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An efficient stereoselective synthesis of enantiomerically pure aziridine derivatives of allyl β-D-glucopyranosides asymmetrically induced by a glucide moiety

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Abstract

The enantiomerically pure title aziridines were obtained by regioselective azidolysis of the 2′,3′-epoxy derivatives of allyl 3,4,6-tri-*O*-benzyl-β-D-glucopyranosides, followed by cyclization of the corresponding azido alcohols by means of the PPh_3 protocol. Enantiomerically pure starting epoxides were prepared by epoxidation of the corresponding allyl 3,4,6-tri-*O*-benzyl-β-D-glucopyranosides asymmetrically induced by a glucide moiety.

1. Introduction

Chiral aziridines form an attractive class of organic compounds because they can be used for asymmetric synthesis in a number of different ways. The chemistry of aziridines is dominated by ring-opening reactions, the driving force for which is relief of ring strain. By a suitable choice of substituents on the carbon and nitrogen atoms, it is possible to obtain stereo- and regiocontrolled ring-opening reactions with a wide variety of nucleophiles; this makes chiral aziridines useful as substrates for the preparation of important bioactive molecules.[1,2] In addition, it is noteworthy that a number of compounds possessing an aziridine ring have been shown to exhibit potent biological activity, which is intimately associated with the reactivity of the strained heterocycle.[3,4]

In the course of our research program studying the use of simple carbohydrates as efficient chiral auxiliaries for asymmetric synthesis, we became interested in evaluating the effectiveness of the glucose-derivative template in the preparation of chiral aziridine derivatives of allylic β-D-glucopyranosides, which may not only have an intrinsic biological activity, but may also represent a source of optically active β-hydroxy α-amino acids, and provide a convenient pathway to a variety of glycosphingolipids.

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Natural glycosphingolipids are indeed an important class of organic compounds, mainly located in the cell membrane, and frequently involved in immunological processes.[5,6] However, only small amounts of glycosphingolipids can be obtained from natural extracts,[6] and consequently the development of efficient synthetic methods for the preparation of these compounds has become one of the most timely problems in synthetic chemistry and biochemistry.[7]

In this work, we report on the application of a general method for the preparation of aziridine derivatives of allylic β-D-glucopyranosides, showing that the completely regioselective ring opening of oxiranes, obtained in an enantiomerically pure form by epoxidation of the corresponding precursors asymmetrically induced by a glucide moiety, represents a highly efficient procedure.

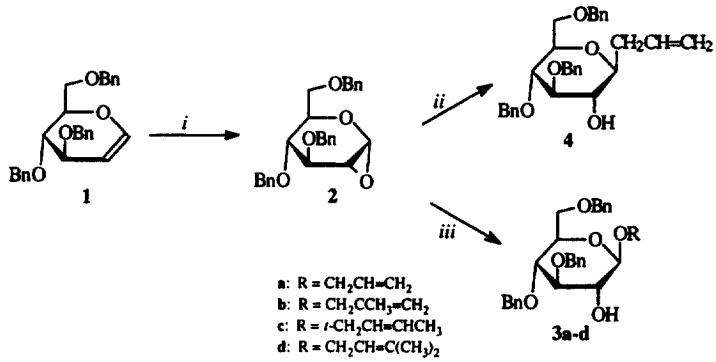
2. Results and discussion

Ring-opening of epoxides by azide ions followed by ring-closure of the resulting 1,2-azido alcohol derivatives is a frequently applied route to aziridines, and when enantiomerically pure epoxides are used in this reaction sequence, access to non-racemic aziridines is feasible.[1] As it has been recently shown[8,9] that oxidation of allyl β-D-glucopyranosides to the corresponding epoxides can be asymmetrically induced by a glucide moiety, the following procedure was applied to obtain enantiomerically pure aziridines derived from allyl β-D-glucopyranosides.

The appropriate allyl β-D-glucopyranosides used as starting materials in this synthetic approach were prepared from the commercially available glucal **1**, which was transformed into the corresponding 1,2-anhydro-3,4,6-tri-*O*-benzyl-α-D-glucose **2** by epoxidation following the MCPBA–KF protocol in anhydrous CH_2Cl_2.[10] The crude epoxide **2** (containing ca. 10% of the corresponding β-anomer)[10] was then subjected to oxirane ring-opening by treatment with the appropriate allyl alcohol in the presence of $ZnCl_2$ to give β-glycosides **3** (Scheme 1). Higher yields were obtained when the reactions were carried out in THF at −78°C, in the presence of molecular sieves as a moisture scavenger, using the inverse addition order of the reagents.[8] The reaction mixtures were then purified by column chromatography to give pure **3** (>80% yield, ^{1}H NMR). C-Glycosides represent a field of noteworthy interest,[11] and in order to verify the possibility of applying the same procedure to obtain enantiomerically pure aziridine derivatives of these compounds, the C-glycoside **4** was synthesized by treatment of the crude epoxide mixture (**2**) with allyl magnesium bromide in the presence of a catalytic amount of $CuBr{\cdot}Me_2S$. The ^{1}H and ^{13}C NMR spectra of **4**, obtained in a satisfactory isolated yield (60%), turned out to be identical to the previously reported data for this compound.[12]

The allyl glycosides **3a–d** and the C-glycoside **4** were treated with anhydrified MCPBA in dichloromethane (Table 1), as previously reported,[8] to give the corresponding epoxides **5**, **6a–d** and **7–8**, respectively (Scheme 2). The stereochemistry at the oxirane C-2′ carbon of the glycidol moiety of the main diastereoisomeric epoxides **5** arising from **3a** and **3c** had previously been established,[8,9] whereas that of epoxide **5b**, arising from **3b**, was tentatively attributed on the basis of the face enantioselection observed in the reaction of **3a** and **3c**.[8,9] It is noteworthy that, although the electrophilic attack of the peracid occurs in **3a–c** on the same face of the double bond of the allylic substituent, the 2′(*R*) stereochemistry of **5a** and **5b** becomes 2′(*S*) in **5c** because of the formal change in the descriptor caused by the CIP priority rule.

