Synthesis of α,β-Cycloeudesmol

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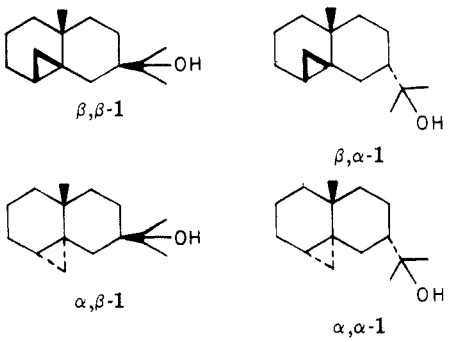
The tricyclic alcohol, α,β-cycloeudesmol (α,β-1) has been prepared in eight steps (36% overall yield) from octalone 3. The final product is not identical with natural cycloeudesmol or the previously synthesized β,β-1 and β,α-1. Natural cycloeudesmol must therefore possess the α,α-1 structure, or the original structural assignment must be revised.

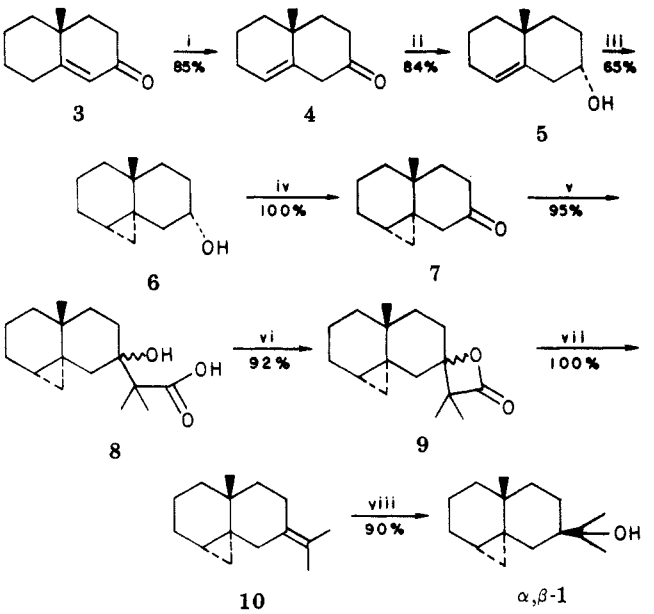
Cycloeudesmol, an antibiotic cyclopropane-containing sesquiterpene alcohol, was isolated from the marine alga *Chondria oppositiclada* Dawson by Fenical and Sims.[1] Acid-catalyzed conversion to (+)-δ-selinene, together with analytical and spectral data, led to formulation of the natural product as one of the four diastereomers of "cycloeudesmol" (1).[1] The depicted absolute stereochemistry about the methyl-substituted quaternary carbon was fixed in analogy to the known stereochemistry of (+)-δ-selinene, but the available data did not permit stereochemical assignments of the cyclopropyl and 2-hydroxypropyl substituents.



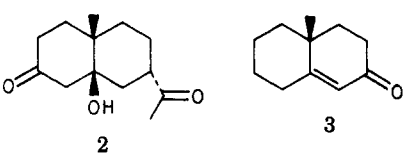
Three laboratories have recently reported stereospecific syntheses of various cycloeudesmol isomers, aiming toward the complete structural elucidation of the natural product. We contributed syntheses of β,β-1 and β,α-1, including an interconversion sequence for β,α-1 → β,β-1.[2] Caine et al. published an independent synthesis of β,β-1,[3] whereas Ando et al. presented syntheses of β,β-1, β,α-1, and α,β-1.[4] All reports are in general agreement concerning the properties of synthetic β,β-1 and β,α-1, and all agree that neither of these materials corresponds to natural cycloeudesmol.[2-4]

Alone, of the three synthesized cycloeudesmol isomers, α,β-1 has been prepared only once,[4] by a sequence of reactions which has no connection to the other diastereomers of structure 1. The important implication of the Ando α,β-1 synthetic work[4] is that natural cycloeudesmol must either have the α,α-1 structure or the original assignment is incorrect. We felt, therefore, that an independent synthesis of α,β-1 was required, together with evidence supporting the assigned stereochemistry. Ando's synthesis began with trifunctional compound 2, preparable in two steps from dihydrocarvone,[5] and proceeded to α,β-1 in ten steps and 5.3% overall yield. We now report a slightly shorter (eight steps), considerably higher yield (36% overall) synthesis which begins with readily available[6] octalone 3.

