ResearchGate

See discussions, stats, and author profiles for this publication at: https://www.researchgate.net/publication/231457457

A convergent total synthesis of (±) colchicine and (±) desacetamidoisocolchicine. J Am Chem Soc

ARTICLE *in* JOURNAL OF THE AMERICAN CHEMICAL SOCIETY · SEPTEMBER 1981

Impact Factor: 12.11 · DOI: 10.1021/ja00409a032

CITATIONS
49

READS
47

3 AUTHORS, INCLUDING:

Steven P Tanis
Singapore Polytechnic
56 PUBLICATIONS **1,129** CITATIONS

SEE PROFILE

Available from: Steven P Tanis
Retrieved on: 24 January 2016

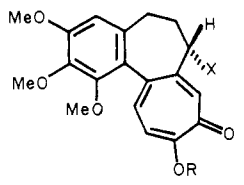
A Convergent Total Synthesis of (±)-Colchicine and (±)-Desacetamidoisocolchicine

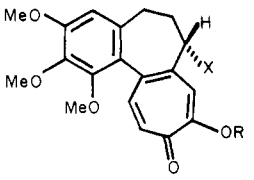
D. A. Evans,* S. P. Tanis, and D. J. Hart

Contribution No. 6363 from the Laboratories of Chemistry, California Institute of Technology, Pasadena, California 91125. *Received December 23, 1981*

Abstract: Total syntheses of (±)-desacetamidoisocolchicine (**2b**) and (±)-colchicine (**1a**) have been achieved. Key features of the synthetic sequence are the facile incorporation of a tropolone dication equivalent via ketone **6** and introduction of the 7-acetamido group. Some of the mechanistic details of the conversion of alcohol **7** to dihydrotropolone **8** and alcohols **14a,b** to ester **19** are discussed.

Colchicine (**1a**), one of the major alkaloid constituents of the





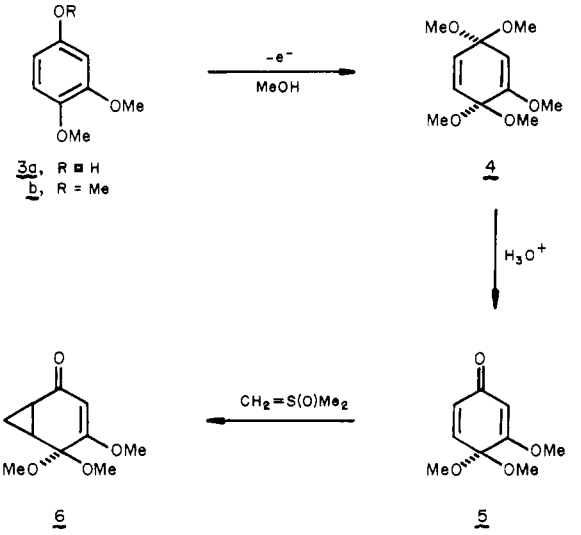
1 **2**

a, R = Me, X = NHAc
b, R = Me, X = H
c, R, X = H
d, R = H, X = NHAc

autumn crocus, *Colchicum automnale L.*, has the interesting property of arresting cell division during mitosis.[1,2] Although colchicine has found extensive use in the treatment of gout,[2] the high toxicity of this alkaloid has precluded its use in cancer chemotherapy.[3] A renewed interest in the pharmacology of colchicine[4] has encouraged us to develop a convergent approach to this natural product which would be readily amenable to the synthesis of structural analogues.

The history of synthetic approaches to colchicine (**1a**) spans more than two decades.[5-7] Despite possessing a deceptively simple structure, colchicine (**1a**) presents several substantial synthetic problems. Noteworthy among these difficulties is the lack of general methodology for the construction of the tropolone nucleus. Although some ten total syntheses of **1a** have been reported to date, several problems associated with the synthesis of this alkaloid have been largely ignored. All but two of the reported syntheses[7] proceed through desacetamidoisocolchicine (**2b**). Since the conversion of **2b** via allylic bromination (12% yield) to colchicine (**1a**) is inefficient,[6a,b] projected syntheses of **1a** would provide for the introduction of the C_7-acetamido group in an alternate manner. In addition, all but one of the syntheses of **2b** proceed through desacetamidocolchiceine (**2c**),[6g] and all of the reported syntheses of colchicine involve the intermediacy of the free tropolone colchiceine (**2d**). This creates severe regiochemical problems since the methylation of **2c** and **2d** produces nearly equal amounts of ethers **1a**, **2a** and **1b**, **2b**, respectively.

Scheme I

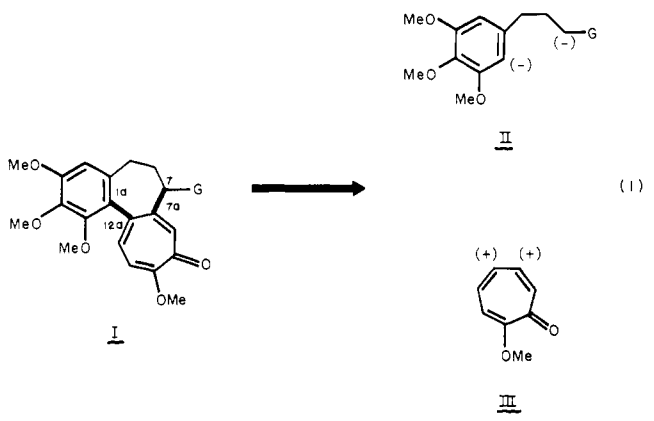


We recently reported our initial efforts directed toward the synthesis of colchicine, culminating in an efficient and convergent construction of desacetamidoisocolchicine (**2b**).[8] Herein we describe the design, development, and execution of a total synthesis of colchicine (**1a**) which acknowledges the pendant C_7-acetamido functionality and illustrates a potentially generalizable annelation process for tropolone ring systems.

The general approach to these target structures is illustrated in eq 1. Disconnection of the C_{12a}–C_{1a} and C_7–C_{7a} bonds reveals two simple subunits, a binucleophilic 3-arylpropyl synthon, **II**, where G = metal or an anion-stabilizing functional group, and a hypothetical tropolone dication **III**. For the projected colchicine synthesis, the functional group interchange, G → NH_2, was envisioned as the basic approach to the incorporation of the requisite C_7 functionality in the target, and carbanion-stabilizing functions such as G = CO_2R, CN, N—NO, and $(SR)_2$ were examined during the course of the investigation. The basic format for this synthesis evolved from our interest in the development of quinone

(1) Olmstead, J. B.; Borisy, G. G. *Annu. Rev. Biochem.* **1973**, *42*, 507–540. Schindler, R. *Nature (London)* **1962**, *196*, 73–74.
(2) Zweig, M. H.; Chignell, C. F. *Biochem. Pharmacol.* **1973**, *22*, 2141–2150 and references cited therein.
(3) For an early report describing the use of deacetyl-*N*-methylcolchicine in the treatment of granulocytic leukemia see: *Chem. Eng. News* **1959**, *37*, 67.
(4) Brossi, A.; Iorio, M.; Chignell, C. F. *Heterocycles* **1978**, *9*, 1–6.
(5) For reviews of the chemistry of colchicine see: (a) Wildman, W. C. "The Chemistry of the Alkaloids"; Pelletier, S. W., Ed.; Van Nostrand-Reinhold: New York, 1970; Chapter 8. (b) Cook, J. W.; Loudon, J. D. "The Alkaloids"; Manske, R. H. F., Ed.; Academic Press: New York, 1952; Vol. 2, pp 261–330. (c) Wildman, W. C. "The Alkaloids"; Manske, R. H. F., Ed.; Academic Press: New York, 1960; Vol. 6, pp 247–288.
(6) For syntheses of colchicine which proceed through desacetamidoisocolchicine **2b**, see: (a) Schreiber, J.; Leimgruber, W.; Pesaro, M.; Schudel, P.; Threefall, T.; Eschenmoser, A. *Helv. Chim. Acta* **1961**, *44*, 540–597. (b) van Tamelen, E. E.; Spencer, T. R.; Allen, D. B.; Orvis, R. L. *Tetrahedron* **1961**, *14*, 8–34. (c) Scott, A. I.; MeCapra, F.; Buchanan, R. L.; Day, A. C.; Young, D. W. *Ibid.* **1965**, *21*, 3605–3631. (d) Martel, J.; Toromonoff, E.; Huynh, C. *J. Org. Chem.* **1965**, *30*, 1752–1759. (e) Kaneko, S.; Matsui, M. *Agric. Biol. Chem.* **1968**, *32*, 995–1001. (f) Kato, M.; Kido, F.; Wu, M. D.; Yoshikoshi, A. *Bull. Chem. Soc. Jpn.* **1974**, *47*, 1516–1521. (g) Kotani, E.; Miyazaki, F.; Tobinaga, S. *J. Chem. Soc., Chem. Commun.* **1974**, 300–301.
(7) For other syntheses of colchicine see: (a) Nakamura, T.; Murase, Y.; Hayashi, R.; Endo, Y. *Chem. Pharm. Bull.* **1962**, *10*, 281–290. Sunagawa, G.; Nakamura, T.; Nakazawa, J.-I. *Ibid.* **1962**, *10*, 291–299. Nakamura, T. *Ibid.* **1962**, *10*, 299–304. (b) Woodward, R. B. "The Harvey Lectures Series 59"; Academic Press: New York, 1965; pp 31–47.
(8) Evans, D. A.; Hart, D. J.; Koelsch, P. M. *J. Am. Chem. Soc.* **1978**, *100*, 4593–4594.

0002-7863/81/1503-5813$01.25/0 © 1981 American Chemical Society



monoketals (cf. **5**) as annelation substrates in the construction of phenanthrenoids.[9,10] These results suggested the possibility of utilizing a cyclopropanated derivative of a quinone monoketal such as **6** as a tropolone dication equivalent (Scheme I). We decided to test this strategy and demonstrate the operational equivalency between **6** and the hypothetical tropolone dication **III** (eq 1) within the context of a synthesis of desacetamidoisocolchicine (**2b**).

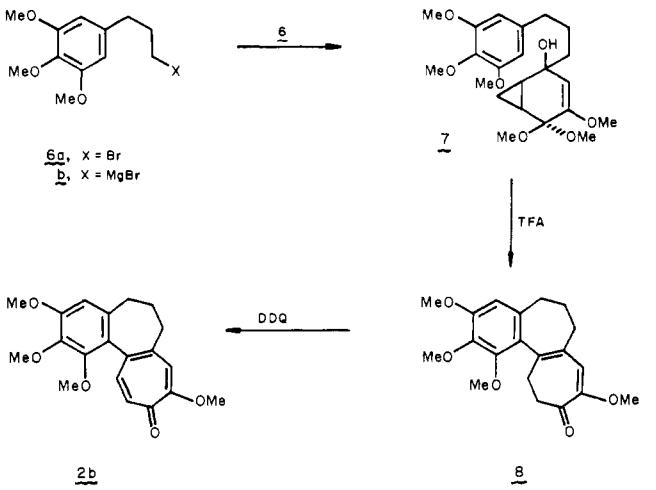
Results and Discussion

Synthesis of Desacetamidoisocolchicine (2b). The cyclopropyl ketone **6** required for the synthesis of **2b** was prepared as outlined in Scheme I. A range of chemical oxidants have been reported for the direct conversion of substituted 4-methoxyphenols to quinone monoketals (e.g., **5**). The yield of quinone ketal has been observed to be highly dependent upon the phenol structure and the nature of the oxidizing agent.[11] To date, the only uniformly high yield chemical oxidant for this transformation has been thallium trinitrate as described by McKillop and Taylor.[12] Oxidation of **3a** with $Tl(NO_3)_3$ provided **5** in 66–85% yields.[8,10] However, difficulties encountered in adapting this method for the production of **5** on a large scale led to the examination of other potential oxidation procedures. Anodic electrochemical oxidation[13,14] was found to be an extremely attractive alternative thus providing quinone bisketal **4** in 88–95% yield from **3b**. Mild acid hydrolysis of **4** readily provided the crystalline quinone monoketal **5**, regiospecifically (Scheme I). In our hands this procedure gave quinone monoketal **5**, from **3b** in 100-g lots in an overall yield of 60–65%. Treatment of **5** with dimethyl oxosulfonium methylide[15,16] afforded the requisite cyclopropyl ketone **6**, in 91–93% yield, as a nicely crystalline solid.

