Communications to the Editor

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STEREOSELECTIVE TOTAL SYNTHESIS OF (±)-EPERUANE-8β,15-DIOL AND (±)-LABDANE-8α,15-DIOL

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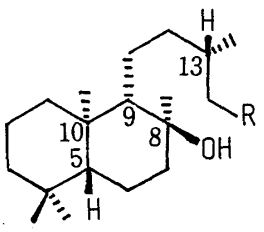
(±)-Eperuane-8β,15-diol (5) and (±)-labdane-8α,15-diol (6), diastereomeric diterpenes to each other, were synthesized stereoselectively, via the same intermediate lactone (7) starting from a known racemic tricyclic compound (8).

KEYWORDS ——— eperuane-8β,15-diol; labdane-8α,15-diol; stereoselective total synthesis; labdane-type diterpenoid

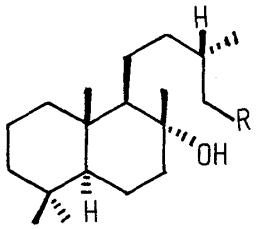
Eperuic acid (1) and labdanolic acid (2) are diterpenes with the same (S)-configuration at C-13. The stereochemistries of the other asymmetric centers (C-5, C-8, C-9, and C-10) are antipodal to each other in these acids.[1] Although total synthesis of methyl labdanolate (3) and its 13-epimer [enantiomer of methyl eperuate (4)] has been described,[2] the final step of the synthesis included no stereoselective formation of these esters. In this paper, we report the stereoselective total synthesis of (±)-eperuane-8β,15-diol (5) and (±)-labdane-8α,15-diol (6) from a common intermediate [(±)-7].

The key compound (7) was obtained unambiguously from the known racemic tricyclic ketone (8)[3,4] by five step reactions in 57% yield as follows. The enolate derived from the α,β-unsaturated ketone (8) by Li-NH_3 reduction was trapped by CH_3I yielding the methylated product (9; mp 139.5-142.5 °C) quantitatively.[5] The Huang-Minlon reduction of 9 gave the unsaturated alcohol (10; 95% yield), which was subjected to catalytic hydrogenation (H_2, PtO_2, CH_3COOH) affording an alcohol (11; 98% yield). The ketone (12; mp 102.5- 103 °C) was obtained in quantitative yield by the Jones' oxidation of 11. The Baeyer-Villiger oxidation of 12 with perbenzoic acid yielded the lactone [7; 61% yield; mp 100.5-102.5 °C; IR (KBr) 1705 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ: 0.83 (6H, s), 0.90 (3H, s), 1.51 (3H, s); $C_{18}H_{30}O_2$ (m/z 278.2238, and elementary analysis: C, 77.81; H, 11.18%)].

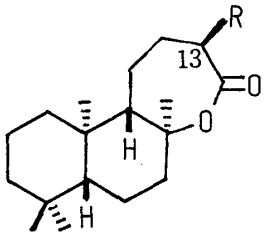
The enolate produced by treatment of 7 with LDA was allylated with allyl bromide to give 13 [mp 78.5-79.5 °C; ^{13}C-NMR ($CDCl_3$) δ: 15.0. 18.7, 19.6, 21.7, 22.9, 24.3, 29.6, 33.3, 33.5, 36.7, 38.7, 39.8, 41.5, 43.6, 45.1, 55.5, 57.9, 85.7, 116.8, 136.3, 176.2] as a sole product[6] in 62% yield. This was the result of an attack by the reagent from the less hindered β-side. Reduction of 13 with $LiAlH_4$ gave the diol (14; mp 109-110 °C) in 97% yield.



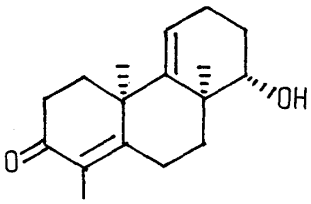
1 : R = CO_2H
4 : R = CO_2CH_3
5 : R = CH_2OH



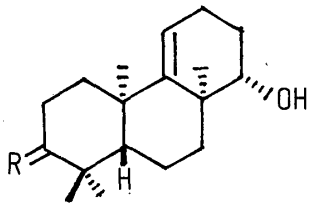
2 : R = CO_2H
3 : R = CO_2CH_3
6 : R = CH_2OH



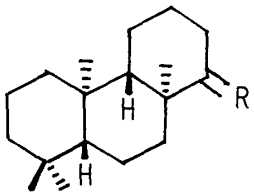
7 : R = H
13 : R = $CH_2CH{=}CH_2$
16 : R = CH_3



