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Tetrahedron: Asymmetry
Tetrahedron: *Asymmetry* 17 (2006) 3030–3036

Practical syntheses of optically active carbagalactose and their potential application to the carbocyclic analogues of KRN7000

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Received 19 October 2006; accepted 7 November 2006

Abstract—Carba-α- and β-D-galactose derivatives were efficiently prepared from a cyclohex-3-ene-1,2-diol derivative **1**. Regioselective inversion of 2-OH, and stereoselective dihydroxylation of **1** were accomplished to provide a carba-β-D-galactose derivative **6** in a good yield and with a high stereoselectivity. Stereo-inversion of 1-OH of **6** via oxidation/reduction gave carba-α-D-galactose derivative **12** with a high stereoselectivity. An efficient coupling of carba-α-galactose **12** with an aziridine derivative of sphingosine has been demonstrated to give 1-*O*-carba-α-galactosyl sphingosine derivative **14**.

1. Introduction

Carbohydrate–protein interactions on cell surfaces are known to initiate or mediate important cell–cell recognition processes such as immune responses, 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 thought to be potential regulators of these biological processes. Among many carbohydrate analogues, non-hydrolyzable analogues such as carbasugar-based carbohydrate mimetics[3] are thought to be more desirable drug candidates than natural sugars since they are expected to provide a prolonged activity due to their stability against ubiquitous glycosidases. Although there have been reported[3a–h,4] a number of synthetic routes to a variety of carbasugars, paucity of efficient synthetic routes has hampered their applications to various useful carbohydrate mimetics.

Recently, we have reported a divergent synthetic route to obtain all optically active 16 (or 32) stereoisomers of carbasugars (carba-aldohexopyranose).[5] The synthetic route comprises of sequential stereoinversions of 3- and/or 4-OH of carba-β-altropyranose and subsequent stereochemical manipulations of 1 and/or 2-OH of the resulting four stereoisomers (carba-β-altrose, carba-β-mannose, carba-β-idose, carba-β-talose), and this sequence of stereoinversions is advantageous in that those four C3 and C4 stereovariants can also be utilized for the preparation of all possible 1,2-olefin and 1,2-epoxides as well as the remaining 12 stereoisomers (Fig. 1). However, due to the linear sequence of stereoinversions, some of the stereoisomers require relatively long synthetic routes. For example, carba-α- and carba-β-galactoses have been synthesized through 13–14 steps from cyclohex-3-ene-1,2-diol derivative **1** because they proceed through a serial inversion of three to four stereocenters of carba-β-altrose.

As KRN-7000 (α-galactosyl ceramide) and its analogues have been known as extremely exciting molecules displaying anticancer and immunomodulatory activities,[6] we have been interested in the synthesis and biological evaluation of carbagalactose-based glycoconjugates. For efficient syntheses of these glycomimetics such as carbasugar analogues of KRN-7000, a more practical and concise synthetic route to carbagalactose would be highly desirable. Although there have been several reports for the synthesis of carbagalactose, only Mehta's norbornyl route[7] appears to be practical in terms of its overall yield and the number of synthetic steps involved. However, it requires an expensive starting material (i.e., 5,5-dimethoxy-1,2,3,4-tetrachlorocyclopentadiene) and a costly enzymatic resolution step[8] of a key intermediate, to its disadvantage. Since the optically active **1** [both (+) and (−) form] can be prepared practically (in a bench scale synthesis, 15–20 g of each enantiomer can be

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doi:10.1016/j.tetasy.2006.11.014

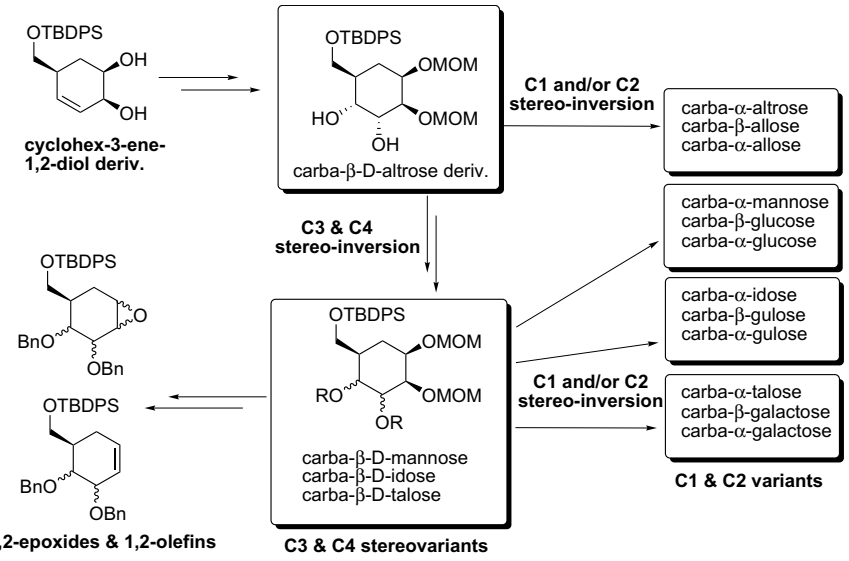


Figure 1. Syntheses of all 16 carbasugar stereoisomers.

readily prepared starting from ca. 50 g of 3-cyclohexene-1-carboxylic acid, which is commercially available at a reasonable price), a synthetic route starting from **1** was envisioned as an efficient way to prepare optically active carbagalactose derivatives.

