ENANTIOSELECTIVE SYNTHESIS OF 16-MEMBERED α,β,γ,δ-UNSATURATED DIOLIDE: A MODEL SYSTEM IN ELAIOPHYLIN

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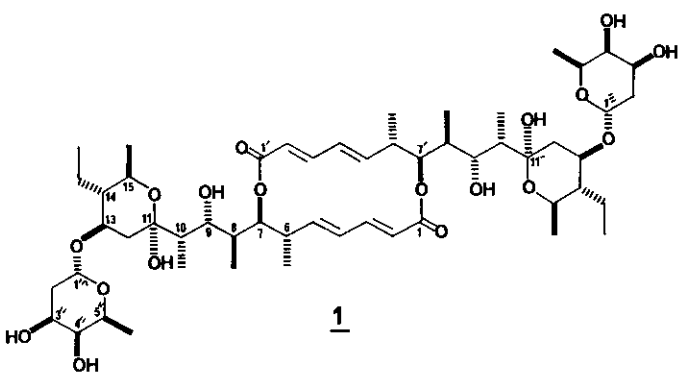
(Dedicated to Professor Gilbert Stork on the occasion of his 65th birthday)

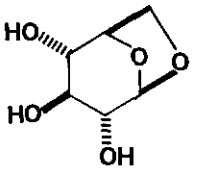
Abstract- The synthesis of the entitled diolide (17) has been achieved starting from levoglucosan(1,6-anhydro-β-D-glucopyranose) (2) via the macrocyclization of the hydroxy acid (16) by reaction of mixed phosphoric anhydride procedure.

Discovery of 16-membered macrodiolides with C_2-symmetry has stimulated widespread interest in synthetic chemistry owing to their antibiotic activity. Elaiophylin(1) [$C_{54}H_{88}O_{18}$, MW 1025] was first isolated from cultures of Streptomyces melanosporus[1a], and exhibits activity against Gram-positive bacteria. Azalomycin B, salbomycin, and antibiotic 255 E, which proved to be identical with elaiophylin were subsequently isolated from other strains of Streptomyces.[1b-e] The structure was elucidated by X-ray crystallographic analysis as 1 that is the bislactone with L-oliose(2-deoxyfucopyranose).[2] Most recently, the first total synthesis of (+)-11,11'-di-O-methylelaiophylidene which is an aglycone of elaiophylin(1) has been published by Seebach and his collaborators.[3a] They have also reported the construction of a model compound such as a 16-membered diolide ring.[3b]



1

In connection with our own program directed toward the synthesis of 1, we report herein the preliminary studies on an effective formation of the hydroxy acid (16) followed by its macrodimerization(16 → 17). We have sought that the structurally rigid and readily available levoglucosan (2) is an ideal carbohydrate building block with the desired chiral centers for the synthesis of the hydroxy acid (16). Thus, the known procedure was partly improved by us to prepare levoglucosan (2)[4], which was converted to the epoxy tosylate (3) by treatment with p-toluenesulfonyl chloride, followed by reaction with sodium methoxide according to the literature procedure.[5] Epoxide ring opening in 3 has been extensively investigated[6a,b,c], and finally the epoxide 3 was found to be opened stereoselectively to give tosylate (4) in a good yield by copper (I) induced reaction with methylmagnesium chloride in tetrahydrofuran(THF). Reductive removal of the tosylate group of 4 was effected by using lithium triethylborohydride to give rise to alcohol (5).[6c]



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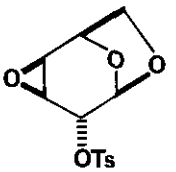

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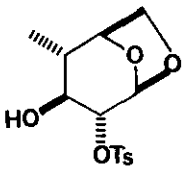

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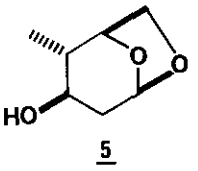
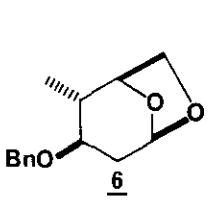


5

Alcohol 5 was cleanly converted to the benzyl ether (6) in a conventional way($C_6H_5CH_2Br$, NaH, n-Bu_4NI, THF, rt,100%). The cleavage of the 1,6-anhydro bridge of 6 was carried out with boron trifluoride ether complex in methanol to afford acetal (7) in 97% yield which is an anomeric mixture in a 5:1 ratio of α- and β-isomers. Treatment of 7 with p-toluenesulfonyl chloride in pyridine at room temperature followed by reduction with lithium triethylborohydride in THF led to the dimethyl acetal(9) in 93% overall yield. Hydrolysis of 9 with 10% sulfuric acid in THF at 50°C for 24 h gave the hemiacetal (10) in 81% yield which was immediately transformed into diol (11) by reaction with lithium aluminum hydride in THF at 0°C for 3 h in 97% yield [IR(film) 3400 cm^{1} ;PMR($CDCl_3$)δ 0.83(d,J=7.0Hz,3H),1.19(d,J=6.1Hz,3H),1.58-2.11(m,3H),2.69(br s, 2H),3.68-3.95(m,4H),4.45(d,J=11.3Hz,1H),4.75(d,J=11.3Hz,1H),7.34(s,5H); $[\alpha]_D$=+47°(c=1.58,$CHCl_3$)]. Selective silylation of diol (11) at the primary hydroxy group with t-butyldimethylchlorosilane containing triethylamine in the presence of catalytic amounts of 4-dimethylaminopyridine(DMAP) in acetonitrile afforded the silyl alcohol (12) in 85% yield.



