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THE TOTAL SYNTHESIS OF (±)-CYCLOEUDESMOL

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Abstract: The highly stereoselective total synthesis of (±)-cycloeudesmol was achieved by the stereoselective cyclopropane ring formation of an epoxy alcohol (7) as a key reaction.

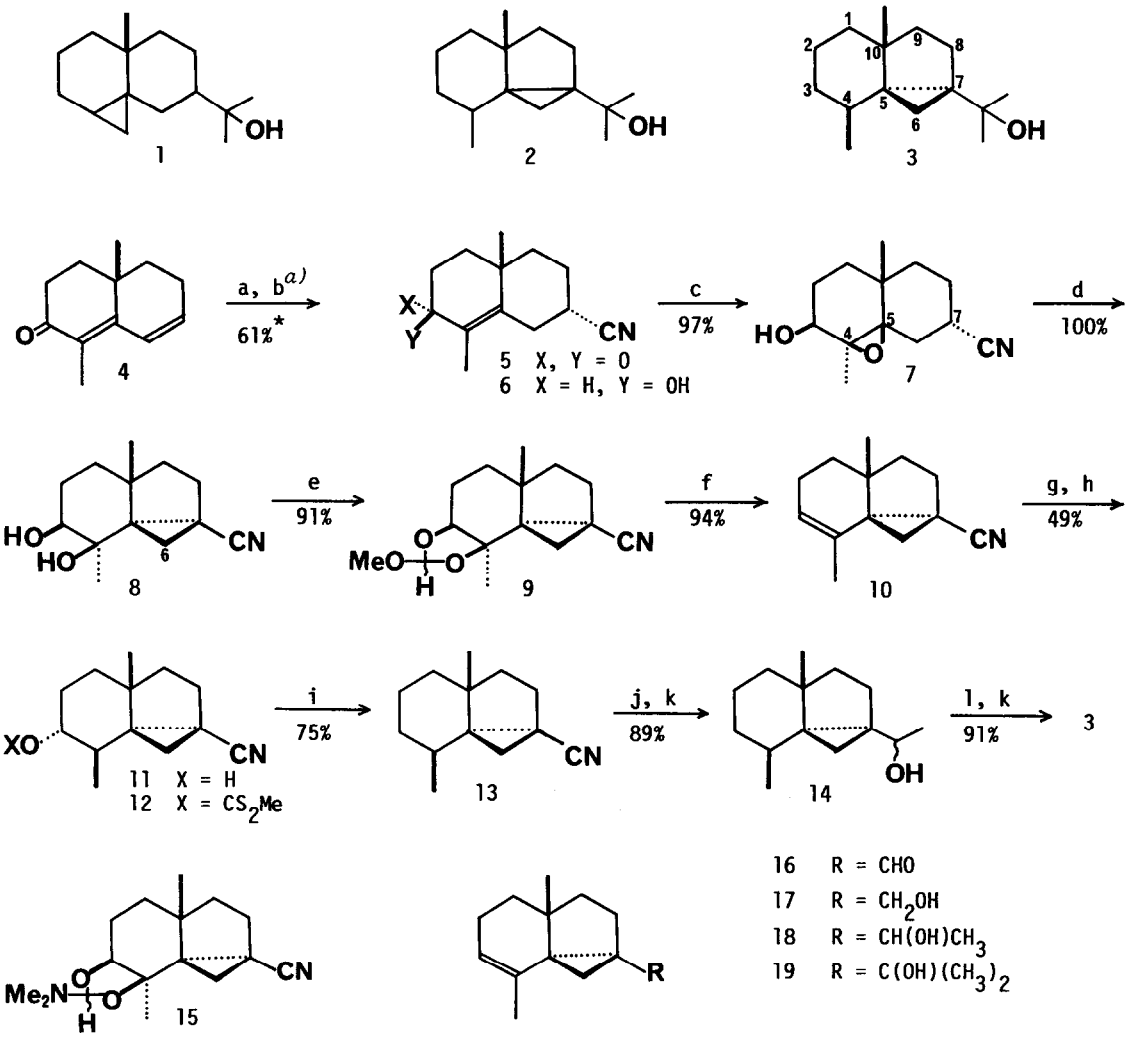
Cycloeudesmol was isolated by Fenical and Sims from the marine alga Chondria oppositiclada Dowson[1] and was shown to be antibiotic toward Staphylococcus aureus, Salmonella choleraesius, Mycobacterium smegmatis, and Candida albicans.[2] The structure of this compound was proposed as shown in structure 1 on the basis of spectral data and its acid-catalyzed transformation to (+)-δ-selinene.[1] Since the stereochemistries of the cyclopropyl and 1-hydroxy-1-methylethyl moieties in 1 were not clear, four stereoisomers were possible for the proposed structure.