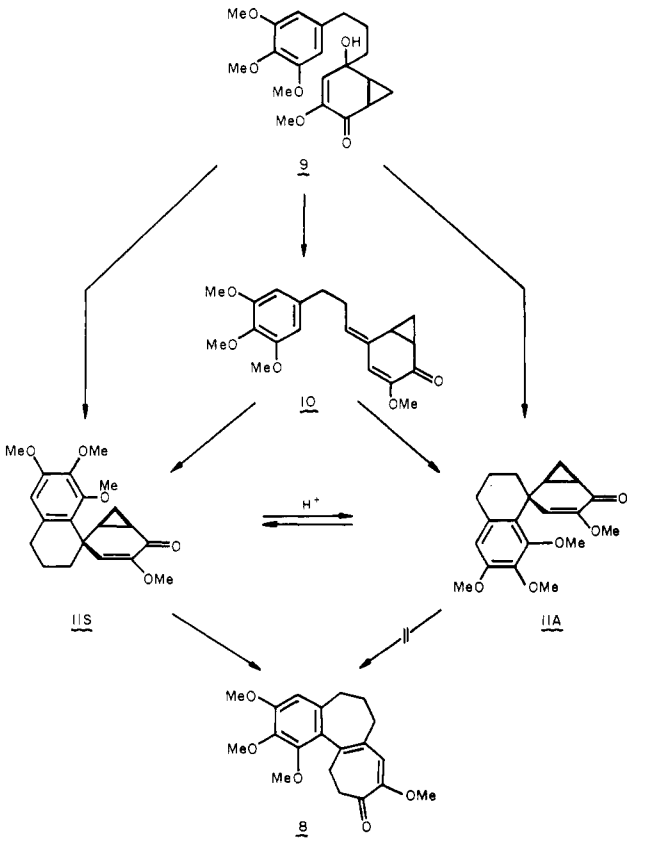
In complete accord with our expectations, the reaction of ketone **6** with 3-(3,4,5-trimethoxyphenyl)-*n*-propylmagnesium bromide (1.5 equiv) (**6b**), prepared from the corresponding bromide **6a**,[6f] provided the vinylogous hemiketal **7** (Scheme II) in 70–90% yield after chromatography over silica gel. In initial cyclization attempts it was found that treatment of **7** with boron trifluoride etherate (CH_3NO_2) afforded a 23% yield of the desired dihydrotropolone methyl ether **8**. Significant improvement was noted in the cyclization process if Brønsted rather than Lewis acids were employed. For example, with trifluoroacetic acid (TFA) a 68% yield of **8** was realized. The reasons for the significant difference in the behavior of **7** when subjected to protic vs. Lewis acids will become apparent from the subsequent discussion. The identity of **8** was confirmed by its subsequent conversion to desacetamidoisocolchicine (**2b**). Oxidation of **8** with DDQ provided a 72% yield of **2b**, mp 147–148 °C[17] (lit.[5b] 148–148.7 °C).

It was gratifying to observe that alcohol **7** did indeed directly provide the desired dihydrotropolone **8**; however, none of the intervening mechanistic intricacies were revealed by this transformation. Careful examination of the crucial cyclization reaction as a function of reaction conditions and time revealed the identifiable intermediates illustrated in Scheme III. Treatment of

Scheme II



Scheme III



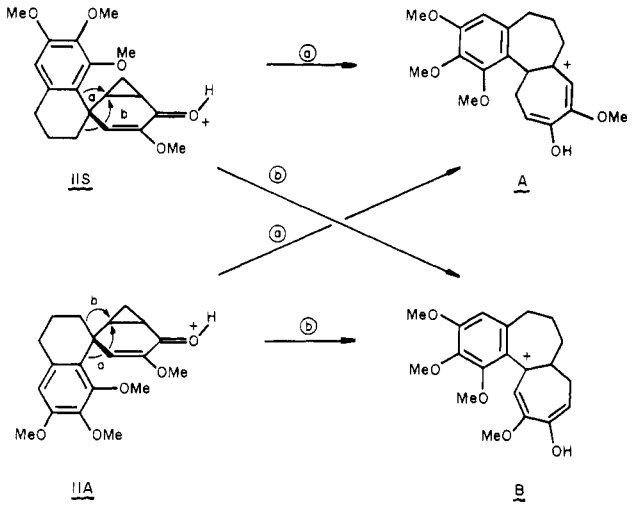
(9) Evans, D. A.; Cain, P. A.; Wong, R. Y. *J. Am. Chem. Soc.* **1977**, *99*, 7083–7085.
(10) Hart, D. J.; Cain, P. A.; Evans, D. A. *J. Am. Chem. Soc.* **1978**, *100*, 1548–1557.
(11) Büchi, G.; Chu, P.-S.; Hoppmann, A.; Mak, C.-P.; Pearce, A. *J. Org. Chem.* **1978**, *43*, 3983–3985 and earlier references.
(12) McKillop, A.; Perry, D. H.; Edwards, M.; Antus, S.; Farkas, L.; Nogradi, M.; Taylor, E. C. *J. Org. Chem.* **1976**, *41*, 282–287.
(13) (a) Belleau, B.; Weinberg, N. L. *J. Am. Chem. Soc.* **1963**, *85*, 2525–2526. (b) Weinberg, N. L.; Belleau, B. *Tetrahedron* **1973**, *29*, 279–285.
(14) (a) Henton, D. R.; Anderson, K.; Manning, M. J.; Swenton, J. S. *J. Org. Chem.* **1980**, *45*, 3422–3433. (b) Henton, D. R.; McCreery, R. L.; Swenton, J. S. *Ibid.* **1980**, *45*, 369–378.
(15) Corey, E. J.; Chaykovsky, M. *J. Am. Chem. Soc.* **1965**, *87*, 1353–1364.
(16) For a relevant study see: Heller, J. E.; Dreiding, A. S.; O'Connor, B. R.; Simmons, G. L.; Buchanan, G. L.; Raphael, R. A.; Taylor, R. *Helv. Chim. Acta* **1973**, *56*, 272–280.
(17) In all respects (mp, mmp, ^1H NMR, IR, and TLC) identical with a sample kindly provided by Professor S. Tobinaga.[6g]

7 with trifluoroacetic acid (TFA) at room temperature for 1 min provided the dienone **10**, as a mixture of *E*- and *Z*-olefin isomers, as well as spirans **11S** and **11A** in the ratio of 10:3:7, respectively. Spectral data (^{1}H NMR and IR) confirmed the structure of dienone **10**. Dienone **10** and the mixture of spirans **11S** and **11A** were efficiently separated by preparative liquid chromatography. The structures of the minor spiran **11S**, mp 169–172 °C, and the major spiran **11A**, mp 155–157 °C, were based on an analysis of spectral data, the mode of synthesis, and behavior in the presence of strong acid (vide infra). A comparison of the ^{1}H NMR spectra of spirans **11A** and **11S** reveals a marked deshielding in the proton resonances assigned to the cyclopropane hydrogens at δ 0.82–1.37 (2 H) and 1.53–2.37 (2 H) for spiran diastereomer **11A** vs. δ 1.22 (1 H) and 1.53–2.77 (3 H) for spiran **11S**, indicating a close spatial relationship between the aryl unit and the cyclopropane in spiran **11S**. The minor spiran **11S** was found to be identical with an intermediate prepared by Tobinaga and co-workers[6g] (^{1}H NMR, IR, mp, mmp).[17] The assignment of structure **11S** to the Tobinaga intermediate was consistent with an analysis of the crucial steps in that synthetic sequence.[18] The assignment of structure **11A** to the *major* kinetic spiran stereoisomer is also consistent with the expectation that the carbocation derived from dienone **10** would undergo preferred electrophilic aromatic substitution from the less sterically congested convex face.

As described in our earlier studies,[8] time-dependent product analysis of the TFA cyclization of **7** revealed that intermediates **10**, **11S**, and **11A** are all intermediates in the cyclization process. In addition, although hydroxy enone **9** was never directly detected in the TFA reaction, the independent hydrolysis of **7** (THF–H_2O, oxalic acid, 25 °C) to **9** and its subsequent behavior under the reaction conditions substantiates it as an additional permissive intermediate. When the acid-catalyzed rearrangement of purified *syn*- and *anti*-spiran isomers **11S** and **11A** were *individually* examined, several important observations were noted. *In trifluoroacetic acid both* **11S** *and* **11A** *not only afford the dihydrotropolone* **8** *but they also interconvert*! Moreover, the observation that spiran **11S** rearranges to **8** more rapidly than does spiran **11A** suggests that the *syn*-spiran **11S** may be the sole penultimate precursor to **8** in the rearrangement process. Support for this assumption were gained by the discovery that, while the *syn*-spiran **11S** is converted to **8** (40%) upon treatment with boron trifluoride etherate in nitromethane (1.0 equiv, 25 °C, 60 min), the *anti*-spiran isomer **11A**, under the same conditions, was recovered unchanged. It is concluded that the preferred syn orientation of the migrating aryl moiety and the cyclopropane ring is a consequence of more favorable bridging geometry with the possible intervention of phenonium ions. A priori, two isomeric dihydrotropolone methyl ethers could have been obtained from the diastereoisomeric spirans (Scheme IV) via either aryl (path a) or alkyl migration (path b). The fact that only *one* of the four potential rearrangement modes was observed (cf. **11S** → **11A**) was gratifying.

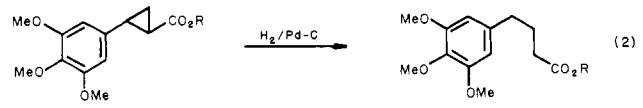
The mechanistic details of the TFA-mediated equilibration of the spiran diastereoisomers **11S** and **11A** remain as an open issue. At least two mechanisms for this interconversion can be proposed. The isomerization could proceed either via a retro-Friedel–Crafts reaction or by way of a homoallylic cation (via cyclopropane scission). The former mechanism should be facilitated by protic acids while it is anticipated that the latter mechanism should be promoted by both protic and Lewis acids. Since spirans **11A** and **11S** are *not* interconverted by boron trifluoride etherate, we tend to favor the equilibration by way of the *retro*-Friedel–Crafts process. The critical observations on the influence of the particular acid catalyst employed in the cyclization process are consistent with our preliminary studies which indicated that low yields of dihydrotropolone **8** resulted from the Lewis acid-catalyzed cyclization of hydroxy ketal **7**. The useful fact that boron trifluoride etherate effectively terminates the complex series of rearrangements at the spiran stage will become significant in the following discussion.

Scheme IV



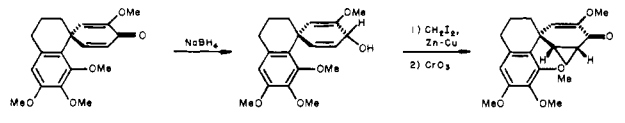
Total Synthesis of (±)-Colchicine (1a). In view of the delicately balanced set of acid-catalyzed rearrangements which were revealed in the desacetamidoisocolchicine synthesis, there was cause for some concern that the added functionality, G, required for colchicine could intervene to disrupt the annelation process. An additional constraint on the extension of the previously delineated plan was the demonstrable weakly electrophilic properties of the tropolone synthon **6**. During the course of these studies it was found that neither ketone enolates, metalloenamines nor metalated nitrosamines could be successfully induced to undergo carbonyl addition to **6**. In addition, although metalated dithianes were observed to undergo successful carbonyl addition, subsequent acid-catalyzed rearrangements afforded intractable products. On the other hand, high-yield carbonyl addition to **6** was observed with the anions derived from esters, amides, and nitriles. The demonstrated capacity of transforming carboxylic acid derivatives to amines via the Curtius–Schmidt reaction suggested that II (G = CO_2R) could serve as the binucleophilic synthon (eq 1).

