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Total Synthesis of the Topopyrones: A New Class of Topoisomerase I Poisons

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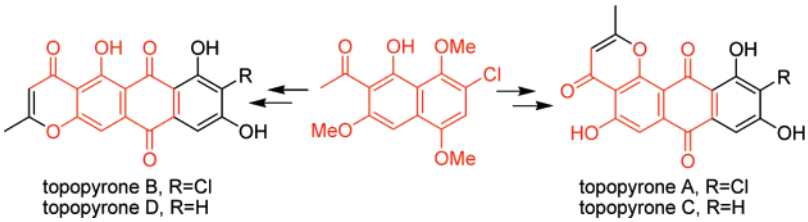

The topopyrones represent a new class of highly cytotoxic topoisomerase I poisons. Efficient total syntheses of all four naturally occurring members of this class have been accomplished. Key elements of the syntheses include Diels−Alder reactions employing two novel dienes and a titanium-mediated ortho-directed Friedel−Crafts acylation. Additionally, the syntheses of two chlorinated analogues accessible from an advanced intermediate are described.

Introduction

DNA topoisomerases are nuclear enzymes which participate in the processing of DNA, including the cleavage, unwinding, and religation of DNA strands. They are thereby essential to support DNA replication and transcription. Interestingly, many anticancer drugs have been found to interact with DNA topoisomerases, including *m*-AMSA, VP-16 (etoposide), and VM-26, all of which poison topoisomerase II.[1] There are also compounds such as saintopin which poison both topoisomerases I and II.[2] However, relatively few compounds potently and selectively poison topoisomerase I.[3] Camptothecin (CPT), two derivatives of which are used clinically as anticancer agents, interacts with topoisomerase I selectively by stabilizing the covalent binary complex formed between the enzyme and DNA.[3a,b] A number of other topoisomerase I poisons have been identified, but most are much less potent.[3c] Given the clinical utility of the CPTs, and the limited number of compounds that function by this mechanism, there is a need for potent new topoisomerase I poisons.

Recently, Kanazawa and co-workers reported the isolation, structural characterization, and biological activity of a new class of topoisomerase I poisons, the topopyrones.[4] The topopyrones (Figure 1) are a family of planar anthraquinone polyphenols, distinguished by the orientation of the pyrone ring appended on one side as well as the presence or lack of a chlorine at C7. Topopyrones A (**1**) and B (**2**) possess a chloro substituent at C7, i.e., that part of the molecule distant from the pyrone ring, while topopyrones C (**3**) and D (**4**) are unsubstituted at C7. Additionally, the pyrone linkage is between C1 or C3, and C13.

The topopyrones were isolated from the culture broths of two fungi, *Phoma* sp. BAUA2861 and *Penicillium* sp. BAUA4206. By using a yeast assay in which topopyrone binding to a topoisomerase I−DNA covalent binary complex resulted in yeast growth inhibition,[5] the workers were able to demonstrate the locus of inhibitory action of these compounds. Specifically, topopyrones A, B, C, and D selectively inhibited the growth of yeast expressing human topoisomerase I with IC_{50} values of 1.22, 0.15, 4.88, and 19.63 ng/mL, respectively. The IC_{50} value of CPT under the same assay conditions was found to be 0.10 ng/mL. No cytotoxicity was observed when the yeasts were grown under conditions that precluded topoisomerase I expres-

(1) (a) Marshall, B.; Darkin, S.; Ralph, R. K. *FEBS Lett.* **1983**, *61*, 75. (b) Tewey, K. M.; Rowe, T. C.; Yang, L.; Hallman, B. D.; Liu, L. F. *Science* **1984**, *226*, 466. (c) Yang, L.; Rowe, T. C.; Liu, L. F. *Cancer Res.* **1985**, *45*, 5872.

(2) Yamashita, Y.; Saitoh, Y.; Ando, K.; Takahashi, K.; Ohno, H.; Nakano, H. *J. Antibiot.* **1990**, *43*, 1344.

(3) (a) Hsiang, Y.-H.; Hertzberg, R.; Hecht, S. M.; Liu, L. F. *J. Biol. Chem.* **1985**, *260*, 14873. (b) Thomas, C. J.; Rahier, N. J.; Hecht, S. M. *Bioorg. Med. Chem.* **2004**, *12*, 1585. (c) Dias, N.; Vezin, H.; Lansiaux, A.; Bailly, C. *Top. Curr. Chem.* **2005**, *253*, 89.

(4) (a) Kanai, Y.; Ishiyama, D.; Senda, H.; Iwatani, W.; Takahashi, H.; Konno, H.; Tokumasu, S.; Kanazawa, S. *J. Antibiot.* **2000**, *53*, 863. (b) Ishiyama, D.; Kanai, Y.; Senda, H.; Iwatani, W.; Takahashi, H.; Konno, H.; Kanazawa, S. *J. Antibiot.* **2000**, *53*, 873.

(5) Wang, J. C.; Bjornsti, M.; Benedetti, P.; Viglianti, G. A. *Cancer Res.* **1989**, *49*, 6318.

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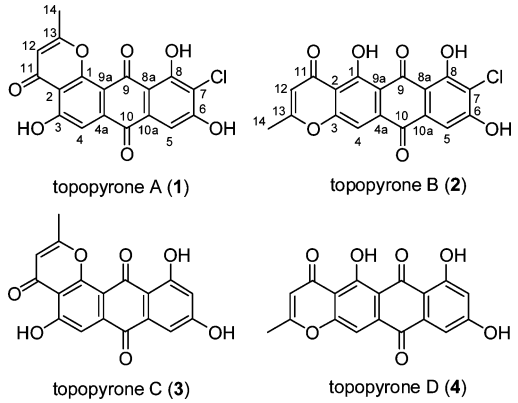


FIGURE 1. Four naturally occurring topopyrones.

sion. It was also shown that topopyrones A and B inhibited the relaxation of supercoiled plasmid DNA by topoisomerase I in a dose-dependent manner that was slightly weaker than CPT but more potent than topopyrones C and D. These results suggest that the chloro substituent may be important for the interaction of the topopyrones with the topoisomerase I−DNA covalent binary complex. The *in vitro* antiproliferative activity of the topopyrones was also evaluated and found to be potent for all of the cell lines tested, albeit somewhat weaker than CPT.

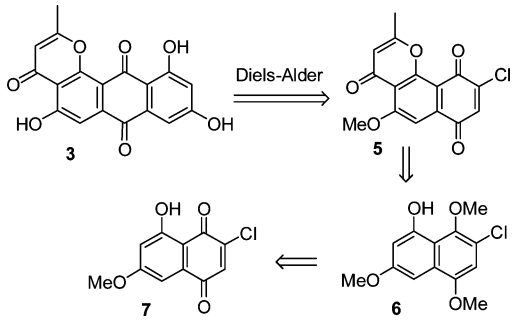
Given the interesting biochemical profile of these compounds and their limited availability, the topopyrones were logical synthetic targets. When this work was initiated, there had been no report of any synthetic work on these compounds. Recently, publications have appeared detailing the total syntheses of topopyrones B and D,[6] as well as topopyrone C.[7] Reported herein is a comprehensive synthetic investigation of the topopyrones, culminating in the efficient syntheses of all four naturally occurring topopyrones as well as two additional chlorinated analogues accessible from an advanced synthetic intermediate.

Results and Discussion

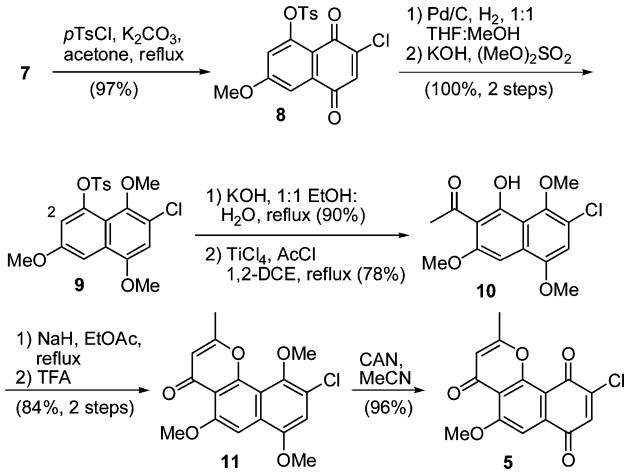
Synthetic Analysis of the Topopyrones. There have been a few reports of research into the synthesis of compounds related to the topopyrones,[8] most of which have focused on the pluramycin class of antibacterial and antitumor agents. Specifically, Hauser and Rhee prepared *O*-methylkidamycinone utilizing a selenium dioxide-mediated ring closure and dehydration sequence as the key step.[9] Later, Krohn and Vitz were able to prepare premithanthramycinone H and some related structures using successive dianion additions followed by an acid-mediated ring closure to form the pyrone.[10] Neither of these general approaches seemed applicable to the present effort given the ring substitution patterns present in the topopyrones.

Non-chlorinated isomers **3** and **4** were studied initially, in the hope that a similar synthetic approach could eventually be used to gain access to chlorinated compounds **1** and **2** as well.

