Quinolizidines. 6.[1] Absolute Stereochemistry of Ankorine: Synthetic Incorporation of Ethyl Cincholoiponate into (-)-Ankorine

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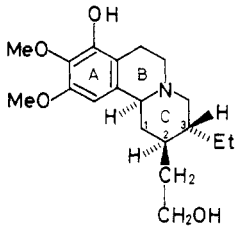
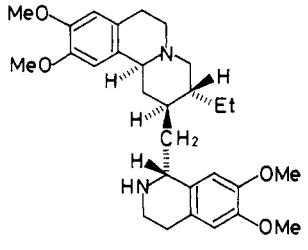
With a view to establishing the absolute configuration of the Alangium alkaloid ankorine, the chiral target molecule **1** was synthesized by means of an initial condensation of 2-(benzyloxy)-3,4-dimethoxyphenacyl bromide with cincholoipon ethyl ester [(+)-**3**], derived from the Cinchona alkaloid cinchonine, and succeeding steps proceeding through the intermediates **9**, **10**, **11**, **13**, **14**, **18**, **17**, **19**, *trans*-**23**, **24**, and **25**. Identity of synthetic (-)-**1** with ankorine unequivocally established the absolute stereochemistry of this alkaloid. In the $Hg(OAc)_2$–EDTA oxidation of the amino alcohol **10**, the desired 6-piperidone derivative **11** was the major product. The successful isomerization of the *cis*-lactam acid (-)-**14** to the *trans*-lactam acid (+)-**18** was based on the finding that the two isomers were convertible to each other through cis–trans equilibration (**14**:**18** = 33:67) at 180 °C in 90 min.

Ankorine is one of the phenolic benzoquinolizidine alkaloids isolated from the Indian medicinal plant *Alangium lamarckii* Thw.[2-4] A partial plane structure of this base was first elucidated by Battersby and co-workers[3] largely on the basis of physical measurements, and the whole structure and relative stereochemistry were recently established as **1** by us[5] and Szántay et al.,[6] who independently accomplished the stereoselective synthesis of (±)-**1**. This paper describes the details of our further synthetic work in this area, which permitted the assignment of the absolute stereoformula **1** to ankorine.[7]



1



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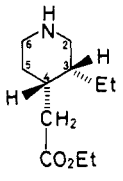

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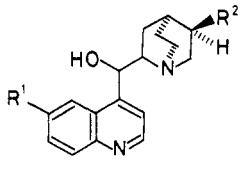

4, R^1 = H or MeO; R^2 = vinyl or Et

5, R^1 = H; R^2 = vinyl

At the commencement of the present study, we selected the chiral target molecule **1** (absolute configuration shown) for synthesis with a view to establishing the absolute stereochemistry of ankorine. This was based on the assumption that the absolute configurations of all three asymmetric centers of this alkaloid correspond to those[4] in the benzoquinolizidine part of the Ipecac alkaloid emetine (**2**), which also occurs[8] in *A. lamarckii*. An appropriate form of the key synthon for the chiral synthesis of **1** would be ethyl cincholoiponate [(+)-**3**],[9] a degradation product of the major *Cinchona* alkaloids **4**,[10] since it already carries the skeleton and side chains necessary for ring C of **1** apart from the wrong configuration at C-4. If chirality could be conserved at C-3 and C-4 in a reaction sequence starting with (+)-**3**, many difficulties in stereochemical control and resolution of racemized intermediates could be avoided. Such synthetic strategy required the following four main operations: (i) introduction of an appropriate phenethyl skeleton into (+)-**3** at N-1; (ii) generation of the lactam carbonyl function at C-6; (iii) epimerization at C-4 to produce the 3,4-trans configuration that must match the relative and absolute configuration of **1** at the 3- and the 2-positions; (iv) ring closure to complete the benzoquinolizidine system.

For trial studies on operation ii, we tried to extend the scope of the mercuric acetate–ethylenediaminetetraacetic acid (EDTA) oxidation method,[11] utilized by Möhrle[12] for conversion of cyclic amines into lactams, to include 1-(3,4-dimethoxyphenyl)-2-(3-substituted piperidino)-ethanols (**6**) that could serve as precursors of the 6-piperidones **7** and/or the 2-piperidones **8**. Previous reports[13] from this laboratory described the results of such oxidation studies with particular emphasis on the effect of various 3-substituents (R in **6**) upon regioselectivity in the formation of the lactam carbonyl function. On the basis of these model experiments, operations i and ii for synthesis of **1** were embodied as follows.

2-(Benzyloxy)-3,4-dimethoxyphenacyl bromide,[14] an appropriate form of the requisite phenethyl synthon, was

