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SYNTHESIS OF CHIRAL 1,2-DIOLS AND RELATED COMPOUNDS OF BIOLOGICAL ACTIVITIES VIA STEPWISE RING FISSION OF 5-ALKYL-6,8-DIOXABICYCLO[3.2.1]OCTANE SKELETON

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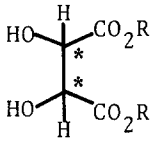
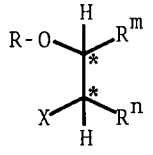
Summary: 5-Alkyl-7-mesyloxymethyl-6,8-dioxabicyclo[3.2.1]octanes, prepared from (+)-tartaric acid, were converted by means of an organoaluminium reagent Et_2AlSPh into the pyranoid monothioacetals, which were utilized via the successive thioacetalization to the synthesis of the insect pheromones (+)-disparlure and (-)-(2S,3S)-octanediol.

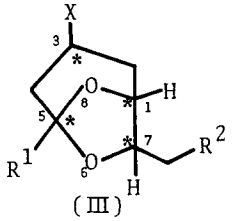
Tartaric acid (I R=H) is one of the few compounds, of which both enantiomers are readily available, and recognized as an ideal source of chiral building blocks particularly for the synthesis of chiral 1,2-diols and related compounds of type (II) including hydroxylactones, aminoalcohols, and epoxides.[1] In the previous papers,[2] we have reported a novel method for transformation of tartaric esters (I R=Me, Et) to 6,8-dioxabicyclo[3.2.1]octanes of type (III), synthetic versatility of which has been demonstrated by successful conversions into the pyranoid natural products. Although several solvolytic methods for the ring opening of the 5-unsubstituted bicyclic systems (III R^1=H) to lead to the functionalized pyranoids of type (IV R^1=H) have been well known in the field of 1,6-anhydrohexopyranose chemistry,[3] there has been no report, to our best knowledge, of successful ring opening of the 5-substituted ones (III R^1= Carbon Substituent) providing selectively the pyranoids (IV R^1=Carbon Substituent) except the reductive cleavage.[4]



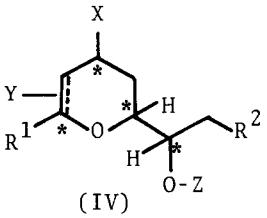
(I) * chiral center



(II)



(III)

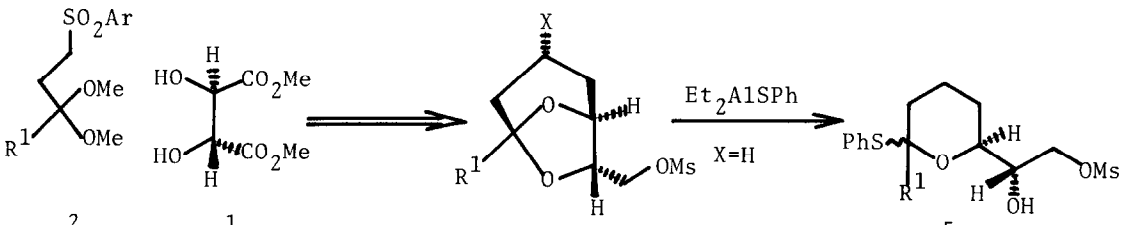


(IV)

In the context, after the extensive trials devoted to transacetalization of 5-alkylated bicyclics (III R^1=Alkyl),[5] we have attained an initial goal thereof and wish to report herein the monothioacetalization of 5-alkyl-7-

mesyloxy-6,8-dioxabicyclo[3.2.1]octanes (4) using an organoaluminium reagent Et_2AlSPh[6] to afford the pyranoids (5) which are recognized as the selectively functionalized, protected, and homologated building blocks derived from (+)-(R,R)-tartaric ester (1) and which were utilized to the enantiospecific synthesis of (2S,3S)-octanediol (12), the sex pheromone of a grape borer Xylotrechus pyrrhoderus,[7] (2S,3R)-2-benzyloxy-3-hydrazononane (14), a synthetic intermediate for (+)-erythro-9-(2S-hydroxy-3R-nonyl)adenine [(+)-EHNA] of potent inhibitory activity of enzyme adenosine deaminase,[8] and (+)-(7R,8S)-disparlure (19), the sex pheromone of a gypsy moth Porthetria dispar.[9]

The 5-alkylated bicyclics (4a–4d) were prepared starting with (+)-(R,R)-dimethyl tartrate (1) and β-arylsulfonyl ketone dimethylacetals (2) by way of the chemoselective reductive desulfonylation of 5-alkyl-3-arylsulfonyl-7-mesyloxymethyl-6,8-dioxabicyclo[3.2.1]octanes (3) according to the reported method in 5 steps.[2a,c] All the attempts for the monothioacetalization of the bicyclic compounds (4a) using thiophenol (PhSH) and Lewis acid (BF_3-Et_2O and $AlCl_3$) were in vain.[5]



