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A New Convergent Route to Aldohexoses from a Common Chiral Building Block

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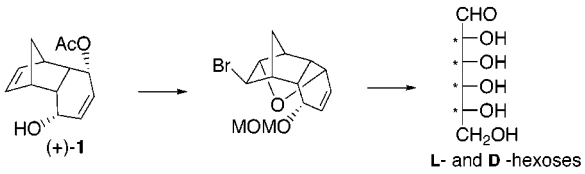
ABSTRACT



A diastereocontrolled route to the eight aldohexoses has been developed starting from a common cyclohexanoid chiral building block.

Although a number of syntheses of aldohexoses have been reported, there are so far two methods that are capable of producing all of the eight possible diastereomers in enantio- and diastereocontrolled manner. Of these, one by the Masamune and the Sharpless groups[1] employed a reagent-controlled method using the Katsuki−Sharpless asymmetric epoxidation reaction[2] as the key step, while the other by our group employed a substrate-controlled method starting from a common chiral building block having a dioxabicyclo[3.2.1]-octane framework.[3] The previous work from our group has shown that the chiral building block, obtained by either a chemical[3] or an enzymatic method,[4] allowed diastereoselective introduction of the requisite functionalities on the basis of the molecular bias of the chiral block, which exerted inherent convex-face selectivity. We report here an alternative substrate-controlled synthesis leading to all of the eight aldohexoses starting from a common cyclohexanoid chiral building block **1** exerting inherent convex-face selectivity. The acetate **1** was prepared in both enantiomeric forms either by an enzymatic[5] or a chemical procedure[6] so as to serve as a chiral equivalent of *cis*-1,4-dihydroxycyclohexane-2,5-diene, and it actually allowed diastereocontrolled construction of a variety of natural products on the basis of its molecular bias and a masked cyclohexene double bond.[7] The present study using (+)-**1** demonstrates the synthesis of four each of the L- and D-diastereomers of aldohexoses via the four conduritol derivatives **3**−**6** generated through the common bromo-ether intermediate,[8,9] (+)-**2** (Scheme 1).

Thus, (+)-**1** was first transformed into bromo-ether[9] **2** to block double bond and hydroxy functionalities on sequential O-protection, deacetylation, and exposure to NBS. Catalytic dihydroxylation of **2** occurred from the convex face to give dibenzyl ether **7**, mp 91−92 °C, $[\alpha]^{29}_{D}$ −63.1 (*c* 1.3, $CHCl_3$), after benzylation. The double bond blocked was regenerated at this point to give alcohol **8**, $[\alpha]^{29}_{D}$ +36.0 (*c* 1.2, $CHCl_3$), on reflux of **7** with zinc in methanolic acetic acid. Thermolysis of **8** in refluxing diphenyl ether followed by benzylation afforded **9**, $[\alpha]^{31}_{D}$ +32.2 (*c* 1.1, $CHCl_3$).

(1) (a) Ko, S. Y.; Lee, A. W. M.; Masamune, S.; Leed, L. A., III; Sharpless, K. B.; Walker, F. J. *Science* **1983**, *220*, 949. (b) Ko, S. Y.; Lee, A. W. M.; Masamune, S.; Leed, L. A., III; Sharpless, K. B.; Walker, F. J. *Tetrahedron* **1990**, *46*, 245.

(2) Johnson, R. A.; Sharpless, K. B. *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I, Eds.; Pergamon: Oxford, 1991; Vol. 7, pp 389−436.

(3) (a) Takeuchi, M.; Taniguchi, T.; Ogasawara, K. *Synthesis* **1999**, 341. (b) Takeuchi, M.; Taniguchi, T.; Ogasawara, K. *Chirality* **2000**, *12*, 338.

(4) Taniguchi, T.; Takeuchi, M.; Kadota, K.; ElAzab, A. S.; Ogasawara, K. *Synthesis* **1999**, 1325.

(5) (a) Takano, S.; Higashi, Y.; Kamikubo, T.; Moriya, M.; Ogasawara, K. *Synthesis* **1993**, 948. (b) Konno, H.; Ogasawara, K. *Synthesis* **1999**, 1135.

(6) Hiroya, K.; Kurihara, Y.; Ogasawara, K. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2287.

(7) Ogasawara, K. J. *Synth. Org. Chem. Jpn.* **1999**, *57*, 957.

(8) Honzumi, M.; Hiroya, K.; Taniguchi, T.; Ogasawara, K. *Chem. Commun.* **1999**, 1985.

(9) Takano, S.; Moriya, M.; Higashi, Y.; Ogasawara, K. *J. Chem. Soc., Chem. Commun.* **1983**, 177.

