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Modular Synthesis of Tetrahydrofluorenones from 5-Alkylidene Meldrum's Acids

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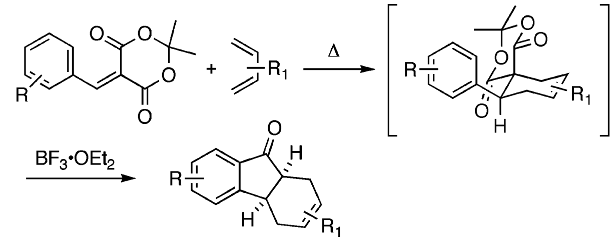

The one-pot synthesis of tetrahydrofluorenones, the core 6-5-6 tricyclic structural motif found in norditerpenoid natural products, from alkylidene Meldrum's acids via thermal Diels−Alder/$BF_3 \cdot OEt_2$-catalyzed Friedel−Crafts acylation reactions is described. A series of tetrahydrofluorenones was assembled in good yields, and the Diels−Alder/Friedel−Crafts acylation protocol allowed modification of the substitution within the rings.

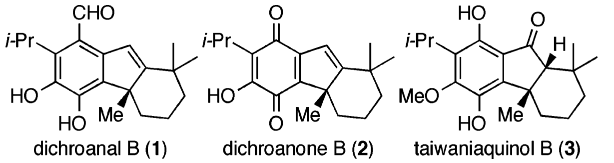

FIGURE 1. Hexahydrofluorene and tetrahydrofluorene natural products.

Several structurally related diterpenoids and norditerpenoids have recently been isolated and identified as possible aromatase inhibitors for the treatment of estrogen-dependent cancers (Figure 1).[1] As such, the total synthesis of these tricyclic natural products has been an area of considerable recent research. An intramolecular Heck reaction was key in the preparation of (±)-dichroanal B (**1**), (±)-dichroanone (**2**), (±)-taiwaniaquinones D and H, and (±)-taiwaniaquinol B (**3**) by Banerjee.[2] A similar strategy was used by Node to accomplish the total synthesis of (±)-dichroanal B (**1**).[3] Stoltz disclosed the first enantioselective synthesis of (+)-dichroanone (**2**) using an elegant asymmetric Tsuji allylation.[4] Very recently, Trauner prepared numerous members of the taiwaniaquinoid family via Nazarov cyclization.[5] Our own work used a unique trimethylsilyl triflate (TMSOTf)-promoted tandem intramolecular Friedel−Crafts acylation/carbonyl α-*tert*-alkylation reaction in the first total synthesis of taiwaniaquinol B (**3**), a highly substituted hexahydrofluorenone.[6,7] However, for the purpose of SAR studies, a rapid and modular method to assemble the core 6-5-6 tricyclic skeleton is desirable. Herein, we describe such an approach based on the thermal Diels−Alder reaction of 5-alkylidene Meldrum's acids followed by in situ $BF_3 \cdot OEt_2$-catalyzed Friedel−Crafts acylation (FC) reaction of the resulting adduct (Scheme 1).[8] (**3**)

Our group has established that Meldrum's acid derivatives are powerful and convenient acylating agents in metal triflate-catalyzed intramolecular FC acylations.[9] Thermal Diels−Alder

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[8] For an example of a Lewis acid-promoted intramolecular Diels−Alder/Friedel−Crafts alkylation sequence: Varseev, G. N.; Maier, M. E. *Angew. Chem., Int. Ed.* **2006**, *45*, 4767−4771.

