Stereoselectivities in Catalytic Hydrogenation of Several Branched-Chain 6-Deoxyhex-5-enopyranosides. A Synthesis of Branched-Chain Methyl 6-Deoxy-β-L-hexopyranoside

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Synopsis. Hydrogenation of several 2-*C*-, 3-*C*-, and 4-*C*-methyl-branched 6-deoxyhex-5-enopyranosides in the presence of palladium–carbon in ethanol showed stereoselective formation of the corresponding 6-deoxy-β-L-hexopyranosides.

Branched-chain 6-deoxy-L-sugars, such as kansosamine and sibirosamine, are biologically important components of not only bacterial saccharides,[1] but also antibiotics.[2] In general, branched-chain 6-deoxy-L-hexopyranoside was synthesized by the introduction of a branched-chain to the corresponding 6-deoxy-L-hexulopyranose. In some cases, though, this procedure has brawbacks regarding the unavailability of L-sugar, which has the required configuration and unexpected stereoselectivity in the introduction of a branched-chain, due to the limited configuration, in general.[3] In this study we examined the stereoselectivity in the catalytic hydrogenation of the five branched-chain methyl 6-deoxy-α-D-hex-5-enopyranosides (**1**, **2**, **3**, **4**, and **5**)[4] in order to provide a novel method for the synthesis of branched-chain methyl 6-deoxy-β-L-hexoses.

Results and Discussion

Branched-chain methyl 6-deoxy-α-D-hex-5-enopyranosides were conveniently synthesized by a one-pot elimination reaction of the corresponding 6-bromo-6-deoxy- or 6-*O*-(*p*-tolylsulfonyl)hexopyranoside in good yields. The catalytic hydrogenation of the above-mentioned branched-chain methyl 6-deoxy-α-D-hex-5-enopyranosides were as follows. A mixture of a methyl branched 6-deoxyhex-5-enopyranoside and 10% palladium–carbon in absolute EtOH was stirred at room temperature under hydrogen until the starting material disappeared. The catalyst was filtered off and the filtrate was evaporated to give quantitatively one or a mixture of isomeric branched-chain 6-deoxyhexopyranosides, which was purified or fractionated on a column of silica gel. The ^{1}H NMR parameters of the branched-chain 6-deoxyhexopyranosides are shown in Table 1.

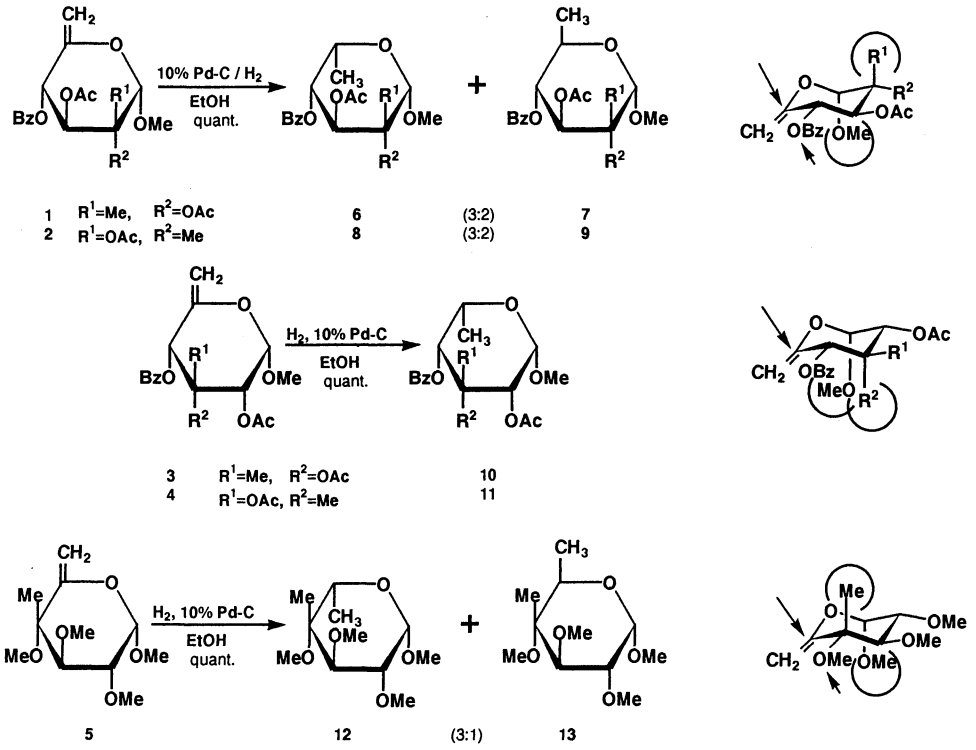
In the case of methyl 2,3-di-*O*-acetyl-4-*O*-benzoyl-6-deoxy-2-*C*-methyl-α-D-*xylo*-hex-5-enopyranoside **1**, two epimeric 6-deoxyhexopyranoside, i.e., L-sugar (**6**) and D-sugar (**7**) were obtained in a ratio of 3:2. Similarly, methyl 2,3-di-*O*-acetyl-4-*O*-benzoyl-6-deoxy-2-*C*-methyl-α-D-*lyxo*-hex-5-enopyranoside **2** also gave two epimeric 6-deoxyhexopyranosides, (**8**) and (**9**), in a ratio of 3:2. On the contrary, methyl 2,3-di-*O*-acetyl-4-*O*-benzoyl-6-deoxy-3-*C*-methyl-α-D-*ribo*-hex-5-enopyranoside **3** and methyl 2,3-di-*O*-acetyl-4-*O*-benzoyl-6-deoxy-3-*C*-methyl-α-D-*xylo*-hex-5-enopyranoside (**4**)