Scheme I[a]



[a] i, *t*-BuOK/*t*-BuOH, ~15 °C, 30 min, then 10% aqueous HOAc; ii, K-Selectride, THF, -77 °C, then 25 °C, 12 h, followed by 2 N NaOH and 30% H_2O_2, 0 °C; iii, CH_2I_2, Zn-Cu, Et_2O, reflux 10 h; iv, CrO_3, aqueous H_2SO_4, acetone, 0-25 °C, 15 min; v, excess *i*-Pr_2NLi, $(CH_3)_2$-CHCOOH, THF, 25 °C, 12 h; vi, $C_6H_5SO_2Cl$, pyridine, 25 °C, 12 h; vii, 130-133 °C, 40 min; viii, $Hg(OAc)_2$, aqueous THF, 0-25 °C, 2 h, then NaOH, $NaBH_4$.



Results and Discussion

Our preparation of α,β-1 is outlined in Scheme I. Enone 3[6] was deconjugated to octalone 4,[7] which was stereoselectively reduced to α-homoallylic alcohol 5, using potassium tri-*sec*-butylborohydride (K-Selectride).[8] About 5% of the epimeric (β) alcohol was also formed (NMR) but was removed by recrystallization. The stereochemical assignment of 5 rests upon its NMR spectrum, which revealed

(1) Fenical, W.; Sims, J. J. *Tetrahedron Lett.* **1974**, 1137.
(2) Moss, R. A.; Chen, E. Y.; Banger, J.; Matsuo, M. *Tetrahedron Lett.* **1978**, 4635.
(3) Caine, D.; Chen, P-C.; Frobese, A. S.; Gupton, J., III *J. Org. Chem.* **1979**, *44*, 4981.
(4) Ando, M.; Sayama, S.; Takase, K. *Chem. Lett.* **1979**, 191.
(5) Humber, D. C.; Pinder, A. R.; Williams, R. A. *J. Org. Chem.* **1967**, *32*, 2335.
(6) Marshall, J. A.; Fanta, W. I. *J. Org. Chem.* **1964**, *29*, 2501. Heathcock, C. H.; Ellis, J. E. *Tetrahedron Lett.* **1962**, 669.
(7) Ringold, H. J.; Malhotra, S. K. *Tetrahedron Lett.* **1962**, 669.
(8) Brown, C. A. *J. Am. Chem. Soc.* **1973**, *95*, 4100. Brown, H. C.; Krishnamurthy, S. *J. Am. Chem. Soc.* **1972**, *94*, 7159.

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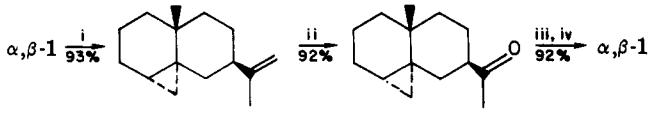
Scheme II[a]



11 12

[a] i, p-$CH_3C_6H_4SO_2NCO$, toluene, reflux 14 h; ii, O_3/CH_2Cl_2-CH_3OH, −77 °C, then Me_2S; iii, CH_3ONa/CH_3OH, 25 °C, 24 h; iv, CH_3MgI, Et_2O, 25 °C, 2 h.

the β (equatorial) methine proton as a broad singlet (δ 4.02), reflecting only axial–equatorial and equatorial–equatorial coupling to the adjacent methylene protons. The epimeric alcohol[9] displayed its α (axial) methine proton as a very broad multiplet (δ 3.83–3.20), indicative of strong axial–axial coupling to the appropriate vicinal methylene protons.[10] Note, also the anticipated[10] greater deshielding of the equatorial methine proton of **5**.

