Grignard reagent prepared from α-chloro-α,α-dideuteriotoluene[15] (0.50 g) and magnesium (0.15 g) in dry ether under nitrogen. The solution was refluxed for 0.5 h, cooled, and worked up in the usual manner to give an oily product (0.60 g), which was chromatographed on silica gel (150 g). Elution with hexane gave tetradeuteriobibenzyl (0.15 g). Elution with benzene gave **5b**-CD_2 as white crystals (0.19 g, 40%), which was crystallized from methylene chloride–hexane, mp 128–129 °C; the NMR spectrum was identical with the protio analogue except for absence of the two-proton signal at 2.9 ppm due to the benzylic methylene protons: MS, *m/e* (relative intensity) 232 (13.6).

The monodeuteriated compound, **5b**-OD was prepared by two crystallizations of **5b** from acetone–D_2O and gave the appropriate NMR spectrum.

The trideuteriated compound **5b**-CD_2-OD was prepared from **5b**-CD_2 in similar manner.

Reactions of 1 with Di-*tert*-butyl Peroxide. A. Thermolysis. A solution of **1** (0.15 g) and di-*tert*-butyl peroxide (0.50 g) in chlorobenzene was refluxed under nitrogen, and samples were withdrawn periodically for GC analysis; this indicated formation of a complex mixture. After 6 h, the solution was cooled and concentrated in vacuo (20 mm) to give a dark oil (0.18 g). Preparative TLC using benzene as eluant afforded recovered starting material (0.11 g) and a mixture (8 mg, 27% based on recovered starting material) of **9**–**11** in the ratio 2.5 (**9**):1 (**10** + **11**) (by NMR and GC analysis).

B. Photolysis. A solution of **7a** (45 mg) and the peroxide (0.50 g) in benzene (3 mL) was irradiated through a Pyrex filter. GC analysis showed peaks with retention time of 10 and 11 min corresponding to **9** and **10** + **11**.

Irradiation of Adducts with CQ or BOD. A solution of **2** (0.22 g) and CQ (0.50 g) in benzene (80 mL) under nitrogen was irradiated with a Hanovia 450-W mercury immersion lamp through a glass tube with a cutoff at approximately 380 nm. After 80 h, additional CQ was added and the irradiation continued for an additional 60 h when GC analysis indicated approximately 50% conversion to **8**. The solution was concentrated to give a yellow oil (1.03 g), which was chromatographed on silica gel (60 g). Elution with 1:2 hexane–benzene gave an oil (0.22 g), which afforded pure **8** (0.075 g, 40%) after preparative TLC (benzene eluant). Elution of the column with 1:9 benzene–hexane gave CQ (0.25 g, 31%), elution with benzene gave recovered **2** (0.11 g, 50%) and elution with ethyl acetate gave CQH_2 (0.38 g, 45%).

In a similar experiment using CQ and **1** there was obtained 35% of a 2:1 mixture of **9** and **10** + **11**, recovered CQ (67%), recovered **1** (50%), and CQH_2 (23%).

Similarly reaction of CQ or of BOD with **5a** afforded **7a**.

Irradiation of Adducts 1, 2, and 5a with Benzophenone. Degassed benzene solutions (3 mL) containing benzophenone (35 mg) and one of the adducts **1**, **2**, or **5a** (30 mg) were irradiated at 366 nm for 6 h. GC analysis indicated conversion of **1** to the mixture **9**, **10**, and **11**, of **2** to **8**, and of **5a** to **7a**.

Registry No. **1b**, 101980-79-4; **2b**, 102045-71-6; **3a**, 538-39-6; **3b**, 103-29-7; **5a**, 68903-63-9; **5b**, 66182-14-7; **5b**-CD_2, 101980-90-9; **6**, 63715-70-8; **7a**, 101980-77-2; **7b**, 61259-29-8; **7b** (alcohol), 101980-78-3; **8**, 101980-80-7; **9**, 101980-81-8; **10**, 101980-82-9; **11**, 101980-83-0; **12**, 101980-84-1; **13**, 101980-85-2; **14**, 101980-86-3; **15**, 101980-87-4; **16**, 101980-88-5; CQ, 465-29-2; CQH_2, 101980-91-0; BOD, 4216-89-1; 4-$CH_3C_6H_4CH_3$, 106-42-3; $C_6H_5CH_3$, 108-88-3; 3-cyclohexene-1-carboxaldehyde, 100-50-5; 4-methylbenzyl chloride, 104-82-5; 3-cyclohexenyl-*p*-methylbenzylcarbinol, 101980-89-6; (chloromethyl-d_2)benzene, 33712-34-4.

(15) Prepared by reduction of methyl benzoate with lithium aluminum deuteride followed by reaction with thionyl chloride according to the procedure of: Newman, M. S. *J. Am. Chem. Soc.* **1940**, *62*, 2295.

Facile Conversion of Natural Colchicine into (±)-Congeners and (+)-Enantiomers Including 2-Demethyl Analogues†

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Racemization of natural colchicine in refluxing acetic anhydride afforded after hydrolysis and chemical manipulation a variety of (±)-colchicinoids. Optical resolution of (±)-deacetylcolchicine and (±)-deacetylisocolchicine afforded the respective optical isomers, readily converted by N-acetylation into (−)- and (+)-colchicine and (−)- and (+)-isocolchicine. Selective ether cleavage of (±)- and (−)-colchicinoids with concentrated sulfuric acid afforded 2-demethyl analogues as major products. A single-crystal X-ray analysis of (±)-**1** showing unusual physical properties is reported.

Most biological effects of natural colchicine (**1b**) on mitosis and inhibition of tumors result from a disruption of the microtubule system. These effects are clearly related to its binding to α-tubulin, the subunit of tubulin protein.[1] Some biological effects of colchicine, however, cannot be explained by this mechanism. 2,3-Didemethylcolchicine (**21b**), i.e.,[2] binds only poorly to tubulin but shows pronounced antiinflammatory responses in artificially inflamed rat pads.[3]