2
a: R^1=Me
b: R^1=Et
c: R^1=i-Pr
d: R^1=n-C_6H_{13}

1

3 X=SO_2Ar

4 X=H

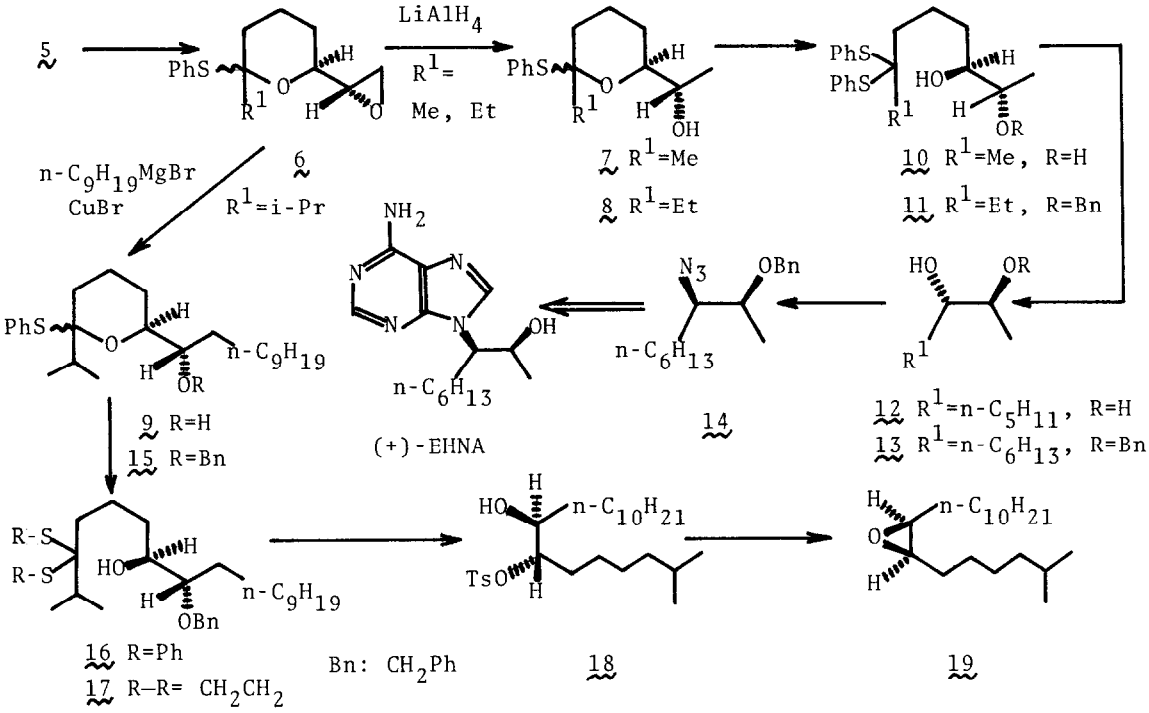
Ar: Ph, Tol

5
a: 78% (at 0 °C)
b: 76% (at −10 °C)
c: 87% (at −70∼−20°C)
d: 89% (at −10 °C)

Recently, the powerful nucleophilicity of the organoaluminium reagent of type R_2AlX (X=OR', NR'$_2$, and SR') on reaction with the oxygen-functionalities (esters, epoxides, and oximesulfonates) have been disclosed.[6] We examined in turn the reaction of the intramolecular bicyclic acetals (4) with diethylaluminiumthiophenoxide Et_2AlSPh aiming at the monothioacetals of type (5). Thus, dropwise addition of a toluene solution of Et_2AlSPh (1.2 equiv) to a cold (0 °C) solution of 4a in toluene under nitrogen followed by stirring the mixture for 30 min at the temperature gave in 78% yield the desired monothioacetal (5a) as a diastereoisomeric mixture after the usual work up and purification. Other 5-alkylated bicyclics (4b,c,d) were also transformed in high yields (76–89%) to the corresponding pyranoids (5b,c,d) by the same reaction at the low temperature (−10∼−70 °C).

Having made this realization, we embarked on a program to transform the pyranoids (5) to the biologically active 1,2-diol (12) and related compounds

(14) and (19). The monothioacetals (5) were converted in high yields (66~81%) to the epoxides (6) upon treatment with K_2CO_3 in MeOH (0 °C/1 h). For 6a and 6b, reduction with $LiAlH_4$ in Et_2O (0 °C/1 h) yielded the alcohols (7) (96%) and (8) (94%), respectively. On the other hand, the epoxide (6c) was alkylated by a Grignard reagent n-$C_9H_{19}MgBr$ in the presence of a catalytic amount of CuBr in THF at −40 °C for 1.5 h to give in 77% yield the alcohol (9), which has the whole carbon chain and the requisite configuration for the synthesis of (+)-disparlure (19).