Herein, we report a practical synthetic route to carba-β-D-galactose derivatives (only five steps from **1**) and its conversion to a carba-α-D-galactose derivative with a high stereoselectivity. We also describe a synthetic method for preparing 1-*O*-carba-α-D-galactosyl sphingosine derivative, which is similarly applicable to the syntheses of various carba-α-D-galactosyl ceramide derivatives as carbocyclic analogues of KRN7000.

2. Result and discussion

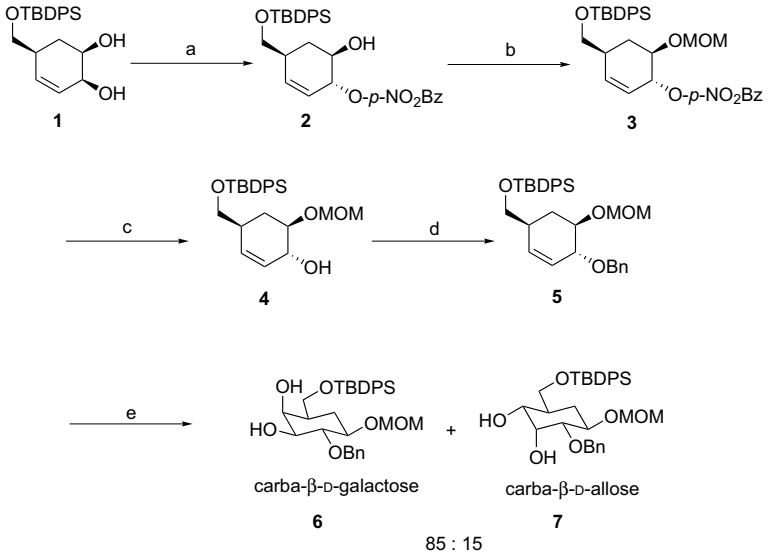
2.1. Synthesis of carba-β-D-galactose derivative 6

In order to prepare carba-β-D-galactose from compound **1**, we needed to place the 3- and 4-OH on the same face as the 1-OH of **1** and to effect stereoinversion of the 2-OH. It was expected that the 2-OH of compound **1** would be more susceptible to the Mitsunobu inversion because of its allylic nature.[9] As imagined, the stereochemistry of the 2-OH in **1** was selectively inverted under Mitsunobu conditions (PPh_3, DEAD, *p*-nitrobenzoic acid in THF) to provide compound **2** in 71% yield. Then, we wanted to transform **2** into the carba-β-galactose configuration by stereoselective dihydroxylation of the 3,4-olefin moiety. Since the effect of a neighboring group to an olefin is often crucial to the stereoselectivity in a dihydroxylation reaction,[10] we decided to introduce the benzyl group onto the 2-OH for a more pronounced effect on dihydroxylation. The 1-OH of compound **2** was first protected as a MOM ether[11] to give compound **3** (93%), which could be orthogonally removed later for selective inversion of the C1 stereochemistry to carba-α-galactose. Then, the *p*-nitrobenzoyl group in compound **3** was replaced by a benzyl group to give compound **5** by treatment with NaOMe in MeOH and subsequent benzylation of the 2-OH in **4** with NaH, BnBr, TBAI in THF. It was gratifying to find that the dihydroxylation of compound **5** with OsO_4 (cat.) and NMO in acetone–water (8:1) gave preferentially carba-β-D-galactose derivative **6** with a minor amount of carba-β-D-allose derivative **7** (**6**:**7** = 85:15, in 99% yield) (Scheme 1).

Structural determinations of compounds **6** and **7** were carried out by ^1H NMR analysis summarized in Figure 2. For compound **6**, the coupling constants $J_{H2-H3} = 9.3$ Hz, $J_{H3-H4} = 2.8$ Hz, and $J_{H4-H5} = 2.4$ Hz in benzene-d_6 indicate that H2 and H3 have axial orientations while H4 occupies an equatorial position. The ^1H–^1H-homonuclear COSY spectrum also corroborated the structure of compound **6**. For compound **7**, the coupling constants $J_{H1-H2} = 9.3$ Hz, $J_{H2-H3} = 2.7$ Hz, $J_{H3-H4} = 2.6$ Hz, and $J_{H4-H5} = 10.3$ Hz in $CDCl_3$ indicated that H1, H2, and H4 have all axial orientations while H3 has an equatorial orientation.

2.2. Synthesis of the carba-α-galactose derivative 12

For the synthesis of a carba-α-galactose derivative, the stereochemistry of **6** was inverted by an oxidation/reduction protocol with PCC and L-Selectride™ (Scheme 2). First, removal of the TBDPS protecting group of the 6-OH in **6** and perbenzylation were carried out.[12] Sequential treatment of compound **6** with TBAF in THF (90%), and the resulting triol **8** with NaH, BnBr, TBAI in THF (92%) provided a fully protected compound **9**. The MOM group of **9** was removed by treatment with MeOH–water–concd HCl (100:10:1) at reflux to provide an alcohol **10** in 94% yield. Compound **10** was oxidized with PCC (3 equiv) to give 1-keto derivative **11** (89%). Reduction of compound **11** with L-Selectride™ gave compound **12** with a high stereoselectivity (**12**:**10** > 40:1, in 82% yield). The structure of compound **12** was assigned by ^1H NMR analysis. The



Scheme 1. Synthesis of carba-β-D-galactose derivative **6**. Reagents and conditions: (a) PPh_3, DEAD, 4-$NO_2C_6H_4CO_2H$, 0 °C, 2 h, 71%; (b) dimethoxymethane, P_2O_5 (4.5 equiv), rt, 2 h, 93%; (c) NaOMe (0.1 equiv), MeOH, rt, 50 min, 97%; (d) BnBr (2 equiv), NaH (2 equiv), Bu_4NI (0.1 equiv), THF, rt, 25 h, 91%; (e) OsO_4 (cat.), NMO (2 equiv), acetone–water (8:1), rt, 22 h, 99%.