(1) For part 5 in this series, see ref 16b.
(2) Dasgupta, B. *J. Pharm. Sci.* **1965**, *54*, 481.
(3) Battersby, A. R.; Kapil, R. S.; Bhakuni, D. S.; Popli, S. P.; Merchant, J. R.; Salgar, S. S. *Tetrahedron Lett.* **1966**, 4965.
(4) For reviews, see: (a) Openshaw, H. T. In "Chemistry of the Alkaloids"; Pelletier, S. W., Ed.; Van Nostrand Reinhold: New York, 1970; Chapter 4. (b) Brossi, A.; Teitel, S.; Parry, G. V. In "The Alkaloids"; Manske, R. H. F., Ed.; Academic Press: New York, 1971; Vol. XIII, Chapter 3.
(5) (a) Fujii, T.; Yoshifuji, S.; Yamada, K. *Tetrahedron Lett.* **1975**, 1527. (b) Fujii, T.; Yoshifuji, S.; Yamada, K. *Tetrahedron*, in press.
(6) Szántay, C.; Szentirmay, E.; Szabó, L.; Tamás, J. *Chem. Ber.* **1976**, *109*, 2420.
(7) A preliminary account of this work has been published: Yoshifuji, S.; Fujii, T. *Tetrahedron Lett.* **1975**, 1965.
(8) Budzikiewicz, H.; Pakrashi, S. C.; Vorbrüggen, H. *Tetrahedron* **1964**, *20*, 399.
(9) For the stereochemistry of this ester, see: (a) Prelog, V.; Zalán, E. *Helv. Chim. Acta* **1944**, *27*, 535. (b) Prelog, V.; Zalán, E. *Ibid.* **1944**, *27*, 545.
(10) Solomon, W. In ref 4a, Chapter 11.
(11) Knabe, J. *Arch. Pharm. Ber. Dtsch. Pharm. Ges.* **1959**, *292*, 416.
(12) Möhrle, H. *Arch. Pharm. Ber. Dtsch. Pharm. Ges.* **1964**, *297*, 474.
(13) (a) Fujii, T.; Yoshifuji, S. *Chem. Pharm. Bull.* **1972**, *20*, 1451. (b) Fujii, T.; Yoshifuji, S.; Michishita, K.; Mitsukuchi, M.; Yoshida, K. *Ibid.* **1973**, *21*, 2695. (c) Fujii, T.; Yoshida, K.; Ohba, M.; Yoshifuji, S. *Ibid.* **1977**, *25*, 2336. (d) Fujii, T.; Ohba, M.; Yoshifuji, S. *Ibid.* **1977**, *25*, 3042.
(14) Fujii, T.; Yoshifuji, S.; Ohba, M. *Chem. Pharm. Bull.* **1978**, *26*, 3218.

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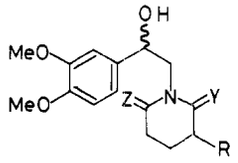
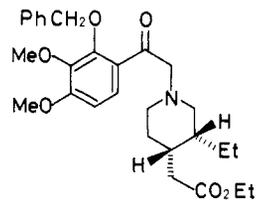


6, Y = H_2; Z = H_2
7, Y = H_2; Z = O
8, Y = O; Z = H_2



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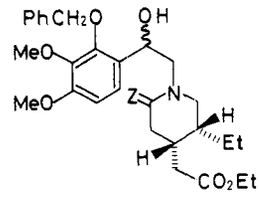
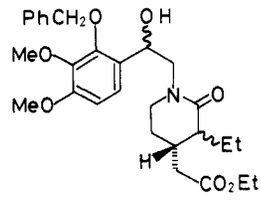


10, Z = H_2
11, Z = O

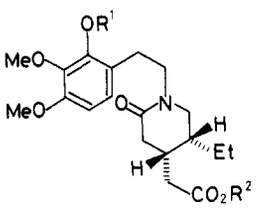


12

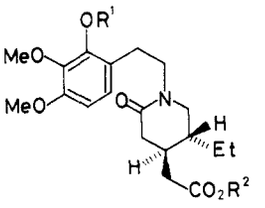
condensed with (+)-3 in benzene containing K_2CO_3 to give the amino ketone (−)-9 in 91% yield. The amino ester (+)-3 was prepared from commercially available cinchonine (5) in 50% overall yield by the known method.[9a,15] On reduction with $NaBH_4$ in EtOH, (−)-9 afforded a diastereoisomeric mixture of the amino alcohol 10 in 92% yield. The $Hg(OAc)_2$–EDTA oxidation of the mixture 10 in boiling 1% aqueous AcOH followed by column chromatography yielded the 6-piperidone 11 as a diastereomeric mixture (57% yield) and an oily substance (19% yield) presumed[16] to be a diastereomeric mixture of the cis and trans 2-piperidones 12. The 6-piperidone structure, assigned in analogy with the similar oxidation products of structurally related systems[16] and simpler 3-alkylpiperidine derivatives (type 6),[13b,c] was also substantiated by the following self-consistent reaction sequence.

Catalytic hydrogenolysis of the diastereomeric mixture of 11 with hydrogen activated on Pd–C catalyst in EtOH in the presence of a little 70% perchloric acid gave the lactam phenol (−)-13 in 98% yield. Hydrolysis of (−)-13 to the lactam acid (−)-14 was effected in 96% yield in EtOH containing 2 M aqueous NaOH at room temperature, concluding operations i and ii in the synthetic plan.

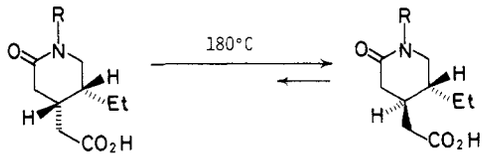
Now that the cis lactam acid (−)-14 had become available, the third main operation was then realized in the form of thermal isomerization of (−)-14 to the trans lactam acid (+)-18. This was patterned after similar isomerizations of the structurally parallel systems (±)-**21a–c** → (±)-**22a–c** and (−)-**21c** → (+)-**22c** which were found[16,17] to proceed through cis–trans equilibration (**21**:**22** = 33:67) under thermal conditions, presumably by a mechanism of intramolecular acidolysis of the lactam bond. The cis lactam acid (−)-14 was thus heated neat at 180 °C for 90 min to give a mixture of the trans and the cis isomers, from which the trans lactam acid (+)-18, identical on spectral comparison with a sample of (±)-18 obtained by alkaline hydrolysis of authentic (±)-17,[5] was isolated by recrystallization. The yield of (+)-18 reached 73% when the cis lactam acid recovered from the reaction mixture was again subjected to the same reaction. In a separate experiment, we followed the progress of isomerization at 180 °C of



