocol furnished the indanone in 73%. [g] The one-pot procedure failed to produce 1-indanone. [h] A yield of 57% was obtained when the slow addition procedure was used.

Regioselectivity of the Friedel-Crafts Acylation with Enolizable Meldrum's Acids

Having established the reactivity of Meldrum's acid derivatives with disubstituted and unsubstituted π-nucleophiles with metal triflate catalysis, the acylation protocol was applied to *meta*-substituted aromatics and the regioselectivity of the process determined. As discussed earlier, the importance of substitution at the benzylic position was prominent for substrates bearing a weak π-nucleophilic moiety. Regioisomeric indanones were obtained from 3-methoxybenzyl and 3-methylbenzyl Meldrum's acids **52** and **58** (table 2.7, entries 1-4) in ratios comparable to classical Friedel-Crafts protocols.[30] There is a noteworthy example in the literature, however, in which the regioselectivity of intermolecular acetylation of 2-methoxynapthalene with acetic anhydride is depended on the amount of catalyst used. While 1-acetylated product was obtained in the presence of a catalytic amount of $Yb(OTf)_3$ or $Sc(OTf)_3$, 6-acetylated product was yielded in the presence of a stoichiometric amount of catalyst.[31] Such a phenomenon was not investigated using the Meldrum's system.

Interestingly, the deactivated 3-chlorobenzyl Meldrum's acid substrate **65** provided a mixture of indanones **66** and **67** in 62% yield (table 2.7, entry 6). Cyclization of the analogous substrate **64** unsubstituted at the benzylic position failed (table 2.7, entry 5). This trend is consistent with the observations discussed above, that benzylic subtituents greatly improve cyclization yields or enolizable substrates.

Table 2.7: Friedel-Crafts acylation of (3-substituted)benzyl Meldrum's acids

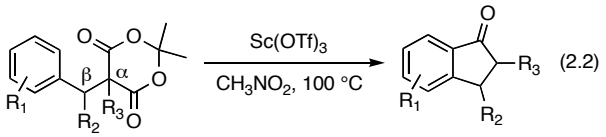


entry	substrate	reaction time (h)	products (*para*:*ortho*)[a]	yield (%)
1	**52,** R_1 = OMe; R_2 = H	1	**53:54 (5.5:1)**	52
2	**55,** R_1 = OMe; R_2 = -$(CH_2)_5$-	2	**56:57 (3.4:1)**	71
3	**58,** R_1 = Me; R_2 = H	1	**59:60 (1:1)**	48
4	**61,** R_1 = Me; R_2 = -$(CH_2)_5$-	2	**62:63 (1:1)**	62
5	**64,** R_1 = Cl; R_2 = H	2		N/A
6	**65,** R_1 = Cl; R_2 = -$(CH_2)_5$-	2	**66:67 (2:1)**	62

[a] Ratio determined by analysis of the crude ^{1}H NMR.

Influence of Substitution at the α-Position of Meldrum's Acids — Intramolecular Friedel-Crafts Acylation with Quaternarized Benzyl Meldrum's Acids

In pursuit of our objective of synthesizing polysubstituted 1-indanones, the influence of substitution at the α-position of Meldrum's acid (5-position) was investigated (Eq. 2.2).



(2.2)

The acylation of quaternarized Meldrum's acid was conducted with substrate **68** using the conditions developed for the cyclization of enolizable benzyl Meldrum's acids. Contrary to the enolizable substrates, no cyclization occurred in the absence of a catalyst. The quaternarized (non-enolizable) Meldrum's are thermally stable, as they cannot enolize and subsequently undergo a retro Diels-Alder reaction.

Intuitively, increased substitution at the position α to the carbonyls was anticipated to result in a decreased reactivity in the catalytic reaction based on steric arguments.[32] The acylation of **68** furnished smoothly 5,7-dimethoxy-2-methyl-1-indanone (**69**) within 45 minutes in 80% yield (table 2.8, entry 1). The potential efficacy of quaternarized Meldrums's acids was confirmed by the high yielding acylation of 5-methyl-5-(3,5-dimethylbenzyl) Meldrum's acid (**70**). In comparison to the analogous 3,5-dimethylbenzyl Meldrum's acid substrates **23** (table 2.6, entry 12), a substantial decrease in reaction time with a markedly increasing yield was observed.

These results on the acylation with quaternarized Meldrum's acid identified a direct and convenient entry into 2-alkyl-1-indanones. The preparation of this type of medicinally relevant structures usually requires several steps starting from 1-indanones due to the propensity for over alkyation. On the basis of these results, the scope of the intramolecular Friedel-Crafts acylation of quaternarized Meldrum's acids was investigated by varying the pattern of substitution and electron-donating ability of the π-nucleophile moiety, giving access to a diversity of functionalized 2-substituted-1-indanones in yields ranging from 66 to 94%.

As shown in table 2.8, excellent results were obtained for the Friedel-Crafts acylation with quaternarized Meldrum's acids for a variety of substrates. π-Nucleophilicity was not as crucial

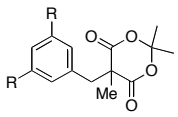
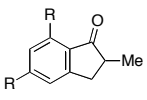
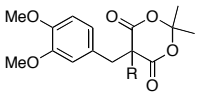
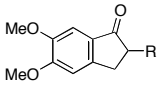
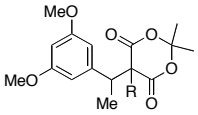
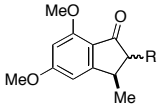
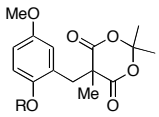
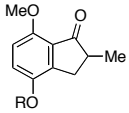
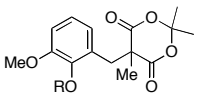
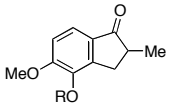
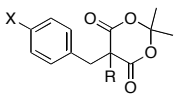
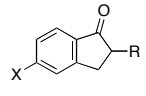
as was observed for the enolizable substrates, and a range of aromatics including 3,4-dimethoxybenzyl, 3,5-dimethoxybenzyl, 2,5-dimethoxybenzyl, and 2,3-dimethoxybenzyl efficiently generated benzocyclic ketones (table 2.8, entries 3-10 and 13-17). The benzyl substrate **102** provided 66% yield of 2-benzyl-1-indanone **103** which is remarkable considering the inability of simple benzyl Meldrum's acid to cyclize in the enolizable series (table 2.8, entries 18 and 19 versus table 2.2, entry 10). In addition to a methyl group, various substituents (allyl, propargyl, aryl, and benzyl) could easily be introduced at the 2-position of the 1-indanones (table 2.8, entries 4-10).

A route to 2,3-disubstituted-1-indanones by the *C*-alkylation of (β-methyl)benzyl Meldrum's acid **11** with iodomethane and benzyl bromide to form substrates **88** and **90** respectively, was developed. Upon treatment with catalytic $Sc(OTf)_3$, the synthesis of indanones **89** and **91** was achieved as diastereomeric mixtures in greater than 90% yield (table 3, entries 11 and 12). An inherent limitation of this strategy is the inability to C-alkylate (α,α-disubstituted)benzyl Meldrum's acid.[33] Although acylation of these precursors would provide access to 2,3,3-trisubstituted-1-indanones, the generation of two contiguous all-carbon quaternary centers in these substrates was prohibitive.

As observed with the enolizable substrates, functional group tolerance was exceptional. Alkenes, alkynes, aryl nitrile, nitro and aryl ethers and silyl ethers were tolerated, all providing α-substituted 1-indanones in good to excellent yields.

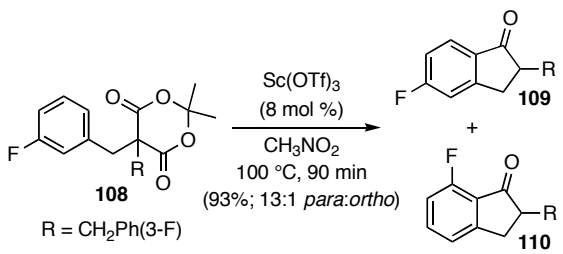
Friedel-Crafts acylation of the electron-deficient 5,5-di-(4-fluorobenzyl) Meldrum's acid (**104**) and the analogous nitro compound **106** failed (table 4, entries 20 and 21). In both cases, complete decomposition of starting material was observed without providing the desired indanones **105** and **107**.

Table 2.8: Quaternarized benzyl Meldrum's acids in Friedel-Crafts acylation

entry	Meldrum's acid substrate	catalyst	loading (mol %)	time (min)	indanone	yield (%)
						
1	**68**, R = OMe	$Sc(OTf)_3$	10	45	**69**, R = OMe	80
2	**70**, R = Me	$Sc(OTf)_3$	11	30	**71**, R = Me	87
						
3	**72**, R = Me	$Sc(OTf)_3$	10	45	**73**, R = Me	77
4	**74**, R = Ph	$Sc(OTf)_3$	10	60	**75**, R = Ph	67
5	**76**, R = Bn	$Sc(OTf)_3$	10	45	**77**, R = Bn	80
6	**78**, R = $CH_2C{=}CH_2$	$Sc(OTf)_3$	10	45	**79**, R = $CH_2C{=}CH_2$	76
7	**80**, R = CH_2CCH	$Sc(OTf)_3$	10	45	**81**, R = CH_2CCH	80
8	**82**, R = $CH_2Ph(4\text{-}CN)$	$Sc(OTf)_3$	17	320	**83**, R = $CH_2Ph(4\text{-}CN)$	78[a]
9	**84**, R = $CH_2Ph(4\text{-}NO_2)$	$Sc(OTf)_3$	10	250	**85**, R = $CH_2Ph(4\text{-}NO_2)$	81
10	**86**, R = CH_2PhF_5	$Sc(OTf)_3$	7	85	**87**, R = CH_2PhF_5	80
						
11	**88**, R = Me	$Sc(OTf)_3$	10	155	**89**, R = Me (*trans*:*cis* 5.6:1)[b]	91
12	**90**, R = Bn	$Sc(OTf)_3$	17[c]	1935 (32 h)	**91**, R = Bn (*trans*:*cis* 12.3:1)[b]	92
						
13	**92**, R = Me	$Sc(OTf)_3$	10	20	**93**, R = Me	69
14	**94**, R = TBDPS	$Sc(OTf)_3$	12	20	**95**, R = TBDPS	94
						
15	**96**, R = Me	$Sc(OTf)_3$	9	20	**97**, R = Me	75
16	**98**, R = TBDPS	$Sc(OTf)_3$	9	30	**99**, R = TBDPS	86
17	**100**, R = TIPS	$Sc(OTf)_3$	10	40	**101**, R = TIPS	77
						
18	**102**, R = Bn; X = H	$Sc(OTf)_3$	10	50	**103**, R = Bn; X = H	66
19	**102**, R = Bn; X = H	TfOH	10	50	**103**, R = Bn; X = H	71
20	**104**, R = $CH_2Ph(4\text{-}F)$; X = F	$Sc(OTf)_3$	10	360	**105**, R = $CH_2Ph(4\text{-}F)$; X = F	N/A
21	**106**, R = $CH_2Ph(4\text{-}NO_2)$; X = NO_2	$Sc(OTf)_3$	10	60	**107**, R = $CH_2Ph(4\text{-}NO_2)$; X = NO_2	N/A

[a] A 73% yield was obtained after 550 minutes when the reaction was run using 11 mol % catalyst. [b] Determined by analysis of the crude ^1H NMR. [c] The catalyst was added in two portions. The reaction was initially started with 7 mol % of catalyst followed by an additional 10 mol % after 23.5 h.

On the other hand, the aromatic substitution of 5,5-di-(3-fluorobenzyl) Meldrum's acid (**108**) resulted in a 93% yield of 1-indanones **109** and **110** in a 13:1 regioisomeric mixture in favor of the *para* product (Eq. 2.3).[34]



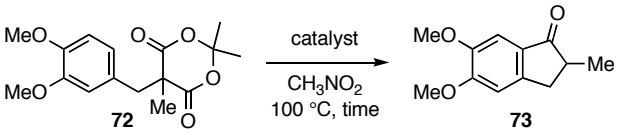
(2.3)

Optimization of the Lewis Acid Catalyst In The Quaternarized Case

The excellent reactivity of quaternarized Meldrum's acid systems prompted the reexamination of the reaction conditions initially developed for the acylation of enolizable substrates. To this end, several Lewis acids were surveyed with 5-(3,4-dimethoxybenzyl)-5-methyl Meldrum's acid (**72**). As depicted in table 2.9, in addition to $Sc(OTf)_3$, numerous metal trifluoromethanesulfonates (aluminum, magnesium, copper, trimethylsilyl) successfully catalyzed the Friedel-Crafts acylation reaction.[35] Other excellent candidates were TfOH, and magnesium bis(trifluoromethanesulfonyl)amide (table 2.9, entries 6, and 11). Unexpectedly, BF_3•OEt_2 was shown to suitably catalyze the acylation reaction (table 2.9, entry 10). This marks the *first* example of BF_3•OEt_2-catalyzed Friedel-Crafts acylation and it appears not to suffer from the catalyst inhibition reported for conventional systems.

The Lewis acids TMSCl and $AlCl_3$ were ineffective at promoting the acylation reaction. The former returned starting material while the latter yielded a trace amount of 1-indanone. With $AlCl_3$, the electrophilic aromatic substitution was sluggish and the main reaction pathway was formation of the acid chloride by the opening of the Meldrum's acid moiety by a chloride ion, following complexation with the carbonyl group. Aqueous workup furnished the corresponding carboxylic acid.

Table 2.9: Optimization of the Lewis acid catalyst



entry	catalyst	loading (mol%)	reaction time (min)	yield (%)
1	$Sc(OTf)_3$	10	20	85
2	$Al(OTf)_3$	10	20	69
3	$Mg(OTf)_2$	10	20	83
4	$Cu(OTf)_2$	10	20	82
5	TMSOTf	10	20	90
6	TfOH	10	20	86
7	LiOTf	10	70	NR
8	KOTf	20-60	90	NR
9	TMSCl	10-35	90	NR
10	BF_3•OEt_2	10	20	90
11	$Mg(NTf_2)_2$	10	30	84

Applying other Lewis acids than $Sc(OTf)_3$ to the dibenzyl Meldrum's acid substrate (**102**) was unproductive. A catalytic amount of BF_3•OEt_2 led to trace formation of 2-benzyl-1-indanone (**103**) and starting material recovery while $Mg(OTf)_2$ was unable to promote this transformation. From these results, the general superiority of $Sc(OTf)_3$ is obvious, particularly for weak π-nucleophiles. Trifluoromethanesulfonic acid was found to be equally competent (table 2.9, entry 19). Further discussion of the relative rates of this reaction with different Lewis acids will be made in chapter 3.

Functional Group Tolerance

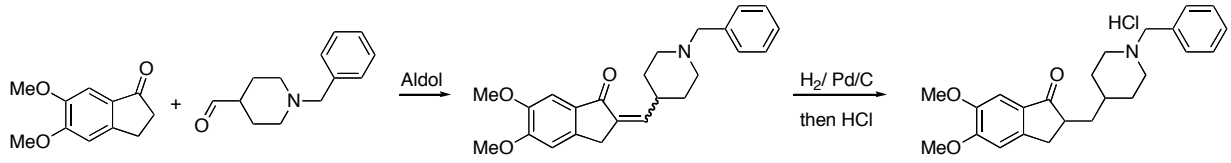
Functional group compatibility was consistent with the results obtained in the enolizable Meldrum's acid series. Again, aryl methyl and aryl TBDPS and TIPS ethers were accommodated (table 2.8, entries 14, 16, and 17). The mild nature of the Friedel-Crafts acylation process was further demonstrated by reacting substrates containing a terminal alkyne or alkene (table 2.8, entries 6 and 7), as well as nitro- and nitrile-substituted aryl groups (table 2.8, entries 8 and 9). Prolonged reaction times were required for Lewis basic functional groups, likely due to partial deactivation of the catalyst.

Compatability of The Methodology With Nitrogen – Synthesis of Donepezil via Intramolecular Catalytic Friedel-Crafts Acylation

The synthesis of the potent acetylcholinesterase inhibitor donepezil (Figure 1.2) was tackled, as it contains a tertiary amine within its structure. Donepezil hydrochloride[36] is a selective inhibitor of acetycholinesterase and is the first agent with this mode of action approved for the treatment of mild to moderate Alzheimer's disease. Originally developed by Eisai Pharmaceuticals, it is licensed to Pfizer and marketed as Aricept®. It was first approved in the US in 1997 and now available all over the world.

Donepezil is synthesized through the Aldol condensation of 5,6-dimethoxy-1-indanone and *N*-benzyl-4-formylpiperidine, followed by double bond reduction (scheme 2.4).[37]

Scheme 2.4: Industrial manufacture of Donepezil



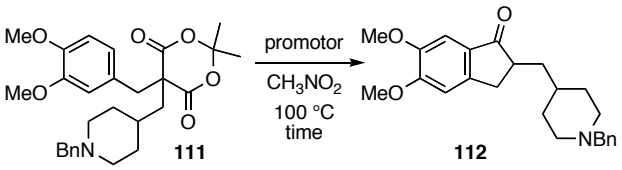
While the industrial route is obviously effective, it begins with the rather expensive 5,6-dimethoxy-1-indanone. The use of this Meldrum's acid Friedel-Crafts methodology would enable an aryl-carbonyl carbon retrosynthetic disconnection. This would greatly facilitate medicinal chemistry investigations and structure-activity studies of this class of inhibitors since both the aromatic and piperidinyl moieties could be easily changed.

Attempts at acylating quaternarized Meldrum's acid **111** with a catalytic amount of $Sc(OTf)_3$ failed (table 2.10, entry 1). It was postulated that the catalyst was inhibited by the Lewis basic tertiary amine[38], though $Sc(OTf)_3$ has been shown to be an effective catalyst in the presence of basic amines in certain transformations.[39] Deactivation of $La(OTf)_3$ by DABCO[38b] has been reported, resulting in significant rate reductions in the Lewis acid catalyzed Baylis-Hillman reaction. Kobayashi reported a significant yield decrease with lower catalyst ($Sc(OTf)_3$) loadings in nucleophilic additions to *N*-acylimino esters, generated *in situ* using triethylamine.[40] This was assumed to be due to coordination of the catalyst with Et_3N. The use of both solid supported tertiary amine and solid supported $Sc(OTf)_3$ resulting in excellent yields. When substrate **111** was treated with excess $Sc(OTf)_3$, donepezil (**112**) was formed but the yield was

undetermined due to its difficult isolation from the reaction mixture (table 2.10, entry 2).

It was considered that protonating the tertiary amine with trifluoromethanesulfonic acid, and conducting the Friedel-Crafts acylation with catalytic $Sc(OTf)_3$ might give the same result, but for the sake of simplicity, a slight excess of TfOH alone was used. Donepezil (**112**) was generated smoothly by the reaction of Meldrum's acid **111** with 120 mol % of TfOH in a 61% yield (table 2.10, entry 3). The use of stoichiometric toluenesulfonic acid with catalytic $Sc(OTf)_3$ gave no reaction and starting material was recovered.

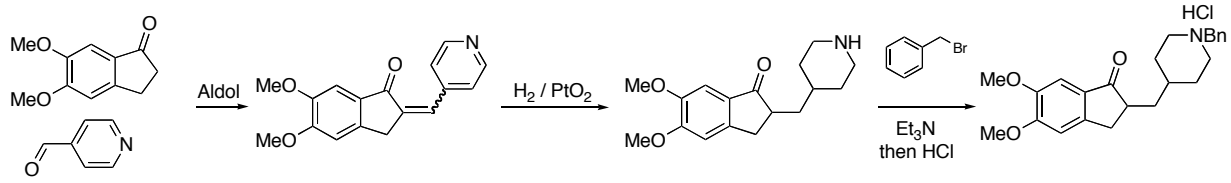
Table 2.10: Donepezil synthesis via intramolecular Friedel-Crafts acylation



entry	promotor	loading (mol %)	reaction time	yield (%)
1	$Sc(OTf)_3$	15	28 h	NR
2	$Sc(OTf)_3$	170	4 h	N/A
3	TfOH	120	30 min	61

The striking observations made with substrate **111** led to the conclusion that the presence of a basic sp^3-hybridized amine was problematic. In an attempt to circumvent this issue, the synthesis of indanone **114** from Meldrum's acid **113** was explored (table 2.11). The sp^2-hybridized nitrogen in **113** should be less prone to interact with the catalyst and reduce its activity. Furthermore, the transformation of indanone **114** into donepezil hydrochloride has been reported (scheme 2.5).[41]

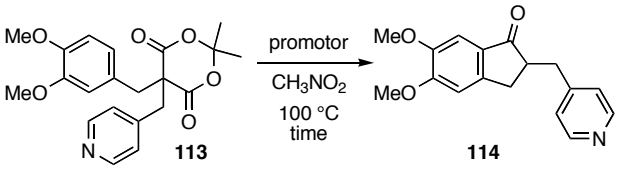
Scheme 2.5: Industrial manufacture of donepezil via a pyridine derivative



Unfortunately, all attempts to form **114** under catalytic conditions were unsuccessful and starting material recovered (table 2.11, entries 1, 2, 6, and 8). Triflic acid cleanly promoted the

formation of indanone **114** in 77% yield (table 2.11, entry 3), but TFA or a 5:1 mixture of TFA/TfOH failed. Decomposition of the starting material (table 2.11, entry 7) was observed with excess BF_3•OEt_2. The volatile TMSOTf, when used in slight excess, induced the Friedel-Crafts acylation and indanone **114** was isolated in a 62% yield (table 2.11, entry 9).

Table 2.11: Acylation of pyridine-containing substrate 113



entry	promotor	loading (mol%)	reaction time (h)	yield (%)
1	$Sc(OTf)_3$	10	0.33	NR
2	$Sc(OTf)_3$	40	14	NR
3	TfOH	120	1	77
4	TFA	120	3	NR
5	TFA/TfOH	100/20	44	NR
6	BF_3•OEt_2	10	19	NR
7	BF_3•OEt_2	120	14	N/A
8	TMSOTf	20	19	NR
9	TMSOTf	120	1.5	62

In light of these results, it is concluded that nitrile and nitro groups are compatible with the catalytic protocol (table 2.8, entries 8 and 9), while sp^2- and sp^3-hybridized nitrogen containing functionalities require excess TfOH or Lewis acid to proceed.

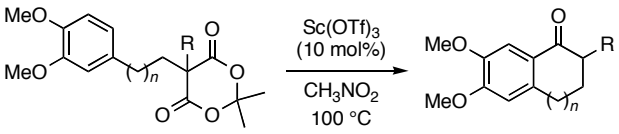
1-Tetralone and 1-Benzosuberone Synthesis

The use of Meldrum's acid derivatives as the acylating agent in the synthesis of 1-tetralones and 1-benzosuberones was examined. Yield enhancement was significant for the enolizable Meldrum's substrate **115**, which furnished tetralone **116** in 82% yield compared with 59% yield for its indanone counterpart **2** (table 2.12, entry 1 and table 2.2, entry 7). Quaternarized Meldrum's acid **117** provided 6,7-dimethoxy-1-tetralone (**118**) in 82% yields (table 2.12, entry 2). Moreover, 1-benzosuberones were efficiently formed for both types of Meldrum's acid precursors (table 2.12, entries 3 and 4). The ability to access 1-indanones, 1-tetralones and 1-benzosuberones using this methodology greatly expands its usefulness.

These results were very pleasing, especially since the enolizable derivatives can produce tetralones and benzosuberones is very good yields. These results are also consistent with the

known difficulty in forming 1-indanones with acid promoted Friedel-Crafts acylations.

Table 2.12: Synthesis of 1-tetralones and 1-benzosuberones

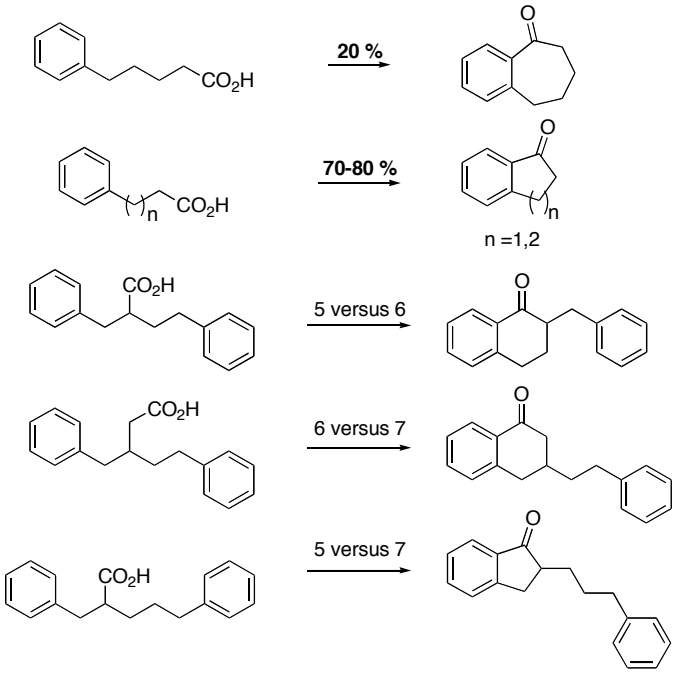


entry	substrate	reaction time (min)	product	yield (%)
1	**115**, R = H; n = 1	45	**116**, R = H; n = 1	82
2	**117**, R = Me; n = 1	15	**118**, R = Me; n = 1	82
3	**119**, R = H; n = 2	45	**120**, R = H; n = 2	78
4	**121**, R = Me; n = 2	15	**122**, R = Me; n = 2	81

Rate of Cyclization as a Function of Ring Size

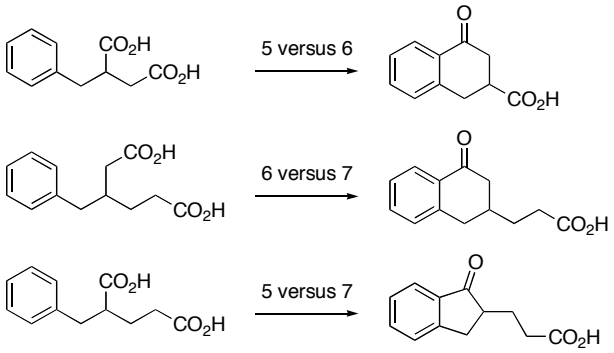
In the Friedel-Crafts acylation, it is well established that 1-tetralones are readily formed in preference to the analogous 1-indanones and 1-benzosuberones.[42] Milder reaction conditions are usually required and higher yields typically obtained. It is widely accepted that the tendency towards formation of various ring sizes favors 6>5>7, as reviewed by Johnson.[43] That review briefly describes the results of competition studies of carboxylic acids are illustrated in scheme 2.6.

Scheme 2.6: Intramolecular ring size competition experiments (1)



Heaney describes another set of competition experiments (scheme 2.7).[44] A particular flaw with this set is that the competing carboxylic acid electrophiles are primary or secondary, making fair comparisons difficult.

Scheme 2.7: Intramolecular ring size competition experiments (2)

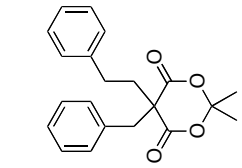
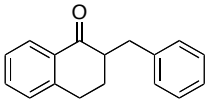
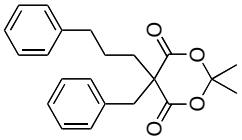
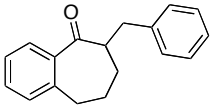
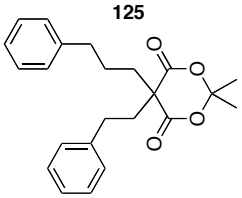
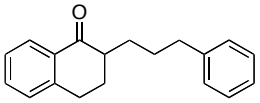
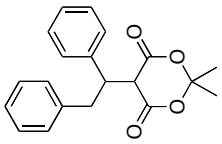
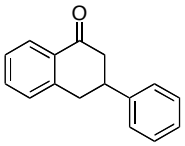
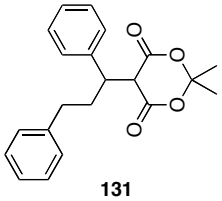
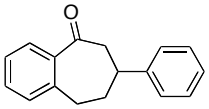
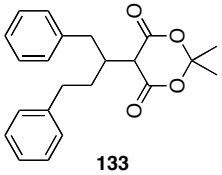
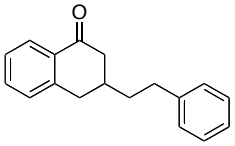


Using the Meldrum's acid electrophile system, the uncompetitive experiments (table 2.12) gave results contrary to the expected order of reactivity; 1-benzosuberone formation was facile for the enolizable Meldrum's substrate, (table 2.12, entries 3 and 4) when compared to the analogous 1-indanone (table 2.2, entry 7).

To probe the effect of tether length on the relative rate of cyclization, substrates that could give mixtures of products of various ring size were synthesized. The study was realized in the

enolizable and non-enolizable Meldrum's acid substrates series using $Sc(OTf)_3$ (10 mol %) in nitromethane at 100 °C. For each of the six models presented in table 2.13, crude ^1H NMR and GC-MS analysis showed the exclusive formation of a *single* benzocyclic ketone.

Table 2.13: Ring size competition experiments with Meldrum's acid derivatives

entry	substrate	product	yield[a] (%)
1	 **123**	 **124**	75[b]
2	 **125**	 **126**	77[b]
3	 **127**	 **128**	76[b]
4	 **129**	 **130**	51[c]
5	 **131**	 **132**	42[c]
6	 **133**	 **134**	59[c]

[a] The acylation was carried out using $Sc(OTf)_3$ (10 mol %) in CH_3NO_2 at 100 °C. [b] Reaction time is 45 min. [c] The substrate was added by syringe pump, over approximately 8 h, followed by an additional ~1 h at reflux.

Quaternarized Meldrum's acids were efficiently acylated (table 2.13, entries 1-3) and 1-tetralones preferentially formed over 1-benzosuberones and 1-indanones. This set of experiments also confirmed that 1-benzosuberones are generated preferentially over 1-indanones (table 2.13, entry 2). An identical trend was observed for the enolizable Meldrum's acids **129**, **131**, and **133** (table 2.13, entries 4-6). Therefore, for the intramolecular Friedel-Crafts acylation with Meldrum's acid derivatives, the ring formation preference is 6>7>5.

Summary

- Exploitation of the exceptional electrophilicity and convenient functionalization of Meldrum's acid provides benzocyclic ketones by catalytic intramolecular Friedel-Crafts acylation.
- Competition experiments determined that the rate of carbocyclization favors 1-tetralone creation, while benzosuberones form in preference to 1-indanones.
- The mild conditions of this method are compatible with a very wide range of functional groups that would not survive the conditions of conventional Friedel-Crafts acylation reactions. The presence of sp^2- and sp^3-hybridized nitrogen within the substrate appears to inhibit catalyst activity, so stoichiometric promoters are required in these cases.
- The synthesis of the pharmaceutical agent donepezil, although using stoichiometric quantities of promoter, demonstrates the usefulness of Meldrum's acid in medicinal research because of its ease of modification, using readily available starting materials.
- The operational simplicity and ready availability of all precursors should make this methodology a useful tool for the assembly of substituted 1-indanones, 1-tetralones and 1-benzosuberones. Mechanistic studies investigating the distinct reactivity of the enolizable versus the quaternarized Meldrum's acid substrates are presented in chapter 3.

Experimental Section

General: All reactions were carried out in flame-dried glassware under a dry nitrogen atmosphere. Nitromethane and DMF were distilled from CaH_2. $Sc(OTf)_3$ was dried under high vacuum (0.5 mmHg) for 2 hours at 180 °C and stored in a dry-box. ^1H NMR spectra were referenced to residual ^1H shift in $CDCl_3$ (7.24 ppm). $CDCl_3$ (77.0 ppm) was used as the internal reference for ^{13}C NMR spectra. Reactions were monitored by thin-layer chromatography (TLC) on commercial silica pre-coated plates with a particle size of 60 Å. Developed plates were viewed by UV lamp (254 nm), and with *p*-anisaldehyde stain. Flash chromatography was performed using 230-400 mesh silica gel. Melting points are uncorrected. Methyl[12b], and dimethyl Meldrum's alkylidenes[11a] were prepared according to literature procedures. Cyclohexyl[45], tetrahydro-4-pyran, tetrahydro-4-thiopyran[46], and 4-cyclohexanone (ethylene ketal)[47] Meldrum's alkylidenes were prepared from their respective ketones according to the method of Baty.[12a]

General Procedure A - Preparation of Mono-Benzylic Meldrum's Acids via a One-Pot Reductive Alkylation: Meldrum's acid (1 eq) and the appropriate benzaldehyde (0.98 eq) were dissolved in absolute EtOH (0.5-1.0 M), followed by the addition of a catalytic amount of piperidinium acetate (0.1 eq). The resulting solution was stirred vigorously for 30 minutes, and then cooled to 0 °C. $NaBH_3CN$ (1.5 eq) was added portion-wise over 60 minutes, and the reaction allowed to warm to room temperature. The reaction was monitored by TLC and upon completion was carefully quenched with 10% HCl (*extreme caution should be exercised due to the evolution of HCN gas*). Vigorous stirring was maintained until gas evolution had ceased, after which time the reaction was concentrated in vacuo to remove EtOH. The residue was re-suspended in 10% HCl and extracted four times with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated. The resulting product was generally found to be of good purity by ^1H NMR, but was recrystallized from MeOH or purified by flash chromatography on silica gel.

General Procedure B - Alkylation of 5-Substituted Meldrum's Acid and Dialkylation of Meldrum's Acid: Equivalents are doubled for the dialkylation. Anhydrous K_2CO_3 (1.5 eq) was added to a solution of 5-substituted Meldrum's acid (1 eq) in dry DMF (1.0 M). To the vigorously stirred suspension was added dropwise the appropriate electrophile, such as

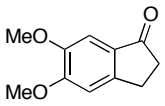
iodomethane (5-10 eq), allyl bromide (1.2 eq), propargyl bromide (1.2 eq), or benzyl bromides (1.1 eq). The reaction was monitored by TLC (typical reaction times are 30-120 minutes for activated electrophiles and 16-24 hours for iodomethane). Upon completion, the mixture was poured into water (15 vol eq relative to DMF) and extracted 3 times with EtOAc. The combined organic layers were washed twice with saturated aqueous $NaHCO_3$, brine, dried over $MgSO_4$, filtered and concentrated. The resulting crude products were typically very pure by ^1H NMR and nearly quantitative in yield, but were purified by recrystallization or flash chromatography on silica gel.

General Procedure C - Conjugate Addition of Grignard Reagents to Meldrum's Alkylidenes: In a typical reaction, Meldrum's alkylidene was suspended in dry THF (0.1 M) and cooled to 0 °C with stirring under inert atmosphere. A solution of the appropriate Grignard reagent (2 eq) in THF (or Et_2O) (0.5 to 3 M) was added dropwise over one hour, and then the reaction allowed to warm to room temperature and monitored by TLC. Upon completion, the reaction was quenched with 5% HCl and extracted three times with EtOAc. The combined organic layers were washed with H_2O, brine, then dried over $MgSO_4$ and filtered. Concentrated provided the crude product that was purified by either recrystallization or by flash chromatography on silica gel.

General Procedure D - Intramolecular Metal Trifluoromethanesulfonate – Catalyzed Friedel-Crafts Acylation of Meldrum's Acid Derivatives: Reactions were typically performed on 200 milligrams of substrate. In a flame-dried round bottomed flask equipped with a magnetic stir bar, a reflux condenser and under inert atmosphere, was placed the substrate and $Sc(OTf)_3$ (0.1 eq) (or other solid catalyst; liquid catalysts were administered to a solution of the substrate in CH_3NO_2). Distilled CH_3NO_2 was added in one portion by syringe, and the resulting suspension immediately placed into an oil bath preheated to 100 °C. The reaction was maintained at this temperature and monitored by TLC until complete consumption of starting material was observed. The reaction was then concentrated under vacuum and directly subjected to flash chromatography, using a small quantity of CH_2Cl_2 to assist column loading.

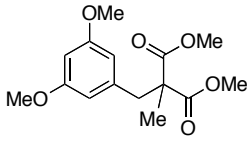
The slow (syringe pump) addition of a substrate solution to a stirring suspension of $Sc(OTf)_3$ at 100 ^oC was found to be advantageous for less activated π-nucleophiles.

5,6-Dimethoxy-1-indanone[48] (2):



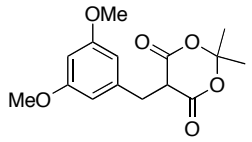
Prepared from **27** in 59% yield using Procedure D in 45 min. Purified by flash chromatography (6:5 hexanes:EtOAc) to provide a white solid. M.p. 116-118 °C (CH_2Cl_2). Lit. 119.5-120.5 °C and 118.8-119.5 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.13 (s, 1H), 6.85 (s, 1H), 3.92 (s, 3H), 3.86 (s, 3H), 3.03-2.99 (m, 2H), 2.65-2.61 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 205.7, 155.3, 150.4, 149.3, 129.8, 107.4, 104.1, 56.1, 56.0, 36.4, 25.5; HRMS *m/z* calcd for $C_{11}H_{12}O_3$ (M^+): 192.0786. Found: 192.0787.

Dimethyl 2-(3,5-dimethoxybenzyl)-2-methylmalonate (4):



Compound (**3**) was alkylated according to Procedure B using iodomethane. Recrystallization from MeOH provided white crystals in 70% yield. M.p. 75-76 °C (MeOH); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.28 (s, 1H), 6.20 (s, 2H), 3.69-3.68 (br s, 12H), 3.12 (s, 2H), 1.31 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 172.1, 160.4, 138.0, 108.1, 98.6, 55.0, 54.6, 52.3, 41.3, 19.6; HRMS(EI) *m/z* calcd for $C_{15}H_{20}O_6$ (M^+): 296.1260. Found: 296.1249.

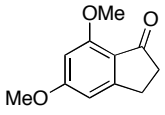
5-(3,5-Dimethoxybenzyl)-2,2-dimethyl-1,3-dioxane-4,6-dione (9):



Prepared by reductive alkylation of Meldrum's acid with 3,5-dimethoxybenzaldehyde using Procedure A. Recrystallization from MeOH provided a fine white solid in 61% yield. M.p. 102-103 °C (MeOH); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.44 (d, J = 2.3 Hz, 2H), 6.29 (app t, J = 2.2 Hz, 1H), 3.73 (t, J = 4.9 Hz, 1H), 3.37 (d, J = 4.9 Hz, 2H), 1.70 (s, 3H), 1.51 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 165.2, 160.7, 139.6, 107.4, 105.1, 99.1, 55.2, 47.9, 32.1, 28.4, 27.0; Anal.

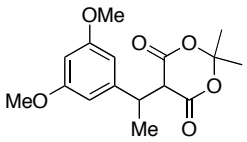
calcd for $C_{15}H_{18}O_6$: C, 61.22; H, 6.16. Found: C, 61.28; H, 6.26.

5,7-Dimethoxy-1-indanone[49] (10):



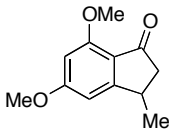
Prepared from **9** in 73% yield using Procedure D in 60 min. Purified by flash chromatography using 2:1 EtOAc:hexanes; M.p. 98-99 °C (benzene/petroleum ether). Lit. 98-99 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.42 (br s, 1H), 6.24 (br s, 1H), 3.85 (s, 3H), 3.82 (s, 3H), 2.98-2.94 (m, 2H), 2.60-2.56 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 203.3, 166.8, 160.3, 159.2, 119.3, 101.5, 97.3, 55.6, 36.8, 25.8. Anal. calcd for $C_{11}H_{12}O_3$: C, 68.74; H, 6.29. Found: C, 69.03; H, 6.30.

5-[1-(3,5-Dimethoxyphenyl)ethyl]-2,2-dimethyl-1,3-dioxane-4,6-dione (11):



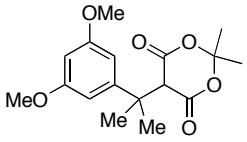
Prepared by conjugate addition of 3,5-dimethoxyphenylmagnesium chloride to methyl Meldrum's alkylidene using Procedure C in 49% yield after recrystallization from MeOH. M.p. 111-112 °C (MeOH); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.53-6.52 (m, 2H), 6.36-6.31 (m, 1H), 3.95 (dq, J = 7.2, 2.9 Hz, 1H), 3.78 (s, 6H), 3.69 (d, J = 3.0 Hz, 1H), 1.69 (s, 3H), 1.64 (d, J = 7.3 Hz, 3H), 1.40 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 164.9, 164.8, 160.8, 143.5, 106.4, 105.2, 99.4, 55.3, 52.4, 39.7, 28.2, 27.9, 17.8; Anal. calcd for $C_{16}H_{20}O_6$: C, 62.33; H, 6.54. Found: C, 62.05; H, 6.61.

5,7-Dimethoxy-3-methyl-1-indanone (12):



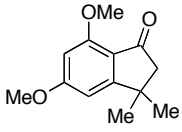
Prepared from **11** in 77% yield using Procedure D in 60 min. Purified by flash chromatography using 2:1 EtOAc:hexanes; M.p. 61-62.5 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.45 (br s, 1H), 6.27 (br s, 1H), 3.87 (s, 3H), 3.85 (s, 3H), 3.28-3.22 (m, 1H), 2.85 (dd, *J* = 18.5, 7.6 Hz, 1H), 2.21 (dd, *J* = 18.5, 3.5 Hz, 1H), 1.32 (d, *J* = 7.6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 202.4, 167.0, 165.2, 159.0, 118.6, 100.4, 97.2, 55.7, 55.6, 45.9, 32.5, 21.3. Anal. calcd for $C_{12}H_{14}O_3$: C, 69.88; H, 6.84. Found: C, 69.82; H, 6.73.

5-[1-(3,5-Dimethoxyphenyl)-1-methylethyl]-2,2-dimethyl-1,3-dioxane-4,6-dione (13):



Prepared by conjugate addition of 3,5-dimethoxyphenylmagnesium chloride to dimethyl Meldrum's alkylidene using Procedure C to provide a 76% yield of white solid after recrystallization from MeOH. M.p. 121-122 °C (MeOH); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.46-6.45 (m, 2H), 6.33-6.31 (m, 1H), 3.75 (s, 6H), 3.59 (s, 1H), 1.63 (s, 3H), 1.61 (s, 6H), 1.34 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 164.0, 160.6, 147.4, 105.0, 104.8, 98.1, 57.1, 55.2, 42.5, 28.9, 27.6, 27.5; Anal. Calcd for $C_{17}H_{22}O_6$: C, 63.34; H, 6.88. Found: C, 63.22; H, 7.06.

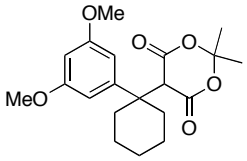
5,7-Dimethoxy-3,3-dimethyl-1-indanone[50] (14):



Prepared from **13** in 82% yield using Procedure D with CH_3CN in 120 min. Purified by flash chromatography using 2:1 EtOAc:hexanes; M.p. 92-94 °C (Et_2O). Lit. 95.5 °C (benzene); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.44 (br s, 1H), 6.27 (br s, 1H), 3.89 (s, 3H), 3.87 (s, 3H), 2.52 (s, 2H), 1.34 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 201.6, 168.9, 167.0, 158.8, 117.5, 98.8, 96.9,

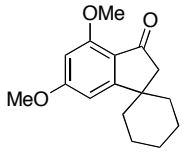
55.7, 55.6, 53.4, 37.9, 29.7. Anal. calcd for $C_{13}H_{16}O_3$: C, 70.89; H, 7.32. Found: C, 70.87; H, 7.49.

5-[1-(3,5-Dimethoxyphenyl)cyclohexyl]-2,2-dimethyl-1,3-dioxane-4,6-dione (15):



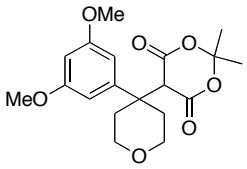
Prepared by conjugate addition of 3,5-dimethoxyphenylmagnesium chloride to cyclohexyl Meldrum's alkylidene using Procedure C to provide a 78% yield of white solid after recrystallization from MeOH. M.p. 124-125 °C (MeOH); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.38 (m, 2H), 6.29 (m, 1H), 3.60 (s, 6H), 3.38 (s, 1H), 2.38-2.33 (m, 2H), 2.00-1.90 (m, 2H), 1.70-1.50 (m, 2H), 1.44 (s, 3H), 1.44-1.30 (m, 4H), 0.84 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 164.3, 160.9, 142.1, 105.9, 105.4, 99.0, 56.6, 55.2, 47.2, 35.6, 30.3, 26.4, 25.4, 22.3; Anal. Calcd for $C_{20}H_{26}O_6$: C, 66.28; H, 7.23. Found: C, 66.36; H, 7.33.

5,7-Dimethoxy-(3.3)-pentamethylene-1-indanone (16):



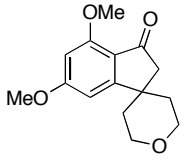
Prepared from **15** in 83% yield using Procedure D with CH_3CN in 120 min. Purified by flash chromatography using 1:1 EtOAc:hexanes; M.p. 132-133 °C (Et_2O); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.45 (d, J = 1.8 Hz, 1H), 6.26 (d, J = 1.8 Hz, 1H), 3.88 (s, 3H), 3.86 (s, 3H), 2.51 (s, 2H), 1.76-1.19 (m, 10H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 201.9, 169.3, 166.9, 159.0, 117.8, 99.3, 97.2, 55.8, 55.7, 49.1, 42.7, 38.2, 25.4, 23.6. Anal. calcd for $C_{16}H_{20}O_3$: C, 73.82; H, 7.74. Found: C, 73.93; H, 7.83.

5-[4-(3,5-Dimethoxyphenyl)tetrahydro-2*H*-4-pyranyl]-2,2-dimethyl-1,3-dioxane-4,6-dione (17):



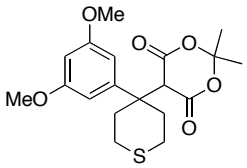
Conjugate addition of 3,5-dimethoxyphenylmagnesium chloride to tetrahydro-4-pyran Meldrum's alkyidene using Procedure C provided a clear, colorless solid after recrystallization from MeOH in 73% yield. M.p. 147-148 °C (MeOH); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.34 (s, 3H), 3.84-3.77 (m, 2H), 3.71 (s, 6H), 3.60-3.47 (m, 2H), 2.50-2.45 (m, 2H), 2.30-2.22 (m, 2H), 1.48 (s, 3H), 0.86 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 163.9, 161.3, 140.9, 105.8, 105.7, 99.4, 64.0, 55.6, 55.3, 45.3, 36.0, 30.2, 26.7; Anal. Calcd $C_{15}H_{18}O_6$: C, 62.63; H, 6.64. Found: C, 62.53; H, 6.71.

5,7-Dimethoxy-[3.3]-(3',4',6',7')tetrahydropyran-1-indanone (18):



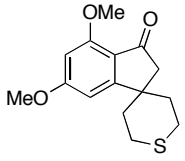
Prepared from **17** in 79% yield using Procedure D with $Yb(OTf)_3$ in 15 min. Purified by flash chromatography (3:1 EtOAc:hexanes) to provide a white solid. M.p. 201-203 °C (EtOAc/hexanes); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.47 (s, 1H), 6.28 (s, 1H), 3.96 (dd, *J* = 11.8, 4.4 Hz, 2H), 3.86 (s, 3H), 3.84 (s, 3H), 3.48 (br t, *J* = 12.3 Hz), 2.58 (s, 2H), 2.06 (dt, *J* = 13.1, 4.6 Hz, 2H), 1.36 (br d, *J* = 13.4 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 200.4, 167.2, 167.1, 159.1, 117.8, 99.3, 97.5, 65.4, 55.8, 55.7, 48.4, 40.2, 38.0; HRMS(EI) *m/z* calcd for $C_{15}H_{18}O_4$ (M^+): 262.1205. Found: 262.1209.

5-[4-(3,5-Dimethoxyphenyl)tetrahydro-2*H*-4-thiopyranyl]-2,2-dimethyl-1,3-dioxane-4,6-dione (19):



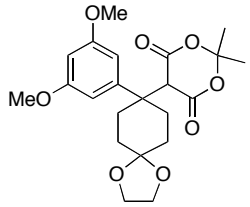
Conjugate addition of 3,5-dimethoxy phenylmagnesium chloride to tetrahydro-4-thiopyranyl Meldrum's alkyidene according to Procedure C produced a 69% yield of the desired product as a white powder after recrystallization from MeOH. M.p. 135-136 °C (MeOH); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.33 (s, 3H), 3.71 (s, 6H), 3.41 (s, 1H), 2.85-2.55 (m, 6H), 2.50-2.30 (m, 2H), 1.47 (s, 3H), 0.89 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 163.8, 161.2, 140.5, 106.0, 105.7, 99.2, 56.4, 55.3, 46.3, 36.5, 30.3, 26.5, 24.1; HRMS(EI) *m/z* calcd for $C_{19}H_{24}O_6S$ (M^+): 380.1293. Found: 380.1302.

5,7-Dimethoxy-[3.3]-(3',4',6',7')tetrahydrothiopyran-1-indanone (20):



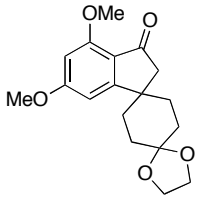
Prepared from **19** in 86% yield using Procedure D with $Yb(OTf)_3$ in 20 min. Purified by flash chromatography (1:1 hexanes:EtOAc) to provide a white solid. M.p. 196-197 °C (CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.49 (d, *J* = 1.8 Hz, 1H), 6.29 (d, *J* = 1.8 Hz, 1H), 3.87 (s, 3H), 3.86 (s, 3H), 2.84-2.74 (m, 2H), 2.59-2.54 (m, 2H), 2.49 (s, 2H), 2.10-2.00 (m, 2H), 1.79-1.72 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 200.4, 167.9, 167.1, 159.2, 117.5, 99.3, 97.7, 55.8, 47.9, 41.7, 38.4, 25.7; HRMS(EI) *m/z* calcd for $C_{15}H_{18}O_3S$ (M^+): 278.0977. Found: 278.0974.

