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SYNTHESIS OF A STEREOISOMER OF PTYCHANOLIDE

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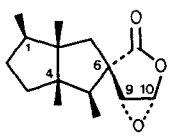
Abstract : A stereoisomer of ptychanolide 1 was synthesized by a method which includes an α-alkynone cyclization.

Ptychanolide, a sesquiterpenoid constituent of the Liverwort Ptychanthus striatus (Lehm. et Lindenb.) Nees isolated by Takeda et al.,[1] was shown by degradation to have structure 1, which contains the diquinane carbon skeleton 2 with four adjacent cis-located methyl groups. Recently, the structure was confirmed and the configuration at the epoxy lactone moiety was determined by x-ray analysis.[2]



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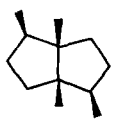
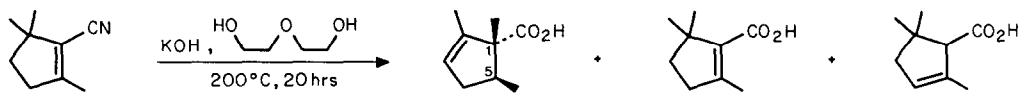


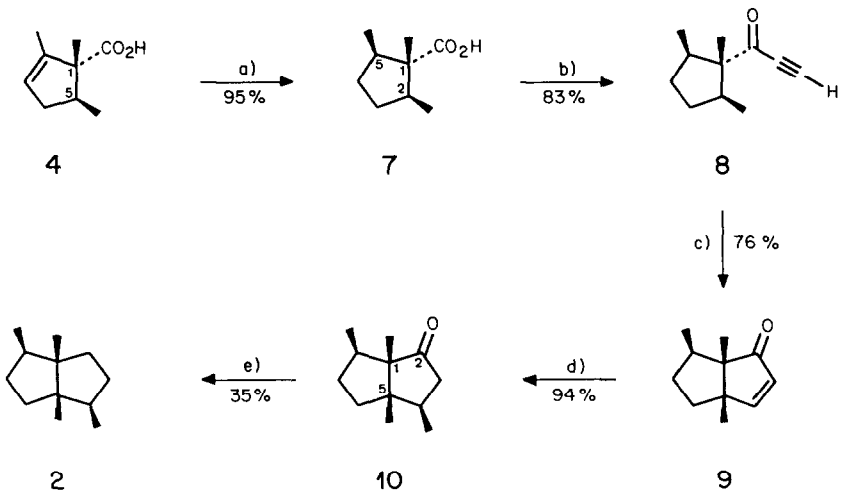
2

Strategies for the synthesis of 1 or its stereoisomers must be concerned with two major problems: a) the construction of the highly methyl substituted bicyclo[3.3.0]octane system and b) the elaboration of the β,γ-epoxy γ-lactone moiety. We envisaged a solution of the former by an application of the α-alkynone cyclization[3] (e.g. 8 → 9), a thermal process with which we had successfully constructed the carbon skeletons of other polycyclopentanoid natural products.[4] A starting material for this approach, the trimethylcyclopentane carboxylic acid 7, became available to us by catalytic hydrogenation of 4, which in turn was an unexpected but reproducible product in the drastic basic hydrolysis of the unsaturated nitrile 3.[5] The new acid 4 was separable from the expected acid 5 and traces of its isomer 6 by repeated column chromatography (silica gel, hexane/EtOAc/AcOH 975:25:10).



3 4 (14%) 5 (12%) 6 (0,4%)

While the methyl migration in 3 → 4 lacks an obvious analogy in the literature and is still unexplained,[6] there is good evidence for the constitution and relative configuration of 4 in its further transformations shown in scheme I. The cis relationship of the two methyl groups at C(2) and C(5) in 7, obtained by hydrogenation of 4, was shown by the NMR expressed molecular symmetry. The cis position of the methyl group at C(1) relative to the other two was evidenced by the ready thermal conversion of the α-alkynone 8, derived from 7, to the bicyclic enone 9, since α-alkynone cyclizations on five membered rings (e.g. 8) are known to proceed exclusively by insertion into cis located β'-C,H-bonds.[7] The structure of 9 was independently confirmed by its methylation to the tetramethyl ketone 10 and by a Wolff-Kishner reduction of the latter to the known[1] symmetrical hydrocarbon 2.