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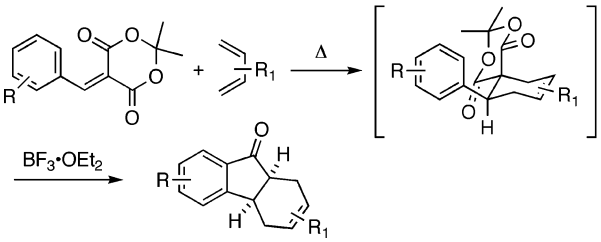
[10] (a) Andreev, G. N.; Shul'ts, E. E.; Volkov, A. A.; Shakirov, M. M.; Bagryyanskaya, I. Yu.; Gatilov, Yu. V.; Tolstikov, G. A. *Russ. J. Org. Chem.* **2004**, *40*, 854−865. (b) Ramachary, D. B.; Barbas, C. F., III *Chem.−Eur. J.* **2004**, *10*, 5323−5331. (c) Ramachary, D. B.; Chowdari, N. S.; Barbas, C. F., III *Angew. Chem., Int. Ed.* **2003**, *42*, 4233−4237. (d) Zitsane, D. R.; Ravinya, I. T.; Riikure, I. A.; Tetere, Z. F.; Gudrinietse, E. Yu.; Kalei, U. O. *Russ. J. Org. Chem.* **1999**, *35*, 1457−1460. (e) Benvegnu, T.; Martelli, J.; Grée, R.; Toupet, L. *Tetrahedron Lett.* **1990**, *31*, 3145−3148. (f) Kraus, G. A.; Liras, S. *Tetrahedron Lett.* **1989**, *30*, 1907−1908. (g) Eberle, M.; Lawton, R. G. *Helv. Chim. Acta* **1988**, *71*, 1974−1982. (h) Kraus, G. A.; Krolski, M. E. *J. Org. Chem.* **1986**, *51*, 3347−3350. (i) Kunz, F. J.; Polansky, O. E. *Monatsh. Chem.* **1969**, *100*, 920−927. Diels−Alder with methylene Meldrum's acid: (j) White, J. D.; Wang, G.; Quaranta, L. *Org. Lett.* **2003**, *5*, 4983−4986. (k) Zia-Ebrahimi, M.; Huffman, G. W. *Synthesis* **1996**, 215−218. (l) Tolstikov, G. A.; Tolstikova, T. G.; Shultz, É. É.; Mukhametyanova, T. Sh.; Popov, V. G.; Davydova, V. A.; Lazareva, D. N.; Zarudii, F. S.; Spirikhin, L. V.; Chertanova, L. F.; Gazikasheva, A. A. *Pharm. Chem. J.* **1992**, *26*, 834−842. (m) Buzinkai, J. F.; Hrubowchak, D. M.; Smith, F. X. *Tetrahedron Lett.* **1985**, *26*, 3195−3198. (n) Brown, R. F. C.; Eastwood, F. W.; McMullen, G. L. *Aust. J. Chem.* **1977**, *30*, 179−193. (o) Brown, R. F. C.; Eastwood, F. W.; McMullen, G. L. *J. Am. Chem. Soc.* **1976**, *98*, 7421−7422. Diels−Alder forming two contiguous all-carbon quaternary centers: (p) Benzing, M.; Vilsmaier, E.; Martini, H.; Michels, G.; Anders, E. *Chem. Ber.* **1989**, *122*, 1277−1284. (q) Bell, V. L.; Holmes, A. B.; Hsu, S.-Y.; Mock, G. A.; Raphael, R. A. *J. Chem. Soc., Perkin Trans. 1* **1986**, 1507−1514. (r) Bell, V. L.; Holmes, A. B. *Synth. Commun.* **1982**, *12*, 323−326. (s) Mock, G. A.; Holmes, A. B.; Raphael, R. A. *Tetrahedron Lett.* **1977**, 4539−4540. (t) Dauben, W. G.; Kozikowski, A. P.; Zimmerman, W. T. *Tetrahedron Lett.* **1975**, 515−517. Diels−Alder with photoenols of *o*-methylbenzaldehyde and related compounds: (u) Tsuno, T.; Sugiyama, K. In *Trends in Heterocyclic Chemistry*; Ramachandran, U., Ed.; Research Trends: Trivandrum, India, 2001; Vol. 7, pp 91−106. (v) Tsuno, T.; Sugiyama, K. *Heterocycles* **1991**, *32*, 1989−2004.