In agreement with the previously observed high facial diastereoselection in the epoxidation of *O*-glycosides **3a** and **3c**, the reaction of **3b** gives pratically only one diastereoisomer (**5b**) (Table 1). However, when the same procedure was applied to the more reactive derivative **3d**, a 1:1 mixture of the two diastereoisomers, **5d** and **6d**, was obtained. Furthermore, in this case, even carrying out the epoxidation



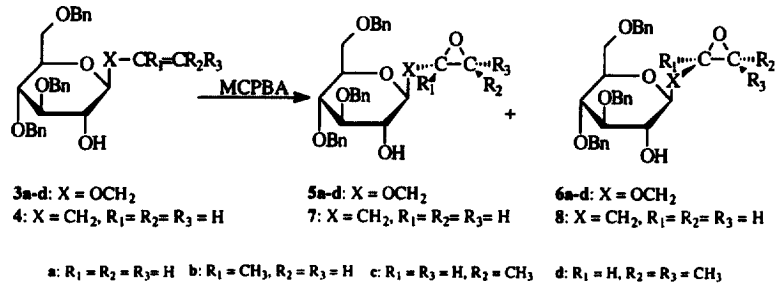
i) MCPBA-KF; *ii)* CH_2=$CHCH_2MgBr$, CuBr-Me_2S; *iii)* ROH-$ZnCl_2$

Scheme 1.

Table 1
Epoxidation of **3a–d** and **4** with MCPBA–KF protocol (1.2 equiv.)

Glycoside	T (°C)	Time (days)	Yield[a]	Ratio (**5**:**6**)[b] or (**7**:**8**)[b]	Abs. Conf.
3a	-18	6	80[c]	90:10	*2'R*[d]
3b	-18	6	95	95:5	*2'R*
3c	-18	7	95	90:10	*2'S,3'S*[e]
3d	-18	2	95	50:50	
3d	-80	20	95	60:40	
4	-18	10[e]	70[c]	50:50	

[a] Determined after column chromatography (SiO_2). [b] Determined by ^1H and ^{13}C NMR. [c] The remainder was unreacted starting material. [d] Ref. 8. [e] Ref. 9.



a: $R_1 = R_2 = R_3 = H$ b: $R_1 = CH_3$, $R_2 = R_3 = H$ c: $R_1 = R_3 = H$, $R_2 = CH_3$ d: $R_1 = H$, $R_2 = R_3 = CH_3$

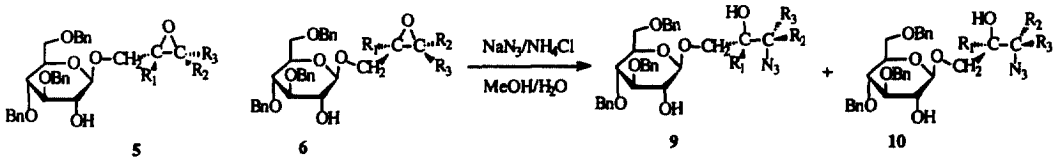
Scheme 2.

at −80°C, the diastereoisomeric ratio remained extremely modest. Finally, no diastereoselection and a very low reaction rate was found in the case of the C-glycoside **4** (Table 1).

As it has been shown[8] that the stereoselectivity of epoxidation, as well as the reaction rate, largely depend on the possibility of forming a hydrogen bond between the peracid and the OH substituent on the C-2 carbon of the glucide moiety, the lack of diastereoface selection observed in the reaction of **4** may be related to the absence of the anomeric oxygen in this compound. This structural feature, reducing the

distance between the hydroxy group on C-2 and the double bond on the allyl substituent, makes the OH group unable to direct the reaction. However, in the case of **3d**, the low facial diastereoselection could be attributed to the higher reactivity of the trisubstituted double bond, which makes the stabilization of the transition state by the formation of a hydrogen bond between the reagent and the directing group on the chiral inductor less important.

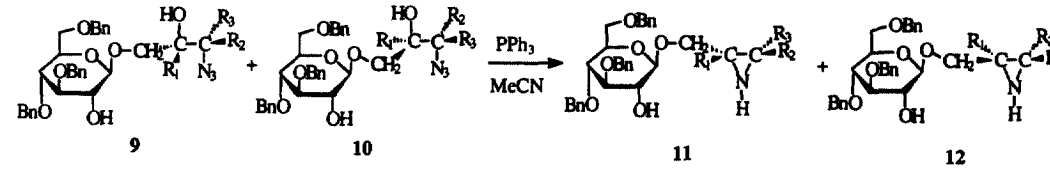
The 90:10 mixtures of the diastereoisomeric epoxides **5a–c** and **6a–c** were then subjected to oxirane ring-opening with NaN_3 in methanol:water in the presence of NH_4Cl. In all cases the reaction occurred in a completely regioselective way to give the diastereoisomeric azido alcohols **9a–c** and **10a–c**, arising from the nucleophilic attack on C-3′, in a practically quantitative yield (>90%), and in a 90:10 ratio (Scheme 3).[13]



a: $R_1 = R_2 = R_3 = H$ b: $R_1 = CH_3$, $R_2 = R_3 = H$ c: $R_1 = R_3 = H$, $R_2 = CH_3$ d: $R_1 = H$, $R_2 = R_3 = CH_3$

Scheme 3.