5-[8-(3,5-Dimethoxyphenyl)-1,4-dioxaspiro[4.5]dec-8-yl]-2,2-dimethyl-1,3-dioxane-4,6-dione (21):



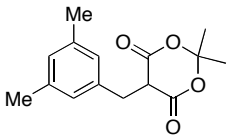
Conjugate addition of 3,5-dimethoxyphenylmagnesium chloride to cyclohexyl-4-one (ethylene ketal) Meldrum's alkylidene using Procedure C produced a 78% yield following recrystallization from MeOH. M.p. 139-140 °C (MeOH); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.25-6.23 (m, 3H), 3.82-3.77 (m, 4H), 3.63 (s, 6H), 3.33 (s, 1H), 2.50-2.40 (m, 2H), 2.20-2.00 (m, 2H), 1.70-1.40 (m, 4H), 1.40 (s, 3H), 0.78 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 164.0, 160.9, 140.6, 107.6, 105.8, 105.4, 99.1, 64.0, 55.7, 55.1, 46.0, 32.7, 31.1, 30.0, 26.4; HRMS(EI) *m/z* calcd for $C_{22}H_{28}O_8$ (M^+): 420.1784. Found: 420.1783.

5,7-Dimethoxy-[3.3]cyclohexan-6'-one (ethylene ketal)-1-indanone (22):



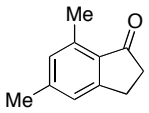
Prepared from **21** in 78% yield using Procedure D with powdered 5Å molecular sieves (100% by weight) and $Yb(OTf)_3$ in 21 hours. Purified by flash chromatography (4:1 hexanes:EtOAc) to provide a pale yellow solid. M.p. 152-154 °C (CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.51 (d, J = 1.6 Hz, 1H), 6.29 (d, J = 1.6 Hz, 1H), 3.98 (d, J = 1.7 Hz, 4H), 3.88 (d, J = 1.8 Hz, 3H), 3.86 (d, J = 1.6 Hz, 3H), 2.57 (d, J = 1.8 Hz, 2H), 2.09-2.05 (m, 2H), 1.82-1.61 (m, 4H), 1.56-1.51 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 201.1, 168.1, 167.1, 159.1, 118.0, 108.0, 99.1, 97.8, 64.4, 64.3, 55.8, 48.3, 41.8, 35.8, 32.6; HRMS(EI) *m/z* calcd for $C_{18}H_{22}O_5$ (M^+): 318.1467. Found: 318.1463.

5-(3,5-Dimethylbenzyl)-2,2-dimethyl-1,3-dioxane-4,6-dione (23):



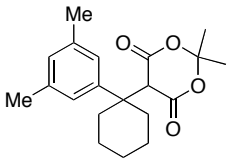
Reductive alkylation of Meldrum's acid according to Procedure A with 3,5-dimethylbenzaldehyde provided a clear colorless oil after flash chromatography (62 %) which solidified on standing. M.p. 69-70 °C (MeOH); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.91 (br s, 2H), 6.85 (br s, 1H), 3.72 (t, J = 4.9 Hz, 1H), 3.39 (d, J = 4.9 Hz, 2H), 2.60 (s, 6H), 1.72 (s, 3H), 1.48 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 165.4, 138.1, 137.2, 128.7, 127.3, 105.2, 48.2, 31.9, 28.4, 27.1, 21.2; HRMS(EI) *m/z* calcd for $C_{15}H_{18}O_4$ (M^+): 262.1205. Found: 262.1206.

5,7-Dimethyl-1-indanone[51] (24):



Prepared from **23** in 52% yield following Procedure D using the slow addition of substrate over 9.5 h. Purified by flash chromatography using 8:1 hexanes:EtOAc; M.p. 75-76 °C (MeOH). Lit. 76-77 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.05 (s, 1H), 6.89 (s, 1H), 3.02-2.98 (m, 2H), 2.64-2.60 (m, 2H), 2.57 (s, 3H), 2.36 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 207.5, 156.5, 145.0, 138.5, 132.2, 130.3, 124.4, 36.1, 25.2, 21.8, 18.2. Anal. calcd for $C_{11}H_{12}O$: C, 82.46; H, 7.55. Found: C, 82.40; H, 7.36.

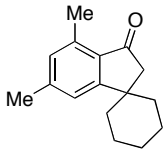
5-[1-(3,5-Dimethylphenyl)cyclohexyl]-2,2-dimethyl-1,3-dioxane-4,6-dione (25):



Prepared by conjugate addition of 3,5-dimethylphenylmagnesium bromide to cyclohexyl Meldrum's alkylidene according to Procedure C, and recrystallized using MeOH to provide a white solid in 88% yield. M.p. 144.5-146 °C (MeOH); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.87 (br s, 3H), 3.42 (s, 1H), 2.46-2.41 (m, 2H), 2.26 (s, 6H), 2.04-1.96 (m, 2H), 2.75-2.60 (m, 2H),

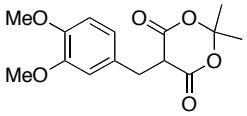
1.46 (s, 3H), 1.46-1.40 (m, 4H), 0.71 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 164.2, 139.5, 137.8, 128.6, 125.1, 105.4, 56.5, 46.7, 38.4, 30.3, 25.8, 25.5, 22.1, 21.2; Anal. Calcd for $C_{20}H_{26}O_4$: C, 72.70; H, 7.93. Found: C, 72.65; H, 7.89.

5,7-Dimethyl-(3.3)-pentamethylene-1-indanone (26):



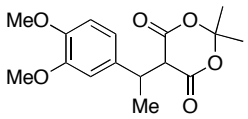
Prepared from **25** in 75% yield using Procedure D in 90 min. Purified by flash chromatography using 10:1 hexanes:EtOAc; M.p. 87.5-88.5 °C (hexanes); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.08 (s, 1H), 6.89 (s, 1H), 2.57 (s, 3H), 2.52 (s, 2H), 2.37 (s, 3H), 1.77-1.23 (m, 10H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 206.5, 165.6, 145.0, 138.2, 130.5, 121.7, 49.1, 42.1, 38.4, 25.6, 23.8, 22.0, 18.3. Anal. calcd for $C_{16}H_{20}O$: C, 84.16; H, 8.83. Found: C, 84.00; H, 9.12.

5-(3,4-Dimethoxybenzyl)-2,2-dimethyl-1,3-dioxane-4,6-dione[52] (27):



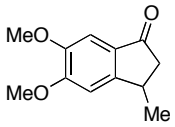
Prepared by reductive alkylation of Meldrum's acid with 3,4-dimethoxybenzaldehyde according to Procedure A. A fine white powder was obtained in 77% yield after recrystallizaton from MeOH. M.p. 136-137 °C (MeOH). Lit. 142-144 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.77-6.64 (m, 3H), 3.75-3.73 (br s, 7H), 3.32 (d, J = 4.8 Hz, 2H), 1.63 (s, 3H), 1.40 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 165.3, 148.4, 147.7, 129.3, 121.7, 112.8, 110.8, 104.9, 55.5, 47.9, 31.5, 28.1, 26.9; HRMS(EI) *m/z* calcd for $C_{15}H_{18}O_6$ (M^+): 294.1103. Found: 294.1106.

5-[1-(3,4-Dimethoxyphenyl)ethyl]-2,2-dimethyl-1,3-dioxane-4,6-dione (28):



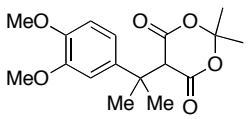
Conjugate addition of methylmagnesium iodide to 3,4-dimethoxyphenyl Meldrum's alkylidene (prepared by condensation of 3,4-dimethoxybenzaldehyde with Meldrum's acid)[15] according to Procedure C produced a 53% yield of a white powder after recrystallization from MeOH. M.p. 137-138 °C (MeOH); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.82-6.79 (m, 2H), 6.72-6.69 (m, 1H), 3.87 (dq, *J* = 7.3, 3.0 Hz, 1H), 3.78 (s, 3H), 3.76 (s, 3H), 3.63 (d, *J* = 3.0 Hz, 1H), 1.59 (s, 6H), 1.26 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 165.2, 164.7, 148.5, 148.0, 133.3, 120.3, 111.4, 110.7, 105.0, 55.6, 55.3, 39.2, 27.9, 27.7, 18.2; HRMS(EI) *m/z* calcd for $C_{16}H_{20}O_6$ (M^+): 308.1260. Found: 308.1269.

5,6-Dimethoxy-3-methyl-1-indanone[48] (29):



Prepared from **28** in 68% yield using Procedure D in 20 min. Purified by flash chromatography (4:1 hexanes:EtOAc) to provide a white solid. M.p. 87-88 °C (hexanes/EtOAc). Lit. 90.5-92 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.12 (s, 1H), 6.86 (s, 1H), 3.95 (s, 3H), 3.88 (s, 3H), 3.36-3.30 (m, 1H), 2.92 (dd, *J* = 7.2, 1.2 Hz, 1H), 2.23 (dd, *J* = 18.8, 1.4 Hz, 1H), 1.35 (d, *J* = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 204.7, 155.4, 155.2, 149.3, 129.1, 106.0, 103.8, 56.1, 56.0, 45.4, 32.4, 21.3; HRMS(EI) *m/z* calcd for $C_{12}H_{14}O_3$ (M^+): 206.0943. Found: 206.0949.

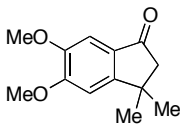
5-[1-(3,4-Dimethoxyphenyl)-1-methylethyl]-2,2-dimethyl-1,3-dioxane-4,6-dione (30):



Conjugate addition of 3,4-dimethoxyphenylmagnesium bromide to dimethyl Meldrum's alkylidene according to Procedure C provided a white solid in 49% yield after recrystallization

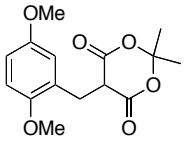
from EtOH. M.p. 137-138 °C (EtOH); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.86-6.75 (m, 3H), 3.83 (s, 3H), 3.81 (s, 3H), 3.46 (s, 1H), 1.63 (s, 6H), 1.56 (s, 3H), 1.19 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 164.4, 148.5, 148.0, 136.5, 118.7, 110.7, 110.1, 105.2, 57.7, 55.9, 55.8, 42.7, 29.5, 28.2, 27.2; Anal. Calcd for $C_{17}H_{22}O_6$: C, 63.34; H, 6.88. Found: C, 63.69; H, 6.93.

5,6-Dimethoxy-3,3-dimethyl-1-indanone[48] (31):



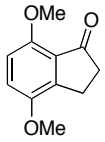
Prepared from **30** in 69% yield using Procedure D in 20 min. Purified by flash chromatography (4:1 hexanes:EtOAc) to provide a pale yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.14 (s, 1H), 6.87 (s, 1H), 4.01 (s, 3H), 3.92 (s, 3H), 2.58 (s, 2H), 1.42 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 204.4, 159.2, 155.6, 149.4, 128.1, 104.3, 103.8, 56.2, 56.1, 52.9, 38.2, 29.9; HRMS(EI) *m/z* calcd for $C_{13}H_{16}O_3$ (M^+): 220.1099. Found: 220.1108.

5-(2,5-Dimethoxybenzyl)-2,2-dimethyl-1,3-dioxane-4,6-dione (32):



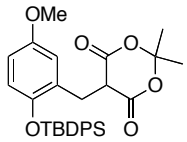
Prepared by the reductive alkyation of Meldrum's acid with 2,5-dimethoxybenzaldehyde according to Procedure A, and recrystallized from MeOH to give a yield of 57%. M.p. 94-95 °C (MeOH); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.91 (s, 1H), 6.74 (d, J = 2.2 Hz, 2H), 4.00 (t, J = 5.8 Hz, 1H), 3.75 (s, 3H), 3.74 (s, 3H), 3.34 (d, J = 5.8 Hz, 2H), 1.75 (s, 3H), 1.70 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 165.3, 153.3, 151.3, 126.7, 117.8, 112.5, 104.8, 60.4, 55.7, 46.1, 28.6, 28.0, 26.4; HRMS(EI) *m/z* calcd for $C_{15}H_{18}O_6$ (M^+): 294.1103. Found: 294.1095.

4,7-Dimethoxy-1-indanone[53] (33):



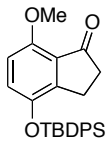
Prepared from **32** in 32% yield using Procedure D in 20 min. Purified by flash chromatography (1:1 hexanes:EtOAc) to provide a white solid. M.p. 122-123 °C (Et_2O). Lit. 125-126 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.96 (d, J = 8.7 Hz, 1H), 6.70 (d, J = 8.7 Hz, 1H), 3.88 (s, 3H), 2.96 (AB m, 2H), 2.65 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 204.3, 151.8, 150.4, 145.9, 126.3, 116.5, 109.4, 55.9, 36.7, 22.2; HRMS(EI) *m/z* for $C_{17}H_{17}NO_3$ (M^+): 192.0786. Found: 192.0782.

5-(2-[1-(*tert*-Butyl)-1,1-diphenylsilyl]oxy-5-methoxybenzyl)-2,2-dimethyl-1,3-dioxane-4,6-dione (34):



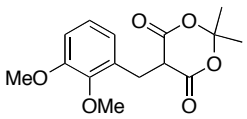
Obtained by reductive alkylation of Meldrum's acid with TBDPS-protected 4-methoxysalicylaldehyde according to Procedure A. Flash chromatography (10:3 hexanes:EtOAc), followed by recrystallization from MeOH gave a white solid in 21% yield. M.p. 128-129 °C (MeOH); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.71-6.80 (m, 4H), 7.46-7.35 (m, 6H), 7.01 (br s, 1H), 6.38-6.36 (m, 2H), 4.49 (t, J = 6.0 Hz, 1H), 3.69 (s, 3H), 3.54 (d, J = 6.0 Hz, 2H), 1.73 (s, 3H), 1.62 (s, 3H), 1.10 (s, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 164.9, 153.3, 147.0, 135.1, 132.5, 130.0, 128.1, 127.9, 118.9, 117.7, 112.4, 124.8, 55.4, 46.7, 48.6, 27.7, 26.5, 25.6, 19.3; HRMS(EI) *m/z* calcd for $C_{30}H_{34}O_6Si$ (M^+): 518.2125. Found: 518.2142.

4-[1-(*tert*-Butyl)-1,1-diphenylsilyl]oxy-7-methoxy-1-indanone (35):



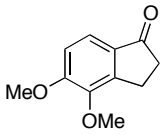
Prepared from **34** in 63% yield using Procedure D in 35 min. Purified by flash chromatography (3:1 hexanes:EtOAc) to provide a pale yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.72 (dd, *J* = 7.9, 1.4 Hz, 4H), 7.42-7.31 (m, 6H), 6.64 (d, *J* = 6.6 Hz, 1H), 6.41 (d, *J* = 8.8 Hz, 1H), 3.82 (s, 3H), 3.11 (t, *J* = 5.8 Hz, 2H), 2.70 (t, *J* = 5.9 Hz, 1H), 1.15 (s, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 205.0, 152.1, 147.3, 146.1, 135.4, 132.5, 130.1, 127.9, 126.1, 125.0, 109.4, 55.8, 36.8, 26.5, 22.8, 19.5; HRMS(EI) *m/z* calcd for $C_{26}H_{28}O_3Si$ (M^+): 416.1808. Found: 416.1799.

5-(2,3-Dimethoxybenzyl)-2,2-dimethyl-1,3-dioxane-4,6-dione (36):



Prepared by the reductive alkylation of Meldrum's acid with veratraldehyde according to Procedure A. Recrystallization from MeOH provided white crystals in 44% yield. M.p. 120-121 °C (MeOH); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.00-6.95 (m, 2H), 6.80 (dd, *J* = 7.5, 2.1 Hz, 1H), 4.11 (t, *J* = 5.6 Hz, 1H), 3.84 (s, 3H), 3.83 (s, 3H), 3.34 (d, *J* = 5.6 Hz, 2H), 1.75 (s, 3H), 1.71 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 165.2, 152.4, 146.9, 131.8, 123.9, 123.4, 111.2, 104.9, 60.4, 55.6, 47.1, 29.6, 27.4, 26.2; Anal. Calcd for $C_{15}H_{18}O_6$: C, 61.22; H, 6.16. Found: C, 61.26; H, 6.17; HRMS(EI) *m/z* calcd for $C_{15}H_{18}O_6$ (M^+): 294.1103. Found: 294.1109.

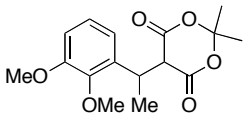
4,5-Dimethoxy-1-indanone[54] (37):



Prepared from **36** in 64% yield using Procedure D in 80 min. Purified by flash chromatography (1:1 hexanes:EtOAc) to provide a pale yellow solid. M.p. 68-70 °C (Et_2O).

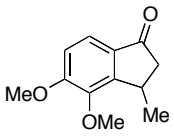
Lit. 74 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.46 (d, *J* = 8.3 Hz, 1H), 6.92 (d, *J* = 8.4 Hz, 1H), 3.90 (s, 3H), 3.87 (s, 3H), 3.07-3.02 (AB m, 2H), 2.63-2.59 (AB m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 205.4, 157.4, 147.8, 145.9, 131.0, 120.1, 112.2, 60.2, 56.1, 36.3, 22.4; HRMS(EI) *m/z* calcd for $C_{11}H_{12}O_3$ (M^+): 192.0786. Found: 192.0782.

5-[1-(2,3-Dimethoxyphenyl)ethyl]-2,2-dimethyl-1,3-dioxane-4,6-dione (38):



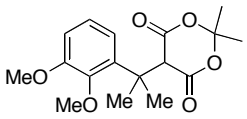
The target material was obtained by the addition of Me_2AlCl to 2,3-dimethoxyphenyl Meldrum's alkylidene (prepared by condensing 2,3-dimethoxybenzaldehyde with Meldrum's acid)**Error! Bookmark not defined.**. A white powder was obtained in 51% yield after flash chromatography (3:1 hexanes:EtOAc) and recrystallization from MeOH. M.p. 123-123.5 °C (MeOH); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.08–7.03 (m, 2H), 6.86-6.82 (m, 1H), 4.29 (d, *J* = 2.9 Hz, 1H), 4.12 (dq, *J* = 7.1, 2.9 Hz, 1H), 3.86 (s, 3H), 3.85 (s, 3H), 1.69 (s, 3H), 1.67 (s, 3H), 1.43 (d, *J* = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 165.5, 163.5, 152.1, 146.3, 135.6, 123.7, 120.9, 110.9, 104.6, 60.6, 55.6, 50.8, 31.6, 28.3, 26.7, 13.9; HRMS(EI) *m/z* calcd for $C_{16}H_{20}O_6$ (M^+): 308.1260. Found: 308.1251.

4,5-Dimethoxy-3-methyl-1-indanone (39):



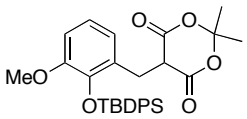
Prepared from **38** in 38% yield using Procedure D in 40 min. Purified by flash chromatography (3:1 hexanes:EtOAc) to provide a clear colorless oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.45 (d, *J* = 8.4 Hz), 6.93 (d, *J* = 8.4 Hz), 3.91 (s, 3H), 3.89 (s, 3H), 3.51 (ddq, *J* = 7.7, 7.0, 2.6 Hz, 1H), 2.87 (dd, *J* = 18.9, 7.7 Hz, 1H), 2.22 (dd, *J* = 18.9, 2.6 Hz, 1H), 1.38 (d, 7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 205.0, 158.0, 152.3, 145.8, 130.6, 119.9, 112.4, 60.5, 56.1, 45.8, 30.8, 21.0; HRMS(EI) *m/z* calcd for $C_{12}H_{14}O_3$ (M^+): 206.0943. Found: 206.0937.

5-[1-(2,3-Dimethoxyphenyl)-1-methylethyl]-2,2-dimethyl-1,3-dioxane-4,6-dione (40):



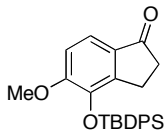
Conjugate addition of 2,3-dimethoxyphenylmagnesium bromide to dimethyl Meldrum's alkylidene according to Procedure C provided a 25% yield of white solid after flash chromatography (6:1 hexanes:EtOAc). M.p. 118-119 °C (CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.02-6.94 (m, 2H), 6.81 (dd, *J* = 7.2, 2.3 Hz, 1H), 5.38 (s, 1H), 3.89 (s, 3H), 3.80 (s, 3H), 1.77 (s, 3H), 1.65 (s, 3H), 1.63 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 163.6, 152.3, 146.4, 140.2, 123.1, 118.7, 110.7, 103.6, 60.4, 55.3, 53.5, 39.5, 28.4, 25.9, 25.5; HRMS(EI) *m/z* calcd for $C_{17}H_{22}O_6$ (M^+): 322.1416. Found: 322.1419.

5-(2-[1-(*tert*-Butyl)-1,1-diphenylsilyl]oxy-3-methoxybenzyl)-2,2-dimethyl-1,3-dioxane-4,6-dione (42):



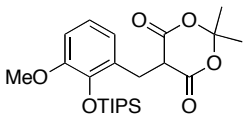
Reductive alkylation of Meldrum's acid with TBDPS-protected *o*-vanillin according to Procedure A, followed by flash chromatography (8:1 hexanes:EtOAc) gave a 32% yield of white solid. M.p. 116-118 °C (Benzene); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.63 (dd, *J* = 7.6, 1.8 Hz, 4H), 7.38-7.28 (m, 6H), 6.98 (dd, *J* = 7.7, 1.3 Hz, 1H), 6.81 (app t, *J* = 7.9 Hz, 1H), 6.49 (dd, *J* = 8.1, 1.4 Hz, 1H), 4.33 (t, *J* = 6.2 Hz, 1H), 3.57 (d, *J* = 6.2 Hz, 2H), 2.76 (s, 1H), 1.72 (s, 3H), 1.61 (s, 3H), 1.02 (s, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 165.0, 148.7, 142.8, 135.3, 134.0, 129.0, 127.2, 123.7, 120.8, 110.3, 104.5, 53.3, 46.7, 28.8, 27.9, 26.8, 25.7, 20.0; HRMS(EI) *m/z* calcd for $C_{30}H_{34}O_6Si$ (M^+-CH_3): 503.1890. Found: 503.1905.

4-[1-(*tert*-Butyl)-1,1-diphenylsilyl]oxy-5-methoxy-1-indanone (43):



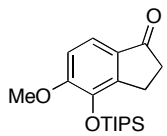
Prepared from **42** in 50% yield using Procedure D in 40 min. Purified by flash chromatography (10:1 hexanes:EtOAc) to provide a pale yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.66 (d, *J* = 7.1 Hz, 4H), 7.37-7.29 (m, 4H), 6.65 (d, *J* = 8.3 Hz, 1H), 3.11-3.07 (m, 2H), 3.09 (s, 3H), 2.66-2.63 (AB m, 2H), 1.09 (s, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 205.8, 154.5, 145.7, 141.5, 134.7, 134.1, 131.1, 129.4, 127.3, 117.6, 111.6, 54.4, 36.5, 26.7, 23.2, 20.0; HRMS(EI) *m/z* calcd for $C_{26}H_{28}O_3Si$ (M^+-CH_3): 401.1573. Found: 401.1581.

5-{3-Methoxy-2-[(1,1,1-triisopropylsilyl)oxy]benzyl}-2,2-dimethyl-1,3-dioxane-4,6-dione (44):



Reductive alkylation of Meldrum's acid with TIPS-protected *o*-vanillin according to Procedure A, followed by flash chromatography (6:1 hexanes:EtOAc) and recrystallization from MeOH gave a 21% yield of white solid. M.p. 77-78 °C (MeOH); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.96 (dd, *J* = 7.5, 1.3 Hz, 1H), 6.83 (app t, *J* = 7.8 Hz, 1H), 6.74 (dd, *J* = 8.1, 1.4 Hz, 1H), 4.15 (t, *J* = 6.0 Hz, 1H), 3.79 (s, 3H), 3.39 (d, *J* = 6.0 Hz, 2H), 1.79 (s, 3H), 1.76 (s, 3H), 1.28 (septet, *J* = 7.7 Hz, 3H), 1.10 (d, *J* = 7.3 Hz, 18H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 165.0, 149.3, 143.5, 128.3, 124.1, 120.3, 109.1, 104.7, 54.5, 46.6, 28.7, 27.7, 25.9, 18.0, 14.2; HRMS(EI) *m/z* calcd for $C_{23}H_{36}O_6Si$ (M^+-CH_3): 421.2046. Found: 421.2056.

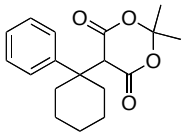
5-Methoxy-4-[(1,1,1-triisopropylsilyl)oxy]-1-indanone (45):



Prepared from **44** in 45% yield using Procedure D in 40 min. Purified by flash

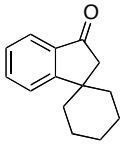
chromatography (12:1 hexanes:EtOAc) to provide a pale yellow solid. M.p. 59-60 °C (Et_2O); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.36 (d, *J* = 8.3 Hz, 1H), 6.88 (d, *J* = 8.3 Hz, 1H), 3.85 (s, 3H), 3.04 (t, *J* = 5.9 Hz, 2H), 2.64 (dd, *J* = 6.1, 4.8 Hz, 2H), 1.24 (septet, *J* = 7.9 Hz, 3H), 1.07 (d, *J* = 7.1 Hz, 18H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 206.0, 154.9, 146.1, 142.2, 131.2, 117.1, 111.4, 55.3, 36.5, 23.1, 18.0, 13.7; HRMS(EI) *m/z* calcd for $C_{19}H_{30}O_3Si$ (M^+): 334.1964. Found: 334.1966.

2,2-Dimethyl-5-(1-phenylcyclohexyl)-1,3-dioxane-4,6-dione (48):



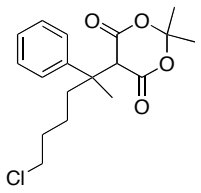
Conjugate addition of phenylmagnesium bromide to cyclohexyl Meldrum's alkylidene according to Procedure C provided a 66% yield of product following recrystallization from hexanes. M.p. 106-107 °C (hexanes); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.35-7.22 (m, 5H), 3.44 (s, 1H), 2.5-2.45 (m, 2H), 2.05-1.97 (m, 2H), 1.66-1.61 (m, 2H), 1.45 (s, 3H), 1.45-1.32 (m, 4H), 0.71 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 164.4, 139.6, 128.7, 127.7, 127.3, 105.7, 57.2, 47.2, 35.5, 30.6, 26.2, 25.7, 22.3; Anal. Calcd for $C_{18}H_{22}O_4$: C, 71.50; H, 7.33. Found: C, 71.40; H, 7.32.

(3.3)-Pentamethylene-1-indanone[55] (49):



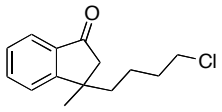
Prepared from **48** in 56% yield using Procedure D in 30 min. Purified by flash chromatography using 7:1 hexanes:EtOAc to provide a colorless oil. Lit. M.p. 58-59 °C (petroleum ether); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.65 (d, *J* = 7.7 Hz, 1H), 7.54 (t, *J* = 7.1 Hz, 1H), 7.45 (d, *J* = 7.7 Hz, 1H), 7.30 (t, *J* = 7.4 Hz, 1H), 2.53 (s, 3H), 1.75-1.20 (m, 10H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 205.9, 164.0, 135.4, 134.7, 127.4, 123.8, 123.3, 48.2, 43.0, 38.2, 25.3, 23.7. Anal. calcd for $C_{14}H_{16}O$: C, 83.96; H, 8.05. Found: C, 83.60; H, 8.12.

5-(5-Chloro-1-methyl-1-phenylpentyl)-2,2-dimethyl-1,3-dioxane-4,6-dione (50):



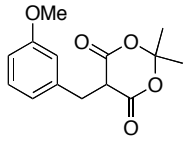
Meldrum's acid and 6-chloro-2-hexanone were condensed according to the procedure of Brown[13], to provide the chlorobutyl methyl Meldrum's alkylidene in quantitative yield and was used without further purification. Subsequent conjugate addition according to Procedure C using phenylmagnesium bromide produced the desired compound in 51% yield as an oil following flash chromatography (5:1 hexanes:EtOAc), that was recrystallized from MeOH. M.p. 84-85 °C (MeOH); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.34-7.20 (m, 5H), 3.60 (s, 1H), 3.46 (t, *J* = 6.6 Hz, 2H), 2.14-2.06 (m, 2H), 1.77-1.68 (m, 2H), 1.64 (s, 3H), 1.59 (s, 3H), 1.42-1.37 (m, 1H), 1.18 (s, 3H), 1.18-1.08 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 164.4, 163.9, 142.3, 128.5, 127.1, 126.6, 105.2, 57.2, 45.8, 44.6, 39.3, 32.8, 29.3, 27.2, 22.3, 21.7; HRMS(EI) *m/z* calcd for $C_{18}H_{23}ClO_4$ (M^+): 338.1285. Found: 338.1292.

3-(4-Chlorobutyl)-3-methyl-1-indanone (51):



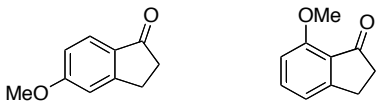
Prepared from **50** in 52% yield using Procedure D in 15 min. Purified by flash chromatography (8:1 hexanes:EtOAc) to provide a pale yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.68 (d, *J* = 7.7 Hz, 1H), 7.59 (t, *J* = 7.1 Hz, 1H), 7.43 (d, *J* = 7.7 Hz, 1H), 7.35 (t, *J* = 7.5 Hz, 1H), 3.43 (t, *J* = 6.6 Hz, 2H), 2.54 (AB quartet, *J* = 18.9 Hz, 2H), 1.76-1.60 (m, 4H), 1.50-1.39 (m, 1H), 1.39 (s, 3H), 1.1-0.95 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 205.8, 162.4, 135.9, 134.9, 127.5, 123.7, 123.3, 50.0, 44.5, 41.9, 41.3, 32.9, 28.3, 22.3; HRMS(EI) *m/z* calcd for $C_{14}H_{17}ClO$ (M^+): 236.0968. Found: 236.0971.

5-(3-Methoxybenzyl)-2,2-dimethyl-1,3-dioxane-4,6-dione (52):



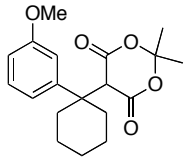
Prepared by reductive alkylation of Meldrum's acid with *m*-anisaldehyde using Procedure A in 45 % yield after recrystallization from MeOH. M.p. 102-104 °C (MeOH); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.15 (t, *J* = 8.0 Hz, 1H), 6.86-6.84 (m, 2H), 6.75-6.72 (m, 1H), 3.77 (t, *J* = 5.0 Hz, 1H), 3.73 (s, 3H), 3.40 (d, *J* = 5.0 Hz, 2H), 1.69 (s, 3H), 1.49 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 165.2, 159.4, 138.7, 129.4, 121.7, 115.1, 112.5, 105.1, 55.0, 47.8, 31.8, 28.2, 26.8; Anal. Calcd for $C_{14}H_{16}O_5$: C, 63.63; H, 6.10. Found: C, 63.70; H, 6.15.

5-Methoxy-1-indanone (53) and 7-Methoxy-1-indanone (54):



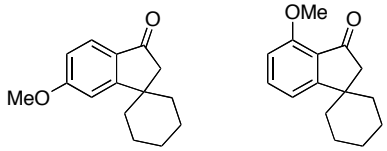
Prepared from **52** in 52% yield as a 5.5:1 ratio of para **53**:ortho **54** products using Procedure D in 60 min. The mixture was separated with 2:1 hexanes:EtOAc; (**53**): Elutes first, M.p. 108-109 °C (MeOH); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.68-7.65 (m, 1H), 6.89-6.87 (m, 2H), 3.86 (s, 3H), 3.07 (m, 2H), 2.65 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 205.3, 165.2, 158.2, 130.4, 125.3, 115.3, 109.7, 55.6, 36.4, 25.8. Anal. calcd for $C_{10}H_{10}O_2$: C, 74.06; H, 6.21. Found: C, 73.90; H, 6.27. (**54**): Elutes second, M.p. 96-97.5 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.50 (t, *J* = 7.9 Hz, 1H), 6.99 (d, *J* = 7.5 Hz, 1H), 6.76 (d, *J* = 8.0 Hz, 1H), 3.93 (s, 3H), 3.08-3.04 (m, 2H), 2.68-2.63 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 204.9, 158.1, 158.0, 136.4, 125.2, 118.4, 108.8, 55.7, 36.8, 25.5. HRMS(EI): *m/z* calcd for $C_{10}H_{10}O_2$ (M^+): 162.0681. Found 162.0685.

5-[1-(3-Methoxyphenyl)cyclohexyl]-2,2-dimethyl-1,3-dioxane-4,6-dione (55):



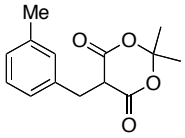
Conjugate addition of 3-methoxyphenylmagnesium bromide to cyclohexyl Meldrum's alkylidene according to Procedure C provided a solid in 36% yield after flash chromatography (4:1 hexanes:EtOAc) and recrystallization from MeOH. M.p. 88-89 °C (MeOH); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.27-7.21 (m, 2H), 6.89-6.76 (m, 3H), 3.76 (s, 3H), 3.43 (s, 1H), 2.55-2.40 (m, 2H), 2.10-1.90 (m, 2H), 1.70-1.50 (m, 2H), 1.52-1.30 (m, 4H), 1.47 (s, 3H), 0.81 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 164.4, 159.9, 141.4, 129.6, 120.0, 113.9, 112.5, 105.6, 57.0, 55.2, 47.2, 35.6, 30.5, 26.4, 25.6, 22.3; Anal. Calcd for $C_{19}H_{24}O_5$: C, 68.66; H, 7.28. Found: C, 68.64; H, 7.39.

5-Methoxy-(3.3)-pentamethylene-1-indanone (56) and 7-Methoxy-(3.3)-pentamethylene-1-indanone[56] (57):



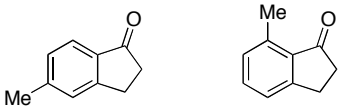
Prepared from **55** in 71% yield as a 3.4:1 ratio of para **56**:ortho **57** products using Procedure D in 120 min. The mixture was separated with 3:1 hexanes:EtOAc; (**56**): Elutes first, M.p. 82-82.5 °C (hexanes). Lit. 83.5-85 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.60 (d, J = 9.0 Hz, 1H), 6.87-6.84 (m, 2H), 3.86 (s, 3H), 2.53 (s, 2H), 1.77-1.26 (m, 10H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 204.2, 167.1, 165.3, 128.8, 125.1, 115.1, 107.4, 55.6, 48.5, 42.9, 38.2, 25.4, 23.7. Anal. calcd for $C_{15}H_{18}O_2$: C, 78.23; H, 7.88. Found: C, 78.38; H, 7.84. (**57**): Elutes second, M.p. 94-96 °C. Lit. 97.5-99 °C (Et_2O); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.52 (t, J = 7.9 Hz, 1H), 7.02 (d, J = 7.7 Hz, 1H), 6.55 (d, J = 8.2 Hz, 1H), 3.92 (s, 3H), 2.55 (s, 2H), 1.77-1.25 (m, 10H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 203.9, 167.0, 157.6, 136.5, 123.6, 115.6, 108.8, 55.8, 48.9, 42.5, 38.3, 25.5, 23.7. HRMS(EI): *m/z* calcd for $C_{15}H_{18}O_2$ (M^+): 230.1307. Found: 230.1304.

2,2-Dimethyl-5-(3-methylbenzyl)-1,3-dioxane-4,6-dione (58):



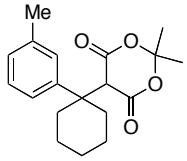
Reductive alkylation of Meldrum's acid with *m*-tolualdehyde according to Procedure A provided a white solid in 69% yield following recrystallization from MeOH. M.p. 81-82.5 °C (MeOH); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.15-7.01 (m, 4H), 3.76 (t, *J* = 4.9 Hz, 1H), 3.41 (d, *J* = 4.9 Hz, 2H), 2.30 (s, 3H), 1.71 (s, 3H), 1.48 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 165.3, 138.1, 137.1, 130.3, 128.3, 127.7, 126.5, 105.1, 47.9, 31.8, 38.3, 27.0, 21.2; Anal. calcd for $C_{14}H_{16}O_4$: C, 67.73; H, 6.50. Found: C, 67.67; H, 6.46.

5-Methyl-1-indanone (59) and 7-Methyl-1-indanone[57] (60):



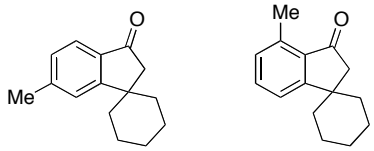
Prepared from **58** in 48% yield as a 1:1 ratio of para **59**:ortho **60** products using Procedure D in 60 min. The mixture was separated with 10:1 hexanes:EtOAc; (**59**): M.p 67-68 °C (petroleum ether). Lit. 68-69 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.62 (d, *J* = 7.8 Hz, 1H), 7.25 (br s, 1H), 7.15 (d, *J* = 7.9 Hz, 1H), 3.08-3.04 (m, 2H), 2.67-2.63 (m, 2H), 2.41 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 206.6, 155.7, 145.7, 134.8, 128.5, 127.0, 123.5, 36.4, 25.6, 22.0. HRMS(EI): *m/z* calcd for $C_{10}H_{10}O$ (M^+): 146.0732. Found: 146.0732. (**60**): M.p. 49-50 °C (petroleum ether). Lit. 52.5-53.5 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.38 (t, *J* = 7.5 Hz, 1H), 7.23 (d, *J* = 7.4 Hz, 1H), 7.04 (d, *J* = 7.4 Hz, 1H), 3.05-3.01 (m, 2H), 2.62-2.58 (m, 2H), 2.59 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 207.8, 155.8, 138.6, 134.3, 133.8, 128.9, 123.9, 36.6, 25.2, 18.2. HRMS(EI): *m/z* calcd for $C_{10}H_{10}O$ (M^+): 146.0732. Found: 146.0728.

2,2-Dimethyl-5-[1-(3-methylphenyl)cyclohexyl]-1,3-dioxane-4,6-dione (61):



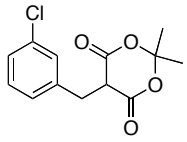
Prepared by conjugate addition of 3-methylphenylmagnesium bromide to cyclohexyl Meldrum's alkylidene according to Procedure C. A white solid was obtained in 35 % yield after flash chromatography (5:1 hexanes:EtOAc) and recrystallization from MeOH. M.p. 124-125 °C (MeOH); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.21-6.90 (m, 4H), 3.42 (s, 1H), 2.50-2.40 (m, 2H), 2.28 (s, 3H), 2.00-1.90 (m, 2H), 1.75-1.55 (m, 2H), 1.44 (s, 3H), 1.44-1.30 (m, 4H), 0.69 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 164.3, 139.6, 138.1, 128.5, 128.1, 127.9, 124.6, 105.5, 56.9, 47.0, 35.5, 30.5, 26.1, 25.6, 22.2, 21.5; Anal. Calcd for $C_{19}H_{24}O_4$: C, 72.13; H, 7.65. Found: C, 72.09; H, 7.63.

5-Methyl-(3.3)-pentamethylene-1-indanone (62) and 7-Methyl-(3.3)-pentamethylene-1-indanone (63):



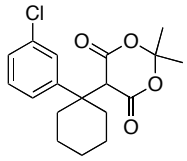
Prepared from **61** in 62% yield as a 1:1 ratio of para **62**:ortho **63** products using Procedure D in 120 min. The resulting mixture of **62** and **63** was separated with 10:1 hexanes:EtOAc; (**62**): M.p. 77.5-78.5 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.58 (d, J = 7.8 Hz, 1H), 7.27 (s, 1H), 7.15 (d, J = 7.8 Hz, 1H), 2.55 (s, 2H), 2.43 (s, 3H), 1.79-1.27 (m, 10H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 205.6, 164.7, 145.9, 133.3, 128.8, 124.3, 123.2, 48.5, 42.9, 38.3, 25.5, 23.8, 22.2. HRMS(EI): *m/z* calcd for $C_{15}H_{18}O$ (M^+) 214.1358. Found 214.1354. (**63**): Oil; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.42 (t, J = 7.5 Hz, 1H), 7.29 (d, J = 7.7 Hz, 1H), 7.07 (d, J = 7.3 Hz, 1H), 2.61 (s, 3H), 2.53 (s, 2H), 1.78-1.23 (m, 10H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 207.1, 165.1 138.5, 134.0, 133.0, 129.3, 121.2, 48.9, 42.3, 38.5, 25.5, 23.8, 18.4. Anal. calcd for $C_{15}H_{18}O$: C, 84.07; H, 8.47. Found: C, 84.19; H, 8.36.

5-(3-Chlorobenzyl)-2,2-dimethyl-1,3-dioxane-4,6-dione (64):



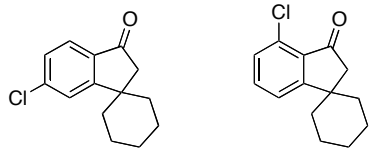
Reductive alkylation of Meldrum's acid with 3-chlorobenzaldehyde according to Procedure A produced white needles in 51% yield following recrystallization from MeOH. M.p. 105-105 °C (MeOH); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.31 (s, 1H), 7.19 (s, 3H), 3.74 (t, J = 5.0 Hz, 1H), 3.41 (d, J = 5.0 Hz, 2H), 1.73 (s, 3H), 1.58 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 164.9, 139.2, 134.2, 129.8, 128.0, 127.3, 105.2, 47.9, 31.3, 28.4, 26.9. HRMS(EI): *m/z* calcd for $C_{13}H_{13}ClO_4$ (M^+): 268.0502. Found 268.0493.

5-[1-(3-Chlorophenyl)cyclohexyl]-2,2-dimethyl-1,3-dioxane-4,6-dione (65):



Conjugate addition of 3-chlorophenylmagnesium bromide to cyclohexyl Meldrum's alkylidene according to Procedure C provided a 51% yield of a white solid following flash chromatography (4:1 hexanes:EtOAc) and recrystallization from MeOH. M.p. 115-116 °C (MeOH); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.29-7.14 (m, 4H), 3.44 (s, 1H), 2.50-2.30 (m, 2H), 2.10-1.90 (m, 2H), 1.75-1.65 (m, 2H), 1.48 (s, 3H), 1.48-1.30 (m, 4H), 0.88 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 164.2, 142.1, 134.7, 129.9, 128.0, 127.5, 126.0, 105.6, 56.9, 47.0, 35.4, 30.4, 26.4, 25.5, 22.2; Anal. Calcd for $C_{18}H_{21}ClO_4$: C, 64.19; H, 6.28. Found: C, 64.16; H, 6.39.

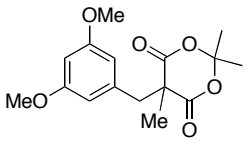
5-Chloro-(3.3)-pentamethylene-1-indanone (66) and 7-Chloro-(3.3)-pentamethylene-1-indanone (67):



Prepared from **65** in 62% yield as a 2:1 ratio of para **66**:ortho **67** products using Procedure D

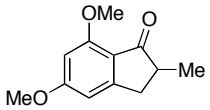
in 120 min. The mixture was separated with 3:1 CH_2Cl_2:hexanes; (**66**): M.p. 74-75 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.61 (d, *J* = 8.2 Hz, 1H), 7.46 (d, *J* = 1.6 Hz, 1H), 7.30 (dd, *J* = 8.1, 1.6 Hz, 1H), 2.57 (3H, s), 1.80-1.22 (m, 10H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 204.5, 165.6, 141.2, 134.0, 128.3, 124.7, 124.4, 48.3, 43.2, 38.2, 25.3, 23.7. HRMS(EI): *m/z* calcd for $C_{14}H_{15}ClO$ (M^+) 234.0811. Found 234.0807. (**67**): M.p. 159-160 °C (hexanes); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.48 (t, *J* = 7.7 Hz, 1H), 7.38 (d, *J* = 7.5 Hz, 1H), 7.27 (d, *J* = 7.6 Hz, 1H), 2.60 (s, 2H), 1.80-1.24 (m, 10H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 202.8, 166.5, 135.1, 131.5, 131.3, 129.1, 122.4, 48.9, 42.3, 38.4, 25.4, 23.7. HRMS(EI): *m/z* calcd for $C_{14}H_{15}ClO$ (M^+): 234.0811. Found 234.0806.

5-(3,5-Dimethoxybenzyl)-2,2,5-trimethyl-1,3-dioxane-4,6-dione (68):



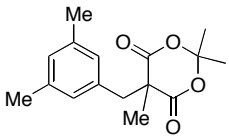
Prepared by alkylation of **9** according to Procedure B using iodomethane. Recrystallization from *i*-PrOH provided a white solid in 79% yield. M.p. 113-114 °C (*i*-PrOH); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.24 (s, 3H), 3.64 (s, 6H), 3.18 (s, 2H), 1.65 (s, 3H), 1.53 (s, 3H), 0.94 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 169.6, 160.7, 137.3, 107.6, 105.1, 99.9, 55.1, 51.9, 44.7, 29.1, 28.3, 26.1; Anal. Calcd for $C_{16}H_{20}O_6$: C, 62.33; H, 6.54. Found: C, 62.29; H, 6.58.

5,7-Dimethoxy-2-methyl-1-indanone[58] (69):



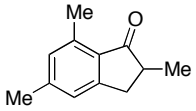
Prepared from **68** in 80% yield using Procedure D in 45 min. Purified with 1:1 hexanes:EtOAc; M.p. 71.5-73 °C (hexanes). Lit. 76-79 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.44 (br s, 1H), 6.28 (br s, 1H), 3.88 (s, 3H), 3.85 (s, 3H), 3.21-3.29 (m, 1H), 2.69-2.55 (m, 2H), 1.25 (d, *J* = 7.3 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 205.6, 166.9, 159.5, 158.6, 118.5, 101.5, 97.4, 55.7, 42.3, 35.0, 17.1. Anal. Calcd. for $C_{12}H_{14}O_3$: C, 69.88; H, 6.84. Found: C, 69.58; H, 6.71.

5-(3,5-Dimethylbenzyl)-2,2,5-trimethyl-1,3-dioxane-4,6-dione (70):



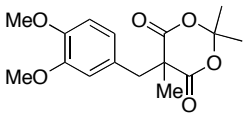
Alkylation of **23** according to Procedure B using iodomethane, followed by recrystallization from MeOH gave a 38% yield of white crystals. M.p. 117-118 °C (MeOH); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.83 (s, 1H), 6.75 (s, 2H), 3.22 (s, 2H), 2.21 (s, 6H), 1.71 (s, 3H), 1.57 (s, 3H), 0.88 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 169.8, 138.2, 135.1, 129.2, 127.7, 105.3, 52.1, 44.7, 29.3, 28.2, 26.0, 21.1; HRMS(EI) *m/z* calcd for $C_{16}H_{20}O_4$ (M^+): 276.1361. Found: 276.1365.

2,5,7-Trimethyl-1-indanone[59] (71):



Prepared from **70** in 87% yield using Procedure D in 30 min. Purified by flash chromatography (10:1 hexanes:EtOAc) to provide a clear colorless oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.24 (s, 1H), 6.85 (s, 1H), 3.23 (dd, J = 18.3, 9.3 Hz, 1H), 2.62-2.53 (m, 5H), 2.33 (s, 3H) 1.24 (d, J = 7.3 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 209.6, 154.5, 144.9, 138.5, 131.3, 130.2, 124.1, 42.2, 34.2, 21.7, 18.0, 16.4; HRMS(EI) *m/z* calcd for $C_{12}H_{14}O$ (M^+): 174.1045. Found: 174.1040.

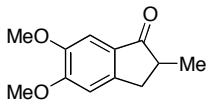
5-(3,4-Dimethoxybenzyl)-2,2,5-trimethyl-1,3-dioxane-4,6-dione (72):



Prepared by alkylation of **27** according to Procedure B using iodomethane. Recrystallization from MeOH provided a white solid in 76% yield. M.p. 88-89 °C (MeOH); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.68-6.60 (m, 3H), 3.74 (s, 3H), 3.73 (s, 3H), 3.18 (s, 2H), 1.64 (s, 3H), 1.52 (s, 3H), 0.90 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 169.8, 148.7, 148.3, 127.6, 122.1, 112.8, 110.9, 105.0, 55.6, 52.2, 44.3, 29.1, 28.3, 25.7; Anal. Calcd for $C_{16}H_{20}O_6$: C, 62.33; H, 6.54.

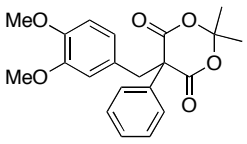
Found: C, 62.68; H, 6.68.

5,6-Dimethoxy-2-methyl-1-indanone[60] (73):



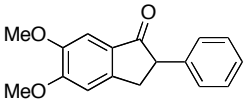
Prepared from **72** in 77% yield using Procedure D in 45 min. Purified by flash chromatography (2:1 hexanes:EtOAc) to provide a white powder. M.p. 131-132 °C (CH_2Cl_2). Lit. 132-133 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.08 (s, 1H), 6.79 (s, 1H), 3.88 (s, 1H), 3.82 (s, 1H), 3.22 (dd, *J* = 16.4, 7.2 Hz, 1H), 2.64-2.51 (m, 2H), 1.20 (d, *J* = 7.2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 207.9, 155.3, 149.3, 148.5, 128.8, 107.3, 104.3, 56.0, 55.9, 42.0, 34.6, 16.5; HRMS *m/z* calcd for $C_{12}H_{14}O_3$ (M^+): 206.0943. Found: 206.0941.

5-(3,4-Dimethoxybenzyl)-2,2-dimethyl-5-phenyl-1,3-dioxane-4,6-dione (74):



Phenyl Meldrum's acid[61] was alkylated with 3,4-dimethoxybenzyl bromide[62] according to Procedure B and purified by recrystallization from MeOH to provide a white solid in 68% yield. M.p. 99-100 °C (MeOH); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.59-7.56 (m, 2H), 7.40-7.36 (m, 3H), 6.88-6.85 (m, 2H), 6.76-6.74 (m, 1H), 3.83 (s, 3H), 3.82 (s, 3H), 3.61 (s, 2H), 1.40 (s, 3H), 1.31 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 167.0, 148.5, 148.3, 136.1, 129.4, 128.8, 127.6, 126.5, 123.3, 114.0, 110.9, 105.4, 61.9, 55.8, 55.7, 45.1, 28.9, 28.4; HRMS(EI) *m/z* calcd for $C_{21}H_{22}O_6$ (M^+): 370.1416. Found: 370.1411.