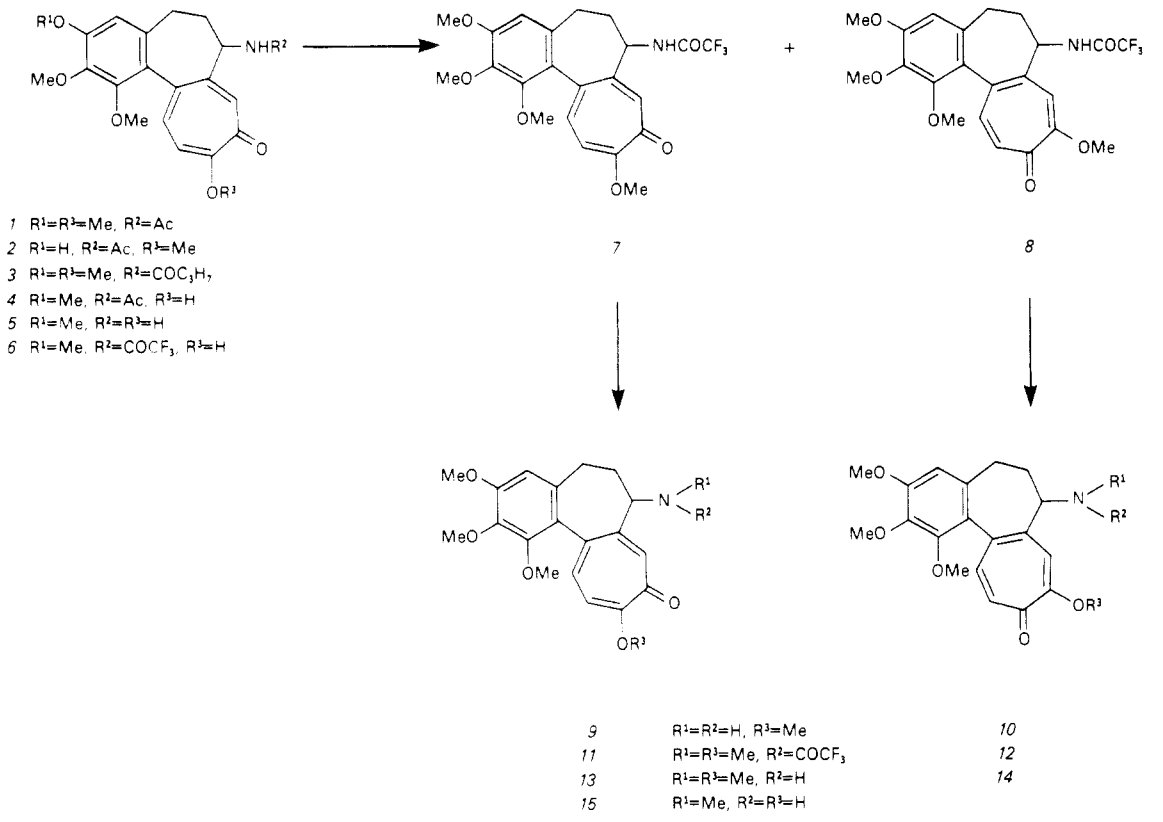
Reevaluation of (±)- and unnatural (+)-colchicinoids in assays measuring antiinflammatory responses necessitated their preparation by more efficient procedures. This has now been accomplished, and the results take credit that several novel (±)-colchicinoids, target molecules of synthetic efforts, are now available for a comparison.

Racemic deacetylcolchiceine (**5**) was first obtained by Corrodi and Hardegger by base-catalyzed equilibration of the Schiff base obtained with benzaldehyde.[4] It was later shown that this process, affording considerable amounts

† Dedicated to Prof. A. Eschenmoser on the occasion of his 60th birthday.

(1) Capraro, H. G.; Brossi, A. *The Alkaloids*; Brossi, A., Ed.; Academic: New York, 1984; Vol. 23, pp 1–70.
(2) Rösner, M.; Hsu, F. L.; Brossi, A. *J. Org. Chem.* **1981**, *46*, 3686.
(3) The antiinflammatory properties of 2,3-didemethylcolchicine will be reported elsewhere.
(4) Corrodi, H.; Hardegger, E. *Helv. Chim. Acta* **1957**, *40*, 193.

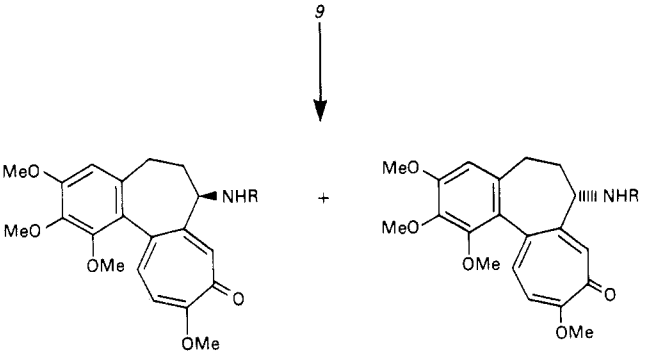
Scheme I



of another product, is the result of aldimine–ketimine tautomerisms.[5] A considerably improved racemization was later achieved by Bladé–Font, treating natural colchicine with refluxing acetic anhydride and hydrolysis of the intermediate triacetate.[6] Repetition of the Bladé–Font racemization afforded in our hand and without isolation of intermediary products **5** in 62% yield.

Racemization by refluxing in acetic anhydride was accomplished also with (−)-3-demethylcolchicine (**2b**), affording **2** after hydrolysis of not isolated intermediates, and from **1b** with butyric anhydride, affording after hydrolysis and chromatographic purification (±)-*N*-butyryldeacetylcolchicine (**3**). Hydrolysis of **1** with 0.1 N HCl at 100 °C gave (±)-colchiceine (**4**) prepared earlier.[4] (±)-Deacetylcolchiceine (**5**) obtained in 60% yield was made from **1** by hydrolysis with 20% H_2SO_4. Treatment of **5** with trifluoroacetic anhydride, followed procedures already executed in the natural series,[7] provided **6** required for an optical resolution after O-methylation and N-deprotection. To achieve this, **6** was O-methylated with ethereal diazomethane in methanol, and the mixture of isomers were separated by preparative chromatography on silica gel with $CHCl_3/CH_3OH$ (100:5) into the faster moving trifluoroacetamide **7** of natural configuration and **8** of isoconfiguration (Scheme I). Both **7** and **8** were found to be identical by TLC and by ^1H NMR with optically active standards.[7] Hydrolysis of **7** and **8** with potassium carbonate in aqueous acetone gave (±)-deacetylcolchicine (**9**) and (±)-deacetylisocolchicine (**10**), respectively. N-Methylation of **7** and **8** with methyl iodide in acetone in the presence of potassium carbonate also following established procedures[7] afforded **11** and **12**, respectively, and (±)-demecolcine (**13**) and (±)-isodemecolcine (**14**) after mild alkaline hydrolysis of the former compounds. Acid hydrolysis of **13** or **14** afforded identical (±)-demecolceine (**15**).

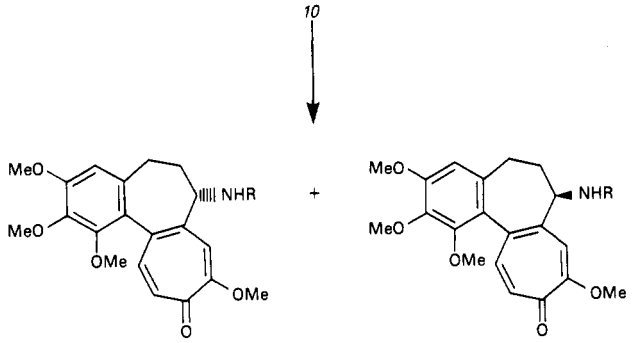
Optical Resolution. Optical resolution of **9** was achieved with (+)-camphorsulfonic acid in methanol, and two crystallizations of the salt from 95% ethanol afforded the camphorsulfonate of (+)-deacetylcolchicine (**9a**). The



camphorsulfonate of **9b**, obtained from the mother liquor, did not change optical rotation after two crystallizations from methanol and showed, like **9a**, by ^1H NMR analysis in $CDCl_3$, when derivatized with (*R*)-(+)-α-methylbenzyl isocyanate no presence of a diastereomer.[8] Both, (+)-colchicine (**1a**) and (−)-colchicine (**1b**), prepared from **9a** and **9b**, respectively, by N-acetylation were optically pure compounds, and showed the expected opposite optical behavior when compared with each other in form of an ethyl acetate complex (**1b**) and a chloroform complex (**1a**). It is interesting to note that (+)-colchicine (**1a**), enantiomeric to (−)-colchicine (**1b**), could not be obtained as

