1,2,3,4-Tetra-*O*-acetyl-α-D-glucopyranose and 1,2,3-Tri-*O*-acetyl-α-D-glucopyranose. To a suspension of α-D-glucose pentaacetate (0.1 g/100 mL) in phosphate buffer (0.05 M, pH 7) containing 10% (v/v) DMF was added CCL (1 g/g substrate), and the reaction was stirred. The reaction progress was monitored by TLC (EtOAc/petroleum ether 2:1). When all starting material had disappeared (~36 h) the reaction was worked up as described in the general procedure above. Yield (1,2,3,4-tetraacetate): 0.23 g, 27% (syrup); ^{1}H NMR ($CDCl_3$) δ 6.32 (d, 1 H, H1, J = 4 Hz), 5.50 (t, 1 H, H3, J = 10 Hz), 5.08 (t, 1 H, H4, J = 10 Hz), 5.04 (dd, 1 H, H2, J = 10 Hz, J = 4 Hz), 3.9 (m, 1 H, H5), 3.71 (dd, 1 H, H6, J = 11 Hz, J = 2 Hz), 3.52 (dd, 1 H, H6′, J = 11 Hz, J = 4 Hz), 2.15 (s, 3 H, acetyl), 2.05 (s, 3 H, acetyl), 2.01 (s, 3 H, acetyl), 1.99 (s, 3 H, acetyl); ^{13}C NMR ($CDCl_3$) 88.67, 71.71, 69.28, 68.95, 67.82, 60.23 ppm; GLC (Me_3Si ether) t_R 3.86 min. Yield (1,2,3-triacetate): 0.51 g, 73% (syrup); ^{1}H NMR ($CDCl_3$) δ 6.25 (d, 1 H, H1, J = 4 Hz), 5.38–5.25 (m, 1 H, H3), 4.96 (d, 1 H, H2, J = 10 Hz, J = 4 Hz), 3.83–3.70 (m, 4 H, H4,5,6,6′), 2.14 (s, 3 H, acetyl), 2.08 (s, 3 H, acetyl), 1.99 (s, 3 H, acetyl); ^{13}C NMR ($CDCl_3$) 89.03, 73.67, 71.85, 69.19, 67.88, 60.83 ppm; GLC (Me_3Si ether) t_R 4.23 min; $[\alpha]^{26}_D$ +104.0° (*c* 2.77, $CHCl_3$).

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Synthesis, X-ray Crystal Structure, and Antimitotic Properties of 6-Chloro-2-methoxy-5-(2′,3′,4′-trimethoxyphenyl)cyclohepta-2,4,6-trien-1-one, a Bicyclic Analogue of Colchicine

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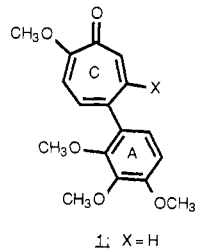
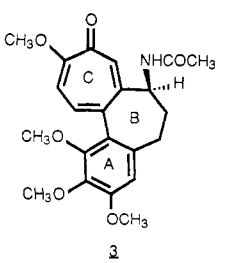
A regiocontrolled synthesis of the bicyclic colchicine analogue **2** has been achieved. Thus, the readily available cyclohexenone **10** was elaborated to the tricyclic compounds **15a**, **16b**, and **17b**, which were converted into the α-methoxy enone **6**. Reaction of **6** with 1,8-diazabicyclo[5.4.0]undec-7-ene gave the title compound (**2**). Subjection of diol **17b** to a Swern reaction, using excess oxidant, afforded the free tropolone **22**, which, on O-methylation, gave a 1:1 mixture of **2** and isomer **23**. An X-ray crystal structure of **2** reveals an angle of 77.5° between the planes of the two rings. Like colchicine, compound **2** is a potent antimitotic agent. Isomer **23** is much less active.

Introduction

In 1976, Fitzgerald reported[1] that the 5-(trimethoxyphenyl)tropolone methyl ether **1** (MTPT) retains the potent antimitotic activity of the alkaloid colchicine (**3**).[2] Subsequent and extensive studies[3] on **1** have helped to provide a better understanding of the mode of biological action of **3**. Interestingly, in spite of several reported attempts,[4] only two successful routes to 5-aryltroponoids have been published[5] since this time. As one of us has recently developed new syntheses of troponoid compounds,[6,7] we sought to prepare systems related to **1** for the purposes of structure–activity studies. We now described a fully regiocontrolled synthesis of the chloro analogue **2**, report its X-ray crystal structure, and detail some of the compound's biological properties. Interest in compound **2** derives not only from its demonstrated antimitotic activity but also from the fact that it is suitably constituted for elaboration to the natural product **3**.



1: X = H
2: X = Cl



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(1) Fitzgerald, T. J. *Biochem. Pharmacol.* **1976**, *25*, 1383.
(2) Boger, D. L.; Brotherton, C. E. *J. Am. Chem. Soc.* **1986**, *108*, 6713 and references therein.
(3) (a) Ray, K.; Bhattacharyya, B.; Biswas, B. B. *J. Biol.* Chem. 1981, *256*, 6241. (b) Schrek, R.; Stefani, S. S. *Exp. Mol. Pathol.* **1981**, *34*, 369. (c) Bane, S.; Puett, D.; Macdonald, T. L.; Williams, R. C. *J. Biol. Chem.* **1984**, *259*, 7391. (d) Andreu, J. M.; Gorbunoff, M. J.; Lee, J. C.; Timasheff, S. N. *Biochemistry* **1984**, *23*, 1742. (e) Rossi, M.; Link, J.; Lee, J. C. *Arch. Biochem. Biophys.* **1984**, *231*, 470. (f) Bhattacharyya, B.; Howard, R.; Maity, S. N.; Brossi, A.; Sharma, P. N.; Wolff, J. *Proc. Natl. Acad. Sci. U.S.A.* **1986**, *83*, 2052. (g) Engelborghs, Y.; Fitzgerald, T. J. *Ann. N.Y. Acad. Sci.* **1986**, *466* (Dyn. Aspects Microtubule Biol.), 709. (h) Bhattacharyya, B.; Ghoshchaudhuri, G.; Maity, S.; Biswas, B. B. *Ann. N.Y. Acad. Sci.* **1986**, 466 (Dyn. Aspects Microtubule Biol.), 791. (i) Choudhury, G. G.; Maity, S.; Bhattacharyya, B.; Biswas, B. B. *FEBS Lett.* **1986**, *197*, 31. (j) Andreu, J. M.; De La Torre, J.; Carrascosa, J. L. *Biochemistry* **1986**, *25*, 5230. (k) Maity, S. N.; Bhattacharyya, B. *FEBS Lett.* **1987**, *218*, 102. (l) Banerjee, A. I.; Barnes, L. D.; Lunduena, R. F. *Biochim. Biophys. Acta* **1987**, *913*, 138. (m) Engelborghs, Y.; Fitzgerald, T. J. *J. Biol. Chem.* **1987**, *262*, 5204.
(4) (a) Mak, C.-P.; Büchi, G. *J. Org. Chem.* **1981**, *46*, 1. (b) Mann, J.; Wilde, P. D.; Finch, M. W. *Tetrahedron* **1987**, *43*, 5431.
(5) (a) Nozoe, J.; Takase, K.; Saito, H.; Yamamoto, H.; Imafuku, K. *Chem. Lett.* **1986**, *1577*. (b) Nair, V.; Powell, D. W.; Suri, S. C. *Synth. Commun.* **1987**, *17*, 1897.
(6) (a) Banwell, M. G.; Lambert, J. N.; Reum, M. E.; Onrust, R. *Org. Prep. Proced. Int.*, in press. (b) Banwell, M. G.; Knight, J. H. *J. Chem. Soc., Chem. Commun.* **1987**, *1082*.
(7) Banwell, M. G.; Onrust, R. *Tetrahedron Lett.* **1985**, *26*, 4543.

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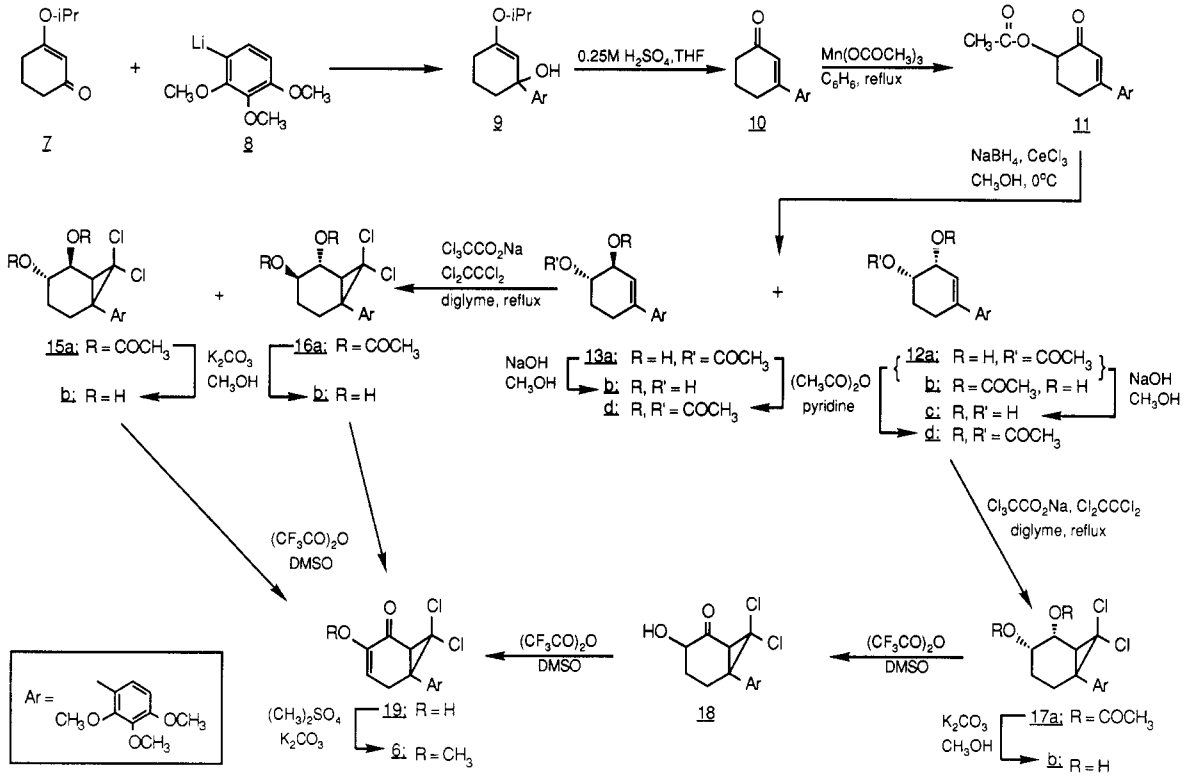
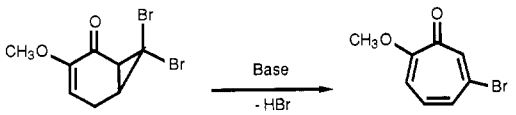
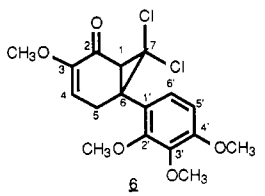
Scheme I