The subsequent transformation of the crude azido alcohol mixtures (**9–10a–c**) into the corresponding aziridines was carried out with triphenylphosphine in acetonitrile. Besides triphenylphosphine oxide, the two diastereoisomeric aziridines **11a–c** and **12a–c** were obtained in a ca. 90:10–95:5 ratio (Scheme 4). A 90:10 mixture of aziridines **11c** and **12c** was isolated, in an 80% yield, after column chromatography, and characterized by ^1H and ^{13}C NMR spectra. In contrast, attempts to purify aziridines **11–12a** and **11–12b** by column chromatography produced only decomposition products.



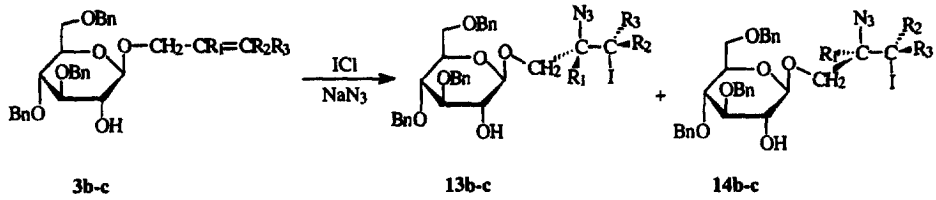
a: $R_1 = R_2 = R_3 = H$ b: $R_1 = CH_3$, $R_2 = R_3 = H$ c: $R_1 = R_3 = H$, $R_2 = CH_3$ d: $R_1 = H$, $R_2 = R_3 = CH_3$

Scheme 4.

The stereochemistry at the aziridine carbon(s) of compounds **11a–c** was finally established, taking into account that the overall reaction sequence implies inversion at both atoms of the original epoxide. On the basis of the absolute configuration of the starting epoxide, it is possible to assign the (*S*) configuration to the C-2′ carbon in compounds **11a** and **11b**, and the (2′*S*,3′*R*) configuration to the aziridine carbons of **11c**.

Another well-established classic method to obtain aziridines is the reduction of haloazides prepared by pseudo halogen addition to olefins.[14] However, attempts to obtain diastereoisomerically pure aziridines, **11–12a–c**, via iodo azides failed because of the very low, if any, face selection which characterizes the IN_3 addition reaction to the double bond of olefins **3b** and **3c** (Scheme 5).

Even at −78°C, the IN_3 (generated in situ from ICl and NaN_3) addition to glycosides **3b** and **3c** carried out in anhydrous CH_3CN, proceeded with a practically complete regioselection, to give the



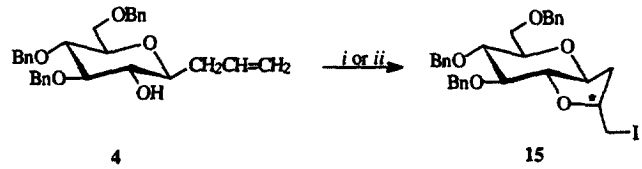
3b-c 13b-c 14b-c

ca. 50:50

a: $R_1 = R_2 = R_3 = H$ b: $R_1 = CH_3$, $R_2 = R_3 = H$ c: $R_1 = R_3 = H$, $R_2 = CH_3$ d: $R_1 = H$, $R_2 = R_3 = CH_3$

Scheme 5.

products arising from addition of the nucleophile to the more substituted carbon,[15] but without face diastereoselection. In both cases, the corresponding compounds **13** and **14** were formed in a ca. 1:1 ratio. In addition, when the reaction was carried out with the C-glycoside **4**, the cyclic iodo ether **15**, arising from the intramolecular nucleophilic attack of the C-2 hydroxy group on the iodonium intermediate, was obtained in a good yield and with a substantial appreciable diastereoisomeric purity (ca. 70%).



4 15

i) ICl, NaN_3, acetonitrile -78 °C; *ii*) ICl, NaN_3, $(Bu)_4NCl$, dichloromethane -78 °C.

It is noteworthy that the same product **15** was also obtained in a practically diastereoisomerically pure form when the reaction was carried out in dichloromethane under two phase conditions, using tetrabutylammonium chloride for the ion transfer.[16]

Finally, aziridination attempts utilizing [*N*-(*p*-toluenesulphonyl)imino]phenylidinane (Ph=NTs) in the presence of catalytic quantities of $Cu(OTf)_2$ under 'standard conditions'[17] failed, giving the unreacted starting material as the sole product.

In conclusion, these results show not only that the high diastereoselection obtained in the epoxidation of allylic alcohols can easily be applied to the preparation of the corresponding aziridines, but also that this method, among those generally used, is the only one able to give satisfactory results with these kinds of compounds.

