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# Total synthesis of (+)-valienamine and (−)-1-*epi*-valienamine via a highly diastereoselective allylic amination of cyclic polybenzyl ether using chlorosulfonyl isocyanate

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ABSTRACT

The total synthesis of (+)-valienamine and (−)-1-*epi*-valienamine was concisely accomplished from readily available D-glucose via a highly diastereoselective amination of chiral benzylic ether using chlorosulfonyl isocyanate, intramolecular olefin metathesis, and diastereoselective reduction of cyclic enone using L-Selectride as the key steps.



## 1. Introduction

Glycosidases are involved in a wide range of important biological processes, such as intestinal digestion, post-translational processing of glycoproteins, and lysosomal catabolism of glycoconjugates.[1] Thus, glycosidase inhibitors have received much attention for the treatment of diabetes,[2] viral infections,[3] malaria,[4] and cancer.[5] The majority of these inhibitors are azasugars, in which an oxygen atom in a monosaccharide is replaced by a nitrogen atom. Azasugars are often found in natural plants and microorganisms. While these azasugars have been extensively studied, the development of carbasugars as glycosidase inhibitors has received little attention.

(+)-Valienamine (**1**) is a polyhydroxylated unsaturated carbasugar that was first isolated from microbial degradation of validoxylamine A (**3**) with *Pseudomonas denitrificans* in 1972.[6] Later, it was derived from degradation of validoxylamine A with *Flavobacterium saccharophilum*[7] or from NBS-mediated selective cleavage of C–N bond in validoxylamine A or its derivatives.[8] (+)-Valienamine is also an essential core unit in many kinds of pseudo-oligosaccharides, e.g., acarbose, validamycins, amylostatins, adiposins, salbostatin, and acarviosin.[9] In particular, acarbose (**4**) is known as a highly potent inhibitor of α-glucosidases in the human digestive tract.[10] Consequently, acarbose can delay the breakdown of ingested carbohydrates and control the resorption of glucose from the intestines. Acarbose (Glucobay™) is currently used as an anti-diabetic drug for the treatment of type II diabetes mellitus (Fig. 1).

Due to the unique structural feature and interesting biological property, a number of efforts have been devoted to the development of various approaches for the efficient synthesis of (+)-valienamine (**1**). Paulsen et al. reported the first synthesis of **1** starting from L-quebrachitol via Mitsunobu-type inversion of an allylic hydroxyl group to an azido group.[11] Since the pioneering work of Paulsen, several approaches have been attempted regarding the preparation of (+)-valienamine (**1**).[12–15] Given the structural relationship of (+)-valienamine with carbohydrates,[12] α-amino acids,[13] and (−)-quinic acid,[14] it is not surprising that most syntheses use these compounds as starting materials. The chiral pool approach can be extremely attractive if nature happens to provide an abundant supply of an inexpensive starting material appropriate for the synthetic target. One of other syntheses relies on a series of Diels–Alder reactions to generate a cyclohexene framework.[15]

In a recent example using a carbohydrate as a chiral pool, Yan and co-workers reported the total synthesis of **1** from D-tartaric acid

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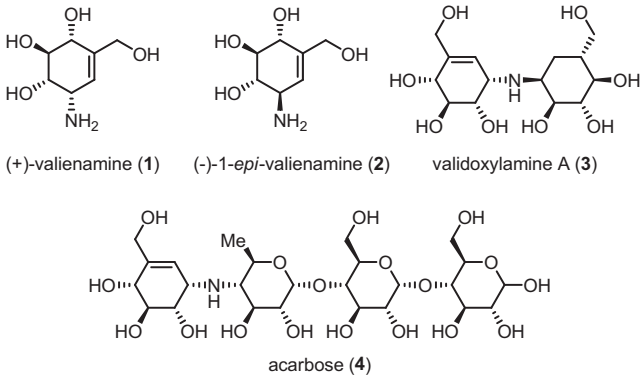


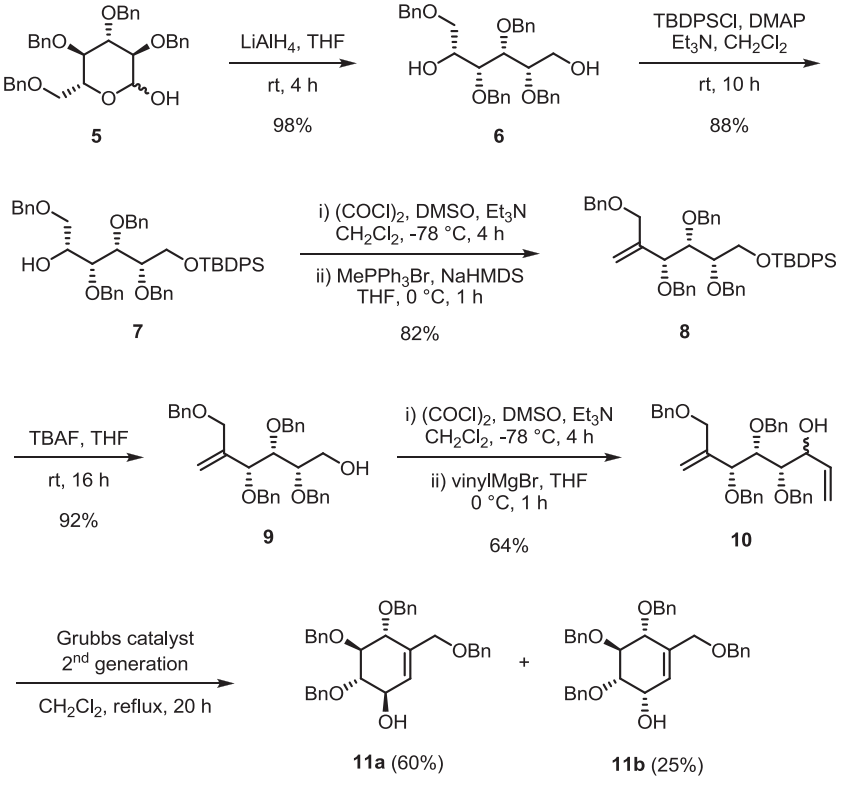

**Fig. 1.** Structures of (+)-valienamine (**1**), (−)-1-*epi*-valienamine (**2**), validoxylamine A, (**3**) and acarbose (**4**).

