DOI: 10.1002/ejoc.200800480

Stereoselective Synthesis of Novel Cyclic γ-Amino Acids and Triazole Derivatives

Verónica F. V. Prazeres,[a] Luis Castedo,[a] and Concepción González-Bello*[a]

In memory of Jonathan Spencer

Keywords: Cyclic γ-amino acids / Regioselectivity / Click chemistry / (–)-Quinic acid

Four polyhydroxylated γ-azido and three γ-amino acids **1**–**4** have been synthesized from (–)-quinic acid. The nitrogen functionality in the reported derivatives was introduced through regioselective ring-opening of cyclic sulfates with azide anion. The synthesis of the 4- and 5-epimers of γ-azido acid **1a** – derivatives **2** and **3a**, respectively – was achieved by regioselective oxidation of dibutylstannylene acetals derived from 1,2-diols, followed by diastereoselective reduction of their corresponding α-hydroxy ketones. The presence of the azide functional group in the reported γ-azido acids was exploited to permit interlinking of bioactive molecular entities.

Introduction

Cyclic amino acids have been shown to play an important role in drug design because they can bear pharmacophoric groups with well defined spatial orientations that can be used to obtain important information about key structural features of receptor ligand complexes.[1] In addition, structural entities possessing polyhydroxylated cyclohexanoid cores are found in many biologically important molecules and natural products.[2] The rich functionality present in polyhydroxylated amino acids also makes them attractive candidates for use as core scaffolds in combinatorial chemistry.

The important applications of cyclic amino acids in biology and materials science have encouraged us to pursue the stereoselective synthesis of a variety of highly functionalized cyclic γ-amino acids derivatives. Here we disclose the stereoselective synthesis of four γ-azido acids and three γ-amino acids **1**–**4** through the use of (–)-quinic acid as a chiral template (Figure 1). Our strategy involved the incorporation of the nitrogen functionalities of cyclitol derivatives **1**–**4** through regioselective ring-opening of cyclic sulfates with azide anion and subsequent azide reduction.

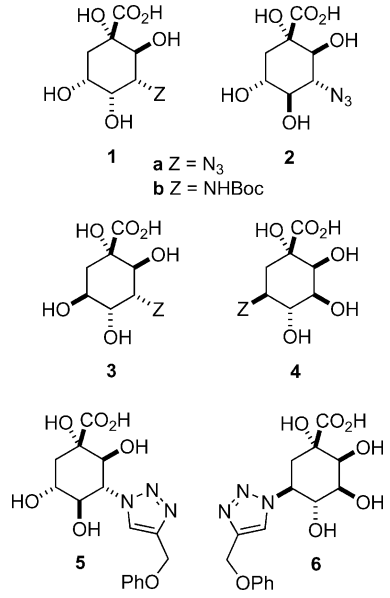


Figure 1. Cyclic γ-azido and γ-amino acids and triazole derivatives.

The high chemoselectivity of azides towards alkynes, together with the stability of the triazole ring toward chemical and enzymatic degradation, makes triazoles useful functional groups for linking bioactive molecular entities.[3] In this context, the improved version of the Huisgen 1,3-dipolar cycloaddition reaction,[4] the copper(I)-catalyzed azide/alkyne cycloaddition, or "Sharpless click reaction",[5] has proven to be a powerful tool in synthetic chemistry. The high regioselectivity and efficiency of the click reaction has been successfully exploited in polymer and material sci-

[a] Laboratorio de Química Orgánica (CSIC) y Departamento de Química Orgánica, Facultad de Química, Universidad de Santiago de Compostela,
Avenida de las Ciencias s/n, 15782 Santiago de Compostela, Spain
Fax: +34-981-595012
E-mail: concepcion.gonzalez.bello@usc.es

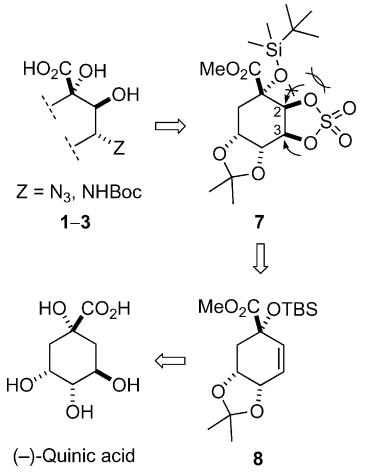
Supporting information for this article is available on the WWW under http://www.eurjoc.org/ or from the author.

ences, particularly in the synthesis of dendrimers containing sugar-binding units (glycodendrimers).[6] In this paper we explore the utility of the azide function present in the reported γ-azido acids as a possible linking group through the use of "Sharpless click chemistry", an approach demonstrated with the synthesis of triazole derivatives **5** and **6**.

Results and Discussion

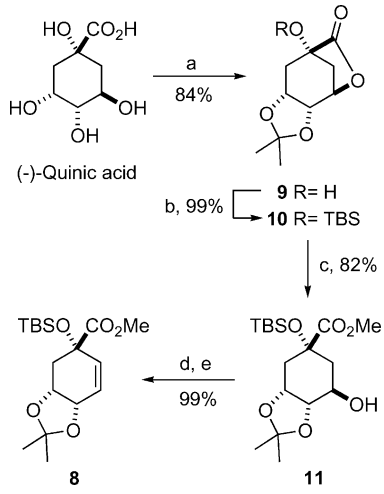
Synthesis of γ-Azido and γ-Amino Acids 1a and 1b

Our synthetic approach was based on the functionalization of the cyclohexene derived from (–)-quinic acid (compound **8**, Scheme 1). This strategy involves the incorporation of the nitrogen functionality by diastereoselective *cis*-dihydroxylation of cyclohexene **8**, followed by cyclic sulfate formation and subsequent regioselective ring-opening with the azide anion. Through the reasoning that the ring-opening reaction should occur mainly at the less hindered side of the cyclic sulfate **7**, a bulky protecting group (TBS) was chosen for protection of the tertiary hydroxy group of sulfate **7**.



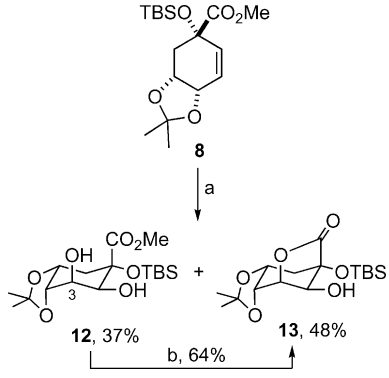
Scheme 1. Strategy for the synthesis of derivatives **1**–**3**.

The synthesis of cyclohexene **8** was carried out in four steps from (–)-quinic acid, as shown in Scheme 2. Firstly, quadruple protection of (–)-quinic acid by a *p*-TsOH acid-catalyzed reaction with acetone dimethyl acetal, followed by TBS protection of the resulting tertiary alcohol **9**[7] with TBSOTf and pyridine, afforded silyl ether **10** in excellent yield. Treatment of lactone **10** with potassium cyanide in methanol gave alcohol **11**, which was finally converted into alkene **8** by a sequential two-step procedure. Initial activation of the free alcohol as a trifluoromethanesulfonate ester with triflic anhydride in the presence of pyridine in dichloromethane and subsequent elimination with DBU in chloroform at reflux afforded the desired cyclohexene derivative **8** in excellent yield.



Scheme 2. Reagents and conditions: (a) $Me_2C(OMe)_2$, $HC(OMe)_3$, acetone, *p*-TsOH (cat.), Δ; (b) TBSOTf, Py, DCM, 0 °C → r.t.; (c) KCN, MeOH, r.t.; (d) Tf_2O, Py, DCM, 0 °C; (e) DBU, $CHCl_3$, Δ.

cis-Dihydroxylation of cyclohexene **8** in the presence of a catalytic amount of osmium tetroxide gave a mixture of two hydroxylated products, diol **12** and carbolactone **13**, resulting, in both cases, from reaction at the sterically less congested face of the double bond, the *Si* face (Scheme 3 and Figure 2). Carbolactone **13** is presumably formed by lactonization of the axial hydroxy group at C-3 and the methyl ester. In fact, diol **12** can also be converted into carbolactone **13** by treatment with sodium hydride. Carbolac-



Scheme 3. Reagents and conditions: (a) OsO_4 (cat), NMO, dioxane/H_2O, r.t.; (b) NaH, THF, 0 °C.

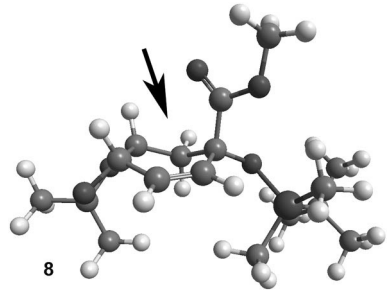
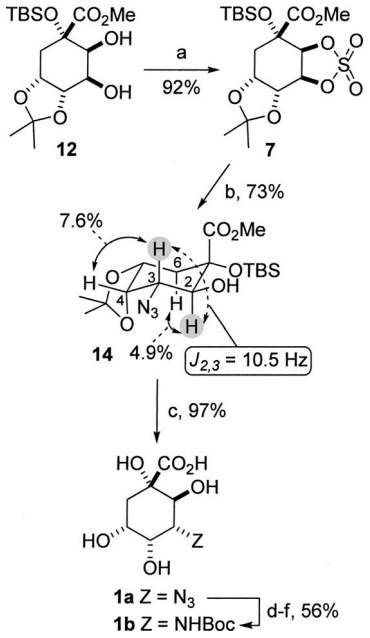


Figure 2. Minimum-energy conformation of cyclohexene **8** obtained by molecular modelling calculations (Gaussian 03W).[8,9]

tone **13** was employed in the synthesis of derivatives **4**, as described below.