Recently we completed the stereoselective total syntheses of the four stereoisomers of 1 and found them to differ from natural cycloeudesmol.[3] By the comparison of the ^{1}H-NMR spectra of the four isomers of synthetic 1 and that of natural cycloeudesmol kindly provided by Fenical and Sims, we concluded that cycloeudesmol had not structure 1 but structure 2,[4] which was identical with the structure proposed by Kurosawa et al. for isocycloeudesmol.[5] Actually the ^{1}H-NMR spectrum of cycloeudesmol was in good accordance with that of isocycloeudesmol reported by them. They also noticed that cycloeudesmol was the same compound with isocycloeudesmol by the comparison of the spectral data, and finally they determined its stereochemistry by X-ray crystallographic analysis as shown in structure 3.[6] More recently, the total synthesis of (±)-cycloeudesmol (3) was reported by Chen.[7] In this communication we want to report the another stereoselective total synthesis of (±)-3 by the completely different approach. The crucial points of our approach were the highly stereoselective formation of cyclopropane ring (6→8) via an epoxy alcohol (7) and the stereoselective transformation of the resulting vicinal cis-diol (8) to the compound (13) possessing the β(axial)-methyl group at C_4.

The starting material is the dienone (4),[8] which was prepared from the corresponding conjugated enone[8] by dehydrogenation with DDQ in the presence of p-toluenesulfonic acid in 79% yield. Hydrocyanation[9] of 4 with triethylaluminum and hydrogen cyanide in THF gave the desired nitrile (5), mp 99 °C, in 73% yield. Reduction of 5 with sodium borohydride gave the desired β-alcohol

(6), mp 115 °C, in 84% yield accompanied by the corresponding α-alcohol, mp 120 °C. Sharpless oxidation[10] of 6 with vanadyl acetylacetonate and t-butyl hydroperoxide in benzene at 10 °C[11] gave a ß-epoxy alcohol (7), mp 95 °C, in 97% yield.

The attempts of the cyclopropane ring formation of 7 by treatment with potassium amide or sodium hydride in various conditions were unsuccessful. We



a) (a) Et_3Al, HCN, THF; (b) $NaBH_4$, EtOH; (c) $VO(acac)_2$, TBHP, benzene, 10 °C; (d) 3.5 eq LDA, THF, -78 °C → 0 °C; (e) $Me_2NCH(OMe)_2$, MeI, CH_2Cl_2, room temperature; (f) Ac_2O, reflux; (g) (i) $BH_3 \cdot Me_2S$, THF; (ii) 2 M NaOH aq soln, 30% H_2O_2; (h) (i) NaH, THF; (ii) CS_2, MeI; (i) Bu_3SnH, cat. AIBN, THF, reflux; (j) (i) DIBAL, CH_2Cl_2; (ii) NH_4Cl, 2 M HCl; (k) MeLi, Et_2O, -78 °C → 0 °C; (l) PCC, AcONa, CH_2Cl_2. *The isolated yields of the analytically pure products.