Simmons–Smith methylenation of **5** afforded α-cyclopropane **6** in 64% yield; the stereochemistry of cyclopropanation was controlled by the α-hydroxyl group.[11] The angular methyl group of **6** (δ 1.12) is indicative of the α-cyclopropyl stereochemistry. Thus, the parent α-cyclopropane (deoxy-**6**) displays its angular methyl resonance at δ 1.11,[12] and the 3α-hydroxyl substituent of **6** should not affect this chemical shift.[13,14] On the other hand, the β-cyclopropyl analogue of **6** would be expected to exhibit an angular methyl resonance at δ ~1.00, as does its deoxy parent.[12-14]

Oxidation of **6** with Jones reagent quantitatively afforded ketone **7**. Although a conventional Wittig reaction did not convert **7** to tetrasubstituted alkene **10**, this transformation could be effected in excellent overall yield by the three-step sequence **7** → **8** → **9** → **10**.[15] Thus, reaction of the α-lithiocarboxylate salt of isobutyric acid with **7** gave oily hydroxy acid **8**, which was directly converted to β-lactone **9** by using benzenesulfonyl chloride in pyridine. Lactone **9** was purified and characterized. Its sharp melting point suggested that only one stereoisomer was in hand, although the (irrelevant) stereochemistry at the lactone/quaternary carbon was not defined. Decarboxylation of **9** quantitatively afforded α-cyclopropyl olefin **10**. The overall yield for the **7** → **10** conversion was a highly satisfactory 87%.

Conversion of **10** to α,β-cycloeudesmol was achieved by oxymercuration/demercuration.[16] Treatment of alkene **10** with 1 equiv of mercuric acetate in aqueous THF, followed by reductive demercuration with excess basic $NaBH_4$ solution, afforded α,β-**1** as a yellow oil, which was readily purified by chromatography over silica gel.

Analytically pure α,β-**1** [mp 74–74.5 °C, after sublimation at 30 °C (0.06 torr)] had IR (melt) 3.0 μm (OH) and NMR ($CHCl_3$, CCl_4) δ −0.10–0.80 (m, 3 H, cyclopropyl), 1.10 (s, 3 H, angular CH_3), 1.15 (s, 6 H, $HOC(CH_3)_2$), and other resonances extending from δ 1.15–2.17. The NMR spectrum was quite similar to that reported for α,β-**1**[4,17] and clearly different from the NMR spectra of natural cycloeudesmol,[1,18] β,β-**1**,[2] or β,α-**1**.[2]

To substantiate the regio- and stereochemistry assigned to α,β-**1**, this material was subjected to the cycle of reactions outlined in Scheme II. Dehydration of α,β-**1** with p-toluenesulfonyl isocyanate afforded α,β-cycloeudesmene, **11**,[19] which was ozonized to ketone **12**. The ketone was completely characterized and then stirred with methoxide/methanol for 1 day at 25 °C. Were the methyl ketone moiety of **12** α (axial), this exposure to base would almost certainly have epimerized it to the more stable equatorial (β) configuration; a similar procedure quantitatively epimerized the analogous β-cyclopropyl-α-acetyl compound to its β,β-epimer.[2] However, ketone **12** was recovered unchanged after attempted basic isomerization. Moreover, reaction of recovered **12** with methyl Grignard reagent returned α,β-**1** in high yield, identical (IR, NMR, TLC) with the initial sample of α,β-**1**.

These results strongly support the regiochemistry and stereochemistry assigned to the hydroxyisopropyl moiety of α,β-**1** in Scheme I. Importantly, it is now clear from the totality of independent, duplicated, published data[2-4] that natural cycloeudesmol must either possess the α,α configuration or a structure other than **1**.[20]

Experimental Section[21]

10-Methyl-1(9)-octal-7-one (4).[7] A mixture of 4.0 g (24 mmol) of 10-methyl-1(9)-octal-2-one (**3**)[6] in 40 mL of *tert*-butyl alcohol was cooled to ~15 °C. Powdered potassium *tert*-butoxide (21.8 g, 194 mmol) was added in three portions, under a nitrogen atmosphere, with stirring which was continued for 30 min. The reaction was quenched by the rapid addition of 250 mL of 10% aqueous acetic acid. The resulting yellow solution was partitioned between 100 mL of ether and 100 mL of water. The aqueous layer was extracted with 30 mL of ether. The combined ether solutions were washed with two 100-mL portions of aqueous sodium bicarbonate solution and two 50-mL portions of water, dried over $MgSO_4$, and freed of solvent under aspirator vacuum to give an orange liquid (3.8 g). This was distilled at 88–90 °C (0.1 mmHg) to give octalone **4** as a slightly yellow liquid (3.4 g, 20.4 mmol,

(9) The epimer of **5** was obtained by $NaBH_4$ reduction of 3-acetoxy-10-methyl-$\Delta^{3,5(6)}$-hexalin; cf.: Vandenheuvel, W. J. A., III; Wallis, E. S. *J. Org. Chem.* **1962**, *27*, 1233.

