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REACTION OF 4,6-O-BENZYLIDENE-3-O-MESYL-ALLAL WITH ALLYLIC GRIGNARD REAGENTS. HIGHLY REGIO- AND STEREOSELECTIVE PREPARATION OF 2,6-DISUBSTITUTED DIHYDROPYRAN RINGS[1)]

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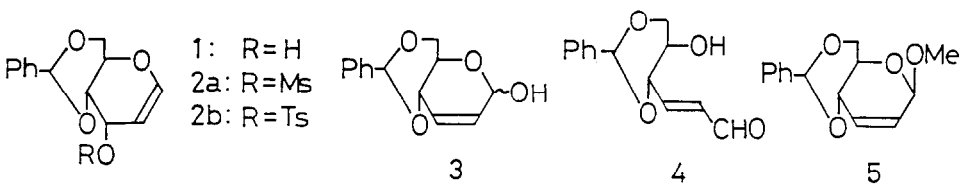
Summary: The reaction of 4,6-O-benzylidene-1,2-dideoxy-3-O-mesyl-D-ribo-hex-1-enopyranose reacted with 2-propenylmagnesium chloride or 2-methyl-2-propenylmagnesium chloride to give 1,5-anhydro-4,6-O-benzylidene-2,3-dideoxy-1-C-prop-2-enyl- (or 2-methylprop-2-enyl)-β-D-erythro-hex-2-enitol in good yield.

Glycals have been utilized as versatile starting materials for the synthesis of carbohydrates and, in recent years, chiral natural products. In order to introduce a carbon chain on the C-1 position, glycals are generally treated with carbon nucleophiles in the presence of Lewis acids or transition metals.[2)] It would be expected, however, that a glycal having a suitable leaving group at the C-3 position reacts with carbanions in the absence of acidic catalysts to give 1,5-anhydro-2,3-dideoxy-1-C-alkyl- (or alkenyl)-hex-2-enitols. In This paper, we wish to report a highly stereo- and regioselective reaction of allylic Grignard reagents with 3-O-mesylate of 4,6-O-benzylidene-1,2-dideoxy-D-ribo-hex-1-enopyranose (1).[3)]

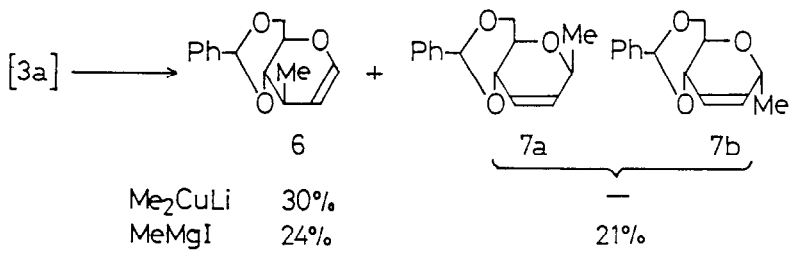
Although 3-O-acyl derivatives of 1 can be readily prepared,[4)] attempts to isolate the mesylate or tosylate of 1 (2a or 2b) were unsuccessful. Thus, when 1 in tetrahydrofuran (THF) was reacted first with small excess of n-butyllithium and then with 1.5~2 molar equivalents of mesyl chloride or tosyl chloride at -70°~-80 °C for 30~80 min, followed by treatment with saturated aqueous sodium bicarbonate, a mixture of 2-enopyranose (3) and α,β-unsaturated aldehyde (4) was obtained in 70~80% yield rather than expected 2a or 2b. When sodium methoxide in methanol was added to the reaction mixture obtained by the reaction of 1 with n-butyllithium and mesyl chloride (-70°~room temperature, 1.5 h), compound 5 was isolated in 91% yield.[5)]



3 4 5

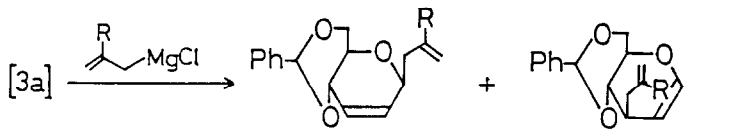
The high yield formation of 5 suggests that 2a or 2b is generated in the solution by the procedure described above and they are susceptible to nucleophilic attack. Therefore, the solution of 2a thus prepared was used in the subsequent reaction with organometallics.