Synthetic Studies

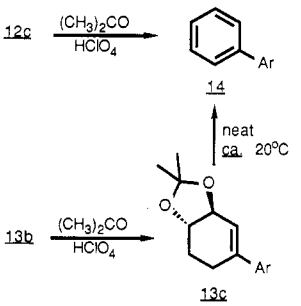
In view of the facile base-promoted ring-opening of bicyclic enone **4** to give tropolone methyl ether **5**,[7] we anticipated that the tricyclic system **6** would undergo a comparable reaction and deliver the target compound **2**. Thus the α-methoxy enone **6** became the major synthetic subtarget in this work. The ultimately successful route to compound **6** is outlined in Scheme I.





Following a procedure described by McMurry and coworkers,[8] we treated the readily available isopropyl enol ether **7** with (2,3,4-trimethoxyphenyl)lithium (**8**). The resulting allylic alcohol **9** was not isolated but immediately subjected to treatment with 0.25 M H_2SO_4 and thereby produced the bicyclic enone **10** (67% from **8**). α'-Acetoxylation of **10** using manganese triacetate[9] in refluxing benzene gave **11** (60%) as a white crystalline solid. Selective 1,2-reduction of the enone moiety in **11** was readily achieved with $NaBH_4$ in the presence of cerium trichloride[10] and gave a ca. 2:1 mixture of *cis*- and *trans*-hydroxy acetates **12** and **13** (89% combined yield), which could be separated by TLC. (Small amounts of the corresponding diols **12c** and **13b** were also isolated.) The cis compound proved to be a ca. 1:1 mixture of regioisomers **12a,b**. Presumably, isomer **12a** is the initial product of reduction and, because of the cis relationship between the adjacent hydroxyl and acetate moieties, this compound undergoes intramolecular acyl transfer to give **12b**. Indeed, the observation of the acyl-transfer product **12b** provided a major basis for the assignment of stereochemistry in these compounds. Confirmation that **12a** and **12b** had the same configuration about C1 and C2 followed from the observation that hydrolysis (with NaOH in methanol) of these compounds gave a single diol, **12c**, in near quantitative yield. Hydrolysis of the *trans*-hydroxy acetate **13a** under similar conditions gave diol **13b** (99%).

Scheme II

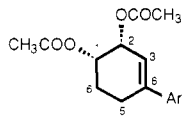


Attemps to convert *cis*-diol **12c** into the corresponding acetonide, prior to the dichlorocarbene addition step, only gave the dehydration product **14**[11] (73%) (Scheme II). Although *trans*-diol **13b** could be converted into **13c** (58%), this latter compound was unstable, reverting to biphenyl **14** on standing. Consequently alternative methods for hydroxyl group protection were sought.

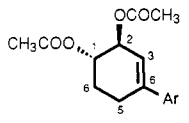
Acetylation (acetic anhydride/pyridine) of the hydroxy acetates **12a,b** (Scheme I) afforded the diacetate **12d**

(8) McMurry, J. E.; Farina, V.; Scott, W. J.; Davidson, A. H.; Summers, D. R.; Shenvi, A. *J. Org. Chem.* **1984**, *49*, 3803.
(9) Dunlap, N. K.; Sabol, M. R.; Watt, D. S. *Tetrahedron Lett.* **1984**, *25*, 5839.
(10) Gemal, A. L.; Luche, J.-L. *J. Am. Chem. Soc.* **1981**, *103*, 5454.
(11) Allan, G.; Bruce, J. M. *J. Chem. Soc.* **1963**, 1757.

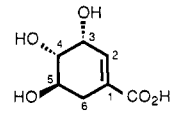
(98%). Similar treatment of *trans*-hydroxy acetate **13a** gave **13d** (81%). Decoupling experiments on diacetate **12d**



12d



13d



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show that $J_{1,2}$ = 3 Hz, which compares favorably with the coupling constant (J = 4 Hz) observed[12] for the analogous cis-related protons (H3 and H4) in shikimic acid (**20**). Similar experiments on the *trans*-diacetate **13d** show $J_{1,2}$ = 7 Hz, a value in good agreement with that observed (J = 8.4 Hz) for the trans-related protons H4 and H5 in **20**. These observations support the stereochemical assignments made earlier.

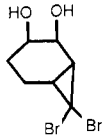
Treatment of **12d** with sodium trichloroacetate, under conditions normally used to generate dichlorocarbene,[13] gave a single cyclopropane (46% yield), which was assigned as stereoisomer **17a**—the compound resulting from carbene addition to the less hindered β-face of the starting alkene. Also formed in this reaction were the biphenyl **14** (22%) and hexachlorocyclopropane[13] (derived from dichlorocarbene addition to the reaction solvent tetrachloroethylene). Addition of dichlorocarbene to *trans*-diacetate **13d** under the same reaction conditions gave an inseparable 3:5 mixture of the expected products **15a** and **16a** (40% combined yield) as well as biphenyl **14** (24%) and hexachlorocyclopropane.

Hydrolysis of the **15a/16a** mixture, using K_2CO_3 in methanol, gave the corresponding mixture of diols **15b** and **16b**, which were readily separated by preparative TLC and obtained as white crystalline solids. Comparable hydrolysis of **17a** gave diol **17b** in 98% yield. The ^1H noise decoupled ^{13}C NMR spectrum of **17b** recorded at 27 °C displayed six, rather than the expected three, carbon resonances (for C1, C4, and C5) in the high-field region (δ 40–20). However, when the same spectrum was recorded at 100 °C, the original six signals coalesced to give three peaks (δ 38.3, 26.1, and 24.9) while the lower field resonances remained unaffected. The ^1H NMR spectrum of **17b** obtained at 27 °C also showed splitting of peaks. Thus, four doublets, rather than two, were observed for the vicinally related aromatic protons in this compound. In addition, four, rather than the anticipated three, methoxyl singlets were observed (δ 4.07, 4.03, 3.86, and 3.84). We have attributed these rather unusual spectral features to restricted rotation about the C6–C1′ bond, which might be caused, at least in part, by hydrogen bonding between the C2′-methoxy oxygen of the aromatic ring and the proximate hydroxyl groups at C2 and C3. Significantly, there is no broadening or splitting of peaks in the ^1H and ^{13}C NMR spectra of the precursor diacetate **17a**. It is noteworthy that there appears to be little comparable splitting of signals in the NMR spectra of the isomeric diols **15b** and **16b**.

Trifluoroacetic anhydride (TFAA) activated dimethyl sulfoxide (DMSO) oxidation[15] of the diol mixture **15b/16b** (using 2.1 mol equiv of oxidant) afforded the expected α-hydroxy enone **19** (69%) as a colorless oil. Oxidation of the *cis*-diol **17b** under the same conditions afforded not only the desired product **19** (63%) but also a hydroxy ketone (as determined by IR and ^{13}C NMR spectroscopy) tentatively identified as **18** (26%). Resubjection of compound **18** to the oxidation reaction (using 1.05 mol equiv of TFAA) gave further quantities of enone **19** (62% at 65% conversion). O-Methylation of compound **19** (using K_2CO_3/dimethyl sulfate) was readily accomplished, and the key intermediate, methoxy enone **6**, was obtained in 87% yield. The ^1H NMR spectrum of **6** was diagnostic, displaying an AB spin system for the aromatic protons, a one-proton triplet (J = 4.5 Hz) at δ 5.64 for H4, four three-proton singlets at δ 3.88, 3.86, 3.62, and 3.46 due to the methoxyl protons, a one-proton doublet of doublet of doublets (J = 21, 4.5, and 1 Hz) due to one of the C5 protons, a one-proton doublet (J = 1 Hz) which is assigned to H1, and a one-proton doublet of doublets due to the remaining C5 proton.

As expected,[7] treatment of a benzene solution of the α-methoxyenone **6** with the weakly nucleophilic base 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) at room temperature resulted in the rapid formation of the target tropolone methyl ether **2** (91%), the structure of which has been confirmed by X-ray crystallographic methods. Accompanying **2** in this reaction was a small quantity of an unidentified yellow oil. High-resolution mass spectral measurements established the molecular formula $C_{25}H_{31}ClN_2O_5$ for this material, suggesting that it was derived (at least in a formal sense) by combination of DBU and **2** with concomitant loss of a methylene unit.

