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STEREOSELECTIVE SYNTHESIS OF C/D/E RINGS IN STEROIDS CONTAINING E (LACTONE) RING. SYNTHESIS OF (±)-1-(1'-HYDROXYETHYL)-7,7a-DIHYDRO-5(6H)-INDANONE-7a-CARBOXYLIC ACID-7a,1'-LACTONE

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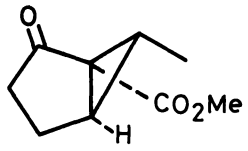
The title compound, a potential intermediate for the synthesis of steroids containing E (lactone) ring, was synthesized stereoselectively using the acid catalyzed homoconjugate addition of methanol to methyl 6-methyl-2-oxobicyclo[3.1.0]hexane-1-carboxylate in four steps.

Recently, organic synthesis based on the cleavage of cyclopropane ring has been noted and this method has been widely applied to the synthesis of natural products.[1-5] We have been previously reported the syntheses of (±)- and optically active dehydroiridodiol[4] and (2R*,3R*)-2-methyl-3-[(1R*)-1,5-dimethylhexyl]-cyclopentanone[5] from methyl 6-methyl-2-oxobicyclo[3.1.0]hexane-1-carboxylate (1)[6] by using the stereoselective cleavage reaction as the key step, respectively. In this communication, we wish to report the stereoselective synthesis of (±)-1-(1'-hydroxyethyl)-7,7a-dihydro-5(6H)-indanone-7a-carboxylic acid-7a,1'-lactone (2), which structure corresponds to the C/D/E rings of steroid hormones (e.g., 3)[7] and steroid alkaloids (e.g., 4),[8] by using acid catalyzed homoconjugate addition of methanol.[9]



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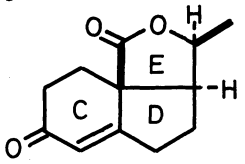

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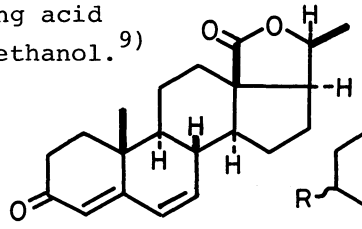

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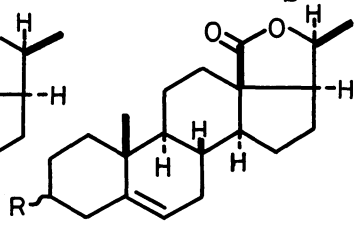
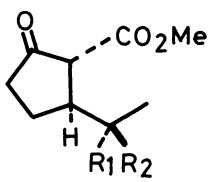


4a R=α-NH_2, 4b R=β-NHMe

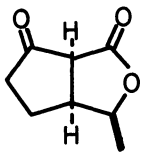
1 was treated with methanol in the presence of *p*-toluenesulfonic acid at reflux for five hours to give the desired methoxy keto ester (5a)[10] and its epimer (5b) with respect to the methoxyl group in a ratio of ca. 7:1 in 86% yield, respectively. The undesired isomer 5b could be removed easily by silica gel chromatography using hexane-ethyl acetate (3:1) as eluent. Treatment of 5a with trimethylsilyl iodide (TMSI) in acetonitrile afforded the known keto lactone (6)[11] in 75% yield. The S configuration at carbon bearing the methoxyl group in 5a was thus ascertained. The Michael reaction of 5a in methanol with methyl vinyl ketone was performed in the presence of sodium methoxide at 0 °C to room temperature for three hours, yielding a single diketo ester (7)[12] in good yield. Since 7 was easily converted to a bicyclic lactone (8)[13] by treatment with TMSI, the relationship of the methoxycarbonyl group and the S-methoxyethyl group was assigned to

a cis disposition. Intramolecular aldol condensation of 7 was carried out with tri-t-butoxyaluminum as base in refluxing benzene for five hours yielding cyclohexenone (9)[14] in 50% yield. The final lactonization of 9 as described above gave the desired tricyclic lactone (2)[15] in 72% yield.

The resulting compound 2 will be a useful intermediate for total syntheses of 3 and 4. In addition, since both enantiomeric isomers of 1 were readily obtained from the corresponding *l*-menthyl ester by chromatographic separation followed by the ester exchange reaction,[4] the optically active 2 would be synthesized by the above process.



5a R_1=OMe, R_2=H
5b R_1=H, R_2=OMe



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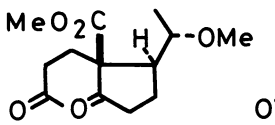

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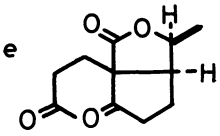

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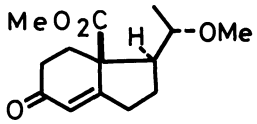

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References

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10) 5a: MS m/z 200 (M^+); IR($CHCl_3$) ν 1760, 1730 cm^{-1}; NMR(CCl_4) δ 1.14(3H, d, J=6 Hz), 3.29, 3.68(each 3H, s).
11) Y.Morizawa, T.Hiyama, K.Oshima, and H.Nozaki, Bull. Chem. Soc. Jpn., 57, 1123 (1984).
12) 7: MS m/z 270.1444 [Calcd for $C_{14}H_{22}O_5$: 270.1446(M^+)]; IR($CHCl_3$) ν 1758, 1739, 1725 cm^{-1}; NMR(CCl_4) δ 1.14(3H, d, J=6), 2.20, 3.10, 3.70(each 3H, s).
13) 8: mp 94-95 °C (colorless prisms); MS m/z 224.1049 [Calcd for $C_{12}H_{16}O_4$: 224.1049 (M^+)]; IR($CHCl_3$) ν 1780, 1739, 1725 cm^{-1}; NMR($CDCl_3$) δ 1.51(3H, d, J=6), 2.10(3H, s), 4.86(1H, dq, J=6, 5).
14) 9: MS m/z 252.1361 [Calcd for $C_{14}H_{20}O_4$: 252.1361 (M^+)]; IR($CHCl_3$) ν 1722, 1661 cm^{-1}; NMR($CDCl_3$) δ 1.10(3H, d, J=6), 3.12, 3.60(each 3H, s), 5.60-5.72(1H, m).
15) 2: mp 43-44 °C (colorless needles); MS m/z 206.0948 [Calcd for $C_{12}H_{14}O_3$: 206.0947(M^+)]; IR($CHCl_3$) ν 1768, 1669 cm^{-1}; ^{1}H-NMR(270 MHz, $CDCl_3$) δ 1.45 (3H, d, J=6.5), 1.83-2.15(2H, m), 2.35-2.53(1H, m), 2.57-2.92(6H, m), 4.84(1H, dq, J=6.5, 5.2), 6.05(1H, t, J=2.0); ^{13}C-NMR δ 198.1, 175.0, 166.3; 57.5 (s), 125.0, 76.1, 51.2 (d), 32.5, 30.5, 29.5, 22.9 (t), 15.9 (q).

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