

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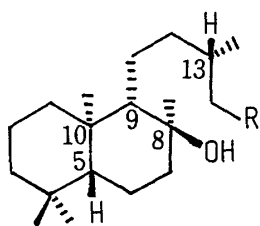
(±)-Eperuane-8β,15-diol (5) and (±)-labdane-8α,15-diol (6), diastereomeric diterpenes to each other, were synthesized stereoselectively, via the same intermediate lactone (7) starting from a known racemic tricyclic compound (8).

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

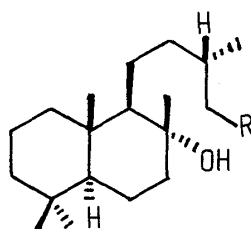
Eperuic acid (1) and labdanolic acid (2) are diterpenes with the same (S)-configuration at C-13. The stereochemistries of the other asymmetric centers (C-5, C-8, C-9, and C-10) are antipodal to each other in these acids.¹⁾ Although total synthesis of methyl labdanolate (3) and its 13-epimer [enantiomer 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-NH₃ reduction was trapped by CH₃I 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 (H₂, PtO₂, CH₃COOH) 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; ¹H-NMR (CDCl₃) δ: 0.83 (6H, s), 0.90 (3H, s), 1.51 (3H, s); C₁₈H₃₀O₂ (m/z 278.2238, and elementary analysis: C, 77.81; H, 11.18%)].

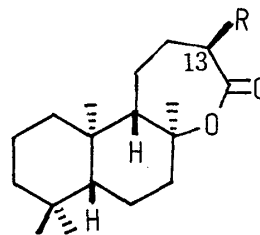
The enolate produced by treatment of 7 with LDA was allylated with allyl bromide to give 13 [mp 78.5-79.5 °C; ¹³C-NMR (CDCl₃) δ: 15.0, 18.7, 19.6, 21.7, 22.9, 24.3, 29.6, 33.3, 33.5, 36.7, 38.7, 39.8, 41.5, 43.6, 45.1, 55.5, 57.9, 85.7, 116.8, 136.3, 176.2] as a sole product⁶⁾ in 62% yield. This was the result of an attack by the reagent from the less hindered β-side. Reduction of 13 with LiAlH₄ gave the diol (14; mp 109-110 °C) in 97% yield.



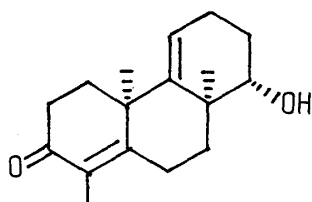
$\tilde{1}$: R = CO₂H
 $\tilde{4}$: R = CO₂CH₃
 $\tilde{5}$: R = CH₂OH



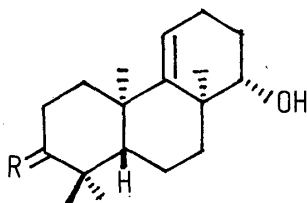
$\tilde{2}$: R = CO₂H
 $\tilde{3}$: R = CO₂CH₃
 $\tilde{6}$: R = CH₂OH



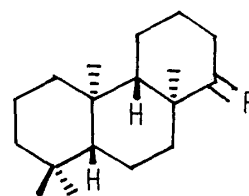
$\tilde{7}$: R = H
 $\tilde{13}$: R = CH₂CH=CH₂
 $\tilde{16}$: R = CH₃



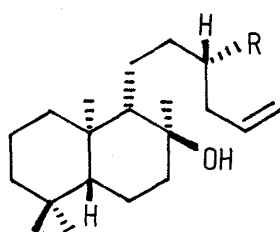
$\tilde{8}$



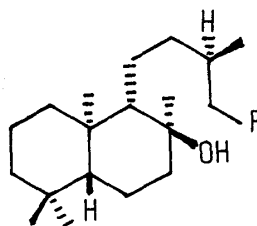
$\tilde{9}$: R = O
 $\tilde{10}$: R = H₂



$\tilde{11}$: R = α-OH, β-H
 $\tilde{12}$: R = O



$\tilde{14}$: R = CH₂OH
 $\tilde{15}$: R = CH₃



$\tilde{17}$: R = OH
 $\tilde{18}$: R = OTs
 $\tilde{19}$: 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-8 β ,15-diol [5; 82% yield; mp 126-128 °C; IR (KBr) 3300 cm^{-1} ; $^1\text{H-NMR}$ (CDCl_3) δ : 0.79 (6H, s), 0.87 (3H, s), 0.91 (3H, d, $J=7.5\text{Hz}$), 1.15 (3H, s), 3.68 (2H, td, $J=6$ and 1.5Hz); $^{13}\text{C-NMR}$ (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; $\text{C}_{20}\text{H}_{38}\text{O}_2$ (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 13 β -methylated compound [16; mp 125.5-127 °C; $^{13}\text{C-NMR}$ (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] stereospecifically⁶⁾ 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 $\text{NaCN-H}_2\text{O-Bu}_3\text{N}$.⁹⁾ Hydrolysis of the nitrile (19) with 30% $\text{H}_2\text{O}_2\text{aq-NaOH-EtOH}$ 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-8 α ,15-diol (6) by known procedures,¹¹⁾ both in almost quantitative yield. [6; mp 111.5-112.5 °C; IR (KBr) 3350 cm^{-1} ; $^1\text{H-NMR}$ (CDCl_3) δ : 0.79 (6H, s), 0.86 (3H, s), 0.90 (3H, d, $J=6.5\text{Hz}$), 1.14 (3H, s), 3.66 (2H, d, $J=6\text{Hz}$); $^{13}\text{C-NMR}$ (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; $\text{C}_{20}\text{H}_{38}\text{O}_2$ (m/z 310.2856)].

The $^1\text{H-}$ and $^{13}\text{C-NMR}$ 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-8 β ,15-diol,^{8,12)} and labdane-8 α ,15-diol.^{12,14,16,17)}

Thus, from the same synthetic intermediate (7), (+)-eperuane-8 β ,15-diol (5) was synthesized by a five step conversion in 39% yield, and (+)-labdane-8 α ,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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