13, R^1 = H; R^2 = Et
14, R^1 = H; R^2 = H
15, R^1 = $PhCH_2$; R^2 = Et
16, R^1 = $PhCH_2$; R^2 = H



17, R^1 = H; R^2 = Et
18, R^1 = H; R^2 = H
19, R^1 = $PhCH_2$; R^2 = Et
20, R^1 = $PhCH_2$; R^2 = H



21a,b,c 22a,b,c

a, R = H
b, R = $PhCH_2$
c, R = 3,4-$(MeO)_2C_6H_3(CH_2)_2$

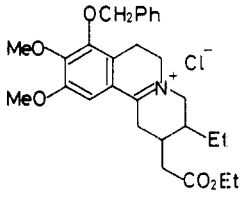
(−)-14 to (+)-18 by determining the isomer ratio in the reaction mixture according to the previously reported[17] carbon-13 NMR spectroscopic method. A rapid decrease of the amount of (−)-14 was observed along with the occurrence and a rapid increase of (+)-18 at earlier stages of the reaction; equilibrium [(−)-14:(+)-18 = 33:67] was attained in 90 min. The equilibration was also confirmed by conducting the reaction in the reverse direction to produce a product mixture of the same composition starting with (+)-18. It is of interest to note that a higher substituent on the N atom of such *cis*- and *trans*-5-ethyl-2-oxo-4-piperidineacetic acid systems tends to cause the rate of isomerization to slow down.[16,17]

Conversion of (+)-18 into the lactam ester (+)-17 was then effected in 96% yield with ethanolic HCl at 17–22 °C for 24 h. Since the model compounds (±)-**21a,b** and (−)-**21c** are known to isomerize to (±)-**22a,b** and (+)-**22c** under acid hydrolytic conditions, presumably via the ring-opened intermediates,[16,17] there might be the possibility that trans → cis isomerization of (+)-18 or (+)-17 occurred during the above Fischer–Speier esterification by means of the mechanistically similar acid-catalyzed alcoholysis of the lactam carbonyl–nitrogen bond. However, our previous work[16,18] has already shown that trans → cis or cis → trans isomerization of the model compounds **22a–c** or **21a–c** does not occur at all under the particular esterification conditions adopted for (+)-18. For protection of the phenolic hydroxyl group, (+)-17 was treated with benzyl bromide in boiling acetone containing K_2CO_3 for 20 h to provide the benzyl ether (+)-19 in 96% yield. The structure of (+)-19 was confirmed by comparison of chromatographic and spectral data with those of authentic (±)-19.[5]

We next concentrated our attention on operation iv that was to complete the benzoquinolizidine system. The following synthetic scheme was essentially the same as adopted recently for the racemic series.[5] Thus, the Bischler–Napieralski cyclization of (+)-19 was carried out with $POCl_3$ in boiling toluene for 2 h, and the resulting iminium salt (*trans*-**23**) was hydrogenated in EtOH with hydrogen

(15) Kaufmann, A.; Rothlin, E.; Brunschweiler, P. *Ber. Dtsch. Chem. Ges.* **1916**, *49*, 2299.
(16) (a) Fujii, T.; Yoshifuji, S. *Tetrahedron Lett.* **1975**, 731. (b) Fujii, T.; Yoshifuji, S. *Tetrahedron*, in press.
(17) Fujii, T.; Yoshifuji, S.; Tai, M. *Chem. Pharm. Bull.* **1975**, *23*, 2094.
(18) Fujii, T.; Yoshifuji, S. *Chem. Pharm. Bull.* **1978**, *26*, 2253.

and Adams catalyst to afford the tricyclic base (−)-**24** in 55% overall yield from (+)-**19**. Spectral identity of (−)-**24** with the racemic base (±)-**24** that was prepared recently[5] by a different stereospecific synthesis proved the stereospecificity of the synthetic operations proceeding from (+)-**3** to (−)-**24**. Our previous success[16] in a parallel synthesis of (−)-**26**, a key intermediate for the synthesis of (−)-emetine (**2**), from (+)-**3** and 3,4-dimethoxyphenacyl bromide also supported the correctness of the stereochemical outcome of the present chiral synthesis.



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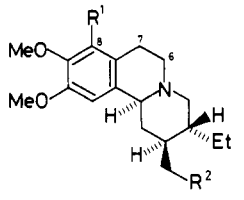

24, R^1 = $PhCH_2O$; R^2 = CO_2Et
25, R^1 = $PhCH_2O$; R^2 = CH_2OH
26, R^1 = H; R^2 = CO_2Et
27, R^1 = H; R^2 = CH_2OH

An alternative step for operation iii was thermal isomerization of the cis lactam acid (−)-**16** to the trans isomer **20**, although it turned out to be less efficient than that of (−)-**14** because of difficulty in separating the two isomers. On treatment with benzyl bromide and K_2CO_3 in boiling acetone, the lactam phenol (−)-**13** gave the benzyl ether **15**, which was then hydrolyzed with aqueous NaOH to provide (−)-**16** in 99% overall yield from (−)-**13**. When heated neat at 180 °C for 80 min, (−)-**16** produced a difficult to separate mixture of the cis (**16**) and trans (**20**) isomers (37:63)[19] in 90% yield. The mixture was subjected to esterification under Fischer–Speier conditions, and the resulting mixture (95% yield) of **15** and **19** was cyclized with $POCl_3$ to a mixture of *cis*- and *trans*-**23**. Catalytic hydrogenation of the mixture of the isomeric iminium salts **23** using hydrogen and Adams catalyst and chromatographic purification of the basic product afforded the tricyclic ester (−)-**24** in 10% overall yield (based on the trans lactam acid **20**).

Finally, reduction of the tricyclic ester (−)-**24** to the alcohol (−)-**25** was effected in 92% yield with $LiAlH_4$ in boiling ether, and debenzylation of (−)-**25** with hydrogen activated on Pd–C catalyst furnished the target molecule (−)-**1** in 99% yield. The synthetic (−)-**1** was identical with a natural sample[3,20] of ankorine.