3. Experimental

All melting points were measured on a Kofler apparatus and are uncorrected. Optical rotations were measured in $CHCl_3$ solution (c=1.0±0.2) at 20±2°C with a Perkin–Elmer 241 polarimeter. NMR spectra were registered with a Bruker AC 200 instrument using tetramethylsilane as the internal standard. All reactions were followed by TLC Alugram® sil G/UV_{254} with detection by UV or with ethanolic 10% sulphuric acid and heating. Kieselgel Macherey-Nagel (70–230 or 230–400 mesh) was used for column and flash chromatography. Solvents were distilled and stored over 4 Å molecular sieves activated by heating for 24 h at 400°C. Reactions in anhydrous conditions were carried out under an argon atmosphere. $MgSO_4$ was used as the drying agent for solutions. Anhydrous KF was obtained by heating at 120°C and 0.1 mmHg for 2 h.

1,2-Anhydro-3,4,6-tri-*O*-benzyl-α-D-glucopyranose **2** was obtained as reported,[8] and transformed into the allyl 3,4,6-tri-*O*-benzyl-β-D-glucopyranosides **3a–d** following the previously described procedure.[8]

3.1. 2′-Methylpropenyl-3,4,6-tri-O-benzyl-β-D-glucopyranoside, 3b

$[\alpha]_D$ −12.8 (*c* 3.6, $CHCl_3$). ^1H NMR ($CDCl_3$) δ: 1.77 (s, 3H, CH_3); 3.48–5.29 (m, 17H, allylic OCH_2, 3 benzylic CH_2, CH_2=, H-6, H-6′, H-5, H-4, H-3, H-2 and H-1); 7.13–7.37 (m, 15H aromatic H). ^{13}C NMR ($CDCl_3$) δ: 20.11 (CH_3); 69.32 (C6); 73.21 (allylic OCH_2); 73.89, 75.39, 75.63 (benzylic CH_2); 75.16, 75.55 (C-2 and C-5); 78.05 (C-4); 85.09 (C-3); 101.98 (C-1); 113.59 (CH_2=); 128.10–128.85 (15 aromatic C); 138.63, 139.17 and 141.65 (3 quaternary aromatic C). Anal. calcd for $C_{31}H_{36}O_6$: C, 73.79; H, 7.19. Found: C, 73.56, H, 7.15.

3.2. trans-2′-Butenyl-3,4,6-tri-O-benzyl-β-D-glucopyranoside, 3c

M.p. 43–45°C. $[\alpha]_D$ 9.0 (*c* 2.1, $CHCl_3$). ^1H NMR ($CDCl_3$) δ: 1.7 (d, 3H, *J*=6.0 Hz, CH_3); 4.50 (m, 12H, allylic OCH_2, 2 benzylic CH_2, H-6, H-6′, H-5, H-4, H-3 and H-2); 4.78–4.97 (m, 3H, benzylic CH_2 and H-1); 5.50–5.90 (m, 2H, CH=); 7.13–7.37 (m, 15 aromatic H). ^{13}C NMR ($CDCl_3$) δ: 17.80 (CH_3); 68.85 (C-6); 70.07 (allylic OCH_2); 73.43, 74.60, 74.96 (benzylic CH_2); 75.09, 75.50 (C-2 and C-5); 78.00 (C-4); 8.50 (C-3); 101.41 (C-1); 126.52 (CH=); 127.59–128.42 (15 CH); 130.73 (CH=); 138.01, 138.06, 138.57 (3 quaternary aromatic C). Anal. calcd for $C_{31}H_{36}O_6$: C, 73.79, H, 7.19. Found: C, 73.91, H, 6.99.

Compounds **3a** and **3d** were identified on the basis of the reported specific rotations and of ^1H and ^{13}C NMR spectra.[8,18]

3.3. C-Allyl 3,4,6-tri-O-benzyl-β-D-glucopyranoside, 4

1 M allyl magnesium bromide in Et_2O (4.6 ml) was added to a solution of CuBr·Me_2S (97 mg, 0.47 mmol) in 3 ml of THF, under an argon atmosphere at −30°C. At the end of the addition, compound **2** (1.30 g, 3.08 mmol) dissolved in THF (2 ml) was added. After 2 h of stirring at 0°C the resulting mixture was poured into aqueous NH_4Cl at 0°C, and extracted with CH_2Cl_2. The organic phase, washed and dried, was evaporated in vacuo to give a residue (1.08 g), which was purified by column chromatography over silica gel (7:3 hexane:AcOEt) to give pure **4** in a ca. 60% yield: m.p. 64–66°C [lit.[12] 63–65°C]. $[\alpha]_D$ +36.6 (*c* 2.1, $CHCl_3$) [lit.[12] $[\alpha]_D$ +37.5 (*c* 2.1, $CHCl_3$)]. ^1H NMR ($CDCl_3$) δ: 3.3–3.1 (m, 8H, allylic CH_2, H-6, H-6′, H-5, H-4, H-3, H-2); 4.5–5.2 (m, 9H, 3 benzylic CH_2, CH_2=, H-1); 5.9 (qt, *J*=17, *J*=10 and *J*=7 Hz, CH=); 7.1–7.4 (m, 15 aromatic H). ^{13}C NMR ($CDCl_3$) δ: 36.05 (CH_2CH=); 68.74 (C-6); 73.32, 74.65 and 75.05 (3 benzylic CH_2); 78.29 and 78.64 (C-5 and C-4); 78.99 (C-3); 86.61 (C-1); 116.94 (CH_2); 127.44–128.51 (15 aromatic CH); 134.50 (CH=); 137.93, 138.13, 138.48 (3 quaternary aromatic C).

