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Tetrahedron: *Asymmetry* 15 (2004) 581–584
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Practical syntheses of enantiopure carbasugars: carba-β-altrose, carba-β-mannose, carba-β-idose, and carba-β-talose derivatives

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Received 22 November 2003; accepted 29 December 2003

Dedicated to Professor D. H. Kim on the occasion of his 70th birthday

Abstract—D and L forms of carba-β-altrose **8**, carba-β-mannose **10a**, carba-β-idose **12**, carba-β-talose **14** derivatives were prepared from (±)-3-cyclohexene-1-carboxylic acid **1**. Homochiral diol compounds D-**5a** and L-**5a**, which were prepared from **1** via enzyme resolution of (±)-**4a**, were efficiently transformed to carba-β-altrose derivatives **8** by stereoselective introduction of hydroxyl groups. Oxidation (PCC)/reduction ($NaBH_4$) of 3-OH and/or 4-OH of **8a** efficiently gave **10a**, **12**, and **14** with good stereoselectivity.

Carbohydrate–protein interactions are known to initiate or mediate important cell–cell recognition processes such as immune response, fertilization, cell growth, cell–cell adhesion, viral infection, and inflammation.[1] Currently, oligosaccharides or their analogues are emerging as potential therapeutic agents,[2] because they are possible regulators of these biological processes. Nonhydrolyzable analogues of oligosaccharides such as carbaoligosaccharides[3] are thought to be more desirable drug candidates than natural sugars because they are stable to hydrolysis by ubiquitous glycosidases.[4]

Recently, we have investigated a practical synthetic route to carbasugar derivatives that can be used as building blocks for nonhydrolyzable oligosaccharide analogues. Although various synthetic routes to carbasugar stereoisomers have been developed since 1966,[5,6] there is no reported general protocol to provide all stereoisomers (*glycosyl acceptor mimics*). Ten out of 16 possible stereoisomers were synthesized by one of the more representative routes,[7] developed by Ogawa et al. but most of them were generated as mixtures.[8] Rather than using a specific route for each stereoisomer, stereoselective conversion of carbasugar stereoisomers to their epimers can be a more practical way to obtain other stereoisomers. Furthermore, carbasugar building blocks should also be made available as *glycosyl donor mimics* such as carbasugar 1,2-epoxide derivatives.[3] We envisioned that a series of operations involving (1) synthesis of *a suitable carbasugar stereoisomer* followed by (2) conversion to its 'C3 and C4 variants', and then (3) conversion of these four stereoisomers to 1,2-epoxides and 'C1 and C2 variants' might be a more practical route to all possible carbasugar building blocks (Fig. 1).

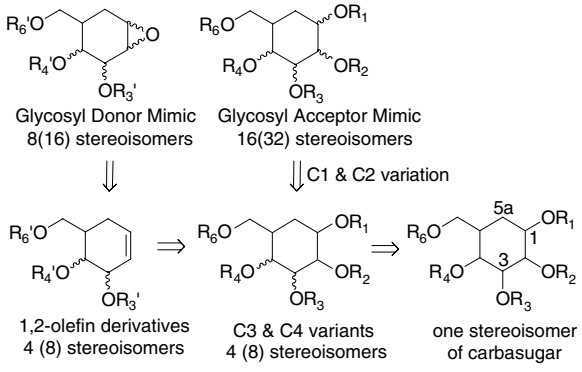

Figure 1.

Herein we report, as a part of our attempts to develop practical synthetic routes to all stereoisomers of monomeric carbasugar, (1) a synthetic route to homochiral 5a-carba-β-altrose derivatives (D and L-**8a**) from racemic 3-cyclohexene-1-carboxylic acid **1** via enzymatic resolution and stepwise introduction of hydroxyl groups at C1∼C4 and (2) regio- and stereo-selective conversion

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doi:10.1016/j.tetasy.2003.12.042

of **8a** to the other three (six as enantiomers) stereoisomers (Fig. 2, only D-form is shown) as 'C3 and C4 variants'.