The results of the above "cincholoipon-incorporating method" have thus defined the absolute configuration of the three asymmetric centers in the Alangium alkaloid ankorine as shown in formula **1**. Interestingly enough, ankorine has proved to be the 8-hydroxy congener of protoemetinol (dihydroprotoemetine) (**27**), which also occurs[3,4] in *Alangium lamarckii*.

Experimental Section

General Notes. All melting points were determined by using a Yamato MP-1 capillary melting point apparatus and are corrected. Unless otherwise noted, the organic solutions obtained after extraction were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Spectra reported herein were recorded on a Hitachi 323 UV spectrophotometer, a JASCO IRA-2 IR spectrophotometer, a JEOL JMS-01SG mass spectrometer, or a JEOL JNM-PS-100 NMR spectrometer at 23 °C with Me_4Si as an internal standard. Optical rotations were measured with a JASCO DIP-SL polarimeter. Microanalyses were performed by Mr. Y. Itatani and his associates at Kanazawa University.

(3*R*,4*S*)-(−)-(2-(Benzyloxy)-3,4-dimethoxyphenacyl)-3-ethyl-4-piperidineacetic Acid Ethyl Ester [(−)-9]. A mixture of ethyl cincholoiponate [(+)-3][9] (9.96 g, 50 mmol), anhydrous K_2CO_3 (6.91 g, 50 mmol), 2-(benzyloxy)-3,4-dimethoxyphenacyl bromide[14] (18.3 g, 50 mmol), and benzene (250 mL) was stirred at room temperature for 8 h and then at 50 °C for 2 h. After cooling, the reaction mixture was poured with stirring into a mixture of H_2O (200 mL) and benzene (200 mL). The benzene layer, after separation from the aqueous layer, was washed successively with 5% aqueous NaOH and H_2O, dried (K_2CO_3), and concentrated to leave a pale brown oil (22.05 g, 91%). A portion of the oil was purified by column chromatography [silica gel, benzene, benzene–EtOH (10:1, v/v)] to give (−)-**9** as a pale yellow oil: $[\alpha]^{20}_D$ −6.0° (*c* 3.00, EtOH); IR (neat) 1728 (ester C=O), 1673 (ketone C=O) cm^{-1}; NMR ($CDCl_3$) δ 0.84 (t, 3, J = 7 Hz, CCH_2CH_3), 1.24 (t, 3, J = 7 Hz, OCH_2CH_3), 3.62 and 3.72 (AB type q, 2, J = 18 Hz, NCH_2COAr), 3.90 and 3.93 (s each, 6, CH_3O's), 4.13 (q, 2, J = 7 Hz, OCH_2CH_3), 5.17 (s, 2, $PhCH_2O$), 6.74 (d, 1, J = 9 Hz, C_5' H), 7.16–7.60 (m, 6, C_6H_5 and C_6' H); mass spectrum, *m/e* 483 (M^+).

The starting ester (+)-**3** was prepared from commercially available cinchonine (**5**) in 50% overall yield according to the literature procedure[9a,15] and characterized as described previously.[17]

(3*R*,4*S*)-1-[2-(2-(Benzyloxy)-3,4-dimethoxyphenyl)-2-hydroxyethyl]-3-ethyl-4-piperidineacetic Acid Ethyl Ester (10). A solution of (−)-**9** (47.0 g, 97.2 mmol) in EtOH (400 mL) was stirred under ice cooling, and $NaBH_4$ (2.75 g, 72.7 mmol) was added portionwise. After the solution was stirred at 0–5 °C for 6 h, acetone (20 mL) was added and the mixture was concentrated in vacuo. The residue was partitioned by extraction with a mixture of H_2O and benzene. The benzene layer was extracted with 10% aqueous HCl. The acid solution was washed with benzene, made basic with anhydrous K_2CO_3, and extracted with benzene. Drying (K_2CO_3) and concentration of the benzene extracts afforded **10** (43.5 g, 92%) as a pale yellow oil: $[\alpha]^{17}_D$ −5.0° (*c* 2.00, EtOH); IR (neat) 3440 (OH), 1730 (ester C=O) cm^{-1}; NMR ($CDCl_3$) δ 0.90 (t, 3, J = 7 Hz, CCH_2CH_3), 1.26 (t, 3, J = 7 Hz, OCH_2CH_3), 3.87 and 3.89 (s each, 6, CH_3O's), 4.13 (q, 2, J = 7 Hz, OCH_2CH_3), 4.78–5.02 [m, 1, CH(OH)Ar], 5.04 and 5.14 (AB type q, 2, J = 11 Hz, $PhCH_2O$), 6.72 (d, 1, J = 9 Hz, C_5' H), 7.10–7.50 (m, 6, C_6H_5 and C_6' H); mass spectrum, *m/e* 485 (M^+). Although the oil (**10**) showed a single spot on a thin-layer chromatography (TLC) plate, it was assumed to be a mixture of the two possible diastereomers due to the difference in configuration at the benzylic position. The crude oil was used directly in the next oxidation step without further purification.