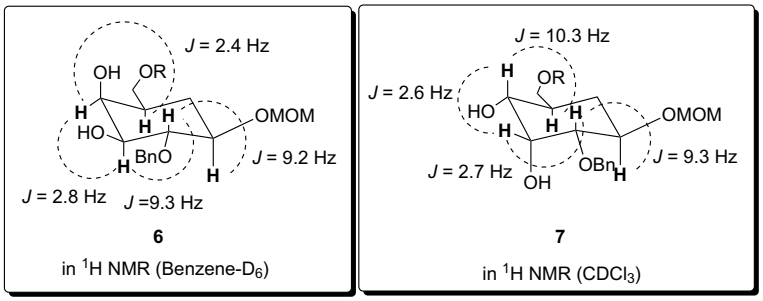


Figure 2. Structural determination of compounds **6** and **7**.

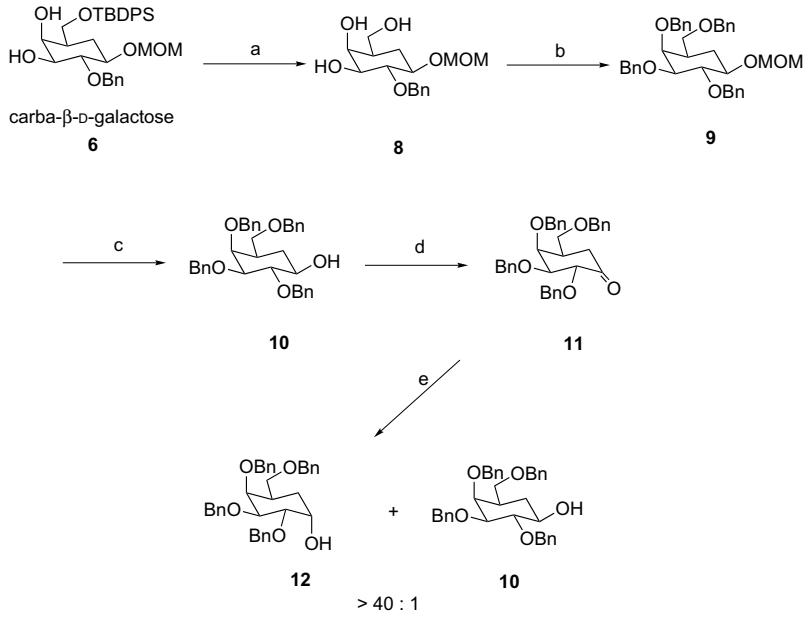
coupling constants $J_{H1–H2} = 3.2$ Hz, $J_{H2–H3} = 9.7$ Hz, and $J_{H3–H4} = 2.3$ Hz in $CDCl_3$ indicate that H1 and H4 have equatorial orientations, whereas H2 and H3 have axial orientations.

2.3. Synthesis of 1-*O*-carba-α-galactosyl sphingosine derivative 14

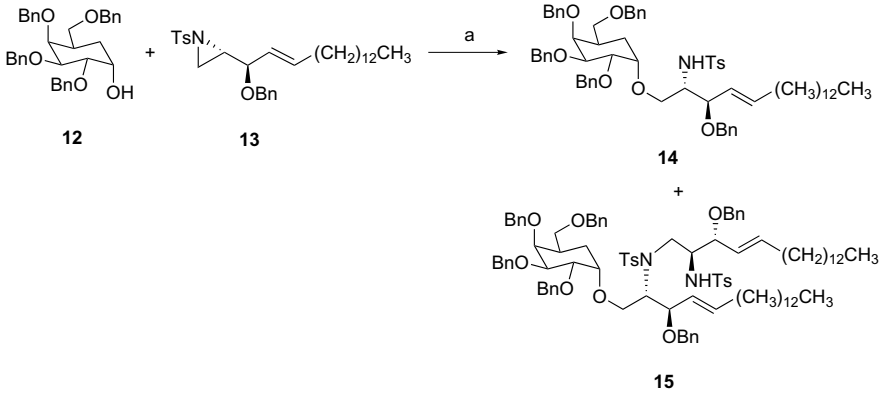
With a good supply of carba-α-D-galactopyranose **12** in hand, we investigated the synthesis of 1-*O*-carba-α-galactosyl sphingoshine derivative **14** via coupling of **12** with an aziridine derivative of sphingosine **13**.[13] Compound **13** in our hands was prepared from D-*erythro*-sphingosine by tritylation, benzylation, detritylation, and cyclization with TsCl, DMAP, Et_3N in CH_2Cl_2 in good overall yield.[14] The reaction of **12** and **13** with NaH in DMF gave the desired product with varying yields depending on the ratio of **12** and **13** employed. When we used 1:1 ratio of **12** and **13**, the yield of the coupled product **14** was only 26% with a by-product **15** (11%). As the reaction progresses under the coupling conditions, obviously the starting material **12** and the desired product **14** were competing for **13**. In order to facilitate the formation of **14** we needed to increase the amount of **12**. When the ratio of **12**:**13** was raised to 4:1, compound **14** was obtained in 85% yield without the formation of **15**, and un-reacted **12** was recovered quantitatively (Scheme 3).