We have previously demonstrated[7] that the bicyclic diol **20** is converted into the tropolone **21** on treatment with 3.1 equiv of TFAA activated DMSO. It was therefore



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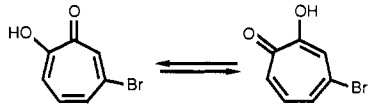
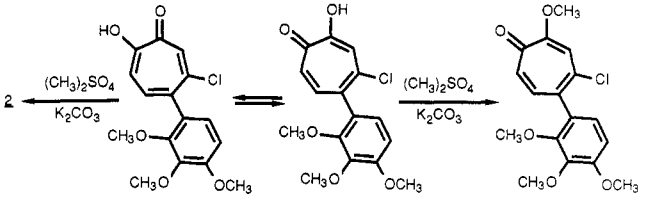


21a 21b

anticipated that oxidation of diol **17b** under the same conditions would give the 5-aryltropolone **22**. Compound **22** was of interest because methylation of this unsymmetrical system should give not only the previously described tropolone methyl ether **2** but also regioisomer **23**. A



22a 22b 23

comparison of the antimitotic properties displayed by these bicyclic colchicine analogues should then provide further insights into the structure–activity relationships of such compounds. In the event, oxidation of diol **17b** under the appropriate conditions afforded the tropolone **22** (76%) as pale yellow needles. O-Methylation of **22** (using K_2CO_3/dimethyl sulfate) then gave a ca. 1:1 mixture of regioisomers **2** and **23**, which could be separated by preparative TLC. Compound **23** was obtained as a crystalline solid.

X-ray Crystallography Study of 2

The molecular geometry of compound **2** is shown in Figure 1. All bond lengths and angles are normal and compare favorably with those found in the unchlorinated analogue **1**.[3e] The structures of **1** and **2** only differ sub-

(12) Jackman, L. M.; Sternhell, S. *Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry*, 2nd ed.; Pergamon: London, 1969; p 296.
(13) Fieser, L. F.; Sachs, D. H. *J. Org. Chem.* **1964**, *29*, 1113.
(14) Seyferth, D.; Burlitch, J. M.; Minasz, R. J.; Mui, J. Y.-P.; Simmons, H. D.; Treiber, A. J. H.; Dowd, S. R. *J. Am. Chem. Soc.* **1965**, *87*, 4259.
(15) Amon, C. M.; Banwell, M. G.; Gravatt, G. L. *J. Org. Chem.* **1987**, *52*, 4851.

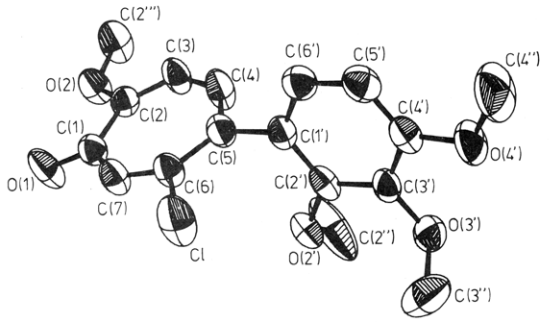
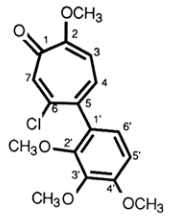
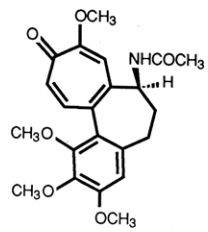


Figure 1. Computer-generated perspective drawing of **2**.

stantially in the angle (as defined by the carbon array 6–5–1′–2′) between the planes of their two rings (77.5° in the title compound, 57.4° in the nonchlorinated analogue). Thus, like MTPT (**1**), compound **2** assumes a solid-state conformation resembling isocolchicine (**24**) (rather than colchicine).[3e]



1: X = H
2: X = Cl



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Biological Studies

The antimitotic properties of colchicine (**3**) and MTPT (**1**) stem from the ability of these molecules to interfere with cellular processes that depend upon microtubule formation.[1-3] Specifically, compounds **1** and **3** bind to tubulin, the major protein subunit of microtubules, thus preventing its polymerization and hence mitosis. The interaction of tubulin with **1** and **3** has been studied extensively,[1-3] and the existence of two partial binding sites on the protein has been established, one for the trimethoxyphenyl ring and one for the tropolone methyl ether ring.

It has been suggested[3f,m] that **1** and **3** undergo reversible binding to tubulin, giving an initial complex, which is then converted into a more stable one. It is frequently argued[1,3] that initial binding of **1** or **3** occurs with a skewed conformation of these molecules, while binding in the more stable complex involves a near planar relationship between the tropone and aryl rings.

If such a model were accurate, then it might be expected that compound **2**, in which the bicyclic system can flatten to produce an atropisomer resembling colchicine, would exhibit significant antimitotic activity. In contrast, isomer **23**, which cannot adopt the comparable atropisomeric planar conformation because severe steric compression between the C4 chlorine and the C2′ methoxy group would result, should be less active. This proved to be the case.

Compounds **2** and **23** were compared to MTPT (**1**)[1,3,20] in several in vitro biological assays (Table I). Tropolone methyl ether **2** was identical to MTPT in the concentration required to inhibit the growth of L1210 murine leukemia cells by 50%, while compound **23** was over 30 times less active (experiment I). Like MTPT, both agents caused a marked rise in cells arrested in mitosis, provided cytotoxic drug concentrations were used (experiment II). Virtually all antimitotic drugs inhibit microtubule assembly, and compound **2** was even more potent than MTPT in inhibiting this reaction (experiment III). Compound **23**, at low concentrations, was much less active, but it, too, inhibited microtubule assembly at high concentrations, consistent with its weaker cytotoxicity. Purified tubulin will polymerize withut other microtubule components in high concentrations of glutamate, and almost all well-described antimitotic agents interact with tubulin rather than the minor microtubule components. Experiment IV demonstrates that compound **2** and **23**, and MTPT, are no exceptions to this generalization. Again, inhibition of tubulin polymerization required a much higher concentration of compound **23** as compared to compound **2** and MTPT. Like MTPT,[1,3] compounds **2** and **23** also inhibit the binding of radiolabeled colchicine to tubulin (experiment V), with a much higher concentration of compound **23** required relative to the other two systems. In summary, compound **2** is a potent antimitotic agent which binds at the colchicine site of tubulin, but compound **23** is much less active.

Table I. Biological Properties of Compounds 2 and 23[a]

agent	expt I: cell growth (IC_{50}, μM)	expt II: % mitoses (drug concn)	% inhibn: expt III: microtubule assembly	% inhibn: expt IV: tubulin polymerization	% inhibn: expt V: colchicine binding
2	0.13	59 (0.5 μM)	100	97	48
23	4.2	46 (15 μM)	9 (74)	2 (51)	5 (39)
MTPT	0.13	62 (0.5 μM)	73	76	47

[a] See Experimental Section for further details.

Experimental Section

General Procedures. Deuteriochloroform was used as solvent for NMR spectra unless otherwise stated. Analytical thin-layer chromatography (TLC) was conducted on aluminum-backed 2-mm-thick silica gel 60 F_{254} plates (Merck). Chromatograms were visualized with iodine vapor, with anisaldehyde/H_2SO_4/EtOH (2:5:93 v/v/v) spray reagent, or under a 254-nm UV lamp. Preparative TLC was conducted on 20 × 20 cm glass plates loaded with Merck Kieselgel 60 GF_{254} (35 g/plate) by using the solvent system indicated. Tetrahydrofuran (THF) and diethyl ether (Et_2O) were distilled from benzophenone ketyl before use. Dichloromethane (CH_2Cl_2) was distilled from CaH_2, and triethylamine (Et_3N) from KOH pellets. Dimethyl sulfoxide (DMSO) was distilled from CaH_2 under reduced pressure. All other solvents and reagents were purified by literature procedures.[16] All reactions requiring anhydrous conditions were run under an argon or nitrogen atmosphere in oven-dried glassware.

3-(2′,3′,4′-Trimethoxyphenyl)cyclohex-2-en-1-one (10). Butyllithium (6.0 mL of a 1.2 M solution in hexane, 7.2 mmol) was added over a period of 45 min (syringe pump) to an ice-cold solution of 1,2,3-trimethoxybenzene (1.15 g, 6.8 mmol) in THF (3.6 mL) containing tetramethylethylenediamine (1.03 mL, 6.8 mmol). The resulting yellow suspension was stirred at room temperature for 2 h and then transferred, via cannula, into a stirred solution of enol ether **7**[8] (1.01 g, 6.55 mmol) in THF (3.6 mL). The material remaining in the original flask was transferred with the aid of additional THF (2.5 mL). The yellow solution thus obtained was stirred at ambient temperatures for 18 h before being poured into water (10 mL) and extracted with CH_2Cl_2 (4 × 10 mL). The combined organic phases were washed with

(16) Perrin, D. D.; Armarego, W. L. F.; Perrin, D. *Purification of Laboratory Chemicals*, 2nd ed.; Pergamon: Oxford, 1980.
(17) *The Dictionary of Organic Compounds*, 5th ed.; Chapman and Hall: New York, 1982.
(18) Scott, L. T.; Brunsvold, W. R.; Kirms, M. A.; Erden, I. *J. Am. Chem. Soc.* **1981**, *103*, 5216.
(19) Programs used for unit cell determinations and initial data processing were part of the CAD-4 SDP structure determination package by B. Frenz. The direct methods structure solution and least-squares refinement were carried out with SHELX on the University of Auckland IBM 4341 computer.
(20) Hamel, E.; Lin, C. M. *Biochem. Pharmacol.* **1983**, *32*, 3864.

