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THE TOTAL SYNTHESIS OF (±)-7α-(1-HYDROXY-1-METHYLETHYL)-4aβ-METHYL-1aβ-DECAHYDROCYCLOPROPA[d]NAPHTHALENE. COMMENT TO THE STRUCTURE OF CYCLOEUDESMOL

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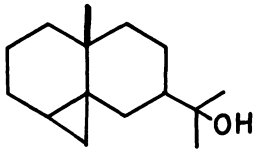
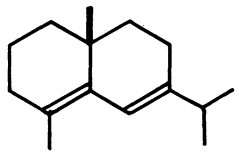
(±)-7α-(1-Hydroxy-1-methylethyl)-4aβ-methyl-1aβ-decahydrocyclopropa[d]naphthalene, which was belived to be the structure of cycloeudesmol, was stereoselectively synthesized and was found to differ from cycloeudesmol.

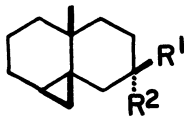
Cycloeudesmol was isolated by Fenical and Sims from the marine alga Chondria oppositiclada Dawson[1] and was shown to be antibiotic toward Staphylococcus aureus, Salmonella cholerasius, Mycobacterium smegmatis, and Candida albicans.[2] The structure of this compound was proposed as shown in structure (I) on the basis of spectral data and its acid-catalyzed transformation to (+)-δ-selinene (II). Since the stereochemistries of the cyclopropyl and 1-hydroxy-1-methylethyl moieties in I are not clear, four stereoisomers (Ia, Ib, Ic, and Id) are possible for the proposed structure. In the previous paper, we have reported the stereoselective total syntheses of Ia, Ib, and Ic.[3] Moss and co-workers[4] have also reported the syntheses of Ia and Ib, and more recently Caine and co-workers[5] have reported the synthesis of Ia by different procedures. Since these stereoisomers were not identical with natural cycloeudesmol, (8aS)-7α-(1-hydroxy-



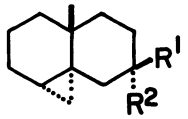
I



II



Ia $R^1=C(CH_3)_2OH$, $R^2=H$
Ib $R^1=H$, $R^2=C(CH_3)_2OH$

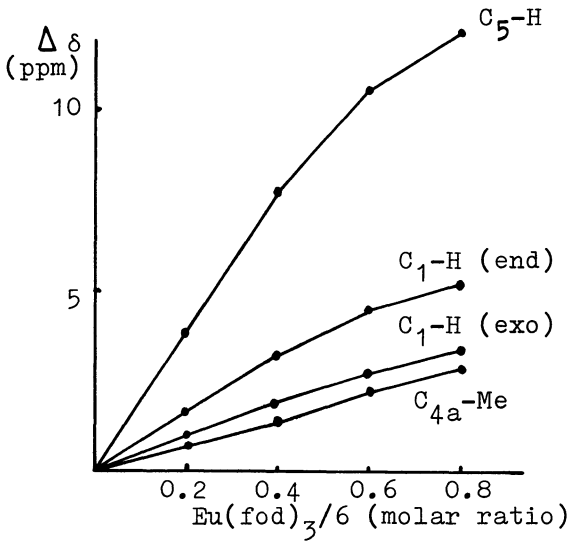


Ic $R^1=C(CH_3)_2OH$, $R^2=H$
Id $R^1=H$, $R^2=C(CH_3)_2OH$

1-methylethyl)-4aβ-methyl-1aβ-decahydrocyclopropa[d]naphthalene (Id) was believed to be the structure of cycloeudesmol at the stage. In this communication, we wish to report the stereoselective total synthesis of (±)-Id.