through iodine-promoted cyclization of an unsaturated carbon-imidothioate for the diastereoselective installation of amine and hydroxyl units.[12e] In another example using a chiral pool, Kim et al. described the asymmetric total synthesis of **1** using readily available D-glucose as a starting material via ring-closing metathesis followed by diastereoselective addition of an azido group under Mitsunobu conditions.[12c] In a representative example of asymmetric synthesis, Trost and co-workers demonstrated the asymmetric total synthesis of **1** via palladium-catalyzed regioselective and diastereoselective *cis*-hydroxyamination of vinyl epoxide and isocyanate as the key steps.[15c] Li et al. reported the asymmetric total synthesis of **1** using *anti*-amino alcohol generated from diastereoselective reductive coupling between alkyne and Garner's aldehyde.[13b]

herein describe an asymmetric total synthesis of (+)-valienamine (**1**) and its 1-epimer **2** starting from commercially available D-glucose via highly regioselective and diastereoselective allylic amination of cyclic polybenzyl ethers using chlorosulfonyl isocyanate, intramolecular olefin metathesis followed by diastereoselective reduction of cyclic enone using L-Selectride as the key steps.

## 2. Results and discussion

The total synthesis of (+)-valienamine (**1**) began with benzyl-protected lactol **5** prepared from commercially available D-glucose according to the reported literature (Scheme 1).[17]



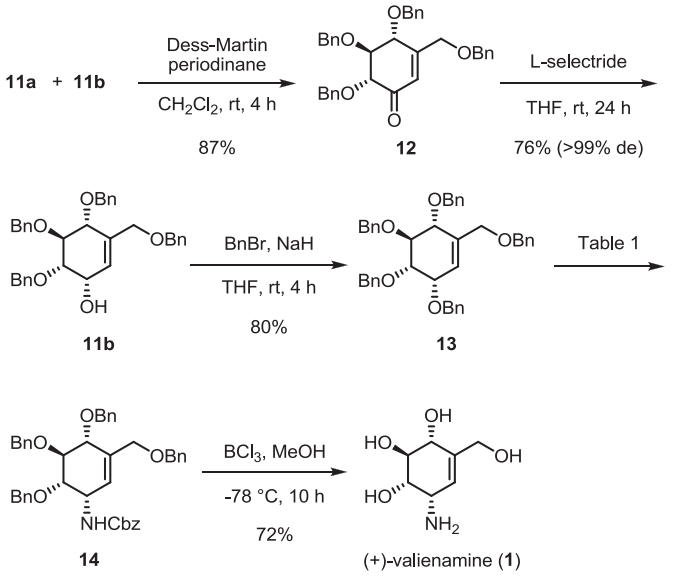

**Scheme 1.**

As part of an ongoing research program aimed at the total synthesis of biologically active polyhydroxylated alkaloids,[16] we

Reduction of **5** and subsequent protection of primary alcohol using TBDPSCl afforded compound **7** in high yields. Swern

oxidation of **7** and subsequent Wittig reaction furnished olefin **7**, which was subjected under standard desilylation conditions to give the corresponding product **9** in 92% yield. After oxidation of primary alcohol, treatment of aldehyde with vinylmagnesium bromide in THF at 0 °C provided an inseparable diastereomeric mixture of allylic alcohol **10** with diastereoselectivity of 2.5:1 ratio by $^1$H NMR analysis. Intramolecular olefin metathesis of diastereomeric diene **10** with second generation Grubbs catalyst in refluxing $CH_2Cl_2$ provided a separable diastereomeric mixture of **11a** and **11b** in 60% and 25% yields, respectively.

To obtain an essential synthetic precursor **13** for the formation of **14**, we then sought selective reduction of enone **12** to alcohol **11b**. Thus, allylic alcohols **11a** and **11b** were oxidized to give enone **12**, which was subjected under reduction conditions using a bulky hydride reagent, such as L-Selectride (Scheme 2). As expected, L-Selectride attacked the ketone exclusively from the sterically accessible β-face of enone **12** to give our desired product **11b** in 80% yield with an excellent level of diastereoselectivity. After benzylation of the primary alcohol, the diastereoselectivity of the reaction




**Scheme 2.**

of cyclic 1,2-*syn*-polybenzyl ether **13** using chlorosulfonyl isocyanate was examined under various reaction conditions. Selected results are summarized in Table 1. As shown in entry 1, the reaction in methylene chloride at 0 °C gave the desired product **14** with a diastereomeric ratio of 6:1. Further study showed that *n*-hexane solvent displayed the increased diastereoselectivity of 15:1, albeit in significantly decreased yield (10%) (Table 1, entry 2). In addition, other solvents, such as $Et_2O$ and $CCl_4$ were less effective under the present conditions (Table 1, entries 3 and 4). After further optimization, the best results were obtained by the use of toluene under otherwise identical conditions, affording cyclic 1,2-*syn*-amino alcohol **14** in 61% yield with a high diastereoselectivity (10:1), as shown in entry 5. Retention of stereochemistry can be explained by $S_Ni$ mechanism through a four-centered transition state.[16g] This observation is consistent with the formation of a tight ion pair in nonpolar *n*-hexane solvent, compared to relatively polar methylene chloride solvent. Finally, debenzylation of **14** using $BCl_3$ in the presence of MeOH afforded (+)-valienamine (**1**) in 72% yield. The spectral data ($^1$H NMR and $^{13}$C NMR) and specific rotation of **1** were in full agreement with the reported values.[12b]

**Table 1**
Selected optimization for the diastereoselective amination of **13**.[a]

| Entry | Solvent | Time (h) | Yield (%)[b] | dr[c] |
|---|---|---|---|---|
| 1 | $CH_2Cl_2$ | 12 | 55 | 6:1 |
| 2 | *n*-Hexane | 24 | 10 | 15:1 |
| 3 | $Et_2O$ | 30 | 31 | 6:1 |
| 4 | $CCl_4$ | 14 | 45 | 8:1 |
| 5 | Toluene | 15 | 61 | 10:1 |

[a] *Reaction conditions*: (i) **13** (1 equiv), chlorosulfonyl isocyanate (3 equiv), $Na_2CO_3$ (4.5 equiv), solvent (0.25 M), 0 °C. (ii) *s*-$Na_2SO_3$, room temperature, 12 h.
[b] Isolated yield by flash column chromatography.
[c] Diastereomeric ratio was determined by $^1$H NMR analysis of a crude reaction mixture.