saturated aqueous NH_4Cl (1 × 20 mL), then dried ($MgSO_4$), and concentrated under reduced pressure to a yellow-brown oil (2.22 g). This material was dissolved in a mixture of THF (5 mL) and 0.25 M aqueous H_2SO_4 (5.1 mL) and the resulting solution stirred at ambient temperatures for 20 h. The reaction mixture was diluted with Et_2O (5 mL) and then washed with brine (2 × 5 mL). The combined aqueous washings were extracted with Et_2O (1 × 5 mL), and the combined organic phases were then dried ($MgSO_4$), filtered, and concentrated under reduced pressure to give an orange oil. Purification by preparative TLC (3:2 Et_2O/hexane elution) gave two major and chromophoric bands A and B (R_f 0.4 and 0.8 respectively). Extraction (Et_2O) of band A gave the title compound (**10**) (0.80 g, 67% based on recovered trimethoxybenzene) as a pale yellow oil: ^1H NMR (90 MHz) δ 2.10 (quintet of d, J = 6 and 2 Hz, 2 H, H5), 2.49 (t of d, J = 6 and 2 Hz, 2 H), 2.75 (t of d, J = 6 and 2 Hz, 2 H), 3.86 (s, 3 H, OCH_3), 3.88 (s, 6 H, 2 × OCH_3), 6.19 (t, J = 2 Hz, 1 H, H2), 6.68 (d, J = 9 Hz, 1 H, H5′), 6.95 (d, J = 9 Hz, 1 H, H6′); ^{13}C NMR (15 MHz) δ 23.4, 30.3, 37.5, 56.0, 60.3, 60.9, 107.3, 123.1, 127.6, 127.4, 142.5, 151.6, 154.6, 161.1, 199.9; IR (neat) 1660, 1595 cm^{-1}; UV (CH_2Cl_2) 228 (log ϵ = 4.1), 304 (4.1) nm; MS, m/e 262 (97) [$[M]^{\cdot+}$], 105 (100) [$[C_7H_5O]^+$]; HRMS, m/e calcd for $[M]^{\cdot+}$ 262.1205, obsd 262.1200. Extraction (Et_2O) of band B gave 1,2,3-trimethoxybenzene (0.39 g, 34% recovery) as a cream solid: mp 42–43 °C (lit.[17] mp 43–45 °C); ^1H NMR (90 MHz) δ 3.86 (s, 9 H, 3 × OCH_3), 6.57 (d, J = 9 Hz, 2 H), 7.00 (d of d, J = 9 and 8 Hz, 1 H); ^{13}C NMR (22.5 MHz) δ 55.7, 60.4, 105.0, 123.3, 137.9, 153.2.

A sample of enone **10** was converted into the corresponding (*p*-tolylsulfonyl)hydrazone [(*p*-tolylsulfonyl)hydrazine in THF for 16 h at ambient temperatures[18]]: mp 160–162 °C (cream needles from EtOH). Anal. Calcd for $C_{22}H_{26}N_2O_5S$: C, 61.38; H, 6.09; N, 6.51; S, 7.45. Found: C, 61.34; H, 6.44; N, 6.57; S, 7.49.

6-Acetoxy-3-(2′,3′,4′-trimethoxyphenyl)cyclohex-2-en-1-one (11). A mixture of cyclohexenone **10** (689 mg, 2.6 mmol) and manganese triacetate (3.47 g, ~15 mmol) in benzene (78 mL) was heated under reflux for 20 h in an apparatus fitted with a Dean–Stark trap. After cooling to room temperature, the reaction mixture was diluted with ethyl acetate (68 mL) and 1 M aqueous HCl (68 mL) and then filtered through Celite. The organic portion of the filtrate was washed with additional acid (68 mL), saturated aqueous $NaHCO_3$ (68 mL), and brine (68 mL), then dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The orange oil thus obtained was dissolved in a minimum volume of ethyl acetate/CH_2Cl_2 (1:9 mixture) and the resulting solution loaded onto the top of a 6-cm-deep pad of TLC grade silica gel. The pad was eluted with additional solvent and the filtrate concentrated under reduced pressure to give a light orange oil, which crystallized on standing. Recrystallization (CH_2Cl_2/hexane) gave the title compound **11** (505 mg, 60%) as white needles: mp 95.5–96.5 °C; ^1H NMR (90 MHz) δ 2.21 (s, 3 H, $OCOCH_3$), 2.24 (m, 2 H), 3.05 (m, 2 H), 3.86 (s, 3 H, OCH_3), 3.88 (s, 3 H, OCH_3), 3.89 (s, 3 H, OCH_3), 5.47 (d of d, J = 12 and 7 Hz, 1 H), 6.25 (broadened s, 1 H), 6.68 (d, J = 9 Hz, 1 H, H5′), 6.96 (d, J = 9 Hz, 1 H, H6′); ^{13}C NMR (100 MHz) δ 20.9, 29.2, 29.6, 56.0, 60.9, 61.3, 73.5, 107.3, 123.3, 126.2, 126.4, 142.5, 151.7, 155.0, 160.6, 170.3, 194.0; IR (KBr) 2945, 1752, 1660, 1591, 1465, 1411, 1235, 1206, 1110, 1055 cm^{-1}; UV (CH_2Cl_2) 230 (log ϵ = 4.1), 304 (4.1) nm; MS, m/e 320 (36) [$[M]^{\cdot+}$], 260 (75) [$[M - CH_3CO_2H]^{\cdot+}$], 219 (100). Anal. Calcd for $C_{17}H_{20}O_6$: C, 63.74; H, 6.29. Found: C, 63.80; H, 6.47.

***cis*- and *trans*-4-(2′,3′,4′-Trimethoxyphenyl)cyclohex-3-ene-1,2-diol 1-Acetate (12a and 13a Respectively) and *cis*-4-(2′,3′,4′-Trimethoxyphenyl)cyclohex-3-ene-1,2-diol 2-Acetate (12b).** Cerium trichloride hexahydrate (0.28 g, 0.8 mmol) was added in one portion to an ice-cold suspension of enone **11** (0.25 g, 0.8 mmol) in anhydrous methanol (5 mL). The mixture was stirred at 0–5 °C for 10 min, then $NaBH_4$ (50 mg, 1.3 mmol) was added in one portion, and the resulting mixture was warmed to room temperature and stirred for 10 min before being diluted with water (5 mL) and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic phases were washed with water (1 × 10 mL), then dried ($MgSO_4$), filtered, and concentrated under reduced pressure to a pale yellow oil. Purification by preparative TLC elution (Et_2O elution, two sweeps) afforded two major and chromophoric bands A and B (R_f 0.5 and 0.6 respectively). Extraction (Et_2O) of band A afforded a ca. 1:1 mixture (as judged by ^{13}C NMR) of hydroxy acetates **12a** and **12b** (154 mg, 61%) as a pale yellow oil: ^1H NMR (90 MHz) δ 1.66–2.30 (complex m, 2 H), 2.13 (s, 3 H, $OCOCH_3$), 2.51 (m, 3 H), 3.82 (s, 3 H, OCH_3), 3.85 (s, 3 H, OCH_3), 3.86 (s, 3 H, OCH_3), 3.95–5.20 (series of m, 2 H), 5.42 and 5.73 (pair of broadened triplets, J = 4.5 and 4 Hz respectively, 1 H), 6.59 (d, J = 9 Hz, 1 H, H5′), 6.84 (d of d, J = 9 Hz and 2 Hz, 1 H, H6′); ^{13}C NMR (15 MHz) δ 21.3, 23.3, 26.8, 27.4, 27.5, 56.0, 60.9, 61.0, 65.6, 67.4, 70.5, 72.2, 107.0, 121.6, 123.3, 125.0, 128.9, 129.1, 140.9, 142.2, 142.7, 151.2, 153.2, 170.6, 171.1 (9 peaks overlapping or obscured); IR (neat) 3455, 2950, 1724, 1592 cm^{-1}; UV (CH_2Cl_2) 228 (log ϵ = 4.2), 2.48 (4.1) nm; MS, m/e 322 (29) [$[M]^{\cdot+}$], 304 (31) [$[M - H_2O]^{\cdot+}$], 262 (100) [$[M - CH_3CO_2H]^{\cdot+}$]. Extraction (Et_2O) of band B afforded hydroxy acetate **13a** (71 mg, 28%) as a pale yellow oil: ^1H NMR (90 MHz) δ 1.56–2.71 (complex m, 5 H), 2.12 (s, 3 H, $OCOCH_3$), 3.83 (s, 3 H, OCH_3), 3.85 (s, 3 H, OCH_3), 3.86 (s, 3 H, OCH_3), 4.36 (m, 1 H, H3), 4.91 (m, 1 H, H4), 5.75 (d of m, J = 10 Hz, 1 H, H2), 6.61 (d, J = 9 Hz, 1 H, H5′) 6.85 (d of d, J = 9 and 1 Hz, 1 H, H6′); ^{13}C NMR (15 MHz) δ 21.3, 26.1, 27.8, 56.0, 60.9, 61.0, 70.4, 75.9, 107.1, 123.4, 126.1, 128.8, 139.2, 142.2, 151.3, 153.1, 171.5; IR (neat) 3450, 2945, 1729, 1592 cm^{-1}; UV (CH_2Cl_2) 228 (log ϵ = 4.1), 248 (4.0 nm); MS, m/e 244 (100) [$[M - CH_3CO_2H - H_2O]^{\cdot+}$].

***cis*-4-(2′,3′,4′-Trimethoxyphenyl)cyclohex-3-ene-1,2-diol (12c).** Sodium hydroxide (~0.1 g, ~2–3 mmol) was added in one portion to a solution of acetates **12a** and **12b** (50 mg, 0.16 mmol) in methanol (1 mL). The resulting solution was stirred at room temperature for 1 h, then diluted with water (2.5 mL), and extracted with CH_2Cl_2 (3 × 2.5 mL). The combined organic phases were washed with water (1 × 2.5 mL), then dried ($MgSO_4$), filtered, and concentrated under reduced pressure to give diol **12c** (44 mg, ~92%) as a pale yellow oil, which crystallized on standing. Recrystallization (hexane/THF) gave diol **12c** monohydrate as white crystals: mp 75–79 °C; ^1H NMR (90 MHz) δ 1.67–2.78 (complex m, 6 H), 3.84 (s, 3 H, OCH_3), 3.86 (s, 6 H, 2 × OCH_3), 4.04 (m, 1 H), 4.33 (m, 1 H), 5.76 (m, 1 H, H3), 6.62 (d, J = 8 Hz, 1 H, H5′), 6.86 (d, J = 8 Hz, 1 H, H6′); ^{13}C NMR (15 MHz) δ 26.7, 27.6, 56.0, 60.8, 61.1, 67.0, 68.5, 107.1, 123.4, 125.5, 129.3, 140.9, 142.1, 151.1, 153.1; IR (KBr) 3380, 2910, 1592, 1495, 1412, 1276, 1098, 1066, 1040, 811 cm^{-1}; UV (CH_2Cl_2) 230 (log ϵ = 4.2), 2.47 (4.1) nm; MS, m/e 280 (48) [$[M]^{\cdot+}$], 262 (40) [$[M - H_2O]^{\cdot+}$], 205 (100); HRMS, m/e calcd for $[M]^{\cdot+}$ 280.1311, obsd 280.1303. Anal. Calcd for $C_{15}H_{20}O_5 \cdot H_2O$: C, 60.39; H, 7.43. Found: C, 60.89; H, 7.62.