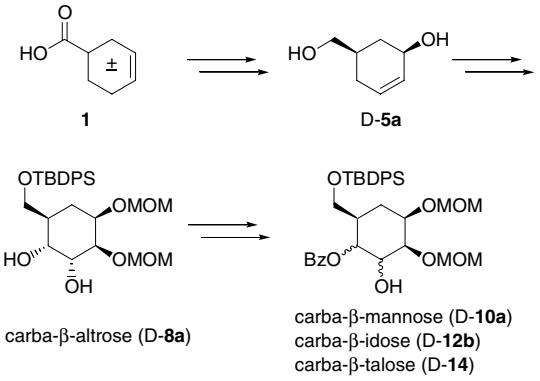
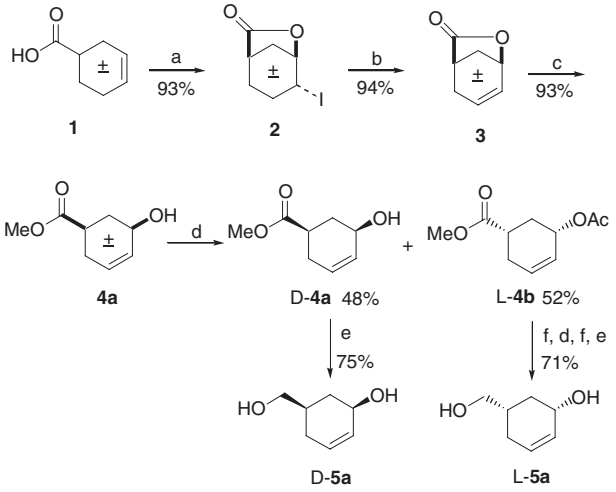


Figure 2.

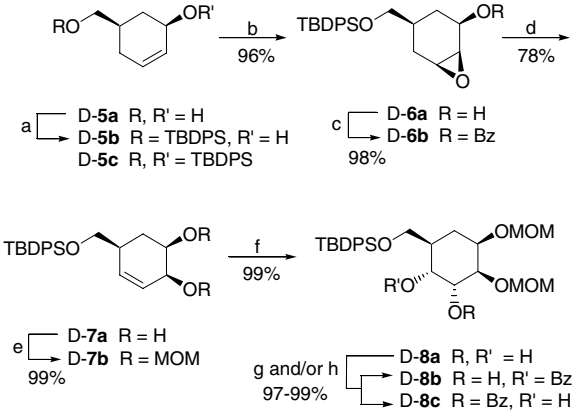
Homochiral diols, D-**5** and L-**5** are key intermediates for the D- and L-form of carba-β-altrose derivative **8a** in our synthetic scheme. Although D-**5a**[9c] and L-**5a**[10] can be derived from optically active 3-cyclohexene-1-carboxylic acid D-**1** and L-**1**, preparation of homochiral D-**1** or L-**1** requires a stoichiometric amount of expensive chiral auxiliaries.[9] We therefore examined a synthetic route to homochiral D-**5a** and L-**5a** from commercially available D/L-**1** based on enzymatic kinetic resolution of compound **4a** with hydrolases (Scheme 1).[11] D/L-**4a** was prepared by iodo-lactonization of D/L-**1** with subsequent elimination and methanolysis according to the literature procedures.[9b] We studied kinetic acetylation reactions of D/L-**4a** with available lipases and vinyl acetate.[12] Treatment of D/L-**4a** with Novozym 435[13] (3–10 mg/mmol of D/L-**4a**) and vinyl acetate (9 equiv) in *t*-BuOMe was found to give the best result at 52% conversion. Depending on the reaction scale, the enantiomeric excess of D-**4a** was in the range of 90–95% ee and the acetylated product, L-**4b** in the range of 80–85% ee.[14] Reduction of D-**4a** (~90% ee) with lithium aluminum hydride was followed by crystallization to obtain enantiomerically pure D-**5a** in 75% yield $\{[\alpha]_D^{24} = +20.8$ (*c* 1.46, MeOH), lit. $[\alpha]_D^{23} = +20.3$ (*c* 1.46, MeOH)[9c]$\}$. A direct reduction of L-**4b** resulted in low % ee, and another cycle of enzyme acetylation was carried out. Thus, methanolysis of L-**4b** (~80% ee) with NaOMe (0.1 equiv) in MeOH gave L-**4a** (~80% ee). The product L-**4a** (~80% ee) upon treatment with Novozym 435 and vinyl acetate again (~86% conversion), followed by deacetylation and reduction gave enantiomerically pure L-**5a** even without recrystallization $\{[\alpha]_D^{24} = -20.6$ (*c* 1.57, MeOH), lit. $[\alpha]_D^{23} = -20.5$ (*c* 2.19, 99.5% EtOH)[10]$\}$. From these runs of operation, were obtained 14.5 g (36% overall yield) of D-**5a** and 15.2 g (37% overall yield) of L-**5a** starting from 49.8 g of D/L-**4a**.