(10) Jackman, L. M.; Sternhell, S. "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry", 2nd. ed.; Pergamon Press: New York, 1969; especially pp 238–241 and 280–289.

(11) Simmons, H. E.; Cairns, T. L.; Vladuchick, S. A.; Hoiness, C. M. *Org. React.* **1973**, *20*, 1 and references therein.

(12) Moss, R. A.; Smudin, D. J. *J. Org. Chem.* **1976**, *41*, 611. Moss, R. A.; Kleinman, R. W.; Williamson, K. L. *J. Chem. Soc. D* **1970**, 927.

(13) Bhacca, N. S.; Williams, D. H. "Applications of NMR Spectroscopy in Organic Chemistry", Holden-Day: San Francisco, 1964; pp 14f.

(14) Decalin derivatives (e.g., **6**) show steroid-like additivity of chemical shifts at the angular methyl resonance; cf.: ref 12; Williamson, K. L.; Sloan, L. R.; Howell, T.; Spencer, T. A. *J. Org. Chem.* **1966**, *31*, 436.

(15) Adam, W.; Barza, J.; Liu, J-C. *J. Am. Chem. Soc.* **1974**, *96*, 2000.

(16) Brown, H. C.; Geoghegan, P., Jr. *J. Am. Chem. Soc.* **1967**, *89*, 1522. Brown, H. C.; Hammar, W. J. *Ibid.* **1967**, *89*, 1524. Brown, H. C.; Kawakami, J. H.; Ikegami, S. *Ibid.* **1967**, *89*, 1525. For a brief mechanistic review of this reaction see: Carey, F. A.; Sundberg, R. J. "Advanced Organic Chemistry, Part B, Reactions and Synthesis"; Plenum Press: New York, 1977; pp 87–90.

(17) We thank Dr. Masayoshi Ando (Tohoku University) for copies of NMR and IR spectra. A small sample of α,β-**1**, kindly supplied by Dr. Ando, melted at 39–41 °C, considerably lower than our (sublimed) sample. TLC comparison of the two materials (silica, 1:2 ether/hexane) revealed identical chromatographic behavior.

(18) We thank Professor J. J. Sims (University of California, Riverside) for copies of NMR and IR spectra of natural cycloeudesmol and cycloeudesmene.

(19) Dehydration of natural cycloeudesmol with p-bromophenyl isocyanate afforded natural cycloeudesmene.[1] The NMR spectrum of this material[18] is quite similar to that of **11**, particularly with respect to the cyclopropyl resonances. The major difference is the presence of a two-proton broad singlet for the terminal methylene group of **11** (δ 4.67), whereas the corresponding protons of natural cycloeudesmene appear as two narrow one-proton multiplets centered at δ 4.83 and 4.67.[18]

(20) Among unsuccessful attempts to convert **10** to α,α-**1**, we cite reaction with basic H_2O_2, which gave α,β-**1** in 14% yield (55% **10** was recovered). Also, reaction of **10** with diborane in a conventional procedure produced a tertiary alcohol in 29% yield which, from its NMR spectrum, appeared to have reversed regiochemistry at C_3 (i.e., OH bonded to the ring carbon). **Note Added in Proof.** Dr. M. Ando has now synthesized α,α-**1** and found it to differ from natural "cycloeudesmol". The natural product must therefore have a noncycloeudesmol structure. Ando, M.; Sayama, S.; Takase, K. *Chem. Lett.*, in press. We thank Dr. Ando for a preprint of this work.

(21) Melting points and boiling points are uncorrected. NMR spectra were recorded on a Varian T-60 instrument, using Me_4Si or $CHCl_3$ as an internal standard and CCl_4 or $CDCl_3$ as solvent. Microanalyses were performed by Robertson Laboratory, Florham Park, NJ.

85%): IR (neat) 1700 (C=O), 1620 (C=C) cm^{-1}; NMR ($CDCl_3$) δ 1.25 (s, 3 H, angular CH_3), 1.43–3.23 (m, 12 H, ring CH_2's), 5.40 (m, 1 H, vinyl).