SCHEME I

a) H_2, 10% Pt/C, EtOAc, rt; b) i: $SOCl_2$, ii: $Me_3SiC{\equiv}CSiMe_3$, $AlCl_3$, CH_2Cl_2,[3] iii: $Na_2B_4O_7$ aq., MeOH, pH 8.5;[5] c) distilled at 14 Torr through a quartz tube[3] at 620°, 6 hrs; d) Me_2CuLi, ether, -20° → 0°; e) K_2CO_3, $H_2NNH_2.H_2O$, triethyleneglycol, 250°, 6 hrs.[8]

The elaboration of the epoxylactone ring (scheme II)[9] started with the methoxycarbonylation of the ketone 10, followed by removal of the keto carbonyl group of 11 by a lithium in ammonia reduction of the enol ether 12 to yield the ester 13. Allylation of 13 led to the two possible stereoisomers of 14 (ratio ca. 86:14 by anal. GC. on SE-52). Although reactions on cis-bicyclo[3.3.0]octane systems are usually expected to occur preferentially from the exo side,[12] the presence of three adjacent methyl groups on this side of the five-membered ring does not allow a prediction of the direction of approach of the electrophile and thus of the configuration of the major isomer of 14. Therefore, the mixture of 14 was ozonolyzed to the ester aldehyde 15 (stereoisomer ratio ca. 82:18). The hydroxylactone 16 was prepared by alkaline hydrolysis of 15, complete removal of the methanol present and subsequent acidification. Since direct dehydration of 16 under various conditions at best gave low yields, the unsaturated lactone 18 (stereoisomer ratio ca. 93:7) was obtained via the thiophenol ether 17, oxidation to the sulfoxide and thermal elimination. Epoxidation of 18 and subsequent crystallization led to one of the diastereoisomers of 1, shown to be different from natural (+)-1 by comparison of its IR, ^1H- and ^{13}C-NMR spectra.[16]

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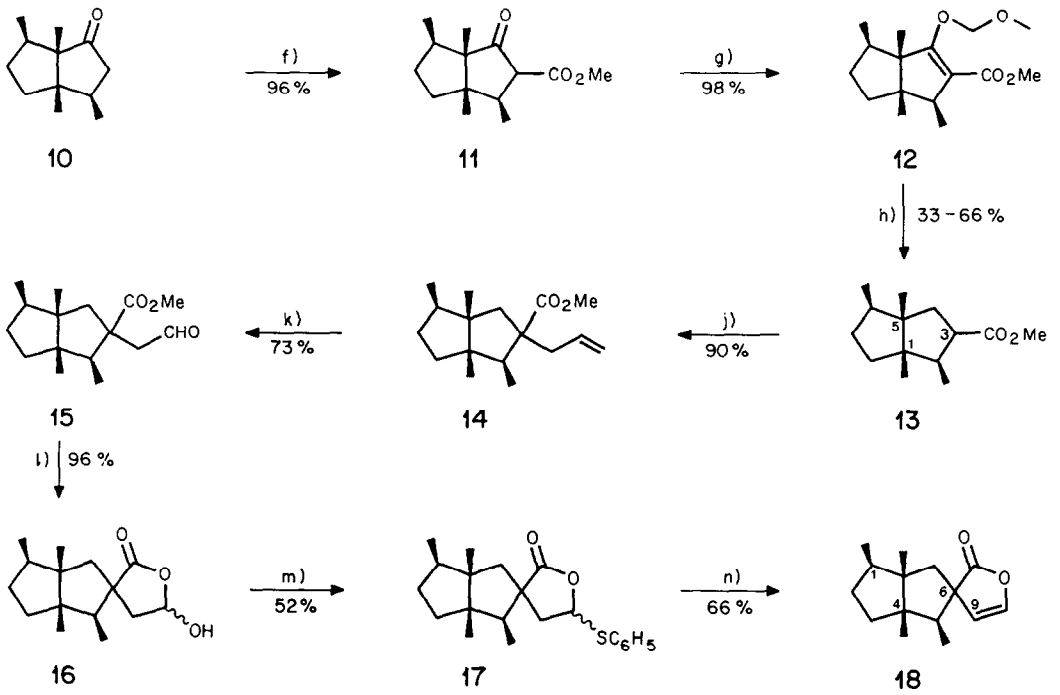