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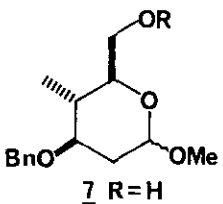
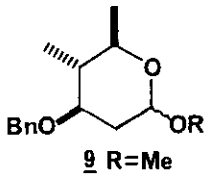
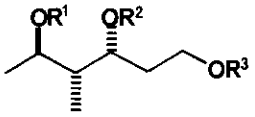


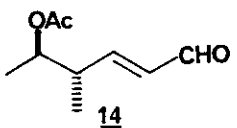
7 R=H
8 R=Ts



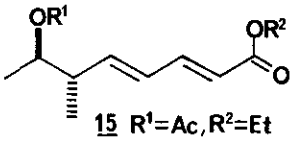
9 R=Me
10 R=H



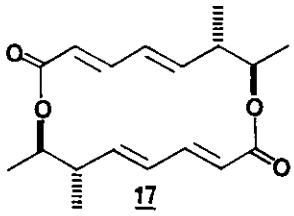
11 R^1=H, R^2=Bn, R^3=H
12 R^1=H, R^2=Bn, R^3=$SiMe_2Bu^t$
13 R^1=R^2=Ac, R^3=$SiMe_2Bu^t$



14



15 R^1=Ac, R^2=Et
16 R^1=R^2=H



17

Debenzylation of 12 (H_2,10%Pd/C, ethyl acetate, 81%) followed by acetylation of diol (Ac_2O, pyridine, DMAP ,rt, 83%) gave diacetate (13). Removal of the silyl protecting group of 13 with HF-CH_3CN(1:19) at 0°C followed by oxidation with pyridinium chlorochromate using 4A molecular sieves in dichloromethane[7] yielded directly the α,β-unsaturated aldehyde (14) in 81% yield after purification by chromatography on Florisil [IR(film) 2700,1740,1690,1640,1240 cm^{-1}; PMR($CDCl_3$)δ 1.13(d,J=7.1Hz,3H),1.22(d,J=6.4Hz,3H),2.04(s,3H),2.55-2.87(m,1H), 4.97(dq,J=12.7 and 6.4Hz,1H),6.13(ddd,J=15.7,7.6,and 1.0Hz,1H),6.78(dd,J=15.7 and 7.8Hz,1H),9.53(d,J=7.8Hz,1H);$[\alpha]_D$=+16°(c=0.5,$CHCl_3$)]. Wittig reaction of 14 with carboethoxymethylenetriphenylphosphorane in dichloromethane at room temperature proceeded smoothly to give an 11:1 mixture of E,E- and E,Z-unsaturated esters, from which the pure E,E-isomer(15) was obtained in 76% yield. Subsequent hydrolysis of 15 with 1N-KOH in THF gave the desired hydroxy acid (16)[8] in nearly quantitative yield. Finally dimerization of 16 was accomplished by the method of mixed phosphoric anhydride generated by reaction of hydroxy acid 16 with diethylphosphorochloridate[9] to afford the 16-membered diolide (17)[10] as crystals in 31% isolated yield after chromatography on silica gel.

Spectral properties of the synthetic diolide 17 obtained in this way were identical with those of reported data.[3b] The synthesis of C(11)-C(15) segment containing L-oliose moiety in both sides is in progress from 2.

ACKNOWLEDGMENT

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8. (16): IR(film) 3600-2400,3400,1690,1640,1620 cm^{-1}; PMR($CDCl_3$)δ 1.07(d,J=6.8Hz,3H),1.19(d,J=6.4Hz,3H),2.21-2.41(m,1H),3.59-3.78(m,1H), 5.82(d,J=15.4Hz,1H),5.99-6.42(m,2H),6.10-6.60(bs.,2H),7.35(dd,J=15.1 and 10.7Hz1H); $[\alpha]_D$=-39°(c=1.8,$CHCl_3$),(lit.[3b] $[\alpha]_D$=-38.7° (c=0.75,$CHCl_3$)).
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10. (17): mp 180-181°C (lit.[3b] 179.5-180.5°C); IR($CDCl_3$)1700,1640,1610 cm^{-1}; PMR($CDCl_3$)δ 1.07(d,J=6.6Hz,6H),1.33(d,J=6.3Hz,6H),2.02-2.34(m,2H), 4.88(dq,J=9.8 and 6.4Hz,2H),5.57(d,J=15.1Hz,2H),5.62(dd,J=15.1 and 9.5Hz ,2H),6.04(dd,J=15.1 and 10.5Hz,2H),6.96(dd,J=15.4 and 10.8Hz,2H); MS m/e 304(M+); $[\alpha]_D$=+82°(c=1.3,$CHCl_3$), (lit.[3b] $[\alpha]_D$=+82.6°(c=0.955,$CHCl_3$)).

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