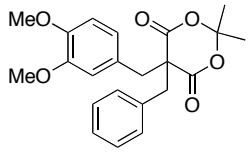
5,6-Dimethoxy-2-phenyl-1-indanone[63] (75):



Prepared from **74** in 67% yield using Procedure D in 60 min. Purified by flash chromatography (4:1 hexanes:EtOAc) to provide a white solid. M.p. 155-157 °C (MeOH). Lit.

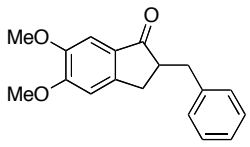
153-156 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.31-7.13 (m, 6H), 6.92 (s, 1H), 3.97 (s, 3H), 3.89 (s, 3H), 3.84 (dd, *J* = 8.0, 3.5 Hz), 3.57 (dd, 17.2, 8.0 Hz, 1H), 3.13 (dd, *J* = 17.2, 3.5 Hz, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 204.6, 155.7, 149.6, 149.9, 140.2, 128.9, 128.7, 127.7, 126.8, 107.2, 104.7, 56.2, 56.1, 53.6, 35.7; HRMS(EI) *m/z* calcd for $C_{17}H_{16}O_3$ (M^+): 268.1099. Found: 268.1107.

5-Benzyl-5-(3,4-dimethoxybenzyl)-2,2-dimethyl-1,3-dioxane-4,6-dione (76):



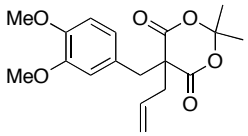
Prepared by the alkylation of **27** according to Procedure B using benzyl bromide. Recrystallization from EtOH provided a clear colorless solid in 70% yield. M.p. 148-149 °C (EtOH); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.24-7.14 (m, 5H), 6.73-6.70 (m, 3H), 3.80 (s, 3H), 3.77 (s, 3H), 3.38 (s, 2H), 3.37 (s, 2H), 0.70 (s, 3H), 0.61 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 168.2, 148.8, 148.4, 134.7, 129.9, 129.6, 128.6, 128.3, 127.6, 127.2, 122.2, 113.0, 111.1, 105.6, 60.0, 55.7, 44.8, 44.4, 28.7, 28.3; Anal. Calcd for $C_{22}H_{24}O_6$: C, 68.74; H, 6.29. Found: C, 68.52; H, 6.34.

2-Benzyl-5,6-dimethoxy-1-indanone[20] (77):



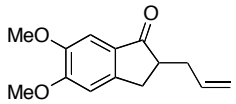
Prepared from **76** in 80% yield using Procedure D in 45 min. Purified by flash chromatography (2:1 hexanes:EtOAc) to provide a white solid. M.p. 125-126 °C (CH_2Cl_2). Lit. 125-126 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.28-7.16 (m, 5H), 7.16 (s, 1H), 6.77 (s, 1H), 3.89 (s, 3H), 3.87 (s, 3H), 3.33 (dd, *J* = 14.0, 4.0 Hz, 1H), 3.07-2.94 (m, 2H), 2.73 (dd, *J* = 16.3, 2.7 Hz, 1H), 2.60 (dd, *J* = 13.9, 10.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 206.3, 155.6, 149.5, 148.8, 139.7, 129.2, 128.8, 128.4, 126.2, 107.4, 104.4, 56.1, 56.0, 49.1, 37.2, 31.8; HRMS *m/z* calcd for $C_{18}H_{18}O_3$ (M^+): 282.1256. Found: 282.1256.

5-Allyl-5-(3,4-dimethoxybenzyl)-2,2-dimethyl-1,3-dioxane-4,6-dione (78):



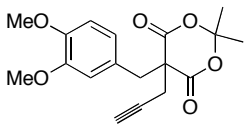
The alkylation of **27** according to Procedure B using allyl bromide provided white crystals in 67% yield following recrystallization from EtOH. M.p. 81-82 °C (EtOH); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.72-6.64 (m, 3H), 5.70-5.56 (m, 1H), 5.19-5.11 (m, 2H), 3.77 (s, 3H), 3.76 (s, 3H), 3.21 (s, 2H), 2.78 (d, J = 7.4 Hz, 2H), 1.48 (s, 3H), 0.73 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 168.4, 148.9, 148.5, 130.5, 127.5, 122.3, 121.2, 113.1, 111.2, 105.7, 58.0, 55.8, 44.2, 43.3, 29.4, 29.0; Anal. Calcd for $C_{18}H_{22}O_6$: C, 64.66; H, 6.63. Found: C, 64.46; H, 6.73.

2-Allyl-5,6-dimethoxy-1-indanone (79):



Prepared from **78** in 76% yield using Procedure D in 45 min. Purified by flash chromatography (2:1 hexanes:EtOAc) to provide a pale yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.07 (s, 1H), 6.78 (s, 1H), 5.77-5.63 (m, 1H), 5.01 (d, J = 17.0 Hz, 1H), 4.94 (d, J = 10.0 Hz, 1H), 3.87 (s, 3H), 3.81 (s, 3H), 3.09 (dd, J = 17.7, 7.9 Hz, 1H), 2.71-2.55 (m, 3H), 2.20-2.10 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 206.4, 155.4, 149.3, 148.8, 135.4, 129.2, 116.6, 107.3, 104.2, 56.0, 55.9, 46.6, 35.6, 31.6; HRMS *m/z* calcd for $C_{14}H_{16}O_3$ (M^+): 232.1099. Found: 232.1093.

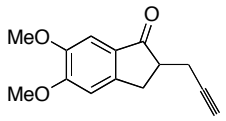
5-(3,4-Dimethoxybenzyl)-2,2-dimethyl-5-(2-propynyl)-1,3-dioxane-4,6-dione (80):



Prepared by alkylation of **27** according to Procedure B using propargyl bromide. Recrystallization from MeOH gave a white powder in 75% yield. M.p. 121-122 °C (MeOH); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.74-6.60 (m, 3H), 3.79 (s, 3H), 3.78 (s, 3H), 3.17 (s, 2H), 2.95

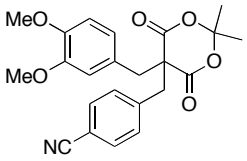
(d, J = 2.7 Hz, 2H), 2.12 (t, J = 2.6 Hz, 1H), 1.61 (s, 3H) 0.81 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 167.6, 148.8, 148.6, 126.4, 122.1, 112.7, 111.1, 106.3, 78.0, 72.9, 56.7, 55.7, 55.7, 44.0, 29.9, 28.4, 28.1; HRMS(EI) *m/z* calcd for $C_{18}H_{20}O_6$ (M^+): 332.1260. Found: 332.1251.

5,6-Dimethoxy-2-(2-propynyl)-1-indanone (81):



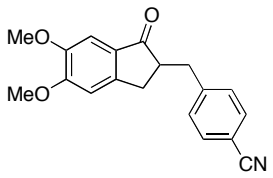
Prepared from **80** in 80% yield using Procedure D in 45 min. Purified by flash chromatography (2:1 hexanes:EtOAc) to provide a white solid. M.p. 109-111 °C (CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.09 (s, 1H), 6.83 (s, 1H), 3.90 (s, 3H), 3.83 (s, 3H), 3.22 (dd, J = 17.0, 7.5 Hz, 1H), 2.92 (dd, J = 17.0, 3.6 Hz, 1H), 2.77-2.64 (m, 2H), 2.45 (ddd, J = 16.6, 7.9 Hz, 2.5 Hz), 1.83 (t, J = 2.1 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 204.7, 155.6, 149.4, 148.8, 129.0, 107.3, 104.3, 81.2, 69.3, 56.1, 55.9, 45.7, 31.6, 20.1; HRMS *m/z* calcd for $C_{14}H_{14}O_3$ (M^+): 230.0943. Found: 230.0948.

4-[5-(3,4-Dimethoxybenzyl)-2,2-dimethyl-4,6-dioxo-1,3-dioxan-5-yl]methylbenzonitrile (82):



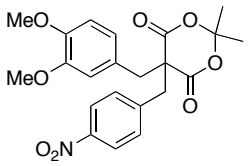
The alkylation of **27** according to Procedure B using α-bromo-*p*-tolunitrile provided a 79% yield of white powder following recrystallization from MeOH. M.p. 158-159.5 °C (MeOH); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.49 (d, J = 8.2 Hz, 2H), 7.21 (d, J = 8.2 Hz, 2H), 6.67-6.60 (m, 3H), 3.72 (s, 3H), 3.71 (s, 3H), 3.37 (s, 2H), 3.31 (s, 2H), 0.65 (s, 3H), 0.60 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 167.7, 148.8, 148.5, 140.0, 132.2, 130.7, 126.5, 122.1, 118.1, 112.8, 111.6, 111.1, 105.8, 59.5, 55.6, 44.5, 44.3, 28.6, 28.5; HRMS(EI) *m/z* calcd for $C_{23}H_{23}NO_6$ (M^+): 409.1525. Found: 409.1531.

4-[(5,6-Dimethoxy-1-oxo-2,3-dihydro-1*H*-2-indenyl)methyl]benzonitrile (83):



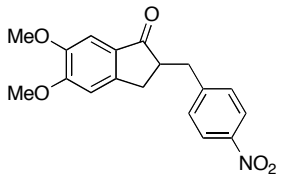
Prepared from **82** in 78% yield using Procedure D with 17 mol % $Sc(OTf)_3$ in 320 min. Purified by flash chromatography (3:1 hexanes:EtOAc) to provide a pale yellow solid. Recrystallization from methanol afforded clear colorless crystals. M.p. 259-260 °C (MeOH); IR(neat) 2224 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.55 (d, *J* = 8.2 Hz, 2H), 7.32 (d, *J* = 8.1 Hz, 2H), 7.15 (s, 1H), 6.78 (s, 1H), 3.91 (s, 1H), 3.88 (s, 3H), 3.35 (dd, *J* = 13.9, 4.2 Hz, 1H), 3.07 (dd, *J* = 16.7, 7.5 Hz, 1H), 2.99-2.91 (m, 1H), 2.79-2.63 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 155.8, 149.7, 148.5, 145.4, 132.3, 129.7, 129.0, 118.9, 110.3, 107.3, 104.4, 56.2, 56.1, 48.4, 37.2, 31.7; HRMS(EI) *m/z* calcd for $C_{19}H_{17}NO_3$ (M^+): 307.1208. Found: 307.1211.

5-(3,4-Dimethoxybenzyl)-2,2-dimethyl-5-(4-nitrobenzyl)-1,3-dioxane-4,6-dione (84):



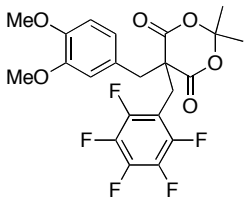
Compound **27** was alkylated according to Procedure B using 4-nitrobenzyl bromide and recrystallized from MeOH to provide a white solid in 81% yield. M.p. 192-193 °C (MeOH); ^1H NMR ($CDCl_3$, 300 MHz) δ 8.09 (d, *J* = 8.7 Hz, 2H), 7.32 (d, *J* = 8.7 Hz, 2H), 6.71-6.64 (m, 3H), 3.78 (s, 3H), 3.76 (s, 3H), 3.46 (s, 3H), 3.37 (s, 2H), 0.71 (s, 3H), 0.64 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 167.8, 148.9, 148.7, 142.4, 142.1, 131.0, 126.6, 123.7, 122.3, 112.9, 111.2, 106.0, 59.5, 55.8, 55.7, 44.5, 44.3, 28.9, 28.6; HRMS(EI) *m/z* calcd for $C_{22}H_{23}NO_8$ (M^+): 429.1424. Found: 429.1418.

5,6-Dimethoxy-2-(4-nitrobenzyl)-1-indanone (85):



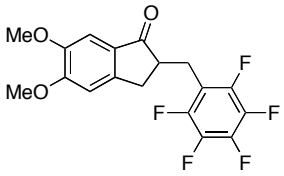
Prepared from **84** in 81% yield using Procedure D in 250 min. Purified by flash chromatography (4:1 hexanes:EtOAc) to provide a pale yellow solid. Recrystallization from MeOH afforded clear, colorless crystals. M.p. 188-190 °C (MeOH); IR(neat) 2361 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 8.15 (d, *J* = 8.6 Hz, 2H), 7.40 (d, *J* = 8.5 Hz, 2H), 7.18 (s, 1H), 6.82 (s, 1H), 3.94 (s, 3H), 3.91 (s, 3H), 3.42 (dd, *J* = 13.8, 4.1 Hz, 1H), 3.12 (dd, *J* = 16.6, 7.5 Hz, 1H), 3.16-2.97 (m, 1H), 2.86 (dd, *J* = 13.8, 9.5 Hz, 1H), 2.73 (dd, *J* = 16.7, 3.2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 205.3. 155.8, 149.6, 148.4, 147.5, 146.7, 129.7, 128.9, 123.7, 107.3, 104.4, 56.2, 56.1, 48.3, 36.9, 31.6; HRMS(EI) *m/z* calcd for $C_{18}H_{17}NO_5$ (M^+): 327.1107. Found: 327.1105.

5-(3,4-Dimethoxybenzyl)-2,2-dimethyl-5-(2,3,4,5,6-pentafluorobenzyl)-1,3-dioxane-4,6-dione (86):



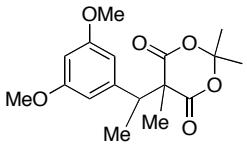
Compound **27** was alkylated according to Procedure B using 2,3,4,5,6-pentafluorobenzyl bromide and recrystallized from MeOH to provide a white powder in 95% yield. M.p. 169-169.5 °C (MeOH); ^1H NMR ($CDCl_3$, 300 MHz) δ 6.75-6.66 (m, 3H), 3.80 (s, 6H), 3.44 (s, 2H), 3.35 (s, 2H), 1.50 (s, 3H), 0.85 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 167.5, 148.8, 148.5, 147.2 (m), 143.9 (m), 139.0 (m), 135.6 (m), 126.6, 122.7, 113.3, 111.0, 108.5 (m), 105.8, 56.4, 55.6, 41.7, 31.9, 28.9, 28.6; HRMS(EI) *m/z* calcd for $C_{22}H_{19}F_5O_6$ (M^+): 474.1102. Found: 474.1108.

5,6-Dimethoxy-2-(2,3,4,5,6-pentafluorobenzyl)-1-indanone (87):



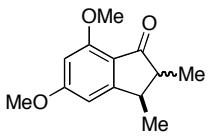
Prepared from **86** in 80% yield using Procedure D in 85 min. Purified by flash chromatography (6:1 hexanes:EtOAc) to provide a white solid. M.p. 163-164 °C (CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.17 (s, 1H), 6.83 (s, 1H), 3.95 (s, 3H), 3.90 (s, 3H), 3.29 (dd, *J* = 13.7 Hz, 5.4 Hz, 1H), 3.14 (dd, *J* = 16.8, 7.5 Hz, 1H), 2.97-2.94 (m, 1H), 2.90-2.82 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 204.3, 155.8, 149.6, 148.1, 146.8 (m), 143.6 (m), 141.5 (m), 139.3-138.2 (m), 135.9-135.7 (m), 128.6, 113.1 (m), 107.3, 104.4, 56.1 (d, *J* = 7.5 Hz), 46.7 (d, *J* = 15.0 Hz), 32.1, 24.3; HRMS(EI) *m/z* calcd for $C_{18}H_{13}F_5O_3$ (M^+): 372.0785. Found: 372.0782.

5-[1-(3,5-Dimethoxyphenyl)ethyl]-2,2,5-trimethyl-1,3-dioxane-4,6-dione (88):



Alkylation of **11** according to Procedure B using iodomethane, followed by flash chromatography (4:1 hexanes:EtOAc) and recrystallization from MeOH gave a white solid in 60% yield. M.p. 72-73 °C (MeOH); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.30 (s, 3H), 3.71 (s, 6H), 3.41 (q, *J* = 7.2 Hz, 1H), 1.63 (s, 3H), 1.54 (s, 3H), 1.51 (d, *J* = 7.2 Hz, 3H), 1.04 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 170.4, 168.6, 160.7, 142.7, 106.5, 104.9, 100.0, 55.3, 54.0, 48.6, 30.0, 27.6, 22.5, 15.2; HRMS(EI) *m/z* calcd for $C_{17}H_{22}O_6$ (M^+): 322.1416. Found: 322.1424.

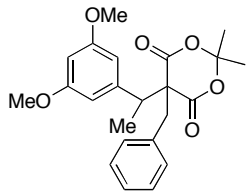
5,7-Dimethoxy-2,3-dimethyl-1-indanone[64] (89):



Prepared from **88** in 91% yield using Procedure D in 155 min. Purified by flash

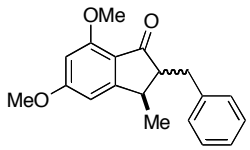
chromatography (6:1 hexanes:EtOAc) to provide a mixture of *trans:cis* isomers (5.6:1) as a clear, colorless oil. *Trans* isomer: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.42 (s, 1H), 6.26 (s, 1H), 3.85 (s, 3H), 3.84 (s, 3H), 2.77-2.71 (m, 1H), 2.11-2.19 (m, 1H), 1.33 (d, J = 7.1 Hz, 3H), 1.19 (J = 6.1 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 204.4, 167.0, 162.9, 159.1, 117.8, 100.2, 97.2, 55.7, 55.6, 51.5, 41.6, 19.4, 15.0. *Cis* isomer: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.42 (s, 1H), 6.26 (s, 1H), 3.85 (s, 3H), 3.84 (s, 3H), 3.35-3.29 (m, 1H), 2.19-2.11 (m, 1H), 1.16 (d, J = 7.3 Hz, 3H), 1.12 (J = 7.6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 205.1, 166.8, 164.2, 159.1, 117.4, 100.6, 97.2, 55.7, 55.6, 46.6, 36.6, 16.8; HRMS(EI) *m/z* calcd for $C_{13}H_{16}O_3$ (M^+)(mixture of isomers): 220.1099. Found: 220.1095.

5-Benzyl-5-[1-(3,5-dimethoxyphenyl)ethyl]-2,2-dimethyl-1,3-dioxane-4,6-dione (90):



Alkylation of **11** according to Procedure B using benzyl bromide, followed by flash chromatography (4:1 hexanes:EtOAc) and recrystallization from MeOH gave a 67% yield of a white powder. M.p. 125-126 °C (MeOH); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.24-7.13 (m, 5H), 6.32-6.29 (m, 3H), 3.69 (s, 6H), 3.57 (q, J = 7.2 Hz, 1H), 3.55 (d, J = 12.5 Hz, 1H), 3.18 (d, J = 12.5 Hz, 1H), 1.62 (d, J = 7.2 Hz, 3H), 0.67 (s, 3H), 0.48 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 168.5, 166.8, 160.7, 142.5, 135.2, 130.5, 128.6, 127.5, 106.4, 105.6, 99.9, 61.8, 55.2, 48.7, 41.5, 28.9, 27.8, 15.5; HRMS(EI) *m/z* calcd for $C_{23}H_{26}O_6$ (M^+): 398.1729. Found: 398.1728.

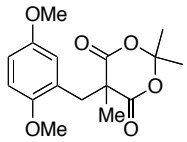
2-Benzyl-5,7-dimethoxy-3-methyl-1-indanone (91):



Prepared from **90** in 92% yield using Procedure D with 17 mol % $Sc(OTf)_3$ in 32 hours. Purified by flash chromatography (6:1 hexanes:EtOAc) to provide a mixture of *trans*:*cis* isomers (12.3:1) as a pale yellow oil. *Trans* isomer: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.29-7.16

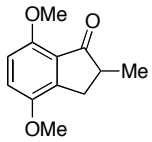
(m, 1H), 6.34 (s, 1H), 6.29 (s, 1H), 3.88 (s, 3H), 3.83 (s, 3H), 3.33 (dd, *J* = 13.6, 4.3 Hz, 1H), 2.96-2.92 (m, 1H), 2.67 (dd, *J* = 13.6, 9.9 Hz, 1H), 2.51-2.46 (m, 1H), 1.06 (d, *J* = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 202.7, 167.0, 163.2, 159.1, 139.7, 128.9, 128.2, 126.0, 117.7, 100.2, 97.2, 57.9, 55.6, 55.5, 38.3, 36.5, 20.1. *Cis* isomer: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.29-7.16 (m, 1H), 6.47 (s, 1H), 6.44 (s, 1H), 3.88 (s, 3H), 3.83 (s, 3H), 3.33 (dd, *J* = 13.6, 4.3 Hz, 1H), 2.96-2.92 (m, 1H), 2.67 (dd, *J* = 13.6, 9.9 Hz, 1H), 2.51-2.46 (m, 1H), 1.13 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 202.4, 166.7, 164.0, 140.5, 128.9, 127.9, 125.7, 117.0, 100.7, 97.2, 60.2, 55.0, 52.9, 31.1, 20.9, 18.7, 14.0; HRMS(EI) *m/z* calcd for $C_{19}H_{20}O_3$ (M^+)(mixture of isomers): 296.1412. Found: 296.1407.

5-(2,5-Dimethoxybenzyl)-2,2,5-trimethyl-1,3-dioxane-4,6-dione (92):



Alkylation of **32** according to Procedure B using iodomethane produced a white solid in 61% yield after recrystallization from MeOH. M.p. 76-77 °C (MeOH); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.75-6.67(3H, m), 3.71 (3H, s), 3.69 (3H, s), 3.27 (2H, s), 1.66 (3H, s), 1.61 (3H, s), 1.32 (3H, s); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 169.4, 153.3, 124.0, 117.8, 113.9, 111.3, 104.8, 55.7, 55.4, 50.1, 40.8, 30.0, 27.9, 23.7; HRMS(EI) *m/z* calcd for $C_{16}H_{20}O_6$ (M^+): 308.1260. Found: 308.1259.

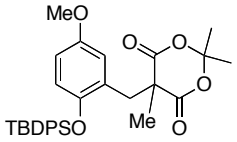
4,7-Dimethoxy-2-methyl-1-indanone[65] (93):



Prepared from **92** in 69% yield using Procedure D in 20 min. Purified by flash chromatography (5:1 hexanes:EtOAc) to provide a white solid. M.p. 78-79 °C (Et_2O). Lit. 79.5-82.5 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.89 (d, *J* = 8.7 Hz, 1H), 6.64 (d, *J* = 8.7 Hz, 1H), 3.81 (s, 3H), 3.76 (s, 3H), 3.16 (dd, *J* = 17.5, 7.7 Hz, 1H), 2.59-2.43 (m, 2H), 1.19 (d, *J* = 7.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 207.2, 151.8, 150.3, 144.1, 125.4, 116.5, 109.5, 55.8, 42.0,

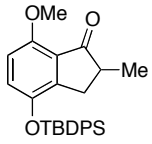
42.1, 31.2, 16.7; HRMS(EI) *m/z* calcd for $C_{12}H_{14}O_3$ (M^+): 206.0943. Found: 206.0937.

5-(2-[1-(*tert*-Butyl)-1,1-diphenylsilyl]oxy-5-methoxybenzyl)-2,2,5-trimethyl-1,3-dioxane-4,6-dione (94):



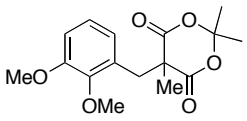
Alkylation of **34** according to Procedure B using iodomethane was followed by flash chromatography using 5:1 (hexanes: EtOAc) to afford a pale yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.75–7.70 (m, 4H), 7.40-7.34 (m, 6H), 6.69-6.68 (m, 1H), 6.31-6.30 (m, 2H), 3.62 (s, 3H), 3.48 (s, 2H), 1.78 (s, 3H), 1.66 (s, 3H), 1.33 (s, 3H), 1.14 (s, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 169.7, 153.1, 147.5, 135.3, 132.5, 129.7, 127.6, 125.2, 119.9, 115.7, 113.6, 104.9, 55.3, 50.6, 39.5, 30.0, 27.8, 26.4, 23.8, 19.2; HRMS(EI) *m/z* calcd for $C_{31}H_{36}O_6Si$ (M^+): 532.2281. Found: 532.2278.

4-[1-(*tert*-Butyl)-1,1-diphenylsilyl]oxy-7-methoxy-2-methyl-1-indanone (95):



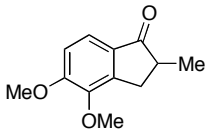
Prepared from **94** in 94% yield using Procedure D in 20 min. Purified by flash chromatography (4:1 hexanes:EtOAc) to provide a pale yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.67 (d, *J* = 6.5 Hz, 4H), 7.45-7.33 (m, 6H), 6.61 (d, *J* = 8.7 Hz, 1H), 6.36 (d, *J* = 8.7 Hz, 1H), 3.77 (s, 3H), 3.37-3.29 (m, A of AB, 1H), 2.65 (m, 1H), 2.56 (m, B of AB, 1H), 1.26 (3H, d, *J* = 7.3 Hz), 1.11 (s, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 207.3, 152.2, 146.1, 145.5, 135.4, 132.5, 130.1, 127.9, 125.2, 125.1, 109.4, 55.8, 42.1, 31.9, 26.5, 19.5, 16.8; HRMS(EI) *m/z* calcd for $C_{27}H_{30}O_3Si$ (M^+): 430.1964. Found: 430.1967.

5-(2,3-Dimethoxybenzyl)-2,2,5-trimethyl-1,3-dioxane-4,6-dione (96):



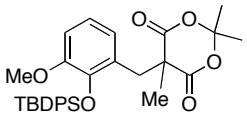
Alkylation of **36** according to Procedure B using iodomethane, followed by flash chromatography (6:1 hexanes:EtOAc) produced a white solid in 50% yield. M.p. 72-73 °C (CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.92 (t, *J* = 7.8 Hz, 1H), 6.82 (d, *J* = 1.5 Hz, 1H), 6.73 (d, *J* = 1.5 Hz, 2H), 3.80 (s, 3H), 3.79 (s, 3H), 3.32 (s, 3H), 1.69 (s, 3H), 1.61 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 169.5, 152.6, 147.9, 128.5, 123.5, 112.5, 105.1, 60.5, 55.6, 50.3, 40.1, 29.9, 28.1, 24.6; HRMS(EI) *m/z* calcd for $C_{16}H_{20}O_6$ (M^+): 308.1260. Found: 308.1249.

4,5-Dimethoxy-2-methyl-1-indanone[66] (97):



Prepared from **96** in 75% yield using Procedure D in 20 min. Purified by flash chromatography (7:1 hexanes:EtOAc) to provide a white solid. M.p. 69-70 °C (Et_2O); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.49 (d, *J* = 8.3 Hz, 1H), 6.94 (d, *J* = 8.4 Hz, 1H), 3.91 (s, 3H), 3.88 (s, 3H), 3.36 (dd, *J* = 18.2, 8.8 Hz, 1H), 2.69-2.60 (m, 2H), 1.25 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 207.8, 157.6, 146.1, 145.3, 130.3, 120.4, 112.3, 60.3, 56.2, 42.1, 31.5, 16.5; HRMS(EI) *m/z* calcd for $C_{12}H_{14}O_3$ (M^+): 206.0943. Found: 206.0947.

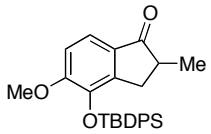
5-(2-[1-(*tert*-Butyl)-1,1-diphenylsilyl]oxy-3-methoxybenzyl)-2,2,5-trimethyl-1,3-dioxane-4,6-dione (98):



Alkylation of **42** according to Procedure B using iodomethane was followed by flash chromatography (5:1 hexanes:EtOAc) and recrystallization from MeOH to give an 84% yield of white powder. M.p. 131-132 °C (MeOH); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.68-7.65 (m, 4H),

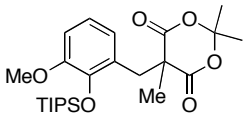
7.33-7.27 (m, 6H), 6.71 (t, *J* = 3.1 Hz, 2H), 6.39 (dd, *J* = 6.1, 3.5 Hz, 1H), 3.64 (s, 2H), 2.73 (s, 3H), 1.75 (s, 3H), 1.66 (s, 3H), 1.35 (s, 3H), 1.10 (s, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 169.7, 149.4, 143.6, 135.0, 134.3, 128.8, 127.1, 125.5, 121.9, 120.7, 110.7, 104.9, 52.4, 51.0, 37.0, 30.0, 28.0, 27.0, 24.3, 20.0; HRMS(EI) *m/z* calcd for $C_{31}H_{36}O_6Si$ (M^+-CH_3): 517.2046. Found: 517.2039.

4-[1-(*tert*-Butyl)-1,1-diphenylsilyl]oxy-5-methoxy-2-methyl-1-indanone (99):



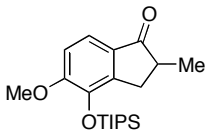
Prepared from **98** in 86% yield using Procedure D in 30 min. Purified by flash chromatography (11:1 hexanes:EtOAc) to provide a clear colorless oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.67-7.65 (m, 4H), 7.37-7.29 (m, 7H), 6.65 (1H, d, *J* = 8.3 Hz), 3.35 (br q, *J* = 8.3 Hz, 1H), 3.09 (s, 3H), 2.85-2.65 (m, 2H), 1.26 (d, *J* = 7.3 Hz, 3H), 1.09 (s, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 208.3, 154.6, 144.0, 141.4, 134.7, 134.1, 130.2, 129.4, 127.3, 117.9, 111.6, 54.4, 42.1, 32.2, 26.7, 20.0, 16.5; HRMS(EI) *m/z* calcd for $C_{27}H_{30}O_3Si$ (M^+-CH_3): 415.1724. Found: 415.1735.

5-(3-Methoxy-2-[(1,1,1-triisopropylsilyl)oxy]benzyl)-2,2,5-trimethyl-1,3-dioxane-4,6-dione (100):



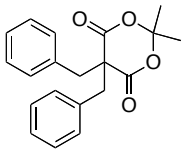
Alkylation of **23** according to Procedure B using iodomethane, followed by flash chromatography (8:1 hexanes:EtOAc) provided a white solid. M.p. 60-61 °C (Benzene); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.74–6.61 (m, 3H), 3.71 (s, 3H), 3.45 (s, 2H), 1.67 (s, 3H), 1.60 (s, 3H), 1.30 (s, 3H), 1.30-1.23 (septet, *J* = 7.3 Hz, 3H), 1.06 (d, *J* = 7.2 Hz, 18H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 169.6, 149.9, 144.4, 125.8, 122.0, 120.1, 110.3, 104.7, 54.6, 50.5, 39.0, 29.9, 28.0, 24.2, 18.1, 14.2; HRMS(EI) *m/z* calcd for $C_{24}H_{38}O_6Si$ (M^+-CH_3): 435.2203. Found: 435.2218.

5-Methoxy-2-methyl-4-[(1,1,1-triisopropylsilyl)oxy]-1-indanone (101):



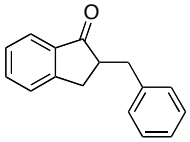
Prepared from **100** in 77% yield using Procedure D in 40 min. Purified by flash chromatography (10:1 hexanes:EtOAc) to provide a pale yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.36 (d, *J* = 8.3 Hz, 1H), 6.88 (d, *J* = 8.3 Hz, 1H), 3.85 (s, 3H), 3.32 (dd, *J* = 16.8, 7.6 Hz, 1H), 2.64-2.59 (m, 2H), 1.27 (d, *J* = 9.0 Hz, 3H), 1.25 (septet, *J* = 6.8 Hz, 3H), 1.07 (d, *J* = 7.1 Hz, 18H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 208.3, 155.0, 144.3, 142.1, 130.4, 117.4, 111.5, 55.3, 42.2, 32.2, 18.0, 16.6, 13.7; HRMS(EI) *m/z* calcd for $C_{20}H_{32}O_3Si$ (M^+): 348.2121. Found: 348.2129.

5,5-Dibenzyl-2,2-dimethyl-1,3-dioxane-4,6-dione[67] (102):



Prepared according to Procedure B from Meldrum's acid and benzyl bromide. The reaction mixture in DMF was poured into H_2O and stirred vigorously for 10 minutes, and the resulting white solid was filtered and dried under high vacuum to provide a white powder in 90% yield. M.p. 225-227 °C (H_2O); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.25-7.17 (m, 10H), 3.42 (s, 4H), 0.60 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 168.1, 134.8, 130.1, 128.7, 127.7, 105.8, 60.0, 44.8, 28.5; Anal. Calcd for $C_{20}H_{20}O_4$: C, 74.06; H, 6.21. Found: C, 73.97; H, 6.18.

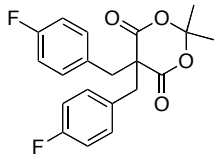
2-Benzyl-1-indanone[66] (103):



Prepared from **102** in 66% yield using Procedure D in 50 min. Using catalytic TfOH gave 71% yield in the same time period. Purified by flash chromatography (10:1 hexanes:EtOAc) to

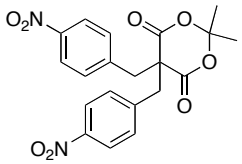
provide a clear colorless oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.77 (d, *J* = 7.6 Hz, 1H), 7.55 (t, *J* = 7.4 Hz, 1H), 7.38-7.20 (m, 7H), 3.39 (dd, *J* = 4.2, 3.9 Hz, 1H), 3.15 (dd, *J* = 17.0, 7.7 Hz, 1H), 3.10-2.90 (m, 1H), 2.84 (dd, *J* = 17.0, 3.9 Hz, 1H), 2.65 (dd, *J* = 13.9, 10.4 Hz, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 207.7, 153.5, 139.6, 136.5, 134.7, 128.8, 128.4, 127.3, 126.5, 126.3, 123.9, 48.8, 36.9, 32.1; HRMS(EI) *m/z* calcd for $C_{16}H_{14}O$ (M^+): 222.1045. Found: 222.1052.

5,5-Di(4-fluorobenzyl)-2,2-dimethyl-1,3-dioxane-4,6-dione (104):



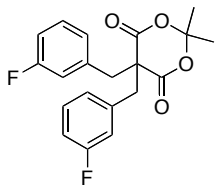
The dialkylation of Meldrum's acid with 4-fluorobenzyl bromide was performed according to Procedure B. The product was precipitated by addition of water, then filtered and dried under high vacuum. Recrystallization from MeOH provided a white solid in 74% yield. M.p. 144-145 °C (MeOH); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.16-7.11 (m, 4H), 6.96-6.90 (m, 4H), 3.67 (s, 4H), 0.68 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 168.0, 164.0, 160.7, 131.8, 131.7, 130.5, 115.8, 105.9, 60.0, 43.9, 28.7; HRMS(EI) *m/z* calcd for $C_{20}H_{18}F_2O_4$ (M^+): 360.1173. Found: 360.1166.

2,2-Dimethyl-5,5-di(4-nitrobenzyl)-1,3-dioxane-4,6-dione[67] (106):



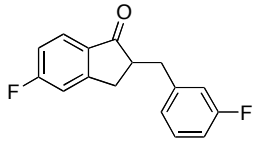
The dialkylation of Meldrum's acid with 4-nitrobenzyl bromide was performed according to Procedure B. The product was precipitated by addition of water, then filtered and dried under high vacuum. Recrystallization from MeOH provided a white solid in 89% yield. M.p. 237-238 °C (MeOH). Lit. 258-259 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.16 (d, *J* = 8.6 Hz, 4H), 7.38 (d, *J* = 8.6 Hz, 4H), 3.56 (s, 4H), 0.72 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 167.3, 147.7, 141.6, 131.3, 130.9, 124.0, 123.8, 106.3, 59.0, 44.4, 29.0.

5,5-Di(3-fluorobenzyl)-2,2-dimethyl-1,3-dioxane-4,6-dione (108):



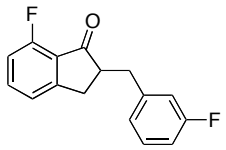
Dialkylation of Meldrum's acid according to Procedure B with 3-fluorobenzyl bromide to provide a white solid in a yield of 58% after recrystallization from MeOH. M.p. 137-138 °C (MeOH); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.27–7.19 (m, 2H), 7.00-6.88 (m, 6H), 3.40 (s, 4H), 0.71 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 167.8, 164.4, 161.1, 136.9, 130.3, 125.9, 117.2 (d, *J* = 22.5 Hz), 114.9 (d, *J* = 15.0 Hz), 106.0, 59.5, 44.5, 28.7; HRMS(EI) *m/z* calcd for $C_{20}H_{18}F_2O_4$ (M^+): 360.1173. Found: 360.1177.

5-Fluoro-2-(3-fluorobenzyl)-1-indanone (109):



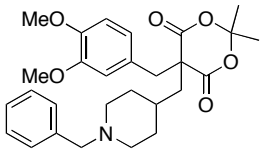
Prepared from **108** in 93% yield as a 13:1 mixture of para **109**:ortho **110** products using Procedure D in 90 min. The mixture was separated by flash chromatography (13:1 hexanes:EtOAc) to provide clear colorless oils. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.78-7.74 (m, 1H), 7.24-7.20 (m, 1H), 7.08-6.90 (m, 5H), 3.35 (dd, *J* = 14.0, 4.3 Hz, 1H), 3.17 (dd, *J* = 17.2, 7.8 Hz, 1H), 3.05-2.90 (m, 1H), 2.80 (dd, *J* = 17.1, 4.2 Hz, 1H), 2.68 (dd, *J* = 13.9, 10.1 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 205.4, 166.8 (d, *J* = 336.2 Hz), 163.4 (d, *J* = 325.7 Hz), 156.3 (d, *J* = 10.0 Hz), 141.9 (d, *J* = 7.1 Hz), 132.8 (d, *J* = 1.7 Hz), 130.0 (d, *J* = 8.4 Hz), 126.3 (d, *J* = 10.5 Hz), 124.5, 115.8 (d, *J* = 23.7 Hz), 115.7 (d, *J* = 20.9 Hz), 113.4 (d, *J* = 20.9 Hz), 113.2 (d, *J* = 22.1 Hz), 48.8, 36.6, 32.0; HRMS(EI) *m/z* calcd for $C_{16}H_{12}F_2O$ (M+): 258.0856. Found: 258.0851.

7-Fluoro-2-(3-fluorobenzyl)-1-indanone (110):



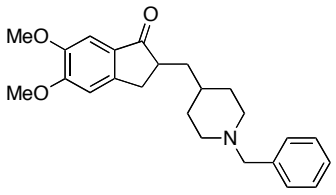
^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.80-7.75 (m, 1H), 7.28-7.24 (m, 1H), 7.09-6.92 (m, 5H), 3.36 (dd, *J* = 14.0, 4.3 Hz, 1H), 3.20-2.99 (m, 1H), 3.18 (dd, *J* = 17.3, 7.8 Hz, 1H), , 2.84 (dd, *J* = 17.3, 3.9 Hz, 1H), 2.70 (dd, *J* = 14.0, 10.1 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 203.4, 162.7 (d, *J* = 244.0 Hz), 159.1 (d, *J* = 262.0 Hz), 155.4 (d, *J* = 20.0 Hz), 141.8 (d, *J* = 7.1 Hz), 136.8 (d, *J* = 8.3 Hz), 130.0 (d, *J* = 8.3 Hz), 124.6, 122.4, 115.7 (d, *J* = 20.9 Hz), 114.4 (d, *J* = 19.1 Hz), 113.4 (d, *J* = 20.9 Hz), 49.1, 36.5, 32.0; HRMS(EI) *m/z* calcd for $C_{16}H_{12}F_2O$ (M^+): 258.0856. Found: 258.0858.

5-[(1-Benzyl-3-piperidyl)methyl]-5-(3,4-dimethoxybenzyl)-2,2-dimethyl-1,3-dioxane-4,6-dione (111):



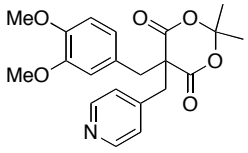
Reductive alkyation of Meldrum's acid according to Procedure A using *N*-benzyl-4-formylpiperidine (prepared by Swern oxidation of (1-benzylpiperidin-4-yl)methanol)[68] provided the monosubstituted derivative in 47% yield after flash chromatography (50:1 CH_2Cl_2:MeOH). This yellow oil was alkylated with 3,4-dimethoxybenzyl bromide[62] according to Procedure B, and the target material was isolated as a pale yellow solid in 44% yield following flash chromatography (5:2 EtOAc:hexanes) and recrystallization from MeOH. M.p. 120-121 °C (MeOH); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.25-7.17 (m, 5H), 6.70-6.64 (m, 3H), 3.78 (s, 3H), 3.77 (s, 3H), 3.39 (s, 2H), 3.17 (s, 2H), 2.80-2.76 (m, 2H), 2.10-2.07 (m, 2H), 1.84-1.80 (m, 2H), 1.60-1.52 (m, 2H), 1.52 (s, 3H), 1.35-1.20 (m, 3H), 0.65 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 169.0, 148.9, 148.5, 138.2, 128.9, 128.0, 127.5, 126.8, 122.5, 113.2, 111.2, 105.8, 63.2, 56.2, 55.8, 55.7, 53.3, 47.9, 44.4, 33.2, 32.7, 29.1, 29.1; HRMS(EI) *m/z* calcd for $C_{28}H_{35}NO_6$ (M^+): 481.2464. Found: 481.2458.

2-[(1-Benzyl-4-piperidyl)methyl]-5,6-dimethoxy-1-indanone (donepezil) (112):



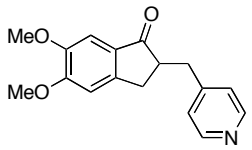
Prepared from **111** in 61% yield using Procedure D with TfOH (1.2 eq) in 30 min. After removal of nitromethane, the crude brown oil was dissolved in CH_2Cl_2 and washed with saturated $NaHCO_3$ (2 times) then the organic layer washed with brine, then dried over $MgSO_4$ and filtered. Concentration, followed by flash chromatography (20:1 CH_2Cl_2:MeOH) provided a pale yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.30-7.14 (m, 5H), 7.14 (s, 3H), 6.83 (s, 1H), 3.93 (s, 3H), 3.88 (s, 3H), 3.51 (s, 2H), 3.21 (dd, *J* = 17.5, 8.1 Hz, 1H), 2.92-2.87 (m, 2H), 2.70-2.63 (m, 2H), 2.02-1.80 (m, 3H), 1.75-1.60 (m, 2H), 1.55-1.20 (m, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 207.7, 155.4, 149.4, 148.7, 138.1, 129.3, 128.1, 127.0, 107.3, 104.4, 63.3, 56.2, 56.1, 53.7, 45.4, 38.7, 34.3, 33.4, 32.8, 31.7; HRMS(EI) *m/z* calcd for $C_{24}H_{29}NO_3$ (M^+): 379.2147. Found: 379.2142.

5-(3,4-Dimethoxybenzyl)-2,2-dimethyl-5-(4-pyridylmethyl)-1,3-dioxane-4,6-dione (113):



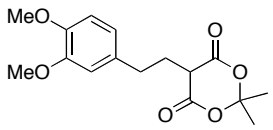
Alkylation of **27** according to Procedure B with (4-bromomethyl)pyridine hydrobromide provided a 74% yield of an off-white solid after recrystallization from MeOH. M.p. 139-141 °C (MeOH); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.51 (d, *J* = 5.8 Hz, 2H), 7.10 (d, *J* = 5.8 Hz, 2H), 6.74-6.68 (m, 3H), 3.82 (s, 3H), 3.80 (s, 3H), 3.39 (s, 2H), 3.38 (s, 2H), 0.74 (s, 3H), 0.68 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 167.5, 149.9, 148.6, 148.4, 143.2, 128.4, 124.7, 122.0, 112.7, 110.9, 105.9, 59.1, 55.5, 44.3, 43.6, 28.5, 28.4; HRMS(EI) *m/z* calcd for $C_{21}H_{23}NO_6$ (M^+): 385.1525. Found: 385.1522.

5,6-Dimethoxy-2-(4-pyridylmethyl)-1-indanone[69] (114):



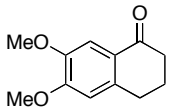
Prepared from **113** using Procedure D, using TfOH (1.2 eq) in 45 min. After removal of nitromethane, the crude brown oil was dissolved in CH_2Cl_2 and washed with saturated $NaHCO_3$ (2 times), brine, then dried over $MgSO_4$ and filtered. Concentration, followed by flash chromatography (20:1 CH_2Cl_2:MeOH) provided a pale yellow solid in 77% yield. The use of TMSOTf (1.2 eq) instead of TfOH provided a 62% yield. Recrystallization from MeOH afforded a white powder. M.p. 190-191 °C (MeOH). Lit. 190-191 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.49-8.48 (m, 2H), 7.17-7.14 (m, 3H), 6.79 (s, 1H), 3.92 (s, 3H), 3.81 (s, 3H), 3.32 (dd, *J* = 14.1 Hz, 4.1 Hz, 1H), 3.09 (dd, *J* = 16.7 Hz, 7.5 Hz, 1H), 3.00-2.90 (m, 1H), 2.71-2.63 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 205.1, 155.4, 149.5, 149.3, 148.5, 148.3, 128.6, 124.0, 107.1, 104.0, 55.9, 55.7, 47.6, 36.1, 31.5; HRMS(EI) *m/z* calcd for $C_{17}H_{17}NO_3$ (M^+): 283.1208. Found: 283.1205.

5-(3,4-Dimethoxyphenethyl)-2,2-dimethyl-1,3-dioxane-4,6-dione (115):



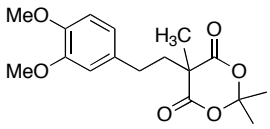
Condensation and reduction of Meldrum's acid and 3,4-dimethoxyphenylacetic acid according to the procedure of Tsukamoto[16] provided a white powder in 79% yield after recrystallization from MeOH. M.p. 138-139.5 °C (MeOH); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.77-6.73 (m, 3H), 3.85 (s, 3H), 3.84 (s, 3H), 3.46 (t, *J* = 5.3 Hz, 1H), 2.81-2.76 (m, 2H), 2.41-2.36 (m, 2H), 1.74 (s, 3H), 1.72 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 165.3, 148.8, 147.3, 132.7, 120.4, 111.6, 111.1, 104.7, 55.7, 55.6, 44.8, 31.8, 28.3, 27.9, 26.4; HRMS(EI) *m/z* calcd for $C_{16}H_{20}O_6$ (M^+): 308.1260. Found: 308.1257.

6,7-Dimethoxy-1,2,3,4-tetrahydro-1-naphthalenone[70] (116):



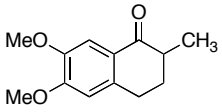
Prepared from **115** in 82% yield using Procedure D in 45 min. Purified by flash chromatography (1:1 hexanes:EtOAc) to provide a white solid. M.p. 96-98 °C (CH_2Cl_2). Lit. 98-99 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.48 (s, 1H), 6.64 (s, 1H), 3.90 (s, 3H), 3.88 (s, 3H), 2.88-2.84 (m, 2H), 2.58-2.54 (m, 2H), 2.10-2.07 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 197.1, 153.3, 147.8, 139.2, 128.7, 110.1, 108.3, 55.9, 38.4, 29.3, 23.5; HRMS(EI) *m/z* calcd for $C_{12}H_{14}O_3$: 206.0943. Found: 206.0950.

5-(3,4-Dimethoxyphenethyl)-2,2,5-trimethyl-1,3-dioxane-4,6-dione (117):



Alkylation of **115** according to Procedure B using iodomethane, followed by recrystallization from MeOH provided an 82% yield of white powder. M.p. 81.5-83 °C (MeOH); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.70-6.57 (m, 3H), 3.76 (s, 6H), 3.74 (s, 3H), 2.43-2.38 (m, 2H), 2.80-2.24 (m, 2H), 1.67 (br s, 6H), 1.57 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 170.0, 148.7, 147.4, 132.1, 120.0, 111.4, 111.1, 104.7, 55.6, 55.6, 49.2, 42.8, 31.2, 29.5, 28.2, 24.0; HRMS(EI) *m/z* calcd for $C_{17}H_{22}O_6$ (M^+): 322.1416. Found: 322.1419.

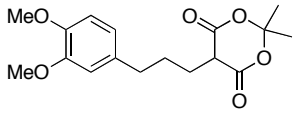
6,7-Dimethoxy-2-methyl-1,2,3,4-tetrahydro-1-naphthalenone[71] (118):



Prepared from **117** in 82% yield using Procedure D in 15 min. Purified by flash chromatography (3:1 hexanes:EtOAc) to provide a pale yellow solid. M.p. 120-121 °C (CH_2Cl_2). Lit. 129-130 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.49 (s, 1H), 6.62 (s, 1H), 3.90 (s, 3H), 3.88 (s, 3H), 3.00-2.80 (m, 2H), 2.53-2.45 (m, 1H), 2.18-2.12 (m, 1H), 1.90-1.75 (m, 1H), 1.23 (d, J = 6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 199.5, 153.1, 147.1, 138.8, 125.3,

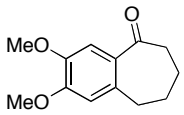
109.9, 108.5, 55.8, 41.7, 31.5, 28.3, 15.4; HRMS(EI) *m/z* calcd for $C_{13}H_{16}O_3$: 220.1099. Found: 220.1107.

5-[3-(3,4-Dimethoxyphenyl)propyl]-2,2-dimethyl-1,3-dioxane-4,6-dione (119):



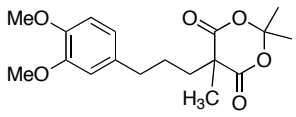
Condensation and reduction of Meldrum's acid and 3,4-dimethoxyhydrocinnamic acid according to Tsukamoto[16] provided a white solid in 68% yield after recrystallization from MeOH. M.p. 113-114.5 °C (MeOH); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.76-6.67 (m, 3H), 3.83 (s, 3H), 3.80 (s, 3H), 3.48 (t, *J* = 4.9 Hz, 1H), 2.60 (t, *J* = 7.6 Hz, 2H), 2.14-2.07 (m, 2H), 1.80-1.68 (m, 2H), 1.69 (br s, 6 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 165.4, 148.7, 147.1, 134.0, 120.1, 111.4, 111.1, 104.7, 55.8, 55.4, 45.9, 35.2, 28.3, 27.8, 26.6, 26.0; HRMS(EI) *m/z* calcd for $C_{17}H_{22}O_6$ (M^+): 322.1416. Found: 322.1407.