(4*S*,5*R*)-1-[2-(2-(Benzyloxy)-3,4-dimethoxyphenyl)-2-hydroxyethyl]-5-ethyl-2-oxo-4-piperidineacetic Acid Ethyl Ester (11). A stirred mixture of **10** (14.57 g, 30 mmol), 1% aqueous AcOH (220 mL), disodium ethylenediaminetetraacetate dihydrate (27.92 g, 75 mmol), and $Hg(OAc)_2$ (23.90 g, 75 mmol) was heated under reflux for 1.5 h, depositing metallic Hg and a brown oil. After cooling, the reaction mixture was extracted with $CHCl_3$. The $CHCl_3$ extracts were washed successively with 5% aqueous HCl, H_2O, 5% aqueous NaOH, and H_2O, dried, and concentrated to leave a reddish brown oil (15.2 g) which was chromatographed on silica gel. Earlier fractions eluted with ether gave a pale yellow oil (2.80 g, 19%) presumed[16] to be a diastereomeric mixture of cis and trans 2-piperidones **12**: IR (neat) 3350 (OH), 1730 (ester C=O), 1615 (lactam C=O) cm^{-1}; IR ($CHCl_3$) 3320 (OH), 1729 (ester C=O), 1606 (lactam C=O) cm^{-1}; mass spectrum, *m/e* 499 (M^+). Later fractions eluted with ether–EtOH (95:5, v/v) furnished the 6-piperidone **11** (8.59 g, 57%) as a pale yellow oil: $[\alpha]^{16}_D$ −5.0° (*c* 1.00, EtOH); IR (neat) 3340 (OH), 1727 (ester C=O), 1620 (lactam C=O) cm^{-1}; IR ($CHCl_3$) 3326 (OH), 1726 (ester C=O), 1613 (lactam C=O) cm^{-1}; NMR ($CDCl_3$) δ 0.78 (t, 3, J = 6.5 Hz, CCH_2CH_3), 1.26 (t, 3, J = 7 Hz, OCH_2CH_3), 3.90 (s, 6, CH_3O's), 4.14 (q, 2, J = 7 Hz, OCH_2CH_3), 4.98 and 5.28 (AB type d, 2, J = 11 Hz, $PhCH_2O$), 4.90–5.20 [m, 2, CH(OH)Ar], 6.74

(19) The isomer ratio was estimated by means of ^{13}C NMR spectroscopy in a manner similar to that employed for model compounds.[16-18] The rate of isomerization was so slow that the two isomers did not equilibrate in at least 100 min.

(20) We are grateful to Professor A. R. Battersby and Dr. R. S. Kapil (Cambridge, U.K.) for the generous gift of this alkaloid.

(d, 1, J = 9 Hz, C_5' H), 7.20–7.60 (m, 6, C_6H_5 and C_6' H); mass spectrum, m/e 499 (M^+).

(4*S*,5*R*)-(−)-1-(2-(2-Hydroxy-3,4-dimethoxyphenyl)-ethyl)-5-ethyl-2-oxo-4-piperidineacetic Acid Ethyl Ester [(−)-13]. A solution of 11 (21.0 g, 42 mmol) in EtOH (220 mL) containing 70% perchloric acid (4.2 mL) was hydrogenated over 10% Pd–C (3.4 g) at atmospheric pressure and 26 °C for 3 h. The catalyst was removed by filtration and the filtrate was concentrated in vacuo. The residue was partitioned between $CHCl_3$ and H_2O. The $CHCl_3$ extracts were washed successively with H_2O, saturated aqueous $NaHCO_3$, and H_2O, dried, and concentrated to leave (−)-**13** (16.25 g, 98%) as a slightly brown oil: $[\alpha]^{17}_D$ −10.5° (c 1.50, EtOH); IR ($CHCl_3$) 3525 (OH), 1725 (ester C=O), 1623 (lactam C=O) cm^{-1}; NMR ($CDCl_3$) δ 0.89 (t, 3, J = 6.5 Hz, CCH_2CH_3), 1.27 (t, 3, J = 7 Hz, OCH_2CH_3), 3.85 and 3.91 (s each, 6, CH_3O's), 4.15 (q, 2, J = 7 Hz, OCH_2CH_3), 6.44 (d, 1, J = 9 Hz, C_5' H), 6.53 (br s, 1, OH), 6.84 (d, 1, J = 9 Hz, C_6' H); mass spectrum, m/e 393 (M^+).

(4*S*,5*R*)-(−)-1-(2-(2-Hydroxy-3,4-dimethoxyphenyl)-ethyl)-5-ethyl-2-oxo-4-piperidineacetic Acid [(−)-14]. A solution of (−)-**13** (16.1 g, 41 mmol) and 2 M aqueous NaOH (50 mL) in EtOH (100 mL) was kept at room temperature for 24 h. The mixture was evaporated in vacuo and H_2O (100 mL) was added to the residue. After being washed with benzene, the aqueous solution was made acidic (pH 1) with aqueous HCl and extracted with benzene. The benzene extracts were washed with H_2O, dried, and concentrated to leave (−)-**14** (14.4 g, 96%) as a brown glass: $[\alpha]^{14}_D$ −8.0° (c 1.00, EtOH); IR ($CHCl_3$) 3544 (OH), 1710 (carboxyl C=O), 1600 (lactam C=O) cm^{-1}; NMR ($CDCl_3$) δ 0.86 (t, 3, J = 7 Hz, CH_2CH_3), 3.84 and 3.89 (s each, 6, CH_3O's), 6.41 (d, 1, J = 8.5 Hz, C_5' H), 6.82 (d, 1, J = 8.5 Hz, C_6' H); mass spectrum, m/e 365 (M^+).