SCHEME 1. Retrosynthetic Analysis of Topopyrone C



SCHEME 2. Synthesis of Quinone 5



It was also anticipated that **4**, the thermodynamically more stable isomer, could be obtained from **3** via a base-catalyzed rearrangement as described in the isolation paper.[4] Retrosynthetically, it was envisioned that two Diels−Alder reactions (Scheme 1) would install the required aromatic rings in a regioselective manner, building upon the observations of Brassard[11] and Kelly.[12] Accordingly, **3** could be obtained after deprotection of the phenols arising from a condensation of quinone **5** and an appropriate diene. Quinone **5** could be obtained from an ortho-directed Friedel−Crafts acylation[13] of phenol **6** followed by chain extension and ring closure to form the pyrone. Access to phenol **6** was envisioned through protecting group manipulations and reductive methylation of previously reported quinone **7**.[11]

Synthesis of Topopyrones C (3) and D (4). Quinone **7**[11] was prepared by the Diels−Alder union of 1,3-dimethoxy-1-trimethylsiloxy-1,3-butadiene[14] and commercially available 2,6-dichloro-1,4-benzoquinone with pyridine added to buffer the reaction.[15] Introduction of a number of different protecting groups for the phenol, including the MOM and allyl ether groups, proved difficult. Finally, the tosylate group was introduced using K_2CO_3 and *p*-TsCl in acetone at reflux to give quinone **8** in 97% yield (Scheme 2). This reaction was somewhat capricious on large scale, but yields were routinely between 80 and 95% on ∼3−5-g scale. Initial reductive conditions ($Na_2S_2O_4$,

(6) Tan, J. S.; Ciufolini, M. A. *Org. Lett.* **2006**, *8*, 4771.
(7) Gattinoni, S.; Merlini, L.; Dallavalle, S. *Tetrahedron Lett.* **2007**, *48*, 1049.
(8) For recent syntheses of related structures, see: (a) Krohn, K.; Tran-Thien, H. T.; Vitz, J.; Vidal, A. *Eur. J. Org. Chem.* **2007**, 1905. (b) Tietze, L. F.; Singidi, R. R.; Gericke, K. M. *Org. Lett.* **2006**, *8*, 5873. (c) Tietze, L. F.; Gericke, K. M.; Singidi, R. R. *Angew. Chem., Int. Ed.* **2006**, *45*, 6990. (d) Fei, Z.; McDonald, F. E. *Org. Lett.* **2005**, *7*, 3617.
(9) Hauser, F. M.; Rhee, R. P. *J. Org. Chem.* **1980**, *45*, 3061.
(10) Krohn, K.; Vitz, J. *Eur. J. Org. Chem.* **2004**, 209.
(11) Savard, J.; Brassard, P. *Tetrahedron* **1984**, *40*, 3455.
(12) Kelly, T. R.; Xu, W.; Ma, Z.; Li, Q.; Bhushan, V. *J. Am. Chem. Soc.* **1993**, *115*, 5843.
(13) Friedel, C.; Crafts, J. M. *Compt. Rend.* **1887**, *84*, 1392.
(14) Available in two steps from commercially available methyl acetoacetate in 85% yield.[11]
(15) (a) Roush, W. R.; Coffey, D. S. *J. Org. Chem.* **1985**, *60*, 4412. (b) Roush, W. R.; Madar, D. J.; Coffey, D. S. *Can. J. Chem.*, **2001**, *79*, 1711.

nBu$_4$NBr, THF−H$_2$O) followed by methylation proved problematic in the presence of the tosylate. Alternatively, reduction of the quinone could be accomplished by Pd/C-catalyzed hydrogenation, followed by methylation of the crude bisphenol, [KOH, $(MeO)_2SO_2$], which afforded **9** quantitatively. Subsequent removal of the tosylate under basic conditions provided the free phenol **6** in 90% yield.

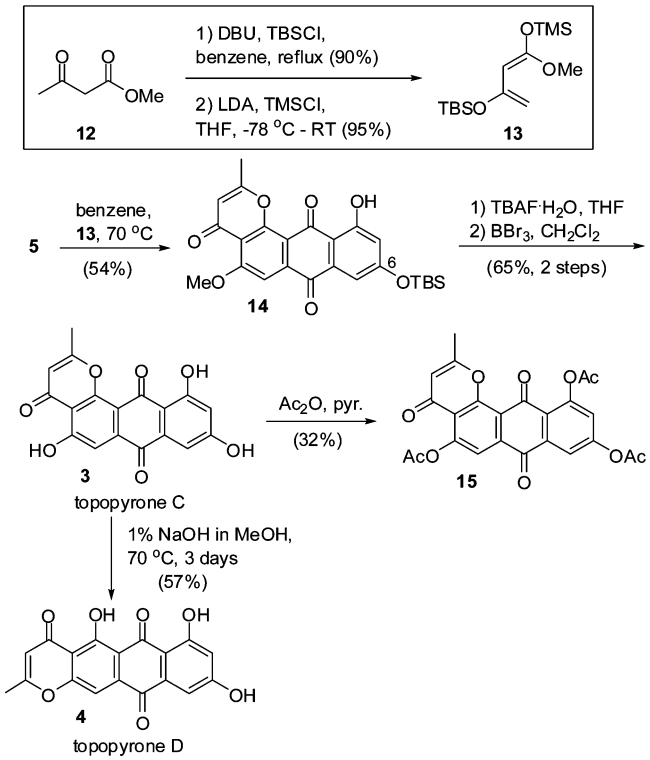
Attention was next turned to the introduction of some functionality at C2, (numbering scheme as in the final target) which could ultimately be converted to the pyrone. Accordingly, phenol **6** was converted to the corresponding *O*-acetate and subjected to Fries rearrangement conditions ($AlCl_3$ or BF_3·Et_2O).[16] Unfortunately, a complex product mixture was obtained. Alternatively, Marschalk reaction conditions[17] were employed according to which phenol **6** was treated with NaOH in MeOH and either acetaldehyde or formaldehyde in hopes of yielding the secondary or primary benzylic alcohol, respectively. Oxidation followed by further elaboration was envisioned to give the desired pyrone. However, no suitable conditions for the conversion were found; only complex product mixtures and low yields resulted.

At this point recent reports[18] regarding the use of $TiCl_4$ to accomplish regiocontrolled Friedel−Crafts[13,19] acylations attracted our attention. In fact, it was found that treatment of **6** in 1,2-dichloroethane with $TiCl_4$ and AcCl at reflux introduced the required acyl side chain selectively at the ortho position (**10**) in 78% yield. Chain extension of the *C*-acetyl group in **10** to the β-diketone was accomplished using NaH in ethyl acetate at reflux.[20] Treatment of this crude material with TFA[10] afforded **11** in 84% yield over two steps. Finally, oxidation with CAN in MeCN afforded the key quinone **5** in 96% yield.

Attempted introduction of the remaining aromatic ring using a Diels−Alder reaction with 1,3-dimethoxy-1-trimethylsiloxy-1,3-butadiene,[11] previously used to prepare **7**, failed to give good conversion to the product. One possible reason may be the thermal instability of this particular diene.[21] Invariably the isolated product was contaminated with starting material (**5**). It seemed possible that a diene having a different protecting group on the incipient C6 phenol might be easier to differentiate chromatographically from the starting material and give the desired product reliably. Accordingly, diene **13** (Scheme 3) was prepared in two steps starting from methyl acetoacetate (**12**). The enol was formed using DBU in benzene and subsequently trapped as the *tert*-butyldimethylsilyl ether in 90% yield. Conversion to the diene was accomplished using LDA, followed by trapping with TMSCl to give **13** in 95% yield. This diene has not been reported previously; the configuration of this diene is presently unknown and is represented arbitrarily in Scheme 3.

Gratifyingly, when quinone **5** was treated with diene **13** in benzene at 70 °C, the desired anthraquinone **14** was obtained in 54% yield. The modest yield may be due in part to the loss of the TBS group during workup and chromatographic purification. A two-stage deprotection involving initial treatment with TBAF followed by BBr_3 afforded topopyrone C (**3**) as an orange-red solid in 65% yield for the two steps. As described in the isolation paper,[4] this material was quite insoluble in organic solvents. In order to obtain an NMR spectrum and confirm the structure, putative **3** was exhaustively acetylated using Ac_2O in pyridine to give **15** in 32% yield. The synthetic material gave ^{1}H and ^{13}C NMR spectra identical to those reported for the derivatized natural product.[4]

SCHEME 3. Completion of the Synthesis of Topopyrone C



Attention was then focused on the preparation of topopyrone D (**4**). Initial efforts to convert topopyrone C to topopyrone D under conditions described in the isolation paper[4] (1% NaOH in MeOH, 25 °C, 4 days) met with failure. Treatment with 1% NaOH in methanol at room temperature for extended periods of time gave only recovered starting material, as confirmed by acetylation and NMR analysis. Eventually, **4** was obtained from **3** using higher temperatures (*vide infra*). It should be noted that the highly insoluble nature of this material made these manipulations difficult. Given these initial results, the preparation of **4** was attempted from an advanced intermediate in the belief that a direct route would be immediately useful for independent structural confirmation and later for analogue preparation (Scheme 4). Beginning with acetophenone **10**, the tosylate group was introduced on the phenol quantitatively using *p*-TsCl and Hünig's base in CH_2Cl_2. Various deprotection strategies were attempted to unmask the phenol at C3; finally it was found that treatment with $AlBr_3$ in MeCN for 9 days gave **16** in 92% yield. Attempts to accelerate this reaction by addition of NaI or increased temperature resulted in multiple unwanted byproducts.

Chain extension conditions as reported above (Scheme 2) gave multiple decomposition products, and so a Baker−Venkataraman rearrangement[22] was employed. Accordingly, the

(16) (a) Fries, K.; Fink, G. *Ber.* **1909**, *41*, 4271. (b) Fries, K.; Pfaffendorf, W. *Chem. Ber.* **1910**, *43*, 212.