7α-Hydroxy-10β-methyl-1(9)-octalin (5). To a solution of K-Selectride (potassium tri-*sec*-butylborohydride, 0.5 M in THF, 24 mL, 12 mmol), cooled in a dry ice–acetone bath, was added dropwise a solution of ketone **4** (1.7 g, 10 mmol) in 10 mL of THF. The resulting orange solution was allowed to warm up and stir at room temperature overnight. To the dark brown product solution, cooled in an ice bath, was added slowly 12 mL of 2 N NaOH solution and then, dropwise, 12 mL of 30% H_2O_2. Diethyl ether workup gave a light orange oil (2.1 g) which solidified on standing and was recrystallized from an ether/hexane mixture to give **5** as colorless, transparent needles (1.0 g), mp 75.5–76.5 °C. A second crop gave slightly yellow crystals (0.4 g) to make a total yield of 1.4 g (8.4 mmol, 84%): IR (neat) 3310 (OH), 1620 (C=C) cm^{-1}; NMR ($CDCl_3$) δ 1.07 (s, 3 H, angular CH_3), 1.33–2.77 (m, 12 H, ring CH_2's), 4.02 (br s, 1 H, HCOH), 5.47 (m, 1 H, vinyl).

Anal. Calcd for $C_{11}H_{18}O$: C, 79.46; H, 10.91. Found: C, 79.70; H, 10.67.

1α,9α-Methylene-7α-hydroxy-10β-methyldecalin (6). To 3.0 g of zinc–copper couple[22] in 12 mL of anhydrous ether was added, with magnetic stirring, a crystal of iodine, followed by 4.0 g (15 mmol) of methylene iodide. The mixture was heated to reflux for 5 min, initiating an exothermic reaction. The heat source was removed and the reaction allowed to subside. Then, a solution of alcohol **5** (2.0 g, 12 mmol) in 12 mL of anhydrous ether was added over 25 min at such a rate as to maintain a gentle reflux. The resulting mixture was refluxed for an additional 10 h. The gray-purple mixture was poured into 25 mL of aqueous ammonium chloride solution and then filtered. The aqueous layer was extracted with 15 mL of ether. The combined ether solutions were washed with 25 mL of aqueous ammonium chloride solution, followed by two 30-mL portions of aqueous sodium chloride solution, dried over $MgSO_4$, and concentrated under reduced pressure.

A light yellow oil was obtained (2.8 g) which was chromatographed over 200 g of silica gel, using 7:3 hexane–ether as the eluant. Product **6** was obtained as a yellow solid (1.4 g, 7.8 mmol, 65%). An analytical sample was prepared by recrystallization from ether–hexane, which gave colorless needles: mp 81.5–82 °C; NMR ($CDCl_3$) δ 0.25–0.97 (m, 3 H, cyclopropyl), 1.10 (s, 3 H, angular CH_3), 1.10–2.43 (m, 12 H, ring CH_2's), 4.03 (m, 1 H, HCOH).

Anal. Calcd for $C_{12}H_{20}O$: C, 79.94; H, 11.18. Found: C, 79.98; H, 11.12.

1α,9α-Methylene-10β-methyloctal-7-one (7). To a solution of cyclopropyl alcohol **6** (0.20 g, 1.1 mmol) in 6 mL of acetone, cooled in an ice bath, was added dropwise a solution of Jones reagent (2.0 mL, 2.0 mmol) prepared by dissolving chromium trioxide (10.0 g, 100 mmol) in 10 mL of concentrated sulfuric acid and diluting with water to 100 mL. A black-green precipitate was formed during the addition. The resulting dark orange mixture was allowed to warm to room temperature and was stirred for 15 min. It was concentrated under aspirator vacuum to half of its original volume and was then partitioned between 20 mL each of ether and water. The combined ether solution was washed twice with 30-mL portions of saturated aqueous sodium chloride solution, dried over $MgSO_4$, and freed of solvent under reduced pressure to afford **7** as an orange oil (0.2 g, 1.1 mmol, 100%), which solidified on standing at room temperature.