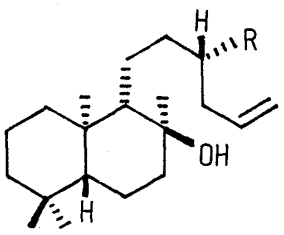
8



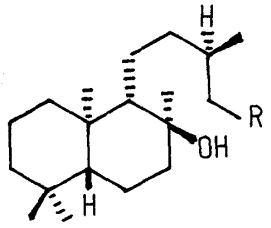
9 : R = O
10 : R = H_2



11 : R = α-OH, β-H
12 : R = O



14 : R = CH_2OH
15 : R = CH_3



17 : R = OH
18 : R = OTs
19 : R = CN

The diol (14) was monotosylated and then reduced with $LiAlH_4$ to give 15 (mp 47-47.5 °C) in 80% yield. The unsaturated alcohol (15) was ozonized with O_3 and treated with $NaBH_4$[7] to afford (±)-eperuane-8β,15-diol [5; 82% yield; mp 126-128 °C; IR (KBr) 3300 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ: 0.79 (6H, s), 0.87 (3H, s), 0.91 (3H, d, J=7.5Hz), 1.15 (3H, s), 3.68 (2H, td, J=6 and 1.5Hz); ^{13}C-NMR ($CDCl_3$) δ: 15.5, 18.5, 20.1, 20.6, 21.5, 22.2, 24.1, 30.1, 33.3, 33.4, 39.2, 39.2, 39.8, 40.4, 42.0, 44.5, 56.2, 61.2, 61.8, 74.5; $C_{20}H_{38}O_2$ (m/z 310.2893)]. This diol (5) was also converted into (±)-eperuic acid (1) and its methyl ester (4; methyl eperuate) by known procedures.[8]

Methylation (LDA; MeI) of the lactone (7) gave the 13β-methylated compound [16; mp 125.5-127 °C; ^{13}C-NMR ($CDCl_3$) δ: 15.1, 18.8, 18.8, 19.7, 21.8, 22.9, 24.4, 32.9, 33.4, 33.6, 38.8, 39.9, 40.3, 41.6, 43.7, 55.6, 57.9, 85.5, 177.4] stereospecifically[6] in 72% yield. The diol (17; mp 114-115 °C) was obtained quantitatively by $LiAlH_4$ reduction of 16. After monotosylation of 17 (87% yield), the obtained tosylate (18; mp 97-98.5 °C) was transformed into the nitrile (19; mp 51-52 °C) in 93% yield by treatment with NaCN-H_2O-Bu_3N.[9] Hydrolysis of the nitrile (19) with 30% H_2O_2aq-NaOH-EtOH[10] gave (±)-labdanolic acid (2; 75% yield; mp 150.5-152 °C). The acid (2) was transformed into (±)-methyl labdanolate (3) and then into (±)-labdane-8α,15-diol (6) by known procedures,[11] both in almost quantitative yield. [6; mp 111.5-112.5 °C; IR (KBr) 3350 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ: 0.79 (6H, s), 0.86 (3H, s), 0.90 (3H, d, J=6.5Hz), 1.14 (3H, s), 3.66 (2H, d, J=6Hz); ^{13}C-NMR ($CDCl_3$) δ: 15.5, 18.5, 19.8, 20.6, 21.5, 23.0, 24.0, 30.6, 33.3, 33.4,.39.2, 39.8, 39.8, 41.2, 42.0, 44.4, 56.2, 60.9, 62.5, 74.4; $C_{20}H_{38}O_2$ (m/z 310.2856)].

The ^{1}H- and ^{13}C-NMR spectra of (±)-3, (±)-4, (±)-5, and (±)-6 were found to be identical respectively with those of natural methyl labdanolate,[2,12-15] methyl enantio-13-epilabdanolate (methyl eperuate),[2,8,12,13] eperuane-8β,15-diol,[8,12] and labdane-8α,15-diol.[12,14,16,17]

Thus, from the same synthetic intermediate (7), (±)-eperuane-8β,15-diol (5) was synthesized by a five step conversion in 39% yield, and (±)-labdane-8α,15-diol (6) by seven step reactions in 43% yield, both stereoselectively. These results provide a synthetic confirmation for the relative stereochemistry at C-13 of these acids (1 and 2), esters (3 and 4), and diols (5 and 6).

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