The required ester **13** was prepared as outlined in eq 2.



3,4,5-Trimethoxycinnamic acid[11] was converted to the corresponding *tert*-butyl ester, in 70% yield, upon treatment of the derived acid chloride with *tert*-butyl alcohol in the presence of *N,N*-dimethylaniline.[19] This ester was converted to cyclopropane **12a** (69%, mp 69–71 °C) with dimethyloxosulfonium methylide.[20] Cyclopropane **12a** was cleaved with hydrogen (50 psi) and 5% palladium on carbon, in methanol to afford butyrate **13a** in a 70% yield, mp 61.5–63 °C. Alternatively, **12b** was prepared from the methyl cinnamate via methylenation with diazomethane in the

(18) We reason that the $NaBH_4$ reduction of the Tobinaga intermediate

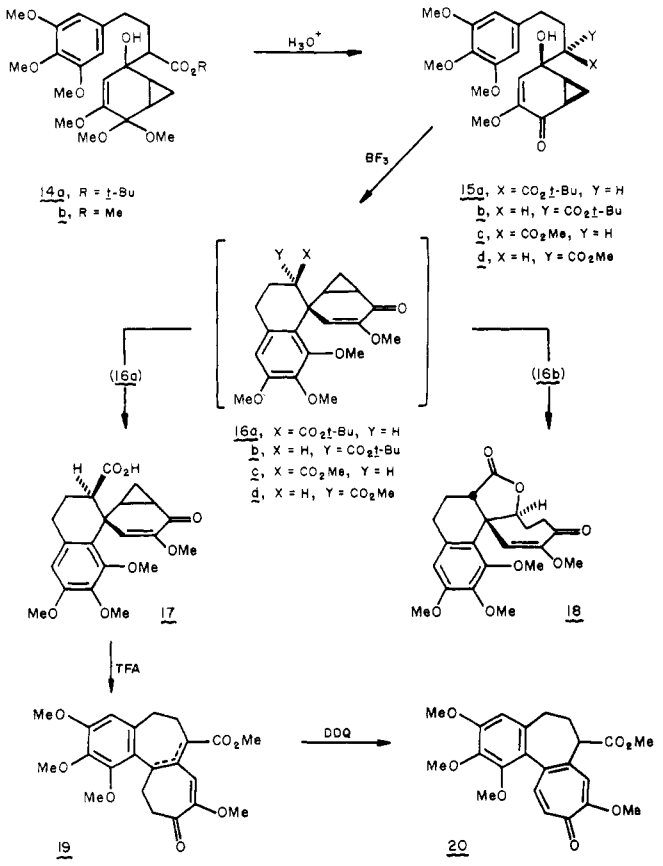


i should give allylic alcohol ii. Thus Simmons–Smith cyclopropanation (cf. Simmons, H. E.; Cairns, T. L.; Vladuchick, S. A.; Hoiness, C. M. *Org. React.* **1973**, *20*, 1–133) and oxidation should given spiran **11S**.

(19) Hauser, C. R.; Hudson, B. E.; Abramovitch, B.; Shivers, J. C. "Organic Syntheses"; Wiley: New York, **1955**; Coll. Vol. III, pp 142–144.

(20) Kaiser, C.; Trost, B. M.; Beeson, J.; Weinstock, J. *J. Org. Chem.* **1965**, *30*, 3972–3975.

Scheme V



presence of palladium(II) acetate in 98% yield, mp 53.5–54.5 °C. Hydrogenolysis of **12b** under similar conditions afforded **13b** in nearly quantitative yield.

Ester **13a** was deprotonated with lithium diisopropylamide (LDA) in tetrahydrofuran and ketone **6** was then added to provide alcohol **14a** (Scheme V) in high yield. The labile alcohol **14a** was immediately hydrolyzed with 5% aqueous oxalic acid in THF to afford a mixture of the diastereoisomeric aldol adducts **15a,b** in 75% yield contaminated with 7% of an enone which is the product of enol ether hydrolysis and dehydration. In assigning structures of the aldol adducts **15a,b** it was assumed that the major direction of attack upon ketone **6** should occur from the face opposite the methylene bridge;[21] therefore, two diastereomers were expected differing at the center bearing the ester function. An examination of the ^{1}H NMR spectrum of the mixture, however, suggested that **15a,b** was a 3:2:1 mixture of three diastereomeric aldol adducts (^{1}H NMR δ 4.73, 4.94, 5.10 (d, J = 2.5 Hz, vinyl H), 6.23, 6.27, 6.33 (s, ArH)), indicating that some addition had probably occurred *syn* to the methylene bridge. The major adduct **15b** (^{1}H NMR δ 4.94 (d, J = 2.5 Hz, vinyl *H*), 6.33 (s, 2, ArH)) could be crystallized directly from the mixture, mp 130–131 °C (CCl_4). The assignment of the structure **15b** was tentatively made as a result of the considerations mentioned above and its subsequent behavior under acidic conditions (vide infra).

Treatment of the mixture of *tert*-butyl esters **15a,b** with boron trifluoride etherate for 5 min at room temperature (CH_3NO_2) afforded a mixture of lactone **18** and acid **17** in 56% and 23%, yields respectively (Scheme V). For convenience of handling, acid **17** was immediately converted to the corresponding methyl ester **16c**. The structures of these compounds were established as follows. ^{1}H NMR studies of lactone **18**, mp 187–190 °C, revealed an absence of proton resonances assignable to the cyclopropane moiety and the appearance of aliphatic CH resonances (δ 1.67–3.07). The ^{13}C NMR spectrum of **18** indicated the presence of a quaternary carbon (δ 46.4) signifying that the spiran center had been retained. The IR spectrum of **18** exhibited a carbonyl absorption at 1775 cm^{-1}, typical of a butyrolactone. These data and the previously observed bias for aryl attack anti to the cyclopropane lead us to propose structure **18**.

Treatment of ester **16c** with boron trifluoride etherate did *not* provide the corresponding dihydrotropolone. This fact establishes the spiran stereochemistry as is illustrated in Scheme V by analogy to the behavior of spirans **11A** and **11S** under similar conditions. The orientation of the ester in **16c** as well as the formation of lactone **18** can be interpreted in the following fashion. We postulate that the mixture of esters **15a,b** initially cyclizes to provide spiro esters **16a** and **16b** (Scheme V) or the derived acids. Spiran isomer **16b** possesses a carboxyl group ideally situated for participation in the acid-catalyzed opening of the cyclopropyl ketone moiety with loss of the *tert*-butyl group. Related examples of participation in the ring opening of a cyclopropylcarbinyl system have been well documented by Marshall[22] and Lawton.[23] In spiran **16a** the carboxyl group is constrained such that participation is precluded and the cyclopropyl ketone unit remains intact, with **17** being the product of acid induced *tert*-butyl ester hydrolysis.

With the identities of compounds **17** and **18** established, we then studied the effect of protic acid (TFA) upon **18** and methyl ester **16c**. It was not surprising to find that spiro ester **16c** did indeed behave as expected, rearranging to a mixture of isomeric dienoic esters **19** upon treatment with TFA at reflux for 75 min. Although not demonstrated, it is likely that a spiro ester, corresponding to **11S**, is an intermediate in the rearrangement of **16c** to **19**, on the basis of our prior studies (Scheme III). Lactone **18**, however, proved to be completely resistant to acid-catalyzed rearrangement. The identity of esters **19** was firmly established as a result of the following transformations.

Esters **19** were oxidized directly with DDQ to a separable 7:3 mixture of tropolone ether **20**, mp 127–128 °C (IR 1735, 1620, 1605 cm^{-1}), and its heptafulvene tautomer, mp 154–155 °C (IR 3500, 1735, 1620, 1575 cm^{-1}), in 64% yield from **16c** (Scheme V). When either tautomer was dissolved in chloroform or ethyl acetate for several hours, a 7:3 mixture of **20** and the corresponding heptafulvene tautomer was obtained.

Although these experiments demonstrated that spiro ester **16c** could be rearranged in a manner analogous to spiran **11A**, it remained to be demonstrated that rearrangement had occurred with aryl rather than alkyl migration (cf. Scheme IV). Alkyl migration would have given a tropolone ether which would not necessarily be readily distinguished from the desired product **19**. The course of the rearrangement was established as follows. A mixture of **20** and the corresponding heptafulvene tautomer were hydrolyzed (NaOH, aqueous MeOH) to afford the crystalline tropolonic acid **21** (cf. Scheme VI), mp 179–180 °C, and a small amount of its heptafulvene tautomer in 85% yield. When acid **21** was warmed to 180 °C for 1–2 min, it melted with concomitant decarboxylation, and desacetamidoisocolchicine (**2b**) was isolated in a 60% yield after crystallization. Although the sequences mentioned above dramatically illustrate the potential utility of spiro ester **16c** in the synthesis of colchicine, the failure of lactone **18**, which constitutes 70% of the total product, to undergo rearrangement presented a severe roadblock to the completion of the synthetic endeavor.

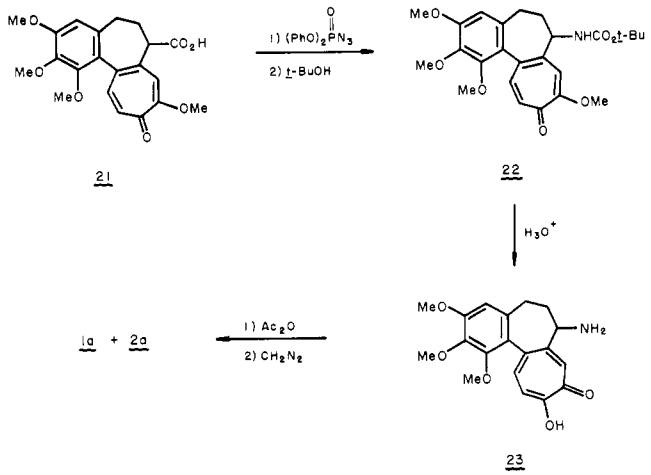
One apparent conclusion from the above studies is that the unfavorable partitioning of the reaction sequence between lactone **18** and spiran **17** had its origin in the stereochemical course of the aldol condensation. This proved *not* to be the case when the acid-catalyzed rearrangement of the methyl esters **15c** and **15d** were explored. Aldol condensation of the enolate derived from **13b** (LDA, THF) with enone **6** followed by aqueous acid hydrolysis afforded the diastereoisomeric β-hydroxy methyl esters **15c** and **15d** in 95% yield after chromatography as a 1:1 mixture

(21) Rocquet, F.; Sevin, A.; Chodkiewicz, W. *C. R. Hebd. Seances Acad. Sci., Ser. C* **1971**, *272*, 417–420. Roequet, F.; Sevin, A. *Bull. Soc. Chim. Fr.* **1974**, 895–899.

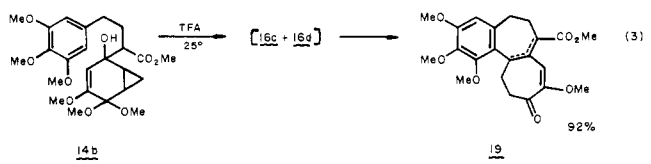
(22) Marshall, J. A.; Ellison, R. H. *J. Org. Chem.* **1975**, *40*, 2070–2073; *J. Am. Chem. Soc.* **1976**, *98*, 4312–4313.

(23) Mueller, L. G.; Lawton, R. G. *J. Org. Chem.* **1979**, *44*, 4741–4742.

