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THE CYCLOEUDESMOLS: SYNTHESES OF THE β-CYCLOPROPYL ISOMERS

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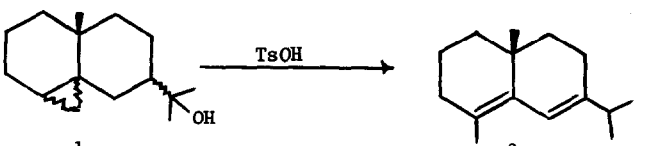
In 1974 Fenical and Sims isolated a cyclopropane-containing sesquiterpene alcohol from the marine alga Chondria oppositiclada Dawson.[1] The compound was strongly antibiotic toward S. aureus and C. albicans, and was assigned the cycloeudesmol structure, 1, on the basis of analytical and spectral data, and its acid-catalyzed transformation to (+)-δ-selinene, 2.



1 2

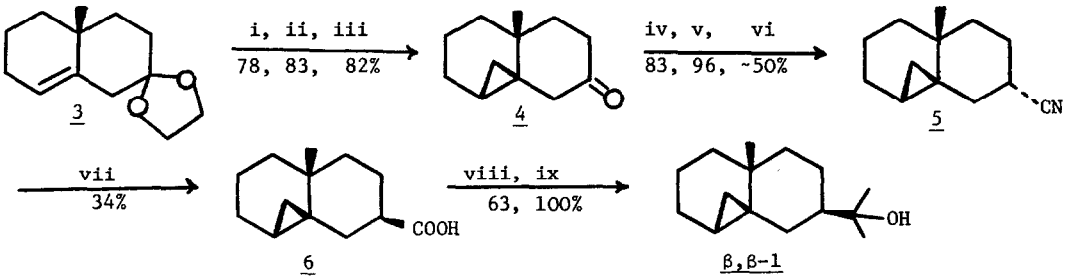
However, the relative stereochemistries of the cyclopropyl and hydroxyisopropyl moieties of 1 were not elucidated. This, together with our interest in carbene-derived relatives of 1,[2] suggested that we synthesize the diastereomers of 1. Restricting ourselves to the β-angular methyl series, the four diastereomers can be designated (cyclopropyl, hydroxyisopropyl) β,β, β,α, α,β, and α,α. In this letter, we describe syntheses of the β,β and β,α isomers.

The synthesis of β,β-1 (Scheme I[3]) crucially involved the β-addition[2a] of CCl_2 to ketal 3.[2d] This stereospecific[2a,b] addition fixed the relative stereochemistry of the cyclopropyl and angular methyl groups. Dechlorination[2a] and hydrolysis then afforded ketone 4, from which nitrile 5 was obtained by sequence iv → vi, previously employed by Marshall and Pike in their synthesis of β-eudesmol.[4,5] Stereochemistry at C_3 was not strictly controlled during this sequence, but was immaterial because of the facile epimerization[4] attending the saponification (vii) of 5, which gave the crystalline β-acid, 6. The acid was purified by sublimation (mp, 69-70°) and fully characterized. Esterification[6] of 6, followed by reaction with CH_3Li afforded β,β-cycloeudesmol, which was purified by gc (5'x0.25", 3% SF-96 on 80/100 Gaschrom R, 150°).

Analytically pure β,β-1, mp, 73 - 75°, had M^+ (weak) at m/e 222, and m/e 204 (M^+-H_2O, strong); ir (film) 2.92μ (OH); and nmr ($\delta^{CHCl_3}_{CCl_4}$) 1.05 (s, 6H, i-Pr), 0.94 (s, 3H, ang. CH_3), 0.64-0.03 (m, 3H, cyclopropyl), and other resonances extending from 2.07-0.64. The β stereochemistry at C_3 rests upon the method of synthesis of 6;[4] failure of the methyl ester of 6 to epimerize after 140 hrs exposure to excess refluxing $NaOCH_3/CH_3OH$;[4] and upon the conversion of β,α-10 to β,β-1 (see below). Synthetic β,β-1 was clearly different from natural 1, which displays its i-Pr methyls as two singlets at $\delta^{TMS}_{CCl_4}$ 1.37 and 1.27, with an angular CH_3 resonance at 1.03.[1,7]