2,3-Dimethoxy-6,7,8,9-tetrahydro-5*H*-benzo[*a*]cyclohepten-5-one[72] (120):



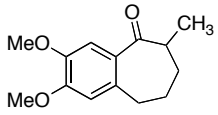
Prepared from **119** in 78% yield using Procedure D in 45 min. Purified by flash chromatography (1:1 hexanes:EtOAc) to provide a white solid. M.p. 61-62.5 °C (CH_2Cl_2). Lit. 63-64 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.35 (s, 1H), 6.65 (s, 1H), 3.91 (s, 3H), 3.88 (s, 3H), 2.90-2.86 (m, 2H), 2.73-2.69 (m, 2H), 1.87-1.74 (m, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 203.7, 152.0, 147.3, 136.6, 130.6, 112.2, 111.1, 55.8, 40.6, 32.4, 25.0, 20.5; HRMS(EI) *m/z* calcd for $C_{13}H_{16}O_3$: 220.1099 Found: 220.1096.

5-[3-(3,4-Dimethoxyphenyl)propyl]-2,2,5-trimethyl-1,3-dioxane-4,6-dione (121):



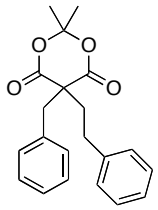
Alkylation of **119** using Procedure B with iodomethane, followed by recrystallization from MeOH provided a 79% yield of a white powder. M.p. 80-81 °C (MeOH); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.77-6.63 (m, 3H), 3.85 (s, 3H), 3.83 (s, 3H), 2.52 (t, J = 7.6 Hz, 2H), 2.06-2.00 (m, 2H), 1.71 (s, 3H), 1.70 (s, 3H), 1.60 (s, 3H), 1.60-1.40 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 170.2, 148.6, 147.1, 133.3, 120.2, 111.2, 111.0, 104.7, 55.7, 55.6, 49.3, 40.5, 34.8, 29.6, 28.3, 27.0, 24.0; HRMS(EI) *m/z* calcd for $C_{18}H_{24}O_6$ (M^+): 336.1573. Found: 336.1585.

2,3-Dimethoxy-6-methyl-6,7,8,9-tetrahydro-5*H*-benzo[*a*]cyclohepten-5-one (122):



Prepared from **121** in 81% yield using Procedure D in 15 min. Purified by flash chromatography (1:1 hexanes:EtOAc) to provide a pale yellow solid. M.p. 80-81 °C (from CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.33 (s, 1H), 6.65 (s, 1H), 3.91 (s, 3H), 3.89 (s, 3H), 3.05-2.84 (m, 3H), 2.10-1.90 (m, 1H), 1.89-1.82 (m, 1H), 1.70-1.50 (m, 2H), 1.20 (d, J = 6.6 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 205.0, 151.2, 147.0, 137.2, 131.3, 112.3, 111.1, 55.8, 43.5, 43.4, 31.2, 25.5, 16.4; HRMS(EI) *m/z* calcd for $C_{14}H_{18}O_3$: 234.1256. Found: 234.1251.

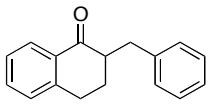
5-Benzyl-2,2-dimethyl-5-phenethyl-1,3-dioxane-4,6-dione (123):



2,2-Dimethyl-5-phenethyl-1,3-dioxane-4,6-dione[16] was alkylated with benzyl bromide according to Procedure B. Purification by recrystallization from MeOH provided a crystalline solid in 22% yield (3 steps from Meldrum's acid); M.p. 117.0-118.0 °C (MeOH); ^{1}H NMR

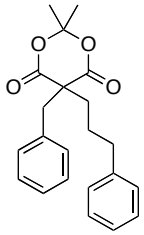
($CDCl_3$, 300 MHz) δ 7.30-7.15 (m, 10H), 3.33 (s, 2H), 2.59-2.38 (m, 4H), 1.58 (s, 3H), 0.65 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 168.8, 139.6, 135.3, 130.3, 128.9, 128.6, 128.3, 127.8, 126.5, 106.0, 57.6, 43.8, 43.1, 31.8, 29.5, 28.8; HRMS(EI) *m/z* calcd for $C_{18}H_{16}O_3$ (M^+-C_3H_6O): 280.1099. Found: 280.1088.

2-Benzyl-1,2,3,4-tetrahydro-1-naphthalenone[73] (124):



Obtained as the exclusive product in 75% yield from **123** using Procedure D in 45 min. Purified by flash chromatography (1:1 CH_2Cl_2:hexanes) to afford a fine white powder. M.p. 50-51 °C (CH_2Cl_2/hexanes). Lit. 53-54 °C (petroleum ether); ^1H NMR ($CDCl_3$, 300 MHz) δ 8.05 (d, *J* = 7.8 Hz, 1H), 7.45 (dt, *J* = 7.1, 1.2 Hz, 1H), 7.32-7.19 (m, 7H), 3.48 (dd, *J* = 13.4, 3.7 Hz, 1H), 2.94-2.89 (m, 2H), 2.74-2.59 (m, 1H), 2.62 (dd, *J* = 13.4, 9.6 Hz, 1H), 2.09 (dq, *J* = 13.4, 4.4 Hz, 1H), 1.84-1.70 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 199.4, 144.0, 140.0, 133.3, 132.5, 129.3, 128.7, 128.4, 127.5, 126.6, 126.1, 49.5, 35.7, 28.6, 27.6; HRMS(EI) *m/z* calcd for $C_{17}H_{16}O$ (M^+): 236.1201. Found: 236.1200.

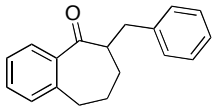
5-Benzyl-2,2-dimethyl-5-(3-phenylpropyl)-1,3-dioxane-4,6-dione (125):



Meldrum's acid was coupled with cinnamic acid using the method of Tsukamoto.[16] The resulting intermediate was hydrogenated over 5% Pd/C, then alkylated with benzyl bromide according to Procedure B, and purified by recrystallization from MeOH to afford a crystalline solid in 25% yield (3 steps); M.p. 126-127 °C (MeOH); ^1H NMR ($CDCl_3$, 300 MHz) δ 7.29-7.11 (m, 10H), 3.29 (s, 2H), 2.61 (t, *J* = 7.6 Hz, 2H), 2.20-2.15 (m, 2H), 1.65-1.54 (m, 2H), 1.51 (s, 3H), 0.60 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 168.9, 140.7, 130.3, 128.9,128.5, 128.3, 127.8, 126.1, 105.9, 57.6, 43.8, 40.8, 35.5, 29.5, 28.9,

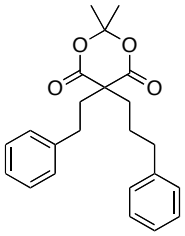
27.0; HRMS(EI) *m/z* calcd for $C_{19}H_{18}O_3$ (M^+- C_3H_6O): 294.1256. Found: 294.1249.

6-Benzyl-6,7,8,9-tetrahydro-5H-benzo[a]cyclohepten-5-one (126):



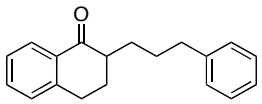
Obtained as the exclusive product in 77% yield from **125** using Procedure D in 45 min. Purified by flash chromatography (9:1 pentane:Et_2O) to afford a clear, colorless oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.73 (d, *J* = 7.6 Hz, 1H), 7.56 (t, *J* = 7.2 Hz, 1H), 7.42 (d, *J* = 7.6 Hz, 1H), 7.34 (t, *J* = 7.4 Hz, 1H), 7.29-7.01 (m, 5H), 3.30 (dd, *J* = 17.2, 7.9 Hz, 1H), 2.78 (dd, *J* = 17.2, 3.9 Hz, 1H), 2.71-2.62 (m, 3H), 2.05-1.93 (m, 1H), 1.74 (quint., *J* = 7.8 Hz, 2H), 1.55-1.45 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 208.8, 153.7, 142.1, 136.8, 134.7, 128.4, 128.3, 127.3, 126.5, 125.8, 123.9, 47.3, 36.0, 32.8, 31.1, 29.3; HRMS(EI) *m/z* calcd for $C_{18}H_{18}O$ (M^+): 250.1358. Found: 250.1358.

2,2-Dimethyl-5-phenethyl-5-(3-phenylpropyl)-1,3-dioxane-4,6-dione (127):



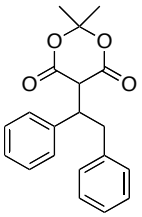
2,2-Dimethyl-5-phenethyl-1,3-dioxane-4,6-dione[16] was alkylated with cinnamyl chloride according to Procedure B, and the resulting intermediate hydrogenated over 5% Pd/C and recrystallized from MeOH to provide a crystalline solid in 72% yield (2 steps); M.p. 94.5-95.5 °C (MeOH); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.28-7.09 (m, 10H), 2.62-2.53 (m, 4H), 2.28-2.03 (m, 4H), 1.74 (s, 3H), 1.70 (s, 3H), 1.70-1.56 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 169.2, 128.6, 128.5, 128.3, 126.1, 105.7, 54.5, 29.8, 27.1; HRMS(EI) *m/z* calcd for $C_{20}H_{20}O_3$ (M^+-C_3H_6O): 308.1412. Found: 308.1407.

2-(3-Phenylpropyl)-1,2,3,4-tetrahydro-1-naphthalenone (128):



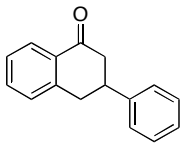
Obtained as the exclusive product in 76% yield from **127** using Procedure D in 45 min. Purified by flash chromatography (9:1 pentane:Et_2O) to afford a clear colorless oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.02 (d, *J* = 7.8 Hz, 1H), 7.44 (dt, *J* = 7.5, 1.3 Hz, 1H), 7.31-7.16 (m, 7H), 2.98-2.95 (m, 2H), 2.66 (dt, *J* = 7.7, 2.4 Hz, 2H), 2.53-2.44 (m, 1H), 2.22 (dq, *J* = 13.3, 4.6 Hz, 1H), 2.06-1.81 (m, 2H), 1.79-1.67 (m, 2H), 1.61-1.49 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 200.2, 143.9, 142.4, 133.1, 132.5, 128.6, 128.4, 128.3, 127.4, 126.5, 125.7, 47.4, 36.1, 29.2, 28.9, 28.3, 28.2; HRMS(EI) *m/z* calcd for $C_{19}H_{20}O$ (M^+): 264.1514. Found: 264.1509.

5-(1,2-Diphenylethyl)-2,2-dimethyl-1,3-dioxane-4,6-dione (129):



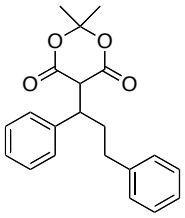
Phenyl Meldrum's alkylidene[12a] was prepared by the conjugate addition of phenylmagnesium bromide to 5-methoxymethylene Meldrum's acid[74] according to Procedure C, followed by acid hydrolysis with 10% HCl for 30 minutes. After standard workup the phenyl Meldrum's alkylidene was acquired as a pale yellow solid in quantitative yield. This was reacted with benzylmagnesium chloride (Procedure C) to produce the desired target material, which was purified by flash chromatography (1:1 hexanes:CH_2Cl_2) to afford a colorless oil in 82% yield. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.39-7.20 (m, 10H), 4.10-4.03 (m, 1H), 3.70 (t, *J* = 12.4 Hz, 1H), 3.53 (d, *J* = 2.8 Hz, 1H), 3.23 (dd, *J* = 13.7, 5.7 Hz, 1H), 1.52 (s, 3H), 1.07 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 166.0, 164.5, 139.5, 139.0, 129.3, 128.9, 128.7, 127.8, 126.7, 105.3, 48.4, 47.7, 38.1, 28.0; HRMS(EI) *m/z* calcd for $C_{17}H_{14}O_3$ (M^+- C_3H_6O): 266.0943. Found: 266.0933.

3-Phenyl-1,2,3,4-tetrahydro-1-naphthalenone (130):



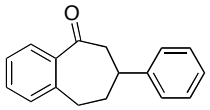
Obtained as the exclusive isomer in 51% yield from **129** using Procedure D with slow addition of substrate by syringe pump over 8 h, followed by an additional one hour of stirring at 100 °C. Purified by flash chromatography (1:1 hexanes:CH_2Cl_2) to afford a colorless oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.07 (d, *J* = 7.8 Hz, 1H), 7.50 (t, *J* = 7.4 Hz, 1H), 7.39-7.24 (m, 7H), 3.51-3.40 (m, 1H), 3.21-3.17 (m, 2H), 2.97 (dd, *J* = 16.7, 3.5 Hz, 1H), 2.83 (dd, *J* = 16.6, 12.9 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 197.8, 143.4, 133.8, 132.1, 128.8, 127.2, 127.0, 126.9, 126.7, 45.9, 41.1, 37.7; HRMS(EI) *m/z* calcd for $C_{16}H_{14}O$ (M^+): 222.1045. Found: 222.1044.

5-(1,3-Diphenylpropyl)-2,2-dimethyl-1,3-dioxane-4,6-dione (131):



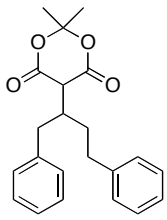
Cinnamaldehyde was condensed with Meldrum's acid using the method of Bigi[15], and the resulting alkylidene reacted with phenylmagnesium bromide according to Procedure C. The resulting product was hydrogenated over 5% Pd/C to afford the target material as a solid in 56% yield (3 steps from Meldrum's acid) after recrystallization from MeOH. M.p. 72.5-73.5 °C (MeOH); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.35-7.12 (m, 10H), 3.80-3.74 (m, 1H), 3.67 (d, *J* = 3.2 Hz, 1H), 2.73-2.51 (m, 3H), 2.36-2.24 (m, 1H), 1.59 (s, 3H), 1.11 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 165.5, 164.6, 141.3, 139.0, 129.1, 128.8, 128.4, 127.8, 126.0, 105.4, 51.4, 45.5, 34.3, 34.1, 28.3, 28.0; HRMS(EI) *m/z* calcd for $C_{21}H_{22}O_4$ (M^+): 338.1518. Found: 338.1519.

7-Phenyl-6,7,8,9-tetrahydro-5H-benzo[a]cyclohepten-5-one (132):



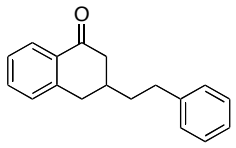
Obtained as the exclusive isomer in 42% yield from **131** using Procedure D with slow addition of substrate by syringe pump over 8 h, followed by an additional one hour of stirring at 100 °C. Purified by flash chromatography (1:1 hexanes:CH_2Cl_2) to afford a colorless oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.73 (d, *J* = 7.6 Hz, 1H), 7.59 (t, *J* = 7.4 Hz, 1H), 7.49 (d, *J* = 7.7 Hz, 1H), 7.36 (t, *J* = 7.4 Hz, 1H), 7.31-7.17 (m, 5H), 3.40-3.34 (m, 1H), 2.89 (dd, *J* = 19.0, 7.5 Hz, 1H), 2.75-2.68 (m, 2H), 2.43 (dd, *J* = 19.0, 3.3 Hz, 1H), 2.32-2.20 (m, 1H), 1.86-1.74 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 206.2, 158.5, 141.4, 136.8, 134.7, 128.5, 128.3, 127.6, 126.1, 125.5, 123.6, 43.0, 37.8, 37.7, 33.9; HRMS(EI) *m/z* calcd for $C_{17}H_{16}O$ (M^+): 236.1201. Found: 236.1194.

5-(1-Benzyl-3-phenylpropyl)-2,2-dimethyl-1,3-dioxane-4,6-dione (133):



Cinnamaldehyde was condensed with Meldrum's acid[15], and the resulting alkylidene reacted with benzylmagnesium chloride according to Procedure C. The resulting product was hydrogenated over 5% Pd/C to afford the target material as a solid in 65% yield (3 steps from Meldrum's acid) after recrystallization from MeOH. M.p. 83.0-84.0 °C (MeOH); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.31-7.14 (m, 10H), 3.29 (d, *J* = 2.4 Hz, 1H), 2.98 (dd, *J* = 8.1, 2.3 Hz, 2H), 2.87-2.74 (m, 2H), 2.65-2.55 (m, 1H), 1.98-1.84 (m, 2H), 1.66 (s, 3H), 1.51 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 165.5, 164.7, 141.5, 139.6, 129.2, 128.7, 128.5, 128.4, 126.7, 126.0, 104.6, 47.4, 40.6, 37.4, 34.3, 32.7, 28.2, 26.7; HRMS(EI) *m/z* calcd for $C_{19}H_{18}O_3$ (M^+- C_3H_6O): 294.1256. Found: 294.1260.

3-Phenethyl-1,2,3,4-tetrahydro-1-naphthalenone (134):



Obtained as the exclusive isomer in 59% yield from **133** using Procedure D with slow addition of substrate by syringe pump over 8 h, followed by an additional one hour of stirring at 100 °C. Purified by flash chromatography (1:1 hexanes:CH_2Cl_2) to afford a colorless oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.02 (d, *J* = 7.8 Hz, 1H), 7.47 (t, *J* = 7.5 Hz, 1H), 7.32-7.18 (m, 7H), 3.05 (d, *J* = 14.0 Hz, 1H), 2.86-2.79 (m, 1H), 2.72 (t, *J* = 7.9 Hz, 2H), 2.37 (dd, *J* = 16.2, 11.9 Hz, 1H), 2.27-2.19 (m, 1H), 1.78 (quintet, *J* = 7.6 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 198.2, 143.5, 141.7, 133.5, 132.3, 128.9, 128.4, 128.3, 126.9, 126.7, 125.9, 45.2, 37.4, 36.1, 34.7, 32.8; HRMS(EI) *m/z* calcd for $C_{18}H_{18}O$ (M^+): 250.1358. Found: 250.1366.

X-Ray data for **36**
From MeOH

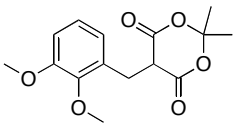


Table 1. Crystal data and structure refinement for ef1233m.

Identification code	ef1233m
Empirical formula	$C_{15}H_{18}O_6$
Formula weight	294.29
Temperature	180(1) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	$P2_1/c$
Unit cell dimensions	a = 7.4134(14) Å alpha = 90° b = 20.429(4) Å beta = 104.548(4)° c = 9.8491(19) Å gamma = 90°
Volume, Z	1443.8(5) $Å^3$, 4
Density (calculated)	1.354 Mg/m^3
Absorption coefficient	0.105 mm^{-1}
F(000)	624
Crystal size	0.34 x 0.29 x 0.10 mm
θ range for data collection	1.99 to 27.88°
Limiting indices	$-9 \le h \le 9$, $-26 \le k \le 26$, $-12 \le l \le 12$
Reflections collected	10218
Independent reflections	3431 (R_{int} = 0.0306)
Completeness to θ = 27.88°	99.7 %
Absorption correction	None
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3431 / 0 / 199
Goodness-of-fit on F^2	2.156
Final R indices [I>2σ(I)]	R1 = 0.0414, wR2 = 0.0756
R indices (all data)	R1 = 0.0480, wR2 = 0.0765
Extinction coefficient	0.0168(12)
Largest diff. peak and hole	0.259 and -0.218 $eÅ^{-3}$

Table 2. Atomic coordinates [x 10^4] and equivalent isotropic displacement parameters [$Å^2$ x 10^3] for ef1233m. U(eq) is defined as one third of the trace of the orthogonalized U_{ij} tensor.

	x	y	z	U(eq)
O(1)	-959(1)	3427(1)	1921(1)	32(1)
C(2)	-1048(2)	3831(1)	704(1)	30(1)
O(3)	801(1)	3941(1)	516(1)	33(1)
C(4)	2093(2)	3457(1)	750(1)	30(1)
C(5)	1549(2)	2817(1)	1293(1)	26(1)
C(6)	205(2)	2911(1)	2204(1)	28(1)
C(7)	-1713(2)	4490(1)	1074(2)	44(1)
C(8)	-2293(2)	3526(1)	-582(1)	35(1)
O(9)	3587(1)	3570(1)	536(1)	44(1)
O(10)	103(1)	2551(1)	3144(1)	38(1)
C(11)	3229(2)	2391(1)	2019(1)	33(1)
C(12)	4062(2)	1990(1)	1041(1)	28(1)
C(13)	5849(2)	2115(1)	890(1)	36(1)
C(14)	6626(2)	1728(1)	41(1)	39(1)
C(15)	5645(2)	1208(1)	-689(1)	36(1)
C(16)	3862(2)	1073(1)	-557(1)	30(1)
C(17)	3087(2)	1464(1)	319(1)	26(1)
O(18)	2761(1)	570(1)	-1223(1)	42(1)
C(19)	3566(2)	130(1)	-2033(1)	48(1)
O(20)	1288(1)	1345(1)	438(1)	32(1)
C(21)	1155(2)	801(1)	1327(2)	51(1)

Table 3. Bond lengths [Å] and angles [°] for ef1233m.

O(1)-C(6)	1.3469(14)	O(1)-C(2)	1.4422(14)
C(2)-O(3)	1.4462(13)	C(2)-C(8)	1.5021(17)
C(2)-C(7)	1.5091(16)	O(3)-C(4)	1.3553(13)
C(4)-O(9)	1.2006(13)	C(4)-C(5)	1.5068(16)
C(5)-C(6)	1.5118(16)	C(5)-C(11)	1.5401(16)
C(6)-O(10)	1.1999(13)	C(11)-C(12)	1.5086(16)
C(12)-C(17)	1.3873(15)	C(12)-C(13)	1.3934(16)
C(13)-C(14)	1.3775(18)	C(14)-C(15)	1.3832(18)
C(15)-C(16)	1.3878(16)	C(16)-O(18)	1.3731(14)
C(16)-C(17)	1.4002(16)	C(17)-O(20)	1.3893(12)
O(18)-C(19)	1.4279(14)	O(20)-C(21)	1.4334(14)

C(6)-O(1)-C(2)	120.92(9)	O(1)-C(2)-O(3)	110.36(9)
O(1)-C(2)-C(8)	110.73(9)	O(3)-C(2)-C(8)	110.92(10)
O(1)-C(2)-C(7)	105.04(10)	O(3)-C(2)-C(7)	105.67(9)
C(8)-C(2)-C(7)	113.86(11)	C(4)-O(3)-C(2)	121.16(9)
O(9)-C(4)-O(3)	118.36(11)	O(9)-C(4)-C(5)	124.70(11)
O(3)-C(4)-C(5)	116.93(10)	C(4)-C(5)-C(6)	112.02(10)
C(4)-C(5)-C(11)	113.45(10)	C(6)-C(5)-C(11)	111.91(10)
O(10)-C(6)-O(1)	118.63(10)	O(10)-C(6)-C(5)	123.98(11)
O(1)-C(6)-C(5)	117.38(10)	C(12)-C(11)-C(5)	115.03(10)
C(17)-C(12)-C(13)	118.29(11)	C(17)-C(12)-C(11)	120.21(10)
C(13)-C(12)-C(11)	121.42(11)	C(14)-C(13)-C(12)	120.91(12)
C(13)-C(14)-C(15)	120.73(12)	C(14)-C(15)-C(16)	119.49(12)
O(18)-C(16)-C(15)	124.71(11)	O(18)-C(16)-C(17)	115.77(10)
C(15)-C(16)-C(17)	119.52(11)	C(12)-C(17)-O(20)	118.71(10)
C(12)-C(17)-C(16)	121.06(10)	O(20)-C(17)-C(16)	120.19(10)
C(16)-O(18)-C(19)	117.16(10)	C(17)-O(20)-C(21)	113.71(9)

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters [$Å^2$ x 10^3] for ef1233m.
The anisotropic displacement factor exponent takes the form:
$-2\pi^2$ [$(ha^*)^2U_{11}$ + ... + 2hka*b*U_{12}]

	U11	U22	U33	U23	U13	U12
O(1)	35(1)	36(1)	29(1)	0(1)	14(1)	-1(1)
C(2)	33(1)	29(1)	33(1)	2(1)	15(1)	0(1)
O(3)	34(1)	26(1)	43(1)	3(1)	17(1)	-1(1)
C(4)	34(1)	29(1)	29(1)	-2(1)	11(1)	-2(1)
C(5)	30(1)	26(1)	22(1)	-1(1)	4(1)	-3(1)
C(6)	30(1)	31(1)	22(1)	-4(1)	4(1)	-9(1)
C(7)	48(1)	34(1)	55(1)	-6(1)	21(1)	5(1)
C(8)	36(1)	35(1)	34(1)	2(1)	9(1)	3(1)
O(9)	36(1)	41(1)	60(1)	4(1)	25(1)	-3(1)
O(10)	42(1)	46(1)	27(1)	8(1)	8(1)	-9(1)
C(11)	35(1)	32(1)	28(1)	0(1)	2(1)	0(1)
C(12)	27(1)	27(1)	26(1)	6(1)	1(1)	2(1)
C(13)	28(1)	34(1)	42(1)	6(1)	1(1)	-3(1)
C(14)	25(1)	43(1)	51(1)	12(1)	11(1)	1(1)
C(15)	35(1)	37(1)	39(1)	8(1)	14(1)	11(1)
C(16)	31(1)	26(1)	31(1)	4(1)	4(1)	3(1)
C(17)	23(1)	26(1)	29(1)	6(1)	5(1)	2(1)
O(18)	42(1)	34(1)	49(1)	-13(1)	12(1)	0(1)
C(19)	64(1)	34(1)	47(1)	-6(1)	15(1)	9(1)
O(20)	26(1)	31(1)	41(1)	4(1)	10(1)	-2(1)
C(21)	46(1)	42(1)	70(1)	17(1)	26(1)	-4(1)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$ x 10^3) for ef1233m.

	x	y	z	U(eq)
H(7X)	-2994	4451	1169	66
H(7Y)	-1677	4805	331	66
H(7Z)	-901	4642	1963	66
H(8X)	-1789	3099	-752	52
H(8Y)	-2356	3812	-1392	52
H(8Z)	-3546	3469	-441	52
H(11X)	4211	2679	2579	39
H(11Y)	2835	2090	2678	39
H(13)	6540	2472	1378	43
H(14)	7849	1820	-44	47
H(15)	6188	944	-1276	43
H(19X)	3903	371	-2794	72
H(19Y)	2663	-213	-2430	72
H(19Z)	4685	-70	-1430	72
H(21X)	1532	399	928	76
H(21Y)	-134	757	1398	76
H(21Z)	1976	875	2262	76
H(5)	815(15)	2588(5)	473(13)	28(3)

X-Ray Data for **38**
From Benzene/Petroleum Ether

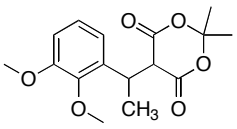


Table 1. Crystal data and structure refinement for ef1268m.

Identification code	ef1268m
Empirical formula	$C_{16}H_{20}O_6$
Formula weight	308.32
Temperature	180(1) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	$P2_1/n$
Unit cell dimensions	a = 11.5072(7) Å alpha = 90° b = 9.0242(6) Å beta = 107.625(1)° c = 15.2500(10) Å gamma = 90°
Volume, Z	1509.27(17) $Å^3$, 4
Density (calculated)	1.357 Mg/m^3
Absorption coefficient	0.104 mm^{-1}
F(000)	656
Crystal size	0.38 x 0.35 x 0.18 mm
θ range for data collection	1.96 to 27.87°
Limiting indices	$-15 \le h \le 15$, $-11 \le k \le 11$, $-20 \le l \le 20$
Reflections collected	15672
Independent reflections	3593 (R_{int} = 0.0384)
Completeness to θ = 27.87°	99.9 %
Absorption correction	None
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3593 / 0 / 209
Goodness-of-fit on F^2	2.700
Final R indices [I>2σ(I)]	R1 = 0.0409, wR2 = 0.0848
R indices (all data)	R1 = 0.0462, wR2 = 0.0853
Extinction coefficient	0.0169(18)
Largest diff. peak and hole	0.257 and -0.259 $eÅ^{-3}$

Table 2. Atomic coordinates [x 10^4] and equivalent isotropic displacement parameters [$Å^2$ x 10^3] for ef1268m. U(eq) is defined as one third of the trace of the orthogonalized U_{ij} tensor.

	x	y	z	U(eq)
O(1)	1898(1)	938(1)	3692(1)	38(1)
C(2)	1035(1)	2123(1)	3404(1)	35(1)
O(3)	1644(1)	3522(1)	3658(1)	35(1)
C(4)	2700(1)	3787(1)	3473(1)	29(1)
C(5)	3401(1)	2472(1)	3273(1)	25(1)
C(6)	2992(1)	993(1)	3538(1)	27(1)
C(7)	177(1)	1981(2)	3972(1)	53(1)
C(8)	421(1)	2087(2)	2389(1)	44(1)
O(9)	3057(1)	5037(1)	3516(1)	40(1)
O(10)	3585(1)	-113(1)	3646(1)	37(1)
C(11)	4787(1)	2750(1)	3726(1)	29(1)
C(12)	5607(1)	1716(1)	3390(1)	28(1)
C(13)	6380(1)	695(1)	3976(1)	35(1)
C(14)	7151(1)	-185(1)	3667(1)	39(1)
C(15)	7191(1)	-77(1)	2770(1)	37(1)
C(16)	6449(1)	933(1)	2179(1)	32(1)
C(17)	5653(1)	1827(1)	2490(1)	29(1)
O(18)	6442(1)	1160(1)	1287(1)	43(1)
C(19)	7246(1)	279(2)	954(1)	49(1)
O(20)	4968(1)	2928(1)	1939(1)	33(1)
C(21)	4098(1)	2459(1)	1092(1)	35(1)
C(22)	5078(1)	2794(1)	4773(1)	40(1)

Table 3. Bond lengths [Å] and angles [°] for ef1268m.

O(1)-C(6)	1.3490(13)	O(1)-C(2)	1.4342(14)
C(2)-O(3)	1.4392(14)	C(2)-C(8)	1.4942(19)
C(2)-C(7)	1.5032(18)	O(3)-C(4)	1.3491(14)
C(4)-O(9)	1.1958(13)	C(4)-C(5)	1.5172(15)
C(5)-C(6)	1.5111(15)	C(5)-C(11)	1.5548(16)
C(6)-O(10)	1.1917(13)	C(11)-C(12)	1.5219(16)
C(11)-C(22)	1.5288(17)	C(12)-C(17)	1.3937(16)
C(12)-C(13)	1.3988(16)	C(13)-C(14)	1.3755(17)
C(14)-C(15)	1.3858(18)	C(15)-C(16)	1.3812(17)
C(16)-O(18)	1.3731(14)	C(16)-C(17)	1.4057(16)
C(17)-O(20)	1.3830(13)	O(18)-C(19)	1.4251(15)
O(20)-C(21)	1.4376(14)		

C(6)-O(1)-C(2)	121.04(9)	O(1)-C(2)-O(3)	109.63(9)
O(1)-C(2)-C(8)	111.54(10)	O(3)-C(2)-C(8)	109.67(10)
O(1)-C(2)-C(7)	105.96(10)	O(3)-C(2)-C(7)	105.70(10)
C(8)-C(2)-C(7)	114.09(11)	C(4)-O(3)-C(2)	119.69(9)
O(9)-C(4)-O(3)	118.15(10)	O(9)-C(4)-C(5)	123.67(11)
O(3)-C(4)-C(5)	118.09(10)	C(6)-C(5)-C(4)	114.15(9)
C(6)-C(5)-C(11)	112.63(9)	C(4)-C(5)-C(11)	108.70(9)
O(10)-C(6)-O(1)	118.12(10)	O(10)-C(6)-C(5)	124.36(10)
O(1)-C(6)-C(5)	117.49(10)	C(12)-C(11)-C(22)	113.91(10)
C(12)-C(11)-C(5)	114.11(9)	C(22)-C(11)-C(5)	109.83(10)
C(17)-C(12)-C(13)	118.05(11)	C(17)-C(12)-C(11)	119.99(10)
C(13)-C(12)-C(11)	121.86(11)	C(14)-C(13)-C(12)	120.84(12)
C(13)-C(14)-C(15)	121.00(12)	C(16)-C(15)-C(14)	119.47(11)
O(18)-C(16)-C(15)	124.20(11)	O(18)-C(16)-C(17)	116.08(11)
C(15)-C(16)-C(17)	119.71(12)	O(20)-C(17)-C(12)	117.74(10)
O(20)-C(17)-C(16)	121.12(11)	C(12)-C(17)-C(16)	120.92(11)
C(16)-O(18)-C(19)	117.37(10)	C(17)-O(20)-C(21)	116.61(9)

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters [$Å^2$ x 10^3] for ef1268m. The anisotropic displacement factor exponent takes the form: $-2\pi^2$ [$(ha^*)^2U_{11}$ + ... + $2hka^*b^*U_{12}$]

	U11	U22	U33	U23	U13	U12
O(1)	30(1)	32(1)	57(1)	11(1)	17(1)	2(1)
C(2)	29(1)	29(1)	47(1)	0(1)	13(1)	1(1)
O(3)	34(1)	32(1)	42(1)	-8(1)	17(1)	0(1)
C(4)	31(1)	29(1)	25(1)	-1(1)	7(1)	1(1)
C(5)	28(1)	25(1)	23(1)	-1(1)	8(1)	0(1)
C(6)	27(1)	28(1)	26(1)	0(1)	6(1)	-1(1)
C(7)	37(1)	60(1)	71(1)	6(1)	28(1)	3(1)
C(8)	35(1)	41(1)	52(1)	-10(1)	4(1)	4(1)
O(9)	44(1)	25(1)	51(1)	-3(1)	16(1)	-1(1)
O(10)	35(1)	26(1)	50(1)	4(1)	12(1)	4(1)
C(11)	29(1)	27(1)	31(1)	-1(1)	7(1)	-3(1)
C(12)	23(1)	27(1)	33(1)	0(1)	6(1)	-5(1)
C(13)	29(1)	40(1)	33(1)	6(1)	6(1)	-2(1)
C(14)	28(1)	38(1)	45(1)	9(1)	4(1)	5(1)
C(15)	25(1)	38(1)	49(1)	0(1)	12(1)	3(1)
C(16)	26(1)	34(1)	37(1)	1(1)	11(1)	-4(1)
C(17)	24(1)	25(1)	36(1)	3(1)	7(1)	-3(1)
O(18)	43(1)	52(1)	41(1)	4(1)	22(1)	8(1)
C(19)	42(1)	60(1)	50(1)	-6(1)	24(1)	2(1)
O(20)	34(1)	28(1)	33(1)	4(1)	5(1)	1(1)
C(21)	32(1)	41(1)	31(1)	2(1)	9(1)	2(1)
C(22)	41(1)	43(1)	31(1)	-7(1)	3(1)	1(1)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$ x 10^3) for ef1268m.

	x	y	z	U(eq)
H(7X)	-235	1019	3852	80
H(7Y)	-431	2776	3807	80
H(7Z)	638	2057	4626	80
H(8X)	1031	2219	2065	67
H(8Y)	-181	2887	2218	67
H(8Z)	12	1130	2218	67
H(11)	4950	3771	3536	35
H(13)	6373	609	4595	42
H(14)	7663	-878	4074	46
H(15)	7724	-693	2564	45
H(19X)	8091	479	1320	73
H(19Y)	7138	523	308	73
H(19Z)	7063	-773	1006	73
H(21X)	4522	2236	639	53
H(21Y)	3502	3251	857	53
H(21Z)	3675	1568	1203	53
H(22X)	4906	1824	4994	60
H(22Y)	4574	3551	4942	60
H(22Z)	5942	3036	5053	60
H(5)	3242(11)	2449(11)	2623(9)	28(3)

X-Ray Data for **40**
From Benzene/ Petroleum Ether
A majorphase change occurs at 291 K
Orthorhombic → Monoclinic
Phase 1 – Orthorhombic

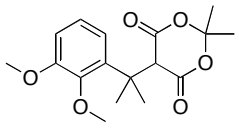


Table 1. Crystal data and structure refinement for ef1267rm.

Identification code	ef1267rm
Empirical formula	$C_{17}H_{22}O_6$
Formula weight	322.35
Temperature	297(1) K
Wavelength	0.71073 Å
Crystal system	Orthorhombic
Space group	Pbcn
Unit cell dimensions	a = 22.5294(12) Å alpha = 90° b = 13.8214(8) Å beta = 90° c = 10.7410(6) Å gamma = 90°
Volume, Z	3344.6(3) $Å^3$, 8
Density (calculated)	1.280 Mg/m^3
Absorption coefficient	0.097 mm^{-1}
F(000)	1376
Crystal size	0.50 x 0.22 x 0.20 mm
θ range for data collection	1.73 to 26.37°
Limiting indices	$-28 \le h \le 27$, $-17 \le k \le 17$, $-13 \le l \le 12$
Reflections collected	22868
Independent reflections	3421 (R_{int} = 0.0591)
Completeness to θ = 26.37°	99.9 %
Absorption correction	None
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3421 / 0 / 219
Goodness-of-fit on F^2	1.992
Final R indices [I>2σ(I)]	R1 = 0.0552, wR2 = 0.1219
R indices (all data)	R1 = 0.0662, wR2 = 0.1239
Extinction coefficient	0.0041(7)
Largest diff. peak and hole	0.236 and -0.165 $eÅ^{-3}$

Table 2. Atomic coordinates [x 10^4] and equivalent isotropic displacement parameters [$Å^2$ x 10^3] for ef1267rm. U(eq) is defined as one third of the trace of the orthogonalized U_{ij} tensor.

	x	y	z	U(eq)
O(1)	934(1)	557(1)	8023(1)	63(1)
C(2)	1091(1)	-31(1)	6981(2)	62(1)
O(3)	1617(1)	343(1)	6416(1)	64(1)
C(4)	1689(1)	1302(1)	6242(2)	50(1)
C(5)	1217(1)	1958(1)	6787(2)	49(1)
C(6)	956(1)	1527(1)	7958(2)	62(1)
C(7)	1258(1)	-1001(2)	7506(3)	99(1)
C(8)	590(1)	-66(2)	6061(2)	85(1)
O(9)	2113(1)	1560(1)	5678(1)	68(1)
O(10)	766(1)	1963(1)	8829(2)	103(1)
C(11)	1418(1)	3036(1)	6895(2)	51(1)
C(12)	1631(1)	3408(1)	5619(2)	46(1)
C(13)	2173(1)	3888(1)	5496(2)	56(1)
C(14)	2365(1)	4239(1)	4372(2)	60(1)
C(15)	2036(1)	4110(1)	3312(2)	54(1)
C(16)	1496(1)	3642(1)	3386(2)	49(1)
C(17)	1289(1)	3323(1)	4543(2)	48(1)
O(18)	1140(1)	3453(1)	2387(1)	63(1)
C(19)	1386(1)	3584(2)	1178(2)	70(1)
O(20)	750(1)	2842(1)	4600(1)	65(1)
C(21)	237(1)	3405(2)	4286(2)	104(1)
C(22)	1908(1)	3095(2)	7885(2)	67(1)
C(23)	895(1)	3686(1)	7304(2)	68(1)

Table 3. Bond lengths [Å] and angles [°] for ef1267rm.

O(1)-C(6)	1.343(2)	O(1)-C(2)	1.428(2)
C(2)-O(3)	1.428(2)	C(2)-C(8)	1.501(3)
C(2)-C(7)	1.502(3)	O(3)-C(4)	1.349(2)
C(4)-O(9)	1.185(2)	C(4)-C(5)	1.515(2)
C(5)-C(6)	1.510(2)	C(5)-C(11)	1.563(3)
C(6)-O(10)	1.192(2)	C(11)-C(22)	1.534(3)
C(11)-C(12)	1.540(2)	C(11)-C(23)	1.547(2)
C(12)-C(17)	1.393(2)	C(12)-C(13)	1.397(2)
C(13)-C(14)	1.371(3)	C(14)-C(15)	1.370(3)
C(15)-C(16)	1.380(2)	C(16)-O(18)	1.365(2)
C(16)-C(17)	1.399(2)	C(17)-O(20)	1.3865(19)
O(18)-C(19)	1.424(2)	O(20)-C(21)	1.432(2)

C(6)-O(1)-C(2)	121.21(14)	O(3)-C(2)-O(1)	109.44(14)
O(3)-C(2)-C(8)	110.89(16)	O(1)-C(2)-C(8)	110.30(16)
O(3)-C(2)-C(7)	106.00(16)	O(1)-C(2)-C(7)	106.01(17)
C(8)-C(2)-C(7)	113.96(19)	C(4)-O(3)-C(2)	120.94(14)
O(9)-C(4)-O(3)	117.53(15)	O(9)-C(4)-C(5)	125.72(17)
O(3)-C(4)-C(5)	116.75(15)	C(6)-C(5)-C(4)	111.10(15)
C(6)-C(5)-C(11)	115.30(14)	C(4)-C(5)-C(11)	113.29(14)
O(10)-C(6)-O(1)	116.77(17)	O(10)-C(6)-C(5)	126.43(18)
O(1)-C(6)-C(5)	116.80(15)	C(22)-C(11)-C(12)	112.10(15)
C(22)-C(11)-C(23)	108.71(15)	C(12)-C(11)-C(23)	107.25(14)
C(22)-C(11)-C(5)	108.06(15)	C(12)-C(11)-C(5)	110.03(13)
C(23)-C(11)-C(5)	110.70(14)	C(17)-C(12)-C(13)	116.46(15)
C(17)-C(12)-C(11)	122.56(15)	C(13)-C(12)-C(11)	120.94(15)
C(14)-C(13)-C(12)	121.76(17)	C(15)-C(14)-C(13)	121.08(17)
C(14)-C(15)-C(16)	119.29(16)	O(18)-C(16)-C(15)	124.25(15)
O(18)-C(16)-C(17)	116.21(15)	C(15)-C(16)-C(17)	119.53(16)
O(20)-C(17)-C(12)	119.25(14)	O(20)-C(17)-C(16)	118.83(14)
C(12)-C(17)-C(16)	121.72(15)	C(16)-O(18)-C(19)	117.58(14)
C(17)-O(20)-C(21)	115.83(17)		

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters [$Å^2$ x 10^3] for ef1267rm. The anisotropic displacement factor exponent takes the form: $-2\pi^2 [(ha^*)^2 U_{11} + ... + 2hka^* b^* U_{12}]$

	U11	U22	U33	U23	U13	U12
O(1)	85(1)	62(1)	40(1)	-1(1)	12(1)	-8(1)
C(2)	67(1)	64(1)	54(1)	-9(1)	17(1)	-7(1)
O(3)	58(1)	57(1)	77(1)	-2(1)	19(1)	2(1)
C(4)	49(1)	61(1)	41(1)	-3(1)	2(1)	5(1)
C(5)	50(1)	62(1)	35(1)	0(1)	6(1)	4(1)
C(6)	79(1)	64(1)	43(1)	-2(1)	16(1)	0(1)
C(7)	120(2)	63(1)	116(2)	8(1)	34(2)	-3(1)
C(8)	78(2)	112(2)	65(1)	-29(1)	13(1)	-29(1)
O(9)	59(1)	70(1)	75(1)	1(1)	24(1)	4(1)
O(10)	168(2)	78(1)	64(1)	-7(1)	62(1)	-4(1)
C(11)	56(1)	58(1)	39(1)	-2(1)	6(1)	4(1)
C(12)	45(1)	52(1)	41(1)	-2(1)	2(1)	3(1)
C(13)	53(1)	65(1)	50(1)	-6(1)	-2(1)	-5(1)
C(14)	51(1)	70(1)	59(1)	-5(1)	6(1)	-14(1)
C(15)	55(1)	61(1)	47(1)	2(1)	12(1)	-4(1)
C(16)	45(1)	60(1)	42(1)	0(1)	1(1)	4(1)
C(17)	37(1)	59(1)	47(1)	2(1)	6(1)	1(1)
O(18)	53(1)	97(1)	39(1)	7(1)	0(1)	-6(1)
C(19)	69(1)	102(2)	40(1)	1(1)	3(1)	-9(1)
O(20)	42(1)	100(1)	54(1)	13(1)	-1(1)	-12(1)
C(21)	42(1)	190(3)	80(2)	31(2)	1(1)	13(1)
C(22)	83(1)	76(1)	42(1)	-3(1)	-4(1)	-5(1)
C(23)	79(1)	66(1)	58(1)	-2(1)	22(1)	12(1)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$ x 10^3) for ef1267rm.

	x	y	z	U(eq)
H(7X)	1578	-925	8088	149
H(7Y)	1381	-1421	6843	149
H(7Z)	921	-1278	7923	149
H(8X)	698	-475	5375	128
H(8Y)	509	575	5762	128
H(8Z)	242	-321	6459	128
H(13)	2411	3971	6196	67
H(14)	2723	4570	4329	72
H(15)	2175	4336	2550	65
H(19X)	1757	3244	1123	105
H(19Y)	1451	4261	1031	105
H(19Z)	1116	3335	565	105
H(21X)	237	3534	3408	156
H(21Y)	247	4005	4736	156
H(21Z)	-115	3053	4505	156
H(22X)	2004	3761	8039	100
H(22Y)	2254	2760	7593	100
H(22Z)	1771	2800	8641	100
H(23X)	554	3550	6795	101
H(23Y)	1003	4354	7212	101
H(23Z)	800	3557	8160	101
H(5)	906(7)	1950(10)	6205(15)	37(4)

Phase 2 - Monoclinic

Table 1. Crystal data and structure refinement for ef1267lm.

Identification code	ef1267lm
Empirical formula	$C_{17}H_{22}O_6$
Formula weight	322.35
Temperature	180(1) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	$P2_1/c$
Unit cell dimensions	a = 10.6791(7) Å alpha = 90° b = 22.3042(15) Å beta = 91.130(1)° c = 13.7749(9) Å gamma = 90°
Volume, Z	3280.4(4) $Å^3$, 8
Density (calculated)	1.305 Mg/m^3
Absorption coefficient	0.099 mm^{-1}
F(000)	1376
Crystal size	0.50 x 0.22 x 0.20 mm
θ range for data collection	1.74 to 27.87°
Limiting indices	$-13 \le h \le 14$, $-29 \le k \le 29$, $-18 \le l \le 17$
Reflections collected	29876
Independent reflections	7791 (R_{int} = 0.0484)
Completeness to θ = 27.87°	99.6 %
Absorption correction	None
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	7791 / 0 / 436
Goodness-of-fit on F^2	2.241
Final R indices [I>2σ(I)]	R1 = 0.0583, wR2 = 0.1208
R indices (all data)	R1 = 0.0689, wR2 = 0.1222
Extinction coefficient	0.0034(5)
Largest diff. peak and hole	0.388 and -0.241 $eÅ^{-3}$

Table 2. Atomic coordinates [x 10^4] and equivalent isotropic displacement parameters [$Å^2$ x 10^3] for ef1267lm. U(eq) is defined as one third of the trace of the orthogonalized U_{ij} tensor.

	x	y	z	U(eq)
O(1)	3684(1)	6602(1)	4977(1)	35(1)
C(2)	3071(2)	6077(1)	5336(1)	34(1)
O(3)	1993(1)	5947(1)	4733(1)	35(1)
C(4)	2059(2)	5959(1)	3755(1)	32(1)
C(5)	3259(2)	6212(1)	3339(1)	26(1)
C(6)	3840(2)	6680(1)	4009(1)	27(1)
C(7)	2579(2)	6245(1)	6319(1)	53(1)
C(8)	3948(2)	5549(1)	5371(1)	43(1)
O(9)	1185(1)	5770(1)	3304(1)	54(1)
O(10)	4423(1)	7107(1)	3760(1)	37(1)
C(11)	3144(2)	6426(1)	2256(1)	28(1)
C(12)	4426(2)	6637(1)	1892(1)	25(1)
C(13)	4548(2)	7192(1)	1425(1)	30(1)
C(14)	5680(2)	7381(1)	1072(1)	32(1)
C(15)	6751(2)	7039(1)	1191(1)	30(1)
C(16)	6668(2)	6489(1)	1660(1)	27(1)
C(17)	5502(2)	6284(1)	1977(1)	26(1)
O(18)	7672(1)	6125(1)	1846(1)	33(1)
C(19)	8885(2)	6384(1)	1746(1)	38(1)
O(20)	5443(1)	5733(1)	2442(1)	34(1)
C(21)	5758(2)	5220(1)	1860(2)	54(1)
C(22)	2155(2)	6925(1)	2198(1)	35(1)
C(23)	2711(2)	5900(1)	1594(1)	36(1)
O(24)	11329(1)	3362(1)	4371(1)	33(1)
C(25)	11929(2)	3893(1)	4757(1)	32(1)
O(26)	12990(1)	4037(1)	4178(1)	33(1)
C(27)	12929(2)	4007(1)	3201(1)	34(1)
C(28)	11724(2)	3763(1)	2751(1)	27(1)
C(29)	11148(2)	3291(1)	3403(1)	27(1)
C(30)	12450(2)	3719(1)	5737(1)	49(1)
C(31)	11025(2)	4409(1)	4785(1)	41(1)
O(32)	13829(2)	4172(1)	2770(1)	60(1)
O(33)	10568(1)	2866(1)	3132(1)	36(1)
C(34)	11808(2)	3564(1)	1664(1)	28(1)
C(35)	10510(2)	3360(1)	1282(1)	26(1)
C(36)	10367(2)	2814(1)	793(1)	31(1)
C(37)	9222(2)	2627(1)	439(1)	33(1)
C(38)	8152(2)	2964(1)	573(1)	29(1)
C(39)	8262(2)	3509(1)	1052(1)	27(1)
C(40)	9434(2)	3713(1)	1376(1)	26(1)
O(41)	7262(1)	3876(1)	1240(1)	34(1)
C(42)	6041(2)	3631(1)	1079(1)	40(1)
O(43)	9510(1)	4255(1)	1866(1)	36(1)
C(44)	9204(2)	4777(1)	1293(2)	59(1)
C(45)	12794(2)	3064(1)	1596(1)	37(1)
C(46)	12225(2)	4098(1)	1027(1)	36(1)

Table 3. Bond lengths [Å] and angles [°] for ef12671m.

