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ENANTIOSPECIFIC SYNTHESIS OF NATURAL (+)-(S,S)-(CIS-6-METHYLTETRAHYDROPYRAN-2-YL)ACETIC ACID, A CONSTITUENT OF CIVET

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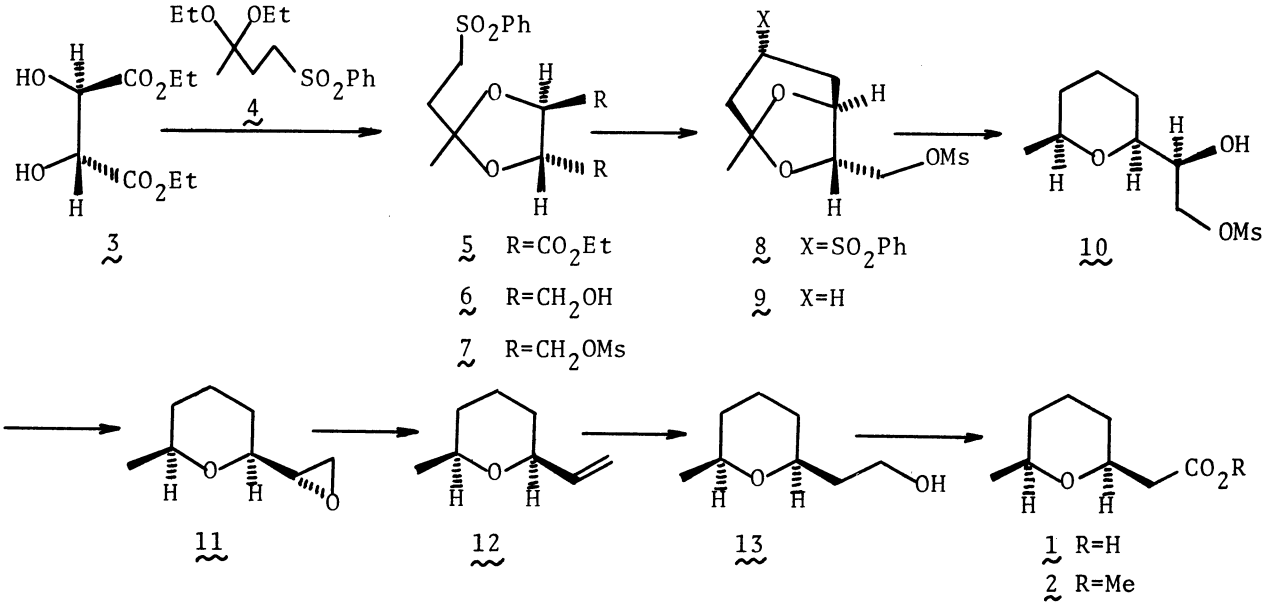
(+)-(S,S)-(cis-6-Methyltetrahydropyran-2-yl)acetic acid, a constituent of the glandular secretion from the civet cat was synthesized enantiospecifically from (+)-(R,R)-diethyl tartrate via stereospecific reductive ring opening of an optically active 5,7-disubstituted 6,8-dioxabicyclo[3.2.1]octane derivative.

(cis-6-Methyltetrahydropyran-2-yl)acetic acid (1) was isolated as a constituent of civet, the glandular secretion of the civet cat (Viverra civetta).[1] It has been found that the natural compound is optically active and has (2S,6S)-configuration of the asymmetric centers by a chiral synthesis and NMR study of the racemic, optically active synthetic, and natural compounds 1 in the presence of a chiral shift reagent.[2]

Recently we reported a short synthesis of (+)-exo-brevicomin in which we developed a new methodology for transformation of optically active tartrate into 6,8-dioxabicyclo[3.2.1]octane derivatives effectively utilizing the inherent C_2-symmetry of tartrate.[3] Here we disclose an enantiospecific synthesis of the titled compound (1) using 6,8-dioxabicyclo[3.2.1]octane derivative (8) as the key intermediate which was prepared from (+)-(R,R)-diethyl tartrate (3) as the chiral starting material, and stereospecific reductive ring opening of the bicyclic carbon framework (9).