(17) Marschalk, C. *Bull. Soc. Chim. Fr.* **1939**, *6*, 655.

(18) (a) Rozenberg, V.; Danilova, T.; Sergeeva, E.; Voronstov, Z. S.; Lysenko, K.; Belokon, Y. *Eur. J. Org. Chem.* **2000**, 3295. (b) Bensari, A.; Zaveri, N. T. *Synthesis* **2003**, *2*, 267.

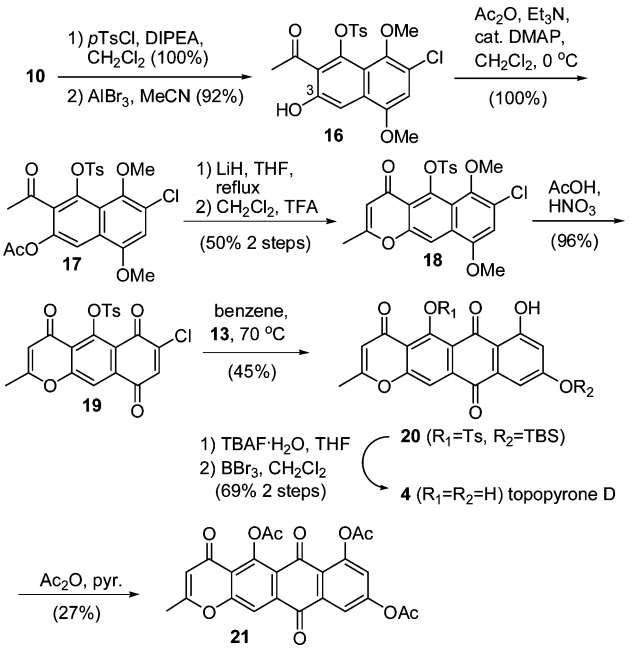
(19) Friedel, C.; Crafts, J. M. *Compt. Rend.* **1887**, *84*, 1450.

(20) Yamashita, A.; Toy, A.; Scahill, T. A. *J. Org. Chem.* **1989**, *54*, 3625.

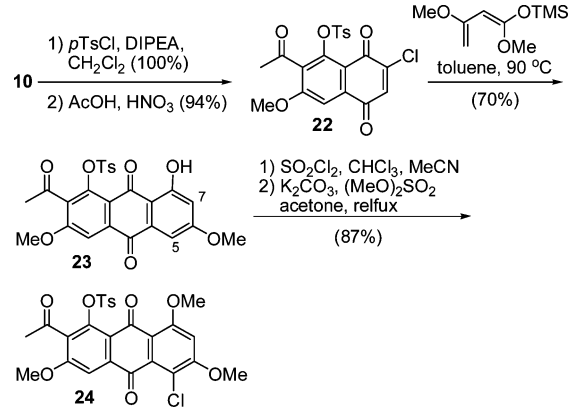
(21) Anderson, G.; Cameron, D. W.; Fetrill, G. I.; Read, R. W. *Tetrahedron Lett.* **1981**, *22*, 4347.

(22) (a) Baker, W. *J. Chem. Soc.* **1933**, *55*, 1381. (b) Mahal, H. S.; Venkataraman, K. *J. Chem. Soc.* **1934**, *56*, 1767.

SCHEME 4. Completion of the Synthesis of Topopyrone D



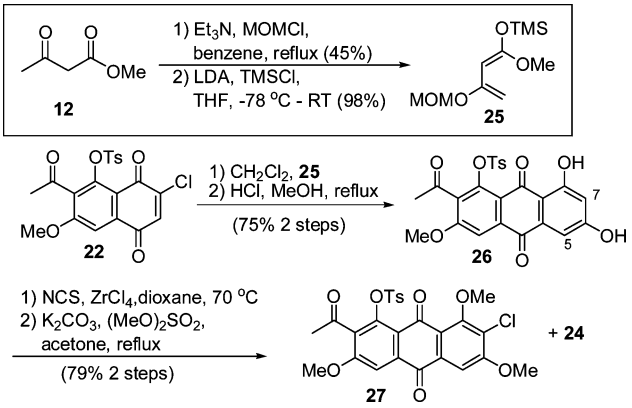
SCHEME 5. Initial Chlorination Attempt



free phenol was acetylated quantitatively using standard conditions to give **17** (Scheme 4). Subsequent treatment of acetate **17** with LiH in THF at reflux gave the desired rearranged product along with deacetylated material (**16**). Treatment of the crude mixture with TFA gave pyrone **18** in 50% yield (76% conversion based on recovered deacetylated material). Attempted oxidation using CAN failed to oxidize the starting material; thus, it was treated with 1:1 AcOH−HNO_3 to give quinone **19** in 96% yield. Treatment with diene **13** in benzene at 70 °C gave anthraquinone **20** in 45% yield. As above, a two-step deprotection procedure using TBAF followed by BBr_3 gave topopyrone D (**4**) in 69% yield. Acetylation to give **21** was required in order to obtain ^{1}H and ^{13}C NMR spectra, which matched those reported in the literature.[4]

Syntheses of Topopyrones A and B. With topopyrones C and D in hand, attention shifted to the chlorinated derivatives. As shown in Scheme 5, initial investigations began with the preparation of quinone **22**. As above, **10** was tosylated and then oxidized with HNO_3 in AcOH to give **22** in 94% overall yield for two steps. There exists limited literature precedent for

SCHEME 6. Synthesis of the Desired Chlorinated Intermediate



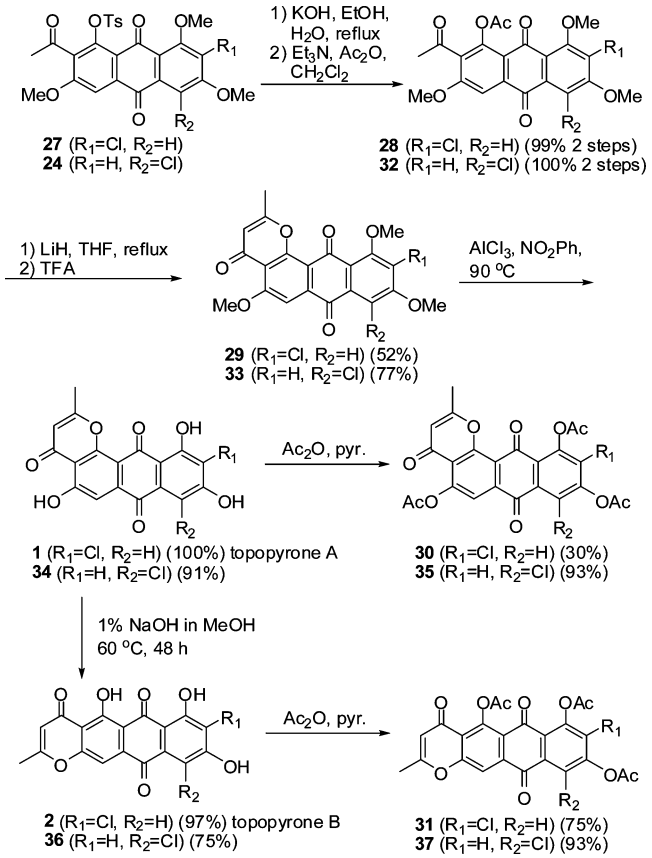
chlorination of anthraquinones.[23] However, these reports along with others detailing the ortho-directing addition of halogens to simple phenolic species[24] suggested that it might be possible to selectively introduce the chlorine in the desired C7 position using the directing effect of a free phenol. Accordingly, anthraquinone **23** was prepared in 70% yield by coupling quinone **22** with 1,3-dimethoxy-1-trimethylsiloxy-1,3-butadiene.[11] Chlorination with sulfuryl chloride in MeCN−$CHCl_3$ proceeded smoothly to give a chlorinated product, which was subsequently methylated with $(MeO)_2SO_2$ and K_2CO_3 in acetone at reflux to give the permethylated product in 87% overall yield for the two steps. ^{1}H NMR analysis (disappearance of the C5 H signal at δ 7.29) indicated that the product was the C5 chlorinated species (**24**) instead of the desired C7 product. This result, while somewhat surprising, is not unprecedented as the para-directing effect of phenols has been documented in simpler systems.[25]

As an alternative strategy chlorination of the diphenol was envisioned, an approach that has proven successful in other systems.[26] Initial attempts to prepare anthraquinone **26** using diene **13** gave consistently low yields, likely due to premature loss of the TBS group leading to complex reaction mixtures. In an effort to improve this reaction, another diene having a MOM protecting group was prepared. Accordingly, diene **25** (Scheme 6) was prepared in two steps starting from acetoacetate **12**. The enol was formed using Et_3N in benzene and subsequently trapped as the MOM ether in 45% yield. Conversion to the diene was accomplished using LDA followed by trapping with TMSCl to give **25** in 98% yield. This diene has not been reported previously. The configuration of **25** is presently unknown; it is drawn arbitrarily in Scheme 6.