O(1)-C(6)	1.3580(19)	O(1)-C(2)	1.434(2)
C(2)-O(3)	1.436(2)	C(2)-C(8)	1.506(3)
C(2)-C(7)	1.510(3)	O(3)-C(4)	1.351(2)
C(4)-O(9)	1.188(2)	C(4)-C(5)	1.523(2)
C(5)-C(6)	1.517(2)	C(5)-C(11)	1.569(2)
C(6)-O(10)	1.1931(19)	C(11)-C(22)	1.537(2)
C(11)-C(12)	1.541(2)	C(11)-C(23)	1.550(2)
C(12)-C(17)	1.397(2)	C(12)-C(13)	1.400(2)
C(13)-C(14)	1.378(2)	C(14)-C(15)	1.381(3)
C(15)-C(16)	1.391(2)	C(16)-O(18)	1.366(2)
C(16)-C(17)	1.404(2)	C(17)-O(20)	1.3876(18)
O(18)-C(19)	1.428(2)	O(20)-C(21)	1.441(2)
O(24)-C(29)	1.3537(19)	O(24)-C(25)	1.442(2)
C(25)-O(26)	1.435(2)	C(25)-C(30)	1.501(2)
C(25)-C(31)	1.504(3)	O(26)-C(27)	1.347(2)
C(27)-O(32)	1.198(2)	C(27)-C(28)	1.518(2)
C(28)-C(29)	1.520(2)	C(28)-C(34)	1.566(2)
C(29)-O(33)	1.1889(19)	C(34)-C(45)	1.538(2)
C(34)-C(35)	1.542(2)	C(34)-C(46)	1.550(2)
C(35)-C(36)	1.398(2)	C(35)-C(40)	1.401(2)
C(36)-C(37)	1.373(3)	C(37)-C(38)	1.384(3)
C(38)-C(39)	1.386(2)	C(39)-O(41)	1.374(2)
C(39)-C(40)	1.397(2)	C(40)-O(43)	1.3857(18)
O(41)-C(42)	1.427(2)	O(43)-C(44)	1.440(2)

C(6)-O(1)-C(2)	120.56(12)	O(1)-C(2)-O(3)	109.43(13)
O(1)-C(2)-C(8)	111.24(16)	O(3)-C(2)-C(8)	110.56(14)
O(1)-C(2)-C(7)	106.04(14)	O(3)-C(2)-C(7)	106.22(17)
C(8)-C(2)-C(7)	113.11(16)	C(4)-O(3)-C(2)	121.02(14)
O(9)-C(4)-O(3)	117.28(16)	O(9)-C(4)-C(5)	126.38(16)
O(3)-C(4)-C(5)	116.34(14)	C(6)-C(5)-C(4)	111.28(13)
C(6)-C(5)-C(11)	113.16(13)	C(4)-C(5)-C(11)	114.83(14)
O(10)-C(6)-O(1)	117.34(14)	O(10)-C(6)-C(5)	125.73(14)
O(1)-C(6)-C(5)	116.93(13)	C(22)-C(11)-C(12)	112.03(13)
C(22)-C(11)-C(23)	108.78(14)	C(12)-C(11)-C(23)	107.28(13)
C(22)-C(11)-C(5)	108.08(13)	C(12)-C(11)-C(5)	110.41(13)
C(23)-C(11)-C(5)	110.25(13)	C(17)-C(12)-C(13)	116.92(15)
C(17)-C(12)-C(11)	122.30(14)	C(13)-C(12)-C(11)	120.74(15)
C(14)-C(13)-C(12)	121.52(16)	C(13)-C(14)-C(15)	121.32(15)
C(14)-C(15)-C(16)	118.71(16)	O(18)-C(16)-C(15)	123.66(16)
O(18)-C(16)-C(17)	116.44(14)	C(15)-C(16)-C(17)	119.89(16)
O(20)-C(17)-C(12)	119.58(14)	O(20)-C(17)-C(16)	118.80(15)
C(12)-C(17)-C(16)	121.48(14)	C(16)-O(18)-C(19)	116.89(13)
C(17)-O(20)-C(21)	115.66(13)	C(29)-O(24)-C(25)	120.84(12)
O(26)-C(25)-O(24)	109.21(13)	O(26)-C(25)-C(30)	106.01(16)
O(24)-C(25)-C(30)	105.87(14)	O(26)-C(25)-C(31)	110.84(14)
O(24)-C(25)-C(31)	110.99(16)	C(30)-C(25)-C(31)	113.64(15)
C(27)-O(26)-C(25)	121.40(14)	O(32)-C(27)-O(26)	117.17(16)
O(32)-C(27)-C(28)	126.13(15)	O(26)-C(27)-C(28)	116.69(15)
C(27)-C(28)-C(29)	110.91(13)	C(27)-C(28)-C(34)	115.35(14)
C(29)-C(28)-C(34)	113.61(13)	O(33)-C(29)-O(24)	117.76(14)
O(33)-C(29)-C(28)	125.50(14)	O(24)-C(29)-C(28)	116.73(13)
C(45)-C(34)-C(35)	112.15(14)	C(45)-C(34)-C(46)	108.54(14)
C(35)-C(34)-C(46)	107.51(13)	C(45)-C(34)-C(28)	108.35(13)
C(35)-C(34)-C(28)	110.02(13)	C(46)-C(34)-C(28)	110.25(13)

C(36)-C(35)-C(40)	116.86(15)	C(36)-C(35)-C(34)	120.71(15)
C(40)-C(35)-C(34)	122.40(14)	C(37)-C(36)-C(35)	121.63(17)
C(36)-C(37)-C(38)	121.25(16)	C(37)-C(38)-C(39)	118.55(16)
O(41)-C(39)-C(38)	123.58(16)	O(41)-C(39)-C(40)	116.13(14)
C(38)-C(39)-C(40)	120.29(16)	O(43)-C(40)-C(39)	118.90(14)
O(43)-C(40)-C(35)	119.64(15)	C(39)-C(40)-C(35)	121.27(14)
C(39)-O(41)-C(42)	116.96(13)	C(40)-O(43)-C(44)	115.34(14)

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters [$Å^2$ x 10^3] for ef1267lm.
The anisotropic displacement factor exponent takes the form:
$-2\pi^2$ [$(ha^*)^2U_{11}$ + ... + $2hka^*b^*U_{12}$]

	U11	U22	U33	U23	U13	U12
O(1)	45(1)	34(1)	27(1)	-1(1)	0(1)	-11(1)
C(2)	34(1)	38(1)	30(1)	4(1)	-4(1)	-11(1)
O(3)	23(1)	49(1)	32(1)	7(1)	1(1)	-5(1)
C(4)	20(1)	40(1)	35(1)	6(1)	-1(1)	-5(1)
C(5)	21(1)	27(1)	29(1)	-1(1)	-1(1)	-4(1)
C(6)	21(1)	28(1)	31(1)	-1(1)	-1(1)	1(1)
C(7)	63(2)	62(1)	33(1)	3(1)	6(1)	-17(1)
C(8)	38(1)	41(1)	51(1)	12(1)	-12(1)	-6(1)
O(9)	36(1)	84(1)	40(1)	12(1)	-8(1)	-29(1)
O(10)	43(1)	34(1)	35(1)	-2(1)	2(1)	-13(1)
C(11)	23(1)	33(1)	26(1)	-1(1)	-1(1)	-4(1)
C(12)	26(1)	27(1)	23(1)	-3(1)	-1(1)	-4(1)
C(13)	30(1)	30(1)	30(1)	2(1)	-3(1)	1(1)
C(14)	34(1)	29(1)	32(1)	7(1)	-2(1)	-5(1)
C(15)	29(1)	31(1)	30(1)	1(1)	2(1)	-8(1)
C(16)	27(1)	26(1)	28(1)	-4(1)	0(1)	-1(1)
C(17)	31(1)	22(1)	27(1)	-1(1)	2(1)	-4(1)
O(18)	24(1)	28(1)	48(1)	1(1)	3(1)	0(1)
C(19)	23(1)	37(1)	52(1)	-1(1)	-1(1)	-2(1)
O(20)	34(1)	23(1)	44(1)	5(1)	6(1)	1(1)
C(21)	50(2)	23(1)	90(2)	-6(1)	26(1)	0(1)
C(22)	27(1)	43(1)	35(1)	4(1)	-1(1)	1(1)
C(23)	34(1)	41(1)	32(1)	-5(1)	-2(1)	-12(1)
O(24)	44(1)	28(1)	28(1)	1(1)	2(1)	-11(1)
C(25)	33(1)	33(1)	30(1)	-4(1)	5(1)	-9(1)
O(26)	23(1)	46(1)	31(1)	-4(1)	1(1)	-6(1)
C(27)	27(1)	42(1)	34(1)	0(1)	3(1)	-8(1)
C(28)	22(1)	31(1)	28(1)	1(1)	2(1)	-5(1)
C(29)	24(1)	26(1)	30(1)	2(1)	3(1)	-1(1)
C(30)	63(2)	53(1)	31(1)	-1(1)	-3(1)	-13(1)
C(31)	33(1)	40(1)	51(1)	-13(1)	10(1)	-5(1)
O(32)	39(1)	101(1)	39(1)	-6(1)	7(1)	-37(1)
O(33)	43(1)	31(1)	35(1)	0(1)	0(1)	-12(1)
C(34)	25(1)	32(1)	27(1)	1(1)	2(1)	-3(1)
C(35)	27(1)	28(1)	23(1)	2(1)	2(1)	-2(1)
C(36)	32(1)	30(1)	31(1)	-3(1)	2(1)	3(1)
C(37)	38(1)	29(1)	32(1)	-7(1)	1(1)	-2(1)
C(38)	28(1)	32(1)	28(1)	-3(1)	-1(1)	-6(1)
C(39)	26(1)	29(1)	25(1)	2(1)	2(1)	1(1)
C(40)	29(1)	23(1)	27(1)	-1(1)	3(1)	-3(1)
O(41)	22(1)	34(1)	46(1)	-5(1)	0(1)	1(1)
C(42)	24(1)	45(1)	53(1)	-8(1)	3(1)	0(1)
O(43)	33(1)	25(1)	51(1)	-9(1)	-1(1)	-1(1)
C(44)	41(1)	26(1)	108(2)	6(1)	0(1)	2(1)
C(45)	27(1)	47(1)	36(1)	-4(1)	2(1)	4(1)
C(46)	32(1)	43(1)	32(1)	4(1)	4(1)	-10(1)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$ x 10^3) for ef1267lm.

	x	y	z	U(eq)
H(7X)	2039	6599	6255	79
H(7Y)	3283	6335	6763	79
H(7Z)	2094	5910	6578	79
H(8X)	4683	5647	5777	65
H(8Y)	4214	5452	4712	65
H(8Z)	3517	5202	5647	65
H(13)	3835	7443	1351	36
H(14)	5724	7753	740	38
H(15)	7530	7178	956	36
H(19X)	8921	6768	2092	56
H(19Y)	9048	6450	1057	56
H(19Z)	9519	6112	2021	56
H(21X)	6657	5137	1930	81
H(21Y)	5550	5302	1177	81
H(21Z)	5283	4870	2077	81
H(22X)	1992	7031	1517	53
H(22Y)	2463	7279	2552	53
H(22Z)	1378	6785	2489	53
H(23X)	3228	5546	1735	54
H(23Y)	2800	6014	912	54
H(23Z)	1832	5807	1718	54
H(30X)	13032	3383	5667	73
H(30Y)	11763	3599	6157	73
H(30Z)	12893	4061	6027	73
H(31X)	10318	4304	5194	62
H(31Y)	10718	4498	4126	62
H(31Z)	11451	4763	5055	62
H(36)	11080	2567	703	37
H(37)	9163	2258	95	40
H(38)	7359	2825	342	35
H(42X)	5980	3245	1414	61
H(42Y)	5891	3573	382	61
H(42Z)	5413	3907	1333	61
H(44X)	8325	4756	1077	88
H(44Y)	9743	4792	726	88
H(44Z)	9335	5138	1687	88
H(45X)	12933	2968	912	55
H(45Y)	12496	2706	1933	55
H(45Z)	13582	3199	1900	55
H(46X)	12126	3992	340	53
H(46Y)	13106	4191	1172	53
H(46Z)	11708	4449	1167	53
H(5)	3845(18)	5878(8)	3352(11)	26(4)
H(28)	11100(20)	4101(8)	2783(12)	34(5)

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Chapter 3
Investigations Into the Mechanism of the Intramolecular Friedel-Crafts Acylation of Meldrum's Acid Derivatives

Introduction

Chapter 2 has described the development and application of a catalytic intramolecular Friedel-Crafts acylation of Meldrum's acid derivatives. While Meldrum's acid has long been used for the acylation of heteroatomic nucleophiles[1], this is the first practical application to π-nucleophiles under mild reaction conditions.

In order to make this methodology as synthetically useful as possible, and to enable its expanded application to more complex systems, a thorough understanding of its mechanism would be advantageous.

There is one aspect of this methodology that makes the mechanism a particularly intriguing area of study – as noted in Chapter 2, Meldrum's acid derivatives that are monosubstituted at carbon 5 are thermally unstable, and can be transformed to 1-indanones even without a catalyst if they contain sufficiently electron rich nucleophiles. The addition of a catalyst accelerates the reaction significantly, and results in higher yields. However, Meldrum's acid derivatives that are disubstituted at carbon 5 are thermally stable, but can also undergo acylation if a catalyst is present, and with typically higher yield.

The investigations began with monosubstituted Meldrum's acid derivatives, which are able to undergo enolization (and thus often referred to as enolizable substrates).

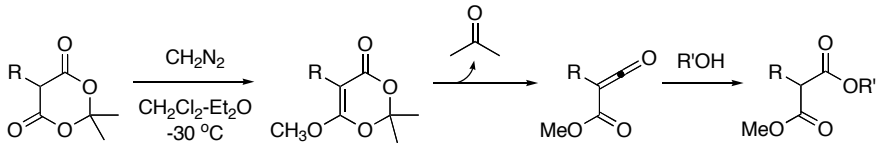
Enolizable Meldrum's acid derivatives (monosubstituted at the 5-position)

In this new methodology of catalytic intramolecular Friedel-Crafts acylation, several mechanisms are possible, particularly when both the thermal case and the Lewis acid catalyzed

cases are considered. The thermal case shall be considered first.

Sato and coworkers have investigated the mechanism of enolizable Meldrum's acid opening with alcohols to give mixed malonates.[2] It was found that following enolization or *O*-methylation, the resultant 3-hydroxy (or 3-methoxy) dioxinones underwent a retro Diels-Alder reaction (cycloreversion) to produce an acyl ketene species that was the reactive acylating agent. Addition of an alcohol produced a mixed malonate product (scheme 3.1).

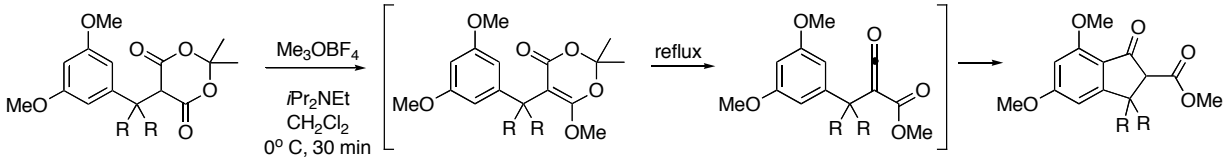
Scheme 3.1: Acylation of Meldrum's acid derivatives via an acyl ketene intermediate



In the course of developing the Friedel-Crafts acylation methodology, it was hypothesized that benzyl Meldrum's acids would react via the same species without a catalyst.

Investigation of the reaction pathway proceeded by methylation of **9** with Meerwein's salt to produce an α-oxoketene intermediate via cycloreversion of the resulting 6-methoxydioxinone. This experiment was based on the work of Sato, though in that case diazomethane or TBDPSCl were used to form the enol ether. Intramolecular arylation of the acylketene intermediate was anticipated to produce a β-ketoester incapable of decarboxylation. Gratifyingly, 1-indanone-2-methyl ester **135** was formed in 52% yield demonstrating the reactivity of acylketenes in acylation reactions (scheme 3.2). Similarly, disubstituted substrate **15** gave indanone **136**. This trend of increased yield with benzylic substituents is consistent with the expected stabilization of the acylketene intermediate reported by Sato.

Scheme 3.2: Synthesis of acyl-1-indanones via intramolecular Friedel-Crafts acylation



9 R = H
15 R = - $(CH_2)_4$-

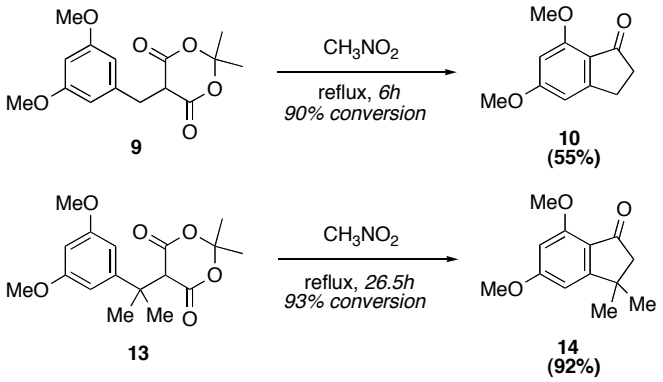
135 R = H **52 %**
136 R = - $(CH_2)_4$- **67 %**

Considering the same electron rich nucleophile, 3,5-dimethoxybenzyl Meldrum's acid **9**, the

direct thermal conversion of **9** to **10** proceeded with excellent conversion of starting material (90% as determined by ^{1}H NMR of the crude reaction mixture), but only a modest 55% isolated yield after flash chromatography (scheme 3.3). The mechanism in this case should be the same as proposed for the acylketene in scheme 3.2 above, but this time the resulting keto-acid rapidly decarboxylates to give the 1-indanone product. No keto-acid could be observed by NMR in the course of this study.

Scheme 3.3 illustrates another interesting result observed for Meldrum's substrates that contain benzylic substituents. Substrate **13** produced 3,3-dimethyl-1-indanone **14** in excellent yield and conversion (92 and 93 %, respectively), but the reaction time was slower: 26.5 hours compared with 6 hours when no benzylic substituents were present.

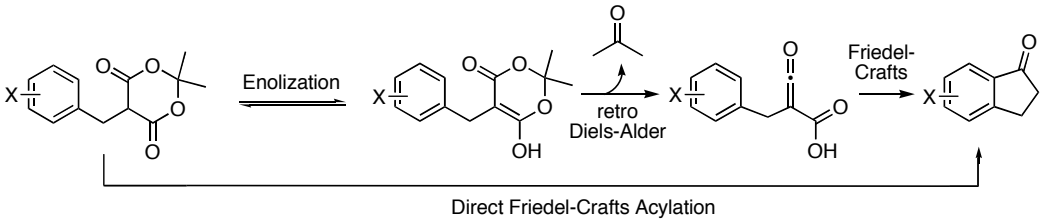
Scheme 3.3: Thermal decomposition of electron rich benzylic Meldrum's acid to 1-indanones



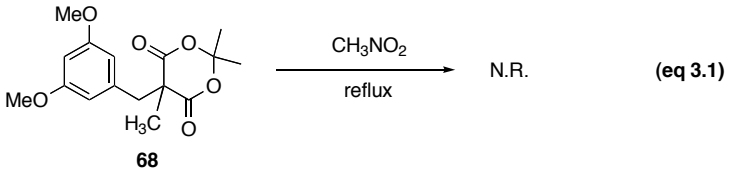
When considering the two substrates **9** and **13** (scheme 3.3), the nucleophile is the same in both substrates, so the rate-differentiating step must be either the tautomerization of the Meldrum's acid, or the retro-Diels Alder reaction that produces the acylketene reactive species. Furthermore, the *gem* dimethyl benzylic subtituents in **13** should facilitate the ring closure based on the *gem* dialkyl effect[3] and the pKa of the α-protons should be nearly identical.

In addition to the retro Diels-Alder pathway that leads to an acylketene reactive species (scheme 3.4), another possibility is the direct attack onto one of the Meldrum's acid carbonyls. This is more likely a possibility with the Lewis acid activated version of the reaction, but still possible in the thermal reaction, especially with very electron rich nucleophiles (scheme 3.4).

Scheme 3.4: Possible reaction pathways for the intramolecular acylation of Meldrum's acid under thermal conditions



An investigation was therefore undertaken to ascertain which step is rate determining. While again maintaining the aromatic nucleophilic portion of the molecule constant, quaternarization of the Meldrum's electrophile in **9** creates a substrate **68** that does not have the ability to enolize under thermal conditions. Therefore, if the acylation is to occur, it must be via a direct acylation mechanism. As expected, the quaternarized Meldrum's derivatives are completely stable under thermal conditions (equation 3.1). No decomposition was observed when they were refluxed in nitromethane under the anhydrous conditions used in the Fiedel-Crafts methodology and the substrate was recovered unchanged. This result supported the enolization/retro Diels-Alder reaction pathway for the enolizable substrates.



68

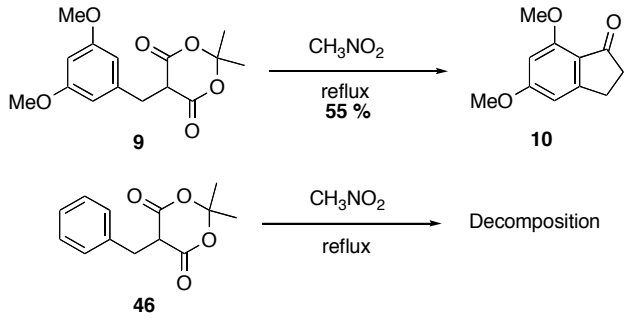
The acquisition of kinetic data was problematic for enolizable Meldrum's acid derivatives. NMR data of crude reaction mixtures was complex, and it was difficult to observe the 1-indanone products from starting materials and by-products in a sealed NMR tube. GC or GC-MS data could not be acquired since thermal decomposition of the substrates occurred in the inlet port (and on the column) that are essentially flash vacuum pyrolysis conditions. It was possible, however, to monitor substrate consumption (disappearance) in a sealed NMR tube, particularly by observing the α and benzylic protons. This method was applied to the comparison of 3,5-dimethoxybenzyl Meldrum's acid **9** and simple benzyl Meldrum's acid **46**. Interpretation of the proton NMR data became complex with time, particularly due to the

emergence of the very intense acetone signal. Ultimately, the data (peak integrations) was tabulated and plotted versus time. An attempt was made to identify trends that might provide some insight into the reaction mechanism, which could benefit synthetic applications and future substrate design.

In a sealable NMR tube, an equimolar amount of substrates **9** and **46** were combined in dry deuterated nitromethane with an internal standard (mesitylene). The tube was immersed in an oil bath at 100 °C and at 15 minute intervals the tube was cooled in an ice bath, then ^{1}H NMR data (integration of starting material relative to the internal standard) were acquired at room temperature.

It was found (chapter 2) that **46** did not produce 1-indanone under thermal conditions, but the substrate did decompose, presumably because it was insufficiently nucleophilic for Friedel-Crafts acylation, and ketene side reactions predominated. The electron rich **9** did produce 5,7-dimethoxy-1-indanone, though in a modest yield of 55% (scheme 3.5). Between these two substrates the only difference is the nucleophilic moiety, so comparison of substrate decomposition rate would demonstrate if the rate-determining step was the acylation of the acylkene intermediate.

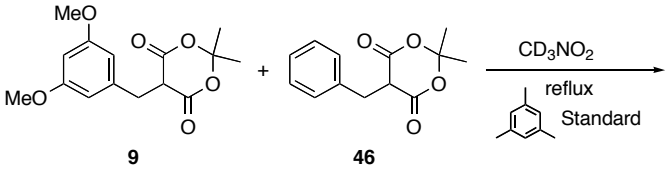
Scheme 3.5: Observed reactivity of enolizable Meldrum's acid models



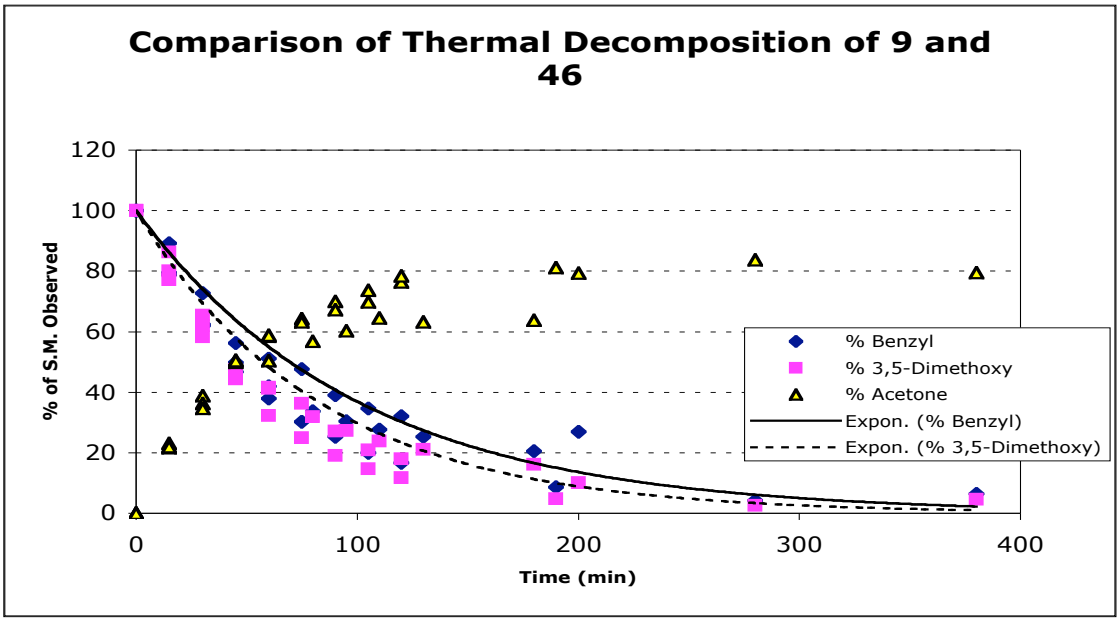
This experiment (performed in triplicate, chart 3.1) showed that both substrates were consumed at essentially the same rate, and that substrate decomposition was a first order process (a plot of the log(data) versus time was linear). What this demonstrates is that the rate determining step for both substrates is the same, and since the nucleophilicity of **9** is about 10000x that of **46**[4], this step cannot be the acylation of the acylketene intermediate or Meldrum's acid, and must be either the tautomerization of Meldrum's acid, or the retro Diels-

Alder reaction. The rate of each of these steps would then be the same for both substrates.

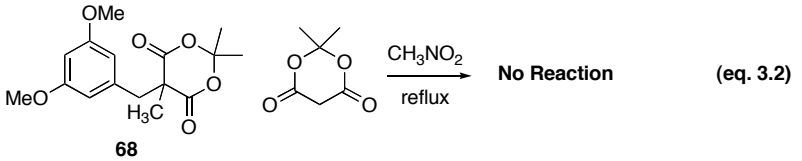
Chart 3.1: Relative consumption of enolizable substrates under thermal conditions



9 **46**



The trend for the 3,5-dimethoxybenzyl substrate **9** is slightly faster than for **46**, but this apparent rate difference is very small with respect to the relative nucleophilicity of the competitors. One possibility considered was that a small amount of direct acylation of the activated Meldrum's acid was occurring for the more nucleophilic of the two reaction components. It was conceived that the high acidity of the α proton of Meldrum's acid might catalyze the intramolecular Friedel-Crafts acylation. A control experiment was conducted using the quaternarized Meldrums acid **68** and a stoichiometric amount of simple Meldrum's acid to serve as promoter (eq. 3.2).

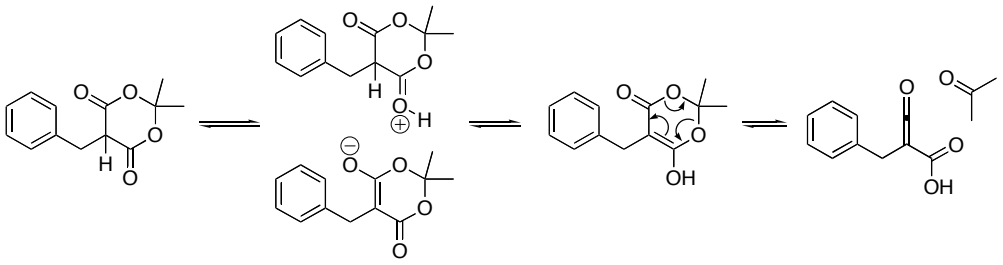


68 **(eq. 3.2)**

After refluxing for 24 hours, no trace of 1-indanone was observed, eliminating the possibility of direct acylation catalyzed by Meldrum's acid itself as a protic acid.

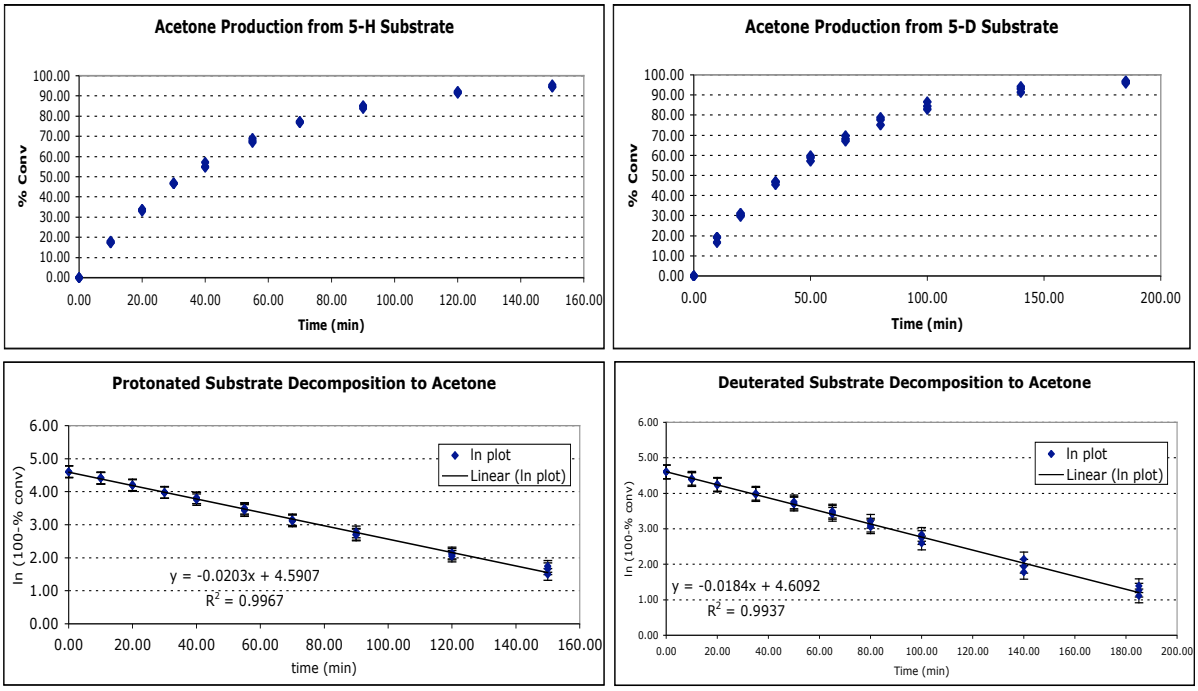
Chart 3.1 suggests a substrate half-life of approximately 50 minutes for both **9** and **46**. Since the rate of decay is equal for each substrate, this is independent of substrate nucleophilicity, so the rate-determining step must either be within the enolization step or the retro Diels-Alder step (scheme 3.4 and 3.6).

Scheme 3.6: Rate determining step of substrate decomposition



Since the rate-determining step of the intramolecular Friedel-Crafts acylation of enolizable Meldrum's acids is independent of the strength of the π-nucleophile, the reaction can be analyzed as presented in scheme **3.6**. If the enolization step is rate-determining, then a primary kinetic isotope effect should exist if the proton at the 5-carbon of Meldrum's acid were replaced with deuterium. Using the 3,5-dimethoxybenzyl Meldrum's acid substrate **9**, the rate equation for production of acetone from substrate by thermal decomposition was determined by NMR observations in a sealed tube. The reaction was performed in triplicate. The same experiment was performed with deuterated substrate **137**, also in triplicate. The plot of ln(conversion) versus time was linear in both cases, indicating their apparent first order nature, and the rate equation extracted from the linear best-fit trend line. The results are presented in chart 3.2.

Chart 3.2: Effect of deuterium substitution on rate constant – evaluation of isotope effect

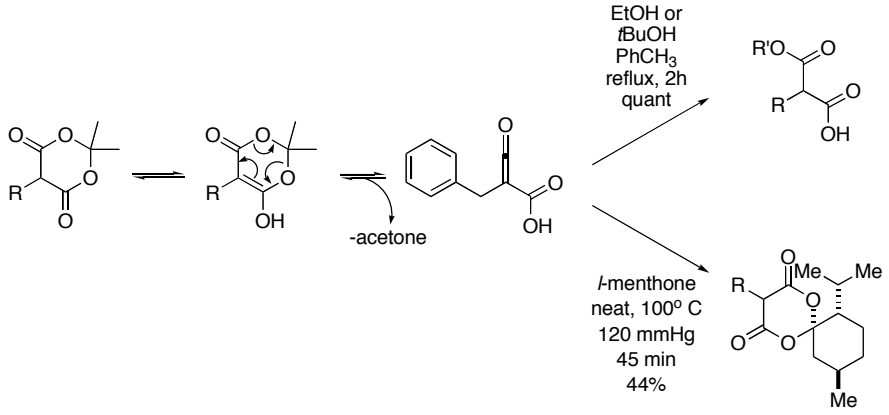


From the data presented in chart 3.2, k_H is 20.3 x 10^{-3} sec^{-1} and k_D is 18.4 x 10^{-3} sec^{-1}, giving an isotope effect k_H/k_D of 1.10. For mechanisms in which the C-H bond is broken in the rate-determining step, substrates of the general type RCD_2COR show deuterium isotope effects of about 5 in acid and base catalyzed processes.[5] Therefore, in the thermal decomposition of Meldrum's acid derivatives to product acyl ketene and acetone, the rate determining step does not involve a C-H (or C-D) bond breaking process at the 5-carbon, and thus enolization of the susbtrate is not rate determining.

Sato and coworkers have conducted extensive investigations on the mechanism of Meldrum's acid ring opening by attacking nucleophiles, particularly alcohols to provide acid/esters and mixed malonates.[2] Previous to that study, the ring opening had been explained by initial attack of the nucleophile at the C4 of Meldrum's acid, but Sato's studies proved that the tautomerization of Meldrum's acid led to the thermal cycloreversion to acylketene. It was found that reaction of monosubstituted Meldrum's acid with ethanol and *tert*-butanol proceeded

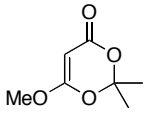
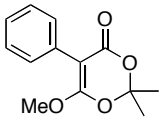
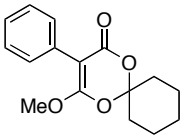
at the same rate, despite their differing nucleophilicity. Furthermore, if a Meldrum's derivative is refluxed in the presence of *l*-menthone, under a slight vacuum to remove the acetone by-product, a [4+2] cycloaddition product was obtained (scheme 3.7). The need to remove acetone is suggestive of a reversible retro Diels-Alder step.

Scheme 3.7: Sato's studies on acylketene reactivity from Meldrum's derivatives



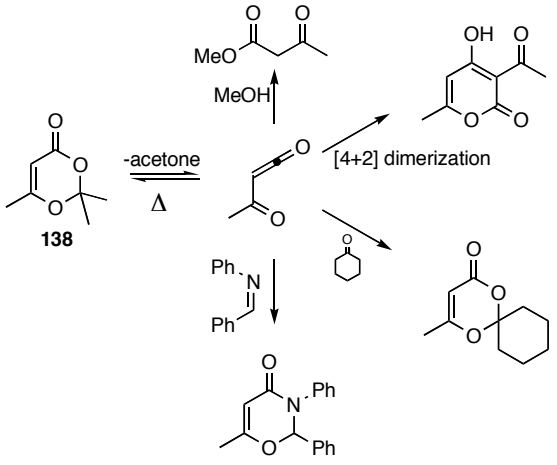
These results are consistent with those observed with the competitive decomposition studies presented above. Nucleophilicity did not affect the rate of substrate decomposition. In all of the synthetic studies conducted (chapter 2) no trace of [4+2] cycloaddition product was ever observed between arylketone product and residual Meldrum's acid substrate. Nonetheless, the increasing presence of acetone in the reaction might slow the rate of progress as the cycloreversion equilibrium is shifted to the left. This would only be an issue if the retro Diels-Alder reaction was, in fact, the rate limiting step. Sato presented some additional evidence to support this possibility (table 3.1).

Table 3.1: Sato's half-life estimations of various methoxydioxinones by NMR

	1/2 Life at 23 °C in $CDCl_3$
	5 min
	20 min
	3 hours

It was found that phenyl acylketenes formed significantly slower, *but* were sufficiently stable that they could be isolated and characterized, while simpler, less substituted acylketenes dimerized and/or oligomerized to produce complex mixtures. Related studies of the thermal decomposition of 2,2,6-trimethyl-4*H*-1,3-dioxin-4-one **138** have been reported with both kinetics experiments[6] and *ab initio* calculations.[7] This compound decomposes to acetylketene and reacts just as described above for acylketenes (scheme 3.8). These dioxinones do not require the initial enolization step, but still involve a retro Diels-Alder and acylation step. The rate-determining step in these reactions was determined to be a reversible, unimolecular loss of acetone to provide a reactive intermediate. It was also concluded that since the decomposition of dioxinone **138** is reversible, acetone is a competitor with other trapping reagents. This rate effect from acetone should be observable with the Meldrum's acid derivatives examined here.

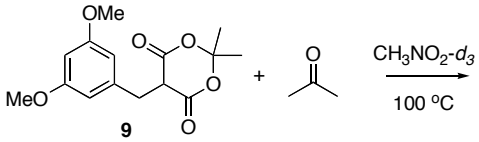
Scheme 3.8: Thermal decomposition and reactivity of dioxinone 138

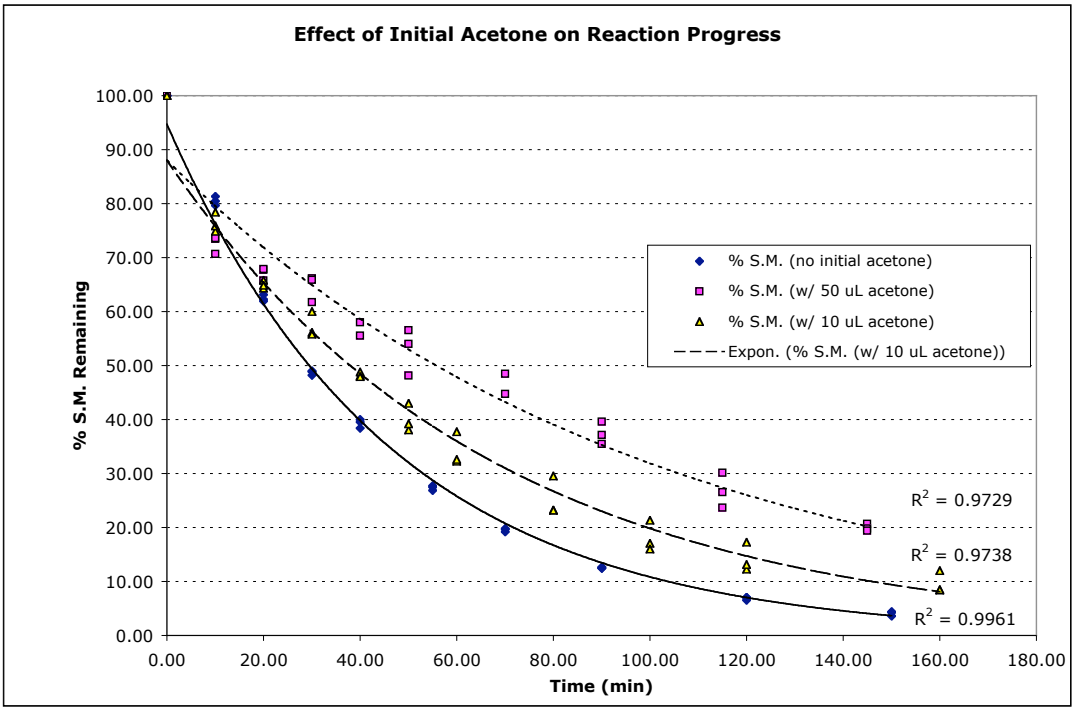


If the rate determining step for the thermal decomposition of benzyl Meldrum's acid derivatives was the retro Diels-Alder reaction, then an increase in initial acetone concentration should decrease the rate of substrate decomposition, since this step is in equilibrium. Sealed NMR tube experiments conducted with 3,5-dimethoxybenzyl Meldrum's acid **9** in the presence of different initial amounts of acetone [0, 10 (4 molar equiv) and 50 μL (20 molar equiv)] were conducted, and the consumption of Meldrum's starting material was observed by integration. The results are presented in chart 3.3.

The addition of acetone does affect the rate of substrate decomposition (and thus acyl ketene formation), but the effect is somewhat small. Even with the addition of 50 μL of acetone (20 molar equivalents), the half-life of the reaction only doubles from about 30 minutes to about 60 minutes. It is additionally noteworthy that this experiment was conducted in a sealed tube in which the acetone is trapped even at high temperatures, although some portion would exist as a vapor in the head space of the NMR tube at the reaction temperature. Allowing the acetone to escape (via reflux condenser) or conducting the reaction under a slight vacuum can reasonably be expected to accelerate the reaction.

Chart 3.3: Effect of acetone concentration on substrate decomposition





Summary

For the thermal decomposition of enolizable benzyl Meldrum's acids, the rate determining step appears to be the retro Diels-Alder reaction of the tautomerized Meldrum's acid. This would be consistent with the known data for nucleophilic attack on dioxinones **138** and Sato's work on the reactivity of Meldrum's acid derivatives via 3-hydroxy dioxinone. Increasing the number of benzylic substituents decreases the rate of the retro Diels-Alder reaction (demonstrated by the half-lives observed in Sato's work), but also produces a more stable acylketene species that is less prone to side reactions that lead to a decreased yield of the desired 1-indanone product.

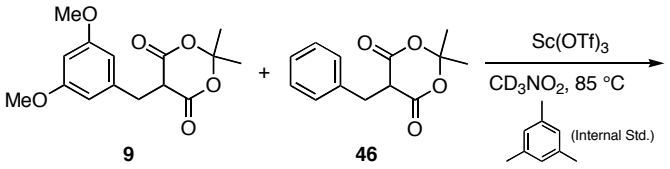
Scandium Triflate Catalyzed Intramolecular Friedel-Crafts Acylation of Enolizable Meldrum's Acid Derivatives

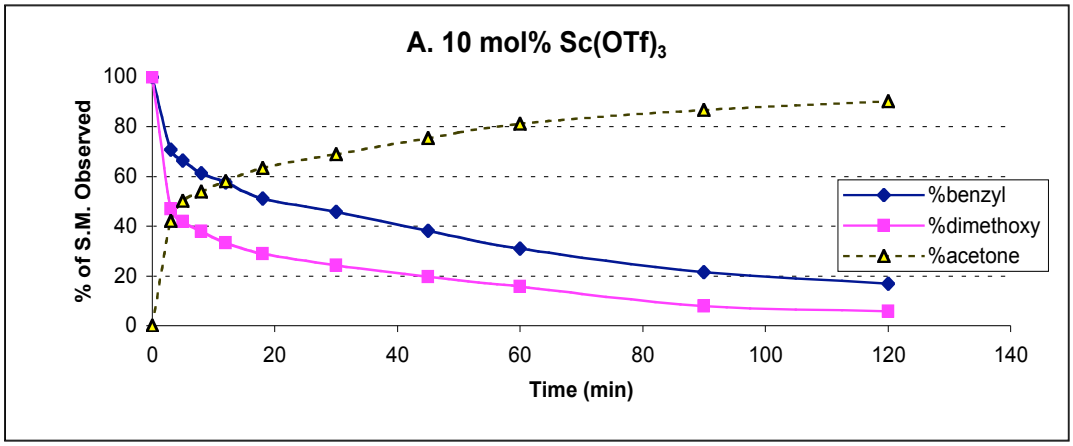
When screening catalytic conditions to improve the reaction time and yield of the Friedel-Crafts reaction with enolizable Meldrum's derivatives, it was found that while $Sc(OTf)_3$ did greatly accelerate the rate of reaction (from 6 hours to 1 hour for **9**), the yield increase was actually quite modest, increasing the isolated yield from 52% to 73% using 12 mol % of catalyst (chapter 2, table 2.1). This result demanded an explanation of the role of scandium triflate (and other catalysts) in this Friedel-Crafts acylation system.

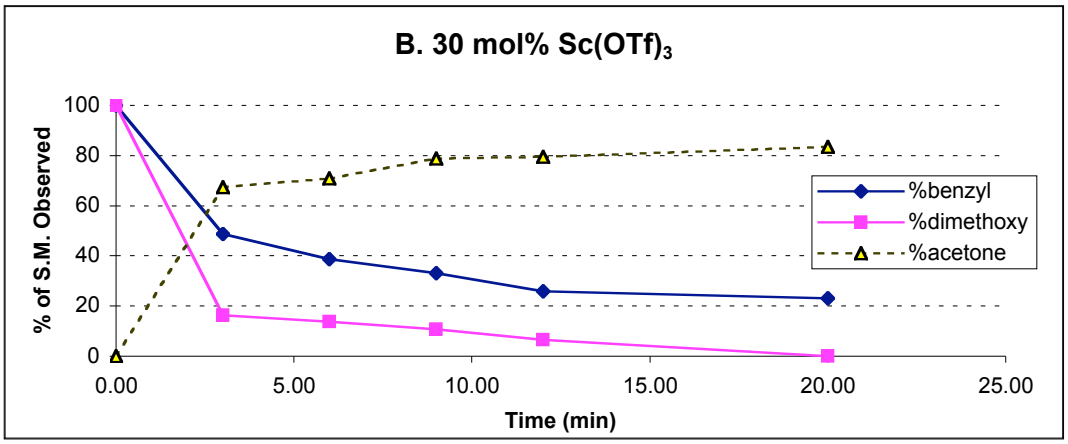
The sealed-tube NMR experiments performed above using **9** and **46** were repeated, but now using 10 and 30 mol % $Sc(OTf)_3$. The reaction temperature was decreased to 85° C since the reaction was considerably faster with catalyst, and acquiring the initial data point was difficult using this NMR technique. Charts 3.4A and 3.4B show the data acquired in this catalyzed reaction.

These results clearly demonstrate a significant impact of the catalyst in the initial few minutes of the reaction, and the more electron rich, more nucleophilic component **9** clearly is consumed about twice as quickly as **46**. This suggests that the addition of $Sc(OTf)_3$ catalyst causes the rate-determining step to be nucleophile dependent, and therefore must be the acylation step itself. After this initial divergence, however, the rates of consumption of the remaining material appear to be very similar, suggesting consumption or destruction of the catalyst, and reversion of the reaction to thermal decomposition described above.

Chart 3.4 A and B: Comparative decomposition of substrates 9 and 46 under catalytic conditions







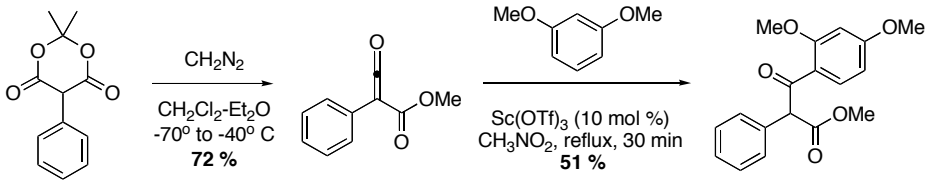
It has been reported that lanthanide triflates could significantly catalyze the enol formation of β-keto esters.[8] While this is indeed likely with Meldrum's acid, the enolization step is not rate determining for this reaction, so accelerating this step would not have an impact on the overall rate, as observed with the Lewis acid catalyzed reaction. There would also not be a preference for one substrate over another as demonstrated in chart 3.4.

The direct effect of $Sc(OTf)_3$ on the reactivity of acylketenes was examined to determine if the Lewis acid catalyst affected this potential reactive species. Acylketene **140** was formed from the phenyl Meldrum's acid derivative **139** and diazomethane at low temperatures. This

ketene is unlikely to undergo any intramolecular Friedel-Crafts acylation due to the formation of a four carbon aryl ketone, and yet is sufficiently stable for isolation and characterization in 72% yield. The acylketene **140** was then refluxed with an external, electron-rich π-nucleophile (1,3-dimethoxybenzene) in nitromethane. In the absence of a catalyst, no product was observed, and the starting material was destroyed, giving an unidentifiable complex mixture by ^{1}H NMR.

In the presence of a catalytic amount of $Sc(OTf)_3$ however, the desired arylketone product **141** was isolated in 51% yield (scheme 3.9).

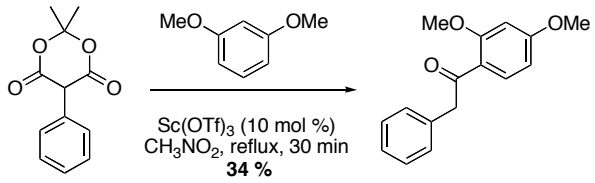
Scheme 3.9: Intermolecular Friedel-Crafts acylation of acylketene 140



139 **140** **141**

Therefore, in the intermolecular acylation case, the acylketene is insufficiently electrophilic for Friedel-Crafts acylation, but when $Sc(OTf)_3$ is used **141** is obtained in good yield. Direct intermolecular acylation of phenyl Meldrum's derivative **139** with the same nucleophile also failed in the absence of catalyst. The catalyzed version did, however, give product **142** in 34% yield (scheme 3.10).