***trans*-4-(2′,3′,4′-Trimethoxyphenyl)cyclohex-3-ene-1,2-diol (13b).** Hydrolysis of acetate **13a** (93 mg, 0.29 mmol) according to the above procedure afforded, on workup, diol **13b** (80 mg, 99%) as a clear colorless oil, which crystallized on standing. Recrystallization (CH_2Cl_2) of this material gave small white plates: mp 129–130 °C (δ sub); ^1H NMR (90 MHz) δ 1.56–2.78 (complex m, 6 H), 3.76 (m, 1 H), 3.83 (s, 3 H, OCH_3), 3.86 (s, 3 H, OCH_3), 3.87 (s, 3 H, OCH_3), 4.24 (m, 1 H), 5.65 (m, 1 H, H3), 6.61 (d, J = 9 Hz, 1 H, H5′), 6.86 (d, J = 9 Hz, 1 H, H6′); ^{13}C NMR (15 MHz, (CD_3CN) δ 29.2, 30.0, 56.7, 61.2, 61.6, 73.4, 73.9, 108.6, 124.4, 128.6, 130.3, 139.0, 143.1, 152.3, 154.2; IR (KBr) 3340, 2950, 1591, 1493, 1459, 1285, 1104, 1072, 1030, 810 cm^{-1}; UV (CH_2Cl_2) 231 (log ϵ variable), 245 (4.0) nm; MS, m/e 280 (40) [$[M]^{\cdot+}$], 262 (40) [$[M - H_2O]^{\cdot+}$], 205 (100); HRMS, m/e calcd for $[M]^{\cdot+}$ 280.1311, obsd 280.1296. Anal. Calcd for $C_{15}H_{20}O_5$: C, 64.27; H, 7.19. Found: C, 64.50; H, 7.70.

2,3,4-Trimethoxybiphenyl (14). Perchloric acid (1 drop of a 60% aqueous solution) was added to a magnetically stirred suspension of diol **12c** (50 mg, 0.18 mmol) in acetone (2 mL). The reaction mixture was stirred at room temperature for 10 min and then diluted with CH_2Cl_2, the resulting solution filtered through a pad of anhydrous K_2CO_3, and the filtrate concentrated under reduced pressure. The light yellow oil thus obtained was purified by preparative TLC (CH_2Cl_2 elution) affording a single major and chromophoric band (R_f 0.6), which on extraction (CH_2Cl_2) gave 2,3,4-trimethoxybiphenyl (**14**) (32 mg, 73%) as a light yellow solid. Recrystallization (hexane) of this material gave white prisms: mp 46–47 °C (lit.[11] mp 46.5 °C); ^1H NMR (60 MHz) δ 3.70 (s, 3 H, OCH_3), 3.96 (s, 3 H, OCH_3), 3.99 (s, 3 H, OCH_3), 6.72 (d, J = 9 Hz, 1 H, H5), 7.07 (d, J = 9 Hz, 1 H, H6), 7.45 (m, 5 H, H2′–6′); ^{13}C NMR (22.5 MHz) δ 56.0 (two peaks overlapping), 61.0, 107.4, 124.8, 126.7, 128.1, 128.7, 129.1, 138.2, 142.5, 151.4, 153.1; IR (KBr)

2950, 1604, 1592 cm^{-1}; MS, *m/e* 224 (100) [$[M]^{\cdot+}$].

(3aα,7aβ)-5-(2′,3′,4′-Trimethoxyphenyl)-2,2-dimethyl-3a,6,7,7a-tetrahydro-1,3-benzodioxole (13c). Reaction of diol **13b** with acetone in the presence of perchloric acid as detailed above gave, following workup, a yellow oil. Purification by preparative TLC (CH_2Cl_2 elution, two sweeps) afforded two major and chromophoric bands A and B (R_f 0.2 and 0.6 respectively). Extraction (Et_2O of band A gave acetonide **13c** (24 mg, 58%) as a colorless oil (this compound is unstable and is converted into biphenyl **14** on standing): ^1H NMR (60 MHz) δ 1.45 (s, 3 H, CH_3), 1.49 (s, 3 H, CH_3), 1.67–2.73 (complex m, 4 H), 3.88 (s, 3 H, OCH_3), 3.91 (s, 3 H, OCH_3), 3.92 (s, 3 H, OCH_3), 4.40 (m, 1 H), 4.62 (m, 1 H), 5.75 (m, 1 H), 6.62 (d, *J* = 8 Hz, 1 H, H5′), 6.88 (d, *J* = 8 Hz, 1 H, H6′); ^{13}C NMR (15 MHz) δ 25.1, 26.4, 26.5, 28.1, 56.0, 60.9, 61.0, 72.4, 72.7, 107.0, 108.3, 123.2, 123.5, 129.9, 141.2, 142.2, 151.3, 153.1; IR (neat) 2940, 1596 cm^{-1}; MS, *m/e* 320 (30) [$[M]^{\cdot+}$], 234 (100). Extraction (CH_2Cl_2) of band B gave biphenyl **14** (2 mg, 6%) identical in all respects with the material obtained from diol **12c**.

***cis*-4-(2′,3′,4′-Trimethoxyphenyl)cyclohex-3-ene-1,2-diol Diacetate (12d).** Acetic anhydride (1.1 mL, 11.8 mmol) was added in one portion to a solution of acetoxy alcohols **12a,b** (117 mg, 0.36 mmol) in dry pyridine (2 mL). The resulting colorless solution was stored at ambient temperatures for 20 h, then diluted with water (2.5 mL), and extracted with CH_2Cl_2 (3 × 5 mL). The combined organic phases were washed with 2 M aqueous HCl (3 × 5 mL), saturated aqueous $NaHCO_3$ (1 × 5 mL), and brine (2 × 5 mL), then dried ($MgSO_4$), filtered, and concentrated under reduced pressure to give diacetate **12d** (130 mg, 98%) as a pale yellow oil: ^1H NMR (90 MHz) δ 1.84 (s, 3 H, $OCOCH_3$), 1.92 (s, 3 H, $OCOCH_3$), 1.98 (m, 2 H), 2.69 (m, 2 H), 3.83 (s, 3 H, OCH_3), 3.86 (s, 3 H, OCH_3) 3.87 (s, 3 H, OCH_3), 5.20 (d of t, *J* = 9.8 and 3 Hz), 5.61 (m, 1 H, H3), 6.62 (d, *J* = 9 Hz, 1 H, H5′), 6.86 (d, *J* = 9 Hz, 1 H, H6′); IR (neat) 2950, 1738, 1595 cm^{-1}; MS, *m/e* 364 (3) [$[M]^{\cdot+}$], 304 (24) [$[M - CH_3CO_2H]^{\cdot+}$], 244 (100) [$[M - 2 \times CH_3CO_2H]^{\cdot+}$].

***trans*-4-(2′,3′,4′-Trimethoxyphenyl)cyclohex-3-ene-1,2-diol Diacetate (13d).** Acetylation of *trans*-diol **13b** according to the procedure used above gave the *trans*-acetate **13d** (81%) as a pale yellow oil: ^1H NMR (60 MHz) δ 1.93 (m, 2 H), 2.08 (s, 6 H, 2 × $OCOCH_3$), 2.76 (m, 2 H), 3.83 (s, 3 H, OCH_3), 3.86 (s, 6 H, 2 × OCH_3), 5.11 (m, 1 H), 5.54 (d, *J* = 7 Hz, 1 H), 5.62 (br s, 1 H, H2), 6.61 (d, *J* = 9 Hz, 1 H, H5′), 6.86 (d, *J* = 9 Hz, 1 H, H6′); IR (neat) 2950, 1732, 1590 cm^{-1}; MS, *m/e* 364 (<1) [$[M]^{\cdot+}$], 304 (56) [$[M - CH_3CO_2H]^{\cdot+}$], 244 (100) [$[M - 2 \times CH_3CO_2H]^{\cdot+}$].

