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

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

The synthesis of synthetic approaches to colchicine (1a) spans more than two decades. 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 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 proceed through desacetamidoisocolchicine (2b). Since the conversion of 2b via allylic bromination (12% yield) to colchicine (1a) is inefficient, projected syntheses of 1a would provide for the introduction of the C7-acetamido group in an alternate manner. In addition, all but one of the syntheses of 2b proceed through desacetamidoisocolchicine (2c) and all of the reported syntheses of colchicine involve the intermediacy of the free tropolone colchicine (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.

We recently reported our initial efforts directed toward the synthesis of colchicine, culminating in an efficient and convergent construction of desacetamidoisocolchicine (2b). Herein we describe the design, development, and execution of a total synthesis of colchicine (1a) which acknowledges the pendant C7-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 C12-C13 and C7-C8 bonds reveals two simple subunits, a binucleophilic 3-arylpropyl synthons, 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 = NH2, was envisioned as the basic approach to the incorporation of the requisite C7 functionality in the target, and carbanion-stabilizing functions such as G = CO2R, 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
monoketals (cf. 5) as annelation substrates in the construction of phananthrenoids.\textsuperscript{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 desacetamidoisorcolchicine (2b).

Results and Discussion

Synthesis of Desacetamidoisorcolchicine (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.\textsuperscript{11} To date, the only uniformly high yield chemical oxidant for this transformation has been thallium trinitrate as described by McKillop and Taylor.\textsuperscript{12} Oxidation of 3a with Tl(NO\textsubscript{3})\textsubscript{3} provided 5 in 66–85% yields.\textsuperscript{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\textsuperscript{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 monoketals 5, from 3b in 100-g lots in an overall yield of 60–65%. Treatment of 5 with dimethyl oxosulfonium methylide\textsuperscript{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,\textsuperscript{16} 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\textsubscript{2}NO\textsubscript{2}) afforded a 23% yield of the desired dihydrotropalone 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 desacetamidoisorcolchicine (2b). Oxidation of 8 with DDQ provided a 72% yield of 2b, mp 147–148 °C\textsuperscript{17} (lit.\textsuperscript{18} 148–148.7 °C). It was gratifying to observe that alcohol 7 did indeed directly provide the desired dihydrotropalone 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

\textsuperscript{(10) Hart, D. J.; Cain, P. A.; Evans, D. A. J. Am. Chem. Soc. 1978, 100, 1548–1557.}
\textsuperscript{(17) In all respects (mp, mmp, H NMR, IR, and TLC) identical with a sample kindly provided by Professor S. Tobinaga.\textsuperscript{46}}
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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 spiras 11S and 11A in the ratio of 10:3:7, respectively. Spectral data ('H NMR and IR) confirmed the structure of dienone 10. Dienone 10 and the mixture of spiras 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 'H NMR spectra of spiras 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 1.53-2.77 (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 (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 spiran steroid isomer is also consistent with the expectation that the carboxylation 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-H2O, oxalic acid, 25 °C) to 9 and its subsequent behavior under the reaction conditions substantiates it as an additional permiscible 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 was 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 spiras (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 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 spiras 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.

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 nitrosoamines could be successfully induced to undergo carboxyl addition to 6. In addition, although metalated dithianes were observed to undergo successful carboxyl addition, subsequent acid-catalyzed rearrangements afforded intractable products. On the other hand, high-yield carboxyl 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 = CO2R) could serve as the binucleophilic synthon (eq 1).

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

3,4,5-Trimethoxycinnamic acid11 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 dimethyloxsulphonium methylide.20 Cyclopropane 12a was cleaved with hydrogen (20 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 methylation with diazomethane in the

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(18) We reason that the NaBH₄ reduction of the Tobinaga intermediate should give allylic alcohol ii. Thus Simmons-Smith cyclopropanation (cf. Simmons, H. E.; Cairns, T. L.; Vluchick, S. A.; Honess, C. M. Org. React. 1973, 20, 1-133) and oxidation should given spiran 11S.

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The assignment of the structure of the aldol adducts of 15a, b, c, and d, X = CO₂Me, Y-H, is precluded and the cyclopropyl ketone unit remains intact, with the spiran stereochemistry as is illustrated in Scheme V.