Table 1. ^{1}H NMR Parameters of Branched-Chain 6-Deoxyhexopyranosides

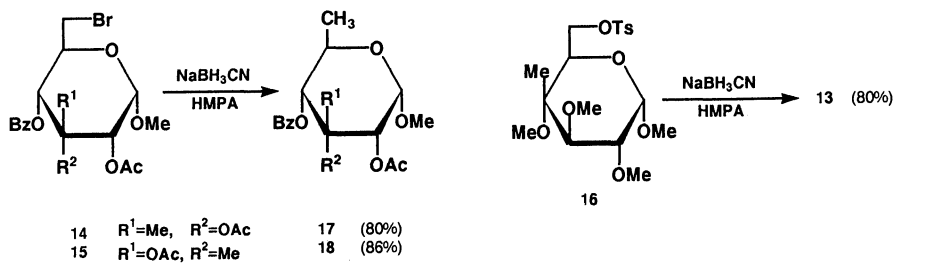
6-Deoxy derivative	Chemical shifts (δ) and coupling constants (Hz)						
	H-1 ($J_{1,2}$)	H-2 ($J_{2,3}$)	H-3 ($J_{3,4}$)	H-4 ($J_{4,5}$)	H-5 ($J_{5,6}$)	H-6	Other protons
6	4.96s		6.05d (7.1)	5.12dd (4.7)	4.36q (6.8)	1.39d	8.07—7.19 (Bz; m), 3.52 (OMe), 1.58 and 1.40 (2×OAc), 1.37 (CMe)
7	5.42s		5.65d (10.0)	5.04dd (10.0)	4.01dq (6.4)	1.23d	8.02—7.19 (Bz; m), 3.39 (OMe), 1.99 and 1.93 (2×OAc), 1.66 (CMe)
8	4.85s		5.81d (4.6)	5.23dd (3.2)	4.35dq (6.6)	1.27d	8.08—7.42 (Bz; m), 3.58 (OMe), 2.11 and 2.03 (2×OAc), 1.73 (CMe)
9	5.42s		5.50d (10.0)	5.27dd (9.7)	3.97dq (6.1)	1.26d	8.02—7.40 (Bz; m), 3.44 (OMe), 2.13 and 1.94 (2×OAc), 1.53 (CMe)
10	4.63d (1.3)	5.49dd ($J_{2,4}$=1.3)		5.57dd (1.3)	3.98dq (6.4)	1.32d	8.24—7.41 (Bz; m), 3.57 (OMe), 1.82 and 1.74 (2×OAc), 2.21 (CMe)
11	4.72d (1.5)	5.47dd ($J_{2,4}$=1.5)		5.57dd (1.5)	4.10dq (6.1)	1.26d	8.23—7.41 (Bz; m), 3.57 (OMe), 2.22 and 2.12 (2×OAc), 1.50 (CMe)
12	4.67d (3.2)	3.30dd (6.4)	3.54d		3.73q (6.8)	1.30d	3.52, 3.52, 3.48, and 3.27 (4×OMe), 1.20 (CMe)
13	4.73d (3.9)	3.18dd (9.8)	3.61d		3.82q (6.6)	1.12d	3.60, 3.49, 3.40, and 3.36 (4×OMe), 1.14 (CMe)
17	4.76d (4.4)	5.00d		4.95d (9.7)	4.36dq (6.3)	1.20d	8.07—7.43 (Bz; m), 3.43 (OMe), 2.18 and 2.12 (2×OAc), 1.66 (CMe)
18	4.89d (4.6)	6.08d		5.90d (10.0)	3.99dq (6.3)	1.25d	8.09—7.43 (Bz; m), 3.41 (OMe), 2.15 and 1.89 (2×OAc), 1.66 (CMe)