(1α,2α,3α,6α)-7,7-Dichloro-6-(2′,3′,4′-trimethoxyphenyl)-bicyclo[4.1.0]heptane-2,3-diol Diacetate (17a). A mixture of cyclohexene **12d** (27 mg, 0.07 mmol), sodium trichloroacetate (400 mg, 2.2 mmol), tetrachloroethylene (0.5 mL), and diglyme (0.3 mL) was heated at reflux (effervescence) for 1.5 h. Additional sodium trichloroacetate (400 mg, 2.2 mmol) was then added and heating continued for a further 1.5 h before cooling of the reaction mixture to room temperature and then addition of water (2.1 mL). The separated aqueous phase was extracted with CH_2Cl_2 (2 × 2 mL), and the combined organic phases were then dried ($MgSO_4$), filtered, and concentrated under reduced pressure to a brown oil. This material was added to the top of a 6-cm-deep pad of TLC grade silica gel, and then the pad was eluted with pentane (~50 mL) followed by CH_2Cl_2 (~100 mL). Concentration of the pentane fraction gave a white solid. Recrystallization (pentane) of this material gave hexachlorocyclopropane (~0.08 g, ~8% based on sodium trichloroacetate) as white plates: mp 102–103 °C (lit.[13] mp 103.5–104.5 °C); IR (KBr) 933, 905, 850, 601, 309 cm^{-1}; MS, *m/e* 219 (3), 217 (20), 215 (65), 213 (100), 211 (62), [[M − $Cl^{\cdot}$]$^+$]. Concentration of the CH_2Cl_2 fraction from elution of the silica gel pad gave a brown oil. Purification by preparative TLC (1:10 ethyl acetate/CH_2Cl_2 elution) gave two mobile and chromophoric bands A and B (R_f 0.7 and 0.9 respectively). Extraction (CH_2Cl_2) of band A afforded the title compound **17a** (15 mg, 46%) as a light yellow oil, which crystallized on standing. Recrystallization (hexane/$CHCl_3$) of this material gave white rectangular prisms: mp 129–131 °C; ^1H NMR (90 MHz) δ 1.21–2.24 (complex m, 4 H), 2.08 (s, 3 H, $OCOCH_3$), 2.14 (s, 3 H, $OCOCH_3$), 2.44 (m, 1 H), 3.86 (s, 3 H, OCH_3), 3.87 (s, 3 H, OCH_3), 4.09 (s, 3 H, OCH_3), 5.03 (t, *J* = 2.7 Hz, 1 H, H2), 5.27 (m, 1 H, H3), 6.58 (d, *J* = 9 Hz, 1 H, H5′), 6.87 (d, *J* = 9 Hz, 1 H, H6′); ^{13}C NMR (15 MHz) δ 21.0, 23.4, 24.4, 34.8, 35.7, 55.9, 60.6, 61.3, 67.2, 67.9, 68.1, 106.0, 122.0, 128.7, 141.8, 152.6, 153.7, 170.0, 170.2; IR (KBr) 2940, 1740, 1596 cm^{-1}; UV (CH_2Cl_2) 228 (log ε = 4.0), 272 (2.7) nm; MS, *m/e* 390 (1), 388 (6), 386 (9), [[M − $CH_3CO_2H]^{\cdot+}$], 43 (100) [$[CH_3CO]^+$]. Anal. Calcd for $C_{20}H_{24}Cl_2O_7$: C, 53.70; H, 5.41; Cl, 15.85. Found: C, 53.67; H, 5.42; Cl, 15.95. Extraction (CH_2Cl_2) of band B gave a pale yellow oil consisting of a mixture of acetate **17a** (~2 mg, 5%) and biphenyl **14** (~4 mg, 22%) as determined by ^1H NMR analysis.

(1α,2α,3β,6α)- and (1α,2β,3α,6α)-7,7-Dichloro-6-(2′,3′,4′-trimethoxyphenyl)bicyclo[4.1.0]heptane-2,3-diol Diacetate (16a and 15a Respectively). Dichlorocarbene addition to the *trans*-diacetate **13d** using the procedure employed above gave hexachlorocyclopropane (~8% based on sodium trichloroacetate) and a brown oil after concentration of the CH_2Cl_2 eluent from the silica gel filtration step. Purification by preparative TLC (1:10 ethyl acetate/CH_2Cl_2 elution) gave two major and chromophoric bands A and B (R_f 0.8 and 0.9 respectively). Extraction (CH_2Cl_2) of band A gave a ca. 2:1 mixture of the cyclopropyl compounds **15a** and **16a** (40% based on recovered starting materials) as a colorless oil: MS, *m/e* 450 (<1), 448 (1), 446 (2) [$[M]^{\cdot+}$], 43 (100) [$[CH_3CO]^+$]. The material was immediately subjected to the hydrolysis reaction detailed below. Extraction (CH_2Cl_2) of band B gave a pale yellow oil consisting of a mixture of acetates **15a** and **16a** (17%) and biphenyl **14** (24%) as determined by ^1H NMR analysis.

(1α,2α,3α,6α)-7,7-Dichloro-6-(2′,3′,4′-trimethoxyphenyl)-bicyclo[4.1.0]heptane-2,3-diol (17b). A solution of diacetate **17a** (78 mg, 0.18 mmol)e in methanol (1 mL) was treated, in one portion, with K_2CO_3 (50 mg, 0.36 mmol) and the resulting suspension stirred at ambient temperatures for 1 h and then diluted with water (1.8 mL). The resulting mixture was extracted with CH_2Cl_2 (3 × 4 mL), and the combined organic phases were dried ($MgSO_4$), filtered, and concentrated under reduced pressure to give diol **17b** (62 mg, 98%) as a yellow foam. Purification by preparative TLC (1:10 ethyl acetate/CH_2Cl_2 elution) gave a single major and chromophoric band (R_f 0.2), which on extraction (ethyl acetate) afforded a crystalline solid. Recrystallization of this material (Et_2O/hexane) gave white needles: mp 111–113 °C; ^1H NMR (90 MHz) δ 0.81–2.53 (complex m, 6 H), 2.66 (m, 1 H), 3.15 (m, 1 H), 3.84, 3.86 4.03, 4.07 (all s, 9 H in toto), 6.54, 6.69, 6.85, 7.08 (all d, *J* = 9 Hz, 2 H in toto) (see discussion section); ^{13}C NMR (15 MHz, $C_2D_2Cl_4$, 100 °C) δ 25.0 (2 peaks superimposed), 26.2, 38.4, 56.2, 60.6, 61.1, 66.4, 67.3, 68.4, 107.3, 123.1, 128.2, 142.3, 152.0, 153.5; IR (KBr) 3540, 2950, 1597 cm^{-1}; UV (CH_2Cl_2) 228 (log ε = 3.9), 273 (2.9) nm; MS, *m/e* 366 (1), 364 (24), 362 (37) [$[M]^{\cdot+}$], 327 (100), 329 (33) [$[M - Cl^{\cdot}]^+$]. Anal. Calcd for $C_{16}H_{20}Cl_2O_5$: C, 52.91; H, 5.55; Cl, 19.52. Found: C, 53.02; H, 5.64; Cl, 19.56.

(1α,2α,3β,6α)- and (1α,2β,3α,6α)-7,7-Dichloro-6-(2′,3′,4′-trimethoxyphenyl)bicyclo[4.1.0]heptane-2,3-diol (16b and 15b Respectively). Preparative TLC (Et_2O elution) of the crude oil obtained from hydrolysis of diacetates **15a** and **16a** according to the procedure outlined above gave two chromophoric bands A and B (R_f 0.1 and 0.2 respectively). Extraction of band A gave a crystalline solid tentatively identified as diol **15b** (100 mg, 25%). Recrystallization (Et_2O/hexane) of this material gave white crystalline needles: mp 128–129 °C; ^1H NMR (90 MHz) δ 1.08–2.67 (complex m, 8 H), 3.87 (s, 6 H, 2 × OCH_3), 4.08 (s, 3 H, OCH_3), 4.10 (br s, 1 H, O*H*), 6.54 (d, *J* = 9 Hz, 1 H, H5′), 6.70 (d, *J* = 9 Hz, 1 H, H6′); ^{13}C NMR (100 MHz) δ 29.6, 30.1, 38.6, 40.7, 55.9, 60.6, 61.2, 69.7, 71.8, 74.2, 105.8, 121.8, 128.9, 141.9, 152.0, 153.8; IR (KBr) 3362, 2942, 1601 cm^{-1}; UV (CH_2Cl_2) 233 (log ε = 3.9), 272 (2.9) nm; MS, *m/e* 366 (1.7), 364 (13), 362 (19) [$[M]^{\cdot+}$], 329 (36), 327 100), [[M − $Cl^{\cdot}]^+$], 328 (32), 326 (47) [[M − HCl]$^{\cdot+}$]. Anal. Calcd for $C_{16}H_{20}Cl_2O_5$: C, 52.91; H, 5.55; Cl, 19.52. Found: C, 53.2; H, 5.6; Cl, 18.8. Extraction of band B gave a crystalline solid tentatively identified as diol **16b** (220 mg, 55%). Recrystallization (Et_2O/hexane) of this material gave fine white needles: mp 118–120 °C; ^1H NMR (90 MHz) δ 1.19–2.97 (complex m, 7 H), 3.75 (m, 1 H), 3.83 (s, 6 H, 2 × OCH_3), 3.99 (br s, 1 H), 4.05 (s, 3 H, OCH_3), 6.54 (d, *J* = 9 Hz, 1 H, H5′), 6.76 (d, *J* = 9 Hz, 1 H, H6′); ^{13}C NMR (22.5 MHz) δ 27.8, 28.0, 36.4, 39.3, 55.9, 60.6, 61.3, 68.1, 71.5, 72.8, 106.1, 122.1, 128.6, 141.8, 152.7, 153.6; IR (KBr) 3289, 2948, 1600 cm^{-1}; UV (CH_2Cl_2) 234 (log ε = 3.9), 263 (2.9 nm); MS, *m/e* 366 (4), 364 (24), 362 (37), [[M]$^{\cdot+}$], 329

(33), 327 (100) [[M − Cl•]+]. Anal. Calcd for $C_{16}H_{20}Cl_2O_5$: C, 52.91; H, 5.55; Cl, 19.50. Found: C, 52.6; H, 5.3; Cl, 19.2.

7,7-Dichloro-3-hydroxy-6-(2′,3′,4′-trimethoxyphenyl)bicyclo[4.1.0]hept-3-en-2-one (19). Trifluoroacetic anhydride (71 μL, 0.50 mmol) was added in a dropwise fashion to a stirred solution of DMSO (44 μL, 0.62 mmol) in CH_2Cl_2 (4.3 mL) maintained at −60 °C. The resulting solution was stirred at this temperature for 10 min, then a solution of the ca. 2:1 mixture of diols **15b** and **16b** (87 mg, 0.24 mmol) in CH_2Cl_2 (0.8 mL) and then DMSO (0.2 mL) were added to the reacton mixture, and stirring was continued at −60 °C for 2 h. NEt_3 (155 μL, 1.10 mmol) was then added to the reaction mixture and the resulting yellow solution stirred for a further 1 h at 60 °C before being diluted with 2 M aqueous HCl (5 mL) and CH_2Cl_2 (6 mL). The separated organic phase was washed with water (2 × 5 mL), then dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Purification of the resulting light yellow oil by preparative TLC (1:19 Et_2O/CH_2Cl_2 elution) afforded a single major and chromophoric band (R_f 0.6). Extraction (Et_2O) of this band gave the hydroxy enone **19** (59 mg, 69%) as a colorless oil: ^1H NMR (90 MHz) δ 2.81 (d of d, J = 22 and 4.5 Hz, 1 H, H5), 2.93 (s, 1 H, H1), 3.53 (d of d of m, J = 22 and 4.5 Hz, 1 H, H5), 3.86 (s, 3 H, OCH_3), 3.87 (s, 3 H, OCH_3), 4.11 (s, 3 H, OCH_3), 5.93 (t, J = 4.5 Hz, 1 H, H4), 5.97 (s, 1 H, O*H*), 6.56 (d, J = 9 Hz, 1 H, H5′), 6.70 (d, J = 9 Hz, 1 H, H6′); IR (neat) 3410, 2940, 1649, 1597 cm^{-1}; MS, m/e 362 (3), 360 (25), 358 (41) [[M]•+], 325 (34), 323 (100), [[M − Cl•]+].