Based on the above results, we next focused on the synthesis of (−)-1-*epi*-valienamine (**2**) from cyclic allylic alcohol **11a** via a three-step synthesis, as illustrated in Scheme 3.

After benzylation of **11a** under standard reaction conditions, cyclic 1,2-*anti*-polybenzyl ether **15** was treated with chlorosulfonyl isocyanate under optimal reaction conditions (toluene, 0 °C, 24 h) to afford the corresponding 1,2-*anti*-amino alcohol **16** in high yield (75%) with an excellent level of diastereoselectivity (dr=27:1). Benzyl and Cbz protection groups were removed using $BCl_3$ to provide (−)-1-*epi*-valienamine (**2**) with specific rotation and spectral data ($^1$H and $^{13}$C NMR) identical to those reported in the literature.[18]

## 3. Conclusion

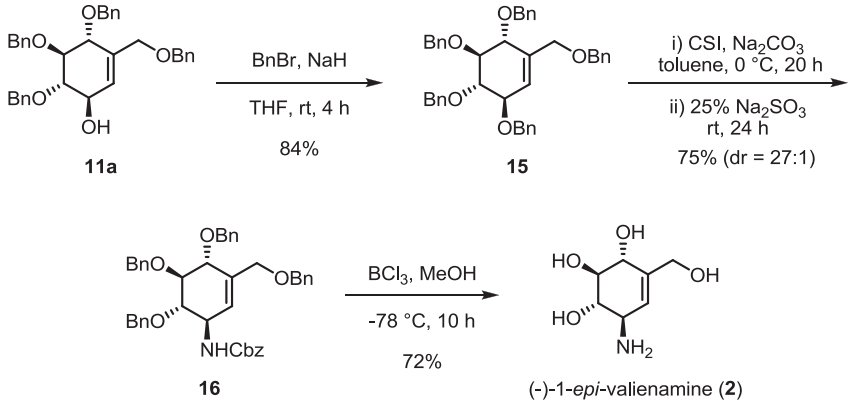
We described a concise total synthesis of (+)-valienamine and (−)-1-*epi*-valienamine starting from readily available D-glucose via highly diastereoselective amination of cyclic benzylic ether with retention of stereochemistry using chlorosulfonyl isocyanate, intramolecular olefin metathesis, and diastereoselective reduction of cyclic enone using L-Selectride as the key steps. It is believed that this synthetic strategy can be applied to the preparation of a broad range of biologically active compounds containing a chiral amine moiety.

## 4. Experimental

### 4.1. General

Commercially available reagents were used without additional purification, unless otherwise stated. All reactions were performed under an inert atmosphere of nitrogen or argon. Nuclear magnetic resonance spectra ($^1$H and $^{13}$C NMR) were recorded on a Bruker Unity 300 MHz and Varian Unit 500 MHz spectrometer for $CDCl_3$ solutions, and chemical shifts are reported as parts per million (ppm) relative to, respectively, residual $CHCl_3$ $\delta_H$ (7.26 ppm) and $CDCl_3$ $\delta_C$ (77.0 ppm) as internal standards. Resonance patterns are reported with the notations s (singlet), d (doublet), t (triplet), q (quartet), and m (multiplet). In addition, the notation br is used to indicate a broad signal. Coupling constants (*J*) are reported in hertz (Hz). IR spectra were recorded on a Bruker Infrared spectrophotometer and are reported as cm$^{-1}$. Optical rotations were measured with a Jasco P1020 polarimeter. Thin layer chromatography was carried out using plates coated with Kieselgel 60$F_{254}$ (Merck). For flash column chromatography, E. Merck Kieselgel 60 (230–400 mesh) was used. LC–mass spectra (LC/MS) were recorded on a Waters 2767 LCMS system. High-resolution mass spectra (HRMS) were recorded on a JEOL JMS-600 spectrometer.

*4.1.1. (2S,3R,4R,5R)-2,3,4,6-Tetrakis(benzyloxy)hexane-1,5-diol (**6**).* To a stirred solution of **5** (8.11 g, 0.015 mol) in anhydrous THF (60 mL) was added $LiAlH_4$ (1.404 g, 0.037 mol) at 0 °C under $N_2$. The




**Scheme 3.**

mixture was stirred for 4 h at room temperature. The reaction mixture was carefully quenched with $H_2O$ and then 1 M HCl (10 mL) was added to make it clear. The aqueous layer was extracted with EtOAc (35 mL×2), and the organic layer was washed with $H_2O$ and brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by column chromatography (*n*-hexanes/EtOAc=2:1) to afford 7.98 g (14.7 mmol, 98% yield) of **6** as a yellow syrup. $R_f$=0.3 (*n*-hexanes/EtOAc=2:1); $[\alpha]_D^{28}$ +3.4 (*c* 1.4, $CHCl_3$); IR (neat) $\nu$ 3450, 3603, 2925, 1605, 1496, 1454, 1397, 1358, 1210, 1092, 736, 699, 605 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) $\delta$ 2.05 (t, *J*=6.0 Hz, 1H), 2.91 (d, *J*=5.0 Hz, 1H), 3.54–3.64 (m, 3H), 3.65–3.81 (m, 3H), 3.87–3.89 (m, 1H), 4.01–4.05 (m, 1H), 4.51–4.72 (m, 8H), 7.21–7.36 (m, 20H); $^{13}C$ NMR (125 MHz, $CDCl_3$) $\delta$ 62.1, 70.9, 71.3, 73.3, 73.5, 73.7, 74.7, 76.9, 79.4, 79.7, 127.9, 128.0, 128.1, 128.2, 128.3, 128.4, 128.6, 128.6, 128.7, 138.1, 138.2, 138.4; HRMS (FAB) calcd for $C_{34}H_{39}O_6$ $[M+H]^+$ 543.2747, found 543.2750.