An analytical sample was prepared by recrystallization from ether–hexane, giving colorless transparent prisms: mp 49–50 °C; IR (neat) 1700 (C=O) cm^{-1}; NMR ($CDCl_3$) δ 0.10–0.50 (m, 2 H, cyclopropyl CH_2), 0.60–0.90 (m, 1 H, cyclopropyl), 1.31 (s, 3 H, angular CH_3), 1.10–3.10 (m, 12 H, ring CH_2's).

Anal. Calcd for $C_{12}H_{18}O$: C, 80.83; H, 10.18. Found: C, 80.84; H, 10.12.

1α,9α-Methylene-7-(2-propylidene)-10β-methyldecalin (10).
(a) Hydroxy Acid 8. To a solution of diisopropylamine (4.5 g, 45 mmol) in 60 mL of tetrahydrofuran (THF), cooled in an ice bath and maintained under a nitrogen atmosphere, was added slowly by syringe 19.5 mL of a 2.3 M hexane solution of *n*-butyllithium (45 mmol). The resulting yellow solution was stirred for 15 min and then isobutyric acid (2.0 g, 23 mmol) was added dropwise. The resulting mixture was stirred for 30 min until a homogeneous solution was obtained. A solution of cyclopropyl ketone **7** (2.7 g, 15 mmol) in 10 mL of THF was added dropwise. The light yellow solution was allowed to warm to room temperature overnight. The final dark orange solution was poured into 100 mL of ice–water. The organic layer was separated and concentrated to near dryness. The residue was combined with reserved aqueous layer and the whole was extracted with three 50-mL portions of ether. The combined ether solutions were washed with two 50-mL portions of saturated aqueous sodium chloride solution, dried over $MgSO_4$, and freed of solvent to give **8** as a tan oil (3.8 g, 14.3 mmol, 95%), which was converted to lactone **9** without purification.

(b) Lactone 9. To a solution of carboxylic acid **8** (360 mg, 1.3 mmol) in 5 mL of pyridine cooled in an ice bath was slowly added a solution of benzenesulfonyl chloride (650 mg, 3.3 mmol) in 1 mL of pyridine. The solution was stirred at room temperature overnight, followed by removal of pyridine under reduced pressure to give a light brown solid (1.2 g). The solid was dissolved in 50 mL of ether and washed with two 30-mL portions of water, dried over $MgSO_4$, and freed of solvent under reduced pressure to give **9** as light yellow crystals (0.3 g, 1.2 mmol, 92%).

An analytical sample was prepared by recrystallization from ether–hexane, affording colorless prisms: mp 129–129.5 °C; IR ($CHCl_3$), 1800 (C=O) cm^{-1}; NMR ($CDCl_3$) δ 0.30–0.87 (m, 3 H, cyclopropyl), 1.08 (s, 3 H, angular CH_3), 1.26 and 1.28 (2 s, 6 H, CH_3's), 1.08–2.43 (m, 12 H, ring CH_2's).

Anal. Calcd for $C_{16}H_{24}O_2$: C, 77.36; H, 9.75. Found: C, 77.23; H, 9.56.

(c) Alkene 10. A sample of β-lactone **9** (230 mg, 0.93 mmol) was heated at 130–133 °C for 40 min, until the cessation of carbon dioxide evolution. The resulting yellow oil (190 mg, 0.93 mmol, 100%) solidified on cooling and was recrystallized from an ethyl acetate/methanol mixture to give colorless needles of **10**, mp 30.5–31 °C.

The hydrocarbon product exhibited the following NMR spectrum ($CDCl_3$): δ 0.13–0.90 (m, 3 H, cyclopropyl), 1.20 (s, 3 H, angular CH_3), 1.60 and 1.70 (2 s, 6 H, allylic CH_3's), 0.90–2.87 (m, 12 H, ring CH_2's).

Anal. Calcd for $C_{15}H_{24}$: C, 88.15; H, 11.85. Found: C, 87.88; H, 11.93.