Oxidation of *cis*-diol **17b** (64 mg, 0.18 mmol) under the conditions described above gave a light yellow oil on workup. Purification by preparative TLC (1:49 Et_2O/CH_2Cl_2 elution) gave two mobile and chromophoric bands A and B (R_f 0.4 and 0.5 respectively). Extraction (Et_2O) of band A gave (1α,3α,6α)-7,7-dichloro-3-hydroxy-6-(2′,3′,4′-trimethoxyphenyl)bicyclo[4.1.0]-heptan-2-one (**18**) (15 mg, 26%) as a pale yellow oil: ^1H NMR (90 MHz) δ 1.51–3.18 (complex m, 5 H), 3.73 (br s, 1 H), 3.86 (s, 3 H, OCH_3), 3.87 (s, 3 H, OCH_3), 4.10 (s, 3 H, OCH_3), 4.36 (m, 1 H), 6.56 (d, J = 9 Hz, 1 H, H5′), 6.71 (d, J = 9 Hz, 1 H, H6′); ^{13}C NMR (22.5 MHz) δ 28.6, 33.9, 44.0, 47.1, 56.0, 60.7, 61.3, 69.8, 72.7, 105.9, 121.8, 127.0, 142.0, 151.5, 154.4, 204.1; IR (neat) 3479, 2944, 1703, 1601 cm^{-1}; UV (CH_2Cl_2) 223 (log ε = 4.2), 271 (3.3) nm; MS, m/e 364 (4), 362 (21), 360 (34) [[M]•+], 49 (100); HRMS m/e calcd for [M]•+ 360.0531, obsd 360.0523. Extraction (Et_2O) of band B gave hydroxy enone **19** (40 mg, 63%) as a clear colorless oil with spectral properties in accord with those reported above.

Resubjection of the hydroxy ketone **18** to the oxidation reaction (using 1.05 molar equiv of trifluoroacetic anhydride) gave, on workup, a yellow oil. Purification by preparative TLC (1:19 Et_2O/CH_2Cl_2 elution) afforded two mobile and chromophoric bands A and B (R_f 0.6 and 0.9 respectively). Extraction (Et_2O) of band A gave hydroxy ketone **18** (35% recovery), and extraction (Et_2O) of band B gave enone **19** (62% based on recovered starting material).

7,7-Dichloro-3-methoxy-6-(2′,3′,4′-trimethoxyphenyl)bicyclo[4.1.0]hept-3-en-2-one (6). A mixture of K_2CO_3 (2.40 g, 17 mmol), hydroxy enone **19** (208 mg, 0.58 mmol), $(CH_3)_2SO_4$ (2.60 mL, 27 mmol), and $(CH_3)_2CO$ (15.4 mL) was stirred at ambient temperatures for 4 h and then diluted with water (25 mL). After standing overnight at room temperature, the resulting solution was extracted with CH_2Cl_2 (2 × 40 mL). The combined organic phases were washed with water (2 × 40 mL), then dried ($MgSO_4$), filtered, and concentrated under reduced pressure to give a yellow oil. Purification by preparative TLC (1:19 Et_2O/CH_2Cl_2 elution) afforded a single major and chromophoric band (R_f 0.6), which on extraction (CH_2Cl_2) gave the title compound **6** (188 mg, 87%) as a cream solid. Recrystallization (Et_2O) of this material afforded colorless prisms: mp 134–135 °C; ^1H NMR (90 MHz) δ 2.86 (d of d, J = 21 and 4.5 Hz, 1 H, H5), 2.93 (d, J = 1 Hz, 1 H, H1), 3.54 (d of d of d, partially obscured, J = 21, 4.5, and 1 Hz, 1 H, H5), 3.62 (s, 3 H, OCH_3), 3.86 (s, 3 H, OCH_3), 3.88 (s, 3 H, OCH_3), 4.12 (s, 3 H, OCH_3), 5.64 (t, J = 4.5 Hz, 1 H, H4), 6.57 (d, J = 9 Hz, 1 H, H5′), 6.72 (d, J = 9 Hz, 1 H, H6′); ^{13}C NMR (22.5 MHz) δ 29.9, 40.2, 43.2, 55.2, 55.9, 60.6, 61.2, 65.0, 106.4 (two peaks superimposed), 115.2, 122.1, 126.5, 149.6, 151.8, 184.1; IR (KBr) 2962, 1678, 1637, 1600 cm^{-1}; UV (CH_2Cl_2) 232 (log ε = 4.0), 272 (3.9) nm. Anal. Calcd for $C_{17}H_{18}Cl_2O_5$: C, 54.71; H, 4.86; Cl, 19.0. Found: C, 54.95; H, 4.63; Cl, 19.4.

6-Chloro-2-methoxy-5-(2′,3′,4′-trimethoxyphenyl)cyclohepta-2,4,6-trien-1-one (2). A stirred solution of enone **6** (100 mg, 0.27 mmol) in anhydrous C_6H_6 (8.6 mL) maintained at room temperature was treated with 1,8-diazabicyclo[5.4.0]undec-7-ene (0.43 mL, 2.9 mmol). After 50 min, the reaction mixture was diluted with CH_2Cl_2 (10 mL) and then washed with 2 M aqueous HCl (2 × 10 mL). The organic phase was washed with saturated aqueous $NaHCO_3$ (10 mL) and water (2 × 10 mL), then dried ($MgSO_4$), filtered, and concentrated under reduced pressure to a light yellow oil. Purification by preparative TLC (1:4 Et_2O/CH_2Cl_2 elution) afforded two major and chromophoric bands A and B (R_f 0.1 and 0.5 respectively). Extraction (Et_2O) of band A gave an unidentified yellow oil (12 mg): IR (neat) 3296, 2931, 1634, 1593, 1547 cm^{-1}; MS, m/e 476 (3), 474 (7), [[M]•+], 105 (100); HRMS m/e calcd [[M]•+] 474.1921, obsd 474.1917. (See discussion section.) Extraction (Et_2O) of band B gave a pale yellow solid. Recrystallization (hexane/CH_2Cl_2) of this material gave the title compound **2** (82 mg, 91%) as pale yellow crystals: mp 200–202 °C; ^1H NMR (90 MHz) δ 3.81 (s, 3 H, OCH_3), 3.90 (s, 3 H, OCH_3), 3.91 (s, 3 H, OCH_3), 3.97 (s, 3 H, OCH_3), 6.66 (d, J = 11 Hz, 1 H, H3), 6.69 (d, J = 9 Hz, 1 H, H5′), 6.86 (d, J = 9 Hz, 1 H, H6′), 7.04 (d, J = 11 Hz, 1 H, H4), 7.65 (s, 1 H, H7); ^{13}C NMR (15 MHz) δ 56.0, 56.4, 60.9, 61.0, 106.7, 110.6, 123.8, 128.8, 132.8, 136.6, 138.5, 141.8, 147.7, 150.9, 154.2, 164.1, 176.7; IR (KBr) 2830, 1605, 1585, 1571 cm^{-1}; UV (CH_2Cl_2) 228 (sh, log ε = 4.1), 250 (4.2), 333 (3.8) nm; MS, m/e 338 (15), 336 (44), [[M]•+], 310 (33), 308 (100) [[M − CO]•+]. Anal. Calcd for $C_{17}H_{17}ClO_5$: C, 60.63; H, 5.09; Cl, 10.53. Found: C, 60.78; H, 4.73; Cl, 10.2. Compound **2** is thermally stable as evidenced by the fact that it is returned unchanged after heating in refluxing in *o*-xylene for 2 h.

4-Chloro-2-hydroxy-5-(2′,3′,4′-trimethoxyphenyl)cyclohepta-2,4,6-trien-1-one (22). Trifluoroacetic anhydride (140 μL, 0.99 mmol) was added in one portion to a magnetically stirred solution of DMSO (90 μL, 1.3 mmol) in CH_2Cl_2 (5.6 mL) maintained at −60 °C. After the mixture was stirred for 10 min, a solution of *cis*-diol **17b** (114 mg, 0.31 mmol) in CH_2Cl_2 (1 mL) and then DMSO (0.3 mL) were added to the reaction mixture and stirring was continued for 2 h at −60 °C. After this time, NEt_3 (0.30 mL, 2.2 mmol) was added and stirring continued for 1 h at −60 °C before the reaction mixture was diluted with 2 M aqueous HCl (5 mL). The organic phase was washed with water (2 × 5 mL), then dried ($MgSO_4$), filtered, and concentrated under reduced pressure to give a yellow solid. Recrystallization (Et_2O) of this material gave tropolone **22** (77 mg, 76%) as pale yellow needles: mp 155–156 °C; ^1H NMR (90 MHz) δ 3.77 (s, 3 H, OCH_3), 3.91 (s, 6 H, 2 × OCH_3), 6.71 (d, J = 8 Hz, 1 H, H5′), 6.87 (d, J = 8 Hz, 1 H, H6′), 7.20 (d, J = 12 Hz, 1 H, H7), 7.39 (d, J = 12 Hz, 1 H, H6), 7.65 (s, 1 H, H3); ^{13}C NMR (100 MHz) δ 56.05, 61.0, 61.1, 107.0, 123.6, 123.7, 124.0, 128.9, 137.7, 139.9, 142.1, 145.5, 150.7, 154.2, 166.1, 172.4; IR (KBr) 3223, 2941, 1613, 1597, 1557 cm^{-1}; UV (CH_2Cl_2) 246 (log ε = 4.5), 334 (4.0) nm; MS, m/e 324 (35), 322 (100) [[M]•+], 296 (9), 294 (29), [[M − CO]•+]. Anal. Calcd for $C_{16}H_{15}ClO_5$: C, 59.54; H, 4.68; Cl, 10.98. Found: C, 59.5; H, 4.6; Cl, 11.3.