(5) Iorio, M. A.; Brossi, A.; Silverton, J. V. *Helv. Chim. Acta* **1978**, *61*, 1213.
(6) Bladé-Font, A. *Tetrahedron Lett.* **1977**, 2977.
(7) Capraro, H. G.; Brossi, A. *Helv. Chim. Acta* **1979**, *62*, 965.
(8) Rice, K. C.; Brossi, A. *J. Org. Chem.* **1980**, *45*, 592.

an ethyl acetate complex but as a chloroform complex. Both showed the opposite optical behavior by CD, but the curves are not completely superimposable, suggesting that they do not represent fully identical solvated molecules.[27] For the optical resolution of (±)-deacetylisocolchicine (**10**), (+)-ditoluoyl-1-tartaric acid was the preferred resolving agent, affording in 95% methanol a salt which was after two crystallizations from methanol optically pure, giving (−)-deacetylisocolchicine (**10b**) and (−)-isocolchicine (**16b**) after N-acetylation. Workup of the mother liquor from

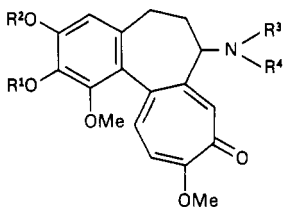


10b R=H *10a*

16b R=Ac *16a*

the ditoluoyltartrate crystallization of **10a** and treatment of the free base with (+)-ditoluoyl-*d*-tartaric acid in 95% methanol afforded after two crystallizations from methanol an optically pure salt and optically pure (+)-deacetylisocolchicine (**10a**) and (+)-isocolchicine (**16a**) after N-acetylation. Hydrolyses of **16a** with 0.1 N HCl at 100 °C afforded **4a** identical by TLC, ^{1}H NMR, and mp with the enantiomer **4b** prepared from natural colchicine **1b**.

Selective O-Demethylation with Concentrated Sulfuric Acid. Treatment of natural colchicine[2] and derived thiocolchicine[9] with concentrated sulfuric acid affords 2-demethylated compounds in good yield and provides congeners which are of interest for studying chemical and biochemical conversions of androcymbine into 2-demethylated colchicinoids.[10] Sulfuric acid catalyzed O-demethylation was therefore carried out with several racemic colchicinoids described here. Similar O-demethylation was performed with (−)-*N*-formyldemecolcine (**17b**), prepared from **7b** by N-formylation with ethyl formate, and with **13b** itself, affording in both cases in about 50% yield the corresponding 2-demethylated analogues **18b** and **19b**, respectively. The latter compound



17b R^1=R^2=R^3=Me, R^4=CHO

18b R^1=H, R^2=R^3=Me, R^4=CHO

19b R^1=R^3=H, R^2=R^4=Me

20 R^1=R^3=H, R^2=Me, R^4=Ac

21 R^1=R^2=R^3=H, R^4=Ac

22 R^1=R^2=$-CH_2-$, R^3=H, R^4=Ac

(9) Sharma, P. N.; Brossi, A. *Heterocycles* **1983**, *20*, 1587.

(10) Battersby, A. R.; Herbert, R. B.; McDonald, E.; Ramage, R.; Clements, J. H. *J. Chem. Soc., Perkin Trans. 1* **1972**, 1741.

Table I. Hydrogen Bonding in Racemic Colchicine

donor	acceptor	H–A, Å	D···A, Å	D–H···A, deg	symmetry operation for A
N	O(9)	2.10 (3)	2.934 (3)	164 (3)	a
O(1s)	O(13)	1.85 (5)	2.955 (3)	179 (5)	1
O(2s)	O(3)	1.94 (4)	2.914	166 (5)	1
O(1s)	O(2s)	1.88 (5)	2.783	153 (4)	a
O(2s)	O(1s)	1.91 (5)	2.791	152 (6)	2_1

is in every respect identical with the natural alkaloid.[11] Similarly (±)-2-demethylcolchicine (**20**) was readily obtained from **1**. Hydrolysis of (±)-3-demethylcolchicine (**2**) with sulfuric acid afforded the 2,3-catechol **21** as a major product, demonstrating again that the formation of catechols in the series of colchicinoids can be accomplished from phenolic precursors by sulfuric acid treatment. Methylenation of **21**, as the previous reaction already accomplished in the natural series,[2] gave **22** in good yield.

X-ray Analysis. The unusual physical properties of **1** when compared with **1a**, expressed by a much higher melting point and a much lower solubility of **1** in several solvents, prompted an investigation of the former after crystallization from aqueous acetic acid by X-ray diffraction. The molecular conformation is shown in Figure 1. There is an extensive three-dimensional pattern of hydrogen bonding linking the molecules, and this is shown in Figure 2. It can be described as that of chains of alternate D and L molecules related by a glide plane and hydrogen bonded by the interaction N–H···O(9). Each colchicine molecule is hydrogen bonded by two donor bonds O(water 1)–H···O(3) and O(water 2)–H···O(acetyl). Each water molecule is hydrogen bonded to another two water molecules, one related by a glide plane to that given in the coordinate table and the other by a twofold screw axis. There is thus extensive linking between the chains. Details of the hydrogen bonds are given in Table I. The final atomic parameters for the heavier atoms are given in Table 2 (supplementary material). The molecular conformation, indicated by the torsion angles of ring B, is within the limits deducible from the average values given in ref 12, and the racemic molecule is a very typical colchinoid even to the orientation of the amide group. The conformations of the methoxyl groups are controlled by the packing and the necessity of close approach to allow the water-O(3) hydrogen bond.

Experimental Section[13]

General. Melting points were measured with a Fisher-Johns or a Thomas-Hoover apparatus. All melting points are corrected. IR spectra were recorded on a Beckmann IR 4230 spectrometer. Data are given in cm^{-1} with only the important diagnostic values reported. ^{1}H NMR spectra were recorded at 220 MHz on a Varian HR-200 spectrometer. Chemical shifts are reported in ppm on the scale, relative to Me_4Si as an internal standard. Data are reported in the form of values of chemical shift (peak multiplicity, number of protons, coupling constant if appropriate). CIMS spectra were recorded on a Finnigan 1015D spectrometer with a Model 6000 data-collection system. Optical rotations were

(11) Šantavý, F.; Talas, M. *Collect. Czech. Chem. Commun.* **1954**, *19*, 141.

(12) Sharma, P. N.; Brossi, A.; Silverton, J. V. *Acta Crystallogr., Sect. C: Cryst. Struct. Commun.* **1985**, *41*, 1069–1071.

(13) Most of the compounds, described here as racemates, are known as optically active compounds.[1,7,14] The purity of each compound was secured by TLC and its structure verified by spectroscopic methods. If spectroscopic data are known for the optically active compound they are not listed separately for the corresponding racemate.

(14) Wildmann, W. C.; Pursey, B. A. *The Alkaloids*; Manske, R. H. F., Holmes, H. L; Eds; Academic: New York 1968; Vol. 11, pp 407–457.