*4.1.2. (3R,4R,5S)-1,3,4,5-Tetrakis(benzyloxy)-6-(tert-butyldiphenylsilyloxy)hexan-2-ol (**7**).* To a stirred solution of **6** (8.682 g, 0.016 mol) in anhydrous $CH_2Cl_2$ (64 mL) was added *tert*-butyldiphenylsilylchloride (4.948 g, 0.018 mol), triethylamine (2.67 mL, 0.019 mol) and *N*,*N*-dimethylaminopyridine (0.078 g, 0.64 mmol) at room temperature under $N_2$. After stirring for 20 h, the reaction mixture was carefully quenched with $H_2O$. The aqueous layer was extracted with $CH_2Cl_2$ (75 mL×3). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by flash column chromatography (*n*-hexanes/EtOAc=8:1) to afford 11.0 g (14.1 mmol, 88% yield) of **7** as a colorless oil. $R_f$=0.27 (*n*-hexanes/EtOAc=8:1); $[\alpha]_D^{28}$ +16.6 (*c* 3.0, $CHCl_3$); IR (neat) $\nu$ 3030, 2930, 2858, 1488, 1454, 1360, 1210, 1111, 824, 737, 700 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) $\delta$ 1.03 (s, 9H), 2.91 (d, *J*=5.0 Hz, 1H), 3.57 (d, *J*=1.5 Hz, 1H), 3.59 (s, 1H), 3.80–3.97 (m, 6H), 4.45–4.54 (m, 5H), 4.61–4.64 (m, 3H), 7.09–7.42 (m, 26H), 7.42–7.64 (m, 4H); $^{13}C$ NMR (125 MHz, $CDCl_3$) $\delta$ 19.4, 27.1, 63.4, 71.2, 71.5, 73.3, 73.5, 73.6, 74.4, 76.8, 76.9, 77.4, 77.5, 77.7, 78.3, 79.9, 127.7, 127.8, 127.9, 128.0, 128.1, 128.2, 128.4, 128.5, 128.6, 128.7, 128.8, 129.9, 130.1, 133.6, 133.7, 135.8, 138.3, 138.4, 138.5, 138.6; HRMS (FAB) calcd for $C_{50}H_{57}O_6Si$ $[M+H]^+$ 781.3924, found 781.3928.

*4.1.3. tert-Butyldiphenyl ((2S,3S,4R)-2,3,4-tris(benzyloxy)-5-(benzyloxymethyl)hex-5-enyloxy)silane (**8**).* To a stirred solution of oxalic chloride (2.2 mL, 0.026 mol) in $CH_2Cl_2$ (60 mL) was carefully added dimethylsulfoxide (3 mL, 0.041 mol) at −78 °C and stirred for 1 h at same temperature. The alcohol **7** (13.28 g, 0.017 mol) in $CH_2Cl_2$ (25 mL) and triethylamine (6.0 mL, 0.043 mol) was added to the reaction mixture at −78 °C. The reaction mixture was stirred for 2 h at room temperature. The resulting mixture was quenched with $H_2O$ and aqueous layer was extracted with $CH_2Cl_2$ (50 mL×2). The organic layer was washed with $H_2O$ and brine, dried over $MgSO_4$, and concentrated in vacuo. Without purification the residue was used in next step. To a stirred solution of methyl triphenylphosphonium bromide (18.2 g, 0.051 mol) in THF (85 mL) was slowly added NaHMDS (51 mL, 0.051 mol) at 0 °C under $N_2$. The reaction mixture was stirred for 2 h at room temperature to generate ylide. A solution of ketone intermediate in THF (25 mL) was added to the reaction mixture at 0 °C. The reaction mixture was stirred for 1 h at room temperature and quenched with $H_2O$. The aqueous layer was extracted with EtOAc (100 mL×2) and the organic layer was washed with $H_2O$ and brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by column chromatography (*n*-hexanes/EtOAc=25:1) to afford 11.6 g (14.96 mmol, 88% yield) of **8** as a colorless oil. $R_f$=0.27 (*n*-hexanes/EtOAc=15:1); $[\alpha]_D^{28}$ +63.3 (*c* 0.07, $CHCl_3$); IR (neat) $\nu$ 3060, 2929, 2856, 1738, 1588, 1428, 1260, 1111, 823, 737, 700, 613, 506 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) $\delta$ 1.01 (s, 9H), 3.62–3.67 (m, 2H), 3.78–3.81 (m, 1H), 3.90 (dd, *J*=7.0, 3.5 Hz, 1H), 4.01 (s, 2H), 4.27–4.37 (m, 3H), 4.44–4.52 (m, 4H), 4.64 (d, *J*=11.0 Hz, 1H), 4.78 (d, *J*=11.0 Hz, 1H), 5.19 (s, 1H), 5.41 (s, 1H), 7.18–7.42 (m, 26H), 7.59–7.62 (m, 4H); $^{13}C$ NMR (125 MHz, $CDCl_3$) $\delta$ 19.4, 27.1, 63.1, 69.9, 71.2, 72.8, 73.1, 75.4, 79.8, 80.3, 82.4, 116.1, 127.5, 127.6, 127.7, 127.8, 127.9, 128.1, 128.2, 128.3, 128.4, 128.5, 128.6, 129.8, 129.9, 133.6, 133.7, 135.8, 135.9, 138.5, 138.6, 139.0, 139.1, 143.2; HRMS (FAB) calcd for $C_{51}H_{57}O_5Si$ $[M+H]^+$ 777.3975, found 777.3979.