Mesylate 2a reacted with lithium dimethylcuprate at -80 °C~room temperature giving compound 6 in 30% yield, while, on treatment with methylmagnesium iodide (0°~10 °C, 12 h), 2a afforded 6 and 1-C-methyl-erythro-hex-2-enitol (7) in 24% and 21% yields, respectively. The stereochemistry at C-3 in 6 was assigned as indicated by coupling constants of $J_{1,2}$ = 6.3 Hz and $J_{2,3}$ =1.8 Hz.[6] The NMR spectrum of 7 showed two methyl proton doublets at δ 1.20 and 1.25 ppm in a ratio of about 1 : 2.5 suggesting a mixture of α- and β-isomers.



The reaction of 2a with 2-propenylmagnesium chloride and with 2-methyl-2-propenylmagnesium chloride proceeded smoothly, with transposition of the double bond to C_2-C_3, giving the corresponding 1-C-prop-2-enyl-β-D-erythro-hex-2-enitols, 8 and 9, in 73% and 77% yields, respectively. The stereochemistry at C-1 in 8 and 9 was determined by NOE experiments. Irradiation of C_1-H in 8 at 400 MHz showed an enhancement of 24 ± 5% in the C_5-H signal. Similarly, irradiation of C_1-H in 9 showed 18 ± 5% enhancement of C_5-H signal.[2d]

In both reactions, small amounts of side products (sirup) were obtained, the structures being tentatively assigned to be 10 (5% yield) and 11 (6% yield) on the bases of NMR measurement. Thus, C_1-H signals of 10 and 11 appeared at δ 6.2 ppm (dd) with $J_{1,2}$ =~6 Hz and $J_{1,3}$=~2 Hz which consistent with the structures suggested.[6]



R=H: 8 (73%) 10 (~5%)
R=Me: 9 (77%) 11 (~6%)

The procedure developed in this paper makes functionalized dihydropyrans, 8 and 9, readily available and suggests interesting possibilities for further work.

Typical procedures are as follows: Reaction of 2a with lithium dimethylcuprate. To a solution of 1 (351 mg, 1.5 mmol) in THF (5 ml) cooled at -70° ~ -80 °C under Ar was added n-BuLi (2.3 mmol). After the mixture had been stirred for 30 min, a solution of mesyl chloride (342 mg, 3 mmol) was added and stirred at 0 °C for 1 h. The solution was then added to lithium dimethylcuprate prepared from CuI (1.5 g) and methyllithium (ether solution) at -80 °C under Ar. The resulting mixture was allowed to warm to 0 °C in 80 min and stirred for 3 h at this temperature. Saturated aqueous NH_4Cl was added and the mixture was filtered through Hyflosupercel. Organic layer was separated, washed with aqueous NH_4Cl, aqueous $NaHCO_3$, dried ($MgSO_4$), and evaporated. The residue was separated by preparative layer chromatography (benzene-ethyl acetate = 3 : 1) giving 6 in 30% yield and 13% of 1 was recovered. An analytical sample of 6 was obtained by recrystallization from ethanol; mp 64°-65 °C, $[\alpha]_D^{16}$ -40.4° (c 0.569, $CHCl_3$). NMR (60 MHz, CCl_4) δ 1.08 (d, CH_3), 2.0-2.8 (m, C_3-H), 3.1-4.6 (m, C_4-H, C_5-H, C_6-H), 4.45 (dd, C_2-H, $J_{1,2}$ = 6.2 Hz, $J_{2,3}$ =1.8 Hz), 5.43 (s, PhCH), 6.18 (dd, C_1-H, $J_{1,3}$ = 2.6 Hz), 7.1-7.5 (m, aromatic-H).

Reaction of 2a with 2-methyl-2-propenylmagnesium chloride. To a solution of 2-methyl-2-propenylmagnesium chloride prepared from 2-methyl-2-propenyl chloride (453 mg, 5.0 mmol) and magnesium (109 mg, 4.5 mmol) in THF (6 ml) was added a solution of 2a prepared as described above at 0 °C. After the mixture had been stirred for 30 min, the reaction was quenched with aqueous NH_4Cl. Organic layer was separated and aqueous layer was extracted with ether. Organic layers were collected, washed successively with aqueous NH_4Cl, $NaHCO_3$, and NaCl, dried ($MgSO_4$), and evaporated. The residue was separated by preparative layer chromatography (benzene) giving 9 (314 mg, 77%) and 11 (23 mg, 6%), and 5% of 1 was recovered. An analytical sample of 9 was obtained by recrystallization from ethanol, mp 52°-53 °C, $[\alpha]_D^{17}$ +92.3° (c 0.542, $CHCl_3$). NMR (400 MHz, $CDCl_3$) δ 1.78 (s, CH_3), 2.2-2.36 (m, $-CH_2-CH=CH_2$), 3.62 (ddd, C_5-H, $J_{5,6e}$ = 4.6 Hz, $J_{5,4}$ = 8.6 Hz, $J_{5,6a}$ = 10.4 Hz), 3.8 (t, C_6-H_a, $J_{5,6a} = J_{6a,6e}$ = 10.4 Hz), 4.18-4.23 (m, C_4-H), 4.32