In the preliminary experiment, the alcohol (7) was converted upon treatment with an excess of PhSH in the presence of an equiv of $AlCl_3$ (CH_2Cl_2/0 °C/1.5 h) into the acyclic thioacetal (10) in 71% yield, and the alcohol (8), after the OH-protection with benzyl ether, was led to the thioacetal (11) in 68% yield under the same reaction conditions. The pheromone (-)-(2S,3S)-octanediol (12) ($[\alpha]_D$−15.8° (c=1.20, $CHCl_3$)) was obtained by desulfurization of 10 with Raney-nickel (W-2) (EtOH/20 °C/30 min) in 70% yield.[10] The thioacetal (11) was transformed also to the diol monobenzyl ether (13) in 72% yield, from which the known azide (14) ($[\alpha]_D$+11.3° (c=0.76, $CHCl_3$))[10] was obtained in 85% yield by the modified Mitsunobu reaction[11] (HN_3/Ph_3P/diethyl azodicarboxylate/benzene) with inversion of configuration at the C(3) position. The azide (14) was used as the optically active aliphatic part for the synthesis of (+)-EHNA by Abushanab and coworkers.[8]

Attempted solvolysis of the benzyl ether (15), derived from the alcohol

(9), using PhSH with $AlCl_3$, however, afforded the desired thioacetal (16) as the minor product and the major one was the corresponding diol, debenzylated product of 16. Ethanedithiol was used in turn in place of PhSH in the reaction ($AlCl_3$ (1 equiv)/CH_2Cl_2/0 °C/30 min) of 15 to furnish successfully the ethylene-thioacetal (17) in 77% yield. Consecutive manipulation of 17 involving desulfurization (Raney-nickel/67% yield), tosylation (TsCl/pyridine/20 °C/2 d/ 78% yield), and debenzylation by catalytic hydrogenation using palladium black (EtOH/20 °C/94% yield) provided the diol monotosylate (18) as a crystalline compound (mp 40-42°, $[\alpha]_D$−11.9° (c=2.56, $CHCl_3$)) which was identified with the authentic compound (mp 41.0-41.5°, $[\alpha]_D$−12.3° (c=2.0, $CHCl_3$))[9b] by spectral comparison. Present synthesis of the diol monotosylate (18) comprises the synthesis of optically and biologically active (+)-(7R,8S)-disparlure (19) since Mori and coworkers achieved the epoxidation of 18 providing 19.[9b]

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References and Notes

1) D. Seebach and E. Hungerbühler, "Modern Synthetic Methods" R. Scheffold, ed., Otto Salle Verlag, Frankfurt am Main (1980), vol. 2, p. 91; K. Mori, "The Total Synthesis of Natural Products" J. ApSimon, ed., Wiley, New York (1981), vol. 4, p. 1.
2) (a) Y. Masaki, K. Nagata, Y. Serizawa, and K. Kaji, Tetrahedron Lett., 23, 5553 (1982); (b) Idem., ibid., 25, 95 (1984); (c) Y. Masaki, Y. Serizawa, K. Nagata, and K. Kaji, Chem. Lett., 1983, 1601; (d) Y. Masaki, K. Nagata, and K. Kaji, ibid., 1983, 1835.
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) Y. Kim and B.P. Mundy, J. Org. Chem., 47, 3556 (1982).
5) Y. Masaki, Y. Serizawa, K. Nagata, and K. Kaji, Chem. Lett., 1984, 2105.
6) K. Oshima and H. Nozaki, J. Synth. Org. Chem. Jpn., 38, 460 (1980); K. Maruoka and H. Yamamoto, ibid., 43, 429 (1985).
7) T. Sakai, Y. Nakagawa, J. Takahashi, K. Iwabuchi, and K. Ishii, Chem. Lett., 1984, 263.
8) E. Abushanab, M. Bessodes, and K. Antonakis, Tetrahedron Lett., 25, 3841 (1984); G. Bastian, M. Bessodes, R.P. Panzica, E. Abushanab, S-F. Chen, J.D. Stoeckler, and R.E. Parks, Jr., J. Med. Chem., 24, 1383 (1981).
9) (a) B.A. Bierl, M. Beroza, and C.W. Collier, Science, 170, 87 (1970); (b) K. Mori, T. Takigawa, and M. Matsui, Tetrahedron, 35, 833 (1979).
10) The pheromone (12) and the azide (14) synthesized were identified respectively with the corresponding authentic samples 12 ($[\alpha]_D$−19.2° (c=1.45, $CHCl_3$))[7] and 14 ($[\alpha]_D$+13.4° (c=1.31))[8] by spectral comparison.
11) H. Loibner and E. Zbiral, Helv. Chim. Acta, 59, 2100 (1976).

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