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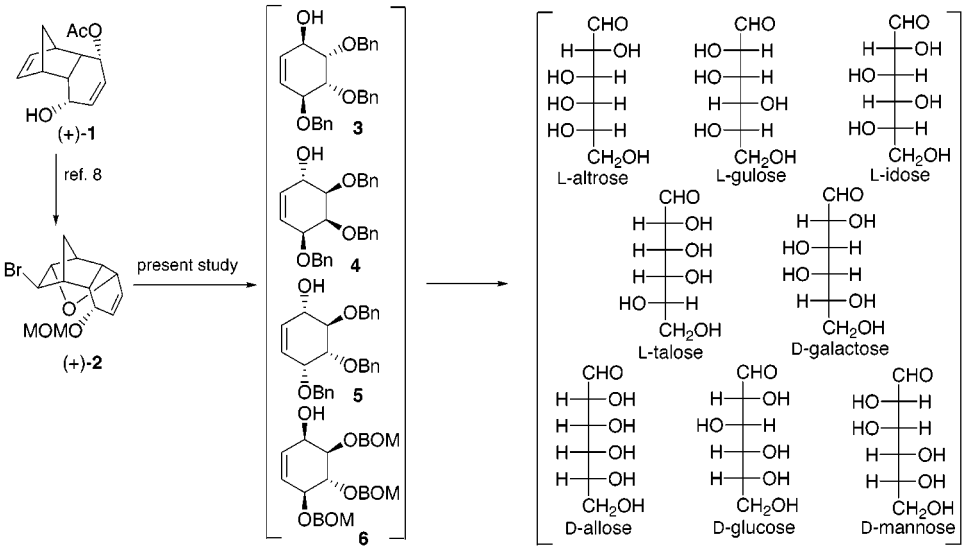
Scheme 1



Removal of the MOM group by acidic methanolysis then gave **3**, $[\alpha]^{30}_D$ +18.1 (*c* 1.2, $CHCl_3$), which would serve as the precursor to L-altrose and D-galactose.

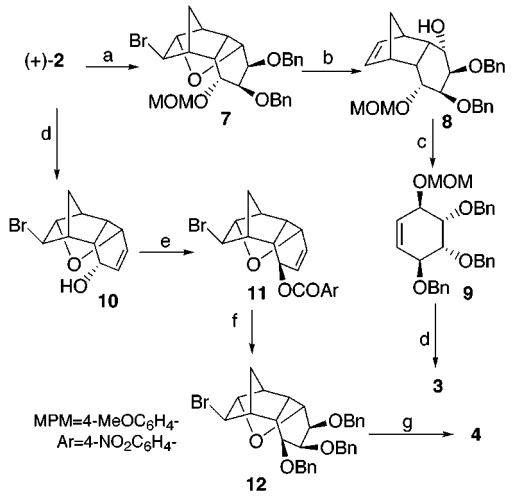
On the other hand, de-O-protection of (+)-**2**, followed by the Mitsunobu reaction[10,11] of the resulting alcohol **10** furnished *exo*-benzoate **11**, which was transformed into tribenzyl ether **12**. Sequential reductive cleavage and thermolysis of **12** furnished cyclopentenol **4**, mp 113−115 °C, $[\alpha]^{30}_D$ +106 (*c* 1.1, $CHCl_3$), which would serve as the precursor to L-talose and D-allose (Scheme 2).

To obtain the cyclohexenols, **5** and **6**, the *endo*-alcohol **10** was first converted into *exo*-epoxy-benzoate **13** by sequential benzoylation and epoxidation. When **13** was exposed to boron trifluoride,[8,12] the benzoate-assisted stereoselective epoxide opening occurred to give a mixture **14** consisting of 1,2- and 1,3-diols (1:1). Without separation, **14** was benzoylated to give single tribenzoate **15**, mp 172−173 °C, $[\alpha]^{29}_D$ −101 (*c* 1.3, $CHCl_3$), which on reductive cleavage gave **16**, $[\alpha]^{27}_D$ −192 (*c* 1.3, $CHCl_3$). After O-protection, the resulting MOM-ether **17** was thermolyzed to give cyclohexene **18**, $[\alpha]^{28}_D$ −245 (*c* 1.2, $CHCl_3$), whose benzoyl functionalities were replaced by benzyl functionalities to give **19**, $[\alpha]^{26}_D$ −62.5 (*c* 1.5, $CHCl_3$), by sequential debenzoylation and benzylation. Finally, the MOM group of **19** was removed to give **5**, mp 68−70 °C, $[\alpha]^{30}_D$ −39.4 (*c* 1.0, $CHCl_3$), serving as the precursor of L-gulose and D-mannose.