Scheme VI



(¹H NMR). Spirocyclization (BF_3·Et_2O, CH_3NO_2) of **15c,d** (1:1) provided a mixture of diastereoisomeric methyl esters **16c** and **16d** (**16c**/**16d** = 1) in 71% yield *uncontaminated* by lactone **18**. The ¹H NMR spectrum of compounds **16c,d** showed two vinyl hydrogen resonances, δ 5.10 (d, 0.5 H, J = 2.5 Hz) and 5.52 (d, 0.5 H, J = 2.5 Hz). The latter resonance and other aspects of the spectrum were superimposable upon the ¹H NMR spectrum of spiro ester **16c** derived from **17** (Scheme V), suggesting that these compounds differed only at the stereocenter bearing the carbomethoxyl group. This conclusion was confirmed by the base-catalyzed equilibration of pure ester **16c**, prepared previously. Treatment of ester **16c** with sodium methoxide in dimethylformamide provided a 40:60 mixture of esters **16c** and **16d**, respectively. Similar equilibration of the 1:1 mixture of esters **16c** and **16d** isolated from the spirocyclization of alcohol **14b**, afforded an



identical 40:60 mixture of **16c** and **16d**, thus securing the stereochemical assignment. These data strongly imply that the origin of the problem in the original cyclization studies of the *tert*-butyl esters **15a,b** was the formation of the carboxylic acid **16** (X = H, Y = CO_2H)[24] which participated in lactone formation. In contrast, the analogous methyl ester **16d** apparently is more resistant to this unwanted reaction path. With an understanding of the intimate details of the annelation process in hand, it was found that treatment of the aldol adduct **14b** with excess trifluoroacetic acid at 25 °C (5 min) followed by an additional 35 min at elevated temperatures (preheated oil bath at 90 °C) afforded a 92% yield of the dihydrotropolone **19**. The overall yield of **19** through the aldol and cyclization steps from **6** and **13b** employing this variation was 87%.

The successful completion of the synthesis of (±)-colchicine is outlined in Scheme VI. Treatment of acid **21**, containing a trace of the corresponding heptafulvene tautomer, with diphenylphosphoryl azide[25] and triethylamine in *tert*-butyl alcohol gave carbamate **22** (54–62%), mp 195–198 °C. The *tert*-butoxycarbonyl group was removed with concomitant hydrolysis of the ether linkage to provide (±)-desacetylcolchiceine (**23**) (72%) which was in all respects (mp, mmp, ¹H NMR, IR, and MS) identical with an authentic sample of (±)-**23** prepared by racemization and degradation of (−)-colchicine **1a**.[26] Since (±)-**23** has been previously converted to colchicine (**1a**)[27–29] (Scheme VI), the reaction sequence outlined above constitutes a total synthesis of (±)-colchicine.

In its present form, the previously described synthesis plan provides an efficient entry into the isocolchicine product manifold (cf. **22**). The isomeric tropolone methyl ether substitution pattern found in colchicine itself does not conveniently evolve from the delineated chemistry. Nonetheless, it is projected that this last obstacle could be addressed by the use of related quinone ketals which would afford isocolchicine benzyl rather than methyl ethers. Since the completion of these studies, the elegant studies of Büchi have further illustrated the potential of quinone ketals in tropolone synthesis.[30]

Experimental Section

Infrared spectra were recorded on a Beckmann 4210 spectrophotometer. ¹H magnetic resonance spectra were recorded on a Varian Associates EM-390 spectrometer (90 MHz) and are reported in parts per million from internal tetramethylsilane on the δ scale. Data are reported as follows: chemical shift (multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, b = broad), integration, coupling constant (Hz), and interpretation). ¹³C magnetic resonance spectra were recorded on Varian Associates XL-100 (25.2-MHz) and JEOL-FX-90Q (22.5-MHz) spectrometers and are reported in parts per million from tetramethylsilane on the δ scale. When multiplicities were determined (by off-resonance decoupling), they are reported by using the abbreviations given above. Melting points were determined with a Büchi SMP-20 melting point apparatus and are uncorrected. Mass spectra were recorded on a Du Pont 21-492B spectrometer by the California Institute of Technology Microanalytical Laboratory. Combustion analyses were performed by the California Institute of Technology Microanalytical Laboratory and Galbraith Laboratories, Inc., Knoxville, TN.

Open column chromatography was performed by utilizing Merck 60-230 mesh silica gel, eluted with the solvents mentioned. Flash chromatography was performed according to the procedure of Still et al.[31] by using Merck Silica Gel 60 (230–400 mesh) and eluted with the solvents mentioned. The column outer diameter (o.d.) is listed in millimeters. Medium-pressure chromatography was performed by using EM Laboratories LoBar Silica Gel 60 prepacked columns on a Chromatronix MPLC apparatus equipped with a Fluid Metering Inc. Model RP lab pump. Column eluate was monitored with an ISCO Model UA-5 absorbance Monitor. Preparative liquid chromatography was performed with a Waters Associates, Inc., Prep LC System 500.

When necessary, solvents and reagents were dried prior to use. Dichloromethane, dimethyl sulfoxide, and diisopropylamine were distilled from calcium hydride. Benzene and tetrahydrofuran were distilled from sodium benzophenone ketyl. Nitromethane was passed through a column of activity I alumina. Dimethylformamide was distilled from phosphorus pentoxide. Pyridine was distilled from barium oxide. Methanol was distilled from magnesium methoxide. *n*-Butyllithium was titrated by the procedure of Watson and Eastham.[32] All other reagents were used as received. All nonaqueous reactions were run under a blanket of argon with rigorous exclusion of moisture unless otherwise noted. Analytical thin-layer chromatographic analysis was performed by using EM Laboratories precoated silica gel 60 F-254 plates.

Lithium diisopropylamide was always prepared in the following manner. A solution of diisopropylamine in tetrahydrofuran was cooled to −70 °C followed by the addition of a hexane solution of *n*-butyllithium via syringe. The mixture was allowed to stir for 10–15 min at −70 °C, and the resulting solution of lithium diisopropylamide was then cooled or warmed to the temperature desired for subsequent operations.

1,2,5-Trimethoxybenzene (3b). A 29.5-g (0.19-mol) sample of phenol **3a**[29] was placed in a 250-mL 3-neck round-bottom flask and heated, with an oil bath, until it liquefied. To the liquid phenol was added, simultaneously with heating, a solution of 16 g (0.28 mol) of potassium hydroxide in 25 mL of water and 30.2 g (0.24 mol) of dimethyl sulfate at such a rate that the reaction mixture remains basic and at a gentle reflux. The mixture was heated at reflux for 1.5 h after the addition was completed, cooled to room temperature, and quenched with 150 mL of 30% ammonium hydroxide. The two-phase mixture was transferred into

(24) Schwyzer, R.; Kappeler, H. *Helv. Chim. Acta* **1961**, *44*, 1991–2002.
(25) Yamada, S.; Shioiri, T.; Ninomiya, K. *Tetrahedron* **1974**, *30*, 2151–2157.
(26) Blade-Font, A. *Tetrahedron Lett.* **1977**, 2977–2980.
(27) Corradi, H.; Hardegger, E. *Helv. Chim. Acta* **1957**, *40*, 193–199. Sarkin, M. *Ibid.* **1946**, *29*, 246–248.
(28) Godfrey, I. M.; Sargent, M. V.; Elix, J. A. *J. Chem. Soc., Perkin Trans. 1* **1974**, 1353–1354.
(29) Hardegger, E.; Steiner, K.; Widmer, E.; Corrodi, H.; Schmidt, T.; Knoepfel, H. P.; Rieder, W.; Meyer, H. J.; Kugler, F.; Gempeler, H. *Helv. Chim. Acta* **1964**, *47*, 1996–2017.
(30) Mak, C.-P.; Büchi, G. *J. Org. Chem.* **1981**, *46*, 1–3.
(31) Still, W. C.; Khan, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923–2925.
(32) Watson, S. L.; Eastham, J. F. *J. Organomet. Chem.* **1967**, *9*, 165–168.

dichloromethane (500 mL), and the organic phase was separated. The aqueous phase was extracted with dichloromethane (150 mL) and the combined organic layers were washed with water (750 mL) and 20% ammonium hydroxide (500 mL), dried (Na_2SO_4), and concentrated in vacuo to provide a yellow liquid. The crude product was purified by filtration through a column of silica gel (150 g, Merck 60–230 mesh, 50-mm o.d.) upon elution with dichloromethane to provide 28.84 g (90%) of **3b**[29] as a colorless liquid.

1,1,2,4,4-Pentamethoxycyclohexa-2,5-diene (4). A solution of 1,2,4-trimethoxybenzene (**3b**) (37.61 g, 0.224 mol) in 220 mL of 3% methanolic KOH was placed in a 400-mL beaker equipped with a magnetic stirrer and an ice-water bath. Into the solution was inserted a platinum anode and cathode, along with a potassium chloride reference electrode. Electrolysis was then carried out at 0 °C for 25 h (initial potential, 4.0 V; initial current, 1.03 A) by using a Princeton Applied Research Model 172 potentiostat/galvanostat as a power source. Methanol was periodically added in order to keep the reaction at its original volume. Completion of electrolysis was confirmed both by observation of a substantial drop in the amount of current being passed through the solution (1.03 → 0.40 A) and by examination of aliquots. The power source and electrodes were removed, and the reaction mixture was freed of solvents in vacuo to leave a tan residue. This material was layered between 300 mL of dichloromethane and 250 mL of half-saturated aqueous NaCl. The resulting organic layer was removed, and the aqueous layer was extracted with 100 mL of dichloromethane. The extract was combined with the initial organic phase, and the solution was washed with 300 mL of brine and dried over Na_2SO_4. Removal of all solvents in vacuo afforded the crude bisketal as an amber oil, of sufficient purity to be used directly in the next reaction: 46.71 g (91%); ^1H NMR ($CDCl_3$) δ 6.18 (dd, 1, J = 11 Hz, J = 2 Hz), 5.89 (d, 1, J = 11 Hz), 5.10 (d, 1, J = 2 Hz), 3.68 (s, 3), 3.30 (s, 6), 3.27 (s, 6).

3,4,4-Trimethoxycyclohexa-2,5-dien-1-one (5). The crude bisketal **4** (46.71 g, 0.203 mol) was dissolved in 250 mL of THF and 60 mL of water at room temperature, and oxalic acid (1.0 g, 0.01 mol) was added. The solution was allowed to stir for 12 min and then was quenched with 5% aqueous Na_2CO_3. After dilution with 400 mL of ether, an organic layer separated. This was removed, and the remaining aqueous layer was extracted with ether (2 × 150 mL). All ether layers were combined and washed with 400 mL of brine, and then the mixture was dried over Na_2SO_4. After removal of solvents in vacuo, the orange residue was eluted rapidly with dichloromethane through a 7-in. column of activity III alumina. This afforded 34.61 g of a crude, yellow solid, which was recrystallized (chloroform–hexane) to afford **5** as a white solid, mp 62–64 °C (lit.[10] 63.5–64.5 °C), 26.86 g (72% from crude bisketal, 65% overall from trimethoxybenzene): IR ($CHCl_3$) 2880–3050, 2825, 1660, 1625, 1600, 1450, 1365, 1350, 1305, 1225, 1170, 1115, 1000, 990, 850 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.60 (d, 1, J = 11 Hz), 6.26 (dd, 1, J = 11 Hz, J = 1.5 Hz), 5.60 (d, 1, J = 1.5 Hz), 3.79 (s, 3), 3.32 (s, 6).

Anal. Calcd for $C_9H_{12}O_4$: C, H.

4,5,5-Trimethoxybicyclo[4.1.0]hept-3-en-2-one (6). To a mixture of 5.27 g (0.22 mmol) of dry sodium hydride and 48.8 g (0.22 mmol) of trimethyloxosulfonium iodide cooled in an ice bath was added 300 mL of dry dimethyl sulfoxide over a 15-min period. The cooling bath was removed, and the resulting suspension was stirred for an additional 30 min. To the chalky mixture was added a solution of 20.5 g (0.11 mol) of dienone **5** in 100 mL of dry dimethyl sulfoxide over a 10-min period. The resulting homogeneous yellow solution was stirred for 2 h at room temperature and poured into 2.0-L of water. The resulting homogeneous yellow solution was extracted with three 1.0-L portions of dichloromethane, and the combined extracts were dried and concentrated in vacuo. The residual dimethyl sulfoxide was removed under high vacuum at 25 °C, and the residue was purified by chromatography on a column of silica gel (200 g, Merck 60–230 mesh, 60-mm o.d., 100-mL fractions) upon elution with ethyl acetate–hexane (9:1) using the flash technique.[30] Combination and concentration of fractions 6–14 provided 19.5 g (91%) of **6** as a white solid, mp 93.5–96 °C. Recrystallization from carbon tetrachloride–hexane afforded **6** as a colorless prisms: mp 94.5–95.5 °C; ^1H NMR ($CDCl_3$) δ 0.92 (m, 1), 1.27 (m, 1), 1.99 (m, 2), 3.30 (s, 3, OCH_3), 3.50 (s, 3, OCH_3), 3.70 (s, 3, OCH_3), 5.11 (s, 1, 2 H); ^{13}C NMR ($CDCl_3$) δ 13.3 (t), 20.0 (d), 23.4 (d), 49.2 (q), 51.4 (q), 55.8 (q), 97.1 (s), 99.7 (d), 166.2 (s), 196.2 (s); IR ($CHCl_3$) 1610 cm^{-1}.