3. Conclusion

We have successfully developed practical synthetic routes to carba-α- and carba-β-galactose derivatives (**6** and **12**) from cyclohex-3-ene-1,2-diol derivative **1**. Since both (+)- and (−)-forms of **1** are readily available, the described synthetic strategy should be also applicable to all four diastereomeric carbagalactoses (D- and L- of the α- and β-forms). By using carba-α-galactose derivative **12**, we have also synthesized a carba-α-galactosyl sphingosine derivative **14**. We are currently investigating the preparation of various aziridine derivatives of all eight stereoisomers of phytosphingosine[14c] and their couplings with carba-α-galactose derivatives for the syntheses of a number of carbocyclic analogues of KRN7000 (α-Galactosyl ceramide). Similarly, the optically active carbagalactose derivatives are also being utilized for the syntheses of carbasugar



Scheme 2. Synthesis of carba-α-galactose derivative **12**. Reagents and conditions: (a) TBAF (1.1 equiv), THF, rt, 2 h, 90%; (b) BnBr (9 equiv), NaH (10 equiv), Bu_4NI (0.3 equiv), THF, rt, 16 h, 92%; (c) MeOH–water–concd HCl (100:10:1), reflux, 20 h, 94%; (d) PCC (3 equiv), molecular sieves 4 Å, CH_2Cl_2, rt, 80 min, 89%; (e) L-Selectride™ (4.3 equiv), THF, −20 °C, 1 h, 82%.



Scheme 3. Synthesis of carba-α-galactosyl sphingosine derivative **14**. Reagents and conditions: (a) NaH (3 equiv), DMF, rt, 3 h, 85%.

glycomimetics for various physiologically important glycoconjugates.

4. Experimental

4.1. General procedure

All non-hydrolytic reactions were carried out in an oven-dried glassware under inert atmosphere of dry argon or nitrogen. All commercial chemicals were used as obtained without further purification, except for solvents, which were purified and dried by standard methods prior to use. Analytical TLC was performed on Merck 60 F254 silica gel plate (0.25 mm thickness) and visualization was done with UV light, and/or by spraying with a 5% solution of phosphomolybdic acid followed by charring with a heat gun. Column chromatography was performed on Merck 60 silica gel (70–230 mesh or 230–400 mesh). NMR spectra were recorded on a Bruker AM 300, DPX 300, or DRX 500 spectrometer. Tetramethylsilane was used as the internal standard for ^1H NMR. High resolution mass spectra (FAB) were determined on a JMS-700 at the Korea Basic Science Center, Daegu, Korea. Optical rotations were measured with a JASCO DIP-360 digital polarimeter. The standard extractive work-up procedure consisted of pouring into a large amount of water, extracting with the organic solvent indicated, washing the combined extracts successively with water and brine, drying the extract over anhydrous $NaSO_4$ or $MgSO_4$, and evaporating the solvent.

4.2. (1*R*,2*R*,5*S*)-5-(*tert*-Butyl-diphenylsilanyloxymethyl)-2-*p*-nitrobenzoyloxy-cyclohex-3-ene-1-ol 2

To a stirred mixture of compound **1**[5a] (2.0 g, 5.23 mmol), triphenylphosphine (1.61 g, 6.14 mmol), 4-nitrobenzoic

acid (1.16 g, 6.94 mmol) in THF (100 ml) at −20 °C was added diethyl azodicarboxylate (1.00 g, 5.75 mmol). After stirring for 2 h at 0 °C, the reaction mixture was partitioned between ethyl acetate and satd aq $NaHCO_3$. The organic layer was dried ($MgSO_4$), concentrated, and chromatographed on silica gel to give compound **2** (1.96 g, 70.7%) as a colorless sticky oil. $[\alpha]_D^{27} = -131.5$ (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 1.09 (s, 9H, $-C(CH_3)_3$), 1.67 (ddd, $J = 13.1$, 10.9, 9.6 Hz, 1H, $H6_\beta$), 2.25 (dt, $J = 13.2$, 4.3 Hz, 1H, $H6_\alpha$), 2.62 (m, 1H, H5), 3.63 (d, $J = 5.9$ Hz, 2H, $H7_a$ and $H7_b$), 4.08 (ddd, $J = 10.9$, 7.0, 3.9 Hz, 1H, H1), 5.54 (ddd, $J = 7.0$, 4.4, 2.6 Hz, 1H, H2), 5.74 (dt, $J = 10.0$, 2.6 Hz, 1H, H3), 5.90 (br d, $J = 10.0$ Hz, 1H, H4), 7.39–7.7 (m, 10H, 2Ph), 8.30 (m, 4H, 4-NO_2Ph); ^{13}C NMR ($CDCl_3$): δ 19.5, 27.0, 32.9, 38.9, 67.4, 70.2, 123.7, 125.0, 127.9, 130.0 (2s), 131.1, 133.4, 133.5, 133.7, 135.7, 135.8 (2s), 150.8, 165.4; HRMS (FAB) *m/z* calcd for $C_{30}H_{34}NO_6Si$ 532.2155, found 532.2149 (M^++1).