10.1021/jo0618876 CCC: $33.50

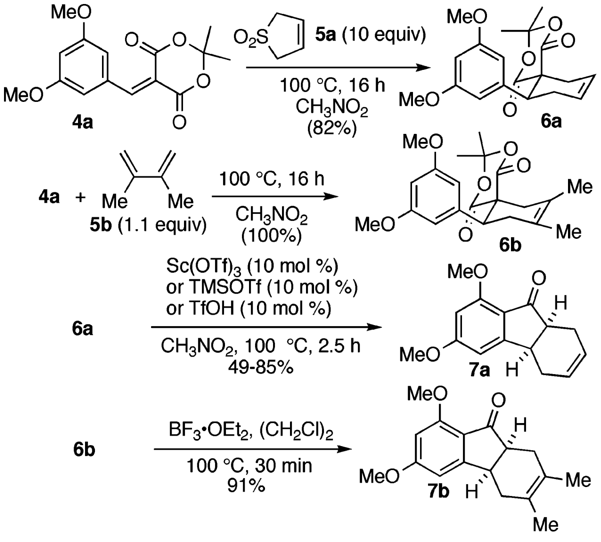
SCHEME 1. One-Pot Tetrahydrofluorenone Synthesis: General Strategy



reactions of 5-alkylidene Meldrum's acids as dienophiles occur readily, as well.[10,11]

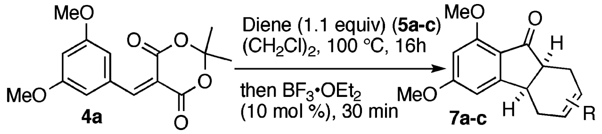
We began our investigation using butadiene generated in situ from butadiene sulfone **5a** and Meldrum's acid **4a**. The Diels–Alder reaction of alkylidene **4a** bearing an electron-rich 3,5-dimethoxybenzene moiety is unprecedented, but **4a** was rationally selected to facilitate the search for effective catalyst and reaction conditions in the subsequent FC acylation reaction. Spiro Meldrum's acid **6a** was isolated in 82% yield from 10 equiv of **5a** and 5-[(3,5-dimethoxyphenyl)methylene] Meldrum's acid (**4a**) after 16 h at 100 °C in CH_3NO_2 in a sealed tube (Scheme 2). The reaction conditions were then applied to 2,3-dimethylbutadiene (**5b**) and **4a**. In this case, only 1.1 equiv of the diene was necessary to furnish a quantitative yield of the [4 + 2] cycloadduct **6b** (Scheme 2).

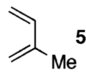
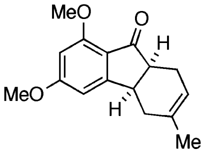
SCHEME 2. Initial Studies



The Friedel–Crafts acylation of **6a** was studied initially. Tetrahydrofluorenone **7a** was obtained in 79% yield after 2.5 h at 100 °C when catalyzed by $Sc(OTf)_3$ in CH_3NO_2, which were the optimal conditions in our previous FC acylations.[9] Triflic acid (10 mol %) provided a 49% yield, and TMSOTf (10 mol %) yielded 85% of **7a** (Scheme 2).[12] However, when the FC acylation conditions were applied to **6b**, decomposition was observed, which was attributed to the high π-nucleophilicity of the tetrasubstituted alkene. The reaction conditions were reexamined, and BF_3·OEt_2 (10 mol %) in $(CH_2Cl)_2$ at 100 °C was found to provide tricycle **7b** in 91% yield from **6b** (Scheme 2).[13]

TABLE 1. One-Pot Tetrahydrofluorenone Synthesis



entry	diene	tetrahydrofluorenone	yield (%)
1	**5a**	**7a**	84[a]
2	**5b**	**7b**	86
3	 **5c**	 **7c**	74[b]

[a] 5 equiv of diene was used. [b] Adduct **7c** and its regioisomer were obtained in a >20:1 ratio.