also examined the cyclopropane ring formation of 7 with lithium diisopropylamide (LDA) in various conditions and finally found the optinum reaction conditions of this transformation as follows. The mixture of 7 and 3.5 molar equivalents of LDA in THF was stirred at -78 °C for 1 h, warmed to 0 °C, and kept at this temperature for additional 1 h to give the desired cyclopropane derivative (8) [mp 103 °C, ^{1}H-NMR ($CDCl_3$) δ 1.05 (1H, d, J=6.0 Hz, C_6-H), 1.43 (1H, d, J=6.0 Hz, C_6-H), 3.47 (1H, dd, J=10.0 and 6.0 Hz, C_3-H)] in a quantitative yield. The stereochemical assignment of 8 was based on the consideration of the reaction mechanism as well as the analysis of the ^{1}H-NMR spectrum. It is noteworthy that more than 3 molar equivalents of LDA was necessary for the completion of this transformation and addition of hexamethylphosphoric triamide (HMPT) inhibited the reaction. Probably lithium atom of LDA interacts with epoxide oxygen of 7 as Lewis acid and promotes the intramolecular attack of the carbanion generated at C_7 to C_5 from the back side of the epoxide ring.

Then we examined the efficient procedure of the conversion of the vicinal cis-diol (8) into the corresponding olefin (10). In literatures[12] the conversion of vicinal cis-diols into the corresponding olefins via 2-dimethylamino-1,3-dioxolan derivatives had been reported and we applied this method to 8. But treatment of 8 with N,N-dimethylformamide dimethyl acetal in various conditions gave the recovered 8 probably because of the severe steric hindrance.

Since we could not get the desired 2-dimethylamino-1,3-dioxolan derivative (15) by the known procedure, we explored a new method. Thus treatment of 8 with excess amounts of N,N-dimethylformamide dimethyl acetal and methyl iodide for 2 h in methylene chloride at ambient temperature gave a 2-methoxy-1,3-dioxolan derivative (9) as a 1:10 diastereomeric mixture in 91% yield at 66% conversion. The products were easily separated by the flash chromatogrphy of silica gel and the recovered 8 was recycled. Treatment of 9 with boiling acetic anhydride gave a tri-substituted olefin (10), mp 117 °C, in 94% yield.

Then our attention was focused on the stereoselective conversion of 10 to 13. The various attempts of the catalytic hydrogenation of 10 and its derivatives such as 16, 17, 18, and 19 were unsuccessful probably because of their severe steric hindrance around the double bond and the unstability of their cyclopropane ring in the reaction conditions. Fortunately the hydroboration of 10 with borane dimethyl sulfide complex in THF and successive treatment with alkaline hydrogen peroxide gave an alcohol (11), mp 101 °C, in 70% yield. The stereochemical assignment of 11 was based on the analysis of the ^{1}H-NMR spectrum ($CDCl_3$) [δ 3.90 (1H, m, $W_{h/2}$=6.0 Hz, C_3-H)] as well as the investigation of its paramagnetic shift induced by $Eu(fod)_3$. The attempts of the direct conversion of the borane adduct of 10 to 13 were unsuccessful. The reductive elimination of the hydroxyl group of 11 was established without epimerization of the axial methyl group at C_4 as follows. Treatment of the sodium alkoxide of 11 with carbon disulfide and methyl iodide gave a methyl xanthate (12). Reduction of 12 with tributyltin hydride in boiling THF in the presence of catalytic amount of azobisisobutyronitrile (AIBN) gave the desired nitrile (13)

in 75% yield.[13)]

The various method of the conversion of 13 to 3 were investigated and the best result was obtained as follows. Reduction of 13 with diisobutylaluminum hydride and reaction of the resulting aldehyde with methyllithium gave a secondary alcohol (14) in 89% yield. Oxidation of 14 with pyridinium chlorochromate (PCC) and the reaction of the resulting methyl ketone with methyllithium gave a 91% yield of 3, which was identical with natural cycloeudesmol in the comparison of the ^{1}H-NMR spectra (200 MHz, CCl_4).

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