4.3. (1*R*,2*S*,5*S*)-5-(*tert*-Butyl-diphenylsilanyloxymethyl)-1-methoxymethoxy-2-*p*-nitrobenzoyloxy-cyclohex-3-ene 3

To a stirred mixture of compound **2** (1.90 g, 3.57 mmol) in dimethoxymethane (20 ml) at rt was added P_2O_5 (2.00 g, 14.1 mmol) in portions over a period of 2 h. After completion of the reaction, satd aq $NaHCO_3$ was added to the reaction mixture until it became homogeneous. Ethyl acetate was added to the mixture and the organic layer was separated. An extractive workup followed by silica gel chromatography gave compound **3** (1.92 g, 93.2%) as a colorless sticky oil. $[\alpha]_D^{27} = -153.7$ (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 1.05 (s, 9H, $-C(CH_3)_3$), 1.56 (m, 1H, $H6_\beta$), 2.18 (dt, $J = 12.9$, 4.4 Hz, 1H, $H6_\alpha$), 2.59 (m, 1H, H5), 3.24 (s, 3H, $-OCH_2OCH_3$), 3.58 (app dd, $J = 6.5$, 1.9 Hz, 2H, $H7_a$ and $H7_b$), 4.00 (ddd, $J = 12.2$, 8.1, 4.0 Hz, 1H, H1), 4.64 and 4.71 (2d, each $J = 6.98$, 6.98 Hz, 2H, $-OCH_2OCH_3$), 5.63 (m, 2H, H2 and H3), 5.86 (br d, $J = 10.3$ Hz, 1H, H4), 7.34–7.70 (m, 10H, 2Ph), 8.26 (m, 4H, 4-NO_2Ph); ^{13}C NMR ($CDCl_3$): δ 19.5, 27.0, 31.0, 39.4, 55.6, 67.4, 75.8, 76.2, 95.7, 123.8, 125.5, 127.9, 129.9, 130.9, 133.1, 133.7 (2s), 135.8 (2s), 136.0, 150.8, 164.6; HRMS (FAB) *m/z* calcd for $C_{32}H_{38}NO_7Si$ 576.2418, found 576.2421 (M^++1).

4.4. (1*R*,2*S*,5*S*)-5-(*tert*-Butyl-diphenylsilanyloxymethyl)-1-methoxymethoxy-2-ol-cyclohex-3-ene 4

To a stirred solution of compound **3** (1.97 g, 3.42 mmol) in MeOH (20 ml) at rt was added NaOMe (25% in MeOH, 80 μl, 0.35 mmol). After stirring for 50 min, acetic acid (41 mg) was added and the resulting mixture was concentrated. The residue was partitioned between ethyl acetate and satd aq $NaHCO_3$. An extractive workup followed by silica gel chromatography gave compound **4** (1.41 g, 96.6%) as a colorless sticky oil. $[\alpha]_D^{26} = -105.7$ (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 1.04 (s, 9H, $-C(CH_3)_3$), 1.67 (app q, $J = 11.8$ Hz, 1H, $H6_\beta$), 2.08 (dt, $J = 12.5$, 4.2 Hz, 1H, $H6_\alpha$), 2.54 (m, 1H, H5), 3.45 (s, 3H, $-OCH_2OCH_3$), 3.46–3.56 (m, 3H, H1, $H7_a$, and $H7_b$), 4.13 (m, 1H, H2), 4.75 and 4.80 (2d, $J = 7.0$ Hz, 2H, $-OCH_2OCH_3$), 5.60–5.70 (m, 2H, H3, H4), 7.34–7.66 (m, 10H, 2Ph); ^{13}C NMR ($CDCl_3$): δ 19.5, 27.0, 31.4, 39.8, 55.8, 67.7, 72.4, 83.6, 97.3, 127.9, 129.2, 129.9, 133.78, 133.84, 135.8; HRMS (FAB) *m/z* calcd for $C_{25}H_{35}O_4Si$ 427.2305, found 427.2307 (M^++1).

4.5. (1*R*,2*S*,5*S*)-5-(*tert*-Butyl-diphenylsilanyloxymethyl)-1-methoxymethoxy-2-benzyloxy-cyclohex-3-ene 5

To a solution of compound **4** (1.37 g, 3.20 mmol) in dry THF (30 ml) at 0 °C was added NaH (280 mg, 55% in paraffin liquid, 6.41 mmol). After stirring for 30 min at rt, BnBr (0.76 ml, 6.41 mmol) and Bu_4NI (118 mg, 0.32 mmol) were added. After stirring for 25 h at rt, the reaction mixture was carefully quenched with satd aq $NaHCO_3$ and worked up by a standard extractive procedure. The crude product was chromatographed on silica gel to give compound **5** (1.50 g, 91%) as a colorless oil. $[\alpha]_D^{26} = -92.2$ (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 1.08 (s, 9H, $-C(CH_3)_3$), 1.44 (app q, $J = 11.0$ Hz, 1H, $H6_\beta$), 2.08 (dt, $J = 12.7$, 4.4 Hz, 1H, $H6_\alpha$), 2.57 (m, 1H, H5), 3.43 (s, 3H, $-OCH_2OCH_3$), 3.56 (m, 2H, $H7_a$ and $H7_b$), 3.86 (ddd, $J = 11.8$, 7.7, 3.8 Hz, 1H, H1), 4.08 (m, 1H, H2), 4.72 and 4.87 (m, 4H, $-OCH_2OCH_3$, $-OCH_2Ph$), 5.74 (m, 2H, H3, H4), 7.27–7.70 (m, 15H, 3Ph); ^{13}C NMR ($CDCl_3$): δ 19.5, 27.0, 31.4, 39.5, 55.6, 67.7, 71.8, 79.8, 96.2, 127.6, 127.7, 127.9, 128.5, 129.9, 131.0, 133.8 (2S), 135.8 (2S), 139.0; HRMS (FAB) *m/z* calcd for $C_{32}H_{41}O_4Si$ 517.2774, found 517.2773 (M^++1).