4-Chloro-2-methoxy-5-(2′,3′,4′-trimethoxyphenyl)cyclohepta-2,4,6-trien-1-one (23). A mixture of K_2CO_3 (1.72 g, 12.4 mmol), tropolone **22** (126 mg, 0.39 mmol), $(CH_3)_2SO_4$ (1.7 mL, 18 mmol), and $(CH_3)_2CO$ (10 mL) was stirred at room temperature for 4 h and then diluted with water (10 mL). The resulting solution was stirred at ambient temperatures for 19.5 h and then extracted with CH_2Cl_2 (3 × 10 mL). The combined organic phases were washed with water (10 mL), then dried ($MgSO_4$), filtered, and concentrated under reduced pressure to a yellow oil. Purification by preparative TLC (Et_2O elution) afforded two major and chromophoric bands A and B (R_f 0.1 and 0.3 respectively). Extraction (Et_2O) of band A gave tropolone methyl ether **2** (42 mg, 32%) as pale yellow crystals with physical and spectral properties in accord with those reported above. Extraction (Et_2O) of band B gave tropolone methyl ether **23** (45 mg, 34%) as a pale yellow oil, which crystallized on trituration with Et_2O. Recrystallization (Et_2O) of this material gave pale yellow crystals: mp 136–137 °C; ^1H NMR (90 MHz) δ 3.78 (s, 3 H, OCH_3), 3.91 (s, 6 H, 2 × OCH_3), 3.98 (s, 3 H, OCH_3), 6.71 (d, J = 9 Hz, 1 H, H5′), 6.87 (d, J = 9 Hz, 1 H, H6′), 6.90 (d, J = 15 Hz, 1 H, H7), 7.13 (s, 1 H, H3), 7.19 (d, J = 15 Hz, 1 H, H6); ^{13}C NMR (100 MHz) δ 56.0, 56.4, 61.0, 61.1, 107.1, 116.1, 124.0, 128.5, 133.5, 136.2, 139.2

(two peaks superimposed), 142.2, 150.6, 154.0, 161.8, 178.7; IR (KBr) 1627, 1614, 1596, 1583, 1568 cm^{-1}; UV (CH_2Cl_2) 246 (log ϵ = 4.9), 334 (4.5) nm; MS, m/e 338 (35), 336 (100), [[M]$^{+\cdot}$], 310 (30), 308 (93), [[M - CO]$^{+\cdot}$]; HRMS m/e calcd for [M]$^{+\cdot}$ 336.0764, obsd 336.0764. Anal. Calcd for $C_{17}H_{17}ClO_5$: C, 60.63; H, 5.09; Cl, 10.53. Found: C, 60.4; H, 5.0; Cl, 10.7.

Single-Crystal X-ray Diffraction Analysis of Tropolone Methyl Ether 2. Crystal data: $C_{17}H_{17}ClO_5$, M_r 336.8, triclinic, space group $P\bar{1}$, a = 10.188 (2) Å, b = 10.720 (1) Å, c = 9.014 (2) Å, α = 107.48 (1)°, β = 95.60 (1)°, γ = 62.09 (1)°, V = 828.66 Å^3, T = 293 ± K, D_{calcd} = 1.35 g cm^{-3}, D_m = 1.37 g cm^{-3} (by flotation in $CHCl_3$/mesitylene), Z = 2, Mo Kα radiation of λ = 0.7107 Å, graphite monochromator, μ = 2.58 cm^{-1}, orange rhomboids. The crystal selected for intensity data collection measured approximately 0.3 × 0.3 × 0.3 mm. Unit cell constants were derived from a least-squares fit to the setting angles of 25 widely dispersed reflections on a Nonius CAD-4 diffractometer. Intensity data were collected by a variable-width, variable-speed $2\theta/\omega$ scan to the practical diffraction limit of θ = 28°. The data were corrected for Lorentz, polarization, and absorption effects (range of transmission factors 1.0000–0.9599). The data set consisted of 3177 unique reflections of which 1820 were deemed observed ($I > 3\sigma(I)$).[19] The structure was solved by using direct methods. The initial E map correctly revealed positions for all 23 non-hydrogen atoms. Refinement was by damped full-matrix least squares. Hydrogen atoms were located in a difference electron density map and their positions refined. Non-hydrogen atoms were assigned anisotropic thermal parameters. The function minimized was $\sum w(|F_o| - |F_c|)^2$. Atomic scattering factors were for neutral atoms. Reflection weights were $w = 3.2968/[\sigma^2(F) + gF^2]$ with final g being 5.51 × 10^{-4}. At convergence, R and Rw were 0.062 and 0.067 respectively. Further results of the crystallographic experiments are available and are described in the supplementary material paragraph.

Biological Studies on Tropolone Methyl Ethers 2 and 23. Biological assays were performed as previously described.[20] In the cell growth experiments (experiment I of Table I), the IC_{50} value cited is the drug concentration that inhibited the growth of L1210 murine leukemia cells by 50%. The percent mitoses values quoted (experiment II) were obtained after 12 h of growth in the presence of the indicated concentration of drug, when cells were harvested and stained and the mitotic index was determined by microscopic examination. Without drug, 4% mitotic figures were observed. In the microtubule assembly experiment (experiment III), reaction mixtures contained 0.1 M 2-morpholinoethanesulfonate (pH 7.0 with NaOH), 0.5 mM $MgCl_2$, 0.4 mM GTP, 1.5 mg/mL (15 μM) tubulin, 0.5 mg/mL microtubule-associated proteins, and 10 μM drug, except that in the experiment indicated by the value in parentheses 100 μM compound **23** was used. In the tubulin polymerization experiment (experiment IV), reaction mixtures contained 1.0 M monosodium glutamate (pH 6.6 with HCl), 1.0 mM $MgCl_2$, 0.4 mM GTP, 1.0 mg/mL (10 μM) tubulin, and 7.5 μM drug, except that in the experiment indicated by the value in parentheses 100 μM compound **23** was used. In the colchicine binding assays (experiment V), reaction mixtures contained 0.1 mg/mL (1 μM) tubulin, 5 μM [^{3}H]colchicine, and 5 μM drug, except that in the experiment indicated by the value in parentheses 50 μM compound **23** was used.

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Registry No. **2**, 116211-76-8; **6**, 116211-75-7; **7**, 58529-72-9; **10**, 116211-56-4; **10** ((*p*-(tolylsulfonyl)hydrazone), 116211-57-5; **11**, 116211-58-6; **12a**, 116211-59-7; **12b**, 116211-60-0; **12c**, 116211-62-2; **12d**, 116211-65-5; **13a**, 116211-61-1; **13b**, 116211-63-3; **13c**, 116211-64-4; **13d**, 116211-66-6; **14**, 95127-11-0; **15a**, 116211-68-8; **15b**, 116211-70-2; **16a**, 116211-69-9; **16b**, 116211-71-3; **17a**, 116211-67-7; **17b**, 116211-73-5; **18**, 116211-74-6; **19**, 116211-72-4; **22b**, 116211-77-9; **23**, 116211-78-0; 1,2,3-trimethoxybenzene, 634-36-6; hexachlorocyclopropane, 2065-35-2.

Supplementary Material Available: Tables of atomic coordinates, thermal parameters, interatomic distances and angles, least-squares planes, and torsion angles for **2** (6 pages). Ordering information is given on any current masthead page.

General Synthetic Approach to Stable Nitrogen Analogues of *S*-Adenosylmethionine

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A general synthetic approach to stable nitrogen alkyl SAM (*S*-adenosylmethionine) analogues, in which the sulfur atom is replaced by a nitrogen atom, is described. This procedure permits the methyl group of SAM to be replaced with larger saturated and unsaturated alkyl groups. The key step is the alkylation of a 5′-(alkylamino)-5′-deoxy-2′,3′-*O*-isopropylideneadenosine with methyl 2(*R*,*S*)-(trifluoroacetamido)-4-iodobutyrate. Subsequent deprotection of the trialkylamine intermediate by alkaline and then acidic hydrolysis provided the final compounds. This procedure has been used to prepare the methyl, ethyl, *n*-propyl, allyl, *n*-butyl, *n*-pentyl, and *n*-octyl nitrogen analogues of SAM. Elaboration of this method allows the synthesis of the 6-amino-1-hexyl nitrogen SAM analogue, a novel potential methyltransferase affinity ligand. Alkylation of 5′-[[6-[[(phenylmethoxy)carbonyl]amino]-1-hexyl]amino]-5′-deoxy-2′,3′-*O*-isopropylideneadenosine with methyl 2(*R*,*S*)-(trifluoroacetamido)-4-iodobutyrate provided the key trialkylamine intermediate. Subsequent deprotection by alkaline hydrolysis, catalytic hydrogenation, and finally acidic hydrolysis provided the final product, N^4-(5′-adenosyl)-N^4-(6-amino-1-hexyl)-2(*R*,*S*),4-diaminobutanoic acid, as a dihydrate.

S-Adenosyl-L-methionine (SAM) is well known as the biological equivalent of methyl iodode. SAM (1) has been found to be a methyl group donor in a wide variety of biochemical processes, including both DNA[1] and RNA

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(1) (a) Santi, D. V.; Garrett, C. E.; Barr, P. J. *Cell* **1983**, *33*, 9. (b) Ehrlich, M.; Wang, R. Y.-H. *Science* (Washington, D.C.) **1981**, *212*, 1350. (c) Doerfler, W. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 919.

0022-3263/88/1953-4952$01.50/0