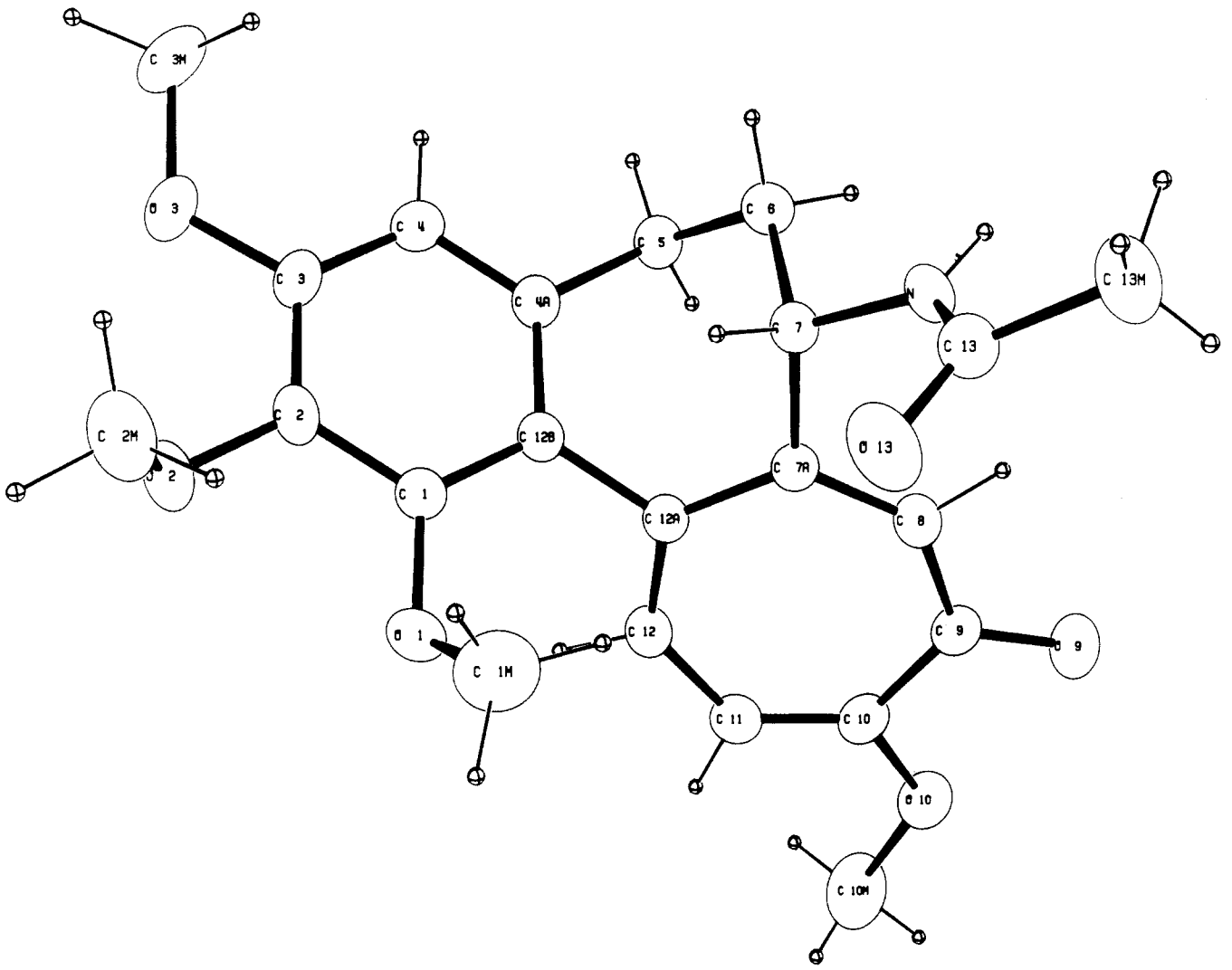


Figure 1. ORTEP drawing of the molecular conformation in 1. (Hydrogen atoms are represented by arbitrary spheres.)

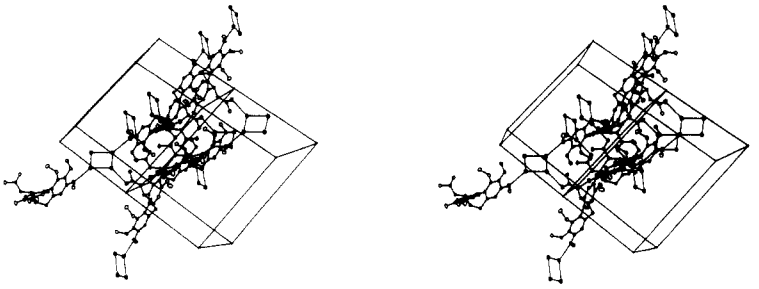


Figure 2. Stereoscopic drawing showing packing. The water molecules we show as filled circles and two unit cell boundaries are indicated although not all molecules of either cell are drawn. The origin is at the center of the left edge, c is upwards to the left, b upwards to right, and the short horizonal line is a.

measured on a Perkin-Elmer 241 MC polarimeter. Elemental analyses were performed by Atlantic Microlab, Inc., or Galbraith Laboratories, Inc. For TLC SiO_2 GHLF plates (Analtech) were used. Detection was done by UV at 254 nm and by I_2 vapor. Flash chromatography refers to the procedure of Still.[15] SiO_2, Merck, grade 60, 230–400 mesh, was used.

Racemization of Colchicine (1b). (±)-Colchicine (1) was prepared according to the procedure of Bladé-Font:[6] 62% yield;[16] mp (from DMF/EtOAc[17] or HOAc/H_2O) 280–282 °C (lit.[6] mp 280 °C).

Racemization of (−)-3-Demethylcolchicine (2b). This racemization was accomplished by using the same procedure as for colchicine (**1b**).[18] After the solvents were evaporated 10 mL of a 10% methanolic K_2CO_3 solution was added and the mixture stirred for 1 h. The MeOH was evaporated, and cold 2 N HCl was added until the pH reached 6–7. Extraction with $CHCl_3$, washing with brine, drying, and evaporation gave a brown residue, which was purified by flash chromatography (100:7 $CHCl_3$/MeOH) and crystallized from $CHCl_3$: **2** as a light yellow solid (51% yield); mp 246–248 °C; $[\alpha]^{25}_D$ 0° (c 0.12, MeOH).