The mixture **14**, on the other hand, was stirred in dichloromethane containing a trace of *p*-toluenesulfonic acid at room temperature for 3 days to give a 5:1 mixture of 1,2-diol **20** and 1,3-diol, which were separated. Since benzylation of **20** could not be attained with the benzoate functionality intact, a benzyloxymethyl (BOM) protecting group removable by catalytic hydrogenolysis[13] was used instead to give di-BOM ether **21**, $[\alpha]^{31}_D$ −62.3 (*c* 1.3, $CHCl_3$), without affection of the benzoate functionality. On reductive cleavage, followed by BOM-protection, **21** afforded tri-BOM ether **22**, $[\alpha]^{31}_D$ −34.9 (*c* 1.0, $CHCl_3$), which was thermolyzed to give **23**, $[\alpha]^{30}_D$ −59.3 (*c* 1.3, $CHCl_3$). Finally, the benzoyl group was removed reductively to give **6**, $[\alpha]_D^{25}$ +23.3 (*c* 1.4, $CHCl_3$), serving as the precursor of D-glucose and L-idose (Scheme 3).

Conversion of the conduritols **3**−**6** into the aldohexoses could be carried out in a rather straightforward way. Thus,

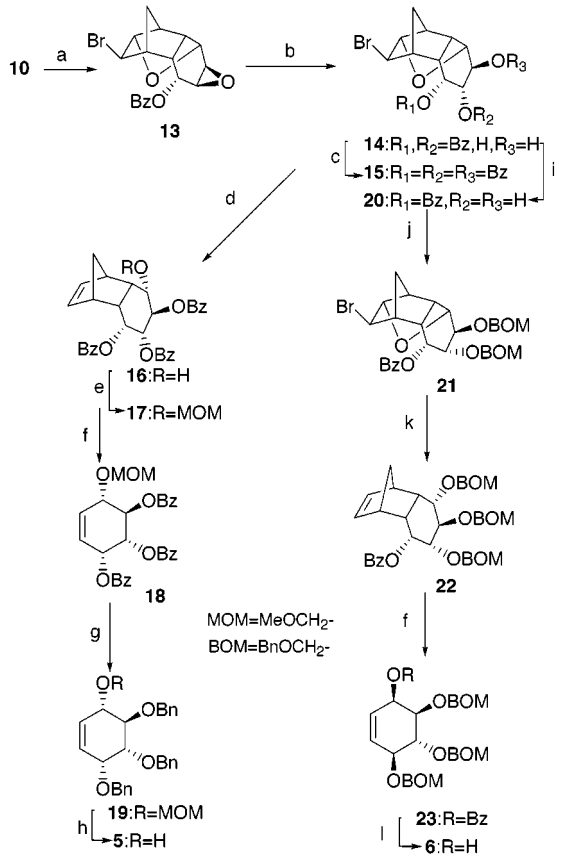
Scheme 2[a]



[a] Reagents and conditions: (a) OsO_4 (cat.), NMO, aq. THF then NaH, BnBr, TBAI (83%). (b) Zn, AcOH/MeOH (97%). (c) Ph_2O, reflux, then NaH, BnBr, TBAI (88%). (d) HCl/MeOH, THF (99% for **3**; 91% for **10**). (e) 4-$NO_2C_6H_4CO_2H$, DIAD, PPh_3 (86%). (f) OsO_4 (cat.), NMO, then NaOMe/MeOH, then BnBr, NaH, TBAI, THF (87%). (g) Zn, AcOH/MeOH (97%)

(10) (a) Mitsunobu, O. *Synthesis* **1981**, 1. (b) Hughes, D. L. *Org. React.* **1992**, *42*, 335.
(11) Martin, S. F.; Dodge, J. A. *Tetrahedron Lett.* **1991**, *32*, 3017.
(12) Prystas, M.; Gustafsson, H.; Sorm, F. *Collect. Czech. Chem. Commun.* **1971**, *36*, 1487.
(13) . Pinnick, H. W.; Lajis, N. H. *J. Org. Chem.* **1978**, *43*, 3964.