Subsequent coupling of **25** with quinone **22** in CH_2Cl_2 at room temperature overnight gave the desired tricyclic product which was partially purified by column chromatography prior to removal of the MOM ether under acidic conditions in methanol

(23) (a) Sargent, M. V.; Smith, D. O. *Tetrahedron Lett.* **1970**, *24*, 2065. (b) Wiley, P. F.; Elrod, D. W.; Harper, D. E. *J. Antibiot.* **1988**, *41*, 343.
(24) (a) Pirrung, M. C.; Brown, W. L.; Rege, S.; Laughton, P. *J. Am. Chem. Soc.* **1991**, *113*, 8561. (b) Cechinel-Filho, V.; Vaz, Z. R.; Zunino, L.; Calixto, J. B.; Yunes, R. A. *Eur. J. Med. Chem.* **1996**, *31*, 833. (c) Bingham, S. J.; Tyman, J. H. P. *Chem. Commun.* **2000**, *11*, 925.
(25) Acton, J. P.; Donnelly, D. J.; Donnelly, J. A. *Monatsh. Chem.* **1982**, *113*, 73.
(26) (a) Hopkins, C. Y.; Chisholm, M. J. *Can. J. Res.* **1946**, *24B*, 208. (b) Safaryn, J. E.; Chiarello, J.; Chen, K. M.; Joullie, M. M. *Tetrahedron* **1986**, *42*, 2635. (c) Nicolaou, K. C.; Boddy, C. N. C. *J. Am. Chem. Soc.* **2002**, *124*, 10451.

SCHEME 7. Completion of the Syntheses of Topopyrones B and D and the C5 Chlorinated Analogues



at reflux. This procedure reproducibly gave the desired anthraquinone **26** in ~75% yield. Initially, treatment of the bisphenol with NCS in dioxane and cat. *p*-TsOH·H_2O[27] at reflux afforded some of the desired product, but as a mixture with what was assumed to be the C5 isomer. Switching to sulfuric acid as the catalyst resulted in no reaction after 18 h, nor did the use of $FeCl_3$ in MeCN afford the desired product.[28] Finally, treatment with cat. $ZrCl_4$ in dioxane with NCS[29] added dropwise over several hours at 70 °C afforded a mixture of products chlorinated at C5 and C7; these could be methylated using $(MeO)_2SO_2$ and K_2CO_3 in acetone at reflux to give the desired **27** mixed with **24** in 79% overall yield for the two steps. The desired C7 chloro derivative **27** could be separated chromatographically from **24** on silica gel to give pure **27** in 42% yield from **26**.

Completion of the syntheses of topopyrones A (**1**) and B (**2**) is outlined in Scheme 7. The tosylate protecting group of **27** was removed under strongly basic conditions to give the free phenol, which was subsequently acetylated to give **28** in 99% overall yield for the two steps. Treatment under rearrangement conditions (LiH, THF, reflux) gave the β-diketone along with the deacetylated free phenol. This crude mixture was treated with TFA to afford pyrone **29** in 52% yield. Removal of the methyl ethers was accomplished with $AlCl_3$ in NO_2Ph at 90 °C for 48 h to give topopyrone A quantitatively. This material was acetylated to give **30** in 30% yield. The NMR data obtained for **30** matched the literature NMR data provided for the acetylated natural material.[4] Conversion of topopyrone A (**1**) to topopyrone B (**2**) was accomplished in 97% yield by heating **1** in 1% NaOH in MeOH at 60 °C for 48 h. Putative topopyrone B (**2**) was also acetylated (affording **31**) which (by comparison with the data for **30**) permitted verification of the rearrangement of **1** → **2**. This demonstrated that the pyrone actually had rearranged to give the desired topopyrone B (**2**). This completed the synthesis of all four of the naturally occurring topopyrones. The successful rearrangement of **1** → **2** at 60 °C prompted further investigation into the analogous rearrangement of **3** → **4**. In fact, the latter rearrangement was realized in 57% yield when the reaction was carried out at 70 °C (Scheme 3).

Synthesis of 5-Chlorotopopyrone Analogues. With intermediate **24** in hand it seemed logical to complete a series of 5-chloro analogues, which would be useful for future biochemical studies. Given the greater potencies of chlorinated species **1** and **2** (vs **3** and **4**) this seemed of special interest. Accordingly, the tosylate group in **24** was removed under basic conditions, and the phenol was acetylated to give **32** quantitatively for the two steps (Scheme 7). Formation of the β-diketone followed by pyrone formation as described above was accomplished in 77% yield. The trimethoxy species **33** was deprotected with $AlCl_3$ to give the 5-chlorinated analogue **34** in 91% yield. Peracetylation to provide **35** was accomplished in good yield and confirmed that the chloro substitution was indeed different than that of the natural topopyrone A. Additionally, analogue **34** was rearranged under basic conditions to give the thermodynamically more stable **36** in 75% yield. Acetylation to provide **37** was accomplished as above, and comparison of ^1H and ^{13}C NMR spectra distinguished this material from the acetylated natural topopyrone B.

Comparison to Previous Synthetic Routes. The approaches described herein are efficient (14−18 steps in length, including all functional group changes whether purification of intermediates was required) with overall yields from commercially available starting materials ranging from 7.7% to 14.7%. Synthetically, access to topopyrones B and D compares well with the routes described by Tan and Cuifolini, which afforded 6.7% and 5.6% yields for topopyrones B and D, respectively, in 12 steps (longest linear sequence).[6] Additionally, by avoiding a late-stage thermal pyrone formation/deprotection step, we were able to access the nonthermodynamic products, topopyrones A and C. While comparatively short with 11 linear steps, the previously published approach to topopyrone C[7] afforded the product in an overall yield of only 0.53%. The present synthesis of topopyrone C was accomplished in 14 steps in 14.7% overall yield.

Conclusions

The preparation of all four naturally occurring topopyrones has been accomplished. The approach employed built upon observations of Savard and Brassard[11] by employing successive Diels−Alder reactions to install the requisite aromatic ring systems of the anthraquinone core. Of synthetic interest is the use of two novel dienes for the required Diels−Alder reactions. These dienes served our purposes well, being more stable to elevated reaction temperatures and ultimately giving the desired products in consistent yields. Additionally, the versatile synthetic approach allows for divergence to the four naturally occurring topopyrones from common intermediates, as well as the preparation of novel analogues of the topopyrones. The ef-

(27) Elix, J. A.; Jiang, H.; Wardlaw, J. H. *Aust. J. Chem.* **1990**, *43*, 1745.
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ficiency of the approach is highlighted by the total synthesis of topopyrone C; the longest linear sequence of 14 steps from commercially available starting materials was accomplished in 14.7% overall yield. In addition to confirming the proposed structures, this work should provide a useful basis for future investigations into this interesting class of topoisomerase I poisons.

Experimental Section

Toluene-4-sulfonic Acid 7-Chloro-3-methoxy-5,8-dioxo-5,8-dihydronaphthalen-1-yl Ester (8). To a solution containing 2.20 g (9.22 mmol) of **7**[11,12] in 500 mL of acetone at room temperature was added 3.51 g (18.4 mmol) of *p*-TsCl and 2.54 g (18.4 mmol) of K_2CO_3. The reaction mixture was heated to reflux for 6 h and filtered while hot through a silica gel plug. The silica gel was washed with 200 mL of ethyl acetate, and excess solvent was removed under diminished pressure to afford a crude residue. The residue was purified by flash chromatography on a silica gel column (20 cm × 6 cm). Step gradient elution with 7:3 $CHCl_3$−hexanes → $CHCl_3$ gave **8** as a yellow solid (eluted with $CHCl_3$): yield 3.51 g (97%); mp 150−152 °C; silica gel TLC R_f 0.45 (1:2 ethyl acetate−hexanes); IR (thin film, CH_2Cl_2) 1678, 1595, 1316, 1177, 1070 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.44 (s, 3H), 3.91 (s, 3H), 7.04 (d, 1H, J = 2.7 Hz), 7.08 (s, 1H), 7.32 (d, 2H, J = 8.1 Hz), 7.48 (d, 2H, J = 2.7 Hz), and 7.84 (d, 1H, J = 8.4 Hz); ^{13}C NMR ($CDCl_3$) δ 21.7, 65.4, 109.5, 110.7, 115.7, 117.2, 128.4, 128.8, 129.7, 132.1, 133.9, 135.0, 145.9, 147.7, 149.5, 164.2, 173.6, and 181.3; mass spectrum (FAB), *m*/*z* 393.0197 $(M + H)^+$ ($C_{18}H_{14}ClO_6S$ requires 393.0200).

Toluene-4-sulfonic Acid 7-Chloro-3,5,8-trimethoxynaphthalen-1-yl Ester (9). To a solution containing 1.13 g (2.87 mmol) of **8** in 50 mL of 1:1 THF−MeOH was added ∼50 mg of Pd/C. The reaction mixture was purged with H_2 and stirred under H_2 for 2 h at room temperature at which time it was filtered through a pad of silica gel and washed with 200 mL of ethyl acetate. The solvent was concentrated, and the resulting residue was dissolved in 100 mL of 1:1 THF−H_2O at room temperature. To this solution was added 1.52 g (28.7 mmol) of KOH and 2.62 mL (3.62 g, 28.7 mmol) of $(MeO)_2SO_2$. The reaction mixture was stirred at room temperature for 1 h and quenched with 100 mL of H_2O. The reaction mixture was extracted with three 100-mL portions of ethyl acetate, and the combined organic phase was dried ($MgSO_4$) and then concentrated under diminished pressure to afford a crude residue. The residue was purified by flash chromatography on a silica gel column (20 cm × 5 cm). Elution with 1:2 ethyl acetate−hexanes gave **9** as a colorless solid: yield 1.21 g (100%); mp 136−138 °C; silica gel TLC R_f 0.59 (1:2 ethyl acetate−hexanes); IR (thin film, CH_2Cl_2) 1625, 1593, 1342, 1177, 1047 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.38 (s, 3H), 3.74 (s, 3H), 3.83 (s, 3H), 3.89 (s, 3H), 6.72 (s, 1H), 6.85 (d, 1H, J = 2.4 Hz), 7.24 (d, 2H, J = 8.1 Hz), 7.43 (d, 1H, J = 2.4 Hz), and 7.78 (d, 2H, J = 8.1 Hz); ^{13}C NMR ($CDCl_3$) δ 21.5, 55.5, 55.8, 61.2, 100.7, 107.0, 113.6, 118.2, 123.0, 127.8, 128.6, 129.4, 132.8, 144.2, 144.6, 145.1, 150.5, and 156.4; mass spectrum (FAB), *m*/*z* 422.0589 (M^+) ($C_{20}H_{19}ClO_6S$ requires 422.0591).