3.4. 2′,3′-Epoxy derivatives of O-allyl and C-allyl 3,4,6-tri-O-benzyl-β-D-glucopyranosides, 5, 6a–d, 7 and 8

Allyl 3,4,6-tri-*O*-benzyl-β-D-glucopyranoside **3a–d** (1 mmol) was added to a CH_2Cl_2 solution (5 ml) of 70% MCPBA (1.2 mmol), previously dried for 20 min over Sikkon and $MgSO_4$ and filtered. The reaction mixture was left at the proper temperature for the time reported in Table 1, then diluted with CH_2Cl_2, washed with an aqueous solution of $NaHSO_3$ and $NaHCO_3$, dried and evaporated in vacuo.

The residues were analyzed by ^{1}H NMR in order to evaluate the conversion by the ratio between the olefinic and oxirane protons, and the diastereoselectivity of the epoxidation, which was given by the ratio between the signals for the diastereoisomeric oxirane H-3′ protons. Yields and diastereoisomeric ratios are reported in Table 1. The crude residues were purified by flash chromatography over silica gel (hexane:AcOEt, 7:3, containing 0.1% Et_3N) to obtain the starting glucoside **3** or **4** and a mixture of the two diastereoisomeric epoxides. The mixture of epoxides **5** and **6**, or **7** and **8**, obtained always as a syrup, showed: Mixture of **5a+6a**: specific rotations and ^{1}H and ^{13}C NMR spectra in agreement with those previously reported.[8] Mixture of **5b+6b**: $[\alpha]_D$ −8.0 (*c* 1, $CHCl_3$). ^{1}H NMR ($CDCl_3$) for **5b** δ: 1.27 (s, 3H, CH_3); 2.54 (d, 1H, *J*=4.8 Hz, H-3′); 2.85 (d, 1H, *J*=4.8 Hz, H-3′); 3.4–3.7 (m, 7H, H-6, H-6′, H-5, H-4, H-3, H-2, H-1′); 3.90 (d, 1H, *J*=11.7 Hz, H-1′); 4.5–5.0 (m, 7H, benzylic CH_2 and H-1). ^{13}C NMR ($CDCl_3$) δ: 18.43 (CH); 51.15 (C-3′); 56.10 (C-2′); 68.74–71.14 (C-6 and C-1′); 73.39, 74.86, 74.93 (benzylic CH_2); 75.06 (C-2 and C-5); 77.22 (C-4); 84.51 (C-3); 103.59 (C-1); 127.59–128.31 (15 aromatic CH); 137.97, 137.97, 138.59 (3 quaternary aromatic C). The following signals were attributed to **6b**: ^{13}C NMR ($CDCl_3$) δ: 102.59 (C-1); 51.7 (C-2′). Anal. calcd for $C_{31}H_{36}O_7$; C, 71.52, H, 6.97. Found: C, 71.35, H, 6.93. Mixture of **5c+6c**: $[\alpha]_D$ −16 (*c* 3.0, $CHCl_3$). ^{1}H and ^{13}C NMR spectra were identical to those previously reported.[9] Mixture of **5d+6d**: ^{1}H NMR ($CDCl_3$) δ: 1.30 (d, 3H, *J*=8.7 Hz, CH_3); 1.33 (d, 3H, *J*=8.8 Hz, CH_3); 3.04 (m, 1H, C-2′); 3.6–4.7 (m, 8H, allylic CH_2, H-6, H-6′, H-5, H-4, H-3, H-2); 4.31 (m, 1H, H-1); 4.4–5.0 (m, 6H, benzylic CH_2). ^{13}C NMR ($CDCl_3$) δ: 25.29 (CH_3); 30.36 (CH_3); 62.64 (C-2′); 69.44–68.64 (C-6, C-1′); 74.15, 75.10, 75.36 (benzylic CH_2); 75.61 (C-2 and C-5); 78.34 (C-4); 85.10 (C-3); 103.57 (C-1); 128.0–129.0 (15 aromatic CH); 138.68, 138.68, 139.26 (3 quaternary aromatic C). Although the spectra of the two diastereoisomeric epoxides were largely identical, it was possible to distinguish the following signals: ^{13}C NMR ($CDCl_3$) δ: 62.00 (C-2′) and 103.40 (C-1). Anal. calcd for $C_{32}H_{38}O_7$: C, 72.89, H, 7.16. Found: C, 71.75, H, 7.26. Mixture of **7+8**: ^{1}H NMR ($CDCl_3$) δ: 2.85 (m, 2H, H-3′); 3.1–3.8 (m, 9H, allylic CH_2, H-6, H-6′, H-5, H-4, H-3, H-2 and H-2′); 4.97–4.70 (m, 7H, 3 benzylic CH_2 and H-1); 7.12–7.40 (m, 15 aromatic H). ^{13}C NMR ($CDCl_3$) δ: 36.38 (C-1′); 48.61 (C-3′); 50.13 (C-2′); 69.44 (C-6); 74.04, 75.45, 75.87 (benzylic CH_2); 77.69 (C-2 and C-5); 78.88 (C-4); 79.32 (C-3); 87.22 (C-1); 117.70–129.30 (15 aromatic carbons). Although the spectra of the two diastereoisomeric epoxides were largely identical, it was possible to distinguish the following signals: ^{13}C NMR ($CDCl_3$) δ: 35.18 (C-1′); 47.40 (C-3′); 49.94 (C-2′); 79.05 (C-4); 79.57 (C-3); 87.32 (C-1). Anal. calcd for $C_{30}H_{34}O_6$: C, 73.45, H, 6.99. Found: C, 73.55, H, 6.95.