(4*S*,5*R*)-(−)-1-(2-(2-(Benzyloxy)-3,4-dimethoxyphenyl)-ethyl)-5-ethyl-2-oxo-4-piperidineacetic Acid [(−)-16]. A stirred mixture of (−)-**13** (5.51 g, 14 mmol) and benzyl bromide (3.59 g, 21 mmol) in acetone (50 mL) containing anhydrous K_2CO_3 (2.90 g, 21 mmol) was heated at reflux for 15 h. The solvent was removed by vacuum distillation and the residue (**15**) was dissolved in a mixture of EtOH (100 mL) and 1 M aqueous NaOH (50 mL). After being kept at 40 °C for 10 h, the ethanolic solution was concentrated in vacuo. The resulting residual oil was partitioned between H_2O (100 mL) and benzene (250 mL). The aqueous extracts were made acidic (pH 1) with 20% aqueous HCl and extracted with benzene. The combined benzene extracts were washed with H_2O, dried, and concentrated to leave (−)-**16** (6.34 g, 99%) as a slightly brown solid, mp 70–75 °C. Recrystallization of the solid from AcOEt–hexane (1:1, v/v) provided an analytical sample as colorless prisms: mp 77–78 °C; $[\alpha]^{25}_D$ −0.4° (c 2.00, EtOH); IR ($CHCl_3$) 1710 (carboxyl C=O), 1597 (lactam C=O) cm^{-1}; NMR ($CDCl_3$) δ 0.83 (t, 3, J = 6.5 Hz, CH_2CH_3), 3.88 and 3.92 (s each, 6, CH_3O's), 5.12 (s, 2, $PhCH_2O$), 6.67 (d, 1, J = 8.5 Hz, C_5' H), 6.93 (d, 1, J = 8.5 Hz, C_6' H), 7.24–7.60 (m, 5, C_6H_5), 11.06 (s, 1, CO_2H); mass spectrum, m/e 455 (M^+). Anal. Calcd for $C_{26}H_{33}NO_6$: C, 68.55; H, 7.30; N, 3.07. Found: C, 68.36; H, 7.41; N, 3.02.

(4*R*,5*R*)-(+)-1-(2-(2-Hydroxy-3,4-dimethoxyphenyl)-ethyl)-5-ethyl-2-oxo-4-piperidineacetic Acid [(+)-18]. The cis lactam acid (−)-**14** (6.80 g, 18.6 mmol) was placed in a small flask and heated neat in an oil bath kept at 180 °C for 90 min. After cooling, the oily reaction mixture was triturated with AcOEt (25 mL), and the insoluble solid [(+)-**18**] (3.77 g) was collected by filtration. The filtrate was evaporated in vacuo, and the residue was again heated at 180 °C for 90 min, yielding a second crop (1.54 g) of (+)-**18**. Recrystallization of the total amount of the crude solid (mp 146–149 °C) from AcOEt furnished (+)-**18** as slightly brown prisms (4.97 g, 73%), mp 152–154 °C. Two more recrystallizations in a similar way produced an analytical sample as colorless prisms: mp 154–155 °C; $[\alpha]^{15}_D$ +86.5° (c 1.00, EtOH); IR ($CHCl_3$) and NMR ($CDCl_3$), identical with those of (±)-**18** (see below); mass spectrum, m/e 365 (M^+). Anal. Calcd for $C_{19}H_{27}NO_6$: C, 62.45; H, 7.45; N, 3.83. Found: C, 62.55; H, 7.47; N, 3.86.

Equilibration of Cis Lactam Acid (−)-14 and Trans Lactam Acid (+)-18. Aliquots (ca. 50 mg) of (−)-**14** or (+)-**18** were separately sealed in ampules and placed in an oil bath kept at 180 ± 1 °C. At intervals the ampules were removed, cooled, and broken, and the relative amounts of (−)-**14** and (+)-**18** in the reaction mixtures were determined by ^{13}C FT NMR spectroscopy as reported previously.[16b,17] In the noise-decoupled ^{13}C NMR spectrum in $CDCl_3$, (−)-**14** showed the methyl and the methylene carbon signals of the C_5-Et group at 11.8 and 20.9 ppm (downfield from internal Me_4Si), whereas in (+)-**18** these signals appeared at 10.7 and 23.2 ppm. For the ^{13}C FT NMR spectroscopic determiantion, relative heights of the methylene carbon signals of the isomeric C_5-Et groups were utilized. The determinations were found to be accurate to ±1%. The results of the equilibration study are summarized in the text.

(±)-*trans*-1-(2-(2-Hydroxy-3,4-dimethoxyphenyl)ethyl)-5-ethyl-2-oxo-4-piperidineacetic Acid [(±)-18]. A solution of (±)-**17**[5] (315 mg, 0.8 mmol) and 1 M aqueous NaOH (2 mL) in EtOH (2 mL) was kept at room temperature for 24 h. The mixture was concentrated in vacuo and H_2O (10 mL) was added to the residue. The resulting aqueous solution was adjusted to pH 1 with 10% aqueous HCl and extracted with $CHCl_3$. The $CHCl_3$ extracts were washed with H_2O, dried, and concentrated to leave a slightly brown glass (254 mg, 87%) which was recrystallized from AcOEt to give (±)-**18** as colorless prisms: mp 156–157 °C; IR ($CHCl_3$) 3542 (OH), 1710 (carboxyl C=O), 1602 (lactam C=O) cm^{-1}; NMR ($CDCl_3$) δ 0.82 (t, 3, J = 7 Hz, CH_2CH_3), 3.86 and 3.92 (s each, 6, CH_3O's), 6.43 (d, 1, J = 8.5 Hz, C_5' H), 6.82 (d, 1, J = 8.5 Hz, C_6' H), 5.90–6.90 (br, 1, OH), 9.5–12.0 (br, 1, CO_2H); mass spectrum, m/e 365 (M^+). Anal. Calcd for $C_{19}H_{27}NO_6$: C, 62.45; H, 7.45; N, 3.83. Found: C, 62.48; H, 7.40; N, 3.79.