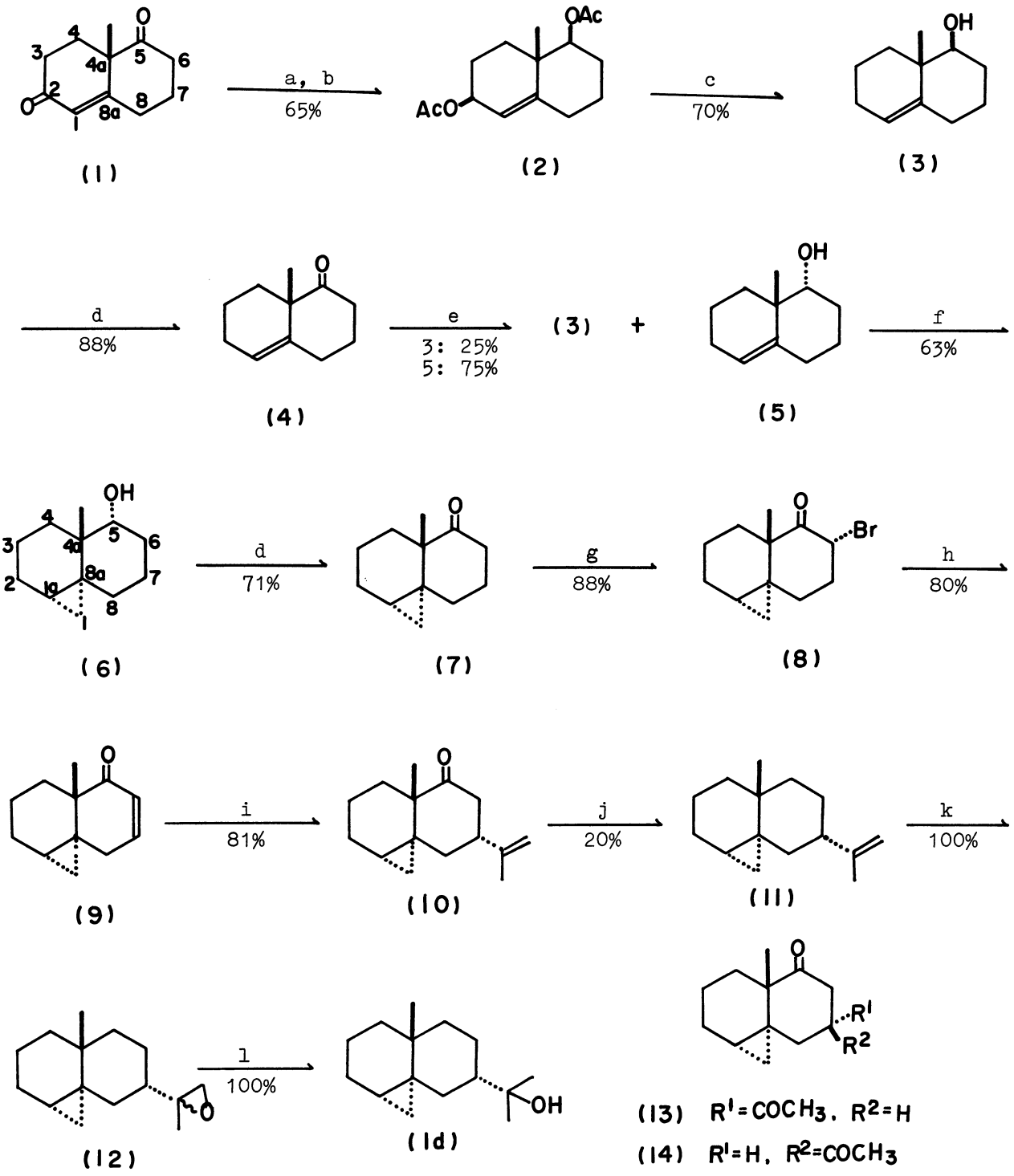
The starting material for our synthesis of (±)-Id is the Wieland-Miescher ketone (1). Reduction of 1 with sodium borohydride and successive acetylation of the resulting 2β,5β-diol gave a diacetate (2), mp 75°C. Reduction of 2 with lithium and liquid ammonia in a small amount of ether gave a 5β-alcohol (3) [NMR ($CDCl_3$, 90 MHz): δ 3.33 (1H, dd, J=4.5 and 10.5 Hz)].[6] An attempt of the direct conversion of 3 to 5 by Mitsunobu's procedure (Ph_3P, $EtO_2C-N=N-CO_2Et$, $PhCO_2H$, THF) was unsuccessful probably because of the steric hindrance at the C_5-position by the angular methyl group. Oxidation of 3 with pyridinium chlorochromate in dichloromethane and successive reduction of the resulting β,γ-unsaturated ketone (4) with L-selectride in THF gave a 3:1 mixture of the desired 5α(ax)-alcohol (5) [NMR ($CDCl_3$, 90 MHz): δ 3.47 (1H, m, $W_{h/2}$=13.5 Hz)] and the recovered 5β(eq)-alcohol (3) in a quantitative yield.