3.5. Oxirane ring-opening of mixtures of epoxides 5a–c+6a–c with NaN_3 and transformation of azido alcohols (9+10) into the corresponding aziridines (11+12)

Anhydrous NaN_3 (4.5 equiv.) and NH_4Cl (2.5 equiv.) were added to a MeOH:H_2O (8:2) solution (2.5 ml) of the ca. 90:10 mixtures of epoxides **5a–c** and **6a–c** (1 equiv.) and the solution was stirred at 80°C. The reactions were monitored by TLC and after 18–20 h, the mixtures were diluted with CH_2Cl_2, washed with an aqueous solution of NaCl, and dried. Evaporation in vacuo of the solvent gave a residue (90–95% yield) which was analyzed by ^{1}H and ^{13}C NMR.

3.5.1. 2′-Hydroxy-3′-azidopropyl-3,4,6-tri-O-benzyl-β-D-glucopyranosides, 9a–10a

$[\alpha]_D$ −3.8 (*c* 1.8, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ: 3.30–3.90 (m, 11H, H-6, H-6′, H-5, H-4, H-2, H-3, allylic OCH_2, C*H*OH, CH_2N_3); 4.40–4.90 (m, 7H, 6H benzylic CH_2, H-1); 7.10–7.40 (15 aromatic H). ^{13}C NMR ($CDCl_3$) δ: 53.09 (C-3′, CH_2N_3); 68.56 (C-6); 69.86 (C-2′, C*H*OH); 73.07 (C-1′, CH_2O); 74.15, 74.80, 74.91 (benzylic CH_2); 77.42 (C-4); 84.33 (C-3); 103.35 (C-1); 127.0–133.0 (15 aromatic

CH); 137.70, 137.96, 138.33 (3 quaternary aromatic C); 74.21, 74.88 (C-2 and C-5). Only the anomeric carbon was attributed to **10a**: ^{13}C NMR ($CDCl_3$) δ: 103.55 (C-1).

*3.5.2. 2′-Hydroxy-2′-methyl-3′-azidopropyl-3,4,6-tri-*O*-benzyl-β-*D*-glucopyranosides, **9b–10b***

$[\alpha]_D$ −3.25 (*c* 2.1, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ: 1.15 (s, 3H, CH_3); 3.25 (AB system, 2H, *J*=12.3 Hz, CH_2N_3); 3.4–4.0 (m, 8H, H-6, H-6′, H-5, H-4, H-3, H-2, OCH_2); 4.2–4.9 (m, 7H, CH_2 benzylic, H-1); 7.10–7.40 (m, 15 aromatic H). ^{13}C NMR ($CDCl_3$) δ: 21.75 (CH_3); 57.27 (CH_2N_3); 68.43 (C-6); 72.40 (quaternary COH); 73.31 (C-1′); 74.77, 75.00, 75.40 (benzylic CH_2); 73.99–74.85 (C-2 and C-5); 77.42 (C-4); 84.36 (C-3); 103.34 (C-1); 127.56–128.39 (15 aromatic C); 137.76, 137.76, 138.33 (3 quaternary aromatic C). The following signals were attributed to **10b**: ^{1}H NMR ($CDCl_3$) δ: 1.22 (d, 3H, CH_3). ^{13}C NMR ($CDCl_3$) δ: 103.53 (C-1); 57.57 (CH_2N_3).

3.5.3. trans-*2′-Hydroxy-3′-azidobutyl-3,4,6-tri-*O*-benzyl-β-*D*-glucopyranosides, **9c–10c***

$[\alpha]_D$ −7.8 (*c* 2.1, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ: 1.28 (d, 3H, *J*=6.6 Hz, CH_3); 3.40–3.95 (m, 10H, H-6, H-6′, H-5, H-4, H-3, H-2, OCH_2, C*H*OH, CHN_3); 4.3–5.0 (m, 7H, benzylic CH_2 and H-1); 7.10–7.40 (15 aromatic H). ^{13}C NMR ($CDCl_3$) δ: 15.14 (CH_3); 58.43 (CHN_3); 68.59 (C-6); 72.60 (C-1′); 73.20 (CHOH); 73.41, 74.88, 75.18 (benzylic CH_2); 74.08–74.88 (C-2 and C-5); 77.44 (C-4); 84.32 (C-3); 103.27 (C-1); 127.83–133.48 (15 aromatic CH); 137.72, 137.72, 138.34 (3 quaternary aromatic C). The following signals were attributed to **10c**: ^{1}H NMR ($CDCl_3$) δ: 1.22 (d, 3H, CH_3). ^{13}C NMR ($CDCl_3$) δ: 103.53 (C-1).