(±)-*N*-Butyryldeacetylcolchicine (3). A mixture of 5 g (1.25 mmol) of colchicine (**1b**) and 50 mL of butyric anhydride was

(15) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2723.
(16) This yield is corrected: (−)-colchicine (**1b**) contains 8% (w/w) of solvent, (±)-colchicine (1), 10%.
(17) According to the ^1H NMR this compound contains 10% (w/w) of DMF as crystal solvent.
(18) After hydrolyses of the tetracetate by adding H_2O a mixture of the desired compound **2** and its 3-acetate was obtained.
(19) This yield is corrected: (±)-colchiceine contains 1 mol of H_2O.[4]

refluxed for 5 h. After the solution was cooled 10 mL of H_2O was added, and the solution was refluxed overnight. After evaporation of the solvents, saturated $NaHCO_3$ solution and 20 mL of ethyl acetate were added, and stirring was continued for 30 min. The two phases were separated, and the organic layer was washed with brine. After evaporation the residue was filtered first through a column of neutral alumina (100:7 $CHCl_3$/MeOH) and then purified by flash chromatography (100:3 $CHCl_3$/MeOH). To get rid of the black color the residue was taken up in $CHCl_3$ and treated with charcoal. Filtration over Celite, evaporation, and crystallization from aqueous acetone gave 1.17 g (23%) of **3** as light yellow crystals: mp 145–147 °C; $[\alpha]^{25}_D$ 0° (*c* 1.23, $CHCl_3$); IR ($CHCl_3$) 1715, 1680, 1620, 1595; ^1H NMR ($CDCl_3$) δ 0.90 (t, 3 H, J = 6 Hz, $COCH_2CH_2CH_3$), 1.59 (m, 2 H, $COCH_2CH_2CH_3$), 2.15 (t, 2 H, J = 6 Hz, $COCH_2CH_2CH_3$), 2.04–2.61 (m, 4 H, H_5 and H_6), 3.65, 3.89, 3.93, and 3.99 (all s, 12 H, OCH_3), 4.65 (m, 1 H, H_7), 6.52 (s, 1 H, H_4), 6.82 (m, 2 H, H_{11} and NH), 7.30 (d, 1 H, J = 11 Hz, H_{12}), 7.43 (s, 1 H, H_8); EIMS, *m/e* (relative intensity) 427 (M^+, 50), 399 (27), 312 (100). Anal. Calcd for $C_{24}H_{29}NO_6 \cdot 0.5H_2O$: C, 66.04; H, 6.93; N, 3.21. Found: C, 66.48; H, 6.94; N, 3.20.

(±)-Colchiceine (4). Compound **1** (500 mg, 1.25 mmol) was dissolved in a minimum amount of HOAc, and then 30 mL of 0.1 N HCl was added. The clear solution was heated at 90–100 °C for 2 h. After the solution was cooled solid Na_2CO_3 was added until the pH reached 6–7. Extraction with $CHCl_3$ (3 × 30 mL), washing with brine, drying, and evaporation gave 480 mg of a yellow solid, which was crystallized from MeOH/H_2O to give 344 mg (76%)[19] of a light yellow solid, mp 162–164 °C (lit.[4] mp 164 °C).

(±)-*N*-Deacetylcolchiceine (5). A mixture of 19.1 g (47.9 mmol) of (±)-colchicine (**1**), 450 mL of 20% H_2SO_4, and 100 mL of HOAc was heated at 80–90 °C for 5 h. The hot solution was neutralized (pH 7–7.5) with solid Na_2CO_3 and allowed to cool to room temperature. The light yellow precipitate was filtered, and the collected solid was washed with cold water and petroleum ether and sucked dry. The remaining H_2O phase was extracted with $CHCl_3$ (3 × 100 mL). The organic extracts were washed with brine, dried, and evaporated. The solids were put together and crystallized from MeOH/$CHCl_3$ to give 9.1 g (50%)[20] of yellow crystals, mp 256–258 °C. Anal. Calcd for $C_{19}H_{21}NO_5 \cdot 0.5H_2O$: C, 64.76; H, 6.29; N, 3.97. Found: C, 65.09; H, 6.10; N, 4.01.

(±)-*N*-(Trifluoroacetyl)deacetylcholchiceine (6). A suspension of 8.3 g (24.2 mmol) of **5** and 25.5 g of Na_2CO_3 (240 mmol) in 700 mL of ether was cooled with ice. While the mixture was stirred, 34 mL of trifluoroacetic anhydride was added in one portion. The cooling bath was removed and the orange solution stirred at room temperature during 2.5 h. Then most of the solvent was evaporated and the residue poured into $CHCl_3$ (250 mL). The organic layer was washed with cold saturated $NaHCO_3$ solution and brine until neutral. After drying and evaporation the crude residue was crystallized from CH_2Cl_2/petroleum ether to give 8.4 g (79%) of **6**, mp 144–145 °C. Anal. Calcd for $C_{21}H_{20}F_3NO_6$: C, 57.40; H, 4.59; N, 3.19; F, 12.98. Found: C, 57.08; H, 4.61; N, 3.08; F, 13.01.

(±)-*N*-(Trifluoroacetyl)deacetylcolchicine (7) and (±)-*N*-(Trifluoroacetyl)deacetylisocolchicine (8). A suspension of 6.5 g (14.8 mmol) of **6** in 100 mL of MeOH was treated with a ethereal solution of CH_2N_2 (from 21.5 g of Diazald). After 3 h the solvents were evaporated, and the remaining dark oil was flash chromatographed (100:5 $CHCl_3$/MeOH) yielding 3.07 g (46%) of the first eluted **7** and 2.55 g (38%) of **8**.

(±)-*N*-(Trifluoroacetyl)deacetylcolchicine (7): mp 230–231 °C (from CH_2Cl_2/petroleum ether). Anal. Calcd for $C_{22}H_{22}F_3NO_6$: C, 58.28; H, 4.88; N, 3.08; F, 12.58. Found: C, 57.89; H, 4.94; N, 3.01; F, 12.15.

(±)-*N*-(Trifluoroacetyl)deacetylisocolchicine (8): mp 265–266 °C (from CH_2Cl_2/petroleum ether).[21]

(±)-*N*-Deacetylcolchicine (9). A mixture of 5.30 g (11.7 mmol) of **7**, 2.3 g of K_2CO_3, and 100 mL of acetone/H_2O (1:1) was heated on an oil bath at 60 °C overnight. The reaction mixture was cooled, diluted with brine, and extracted several times with $CHCl_3$. The organic extracts were dried and evaporated, and the residue was purified by flash chromatography (100:8 $CHCl_3$/MeOH) to afford 2.84 g (70%) of **9** after crystallization from MeOH/ether: mp 158–160 °C (lit.[22] mp 147 °C).

(±)-*N*-Deacetylisocolchicine (10). Compound **8** was hydrolyzed in the usual way (see preparation of **9** from **7**) to give after flash chromatography (100:7 $CHCl_3$/MeOH) and crystallization from MeOH/ether **10** in 70% yield: mp 164–165 °C (lit.[22] mp 164–165 °C); ^1H NMR ($CDCl_3$) δ 1.82–1.98 and 2.20–2.50 (both m, 4 H, H_5 and H_6), 3.70, 3.89, 3.91, and 4.05 (all s, 12 H, OCH_3), 6.55 (s, 1 H, H_4), 7.15 and 7.34 (both d, 2 H, J = 12 Hz, H_{11} and H_{12}), 7.95 (s, 1 H, H_8); CIMS, *m/e* (relative intensity) 358 (M^+ + 1, 100).

(±)-*N*-(Trifluoroacetyl)demecolcine (11). A mixture of 300 mg (0.66 mmol) of **7**, 0.5 mL of MeI, and 0.5 g of K_2CO_3 in 10 mL of acetone was stirred at room temperature for 3 days. The reaction mixture was poured into $CHCl_3$, then washed neutral with brine, dried, and evaporated. Crystallization from MeOH/petroleum ether afforded 237 mg (77%) of **11** as white crystals, mp 174–175 °C. Anal. Calcd for $C_{23}H_{24}F_3NO_6 \cdot 1CH_3OH$: C, 57.71; H, 5.65; N, 2.80; F, 11.42. Found: C, 57.38; H, 5.57; H, 2.87; F, 11.83.