Diol **12** was efficiently converted into the desired cyclic sulfate **7** by the Sharpless method (Scheme 4).[10] Azidolysis of **7** with sodium azide in the presence of a catalytic amount of 15-crown-5 ether in *N*,*N*-dimethylformamide at 90 °C regioselectively afforded the desired azido alcohol **14** as a single diastereoisomer. The regioselectivity of the reaction was confirmed by NOE experiments. Irradiation of 2-H led to enhancement of the signal for 6-H_{axial} (4.9%), whereas irradiation of 3-H led to enhancement of the signal for 4-H (7.6%). The structure of azido alcohol **14** is also consistent with a diaxial coupling constant between 2-H and 3-H ($J_{2,3}$ = 10.5 Hz). Azido alcohol **14** was directly converted into the desired acid **1a** by treatment with trifluoroacetic acid (50%) at 70 °C, followed by basic hydrolysis of the methyl ester and subsequent protonation with an ion-exchange resin to afford acid **1a** in 97% yield.

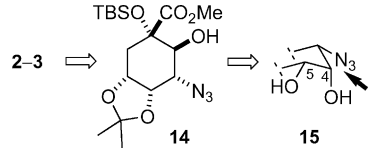


Scheme 4. Reagents and conditions: (a) (i) $SOCl_2$, Et_3N, DCM, r.t., (ii) $RuCl_3{\cdot}3H_2O$ (cat.), $NaIO_4$, H_2O, CCl_4, CH_3CN, r.t.; (b) (i) NaN_3, 15-crown-5 ether, DMF, 90 °C, (ii) H_2SO_4 (aq., 70%), THF, 50 °C; (c) (i) TFA (aq., 50%), 70 °C, (ii) LiOH, r.t., (iii) Amberlite IR-120 (H^+), r.t.; (d) Ac_2O, Py, 0 °C to r.t.; (e) H_2, PtO_2 (cat.), Boc_2O, THF, r.t.; (f) (i) LiOH, r.t.; (ii) Amberlite IR-120 (H^+), r.t.

The conversion of azide **1a** into the desired γ-amino acid **1b** was found to be difficult. Catalytic hydrogenolysis of azide **1a** in acidic media (HCl, HOAc, etc.) or in the presence of di-*tert*-butyl dicarbonate to avoid decomposition of the free amine either did not give any reaction or gave only low yields of the desired product. Azide reduction could only be achieved by acetylation of **1a**, which was carried out by treatment of **1a** with acetic anhydride and pyridine, followed by catalytic hydrogenolysis with platinum oxide as catalyst and in the presence of di-*tert*-butyl dicarbonate. Finally, removal of the acetyl groups by basic hydrolysis and acidification with an acidic ion-exchange resin afforded Boc-γ-amino acid **1b** in 56% overall yield.

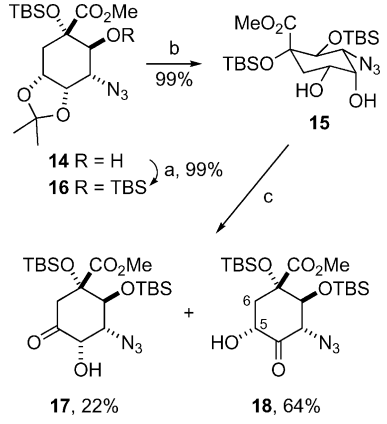
Synthesis of γ-Azido (2–3a) and γ-Amino (3b) Acids

The strategy for the synthesis of 4- and 5-epimers of **1a** – derivatives **2** and **3a**, respectively – consisted of the regioselective oxidation of C-4 and C-5 of **15**, respectively, followed by diastereoselective reduction of the corresponding ketone. Bearing in mind that dibutylstannylene acetals derived from 1,2-diols can be regioselectively oxidized to α-hydroxy ketones by bromine,[11] *N*-bromosuccinimide[12] or 1,3-dibromo-5,5-dimethylhydantoin,[13] we investigated the utility of this reaction for the synthesis of compounds **2** and **3** (Scheme 5). Moreover, considering that Sn-mediated oxidation of cyclic 1,2-diols usually occurs at the axial hydroxy group, one would expect that in our case the oxidation should take place preferentially at C-4, the more hindered side of diol **15**.[14]



Scheme 5. Strategy for the synthesis of derivatives **2**–**3**.

Firstly, TBS protection of the free hydroxy group of **14**, followed by selective deprotection of the isopropylidene acetal **16** by treatment with aqueous acetic acid (80%) at 65 °C, led to diol **15** in excellent yield (Scheme 6). Oxidation of the dibutylstannylene acetal derived from **15** (obtained by treatment of diol **15** with dibutyltin oxide in toluene with azeotropic removal of water) with *N*-bromosuccinimide in chloroform at room temperature gave a chromatographically separable mixture of the two α-hydroxy ketones **17** and **18**, the structures of which were confirmed by analysis of their ^1H NMR spectra. The diaxial coupling constant between 5-H and 6-H_{axial} ($J_{5,6ax}$ = 11.0 Hz) confirmed the structure of ketone **18**. As expected, ketone **18** was the main product of the reaction and was obtained in 64% yield.

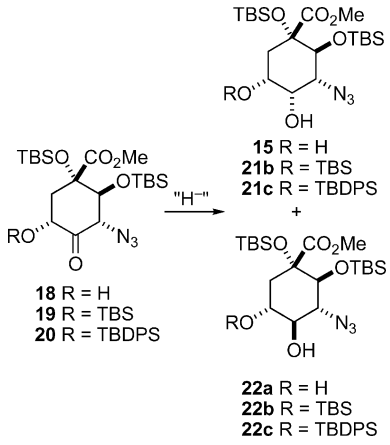


Scheme 6. Reagents and conditions: (a) TBSOTf, Py, DCM, 0 °C → r.t.; (b) AcOH (aq., 80%), 65 °C; (c) (i) Bu_2SnO, PhMe, Δ, (ii) NBS, $CHCl_3$, r.t.

The stereoselective reduction of ketone **18** by several reducing agents was then studied (Table 1). Use of a sterically hindered reducing agent, such as Li-selectride, provided ex-

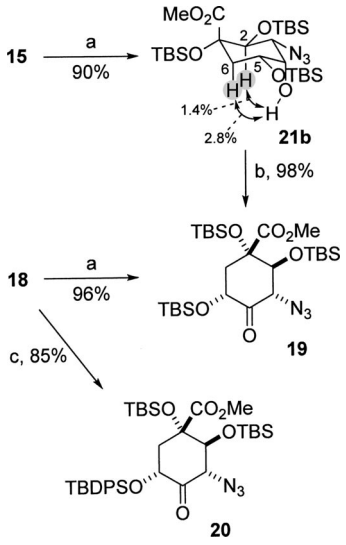
clusive equatorial hydride delivery. Only with use of a small hydride, such as sodium borohydride, was a modest preference for axial hydride attack obtained.

Table 1. Reduction of ketones **18**, **19** and **20**.



Ketone	Reducing agent	**15/21**, yield (%)	**22**, yield (%)
18	L-Selectride	94	0
18	$NaBH_4$	57	43
19	L-Selectride	100	0
19	$NaBH_4$	34	51
20	$NaBH_4$	41	42

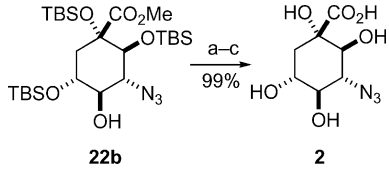
The influence of hydroxy group protection of **18** on the reaction diastereoselectivity was also investigated, with TBS- and TBDPS-protected ketones **19** and **20**, respectively, being synthesized. TBS derivative **19** was prepared from diol **15** or ketone **18** as shown in Scheme 7. Treatment of diol **15** with TBSOTf at 0 °C regioselectively afforded TBS ether **21b** in 90% yield. The regiochemistry of the protection was confirmed by NOE experiments. Inversion of the hydroxy group led to enhancement of the signals for 6-H_{axial} (2.8%) and for 2-H (1.4%). Swern oxidation of the



Scheme 7. Reagents and conditions: (a) TBSOTf, Py, DCM, 0 °C → r.t.; (b) (i) DMSO, TFAA, DCM, –60 °C, (ii) Et_3N, –60 °C → r.t.; (c) TBDPSCl, Im, DMF, 0 °C → r.t.

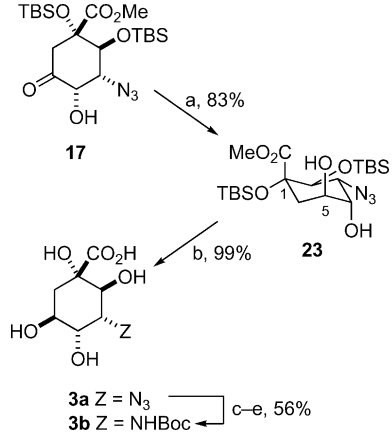
free secondary hydroxy group gave ketone **19** in excellent yield. Alternatively, treatment of ketone **18** with TBSOTf/pyridine or TBDPSCl/imidazole provided ketones **19** and **20**, respectively. However, protection of the hydroxy groups in ketones **19** and **20** as TBS or TBDPS ethers did not show any significant influence on the diastereoselectivity of the sodium borohydride reduction, which seems to be unaffected by the size of the equatorial substituent in the α-position (Table 1).

Finally, γ-azido acid **2** was obtained from alcohol **22b** in the same way as compound **1a** from **14** (Scheme 8).



Scheme 8. Reagents and conditions: (a) TFA (aq., 50%), 70 °C; (b) LiOH, r.t.; (c) Amberlite IR-120 (H^+), r.t.

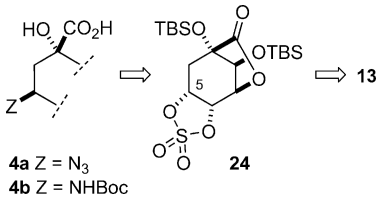
The desired compounds **3** were obtained from ketone **17** by the reaction sequence shown in Scheme 9. Reduction of **17** with sodium borohydride in methanol afforded mainly axial hydride delivery. In this case, the free hydroxy group, which is in an axial orientation, directs the hydride attack to give diaxial diol **23** in 83% yield. Equatorial hydride delivery was obtained in only 16% yield. Acidic hydrolysis of diol **23** with aqueous trifluoroacetic acid at 70 °C gave the corresponding 1,5-carbolactone, and basic hydrolysis followed by ion exchange gave azido acid **3a** in excellent yield. Finally, reduction of **3a** in the same way as compound **1b** from **1a** afforded amino acid **3b** in 56% yield.