With this set of optimal conditions in hand, the development of a one-pot protocol was explored. Carrying out the Diels–Alder reaction in $(CH_2Cl)_2$ at 100 °C for 16 h followed by the addition of BF_3·OEt_2 (10 mol %) generated **7b** in 86% yield (Table 1, entry 2) from **4a** and **5b**.[14] Similar results were obtained with **5a** and **4a** (entry 1). Excellent regioselectivity was observed when **4a** was reacted with isoprene **5c** (entry 3).[15]

The π-nucleophilicity of the aromatic moiety and its impact on the FC acylation were investigated for a series of alkylidene Meldrum's acids using 2,3-dimethylbutadiene (**5b**). As shown in Table 2, the electron-rich 3,4-dimethoxyphenyl and 3,4,5-trimethoxyphenyl substituted alkylidenes **4b** and **4c** provided excellent yields of tetrahydrofluorenones **7d** and **7e**, respectively (Table 2, entries 1 and 2). Alkylidene **4d** furnished a mixture of regioisomers **7f** and **7g**. Of note, 5-(phenylmethylene) and 5-[(4-methoxyphenyl)methylene] Meldrum's acids **4h** and **4i** were ineffective in the one-pot transformation; both gave good conversion to the Diels–Alder cycloadduct, but the FC acylation failed.

Complex benzocyclic ketones were generated from alkylidene Meldrum's acids **4a** and **4e–g** and *o*-quinodimethane generated in situ from sultine **5d** (Table 3). In order for SO_2 to escape, the one-pot process was carried out in an open vessel.[16] As a result, longer reaction times were required for the FC acylations to go to completion. The products were formed in good to excellent yields, and the process was compatible with an aryl

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(11) Functionalized tetrahydrofluorenones are generally prepared via multistep sequences: Lomberget, T.; Bentz, E.; Bouyssi, D.; Balme, G. *Org. Lett.* **2003**, *5*, 2055–2057 and references therein

(12) The one-pot procedure furnished tricycle **7a** in 79% yield when **5a** (10 equiv) was heated in the presence of **4a** in CH_3NO_2 for 16 h followed by the addition of TMSOTf (10 mol %).

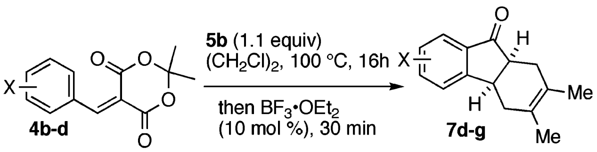
(13) BF_3·OEt_2 (10 mol %) in $MeNO_2$ gave **7b** after 10 min, which was contaminated with numerous alkene isomers. $Sc(OTf)_3$, $Cu(OTf)_2$, $Al(OTf)_3$, and $Sn(OTf)_2$ gave unsactifactory results. $Mg(OTf)_2$ was effective under stoichiometric conditions. $Zn(OTf)_2$ in $(CH_2Cl)_2$ cleanly converted **6b** to **7b**. CH_3CN, toluene, and benzene were unsuitable solvents for the FC acylation reactions.

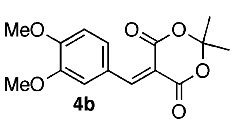
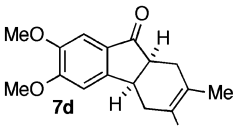
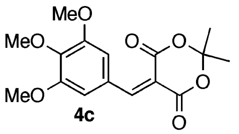
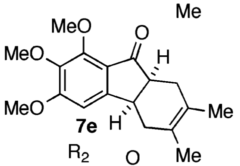
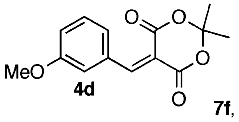
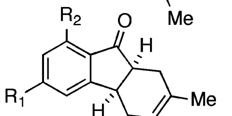
(14) The development of a BF_3·OEt_2-catalyzed Diels–Alder/Friedel–Crafts acylation protocol was unsuccessful. In most cases, the alkylidene Meldrum's acid was recovered and the diene polymerized.

(15) Analysis of the ^1H NMR of the crude revealed a 9:1 ratio of regioisomers after the initial Diels–Alder reaction.

(16) In a closed vessel, *o*-quinodimethane was rapidly trapped by SO_2 to generate a cyclic sulfone, and a large excess of sultine was required for the cycloaddition to go to completion, making purification of the FC acylation product tedious.