Synthesis of D-**8a** was accomplished from diol D-**5a** by applying the modified 'Sharpless procedure' for transforming an epoxide to an allyl alcohol (Scheme 2).[15] The primary hydroxyl group of D-**5a** was protected with *t*-butyldiphenylsilyl group to D-**5b** and treatment of



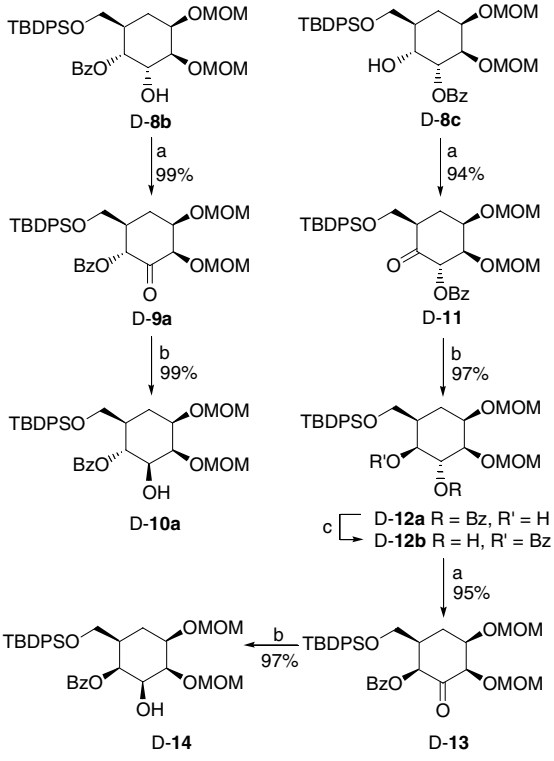
Scheme 1. Reagents and conditions: (a) $NaHCO_3$, KI, I_2, water, rt; (b) DBU, THF, reflux; (c) $NaHCO_3$, MeOH, reflux; (d) Novozym 435, vinyl acetate, *t*-BuOMe, rt; (3) LAH, THF, 0 °C, crystallization; (f) NaOMe (0.1 equiv) MeOH, rt.

D-**5b** with mCPBA gave the *cis*-epoxide D-**6a** as major product (*cis*:*trans* = 20:1 by ^1H NMR) presumably due to the directing effect of the allylic hydroxyl group.[16] After protection of 1-OH of D-**6a** as a benzoate, successive treatments with TMSBr, DBU, 1 M HCl, and NaOMe–MeOH resulted in compound D-**7a** via an elimination reaction of the transient bromohydrin.[15b] Treatment of D-**7a** with MOMCl and diisopropylethylamine gave compound D-**7b** and the subsequent dihydroxylation with a catalytic amount of OsO_4[17] and *N*-methylmorpholine N-oxide in acetone–water (6:1) gave compound D-**8a** as the sole product. L-**8a** was similarly prepared from L-**5a**.



Scheme 2. Reagents and conditions: (a) TBDPS-Cl (1.0 equiv), imidazole, DMF, 0 °C, D-**5b**:D-**5c** = 70%: 14%; (b) mCPBA, CH_2Cl_2, 0 °C, *cis*:*trans* = 20:1; (c) BzCl (1.5 equiv), pyridine, 0 °C; (d) (i) TMSBr (4 equiv), 0 °C, (ii) DBU (4 equiv), 80 °C, 5 days, (iii) 1 N HCl, rt, (iv) NaOMe (0.1 equiv), MeOH, rt; (e) MOMCl (4 equiv), $(i\text{-Pr})_2$ NEt (4 equiv), CH_2Cl_2, 40 °C; (f) OsO_4 (cat.), NMO (2 equiv), rt; (g) (i) triethyl orthobenzoate (2 equiv), *p*-TSA monohydrate (0.1 equiv), CH_2Cl_2, rt, (ii) 80% aq AcOH; (h) TEA (2 equiv), Me_2SnCl_2 (2 mol %), BzCl (1.2 equiv), 0 °C.