Scheme 9. Reagents and conditions: (a) $NaBH_4$, MeOH, r.t.; (b) (i) TFA (aq., 50%), 70 °C, (ii) LiOH, r.t., (iii) Amberlite IR-120 (H^+), r.t.; (c) Ac_2O, Py, 0 °C → r.t.; (d) H_2, PtO_2 (cat.), Boc_2O, THF, r.t.; (e) (i) LiOH, r.t., (ii) Amberlite IR-120 (H^+), r.t.

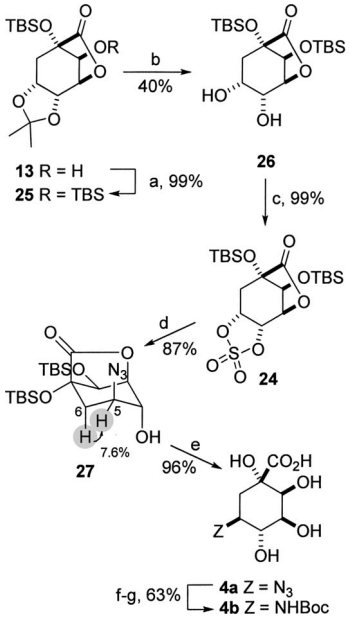
Synthesis of Compounds 4

γ-Amino acid **4b** was synthesized via γ-azido acid **4a**, which was obtained by nucleophilic ring opening of cyclic sulfate **24** (Scheme 10). This key step was expected to take place mainly at C-5, the less congested side of the sulfate **24**.



Scheme 10.

The key intermediate **24** was prepared in three steps from carbolactone **13** (Scheme 11). Initial protection of the free hydroxy group of **13**, followed by acid removal of the isopropylidene acetal of **25**, gave diol **26**, which was converted into cyclic sulfate **24** as described above. Subsequent azidolysis of sulfate **24** with sodium azide in the presence of a catalytic amount of 15-crown ether in DMF at 90 °C afforded azido alcohol **27** as a single regioisomer. The stereochemistry of the azidolysis was confirmed by NOE experiments. Irradiation of 6-H_{axial} led to enhancement of the signal for 5-H (7.6%). The regiochemistry of the reaction can be explained in terms of an axial attack of the azide anion from the less hindered side of the cyclic sulfate.

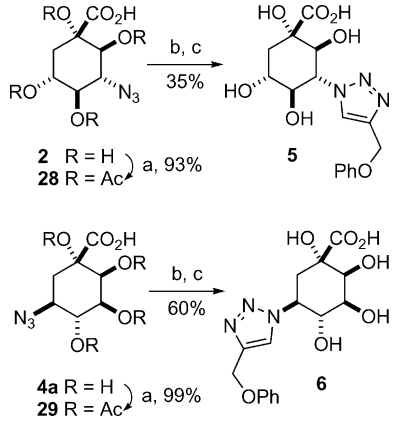


Scheme 11. Reagents and conditions: (a) TBSOTf, Py, DCM, 0 °C → r.t.; (b) AcOH (aq., 80%), 65 °C; (c) (i) $SOCl_2$, Et_3N, DCM, r.t., (ii) $RuCl_3·3H_2O$ (cat.), $NaIO_4$, H_2O, CCl_4, CH_3CN, r.t.; (d) (i) NaN_3, DMF, 90 °C, (ii) H_2SO_4 (70%), THF, r.t.; (e) (i) TFA (aq., 50%), 70 °C, (ii) LiOH, r.t., (iii) Amberlite IR-120 (H^+), r.t.; (f) Ac_2O, Py, 0 °C → r.t.; (g) H_2, PtO_2 (cat.), Boc_2O, THF, r.t.; (h) (i) LiOH, r.t., (ii) Amberlite IR-120 (H^+), r.t.

Acid removal of the TBS protecting groups, basic hydrolysis of the carbolactone and protonation with an ion-exchange resin led to azido acid **4a**. Finally, catalytic hydrogenolysis of the acetyl-protected derivative of **4a** in the presence of di-*tert*-butyl dicarbonate, followed by hydrolysis of the acetyl groups, afforded the desired γ-amino acid **4b** in 63% yield.

Synthesis of Triazoles 5 and 6

Finally, we explored the reactivities of azides **2** and **4a** in 1,3-cycloaddition reactions with alkynes to form triazoles (Scheme 12). Copper(I)-catalyzed cycloaddition reactions between alkynes and azides do not usually require protection of any hydroxy groups that may be present in both reagents. In our case, however, purification of the corresponding triazoles **5** and **6** proved difficult, so we decided to carry out the cycloaddition reactions on the acetyl-protected azides **28** and **29**, which would be expected to provide less polar triazole derivatives. Indeed, treatment of acetyl-protected azides **28** and **29** with phenyl propargyl ether under standard Sharpless click conditions efficiently afforded the corresponding triazoles. The reactions were regioselective in both cases, and only single regioisomers were obtained. Finally, basic removal of the acetyl protecting groups from the resulting cycloadducts, followed by protonation with an ion-exchange resin, led to triazoles **5** and **6**, respectively, in 33% and 60% overall yields.



Scheme 12. Reagents and conditions: (a) Ac_2O, Py, 0 °C → r.t.; (b) $PhOCH_2C{\equiv}CH$, sodium ascorbate, *t*BuOH/H_2O, $CuSO_4$, r.t.; (c) (i) LiOH, r.t., (ii) Amberlite IR-120 (H^+), r.t.

Conclusions

Regioselective ring-opening of cyclic sulfates **7** and **24**, derived from inexpensive, commercially available (–)-quinic acid, with azide anion can be used for the efficient synthesis of azido acids and Boc-γ-amino acids **1**–**4**. The equatorial substituent at the C-1 position has been successfully used to control the facial selectivity of the ring-opening reaction, as well as to direct the regioselective formation of the cyclic sulfate **7**.

The Sn-mediated oxidation of cyclic-1,2-diol **15** by *N*-bromosuccinimide and the stereoselective reduction of the corresponding α-hydroxy ketones **17** and **18** have been studied and used in the synthesis of compounds **2** and **3** – 4- and 5-epimers of **1** –, respectively. The axial free hydroxy group of α-hydroxy ketone **17** directs the hydride attack from the same side of the hydroxy group. However, no significant influence was observed for the reduction of α-hydroxy ketone **18**.

Finally, the reactivities of azides **2** and **4a** with alkynes in click chemistry techniques was explored and is demonstrated with triazoles **5** and **6**. The efficiency and high regioselectivity achieved make the azide functions present in derivatives **2** and **4a** an attractive means to link these highly hydroxylated acid moieties to polymers or bioactive molecular entities.

The *cis*- and *trans*-γ-cyclohexane amino acid entities reported here, functionalized with many stereochemically diverse hydroxy groups, may be used in the stereocontrolled assembly of simple or complex molecules with tailored properties, as well as in the synthesis of new oligosaccharides, such as validamycin derivatives,[15] and peptidomimetics.

Experimental Section

General Procedures: All starting materials and reagents were commercially available and used without further purification. FT-IR spectra were recorded as NaCl plates or KBr discs. $[a]_D$ values are given in 10^{-1} deg cm^2 g^{-1}. ^{1}H NMR spectra (250, 300, 400 and 500 MHz) and ^{13}C NMR spectra (63, 75, 100 and 125 MHz) were measured in deuterated solvents. *J* values are given in Hertz. NMR assignments were determined by a combination of 1D, NOE, COSY, and DEPT-135 experiments. All procedures involving the use of ion-exchange resins were carried out at room temperature, with use of Mili-Q deionized water. Amberlite IR-120 (H^+) (cation exchanger) was washed alternately with water, NaOH (10%), water, HCl (10%), and finally water before use.

(1*S*,3*R*,4*R*,5*R*)-1-(*tert*-Butyldimethylsilyloxy)-4,5-*O*-isopropylidenecyclohexane-1,3-carbolactone (10): *tert*-Butyldimethylsilyl trifluoromethanesulfonate (6.44 mL, 28.04 mmol) was added under an inert gas and at 0 °C to a stirred solution of the alcohol **9**[7] (4.0 g, 18.69 mmol) in dry dichloromethane (62 mL) and pyridine (2.64 mL, 32.70 mmol). The resulting solution was stirred at 0 °C for 30 min and at room temperature for 15 h. The reaction mixture was diluted with dichloromethane and water. The aqueous layer was acidified with HCl (10%), and the organic phase was separated. The aqueous layer was extracted twice with dichloromethane. All the combined organic extracts were dried (anh. Na_2SO_4) and filtered, and the solvents were evaporated. The obtained residue was purified by flash chromatography, with elution with ethyl acetate/hexanes (10:90) to yield silyl ether **10** (6.06 g, 99%) as white needles. $[a]_D^{20}$ = +1.9 (*c* = 1.1, $CHCl_3$). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 4.56 (dd, *J* = 6.0, 2.5 Hz, 1 H, 4-H), 4.40 (td, *J* = 7.5, 2.9 Hz, 1 H, 5-H), 4.19 (m, 1 H, 3-H), 2.47 (d, *J* = 11.7 Hz, 1 H, 2-H_{ax}), 2.35 (ddd, *J* = 14.7, 7.5, 2.2 Hz, 1 H, 6-H_{ax}), 2.23–2.15 (m, 1 H, 2-H_{eq}), 1.99 (dd, *J* = 14.7, 2.9 Hz, 1 H, 6-H_{eq}), 1.44 (s, 3 H, CH_3), 1.24 (s, 3 H, CH_3), 0.82 [s, 9 H, $C(CH_3)_3$], 0.10 (s, 3 H, $SiCH_3$), 0.06 (s, 3 H, $SiCH_3$) ppm. ^{13}C NMR (63 MHz, $CDCl_3$): δ = 176.9 (C), 109.3 (C), 74.7 (CH), 73.1 (C), 72.0 (CH), 71.4 (CH), 39.1 (CH_2), 35.3 (CH_2), 26.9 (CH_3), 25.4 [$C(CH_3)_3$], 24.1 (CH_3), 17.8 [$C(CH_3)_3$], –3.1 ($SiCH_3$) and –3.2 ($SiCH_3$) ppm. IR (KBr): $\tilde{\nu}$ = 1804 (C=O) cm^{-1}. MS (CI): *m*/*z* = 329 $[M + H]^+$. HRMS: calcd. for $C_{16}H_{29}O_5Si$ $[M + H]^+$ 329.1784; found 329.1796. $C_{16}H_{28}O_5Si$ (328.48): calcd. C 58.50, H 8.59; found C 58.55, H 8.91.

