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SHORT-STEP SYNTHESIS OF OPTICALLY AND BIOLOGICALLY ACTIVE EXO-BREVICOMIN

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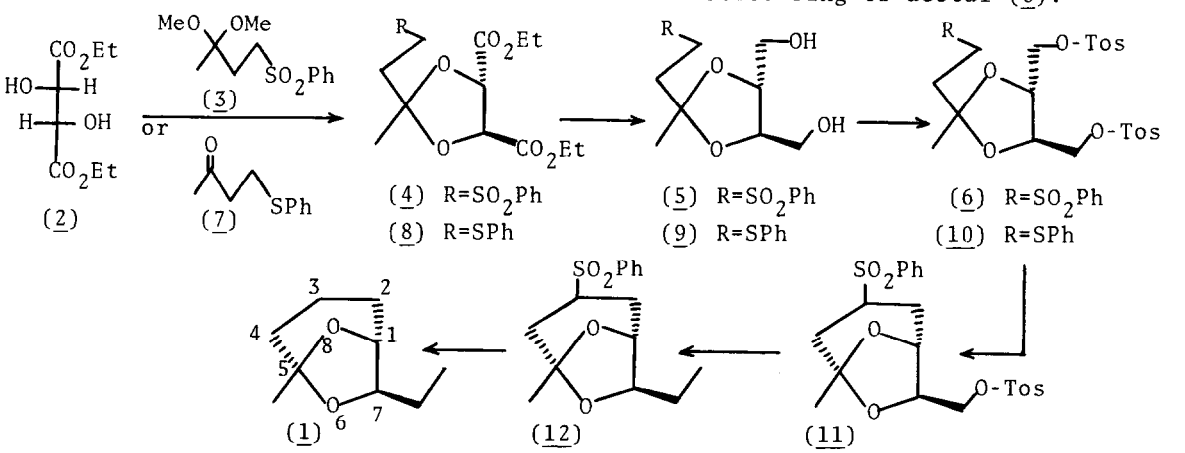
Summary: Optically and biologically active (1R,5S,7R)-(+)-exo-brevicomin was synthesized in the six-step sequence starting from diethyl (S,S)-(-)-tartrate.

Exo-brevicomin (1), one of the attractant pheromones of the western pine beetle, Dendroctonus brevicomis Le Conte, was isolated and identified as exo-7-ethyl-5-methyl-6,8-dioxabicyclo[3,2,1]octane by Silverstein[1] and the absolute stereochemistry of biologically active one was determined as (1R,5S,7R)-(1) by Mori's energetic synthetic study of both enantiomers[2] and biological evaluation.[3] Among the syntheses of exo-brevicomin,[4] the optically active version was limited to Mori's, Meyer's, and Bernardi's reports.[2,5,6] Except the last one,[6] steps involving the protection and regeneration of asymmetric glycol and steps required for the partial elongation of the carbon chain made the synthetic schemes relatively long in the former two reports although the asymmetric center of easily accessible tartaric acid was effectively took in the basic structure 6,8-dioxabicyclo[3,2,1]-octane of (1 and the enantiomer). Now we describe a short and practical synthesis of optically and biologically active exo-brevicomin (1) starting from diethyl (S,S)-(-)-tartrate (2) with a new concept in which the construction of the acetal functionality with the requisite carbon chain in the structure (1) on the first step of the synthesis requires no tedious protection and deprotection of diol portion of (2), and no differentiation of the two carboxylates in (2) is employed by intramolecular carbon-carbon coupling between the nucleophilic and the electrophilic partners located on the same face of the five membered ring of acetal (6).



Acetalization of (2)[2] with 4-phenylsulfonyl-2-butanone dimethyl acetal (3)[7] was carried out by heating at 80~90 °C in benzene for 20 h in the presence of catalytic amount of p-TsOH to give the sulfone-ester (4) as a syrup in 87% yield. Reduction of the ester functions with $NaBH_4$[8] in EtOH at 5 °C for 1 h gave nearly quantitatively the diol (5) which without purification was treated with 2.2 equiv. of p-TsCl in pyridine at 15 °C for 20 h to furnish the ditosylate (6) as a crystalline compound, mp. 98-100°C, $[\alpha]_D$+3.3°($CHCl_3$), in 90% yield from (4). This ditosylate (6) was also obtained by way of the other acetal (8) prepared from (2) and 4-phenylthio-2-butanone (7)[9] analogously (p-TsOH/benzene/reflux/2 d), reduction with $NaBH_4$ to the diol (9), mp. 60-61°C, $[\alpha]_D$-10.8°($CHCl_3$), tosylation to (10), and finally oxidation with m-Cl-perbenzoic acid (CH_2Cl_2/5 °C/1 h) in 62% overall yield. Intramolecular carbon-carbon coupling, the crucial step of the present synthesis was realized by treatment of (6) with 1.5 equiv. of n-BuLi in THF at -20~0 °C for 1 h, providing the desired 6,8-dioxabicyclo[3,2,1]octane (11) in 81% yield, mp. 138-139°C, $[\alpha]_D$+27.5°($CHCl_3$). The remaining tosylate functionality in (11) was effectively utilized for intermolecular alkylation. Thus, methylation of (11) by treatment with Me_2CuLi in Et_2O and Me_2S at -20~20 °C for 5 h produced 3-phenylsulfonyl-exo-brevicomin (12) (76%), mp. 85-87°C, $[\alpha]_D$+49.5° ($CHCl_3$). The final step, reductive desulfonylation was conveniently achieved on treatment of (12) with Na and EtOH in THF at 0~5 °C for 1.5 h. Purification of the product by chromatography on silica gel eluted with pentane-Et_2O and distillation gave pure (+)-exo-brevicomin (1) (67%), bp. 95-100°C/105 Torr.(bath temp.), $[\alpha]_D$+81.6°(Et_2O), which was identified with the authentic one by spectral comparisons (IR, NMR,and MS).[2]

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References and Notes.

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4) T. Cohen and J.R. Matz, J. Am. Chem. Soc., 102, 6900 (1980) and references cited therein.
5) H.H. Meyer, Liebigs Ann. Chem., 1977, 732.
6) Bernardi's synthesis of (1) was not so convergent due to low diastereoselectivities of double Grignard reactions of optically active α-oxy-aldehydes providing the desirable glycol; R. Bernardi, C. Fuganti, and P. Grasselli, Tetrahedron Lett., 22, 4021 (1981).
7) The compound (3) was prepared from methylvinyl ketone in 83% yield, mp.65-68°C, ($PhSO_2Na$/EtOH/AcOH/15 °C/20 h, then $HC(OMe)_3$/MeOH/c. H_2SO_4/15 °C/3 h).
8) Yamada reported that esters bearing oxygen functionality on the α position are generally reduced to alcohols with $NaBH_4$ in EtOH; M. Tniguchi, K. Koga, and S. Yamada, Tetrahedron, 30, 3547 (1974), and reference cited therein.
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