Anal. ($C_{10}H_{14}O_4$): C, H.

4,5,5-Trimethoxy-2-[3-(3,4,5-trimethoxyphenyl)prop-1-yl]bicyclo[4.1.0]hept-3-en-2-ol (7). To 0.86 g (36.0 mmol) of dry magnesium turnings covered with 9.0 mL of dry tetrahydrofuran at room temperature was added 10–15% of a solution of 8.67 g (30.0 mmol) of 3-(3,4,5-trimethoxyphenyl)-*n*-propyl bromide[6f] in 15 mL of tetrahydrofuran. After 10 min the solution became warm and the remaining halide was added over a 55-min period. The mixture was stirred for an additional 60 min and transferred via syringe to a dry addition funnel.

To a solution of 2.97 g (15.0 mmol) of ketone **6** in 30 mL of dry tetrahydrofuran was added the straw-colored solution of Grignard reagent over a 35-min period with concomitant cooling in an ice bath. The cooling bath was removed, and the mixture was stirred for an additional 2 h followed by pouring into 100 mL of water. The mixture was rapidly extracted with two 100-mL portions of dichloromethane. The combined extracts were dried and concentrated in vacuo. The residue was purified by chromatography on a column of silica gel (125 g, Merck 60–230 mesh, 15-mL fractions) upon elution with ethyl acetate. Combination and concentration of fractions 18–41 provided 5.5 g (90%) of vinylogous hemiketal **7** as a pale yellow liquid: ^1H NMR (CCl_4) δ 0.23–0.67 (m, 2), 1.07–2.10 (m, 2), 2.47 (m, 2), 3.07 (s, 3, OCH_3), 3.23 (s, 3, OCH_3), 3.37 (s, 3, OCH_3), 3.62 (s, 3, OCH_3), 3.73 (s, 6, OCH_3), 4.26 (b s, 1, 3-H), 6.24 (s, 2, ArH); IR (CCl_4) 3600, 3510, 1650, 1580, 1125 cm^{-1}. Alcohol **7** is sensitive to acids and should be kept from contact with any solvent which may be acidic (e.g., chloroform). Samples of **7** were stored at 0 °C for up to 2 weeks without extensive decomposition, but immediate use in subsequent reactions is recommended.

11,12-Dihydrodesacetamidoisocolchicine (8). A solution of unpurified ketal **7** [prepared from 8.67 g (30 mmol) of 3-(3,4,5-trimethoxyphenyl)-*n*-propyl bromide and 3.96 g (20 mmol) of ketone **6** as described above] in 100 mL of trifluoroacetic acid was allowed to stir at room temperature for 18 h. The resulting red solution was poured into 400 mL of dichloromethane–water (1:1). The organic phase was washed with 200 mL of water and two 200-mL portions of saturated aqueous sodium bicarbonate, dried (Na_2SO_4), and concentrated in vacuo. The residual oil was chromatographed on silica gel at medium pressure (Lobar, size B; eluted with hexane–ethyl acetate (3:2); 18-mL fractions; 9-mL flow/min). Fractions 10–14 were concentrated to afford 4.7 g (68%) of dihydrotropolone ether **8** as a yellow solid, mp 105–111 °C. Recrystallization from hexane–ethyl acetate (2:1) gave **8** as a pale yellow solid: mp 111–112 °C; ^1H NMR ($CDCl_3$) δ 1.67–2.79 (m, 10), 3.63 (s, 3, OCH_3), 3.76 (s, 3, OCH_3), 3.78 (s, 3, OCH_3), 3.81 (s, 3, OCH_3), 5.83 (s, 1, 8-H), 6.39 (s, 1, 4-H); ^{13}C NMR ($CDCl_3$) δ 27.7 (t), 31.9 (t), 32.7 (t), 33.4 (t), 42.6 (t), 55.5 (q), 55.8 (q), 60.7 (q), 60.8 (q), 107.2 (d), 116.7 (d), 127.8 (s), 131.6 (s), 135.4 (s), 138.8 (s), 140.5 (s), 150.5 (s), 152.2 (s), 152.4 (s), 195.5 (s); IR (CCl_4) 1670 cm^{-1}.

Anal. ($C_{20}H_{24}O_5$): C, H.

Desacetamidoisocolchicine (2b). A solution of 4.6 g (13.3 mmol) of dienone **8** and 3.18 g (14.0 mmol) of DDQ in 60 mL of benzene was heated at reflux for 18 h. The solution was filtered, and the filter cake was rinsed with 30 mL of benzene. The filtrate was concentrated in vacuo, and the black residue was purified by chromatography on a column of alumina (230 g, Woelm activity III, 20-mL fractions) upon elution with ethyl acetate. Combination and concentration of fractions 14–44 provided a viscous oil which was crystallized from diethyl ether to give 3.28 g (72%) of desacetamidoisocolchicine **2b**: mp 147–148 °C (lit.[5b] 148–148.7 °C); ^1H NMR ($CDCl_3$) δ 1.93–2.60 (m, 6), 3.63 (s, 3, OCH_3), 3.89 (s, 6, OCH_3), 3.93 (s, 3, OCH_3), 6.50 (s, 1, 8-H), 6.72 (s, 1, 4-H), 7.07 (d, 1, J = 12 Hz, 11-H), 7.33 (d, 1, J = 12 Hz, 12-H); ^{13}C NMR ($CDCl_3$) δ 30.8 (t), 33.1 (t), 37.4 (t), 56.1 (q), 56.1 (q), 60.8 (q), 61.0 (q), 107.4 (d), 116.9 (d), 126.9 (s), 133.1 (s), 135.4 (s), 135.7 (s), 140.9 (s), 141.2 (s), 144.1 (s), 150.3 (s), 153.2 (s), 163.1 (s), 179.2 (s); IR ($CHCl_3$) 1610, 1595, 1560 cm^{-1}.

Exact mass calcd for $C_{20}H_{22}O_5$: 342.147. Found: 342.145.

2-[3-(3,4,5-Trimethoxyphenyl)prop-1-yl]-4-methoxybicyclo[4.1.0]hept-3-en-5-on-2-ol (9). To a stirred solution of 3.45 g (8.45 mmol) of ketal **7** in 72 mL of tetrahydrofuran–water (5:1) was added 30 mg of oxalic acid. The solution was stirred at room temperature for 60 min, poured into 150 mL of dichloromethane, and washed with two 75-mL portions of saturated aqueous sodium bicarbonate. The organic phase was dried (Na_2SO_4) and concentrated in vacuo, and the residual yellow oil was chromatographed on a column of silica gel (125 g, Merck 60–230 mesh, 20 mL fractions, ethyl acetate). Fractions 22–42 gave 1.79 g (58%) of γ-hydroxyenone **9** as a colorless oil: ^1H NMR (CCl_4) δ 0.61–2.61 (m, 11), 3.40 (s, 3, OCH_3), 3.64 (s, 3, OCH_3), 3.74 (s, 3, OCH_3), 3.76 (s, 3, OCH_3), 4.90 (d, 0.6 H, J = 2 Hz, 3-H), 5.04 (s, 0.4 H, 3-H), 6.20 (s, 0.6 H, ArH), 6.28 (s, 0.4 H, ArH); IR ($CHCl_3$) 1675 cm^{-1}. This material is acid sensitive, and immediate use in subsequent reactions is recommended.

***rel*-(1*S*,2*R*,6*R*)-3,4′-Dihydro-4,6′,7′,8′-tetramethoxyspiro[bicyclo[4.1.0]hept-3-ene-2,1′-(2′*H*)-naphthalen]-5-one (11A) and *rel*-(1*S*,2*S*,6*R*)-3,4′-dihydro-4,6′,7′,8′-tetramethoxyspiro[bicyclo[4.1.0]hept-3-ene-2,1′-(2′*H*)-naphthalen]-5-one (11S).** To a solution of 0.72 g (1.96 mmol) of enone **9** in 15 mL of dry nitromethane was added 0.35 mL of boron trifluoride etherate. The mixture was stirred at room temperature for 1 min, poured into 50 mL of dichloromethane, and washed with 50 mL of saturated aqueous sodium bicarbonate. The organic phase was dried (Na_2SO_4) and concentrated, and the residue was chromatographed on silica gel at medium pressure (Lobar, size B; eluted

with ethyl acetate–hexane (3:7); 10-mL fractions; 6.0-mL flow/min). Fractions 56–97 gave 588 mg (84%) of a 3:1 mixture of spiranes **11A** and **11S**, respectively, as a white solid. Spiranes **11A** and **11S** were separated by preparative liquid chromatography (Waters Prep 500) on silica gel upon elution with dichloromethane–ethyl acetate (9:1). Collection (retention time 28–34 min), and concentration in vacuo provided 140 mg of spirane **11S** as a white solid: mp 167–170 °C; ^{1}H NMR ($CDCl_3$) δ 1.22 (m, 1), 1.53–2.20 (m, 7), 2.77 (m, 2), 3.57 (s, 3, OCH_3), 3.80 (s, 3, OCH_3), 3.86 (s, 6, OCH_3), 5.50 (s, 1, 3-H), 6.40 (s, 1, 9-H); ^{13}C NMR ($CDCl_3$) δ 14.5 (t), 18.0 (t), 25.0 (d), 25.5 (d), 30.4 (t), 38.4 (s), 42.0 (t), 54.8 (q), 55.7 (q), 60.2 (q), 60.4 (q), 107.3 (d), 123.7 (d), 126.0 (s), 133.5 (s), 140.7 (s), 146.1 (s), 152.4 (s), 153.0 (s), 193.1 (s); IR ($CHCl_3$) 1654, 1614 cm^{-1}.

Anal. ($C_{20}H_{24}O_5$): C, H.

Collection (retention time 40–53 min) and concentration in vacuo gave 440 mg of spirane **11A** as a white solid: mp 158–159 °C; ^{1}H NMR ($CDCl_3$) δ 0.83–1.37 (m, 2), 1.53–2.37 (m, 6), 2.67–2.90 (m, 2), 3.50 (s, 3, OCH_3), 3.67 (s, 3, OCH_3), 3.73 (s, 3, OCH_3), 3.83 (s, 3, OCH_3), 5.10 (d, 1, J = 2.5 Hz, 3-H), 6.40 (s, 1, 9-H); ^{13}C NMR ($CDCl_3$) δ 12.4 (t), 19.5 (t), 27.5 (d), 27.9 (d), 31.5 (t), 37.6 (s), 39.4 (t), 54.6 (q), 55.6 (q), 59.9 (q), 60.3 (q), 107.1 (d), 115.1 (d), 130.0 (s), 132.6 (s), 140.6 (s), 147.0 (s), 152.3 (s), 154.2 (s), 193.0 (s); IR ($CHCl_3$) 1664, 1624, 1590 cm^{-1}.

Anal. ($C_{20}H_{24}O_5$): C, H.