*4.1.4. (2S,3S,4R)-2,3,4-Tris(benzyloxy)-5-(benzyloxymethyl)hex-5-en-1-ol (**9**).* To a stirred solution of **8** (10.88 g, 0.014 mol) in THF (56 mL) was added tetra-*n*-butylammonium fluoride (21 mL, 0.021 mol), stirred for 18 h at room temperature under $N_2$. The resulting mixture was quenched with $H_2O$. The aqueous layer was extracted with EtOAc (60 mL×2) and the organic layer was washed with $H_2O$ and brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by column chromatography (*n*-hexanes/EtOAc=4:1) to afford 6.94 g (0.013 mol, 92% yield) of **9** as a yellow oil. $R_f$=0.45 (*n*-hexanes/EtOAc=4:1); $[\alpha]_D^{28}$ −23.5 (*c* 0.77, $CHCl_3$); IR (neat) $\nu$ 3466, 3063, 2863, 1723, 1604, 1496, 1454, 1361, 1269, 1209, 1072, 916, 736, 698, 605 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) $\delta$ 2.03 (br s, 1H), 3.46–3.48 (m, 1H), 3.61–3.67 (m, 2H), 3.78 (dd, *J*=11.0, 5.0 Hz, 1H), 3.98 (d, *J*=12.5 Hz, 1H), 4.07 (d, *J*=12.5 Hz, 1H), 4.28 (d, *J*=5.0 Hz, 1H), 4.33 (d, *J*=11.5 Hz, 1H), 4.47–4.74 (m, 7H), 5.32 (d, *J*=1.0 Hz, 1H), 5.42 (d, *J*=1.0 Hz, 1H), 7.24–7.34 (m, 20H); $^{13}C$ NMR (125 MHz, $CDCl_3$) $\delta$ 61.8, 70.6, 71.2, 72.8, 72.9, 73.5, 74.7, 75.1, 79.3, 80.8, 81.2, 116.9, 127.8, 127.7, 127.9, 128.0, 128.1, 128.2, 128.4, 128.5, 128.6, 128.7, 128.8, 138.2, 138.4, 138.5, 138.7, 142.7; HRMS (FAB) calcd for $C_{35}H_{39}O_5$ $[M+H]^+$ 539.2797, found 539.2797.

*4.1.5. (2R,3S,4R)-2,3,4-Tris(benzyloxy)-5-(benzyloxymethyl)hex-5-enal (**10**).* To a stirred solution of oxalic chloride (2.1 mL, 0.024 mol)

in $CH_2Cl_2$ (70 mL) was carefully added dimethylsulfoxide (2.7 mL, 0.038 mol) at −78 °C and stirred for 1 h at same temperature. The alcohol **9** (8.62 g, 0.016 mol) and triethylamine (5.6 mL, 0.04 mol) in $CH_2Cl_2$ (10 mL) was added to the reaction mixture at −78 °C. The reaction mixture was stirred for 2 h at room temperature. The resulting mixture was quenched with $H_2O$ and the aqueous layer was extracted with $CH_2Cl_2$ (100 mL×2). The organic layer was washed with $H_2O$ (20 mL×2) and brine, dried over $MgSO_4$, and concentrated in vacuo. Without purification the residue was used for next step. To a stirred mixture of the reaction intermediate in THF (50 mL) was slowly added vinylmagnesium bromide (32 mL, 0.032 mol, 1.0 M in THF solution) at 0 °C. After stirring for 1 h at room temperature, the reaction mixture was quenched by aqueous saturated $NH_4Cl$ (30 mL) and extracted with $CH_2Cl_2$ (60 mL×2). The organic layer was washed with $H_2O$ (30 mL×2), dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by column chromatography (*n*-hexanes/EtOAc=8:1) to afford 5.78 g (0.01 mol, 64% yield, dr=2.5:1) of **10** as a colorless oil. $R_f$=0.3 (*n*-hexanes/EtOAc=10:1); IR (neat) $\nu$ 3454, 3031, 1497, 1454, 1387, 1348 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) $\delta$ 2.51 (d, *J*=6.5 Hz, 0.7H), 3.21 (d, *J*=6.5 Hz, 0.3H), 3.55 (dd, *J*=6.0, 4.5 Hz, 0.3H), 3.64 (dd, *J*=6.0, 3.0 Hz, 0.7H), 3.81 (dd, *J*=6.0, 4.5 Hz, 0.7H), 3.92 (m, 0.3H), 3.96–4.06 (m, 3H), 4.23–4.36 (m, 2.3H), 4.45–4.53 (m, 6.4H), 4.83 (d, *J*=11.0 Hz, 0.3H), 5.07–5.45 (m, 4H), 5.71–5.78 (m, 1H), 7.23–7.36 (m, 20H); $^{13}C$ NMR (125 MHz, $CDCl_3$) $\delta$ 70.1, 70.7, 71.1, 71.9, 72.4, 72.5, 72.9, 73.1, 74.9, 75.4, 80.1, 80.2, 80.8, 81.1, 81.9, 82.7, 115.6, 116.1, 116.8, 117.8, 127.7, 127.8, 127.9, 128.0, 128.1, 128.2, 128.3, 128.4, 128.5, 128.6, 128.7, 128.8, 138.1, 138.4, 138.5, 138.7, 138.8, 142.7; HRMS (FAB) calcd for $C_{37}H_{41}O_5$ $[M+H]^+$ 565.2954, found 565.2955.