The Simmons-Smith reaction of 5 gave an α-cyclopropyl derivative (6) [NMR ($CDCl_3$, 60 MHz): δ 0.23-0.80 (2H, m), 1.20 (3H, s), and 3.43 (1H, m, $W_{h/2}$=6.0 Hz)] as a single stereoisomer. The stereochemistry of the newly introduced cyclopropyl moiety in 6 was confirmed by the investigation of paramagnetic shifts in ^{1}H-NMR induced by lanthanide shift reagent, $Eu(fod)_3$. The highly stereochemical control in this reaction results from the directive effect of the hydroxyl group at the homoallylic position.[7] Oxidation of 6 with pyridinium chlorochromate gave a ketone (7) [NMR ($CDCl_3$, 200 MHz): δ 0.16 (1H, dd, J=5.0 and 8.5 Hz), 0.36 (1H, ddd, J=2.0, 5.0, and 5.0 Hz), 0.91 (1H, m), 1.40 (3H, s)], which on treatment with phenyltrimethylammonium tribromide gave an α-bromoketone (8) [NMR (CCl_4, 60 MHz): δ 5.07 (1H, dd, J=6.0 and 12.0 Hz)]. Dehydrobromination of 8 gave an α,β-unsaturated ketone (9) [IR ($CHCl_3$): 1660 cm^{-1}; NMR (CCl_4, 90 MHz): δ 0.23 (1H, dd, J=4.5 and 9.0 Hz), 0.45 (1H, ddd, J=1.5, 4.5, and 4.5 Hz), 0.93 (1H, m), 5.85 (1H, dd, J=3.0 and 10.5 Hz), and 6.73 (1H, ddd, J=2.0, 4.5, and 10.5 Hz)].



Change in Chemical Shift in the ^{1}H-NMR spectrum of 6

Conjugate addition of lithium diisopropenylcuprate to 9 gave a ketone (10) [IR (neat): 1705 cm^{-1}; NMR (CCl_4, 60 MHz): δ 0.10-1.13 (3H, m), 1.33 (3H, s), 1.73 (3H, broad s), and 4.73 (2H, broad s)],



a: $NaBH_4$, EtOH, 0°C; b: Ac_2O, Py, room temp; c: Li, liq NH_3, ether, -70°C; d: PCC, CH_2Cl_2, 0°C; e: L-Selectride, THF, -70°C; f: Zn(Cu), CH_2I_2, ether, DME, room temp, 1 h; g: PTAB, THF, 0°C; h: LiBr, Li_2CO_3, DMF, 120°C, 4h; i: $LiCu(\rangle\!\!-)_2$, -60°C - 0°C, 4h; j: $NH_2NH_2 \cdot H_2O$, KOH, DEG, 110°C (30 min), 200°C (3 h); k: m-Cl-$C_6H_4CO_3H$, CH_2Cl_2, 0°C - room temp; l: $LiAlH_4$, 0°C, 1.5 h

possessing an α(ax)-isopropenyl group, as a single stereoisomer. The highly stereochemical control in this reaction results from the stereoelectronic factor.[8] Further stereochemical evidence was obtained by the following transformation. Ozonolysis of 10 gave the corresponding α(ax)-acetyl derivative (13), which gave a 1:3 mixture of 13 and a thermodynamically more stable β(eq)-acetyl derivative (14) by treatment with 2 M KOH in methanol at room temperature.

The Wolff-Kishner reduction of 10 gave the corresponding hydrocarbon (11) [NMR (CCl_4, 60 MHz): δ 1.13 (3H, s), 1.73 (3H, broad s), 4.76 (1H, broad s) and 4.83 (1H, broad s)]. Since the carbonyl group of 10 is highly hindered by the angular methyl group and the α(ax)-isopropenyl group as well as the cyclopropyl moiety, the yield of this reaction is rather poor. Epoxidation of 11 and successive reduction of the resulting epoxide (12) with lithium aluminium hydride afforded (±)-Id, oil, [NMR (CCl_4, 90 MHz): δ 0.20 (1H, dd, J=4.5 and 9.0 Hz), 0.47 (1H, ddd, J=1.5, 4.5, and 4.5 Hz), 0.70 (1H, m), 1.15 (6H, s), and 1.17 (3H, s)]. The NMR spectrum of (±)-Id was found to differ from the reported spectrum of cycloeudesmol.

Since the total syntheses of the four stereoisomers of I have been completed and they are found to differ from natural cycloeudesmol, it is concluded that the structure proposed by Fenical and Sims is wrong.

References

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