α,β-Cycloeudesmol (α,β-1). To a sample of powdered mercury(II) acetate (191 mg, 0.6 mmol) was added 0.6 mL of water. This was stirred until a clear solution was obtained. To the cooled solution (ice bath) was added slowly 0.4 mL of THF, which yielded a yellow solution after brief warming on a steam bath. To this solution, cooled in an ice bath, was added slowly a solution of olefin **10** (100 mg, 0.49 mmol) in 0.4 mL of THF. The resulting yellow mixture was allowed to warm to room temperature and stirred for 2 h. To the then colorless mixture was added 0.5 mL of 3 N soldium hydroxide solution, followed by a solution of 0.2 g of sodium borohydride in 1 mL of 3 N sodium hydroxide solution. The aqueous layer was extracted with 5 mL of ether. The combined organic solutions were dried over $MgSO_4$ and freed of solvent to give a light yellow syrup (110 mg) which was chromatographed over silica gel (35 g), using 1:3 ether/hexane as the eluant. The fractions with R_f 0.32 were collected to give a colorless solid (98 mg, 0.44 mmol, 90%) which was identified as α,β-cycloeudesmol. Properties of this material are described above.

Anal. Calcd for $C_{15}H_{26}O$: C, 81.00; H, 11.79. Found: C, 81.28; H, 11.90.

1α,9α-Methylene-7β-isopropenyl-10β-methyldecalin (11). To a solution of *p*-toluenesulfonyl isocyanate (0.45 g, 2.2 mmol) in 2 mL of toluene, cooled in an ice bath, was added dropwise by means of a syringe a solution of α,β-cycloeudesmol (0.48 g, 2.2 mmol) in 2 mL of toluene. The resulting colorless solution was then refluxed for 14 h. Most of the solvent was removed under reduced pressure. The residue was diluted with 30 mL of hexane and filtered. The hexane filtrate was concentrated to give an oil which was purified by bulb-to-bulb distillation at 85–90 °C (0.1 mmHg) to give a colorless oil (0.40 g, 1.95 mmol, 93%). The oil was identified as olefin **11**.

Spectral properties included the following: IR (neat) 1640 (C=C) cm^{-1}; NMR ($CDCl_3$) δ 0.00–0.77 (m, 3 H, cyclopropyl), 1.12

(22) Shank, R. S.; Shechter, H. *J. Org. Chem.* **1959**, *24*, 1825.

(s, 3 H, angular CH_3), 1.72 (s, 3 H, allylic CH_3), 4.67 (s, 2 H, C=CH_2), 0.76–2.30 (m, 13 H, ring protons).

In one case the intermediate *N*-tosylurethane was isolated by cooling and filtering the reaction mixture as soon as the addition of tosyl isocyanate had been completed. The solid was recrystallized from ether and melted at 132–133 °C.

1α,9α-Methylene-7β-acetyl-10β-methyldecalin (12). A sample of olefin **11** (1.0 g, 4.9 mmol) in 38 mL of methylene chloride and 9 mL of methanol was cooled in a dry ice–acetone bath and ozonized until a light blue solution was obtained. The excess ozone was flushed with a slow stream of nitrogen gas. Dimethyl sulfide (3 mL) was added dropwise to the colorless solution. The reaction solution was allowed to warm and stirred at room temperature overnight. Then it was washed with water (2 × 50 mL) and dried over $MgSO_4$, and the solvent was removed under reduced pressure. The residue was passed through a short column (60 g of SiO_2), using 1:2 methylene chloride/hexane as the eluant, to afford **12** as a colorless liquid (0.93 g, 4.5 mmol, 92%), bp 90 °C (0.1 mmHg). The structure was assigned on the basis of spectral properties: IR (neat) 1700 (C=O) cm^{-1}; NMR ($CDCl_3$) δ 0.00–0.90 (m, 3 H, cyclopropyl) 1.10 (s, 3 H, angular CH_3), 2.10 (s, 3 H, $COCH_3$), 0.90–3.00 (m, 13 H, ring protons).

Anal. Calcd for $C_{14}H_{22}O$: C, 81.48; H, 10.76. Found: C, 81.79; H, 10.66.

α,β-Cycloeudesmol (α,β-1) from Ketone 12. To a solution of methylmagnesium iodide, prepared by dissolving magnesium turnings (24 mg, 1.0 mmol) in methyl iodide (150 mg, 1.0 mmol) and 4 mL of anhydrous ether, was added dropwise, under a nitrogen atmosphere, a solution of ketone **12** (100 mg, 0.49 mmol) in 2 mL of anhydrous ether. The resulting white mixture was allowed to stir at room temperature for 2 h and then was partitioned between 6 mL of dilute aqueous hydrochloric acid and 10 mL of ether. The ether layer was washed with two 10-mL portions of water and dried over $MgSO_4$ to give, after removal of solvent under reduced pressure, a slightly yellow oil (100 mg, 0.45 mmol, 92%). This was identified as α,β-cycloeudesmol (α,β-1) on the basis of IR and NMR spectral comparisons with the material prepared according to Scheme I.