Methyl (1*R*,3*R*,4*S*,5*R*)-1-(*tert*-Butyldimethylsilyloxy)-3-hydroxy-4,5-*O*-isopropylidenecyclohexane-1-carboxylate (11): Potassium cyanide (95 mg, 1.46 mmol) was added under argon to a stirred solution of the carbolactone **10** (400 mg, 1.22 mmol) in dry methanol (12.2 mL). The resulting solution was stirred at room temperature for 1 h. Dichloromethane and water were added. The organic layer was separated, and the aqueous layer was extracted with dichloromethane (3×). All the combined organic extracts were dried (anh. Na_2SO_4) and filtered, and the solvents were evaporated. The obtained residue was purified by flash chromatography, with elution with a gradient of ethyl acetate/hexane (25:75 to 50:50) to yield alcohol **11** (358 mg, 82%) as a light yellow, amorphous solid. $[a]_D^{20}$ = –12.8 (*c* = 1.3, $CHCl_3$). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 4.36 (dd, *J* = 11.3, 5.6 Hz, 1 H, 4-H), 4.13–4.04 (m, 1 H, 5-H), 3.90 (t, *J* = 6.2 Hz, 1 H, 3-H), 3.70 (s, 3 H, OCH_3), 2.94 (d, *J* = 3.0 Hz, 1 H, OH), 2.23 (dd, *J* = 14.8, 5.6 Hz, 1 H, 2-H_{ax}), 2.03 (m, 2 H, 2-H_{eq} + 6-H_{eq}), 1.87 (dd, *J* = 13.8, 9.8 Hz, 1 H, 6-H_{ax}), 1.47 (s, 3 H, CH_3), 1.32 (s, 3 H, CH_3), 0.85 [s, 9 H, $C(CH_3)_3$], 0.04 (s, 6 H, 2× $SiCH_3$) ppm. ^{13}C NMR (63 MHz, $CDCl_3$): δ = 175.0 (C), 108.7 (C), 79.6 (CH), 75.7 (C), 72.7 (CH), 67.8 (CH), 52.2 (CH_3), 39.7 (CH_2), 37.2 (CH_2), 28.1 (CH_3), 25.7 [$C(CH_3)_3$], 25.5 (CH_3), 18.2 [$C(CH_3)_3$], –3.3 ($SiCH_3$), –3.4 ($SiCH_3$) ppm. IR (KBr): $\tilde{\nu}$ = 3565 (O–H) and 1725 (C=O) cm^{-1}. MS (CI): *m*/*z* = 361 $[M + H]^+$. HRMS: calcd. for $C_{17}H_{33}O_6Si$ $[M + H]^+$ 361.2046; found 361.2034. $C_{17}H_{32}O_6Si$ (360.52): calcd. C 56.64, H 8.95; found C 56.30, H 9.02.

Methyl (1*S*,4*S*,5*R*)-1-(*tert*-Butyldimethylsilyloxy)-4,5-*O*-isopropylidenecyclohex-2-ene-1-carboxylate (8): Freshly distilled trifluoroacetic anhydride (55 μL, 0.32 mmol) was added at 0 °C under argon to a stirred solution of the alcohol **11** (653 mg, 1.82 mmol) in dry dichloromethane (18.2 mL) and dry pyridine (0.37 mL, 4.55 mmol). The resulting mixture was stirred at this temperature for 45 min and then diluted successively with dichloromethane and water. The organic phase was separated, and the aqueous layer was extracted with dichloromethane (2×). All combined organic extracts were washed with $CuSO_4$ (sat.), dried (anh. Na_2SO_4), filtered and concentrated under reduced pressure. The obtained yellow oil was dissolved in dry chloroform (9.1 mL), DBU (0.35 mL, 2.37 mmol) was added, and the mixture was heated at reflux under argon for 24 h. After the mixture had cooled to room temperature, water and dichloromethane were added. The organic layer was separated, and the aqueous phase was extracted with dichloromethane (2×). All the combined organic extracts were washed twice with $NaHCO_3$ (sat.), dried (anh. Na_2SO_4) and filtered, and the solvents were evaporated. The obtained residue was purified by flash chromatography, with elution with ethyl acetate/hexane (5:95) to afford alkene **8** (615 mg, 99%) as a colourless oil. $[a]_D^{20}$ = +104.4 (*c* = 1.2, $CHCl_3$). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 5.90 (br. s, 2 H, 2-H, 3-H), 4.56–4.44 (m, 2 H, 4-H, 5-H), 3.68 (s, 3 H, OCH_3), 2.43 (dd, *J* = 12.3, 5.3 Hz, 1 H, 6-H_{eq}), 1.71 (ddd, *J* = 12.3, 10.7, 3.5 Hz, 1 H, 6-H_{ax}), 1.47 (s, 3 H, CH_3), 1.35 (s, 3 H, CH_3), 0.86 [s, 9 H, $C(CH_3)_3$], 0.09 (s, 3 H, $SiCH_3$), 0.07 (s, 3 H, $SiCH_3$) ppm. ^{13}C NMR (63 MHz, $CDCl_3$): δ = 173.0 (C), 135.2 (CH), 125.6 (CH), 109.8 (C), 76.0 (CH), 71.6 (CH), 70.0 (C), 52.2 (OCH_3), 38.2 (CH_2), 28.0 (CH_3), 25.6 [$C(CH_3)_3$], 25.6 (CH_3), 18.1 [$C(CH_3)_3$], –2.9 ($SiCH_3$),–3.3 ($SiCH_3$) ppm. IR (film): $\tilde{\nu}$ = 1739 (C=O) cm^{-1}. MS (CI): *m*/*z* = 343 $[M + H]^+$. HRMS: calcd. for $C_{17}H_{31}O_5Si$ $[M + H]^+$ 343.1941; found 343.1939. A small amount of the triflate intermediate was purified by flash chromatography, with elution with ethyl acetate/hexane (10:90 to 15:85), and characterized. Data for triflate intermediate: $[a]_D^{20}$ = –46.8 (*c* = 1.9, $CHCl_3$). ^{19}F NMR (282 MHz, $CDCl_3$): δ = –75.5 (s, 3 F, CF_3) ppm. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 5.26 (ddd, *J* = 11.8, 7.8, 4.0 Hz, 1 H, 5-H), 4.48 (td, *J* = 5.5, 2.3 Hz, 1 H, 3-H), 4.09 (dd, *J* = 7.8, 5.5 Hz, 1 H, 4-H), 3.75 (s, 3 H, OCH_3), 2.45–2.34 (m, 2 H, 6-H_{eq}, 2-H_{eq}), 2.22 (dd, *J* = 16.0, 5.5 Hz, 1 H, 6-H_{ax}), 2.00 (t, *J* = 12.6 Hz, 1 H, 2-H_{ax}), 1.52 (s, 3 H, CH_3), 1.36 (s, 3 H, CH_3), 0.90 [s, 9 H, $C(CH_3)_3$], 0.09 (s, 3 H, $SiCH_3$), 0.06 (s, 3 H, $SiCH_3$) ppm. ^{13}C

NMR (63 MHz, $CDCl_3$): δ = 172.8 (C), 118.4 (J_{CF} = 317 Hz, C), 109.8 (C), 87.6 (CH), 76.4 (CH), 76.3 (C), 73.6 (CH), 52.4 (OCH_3), 39.2 (CH_2), 35.1 (CH_2), 27.8 (CH_3), 25.6 [C(CH_3)$_3$], 25.6 (CH_3), 18.3 [C(CH_3)$_3$], –3.3 ($SiCH_3$), –4.0 ($SiCH_3$) ppm. IR (film): $\tilde{\nu}$ = 1743 (C=O) cm^{-1}. MS (CI): m/z = 493 $[M + H]^+$. HRMS: calcd. for $C_{18}H_{32}O_8SiSF_3$ $[M + H]^+$ 493.1539; found 493.1558.

Methyl (1*S*,2*S*,3*R*,4*S*,5*R*)-1-(*tert*-Butyldimethylsilyloxy)-2,3-dihydroxy-4,5-*O*-isopropylidenecyclohex-2-ene-1-carboxylate (12) and (1*S*,2*S*,3*S*,4*R*,5*R*)-1-(*tert*-Butyldimethylsilyloxy)-2-hydroxy-4,5-*O*-isopropylidenecyclohexane-1,3-carbolactone (13): A freshly made aqueous solution of osmium tetroxide (0.12 M, 3.8 mL, 0.46 mmol) was added at room temperature to a stirred solution of the alkene **8** (1.05 g, 3.07 mmol) and NMO (431 mg, 3.68 mmol) in dioxane/water (1:1, 36 mL). After the system had been stirred for about 20 h, ethyl acetate and then $Na_2S_2O_3$ (10%, 10 mL) were added. The resulting reaction mixture was stirred for 20 min. The organic layer was separated, and the aqueous layer was extracted with ethyl acetate (2×). All combined organic layers were dried (anh. Na_2SO_4), filtered and concentrated under reduced pressure. The obtained residue was purified by flash chromatography, with elution with ethyl acetate/hexane (30:70 then 50:50) to yield diol **12** (430 mg, 37%) as white needles and hydroxy lactone **13** (506 mg, 48%) as a light yellow amorphous solid.

