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ENANTIO- AND STEREO-SELECTIVE SYNTHESIS OF 2,6-DIDEOXYHEXOSES FROM DIVINYLCARBINOL

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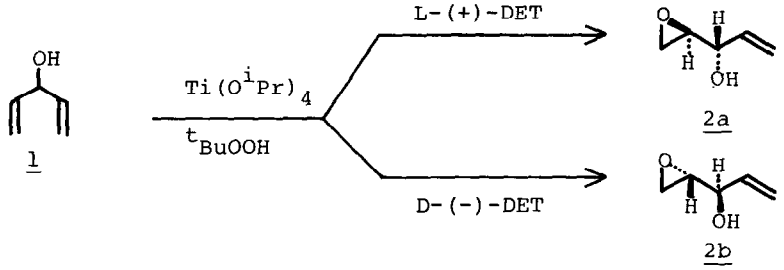
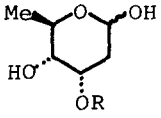
Summary: Four 2,6-dideoxyhexoses; D-(+)-digitoxose, D-(+)-cymarose, D-(+)-olivose, and D-(-)-oleandrose have been synthesized stereo- and enantioselectively starting with (+)-(2R,3S)-1,2-epoxypent-4-en-3-ol prepared by asymmetric epoxidation of divinylcarbinol.

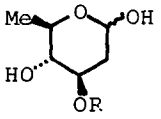
In recent years the synthesis of deoxysugars has attracted great attention because of their broad existence as a sugar component in various antibiotics as well as their characteristic 2,3,4-triol systems which present in a number of polyhydroxylated natural products.[1] We have recently reported[2,3] that the titanium-tartrate mediated asymmetric epoxidation[4] of prochiral divinylcarbinol (1) having a σ-symmetrical nature proceeded with high diastereoselectivity (erythro/threo=97/3) and enantioselectivity (>90% ee)[5] to produce either (2R,3S)-1,2-epoxypent-4-en-3-ol (2a) or it's enantiomer 2b, depending on the chirality of the tartrate used. We now wish to describe a novel enantio- and stereo-selective synthesis of four 2,6-dideoxyhexoses; D-(+)-digitoxose (3),[1b,6,7] D-(+)-cymarose (4),[1b] D-(+)-olivose (5),[1b,8] and D-(-)-oleandrose (6)[9,10] using (2R,3S)-1,2-epoxypent-4-en-3-ol (2a) as a chiral building block.



1 2a 2b



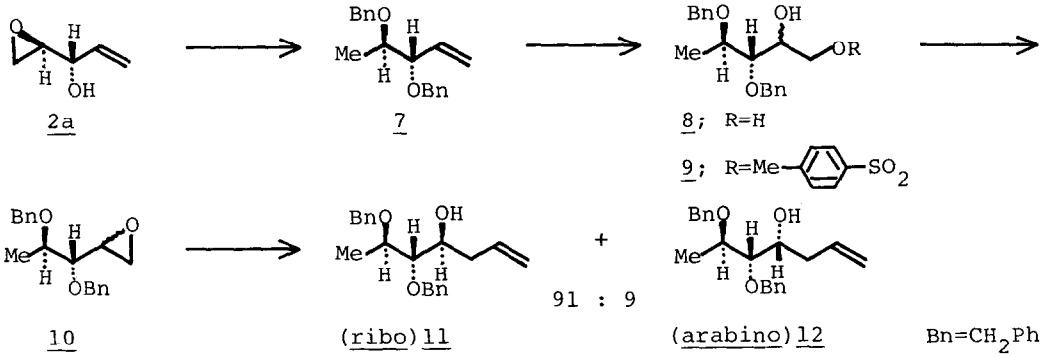
R=H; D-(+)-digitoxose (3)
R=Me, D-(+)-cymarose (4)



R=H; D-(+)-olivose (5)
R=Me; D-(-)-oleandrose (6)