The 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 provide a mixture of the diastereomeric 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; therefore, two diastereomers were expected differing at the center bearing the ester function. An examination of the 1H NMR spectrum of the mixture, however, suggested that 15a, b was a 3:2:1 mixture of three diastereomeric aldol adducts (1H 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 (1H 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 (CCl₄). 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-buty1 esters 15a, b with boron trifluoride etherate for 5 min at room temperature (CH₂O₂) afforded a mixture of lactone 18 and acid 17 in 56% and 23%, 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. 1H NMR studies of lactone 18, mp 187-190 °C, revealed an absence of proton resonances assignable to the cyclopropanone moiety and the appearance of aliphatic CH resonances (δ 1.67-3.07). The 13C NMR spectrum of 18 indicated the presence of a quaternary carbon (δ 46.4) signifying that the spiro center had been retained. The IR spectrum of 18 exhibited a carbonyl absorption at 1775 cm⁻¹, typical of a butyro lactone. 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 dihydro tropolone. This fact establishes the spiro stereochemistry as is illustrated in Scheme V by analogy to the behavior of spirans 11a and 11b 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 carbonyl 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 cyclopolyketinyl system have been well documented by Marshall22 and Lawton.23 In spiran 16a the carbonyl group is constrained such that participation is precluded and the cycloprolyl 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 dienolic 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 spiron 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 desacetylaminosocochelocine (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 spiron 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 diastereomeric β-hydroxy methyl esters 15c and 15d in 95% yield after chromatography as a 1:1 mixture

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unaltered 18D, 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 stereocchemical 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 = CO₂H) 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 heptafuvene tautomer, with diphenylphosphoryl azide and triethylamine in tert-butyl alcohol gave carbamate 22 (54-62%), mp 195-198 °C. The tert-butyloxy carbonyl group was removed with concomitant hydrolysis of the ether linkage to provide (+)-desacetylcolchicine (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 1e. Since (+)-23 has been previously converted to colchicine (1a)24-28, the reaction sequence outlined above constitutes a total synthesis of (+)-colchicine.

In its present form, the previously described synthesis 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 ketal schemes reported in part 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. 1C 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 11-492B 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 Chromatotron Model 5920, apparatus equipped with a Fluid Metering Model R2 RP 54 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 disopropylamine were distilled from calcium hydride. Benzene and tetrahydrofuran were distilled from sodium benzenophenone 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 Easteal.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 disopropylamide was always prepared in the following manner. A solution of disopropylamine 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 disopropylamide was then cooled or warmed to the temperature desired for subsequent operations.

The residual dimethyl sulfoxide was removed under high vacuum. The resulting homogeneous yellow solution was stirred for 2 h at room temperature and poured into 2.0-L of water. The solution was allowed to stir for 12 min and then was quenched with oxalic acid. The mixture was stirred at room temperature for 60 min and then was filtered, and the filter cake was rinsed with 30 mL of benzene. The filtrate was concentrated in vacuo, leaving a residue of dienone 6 as a colorless oil: $^{1}H$ NMR (CDCl$_3$) $\delta$ 30.8 (t), 33.1 (t), 37.4 (t), 56.1 (q), 56.1 (q), 61.0 (q), 107.4 (d), 116.9 (d), 126.9 (s), 131.3 (s), 135.4 (d), 150.3 (s), 152.3 (s), 152.4 (d), 195.5 (s); IR (CCl$_4$) 1675 cm$^{-1}$. Anal. Calcd for C$_{22}$H$_{20}$O$_4$: C, H.

4.5,5-Trimethoxybicyclo[4.1.0]hept-3-en-2-one (6). A mixture of $^{5.27}$ g (0.022 mmol) of dry sodium hydride and $48.8$ g (0.22 mmol) of 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 a thermometer. The mixture was refluxed for 18 h. The solution was allowed to stir for 12 min and then was quenched with oxalic acid. The mixture was stirred at room temperature for 60 min and then was filtered, and the filter cake was rinsed with 30 mL of benzene. The filtrate was concentrated in vacuo, leaving a residue of dienone 6 as a colorless liquid. An exact mass calcd for C$_{22}$H$_{20}$O$_4$: C, H.

11.12-Dihydrodesacetamidoisacolchicine (8). A solution of unpurified ketal 7 [prepared from 8.67 g (30 mmol) of 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 up to 2 weeks without extensive decomposition. The mixture was concentrated in vacuo, and the residue was chromatographed on silica gel (125 g, Merck 60–230 mesh, 15-mm fractions) upon elution with ethyl acetate. Combination and concentration of fractions 18–41 provided 5.5 g (90%) of 11,12-Dihydrodesacetamidoisacolchicine (8).