5-[3-(3,4,5-Trimethoxyphenyl)propylidene]-3-methoxybicyclo[4.1.0]-hept-3-en-2-one (10). To a solution of 200 mg (0.49 mmol) of ketal **7** in 5.0 mL of dichloromethane was added 0.96 mL of boron trifluoride etherate via syringe. The mixture was stirred at room temperature for 10 min and diluted with dichloromethane and the solution washed with saturated aqueous sodium bicarbonate, dried (Na_2SO_4), and concentrated in vacuo. The residue was chromatographed on a column of silica gel (50 g, Merck 60–230 mesh, 10-mL fractions) upon elution with ethyl acetate–hexane (1:2). Combination and concentration of fractions 31–45 provided 12 mg (7%) of a 3.5:1 mixture (^{1}H NMR) of spirans **11A** and **11S**, respectively. Fractions 53–56 afforded 15 mg of a single stereoisomer of dienone **10** as a yellow oil: ^{1}H NMR (CCl_4) δ 0.83 (m, 1), 1.20 (m, 1), 1.93–2.73 (m, 6), 3.44 (s, 3, OCH_3), 3.61 (s, 3, OCH_3), 3.73 (s, 6, OCH_3), 5.47 (t, 1, J = 6 Hz, 1′-H), 5.72 (b s, 1, 4-H), 6.21 (s, 2, ArH); IR (CCl_4) 1674, 1582, 1060 cm^{-1}.

Exact mass calcd for $C_{20}H_{24}O_5$: 344.163. Found: 344.164.

Fractions 57–75 gave 120 mg of a 1:1 mixture of stereoisomeric dienones **10**. Fractions 76–80 provided 16 mg (88% overall) of the other stereoisomer: ^{1}H NMR (CCl_4) δ 0.79 (m, 1), 1.27 (m, 1), 1.90–2.73 (m, 6), 3.50 (s, 3, OCH_3), 3.63 (s, 3, OCH_3), 3.74 (s, 6, OCH_3), 5.50 (t, 1, J = 6 Hz, 1′-H), 5.67 (b s, 1, 4-H), 6.26 (s, 2, ArH); IR (CCl_4) 1674, 1582, 1060 cm^{-1}.

Exact mass calcd for $C_{20}H_{24}O_5$: 344.163. Found: 344.165.

***tert*-Butyl 3,4,5-Trimethoxycinnamate.** To a suspension of 11.5 g (48.5 mmol) of 3,4,5-trimethoxycinnamic acid in 300 mL of benzene was added 15.4 g (0.12 mol) of oxalyl chloride. The solution was stirred at room temperature for 3 h and concentrated in vacuo to give the crude acid chloride as a yellow solid.

A mixture of the crude acid chloride, 3.7 g (50 mmol) of *tert*-butyl alcohol, and 6.66 g (55 mmol) of *N*,*N*-dimethylaniline in 50 mL of ether was warmed under reflux for 14 h.[19] The solution was diluted with 150 mL of dichloromethane and washed with 100 mL of water, 100 mL of dilute aqueous sulfuric acid, and 100 mL of saturated aqueous sodium bicarbonate. The organic phase was dried (Na_2SO_4) and concentrated in vacuo, and the residual liquid was purified by chromatography on a column of silica gel (150 g, Merck 60–230 mesh, 100-mL fractions) upon elution with hexane–ethyl acetate (4:1). Combination and concentration of fractions 5–9 provided 9.1 g (70%) of the *tert*-butyl ester as a white solid, mp 79–81 °C. Recrystallization afforded the *tert*-butyl ester as fine white needles: mp 79.5–81 °C; ^{1}H NMR ($CDCl_3$) δ 1.53 (s, 9, *t*-Bu), 3.87 (s, 9, OCH_3), 6.23 (d, 1, J = 15 Hz), 6.71 (s, 2, ArH), 7.48 (d, 1, J = 15 Hz); IR ($CHCl_3$) 1695, 1631 cm^{-1}.

Anal. ($C_{16}H_{22}O_5$): C, H.

***tert*-Butyl 2-(3,4,5-Trimethoxyphenyl)cyclopropanecarboxylate (12a).** To a solution of dimethyloxosulfonium methylide [prepared as previously described[15] from 8.8 g (40 mmol) of trimethyloxosulfonium iodide and 0.96 g (40 mmol) of sodium hydride] in 50 mL of dimethyl sulfoxide was added a solution of 9.1 g (33.8 mmol) of *tert*-butyl 3,4,5-trimethoxycinnamate in 50 mL of dimethyl sulfoxide over a 10-min period. The mixture was warmed in an oil bath at 55 °C for 2 h, cooled to room temperature, and poured into 500 mL of water and the solution extracted with three 250-mL portions of dichloromethane. The extracts were dried and concentrated in vacuo, and the residual oil was chromatographed on a column of silica gel (170 g, Merck 60–230 mesh). Elution with ethyl acetate afforded 6.5 g (68%) of **12a** as a white solid, mp 69–71 °C. Recrystallization from hexane–ethyl acetate (9:1) afforded **12a** as colorless needles: mp 71–72.5 °C; ^{1}H NMR δ 1.17 (m, 1), 1.47 (s, 9, *t*-Bu), 1.47 (m, 1), 1.77 (m, 1), 2.33 (m, 1), 3.77 (s, 3, OCH_3), 3.80 (s, 6, OCH_3), 6.28 (s, 2, ArH); IR ($CHCl_3$) 1707, 1585 cm^{-1}.

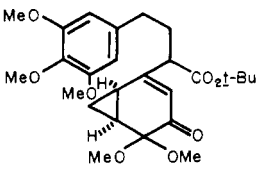
Anal. ($C_{17}H_{24}O_5$): C, H.

***tert*-Butyl 4-(3,4,5-Trimethoxyphenyl)butyrate (13a).** A solution of 6.0 g of cyclopropane **12a** in 100 mL of methanol was hydrogenated over 6.0 g of 5% palladium on charcoal in a Parr apparatus at 50 psi for 48 h. The mixture was filtered through Celite, concentrated in vacuo, and crystallized from ethyl acetate–hexane (1:9) to afford 4.3 g (72%) of ester **13a**: mp 61.5–63 °C; NMR ($CDCl_3$) δ 1.44 (s, 9), 1.90 (m, 2), 2.20 (m, 2), 2.57 (t, 2), 3.78 (s, 3, CH_3), 3.81 (s, 6, CH_3), 6.37 (s, 2, ArH); IR ($CHCl_3$) 1715, 1585 cm^{-1}.

Anal. ($C_{17}H_{26}O_5$): C, H.

***tert*-Butyl α-(2-Hydroxy-4-methoxy-5-oxobicyclo[4.1.0]hept-3-en-1-yl)-α-(β-(3,4,5-trimethoxyphenyl)ethyl)acetate (15a,b).** To a solution of lithium diisopropylamide, prepared in the usual manner from 45 mmol of diisopropylamine and 40.0 mmol of *n*-butyllithium, in 150 mL of tetrahydrofuran cooled to −70 °C was added a solution of 11.73 g (38.0 mmol) of ester **13a** in 60 mL of tetrahydrofuran over a 15-min period. The temperature of the reaction was maintained below −65 °C during the addition. The mixture was stirred below −65 °C for 50 min followed by the addition of 7.55 g (38.0 mmol) of ketone **6** over a 5-min period. The mixture was stirred below −60 °C for 15 min, warmed to 10 °C over a 30-min period, and poured into 1-L of water–dichloromethane (1:1). The organic phase was separated, and the aqueous phase was extracted with 250 mL of dichloromethane. The combined extracts were dried (Na_2SO_4) and concentrated in vacuo to provide crude **14a**.

To a solution of the unpurified ketal **14a** in 240 mL of tetrahydrofuran–water (5:1) was added 200 mg of oxalic acid. The mixture was stirred at room temperature for 4 h and partitioned between 500 mL of dichloromethane and 500 mL of water. The aqueous phase was extracted with 250 mL of dichloromethane, and the combined organic phases were dried (Na_2SO_4) and concentrated in vacuo. The residual oil was chromatographed on a column of silica gel (400 g, Merck 60–230 mesh, 250-mL fractions, ethyl acetate–hexane (1:1)). Fractions 3–4 gave 1.5 g (13%) of starting ester **13a**. Fractions 5–8 afforded 1.25 g (7%) of ketal **iii** as a yellow oil: ^{1}H NMR ($CDCl_3$) δ 0.50 (m, 1), 1.33–2.83 (m, 8),



iii

1.47 (s, 9, *t*-Bu), 3.20 (s, 3, OCH_3), 3.43 (s, 3, OCH_3), 3.80 (s, 3, OCH_3), 3.83 (s, 6, OCH_3), 5.70 (s, 1, 3-H), 6.33 (s, 2, ArH); IR ($CHCl_3$) 1722, 1670, 1620, 1585 cm^{-1}.

Exact mass calcd for $C_{26}H_{36}O_8$: 476.242. Found: 476.240.

Fractions 9–19 gave 12.1 g (71%) of γ-hydroxy enones **15a,b** as a 3:2:1 mixture of diastereomers: ^{1}H NMR ($CDCl_3$) δ 0.7–2.8 (m, 9), 1.44 (s), 1.48 (s), 1.51 (s, total = 9 H), 3.33, 3.47, 3.67, 3.78 (s's, OCH_3), 4.73, 5.10 (d's, 1, J = 2 Hz, 3-H's), 6.23, 6.27, 6.31 (s's, ArH's); IR ($CHCl_3$) 1725, 1683, 1630, 1589 cm^{-1}. A sample of the major enone **15b** was obtained by crystallization from carbon tetrachloride. This material (2.31 g) exhibited the following properties: mp 130–131 °C; ^{1}H NMR ($CDCl_3$) δ 1.20 (m, 1), 1.52 (s, 9, *t*-Bu), 1.73–2.73 (m, 8), 2.98 (s, 1), 3.47 (s, 3, OCH_3), 3.78 (s, 3, OCH_3), 3.81 (s, 6, OCH_3), 4.94 (d, 1, J = 2.5 Hz, 3-H), 6.33 (s, 2, ArH); IR ($CHCl_3$) 3500, 1710 (sh), 1680, 1626 cm^{-1}.

Exact mass calcd for $C_{25}H_{34}O_8$: 462.225. Found: 462.219.

***rel*-(1*R*,2′*S*,7*S*)-3′,4′-Dihydro-3,6′,7′,8′-tetramethoxyspiro[cyclohept-2-ene-1,1′-(2′*H*)-naphthalen]-4-on-7-ol-2′-carboxylic Acid Lactone (18) and Methyl *rel*-(1*S*,2*R*,2′*R*,6*R*)-3′,4′-Dihydro-4,6′,7′,8′-tetramethoxyspiro[bicyclo[4.1.0]hept-3-ene-2,1′-(2′*H*)-naphthalen]-5-one-2′-carboxylate (16c).** To a solution of 9.79 g (21.1 mmol) of γ-hydroxy enones **15a,b** in 70 mL of nitromethane was added 2.7 mL of boron trifluoride etherate. The mixture was stirred at room temperature for 5 min, diluted with 500 mL of dichloromethane, and extracted with two 200-mL portions of saturated aqueous sodium bicarbonate. The organic phase was dried (Na_2SO_4) and concentrated in vacuo to give 6.2 g of a yellow oil. This oil was dissolved in 40 mL of hexane–ethyl acetate (1:1), and the resulting crystalline lactone **18** was collected (3.7 g, 50%): mp 187–190 °C; ^{1}H NMR ($CDCl_3$) δ 1.67–3.07 (m, 10), 3.53 (s, 3, OCH_3), 4.87 (dd, 1, J = 8.5 Hz, 7-H), 5.37 (s, 1, 2-H), 6.37 (s, 1, ArH); ^{13}C NMR ($CDCl_3$) δ 18.1 (t), 25.3 (t), 26.2 (t), 36.6 (t), 46.4 (s), 47.2 (d), 55.7 (q), 55.7 (q), 60.1 (q), 60.6 (q), 86.8 (d), 106.7 (d), 116.7 (d), 123.1 (s), 131.3 (s), 140.5 (s), 148.1 (s), 151.7 (s), 153.2 (s), 175.0 (s), 196.6

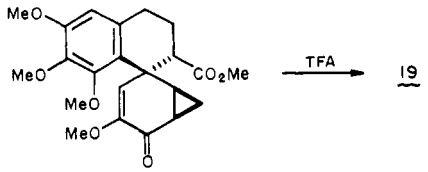
(s); IR ($CHCl_3$) 1775, 1680, 1620 cm^{-1}.