SCHEME II

f) 4 eq NaH, $CO(OMe)_2$, 80-90°, 6 hrs [10] g) 4 eq NaH, HMPT, 2 eq $MeOCH_2Cl$, rt, 12 hrs;[11] h) Li, NH_3, -70°;[11] j) 1.2 eq LDA, THF, 3 eq CH_2=CH-CH_2Br, -78° → 25°, 12 hrs; k) i: O_3, CH_2Cl_2, pyridine (trace), -78°, ii: Me_2S, 3 days, rt; l) i: KOH, H_2O, MeOH, THF, rt, ii: H_2SO_4, H_2O;[13] m) C_6H_5SH, $MeSO_3H$, C_6H_6; n) i: m-CPBA, CH_2Cl_2, -20°, 12 hrs,[14] ii: CCl_4, 2 eq $P(OMe)_3$, 75°, 2 days;[14,15] o) 5.8 eq m-CPBA, CH_2Cl_2, rt, 2 days.

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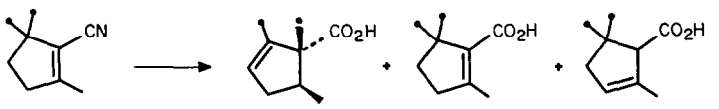
6. A preliminary investigation of the hydrolysis of 3-d_6 revealed the migration of one of the perdeuterated geminal methyl groups (CD_3 = •) with introduction of the double bond at the abandoned position. 3-d_6 was obtained by bis-deuteromethylation of 2-carb-

ethoxy-2-methylcyclopentanone with d_3-methyl iodide, followed by the same reaction sequence as described for 3.[5]



3-d_6 4-d_6 5-d_6 6-d_6

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9. Satisfactory elemental analyses were obtained for all new compounds except 16, 17 and 18, which were not analyzed. The data on a few representative key compounds (numbering of 18 and iso-1 according to[2]) are as follows:

   4: mp. 48.5 - 51°; IR (film): ν 3600 - 2700br, 1700s, 1660m cm^{-1}; ^{1}H-NMR (200 MHz, $CDCl_3$): δ 5.44 (br s, 1 H, H-C(3)); 2.74 (sext, J ca. 7.5 Hz, 1 H, H-C(5)); 2.58 - 2.37 (m, 1 H, H-C(4)); 2.03 - 1.82 (m, 1 H, H-C(4)); 1.76 - 1.66 (m, 3 H, H_3C-C(2)); 1.10 (s, 3 H, H_3C-C(1)); 1.03 (d, J = 6.9 Hz, 3 H, H_3C-C(5)) ppm.

   7: mp. 71 - 73°; IR ($CHCl_3$): ν 3600 - 2200br, 1695s cm^{-1}; ^{1}H-NMR (200 MHz, $CDCl_3$): δ 2.56 - 2.28 (m, 2 H, H-C(2) and H-C(5)); 2.00 - 1.76 (m, 2 H); 1.40 - 1.10 (m, 2 H); 0.93 (d, J = 7.0 Hz, 6 H, H_3C-C(2) and H_3C-C(5)); 0.89 (s, 3 H, H_3C-C(1)) ppm. ^{13}C-NMR (25.2 MHz, $CDCl_3$): δ 184.8 (s, CO_2H); 54.4 (s, C(1)); 43.1 (d, C(2) and C(5)); 30.7 (t, C(3) and C(4)); 14.8 (q, CH_3-C(2) and CH_3-C(5)); 9.1 (q, CH_3-C(1)) ppm.