4,5,5-Trimethoxybicyclo[4.1.0]hept-3-en-2-one (6). To a solution of 3.45 g (8.45 mmol) of ketoaldehyde 7 in 72 mL of tetrahydrofuran-water (5:1) was added 30 mmol 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$_2$SO$_4$) and concentrated to the residue which was chromatographed on silica gel at medium pressure (Lobar, size B; eluted with hexane-ethyl acetate (3:2); 18-mm fractions) upon elution with ethyl acetate.

7.11-Desacetoamidoisacolchicine (2b). A solution of 4.6 g (13.3 mmol) of dienone 6 with 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, leaving a residue of dienone 6 as a colorless solid, mp 105–111 °C. Recrystallization from ethane-ethyl acetate (2:1) gave 8 as a pale yellow solid: mp 111–112 °C; $^{1}H$ NMR (CDCl$_3$) $\delta$ 1.67–2.79 (m, 10), 3.63 (s, 3, OCH$_3$), 3.76 (s, 3, OCH$_3$), 3.81 (s, 3, OCH$_3$), 5.83 (s, 1-H), 6.39 (s, 1, H), 15.11 (s, OCH$_3$), 20.1 (s, OCH$_3$), 25.2 (s, OCH$_3$), 30.5 (s, OCH$_3$), 35.1 (s, OCH$_3$), 56.7 (s, OCH$_3$), 60.7 (s, OCH$_3$), 60.8 (s, OCH$_3$), 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. Calcd for C$_{22}$H$_{20}$O$_4$: C, H.
with ethyl acetate-hexane (3:7); 10 mL fractions; 6.0 mL flow/min. Fractions 56-97 gave 588 mg (84%) from 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 11a as a white solid: mp 167-170 °C; IR (KBr) 1785, 1754, 1670, 1620 cm⁻¹; ¹H NMR (CDCl₃) 6 1.64 (t, 3H, J = 7.5 Hz), 2.47 (m, 1H), 3.16, 3.33, 3.67, 3.80 (s, OCH₃), 4.94 (d, 1H, J = 6 Hz, 1'H), 5.72 (t, 1H), 6.17 (s, 2H), 12.26 (s, 1H). Anal. (C₁₆H₂₂O₅) C, H.

Recrystallization from hexane-ethyl acetate (9:1) afforded 12a as colorless needles: mp 71-72.5 °C; ¹H NMR 8.17 (1H, m), 1.47 (s, 9, t-Bu), 1.47 (m, 1H), 1.77 (m, 1H), 2.33 (m, 1H), 3.77 (s, 3, OCH₃), 3.80 (s, 6, OCH₃), 6.28 (s, 2, ArH); IR (CHC≡H) 1707, 1585 cm⁻¹.

Anal. (C₁₆H₂₂O₅): C, H.

terr-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 4 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 61-63 °C; ¹H NMR (CDCl₃) 6 1.44 (s, 9), 1.90 (m, 2), 2.20 (m, 2), 2.57 (t, 2), 3.78 (s, 3, CH₃), 3.81 (s, 6, CH₂), 6.37 (s, 2, ArH); IR (CHC≡H) 1715, 1585 cm⁻¹.

Anal. (C₁₇H₂₄O₅): C, H.

terr-butyl 4-(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-butyl lithium, in 150 mL of tetrahydrofuran-water (3:7) was added 1.12 g (3.80 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 (Na₂SO₄) 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 (Na₂SO₄) and concentrated in vacuo. The residual oil was chromatographed on a column of silica gel (400 g, Merck 60-230 mesh, 250 mL) of tetrahydrofuran–water (5:1). The mixture was stirred below 4 °C 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 (Na₂SO₄) and concentrated in vacuo. The residual oil was chromatographed on a column of silica gel (400 g, Merck 60-230 mesh, 250 mL). Fractions 5-8, ethyl acetate–hexane (1:1) provided 1.2 g of a 1:1 mixture of stereoisomeric dienes 10 as a yellow oil: ¹H NMR (CDCl₃) 6 0.50 (m, 1), 1.33–2.83 (m, 8), 4.73 (s, 3, OCH₃), 3.63 (s, 3, OCH₃), 3.74 (s, 6, OCH₃), 5.50 (t, 1, J = 6 Hz, 1'H), 5.67 (b, 1, 1H), 6.26 (s, 2, ArH); IR (CHC≡H) 1674, 1582, 1060 cm⁻¹.