Anal. Calcd for $C_{21}H_{24}O_7$: C, H.

The mother liquor was dissolved in 20 mL of trifluoroacetic acid and allowed to stand at room temperature for 20 min. The solution was diluted with 100 mL of dichloromethane and the mixture washed with three 50-mL portions of water and extracted with two 75-mL portions of saturated aqueous sodium bicarbonate. The organic phase was worked up as described above to give an additional 0.13 g of lactone **18**. The spiran carboxylic acid **17** was isolated from the aqueous base extract, dissolved in benzene (100 mL), and esterified with 4.7 mL of dimethylformamide dimethylacetal upon heating at reflux (20 min). The mixture was diluted with dichloromethane and the solution washed with water, dried (Na_2SO_4), and concentrated in vacuo to provide 4.9 g of an orange oil. The residual oil was dissolved in 20 mL of hexane–ethyl acetate (1:1), and 2.23 g (20%) of crystalline spiro ester **16c** was collected: mp 174–177 °C; ^1H NMR ($CDCl_3$) δ 0.83 (m, 1), 1.23 (m, 1), 1.67 (m, 1), 2.13 (m, 3), 2.83 (m, 3), 3.54 (s, 3, OCH_3), 3.67 (s, 6, OCH_3), 3.71 (s, 3, OCH_3), 3.79 (s, 3, OCH_3), 5.54 (d, 1, J = 2.5 Hz, 3-H), 6.37 (s, 1, ArH); ^{13}C NMR ($CDCl_3$) δ 12.2, 23.7, 26.6, 26.6, 29.9, 40.5, 51.5, 52.6, 54.6, 55.6, 60.0, 60.3, 107.0, 111.9, 124.8, 131.3, 140.9, 146.5, 152.4, 154.4, 174.6, 192.7; IR ($CHCl_3$) 1725, 1670 cm^{-1}.

Exact mass calcd for $C_{22}H_{26}O_7$: 402.169. Found: 402.164.

The mother liquor was chromatographed over silica gel to give an additional 180 mg of spiro ester **16c** (28% total) and 200 mg (2%) of diastereomeric spiro ester iv: mp 167–170 °C; ^1H NMR ($CDCl_3$) δ



iv

0.87–1.20 (m, 1), 1.73–3.07 (m, 8), 3.52 (s, 3), 3.62 (s, 3), 3.77 (s, 3), 3.80 (s, 3), 3.82 (s, 3), 5.42 (s, 1), 6.39 (s, 1); ^{13}C NMR ($CDCl_3$): δ 11.6, 20.5, 22.0, 27.2, 29.1, 41.3, 52.1, 52.6, 55.0, 55.8, 60.4, 107.2, 120.5, 125.9, 131.3, 146.9, 152.6, 173.3, 192.1; IR ($CHCl_3$) 1722, 1660, 1622 cm^{-1}; mass spectrum (75 eV), m/e 402 (M^+, 60), 371 (27), 194 (100).

Exact mass calcd for $C_{22}H_{26}O_7$: 402.169. Found: 402.171.

The *syn*-arylmethylene relationship in iv was given qualitative support by the following comparative study. In THF (25 °C) the half-life for its rearrangement to **19** was 20 min. In contrast, **16c** rearranged with a half-life of 24 h to **19** under identical conditions.

7-Carbomethoxydesacetamidoisocolchicine (20) and Heptafulvene (v). A solution of 1.0 g (2.5 mmol) of spiro ester **16c** in 10 mL of trifluoroacetic acid was heated at reflux for 75 min. The solution was poured into 75 mL of dichloromethane and the mixture washed with two 100-mL portions of water, dried, and concentrated in vacuo to afford a mixture of esters **19**.

A benzene solution of the crude esters and 570 mg (2.5 mmol) of DDQ was warmed under reflux for 13 h. The solution was cooled and filtered, and the filter cake was rinsed with benzene. The filtrate was concentrated, and the residue was chromatographed over alumina (80 g, activity III). Elution with ethyl acetate afforded 0.64 g (64%) of a 7:3 mixture of dihydrotropolone ether **20** and heptafulvene v, respectively. These tautomers were easily separated by chromatography over activity III alumina. Elution with hexane–ethyl acetate (3:5), afforded pure samples of **20**: mp 127–130 °C; ^1H NMR ($CDCl_3$) δ 2.33 (m, 4), 3.44 (m, 1), 3.70 (s, 6, OCH_3), 3.90 (s, 9, OCH_3), 6.57 (s, 1, 4-H), 6.74 (s, 1, 8-H), 7.11 (d, 1, J = 13 Hz, 11-H), 7.38 (d, 1, J = 13 Hz, 12-H); IR ($CHCl_3$) 1722, 1608 cm^{-1}.

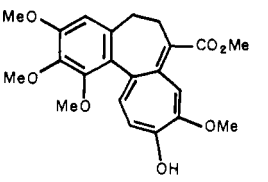
Exact mass calcd for $C_{22}H_{24}O_7$: 400.153. Found: 400.152.

Heptafulvene v: mp 155–156 °C; ^1H NMR ($CDCl_3$) δ 2.11–2.57 (m, 4), 3.30 (s, 3, OCH_3), 3.84 (s, 6, OCH_3), 3.87 (s, 3, OCH_3), 3.97 (s, 3, OCH_3), 6.50 (s, 1, 4-H), 6.67 (s, 1, 8-H), 7.10 (d, 1, J = 13 Hz), 7.30 (d, 1, J = 13 Hz); IR ($CHCl_3$) 1725 cm^{-1}.

Exact mass calcd for $C_{22}H_{24}O_7$: 400.153. Found: 400.152.

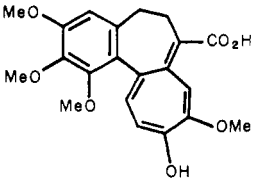
When the solution was left standing at room temperature in deuteriochloroform for 24 h, pure **20** or v was converted to a 7:3 mixture of **20** and vi, respectively.

Desacetamidoisocolchicine-7-carboxylic Acid (21). A solution of 0.64 g (1.6 mmol) of an equilibrium mixture of **20** and v in 18 mL of methanol–water (5:1) containing 115 mg (4.8 mmol) of dissolved sodium hydride was warmed at 75 °C for 45 min. The solution was cooled, acidified with concentrated hydrochloric acid, diluted with water, and extracted with dichloromethane. The extracts were dried (Na_2SO_4), concentrated in vacuo, and the residue was crystallized from ethyl acetate to give 0.52 g (85%) of acid **21** as an off-white solid: mp 179–180 °C



v

(decomposition with loss of CO_2); NMR ($CDCl_3$) δ 2.37 (m, 4), 3.70 (s, 3, OCH_3), 3.84 (s, 3, OCH_3), 3.90 (s, 6, OCH_3), 6.57 (s, 1), 6.57 (b s), 7.00 (s, 1), 7.17 (d, 1, J = 12 Hz, 11-H), 7.43 (d, 1, J = 12 Hz, 12-H); IR ($CHCl_3$) 1710, 1610, 1596 cm^{-1}. The tropolonoid acid described above was contaminated by a small amount of its heptafulvene tautomer vi (signals at δ 6.47 and 6.73 for 4-H and 8-H, respectively). A 7:3 mixture of **21** and vi was obtained after **21** was allowed to stand in $CDCl_3$



vi

for several hours. When 30 mg of **21** was warmed at 180 °C for 1–2 min, 16 mg (60%) of desacetamidoisocolchicine (**2b**) was obtained after purification (mp 146.5–148 °C; mmp 146–148 °C).

Methyl 2-(3,4,5-Trimethoxyphenyl)cyclopropanecarboxylate (12b). Into a solution of 6 g (23.8 mmol) of methyl 3,4,5-trimethoxycinnamate in ether–dichloromethane (3:1), containing 50 mg of palladium (II) acetate, cooled in an ice-water bath, was distilled diazomethane, prepared from 10 g of *N*-nitroso-*N*-methyl urea and 29 mL of 50% aqueous potassium hydroxide in 100 mL of ether. The mixture was stirred for 15 min at 0 °C after the distillation was completed and concentrated in vacuo to provide a pale green oil. The crude product was purified by chromatography on a column of silica gel (100 g, Merck 60–230 mesh, 50-mm o.d., 125-mL fractions) upon elution with ether–petroleum ether (1:1), by using the flash technique.[30] Fractions 6–9 provided 6.2 g (98%) of cyclopropyl ester **12b** as a colorless oil which solidifed on cooling. Recrystallization from ether–hexane (1:9) provided **12b** as colorless prisms: mp 53.5–54.5 °C; ^1H NMR ($CDCl_3$) δ 1.27 (m, 1), 1.56 (m, 1), 1.85 (m, 1), 2.46 (m, 1), 3.70 (s, 3, OCH_3), 3.80 (s, 9, OCH_3), 6.27 (s, 2, ArH); IR ($CHCl_3$) 3000, 1720, 1715, 1680, 1000 cm^{-1}.

Anal. ($C_{14}H_{18}O_5$): C, H.

Methyl 4-(3,4,5-Trimethoxyphenyl)butyrate (13b). A solution of 13 g (48.9 mmol) of cyclopropyl ester **12b** in 175 mL of methanol containing 4 g of 10% palladium on carbon was hydrogenolized under 51 psi of hydrogen. The catalyst was removed by filtration through a pad of Celite, the filter cake was rinsed with ether, and the combined filtrates were concentrated in vacuo to provide a pale yellow liquid. Bulb-to-bulb distillation (165 °C (0.015mmHg)) provided 12.68 g (97%) of **13b** as a colorless liquid: ^1H NMR ($CDCl_3$) δ 1.93 (m, 2), 2.30 (m, 2), 2.52 (m, 2), 3.60 (s, 3, OCH_3), 3.80 (s, 9, OCH_3), 6.25 (s, 2, ArH); IR (neat) 2920, 1715, 1570 cm^{-1}.

Anal. ($C_{14}H_{20}O_5$): C, H.

Methyl α-(2-Hydroxy-4-methoxy-5-oxobicyclo[4.1.0]hept-3-en-1-yl)-α-(β-(3,4,5-trimethoxyphenyl)ethyl)acetate (15c,d). To a solution of 8.4 mmol of lithium diisopropylamide, prepared in the usual way from 5.26 mL of 1.61 M *n*-butyllithium and 0.848 g (8.4 mmol) of diisopropylamine, in 20 mL of tetrahydrofuran, cooled in a dry ice–2-propanol bath under argon, was added 2.14 g (8 mmol) of **13b** in 12.5 mL of tetrahydrofuran over a period of 15 min. The resulting pale yellow solution was stirred for 20 min and 1.58 g (8 mmol) of **6** in 10 mL of tetrahydrofuran was added over 15 min. The mixture was allowed to stir for 30 min, and then the cooling bath was replaced with an ice-water bath. After 30 min the reaction was quenched with 10 mL of saturated aqueous ammonium chloride and transferred into dichloromethane (500 mL) and the mixture was washed with brine (500 mL) and dried (Na_2SO_4). Concentration in vacuo provided crude **14b**, a 1:1 mixture of diastereomers, as a yellow oil: ^1H NMR δ 0.5–2.8 (10), 3.05–3.85 (21), 4.25 (d, 0.5 H, J = 0.5 Hz, 3-H), 4.50 (d, 0.5 Hz, J = 1.5 Hz, 3-H), 6.33 (s, 2, ArH). Crude **14b** was dissolved in 160 mL of tetrahydrofuran, and 30 mL of 5% aqueous oxalic acid solution was added. The solution was stirred for 5 h at room temperature and concentrated in vacuo. The residue was transferred into dichloromethane (500 mL) and water (500 mL), and the organic phase was dried (Na_2SO_4). Concentration in vacuo

provided the crude enone **15c,d** as a yellow foam which was purified by chromatography on a column of silica gel (165 g, Merck 230–400 mesh), 60-mm o.d., 75 mL fractions) upon elution with ether–dichloromethane–methanol (20:4:1), using the flash technique.[30] Fractions 12–17 provided 3.2 g (95%) of **15c,d** as a white foam: ^{1}H NMR ($CDCl_3$) δ 1.0–2.9 (10), 3.48 (s, 1.5 H, OCH_3), 3.62 (s, 1.5 H, OCH_3), 3.72 (s, 3, OCH_3), 3.80 (s, 9, OCH_3), 4.86 (d, 0.5 H, J = 2 Hz, 3-H), 5.23 (d, 0.5 H, J = 2 Hz, 3-H), 6.29 (s, 2, ArH); IR ($CHCl_3$) 3600 (sh), 3460 (br), 1725, 1680, 1630, 1030 cm^{-1}.