gave exclusively the L-isomers, (**10**) and (**11**), respectively. Further, methyl 6-deoxy-4-*C*-methyl-2,3,4-tri-*O*-methyl-α-D-*xylo*-hex-5-enopyranoside **5** gave a 3:1 mixture of the corresponding 6-deoxyhexopyranoside (Scheme 1). In the case of **6**, **7**, **8**, and **9**, the configuration at *C*-5 was clearly determined by a comparison of the coupling constants, $J_{3,4}$ and $J_{4,5}$, of both epimers. While the large coupling constants of the D-isomers, **7** and **9**, indicate a *trans*-diaxial relationship between *H*-3 and *H*-4, as well as *H*-4 and *H*-5 in the $^4C_1$ (D) conformation, smaller values of the L-isomers suggest that the $^1C_4$ (L) conformation is strongly favored, and that *H*-4 and *H*-5 have a *cis* relationship. Similarly, in the case of compounds **10** and **11**, the small values of $J_{1,2}$ and $J_{4,5}$ (1.3—1.5 Hz) indicated the $^1C_4$ (L) conformation and the L configuration at *C*-5. The epimers of **10** and **11** (**17** and **18**) were also derived from methyl 2,3-di-*O*-acetyl-4-*O*-benzoyl-6-bromo-6-deoxy-3-*C*-methyl-α-D-allopyranoside (**14**) and methyl 2,3-di-*O*-acetyl-4-*O*-benzoyl-6-bromo-6-deoxy-3-*C*-methyl-α-D-glucopyranoside (**15**), respectively, in order to confirm their structure (Scheme 2). A hydride reduction of **14** (100 mg) with Na[BH_3CN] (81 mg) in hexamethylphosphoric triamide (HMPA, 2.0 cm^3) at 120°C gave **17** in 80% yield. In a similar manner, **15** gave **18** in 86% yield. In the case of compound **5**, the structure of products (**12**) and (**13**) could not be determined by ^1H NMR, because of the absence of *H*-4. Then, **13** was also prepared by a hydride reduction of methyl 4-*C*-methyl-2,3,4-tri-*O*-methyl-6-*O*-(*p*-tolylsulfonyl)-α-D-glucopyranoside (**16**) in 80% yield.

If each starting 5-enopyranoside is assumed to have the $^4C_1$ (D) conformation,[4] as is shown at the right side of Scheme 1, the stereoselectivity can be rationalized by a steric repulsion caused by the axial substituents. Their bulkiness may decreased in the following order: *C*-1(OMe),*C*-3(Me,OAc)>*C*-2(Me,OAc)>*C*-4(Me). This indicates that the axial substituents at the β-position is most important for controlling the perfect selectivity observed in the cases of **3** and **4**. The method proposed



Scheme 1.