   10: bp. 115°/14 mm (bulb-to-bulb); IR (film): ν 1735s cm^{-1}; ^{1}H-NMR (200 MHz, $CDCl_3$): δ 2.53 (dd, J = 18.2 & 7.6 Hz, 1 H, H-C(3)); 2.40 - 2.08 (m, 2 H); 2.06 - 1.60 (m, 3 H), 1.58 - 1.30 (m, 2 H); 0.97 (d, J = 6.8 Hz, 3 H); 0.87 (d, J = 6.6 Hz, 3 H); 0.83 (s, 3 H); 0.81 (s, 3 H) ppm.

   13: colorless oil; IR (film): ν 1740s cm^{-1}; ^{1}H-NMR (200 MHz, $CDCl_3$): δ 3.67 (s, 3 H, H_3C-O); 2.60 - 2.40 (m, 1 H, H-C(3)); 2.28 - 1.98 (m, 2 H); 1.96 - 1.75 (m, 2 H); 1.74 - 1.50 (m, 2 H); 1.44 - 1.20 (m, 2 H); 0.87 (d, J = 6.6 Hz, 3 H); 0.84 (d, J = 6.8 Hz, 3 H); 0.75 (s, 6 H, H_3C-C(1) and H_3C-C(5)) ppm.

   18: colorless oil; IR (film): ν 1790s, 1620m cm^{-1}; ^{1}H-NMR (200 MHz, $CDCl_3$, major isomer): δ 6.75 (d, J = 3.5 Hz, 1 H, H-C(10)); 5.59 (d, J = 3.5 Hz, 1 H, H-C(9)); 2.54 - 2.25 (m, 2 H); 2.10 (d, J = 14 Hz, 1 H); 2.05 - 1.10 (m, 5 H) including at 1.54 (d, J = 14 Hz); 0.87 (d, J = 7.0 Hz, 3 H); 0.84 (s, 3 H); 0.82 (s, 3 H); 0.71 (d, J = 7.1 Hz, 3 H) ppm.

   iso-1: mp. 91 - 93°; IR ($CHCl_3$): ν 3030w, 2970s, 2880s, 1795s, 1460m, 1405m, 1385m, 1325m, 1165m, 1155m, 1080s, 1070s, 1050m, 1015m, 985m, 860s cm^{-1}; ^{1}H-NMR (200 MHz, $CDCl_3$): δ 5.57 (d, J = 2.2 Hz, 1 H, H-C(10)); 3.79 (d, J = 2.2 Hz, 1 H, H-C(9)); 2.42 (q, J = 7.6 Hz, 1 H, H-C(5)); 2.35 - 2.15 (m, 1 H); 2.04 (d, J = 14.2 Hz, 1 H, H-C(7)); 2.0 - 1.80 (m, 2 H) including at 1.86 (d, J = 14.2 Hz, ca. 1 H, H-C(7)); 1.74 - 1.24 (m, 3 H); 0.95 (s, 3 H); 0.91 (d, J = 7.6 Hz, 3 H); 0.89 (s, 3 H); 0.88 (d, J = 6.9, 3 H) ppm; ^{13}C-NMR (20 MHz, $CDCl_3$): δ 180.5 (s, C=O), 78.1 (d), 57.2 (d), 56.1 (s), 55.7 (s), 53.9 (s), 50.6 (d), 45.6 (t), 43.1 (d), 37.2 (t), 30.6 (t), 18.7 (q), 17.6 (q), 14.7 (q), 8.9 (q) ppm.

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16. We thank Professor R. Takeda for providing us with copies of the IR, ^{1}H- and ^{13}C-NMR spectra of natural (+)-1.

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