Scheme 3[a]

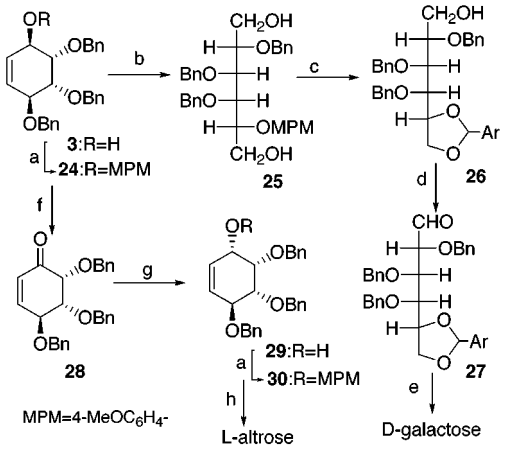


[a] Reagents and conditions: (a) BzCl, pyridine then *m*-CPBA (91%). (b) BF_3/OEt_2, toluene (100%). (c) BzCl, pyridine, DMAP, CH_2Cl_2 (100%). (d) Zn, AcOH/MeOH (98%). (e) MOM-Cl, Hünig base, $(CH_2Cl)_2$ (99%). (f) Ph_2O, $NaHCO_3$, reflux (83% for **18**, 92% for **23**). (g) NaOMe/MeOH, then BnBr, NaH, TBAI, THF (78%). (h) HCl-MeOH (99%). (i) *p*-TsOH, CH_2Cl_2, rt, 3 d (76%). (j) BOM-Cl, Hünig base, TBAI, $(CH_2Cl)_2$ (89%). (k) Zn, AcOH/MeOH, then BOM-Cl, Hünig base, TBAI, $(CH_2Cl)_2$ (86%). (l) DIBAL, CH_2Cl_2 (92%).

3 was transformed into *p*-methoxybenzyl (MPM) ether **24**, $[\alpha]_D^{25}$ −1.2 (*c* 1.3, $CHCl_3$), which was sequentially ozonized and reduced in the same flask to give diol **25**, $[\alpha]^{28}_D$ −3.1 (*c* 1.3, $CHCl_3$). On stirring with DDQ[14] in dichloromethane in the presence of molecular sieves (4Å) at 0 °C, **25** afforded a 1,3-dioxolane **26** whose primary alcohol was oxidized[15] to give aldehyde **27**. Catalytic hydrogenolysis of **27** furnished D-galactose, $[\alpha]^{31}_D$ +75.2 (*c* 0.4, H_2O){lit.[1] $[\alpha]_D^{23}$ −72.2 (*c* 0.7, H_2O) for L-isomer}.

On the other hand, **3** was oxidized to cyclohexenone **28**, $[\alpha]^{30}_D$ +181 (*c* 1.1, $CHCl_3$), which on reduction with DIBAL afforded diastereoselectively cyclohexenol **29**, $[\alpha]^{28}_D$ +121 (*c* 1.1, $CHCl_3$), isomeric to **3**. Employing exactly the same procedure as for **3**, **29** was transformed into L-altrose, $[\alpha]^{29}_D$ −29.2 (*c* 0.7, H_2O){lit.[16] $[\alpha]^{20}_D$ +32.6 (*c* 7.6, H_2O) for D-isomer}, in comparable overall yield via MPM-ether **30**, $[\alpha]^{25}_D$ +75.8 (*c* 1.4, $CHCl_3$) (Scheme 4).

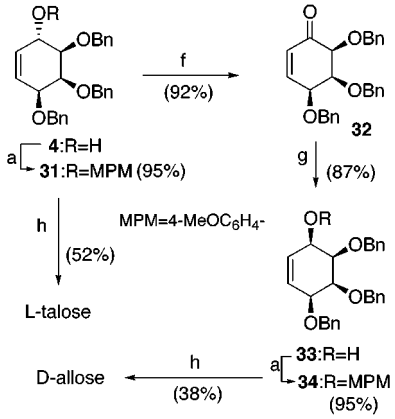
Scheme 4[a]



[a] Reagents and conditions: (a) MPM-Cl, NaH, TBAI, DMF (95% for **24**, 100% for **30**). (b) O_3 then $NaBH_4$, CH_2Cl_2/MeOH (81%). (c) DDQ, 4Å sieves, CH_2Cl_2, (78%). (d) Dess−Martin oxidation (86%). (e) H_2, $Pd(OH)_2$, aq. THF (81% from **27**). (f) PCC, CH_2Cl_2 (92%). (g) DIBAL, CH_2Cl_2 (87%). (h) (b)−(e) (46%)