PPh_3 (1 equiv.) was added to the crude azido alcohols (**9+10a–c**) dissolved in CH_3CN (2 ml) and the mixture was kept at room temperature with stirring until the evolution of N_2 was observed (ca. 30 min) and then refluxed for ca. 16 h. After cooling, the solvent was removed in vacuo and the residue, consisting of a mixture of aziridines **11+12** and triphenylphosphine oxide was analyzed by ^{1}H and ^{13}C NMR. Purification by column chromatography over silica gel (4:4:2 hexane:CH_2Cl_2:Et_3N) made it possible to obtain, only in the case of **11c** and **12c**, a pure fraction containing the two corresponding diastereoisomeric aziridines in a 90:10 ratio. Attempts to purify aziridines **11a+12a** and **11b+12b** by column chromatography failed because of the products' instability. **11c** and **12c** (90:10 ratio): $[\alpha]_D$ +2.0 (*c* 2.1, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ: 1.19 (d, 3H, *J*=5.4 Hz, CH_3); 1.92 [m, 2H, C*H*(NH)–C*H*]; 3.3–3.7 (m, 9H, H-6, H-6′, H-5, H-4, H-3, H-2, allylic CH_2, OH, NH); 4.1 (dd, 1H, *J*=11.3 and 3.2 Hz, OCH_2); 4.27 (d, 1H, *J*=6.9 Hz, OCH_2); 4.5–5.1 (m, 6H, benzylic CH_2). ^{13}C NMR ($CDCl_3$) δ: 18.38 (C-4′, CH_3); 29.75 (C-3′, CHN); 37.00 (CHN); 68.77 (C-6); 69.57 (OCH_2); 73.24, 74.75, 74.78 (benzylic CH_2); 74.78, 73.89 (C-2 and C-5); 77.26 (C-4); 84.65 (C-3); 102.90 (C-1); 127.00–132.00 (15 aromatic C); 138.00, 138.00, 138.73 (3 quaternary aromatic C). The following signals were attributed to **12c**: ^{13}C NMR ($CDCl_3$) δ: 103.90 (C-1); 69.38 (OCH_2); 36.60, 29.37 (CHN). Anal. calcd for $C_{31}H_{37}O_6N$: C, 71.65; H, 7.18; N, 2.70. Found: C, 71.53; H, 7.25; N, 2.55.

*3.6. Iodine azide addition reaction to **3b–c** and **4**. General procedure*

3.6.1. In acetonitrile

ICl (1.12 mmol), previously dissolved in CH_3CN (2 ml), was added to a stirred slurry of NaN_3 (2.5 mmol) in CH_3CN (2 ml) cooled at −78°C. The reaction mixture was stirred for 10 min and then, after the addition of the glycoside (1 mmol), allowed to warm to room temperature. At the end of the reaction, which in all cases was followed by TLC, the reaction mixture was diluted with CH_2Cl_2 and washed with aqueous $NaHSO_3$. The organic phase was dried and evaporated in vacuo to give a residue (90% yield), which was analyzed by ^{1}H and ^{13}C NMR.

*3.6.2. From **3b**: 3′-iodo-2′-methyl-2′-azidopropyl-3,4,5-tri-O-benzyl-β-D-glucopyranoside (**13b+14b**)*

^{1}H NMR ($CDCl_3$) δ: 1.39 (s, 3H, CH_3); 1.44 (s, 3H, CH); (m, 10H, OCH_2, H-6′, H-6, H-5, H-3, H-2, CH_2I); 4.50–5.00 (m, 7H, 3 benzylic CH_2 and H-1); 7.20–7.50 (m, 15 aromatic H). ^{13}C NMR ($CDCl_3$) δ: 12.40 (CH_2I); 22.55 (CH_3); 62.50 (CN_3); 69.28 (C-6); 74.72 (OCH_2); 74.10, 75.83, 75.83 (benzylic CH_2); 75.62 (C-2 and C-5); 77.93 (C-4), 84.99 (C-3); 103.67 (C-1); 127.00–132.00 (15 aromatic C); 138.00, 138.00, 138.73 (3 quaternary C). Although the spectra of the two diastereoisomeric iodo azido derivatives were largely identical, it was possible to distinguish the following signals: ^{13}C NMR ($CDCl_3$) δ: 12.16 (CH_2I); 22.13 (CH_3); 62.15 (CN_3). On the basis of the intensity of these signals a 60:40 ratio between the two diastereoisomeric products was evaluated.

*3.6.3. From **3c**: 3′-iodo-2′-azidobutyl-3,4,6-tri-O-benzyl-β-D-glucopyranoside or 2′-iodo-3′-azidobutyl-3,4,6-tri-O-benzyl-β-D-glucopyranoside (**13c+14c**)*

^{1}H NMR ($CDCl_3$) δ: 1.60 (d, 3H, CH_3); 3.40–4.40 (m, 10H, OCH_2, H-6′, H-6, H-5, H-3, H-2, CHI, CHN_3); 4.50–5.00 (m, 7H, 3 benzylic CH_2 and H-1); 7.20–7.50 (m, 15 aromatic H). ^{13}C NMR ($CDCl_3$) δ: 24.42 (CH_3); 38.87 (CHI); 56.94 (CHN_3); 68.50 (C-6); 72.58 (CH_2O); 73.42, 74.46, 74.95 (benzylic CH_2); 75.01 (C-2 and C-5); 77.19 (C-4); 84.25 (C-3); 102.66 (C-1); 127.00–132.00 (15 aromatic C); 138.00, 138.00, 138.73 (3 quaternary C). Although the spectra of the two diastereoisomeric iodo azido derivatives were largely identical, it was possible to distinguish the following signals: ^{13}C NMR ($CDCl_3$) 24.58 (CH_3); 39.72 (CHI); 57.25 (CN_3); 103.24 (C-1). On the basis of the intensity of these signals a 50:50 ratio between the two diastereoisomeric products was evaluated.