7-Chloro-3,5,8-trimethoxynaphthalen-1-ol (6). A solution containing 2.87 g (6.81 mmol) of **9** in 200 mL of 10% KOH in 1:1 EtOH−H_2O was heated at reflux for 4 h, and excess EtOH was then removed. The remaining solution was poured into 100 mL of 6 N HCl−ice and extracted with three 100-mL portions of ethyl acetate. The combined organic phase was dried over anhydrous $MgSO_4$ and filtered, and excess solvent was removed under diminished pressure to afford a crude oil. The residue was purified by flash chromatography on a silica gel column (20 cm × 5 cm). Elution with 1:3 ethyl acetate−hexanes gave **6** as a colorless solid: yield 1.65 g (90%); mp 115−117 °C; silica gel TLC R_f 0.65 (1:2 ethyl acetate−hexanes); IR (thin film, CH_2Cl_2) 3355, 1635, 1601, 1516, 1368, 1149, 1053 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.88 (s, 3H), 3.91 (s, 3H), 4.01 (s, 3H), 6.63 (m, 2H), 7.00 (d, 1H, J = 2.4 Hz), and 9.45 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 55.2, 55.6, 62.1, 93.3, 103.6, 106.0, 113.5, 118.3, 127.5, 144.8, 151.5, 154.3, and 158.9; mass spectrum (FAB), *m*/*z* 268.0503 $(M)^+$ ($C_{13}H_{13}ClO_4$ requires 268.0502).

1-(7-Chloro-1-hydroxy-3,5,8-trimethoxynaphthalen-2-yl)ethan-2-one (10). To a solution containing 0.824 g (3.06 mmol) of **6** in 25 mL of 1,2-dichloroethane at −10 °C was added 3.37 mL (3.37 mmol) of $TiCl_4$ (1.0 M in CH_2Cl_2). The reaction mixture was stirred for 5 min at −10 °C, and 0.42 mL (0.48 g, 6.12 mmol) of acetyl chloride was added. The reaction mixture was stirred at reflux for 2 h and, while hot, was poured into 500 mL of 1:1 2 N HCl−saturated aq potassium sodium tartrate, filtered through a pad of Celite, and washed with 200 mL of ethyl acetate. The organic phase was separated, and the aqueous phase was extracted with three 300-mL portions of ethyl acetate. The combined organic phase was dried ($MgSO_4$) and concentrated under diminished pressure to afford a crude residue. The residue was purified by flash chromatography on a silica gel column (20 cm × 5 cm). Elution with 1:5 ethyl acetate−hexanes gave **10** as a yellow solid: yield 0.74 g (78%); mp 128−130 °C; silica gel TLC R_f 0.59 (1:2 ethyl acetate−hexanes); IR (thin film, CH_2Cl_2) 1661, 1497, 1395, 1362, 1280, 1084, 1064 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.68 (s, 3H), 3.88 (s, 3H), 3.89 (s, 3H), 3.90 (s, 3H), 6.77 (s, 1H), 6.83 (s, 1H), and 13.66 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 33.3, 55.3, 55.8, 61.6, 91.2, 109.5, 110.3, 115.7, 121.7, 129.2, 147.3, 150.1, 156.4, 163.0, and 204.9; mass spectrum (FAB), *m*/*z* 310.0610 $(M)^+$ ($C_{15}H_{15}ClO_5$ requires 310.0608).

9-Chloro-2-methyl-5,7,10-trimethoxybenzo[h]chromen-4-one (11). To a solution containing 0.40 g (1.28 mmol) of **10** in 20 mL of ethyl acetate was added 0.52 g (12.8 mmol) of NaH (60% dispersion in mineral oil). The reaction mixture was heated at reflux for 1 h and quenched while hot with 100 mL of 2 N HCl−ice. The solution was extracted with three 300-mL portions of $CHCl_3$, and the combined organic phase was dried ($MgSO_4$) and concentrated under diminished pressure to afford a crude residue. The residue was dissolved in 15 mL of TFA at 0 °C and stirred for 15 min at 0 °C, and then for 30 min at room temperature. The solvent was concentrated under diminished pressure, and the resulting residue was coevaporated with two 50-mL portions of toluene. The resulting residue was purified by flash chromatography on a silica gel column (20 cm × 5 cm). Step-gradient elution with 1:1 ethyl acetate−hexanes → 20% MeOH in $CHCl_3$ gave **11** as a brown solid: yield 0.36 g (84%); mp 182−184 °C; silica gel TLC R_f 0.38 (15% MeOH in 1:1 ethyl acetate−hexanes); ^1H NMR ($CDCl_3$) δ 2.48 (s, 3H), 3.94 (s, 3H), 4.00 (s, 3H), 4.05 (s, 3H), 6.31 (s, 1H), 6.95 (s, 1H), and 7.40 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 19.7, 55.9, 56.1, 61.0, 97.0, 109.2, 113.4, 114.5, 123.5, 127.8, 128.1, 145.3, 150.0, 155.0, 155.6, 163.4, and 177.4; mass spectrum (FAB), *m*/*z* 335.0687 $(M + H)^+$ ($C_{17}H_{16}ClO_5$ requires 335.0686).

9-Chloro-5-methoxy-2-methylbenzo[h]chromene-4,7,10-trione (5). To a solution containing 0.030 g (0.090 mmol) of **11** in 5 mL of MeCN at 0 °C was added 0.098 g (0.179 mmol) of CAN in 1 mL of H_2O. The reaction mixture was warmed to room temperature and stirred for 0.5 h at which time 50 mL of H_2O was added. The reaction mixture was extracted with three 50-mL portions of $CHCl_3$, and the combined organic phase was dried (anhydrous $MgSO_4$) and concentrated under diminished pressure to afford a crude residue. The residue was purified by flash chromatography on a silica gel column (15 cm × 2 cm). Elution with 10% MeOH in $CHCl_3$ gave **5** as a yellow solid: yield 0.026 g (96%); mp 257−259 °C; silica gel TLC R_f 0.50 (15% MeOH in 1:1 ethyl acetate−hexanes); IR (thin film, CH_2Cl_2) 1669, 1576, 1558 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.45 (s, 3H), 4.15 (s, 3H), 6.21 (s, 1H), 7.22 (s, 1H) and 7.49 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 19.9, 57.4, 104.0, 112.7, 113.3, 117.3, 133.5, 136.5, 148.7, 157.8, 164.7, 165.2, 174.0, 176.5, and 181.6; mass spectrum (FAB), *m*/*z* 305.0218 $(M + H)^+$ ($C_{15}H_{10}ClO_5$ requires 305.0217).

3-(*tert*-Butyldimethylsilyloxy)but-2-enoic Acid Methyl Ester (13a). To a solution containing 10.0 mL (10.7 g, 92.0 mmol) of

methyl acetoacetate (**12**) in 150 mL of benzene at room temperature was added 16.5 mL (16.7 g, 110 mmol) of DBU followed by 15.3 g (101 mmol) of TBSCl. The reaction mixture was heated to reflux for 1 h, quenched while hot with 100 mL of 2 N HCl−ice and extracted with three 100-mL portions of ethyl acetate. The combined organic extract was dried over anhydrous $MgSO_4$, filtered, and concentrated under diminished pressure to afford a crude residue. The residue was purified by flash chromatography on a silica gel column (20 cm × 5 cm). Elution with 1:9 ethyl acetate−hexanes as eluant gave **13a** as a colorless oil: yield 19.1 g (90%); silica gel TLC R_f 0.76 (1:3 ethyl acetate−hexanes); ^{1}H NMR ($CDCl_3$) δ 0.16 (s, 6H), 0.88 (s, 9H), 2.21 (s, 3H), 3.59 (s, 3H), and 5.09 (s, 1H); ^{13}C NMR ($CDCl_3$) δ −4.7, 17.9, 20.4, 25.3, 50.5, 99.4, 168.2, and 170.0; mass spectrum (FAB), *m*/*z* 231.1415 $(M + H)^+$ ($C_{11}H_{23}O_3Si$ requires 231.1417).