(4*R*,5*R*)-(+)-1-(2-(2-Hydroxy-3,4-dimethoxyphenyl)-ethyl)-5-ethyl-2-oxo-4-piperidineacetic Acid Ethyl Ester [(+)-17]. A solution of (+)-**18** (600 mg, 1.64 mmol) in 10% (w/w) ethanolic HCl (12 mL) was kept at 17–22 °C for 24 h. The mixture was evaporated in vacuo and the residue was partitioned by extraction with a mixture of $CHCl_3$ (30 mL) and H_2O (10 mL). The $CHCl_3$ extracts were washed sequentially with saturated aqueous $NaHCO_3$ and H_2O, dried, and concentrated to afford a colorless solid (622 mg, 96%), mp 85–88 °C. Recrystallization of the solid from isopropyl ether gave (+)-**17** as colorless needles: mp 88–89 °C; $[\alpha]^{16}_D$ +78.6° (c 1.00, EtOH); IR ($CHCl_3$) and NMR ($CDCl_3$), identical with those[5b] of authentic (±)-**17**.[5] Anal. Calcd for $C_{21}H_{31}NO_6$: C, 64.10; H, 7.94; N, 3.56. Found: C, 64.22; H, 7.93; N, 3.68.

(4*R*,5*R*)-(+)-1-(2-(2-(Benzyloxy)-3,4-dimethoxyphenyl)-ethyl)-5-ethyl-2-oxo-4-piperidineacetic Acid Ethyl Ester [(+)-19]. A stirred mixture of (+)-**17** (3.54 g, 9 mmol), benzyl bromide (1.85 g, 10.8 mmol), anhydrous K_2CO_3 (1.49 g, 10.8 mmol), and acetone (36 mL) was heated at reflux for 20 h. The solvent was removed by vacuum distillation, and the residue was partitioned by extraction with a mixture of benzene (80 mL) and H_2O (30 mL). The benzene extracts were washed successively with 5% aqueous NaOH and H_2O, dried, and concentrated to leave a brown oil which was dissolved in benzene (30 mL) containing pyridine (800 mg). The resulting solution was kept at 16–20 °C for 16 h, diluted with benzene (30 mL), washed sequentially with 5% aqueous HCl, H_2O, saturated aqueous $NaHCO_3$, and H_2O, dried, and evaporated to yield (+)-**19** (4.17 g, 96%) as a faint brown oil: $[\alpha]^{16}_D$ +53.3° (c 1.00, EtOH); IR (neat), NMR ($CDCl_3$), and TLC behavior identical with that[5b] of authentic (±)-**19**.[5]

(2*R*,3*R*,11b*S*)-(−)-8-(Benzyloxy)-3-ethyl-1,3,4,6,7,11b-hexahydro-9,10-dimethoxy-2*H*-benzo[*a*]quinolizine-2-acetic Acid Ethyl Ester [(−)-24]. A solution of (+)-**19** (3.97 g, 8.21 mmol) and $POCl_3$ (6.30 g, 41.1 mmol) in toluene (40 mL) was heated at reflux for 2 h. After the solution was cooled, the solvent and $POCl_3$ were removed by vacuum distillation, and the residue was partitioned by extraction with a mixture of $CHCl_3$ (50 mL) and H_2O (15 mL). The $CHCl_3$ extracts were washed with H_2O, dried, and evaporated to leave crude *trans*-**23** (4.16 g) as a brown thick oil. The oil was dissolved in EtOH (35 mL), and the solution was hydrogenated over Adams catalyst (150 mg) at atmospheric pressure and 20 °C for 20 min. The catalyst was filtered off and the filtrate was concentrated in vacuo to leave an oil to which cold 5% aqueous NaOH was added. The mixture was then extracted with benzene, and the benzene extracts were washed with H_2O, dried (K_2CO_3) for 2.5 h, and evaporated to leave a reddish orange oil (3.77 g). The oil was purified, without delay, by column chromatography [Al_2O_3, AcOEt–hexane (1:2, v/v)] to afford (−)-**24** [2.11 g, 55% overall yield from (+)-**19**] as an unstable, yellow oil: $[\alpha]^{16}_D$ −16.0° (c 1.60, EtOH); IR (neat or $CHCl_3$), NMR ($CDCl_3$),

and TLC behavior identical with that[5b] of authentic (±)-24;[5] mass spectrum, m/e 467 (M^+).

Epimerization of the Cis Lactam Acid (-)-16 to the Trans Isomer 20. (-)-16 (4.56 g, 10 mmol) was heated neat at 180 °C for 80 min to give a brown solid. Recrystallization of the solid from AcOEt–hexane (1:1, v/v) produced almost colorless prisms (4.10 g, 90%), mp 118–119 °C, presumed to be a 37:63 mixture[19] of (-)-16 and 20.[21] A portion (3.00 g, 6.59 mmol) of the mixture was esterified [10% (w/w) ethanolic HCl (60 mL), 17 °C, 12 h] as described above for (+)-17, giving a mixture of 15 and 19 as a pale yellow oil (3.01 g, 95%): IR (neat) 1730 (ester C=O), 1643 (lactam C=O) cm^{-1}. The oil (2.98 g, 6.16 mmol) was subjected to the Bischler–Napieralski cyclization [$POCl_3$ (5.35 g, 34.9 mmol), boiling benzene (30 mL), 2.5 h] followed by catalytic hydrogenation [Adams catalyst (200 mg), EtOH (20 mL), atmospheric pressure, 20 °C, 150 min] as described above for (-)-24, and the basic product obtained was chromatographed [silica gel, AcOEt–hexane (1:2, v/v)] to afford (-)-24 (170 mg, 10% overall yield based on 20) as a yellow oil which was identical (by comparison of TLC behavior and IR and NMR spectra) with authentic (-)-24.