The carba-β-altrose derivative D-**8a** was transformed into its regioisomeric monobenzoates D-**8b** and D-**8c**. Treatment of D-**8a** with triethyl orthobenzoate[18] and *p*-TSA, followed by hydrolysis in 80% aqueous AcOH gave a mixture of benzoates (D-**8b**:D-**8c** = 25:75) in 99% yield. On the other hand, D-**8a** upon treatment with benzoyl chloride, triethylamine, and Me_2SnCl_2[19] gave 4-O-benzoate D-**8b** as the major product (D-**8b**:D-**8c** = 88:12, 97%). Oxidation of 4-O-benzoate D-**8b** with PCC[3b,20] gave the 3-keto compound D-**9a**, which was then reduced with $NaBH_4$ (5 equiv) and MeOH (50 equiv) in dichloromethane to give the carba-β-mannose derivative D-**10a** with a high stereoselectivity (D-**10a**:D-**8b** = 96:4 by ^1H NMR) (Scheme 3). Similarly, oxidation of 3-O-benzoate D-**8c** with PCC gave the 4-keto compound D-**11** and subsequent reduction of D-**11** with $NaBH_4$ gave the carba-β-idose derivative D-**12a** with a high stereoselectivity (D-**12a**:D-**8c** = 95:5 by ^1H NMR). Benzoyl migration of D-**12a** was effected in 60% aqueous pyridine for 4 days[21,22] at 100 °C to give a mixture of D-**12a** and D-**12b** (30:70). By repeating the migration reaction of D-**12a**, the 4-O-benzoate D-**12b** was obtained in 83% overall yield. Further inversion of 3-OH of the carba-β-idose derivative D-**12b** by the similar oxidation/reduction strategy provided the carba-β-talose derivative D-**14** with a high stereoselectivity (D-**14**:D-**12b** = 95:5 by ^1H NMR).



Scheme 3. Reagents and conditions: (a) PCC (3.0 equiv), molecular sieve 4 Å, CH_2Cl_2, reflux; (b) $NaBH_4$ (5.0 equiv), MeOH (50 equiv), CH_2Cl_2, 0 °C; (c) 60% aq pyridine, 100 °C, 4 days, D-**12a**:D-**12b** = 27%:66%.

All keto derivatives in this series were attacked by the hydride from the bottom side when treated with $NaBH_4$ in CH_2Cl_2–MeOH. These results might be attributable to the steric hindrance of the axial 2-OMOM groups. Initially, we examined the reduction of the 4-OBn-3-keto derivative D-**9b** in order to obtain the carba-β-mannose derivative D-**10b**, but a poor stereoselectivity was observed (D-**10b**:D-**8d** = ~1:2 with $NaBH_4$, D-**10b**:D-**8d** = ~1:1 with BH_3–SMe_2) (Fig. 3). Apparently, for some reasons, the benzoyl groups of D-**9a** and D-**11** do not hinder the bottom-side approach by the hydride, whereas the benzyl group of D-**9b** substantially does. In a recent report by Chang et al.[23] many examples were described concerning the stereoselectivities versus vicinal functional groups in the reduction of ketosugars (hexosulose) with $NaBH_4$. Several of these examples also imply that vicinal benzoate might not affect the steric approach of hydride even though there has been no obvious explanation for these results.

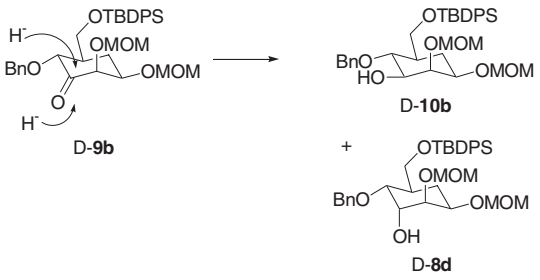


Figure 3.