Scheme 3.10: Intermolecular Friedel-Crafts acylation of phenyl Meldrum's Acid



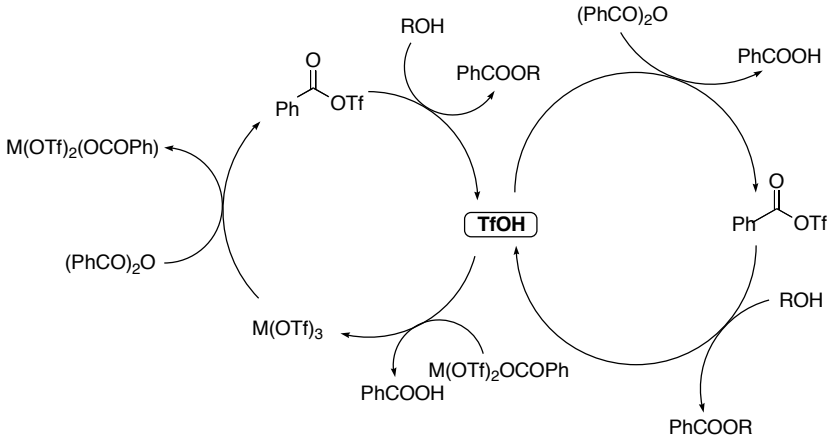
139 **142**

The above results demonstrate that in the presence of a catalyst, the intermolecular Friedel-Crafts acylation of Meldrum's acid derivatives proceeds. From a mechanistic point of view, however, it does not contribute much information aside from the apparent activation of an acylketene by Lewis acid. For enolizable Meldrum's acid derivatives the rate determining step in the thermal decomposition is the retro Diels-Alder reaction step, but in the presence of a

Lewis acid ($Sc(OTf)_3$ in particular for these investigations) an alternative reaction pathways appears to be predominating.

The role of metal triflate catalysts in the acylation of alcohols has recently been studied by Markó.[9] Using benzoic anhydride, benzoyl chloride, and acetic anhydride, it was revealed that with $Sc(OTf)_3$, $Bi(OTf)_3$, $In(OTf)_3$ and $Yb(OTf)_3$, the acylation of alcohols is actually promoted by TfOH, which is the true catalytic species. It was proposed that a triflic anhydride intermediate is formed from the acylating agent and the metal-triflate, and upon acylation, triflic acid is produced which then assumes the role of active catalyst. Catalytic inhibition could be obtained by addition of various proportions of 2,6-di-*tert*-butyl-4-methyl pyridine (DTBMP). DTBMP is a hindered organic base that is known not to interact with metal catalysts.[10] Additional water also diminished catalytic activity by sequestration of triflic acid. Markó proposed the catalytic cycle presented in figure 3.1.

Figure 3.1: Markó's proposed catalytic cycle for the acylation of alcohols using metal-triflates



Friedel-Crafts acylations catalyzed by $Bi(OTf)_3$ have also been studied,[11] and in that case it was found that benzoyl chloride undergoes exchange to produce a triflic anhydride species, while benzoic anhydride was directly activated by the metal centre.

Based on the observed rapid substrate consumption that is proportional to catalyst loading (chart 3.4 A/B), as well as the observed intermolecular Friedel-Crafts acylation with Meldrum's acid in the presence of catalyst, an alternative pathway is that a triflic anhydride species is being formed. Triflic anhydrides have known potency in the Friedel-Crafts acylation.[12] Chart

3.4 A/B also shows that the nucleophilic difference between the two substrates significantly affects the rates of substrate decomposition, so formation of the reactive species must be very rapid, followed by the rate limiting acylation step. In the presence of a metal-triflate Lewis acid catalyst, the major acylation pathway would involve a triflic anhydride species generated directly from Meldrum's acid. The active catalytic species could be triflic acid in this case, and the activity would diminish as the acetone side product and indanone product increase in concentration.

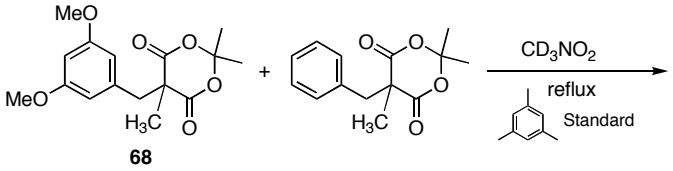
The mechanism of catalytic acylation for the enolizable substrates is complicated by the continued presence of the thermal pathway that was discussed earlier, that occurs with and without active catalyst. This underlying thermal instability of the substrates is a possible contributor to the lower yields generally observed for enoliable substrates. The catalytic pathway was therefore better studied with the quarternarized Meldrum's acids that proceed via only one manifold.

Quaternarized Meldrum's Acid Derivatives In The Catalytic Intramolecular Friedel-Crafts Acylation Reaction

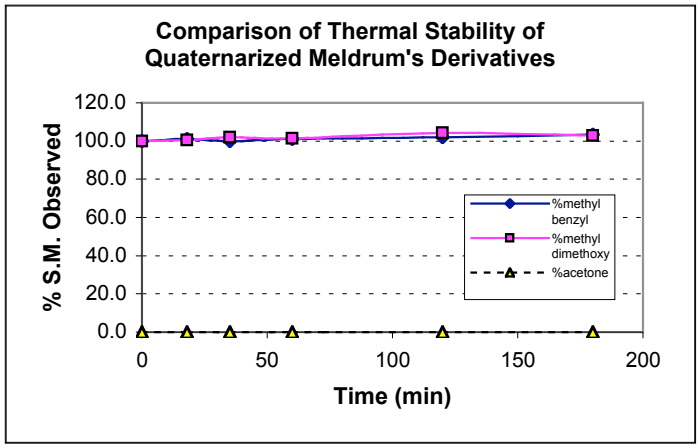
Quaternarized Meldrum's acid derivatives are unable to enolize, and so do not undergo retro Diels-Alder to generate acylketenes. As a result, these compounds are completely stable under thermal conditions, and the starting material is quantitatively recovered even after refluxing for 24 hours (chart 3.5).

The reactivity of the non-enolizable derivatives of Meldrum's acid is simplified by their thermal stability, and these substrates can even be analyzed with GC and GC-MS without FVP occurring. It was hypothesized that upon activation by a Lewis acid, a zwitterionic resonance structure could be formed that would rapidly lose acetone and decarboxylate to produce a ketene intermediate. This might undergo Friedel-Crafts acylation to produce the desired arylketone (scheme 3.11).

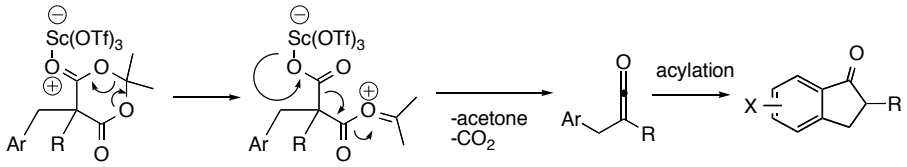
Chart 3.5: Thermal stability of quaternarized Meldrum's acid derivatives



68



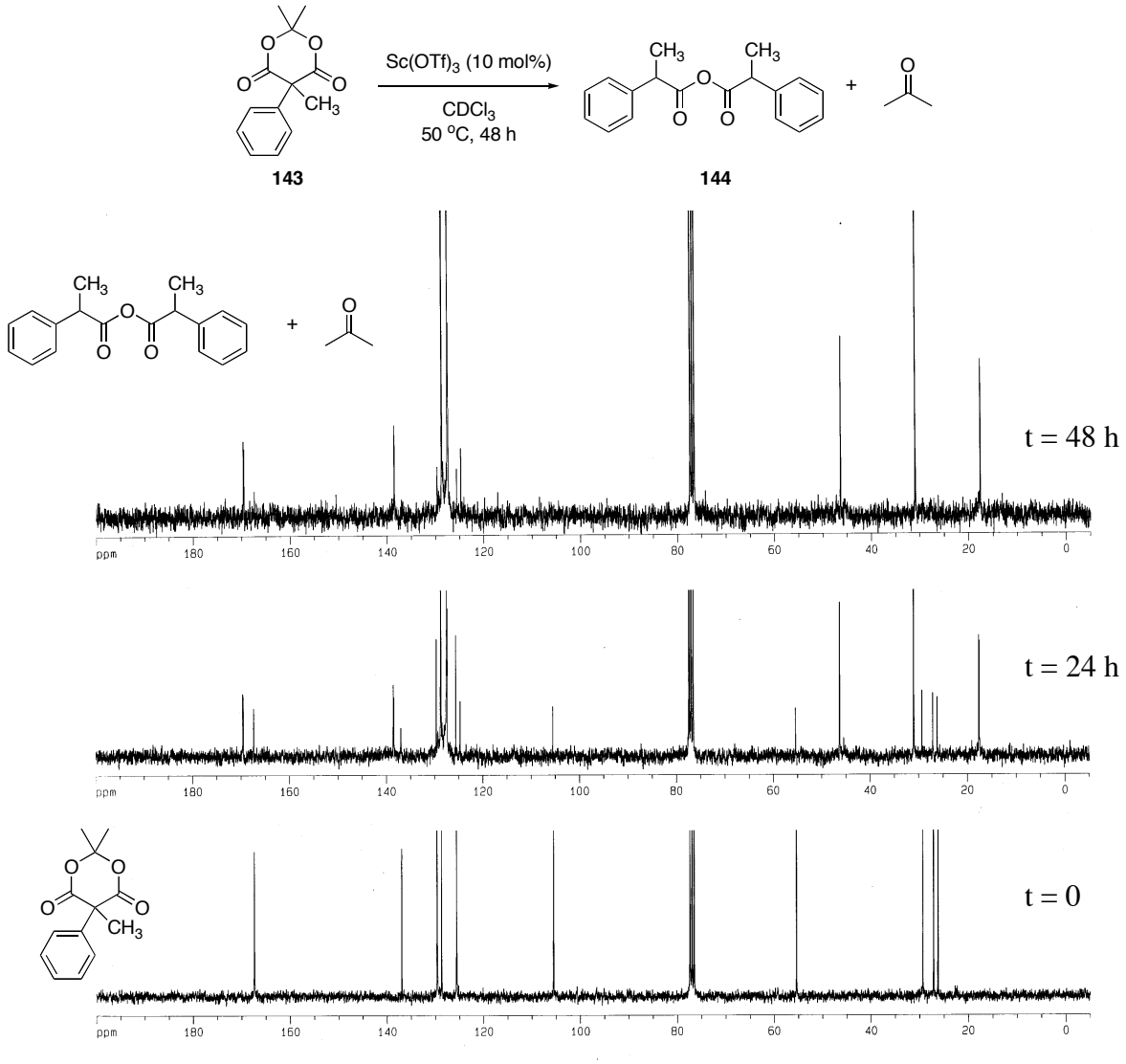
Scheme 3.11: Possible decomposition of quarternarized Meldrum's acid to ketene



To observe such a ketene, 5,5-phenyl methyl Meldrum's acid **143** was heated alone with catalytic scandium triflate in dry deuterated chloroform in a sealed NMR tube and the ^{13}C NMR frequently observed. Phenyl methylketene is a known stable compound that is a distillable oil. It was prepared independently from 2-phenyl propionyl chloride and triethylamine[13], and its ^{1}H and ^{13}C NMR data acquired.

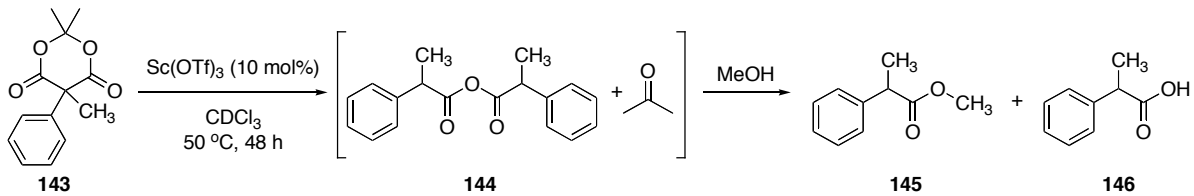
The result of this experiment was very surprising. This substrate is structural constrained such that the intramolecular acylation is not possible (due to the formation of a four carbon aryl ketone ring). The species that slowly arose (illustrated in figure 3.2) is the anhydride **144** as a mixture of diastereoisomers. After 48 hours, complete and clean conversion had occurred, as observed by ^{1}H and ^{13}C NMR, with the production of acetone.

Figure 3.2: Anhydride formation from quaternarized Meldrum's acid derivative 143



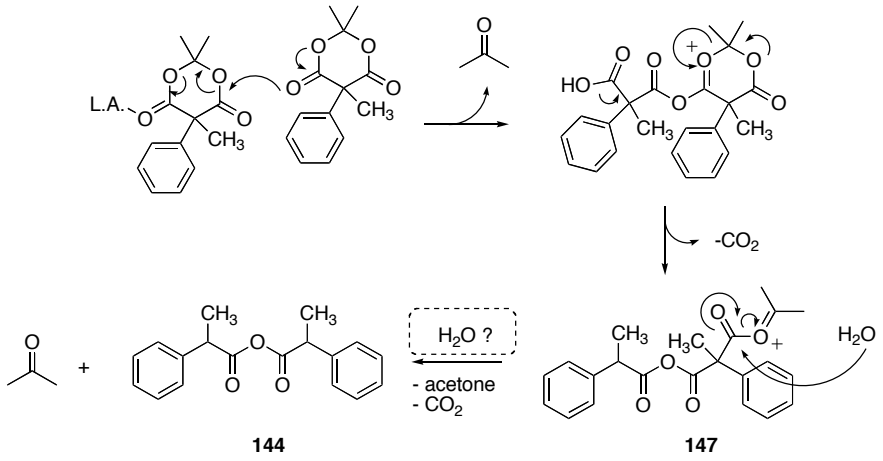
After unsealing the NMR tube and treatment of the reaction mixture with excess methanol, GC-MS analysis GC-MS revealed methyl hydratropate **145** and 2-phenyl propanoic acid **146** (scheme 3.12). Further isolation and analysis was not undertaken.

Scheme 3.12: Reaction of the proposed anhydride species with methanol



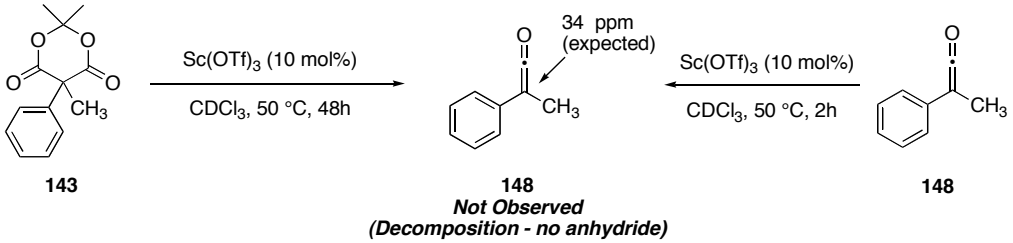
The formation of **144** is difficult to rationalize considering the strictly anhydrous reaction conditions. The scandium catalyst was predried under high vacuum and handled in a glove box under argon, and the chloroform-d_3 was distilled from CaH_2 and stored in a Schlenk tube. Recall, however, that in chapter 2, the ketal containing substrate **21** also suffered from the presence of trace amounts of water. Theoretically, one molecule of **143** could attack another Lewis acid activated molecule of **143**, and subsequent decarboxylation would produce a species **147**, which would require a molecule of water for conversion to the observed anhydride **144** (scheme 3.13).

Scheme 3.13: Hypothetical formation of anhydride 144



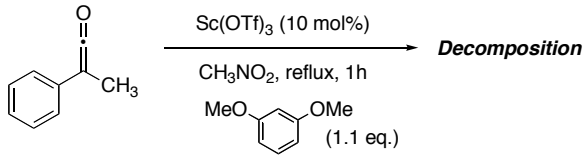
In spite of this unusual observation, phenyl methyl Meldrum's acid did not provide the corresponding ketene by NMR. To confirm that phenyl methylketene **148** was not forming transiently and transforming into the anhydride, **148** was treated under the same conditions, but after 2 hours, complete decomposition had occurred with no recognizable peaks by ^{1}H or ^{13}C NMR. Scheme 3.14 summarizes the direct attempts to observe a ketene intermediate.

Scheme 3.14: Attempts to observe the suspected ketene intermediate



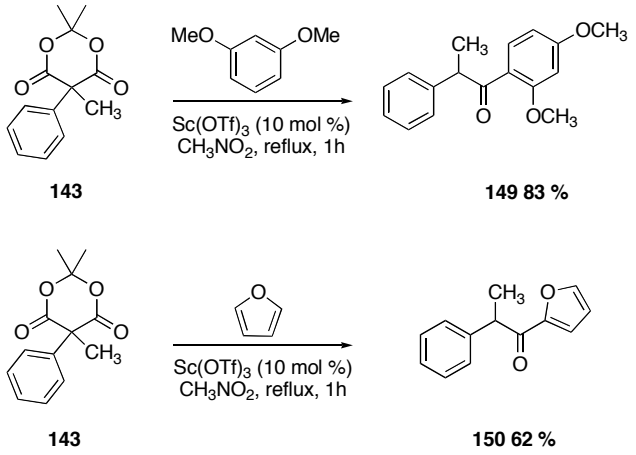
Since direct observation methods were unsuccessful, indirect methods were attempted. Phenyl methylketene **148** was combined with 1,3-dimethoxybenzene in nitromethane and a catalytic quantity of scandium triflate. After refluxing for 1 hour, complete decomposition of the starting material was observed, and none of the desired product was detected (scheme 3.15). It is conceivable that under these conditions the ketene more readily undergoes side reactions compared with acylketene that was successfully acylated under similar conditions above (scheme 3.9).

Scheme 3.15: Attempted Friedel-Crafts acylation of Lewis acid activated ketene



The failure of ketene to undergo Friedel-Crafts acylation under these conditions is in stark contrast to the intermolecular reactivity of **143** under the same reaction conditions (scheme 3.16). Both 3,5-dimethoxybenzene and furan served as effective intermolecular π-nucleophiles, providing the arylketones **149** and **150** in 83% and 62% yield, respectively.

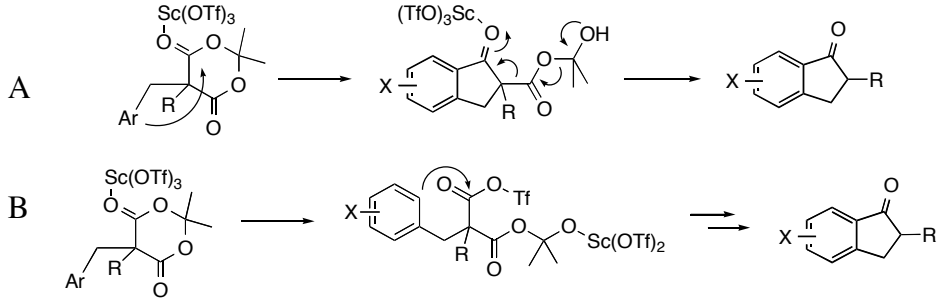
Scheme 3.16: Intermolecular Friedel-Crafts acylation of quarternarized Meldrum's acids.



The above results strongly suggest that a ketene (or Lewis acid activated ketene) is not the reactive species in this reaction. The possibilities that remain are the direct acylation of a Lewis

acid activated carbonyl (scheme 3.17A), or (in the case of metal triflates) the formation of a triflic anhydride reactive intermediate as proposed earlier (scheme 3.17B).

Scheme 3.17: Proposed mechanisms of Friedel-Crafts acylation of quaternarized Meldrum's acids (excluding ketene)



This latter route (via an anhydride) does not explain, however, the excellent results observed with BF_3•OEt_2 with quaternarized Meldrum's derivatives (table 2.9).

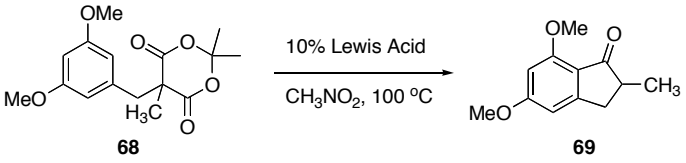
With BF_3•OEt_2 it was observed that the electron rich nucleophile **72** provided the desired indanone **73**, but the dibenzyl Meldrum's derivative **102** provided only recovered starting material. This suggests a direct acylation mechanism, as there is no report of acid fluoride formation (from any substrate) using BF_3•OEt_2 in the literature. If an acyl fluoride were to form, the Meldrum's substrate would be observed to decompose (in the base of **102**) if the strength of the nucleophilic portion were insufficient for a productive Friedel-Crafts acylation.

Comparison of Lewis Acid Reaction Profiles

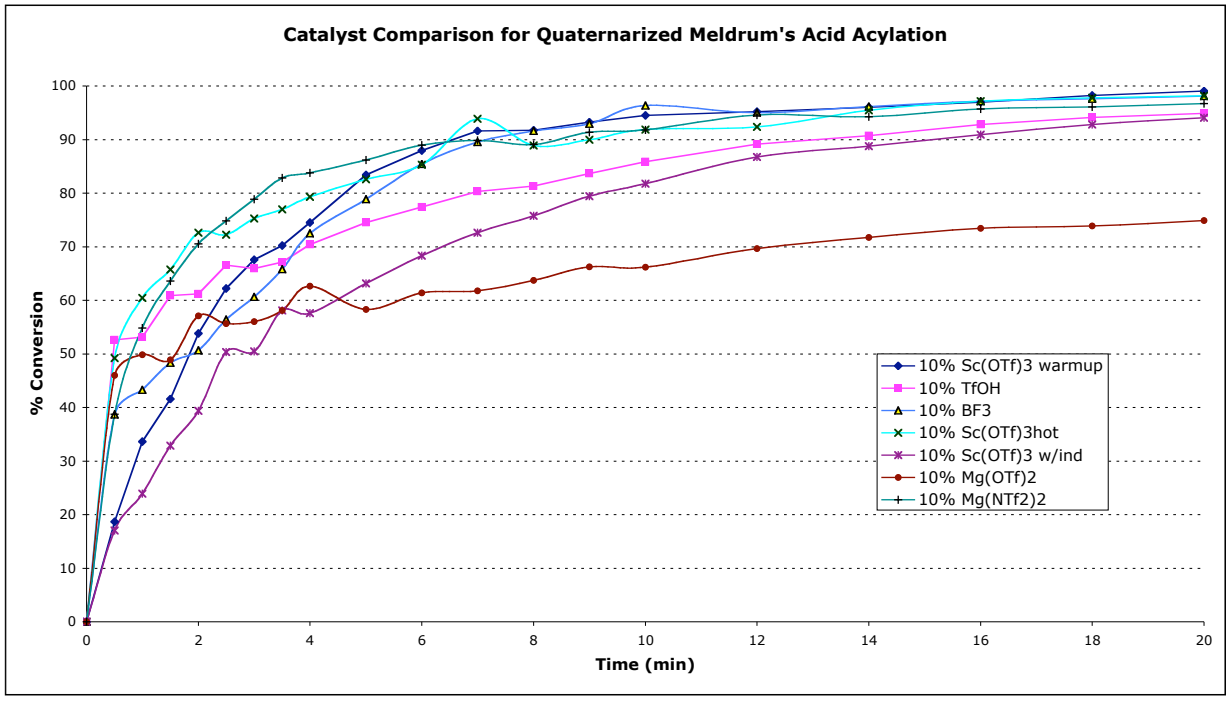
One distinct advantage of the quaternarized Meldrum's derivatives is their thermal stability in the absence of Lewis acid catalyst. This feature greatly simplifies their analysis since it eliminates the underlying background reaction due to the retro Diels-Alder reaction observed in the enolizable cases. This allows for the direct observation of reaction progress by gas chromatography. Using a stock solution of (3,5-dimethoxybenzyl)-5-methyl Meldrum's acid **68** as the substrate, a number of Lewis acids were used to catalyze the intramolecular Friedel-Crafts reaction. At fixed time intervals, aliquots were drawn from the reaction mixture and immediately quenched in a triethylamine/methylene chloride solution. These samples were then filtered through plugs of silica, and then injected into a GC equipped with a flame ionization

detector. The progression of the reaction was judged by the simple percent conversion as determined by the direct comparison of integration areas of the starting material with the product. Since no internal standard was used in the analysis, percent yields are not determined. The objective of this experiment was the comparison of reaction profiles for different Lewis acids. All other reaction and analysis conditions are identical between each Lewis acid. The profiles are presented in chart 3.6. Point to point line connections are provided solely for the purpose of clarity.

Chart 3.6: Relative reaction progress for different Lewis acids



68 69



The data presented in Chart 3.6 is remarkable in that all the Lewis acids displayed extremely similar reaction profiles. All of the reactions were very fast, with the bulk of substrate conversion occurring within the first 5 minutes of the reaction. From this data can be gleaned some useful details that can influence the application of this methodology in practical synthetic applications. These are described below.

Scandium triflate was utilized for three different experiments. [$Sc(OTf)_3$ (warmup)] allowed the reaction solution to warm up to 100 ^oC in the presence of catalyst, and so the initial 2 minutes show a much slower progress than when then catalyst is added to a preheated solution of substrate [$Sc(OTf)_3$ (hot)]. It is clearly advantageous, therefore, to add catalyst to a preheated solution of quaternarized derivative. The final scandium experiment [$Sc(OTf)_3$ w/ind] examined the catalyst inhibition by benzocyclic ketone produced in the reaction. 1-Indanone was used as a conveniently available surrogate for the indanone product **69** without complicating the GC analysis (a distinct new peak is produced). While this reaction still proceeded rapidly and with near complete conversion within 20 minutes, the rate was much slower than all of the other conditions examined. Clearly the Lewis acid is partially sequestered by the 1-indanone (and likely acetone as well) that is produced in the reaction. This experiment with 1-indanone (4 equivalents) is an extreme demonstration of this phenomenon, however. For a large-scale synthesis, the removal of the acetone byproduct by reduced pressure could be expected to acclerate the reaction, but this was never explored in this study.

BF_3•Et_2O and triflic acid are both very convenient Lewis/protic acids since they are distillable liquids, and relatively inexpensive. These are both highly effective catalysts in the acylation of quaternarized derivatives.

The most profound observation was in the comparison between magnesium triflate $Mg(OTf)_2$ and magnesium bistriflamide $Mg(NTf_2)_2$.[14] In chapter 2, table 2.9, it was reported that $Mg(OTf)_2$ was an effective catalyst, providing an excellent yield of 2-methyl indanone product in refluxing nitromethane. In this controlled experiment at precisely 100 ^oC it was found that $Mg(OTf)_2$ provided the lowest overall conversion of the Lewis acids examined, even though it rapidly converted about half of the substrate within a minute of the reaction beginning. On the other hand, magnesium bistriflamide was amongst the best catalysts examined, being comparable to scandium triflate.

In general, metal triflamides are considered to be more Lewis acidic than their triflate counterparts.[15] Aluminum, ytterbium and titanium bistriflamides have been used in the Friedel-Crafts reaction of acetic anhydride with anisole to give acetyl anisole.[16] Benzoyl chloride was reacted with toluene promoted by a large variety of metal bistriflamide salts with excellent results.[14] In that report it was noted that $HNTf_2$ was also a good acylation catalyst, and addition of this as a co-catalyst with metal bistriflamides greatly accelerated the reaction rate. Finally,

the benzoylation of toluene using $Bi(NTf_2)_3$ was studied.[15]

This data with the magnesium based catatlysts is especially revealing when one considers the possible mechanism of acylation in scheme 3.17 (A and B). If route B was followed, then $Mg(NTf_2)_2$ would produce a *N,N*-bis(trifluoromethanesulfonyl)amide species, which, as an acylating agent, would be less powerful than the mixed anhydride formed with $Mg(OTf)_2$.[15] This would result in a faster and more effective reaction with $Mg(OTf)_2$ which is not observed in this reaction. These results would, therefore, support mechanistic route A in scheme 3.17, direct acylation of a Lewis acid activated Meldrum's acid derivative. This would be supported by the observed effectiveness of $BF_3 \bullet Et_2O$ (though this could theoretically produce an acid fluoride acylating species in the hypothetical route B).

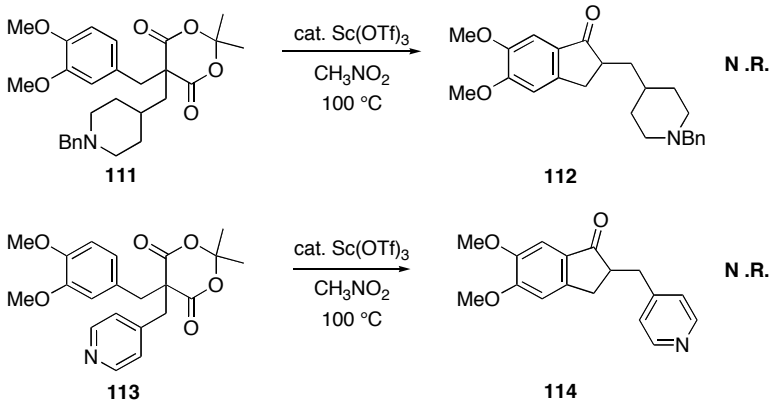
Summary For The Catalytic Intramolecular Friedel-Crafts Acylation of Quaternarized Meldrum's Acid Derivatives

It is proposed, based on the evidence presented in the preceding sections, that the acylation of quaternarized Meldrum's acid derivatives could occur either via an activated carboxylic acid derivative or by direct acylation of a Lewis acid activated carbonyl of Meldrum's acid itself. The adoption of the direct acylation pathway as a functional mechanism is consistent with the observations presented, and at a synthetic level, provides an operationally useful model for reaction design and product prediction.

Catalyst Inhibition by Amine Bases – Donepezil Synthesis Revisited

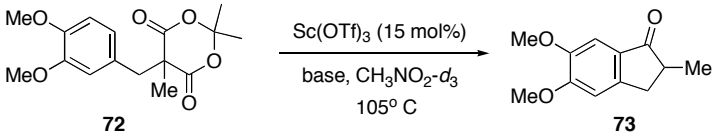
In chapter 2, the synthesis of Donepezil was presented using a stoichiometric quantity of promoter. The use of catalytic scandium triflate failed to produce any product and starting material was recovered (scheme 3.18).

Scheme 3.18: Attempts at the catalytic synthesis of Donepezil



The apparent inhibition of catalytic activity by sp^2- and sp^3-hybridized nitrogen in these quarternarized Meldrum's acids was further examined by intermolecular competition experiments with substrate **72**. This non-enolizable derivative provides **73** in high yields with a variety of catalysts. Running the same reaction with various proportions of pyridine or 2,6-di-*tert*-butyl-4-methylpyridine (DTBMP) revealed that low amounts of pyridine are tolerated, but a threshold is reached such that no substrate conversion is obtained (table 3.2). The experiment was performed in a sealed NMR tube containing an internal standard (mesitylene) and the reaction heated at 105° C. After a fixed time interval (1 or 2 hours) the reaction was observed by ^{1}H NMR to determine the substrate conversion by integration.

Table 3.2: Catalytic acylation of 72 in the presence of amine

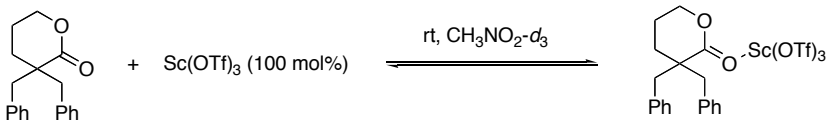


Base		Loading (mol%)	Time (h)	Conversion (%)
pyridine		0	1	100
pyridine		15	1	100
pyridine		30	1	55
pyridine		45	1	0
pyridine		100	1	0
DTBMP		15	2	100
DTBMP		30	1	50
DTBMP		30	2	75
DTBMP		45	18	0

These results are virtually identical to the results obtained by Markó in a comparable experiment examining the acylation of alcohols with metal triflates.[9] DTBMP is unable to interact with the Lewis acid, but it is capable of scavenging triflic acid.[9,17] These results for quaternarized derivatives further supports the role of triflic acid as the active catalytic species.

The Lewis acidity of scandium triflate in the presence of DTBMP was directly assessed using α,α-dibenzyl-δ-valerolactone **151**. An equimolar amount of catalyst and substrate were combined in a sealed NMR tube and the chemical shift of the lactone carbonyl examined. With increased loading of DTBMP, the downfield shift was diminished, and essentially disappeared with 2 equivalents of DTBMP (table 3.3).

Table 3.3: Effect of DTBMP on scandium triflate Lewis acidity



151

Mixture	δ ^{13}C=O (ppm)	Δδ	δ $^{19}F_3C$ (ppm)
α,α-dibenzyl-δ-valerolactone (**151**)	176.8	–	–
$Sc(OTf)_3$	–	–	-78.0
151 + $Sc(OTf)_3$	190.5 (s)	13.7	-78.2
151 + TfOH	190.8 (s)	14.1	-79.2
151 + $Sc(OTf)_3$ + DTBMP (1 eq.)	178.6 (vb)	1.8	-78.8
151 + $Sc(OTf)_3$ + DTBMP (2 eq.)	176.9 (b)	0.1	-79.3
151 + $Sc(OTf)_3$ + DTBMP (3 eq.)	176.9 (s)	0.1	-79.3

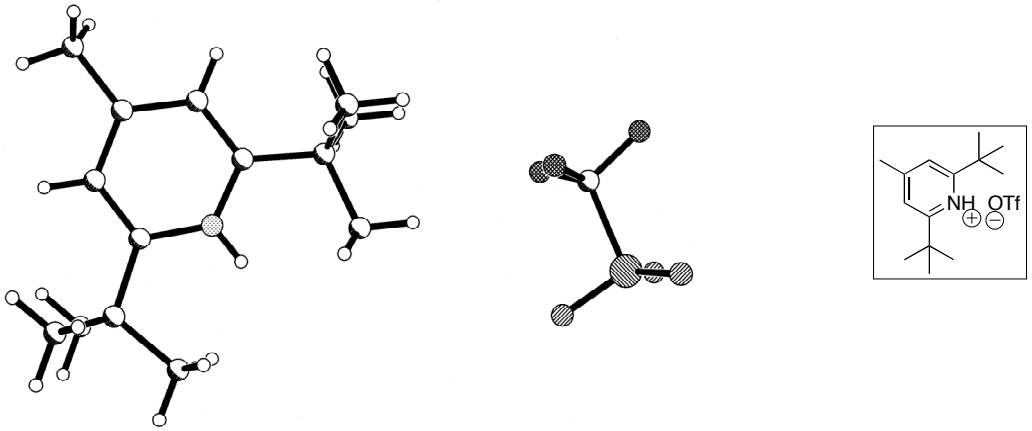
b = broad, s = sharp, vb = very broad

Regardless whether the carbonyl activation (downfield shift) was due to triflic acid or scandium triflate, the addition of only 1 molar equivalent of non-nucleophilic base led to a significant decrease of Lewis acidity, as evidenced by the chemical shift of the lactone carbonyl. The fluorine NMR also indicated that upon combination with increasing amounts of DTBMP, the triflate moiety was more like that of a free triflate anion than in its scandium complex state.

It was speculated that perhaps DTBMP was, in fact, able to serve as a ligand to $Sc(OTf)_3$. A solution of dry $Sc(OTf)_3$ was made with 3 equivalents of DTBMP in dry chloroform, and crystals were grown by the diffusion method in a dry hexane atmosphere. X-ray

crystallography of the clear needles were obtained, revealing them to be $DTBMPH^{+}$ ^{-}OTf salt (Figure 3.3).

Figure 3.3: X-Ray structure of salt obtained from DTBMP and $Sc(OTf)_3$



Based on the results discussed above, it appears as though $Sc(OTf)_3$ is practically challenging to obtain in a truly anhydrous form. In the catalytic Friedel-Crafts acylation of Meldrum's acids, triflic acid appears to be the active catalytic species, and metal triflates appear to serve as a very mild and convenient method for its delivery.

Summary

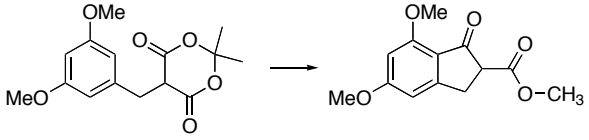
- Benzyl Meldrum's acid derivatives are potent acylating in the intramolecular Friedel-Crafts acylation. Under thermal conditions, without catalyst, monosubstituted Meldrum's acids can enolize, then undergo a rate limiting retro Diels-Alder reaction to form an acyl ketene reactive species. This can react with heteroatomic nucleophiles, or intramolecularly with π-nucleophiles.
- For both quaternarized and enolizable Meldrum's acid derivatives, the addition of a Lewis acid is capable of activating one of the Meldrum's carbonyls. This activated complex is either attacked directly, or undergoes a ligand transfer from the Lewis acid to generate an activated carboxylic acid derivative. Enolizable Meldrum's acids can still enolize and undergo retro Diel-Alder to generate the acyl ketene, which can also interact with the Lewis acid in this dichotomous manner. Quaternarized derivatives (in their Lewis acid activated form) immediately undergo acylation without the possibility

of enolization (and further decomposition), resulting in faster and high yielding reactions to generated 2-substituted 1-indanones.

- Quaternarized derivatives are quite poorly Lewis basic, such that the addition of even small quantities of a stronger Lewis base (such as amines) inhibits catalyst activity for this class of substrates. This is particularly true for scandium triflate, which appears to behave as a triflic acid delivery device, based on the results presented here and the references cited.

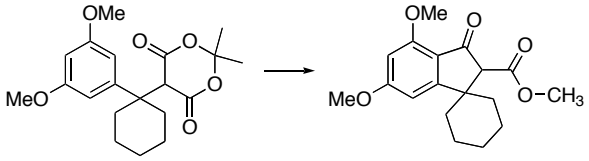
Experimental Section

5,7-Dimethoxy-1-indanone-2-carboxylic acid methyl ester[18] (135)



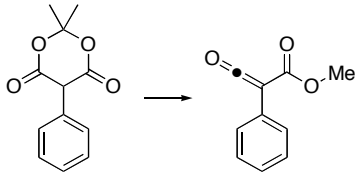
Meldrum's acid derivative **9** (100 mg, 0.34 mmol) and trimethyloxonium tetrafluoroborate (Meerwein's salt) (70 mg, 0.47 mmol) were combined in a round bottom flask equipped with a reflux condenser, magnetic stir bar and a rubber septum under a dry nitrogen atmosphere. At 0 $^{\circ}$C, CH_2Cl_2 (5 mL) was added via syringe with stirring, followed by diisopropylethylamine (65 μL, 0.38 mmol). The resulting suspension was stirred for 30 minutes at 0 $^{\circ}$C and then heated at reflux for 1.5 hours, at which time no starting material was observed by TLC. The crude reaction mixture was quenched with aqueous 10% HCl then diluted with additional CH_2Cl_2. The layers were partitioned and the aqueous phase was extracted with CH_2Cl_2 (3x). The combined organic fractions were dried over $MgSO_4$, then filtered and concentrated. The yellow oil was purified by flash chromatography (2:1 EtOAc:Hex) on silica gel to provide 4 mg (52 %) of the desired β-keto ester **135** as an oil that solidified on standing. M.p. 103-104 $^{\circ}$C. Lit. 104-105 $^{\circ}$C (EtOAc/ Et_2O); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.48 (1H, br s), 6.28 (1H, br s), 3.88 (3H, s), 3.86 (3H, s), 3.74 (3H, s), 3.66 (1H, dd, *J* = 8.2 Hz, 3.8 Hz), 3.41 (1H, dd, *J* = 17.2 Hz, 3.4 Hz), 3.20 (1H, dd, *J* = 17.3 Hz, 8.3 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 195.1, 170.0, 167.6, 160.0, 158.8, 117.6, 101.6, 97.8, 55.8, 53.7, 52.7, 30.2. HRMS (EI): *m/z* Calcd. for $C_{13}H_{14}O_5$ (M^+) 250.0841. Found 250.0839.

5,7-Dimethoxy-(3.3)-pentamethylene-1-indanone-2-carboxylic acid methyl ester (136)



Meldrum's acid derivative **15** (200 mg, 0.55 mmol) and trimethyloxonium tetrafluoroborate (Meerwein's salt) (114 mg, 0.77 mmol) were combined in a round bottom flask equipped with a reflux condenser, magnetic stir bar and a rubber septum under a dry nitrogen atmosphere. At 0 °C, CH_2Cl_2 (5 mL) was added via syringe with stirring, followed by diisopropylethylamine (0.13 mL, 0.75 mmol). The resulting suspension was stirred for 30 minutes at 0 °C then heated at reflux for 1 hour. An additional portion of Meerwein's salt (114 mg, 0.77 mmol) was added and the reflux continued for an additional 30 minutes. The crude reaction mixture was quenched with aqueous 10% HCl then diluted with additional CH_2Cl_2. The layers were partitioned and the aqueous phase was extracted with CH_2Cl_2 (3x). The combined organic fractions were dried over $MgSO_4$, then filtered and concentrated. The yellow oil was purified by flash chromatography (1:1 Hex:EtOAc) on silica gel to provide the desired β-keto ester **136** as 112 mg (67 %) of white solid. M.p. 168-170 °C (Et_2O); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.46 (1H, d, *J* = 1.7 Hz), 6.28 (1H, d, *J* = 1.6 Hz), 3.88 (6H, s), 3.67 (3H, s), 3.56 (1H, s), 2.04-2.09 (1H, m), 1.77-1.16 (9H, m); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 196.0, 170.0, 168.3, 167.4, 159.6, 116.6, 99.4, 97.4, 64.1, 55.8, 55.7, 52.0, 46.6, 41.8, 31.9, 25.3, 23.6, 22.7; HRMS (EI): *m/z* Calcd. for $C_{18}H_{22}O_5$ (M^+): 318.1467. Found: 318.1470.

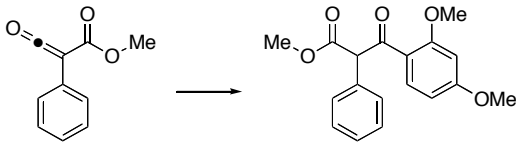
3-Oxo-2-phenyl-acrylic acid methyl ester (140)



Phenyl Meldrum's acid[19] **139** (337 mg, 1.53 mmol) was dissolved in dry CH_2Cl_2 (5 mL) and cooled to –70° C in a Schlenk tube under a dry argon atmosphere. An excess of dry ethereal diazomethane solution (generated under ethanol free conditions) was added and the reaction stirred at this temperature for 30 minutes. The reaction was then maintained at a temperature between -50° and -40° C as the solvent was removed under high vacuum (0.3 torr) with

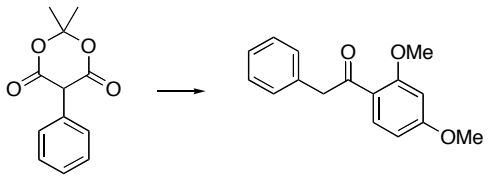
vigorous stirring. The resulting yellow oil was warmed to room temperature under vacuum and then purged with argon. The acyl ketene **140** was obtained as 195 mg of yellow oil (72 %) and used immediately without purification. Crude ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40-7.25 (5H, m), 3.81 (3H, s); IR ($CDCl_3$, liquid cell) ketene 2130, ester 1721 cm^{-1}.

Methyl 3-(2,4-dimethoxyphenyl)-3-oxo-2-phenylpropanoate (141)



To solution of 1,3-dimethoxybenzene (76 mg, 0.55 mmol) in dry CH_3NO_2 (1 mL) was added dry $Sc(OTf)_3$ (27 mg, 0.055 mmol), and the resulting suspension brought to reflux in an oil bath under argon atmosphere. A solution of acyl ketene **140** (97 mg, 0.55 mmol) in CH_3NO_2 (1 mL) was added in one portion to the refluxing reaction mixture via syringe. After 30 minutes the reaction mixture was cooled and concentrated by rotary evaporation, and then purified by flash chromatography (4:1 hex:EtOAc) to provide 88 mg (51 %) of **141** as a pale yellow oil. If the reaction was performed in the absence of $Sc(OTf)_3$ then no product or starting material was obtained. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.86 (1H, d, *J* = 8.8 Hz), 7.24-7.30 (5H, m), 6.50 (1H, dd, *J* = 8.8, 2.1 Hz), 6.37 (1H, d, *J* = 2.1 Hz), 5.64 (1H, s), 3.83 (3H, s), 3.81 (3H, s), 3.71 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 193.2, 170.1, 165.1, 160.4, 133.9, 133.8, 129.7, 128.3, 127.6, 119.5, 105.7, 198.1, 64.1, 55.5, 55.2, 52.3; IR (NaCl) ester 1734, ketone 1668 cm^{-1}; EI *m/z (rel. int.)* 314 (3), 179 (4), 166 (10), 165 (100); HRMS (EI) calcd for $C_{18}H_{18}O_5$: 314.1154; found 314.1159.

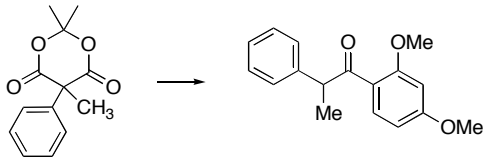
1-(1,4-Dimethoxyphenyl)-2-phenyl-1-ethanone (142)



A solution of 1,3-dimethoxybenzene (140 mg, 1.01 mmol) and $Sc(OTf)_3$ (50 mg, 0.10 mmol) in dry CH_3NO_2 (5 mL) was brought to reflux under a dry nitrogen atmosphere. Phenyl Meldrum's acid **139** (223 mg, 1.01 mmol) was added in one portion and the reaction refluxed

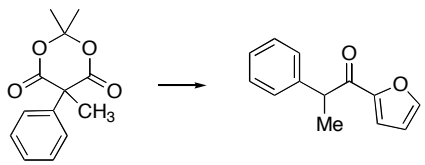
for 30 minutes. The dark brown mixture was cooled, concentrated and then purified by flash chromatography (4:1 Hex:EtOAc) to provide 88 mg (34%) of **142** as a pale yellow oil. If the reaction was performed in the absence of $Sc(OTf)_3$ then no product or starting material was obtained. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.79 (1H, d, *J* = 8.7 Hz), 7.27-7.19 (5H, m), 6.5 (1H, dd, *J* = 8.7, 2.1 Hz), 6.43 (1H, d, *J* = 2.1 Hz), 4.26 (2H, s), 3.87 (3H, s), 3.82 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 197.7, 164.5, 160.6, 135.7, 133.1, 129.6, 128.2, 126.4, 120.8, 105.2, 98.3, 55.5, 55.4, 50.0; IR (NaCl) C=O 1665 cm^{-1}; EI *m/z (rel. int.)* 256 (1), 179 (3), 166 (10), 165 (100); HRMS (EI) calcd for $C_{16}H_{16}O_3$: 256.1099; found 256.1106.

1-(2,4-Dimethoxyphenyl)-2-phenyl-1-propanone (149)



To a refluxing solution of 1,3-dimethoxybezene (128 mg, 0.93 mmol) and phenyl methyl Meldrum's acid[20] **143** (200 mg, 0.85 mmol) in CH_3NO_2 (5 mL) under nitrogen was added $Sc(OTf)_3$ (42 mg, 0.09 mmol). The reaction was allowed to stir for 1 hour and then cool and concentrated. Purification by flash chromatography (5:1 Hex:EtOAc) provided 191 mg (83 %) of **149** as a pale yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.65 (1H, d, *J* = 8.7 Hz), 7.25-7.11 (5H, m), 6.43 (1H, dd, *J* = 8.7, 2.2 Hz), 6.34 (1H, d, *J* =2.2 Hz), 4.75 (1H, q, *J* = 6.9 Hz), 3.79 (3H, s), 3.78 (3H, s), 1.46 (3H, d, *J* = 6.9 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.9, 159.8, 142.0, 132.9, 128.2, 128.0, 126.3, 121.2, 105.0, 98.2, 55.3, 55.2, 51.1, 19.2; IR (NaCl) C=O 1663 cm^{-1}; EI *m/z (rel. int.)* 270 (<1), 179 (8), 166 (10), 165 (100), 122 (7), 77 (6); HRMS (EI) calcd for $C_{17}H_{18}O_3$: 270.1256; found 270.1258.

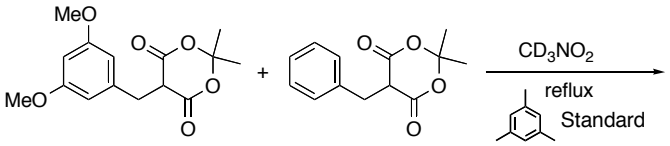
1-(2-Furyl)-2-phenyl-1-propanone (150)



In a Schlenk tube containing phenyl methyl Meldrum's acid **143** (200 mg, 0.85 mmol) and

$Sc(OTf)_3$ (42 mg, 0.09 mmol) in CH_3NO_2 (5 mL) under nitrogen was added furan (64 mg, 0.94 mmol). The Schlenk tube was sealed and immediately placed in an oil bath at 105° C for 1 hour. The resulting black reaction mixture was cooled and concentrated, and then purified by flash chromatography (5:1 Hex:EtOAc) to provide 106 mg (62 %) of **150** as a yellow oil. ^1H NMR (300 MHz, $CDCl_3$) δ 7.50 (1H, dd, *J* = 0.8, 0.8 Hz), 7.50-7.15 (5H, m), 7.12 (1H, br d, *J* = 3.6 Hz), 6.43 (1H, dd, *J* = 3.6, 1.6 Hz) 4.47 (1H, q, *J* = 7.0 Hz), 1.50 (3H, d, *J* = 7.0 Hz); $CDCl_3$ (75 MHz, $CDCl_3$) δ 189.4, 152.2, 146.3, 140.8, 128.8, 127.9, 127.0, 117.8, 112.2, 47.9, 18.3; IR (NaCl) C=O 1674 cm^{-1}; EI *m/z (rel. int.)* 200 (41), 105 (100), 95 (61), 77 (18); HRMS (EI) calcd for $C_{13}H_{12}O_2$: 200.0837; found 200.0840.

The thermal intramolecular Friedel-Crafts acylation of enolizable substrates (competition) – for chart 3.1



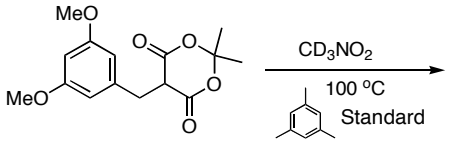
3,5-Dimethoxybenzyl Meldrum's acid **9** (10 mg, 0.034 mmol) and benzyl Meldrum's acid **46** (8.0 mg, 0.034 mmol) were placed in a sealable Schlenk NMR tube, to which was added 4.7 μL of mesitylene and CD_3NO_2 (0.5 mL). The tube was sealed under a dry nitrogen atmosphere, then the *t=0* data acquired on a 300 MHz NMR. Integration of the mesitylene peak was defined as 9 protons, and integrations of the 2 benzylic protons of the two substrates were recorded according to this standard. The NMR tube was placed in an oil bath maintained at precisely 100 ^oC. At the given time points, the tube was removed and placed in an ice/water bath for 1 minute, then dried. The new NMR data for that time point was acquired. The NMR tube was kept tightly sealed throughout the experiment, and the reaction times refer only to the time that the tube was heated in the oil bath. This experiment was performed in triplicate.