*3.6.4. From **4**: compound **15** (85:15 mixture of the two diastereoisomers)*

^{1}H NMR ($CDCl_3$) δ: 1.70–2.20 (m, 2H, CH_2); 2.50 (m, 1H, CH); 3.10–3.70 (m, 8H, CH_2, H-6, H-6′, H-5, H-4, H-3, H-2); 4.30–5.00 (m, 7H, 3 benzylic CH_2 and H-1); 7.20–7.50 (m, 15 aromatic H). ^{13}C NMR ($CDCl_3$) δ: 10.15 (CH_2I); 35.66 (CH_2); 72.87, 73.35, 75.25 (benzylic CH_2); 68.94 (C-6); 77.25 (C-2); 78.0 (C-5); 78.38 (C-4); 80.49 (C-3); 81.92 (CH); 84.07 (C-1); 127.00–132.00 (15 aromatic C); 138.00, 138.00, 138.73 (3 quaternary C). Although the spectra of the two diastereoisomers were largely identical, it was possible to distinguish the following signals: ^{13}C NMR ($CDCl_3$) δ: 83.70 (C-1); 34.08 (CH_2); 11.28 (CH_2I). On the basis of the intensity of these signals an 85:15 ratio between the two diastereoisomeric products was evaluated. [Lit.[12]: ^{13}C NMR of the major isomer δ: 11.2 (t); 34.3 (t); 73.0 (t), 73.5 (t), 75.3 (t); 69.3 (t); 77.5 (d); 77.6 (d); 78.0 (d); 80.9 (d); 83.8 (d); 83.9 (d).]

3.7. In dichloromethane

ICl (1.5 mmol) was added to a stirred slurry of NaN_3 (3 mmol) in anhydrous CH_2Cl_2 (4 ml), containing tetrabutylammonium chloride (0.03 mmol). After 2 h at room temperature, the mixture was cooled at −78°C and **4** (1 mmol) was added with stirring. The reaction mixture was stirred for another 4 h and then allowed to warm to room temperature. After 1 h at room temperature the reaction mixture was washed with aqueous $NaHSO_3$, dried and evaporated in vacuo to give **15** (90% yield; ≥98% d.r.), which was analyzed by ^{1}H and ^{13}C NMR.

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References

1. Osborn, H. M. I.; Sweeney, J. *Tetrahedron: Asymmetry* **1997**, 8, 1693.
2. Tanner, D. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 599.
3. Kasai, M.; Kono, M. *Synlett* **1992**, 778.
4. Skibo, E. B.; Islam, I.; Heileman, M. J.; Schulz, W. G. *J. Med. Chem.* **1994**, *37*, 78.
5. Motoki, K.; Kobayashi, E.; Uchida, T.; Fukushima, H.; Koezuda, Y. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 705.
6. Costantino, V.; Fattorusso, E.; Mangoni, A.; Di Rosa, M.; Ianaro, A. *J. Am. Chem. Soc.* **1997**, *119*, 12465.
7. Liu, K. K.-C.; Danishefsky, S. J. *Chem. Eur. J.* **1996**, *2*, 1359.
8. Bellucci, G.; Catelani, G.; Chiappe, C.; D'Andrea, F.; Grigò, G. *Tetrahedron: Asymmetry* **1997**, *8*, 765.
9. Charette, A. B.; Côté, B. *Tetrahedron: Asymmetry* **1993**, *4*, 2283.
10. Bellucci, G.; Catelani, G.; Chiappe, C.; D'Andrea, F. *Tetrahedron Lett.* **1994**, *35*, 8433.
11. Levy, D. E.; Tang, C. *The Chemistry of C-Glycosides*; Baldwin, J. E.; Magnus, P. D., Eds; Elsevier Science: Oxford, 1995.
12. Cipolla, L.; Lay, L.; Nicotra, F. *J. Org. Chem.* **1997**, *62*, 6678.
13. While the regiochemistry of **9–10a,b** was well established by ^{1}H NMR, examination of the 9:1 mixture of these compounds obtained from epoxides **5–6a,b**, the regiochemistry of **9–10c**, obtained from **5–6c**, was arbitrarily assumed on the basis of the complete C-3′ regioselectivity observed in the azidolysis of the related epoxides **5–6a,b**.
14. Hassner, A.; Matthews, G. J. *J. Am. Chem. Soc.* **1969**, *91*, 5046.
15. While the regiochemistry of compounds **13b** and **14b** was unambigously established on the basis of the NMR spectra, those of **13c** and **14c** were tentatively attributed.
16. Napolitano, E.; Fiaschi, R. *Gazz. Chim. Ital.* **1992**, *122*, 233.
17. (a) Evans, D. A.; Faul, F. M.; Bilodeau, M. T. *J. Org. Chem.* **1991**, *56*, 6744. (b) Evans, D. A.; Faul, F. M.; Bilodeau, M. T. *J. Am. Chem. Soc.* **1994**, *116*, 2742.
18. Charette, A. B.; Turcotte, N.; Côté, B. *J. Carbohydr. Chem.* **1994**, 421.