(±)-*N*-(Trifluoroacetyl)isodemecolcine (12). From 8. See preparation of **11** from **7**: yield, 92% after crystallization from acetone/ether; mp 211–213 °C. Anal. Calcd for $C_{23}H_{24}F_3NO_6$: C, 59.10; H, 5.17; N, 2.99; F, 12.20. Found: C, 58.62; H, 5.14; N, 2.97; F, 12.27.

(±)-Demecolcine (13). Compound **11** was hydrolyzed in the usual way (see preparation of **9** from **7**) to give after flash chromatography (100:8 $CHCl_3$/MeOH) and crystallization from MeOH/ether **13** in 89% yield: mp 178–179 °C. Anal. Calcd for $C_{21}H_{25}NO_5$: C, 67.91; H, 6.77; N, 3.77. Found: C, 67.79; H, 6.82; N, 3.75.

(±)-Isodemecolcine (14). Compound **12** was treated in the same way as **11**. After workup and filtration over SiO_2 the residue was crystallized from MeOH/petroleum ether to give **14** in 73% yield, mp 111–112 °C. Anal. Calcd for $C_{21}H_{25}NO_5$: C, 67.91; H, 6.77; N, 3.77. Found: C, 67.77; H, 6.83; N, 3.74.

(±)-Demecolcine (15). A mixture of 180 mg (0.48 mmol) of **14** and 20 mL of half concentrated HCl was stirred at 100 °C for 5 h. After the mixture was cooled, solid Na_2CO_3 was added until the pH reached 6–7. Extraction with $CHCl_3$ (5 × 20 mL), drying, and evaporation yielded a dark yellow solid, which was crystallized from MeOH/ether to give 140 mg of light yellow crystals, mp 245–247 °C.[21]

Optical Resolution of (±)-*N*-Deacetylcolchicine (9). To a hot solution (50–60 °C) of 1.37 g (3.84 mmol) of **9** in 50 mL of MeOH was added 1.0 g (4.3 mmol of *d*-10-camphorsulfonic acid in 10 mL of MeOH. Crystallization began immediately. After slowly cooling down, the mixture was kept at 4 °C overnight.[23] After two more crystallizations from 95% EtOH an optical rotation was obtained which could not be increased by further crystallizations: $[\alpha]^{25}_D$ +120° (*c* 0.33, H_2O);[24] 1.0 g (88%) of **9a** *d*-camphorsulfonate; mp 220–222 °C.[25] From the first mother liquor, after two crystallizations from MeOH, 890 mg (78%) of **9b** *d*-camphorsulfonate was obtained: $[\alpha]^{25}_D$ −97° (*c* 0.345, H_2O); mp 220–225 °C.[25] Both camphorsulfonates were >99% optically pure.[26] Compound **9a** camphorsulfonate was converted to the (+)-*N*-deacetylcolchicine (**9a**) in the following way: The salt was dissolved in H_2O, rendered alkaline with concentrated aqueous NH_3, and extracted with $CHCl_3$ (4 × 10 mL). The organic layer was washed with brine, dried, and evaporated to give **9a** in a quantitative yield: light yellow foam; $[\alpha]^{25}_D$ +175° (*c* 1.2, $CHCl_3$)

(20) This yield is corrected.
(21) No satisfactorily combustion analysis could be obtained.
(22) Schreiber, J.; Leimgruber, W.; Pesaro, M.; Schudel, P.; Threlfall, T.; Eschenmoser, A. *Helv. Chim. Acta* **1961**, *44*, 540.
(23) It is important to keep the mixture at 4 °C overnight, although one might think that the crystallization was complete within a short time at room temperature.
(24) After the first crystallization the $[\alpha]^{25}_D$ was +47° (*c* 0.285, H_2O), after the next from 95% EtOH +77° (*c* 0.295, H_2O), and finally +120° (*c* 0.33, H_2O).
(25) This compound shrinks at 170–172 °C, then changes color from yellow to red at 190–192 °C, and then melts at 220–222 °C.
(26) The optical purity was determined either by reaction of the bases **9a** and **9b** or **10a** and **10b** with (*R*)-(+)-α-methylbenzyl isocyanate in $CDCl_3$ followed by ^1H NMR analyses of the resulting diastereoisomeric urea derivatives.[8]

(lit.[7] for **9b**, $[\alpha]^{25}_D$ −152° (*c* 1.17, $CHCl_3$)). Compound **9b** camphorsulfonate was converted to (−)-N-deacetylcolchicine (**9b**) as described above: light yellow foam; $[\alpha]^{20}_D$ −164° (*c* 1.03, $CHCl_3$).

(+)-Colchicine (1a). To a vigorously stirred and cooled mixture of 145 mg (0.41 mmol) of **9a**, 210 mg of $NaHCO_3$, 5 mL of H_2O, and 20 mL of $CHCl_3$ was added 120 μL of acetic anhydride at once. After 2.5 h the cooling bath was removed, and 10 ml of saturated $NaHCO_3$ solution was added and stirred for 30 min to hydrolyze excess acetic anhydride. After separation of the phases the H_2O phase was extracted with two 20-mL portions of $CHCl_3$. The combined $CHCl_3$ fractions were washed once with brine, dried, and evaporated to yield 145 mg of a light yellow solid which was crystallized from $CHCl_3$:[27] 130 mg (80%); mp 146–148 °C (lit.[4] mp 140 °C);[29] $[\alpha]^{25}_D$ +190° (*c* 1, MeOH) (lit.[4] $[\alpha]^{25}_D$ +215°[30] (*c* 1, MeOH). Anal. Calcd for $C_{22}H_{25}NO_6 \cdot 0.5CHCl_3$: C, 56.64; H, 5.81; N, 2.94. Found: C, 57.15; H, 5.83; N, 2.74.

Similar N-acetylation of **9b** gave (−)-colchicine (**1b**), identical in every respect with the natural alkaloid.

Optical Resolution of (±)-*N*-Deacetylisocolchicine (10). To a solution of 640 mg (1.80 mmol) of **10** in 20 mL of 95% MeOH a solution of 870 mg (2.15 mmol) of (+)-di-*p*-toluoyl-1-tartaric acid monohydrate in 7 mL of 95% MeOH was added. After being heated shortly to 50–60 °C the mixture was allowed to cool slowly and then kept overnight at 4 °C. Crystallization began after 10 min. Two more crystallizations from MeOH were necessary to obtain a pure **10b** di-*p*-toluoyl-1-tartrate: 550 mg (41%); $[\alpha]^{25}_D$ −19° (*c* 0.29, 95% EtOH); mp 200–202 °C dec. The first mother liquor was converted to the free base as described before. This 300 mg of optically impure **10a** was dissolved in 10 mL of 95% MeOH, and 360 mg (0.93 mmol) of (−)-di-*p*-toluoyl-*d*-tartaric acid in 4 ml of 95% MeOH was added. After being heated to 50–60 °C and slowly cooled down, the mixture was stored overnight at 4 °C. Another crystallization from 95% MeOH gave pure **10a** di-*p*-toluoyl-*d*-tartrate: 562 mg (45%); $[\alpha]^{25}_D$ +25° (*c* 0.185, 95% EtOH); mp 201–202 °C dec. Both tartrate salts were >99% optically pure.[26] Both compounds were converted in the usual way to the free bases which were crystallized from EtOH/ether to give 230 mg (36%) of **10b**, mp 175–177 °C, $[\alpha]^{25}_D$ −236° (*c* 1, $CHCl_3$) (lit.[31] mp 176–178 °C, $[\alpha]^{25}_D$ −240° (*c* 1, $CHCl_3$)), and respectively 260 mg (41%) of **10a**, mp 176–178 °C, $[\alpha]^{25}_D$ +238° (*c*, 1.1, $CHCl_3$).[32]