(dd, C_6-H_e, $J_{5,6e}$ = 4.6 Hz, $J_{6a,6e}$ = 10.4 Hz), 4.44-4.51 (m, C_1-H), 4.79, 4.86 (two peaks, CH=CH_2), 5.60 (s, PhCH), 5.74 (ddd, C_2-H, $J_{1,2} = J_{2,4}$ = 2.0 Hz, $J_{2,3}$ = 10.4 Hz), 5.96 (d, C_3-H), 7.35-7.4 (m, 3H, aromatic-H), 7.5-7.53 (m, 2H, aromatic-H).

Similarly, the reaction of 2a with 2-propenylmagnesium chloride afforded 8 [mp 72°-73 °C, $[\alpha]_D^{16}$ +104° (c 0.694, $CHCl_3$)] and 10 in 73% and 5% yields, and 9% of 1 was recovered.

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References

1) Stereospecific and Stereoselective Reactions. X. Part IX; S. Yokota, M. Nishida, and O. Mitsunobu, Bull. Chem. Soc. Jap., in press.

2) a) B. Fraser-Reid and B. Radatus, Can. J. Chem., 47, 4095 (1969). b) K. Heyns and J. I. Park, Chem. Ber., 109, 3262 (1976). c) R. D. Dawe and B. Fraser-Reid, J. Chem. Soc. Chem. Commun., 1981, 1180. d) S. Danishefsky and J. F. Kerwin, Jr., J. Org. Chem., 47, 3805 (1982). e) S. Czernecki and F. Gruy, Tetrahedron Lett., 22, 432 (1981). f) I. Arai and G. D. Daves, Jr., J. Am. Chem. Soc., 103. 7683 (1981). g) L. V. Dunkerton and A. J. Serino, J. Org. Chem., 47, 2812 (1982). h) B. Fraser-Reid, R. D. Dawe, and D. B. Tulshian, Can. J. Chem., 57, 1746 (1979). i) R. E. Ireland, S. Thaisrivongs, N. Vanier, and C. S. Wilcox, J. Org. Chem., 45, 48 (1980). j) G. Grynkiewicz and A. Zamojski, Z. Naturforsch., 35b, 1024 (1980).

3) Compound 1 can be readily prepared from methyl 2,3-anhydro-4,6-O-benzylidene-α-D-allopyranoside. N. Tsuda, S. Yokota, T. Kudo, and O. Mitsunobu, Chem. Lett., 1983, 289.

4) See for example, M. Sharma and R. K. Brown, Can. J. Chem., 44, 2825 (1966).

5) Compound 5 was purified by recrystallization from ethanol (63% yield); mp 94°-95 °C, $[\alpha]_D^{17}$ +49.1° (c 0.531, $CHCl_3$). Lit.[7] mp 94°-95 °C, $[\alpha]_D^{25}$ +45° (c 1.3, $CHCl_3$). α-Isomer has been reported to have mp 119.5°-120 °C, $[\alpha]_D^{25}$ +129.0° (c 1.4, $CHCl_3$).[7]

6) Fraser-Reid et al. have reported the values $J_{1,2}$ = 6.0 Hz and $J_{2,3}$ = 2.0 Hz for compound 6, while $J_{1,2} = J_{2,3}$ = 6.0 Hz for 4,6-O-benzylidene-1,2,3-trideoxy-3-C-methyl-D-ribo-hex-1-enopyranose (mp 85°-86 °C, $[\alpha]_D^{23}$ +158.4° (c 4.95, $CHCl_3$). B. Fraser-Reid, B. J. Carthy, and B. Radatus, Tetrahedron, 28, 2741 (1972). B. Fraser-Reid and B. Radatus, Can. J. Chem., 50, 2919 (1972).

7) R. U. Lemieux, E. Frage, and K. A. Watanabe, Can. J. Chem., 46, 61 (1968).

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