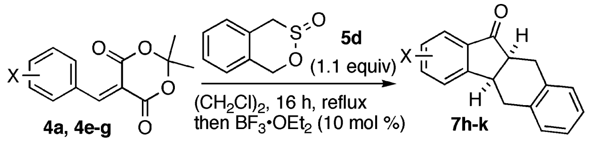
TABLE 2. Scope of the Alkylidene Meldrum's Acids

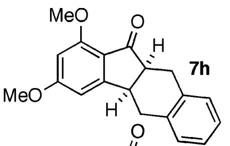
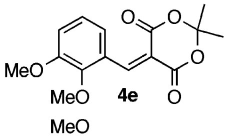
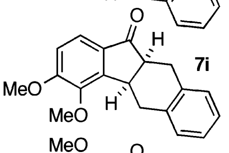
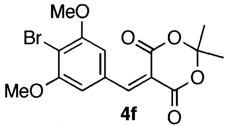
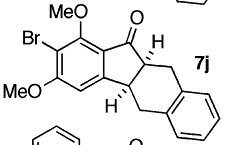
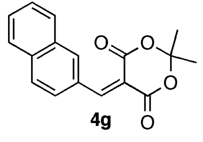
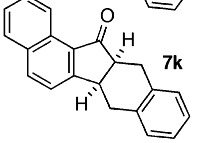


entry	alkylidene	tetrahydrofluorenone	yield (%)
1	 **4b**	 **7d**	76
2	 **4c**	 **7e**	90
3	 **4d**	 **7f**, R_1 = OMe; R_2 = H **7g**, R_1 = H; R_2 = OMe	64[a]

[a] Compounds **7f** and **7g** were obtained in a 67:33 ratio.

TABLE 3. Reaction of Alkylidene Meldrum's Acids with *o*-quinodimethane



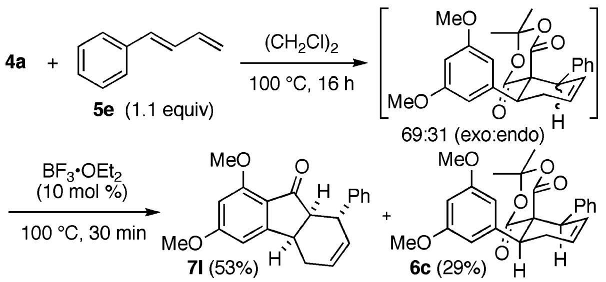
entry	Meldrum's acid	ketone	yield (%)[a]
1	**4a**	 **7h**	87 (3.5)
2	 **4e**	 **7i**	52 (6.5)[b]
3	 **4f**	 **7j**	74 (4.0)
4	 **4g**	 **7k**	71 (5.5)

[a] FC acylation reaction times are in parentheses. [b] 2.0 equiv of sultine was used.

bromide (entry 3). 5-(2-Naphthylmethylene) Meldrum's acid (**4g**) furnished pentacycle **7k** in 71% yield (entry 4).[17]

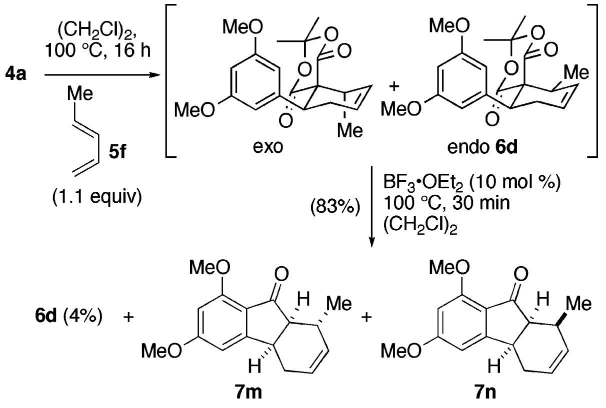
Functionalization of the cyclohexene moiety was then investigated by reacting alkylidene Meldrum's acid **4a** with 1-((*E*)-buta-1,3-dienyl)benzene (**5e**). The stereoselectivity of the Diels−Alder reaction was modest, but the large reactivity difference of the cycloadducts in the FC acylation allowed for the isolation of tricycle **7l** in 53% yield as a single diastereomer from **4a** and **5e**; unreacted endo-adduct **6c** was obtained in 29% yield (Scheme 3).[18] On the basis of the X-ray structure of **6c**, it seems likely that the two aryl groups flanking the Meldrum's acid moiety encumber Lewis acid complexation, preventing activation of the electrophile.