*4.1.6. (1R,4R,5S,6S)-4,5,6-Tris(benzyloxy)-3-(benzyloxymethyl)cyclohex-2-enol (**11a**) and (1S,4R,5S,6S)-4,5,6-tris(benzyloxy)-3-(benzyloxymethyl)cyclohex-2-enol (**11b**).* To a stirred solution of **10** (3.95 g, 0.007 mol) in $CH_2Cl_2$ (70 mL) was added Grubbs second generation (0.594 g, 0.7 mmol) at room temperature. The reaction mixture was stirred for 8 h at 50 °C. The solution was evaporated to dryness and the residue was purified by column chromatography (*n*-hexanes/EtOAc=6:1) to afford a separable mixture (3.19 g, 5.95 mmol, 85% yield) of **11a** and **11b** as a colorless oil. **11a**: $R_f$=0.15 (*n*-hexane/EtOAc=4:1); mp 73–75 °C; $[\alpha]_D^{28}$ −65.8 (*c* 1.3, $CHCl_3$); IR (neat) $\nu$ 3442, 3030, 1496, 1454, 1360 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) $\delta$ 2.08 (d, *J*=4.5 Hz, 1H), 3.56 (dd, *J*=10.0,7.5 Hz, 1H), 3.84 (dd, *J*=9.5, 7.0 Hz, 1H), 3.90 (d, *J*=12.0 Hz, 1H), 4.23 (d, *J*=12.0 Hz, 1H), 4.28–4.32 (m, 2H), 4.45 (d, *J*=12.0 Hz, 1H), 4.51 (d, *J*=12.0 Hz, 1H), 4.68–4.73 (m, 2H), 4.78–4.82 (m, 2H), 4.90–4.97 (m, 2H), 5.73 (s, 1H), 7.24–7.35 (m, 20H); $^{13}C$ NMR (125 MHz, $CDCl_3$) $\delta$ 70.2, 71.5, 72.5, 74.7, 75.1, 75.3, 79.9, 83.7, 84.1, 127.4, 127.8, 127.9, 128.0, 128.1, 128.2, 128.3, 128.4, 128.5, 128.6, 128.7, 128.8, 136.2, 138.3, 138.5, 138.6, 138.7; HRMS (CI) calcd for $C_{35}H_{35}O_5$ $[M-H]^+$ 535.2484, found 535.2478. **11b**: $R_f$=0.2 (*n*-hexane/EtOAc=2:1); $[\alpha]_D^{28}$ −40.3 (*c* 1.2, $CH_2Cl_2$); IR (neat) $\nu$ 3446, 3063, 2923, 1730, 1604, 1496, 1454, 1365, 1250, 1208, 1142, 1071, 910, 737, 698, 605 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) $\delta$ 2.56 (d, *J*=3.5 Hz, 1H), 3.60 (dd, *J*=9.5, 4.0 Hz, 1H), 3.94 (d, *J*=12.0 Hz, 1H), 4.06 (dd, *J*=9.5, 7.0 Hz, 1H), 4.23 (m, 1H), 4.31 (t, *J*=4.0 Hz, 1H), 4.46 (d, *J*=12.0 Hz, 2H), 4.64–4.80 (m, 6H), 4.87 (d, *J*=12.0 Hz, 1H), 5.91 (br s, 1H), 7.17–7.38 (m, 20H); $^{13}C$ NMR (125 MHz, $CDCl_3$) $\delta$ 31.1, 65.3, 70.5, 72.8, 73.1, 74.2, 74.9, 79.1, 79.2, 79.3, 124.8, 127.7, 127.8, 127.9, 128.0, 128.1, 128.2, 128.3, 128.5, 128.6, 128.7, 128.8, 138.2, 138.3, 138.7, 138.8, 139.9; HRMS (CI) calcd for $C_{35}H_{35}O_5$ $[M-H]^+$ 535.2484, found 535.2477.

*4.1.7. (4R,5S,6R)-4,5,6-Tris(benzyloxy)-3-(benzyloxymethyl)cyclohex-2-enone (**12**).* To a stirred solution of **11** (1.667 g, 0.003 mol) in $CH_2Cl_2$ (15 mL) was added Dess–Martin periodinane (3.181 g, 7.5 mmol) at 0 °C. The reaction mixture was stirred for 4 h at room temperature. The mixture was quenched with a solution of aqueous saturated $NaHCO_3$ (5 mL) and filtered with Celite pad. The aqueous layer was extracted with $CH_2Cl_2$ (10 mL×2). The organic layer was washed with $H_2O$ (5 mL×2), dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by column chromatography (*n*-hexane/EtOAc=6:1) to afford 1.394 g (2.61 mmol, 64% yield) of **12** as a colorless oil. $R_f$=0.25 (*n*-hexane/EtOAc=6:1); $[\alpha]_D^{28}$ +65.4 (*c* 1.2, $CHCl_3$); IR (neat) $\nu$ 3062, 3030, 2921, 2860, 1729, 1604, 1496, 1454, 1365, 1089, 1072, 736, 698 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) $\delta$ 4.06 (d, *J*=9.0 Hz, 2H), 4.10 (t, *J*=1.5 Hz, 1H), 4.24 (s, 0.6H), 4.27 (d, *J*=1.0 Hz, 0.4H), 4.36 (t, *J*=1.0 Hz, 0.5H), 4.37 (t, *J*=1.0 Hz, 0.5H), 4.51 (d, *J*=2.0 Hz, 2H), 4.68 (d, *J*=11.0 Hz, 1H), 4.73 (d, *J*=4.5 Hz, 1H), 4.76 (d, *J*=4.0 Hz, 1H), 4.91 (d, *J*=11.0 Hz, 1H), 5.00 (d, *J*=11.0 Hz, 1H), 5.10 (d, *J*=11.0 Hz, 1H), 6.21 (dd, *J*=4.0, 2.0 Hz, 1H), 7.21–7.44 (m, 20H); $^{13}C$ NMR (125 MHz, $CDCl_3$) $\delta$ 69.2, 73.4, 74.6, 75.8, 75.9, 77.4, 79.4, 84.1, 85.1, 124.1, 127.9, 128.0, 128.1, 128.2, 128.3, 128.4, 128.5, 128.6, 128.7, 128.8, 137.6, 137.9, 138.1, 138.3, 159.2, 196.9; HRMS (FAB) calcd for $C_{35}H_{35}O_5$ $[M+H]^+$ 535.2484, found 535.2483.

*4.1.8. (1S,4R,5S,6S)-4,5,6-Tris(benzyloxy)-3-(benzyloxymethyl)cyclohex-2-enol (**11b**).* To a stirred solution of **12** (1.07 g, 0.002 mol) in THF (50 mL) was added L-Selectride (3 mL, 0.003 mol) at 0 °C under $N_2$. The reaction mixture was stirred for 2 h at 0 °C. The reaction mixture was quenched with $H_2O$ and extracted with EtOAc (50 mL×2). The organic layer was washed with $H_2O$ and brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by column chromatography (*n*-hexane/EtOAc=4:1) to afford 0.816 g (1.56 mmol, 76% yield) of **11b** as a colorless oil.