(+)-Isocolchicine (16a). From 10a. See preparation of (+)-colchicine (**1a**): crystallized from EtOAc/ether; yield 71%; mp 221–223 °C (lit.[33] mp 225–226 °C); $[\alpha]^{25}_D$ +304° (*c* 1, $CHCl_3$). Anal. Calcd for $C_{22}H_{25}NO_6 \cdot 0.25EtOAc$: C, 65.54; H, 6.46; N, 3.32. Found: C, 65.48; H, 6.44; N, 3.40. Hydrolyses of **16a** with 0.1 N HCl at 100 °C afforded **4a**, identical by TLC, ^1H NMR, and mp with **4b**, prepared from natural colchicine **1b**.

(−)-Isocolchicine (16b). From 10b. See preparation of (+)-colchicine (**1a**): yield 75%; (after crystallization from EtOAc/ether) mp 222–223 °C (lit.[33] mp 225–226 °C); $[\alpha]^{25}_D$ −312° (*c* 1, $CHCl_3$) (lit.[33] $[\alpha]^{25}_D$ −306.7° (*c* 1.063, $CHCl_3$)). Anal. Calcd for $C_{22}H_{25}NO_6$: C, 66.15; H, 6.31; N, 3.51. Found: C, 66.08; H, 6.35; N, 3.49.

(−)-*N*-(Trifluoroacetyl)deacetylcolchicine (7b). From 9b. See the preparation of **6** from **5**. Crystallization from CH_2Cl_2/petroleum ether afforded a slightly yellow powder in 75% yield: mp 202–203 °C, $[\alpha]^{25}_D$ −78° (*c* 1.5, $CHCl_3$) (lit.[7] mp 203–205 °C, $[\alpha]^{25}_D$ −79° (*c* 1.43, $CHCl_3$).

(−)-*N*-Formyldemecolcine (17b). A mixture of 928 mg (2.5 mmol) of (−)-demecolcine (**13b**)[34] and 30 mL of ethyl formate was refluxed under argon during 20 h. After evaporation the residue was crystallized from ethyl acetate/ether to give 810 mg (81%) of a yellow powder as mixture of rotamers: mp 182–183°C (lit.[35] mp 187–189 °C); $[\alpha]^{25}_D$ −185° (*c* 1.03, $CHCl_3$) (lit.[36] $[\alpha]^{25}_D$ −189° (*c* 1.02, $CHCl_3$)); ^1H NMR ($CDCl_3$)[37] δ 2.05–2.77 (m, 4 H, H_5 and H_6), 2.84 and 3.24 (both s, together 3 H, NCH_3), 3.63, 3.66, 3.89, 3.92, 3.94, 3.97, and 4.00 (all s, together 12 H, OCH_3), 4.11 and 4.82 (both m, together 1 H, H_7), 6.53 and 6.57 (both s, together 1 H, H_4), 6.79 and 6.81 (both d, together 1 H, J = 11 Hz, H_{11}), 7.10 and 7.17 (both s, together 1 H, H_8), 7.28 (d, 1 H, J = 11 Hz, H_{12}), 8.09 and 8.28 (both s, together 1 H, NCHO); CIMS, *m/e* (relative intensity) 400 (M^+ + 1, 100).

(−)-2-Demethyl-*N*-formyldemecolcine (18b). See the preparation of **20** from **1**. After workup the residue was purified by flash chromatography (100:7 $CHCl_3$/MeOH). Crystallization from isopropyl alcohol/ether gave a yellow powder in 46% yield: mp 149–151 °C; $[\alpha]^{25}_D$ −180° (*c* 0.9, $CHCl_3$); IR ($CHCl_3$) 3570, 1680, 1628, 1600, 1570 cm^{-1}; ^1H NMR ($CDCl_3$)[37] δ 2.05–2.73 (m, 4 H, H_5 and H_6), 2.82 and 3.23 (both s, together 3 H, NCH_3), 3.57 and 3.63 (both s, together 3 H, OCH_3), 3.91 and 3.92 (both s, together 3 H, OCH_3), 3.97 and 3.99 (both s, together 3 H, OCH_3), 4.13 and 4.79 (both m, together 1 H, H_7), 6.50 and 6.53 (both s, together 1 H, H_4), 6.77 and 6.79 (both d, together 1 H, J = 11 Hz, H_{11}), 7.09 and 7.16 (both s, together 1 H, H_8), 7.25 and 7.27 (both d, together 1 H, J = 11 Hz, H_{12}), 8.07 and 8.27 (both s, together 1H, NCHO); CIMS, *m/e* (relative intensity) 386 (M^+ + 1, 100).[21]

(−)-2-Demethyldemecolcine (19b). See the preparation of **20** from **1**. After workup the residue was purified by flash chromatography (100:6 $CHCl_3$/MeOH) and then crystallized to give light yellow crystals in 47% yield: mp 137–139 °C (lit.[38] mp 137–139 °C); $[\alpha]^{25}_D$ −111° (*c* 1, $CHCl_3$) (lit.[39] $[\alpha]^{25}_D$ −109° (*c* 1, $CHCl_3$), −119° (*c* 1, $CHCl_3$)).

(±)-2-Demethylcolchicine (20). A solution of 562 mg (1.41 mmol) of **1** in 5 mL of concentrated H_2SO_4 and 12 mL of HOAc was stirred at 55 °C for 4 h. Then the reaction was stopped, although not all starting material has gone, because the amount of polar side products began to increase. After the mixture was cooled, solid Na_2CO_3 was added and eventually some H_2O until the pH reached 5–6. Extraction with $CHCl_3$ (4 × 30 mL), washing with brine, drying, and evaporation yielded 400 mg of a dark yellow solid. This was purified by flash chromatography (100:7 $CHCl_3$/MeOH) and then crystallized from MeOH/ether: slightly yellow powder (260 mg, 47%), mp 286–288 °C.[21]

(±)-2,3-Didemethylcolchicine (21). A mixture of 125 mg (0.32 mmol) of **2** and 5 mL of concentrated H_2SO_4 was heated at 55–60 °C for 7 h. The reaction mixture was cooled, extracted with seven portions of $CHCl_3$/isopropyl alcohol (3:1), washed with brine, dried, and evaporated. The dark yellow residue was purified by flash chromatography (100:8 $CHCl_3$/MeOH) and crystallized from MeOH/ether to yield 20 mg (17%) of **21** as yellow crystals, mp 277–279 °C dec.