The same procedure was applied to the conversion of **4**. Thus, L-talose, $[\alpha]^{29}_D$ −18.1 (*c* 0.4, H_2O) {lit.[3] $[\alpha]^{28}_D$ −17.6 (*c* 1.0, H_2O)}, was obtained via MPM-ether **31**, mp 50−51 °C, $[\alpha]^{27}_D$ +83.5 (*c* 1.3, $CHCl_3$), while D-allose, $[\alpha]^{27}_D$ +9.9 (*c* 0.4, H_2O) {lit.[1] $[\alpha]^{21}_D$ −10.8 (*c* 0.4, H_2O) for L-isomer}, was obtained via MPM-ether **34**, $[\alpha]^{23}_D$ +2.2 (*c* 1.2, $CHCl_3$), after the inversion through enone **32**, $[\alpha]^{29}_D$ +16.3 (*c* 1.0, $CHCl_3$), and alcohol **33**, mp 74−75 °C, $[\alpha]^{27}_D$ −13.4 (*c* 1.3, $CHCl_3$) (Scheme 5).

Scheme 5[a]



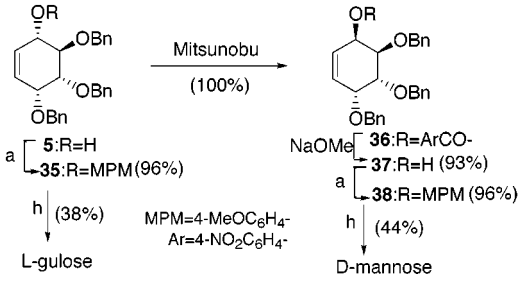
[a] Reagents and conditions: see Scheme 4.

The same method coverted **5** into L-gulose, $[\alpha]^{27}_D$ +19.2 (*c* 0.6, H_2O) {lit.[3] $[\alpha]^{31}_D$ +20.9 (*c* 1.0, H_2O)}, via MPM-

(14) . Oikawa, Y.; Yoshioka, T.; Yonemitsu, O. *Tetrahedron Lett*. **1982**, *23*, 889.
(15) . Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155.
(16) *The Merck Index*, 12th ed.; Merck & Co.: Whitehouse Station, NJ, 1996; p 327.

ether **35**, $[\alpha]^{26}_D$ −11.5 (*c* 1.7, $CHCl_3$). However, the same procedure could not be applied to its isomerization into **33**. Instead, the Mitsunobu reaction using 4-nitrobenzoic acid brought about a clear-cut inversion to give **36**, $[\alpha]^{26}_D$ −143 (*c* 1.4, $CHCl_3$), which gave the epimeric alcohol **37**, $[\alpha]^{27}_D$ −102 (*c* 1.3, $CHCl_3$), on alkaline methanolysis. By employing the same procedure above, **37** gave D-mannose, $[\alpha]^{25}_D$ +13.8 (*c* 0.7, H_2O) {lit.[1] $[\alpha]_D$ −13.5 (*c* 1.0, H_2O) for L-isomer}, via the MPM-ether **38**, $[\alpha]^{25}_D$ −100 (*c* 1.7, $CHCl_3$) (Scheme 6).

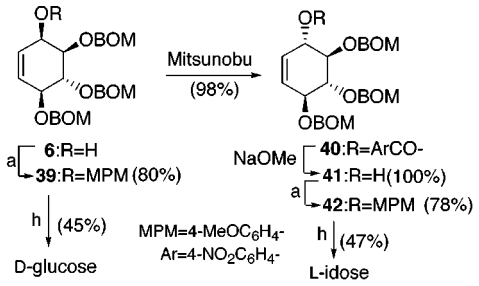
Scheme 6[a]



[a] Reagents and conditions: see Scheme 4.

Tri-BOM-ether **6**, after converion to the MPM-ether **39**, $[\alpha]^{29}_D$ −11.3 (*c* 1.3, $CHCl_3$), gave D-glucose, $[\alpha]^{28}_D$ +47.7 (*c* 0.6, H_2O) {lit.[1] $[\alpha]^{31}_D$ −47.2 (*c* 0.8, H_2O) for L-isomer} on the same treatment for the benzyl ethers as above. Epimerization was carried out by the Mitsunobu reaction to give **41**, via benzoate **40**, which furnished L-idose, $[\alpha]^{28}_D$ −9.2 (*c* 0.6, H_2O) {lit.[1] $[\alpha]^{25}_D$ −10.6 (*c* 1.0, H_2O)}, via MPM-ether **42**, $[\alpha]^{30}_D$ +60.8 (*c* 1.5, $CHCl_3$) on the same treatment as above for the benzyl ethers (Scheme 7).

Scheme 7[a]



[a] Reagents and conditions: see Scheme 4.

In conclusion, we have demonstrated the synthesis of four L- and four D-aldohexoses from a single cyclohexanoid chiral building block. The enantiomers of these may be also accessible as we have obtained the enantiomer of the starting chiral building block.

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