(2R,3S)-1,2-Epoxypent-4-en-3-ol (2a), prepared from divinylcarbinol (1) as mentioned above, was subjected to reduction ($LiAlH_4$, THF,-20°C) followed by benzylation[11] ($PhCH_2Br$, NaH, 10 mol % $^{n}Bu_4NI$, THF, 25°C) in the same flask to give the benzyl ether 7,[12] $bp_{0.25}$ 120°C (Kugelrohr), $[\alpha]_D^{17}$ +37.4° (c 1.129, $CHCl_3$), in 87% yield. In order to achieve stereoselective introduction of the requisite hydroxyl group either with ribo-configuration or with arabino-configuration, the following routes were examined. Thus, hydroxylation[13] of 7 (1 mol %

OsO_4, N-methylmorpholine N-oxide monohydrate, 50% aq. acetone, 25°C) afforded an inseparable epimeric mixture of the diol 8 in 90% yield. The diol was then converted into the epoxide 10, $bp_{0.45}$ 170°C, by tosylation (p-TsCl, pyridine, 25°C) followed by treatment with potassium carbonate (MeOH, 25°C) in 79% overall yield. Reaction of 10 with vinylmagnesium bromide in the presence of copper(I) iodide (THF, -78°C) yielded the ribo-alcohol 11,[14] $[\alpha]_D^{19}$ -43.2° (c 1.024, $CHCl_3$), and the arabino-alcohol 12,[15] $[\alpha]_D^{19}$ -24.0° (c 0.716, $CHCl_3$), in a ratio of 91:9[16] in 93% yield.[17]

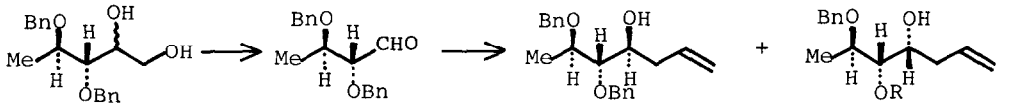


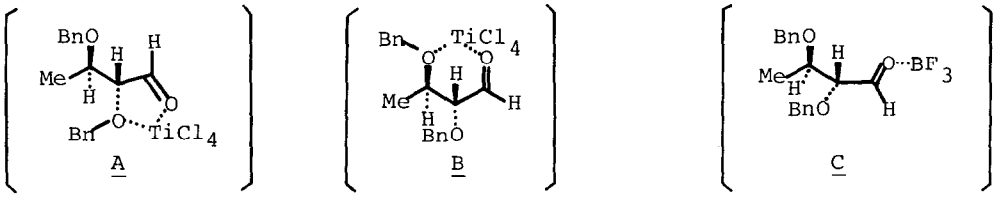
2a 7 8; R=H 9; R=Me-C6H4-SO2 10 (ribo) 11 (arabino) 12 Bn=CH2Ph

On the other hand, addition of allyltrimethylsilane to the aldehyde 13, prepared by oxidative cleavage of the diol 8 ($Pb(OAc)_4$, THF, -30°C), in the presence of titanium tetrachloride (CH_2Cl_2, -90°C) according to the Reetz's procedure[18] afforded the ribo-alcohol 11 and the arabino-alcohol 12 in a ratio of 5:>95[16] in 80% overall yield from 8. It is interesting to add that upon this addition reaction at -78°C instead of -90°C, concomitant regioselective cleavage of the benzyl group took place to give the diol 14, mp 53°C (^{n}hexane), $[\alpha]_D^{17}$ -22.3° (c 1.057, $CHCl_3$), in 29% yield together with 46% yield of 12. These results reveal that the chelated transition state A predominated over the other possible chelated structure B in this titanium mediated addition of allyltrimethylsilane to 13. Moreover, this addition reaction was also examined using tin tetrachloride or boron trifluoride etherate in place of titanium tetrachloride. The results are summarized in the Table which shows that boron trifluoride etherate mediated addition resulted in the opposite diastereofacial selection reflecting the nonchelated transition state C as postulated by Reetz.[18]