4.6. Methoxymethyl 2-*O*-benzyl-6-*O*-(*tert*-butyl-diphenyl)-silyl-5a-carba-β-D-galactopyranoside 6 and methoxymethyl 2-*O*-benzyl-6-*O*-(*tert*-butyl-diphenyl)silyl-5a-carba-β-D-allo-pyranoside 7

To a solution of **5** (1.40 g, 2.71 mmol) and 4-methylmorpholine-*N*-oxide (NMO, 635 mg, 5.42 mmol) in acetone–water (28 ml, 6:1) at rt was added a catalytic amount of OsO_4. After stirring for 22 h, Na_2SO_3 (3.41 g, 27.1 mmol) was added and the resulting mixture was further stirred for 30 min at rt. The reaction mixture was extractively worked up with ethyl acetate, and chromatographed on silica gel to give compound **6** (1.26 g, 84.6%) and compound **7** (219 mg, 14.7%) as colorless oils.

Compound **6**: $[\alpha]_D^{27} = +29.2$ (*c* 1.0, $CHCl_3$); ^1H NMR (C_6D_6): δ 1.28 (s, 9H, $-C(CH_3)_3$), 1.53 (m, 1H, H5), 1.82 (m, 2H, $H5a_\alpha$ and $H5a_\beta$), 3.31 (s, 3H, $-OCH_2OCH_3$), 3.42 (dd, $J = 9.3$, 2.8 Hz, 1H, H3), 3.67 (app td, $J = 9.3$, 7.1 Hz, 1H, H1), 3.73 (dd, $J = 9.8$, 5.8 Hz, 1H, $H6_a$), 3.85 (t, $J = 9.2$ Hz, 1H, H2), 3.98 (dd, $J = 9.7$, 7.7 Hz, 1H, $H6_b$), 4.24 (t, $J = 2.4$ Hz, 1H, H4), 4.67–5.08 (4d, each $J = 6.7$, 11.8, 6.7, 11.8 Hz, 4H, $-OCH_2OCH_3$, $-OCH_2Ph$), 7.25–7.91 (m, 15H, 3Ph); ^{13}C NMR (C_6D_6): δ 19.5, 27.1, 28.3, 39.3, 55.2, 65.1, 69.2, 75.1, 75.3, 78.8, 83.3, 96.0, 128.7, 130.0, 134.0, 134.1, 136.0, 136.1, 139.8; HRMS (FAB) *m/z* calcd for $C_{32}H_{43}O_6Si$ 551.2829, found 551.2831 (M^++1).

Compound **7**: $[\alpha]_D^{27} = +0.64$ (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 1.07 (m, 10H, $-C(CH_3)_3$, $H5a_\beta$), 1.85 (dt, $J = 13.2$, 4.3 Hz, 1H, $H5a_\alpha$), 2.16 (m, 1H, H-5), 2.38 (br s, 2H, OH's), 3.30 (dd, $J = 9.3$, 2.7 Hz, 1H, H2), 3.37 (s,

3H, –OCH_2OCH_3), 3.60 (dd, $J = 10.3$, 2.6 Hz, 1H, H4), 3.67 (dd, $J = 10.0$, 7.0 Hz, 1H, $H6_a$), 3.81 (dd, $J = 10.0$, 4.4 Hz, 1H, $H6_b$), 3.98 (ddd, $J = 11.5$, 9.4, 4.7 Hz, 1H, H1), 4.20 (t, $J = 2.6$ Hz, 1H, H3), 4.68–4.85 (m, 4H, –OCH_2OCH_3, –OCH_2Ph), 7.27–7.70 (m, 15H, 3Ph); ^{13}C NMR ($CDCl_3$): δ 19.3, 27.0, 30.5, 37.8, 55.5, 67.0, 71.1, 72.5, 73.2, 74.9, 82.0, 96.8, 127.9 (2s), 128.0, 128.6, 130.0, 132.9, 133.1, 135.7, 138.4; HRMS (FAB) m/z calcd for $C_{32}H_{43}O_6Si$ 551.2829, found 551.2821 (M^++1).

4.7. Methoxymethyl 2-*O*-benzyl-5a-carba-β-D-galacto-pyranoside 8

To the solution of compound **6** (1.24 g) in THF (25 ml) at 0 °C was added tetrabutylammonium fluoride (1 M in THF, 2.48 ml, 2.48 mmol). After stirring for 2 h at rt, the reaction mixture was concentrated and chromatographed on silica gel (sequential elution with CH_2Cl_2 to remove TBDPS-F followed by elution with ethyl acetate) to give the desired triol compound **8** (634 mg, 90.2%) as a colorless foam. $[\alpha]_D^{27} = +51.3$ (c 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 1.61 (m, 1H), 1.80 (m, 2H), 3.38 (m, 4H), 3.57–3.79 (m, 4H), 4.10 (pseudo t, $J = 2.4$ Hz, 1H, H4), 4.63–4.99 (m, 4H, –OCH_2OCH_3, –OCH_2Ph), 7.24–7.37 (m, 5H, Ph); ^{13}C NMR ($CDCl_3$): δ 28.0, 38.3, 55.7, 64.4, 70.6, 74.5, 75.5, 78.8, 82.7, 96.2, 128.1, 128.8, 139.0; HRMS (FAB) m/z calcd for $C_{16}H_{25}O_6$ 313.1651, found 313.1648 (M^++1).