12: $[\alpha]_D^{20}$ = –21.5 (c = 1.1, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$): δ = 4.43 (td, J = 5.5, 3.5 Hz, 1 H, 5-H), 4.14 (dd, J = 7.0, 5.5 Hz, 1 H, 4-H), 4.10–4.06 (m, 2 H, 2-H, 3-H), 3.75 (s, 3 H, OCH_3), 2.88 (d, J = 3.0 Hz, 1 H, OH), 2.58 (d, J = 5.0 Hz, 1 H, OH), 2.44 (dd, J = 15.5, 5.5 Hz, 1 H, 6-H_{ax}), 2.19 (dd, J = 15.5, 3.5 Hz, 1 H, 6-H_{eq}), 1.48 (s, 3 H, CH_3), 1.34 (s, 3 H, CH_3), 0.88 [s, 9 H, C(CH_3)$_3$], 0.08 (s, 3 H, $SiCH_3$), 0.04 (s, 3 H, $SiCH_3$) ppm. ^{13}C NMR (63 MHz, $CDCl_3$): δ = 173.2 (C), 108.7 (C), 77.9 (C), 77.9 (CH), 75.4 (CH), 72.9 (CH), 70.4 (CH), 52.2 (OCH_3), 31.8 (CH_2), 28.4 (CH_3), 25.8 (CH_3), 25.6 [C(CH_3)$_3$], 18.2 [C(CH_3)$_3$], –3.3 ($SiCH_3$),–4.0 ($SiCH_3$) ppm. IR (KBr): $\tilde{\nu}$ = 3385 (O–H), 1754 and 1735 (C=O) cm^{-1}. MS (CI): m/z = 377 $[M + H]^+$. HRMS: calcd. for $C_{17}H_{33}O_7Si$ $[M + H]^+$ 377.1996; found 377.1996. $C_{17}H_{32}O_7Si{\cdot}1/4H_2O$ (394.56): calcd. C 53.59, H 8.60; found C 53.67, H 8.98.

13: $[\alpha]_D^{20}$ = +14.9 (c = 1.2, $CHCl_3$). ^1H NMR (250 MHz, $CDCl_3$): δ = 4.52 (s, 1 H, 2-H), 4.46 (dd, J = 7.0, 2.0 Hz, 1 H, 5-H), 4.40 (m, 2 H, 4-H, 3-H), 2.82 (br. s, 1 H, OH), 2.51 (dd, J = 15.5, 7.0 Hz, 1 H, 6-H_{ax}), 2.25 (dd, J = 15.5, 2.0 Hz, 1 H, 6-H_{eq}), 1.51 (s, 3 H, CH_3), 1.31 (s, 3 H, CH_3), 0.90 [s, 9 H, C(CH_3)$_3$], 0.14 (s, 6 H, 2×$SiCH_3$) ppm. ^{13}C NMR (63 MHz, $CDCl_3$): δ = 177.2 (C), 109.4 (C), 81.0 (CH), 74.2 (CH), 74.0 (C), 72.4 (CH), 70.9 (CH), 36.0 (CH_2), 26.8 (CH_3), 25.6 [C(CH_3)$_3$], 23.9 (CH_3), 18.1 [C(CH_3)$_3$], –4.8 (2×CH_3) ppm. IR (KBr): $\tilde{\nu}$ = 3525 (O–H), 1800 (C=O) cm^{-1}. MS (CI): m/z = 345 $[M + H]^+$. HRMS: calcd. for $C_{16}H_{29}O_6Si$ $[M + H]^+$ 345.1733; found 345.1725. $C_{16}H_{28}O_6Si$ (344.48): calcd. C 55.79, H 8.19; found C 55.55, H 8.48.

(1*S*,2*S*,3*S*,4*R*,5*R*)-1-(*tert*-Butyldimethylsilyloxy)-2-hydroxy-4,5-*O*-isopropylidenecyclohexane-1,3-carbolactone (13) by Lactonisation of 12: Sodium hydride (1.6 mg, 65 μmol, ca. 60% in mineral oil) was added at 0 °C under argon to a stirred solution of the diol **12** (48 mg, 0.13 mmol) in dry THF (0.5 mL). The resulting suspension was stirred for 15 min. Diethyl ether and then water were added. The organic layer was separated, and the aqueous layer was extracted with diethyl ether (3×5 mL). All combined organic layers were dried (anh. Na_2SO_4) and concentrated under reduced pressure. The crude residue was purified by flash chromatography, with elution with diethyl ether/hexane (50:50), to afford carbolactone **13** (28.5 mg, 64%).

Sulfate 7: Thionyl chloride (575 μL, 7.91 mmol) was added at 0 °C under argon to a stirred solution of diol **12** (850 mg, 2.26 mmol) and dry triethylamine (1.26 mL, 9.04 mmol) in dry dichloromethane (45 mL). The ice bath was removed, and the resulting solution was stirred at room temperature for 3 h. The reaction mixture was cooled to 0 °C and diluted with dichloromethane and water. The organic phase was separated, and the aqueous layer was extracted with dichloromethane (3×). All the combined organic extracts were dried (anh. Na_2SO_4) and filtered, and the solvents were evaporated. The obtained residue was dissolved in a CCl_4/CH_3CN mixture (1:1, 45 mL) and cooled to 0 °C. Aqueous $NaIO_4$ (22.6 mL, 0.4 M) and $RuCl_3{\cdot}3H_2O$ (48 mg, 0.23 mmol) were then added. The resulting reaction mixture was stirred at this temperature for 2 h and then diluted with diethyl ether and water. The organic phase was separated and successively washed with water, $NaHCO_3$ (sat.) and NaCl (sat.). The organic extract was dried (anh. Na_2SO_4) and filtered, and the solvents were evaporated. The obtained residue was purified by flash chromatography, with elution with ethyl acetate/hexanes (10:90) to yield sulfate **7** (907 mg, 92%) as a white amorphous solid. $[\alpha]_D^{20}$ = –31.2 (c = 1.0, $CHCl_3$). ^1H NMR (250 MHz, $CDCl_3$): δ = 5.05 (br. s, 2 H, 2-H, 3-H), 4.58 (br. s, 2 H, 4-H, 5-H), 3.81 (s, 3 H, OCH_3), 2.50 (br d, J = 15.0 Hz, 1 H, 6-H_{ax}), 2.10 (br. d, J = 15.0 Hz, 1 H, 6-H_{eq}), 1.48 (s, 3 H, CH_3), 1.34 (s, 3 H, CH_3), 0.87 [s, 9 H, C(CH_3)$_3$], 0.12 (s, 3 H, $SiCH_3$), 0.09 (s, 3 H, $SiCH_3$) ppm. ^{13}C NMR (63 MHz, $CDCl_3$): δ = 169.9 (C), 110.0 (C), 85.3 (CH), 84.6 (CH), 75.8 (C), 74.6 (CH), 71.5 (CH), 52.8 (OCH_3), 33.4 (CH_2), 27.5 (CH_3), 25.6 [C(CH_3)$_3$], 24.7 (CH_3), 18.2 [C(CH_3)$_3$], –3.0 ($SiCH_3$), –3.9 ($SiCH_3$) ppm. IR (KBr): $\tilde{\nu}$ = 1740 (C=O) cm^{-1}. MS (CI): m/z = 439 $[M + H]^+$. HRMS: calcd. for $C_{17}H_{31}O_9SiS$ $[M + H]^+$ 439.1458; found 439.1464. $C_{17}H_{30}O_9SSi$ (438.57): calcd. C 46.56, H 6.89; found C 46.58, H 6.87.

Methyl (1*S*,2*S*,3*S*,4*S*,5*R*)-3-Azido-1-(*tert*-butyldimethylsilyloxy)-2-hydroxy-4,5-*O*-isopropylidenecyclohexane-1-carboxylate (14): A solution of sulfate **7** (804 mg, 1.84 mmol) in dry DMF (46 mL) was treated with sodium azide (471 mg, 7.36 mmol) and 15-crown-5 ether (35 μL, 0.18 mmol), and the resulting mixture was heated at 90 °C for 2.5 h. After the mixture had cooled to room temperature, the solvent was removed under reduced pressure. The obtained residue was dissolved in THF (92 mL) and aqueous H_2SO_4 (136 μL, 70%) and then heated at 50 °C for 1 h. After the mixture had cooled to room temperature, powdered $NaHCO_3$ (1.68 g) was added, and the resulting mixture was stirred for 20 min. The suspension was filtered through a plug of Celite, and the residue was washed with ethyl acetate. The filtrate and washings were concentrated under reduced pressure. The obtained residue was purified by flash chromatography, with elution with ethyl acetate/hexanes (20:80), to yield azide **14** (542 mg, 73%) as a white amorphous solid. $[\alpha]_D^{20}$ = +8.0 (c = 1.1, $CHCl_3$). ^1H NMR (250 MHz, $CDCl_3$): δ = 4.54–4.46 (m, 1 H, 5-H), 4.40 (dd, J = 4.0, 4.7 Hz, 1 H, 4-H), 4.04 (d, J = 10.5 Hz, 1 H, 2-H), 3.84 (dd, J = 4.0, 10.5 Hz, 1 H, 3-H), 3.76 (s, 3 H, OCH_3), 2.76 (br. s, 1 H, OH), 2.29 (dd, J = 13.5, 6.8 Hz, 1 H, 6-H_{ax}), 1.79 (dd, J = 9.5, 13.5 Hz, 1 H, 6-H_{eq}), 1.51 (s, 3 H, CH_3), 1.36 (s, 3 H, CH_3), 0.89 [s, 9 H, C(CH_3)$_3$], 0.13 (s, 3 H, $SiCH_3$), 0.09 (s, 3 H, $SiCH_3$) ppm. ^{13}C NMR (63 MHz, $CDCl_3$): δ = 172.8 (C), 109.6 (C), 80.0 (C), 76.1 (CH), 75.3 (CH), 72.6 (CH), 59.7 (CH), 52.3 (OCH_3), 38.8 (CH_2), 28.4 (CH_3), 26.2 (CH_3), 25.7 [C(CH_3)$_3$], 18.2 [C(CH_3)$_3$], –2.8 ($SiCH_3$),–3.3 ($SiCH_3$) ppm. IR (film): $\tilde{\nu}$ = 3504 (O–H), 2106 (N≡N), 1729 (C=O) cm^{-1}. MS (ESI): m/z = 424 $[M + Na]^+$. HRMS: calcd. for $C_{17}H_{31}O_6SiN_3Na$ $[M + Na]^+$ 424.1884; found 424.1874.