*4.1.9. ((1S,2S,3S,4R)-5-(Benzyloxymethyl)cyclohex-5-ene-1,2,3,4-tetrayl)tetrakis(oxy)tetrakis(methylene)tetrabenzene (**13**).* To a stirred solution of **11b** (0.63 g, 0.001 mol) in anhydrous THF (6.67 mL) was added NaH (0.08 g, 0.002 mol, 60% in mineral oil) and BnBr (0.17 mL, 0.002 mol) at 0 °C under $N_2$. The reaction mixture was stirred for 12 h at room temperature. The reaction mixture was carefully quenched with a cold aqueous solution of 10% $NH_4Cl$ (10 mL). The aqueous layer was extracted with EtOAc (15 mL×2). The organic layer was washed with $H_2O$ and brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by column chromatography (*n*-hexane/EtOAc=8:1) to afford 0.501 g (0.8 mmol, 80% yield) of **13** as a colorless oil. $R_f$=0.28 (*n*-hexane/EtOAc=8:1); $[\alpha]_D^{28}$ +238.3 (*c* 0.04, $CHCl_3$); IR (neat) $\nu$ 3030, 2921, 2860, 1729, 1604, 1496, 1454, 1365, 1208, 1088, 908, 736, 698, 605 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) $\delta$ 3.58 (dd, *J*=10.0, 3.5 Hz, 1H), 3.94 (d, *J*=12.0 Hz, 1H), 4.07–4.09 (m, 1H), 4.17 (dd, *J*=12.0, 7.0 Hz, 2H), 4.42 (d, *J*=12.0 Hz, 1H), 4.62 (d, *J*=12.0 Hz, 1H), 4.64–4.80 (m, 8H), 5.01 (d, *J*=12.0 Hz, 1H), 5.89–5.90 (m, 1H), 7.04–7.46 (m, 25H); $^{13}C$ NMR (125 MHz, $CDCl_3$) $\delta$ 70.5, 71.1, 71.9, 72.7, 72.8, 73.8, 75.1, 79.9, 80.1, 80.7, 123.7, 127.5, 127.6, 127.7, 127.8, 127.9, 128.0, 128.1, 128.2, 128.3, 128.5, 128.6, 128.7, 128.8, 129.9, 138.3, 138.8, 138.9, 139.0, 139.1, 140.3; HRMS (CI) calcd for $C_{42}H_{41}O_5$ $[M-H]^+$ 625.2954, found 625.2954.

*4.1.10. Benzyl (1S,4R,5S,6S)-4,5,6-tris(benzyloxy)-3-(benzyloxymethyl)cyclohex-2-enylcarbamate (**14**).* To a stirred solution of **13** (0.069 g, 0.11 mmol) in anhydrous toluene (0.74 mL) was added $Na_2CO_3$ (0.132 g, 1.247 mmol) and chlorosulfonyl isocyanate (0.07 mL, 0.831 mmol) at 0 °C under $N_2$. The reaction mixture was stirred for 15 h at 0 °C and quenched with $H_2O$ (1 mL). The aqueous layer was extracted with EtOAc (2 mL×2). The organic layer was added to a solution of a solution of aqueous 25% $Na_2SO_3$ (2 mL), and the reaction mixture was stirred for 24 h at room temperature. The organic layer was washed with $H_2O$ and brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by column chromatography (*n*-hexane/EtOAc=6:1) to afford 0.049 g (0.074 mmol, 61% yield) of **14** as a colorless oil. $R_f$=0.23 (*n*-hexane/

EtOAc=6:1); $[\alpha]_D^{28}$ +32.1 (*c* 1.69, $CHCl_3$); IR (neat) $\nu$ 3322, 3031, 2862, 1719, 1498, 1454, 1296, 1238, 1069, 910, 738, 698, 605 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) $\delta$ 3.74 (br s, 1H), 3.81 (dd, *J*=9.0, 4.5 Hz, 1H), 3.90 (d, *J*=12.0 Hz, 1H), 4.06 (br s, 1H), 4.24 (d, *J*=12.0 Hz, 1H), 4.41 (d, *J*=12.0 Hz, 1H), 4.48 (d, *J*=12.0 Hz, 1H), 4.57–4.77 (m, 7H), 5.06 (d, *J*=9.0 Hz, 1H), 5.12 (s, 2H), 5.82 (s, 1H), 7.17–7.38 (m, 25H); $^{13}C$ NMR (125 MHz, $CDCl_3$) $\delta$ 47.3, 67.0, 70.1, 72.2, 72.3, 73.9, 74.4, 76.1, 77.3, 77.5, 125.3, 127.6, 127.7, 127.9, 128.0, 128.1, 128.2, 128.3, 128.4, 128.5, 128.6, 128.7, 136.8, 137.3, 138.1, 138.4, 138.5, 156.3; HRMS (FAB) calcd for $C_{43}H_{44}NO_6$ $[M+H]^+$ 670.3169, found 670.3170.

*4.1.11. (1S,2S,3R,6S)-6-Amino-4-(hydroxymethyl)cyclohex-4-ene-1,2,3-triol (**1**).* To a stirred solution of **14** (0.6 g, 0.89 mmol) in anhydrous $CH_2Cl_2$ (18 mL) was added $BCl_3$ (80 mL, 1.0 M in $CH_2Cl_2$ solution) at −78 °C. The reaction mixture was stirred for 24 h at −78 °C. The reaction mixture was quenched with MeOH (30 mL) and further stirred at −78 °C for 1 h. The resulting mixture was warmed to room temperature and concentrated in vacuo. The residue was purified by ion-exchange resin DOWEX 50WX8-100 using 0.5 M $NH_4OH$ as eluent to afford 109 mg (0.62 mmol, 70% yield) of **1** as colorless syrup. $R_f$=0.29 ($CH_2Cl_2$/$CH_3OH$/$NH_4OH$=3:1:0.1); $[\alpha]_D^{28}$ +85.7 (*c* 0.04, $CH_3OH$); IR (neat) $\nu$ 3727, 3333, 2923, 1737, 1611, 1516, 1372, 1244, 1093, 1053, 930, 722, 700, 618, 514 $cm^{-1}$; $^1H$ NMR (500 MHz, $D_2O$) $\delta$ 3.52–3.69 (m, 2H), 3.83–3.94 (m, 1H), 4.00–4.02 (m, 1H), 4.07–4.13 (m, 1H), 4.16 (s, 1H), 5.70 (dd, *J*=7.0, 3.5 Hz, 1H); $^{13}C$ NMR (125 MHz, $CDCl_3$) $\delta$ 49.5, 61.2, 66.8, 71.1, 71.8, 115.7, 146.1; HRMS (CI) calcd for $C_7H_{14}NO_4$ $[M+H]^+$ 176.0923, found 176.0923.