Fractions 7-15 provided 120 mg of a 1:1 mixture of stereoisomeric dienes 10. Fractions 76-80 provided 16 mg (88% overall) of the other stereoisomers: ¹H NMR (CDCl₃) 6 0.79 (s, 1), 1.27 (m, 1), 1.90-2.73 (m, 6), 3.50 (s, 3, OCH₃), 3.63 (s, 3, OCH₃), 3.74 (s, 6, OCH₃), 5.50 (t, 1, J = 6 Hz, 1'H), 5.72 (t, 1H), 6.17 (s, 2, ArH); IR (CHC≡H) 1674, 1582, 1060 cm⁻¹.


Recrystallization from hexane-ethyl acetate (9:1) afforded 12a as colorless needles: mp 71-72.5 °C; ¹H NMR 8.17 (1H, m), 1.47 (s, 9, t-Bu), 1.47 (m, 1H), 1.77 (m, 1H), 2.33 (m, 1H), 3.77 (s, 3, OCH₃), 3.80 (s, 6, OCH₃), 6.28 (s, 2, ArH); IR (CHC≡H) 1707, 1585 cm⁻¹.

Anal. (C₁₆H₂₂O₅): C, H.

terr-Butyl 2-(3,4,5-Trimethoxyphenyl)cyclopropanecarboxylate (12a). To a solution of dimethylmethylene in methylene chloride [prepared as previously described from 8.8 g (40 mmol) of trimethylsulfoxonium 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 stirred at 55 °C 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 9.5 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; ¹H NMR 8.17 (1H, m), 1.47 (s, 9, t-Bu), 1.47 (m, 1H), 1.77 (m, 1H), 2.33 (m, 1H), 3.77 (s, 3, OCH₃), 3.80 (s, 6, OCH₃), 6.28 (s, 2, ArH); IR (CHC≡H) 1707, 1585 cm⁻¹.

Anal. (C₁₆H₂₂O₅): C, H.
saturated aqueous sodium bicarbonate. The organic phase was worked up as described above to give an additional 0.13 g of lactone 18. The spiro carbonylic 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 distilled with dichloromethane and the solution washed with water, dried (Na₂SO₄), and concentrated in vacuo. The residue was chromatographed over alumina (200 g), then eluted with an ascending flow of orange oil. The residual oil was dissolved in 20 mL of hexane-etanly acetate (1:1), and 2.23 g (20%) of crystalline spiro ester 16c was collected: mp 174–177 °C; 1H NMR (CDCl₃) 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, OCH₂), 3.67 (s, 6, OCH₃), 3.71 (s, 3, OCH₂), 3.79 (s, 3, OCH₃), 5.54 (d, J = 2.5 Hz, 3-H), 6.37 (s, 1, ArH); 13C NMR (CDCl₃) δ 12.2, 23.7, 26.6, 26.9, 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 (CHCl₃) 1725, 1670 cm⁻¹.

Exact mass calcd for C₁₂H₂₃O₇: C, H.

Desacetamidoisococillin-7-carboxylic acid 21b was obtained after purification (mp 146.5–148 °C; mnp 146–148 °C)

Methyl 2-(3,4,5-Trimethoxyphenyl)cyclopropene carboxylate (12b).

To a solution of 1 g (23.8 mmol) of methyl 3,4,5-trimethoxyphenylcarboxylate in ether–dichloromethane (3:1), containing 50 mg of palladium (II) acetate, cooled in an ice-water bath, was distilled dichloromethane, 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. Fraction 6–9 provided 6.2 g (98%) of cyclopropyl ester 12b as a colorless oil which solidified on cooling. Recrystallization from ether–hexane (1:9) provided 12b as colorless prisms: mp 53.5–54.5 °C; 1H NMR (CDCl₃) δ 1.27 (m, 1), 1.56 (m, 1), 1.85 (m, 1), 2.46 (m, 1), 3.70 (s, 3, OCH₃), 3.80 (s, 9, OCH₃), 6.27 (s, 2, ArH); IR (CHCl₃) 3000, 1720, 1715, 1600, 1500 cm⁻¹.

Anal. (C₁₃H₁₆O₇): 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 hydrogenized under 51 psi of hydrogen. The catalyst was removed by filtration through a bed of Celite. The filter cake was washed with ether, and the combined filtrates were concentrated in vacuo to provide a pale yellow liquid. Bulb-to-bulb distillation (165 °C (0.015 mmHg)) provided 12.68 g (97%) of 13b as a colorless liquid: 1H NMR (CDCl₃) δ 1.93 (m, 2), 2.30 (m, 2), 2.52 (m, 2), 2.60 (s, 3, OCH₃), 3.80 (s, 9, OCH₃), 6.25 (s, 2, ArH); IR (neat) 2920, 1715, 1570 cm⁻¹.