Exact mass calcd for $C_{22}H_{28}O_8$: 420.178. Found: 420.178.

Methyl *rel*-(1*S*,2*R*,2′*RS*,6*R*)-3′,4′-Dihydro-4,6′,7′,8′-tetramethoxyspiro[bicyclo[4.1.0]hept-3-ene-2,1′-(2′*H*)-naphthalen]-5-one-2′-carboxylate. Spiro Esters 16c and 16d. To 2.78 g (6.62 mmol) of alcohol **15c,d** was added 30 mL of trifluoroacetic acid. The resulting red solution, which gradually became green, was stirred at room temperature under argon, for 20 min. The green solution was transferred into dichloromethane (300 mL), washed with water (300 mL) and saturated aqueous sodium bicarbonate (2 × 250 mL), dried (Na_2SO_4), and concentrated in vacuo to provide crude **16c** and **16d** as an orange solid. The orange solid was chromatographed on a column of silica gel (175 g, Merck 230–400 mesh, 60-mm o.d., 100-mL fractions) upon elution with ethyl acetate–hexane (45:55), using the flash technique.[30] Fractions 22–32 provided 2.17 g (71%) of a 1:1 mixture of spiro esters **16c** and **16d** as a pale yellow solid. Recrystallization from ethyl acetate–hexane (1:9) afforded the mixture of spiroesters as colorless needles: mp 138–139 °C; ^{1}H NMR ($CDCl_3$) δ 0.8–1.5 (m, 2), 2.15 (m, 3), 2.83 (m, 3), 3.46 (s, 1.5 H, OCH_3), 3.56 (s, 1.5 H, OCH_3), 3.63 (s, 4.5 H, OCH_3), 3.67 (s, 1.5 H, OCH_3), 3.70 (s, 3, OCH_3), 3.79 (s, 3, OCH_3), 5.10 (d, 0.5 H, J = 2.5 Hz, **16d**, 3-H), 5.52 (d, 0.5 H, J = 2.5 Hz, **16c**, 3-H), 6.33 (s, 1, ArH); ^{13}C NMR ($CDCl_3$) δ 12.3, 12.6, 22.0, 23.9, 25.4, 26.7, 27.6, 30.0, 39.2, 40.6, 51.4, 41.6, 51.7, 52.8, 54.8, 55.7, 59.9, 60.2, 60.6, 61.3, 107.3, 112.2, 113.8, 124.8, 125.1, 131.4, 131.7, 141.0, 141.2, 146.6, 146.8, 152.3, 152.4, 154.1, 154.5, 173.1, 174.7, 192.8, 192.9; IR ($CHCl_3$) 3000, 2820, 1725, 1670, 1620, 1590, 1210, 1115 cm^{-1}.

Anal. ($C_{22}H_{26}O_7$): C, H.

Equilibration of Spiro Ester 16c. To a solution of 50 mg (0.124 mmol) of spirane **16c** in 5 mL of dimethylformamide was added 67 mg (1.24 mmol) of sodium methoxide. The resulting pale yellow suspension was stirred for 16 h at room temperature, quenched with 5 mL of 5% aqueous hydrochloric acid, transferred into 1,1,1-trichloroethane (50 mL), washed with water (50 mL), and dried (Na_2SO_4). Concentration in vacuo afforded 44 mg (88%) of a (40:60) mixture of spirans **16c** and **16d**, respectively: ^{1}H NMR ($CDCl_3$) δ 5.12 (d, 0.6 H, J = 2.5 Hz, 3-H, **16d**), 5.52 (d, 0.4 H, J = 2.5 Hz, 3-H, **16c**).

Equilibration of a (1:1) Mixture of Spiro Esters 16c and 16d. To a solution of 50 mg (0.124 mmol) of a (1:1) mixture of **16c** and **16d** was added 67 mg (1.24 mmol) of sodium methoxide. The mixture was stirred for 16 h at room temperature, quenched with 5 mL of 5% aqueous HCl, transferred into 1,1,1-trichloroethane (50 mL), washed with water (50 mL), and dried (Na_2SO_4). Concentration in vacuo provided 45 mg (90%) of a (40:60) mixture of spiranes **16c** and **16d**, respectively: ^{1}H NMR δ 5.12 (d, 6.6 H, J = 2.5 Hz, 3-H, **16d**), 5.52 (d, 6.4 H, J = 2.5 Hz, 3-H, **16c**).

Preparation of Esters 19 from Spiro Esters 16c and 16d. A solution of 0.84 g (2 mmol) of spiro esters **16c** and **16d** in 20 mL of trifluoroacetic acid (initially green) was heated at reflux under argon, for 35 min. As the reaction proceeded the color of the solution gradually became red-red-orange. The red-orange solution was cooled to room temperature and transferred into dichloromethane (250 mL) and the mixture washed with water (250 mL), saturated aqueous $NaHCO_3$ (2 × 250 mL), and dried (Na_2SO_4). Concentration in vacuo provided the crude product as a yellow foam. The crude material was purified on a column of silica gel (100 g, Merck 230–400 mesh, 50-mm o.d., 20-mL fractions) packed in ether–dichloromethane (80:20) upon elution with ether–dichloromethane–methanol (40:8:1), using the flash technique. Combination and concentration of fractions 14–22 afforded 0.624 g (78%) of esters **19**: ^{1}H NMR ($CDCl_3$) δ 1.8–3.3 (8), 3.30 (s, 0.6 H, $COCH_3$), 3.55–3.9 (14.4), 5.86 (s, 0.2 H, 8-H), 5.88 (s, 0.8 H, 8-H), 6.43 (s, 0.2 H, ArH), 6.46 (s, 0.8 H, ArH); IR ($CHCl_3$) 2950, 2840, 1730, 1675, 1600 cm^{-1}.

Exact mass calcd for $C_{22}H_{26}O_7$: 402.168. Found: 402.169.

Preparation of Esters 19 from Alcohol 15c,d. To 0.9 g (2.14 mmol) of **15c,d** was added 20 mL of trifluoroacetic acid. The pale red solution was maintained at reflux for 35 min, during which time the color changed to deep red. The solution was cooled to room temperature and transferred into dichloromethane (300 mL) and the mixture washed with water (2 × 300 mL), saturated aqueous sodium bicarbonate (300 mL), and dried (Na_2SO_4). Concentration in vacuo provided the crude product as an orange foam. The product was chromatographed on a column of silica gel (100 g, Merck 230–400 mesh, 50-mm o.d., 50-mL fractions), packed in ether–dichloromethane (4:1) upon elution with ether–dichloromethane–methanol (40:8:1). Fractions 17–27 provided 0.79 g (92%) of esters **19** as a pale yellow foam.

7-Carbomethoxydesacetamidoisocolchicine (20) and Heptafulvene (v). To a solution of 0.867 g (2.15 mmol) of esters **19** in 25 mL of dry benzene was added 0.489 g (2.15 mmol) of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ). The resulting greenish solution was heated to reflux for 18 h under argon and cooled to room temperature, and the hydroquinone was removed by filtration through a pad of celite. The filter cake was rinsed with benzene, and the combined filtrates were concentrated in vacuo affording a brown oil. The crude product was purified by chromatography on a column of Activity III alumina (80 g, Woelm, 30-mm o.d., 10-mL fractions) upon elution with ethyl acetate–hexane (3:5). Combination and concentration of fractions 6–11 provided 0.269 g (31%) of tropolone **20** as a brown solid. Recrystallization, ethyl acetate–hexane, gave **20** as pale brown needles: mp 127–128 °C; IR ($CHCl_3$) 3000, 2860, 1735, 1620, 1605, 1570, 1495, 1470, 1455 cm^{-1}.

Anal. ($C_{22}H_{24}O_7$): C, H.

Fractions 17–36 gave 0.083 g (9.7%) of heptafulvene **v** as a yellow solid. Recrystallization from ethyl acetate–hexane afforded **v** as pale yellow needles: mp 154–155 °C; IR ($CHCl_3$) 3500 (br), 3020, 1735, 1620, 1575, 1460, 1400 cm^{-1}.

Anal. ($C_{22}H_{26}O_7$): C, H.

Fractions 12–16 provided 0.108 g (13%) of a 1:1 mixture (by ^{1}H NMR) of tropolone **20** and heptafulvene **v**. Overall yield 0.46 g (54%) of **20** and **v** in the ratio of 7:3, respectively.

***N*-*tert*-Butoxycarbonyldesacetylisocolchicine (22).** A solution of 465 mg (1.2 mmol) of acid **21**, 348 mg (1.26 mmol) of diphenylphosphoryl azide, and 126 mg (1.26 mmol) of triethylamine in 15 mL of *tert*-butyl alcohol was warmed at reflux for 17 h. The solution was diluted with 100 mL of dichloromethane, washed with 100 mL of water, dried, and concentrated in vacuo. The residual oil was chromatographed at medium pressure (Lobar, size B; eluted with ethyl acetate–methanol (20:1); 14-mL fractions; 7-mL flow/min). Fractions 15–20 afforded 290 mg (54%) of carbamate **22** after crystallization from ethyl acetate: mp 195–198 °C; ^{1}H NMR ($CDCl_3$) δ 1.34 (s, 9), 2.37 (m, 4), 3.63 (s, 3, OCH_3), 3.89 (s, 3, OCH_3), 3.90 (s, 3, OCH_3), 3.93 (s, 3, OCH_3), 4.30 (m, 1), 4.92 (br d, 1), 6.51 (s, 1), 7.09 (d, 1, J = 12 Hz, 11-H), 7.10 (s, 1), 7.36 (d, 1, J = 12 Hz, 12-H); IR ($CHCl_3$) 3442, 1705, 1611 cm^{-1}.

Exact mass calcd for $C_{25}H_{31}NO_7$: 457.210. Found: 457.212.

***d,l*-Desacetylcholciceine (23).** A mixture of 80 mg (0.17 mmol) of carbamate **22** and 2.0 mL of 3 N aqueous hydrochloric acid was warmed at 110 °C for 90 min. The resulting yellow solution was cooled, neutralized with saturated aqueous sodium bicarbonate, and extracted with dichloromethane. The extracts were dried and concentrated in vacuo to give a yellow solid: mp 238–242 °C. The residue was recrystallized from ethanol to give 42 mg (72%) of desacetylcolchiceine **23** as a yellow solid: mp 244–246 °C; ^{1}H NMR ($CDCl_3$) δ 1.60–3.37 (m, 7), 3.63 (s, 3, OCH_3), 3.90 (s, 6, OCH_3), 6.53 (s, 1), 7.27 (d, 1, J = 12 Hz, 11-H), 7.50 (d, 1, J = 12 Hz, 12-H), 8.07 (s, 1); IR ($CHCl_3$) 1610, 1540, 1485, 1450 cm^{-1}.

Exact mass calcd for $C_{19}H_{21}NO_5$: 343.383. Found: 343.381.

This material was identical (NMR, IR, mass spectrum, mp, mmp, and TLC) with an authentic sample of **23** prepared from colchicine via established procedures.[27]

Acknowledgment. This research was supported by the National Institutes of Health. We wish to acknowledge Peter M. Koelsch for developing the quinone oxidation procedure reported herein.