Time in minutes; 'benzyl', 'dimethoxy' and 'acetone' are the standardized integration values for each signal in each run; %benzyl, %dimethoxy, and %acetone = $100(value_t/value_0)$ for each experiment.

time	Benzyl integration	Dimethoxy integration	Acetone integration	%benzyl remaining	%dimethoxy remaining	%acetone formed
0.00	2.21	2.32	0.00	100.00	100.00	0.00
0.00	2.31	2.40	0.00	100.00	100.00	0.00

0.00	2.93	2.60	0.00	100.00	100.00	0.00
15.00	1.74	1.79	3.14	78.73	77.16	23.11
15.00	2.06	2.07	3.05	89.18	86.25	21.59
15.00	2.33	2.08	3.64	79.52	80.00	21.94
30.00	1.37	1.35	5.28	61.99	58.19	38.85
30.00	1.68	1.57	5.12	72.73	65.42	36.23
30.00	1.83	1.61	5.75	62.46	61.92	34.66
45.00	1.10	1.03	6.78	49.77	44.40	49.89
45.00	1.30	1.14	7.15	56.28	47.50	50.60
45.00	1.37	1.16	8.36	46.76	44.62	50.39
60.00	0.84	0.75	7.94	38.01	32.33	58.43
60.00	1.18	0.99	8.30	51.08	41.25	58.74
60.00	1.23	1.08	8.37	41.98	41.54	50.45
75.00	0.67	0.58	8.73	30.32	25.00	64.24
75.00	1.10	0.87	8.94	47.62	36.25	63.27
80.00	0.99	0.83	9.42	33.79	31.92	56.78
90.00	0.56	0.44	9.51	25.34	18.97	69.98
90.00	0.90	0.65	9.50	38.96	27.08	67.23
95.00	0.89	0.71	10.00	30.38	27.31	60.28
105.00	0.44	0.34	10.00	19.91	14.66	73.58
105.00	0.80	0.50	9.86	34.63	20.83	69.78
110.00	0.81	0.62	10.69	27.65	23.85	64.44
120.00	0.37	0.27	10.37	16.74	11.64	76.31
120.00	0.74	0.43	11.07	32.03	17.92	78.34
130.00	0.74	0.55	10.50	25.26	21.15	63.29
180.00	0.60	0.42	10.59	20.48	16.15	63.83
190.00	0.19	0.11	11.04	8.60	4.74	81.24
200.00	0.62	0.24	11.21	26.84	10.00	79.33
280.00	0.10	0.06	11.37	4.30	2.59	83.66
380.00	0.15	0.11	11.23	6.49	4.58	79.48

Consumption of Enolizable Meldrum's Acid Derivative Under Thermal Conditions – Determination of Rate Constant (k_H) (for Chart 3.2)



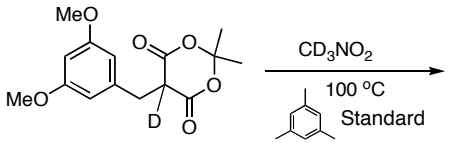
3,5-Dimethoxybenzyl Meldrum's acid **9** (10.0 mg, 0.034 mmol) was placed in a sealable Schlenk NMR tube, to which was added 5 μL of mesitylene and CD_3NO_2 (0.5 mL). The tube was sealed under a dry nitrogen atmosphere, then the *t=0* data acquired on a 300 MHz NMR. Integration of the mesitylene peak was defined as 9 protons, and integration of the Meldrum's methyl peak (3 protons) farthest upfield was recorded according to this standard. The NMR tube was placed in an oil bath maintained at precisely 100 °C. At the given time points, the tube

was removed and placed in an ice/water bath for 1 minute, then dried. The new NMR data for that time point was acquired. The NMR tube was kept tightly sealed throughout the experiment, and the reaction times refer only to the time that the tube was heated in the oil bath. This reaction was performed in triplicate.

Time in minutes; 'acetone' and 'methyl' are the standardized integration values for the acetone and Meldrum's acid methyl signal in each run; %conv = 100(acetone/(acetone+methyl)) for each experiment; ln plot = ln(100-%conv).

time	Acetone integration	Meldrum's methyl\ integration	% conv	ln plot
0.00	0.00	3.39	0.00	4.61
0.00	0.00	3.05	0.00	4.61
0.00	0.00	3.28	0.00	4.61
10.00	1.20	2.70	18.18	4.40
10.00	1.04	2.48	17.33	4.41
10.00	1.11	2.64	17.37	4.41
20.00	2.15	2.10	33.86	4.19
20.00	1.92	1.90	33.57	4.20
20.00	2.03	2.07	32.90	4.21
30.00	2.88	1.66	46.45	3.98
30.00	2.60	1.49	46.59	3.98
30.00	2.79	1.58	46.89	3.97
40.00	3.26	1.34	54.88	3.81
40.00	2.96	1.22	54.81	3.81
40.00	3.35	1.26	57.07	3.76
55.00	3.81	0.94	66.96	3.50
55.00	3.66	0.82	69.06	3.43
55.00	3.80	0.90	67.86	3.47
70.00	4.37	0.65	77.07	3.13
70.00	4.12	0.60	77.44	3.12
70.00	4.26	0.65	76.62	3.15
90.00	4.46	0.43	83.83	2.78
90.00	4.30	0.38	84.98	2.71
90.00	4.73	0.41	85.23	2.69
120.00	5.13	0.24	91.44	2.15
120.00	4.77	0.20	92.26	2.05
120.00	5.13	0.23	91.77	2.11
150.00	4.96	0.15	94.30	1.74
150.00	4.71	0.11	95.54	1.50
150.00	5.02	0.14	94.72	1.66

Consumption of Deuterium Labeled Enolizable Meldrum's Acid Derivative Under Thermal Conditions – Determination of Rate Constant (k_D) (for Chart 3.2)



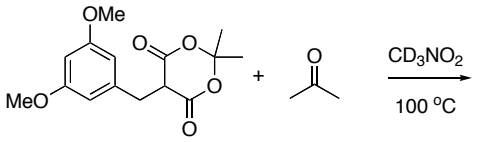
3,5-Dimethoxybenzyl 5-deutero Meldrum's acid **137** (10.0 mg, 0.034 mmol) was placed in a sealable Schlenk NMR tube, to which was added 5 μL of mesitylene and CD_3NO_2 (0.5 mL). The tube was sealed under a dry nitrogen atmosphere, then the *t=0* data acquired on a 300 MHz NMR. Integration of the mesitylene peak was defined as 9 protons, and integration of the Meldrum's methyl peak (3 protons) farthest upfield was recorded according to this standard. The NMR tube was placed in an oil bath maintained at precisely 100 °C. At the given time points, the tube was removed and placed in an ice/water bath for 1 minute, then dried. The new NMR data for that time point was acquired. The NMR tube was kept tightly sealed throughout the experiment, and the reaction times refer only to the time that the tube was heated in the oil bath. This reaction was performed in triplicate.

Time in minutes; 'acetone' and 'methyl' are the standardized integration values for each signal in each run; %conv = 100(acetone/(acetone+methyl)) for each experiment; ln plot = ln(100-%conv).

time	Acetone integration	Meldrum's Methyl integration	% conv	ln plot
0.00	0.00	3.27	0.00	4.61
0.00	0.00	3.40	0.00	4.61
0.00	0.00	3.28	0.00	4.61
10.00	1.22	2.55	19.30	4.39
10.00	1.28	2.70	19.16	4.39
10.00	1.07	2.67	16.69	4.42
20.00	1.86	2.12	30.49	4.24
20.00	1.99	2.20	31.14	4.23
20.00	1.82	2.16	29.64	4.25
35.00	2.72	1.55	46.74	3.98
35.00	2.91	1.64	47.01	3.97
35.00	2.71	1.62	45.55	4.00
50.00	3.36	1.13	59.79	3.69
50.00	3.45	1.21	58.77	3.72
50.00	3.22	1.21	57.09	3.76

65.00	3.78	0.82	69.74	3.41
65.00	3.91	0.91	68.24	3.46
65.00	3.70	0.91	67.03	3.50
80.00	4.31	0.58	78.79	3.05
80.00	4.38	0.63	77.66	3.11
80.00	4.04	0.67	75.09	3.22
100.00	4.63	0.36	86.54	2.60
100.00	4.74	0.44	84.34	2.75
100.00	4.36	0.45	82.89	2.84
140.00	4.78	0.15	94.09	1.78
140.00	5.06	0.19	93.01	1.94
140.00	4.47	0.21	91.41	2.15
185.00	5.11	0.08	96.96	1.11
185.00	5.43	0.10	96.45	1.27
185.00	4.75	0.10	95.96	1.40

Relative Effect of Initial acetone concentration on Reaction rate – Data for chart 3.3



3,5-Dimethoxybenzyl Meldrum's acid **9** (10.0 mg, 0.034 mmol) was placed in a sealable Schlenk NMR tube, to which was added 5 μl of mesitylene and CD_3NO_2 (0.5 mL). Acetone (10 μL or 50 μL) was added to the tube, which was then sealed under a dry nitrogen atmosphere, and the *t=0* data acquired on a 300 MHz NMR. Integration of the mesitylene methyl peak was defined as 9 protons, and integration of the Meldrum's methyl peak farthest upfield was recorded according to this standard. The NMR tube was placed in an oil bath maintained at precisely 100 °C. At the given time points, the tube was removed and placed in an ice/water bath for 1 minute, then dried. The new NMR data for that time point was acquired. The NMR tube was kept tightly sealed throughout the experiment, and the reaction times refer only to the time that the tube was heated in the oil bath. This experiment was repeated in triplicate (for each acetone amount). Acetone-free data was used from the kinetics experiment above (chart 3.2 data)

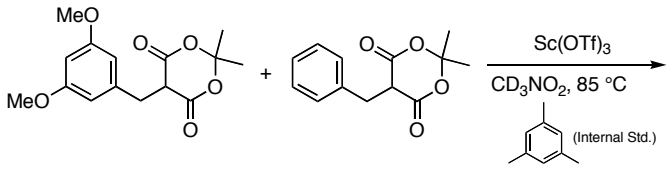
Time in minutes; 'methyl' is the standardized integration value for that signal in each run; % S.M. = 100($methyl_t$/$methyl_0$) for each experiment.

10mg **9** in 0.5ml CD_3NO_2		
time	methyl	% S.M.
0.00	3.39	100.00
0.00	3.05	100.00
0.00	3.28	100.00
10.00	2.70	79.65
10.00	2.48	81.31
10.00	2.64	80.49
20.00	2.10	61.95
20.00	1.90	62.30
20.00	2.07	63.11
30.00	1.66	48.97
30.00	1.49	48.85
30.00	1.58	48.17
40.00	1.34	39.53
40.00	1.22	40.00
40.00	1.26	38.41
55.00	0.94	27.73
55.00	0.82	26.89
55.00	0.90	27.44
70.00	0.65	19.17
70.00	0.60	19.67
70.00	0.65	19.82
90.00	0.43	12.68
90.00	0.38	12.46
90.00	0.41	12.50
120.00	0.24	7.08
120.00	0.20	6.56
120.00	0.23	7.01
150.00	0.15	4.42
150.00	0.11	3.61
150.00	0.14	4.27

10 mg **9** in 0.5 CD_3NO_2 plus 10 μL acetone		
time	methyl	% S.M.
0.00	3.10	100.00
0.00	3.42	100.00
0.00	3.19	100.00
10.00	2.43	78.39
10.00	2.56	74.85
10.00	2.42	75.86
20.00	2.04	65.81
20.00	2.20	64.33
20.00	2.07	64.89
30.00	1.86	60.00
30.00	1.92	56.14
30.00	1.78	55.80
40.00	1.49	48.06
40.00	1.67	48.83
40.00	1.53	47.96
50.00	1.18	38.06
50.00	1.47	42.98
50.00	1.25	39.18
60.00	1.00	32.26
60.00	1.29	37.72
60.00	1.04	32.60
80.00	0.72	23.23
80.00	1.01	29.53
80.00	0.74	23.20
100.00	0.53	17.10
100.00	0.73	21.35
100.00	0.51	15.99
120.00	0.38	12.26
120.00	0.59	17.25
120.00	0.42	13.17
160.00	0.26	8.39
160.00	0.41	11.99
160.00	0.27	8.46

10 mg **9** in 0.5 ml CD_3NO_2 plus 50 μL acetone		
time	methyl	% S.M.
0.00	3.24	100.00
0.00	3.13	100.00
0.00	2.99	100.00
10.00	2.29	70.68
10.00	2.30	73.48
10.00	2.20	73.58
20.00	2.13	65.74
20.00	2.12	67.73
20.00	2.03	67.89
30.00	2.00	61.73
30.00	2.07	66.13
30.00	1.97	65.89
40.00	1.88	58.02
40.00		
40.00	1.66	55.52
50.00	1.75	54.01
50.00	1.77	56.55
50.00	1.44	48.16
70.00	1.57	48.46
70.00	1.40	44.73
70.00		
90.00	1.15	35.49
90.00	1.24	39.62
90.00	1.11	37.12
115.00	0.86	26.54
115.00	0.74	23.64
115.00	0.90	30.10
145.00	0.67	20.68
145.00	0.62	19.81
145.00	0.58	19.40

The catalytic intramolecular Friedel-Crafts acylation of enolizable substrates (competition) – for charts 3.4 A and B



3,5-Dimethoxybenzyl Meldrum's acid **9** (10 mg, 0.034 mmol) and benzyl Meldrum's acid **46** (8 mg, 0.034 mmol) were placed in a sealable Schlenk NMR tube containing $Sc(OTf)_3$ (2 mg, 0.1 eq) or (6 mg, 0.3 eq), to which was added 4.7 μL of mesitylene and CD_3NO_2 (0.6 mL). The tube was sealed under a dry nitrogen atmosphere, then the *t=0* data acquired on a 300 MHz NMR. Integration of the mesitylene methyl peak was defined as 9 protons, and integrations of the 2 benzylic protons of the two substrates were recorded according to this standard. The NMR tube was placed in an oil bath maintained at precisely 85 ^{o}C. At the given time points, the tube was removed and placed in an ice/water bath for 1 minute, then dried. The new NMR data for that time point was acquired. The NMR tube was kept tightly sealed throughout the experiment, and the reaction times refer only to the time that the tube was heated in the oil bath

Time in minutes; 'benzyl', 'dimethoxy' and 'acetone' are the standardized integration values for each signal in each run; %benzyl, %dimethoxy, and %acetone = 100(value$_t$/value$_0$) for each experiment.

A: **9** + **46** w/ std, 85 ^{o}C 10% scandium

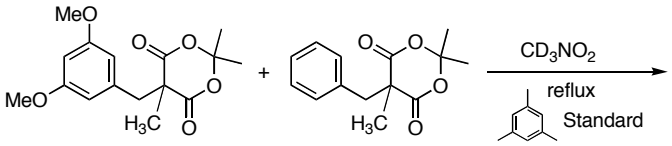
Time	Benzyl integration	Dimethoxy Integration	Acetone integration	%benzyl remaining	%dimethoxy remaining	%acetone produced
0.00	2.36	2.55	0.00	100.00	100.00	0.00
3.00	1.67	1.20	6.21	70.76	47.06	42.04
5.00	1.57	1.07	6.82	66.53	41.96	50.18
8.00	1.45	0.97	7.32	61.44	38.04	53.86
12.00	1.36	0.85	7.91	57.63	33.33	58.20
18.00	1.21	0.74	8.62	51.27	29.02	63.43
30.00	1.08	0.62	9.37	45.76	24.31	68.95
45.00	0.90	0.50	10.25	38.14	19.61	75.42
60.00	0.73	0.40	11.04	30.93	15.69	81.24
90.00	0.51	0.20	11.80	21.61	7.84	86.83
120.00	0.40	0.15	12.26	16.95	5.88	90.21

B: **9** + **46** w/ std, 85 ^{o}C 30% scandium

Time	Benzyl integration	Dimethoxy integration	Acetone integration	%benzyl remaining	%dimethoxy remaining	%acetone produced
0.00	2.09	2.32	0.00	100.00	100.00	0.00

3.00	1.02	0.38	8.08	48.80	16.38	67.33
6.00	0.81	0.32	8.49	38.76	13.79	70.75
9.00	0.69	0.25	9.46	33.01	10.78	78.83
12.00	0.54	0.15	9.53	25.84	6.47	79.42
20.00	0.48	0.00	10.00	22.97	0.00	83.33

Quarternarized thermal reaction – no reaction (for chart 3.5)

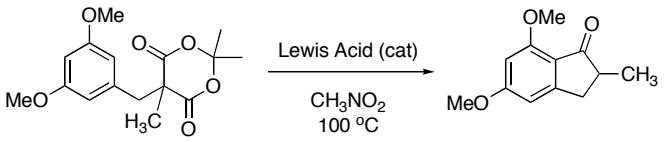


3,5-Dimethoxybenzyl Meldrum's acid **68** (10 mg, 0.032 mmol) and benzyl Meldrum's acid (8 mg, 0.032 mmol) were placed in a sealable Schlenk NMR tube, to which was added 4.7 μL of mesitylene and CD_3NO_2 (0.5 mL). The tube was sealed under a dry nitrogen atmosphere, then the *t=0* data acquired on a 300 MHz NMR. Integration of the mesitylene methyl peak was defined as 9 protons, and integrations of the 2 benzylic protons of the two substrates were recorded according to this standard. The NMR tube was placed in an oil bath maintained at precisely 100 ^{o}C. At the given time points, the tube was removed and placed in an ice/water bath for 1 minute, then dried. The new NMR data for that time point was acquired. The NMR tube was kept tightly sealed throughout the experiment, and the reaction times refer only to the time that the tube was heated in the oil bath.

Time in minutes; benzyl, dimethoxy and acetone are the standardized integration values for each signal in each run; %benzyl, %dimethoxy, and %acetone = 100(value$_t$/value$_0$) for each experiment.

time	Benzyl integration	Dimethoxy integration	Acetone integration	%benzyl remaining	%dimethoxy remaining	%acetone produced
0.00	2.62	2.18	0.00	100.00	100.00	0.00
18.00	2.65	2.19	0.00	101.15	100.46	0.00
35.00	2.62	2.22	0.00	100.00	101.83	0.00
60.00	2.65	2.21	0.00	101.15	101.38	0.00
120.00	2.67	2.27	0.00	101.91	104.13	0.00
180.00	2.71	2.24	0.00	103.44	102.75	0.00

Relative Reaction Progressions for Various Lewis Acids in the Intramolecular Friedel-Crafts Acylation of Quaternarized Meldrum's Acid Derivatives (for Chart 3.6)



A 0.095M stock solution containing of (3,5-dimethoxybenzyl)-5-methyl Meldrum's acid **68** (2.94 g, 9.55 mmol) in CH_3NO_2 (100 mL) was prepared.

In a glove box, the solid catalyst was weighed into a dry screwcap vial. A dry two-necked round bottom flask equipped with a reflux condenser and a stir bar was placed into an oil bath preheated to 100 ^oC under a dry nitrogen atmosphere, and the 5 mL of the stock solution was added via syringe. After 5 minutes, the t = 0 sample was taken.

For the liquid catalysts [(TfOH 5 μL, 10 mol%), BF_3•OEt_2 (9 μL, 10 mol%)], the catalyst was added by microsyringe and timing of the reaction immediately begun.

For solid catalysts [$Sc(OTf)_3$ (25 mg, 10 mol%), $Mg(OTf)_2$ (16 mg, 10 mol%), $Mg(NTf_2)_2$ (27 mg, 10 mol%)] the solid was added rapidly through the available neck of the round bottom flask and then then flask immediately resealed and timing begun.

Three experiments were performed using scandium triflate. One is as described above, but in another the catalyst was added to the flask first, before the stock solution was added. In this experiment the solution needed to warm up to the oil bath temperature while being exposed to catalyst. In the third experiment the stock solution was used to dissolve 1-indanone (252 mg, 400 mol%), and the catalyst added after the initial warming period.

Samples were taken every 30 seconds for the first 4 minutes, then every minute for the next 6 minutes, then every two minutes for the next 10 minutes, for a total reaction time of 20 minutes. This distribution ensured a large sampling rate at the beginning of the reaction. At each time point, 100 μL aliquots were withdrawn using a clean and dry disposable syringe, and immediately injected into 10 uL of distilled Et_3N in 100 uL of methylene chloride. At end of experiment, each sample was filtered through a short plug of silica gel and eluted with ethyl acetate. The samples were then run on a gas chromatograph equipped with a flame ionization detector, with a temperature gradient of 50 ^oC for 3 minutes, then 50 to 270 ^oC over 10 minutes.

The indanone product peak eluted at 11.7 minutes, and the Meldrum's acid derivative starting material at 12.9 minutes.

In the following tables of raw data, the 'time' column is the reaction time elapsed in minutes, the 'product' column is the integration value for 1-indanone, 'sm' is the Meldrum's acid derivative **68**, and the '%conv'= 100 x 'prod'/('prod'+'sm').

$Sc(OTf)_3$ (10 mol%) (warmup) – Catalyst in dry flask warmed to 100 ^oC then stock solution added at time 0 (solution therefore warms up with beginning of reaction).

time	Prod integration	Sm integration	% conversion of peak areas
0.00	0.00	8928.40	0.00
0.50	1173.20	5115.50	18.66
1.00	1128.30	2224.30	33.65
1.50	806.20	1133.50	41.56
2.00	1831.10	1572.90	53.79
2.50	1343.00	816.50	62.19
3.00	2106.10	1009.70	67.59
3.50	1610.50	682.60	70.23
4.00	2390.50	816.50	74.54
5.00	1996.30	396.40	83.43
6.00	1800.10	246.50	87.96
7.00	2168.00	198.30	91.62
8.00	1339.70	120.80	91.73
9.00	3003.90	216.90	93.27
10.00	2334.30	135.60	94.51
12.00	2028.40	101.50	95.23
14.00	2342.40	96.60	96.04
16.00	3822.70	118.20	97.00
18.00	3482.50	62.20	98.25
20.00	2162.20	20.40	99.07

Trifluoromethansulfonic acid (10 mol%)

time	prod	sm	% conversion of peak areas
0.00	0.00	5168.90	0.00
0.50	1417.60	1277.80	52.59
1.00	1239.60	1095.00	53.10
1.50	1983.20	1273.20	60.90
2.00	1092.30	692.50	61.20
2.50	2227.00	1119.00	66.56
3.00	2212.60	1144.40	65.91
3.50	1055.40	516.40	67.15
4.00	1808.40	758.90	70.44
5.00	1900.60	651.10	74.48

6.00	1641.80	478.70	77.43
7.00	1874.30	459.60	80.31
8.00	2331.70	535.90	81.31
9.00	2022.20	395.00	83.66
10.00	1902.40	313.30	85.86
12.00	2950.00	359.50	89.14
14.00	1931.20	197.60	90.72
16.00	2410.60	187.50	92.78
18.00	2126.20	133.20	94.10
20.00	1972.60	105.60	94.92

BF_3 OEt_2 (10 mol%)

time	prod	sm	% conversion of peak areas
0.00	0.00	4189.20	0.00
0.50	1106.30	1754.90	38.67
1.00	1416.80	1857.40	43.27
1.50	2236.50	2389.30	48.35
2.00	1512.20	1473.20	50.65
2.50	1792.90	1387.10	56.38
3.00	1269.10	824.60	60.62
3.50	1636.10	850.30	65.80
4.00	2540.60	963.60	72.50
5.00	2009.90	539.00	78.85
6.00	3004.10	512.40	85.43
7.00	4619.60	541.20	89.51
8.00	3517.60	322.40	91.60
9.00	3331.20	253.20	92.94
10.00	3333.20	125.50	96.37
12.00	3306.40	172.30	95.05
14.00	3789.40	150.50	96.18
16.00	4053.70	119.40	97.14
18.00	3359.70	81.70	97.63
20.00	4407.70	84.40	98.12

$Sc(OTf)_3$ (10 mol%) (hot) – Stock solution preheated, then dry catalyst added at time 0.

time	prod	sm	% conversion of peak areas
0.00	0.00	3776.90	0.00
0.50	1834.60	1895.50	49.18
1.00	4109.00	2688.40	60.45
1.50	3860.10	2010.10	65.76
2.00	5462.00	2058.40	72.63
2.50	2993.20	1151.20	72.22
3.00	3220.30	1059.60	75.24
3.50	3692.90	1103.80	76.99
4.00	3697.00	963.60	79.32
5.00	4281.60	901.90	82.60

6.00	4199.30	723.90	85.30
7.00	3531.90	231.10	93.86
8.00	4268.20	534.20	88.88
9.00	6394.60	711.40	89.99
10.00	7192.40	635.30	91.88
12.00	3604.60	297.50	92.38
14.00	5322.70	253.50	95.45
16.00	7774.80	226.50	97.17
18.00	6307.20	140.80	97.82
20.00	3702.90	68.50	98.18

$Sc(OTf)_3$ (10 mol%) with 1-indanone (400 mol%)

time	prod	sm	% conversion of peak areas
0.00	0.00	5306.70	0.00
0.50	696.60	3397.90	17.01
1.00	1202.90	3831.00	23.90
1.50	1610.50	3286.10	32.89
2.00	1911.50	2942.50	39.38
2.50	1698.00	1675.80	50.33
3.00	2030.90	1995.10	50.44
3.50	1803.20	1298.80	58.13
4.00	2038.90	1500.10	57.61
5.00	2514.40	1465.10	63.18
6.00	1480.00	685.20	68.35
7.00	2280.40	859.80	72.62
8.00	2993.70	958.20	75.75
9.00	3683.90	954.70	79.42
10.00	2363.50	528.10	81.74
12.00	4201.70	642.80	86.73
14.00	4176.70	528.10	88.78
16.00	3780.70	378.20	90.91
18.00	3380.50	260.80	92.84
20.00	2710.10	171.00	94.06

$Mg(OTf)_2$ (10 mol%)

time	prod	sm	% conversion of peak areas
0.00	0.00	984.40	0.00
0.50	528.80	621.70	45.96
1.00	598.50	602.80	49.82
1.50	819.80	855.80	48.93
2.00	1179.10	885.50	57.11
2.50	1135.90	906.20	55.62
3.00	491.30	385.60	56.03
3.50	816.70	588.20	58.13
4.00	690.20	411.80	62.63
5.00	807.50	577.60	58.30

6.00	738.50	464.90	61.37
7.00	808.70	500.10	61.79
8.00	1120.00	638.10	63.71
9.00	1404.50	716.30	66.23
10.00	1008.40	515.80	66.16
12.00	988.10	431.00	69.63
14.00	1880.50	740.00	71.76
16.00	1366.80	494.10	73.45
18.00	1786.10	631.50	73.88
20.00	3493.20	1172.20	74.87

$Mg(NTf_2)_2$ (10 mol%)

time	prod	sm	% conversion of peak areas
0.00	0.00	5287.10	0.00
0.50	1130.20	1788.80	38.72
1.00	2515.80	2074.60	54.81
1.50	2156.00	1234.10	63.60
2.00	2034.30	850.20	70.53
2.50	2883.80	971.80	74.80
3.00	3222.40	862.60	78.88
3.50	2113.60	438.30	82.82
4.00	2015.60	390.50	83.77
5.00	4049.80	649.70	86.18
6.00	2124.70	262.90	88.99
7.00	2345.90	264.80	89.86
8.00	5661.20	692.80	89.10
9.00	3124.80	294.70	91.38
10.00	3696.70	331.20	91.78
12.00	3615.60	207.40	94.57
14.00	5045.20	306.00	94.28
16.00	4157.00	185.20	95.73
18.00	3498.60	141.40	96.12
20.00	4398.30	148.80	96.73

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Chapter 4
The Total Synthesis of (±)-Taiwaniaquinol B

Introduction

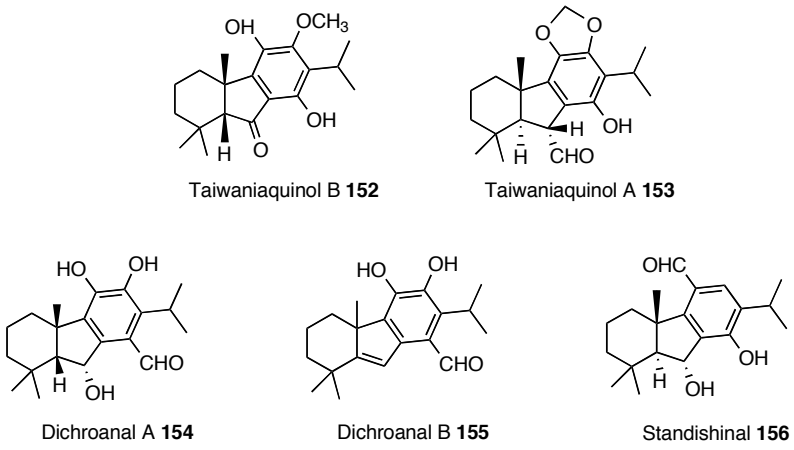
While Meldrum's acid has established synthetic utility as an acylating agent for heteroatomic nucleophiles[1], the preceeding chapters have described its application to the catalytic carbon-carbon bond formation via intramolecular Friedel-Crafts acylation.

Chapter 3 illustrates that the Friedel-Crafts acylation with monosubstituted Meldrum's acid derivatives (enolizable derivatives) occurs via the intermediacy of an acyl ketene that produces 1-indanone-2-carboxylic acid which decarboxylates to provide the 1-indanone products. It was envisaged that this unique reactivity of Meldrum's acid could be exploited in the design of a multiple carbon-carbon bond forming reaction. This chapter describes a conceptually new approach to sterically congested 1-indanones via Lewis acid-mediated intramolecular Friedel–Crafts acylation/carbonyl α–*tert*-alkylation domino reaction, and its application to the concise total synthesis of taiwaniaquinol B.

Background

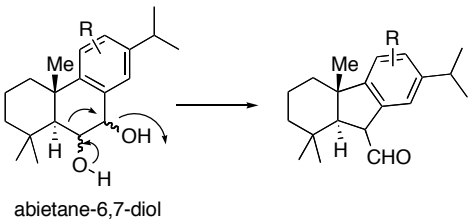
Taiwaniaquinol B (**1)** is a member of the 5(6→7)abeoabietane-type diterpenoid family (figure 4.1), and was amongst the first natural products exhibiting the uncommon fused 6-5-6 tricyclic carbon skeleton.

Figure 4.1: The 5(6→7)abeoabietane-type diterpenoid family



These structurally related natural products have been isolated from various sources. Taiwaniaquinol B (**152**) and A (**153**) were isolated in 1995 from *Taiwania cryptomeriodes*, a common Taiwanese pine tree (Figure 1).[2] Examination of extracts from the root of *Salvia dishroantha* led to the isolation and identification of dichroanal A (**154**) and B (**155**).[3] Standishinal (**156**) was isolated from the bark of *Thuja standishii* by Tanaka and coworkers in 1999.[4] Biogenetically, the 6-5-6 fused ring skeleton is thought to arise from the pinacol rearrangement of abietane-6,7-diol (scheme 4.1).[2]

Scheme 4.1: Proposed biosynthesis of 6-5-6 system



The bioactivity of these natural products remains to be studied in detail, but promising results have been obtained for standishinal (**156**) for which aromatase inhibitory activity has been determined which may lead to the development of valuable therapeutic agents in the treatment of estrogen-dependant cancers.[5]

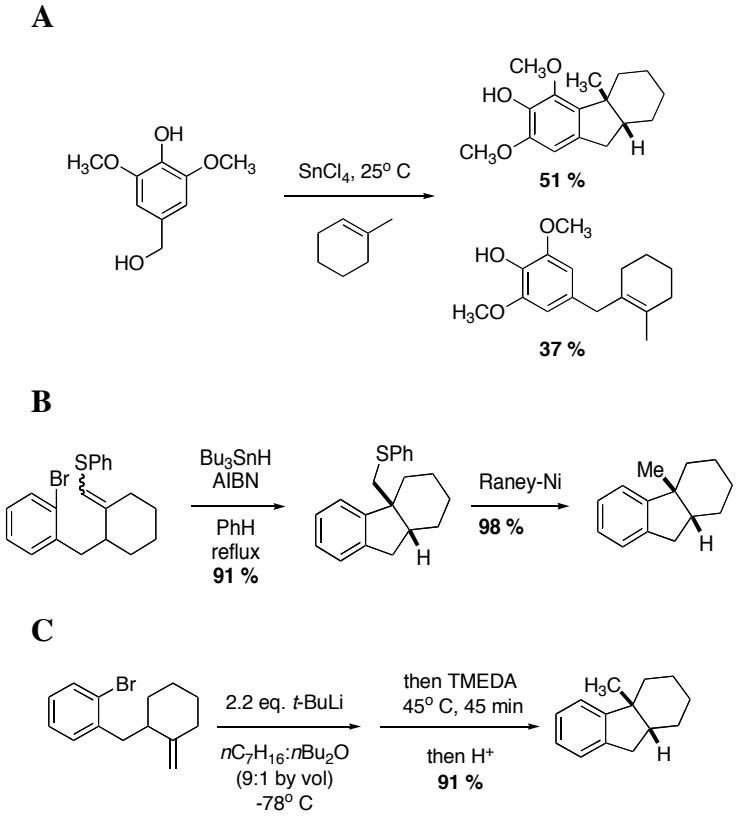
In light of this potential bioactivity, total synthesis would not only surpass isolation as a means to access quantities of material suitable for evaluation of biological activity, but also

facilitate structure-activity relationship studies, potentially leading to the development of novel pharmaceutical agents. Therefore a synthetic route to this class of compounds must be sufficiently flexible to enable easy modification within all three of the ring systems.

Previous Synthetic Investigations

The synthesis of the 6-5-6 fused ring (4*a*-methylhydrofluorene) core of this family has received previous synthetic attention including intermolecular [3+2] cycloaddition[6] (scheme 4.2 A), and cyclization of arylradical[7] and aryllithium[8] tethered to methylene cyclohexane (scheme 4.2 B and C respectively). None of these approaches was extended to the total synthesis of the targets discussed here, and most lack any large degree of functionalization, and the appropriate oxidation of the benzylic carbon in particular.

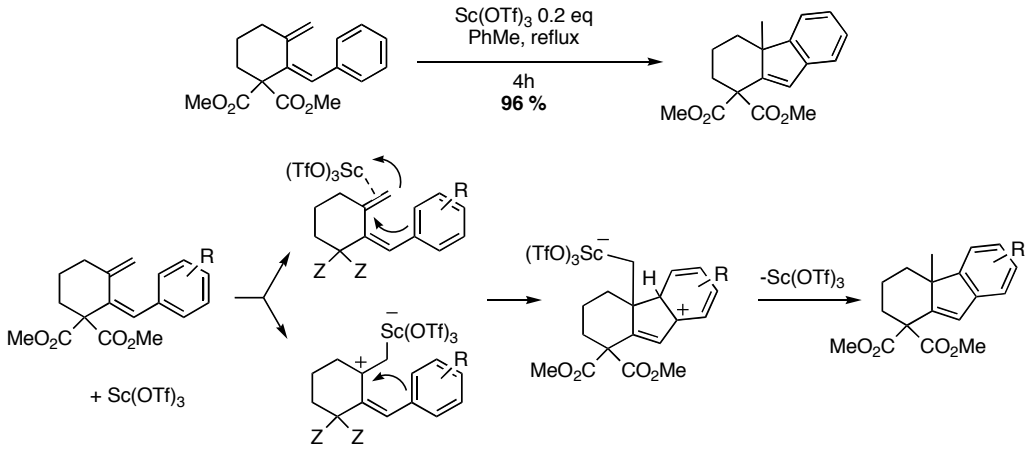
Scheme 4.2: Previous routes to the 4*a*-methylhydrofluorene ring system



Studies more specifically aimed at the family of compounds addressed here have also been reported. Balme's group has reported methodology for the synthesis of the 4*a*-

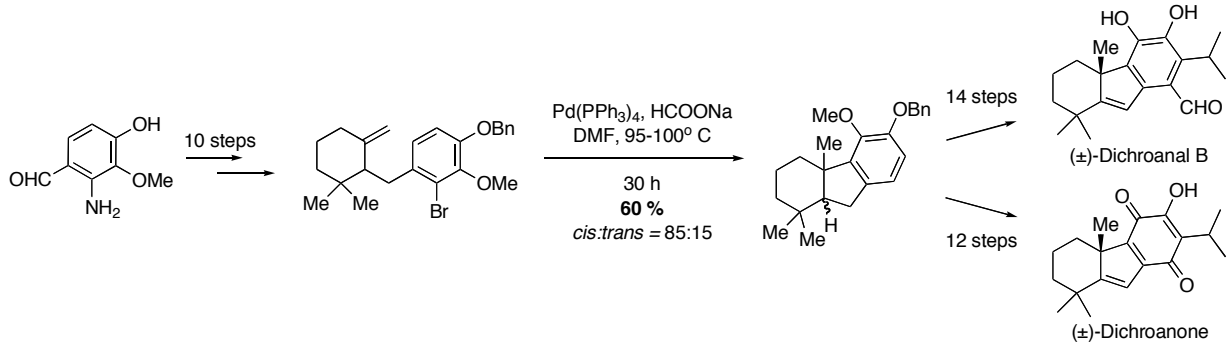
methylhexahydrofluorene core (scheme 4.3). The tricyclic skeleton was constructed via a $Sc(OTf)_3$-catalyzed intramolecular Friedel-Crafts alkylation of 1,3-bis-exocyclic dienes.[9]

Scheme 4.3: Intramolecular Friedel-Crafts alkyation to access the 6-5-6 ring system



The Banerjee's group reported the first total synthesis of the diterpenoids dichroanone and dichroanal B[10], utilizing a strategy based on palladium-catalyzed reductive cyclization[11] of a substituted methylene cyclohexane (scheme 4.4).

Scheme 4.4: Banerjee's approach to 6-5-6 core containing natural products

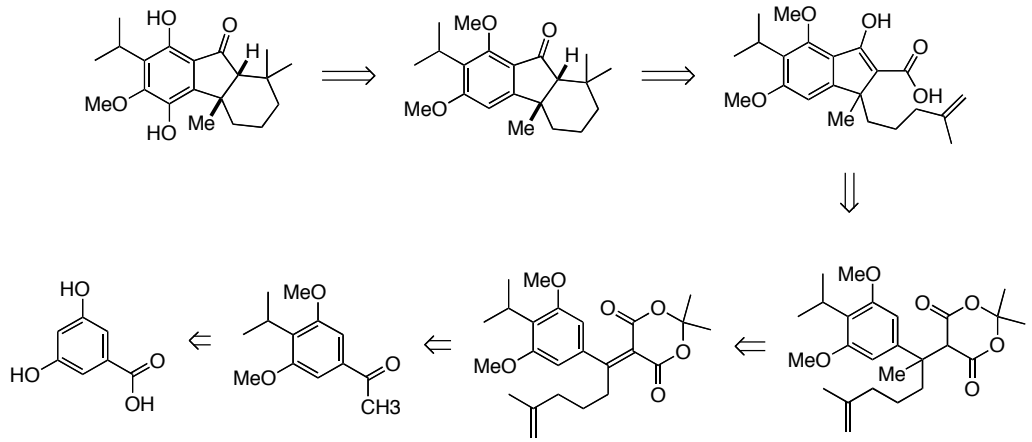


This synthesis suffers from a lengthy and linear route, and the key step of the synthesis enjoys only a modest yield of 60%. It is also not amenable to SAR studies, particularly due to the number of late-stage functional group manipulations.

Retrosynthetic analysis of Taiwaniaquinol B

Aside from the 6-5-6 ring system, Taiwaniaquinol B presents the additional synthetic challenge of a hexasubstituted aromatic core, and two all-carbon quaternary centers. As illustrated in scheme 4.5, it was envisaged that the tricyclic carbon skeleton could emanate from the intramolecular α-tert-alkylation of a 1-indanone, with an appropriately tethered alkene. This pivotal intermediate would arise from the intramolecular acylation of a symmetrically substituted aromatic with Meldrum's acid. The Friedel-Crafts acylation and the α-*tert* alkylation could be catalyzed in a single operation by the same catalyst.

Scheme 4.5: Retrosynthetic analysis of Taiwaniaquinol B



The necessary key step precursor would be obtained by conjugate Grignard addition to a Meldrum's arylidene, which assembled from an appropriately substituted ketone and Meldrum's acid by Knoevenagel condensation. This strategy is flexible and should be amenable to structure activity relationship studies of this family of natural products, beginning from the inexpensive 3,5-dihydroxybenzoic acid starting material.

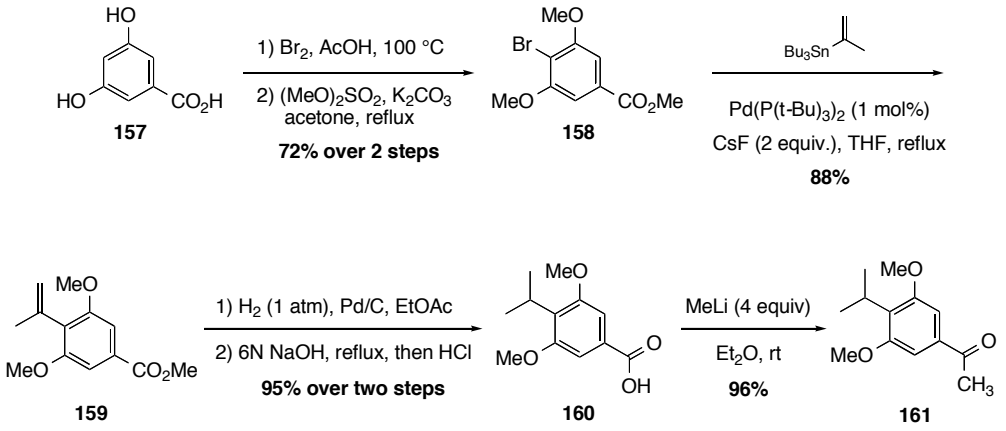
A key transformation that is required for the successful application of this proposed sequence is the α-*tert*-alkylation of the intermediate ketoacid or enol form of the 1-indanone formed in the course of the Friedel-Crafts acylation. The α–*tert*-butylation of ketones with *tert*-butyl chloride by the Friedel-Crafts alkylation of trimethylsilyl enol ethers promoted by Lewis acids was reported independently by the groups of Chan[12] and Reetz.[13] However, the proposed route in scheme 4.5 utilizes a tethered alkene as the electrophile. Intramolecular α-*tert*-alkylations of

β-ketoesters with alkenes to generate a β-quaternary carbon center have been mentioned in the literature utilizing stoichiometric amounts of stannic chloride.[14]

Substrate Preparation

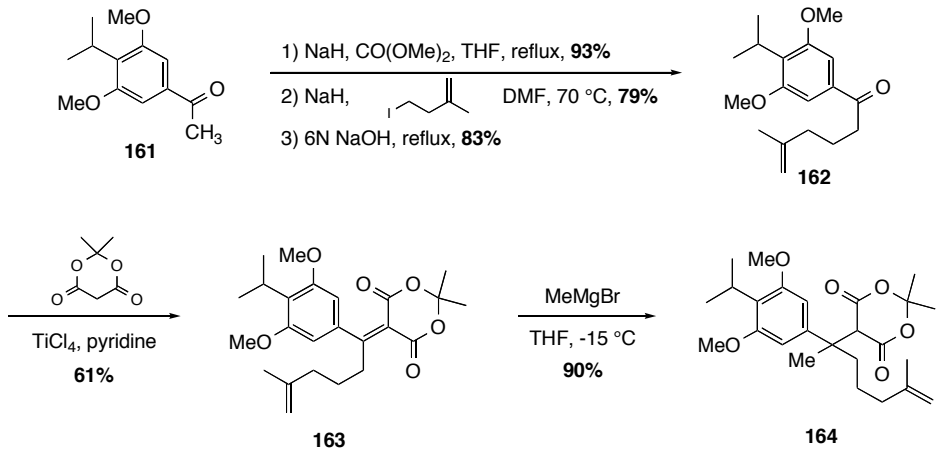
The assembly of taiwaniaquinol B started with the commercially available 3,5-dihydroxybenzoic acid **157**, which upon regioselective mono-bromination with bromine in boiling acetic acid[15], followed by permethylation, furnished ester **158** as a solid in 72% yield over two steps. The isopropyl moiety was then introduced in two steps via a Stille cross-coupling with 2-propene-2-tributyltin using Fu's protocol[16] in refluxing THF followed by catalytic hydrogenation. The Stille coupling step was very efficient (88% yield) and scalable, but it was found to be critical to ensure that all traces of residual vinyl stannane or stannous salts were removed for successful catalytic hydrogenation with palladium on charcoal. The bulk of the Bu_3SnF salts were removed by filtration through celite, but a further recrystallization from EtOAc/Hex was necessary. The mother liquor could also be flashed on silica gel. Hydrogenation followed by saponification of the ester **159** provided the acid **160** as a solid by filtration following workup with aqueous acid, in 95% over these two steps. After thorough drying under high vacuum, treatment with excess MeLi provided methyl ketone **161** in 96% yield. It is noteworthy that the synthesis of this acetophenone derivative (scheme 4.6) from 3,5-dihydrobenzoic acid can be accomplished on large scale without the requirement of any silica gel chromatography. Each intermediate is isolated by filtration of the resultant precipitate, or crystallization.

Scheme 4.6: Synthesis of acetophenone derivative 161



The installation of the tethered alkene was accomplished in three steps. The acetophenone **161** was converted to the corresponding β-ketoester and then alkylated with 3-methyl-1-iodobut-3-ene.[17] Attempts to alkylate **161** directly failed and the homoallylic iodide was destroyed by the competing E_2 reaction. Saponification and decarboxylation on workup produced the arylketone **162** (61% from **161**). Knoevenagel condensation[18] of ketone **162** with Meldrum's acid yielded the alkylidene in 61% yield, which was further reacted with methylmagnesium bromide to efficiently form substrate **164** containing the all-carbon benzylic quaternary center in 90% yield, and set the stage for the key tandem dicyclization reaction.

Scheme 4.7: Final preparation of key step substrate 164



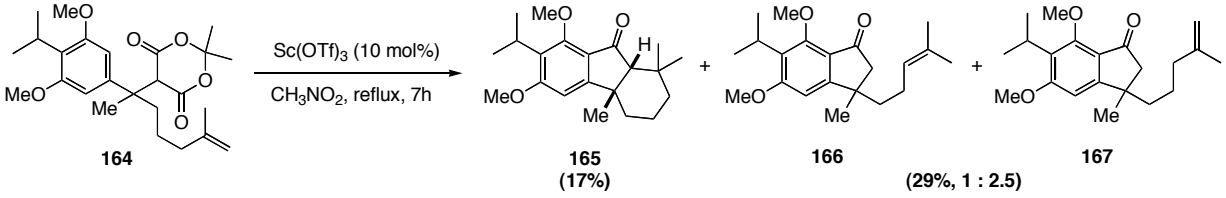
In the course of the substrate preparation described above, there are three main points at which diversity can be introduce should analogues be prepared: replacement of the isopropyl group on the aromatic ring by variation of the stannane partner in the Stille coupling, variation of the alkene tether in the β-ketoester alkylation step, and any number of Grignard reagents or a hydride could be added instead of a methyl group.

Domino Intramolecular Friedel-Crafts Acylation/α-*tert*-alkylation Reaction

The initial attempt to form the 6-5-6 tricycle in one step involved the treatment of **164** with 10 mol % $Sc(OTf)_3$ in refluxing nitromethane and, gratifyingly, the tricycle **165** was obtained in 17% yield accompanied with a mixture of indanones **167** and **168** in a 2.5:1 ratio and 29% yield. Similar results were obtained when the reaction was catalyzed by either TfOH or

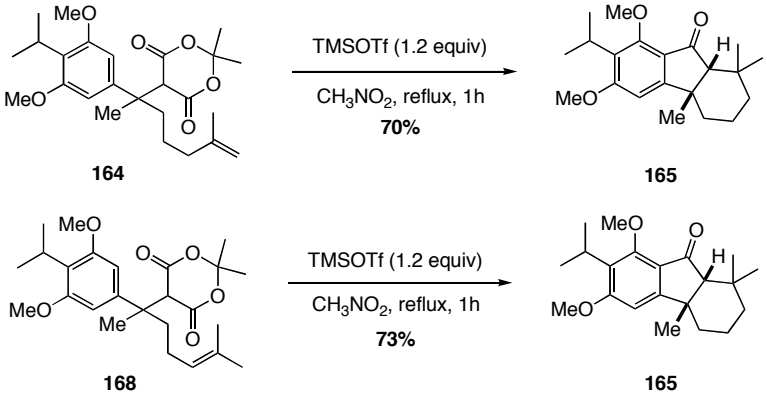
TMSOTf (scheme 4.8). From these results, it was rationalized that the Friedel-Crafts acylation reaction was indeed proceeding smoothly as found in the methodology development described in chapter 2. Unfortunately the α-*tert*-alkylation step was not occurring efficiently. While some of the desired product was formed, the presence of 1-indanones containing the tethered alkene suggested that a low concentration of the reactive reactive species (either a silylenol ether or β-keto ester and its enol form) was present under catalytic conditions. Longer reaction times did not ameliorate this problem. The scandium triflate catalyzed Friedel-Crafts alkylation studies of Balme also reported that poor π-nucleophiles resulted in incomplete reactions and double bond migrated side products.[9]

Scheme 4.8: Attempted catalytic domino reaction



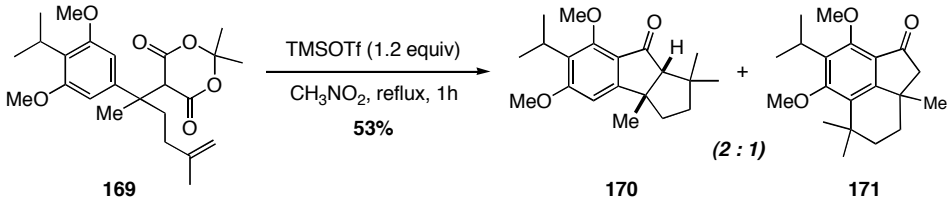
When TMSOTf was used as a stoichoimetric promoter, the tricycle **165** was isolated in 70% yield, and no trace of indanones **166** and **167** were observed by analysis of the crude reaction mixtures by ^{1}H NMR and GC-MS (scheme 4.9). Application of these conditions to substrate **168** shows that the placement of the unsaturation within the tether does not affect the success of the cyclization and the expected product **165** was obtained in 73% yield (scheme 4.9).

