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FACILE AND RAPID ENTRY TO FUNCTIONALIZED AND OPTICALLY ACTIVE PYRANS FROM TARTARIC ACID BY WAY OF 6,8-DIOXABICYCLO[3.2.1]OCTANES. APPLICATION TO THE SYNTHESIS OF (-)-(6S,1'S)-PESTALOTIN

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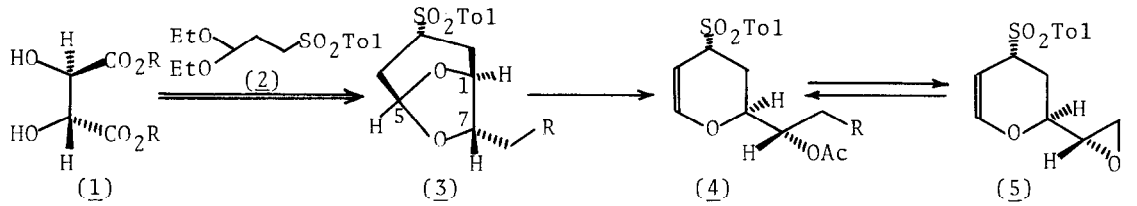
Summary: Optically active 7-exo-substituted-3-p-tosyl-6,8-dioxabicyclo[3.2.1]-octanes prepared from (+)-(R,R)-diethyl tartrate in four or five steps sequence effectively utilizing the inherent C_2 symmetry of tartrate, underwent acetolysis to lead to the new type of functionalized and optically active 3,4-dihydro-2H-pyrans in high yields. An application to the unambiguous synthesis of (-)-(6S,1'S)-pestalotin is reported.

We have recently reported a short-step synthesis of (+)-exo-brevicomin from (-)-(S,S)-diethyl tartrate (enantiomer of 1). In the synthesis, the inherent C_2 symmetry of tartrate (1) was effectively utilized for the differential homologation of the two carboxylate groups in 1.[1] Here we disclose a facile method for preparation of functionalized and optically active 3,4-dihydro-2H-pyrans (4), which have a broad spectrum for the synthesis of biologically important natural products, particularly of δ-lactones,[2] via acetolysis of intermediate 6,8-dioxabicyclo-[3.2.1]octanes (3) easily prepared from (+)-(R,R)-diethyl tartrate (1 R=Et).

6,8-Dioxabicyclo[3.2.1]octanes (3) with 7-exo-substituents were prepared from 1 (R=Et) and 3-p-tosylpropanal diethyl acetal (2) by four-steps sequence of reactions (acetalization, reduction, sulfonation, and intramolecular alkylation) and additional homologations with cuprate reagents R_2CuLi (R=Me, n-Pr, n-C_9H_{19}, and Ph) of the sulfonate terminus of 3a as analogously as the previous case.[1]



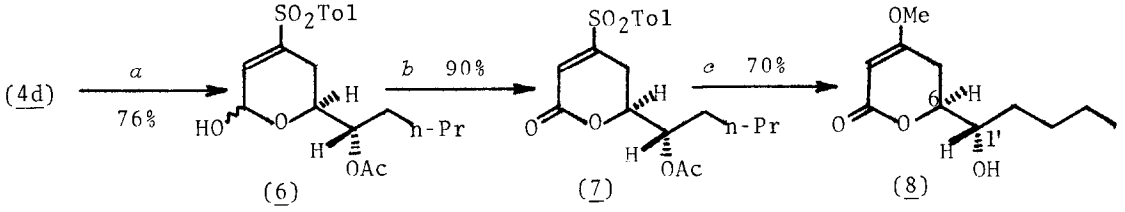
(1) (3) (4) (5)

Compound	a: R=O-Ts	b: R=O-Ms	c: R=Me	d: R=n-Pr	e: R=n-C_9H_{19}	f: R=Ph
3	58%*1	54%*1	73%*2	71%*2	78%*2	53%*2
4	71%*3	89%*3	80%*3	75%*3	72%*3	72%*3

*1 overall yield from diethyl tartrate (1). *2 yield from the tosylate (3a).
*3 yield from the bicyclic compound (3).