Acknowledgment. We thank the National Science Foundation for support of this research. E.Y.C. is grateful to Hoffmann-LaRoche, Inc., for financial support.

Registry No. α,β-1, 76548-19-1; α,β-1 *N*-tosylurethane, 76480-40-5; **3**, 63975-59-7; **4**, 76480-41-6; **5**, 76548-20-4; **6**, 76480-42-7; **7**, 76548-21-5; **8**, 76480-43-8; **9**, 76480-44-9; **10**, 76480-45-0; **11**, 53767-96-7; **12**, 76548-22-6.

Antileukemic Alkaloids from *Taxus wallichiana* Zucc.

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A new antileukemic taxane alkaloid, cephalomannine (**1a**), has been isolated from leaves, stems, and roots of *Taxus wallichiana* Zucc. Cephalomannine is closely related to taxol (**1b**), a previously characterized antileukemic alkaloid, which also occurs in *T. wallichiana* but in lesser amounts than cephalomannine. The new alkaloid and its hydrolysis products were characterized by nuclear magnetic resonance, mass spectroscopy, and X-ray crystallography; taxol and two cytotoxic taxane congeners were also identified.

During a search for antitumor agents from plants, we encountered KB and PS activity[2] in extracts of a coniferous tree collected in the Shillong Forest of India and shipped to us under the name *Cephalotaxus mannii*. Our putative *C. mannii* contains none of the alkaloids characteristic of other *Cephalotaxus* sp.,[3] and its antitumor properties are associated with alkaloids of the taxane series; the plant now is considered to be *Taxus wallichiana* Zucc.[4] This paper describes the isolation and characterization of a new antitumor alkaloid, cephalomannine, and the identification of some other taxanes. A portion of this work has been published previously in preliminary form.[5]

The ethanolic extract of the ground plant material was processed in a solvent-partitioning scheme (Figure 1). KB activity was found to reside exclusively in material from the chloroform phase (F188) after chloroform–water partitioning, and this fraction was subjected to column chromatography on silica gel. This procedure afforded a series of fractions (F191–F196), most of which were KB active. We noted that analytical thin-layer chromatography (TLC) of F193 revealed a component that had an R_f similar to that of taxol,[6,7] and this observation led to the

(1) The mention of firm names or trade products does not imply that they are endorsed or recommended by the U.S. Department of Agriculture over other firms or similar products not mentioned.

(2) Cytotoxic and antileukemic activities were assayed under the auspices of the National Cancer Institute by the procedures described by: Geran, R. I.; Greenburg, N. H.; MacDonald, M. M.; Schumacher, A. M.; Abbott, B. J. *Cancer Chemother. Rep., Part 3* **1972**, *3*(2), 1.

(3) Smith, C. R.; Powell, R. G.; Mikolajczak, K. L. *Cancer Treat. Rep.* **1976**, *60*, 1157.

(4) After examining leaves and woody portions of the plant, Dr. Richard Eyde of the Smithsonian Institute, Washington, DC, has tentatively reidentified our material as *Taxus wallichiana* Zucc.

(5) Powell, R. G.; Miller, R. W.; Smith, C. R., Jr. *J. Chem. Soc., Chem. Commun.* **1979**, 102.

(6) Wani, M. C.; Taylor, H. L.; Wall, M, E.; Coggon, P.; MacPhail, A. T. *J. Am. Chem. Soc.* **1971**, *93*, 2325.

(7) Cephalomannine (**1a**) gave typical T/C values in the range 152–180 at dose levels of 1–3.3 mg/kg against PS. Taxol (**1b**) showed T/C values of 148–152 in the dosage range 1.4–2.2 mg/kg. Both compounds showed cytotoxicity (ED_{50}) against KB cell culture at 10^{-3} μg/mL, whereas baccatin III (**1c**) had an ED_{50} of 2.0 μg/mL and 1β-hydroxybaccatin I (**2**) had an ED_{50} of 2.9 μg/mL.

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