Scheme 4.9: Domino Intramolecular Friedel-Crafts Acylation/α-*tert*-alkylation Reaction



The methodology was applied to the synthesis of the analogous fused 6-5-5 tricyclic carbon skeleton simply by varying the length of the alkene tether in the substrate. When **169** was treated with TMSOTf, a 53% yield of two products was isolated in a 2:1 ratio (scheme 4.10).

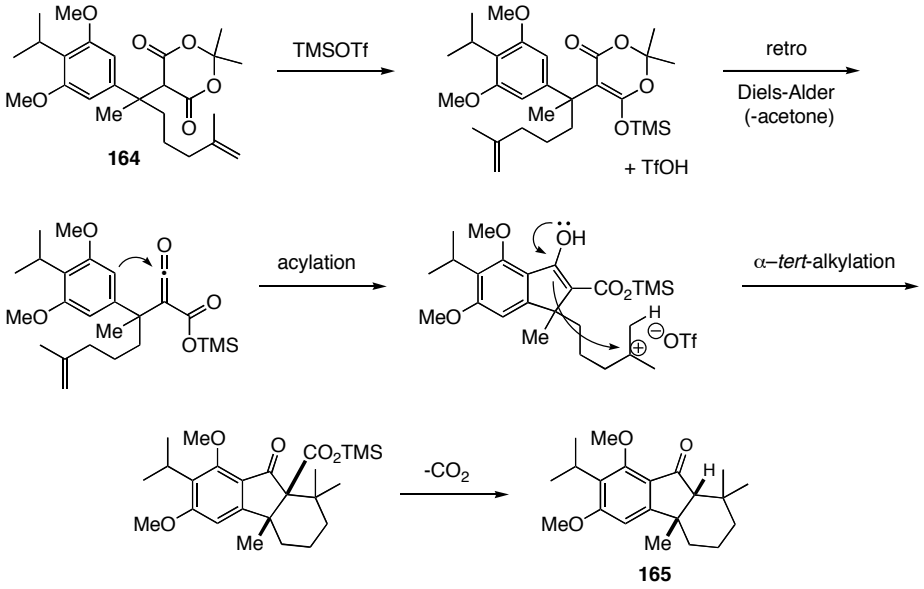
Scheme 4.10: Domino Friedel-Crafts Acylation/Alkylation



Tricycle **170** was the major product and tricycle **171** the minor component. These compounds could not be separated by silica gel chromatography, but fractional crystallization from methanol provided pure samples of each component for characterization. Product **171** arose from a competing Friedel-Crafts alkylation reaction at the highly congested 4-position of the 1-indanone intermediate, installing two contiguous all-carbon quaternary centre on the aromatic moiety.[19]

Application of the optimized reaction conditions to the 1-indanone by-products (**166** and **167**) from the catalytic attempt of the key step resulted in no tricyclic product being formed and decomposition of the substrates to unrecognizable material by ^{1}H NMR. This result strongly suggests that the silylenol ether of the 1-indanone is not an intermediate in the domino reaction, but that the enol form of a 1-indanone 2-carboxylic acid TMS ester is the transient reactive species in the domino reaction (scheme 4.11). This mechanism is also supported by the failure of the 1-indanone to cyclize in the catalytic reaction. In that case, the acyl ketene is formed that undergoes Friedel-Crafts acylation and then undergoes decarboxylation more rapidly to produce the 1-indanone byproducts **166** and **167**. In the presence of a stoichiometric quantity of TMSOTf, however, the TMS ketoester is perhaps more persistent and decarboxylates more slowly. This transient nucleophile is alkylated by the tethered, triflic acid activated alkene.

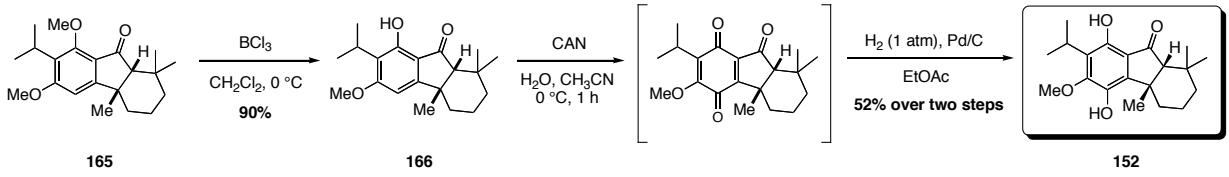
Scheme 4.11: Proposed mechanism of the domino reaction



Completion of Taiwaniaquinol B

The total synthesis of **152** was completed by selective deprotection of the methoxy group adjacent to the carbonyl group in 90% yield (scheme 4.12).[20] Installation of the phenoxy group was realized by treating **166** with cerium ammonium nitrate in water/acetonitrile to provide a high-energy quinone[21] intermediate that was reduced using H_2 to provide taiwaniaquinol B (**152**) in 52% for the two steps (scheme 4.12). The use of Fremy's salt in the oxidation of **166** was unsuccessful, even with stirring for 24 hours at room temperature.

Scheme 4.12: Completion of taiwaniaquinol B



The proton and carbon (JMOD) NMR spectra for the synthetic, racemic **152** are presented in figure 4.2. The carbon and proton peaks, as well as coupling constants, match the isolated product perfectly (table 4.1).[2]

Figure 4.2: ^{1}H and JMOD NMR spectra for synthetic 152

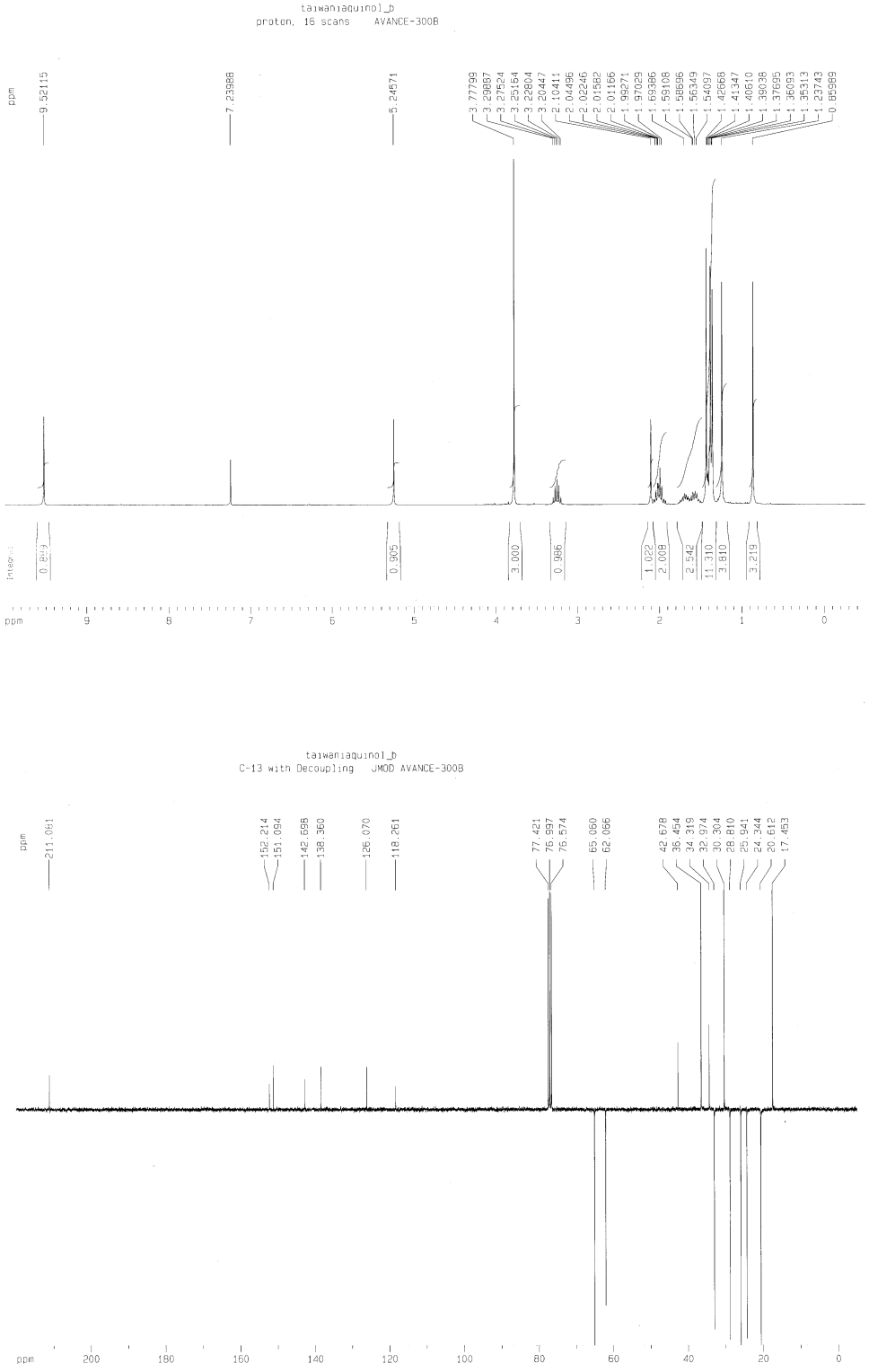
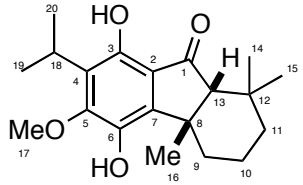


Table 4.1: Spectral data for taiwaniaquinol B (152)



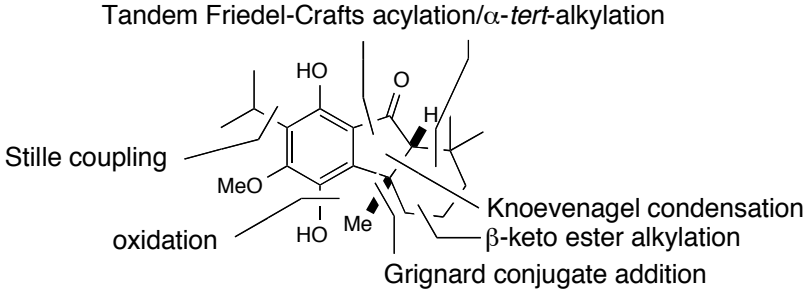
Carbon	^{13}C NMR (ppm)	^{1}H NMR (ppm)	
1	211.1	-	
2	118.3	-	
3	151.1	-	(Ar-OH) 9.52 (s)
4	126.1	-	
5	152.2	-	
6	138.4	-	(Ar-OH) 5.25 (s)
7	142.7	-	
8	42.7	-	
9	30.3	2.02 (m)	
10	17.5	1.69 (m)	
11	36.5	1.41 (m)	
12	34.3	-	
13	65.1	2.10 (s)	
14	24.4	0.86 (s)	
15	33.0	1.24 (s)	
16	28.8	1.42 (s)	
17	62.1	3.78 (s)	
18	25.9	3.25 (sept, J = 7 Hz)	
19	20.6	1.36 (d, J = 7 Hz)	
20	20.6	1.36 (d, J = 7 Hz)	

Summary

Taiwaniaquinol B has been synthesized in 15 steps from 3,5-dihydroxybenzoic acid in 6% overall yield. The crux of the approach presented here is a Lewis acid-mediated intramolecular Friedel–Crafts acylation/carbonyl α–*tert*-alkylation domino reaction that employs the unique reactivity of Meldrum's acid. Two carbon carbon bonds are formed in a one pot process in high yield. The ease of substrate assembly simplifies modification of ring substituents and control of ring size, making this a useful methology for the construction of polycylic carbon skeletons. Scheme 4.13 summarizes the synthesis and the disconnections made.

Although the synthesis is racemic as presented, an enantioselective one could be performed if a chiral conjugate addition methodology for disubstituted Meldrum's acid arylidenes existed.

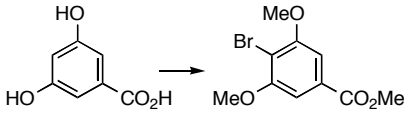
Scheme 4.13: Summary of disconnections employed in the synthesis of taiwaniaquinol B



Experimental Section

General: All reactions were carried out in flame-dried glassware under a dry nitrogen atmosphere. Nitromethane was distilled from CaH_2. TMSOTf was used as received from Aldrich. $Sc(OTf)_3$ was dried under high vacuum (0.5 mmHg) for 2 hours at 180 °C and stored in a dry-box. ^1H NMR spectra were referenced to residual ^1H shift in $CDCl_3$ (7.24 ppm) or C_6D_6 (7.15 ppm). $CDCl_3$ (77.0 ppm) or C_6D_6 (128.0 ppm) was used as the internal reference for ^{13}C NMR spectra. Reactions were monitored by thin-layer chromatography (TLC) on Silica Gel 60 F_{254} precoated plates from EMD/Merck. Developed plates were viewed by UV lamp (254 nm), and with *p*-anisaldehyde stain. Flash chromatography was performed using 230-400 mesh silica gel. Melting points are uncorrected.

Methyl 4-bromo-3,5-dimethoxybenzoate (158)

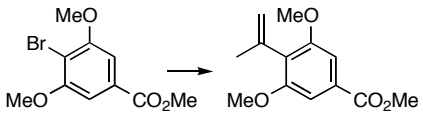


A solution of 3,5-dihydroxybenzoic acid **157** (25.5 g, 0.166 moles) in glacial acetic acid (90 mL) was heated to 110 °C in an oil bath with vigorous stirring. A solution of bromine (27.5 g, 0.173 moles) in acetic acid (10 mL) was added drop-wise over 1 hour. The mixture was stirred for an additional 1.5 hours, then cooled to ~10 °C. The resulting pink solid was filtered and the filter cake was washed with hexanes, and then dried under high vacuum at room temperature (0.3 torr). The crude yield of 4-bromo-3,5-dihydroxybenzoic acid[15] was 38.8 g (quant.) and was used in the next step without purification.

Acetone (500 mL) was combined with potassium carbonate (75.0 g, 0.54 moles), 4-bromo-3,5-dihydroxybenzoic acid (38.8 g, 0.166 moles) and dimethyl sulfate (52.0 mL, 0.55 moles) and the resulting solution brought to a gentle reflux under nitrogen for 4 hours. The reaction was cooled then concentrated by rotary evaporator. The crude material was dissolved in water and Et_2O, then the layers partitioned. The aqueous phase was extracted with Et_2O (x4) and the combined organic fractions dried over $MgSO_4$, filtered and then concentrated to provide a crude solid. Recrystallization from methanol provided 32.8 g (72 % over 2 steps) of **158** as fine white needles. M.p. 121-122 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 7.18 (2H, s), 3.90 (6H, s), 3.88 (3H,

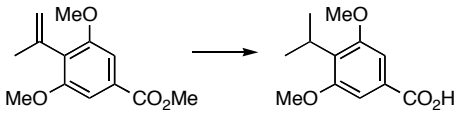
s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.3, 156.9, 130.1, 106.5, 105.4, 56.5, 52.3; EI *m/z (rel. int.)* 276 (100), 274 (100), 245 (62), 243 (62).

Methyl 4-isoprenyl-3,5-dimethoxybenzoate



To a solution of bromo ester **158** (4.0 g, 14.3 mmol) in THF (100 mL) was added 2-propene-2-tributyltin (5.0 g, 15 mmol), cesium fluoride (4.4 g, 28.7 mmol) and $Pd(tBu_3P)_2$ (73 mg, 0.143 mmol). The solution was brought to reflux and maintained at this temperature for 12 hours. The cooled reaction mixture was filtered through a pad of silica gel to remove a fine tan powder, and the filter cake was washed thoroughly with diethyl ether. The resulting filtrate was concentrated then crystallized from EtOAc/Hex to provide 2.56 g of methyl 4-isoprenyl-3,5-dimethoxybenzoate as fine white needles. Flash chromatography (5:1 Hex:EtOAc) of the mother liquor provided an additional 399 mg for a combined yield of 88%. M.p. 93-94 ºC; R.f. 0.45 (4:1 Hex:EtOAc); ^{1}H NMR (300 MHz, C_6D_6) δ 7.43 (2H, s), 5.39 (1H, s), 5.08 (1H, s), 3.58 (3H, s), 3.32 (6H, s), 2.12 (3H, s); ^{13}C NMR (75 MHz, C_6D_6) δ 166.7, 157.7, 138.3, 130.5, 126.8, 116.5, 105.7, 55.4, 51.7, 23.4; IR (NaCl) C=O 1719.5 cm^{-1}; EI *m/z (rel. int.)* 236 (86), 221 (100), 189 (69) 162 (64); HRMS (EI) calcd for $C_{13}H_{16}O_4$: 236.1049; found 236.1052.

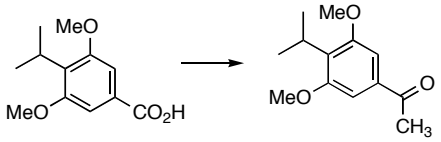
4-Isopropyl-3,5-dimethoxybenzoic acid (160)



To a degassed solution of methyl 4-isoprenyl-3,5-dimethoxybenzoate (2.2 g, 9.32 mmol) in EtOAc (50 mL) was added 5% Pd/C (0.2 g, 10% w/w) and H_2 (1 atm). The suspension was stirred vigorously for 4 hours at room temperature. The reaction was filtered though a pad of celite and concentrated to provide a white solid. This was suspended in 6M NaOH (50 mL) and refluxed for 30 minutes then allowed to cool. The reaction mixture was poured into 6M HCl (100 mL), and then this suspension was cooled on ice. The resulting white solid was filtered

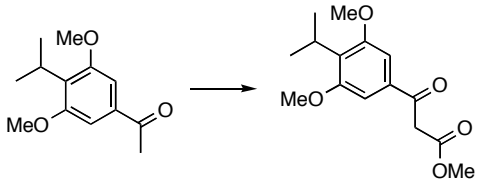
and washed with ice-cold water. The fine white powder was dried under vacuum (0.3 torr) to provide 1.81 g of **160** (87 % over 2 steps). M.p. 182-184 ºC; R.f. 0.1 (streak) (4:1 Hex:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.27 (2H, s), 3.85 (6H, s), 3.63 (1H, septet, *J* = 7.1 Hz), 1.27 (6H, d, *J* = 7.1 Hz); ^{13}C (75 MHz, $CDCl_2$) 172.6, 158.4, 131.0, 127.4, 106.1, 55.8, 24.2, 20.2; IR (NaCl) C=O 1687 cm^{-1}; EI *m/z (rel. int.)* 224 (77), 210 (36), 209 (100), 105 (23); HRMS (EI) calcd for $C_{12}H_{16}O_4$: 224.1049; found 224.1056.

4-Isopropyl-3,5-dimethoxyacetophenone (161)



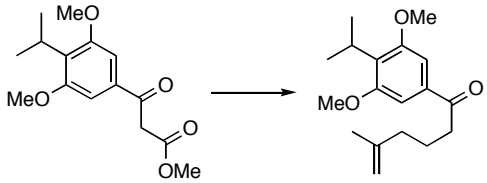
A solution of acid **160** (5.9 g, 26.3 mmol) was dissolved in dry diethyl ether (200 mL) and cooled to 0 °C. Methyl lithium (1.6 M in ether, 66 mL, 106 mmol) was added drop-wise with vigorous stirring, then the reaction was allowed to warm to room temperature and stir for an additional 3.5 hours. The reaction formed a white suspension that eventually redissolved. The reaction was quenched by pouring into ice cold 10% HCl and then extracted to Et_2O (3x). The ethereal solution was washed with brine, then dried over $MgSO_4$, filtered, and concentrated by rotary evaporation to provide a white solid. Recrystallization from EtOAc/Hex provided white crystals, and the mother liquor was additionally purified by flash chromatography (4:1 Hex:EtOAc) to provided a total yield of 5.6 g (96%). M.p. 103-104 °C; R.f. 0.35 (4:1 Hex:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.10 (2H, s), 3.83 (6H, s), 3.61 (1H, septet, *J* = 7.1 Hz), 2.55 (3H, s), 1.25 (6H, d, *J* = 7.1 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 197.4, 158.4, 135.6, 130.3, 104.3, 55.7, 26.4, 24.3, 20.2; IR (NaCl) C=O 1672 cm^{-1}; EI *m/z (rel. int.)* 222 (67), 207 (100), 208 (29), 79 (16), 137 (14), 91 (11); HRMS (EI) calcd for $C_{13}H_{18}O_3$: 222.1256; found 222.1250.

Methyl 3-(4-isopropyl-3,5-dimethoxyphenyl)-3-oxopropanoate



Acetophenone **161** (2.9 g, 13 mmol) was combined with NaH (1.3 g, 60% dispersion in mineral oil, 40 mmol) in dry THF (20 mL) and brought to reflux with stirring under nitrogen atmosphere. Dimethyl carbonate (6.6 mL, 78 mmol) was added drop-wise. After an additional 1.5 hours of reflux the reaction was allowed to cool, then cooled on ice before quenching with 5% HCl. The mixture was extracted with EtOAc (3x). The combined organic layers were washed with brine, then dried over $MgSO_4$, filtered, then concentrated to a yellow oil. Flash chromatography (4:1 Hex:EtOAc) provided 3.4 g (93%) of a yellow oil. R.f. 0.32 (4:1 Hex:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 15% enol form: 12.49 (1H, s), 6.91 (2H, s), 5.60 (1H, s), 3.81 (6H, s), 3.77 (3H, s), 3.59 (1H, septet, *J* = 7.1 Hz), 1.24 (6H, d, *J* = 7.1 Hz); keto form: 7.09 (2H, s), 3.95 (2H, s), 3.82 (6H, s), 3.72 (3H, s), 3.59 (1H, septet, *J* = 7.1 Hz), 1.24 (6H, d, *J* = 7.1 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 191.6, 173.5 (enol), 171.7 (enol), 168.0, 158.5, 158.4 (enol), 134.3, 131.1, 128.2 (enol), 104.2, 102.2 (enol), 86.5 (enol), 55.7, 52.4, 51.3 (enol), 45.8, 24.4, 24.2 (enol), 20.3 (enol), 20.1; IR (NaCl) C=O 1746, 1684 cm^{-1}; EI *m/z (rel. int.)* 280 (76), 265 (100), 233 (34), 207 (24), 191 (15); HRMS (EI) calcd for $C_{15}H_{20}O_5$: 280.1311; found 280.1304.

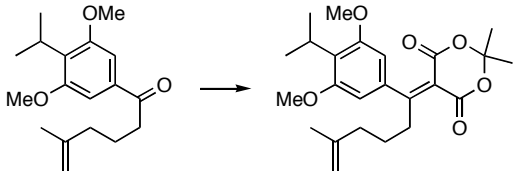
1-(4-Isopropyl-3,5-dimethoxyphenyl)-5-methyl-5-hexen-1-one (162)



To a stirring suspension of NaH (580 mg, 60% dispersion, 14. 6 mmol) in dry DMF (5 mL) at 0 °C was added drop-wise a solution of methyl 3-(4-isopropyl-3,5-dimethoxyphenyl)-3-oxopropanoate (3.4 g, 12.1 mmol) in DMF (40 mL) under nitrogen atmosphere. The ice bath was removed when addition was complete and the reaction stirred at room temperature for 3

hours. 4-Iodo-2-methylbutene[17] (2.9 g, 14.8 mmol) was then added and the reaction warmed to 70 °C and stirred at this temperature for 13 hours. The reaction was cooled to room temperature and then poured into an ice cold saturated NH_4Cl solution (400 mL). This mixture was extracted to EtOAc (x3), and the combined organic layers washed with brine (x3), dried over $MgSO_4$, filtered, and then concentrated by rotary evaporator. The resulting oil was purified by flash chromatography (10:1 Hex:EtOAc) to provide 3.36 g of yellow oil (79%). R.f. 0.50 (4:1 Hex:EtOAc). This oil was suspended in 6M NaOH (25 mL) and refluxed for 4 hours, then cooled, and poured into 10% HCl (150 mL). This mixture was extracted with EtOAc (x3), and the combined organic layers dried over $MgSO_4$, filtered and concentrated. Flash chromatography (10:1 Hex:EtOAc) provided 2.33 g (83%) of **162** (66% for 2 steps) as a pale yellow oil that solidified on standing. M.p. 38-39 °C; R.f. 0.63 (4:1 Hex:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.11 (2H, s), 4.74 (1H, br s), 4.70 (1H, br s), 3.84 (6H, s), 3.61 (1H, septet, *J* = 7.1 Hz), 2.91 (2H, t, *J* = 7.3 Hz), 2.10 (2H, br t, *J* = 7.3 Hz), 1.87 (2H), br quint, *J* = 7.3 Hz), 1.73 (3H, s), 1.26 (6H, d, *J* = 7.1 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 199.4, 158.3, 144.9, 135.5, 129.9, 110.4, 104.0, 55.6, 37.4, 37.0, 24.2, 22.1, 22.0, 20.1; IR (NaCl) C=O 1683 cm^{-1}; EI *m/z (rel. int.)* 290 (70), 275 (25), 247 (22), 222 (91), 208 (45), 207 (100); HRMS (EI) calcd for $C_{18}H_{26}O_3$: 290.1882; found 290.1876.

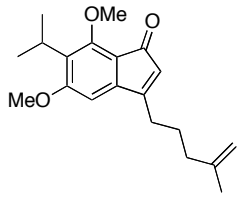
5-[1-(4-isopropyl-3,5-dimethoxyphenyl)-5-methyl-5-hexenylidene]-2,2-dimethyl-1,3-dioxane-4,6-dione (163)



A solution of $TiCl_4$ (0.76 mL, 6.93 mmol) in CH_2Cl_2 (2 mL) was added slowly drop-wise to THF (2 mL) at 0 °C under a nitrogen atmosphere. After stirring for 5 minutes, a solution of ketone **162** (1.0 g, 3.45 mmol) and Meldrum's acid (0.55 g, 3.8 mmol) in THF (10 mL) was added drop-wise. After addition was complete the mixture was stirred an additional 15 minutes, then pyridine (1.4 mL, 17.3 mmol) was added. The ice bath was removed and the reaction was allowed to warm to room temperature and stir 20 hours, after which time it was quenched by the addition of H_2O and stirred until the reaction became clear. The mixture was extracted with

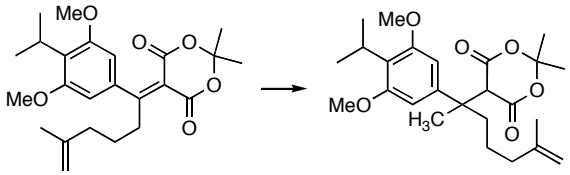
diethyl ether (x5) and the combined organic layers washed with saturated NH_4Cl (x2), H_2O (x1), then saturated $NaHCO_3$ (x2), and then dried over $MgSO_4$, filtered and concentrated. The crude solid was recrystallized from methanol and the mother liquor flashed on silica gel (4:1 Hex:EtOAc) to provide a combined yield of 868 mg (61%) as pale yellow crystals. M.p. 129-130 °C; R.f. 0.29 (4:1 Hex:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.30 (1H, s), 4.68 (1H, br s), 4.60 (1H, br s), 3.76 (6H, s), 3.56 (1H, septet, *J* = 7.1 Hz), 3.08-3.03 (2H, m), 2.04 (2H, br t, *J* = 7.3 Hz), 1.81 (6H, s), 1.62 (2H, s), 1.62-1.55 (2H, m), 1.25 (6H, d, *J* = 7.1 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.8, 161.1, 160.4, 158.2, 144.6, 138.2, 125.9, 116.9, 110.8, 103.6, 103.1, 55.7, 37.7, 37.4, 27.2, 26.2, 24.1, 22.0, 20.5; IR (NaCl) C=O 1738 cm^{-1}; EI *m/z (rel. int.)* 416 (5), 358 (100), 343 (29), 299 (26), 271 (46), 243 (32), 231 (28); HRMS (EI) calcd for $C_{24}H_{32}O_6$: 416.2199; found 416.2209.

A small amount of indenone **6-Isopropyl-5,7-dimethoxy-3-(5-methyl-5-hexenyl)-1*H*-1-indenone** (61 mg, 5% yield) was isolated as the only other major UV active component during flash chromatography.



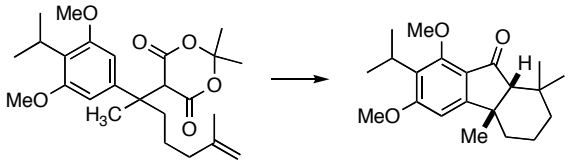
Yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.99 (1H, s), 5.71 (1H, m), 4.79 (1H, s), 4.76 (1H, s), 3.90 (6H, s), 3.60 (1H, septet, *J* = 7.0 Hz), 3.20 (2H, d, *J* = 1.2 Hz), 2.66 (2H, m), 2.26 (2H, app t, *J* = 7.5 Hz), 1.76 (3H, s), 1.28 (6H, d, *J* = 7.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 199.2, 164.8, 157.1, 150.5, 144.8, 131.0, 130.1, 127.1, 124.3, 110.6, 102.8, 62.3, 55.6, 44.6, 37.3. 27.2, 24.5, 22.5, 20.9; IR (NaCl) C=O 1703 cm^{-1}; EI *m/z (rel. int.)* 314 (85), 294 (45), 259 (93), 246 (100), 231 (41), 217 (48); HRMS (EI) calcd for $C_{20}H_{26}O_3$: 314.1882; found 314.1878.

(±)-5-[1-(4-isopropyl-3,5-dimethoxyphenyl)-1,5-dimethyl-5-hexenyl]-2,2-dimethyl-1,3-dioxane-4,6-dione (164)



A solution of Meldrum's benzylidene **163** (590 mg, 1.42 mmol) in dry THF (30 mL) under nitrogen atmosphere was cooled to –20 °C using a dry ice/acetone bath. Methylmagnesium bromide (0.57 mL, 3M in diethyl ether, 1.71 mmol) was added drop-wise over 5 minutes, and the reaction was allowed to stir at this temperature for an additional 15 minutes. The reaction was quenched with 10% HCl and then allowed to warm to room temperature before being diluted with 5% HCl and extracted with ether (x3). The combined organic fractions were washed with brine and dried over $MgSO_4$, filtered and concentrated by rotary evaporator. The crude oil was purified by flash chromatography (8:1 hexanes:EtOAc) to provide 552 mg (90%) of **164** as a pale yellow oil. R.f. (4:1 Hex:EtOAc) 0.35; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.41 (2H, s), 4.69 (1H, br s), 4.65 (1H, br s), 3.74 (6H, s), 3.50 (1H, septet, J = 7.1 Hz), 3.41 (1H, s), 2.16-1.98 (4H, m), 1.65 (6H, s), 1.53 (3H, s), 1.52-1.42 (1H, m), 1.35-1.18 (1H, m), 1.19 (6H, d, J = 7.1 Hz), 0.97 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.6, 164.2, 158.2, 145.2, 139.9, 123.6, 110.2, 105.4, 103.6, 57.1, 55.6, 46.6, 39.2, 37.9, 29.9, 26.5, 23.7, 23.4, 22.2, 22.2, 20.4; IR (NaCl) C=O 1747 cm^{-1}; EI *m/z (rel. int.)* 432 (51), 315 (56), 247 (100), 205 (80); HRMS (EI) calcd for $C_{25}H_{36}O_6$: 432.2512; found 432.2508.

Tandem Friedel-Crafts Acylation/α-*tert* Alkylation – 6-5-6 Tricycle Synthesis: (±)-7-Isopropyl-6,8-dimethoxy-1,1,4a-trimethyl-2,3,4,4a,9,9a-hexahydro-1*H*-9-fluorenone (165)

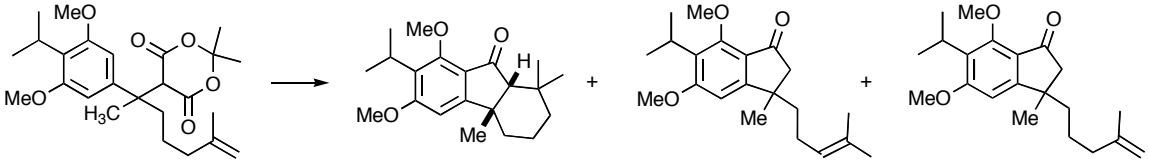


A Schlenk tube containing a stirred solution of dry CH_3NO_2 (2 mL) containing TMSOTf (63 μL, 0.35 mmol) under nitrogen atmosphere was heated to 105 °C in an oil bath. A solution of

Meldrum's derivative **164** (137 mg, 0.32 mmol) in CH_3NO_2 (2 mL) was added drop-wise over 5 minutes, after which time the Schlenk tube was sealed and stirred for an additional 1 hour. The reaction was cooled using an ice bath then diluted with a saturated NH_4Cl solution then concentrated using a rotary evaporator. The resulting residue was dissolved in EtOAc and H_2O, and the organic layer removed. The aqueous portion was extracted with EtOAc (x3) and the combined organic fractions washed with brine, then dried over $MgSO_4$. After filtration and concentration, the crude oil was purified by flash chromatography (12:1 Hex:EtOAc) to provide 73 mg (70%) of tricycle **165** as an off-white solid. M.p. 132-133.5 °C (CH_2Cl_2). R.f. 0.55 (4:1 Hex:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.55 (1H, s), 3.89 (3H, s), 3.87 (3H, s), 3.55 (1H, septet, J = 7.1 Hz), 2.09 (1H, s), 2.09-2.0 (1H, m), 1.20-1.63 (5H, m), 1.26 (6H, d, J = 7.1 Hz), 1.23 (3H, s), 1.21 (3H, s), 0.68 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 204.3, 164.7, 163.8, 156.9, 127.9, 121.5, 99.6, 65.6, 61.9, 55.6, 41.2, 38.4, 34.4, 33.8, 33.2, 32.4, 24.5, 24.3, 21.0, 18.3; IR (NaCl) C=O 1685 cm^{-1}; EI *m/z (rel. int.)* 330 (45), 315 (100), 248 (80); HRMS (EI) calcd for $C_{21}H_{30}O_3$: 330.2195; found 330.2199.

Attempted Catalytic Tandem Friedel-Crafts Acylation/α-*tert* Alkylation:

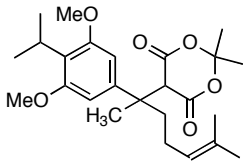
6-Isopropyl-5,7-Dimethoxy-3-Methyl-3-(4-Methyl-3-pentenyl)-1-indanone (166)
6-Isopropyl-5,7-Dimethoxy-3-Methyl-3-(4-Methyl-4-pentenyl)-1-indanone (167)



A Schlenk tube containing a stirred solution of dry CH_3NO_2 (1 mL) containing $Sc(OTf)_3$ (17 mg, 0.035 mmol) under nitrogen atmosphere was heated to 105 °C in an oil bath. A solution of Meldrum's derivative **164** (148 mg, 0.34 mmol) in CH_3NO_2 (7 mL) was added drop-wise at a rate of 0.5 mL/hr, after which time the Schlenk tube was sealed and stirred for an additional 7 hours. The reaction was cooled then concentrated and immediately purified by flash chromatography (12:1 hexanes:EtOAc). A small amount of the desired tricycle **165** was obtained (19 mg, 17%), as well as an inseparable mixture of two indanones **166** and **167** (in 1:2.5 ratio) that failed to undergo α-*tert* alklation (33 mg, 29%): Yellow oil; R.f. 0.42 (4:1

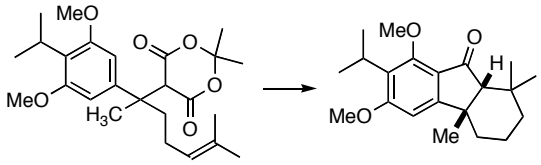
Hex:EtOAc); Internal alkene **166**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.55 (1H, s), 5.0 (1H, m), 3.89 (3H, s), 3.86 (3H, s), 3.55 (1H, septet, *J* = 7.1 Hz), 2.50 (2H, AB quartet, *J* = 18.4 Hz), 2.0-1.8 (1H, m), 1.7-1.4 (3H, m), 1.61 (3H, s), 1.48 (3H, s), 1.34 (3H, s), 1.25 (6H, d, *J* = 7.1 Hz); Terminal alkene **167**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.53 (1H, s), 4.65 (1H, br s), 4.59 (1H, br s), 3.89 (3H, s), 3.86 (3H, s), 3.55 (1H, septet, *J* = 7.1 Hz), 2.48 (2H, AB quartet, *J* = 18.4 Hz), 2.0-1.8 (1H, m), 1.7-1.2 (5H, m), 1.61 (3H, s), 1.34 (3H, s), 1.25 (6H, d, *J* = 7.1 Hz); ^{13}C NMR (for mixture) (75 MHz, $CDCl_3$) δ 201.6, 165.1, 164.7, 156.7, 131.89, 128.2, 123.8, 121.6, 110.2, 100.7, 62.1, 55.6, 50.7, 50.6, 42.0, 41.5, 41.2, 37.9, 28.4, 25.6, 24.1, 23.7, 22.6, 22.2, 21.0, 17.5; Internal db **166** EI *m/z (rel. int.)* 330 (79), 315 (88), 248 (100), 205 (75); External db **167** EI *m/z (rel. int.)* 330 (45), 315 (88), 248 (53), 247 (44); HRMS (EI) calcd for $C_{21}H_{30}O_3$: 330.2195; found 330.2199.

(±)-5-[1-(4-Isopropyl-3,5-dimethoxyphenyl)-1,5-dimethyl-4-hexenyl]-2,2-dimethyl-1,3-dioxane-4,6-dione (168)



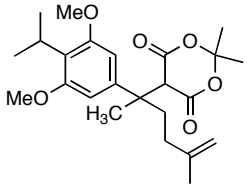
Meldrum's acid derivative **168** was prepared in an analogous manner to **164** beginning with methyl 3-(4-isopropyl-3,5-dimethoxyphenyl)-3-oxopropanoate and 3,3-dimethylallyl bromide. M.p. 53-55 °C (EtOAc/Hex); R.f. 0.35 (4:1 Hex:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.42 (2H, s), 5.12 (1H, m), 3.75 (6H, s), 3.50 (1H, septet, *J* = 7.1 Hz), 3.42 (1H, s), 2.25-1.75 (4H, m), 1.66 (3H, s), 1.66 (3H, s), 1.52 (6H, s), 1.17 (6H, d, *J* = 7.1 Hz), 0.97 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.7, 164.3, 158.4, 139.8, 131.8, 123.8, 123.7, 105.5, 103.7, 57.3, 55.8, 46.7, 39.8, 30.1, 26.6, 25.7, 23.8, 23.4, 23.2, 20.5, 17.5; EI *m/z (rel. int.)* 432 (10), 315 (29), 264 (37), 247 (33), 248 (100), 205 (71); HRMS (EI) calcd for $C_{25}H_{36}O_6$: 432.2512; found 432.2503.

Tandem Friedel-Crafts Acylation/α-*tert* Alkylation – 6-5-6 Tricycle (165) From Internal Alkene:



A Schlenk tube containing a stirred solution of dry CH_3NO_2 (2 mL) containing TMSOTf (82 μL, 0.46 mmol) under nitrogen atmosphere was heated to 105 °C in an oil bath. A solution of Meldrum's derivative **168** (178 mg, 0.41 mmol) in CH_3NO_2 (3 mL) was added drop-wise over 5 minutes, after which time the Schlenk tube was sealed and stirred for an additional 1 hour. The reaction was cooled using an ice bath then diluted with a saturated NH_4Cl solution then concentrated using a rotary evaporator. The resulting residue was dissolved in EtOAc and H_2O, and the organic layer removed. The aqueous portion was extracted with EtOAc (x3) and the combined organic fractions washed with brine, then dried over $MgSO_4$. After filtration and concentration, the crude oil was purified by flash chromatography (9:1 Hex:EtOAc) to provide 99 mg (73%) of **165**.

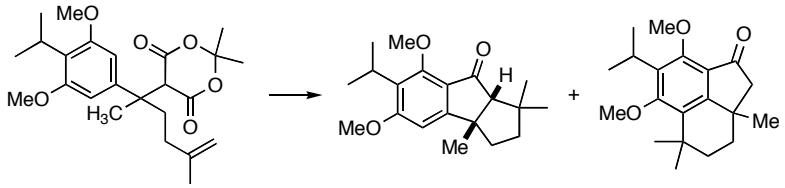
(±)-5-[1-(4-Isopropyl-3,5-dimethoxyphenyl)-1,4-dimethyl-4-pentenyl]-2,2-dimethyl-1,3-dioxane-4,6-dione (169)



Meldrum's acid derivative **169** was prepared in an analogous manner to **164** beginning with methyl 3-(4-isopropyl-3,5-dimethoxyphenyl)-3-oxopropanoate and 3-bromo-2-methyl-propene. Clear, colourless oil; R.f. 0.29 (4:1 Hex:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.42 (2H, s), 4.70 (2H, br s), 3.75 (6H, s), 3.49 (1H, septet, J = 7.1 Hz), 3.41 (1H, s), 2.50-2.30 (1H, m), 2.15-1.95 (1H, m), 1.90-1.73 (1H, m), 1.73 (3H, s), 1.66 (3H, s), 1.53 (3H, s), 1.20 (6H, d, J = 7.1 Hz), 0.98 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.6, 164.2, 158.4, 145.5, 139.6, 123.8, 110.2, 105.5, 103.8, 57.5, 55.8, 46.7, 38.1, 32.6, 30.0, 26.6, 23.8, 23.4, 22.6, 20.5; IR (NaCl) C=O 1748 cm^{-1} EI *m/z (rel. int.)* 418 (44), 301 (100), 264 (46), 259 (58), 247 (61), 205 (87); HRMS (EI) calcd for $C_{24}H_{34}O_6$: 418.2355; found 418.2364.

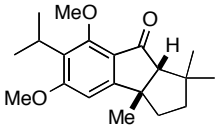
Tandem Friedel-Crafts Acylation/α-*tert* Alkylation – 6-5-5 Tricycle (170)

And Tandem Friedel-Crafts Acylation/Friedel-Crafts Alkylation – 6-6-5 Tricycle (171)



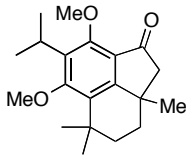
A Schlenk tube containing a stirred solution of dry CH_3NO_2 (1 mL) containing TMSOTf (55 μL, 0.304 mmol) under nitrogen atmosphere was heated to 105 °C in an oil bath. A solution of Meldrum's derivative **169** (116 mg, 0.28 mmol) in CH_3NO_2 (2 mL) was added drop-wise over 5 minutes, after which time the Schlenk tube was sealed and stirred for an additional 30 minutes. The reaction was cooled using an ice bath then diluted with a saturated NH_4Cl solution then concentrated using a rotary evaporator. The resulting residue was dissolved in EtOAc and H_2O, and the organic layer removed. The aqueous portion was extracted with EtOAc (x3) and the combined organic fractions washed with brine, then dried over $MgSO_4$. After filtration and concentration, the crude oil was purified by flash chromatography (5:1 Hex:EtOAc) to provide 47 mg (53%) of **170**:**171** in a 2:1 ratio. These could be separated by crystallization from MeOH:

6-Isopropyl-5,7-dimethoxy-1,1,3a-trimethyl-1,2,3,3a,8,8a-hexahydrocyclopenta[*a*]inden-8-one (170)



Crystallization from methanol provided pure Friedel-Crafts acylation/α-*tert* alkylation product **170** as clear, colourless crystals. M.p. 155-157° C; R.f. 0.51 (4:1 Hex:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.54 (1H, s), 3.88 (3H, s), 3.87 (3H, s), 3.55 (1H, septet, J = 7.1 Hz), 2.16 (1H, s), 1.95-1.89 (2H, m), 1.16-1.55 (2H, m), 1.42 (3H, s), 1.27 (6H, d, J = 7.1 Hz), 1.17 (3H, s), 0.99 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 203.3, 165.2, 164.7, 128.0, 122.2, 100.7, 70.2, 62.0, 55.6, 51.3, 43.2, 41.4, 38.3, 30.6, 28.9, 25.6, 24.3, 21.0; IR (NaCl) C=O 1687 cm^{-1}; EI *m/z (rel. int.)* 316 (30), 301 (100), 248 (28); HRMS (EI) calcd for $C_{20}H_{28}O_3$: 316.2038; found 316.2031.

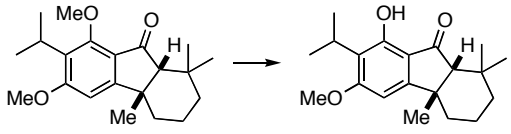
7-Isopropyl-6,8-dimethoxy-2a,5,5-trimethyl-1,2,2a,3,4,5-hexahydro-1-acenaphthylenone (171)



Purification of the mother liquor from the **170** crystallization by flash chromatography (9:1 Hex:EtOAc) provided the pure Friedel-Crafts acylation/alkylation product **171** as a clear, colourless oil. R.f. 0.51 (4:1 Hex:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.05 (3H, s), 3.76 (3H, s), 3.26 (1H, septet, *J* = 7.1 Hz), 2.49 (2H, AB quartet, *J* = 16.5 Hz), 2.07 (1H, dt, *J* = 13.5, 4.0 Hz), 1.78-1.49 (3H, m), 1.49 (3H, s), 1.36 (3H, d, *J* = 7.1 Hz), 1.29 (3H, d, *J* = 7.1 Hz), 1.26 (3H, s), 1.21 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.3, 164.1, 159.8, 158.1, 133.4, 130.5, 122.2, 63.1, 62.8, 56.2, 39.0, 38.2, 34.0, 31.8, 31.2, 30.6, 30.1, 29.7, 26.4, 21.8, 21.7; IR (NaCl) C=O 1702 cm^{-1}; EI *m/z (rel. int.)* 316 (31), 301 (100), 302 (35), 283 (8); HRMS (EI) calcd for $C_{20}H_{28}O_3$: 316.2038; found 316.2044.

Completion of Taiwaniaquinol B Synthesis:

(±)-8-Hydroxy-7-isopropyl-6-dimethoxy-1,1,4a-trimethyl-2,3,4,4a,9,9a-hexahydro-1*H*-9-fluorenone (172)

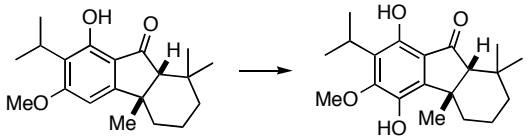


Tricycle **165** (342 mg, 1.04 mmol) was dissolved in dry CH_2Cl_2 (25 ml) and cooled to 0 °C in an ice bath under a nitrogen atmosphere. Boron trichloride (1.25 mL, 1M in hexanes, 1.25 mmol) was added drop-wise and the reaction stirred an additional 15 minutes. The reaction was quenched with water and extracted to CH_2Cl_2 (x3). The combined organic fractions were washed with brine then dried over $MgSO_4$, filtered and concentrated. Purification by flash chromatography (9:1 hexanes:EtOAc) provided 295 mg (90%) of an off-white solid. M.p. 123-124 °C; R.f. 0.46 (9:1 Hex:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.57 (1H, s), 6.32 (1H, s), 3.86 (3H, s), 3.47 (1H, septet, *J* = 7.1 Hz), 2.13 (1H, s), 1.95-1.80 (1H, m), 1.75-1.60 (2H, m),

1.60-1.40 (1H, m), 1.40-1.30 (1H, m), 1.35-1.20 (1H, m), 1.29 (3H, s), 1.27 (6H, d, *J* = 7.1 Hz), 1.22 (3H, s), 0.81 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 209.4, 165.5, 162.2, 156.5, 120.2, 115.7, 96.4, 64.8, 55.7, 42.5, 37.2, 34.0, 33.1, 32.7, 31.95, 24.4, 23.6, 20.4, 17.8; IR (NaCl) OH 3319 C=O 1667 cm^{-1}; EI *m/z (rel. int.)* 316 (43), 301 (100), 234 (92); HRMS (EI) calcd for $C_{20}H_{28}O_3$: 316.2038; found 316.2043.

(±)-Taiwaniaquinol B (152)

[(±)-5,8-Dihydroxy-7-isopropyl-6-dimethoxy-1,1,4a-trimethyl-2,3,4,4a,9,9a-hexahydro-1*H*-9-fluorenone]



Phenol **166** (20 mg, 0.063 mmol) was dissolved in CH_3CN/CH_2Cl_2 (2 mL/0.1 mL) and cooled to 0 °C in an ice bath. A solution of cerium ammonium nitrate (134 mg, 0.24 mmol) in water (1 mL) was added drop-wise and the reaction monitored by TLC while maintaining the reaction at 0°C. After 3 hours the TLC showed complete consumption of starting material and the intense yellow solution was diluted with brine and extract to EtOAc (x4). The combined organic fractions were dried over $MgSO_4$ and filtered, the partially concentrated by rotary evaporator to a volume of about 10-15 mL. This solution was degassed and then 10 % Pd/C (20 mg) was added, followed by H_2 (1 atm). The reaction mixture was stirred vigorously at room temperature for 19 hours then filtered through celite. Concentration, followed by flash chromatography (9:1 hexanes:EtOAc) provided 11 mg (52%) of a pale yellow solid. M.p. 133-134 °C (EtOAc/Hex) (Lit. for (-)-enantiomer 142-144 °C (EtOAc/Hex))[2]; R.f. 0.26 (9:1 Hex:EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.52 (1H, s), 5.25 (1H, s), 3.78 (3H, 3.25 (1H, septet, *J* = 7.1 Hz), 2.10 (1H, s), 2.05-1.97 (2H, m), 1.80-1.50 (2H, m), 1.43-1.23 (2H, m), 1.42 (3H, s), 1.36 (6H, d, *J* = 7.1 Hz), 1.24 (3H, s), 0.86 (3H, s); ^{13}C NMR (75 MHZ, $CDCl_3$) δ 211.1, 152.2, 151.1, 142.7, 138.4, 126.1, 118.3, 65.1, 62.1, 42.7, 36.5, 34.3, 33.0, 30.3, 28.8, 25.9, 24.3, 20.6, 17.5; IR (NaCl) OH 3436.3, C=O 1661 cm^{-1}; EI *m/z (rel. int.)* 332 (100), 317 (38), 263 (11), 249 (41), 233 (13), 219 (7), 149 (8); HRMS (EI) calcd for $C_{20}H_{28}O_4$: 332.1988; found 332.1982.

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