Considering the reactions of 1,6-anhydrohexoses in the literature,[3] the skeleton 3 might be cleft to furnish a new type of functionalized pyran framework bearing an additional asymmetric carbon substituent on the C(2)-position. Thus, treatment of the bicyclic compounds (3) with Ac_2O (excess) and 1.2 equiv of BF_3-Et_2O (CH_2Cl_2/0 °C/1.5 h) afforded in high yields 3,4-dihydro-2H-pyran derivatives (4) whose structures were supported by ^1H NMR analysis.[4] Homologation at the sulfonate terminus of 4a and 4b providing 4c-4f was achieved via the epoxide (5) which was obtained by treatment of 4a and 4b with K_2CO_3 in MeOH (0 °C/30 min/89-95%), on treatment with cuprate reagents (R_2CuLi) followed by acetylation.

A utilization of the compound 4d (mp 61-63 °C, $[\alpha]_D$+184.6° ($CHCl_3$)) in the synthesis of (-)-(6S,1'S)-pestalotin (8), a gibberellin synergist isolated from microorganisms,[2a] is illustrated below. Resultant crystalline pestalotin (8) showed mp 85-86 °C and $[\alpha]_D$-93.0° (MeOH) (lit.[2a] mp 88-89, 84-85 °C, $[\alpha]_D$-86.2°), and was identified with the natural one in the spectral comparison (IR, NMR, and mass). By the present synthesis of natural pestalotin (8) incorporating both asymmetric carbons of 1, the absolute configuration of the C(1')-carbon in 8 was determined chemically as (S).[5]



Conditions: *a* i) Br_2 (1 equiv), CH_2Cl_2, 0 °C, 5 min; ii) 5% aq. K_2CO_3, THF, 0 °C, 15 min: iii) NaOMe (1.5 equiv), THF, 0 °C, 0.5 h. *b* Jones reagent, acetone, 0 °C, 3 h. *c* K_2CO_3 (2 equiv), MeOH, r.t, 0.5 h.

References and Notes

1) Y. Masaki, K. Nagata, Y. Serizawa, and K. Kaji, Tetrahedron Lett., 23, 5553 (1982).
2) (a) Y. Kimura, K. Katagiri, and S. Tamura, Tetrahedron Lett., 1971, 3137; Y. Kimura and S. Tamura, Agr. Biol. Chem., 36, 1925 (1972); G. A. Ellestad, W. J. McGahren, and M. P. Kunstmann, J. Org. Chem., 37, 2045 (1972); (b) B. R. Laurence and J. A. Pickett, J. Chem. Soc., Chem. Commun., 1982, 59; (c) G. Snatzke and R. Hänsel, Tetrahedron Lett., 1968, 1797.
3) M. Cerny and J. Stanek, Jr., "Advance in Carbohydrate Chemistry and Biochemistry" R. S. Tipson and D. Horton, ed., Academic Press, New York (1977), Vol. 34, p. 23.
4) The diagnostic signals of C(6)- and C(5)-olefinic protons of the glycal system appeared at δ 6.66-6.73 as a split doublet (J=6.5 and 1.5 Hz) and at 4.57-4.88 as a multiplet respectively: B. Fraser-Reid and B. Radatus, J. Am. Chem. Soc., 92, 6661 (1970); S. Danishefsky, J. F. Kerwin, Jr., and S. Kobayashi, Ibid., 104, 358 (1982); O. Achmatowicz, Jr. and B. Szechner, Tetrahedron Lett., 1972, 1205.
5) Although several efforts concerning the determination of the absolute configuration of the two asymmetric centers in 8 have appeared, any clear chemical assignment of the absolute configuration of the C(1')-carbon has not been reported: J. Dillon and K. Nakanishi, J. Am. Chem. Soc., 96, 4055 (1974); K. Mori, M. Oda, and M. Matsui, Tetrahedron Lett., 1976, 3173 and ref. 2a).

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