Diastereomer β,α-1 was synthesized in two different ways. In the first approach (Scheme II[3]), octalone 7 (from dihydrocarvone and methyl vinyl ketone[8]) was reduced with $LiAlH_4$ to give 3β-alcohol, 8.[9] Directed[10] Simmons-Smith cyclopropanation (ii) then afforded the β-cyclopropanated

SCHEME I[3]



3 4 5 6 β,β-1

Reagents: i,[2a] $CHCl_3$, 50% aq. NaOH, $C_6H_5CH_2\overset{+}{N}Et_3Cl^-$, 100h; ii,[2a] Na, NH_3, THF, -78°, 5h, then NH_4Cl; iii, HCl, MeOH, refl. 3h; iv, $LiAlH_4$, Et_2O, refl. 1h; v, TsCl, C_5H_5N, 25°, 44h; vi, KCN, HMPA, 90°, 23h; vii, KOH, $HOCH_2CH_2OH$, 150°, 15.5h, then HCl; viii, CH_3I, aq. NaOH, HMPA, 25°, 20h; ix, CH_3Li,Et_2O, 0-5°, then 25°, 24h.

derivative which, without purification, was readily converted to 9 via Jones oxidation.[11] Wolff-Kishner reduction of 9 gave β,α-cycloeudesmene, 10, which was converted to β,α-cycloeudesmol by epoxidation (v) of the isopropenyl group, followed by reaction of the crude oxirane with $LiAlH_4$ (vi).[12]

Analytically pure β,α-1 (bp, 120°/0.06 mm-Hg) had M^+-18 at m/e 204; ir (film) 3.0μ (OH); and nmr ($\delta^{CHCl_3}_{CCl_4}$) 1.01 (s, 6H, i-Pr), 0.84 (s, 3H, ang. CH_3), 0.83-0.03 (m, 2H, cyclopropyl), and other resonances extending from 2.07-0.50. β,α-1 was clearly different from both β,β-1 and natural 1 (see above).

A second synthesis of β,α-1 began with 11 (Scheme III[3]), prepared by the $Me_4N^+OH^-$ catalyzed cyanoethylation of dihydrocarvone with acrylonitrile (25°, 16h).[13] Wittig olefination (i) then gave diene-nitrile 12 ($\delta^{TMS}_{CDCl_3}$ 4.87, 4.70, m, 4H, two $=CH_2$). In a conventional sequence, 12 was converted to diazoketone 13 by hydrolysis (ii, CN → COOH), reaction with oxalyl chloride (iii, COO^-K^+ → $COCl$[14]), and subsequent reaction with diazomethane (iv, $COCl$ → $COCHN_2$[14]). Catalytic decomposition of 13 (v) afforded 9 via ketocarbene cyclization.[15,16] The pure cyclopropylketone, isolated in 62% yield by chromatography on silica gel (n-$C_6H_{14}/CHCl_3$, 1:3), was identical by ir and nmr to 9 obtained via Scheme II, and was subsequently converted to β,α-1 by reactions iv-vi of Scheme II.

Further stereochemical evidence was obtained by the facile conversion of β,α-cycloeudesmene, 10, to β,β-1 (cf., Scheme IV). A key feature of this sequence was the easy base-catalyzed epimerization of α-methylketone 14 to its β-isomer, 15.[17] Ketone 15 was converted to β,β-1 which was purified by chromatography (SiO_2; eluent, n-$C_6H_{14}/CH_2Cl_2/Et_2O$, 10:4:1) and identified by nmr and ir comparisons with the product of Scheme I.

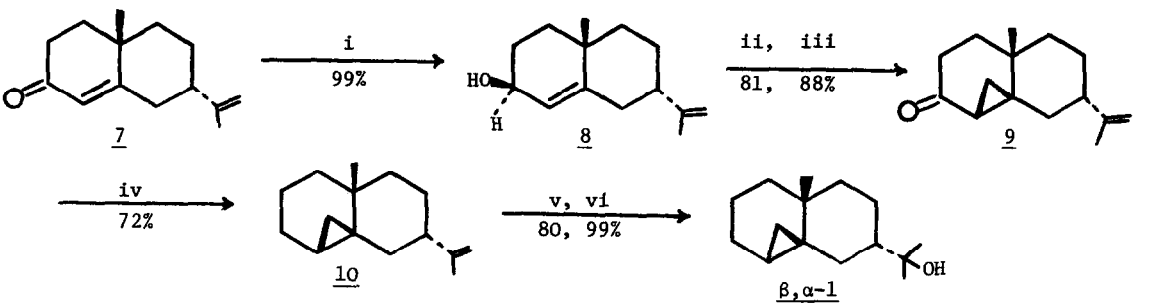
Efforts directed toward the syntheses of α,α- and α,β-cycloeudesmols are under way in our laboratory.