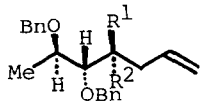
Having developed the stereoselective routes to the ribo-alcohol 11 and the arabino-alcohol 12, conversion of 11 and 12 into 2,6-dideoxyhexoses was then investigated. Thus, the ribo-alcohol 11 was subjected to debenzylation (Li, liq. NH_3-THF, -33°C) followed by ozonolysis (O_3, MeOH, -20°C, then Me_2S, 25°C) to furnish D-(+)-digitoxose (3), mp 104-106°C (AcOEt) (lit.[1b] 102-103°C), $[\alpha]_D^{24}$ +46.0° (c 1.807, H_2O, equilibrated) (lit.[1b] +48.8°), in 74% overall yield. Furthermore, 11 was converted into D-(+)-cymarose (4), mp 84-85°C (Et_2O/^{n}hexane) (lit.[1b] 84-85°C), $[\alpha]_D^{20}$ +51.2° (c 2.112, H_2O, equilibrated) (lit.[19] +54.9°), via the methyl ether 15, $[\alpha]_D^{19}$ -3.8° (c 1.197, $CHCl_3$), in 77% overall yield by three

steps (i. methylation (MeI, NaH, THF, 25°C), ii. debenzylation (Li, liq. NH_3-THF, -33°C), iii. ozonolysis (O_3, MeOH, -20°C, then Me_2S, 25°C)). Similarly, the arabino-alcohol 12 was transformed into D-(+)-olivose (5), $[\alpha]_D^{22}$ +15.7° (c 1.590, H_2O, equilibrated) (lit.[1b] +19.4°), (70% yield) and D-(-)-oleandrose (6), $[\alpha]_D^{22}$ -11.8° (c 1.150, H_2O, equilibrated) (lit.[9b] +11.9° for it's antipode), (60% yield) via the methyl ether 16, $[\alpha]_D^{19}$ -18.5° (c 1.017, $CHCl_3$). Each of these synthetic 2,6-dideoxyhexoses exhibited spectral properties (^{1}H-NMR and ^{13}C-NMR in D_2O) in accord with those reported.[1b,10]

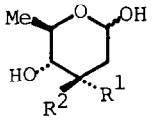




Lewis acid	temp, °C	yield from 8, %	product ratio[16] 11/12
$TiCl_4$	-90	80	5/95
$SnCl_4$	-90	63	19/81
BF_3 Et_2O	-90	39	88/12
BF_3 Et_2O	-78	52	88/12



11; R^1=OH, R^2=H
12; R^1=H, R^2=OH
15; R^1=OMe, R^2=H
16; R^1=H, R^2=OMe



3; R^1=OH, R^2=H
4; R^1=OMe, R^2=H
5; R^1=H, R^2=OH
6; R^1=H, R^2=OMe

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References and Notes

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14. ^{1}H-NMR ($CDCl_3$): δ 1.33 (3H, d, 6 Hz), 2.10-2.60 (3H, m, 1H exchangeable with D_2O), 3.30-4.03 (3H, m), 4.30-4.85 (4H, m), 4.90-5.40 (2H, m), 5.45-6.25 (1H, m), 7.30 (10H, s).
15. ^{1}H-NMR ($CDCl_3$): δ 1.28 (3H, d, 7 Hz), 2.31 (2H, br.t, 6 Hz), 2.89 (1H, d, 6 Hz, exchangeable with D_2O), 3.38 (1H, dd, 3 Hz and 5 Hz), 3.60-4.13 (2H, m), 4.35-5.30 (6H, m), 5.50-6.30 (1H, m) 7.33 (10H, s).
16. The ratio was determined by HPLC (column LS 410K, 3:1 MeCN-H_2O).
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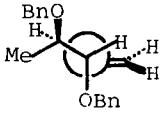
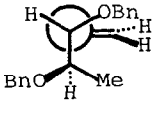


A



B

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