(1*S*,2*S*,3*R*,4*S*,5*R*)-3-Azido-1,2,4,5-tetrahydroxycyclohexane-1-carboxylic Acid (1a): A solution of acetal **14** (60 mg, 0.15 mmol) in aqueous TFA (1.5 mL, 50%) was heated at 70 °C for 3 h. The reac-

tion mixture was cooled to room temperature, and the solvent was removed under reduced pressure. A solution of the crude product in water was washed with ethyl acetate (3×) and lyophilised. The obtained residue was dissolved in water (1.4 mL), treated with aqueous lithium hydroxide (0.8 mL, 0.5 M) and stirred at room temperature for 4 h. The aqueous solution was treated with Amberlite IR-120 until pH = 6 was reached. The resin was filtered and washed with water. The filtrate and the washings were lyophilised to afford azido acid **1a** (34 mg, 97%) as a beige, amorphous solid. $[\alpha]_D^{20}$ = –4.5 (*c* = 1.3, H_2O). ^1H NMR (250 MHz, D_2O): δ = 4.15 (m, 2 H, 4-H, 5-H), 3.99 (dd, *J* = 10.8, 2.5 Hz, 1 H, 3-H), 3.85 (d, *J* = 10.8 Hz, 1 H, 2-H), 2.04 (m, 1 H, 6-H_{eq}), 1.91 (m, 1 H, 6-H_{ax}) ppm. ^{13}C NMR (100 MHz, D_2O): δ = 178.5 (C), 79.7 (C), 76.9 (CH), 74.1 (CH), 69.0 (CH), 66.2 (CH), 38.8 (CH_2) ppm. IR (KBr): $\tilde{\nu}$ = 3453 (O–H), 3391 (O–H), 3351 (O–H), 3297 (O–H), 2115 (N≡N), 1743 (C=O) cm^{-1}. MS (ESI) *m*/*z* = 256 $[M + Na]^+$. HRMS: calcd. for $C_7H_{11}O_6N_3Na$ $[M + Na]^+$ 256.0540; found 256.0540. A small amount of the **1a** methyl ester intermediate was characterized. White foam. $[\alpha]_D^{20}$ = –8.6 (*c* = 1.7, MeOH). ^1H NMR (400 MHz, D_2O): δ = 4.18 (m, 2 H, 4-H, 5-H), 4.02 (dd, *J* = 10.8, 2.8 Hz, 1 H, 3-H), 3.91 (d, *J* = 10.8 Hz, 1 H, 2-H), 3.84 (s, 3 H, OCH_3), 2.09 (dd, *J* = 13.2, 4.8 Hz, 1 H, 6-H_{eq}), 1.98 (dd, *J* = 13.2, 12.0 Hz, 1 H, 6-H_{ax}) ppm. ^{13}C NMR (100 MHz, D_2O): δ = 177.0 (C), 80.2 (C), 77.1 (CH), 74.0 (CH), 68.9 (CH), 66.2 (CH), 55.9 (CH_3), 38.7 (CH_2) ppm. IR (KBr): $\tilde{\nu}$ = 3410 (O–H), 2112 (N≡N), 1732 (C=O) cm^{-1}. MS (ESI): *m*/*z* = 270 $[M + Na]^+$. HRMS: calcd. for $C_8H_{13}O_6N_3Na$ $[M + Na]^+$ 270.0697; found 270.0706.

(1*S*,2*S*,3*R*,4*S*,5*R*)-3-(*tert*-Butoxycarbonylamino)-1,2,4,5-tetrahydroxycyclohexane-1-carboxylic Acid (1b): A solution of acid **1a** (13.6 mg, 0.058 mmol) in dry pyridine (0.2 mL) was treated under argon and at 0 °C with acetic anhydride (0.2 mL). The ice bath was removed, and the resulting mixture was stirred at room temperature for 36 h. The solvents were removed under reduced pressure through successive addition of toluene and acetonitrile and subsequent concentration. A suspension of the obtained residue, di-*tert*-butyl dicarbonate (16.4 mg, 0.075 mmol) and platinium(IV) oxide (5 mg) in dry THF (0.7 mL) was shaken under hydrogen at room temperature for 19 h. The mixture was filtered through a plug of Celite, and the residue was washed with methanol. The filtrate and washings were diluted with ethyl acetate and water. The organic layer was separated, washed with water (2×), dried (anh. Na_2SO_4) and concentrated under reduced pressure. A solution of the crude reaction mixture in THF (0.4 mL) was treated with aqueous lithium hydroxide (0.7 mL, 0.5 M) and stirred at room temperature for 30 min. THF was removed under reduced pressure, and the aqueous solution was then diluted with water and washed with ethyl acetate (3×). The aqueous extract was treated with Amberlite IR-120 until pH = 6 was reached. The resin was filtered and washed with water. The filtrate and the washings were lyophilised to afford Boc-amino acid **1b** (10 mg, 56%) as an amorphous, beige solid. $[\alpha]_D^{20}$ = –10.6 (*c* = 1.0, H_2O). ^1H NMR (400 MHz, D_2O): δ = 4.21 (m, 2 H, 4-H, 5-H), 4.01 (m, 1 H, 3-H), 3.64 (d, *J* = 11.2 Hz, 1 H, 2-H), 1.99 (m, 1 H, 6-H_{eq}), 1.87 (t, *J* = 12.4 Hz, 1 H, 6-H_{ax}), 1.47 {s, 9 H, $[C(CH_3)_3]$} ppm. ^{13}C NMR (100 MHz, D_2O): δ = 180.8 (C), 160.9 (C), 84.1 (C), 79.6 [*C*$(CH_3)_3$], 76.6 (CH), 74.7 (CH), 69.9 (CH), 56.8 (CH), 39.4 (CH_2) and 30.7 [C(*C*$H_3)_3$] ppm. IR (KBr): $\tilde{\nu}$ = 3400 (O–H), 1684 (C=O), 1616 (C=O) cm^{-1}. MS (ESI): *m*/*z* = 330 $[M + Na]^+$. HRMS: calcd. for $C_{12}H_{21}O_8NNa$ $[M + Na]^+$ 330.1159; found 330.1158.

Methyl (1*S*,2*S*,3*R*,4*S*,5*R*)-3-Azido-1,2-bis(*tert*-butyldimethylsilyloxy)-4,5-*O*-isopropylidenecyclohexane-1-carboxylate (16): A stirred solution of the alcohol **14** (402 mg, 1.00 mmol) and dry pyridine (0.14 mL, 1.75 mmol) in dry dichloromethane (3.3 mL) was cooled to 0 °C under argon and was then treated with TBSOTf (344 μL, 1.5 mmol). The resulting mixture was stirred at this temperature for 12 h and then diluted successively with dichloromethane and water. The aqueous layer was acidified with HCl (10%), and the organic phase was separated. The aqueous layer was extracted twice with dichloromethane. All combined organic extracts were dried (anh. Na_2SO_4), filtered and concentrated under reduced pressure. The obtained residue was purified by flash chromatography, with elution with ethyl acetate/hexane (10:90), to afford ether **16** (515 mg, 99%) as a light yellow oil. $[\alpha]_D^{20}$ = –21.6 (*c* = 1.0, $CHCl_3$). ^1H NMR (250 MHz, $CDCl_3$): δ = 4.48 (m, 2 H, 4-H, 5-H), 3.90 (d, *J* = 10.0 Hz, 1 H, 2-H), 3.81 (dd, *J* = 10.0, 3.3 Hz, 1 H, 3-H), 3.73 (s, 3 H, OCH_3), 2.27 (m, 1 H, 6-H_{ax}), 1.93 (m, 1 H, 6-H_{eq}), 1.51 (s, 3 H, CH_3), 1.35 (s, 3 H, CH_3), 0.88 [s, 9 H, $C(CH_3)_3$], 0.86 [s, 9 H, $C(CH_3)_3$], 0.19 (s, 3 H, $SiCH_3$), 0.18 (s, 3 H, $SiCH_3$), 0.12 (s, 3 H, $SiCH_3$), 0.05 (s, 3 H, $SiCH_3$) ppm. ^{13}C NMR (63 MHz, $CDCl_3$): δ = 173.6 (C), 109.3 (C), 81.4 (C), 76.3 (CH), 75.4 (CH), 72.3 (CH), 63.2 (CH), 51.7 (OCH_3), 38.6 (CH_2), 27.8 (CH_3), 26.2 (CH_3), 25.8 [C(*C*$H_3)_3$], 25.6 [C(*C*$H_3)_3$], 18.6 [*C*$(CH_3)_3$], 17.9 [*C*$(CH_3)_3$], –2.4 ($SiCH_3$), –3.1 ($SiCH_3$), –4.0 ($SiCH_3$), –4.7 ($SiCH_3$) ppm. IR (film): $\tilde{\nu}$ = 2104 (N≡N), 1761 and 1731 (C=O) cm^{-1}. MS (ESI): *m*/*z* = 538 $[M + Na]^+$. HRMS: calcd. for $C_{23}H_{45}O_6Si_2N_3Na$ $[M + Na]^+$ 538.2739; found 538.2734.