Acknowledgments. We thank the National Science Foundation and the Public Health Service (Research Grant CA-14912 from the National Cancer Institute) for financial support.

References and Notes

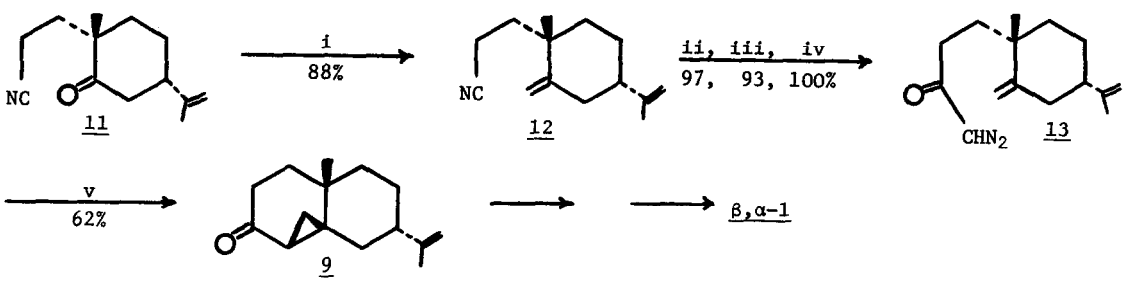
(1) W. Fenical and J. J. Sims, Tetrahedron Lett., 1137 (1974).
(2) (a) R. A. Moss and D. J. Smudin, J. Org. Chem., 41, 611 (1976); (b) R. A. Moss and P.

SCHEME II[3]



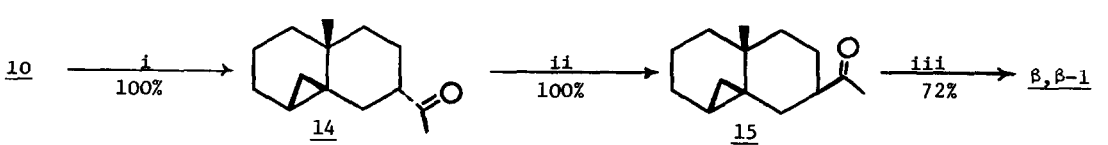
Reagents: i, $LiAlH_4$, Et_2O, refl. 6h; ii, CH_2I_2, Zn-Cu, DME-Et_2O, 65°, 4h; iii, CrO_3, aq. H_2SO_4, acetone, -20° to 0°, 10 min; iv, 85% N_2H_4-H_2O, KOH, DEG, 110°, 1h, then 190-200°, 3.5h; v, m-$ClC_6H_4CO_3H$, CH_2Cl_2, 25°, 15h; vi, $LiAlH_4$, Et_2O, refl. 3h.

SCHEME III[3]



Reagents: i, NaH, DMSO, $\phi_3\overset{+}{P}CH_3Br^-$, 25°, 12h; ii, KOH, $HOCH_2CH_2OH$, 150°, 30h, then conc. HCl; iii, KOH, lyophilization, then $(COCl)_2$, C_5H_5N, C_6H_6, 0°, then 25°, 4h; iv, CH_2N_2,Et_2O, 10°, 40 min; v, $CuSO_4$, C_6H_{12}, refl. 7h.

SCHEME IV



Reagents: i, O_3, CH_2Cl_2-MeOH, -77°, then Me_2S; ii, NaOMe/MeOH, 0°, 2h, then 25°, 15h; iii, MeMgI, Et_2O, 25°, 6h.

Bekiarian, Tetrahedron Lett., 993 (1975); (c) R. A. Moss and D. J. Smudin, ibid., 1829 (1974); and (d) R. A. Moss, R. W. Kleinman, and K. L. Williamson, Chem. Commun., 927 (1970).