Scheme 2.

herein may provide wide applications to the preparation of the naturally occurring branched-chain 6-deoxy-L-hexopyranoside.

Experimental

All melting points are uncorrected. The solutions were evaporated under reduced pressure at a bath temperature not exceeding 40°C. The optical rotations were measured in a 0.5 dm tube with a JASCO DIP-140 polarimeter in chloroform. The ^{1}H NMR spectra were recorded in chloroform-*d* with a JEOL FX-200 spectrometer, with tetramethylsilane used as an internal standard. IR spectra were recorded with Hitachi 270—30 spectrometer. The chemical shifts, coupling constants, and IR frequencies were recorded in δ, Hz, and cm^{-1} units respectively.

Catalytic Hydrogenation of (1—5) with 10% Palladium-Carbon. Methyl 2,3-Di-*O*-acetyl-4-*O*-benzoyl-6-deoxy-2-*C*-methyl-β-L-idopyranoside (6) and Methyl 2,3-Di-*O*-acetyl-4-*O*-benzoyl-6-deoxy-2-*C*-methyl-α-D-glucopyranoside (7). To a suspension of methyl 2,3-di-*O*-acetyl-4-*O*-benzoyl-6-deoxy-2-*C*-methyl-α-D-*xylo*-hex-5-enopyranoside **1** (50 mg) and 10% palladium-carbon (15 mg) in absolute EtOH (10 cm^3), hydrogen gas was passed with efficient stirring until the starting material was completely consumed. The catalyst was filtered off and the filtrate was evaporated to give a mixture of epimeric **6** and **7** in a ratio of 3:2, quantitatively, which was fractionated on a column of silica gel (Kieselgel 60, Merck). **6**: Mp 93—94°C (ethanol–hexane); $[\alpha]_D^{25}$−11° (*c* 1.8); IR: 1760 and 1740 (C=O). Found: C, 60.19; H, 6.27%. Calcd for $C_{19}H_{24}O_8$: C, 60.00; H, 6.32%. **7**: Mp 79—80°C (ethanol–hexane); $[\alpha]_D^{25}$+67° (*c* 1.3); IR: 1755 and 1733 (C=O). Found: C, 59.91; H, 6.32%. Calcd for $C_{19}H_{24}O_8$: C, 60.00; H, 6.32%.

Methyl 2,3-Di-*O*-acetyl-4-*O*-benzoyl-6-deoxy-2-*C*-methyl-β-L-gulopyranoside (8) and Methyl 2,3-Di-*O*-acetyl-4-*O*-benzoyl-6-deoxy-2-*C*-methyl-α-D-mannopyranoside (9). In a similar manner as mentioned above, methyl 2,3-di-*O*-acetyl-4-*O*-benzoyl-6-deoxy-2-*C*-methyl-α-D-*lyxo*-hex-5-enopyranoside (**2**) gave two epimeric **8** and **9** in a 3:2 ratio, quantitatively. **8**: Mp 87—88°C (ethanol–hexane); $[\alpha]_D^{25}$−42° (*c* 0.3); IR: 1730 (C=O). Found: C, 59.85; H, 6.26%. Calcd for $C_{19}H_{24}O_8$: C, 60.00; H, 6.32%. **9**: Mp 168—170°C (ethanol–hexane); $[\alpha]_D^{25}$+22° (*c* 0.5); IR: 1740 (C=O). Found: C, 59.84; H, 6.47%. Calcd for $C_{19}H_{24}O_8$: C, 60.00; H, 6.32%.

Methyl 2,3-Di-*O*-acetyl-4-*O*-benzoyl-6-deoxy-3-*C*-methyl-β-L-talopyranoside (10). The reduction of methyl 2,3-di-*O*-acetyl-4-*O*-benzoyl-6-deoxy-3-*C*-methyl-α-D-*ribo*-hex-5-enopyranoside **3** gave **10** exclusively in quantitative yield. **10**: Mp 154—155°C (ethanol–hexane); $[\alpha]_D^{25}$−38° (*c* 0.8); IR: 1749 and 1731 (C=O). Found: C, 60.06; H, 6.37%. Calcd for $C_{19}H_{24}O_8$: C, 60.00; H, 6.32%.