(2*R*,3*R*,11b*S*)-(-)-8-(Benzyloxy)-3-ethyl-1,3,4,6,7,11b-hexahydro-9,10-dimethoxy-2*H*-benzo[*a*]quinolizine-2-ethanol [(-)-25]. To a stirred, ice-cooled suspension of $LiAlH_4$ (140 mg, 3.7 mmol) in dry ether (10 mL) was added dropwise a solution of (-)-24 (865 mg, 1.85 mmol) in dry ether (10 mL) over a period of 15 min. After the mixture had been heated under reflux for 4 h, H_2O (0.15 mL), 10% aqueous NaOH (0.2 mL), and H_2O were sequentially added under ice cooling. The supernatant ethereal solution was separated from the resulting insoluble inorganic materials by decantation, dried (K_2CO_3), and concentrated in vacuo to give (-)-25 (725 mg, 92%) as an unstable, pale yellow oil: $[\alpha]^{20}_D$ -33.4° (*c* 1.00, EtOH); IR ($CHCl_3$) and NMR ($CDCl_3$) spectra superimposable with those[5b] of authentic (±)-25.[5]

(2*R*,3*R*,11b*S*)-(-)-3-Ethyl-1,3,4,6,7,11b-hexahydro-8-hydroxy-9,10-dimethoxy-2*H*-benzo[*a*]quinolizine-2-ethanol (Ankorine) [(-)-1]. A solution of (-)-25 (660 mg, 1.55 mmol) in EtOH (25 mL) was hydrogenated over 10% Pd–C (300 mg) at ordinary pressure and 20 °C for 60 min. Removal of the catalyst by filtration and concentration of the filtrate under reduced pressure furnished (-)-1 (515 mg, 99%) as a colorless solid, mp 173–177 °C. Recrystallization of the solid from acetone yielded an analytical sample as colorless prisms: mp 176–177 °C; $[\alpha]^{16}_D$ -58 ± 1° (*c* 0.23, $CHCl_3$); UV max (99% EtOH) 273 nm (log ε 2.98); UV max (0.1 M aqueous NaOH) 287 (3.37); IR ($CHCl_3$) 3630, 3530 (OH), 2800, 2750 (*trans*-quinolizidine ring)[22] cm^{-1}; NMR ($CDCl_3$) δ 0.91 (t, 3, *J* = 6.5 Hz, CH_2CH_3), 3.84 and 3.87 (s each, 6, CH_3O's), 5.90 (br, OH's), 6.33 (s, 1, C_{11} H); mass spectrum, m/e (relative intensity) 335 (M^+) (75), 334 (100), 320 (32), 318 (43), 306 (10), 304 (8), 290 (17), 278 (15), 262 (67), 248 (10), 221 (54), 207 (54). Anal. Calcd for $C_{19}H_{29}NO_4$: C, 68.03; H, 8.71; N, 4.18. Found: C, 68.24; H, 8.56; N, 4.19. This sample was identical [by mixture melting point test (mmp 175–177 °C) and comparison of UV, IR ($CHCl_3$ or KBr), NMR, and mass spectra, TLC behavior, and specific rotation] with a natural sample of ankorine [mp 175–177 °C; $[\alpha]^{16}_D$ -54 ± 2° (*c* 0.18, $CHCl_3$)].[3,20]

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Registry No. (-)-1, 13849-54-2; (+)-3, 56246-53-8; 5, 118-10-5; (-)-9, 57103-62-5; 10, isomer 1, 73090-15-0; 10, isomer 2, 73090-16-1; 11, isomer 1, 73090-17-2; 11, isomer 2, 73090-18-3; 12, isomer 1, 73090-19-4; 12, isomer 2, 73090-20-7; 12, isomer 3, 73090-21-8; 12, isomer 4, 73090-22-9; (-)-13, 57130-36-6; (-)-14, 65929-06-8; (-)-16, 57103-66-9; (±)-17, 56774-69-7; (+)-17, 65942-29-2; (±)-18, 73173-72-5; (+)-18, 65929-07-9; (+)-19, 57130-38-8; 20, 57103-67-0; *trans*-23, 73136-35-3; (-)-24, 57130-35-5; (-)-25, 73136-36-4.

(21) Further recrystallizations from AcOEt or MeCN did not improve the isomeric purity of this mixture.

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Carbohydrate Models of α-Methylene-γ-butyrolactones[1]

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The α-methylene-γ-butyrolactone moiety is a characteristic component of a large class of sesquiterpenes many of which possess marked cytotoxic, antitumor, and other biological activities. The activity of these lactones apparently derives from their chemical affinity for the thiol groups of sulfhydryl enzymes. Although the enone component is essential for biological activity, there are additional factors which may enhance these properties. These enhancement factors include the presence of hydroxyl groups in stereochemically strategic positions and the presence of various conjugated ester side chains. The built-in functionality of carbohydrates was utilized for the synthesis of such analogues. The target molecule was 2-deoxy-2-*C*-methylene-D-*threo*-pentono-1,4-lactone (2), the D-xylose analogue of α-methylene-γ-butyrolactone. Synthesis of 2 commenced with the protection of D-xylose at the 1, 3, and 5 positions to give methyl 3,5-*O*-isopropylidene-α-D-xylofuranoside (3). Compound 3 was oxidized with RuO_4 to the 2-keto sugar which was condensed with $NaCH_2NO_2$. Treatment of the resulting nitro alcohols with Ac_2O in Me_2SO followed by quantitative reduction with $NaBH_4$ gave the protected 2-deoxy-2-*C*-nitromethyl derivative of D-xylose. Removal of the protecting groups followed by oxidation with bromine in water–acetic acid and then treatment with $BaCO_3$ gave the target molecule 2 as evidenced by IR, ^1H NMR, and ^{13}C NMR data. The reaction of 2 was carried out with the model sulfhydryl compounds cysteine and glutathione. In each case the reaction was complete in less the 15 min and gave crystalline adducts quantitatively. In addition, these sulfhydryl compounds added stereospecifically, as evidenced by ^{13}C NMR data.

The potent cytotoxic action of many sesquiterpene plant products and their ability to inactivate certain selected enzymes have been attributed to the presence of the α-methylene-γ-butyrolactone moiety.[2-5] The activity of these compounds apparently derives from the extreme ease

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