(3) Structural assignments on purified samples were supported by ir and nmr spectra, and by acceptable elemental analyses. Unless otherwise indicated all relay compounds (not shown in Scheme) were similarly purified and characterized. For convenience, all structures are drawn in the natural (i.e., β-CH_3) configurational series.

(4) J. A. Marshall and M. T. Pike, Tetrahedron Lett., 3107 (1965); J. A. Marshall, M. T. Pike, and R. D. Carroll, J. Org. Chem., 31, 2933 (1966).

(5) Reaction vi affords 5 grossly contaminated with an apparent elimination product. Pure 5 could be obtained by gc, but crude 5 was used for reaction vii.

(6) J. E. Shaw, D. C. Kunerth, and J. J. Sherry, Tetrahedron Lett., 689 (1973).

(7) Private communications from J. J. Sims, University of California, Riverside, 13 Dec. 1974, 5 Feb., 1975. We thank Professor Sims for copies of the nmr and ir spectra of 1 and related compounds.

(8) J. A. Marshall, W. I. Fanta, and H. Roebke, J. Org. Chem., 31, 1016 (1966); J. A. Marshall and H. Roebke, ibid., 33, 840 (1968).

(9) Only 8 (mp, 54.5-55°) was obtained in this reaction. Reduction with Li(s-Bu)$_3$BH in THF gave 8 (48%) and its 3α-OH epimer (34%), which could be separated by chromatography on silica gel. The analytically pure isomers were differentiated by nmr: whereas 8 displays the C_4 vinyl proton (δ5.33) as a broadened singlet, indicating little coupling to the vicinal, near-perpendicular (ϕ~82°) 3α-proton, its 3α-OH isomer displays H_4 (δ5.43) as a doublet (J=5 Hz), due to stronger coupling to the vicinal 3β proton (ϕ~34°).

(10) Cf., H. E. Simmons, T. L. Cairns, and S. A. Vladuchick, Org. React., 20, 1 (1973); especially pp. 23-31 and 53-60.

(11) A semicarbazone derivative (mp, 222-223°) gave a satisfactory elemental analysis.

(12) Cf., J. A. Marshall and M. T. Pike, J. Org. Chem., 33, 435 (1968) for an analogous isopropenyl to hydroxyisopropyl conversion.

(13) (a) For the related cyanoethylation of 2-methylcyclohexanone, see R. L. Frank and R. C. Pierle, J. Amer. Chem. Soc., 73, 724 (1951). (b) Adduct 11 was obtained in 81% yield after chromatography on silica gel. It had bp 110-112°/0.1 mm-Hg; λ^{CHCl_3} 4.5 (CN), 5.95 (C=O), 6.15, and 11.1 (C=CH_2)μ ; and a structurally consistent nmr spectrum which included $\delta^{TMS}_{CDCl_3}$ 4.76 (m, 2H, =CH_2), 1.77 (S, 3H, =CCH_3), and 1.08 (s, 3H, CH_3). A semicarbazone derivative (mp, 121-122°) gave an acceptable elemental analysis. The chromatographed adduct appeared to be very largely a single isomer, although the condensation afforded a mixture (77:23) of isomers. The stereochemistry of the major product (11) is assigned by analogy to that observed in the dihydrocarvone - methylvinyl ketone condensation, and is supported by the synthetic outcome (see below).

(14) These compounds were not purified, but had structurally consistent ir and nmr spectra.

(15) For a brief review of ketocarbene cyclizations, see W. Kirmse, "Carbene Chemistry," 2nd Ed., Academic Press, New York, 1971, pp. 338-342.

(16) Dreiding models indicate that in the favored e-CH_3, e-isopropenyl conformation of the ketocarbene generated from 13, the carbenic carbon can only attack the =CH_2 function from the α-face, leading to a β-cyclopropane product (i.e., 9).

(17) Indeed, the preparation of β,β-1 by the initial 4 steps of Scheme II, followed by the 3 steps of Scheme IV (overall yield, 37%) is more direct than the 9-step sequence of Scheme I (overall yield, 4.5%), and thus constitutes a second synthesis of β,β-cycloeudesmol.

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