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An Efficient Synthesis of 6-Deoxy-D-allose from Simple Achiral Starting Materials

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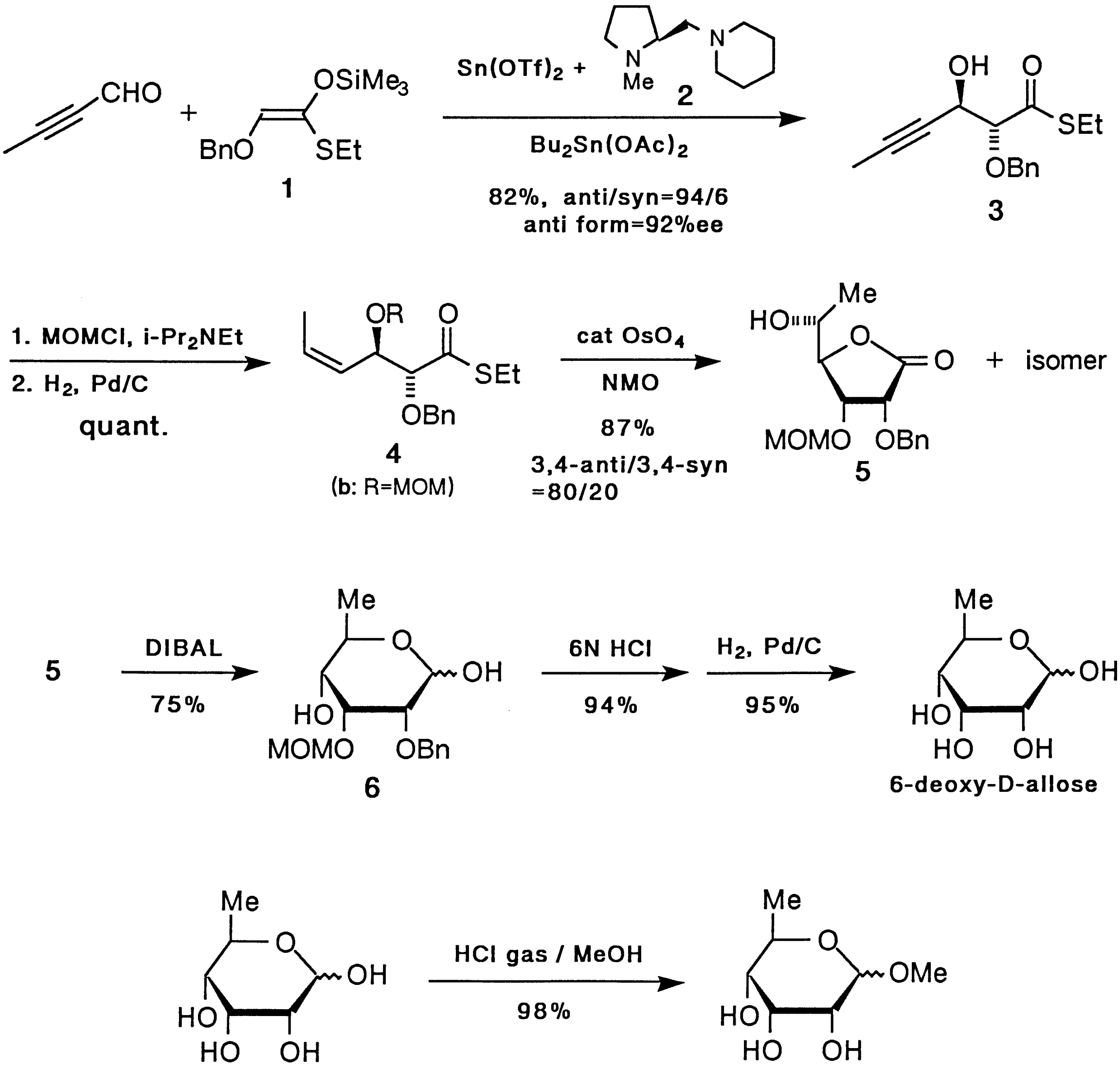
6-Deoxy-D-allose is prepared from simple achiral starting materials, butynal and chloroacetic acid, via two key steps of the chiral tin(II) triflate mediated asymmetric aldol reaction and the dihydroxylation using osmium tetroxide.

6-Deoxy-D-allo-glycosides such as ascleposide, gofruside and frugoside, etc. are steroidal class of glycosides and their cardiac activity is now of great interest.$^{1)}$ Moreover, it was recently reported that 6-thiopurine nucleosides of 6-deoxy-D-allose showed strong inhibition of growth of a mouse leukemia both in vivo and in vitro, and they are expected as promising antitumor agents.$^{2)}$ In these glycosides and nucleosides, 6-deoxy-D-allose is involved as a common sugar, which is classified into deoxyaldohexoses. Concerning the synthesis of 6-deoxy-D-allose, derivations of easily available sugars (D-glucose derivatives) were reported in the literatures, however, rather complicated multistep conversions were required.$^{3)}$ In this communication, we would like to report an efficient synthesis of 6-deoxy-D-allose starting from simple achiral compounds, butynal and chloroacetic acid, via two key steps of asymmetric aldol reaction and dihydroxylation.