Acetalization of 3 with 4-phenylsulfonyl-2-butanone diethyl acetal (4) in the presence of p-TsOH (benzene/reflux/20 h) gave the sulfone-ester (5) as a syrup ($[\alpha]_D$-16.0°)[4] in 85% yield. Reduction of the ester function with $NaBH_4$[5] (EtOH/0-5 °C/1 h) providing the diol (6) followed by mesylation on treatment of 6 with 2.2 equiv. of MsCl in pyridine (0-5 °C/3 h) gave the crystalline dimesylate (7) (mp 96-98 °C) in 77% overall yield from 5. The dimesylate (7) underwent smoothly intramolecular alkylation on treatment with 1.2 equiv. of n-BuLi in THF at -20 °C for 1.5 h to furnish a 6,8-dioxabicyclo[3.2.1]octane derivative (8) ($[\alpha]_D$-34.5°) as a viscose in 82% yield.

Mundy has found recently that 5,7-dimethyl-6,8-dioxabicyclo[3.2.1]octane underwent reductive cleavage by use of AlH_3 to give stereospecifically 2,6-cis-tetrahydropyran derivative from which the racemate of 1 was synthesized.[6] The bicyclic compound (8) contains the whole carbons for construction of 1 and the requisite configuration of one (β-position to carbonyl) of the two asymmetric centers in 1.

After selective desulfonylation of 8 by treatment with Na and EtOH in THF (-20 °C/2 h/60%), the resultant bicyclic compound (9) ($[\alpha]_D$-45.5°) was submitted to the Mundy's condition (excess $AlCl_3$-$LiAlH_4$(4:1) complex/Et_2O/reflux/3 h) to afford the desired alcohol (10) ($[\alpha]_D$+10.0°) in high (80%) yield as the stereochemically homogeneous compound which exhibited a single doublet at 1.17 (3H, J= 6.0 Hz, CH_3-CH-O), a singlet at 3.10 (3H, CH_3SO_2), and a doublet at 4.34 (2H, J= 5.0 Hz, (OH)CH-CH_2-OMs) in NMR.[4] Treatment of 10 with K_2CO_3 in MeOH (0-5 °C/1.5 h) gave the epoxide (11) (79%), which showed also a single doublet at 1.20 (3H, J=6.0 Hz, CH_3-CH-O). The epoxide (11) was converted to the alcohol (13) ($[\alpha]_D$ +24.6°) in 48% overall yield via the vinylic compound (12) by deoxygenation of 11 with KSeCN[7] (excess) in aqueous MeOH (20 °C/20 h) followed by hydroboration (BH_3/THF/20 °C/2 h then 3 mol dm^{-3} NaOH/30% H_2O_2/20 °C/3 h). Jones oxidation of 13 at 20 °C for 1 h gave the desired carboxylic acid (1) ($[\alpha]_D$+46.8°(benzene)) in 71% as a syrup, which was esterified with CH_2N_2 in Et_2O to provide the methyl ester (2). The spectral data (NMR, IR) of the carboxylic acid (1) and the methyl ester (2) ($[\alpha]_D$+41.2°(benzene)) were identical with those of the authentic compounds[1,2] respectively.

References

1) B. Maurer, A. Grieder, and W. Thommen, Helv. Chim. Acta, 62, 44 (1979).
2) D. Seebach and M. Pohmakotr, Helv. Chim. Acta, 62, 843 (1979); B. Maurer and W. Thommen, ibid., 62, 1096 (1979).
3) Y. Masaki, K. Nagata, Y. Serizawa, and K. Kaji, Tetrahedron Lett., 23, 5553 (1982).
4) The specific optical rotations $[\alpha]_D$ were measured in 0.2 dm quartz cell usually as $CHCl_3$ solution unless otherwise noted. The NMR spectra were obtained at 60 MHz in $CDCl_3$ and the chemical shifts are reported in δ (ppm).
5) M. Taniguchi, K. Koga, and S. Yamada, Tetrahedron, 30, 3547 (1974).
6) Y. Kim and B. P. Mundy, J. Org. Chem., 47, 3556 (1982).
7) J. M. Behan, R. A. W. Johnstone, and M. J. Wright, J. Chem. Soc., Perkin 1, 1975, 1216.

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