Anal. (C₁₄H₂₀O₄): C, H.

Methyl α-(2-Hydroxy-4-methoxy-5-oxobycycl[4.1.0]hept-3-en-1-yl)-α-(β-(3,4,5-trimethoxyphenyl)ethyl)acetate (15b,c,d). To a solution of 8.4 mmol of lithium diisopropanolamide, prepared in the usual way from 5.26 mL of 1.61 M n-butyllithium and 0.849 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 1.38 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 (Na₂SO₄). Concentration in vacuo provided crude 14b, a 1:1 mixture of diastereomers, as a yellow oil: 1H NMR δ 0.5–2.8 (10), 3.03–3.85 (4), 4.25 (d, 0.5 H, J = 0.5 Hz, 3-H), 4.50 (d, 0.5 H, J = 1.5 Hz, 3-H), 6.33 (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 (Na₂SO₄). 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, 60–200 mm, 0.01 mm fractions) upon elution with diethyl-dichloro-methane-methanol (20:4:1), using the flash technique.20 Fractions 12–17 provided 3.2 g (95%) of 15c,d as a white foam: 1H NMR (CDCl3) δ 10.0–2.9 (10), 3.48 (s, 2.5 H, OCH3), 3.62 (s, 2.5 H, OCH3), 3.72 (s, 3.0 H, OCH3), 3.80 (s, 3.0 H, OCH3), 4.86 (d, 0.5 H, J = 2.7 Hz, 3-H), 5.23 (d, 0.5 H, J = 2 Hz, 3-H), 6.29 (s, 2, ArH); IR (CHCl3) 3600 (sh), 3460 (br), 1725, 1680, 1630, 1300 cm−1.


Methyl (R,R,2R,5S,6R)-3'-4'-Dihydro-4,6,7,8-tetramethoxyspirobicyclo[4.1.0]hept-3-ene-2,1'-((2'H)-naphthalen)-5-one-2'-(2'H), solid was chromatographed in vacuo to provide crude methane (300 mL), washed with water (300 mL) and saturated aqueous sodium bicarbonate (300 mL), and dried (Na2SO4). Concentration in vacuo provided the crude product as a pale yellow solid. The product was chromatographed on a column of silica gel (100 g, Merck 230–400 mesh, 50–mm o.d., 50–mm 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-(tert-Butyloxycarbonyl)-desacetylcolchicine (20) and Heptafuvlene (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 green 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-mm fractions) upon elution with ethyl acetate–hexane (3:5). Combination and concentration of fractions 6–11 provided 0.269 g (31%) of tropoline 20 as a brown solid. Recrystallization, ethyl acetate–hexane, gave 20 as pale brown needles: mp 127–128 °C; IR (CHCl3) 3080, 2860, 1735, 1620, 1605, 1570, 1495, 1470, 1455 cm−1. Anal. (C22H24O7): C, H.

Fractions 17–36 gave 0.083 g (9.7%) of heptafuvlene v as a yellow solid. Recrystallization from ethyl acetate–hexane afforded v as pale yellow needles: mp 154–155 °C; IR (CHCl3) 3500 (br), 3020, 1735, 1620, 1575, 1460, 1400 cm−1. Anal. (C19H18O7): C, H.

Equilibration of Spiro Ester 16c. To a solution of 0.50 mmol (0.124 mmol) of spiro 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-trichloroethane (50 mL), washed with water (50 mL), and dried (Na2SO4). Concentration in vacuo afforded 44 mg (88%) of a (40:60) mixture of spiro 16c and 16d, respectively: 1H NMR (CDCl3) 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 hydrochloric acid, transferred into 1,1-trichloroethane (50 mL), washed with water (50 mL), and dried (Na2SO4). Concentration in vacuo provided 45 mg (90%) of a (40:60) mixture of spiro 16c and 16d, respectively: 1H NMR (CDCl3) 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). Preparation of Ester 19 from Spiro Ester 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-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 NaHCO3 (2 × 250 mL), and dried (Na2SO4). 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, 60–200 mm, 0.01 mm fractions) packed in ether–dichloromethane (80%) 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: 1H NMR (CDCl3) δ 1.8–3.3 (8), 3.30 (s, 0.6 H, CH3O), 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), 6.64 (s, 0.8 H, ArH); IR (CHCl3) 2950, 2840, 1730, 1675, 1600 cm−1.


Preparation of Ester 19 from Alcohol 15c,d. To 0.9 g (2.14 mmol) of alcohol 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 (Na2SO4). 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–mm 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.

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