The synthetic route of 6-deoxy-D-allose is shown in Scheme 1. In our preliminary strategy, the intermediate **4a** (R=H) was planned to prepare directly from cis-crotonaldehyde and the silyl enol ether derived from S-ethyl 2-benzyloxyethanethioate (**1**)$^{4)}$ via asymmetric aldol reaction. However, cis-crotonaldehyde is unstable and difficult to obtain as a pure geometrical isomer,$^{5)}$ therefore, our strategy was altered to the asymmetric aldol reaction of butynal with **1**, followed by reduction of the acetylenic compound **3** to the corresponding cis olefin **4**.

At first, asymmetric aldol reaction of butynal with **1** was examined. We have already reported that the asymmetric aldol reaction of acetylenic aldehydes with the silyl enol ether derived from *S*-ethyl propanethioate proceeded smoothly in the presence of the chiral three components promoter, consisting of tin(II) triflate, a chiral diamine and a tin(IV) additive, to give the corresponding propargyl alcohols in high diastereo- and enantioselectivities.$^{6)}$ In the reaction of butynal with **1** in the presence of tin(II) triflate, (*S*)-1-methyl-2-[(piperidin-1-yl)methyl]pyrrolidine (**2**) and dibutyltin diacetate, the corresponding anti aldol-type adduct **3** was obtained in high yield with high diastereo- and enantioselectivities.$^{7)}$ This high anti selectivity was consistent with those observed in the reaction of **1** with aromatic, aliphatic aldehydes and enals.$^{8)}$ Then reduction of the adduct **3** thus obtained was tried under the Lindlar condition, however, no reduction product was obtained and only the starting material was recovered. The hydrogenation of **3** using Pd/C as a catalyst gave the corresponding cis olefin (**4a**, R=H) along with a small amount of trans olefin (quantitative yield, cis/trans=93/7). Further reduction of the olefinic compound (hydrogenation of the cis or trans olefin) was not observed. The yield and selectivity were improved when the reduction was carried out after protection of the free hydroxyl group of **3** as a methoxymethyl ether (MOM ether), and the desired cis olefin **4b** was quantitatively obtained (cis/trans=100/0).[9]

Next, dihydroxylation of **4** was investigated and it was found that the protective group of the alcohol at 3-position strongly affected the diastereoselectivity (Table 1). When the MOM ether **4b** was treated with 10 mol% of osmium tetroxide and *N*-methylmorphorine oxide (NMO), two diastereomeric lactones, separable by column chromatography on silica gel, were obtained in 87% yield with a ratio of 80/20 (3,4-anti/3,4-syn). The major diastereomer was assigned to be the lactone 5,[10] which was produced by the dihydroxylation followed by lactonization. When the dihydroxylation was carried out by using the β-hydroxy thioester **4a** as a substrate, the diastereomeric ratio was low (3,4-anti/3,4-syn=48/52).



Scheme 1. Synthesis of 6-deoxy-D-allose.

Table 1. Effect of the Protective Group in the Dihydroxylation of **4**

Entry	Protective group		Yield/%	3,4-anti / 3,4-syn
1	H	(**4a**)	73	48/52
2	MOM [a)]	(**4b**)	87	80/20
3	Ac	(**4c**)	61	79/21 [c)]
4	TMS	(**4d**)	65	76/24
5	TBS	(**4e**)	70	75/25
6	BOM [b)]	(**4f**)	65	60/40

a) Methoxymethyl. b) Benzyloxymethyl. c) Relative configuration assignment was not made.

The lactone **5** thus obtained is a versatile intermediate for the synthesis of monosaccharides including 6-deoxy-D-allofuranoside,[2,3c)] D-mycinose (2,3-di-O-methyl-6-deoxy-D-allose),[11)] etc., because three hydroxy groups are discriminated and can be respectively converted to desired functional groups without tedious protection and deprotection procedures. Next, this lactone **5** was reduced with diisobutylaluminum hydride (DIBAL) in dichloromethane at -78 °C to give the hemiacetal **6** (75% yield). The protective groups of **6** were successively removed with 6 mol dm^{-1} HCl in THF (94% yield) followed by hydrogenolysis using Pd/C in methanol (95% yield) to afford 6-deoxy-D-allose[12)] (mp 145-146 °C. lit. 146 °C,[3a)] 151-152 °C[3b)]). The 6-deoxy-D-allose thus synthesized was converted to the corresponding methyl glycoside (HCl gas in MeOH, 98% yield, α/β=32/68),[13)] whose optical rotation was consistent with those in the literature (β-form; $[\alpha]_D^{30}$ -60.8 ° (c 0.026, H_2O); lit. $[\alpha]_D^{25}$ -61.26 ° (c 2.024, H_2O)[3b)]).