3-(*tert*-Butyldimethylsilyloxy)-1-methoxy-1-trimethylsilyloxybuta-1,3-diene (13). To a solution containing 1.80 mL (1.32 g, 13.0 mmol) of *i*Pr_2NH in 20 mL of THF at 0 °C was added 5.21 mL (13.0 mmol) of *n*BuLi (2.5 M in hexanes). The reaction mixture was stirred for 30 min at which time the reaction mixture was chilled to −78 °C and stirred for an additional 30 min. At this time a solution of 2.00 g (8.69 mmol) of **13a** in 10 mL of THF was added dropwise over a period of 15 min; the reaction mixture was stirred for 30 min. The reaction mixture was warmed to room temperature for 1 h, then cooled to −78 °C. A solution of 2.20 mL (1.89 g, 17.4 mmol) of TMSCl in 10 mL of THF at 25 °C was added dropwise over 15 min. The reaction mixture was stirred for 30 min at −78 °C and then for 1 h at room temperature. The solvent was concentrated under diminished pressure, and the residue was dissolved in hexanes and filtered through a pad of Celite. The solvent was concentrated under diminished pressure to afford pure **13** as a light-yellow oil: yield 2.51 g (95%); silica gel TLC R_f not recorded due to decomposition on SiO_2; ^{1}H NMR ($CDCl_3$) δ 0.15 (s, 6H), 0.23 (s, 9H), 0.93 (s, 9H), 3.53 (s, 3H), 3.88 (d, 1H, J = 1.5 Hz), 4.16 (d, 1H, J = 1.5 Hz), and 4.51 (s, 1H); ^{13}C NMR ($CDCl_3$) δ −4.6, 0.4, 18.1, 25.7, 54.8, 77.6, 89.3, 53.3, and 158.6; mass spectrum (FAB), *m*/*z* 303.1811 $(M + H)^+$ ($C_{14}H_{31}O_3Si_2$ requires 303.1812).

9-(*tert*-Butyldimethylsilyloxy)-11-hydroxy-5-methoxy-2-methyl-1-oxabenzo[*a*]anthracene-4,7,12-trione (14). To a solution containing 0.030 g (0.099 mmol) of **5** in 10 mL of benzene was added 0.30 g (0.99 mmol) of **13**. The reaction mixture was heated to 70 °C for 2 h at which time the reaction mixture was quenched while hot with 100 mL of 2 N HCl−ice and extracted with three 50-mL portions of $CHCl_3$. The combined organic layer was dried ($MgSO_4$) and concentrated under diminished pressure to afford a crude brown solid. The residue was purified by flash chromatography on a silica gel column (25 cm × 2 cm). Elution with 5% MeOH in 1:1 ethyl acetate−hexanes gave **14** as an orange solid: yield 0.026 g (54%); mp >300 °C dec; silica gel TLC R_f 0.69 (10% MeOH in 1:1 ethyl acetate−hexanes); ^{1}H NMR ($CDCl_3$) δ 0.30 (s, 6H), 1.01 (s, 9H), 2.47 (s, 3H), 4.16 (s, 3H), 6.22 (s, 1H), 6.69 (d, 1H, J = 2.4 Hz), 7.21 (d, 1H, J = 2.4 Hz), 7.66 (s, 1H), and 13.06 (s, 1H); ^{13}C NMR ($CDCl_3$) δ −4.3, 18.2, 20.0, 25.5, 57.3, 104.4, 111.7, 112.4, 113.2, 114.4, 114.6, 117.6, 133.5, 138.2, 158.2, 162.5, 164.2, 165.0, 165.3, 176.8, 181.7, and 185.1; mass spectrum (FAB), *m*/*z* 467.1528 $(M + H)^+$ ($C_{25}H_{27}O_7Si$ requires 467.1526).

Topopyrone C (3). To a solution containing 0.055 g (0.12 mmol) of **14** in 10 mL of THF at room temperature was added 0.034 g (0.13 mmol) of TBAF·H_2O. The reaction mixture was stirred for 0.5 h at room temperature, quenched with 100 mL of 2 N HCl, and extracted with three 150-mL portions of ethyl acetate and two 100-mL portions of $CHCl_3$. The combined organic phase was dried ($MgSO_4$) and concentrated under diminished pressure to afford a crude orange-yellow solid. The residue was dissolved in 10 mL of CH_2Cl_2 at −78 °C, and 1.18 mL (1.18 mmol) of BBr_3 (1.0 M in CH_2Cl_2) was added. The reaction mixture was warmed to room temperature and stirred for 18 h. The reaction was quenched with 100 mL of 2 N HCl and extracted with three 150-mL portions of ethyl acetate. The combined organic layer was dried ($MgSO_4$) and concentrated under diminished pressure to afford a crude orange-yellow solid. The crude product was purified by flash chromatography on a silica gel column (25 cm × 2 cm). Elution with 94:5:1 $CHCl_3$−MeOH−AcOH gave **3** as an orange solid: yield 0.026 g (65%); mp 133−135 °C; silica gel TLC R_f 0.51 (94:5:1 $CHCl_3$−MeOH−AcOH). All attempts at obtaining an ^{1}H NMR of **3** met with failure in a variety of solvent systems due to insufficient solubility; mass spectrum (FAB), *m*/*z* 339.0507 $(M + H)^+$ ($C_{18}H_{11}O_7$ requires 339.0505).

Topopyrone D (4). A solution containing 0.023 g (0.068 mmol) of **3** in 15 mL of 1% NaOH in MeOH was heated to 70 °C for 72 h. The reaction was quenched while hot with 2 N HCl and extracted with three 100-mL portions of $CHCl_3$. The combined organic phase was dried ($MgSO_4$) and concentrated under diminished pressure to afford a crude residue. The residue was purified by flash chromatography on a silica gel column (15 × 2 cm). Elution with 94:5:1 $CHCl_3$−MeOH−AcOH gave **4** as a red orange solid: yield 0.013 g (57%); mp >320 °C (dec); silica gel TLC R_f 0.22 (10% MeOH in 1:1 ethyl acetate−hexanes). All attempts at obtaining an ^{1}H NMR spectrum were unsuccessful in a variety of solvent systems due to the insolubility of **4**; mass spectrum (FAB), *m*/*z* 339.0507 $(M + H)^+$ ($C_{18}H_{11}O_7$ requires 339.0505).

Toluene-4-sulfonic Acid 2-Acetyl-7-chloro-3,5,8-trimethoxynaphthalen-1-yl Ester (16a). To a solution containing 0.045 g (0.14 mmol) of **10** in 5 mL of CH_2Cl_2 at room temperature was added 0.055 g (0.29 mmol) of *p*-TsCl, 0.05 mL (0.037 g, 0.29 mmol) of DIPEA, and cat. DMAP. The reaction mixture was stirred at room temperature for 1 h, quenched with 100 mL of brine and extracted with three 50-mL portions of ethyl acetate. The combined organic phase was dried ($MgSO_4$) and concentrated under diminished pressure to afford a crude residue. The residue was purified by flash chromatography on a silica gel column (15 cm × 2 cm). Elution with 1:3 ethyl acetate−hexanes gave **16a** as a colorless solid: yield 0.067 g (100%); mp 150−152 °C; silica gel TLC R_f 0.39 (1:2 ethyl acetate−hexanes); IR (thin film, CH_2Cl_2) 1700, 1594, 1325, 1177, 1084, 1042 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.42 (s, 3H), 2.51 (s, 3H), 3.50 (s, 3H), 3.92 (s, 3H), 3.93 (s, 3H), 6.77 (s, 1H), 7.26 (d, 2H, J = 8.4 Hz), 7.54 (s, 1H), and 7.78 (d, 2H, J = 8.4 Hz); ^{13}C NMR ($CDCl_3$) δ 21.6, 32.1, 55.9, 56.0, 61.0, 101.0, 107.8, 118.5, 123.7, 127.5, 129.0, 129.1, 129.3, 132.3, 139.3, 144.9, 145.3, 150.2, 153.6, and 199.4; mass spectrum (FAB), *m*/*z* 464.0695 $(M)^+$ ($C_{22}H_{21}ClO_7S$ requires 464.0697).

Toluene-4-sulfonic Acid 2-Acetyl-7-chloro-3-hydroxy-5,8-dimethoxynaphthalen-1-yl Ester (16). A solution containing 0.850 g (1.83 mmol) of **16a** in 50 mL of 16% $AlBr_3$ in MeCN was stirred at room temperature for 9 days. The reaction was quenched with 50 mL of 6 N HCl and extracted with three 50-mL portions of ethyl acetate. The combined organic extract was dried ($MgSO_4$) and concentrated under diminished pressure to afford a crude residue. The residue was purified by flash chromatography on a silica gel column (20 cm × 5 cm). Elution with 1:4 ethyl acetate−hexanes gave **16** as a yellow oil which crystallized on standing: yield 0.757 g (92%); mp 120−122 °C; silica gel TLC R_f 0.47 (1:2 ethyl acetate−hexanes); IR (thin film, CH_2Cl_2) 1653, 1506, 1335, 1200, 1177, 1038 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.35 (s, 3H), 2.77 (s, 3H), 3.65 (s, 3H), 3.89 (s, 3H), 6.62 (s, 1H), 7.10 (d, 2H, J = 8.4 Hz), 7.45 (d, 2H, J = 8.1 Hz), 7.64 (s, 1H), and 10.69 (br, 1H); ^{13}C NMR ($CDCl_3$) δ 21.6, 32.1, 56.0, 60.9, 107.8, 108.1, 117.3, 120.5, 122.9, 129.0, 129.3, 129.8, 130.0, 144.1, 144.3, 146.0, 150.0, 155.0, and 204.3; mass spectrum (FAB), *m*/*z* 450.0537 $(M)^+$ ($C_{21}H_{19}ClO_7S$ requires 450.0540).