4.8. Methoxymethyl 2,3,4,6-tetra-*O*-benzyl-5a-carba-β-D-galactopyranoside 9

To a solution of compound **8** (611 mg, 1.96 mmol) in dry THF (35 ml) at 0 °C, was added NaH (860 mg, 55% in paraffin liquid, 19.7 mmol). After stirring for 25 min at rt, BnBr (2.09 ml, 17.6 mmol) and Bu_4NI (217 mg, 0.59 mmol) were added. After stirring for 16 h at rt, the reaction mixture was carefully quenched with satd aq $NaHCO_3$ and worked up by a standard extractive procedure. The crude product was chromatographed on silica gel to give compound **9** (1.05 g, 92.0%) as a colorless oil. $[\alpha]_D^{27} = +29.7$ (c 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 1.59–1.75 (m, 3H, H5, $H5a_\alpha$, $H5a_\beta$), 3.32 (dd, $J = 9.0$, 5.0 Hz, 1H, $H6_a$), 3.35 (s, 3H, –OCH_2OCH_3), 3.41 (dd, $J = 9.7$, 2.4 Hz, 1H, H3), 3.50 (t, $J = 9.0$ Hz, 1H, $H6_b$), 3.58 (ddd, $J = 11.1$, 9.2, 5.3 Hz, 1H, H1), 3.91 (t, $J = 9.4$ Hz, 1H, H2), 4.11 (br s, 1H, H4), 4.42–5.05 (m, 10H, –OCH_2OCH_3, 4 × –OCH_2Ph), 7.29 (m, 20H, 4Ph); ^{13}C NMR ($CDCl_3$): δ 28.9, 37.7, 55.5, 70.8, 73.1, 73.4, 74.6, 74.8, 76.0, 78.7, 83.3, 84.9, 96.8, 127.4, 127.6, 127.9, 128.0, 128.2, 128.3, 128.4, 128.5, 128.6, 138.4, 139.0, 139.3, 139.6; HRMS (FAB) m/z calcd for $C_{37}H_{43}O_6$ 583.3060, found 583.3059 (M^++1).

4.9. 2,3,4,6-Tetra-*O*-benzyl-5a-carba-β-D-galactopyranose 10

The solution of compound **9** (1.02 g, 1.76 mmol) in MeOH–water–concd HCl (100:10:1, 40 ml) was refluxed for 20 h. The reaction mixture was concentrated and partitioned between ethyl acetate and satd aq $NaHCO_3$. The organic layer was dried ($MgSO_4$), concentrated, and chromatographed to give compound **10** (887 mg, 93.7%) as a colorless sticky oil. $[\alpha]_D^{27} = -12.6$ (c 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 1.59 (app q, $J = 12.2$ Hz, 1H, $H5a_\beta$), 1.72 (dt, $J = 12.3$, 4.4 Hz, 1H, $H5a_\alpha$) 1.83 (m, 1H, H5), 2.03 (br s, 1H, –OH), 3.37 (dd, $J = 8.8$, 5.1 Hz, 1H, $H6_a$), 3.46 (dd, $J = 9.6$, 2.3 Hz, 1H, H3), 3.55 (t, $J = 9.1$ Hz, 1H, $H6_b$), 3.57 (m, 1H, H1), 3.84 (t, $J = 9.3$ Hz, 1H, H2), 4.17 (br s, 1H, H4), 4.46–5.08 (m, 8H, 4 × –OCH_2Ph), 7.33 (m, 20H, 4Ph); ^{13}C NMR ($CDCl_3$): δ 29.8, 38.4, 71.4. 72.6. 73.1. 74.0. 75.2. 75.3. 76.2. 84.5. 85.5. 128.0, 128.1, 128.2, 128.3, 128.4, 128.47, 128.54, 128.7, 128.9, 129.1, 129.2, 138.9, 139.2, 139.5, 140.1; HRMS (FAB) m/z calcd for $C_{35}H_{39}O_5$ 539.2797, found 539.2794 (M^++1).

4.10. (2*R*,3*S*,4*S*,5*R*)-2,3,4-Tri-benzyloxy-5-benzyloxy-methyl-cyclohexanone 11

To a stirred mixture of **10** (850 mg, 1.58 mmol), molecular sieves 4 Å (powder, 1 g) in CH_2Cl_2 (30 ml) at rt, was added PCC (1.02 g, 4.73 mmol). After stirring for 80 min, the reaction mixture was filtered through a silica gel column and washed with EtOAc–n-hexane (1:4–1:2). The filtrate was concentrated to give **11** (753 mg, 1.40 mmol, 89.0%) as a colorless oil. $[\alpha]_D^{27} = +10.1$ (c 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 2.05 (m, 1H, H5), 2.24 (dd, $J = 13.6$, 3.8 Hz, 1H, $H6_\alpha$) 2.56 (t, $J = 13.8$ Hz, 1H, $H6_\beta$), 3.36 (dd, $J = 8.9$, 5.2 Hz, 1H, $H7_a$), 3.58 (t, $J = 8.9$ Hz, 1H, $H7_b$), 3.70 (dd, $J = 10.2$, 2.3 Hz, 1H, H3), 4.29 (br s, 1H, H4), 4.46–5.08 (m, 9H, H2, 4 × –OCH_2Ph), 7.36 (m, 20H, 4Ph); ^{13}C NMR ($CDCl_3$): δ 38.3, 38.4, 70.2, 73.4, 73.9, 74.0, 75.2, 75.3, 84.57, 84.65, 127.7, 127.8, 128.0, 128.1, 128.3, 128.5 (2S), 128.7, 138.1, 138.2, 138.7, 139.0; HRMS (FAB) m/z calcd for $C_{35}H_{37}O_5$ 537.2641, found 537.2643 (M^++1).