*4.1.12. ((1R,2S,3S,4R)-5-(Benzyloxymethyl)cyclohex-5-ene-1,2,3,4-tetrayl)tetrakis(oxy)tetrakis(methylene)tetrabenzene (**15**).* To a stirred solution of **11a** (0.45 g, 0.84 mmol) in anhydrous THF (4.2 mL) was added NaH (0.05 g, 1.26 mmol, 60% in mineral oil) and BnBr (0.1 mL, 1.26 mmol) at 0 °C under $N_2$. The reaction mixture was stirred for 12 h at room temperature. The reaction mixture was carefully quenched with a cold aqueous solution of 10% $NH_4Cl$ (4 mL). The aqueous layer was extracted with EtOAc (10 mL×2). The organic layer was washed with $H_2O$ and brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by column chromatography (*n*-hexane/EtOAc=8:1) to afford 0.44 g (0.71 mmol, 84% yield) of **15** as a colorless oil. $R_f$=0.30 (*n*-hexane/EtOAc=8:1); $[\alpha]_D^{28}$ −234.4 (*c* 0.62, $CHCl_3$); IR (neat) $\nu$ 3063, 3030, 2859, 1605, 1497, 1454, 1359, 1069, 1027, 735, 697, 605 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) $\delta$ 3.77–3.83 (m, 2H), 3.94 (dd, *J*=10.0, 6.0 Hz, 1H), 4.18–4.22 (m, 2H), 4.29 (d, *J*=8.0 Hz, 1H), 4.31 (d, *J*=6.0 Hz, 1H), 4.43–4.53 (m, 2H), 4.65–4.94 (m, 6H), 4.98 (d, *J*=11.0 Hz, 1H), 5.78 (s, 1H), 7.18–7.39 (m, 25H); $^{13}C$ NMR (125 MHz, $CDCl_3$) $\delta$ 70.1, 72.4, 72.7, 75.2, 75.7, 75.8, 80.1, 83.9, 84.7, 125.4, 127.6, 127.7, 127.8, 127.9, 128.0, 128.1, 128.2, 128.3, 128.4, 128.5, 128.6, 128.7, 128.8, 128.9, 136.6, 138.3, 138.5, 138.6, 138.8, 138.9; HRMS (EI) calcd for $C_{42}H_{42}O_5$ $[M]^+$626.3032, found 626.3031.

*4.1.13. Benzyl (1R,4R,5S,6S)-4,5,6-tris(benzyloxy)-3-(benzyloxymethyl)cyclohex-2-enylcarbamate (**16**).* To a stirred solution of **15** (0.07 g, 0.112 mmol) in anhydrous toluene (0.45 mL) was added $Na_2CO_3$ (0.134 g, 1.26 mmol) and chlorosulfonyl isocyanate (0.07 mL, 0.84 mmol) at 0 °C under $N_2$. The reaction mixture was stirred for 12 h at 0 °C and quenched with $H_2O$ (1 mL). The aqueous layer was extracted with EtOAc (3 mL×2). The organic layer was added to a solution of a solution of aqueous 25% $Na_2SO_3$ (8 mL). The reaction mixture was stirred for 24 h at room temperature. The organic layer was washed with $H_2O$ and brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by column chromatography (*n*-hexane/EtOAc=4:1) to afford 0.056 g (0.084 mmol, 75% yield) of **16** as a white solid. $R_f$=0.29 (*n*-hexane/EtOAc=4:1); mp 116–119 °C; $[\alpha]_D^{28}$ −15.5 (*c* 0.64, $CHCl_3$); IR (neat) $\nu$ 3323, 3031, 2924, 2855, 1720, 1605, 1498, 1454, 1361, 1204, 1068, 736, 698, 608 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) $\delta$ 3.57 (t, *J*=8.0 Hz, 1H), 3.89 (d, *J*=4.0 Hz, 1H), 3.91 (d, *J*=8.0 Hz, 1H), 4.24 (d, *J*=8.0 Hz, 2H), 4.43–4.51 (m, 3H), 4.71–4.84 (m, 7H), 5.08–5.16 (m, 2H), 5.68 (s, 1H), 7.23–7.39 (m, 25H); $^{13}C$ NMR (125 MHz, $CDCl_3$) $\delta$ 52.3, 66.9, 70.5, 72.7, 74.3, 74.4, 74.7, 78.1, 79.9, 82.4, 126.2, 127.8, 127.9, 128.0, 128.1, 128.2, 128.3, 128.4, 128.5, 128.6, 128.7, 128.8, 136.5, 136.7, 138.3, 138.4, 138.5, 138.6, 156.1; HRMS (FAB) calcd for $C_{43}H_{44}NO_6$ $[M+H]^+$ 670.3169, found 670.3163.

*4.1.14. (1S,2S,3R,6R)-6-Amino-4-(hydroxymethyl)cyclohex-4-ene-1,2,3-triol (**2**).* To a stirred solution of **16** (262 mg, 0.39 mmol) in anhydrous $CH_2Cl_2$ (8 mL) was added $BCl_3$ (39 mL, 1.0 m in $CH_2Cl_2$ solution) at −78 °C. The reaction mixture was stirred at for 24 h −78 °C. The reaction mixture was quenched with MeOH (10 mL) and further stirred at −78 °C for 1 h. The resulting mixture was warmed to room temperature and concentrated in vacuo. The residue was purified by ion-exchange resin DOWEX 50WX8-100 using 0.5 M $NH_4OH$ as eluent to afford 45.8 mg (0.26 mmol, 67% yield) of **2** as colorless syrup. $R_f$=0.28 ($CH_2Cl_2$/$CH_3OH$/$NH_4OH$=3:1:0.1); $[\alpha]_D^{28}$ +26.7 (*c* 0.08, $CH_3OH$); IR (neat) $\nu$ 3713, 3333, 2923, 1737, 1609, 1512, 1375, 1102, 1054, 1033, 1014, 897, 822, 773, 621 $cm^{-1}$; $^1H$ NMR (500 MHz, $D_2O$) $\delta$ 3.54–3.59 (m, 2H), 3.84–3.89 (m, 1H), 4.08–4.18 (m, 3H), 5.71–5.58 (m, 1H); $^{13}C$ NMR (125 MHz, $CDCl_3$) $\delta$ 53.8, 60.9, 71.6, 71.8, 116.9, 143.4; HRMS (CI) calcd for $C_7H_{14}NO_4$ $[M+H]^+$ 176.0923, found 176.0924.

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## Supplementary data

Supplementary data available: $^1H$ NMR and $^{13}C$ NMR copies of all compounds. Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.tet.2013.09.098.

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