Methyl (1*S*,2*S*,3*R*,4*S*,5*R*)-3-Azido-1,2-bis(*tert*-butyldimethylsilyloxy)-4,5-dihydroxycyclohexane-1-carboxylate (15): A solution of isopropylidene acetal **16** (160 mg, 0.31 mmol) in aqueous acetic acid (5.2 mL, 80%) was heated at 65 °C for 3 h. The reaction mixture was cooled to room temperature, and the solvent was removed under reduced pressure. The obtained residue was purified by flash chromatography, with elution with ethyl acetate/hexane (30:70), to afford diol **15** (147 mg, 99%) as a light yellow oil. $[\alpha]_D^{20}$ = +0.8 (*c* = 1.6, $CHCl_3$). ^1H NMR (250 MHz, $CDCl_3$): δ = 4.11 (m, 2 H, 4-H, 5-H), 3.93 (d, *J* = 8.3 Hz, 1 H, 2-H), 3.75 (dd, *J* = 8.3, 3.3 Hz, 1 H, 3-H), 3.71 (s, 3 H, OCH_3), 3.04 (d, *J* = 4.0 Hz, 1 H, OH), 2.77 (d, *J* = 7.3 Hz, 1 H, OH), 2.07 (m, 2 H, 6-H), 0.88 [s, 9 H, $C(CH_3)_3$], 0.82 [s, 9 H, $C(CH_3)_3$], 0.18 (s, 3 H, $SiCH_3$), 0.14 (s, 3 H, $SiCH_3$), 0.08 (s, 3 H, $SiCH_3$), 0.06 (s, 3 H, $SiCH_3$) ppm. ^{13}C NMR (63 MHz, $CDCl_3$): δ = 172.8 (C), 80.2 (C), 75.5 (CH), 70.5 (CH), 67.3 (CH), 65.8 (CH), 51.8 (OCH_3), 37.4 (CH_2), 26.1 [C(*C*$H_3)_3$], 25.7 [C(*C*$H_3)_3$], 18.5 [*C*$(CH_3)_3$], 17.9 [*C*$(CH_3)_3$], –2.8 ($SiCH_3$), –3.0 ($SiCH_3$), –4.3 ($SiCH_3$), –4.7 ($SiCH_3$) ppm. IR (film): $\tilde{\nu}$ = 3417 (O–H), 2105 (N≡N), 1731 (C=O) cm^{-1}. MS (ESI): *m*/*z* = 498 $[M + Na]^+$. HRMS: calcd. for $C_{20}H_{41}O_6Si_2N_3Na$ $[M + Na]^+$ 498.2426; found 498.2421.

Methyl (1*S*,2*S*,3*R*,4*S*)-3-Azido-1,2-bis(*tert*-butyldimethylsilyloxy)-4-hydroxy-5-oxocyclohexane-1-carboxylate (17) and Methyl (1*S*,2*S*,3*S*,5*R*)-3-Azido-1,2-bis(*tert*-butyldimethylsilyloxy)-5-hydroxy-4-oxocyclohexane-1-carboxylate (18) by Sn-Mediated Oxidation of Diol 15: A solution of diol **15** (100 mg, 0.21 mmol) and Bu_2SnO (52 mg, 0.21 mmol) in dry toluene (10 mL) was heated under reflux with azeotropic removal of water in a Dean–Stark apparatus. After 24 h, the solution was cooled to room temperature, and the solvent was removed under reduced pressure. The obtained residue was dissolved, under an inert gas, in dry chloroform (2.3 mL) and then treated with NBS (41 mg, 0.23 mmol). The resulting mixture was stirred at room temperature for 1.5 h and then concentrated under reduced pressure. The obtained residue was purified by flash chromatography, with elution with ethyl acetate/hexane [(1) 5:95; (2) 10:90] to afford ketones **17** (22 mg, 22%) and **18** (64 mg, 64%).

17: Light orange oil. $[\alpha]_D^{20}$ = –1.8 (*c* = 2.3, $CHCl_3$). ^1H NMR (250 MHz, $CDCl_3$): δ = 4.64 (t, *J* = 4.5 Hz, 1 H, 3-H), 4.31 (m, 2

H, 4-H, 2-H), 3.74 (s, 3 H, OCH_3), 3.52 (d, J = 5.0 Hz, 1 H, OH), 3.29 (dd, J = 14.5, 1.0 Hz, 1 H, 6-H_{eq}), 2.76 (dd, J = 14.5, 1.3 Hz, 1 H, 6-H_{ax}), 0.87 [s, 9 H, $C(CH_3)_3$], 0.85 [s, 9 H, $C(CH_3)_3$], 0.21 (s, 3 H, $SiCH_3$), 0.09 (s, 3 H, $SiCH_3$), 0.03 (s, 6 H, 2×$SiCH_3$) ppm. ^{13}C NMR (63 MHz, $CDCl_3$): δ = 205.7 (C), 170.7 (C), 83.6 (C), 73.0 (CH), 73.0 (CH), 67.4 (CH), 52.4 (CH_3), 44.3 (CH_2), 25.5 [$C(CH_3)_3$], 25.4 [$C(CH_3)_3$], 18.2 [$C(CH_3)_3$], 17.7 [$C(CH_3)_3$], –3.5 ($SiCH_3$), –4.2 (2×$SiCH_3$),–5.5 ($SiCH_3$) ppm. IR (film): $\tilde{\nu}$ = 3481 (O–H), 2112 (N≡N), 1745 (C=O) cm^{-1}. MS (ESI): m/z = 496 [M + Na]$^+$. HRMS: calcd. for $C_{20}H_{39}O_6Si_2N_3Na$ [M + Na]$^+$ 496.2270; found 496.2262.

18: Light yellow oil. $[\alpha]_D^{20}$ = –36.0 (c = 2.0, $CHCl_3$). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 4.75 (dd, J = 11.0, 8.0 Hz, 1 H, 5-H), 4.41 (d, J = 8.0 Hz, 1 H, 2-H), 3.80 (s, 3 H, OCH_3), 3.74 (d, J = 8.0 Hz, 1 H, 3-H), 3.37 (br. s, 1 H, OH), 2.77 (dd, J = 14.0, 8.0 Hz, 1 H, 6-H_{eq}), 1.73 (dd, J = 11.0, 14.0 Hz, 1 H, 6-H_{ax}), 0.86 [s, 9 H, $C(CH_3)_3$], 0.85 [s, 9 H, $C(CH_3)_3$], 0.17 (s, 3 H, $SiCH_3$), 0.14 (s, 3 H, $SiCH_3$), 0.09 (s, 3 H, $SiCH_3$), 0.08 (s, 3 H, $SiCH_3$) ppm. ^{13}C NMR (63 MHz, $CDCl_3$): δ = 204.4 (C), 172.5 (C), 81.3 (CH), 79.2 (C), 69.7 (CH), 69.1 (CH), 52.2 (OCH_3), 40.5 (CH_2), 26.0 [$C(CH_3)_3$], 25.7 [$C(CH_3)_3$], 18.4 [$C(CH_3)_3$], 17.9 [$C(CH_3)_3$], –2.9 (2×$SiCH_3$), –4.6 (2×$SiCH_3$) ppm. IR (film): $\tilde{\nu}$ = 3454 (O–H), 2111 (N≡N), 1760 (C=O), 1732 (C=O) cm^{-1}. MS (ESI): m/z = 496 [M + Na]$^+$. HRMS: calcd. for $C_{20}H_{39}O_6Si_2N_3Na$ [M + Na]$^+$ 496.2270; found 496.2261.

Methyl (1*S*,2*S*,3*R*,4*S*,5*R*)-3-Azido-1,2,5-tris(*tert*-butyldimethylsilyloxy)-4-hydroxycyclohexane-1-carboxylate (21b): A stirred solution of the diol **15** (134 mg, 0.28 mmol) and dry pyridine (30 μL, 0.36 mmol) in dry dichloromethane (0.9 mL) was cooled to 0 °C under argon and was then treated with TBSOTf (64 μL, 0.28 mmol). The resulting mixture was stirred at this temperature for 1 h, and dry pyridine (10 μL, 0.12 mmol) and TBSOTf (20 μL, 0.09 mmol) were then added. The resulting mixture was stirred at room temperature for 2 h and then diluted successively with dichloromethane and water. The aqueous layer was acidified with HCl (10%), and the organic phase was separated. The aqueous layer was extracted with dichloromethane (2×). All combined organic extracts were dried (anh. Na_2SO_4), filtered and concentrated under reduced pressure. The obtained residue was purified by flash chromatography, with elution with ethyl acetate/hexane (5:95), to afford silyl ether **21b** (149 mg, 90%) as a light yellow oil. $[\alpha]_D^{20}$ = –24.4 (c = 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.31 (ddd, J = 11.2, 5.2, 2.8 Hz, 1 H, 5-H), 4.10 (t, J = 2.8 Hz, 1 H, 4-H), 3.90 (d, J = 10.0 Hz, 1 H, 2-H), 3.72 (s, 3 H, OCH_3), 3.58 (dd, J = 10.0, 2.8 Hz, 1 H, 3-H), 2.44 (br. s, 1 H, OH), 2.03 (dd, J = 11.2, 13.2 Hz, 1 H, 6-H_{ax}), 1.91 (dd, J = 5.2, 13.2 Hz, 1 H, 6-H_{eq}), 0.89 [s, 9 H, $C(CH_3)_3$], 0.88 [s, 9 H, $C(CH_3)_3$], 0.86 [s, 9 H, $C(CH_3)_3$], 0.19 (s, 3 H, CH_3), 0.17 (s, 3 H, CH_3), 0.11 (s, 3 H, $SiCH_3$), 0.08 (s, 3 H, $SiCH_3$), 0.06 (s, 3 H, $SiCH_3$), 0.06 (s, 3 H, $SiCH_3$) ppm. ^{13}C NMR (63 MHz, $CDCl_3$): δ = 173.7 (C), 80.8 (C), 76.0 (CH), 72.5 (CH), 67.7 (CH), 64.7 (CH), 51.5 (OCH_3), 39.1 (CH_2), 26.2 [$C(CH_3)_3$], 25.8 [$C(CH_3)_3$], 25.7 [2×$C(CH_3)_3$], 18.5 [$C(CH_3)_3$], 18.0 [2×$C(CH_3)_3$], –2.5 (CH_3), –2.8 (CH_3), –4.0 ($SiCH_3$),–4.8 (3×$SiCH_3$) ppm. IR (film): $\tilde{\nu}$ = 3466 (O–H), 2102 (N≡N), 1732 (C=O) cm^{-1}. MS (ESI): m/z = 590 [M + H]$^+$. HRMS: calcd. for $C_{26}H_{56}O_6Si_3N_3$ [M + H]$^+$ 590.3471; found 590.3470.