Toluene-4-sulfonic Acid 7-Chloro-6,9-dimethoxy-2-methyl-4-oxo-4*H*-benzo[g]chromen-5-yl Ester (18). To a solution containing 1.32 g (2.67 mmol) of **17** in 20 mL of THF at 0 °C was added 0.43 g (53.6 mmol) of LiH. The reaction mixture was heated to reflux and stirred for 18 h, at which time it was cooled and then quenched with 100 mL of 2 N HCl and extracted with three 100-mL portions of ethyl acetate. The combined organic extract was

dried ($MgSO_4$) and concentrated under diminished pressure to afford a crude residue. The residue was dissolved in 10 mL of CH_2Cl_2 at 0 °C and 1 mL of TFA was added dropwise. The reaction mixture was stirred at room temperature for 1 h and concentrated under diminished pressure, and the residue was coevaporated with 50 mL of toluene. The resulting crude residue was purified by flash chromatography on a silica gel column (15 cm × 2 cm). Step-gradient elution with 1:1 ethyl acetate−hexanes → 100% ethyl acetate gave **18** as a yellow-brown solid (eluted with ethyl acetate): yield 0.63 g (50%); mp 192−194 °C; silica gel TLC R_f 0.08 (1:2 ethyl acetate−hexanes); IR (thin film, CH_2Cl_2) 1662, 1653, 1330, 1042 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.31 (s, 3H), 2.38 (s, 3H), 3.70 (s, 3H), 3.96 (s, 3H), 5.89 (s, 1H), 6.76 (s, 1H), 7.17 (d, 2H, J = 8.1 Hz), 7.60 (d, 2H, J = 8.1 Hz), and 8.17 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 20.2, 21.6, 56.1, 61.2, 108.0, 109.7, 110.4, 118.2, 120.7, 125.2, 128.5, 128.8, 129.1, 132.4, 141.4, 144.9, 145.1, 150.4, 152.5, 164.9, and 176.2; mass spectrum (FAB), m/z 475.0620 $(M + H)^+$ ($C_{23}H_{20}ClO_7S$ requires 475.0618).

Toluene-4-sulfonic Acid 7-Chloro-2-methyl-4,6,9-trioxo-6,9-dihydro-4*H*-benzo[*g*]chromen-5-yl Ester (19). To a solution containing 0.020 g (0.042 mmol) of **18** in 2 mL of AcOH at room temperature was added 2 mL of HNO_3. The reaction mixture was stirred at room temperature for 1 h, then quenched carefully with sat. aq $NaHCO_3$, and extracted with three 50-mL portions of ethyl acetate. The combined organic phase was dried ($MgSO_4$) and concentrated under diminished pressure to afford a crude yellow solid. The crude residue was purified by flash chromatography on a silica gel column (15 cm × 2 cm). Elution with 10% MeOH in 1:1 ethyl acetate−hexanes gave **19** as an orange solid: yield 0.018 g (96%); mp 202−204 °C; silica gel TLC R_f 0.41 (10% MeOH in 1:1 ethyl acetate−hexanes); IR (thin film, CH_2Cl_2) 1690, 1539, 1348, 1065 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.40 (s, 3H), 2.46 (s, 3H), 6.16 (s, 1H), 7.21 (s, 1H), 7.34 (d, 2H, J = 8.7 Hz), 7.84 (d, 2H, J = 8.4 Hz), and 8.09 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 20.1, 21.8, 113.1, 116.4, 121.6, 122.9, 128.9, 129.8, 132.3, 134.4, 135.1, 146.0, 146.7, 148.8, 159.6, 165.3, 173.2, 174.5, and 179.9; mass spectrum (FAB), m/z 445.0147 $(M + H)^+$ ($C_{21}H_{14}ClO_7S$ requires 445.0149).

2-Acetyl-3,6-dimethoxy-8-hydroxy-1-tosyloxyanthraquinone (23). To a solution containing 0.44 g (1.01 mmol) of **22** in 20 mL of toluene at room temperature was added 0.41 g (2.01 mmol) of 1,3-dimethoxy-1-trimethylsiloxy-1,3-butadiene.[11] The reaction mixture was heated to 90 °C for 2 h at which time the reaction was quenched while hot with 100 mL of 6 N HCl−ice and extracted with three 100-mL portions of ethyl acetate. The combined organic phase was dried ($MgSO_4$) and concentrated under diminished pressure to afford a crude brown solid. The residue was purified by flash chromatography on a silica gel column (20 cm × 5 cm). Elution with 1:3 ethyl acetate−hexanes gave **23** as a yellow-orange solid: yield 0.35 g (70%); mp 224−226 °C; silica gel TLC R_f 0.27 (1:2 ethyl acetate−hexanes); IR (thin film, CH_2Cl_2) 1684, 1338, 1213, 1178 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.45 (s, 3H), 2.52 (s, 3H), 3.92 (s, 3H), 4.03 (s, 3H), 6.69 (d, 1H, J = 2.4 Hz), 7.29 (d, 1H, J = 2.7 Hz), 7.33 (d, 2H, J = 8.1 Hz), 7.80 (s, 1H), 7.83 (d, 2H, J = 8.4 Hz), and 12.65 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 21.8, 31.9, 56.0, 56.9, 107.4, 108.5, 110.9, 120.8, 128.8, 129.7, 132.5, 132.7, 133.6, 136.7, 144.8, 146.0, 160.6, 165.2, 165.6, 181.1, 184.2, and 197.6; mass spectrum (FAB), m/z 497.0907 $(M + H)^+$ ($C_{25}H_{21}O_9S$ requires 497.0906).

2-Acetyl-5-chloro-1-tosyloxy-3,6,8-trimethoxyanthraquinone (24). To a solution containing 0.29 g (0.58 mmol) of **23** in 30 mL of 5:1 $CHCl_3$−MeCN at room temperature was added 0.24 mL (0.39 g, 2.92 mmol) of SO_2Cl_2. The reaction mixture was stirred for 3 h, quenched with 200 mL sat. aq $NaHCO_3$, and extracted with three 100-mL portions of ethyl acetate. The combined organic phase was dried over anhydrous $MgSO_4$ and filtered, and excess solvent was removed under diminished pressure to afford a crude brown residue. The residue was dissolved in 200 mL of acetone, and 0.81 g (5.84 mmol) of K_2CO_3 was added followed by 0.53 mL (5.84 mmol) of $(MeO)_2SO_2$. The reaction mixture was stirred at reflux for 18 h at which time it was filtered though a silica gel plug and washed with ethyl acetate. The excess solvent was removed under diminished pressure to afford a crude brown residue. The residue was purified by flash chromatography on a silica gel column (20 cm × 5 cm). Elution with 2% MeOH in $CHCl_3$ as eluant gave **24** as a yellow solid: yield 0.277 g (87%); mp 218−220 °C; silica gel TLC R_f 0.42 (1:1 ethyl acetate−hexanes); IR (thin film, CH_2Cl_2) 1683, 1558, 1317, 1081 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.43 (s, 3H), 2.48 (s, 3H), 3.96 (s, 3H), 3.99 (s, 3H), 4.01 (s, 3H), 6.79 (s, 1H), 7.33 (d, 2H, J = 8.1 Hz), 7.58 (s, 1H), and 7.88 (d, 2H, J = 8.4 Hz); ^{13}C NMR ($CDCl_3$) δ 21.7, 31.8, 56.6, 56.7, 57.0, 101.3, 107.1, 114.7, 118.1, 124.3, 128.9, 129.6, 131.7, 131.9, 132.0, 136.8, 142.0, 145.7, 159.3, 159.5, 160.0, 179.3, 182.1, and 197.9; mass spectrum (FAB), m/z 545.0676 $(M + H)^+$ ($C_{26}H_{22}ClO_9S$ requires 545.0673).

3-Methoxymethoxybut-2-enoic Acid Methyl Ester (25a). To a solution containing 5.0 mL (5.38 g, 46.3 mmol) of methyl acetoacetate (**12**) in 150 mL of benzene at room temperature was added 8.29 mL (8.44 g, 55.6 mmol) of DBU followed by 3.86 mL (4.09 g, 50.9 mmol) of MOMCl. The reaction mixture was heated to reflux for 1 h, quenched while hot with 100 mL of brine, and extracted with three 100-mL portions of ethyl acetate. The combined organic extract was dried ($MgSO_4$) and concentrated under diminished pressure to afford a crude residue. The residue was purified by flash chromatography on a silica gel column (20 cm × 5 cm). Elution with 1:3 ethyl acetate−hexanes gave **25a** as a colorless oil: yield 3.37 g (45%); silica gel TLC R_f 0.83 (1:2 ethyl acetate−hexanes); ^1H NMR ($CDCl_3$) δ 2.21 (s, 3H), 3.33 (s, 3H), 3.55 (s, 3H), 4.91 (s, 2H), and 5.13 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 18.2, 50.5, 56.4, 93.4, 93.4, 167.8, and 169.8; mass spectrum (FAB), m/z 161.0815 $(M + H)^+$ ($C_7H_{13}O_4$ requires 161.0814).