SCHEME 3. Reaction of 1-((*E*)-Buta-1,3-dienyl)benzene with 4a



The steric argument was tested by the reaction of *trans*-piperylene **5f** with **4a**, which gave a similar exo/endo ratio, but the difference in reactivity in the FC acylation step was far less pronounced. After treatment with $BF_3\cdot OEt_2$ (10 mol %), a small amount of unreacted endo-isomer **6d** was recovered, along with a 69:31 mixture of **7m**/**7n** in 83% yield (Scheme 4).[19]

SCHEME 4. Reaction of *trans*-Piperylene with 4a



In order to make later derivatization as diverse as possible, the placement of the alkene in the tetrahydrofluorenone was modified by simply incorporating the most reactive π-nucleophile in the diene (Table 4). Reacting diene **5g** with alkylidene **4h** provided tricycle **7o** in 58% yield, in addition to a 20% yield of endo cycloadduct **6e**.[20] The one-pot process was then applied to a variety of alkylidene Meldrum's acids **4h**−**k** as depicted in Table 4. Arylbutadiene **5h** reacted similarly with **4h**, yielding **7s** as a single regioisomer (entry 5).

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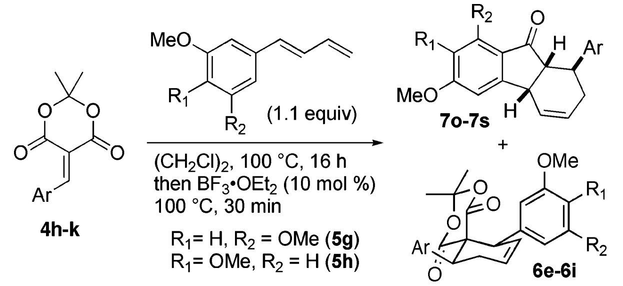
[17] Once again, 5-(phenylmethylene) Meldrum's acid **4h** underwent [4 + 2] cycloaddition but the acylation failed, likely due to the low π-nucleophilicity of the phenyl moiety.

[18] The exo and endo cycloadducts were separated and their respective structures determined by nOe's experiments. The structure of the endo adduct **6c** was further confirmed by X-ray crystallography. See the Supporting Information.

[19] The diastereomers were separated by flash chromatography for characterization; see Supporting Information.

[20] Preliminary experiments have shown that the conversion of the endo adducts to the corresponding tetrahydrofluorenone is slow. For example, a 50% conversion for **6e** after 8 h at 100 °C was observed.

TABLE 4. Reactivity of 1-Arylbutadienes 5g and 5h

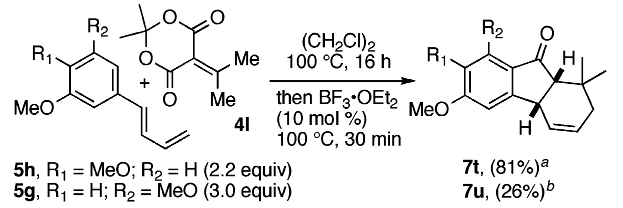


entry	Ar (**4**)	diene (**5**)	exo/endo[a]	yield of (**7**) (%)[b]	yield of (**6**) (%)[b]
1	Ph (**4h**)	**5g**	66:34	58 (**7o**)	20 (**6e**)
2	4-MeOPh (**4i**)	**5g**	69:31	42 (**7p**)	24 (**6f**)
3	3-ClPh (**4j**)	**5g**	65:35	55 (**7q**)	23 (**6g**)
4	4-ClPh (**4k**)	**5g**	64:36	51 (**7r**)	24 (**6h**)
5	**4h**	**5h**	65:35	45 (**7s**)	21 (**6i**)

[a] Determined by analysis of the ^{1}H NMR of the crude Diels−Alder reaction mixture. [b] R$_1$ and R$_2$ identical to **5g** or **5h**, respectively.