4.11. 2,3,4,6-Tetra-*O*-benzyl-5a-carba-α-D-galactopyranose 12

To a stirred solution of compound **11** (4.0 g, 7.45 mmol) in THF (250 ml) at 0 °C, was slowly added L-Selectride™ (32.4 ml, 1 M solution in THF, 32.4 mmol) over 25 min with a syringe. After 1 h, the reaction mixture was carefully quenched by dropwise addition of 5% KOH (2.5 ml). The reaction mixture turned to be turbid and a white precipitate was formed. To the resulting mixture at 0 °C, H_2O_2 (4 ml) was slowly added and stirred for 1 h and 30 min. The resulting mixture was filtered, washed with CH_2Cl_2, and the filtrate was concentrated. The residue was dissolved in ethyl acetate, washed with water and brine, dried ($MgSO_4$), concentrated, and chromatographed to give compound **12** (3.10 g, 77.2%) as a colorless oil together with recovered **11** (217 mg, 5.4 %). $[\alpha]_D^{25} = +20.8$ (c 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 1.64 (m, 2H, $H5a_\alpha$ and $H5a_\beta$), 2.32 (m, 1H, H5), 2.62 (br s, 1H, –OH), 3.34 (dd, $J = 8.9$, 5.1 Hz, 1H, $H6_a$), 3.54 (t, $J = 9.2$ Hz, 1H, $H6_b$), 3.80 (dd, $J = 9.7$, 2.3 Hz, 1H, H3), 3.94 (dd, $J = 9.7$, 3.2 Hz, 1H, H2), 4.20 (app q, $J = 2.9$ Hz, 1H, H1), 4.23 (pseudo t, $J = 1.8$ Hz, 1H, H4), 4.77–5.05 (m, 8H, 4 × –OCH_2Ph), 7.36 (m, 20H, 4Ph); ^{13}C NMR ($CDCl_3$): δ 27.8, 35.3, 67.4, 70.8, 72.9, 73.1, 73.2, 74.7, 75.7, 80.3, 81.2, 127.4, 127.5, 127.6, 127.8, 127.86, 127.95, 128.0, 128.3, 128.5, 128.6, 128.7, 138.6, 138.7, 139.2, 139.7; HRMS (FAB) m/z calcd for $C_{35}H_{39}O_5$ 539.2797, found 539.2795 (M^++1).

4.12. (2*S*,3*R*,4*E*)-3-Benzyloxy-1-(2′,3′,4′,6′-tetra-*O*-benzyl-5a-carba-α-D-galactopyranosyloxy)-2-(*p*-toluenesulfonylamino)-4-octadecene 14

To carbasugar derivative **12** (1.31 g, 2.43 mmol) in DMF (4 ml) at 0 °C, was added NaH (55%, 108 mg, 2.47 mol). After stirring for 20 min, aziridine derivative **13** (315 mg, 0.60 mmol) in DMF (2 ml) was added with a syringe. After stirring for 1.5 h at rt, the reaction mixture was partitioned between CH_2Cl_2 and satd aq $NaHCO_3$. The organic layer was dried ($MgSO_4$), concentrated, and chromatographed to give the coupled product **14** (540 mg, 0.51 mmol, 85.0%) as an oil, together with recovered **12** (1.03 g, 1.91 mmol).

Compound **14**: $[\alpha]_D^{25} = +13.1$ (*c* 1.0, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) and ^1H–^1H homonuclear COSY NMR (500 MHz, $CDCl_3$): δ 0.92 (t, $J = 7.0$ Hz, 3H, –CH=$CHCH_2(CH_2)_{11}CH_3$), 1.29 (m, 22H, –CH=$CHCH_2$-$(CH_2)_{11}CH_3$), 1.45 (br t, $J = 13.0$ Hz, 1H, H5a$_\beta$), 1.52 (m, 1H, 1H, H5a$_\alpha$), 1.98 (app q, $J = 7.5$ Hz, 2H, H6$_a$ and H6$_b$), 2.07 (m, 1H, H5′), 2.37 (s, 3H, Ph–CH_3), 3.29 (dd, $J = 8.5$, 5.0 Hz, H6′$_a$), 3.44 (m, 1H, H2), 3.48 (t, $J = 9.0$ Hz, 1H, H6′$_b$), 3.59 (dd, $J = 9.5$ Hz, 1H, H1$_a$), 3.67 (pseudo q, $J = 2.5$ Hz, 1H, H1′), 3.82 (dd, $J = 10.0$, 2.5 Hz, 1H, H3′), 3.85 (dd, $J = 10.0$, 5.5 Hz, 1H, H1$_b$), 3.89 (dd, $J = 9.5$, 2.5 Hz, 1H, H2′), 3.95 (dd, $J = 8.0$, 5.5 Hz, 1H, H3), 4.1 (br s, 1H, H4′), 4.16–5.00 (m, 10H, 5 × –OCH_2Ph), 5.19 (dd, $J = 15.5$, 8.0 Hz, 1H, H4), 5.44 (d, $J = 6.0$ Hz, 1H, NH), 5.59 (dt, $J = 15.5$, 6.5 Hz, 1H, H5), 7.14–7.72 (m, 29H, 5 × Ph, tosyl); ^{13}C NMR ($CDCl_3$): δ 14.3, 21.7, 22.9, 27.2, 29.3, 29.5, 29.6, 29.7, 29.90, 29.94, 32.1, 32.6, 35.9, 57.7, 68.9, 70.8, 73.1, 73.4, 74.8, 76.0, 79.5, 80.2, 81.7, 126.7, 127.4, 127.6, 127.8, 127.9, 128.1, 128.4, 128.5, 128.6, 129.6, 136.8, 138.3, 138.6, 138.7, 139.0, 138.4, 139.8, 143.1; MS (FAB) *m*/*z* 1087 (M^++Na); HRMS (FAB) *m*/*z* calcd for $C_{67}H_{86}NO_8S$ 1064.6074, found 1064.6077 (M^++1).

Acknowledgment

This work was supported by the Korea Research Foundation Grant funded by the Korean Government (MOEHRD) (KRF-2005-070-C00078).

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