Methyl 2,3-Di-*O*-acetyl-4-*O*-benzoyl-6-deoxy-3-*C*-methyl-β-L-idopyranoside (11). The reduction of methyl 2,3-di-*O*-acetyl-4-*O*-benzoyl-6-deoxy-3-*C*-methyl-α-D-*xylo*-hex-5-enopyranoside **4** gave **11** exclusively in quantitative yield. **11**: Mp 152—153°C (ethanol–hexane); $[\alpha]_D^{25}$−67° (*c* 0.2); IR: 1755 and 1725 (C=O). Found: C, 60.06; H, 6.35%. Calcd for $C_{19}H_{24}O_8$: C, 60.00; H, 6.32%.

Methyl 6-Deoxy-4-*C*-methyl-2,3,4-tri-*O*-methyl-β-L-idopyranoside (12) and Methyl 6-Deoxy-4-*C*-methyl-2,3,4-tri-*O*-methyl-α-D-glucopyranoside (13). The reduction of methyl 6-deoxy-4-*C*-methyl-2,3,4-tri-*O*-methyl-α-D-*xylo*-hex-5-enopyranoside **5** gave a mixture of **12** and **13** in a 3:1 ratio, quantitatively, which was purified on a column of silica gel (Kieselgel 60, Merck). **12**: Syrup; $[\alpha]_D^{25}$−15° (*c* 0.4). Found: C, 56.43; H, 9.32%. Calcd for $C_{11}H_{22}O_5$: C, 56.39; H, 9.47%. **13**: Syrup; $[\alpha]_D^{25}$+50° (*c* 0.8). Found: C, 55.99; H, 9.52%. Calcd for $C_{11}H_{22}O_5$: C, 56.39; H, 9.47%.

Hydride Reduction of (14, 15, and 16) for Determining of the Structures of 10, 11, and 12. Methyl 2,3-Di-*O*-acetyl-4-*O*-benzoyl-6-deoxy-3-*C*-methyl-α-D-allopyranoside (17). Methyl 2,3-di-*O*-acetyl-4-*O*-benzoyl-6-bromo-6-deoxy-3-*C*-methyl-α-D-allopyranoside **14** (100 mg) was reduced with sodium cyanotrihydroborate ($Na[BH_3CN]$, 81 mg) in hexamethylphosphoric triamide (HMPA, 2.0 cm^3) at 120°C, with stirring until the starting material was completely consumed. The mixture was then poured into saturated brine and extracted with ethyl acetate several times, washed with water, dried and evaporated to give crude **17**, which was purified on a column of silica gel (Kieselgel 60, Merck). The yield was 80%. **17**: Amorphous; $[\alpha]_D^{25}$+30° (*c* 0.5). Found: C, 60.06; H, 6.37%. Calcd for $C_{19}H_{24}O_8$: C, 60.00; H, 6.32%.

Methyl 2,3-Di-*O*-acetyl-4-*O*-benzoyl-6-deoxy-3-*C*-methyl-α-D-glucopyranoside (18). A similar reduction of methyl 2,3-di-*O*-acetyl-4-*O*-benzoyl-6-bromo-6-deoxy-3-*C*-methyl-α-D-glucopyranoside **15** gave **18** in 86% yield. **18**: Mp 54—56°C; $[\alpha]_D^{22}$+49° (*c* 1.0); IR: 1760 and 1730 (C=O). Found: C, 59.93; H, 6.28%. Calcd for $C_{19}H_{24}O_8$: C, 60.00; H, 6.32%.

Methyl 6-Deoxy-2,3,4-tri-*O*-methyl-4-*C*-methyl-α-D-glucopyranoside (13). A similar reduction of methyl 2,3,4-tri-*O*-methyl-4-*C*-methyl-6-*O*-(*p*-tolylsulfonyl)-α-D-glucopyranoside **16** gave **13** in 80% yield, of which the physical constants were identical with that obtained in the reduction of compound **5**.

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