A common feature of these natural products is the *gem*-dimethyl group (Figure 1), which can be introduced using alkylidene **4l**. An 81% yield of tricycle **7t** was obtained with electron-rich diene **5h**, but the less reactive diene **5g** provided a 26% yield of **7u** (Scheme 5).[21]

SCHEME 5. Gem-Dimethyl Substituted Tetrahydrofluorenones



[a] Diels−Alder reaction 89% complete. [b] Diels−Alder reaction 78% complete.

In summary, a modular strategy for the expedient assembly and modification of structurally diverse tetrahydrofluorenones from alkylidene Meldrum's acids was described.

Experimental Section

Synthesis of Tetrahydrofluorenones 7a−g, 7o−s (Procedure A). An oven-dried Schlenk tube cooled under N$_2$ was charged with alkylidene Meldrum's acid (200 mg, 1.0 equiv) and the diene (1.1 equiv, 5.0 equiv of butadiene sulfone for the preparation of **7a**) and was washed into the tube with (CH$_2$Cl)$_2$ (0.2 M relative to the alkylidene). The tube was sealed, heated in an oil bath at 100 °C for 16 h, and removed from the bath to cool to rt. A 50 μL aliquot was removed and concentrated to determine conversion and endo/exo ratio (where applicable) of the Diels−Alder reaction by ^{1}H NMR. A solution of BF$_3$•OEt$_2$ in (CH$_2$Cl)$_2$ (0.1 equiv/100 μL) was washed into the tube with sufficient (CH$_2$Cl)$_2$ to bring the total concentration to 0.15 M. The tube was reheated to 100 °C for 30 min and cooled to rt, and the contents were transferred into a separatory funnel with CH$_2$Cl$_2$ (*Caution: A small amount of pressure builds up in the tube during the FC acylation as CO$_2$ is evolved.*) The organic phase was washed with brine, dried with MgSO$_4$, filtered, and concentrated. Purification by flash chromatography eluting with EtOAc/hexanes solvent mixtures yielded the product.

Synthesis of Benzotetrahydrofluorenones 7h−k (Procedure B). A flame-dried round-bottom flask equipped with a condenser under N$_2$ with an outlet for SO$_2$ was charged with alkylidene Meldrum's acid (200 mg, 1.0 equiv). Sultine **5d**[22] (1.1 equiv) was weighed into a vial and rinsed into the flask with (CH$_2$Cl)$_2$ (0.2 M relative to the alkylidene). The contents were heated to reflux for 16 h and cooled to rt before removing a 50 μL aliquot to check the reaction progress by ^{1}H NMR. A solution of BF$_3$•OEt$_2$ (CH$_2$Cl)$_2$ in (0.1 equiv/100 μL) was added to the flask, as well as enough (CH$_2$Cl)$_2$ to bring the total volume to 0.15 M. The reaction was heated to reflux for the indicated times and then cooled to rt. The remainder of the procedure is identical to procedure A.

Synthesis of Tetrahydrofluorenones 7t−u (Procedure C). An oven-dried Schlenk tube cooled under N$_2$ was charged with 5-(1-methylethylidene) Meldrum's acid **4l** (100 mg, 0.54 mmol, 1.0 equiv). The arylbutadiene (2.2−3.0 equiv) was weighed into a vial, then transferred into the tube with (CH$_2$Cl)$_2$ (0.4 M). The tube was sealed and heated to 100 °C for 16 h and then cooled to rt. A 50 μL aliquot was removed to check conversion by ^{1}H NMR, then a solution of BF$_3$•OEt$_2$ in (CH$_2$Cl)$_2$ (0.1 equiv/100 μL) was washed into the tube with sufficient (CH$_2$Cl)$_2$ to bring the concentration to 0.15 M. The reaction was reheated to 100 °C for 30 min, cooled to rt, and worked up as in procedure A. Flash chromatography eluting with 1:9 to 1:4 EtOAc/hexanes afforded a yellow powder, which was recrystallized from Et$_2$O to remove colored impurities.

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Supporting Information Available: Detailed experimental procedures and NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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(21) All attempts to react 5-(1-arylethylidene) Meldrum's acids for the formation of tetrahydrofluorenones bearing an all-carbon benzylic quaternary center failed.

(22) Hoey, M. D.; Dittmer, D. C. *J. Org. Chem.* **1991**, *56*, 1947−1948.