In conclusion, we have developed a practical route to optically active carba-β-altrose derivative, D and L-**8a**, from 3-cyclohexen-1-carboxylic acid via stepwise, stereoselective introductions of hydroxyl groups and enzymatic resolution. We have also developed facile transformation routes from **8a** to other stereoisomers [D and L of carba-β-mannose **10a**, carba-β-idose **12**, carba-β-talose derivatives **14**] via regio- and stereo-selective inversions of the C3 and/or C4 stereochemistry of **8a**. We are currently examining these eight carbasugar stereoisomers as convenient precursors to all other possible carbasugar stereoisomers and their derivatives, as well as the utility of these derivatives as building blocks of carbasugar-containing oligosaccharide mimics as potential drug candidates.

Acknowledgements

Financial support from the Ministry of Education/BSRI Fund is gratefully acknowledged.

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8. For examples: carba-β-glucose and carba-α-galactose as mixture (34% and 27% isolated yield), carba-α-mannose and carba-β-altrose as mixture (29% and 27% isolated yield), and carba-α-galactose and carba-α-idose as mixture (29% and 27% isolated yield).
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12. Preliminary hydrolysis reactions of **4b** with *Candida rugosa* (CRL; Sigma), *Pseudomonas cepacia*(PCL; Amano), Novozym 435 (CAL, immobilized lipasae from *Candida antarctica*; Novo Nordisk), Lipozyme RM IM (RML, immobilized lipase from *Rhizomucor miehei*; Novo Nordisk) in phosphate buffer (pH 7) resulted in undesired saponification of the methyl ester.
13. Preliminary acetylations of **4a** showed that Novozym 435 had the best ability to distinguish L-**4a** from D-**4a** among the four enzymes tested.[12]
14. Although we obtained D-**4a** with ~95% ee from small scale reaction (1 mmol scale), enantiomeric excess of D-**4a** was ~90% ee from large scale reaction (150 mmol scale). The enantiomeric purity of D-**4a** was determined by measuring the specific rotation of its oxidized compound, that is methyl (1*R*)-3-oxo-4-cyclohexen-1-carboxylate {determined as 95% ee from $[\alpha]_D^{24} = -79.7$ (*c* 1.06, $CHCl_3$) for small scale reaction and as 90% ee from $[\alpha]_D^{20} = -75.5$ (*c* 1.05, $CHCl_3$) for large scale reaction, lit. $[\alpha]_D^{25} = +82.3$ (*c* 1.0, $CHCl_3$) 98% ee for its antipode [24]}. Enantiomeric purities of D-**4a** (~ 90% ee) and L-**4a** (~80% ee) were also determined by ^1H NMR ($CDCl_3$) and ^{19}F NMR ($CDCl_3$) analysis of their corresponding *O*-(−)-MTPA esters[25] (D-**4a**′ and L-**4a**′) Compound D-**4a**′: ^1H NMR ($CDCl_3$) δ 1.83 (td, $J = 12.3$, 9.5 Hz, 1H), 2.29 (m, 2H), 2.49 (dm, $J = 12.0$ Hz, 1H), 2.73 (m, 1H), 3.53 (s, 3H), 3.66 (s, 3H), 5.57 (bd, $J = 10.1$ Hz, 1H), 5.65 (m, 1H), 5.87 (dm, $J = 10.1$ Hz, 1H), 7.35–7.55 (m, 5H), ^{19}F NMR ($CDCl_3$) δ 4.77 (95%). Compound L-**4a**′: ^1H NMR ($CDCl_3$) δ 1.77 (td, $J = 12.1$, 9.1 Hz, 1H), 2.29 (m, 2H), 2.40 (dm, $J = 12.2$ Hz, 1H), 2.73 (m, 1H), 3.53 (s, 3H), 3.61 (s, 3H), 5.62 (m, 1H), 5.70 (bd, $J = 10.3$ Hz, 1H), 5.93 (dm, $J = 10.2$ Hz, 1H), 7.35–7.55 (m, 5H), ^{19}F NMR ($CDCl_3$) δ 4.80 (90%).
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