(±)-2,3-(Methylenedioxy)-2,3-didemethoxycolchicine, Cornigerine (22). A stirred mixture of 17 mg (0.05 mmol) of **21**, 100 mg of K_2CO_3, 0.1 mL of bromochloromethane, and 1 mL of 1-methyl-2-pyrrolidone was heated under argon at 70 °C for 18 h. After the mixture was cooled 3 mL H_2O was added and the solution extracted 4× with CH_2Cl_2. The combined organic phase was washed with brine, dried, and evaporated. Residual solvent was stripped at high vacuum. The slightly brown residue was crystallized from MeOH/petroleum ether: 12 mg (70%) of **22**

(27) Note added in proof: There is considerable evidence that colchicine in solution aggregates with solvent molecules to form atropisomer–solvent complexes. This is demonstrated by the finding that TLC-pure (+)-colchicine crystallized from chloroform, whereas (−)-colchicine was obtained crystalline from ethyl acetate, in full agreement with similar findings made by Corrodi and Hardegger.[4] CD spectra of (+)- and (−)-colchicine solvents are for this reason also not fully superimposable.[28] As suggested by one of the referees, 10 mg of (−)-colchicine–ethyl acetate complex and 10 mg of (+)-colchicine–chloroform complex dissolved in methanol, evaporated to dryness, and crystallized from acetic acid–water afforded 18 mg of (±)-colchicine, identical with material prepared differently by MP and IR (Nujol).

(28) Brossi, A. *J. Nat. Prod.* **1986**, *49*, 878.

(29) Melting point reported for amorphous (+)-colchicine (**1a**).

(30) These two optical rotations cannot be compared because the reported data is for amorphous colchicine, whereas in this work (+)-colchicine with $0.5CHCl_3$ is reported.

(31) Raffauf, R. F.; Farren, A. L.; Ullyot, G. E. *J. Am. Chem. Soc.* **1953**, *75* 5292.

(32) With (−)-di-*p*-toluoyl-*d*-tartaric acid (+)-*N*-deacetylisocolchicine is directly obtained.

(33) Sorkin, M. *Helv. Chim. Acta* **1946**, *29*, 246.

(34) (−)-Demecolcine (**13b**) was synthesized from **7b** according to Capraro.[7]

(35) Battersby, A. R.; Rainage, R.; Cameron, A. F.; Hannaway, C.; Santavý, F. *J. Chem. Soc. C* **1971**, 3514.

(36) Šantavý, F.; Winkler, R.; Reichstein, T. *Helv. Chim. Acta* **1953**, *36*, 1319.

(37) This compound is a 65:35 mixture of rotamers (according to the ^1H NMR spectrum).

(38) Malichová, V.; Potesilá, H.; Preininger, V.; Šantavý, F. *Planta Med.* **1979**, *36*, 119.

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as slightly yellow crystals, mp 343–345 °C.

X-ray Crystallography. Crystals were colorless prisms and preliminary X-ray investigation indicated a monoclinic unit cell. The crystal used for data collection was approximately 0.3 × 0.15 × 0.1 mm.[3] With 15 reflections, measured at ±θ angles between 20° and 30°, least-squares refinement produced a cell with dimensions a = 11.982 (1) Å, b = 16.383 (1) Å, c = 12.509 (1) Å, β = 116.71 (1)° (assumed wavelength for Cu Kα: 1.5418 Å). The space group was uniquely determined as $P2_1/a$. Assuming four molecules of colchicine, the calculated crystal density of 1.209 g cm^{-3} was reasonable. The phase problem was solved with MITHRIL.[40] The distribution of intensities was centric, and all heavy atoms of the molecule were visible in the E-map. The structure was refined by standard methods using the programs of XRAY72[41] (isotropic followed by anisotropic refinement of heavy atoms, finding H atoms in a difference map, and finally refinement of all atoms with isotropic H thermal parameters). The anisotropic temperature factor used had the form $\exp-(2\pi^2(\sum_i\sum_j(U_{ij}h_ih_ja^*_ia^*_j)))$.

In the course of refinement, two large peaks at a separation of 2.8 Å were found and assigned as O atoms of water molecules. The appropriate H atoms were found after refinement. With 4436 observations (2750 with $I > \sigma(I)$) and a maximum $\sin\theta/\lambda$ of 0.6233 Å^{-1}, the final conventional R factor was 4.7%. The final molecular dimensions are given in Table 3 (supplementary material), and it can be seen that they are as might be expected from the formula. The crystal density calculated on a basis of the final deduced crystal contents is 1.318 g cm^{-3}.

(40) Gilmore, C. J. MITHRIL. A computer program for the automatic solution of crystal structures from X-ray data, University of Glasgow, 1983.

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Supplementary Material Available: Tables of final atomic coordinates for the heavier atoms and of bond distances and angles (2 pages). Ordering information is given on any current masthead page.

Conformations of Germacra-1(10),4-dien-6,12-olides and -8,12-olides. A Comparison of X-ray Diffraction, NMR, and Molecular Mechanics Derived Conformations

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Conformations of the ten-membered ring *trans,trans*-germacradiene lactones have been investigated. X-ray diffraction, NMR, and molecular mechanics all indicate that the 6,12-olides exist in solution and in the solid state as the 1UU conformer with crossed double bonds and an up–up arrangement of the two ring methyl groups. In costunolide this conformer is more stable by 3.55 kcal/mol. Molecular mechanics predicts the barrier between 1UU and the next lowest conformer to be 22.1 kcal/mol. In the 8,12-olides the 2DD (both methyl groups down) and 2UD are almost isoenergetic with a calculated barrier of 18.4 kcal/mol. In this series the ring substituents determine which conformer is of lowest energy. Line broadening or multiple NMR signals are common. The crystal structure of 3-acetoxy-6-hydroxygermacra-1(10),4-dien-8,12-olide is reported.

A wide variety of germacra-1(10),4-dien-6,12-olides, -8,12-olides, and their derivatives have been isolated from plant sources.[1] These ten-membered ring sesquiterpenes have been investigated by NMR, X-ray diffraction, and other spectroscopic techniques. X-ray diffraction studies provide a detailed analysis of the ten-membered ring conformation in the solid state; however, a number of the germacranolides show broadened NMR signals or even multiple NMR signals indicative of conformational equilibria in solution. A few of the conformational mixtures have been investigated by low temperature and NOE methods and the structures of the solution conformers assigned. The conformations of ten-membered rings have been the subject of a number of earlier investigations,[2] and the stable conformations are those which tend to follow the diamond lattice. In germacratrienes, such as agerol, the double bonds are in a crossed orientation with the methyl groups syn with respect to the ring.[2a,d] The influence of lactone rings and ring substituents has not been systematically investigated. Molecular mechanics (MM) calculations have been applied successfully to the study of many hydrocarbons including ten-membered rings,[2a,c–h] and reliable predictions of conformations, heats of formation, steric energies, and in some cases estimates of energy barriers between conformers have resulted. Enough data are now available on germacradienolide-type terpenes to permit a comparison of the low energy conformers identified by X-ray diffraction, NMR, and molecular mechanics studies and to estimate the relative magnitudes of conformational barriers.

Discussion

The *trans,trans*-germacradienolides are usually discussed in terms of the four conformations which are labeled in Figure 1 as 1UU, 1UD, 1DU, 1DD and 2UU, 2UD, 2DU, 2DD. The 1 and 2 refer to the 6,12-and 8,12-olides, respectively, while U (up) and D (down) refer to the orientation of the C(10) and C(4) methyl groups on the ten-membered ring.[3] The lowest energy conformers corre-

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