(1-Methoxy-3-methoxymethoxybuta-1,3-dienyloxy)trimethylsilane (25). To a solution containing 1.91 mL (1.38 g, 13.8 mmol) of iPr$_2$NH in 20 mL of THF at 0 °C was added 5.51 mL (13.8 mmol) of nBuLi (2.5 M in hexanes). The reaction mixture was stirred at 0 °C for 30 min, at which time the reaction mixture was chilled to −78 °C and stirred for an additional 30 min. A solution containing 2.00 g (12.5 mmol) of **25a** in 10 mL of THF at 25 °C was added dropwise over a period of 15 min, and the reaction mixture was stirred for 30 min at −78 °C. A solution containing 2.36 mL (2.01 g, 18.8 mmol) of TMSCl in 10 mL of THF at 25 °C was added dropwise over a period of 15 min. The reaction mixture was stirred at −78 °C for 30 min and then at room temperature for an additional 1 h. The solvent was concentrated under diminished pressure, and the residue was dissolved in hexanes and filtered through a pad of Celite. The solvent was concentrated under diminished pressure to afford pure **25** as a light yellow oil: yield 2.83 g (98%); silica gel TLC R_f was not recorded due to decomposition on SiO_2; ^1H NMR ($CDCl_3$) δ 0.21 (s, 9H), 3.39 (s, 3H), 3.53 (s, 3H), 3.99 (s, 1H), 4.18 (s, 1H), 4.40 (m, 1H), and 4.92 (s, 2H); ^{13}C NMR ($CDCl_3$) δ 0.2, 54.9, 55.9, 75.0, 83.0, 93.4, 155.8, and 158.9. *Note: compound decomposes rapidly, and must be used immediately.*

2-Acetyl-6,8-dihydroxy-3-methoxy-1-tosyloxyanthraquinone (26). To a solution containing 0.40 g (0.90 mmol) of **22** in 20 mL of benzene at room temperature was added 0.84 g (3.60 mmol) of **25**. The reaction mixture was stirred at room temperature for 18 h, quenched with 100 mL of 2 N HCl, and extracted with three 100-mL portions of ethyl acetate. The combined organic phase was dried and concentrated under diminished pressure to afford a crude brown solid. The residue was purified by flash chromatography on a silica gel column (20 cm × 5 cm). Elution with 1:2 ethyl acetate−hexanes gave a yellow oil which was dissolved in 20 mL of MeOH at room temperature and treated with ∼1 mL of conc HCl. The reaction mixture was heated to reflux and stirred for 18 h, and then MeOH was removed under diminished pressure. The residue was dissolved in 50 mL of H_2O and extracted with three 100-mL portions of $CHCl_3$. The combined $CHCl_3$ extract was dried ($MgSO_4$) and concentrated under diminished pressure to afford a crude brown

solid. The residue was purified by flash chromatography on a silica gel column (30 cm × 2 cm). Elution with 2% MeOH in $CHCl_3$ gave **26** as a yellow solid: yield 0.32 g (75%); mp 223−225 °C; silica gel TLC R_f 0.42 (1:1 ethyl acetate−hexanes); IR (thin film, CH_2Cl_2) 1717, 1558, 1317, 1229 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.46 (s, 3H), 2.55 (s, 3H), 4.04 (s, 3H), 6.59 (d, 1H, J = 2.7 Hz), 7.16 (d, 1H, J = 2.7 Hz), 7.34 (d, 2H, J = 8.4 Hz), 7.77 (s, 1H), 7.85 (d, 2H, J = 8.4 Hz), and 12.60 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 21.1, 31.5, 57.2, 107.7, 108.2, 108.9, 109.5, 120.0, 128.6, 129.9, 131.1, 131.7, 133.6, 136.3, 144.0, 146.2, 160.5, 164.1, 164.6, 180.4, 183.5, and 197.3; mass spectrum (FAB), *m*/*z* 483.0753 $(M + H)^+$ ($C_{24}H_{19}O_9S$ requires 483.0750).

2-Acetyl-7-chloro-1-tosyloxy-3,6,8-trimethoxyanthraquinone (27). To a solution containing 0.32 g (0.67 mmol) of **26** in 30 mL of dioxane at room temperature was added ∼15 mg of $ZrCl_4$. The reaction mixture was slowly heated to 70 °C while 0.11 g (0.81 mmol) of NCS in 10 mL of dioxane was added dropwise over a period of 2 h. The reaction mixture was stirred at 70 °C for 18 h and then concentrated under diminished pressure. The residue was purified by flash chromatography on a silica gel column (30 × 2 cm). Elution with 5% MeOH in 1:1 ethyl acetate−hexanes afforded a major red band (R_f slightly smaller than the starting material) which was collected and concentrated to afford an orange-yellow residue. The residue was dissolved in 20 mL of acetone, and 0.93 g (6.72 mmol) of K_2CO_3 and 0.62 mL (6.72 mmol) of dimethyl sulfate was added. The reaction mixture was stirred at reflux for 3 h, quenched after cooling with 100 mL of 2 N HCl, and extracted with three 100-mL portions of ethyl acetate. The combined organic extract was dried ($MgSO_4$) and concentrated under diminished pressure to afford a crude residue. The residue was purified by flash chromatography on a silica gel column (30 cm × 2 cm). Step-gradient elution with 2:1 ethyl acetate−hexanes → 100% ethyl acetate afforded **27** as a yellow solid (eluted with 1:1 ethyl acetate−hexanes): yield 0.13 g (42%); (also obtained was 0.12 g of **24** (37%) (eluted with 100% ethyl acetate)); mp 232−235 °C; silica gel TLC R_f 0.81 (1:1 ethyl acetate−hexanes); IR (thin film, CH_2Cl_2) 1684, 1338, 1213 cm^{-1}; ^1H NMR ($CDCl_3$) δ2.47 (s, 3H), 2.53 (s, 3H), 4.02 (s, 6H), 4.09 (s, 3H), 7.36 (d, 2H, J = 8.7 Hz), 7.57 (s, 1H), 7.71 (s, 1H), and 7.91 (d, 2H, J = 8.4 Hz); ^{13}C NMR ($CDCl_3$) δ 21.8, 31.9, 56.8, 57.0, 62.1, 105.1, 107.4, 122.6, 124.0, 125.8, 128.8, 129.8, 132.1, 132.7, 132.8, 135.4, 143.3, 146.0, 157.9, 159.5, 159.7, 179.0, 181.4, and 197.8; mass spectrum (FAB), *m*/*z* 545.0675 $(M + H)^+$ ($C_{26}H_{22}ClO_9S$ requires 545.0673).

1-*O*-Acetyl-2-acetyl-7-chloro-3,6,8-trimethoxyanthraquinone (28). To a solution containing 0.24 g (0.44 mmol) of **27** in 60 mL of 1:1 EtOH−H_2O was added 0.23 g (4.40 mmol) of KOH. The reaction mixture was stirred at reflux for 4 h. The cooled solution was poured into 50 mL of 2 N HCl and extracted with three 100-mL portions of ethyl acetate. The combined organic phase was dried ($MgSO_4$) and concentrated under diminished pressure to afford a crude residue. The residue was purified by flash chromatography on a silica gel column (15 cm × 2 cm). Elution with 2% MeOH in $CHCl_3$ afforded the free phenol. This material was dissolved in 20 mL of CH_2Cl_2, and 0.08 mL (0.090 g, 0.88 mmol) of Ac_2O was added followed by 0.12 mL (0.089 g, 0.88 mmol) of Et_3N and ∼10 mg of DMAP. The reaction mixture was stirred at room temperature for 18 h, then quenched with 100 mL of 2 N HCl, and extracted with three 50-mL portions of ethyl acetate. The combined organic extract was dried ($MgSO_4$) and concentrated under diminished pressure to afford a crude residue. The residue was purified by flash chromatography on a silica gel column (15 cm × 2 cm). Elution with 2% MeOH in $CHCl_3$ gave **28** as a yellow solid: yield 0.189 g (99%); mp 198−200 °C; silica gel TLC R_f 0.53 (ethyl acetate); IR (thin film, CH_2Cl_2) 1771, 1592, 1339, 1215, 1137 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.42 (s, 3H), 2.50 (s, 3H), 3.93 (s, 3H), 4.03 (s, 3H), 4.07 (s, 3H), 7.58 (s, 1H), and 7.65 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 21.0, 31.7, 56.6, 56.9, 61.7, 105.2, 106.5, 120.2, 121.5, 125.9, 131.3, 132.9, 135.4, 147.5, 158.2, 159.6, 159.7, 169.1, 178.9, 181.7, and 199.0; mass spectrum (FAB), *m*/*z* 433.0692 $(M + H)^+$ ($C_{21}H_{18}ClO_8$ requires 433.0690).

Topopyrone A (1). A solution containing 0.026 g (0.063 mmol) of **29** in 4 mL of 1.0 M $AlCl_3$ in nitrobenzene was heated to 90 °C for 48 h. The reaction was quenched while hot with 50 mL of 6 N HCl and stirred at 90 °C for 1 h. The cooled mixture was extracted with three 100-mL portions of $CHCl_3$. The combined organic extract was dried ($MgSO_4$) and concentrated under diminished pressure to afford a crude orange-yellow solid. The crude product was purified by flash chromatography on a silica gel column (15 cm × 2 cm). Step-gradient elution with 4:1 ethyl acetate−hexanes → 94:5:1 $CHCl_3$−MeOH−AcOH gave **1** as a brown solid: yield 0.023 g (100%); mp >320 °C dec; silica gel TLC R_f 0.78 (10% MeOH in 1:1 ethyl acetate−hexanes). All attempts at obtaining an ^1H NMR spectrum met with failure in a variety of solvent systems due to insufficient solubility; mass spectrum (FAB), *m*/*z* 373.0113 $(M + H)^+$ ($C_{18}H_{10}ClO_7$ requires 373.0115).

Supporting Information Available: General experimental details for all new compounds and copies of ^1H and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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