Thus, 6-deoxy-D-allose was prepared from butynal in 36% overall yield (7 steps).

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4) The compound **1** was prepared from chloroacetic acid: i) Na, BnOH, 150 °C, 4 h; ii) PCl_5, CH_2Cl_2, rt, 1 h; iii) EtSH, py, CH_2Cl_2, rt, 12 h; iv) lithium tetramethylpiperidylamide, THF, -78 °C, 1 h, then TMSCl, rt, 1 h. Z/E=9/1. Cf. Ref. 8.

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7) Syn and anti aldol-type adducts could be separated by silica gel column chromatography. Anti form: mp 71.0-72.0 °C. $[\alpha]_D^{29}$ +86.7 ° (c 1.27, benzene); 94% ee determined by HPLC analysis using Daicel Chiralcel OD. ^{1}H NMR ($CDCl_3$) δ 1.27 (t, 3H, J=7.4 Hz), 1.84 (d, 3H, J=2.0 Hz), 2.50 (d, 1H, J=7.9 Hz), 2.91 (q, 2H, J=7.4 Hz), 4.07 (d, 1H, J=5.0 Hz), 4.60-4.67 (m, 1H), 4.62 (d, 1H, J=11.5 Hz), 4.92 (d, 1H, J=11.5 Hz), 7.32-7.45 (m, 5H). ^{13}C NMR ($CDCl_3$) δ 3.6, 14.4, 22.6, 63.8, 74.5, 75.6, 83.4, 86.2, 128.2, 128.3, 128.5, 136.6, 200.7.

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9) **4b**: ^{1}H NMR ($CDCl_3$) δ 1.24 (t, 3H, J=7.4 Hz), 1.63 (dd, 3H, J=6.9, 1.7 Hz), 2.86 (q, 2H, J=7.4 Hz), 3.33 (s, 3H), 4.12 (d, 1H, J=4.3 Hz), 4.53 (d, 1H, J=6.9 Hz), 4.64 (d, 1H, J=6.9 Hz), 4.65 (d, 1H, J=11.5 Hz), 4.80 (ddd, 1H, J=9.5, 4.3, 1.0 Hz), 4.81 (d, 1H, J=11.5 Hz), 5.45 (ddq, 1H, J=10.9, 9.6, 1.7 Hz), 5.80 (ddq, 1H, J=10.9, 6.9, 1.0 Hz), 7.29-7.43 (m, 5H). ^{13}C NMR ($CDCl_3$) δ 13.4, 14.5, 22.6, 55.4, 71.6, 73.8, 86.6, 93.5, 125.3, 127.8,127.9, 128.3, 130.7, 137.3, 201.1.

10) **5**: $[\alpha]_D^{30}$ +78.6 ° (c 1.11, benzene); 96% ee determined by HPLC analysis using Daicel Chiralcel AD. ^{1}H NMR ($CDCl_3$) δ 1.27 (d, 3H, J=6.9 Hz), 2.30-2.60 (brs, 1H), 3.37 (s, 3H), 4.07 (dq, 1H, J=6.9, 3.3 Hz), 4.33 (dd, 1H, J=3.3, 1.7 Hz), 4.40 (d, 1H, J=5.9 Hz), 4.44 (dd, 1H, J=5.9, 1.7 Hz), 4.68 (d, 1H, J=6.9 Hz), 4.73 (d, 1H, J=6.9 Hz), 4.76 (d, 1H, J=11.9 Hz), 4.96 (d, 1H, J=11.9 Hz), 7.30-7.40 (m, 5H). ^{13}C NMR ($CDCl_3$) δ 18.7, 55.9, 66.6, 71.3, 72.9, 73.8, 87.0, 96.5, 128.1, 128.5, 136.8, 173.8.

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12) ^{1}H NMR (DMSO-d_6) δ 1.10 (d, 3H, J=6.3 Hz), 3.00 (dd, 1H, J=9.5,2.6 Hz), 3.05 (dd, 1H, J=7.9,2.6 Hz), 3.56 (dq, 1H, J=9.5,6.3 Hz), 3.81 (dd, 1H, J=2.6, 2.6 Hz), 4.59 (d, 1H, J=7.9 Hz), 4.65-4.75 (brs, 3H), 6.34-6.36 (brs, 1H). ^{13}C NMR (DMSO-d_6) δ 18.1, 68.7, 71.5, 72.2, 73.0, 94.0.

13) β-form: ^{1}H NMR (acetone-d_6-D_2O) δ 1.25 (d, 3H, J=6.3 Hz), 3.25 (dd, 1H, J=9.6,2.6 Hz), 3.36 (dd, 1H, J=7.9,3.0 Hz), 3.48 (s, 3H), 3.76 (dq, 1H, J=9.6,6.3 Hz), 4.10 (dd, 1H, J=3.0,2.6 Hz), 4.53 (d, 1H, J=7.9 Hz). ^{13}C NMR (acetone-d_6-D_2O) δ 18.0, 56.8, 70.0, 71.7, 72.0, 73.5, 102.2.

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