Methyl (1*S*,2*S*,3*S*,5*R*)-3-Azido-1,2,5-tris(*tert*-butyldimethylsilyloxy)-4-oxocyclohexane-1-carboxylate (19) by Swern Oxidation of 21b: A flame-dried round-bottomed flask was charged with dry DMSO (27 μL, 0.38 mmol) and dry dichloromethane (1.5 mL). The resulting solution was cooled to –60 °C, and then freshly distilled TFAA (48 μL, 0.34 mmol) was added. After the mixture had been stirred for 20 min, a solution of the alcohol **21b** (113 mg, 0.19 mmol) in dry dichloromethane (0.4 mL) was added by cannula. Dry triethylamine (0.11 mL, 0.78 mmol) was added after 1.5 h, and the reaction mixture was allowed to warm slowly to room temperature. After 8 h, the reaction mixture was diluted successively with dichloromethane and water. The aqueous layer was acidified with HCl (10%), and the organic phase was separated. The aqueous layer was extracted three times with dichloromethane. All combined organic extracts were dried (anh. Na_2SO_4), filtered and concentrated under reduced pressure. The obtained residue was purified by flash chromatography, with elution with ethyl acetate/hexane (5:95), to afford ketone **19** (109 mg, 98%) as a colourless oil. $[\alpha]_D^{20}$ = –28.4 (c = 1.4, $CHCl_3$). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 4.79 (dd, J = 11.0, 7.8 Hz, 1 H, 5-H), 4.19 (d, J = 8.0 Hz, 1 H, 3-H), 3.78 (s, 3 H, OCH_3), 3.69 (d, J = 8.0 Hz, 1 H, 2-H), 2.57 (dd, J = 14.0, 7.8 Hz, 1 H, 6-H_{eq}), 1.87 (dd, J = 14.0, 11.0 Hz, 1 H, 6-H_{ax}), 0.88 [s, 9 H, $C(CH_3)_3$], 0.85 [s, 18 H, 2×$C(CH_3)_3$], 0.15 (s, 3 H, $SiCH_3$), 0.12 (s, 3 H, $SiCH_3$), 0.11 (s, 3 H, $SiCH_3$), 0.07 (s, 6 H, 2×$SiCH_3$), 0.03 (s, 3 H, CH_3) ppm. ^{13}C NMR (63 MHz, $CDCl_3$): δ = 201.7 (C), 172.8 (C), 80.7 (CH), 79.2 (C), 71.1 (CH), 69.1 (CH), 52.0 (CH_3), 41.6 (CH_2), 26.0 [$C(CH_3)_3$], 25.7 [2×$C(CH_3)_3$], 18.4 [$C(CH_3)_3$], 18.3 [$C(CH_3)_3$], 17.9 [$C(CH_3)_3$], –2.9 (2×$SiCH_3$), –4.6 (3×$SiCH_3$), –5.4 ($SiCH_3$) ppm. IR (film): $\tilde{\nu}$ = 2109 (N≡N), 1747 (C=O), 1732 (C=O) cm^{-1}. MS (ESI): m/z = 610 [M + Na]$^+$. HRMS: calcd. for $C_{26}H_{53}O_6Si_3N_3Na$ [M + Na]$^+$ 610.3134; found 610.3137.

Methyl (1*S*,2*S*,3*S*,5*R*)-3-Azido-1,2,5-tris(*tert*-butyldimethylsilyloxy)-4-oxocyclohexane-1-carboxylate (19) by Preparation from 18: A stirred solution of the α-hydroxy ketone **18** (167 mg, 0.35 mmol) and dry pyridine (50 μL, 0.61 mmol) in dry dichloromethane (1.5 mL) was cooled to 0 °C under argon and was then treated with TBSOTf (122 μL, 0.53 mmol). The resulting mixture was stirred at this temperature for 20 min and 4 h at room temperature. The resulting mixture was diluted successively with dichloromethane and water. The aqueous layer was acidified with HCl (10%), and the organic phase was separated. The aqueous layer was extracted with dichloromethane (2×). All combined organic extracts were dried (anh. Na_2SO_4), filtered and concentrated under reduced pressure. The obtained residue was purified by flash chromatography, with elution with ethyl acetate/hexane (5:95), to afford silyl ether **19** (197 mg, 96%).

Methyl (1*S*,2*S*,3*S*,5*R*)-3-Azido-1,2-bis(*tert*-butyldimethylsilyloxy)-5-(*tert*-butyldiphenylsilyloxy)-4-oxocyclohexane-1-carboxylate (20): A stirred solution of the alcohol **18** (34 mg, 0.07 mmol) and imidazole (15 mg, 0.22 mmol) in dry *N*,*N*-dimethylformamide (0.5 mL) was cooled to 0 °C under argon and was then treated with *tert*-butylchlorodiphenylsilane (22 μL, 0.09 mmol). The resulting mixture was stirred at room temperature for 48 h and was then diluted successively with diethyl ether and water. The aqueous layer was acidified with HCl (10%), and the organic phase was separated. The aqueous layer was extracted with diethyl ether (2×). All combined organic extracts were dried (anh. Na_2SO_4), filtered and concentrated under reduced pressure. The obtained residue was purified by flash chromatography, with elution with ethyl acetate/hexane [(1) 1:99; (2) 2:98] to afford silyl ether **20** (43 mg, 85%) as a light yellow oil. $[\alpha]_D^{20}$ = +5.1 (c = 1.3, $CHCl_3$). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.67 (m, 4 H, 4×ArH), 7.47–7.33 (m, 6 H, 6×ArH), 4.65 (ddd, J = 11.8, 7.3, 1.0 Hz, 1 H, 5-H), 4.05 (dd, J = 8.5, 1.0 Hz, 1 H, 3-H), 3.62 (d, J = 8.5 Hz, 1 H, 2-H), 3.54 (s, 3 H, OCH_3), 2.29 (dd, J = 13.5, 7.3 Hz, 1 H, 6-H_{eq}), 1.86 (dd, J = 13.5, 11.8 Hz, 1 H, 6-H_{ax}), 1.10 [s, 9 H, $C(CH_3)_3$], 0.84 [s, 9 H, $C(CH_3)_3$], 0.78 [s, 9 H, $C(CH_3)_3$], 0.12 (s, 3 H, $SiCH_3$), 0.08 (s, 3 H, $SiCH_3$), 0.02 (s, 3 H, $SiCH_3$), –0.10 (s, 3 H, $SiCH_3$) ppm. ^{13}C NMR (63 MHz,

$CDCl_3$): δ = 201.0 (C), 172.1 (C), 135.8 (2×CH), 135.7 (2×CH), 133.2 (C), 132.6 (C), 130.0 (2×CH), 127.8 (2×CH), 127.7 (2×CH), 80.8 (CH), 79.2 (C), 71.4 (CH), 69.3 (CH), 51.9 (OCH_3), 41.3 (CH_2), 26.8 [C(CH_3)$_3$], 26.0 [C(CH_3)$_3$], 25.6 [C(CH_3)$_3$], 19.2 [C(CH_3)$_3$], 18.4 [C(CH_3)$_3$], 17.9 [C(CH_3)$_3$], –2.9 ($SiCH_3$), –3.0 ($SiCH_3$), –4.6 ($SiCH_3$), –4.7 ($SiCH_3$) ppm. IR (film): $\tilde{\nu}$ = 2112 (N≡N), 1747 (C=O), 1726 (C=O) cm^{-1}. MS (ESI): *m/z* = 734 [M + Na]$^+$. HRMS: calcd. for $C_{36}H_{57}O_6Si_3N_3Na$ [M + Na]$^+$ 734.3447; found 734.3443.

Reduction of Ketones 18–20 with $NaBH_4$. General Procedure: Sodium borohydride (1 mmol) was added under argon to a stirred solution of the ketone (1 mmol) in dry methanol (0.1 M). The resulting reaction mixture was stirred at room temperature for 1–2 h and was then diluted with ethyl acetate and water. The resulting mixture was treated with aqueous H_2SO_4 (5%) until pH = 5 was reached, and the organic layer was separated. The aqueous phase was extracted with ethyl acetate (3×). All the combined organic extracts were dried (anh. Na_2SO_4), filtered and concentrated under reduced pressure. The resulting residue was purified by flash chromatography.

22a: Colourless oil. $[\alpha]_D^{20}$ = +15.5 (*c* = 1.3, $CHCl_3$). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 4.10 (m, 1 H, 5-H), 3.76 (s, 3 H, OCH_3), 3.64 (t, *J* = 9.5 Hz, 1 H, 4-H), 3.40 (d, *J* = 9.5 Hz, 1 H, 2-H), 3.32 (t, *J* = 9.5 Hz, 1 H, 3-H), 2.89 (br. s, 1 H, OH), 2.58 (br. s, 1 H, OH), 2.29 (dd, *J* = 4.8, 13.5 Hz, 1 H, 6-H_{eq}), 1.57 (dd, *J* = 12.0, 13.5 Hz, 1 H, 6-H_{ax}), 0.87 [s, 9 H, C(CH_3)$_3$], 0.86 [s, 9 H, C(CH_3)$_3$], 0.21 (s, 3 H, $SiCH_3$), 0.15 (s, 3 H, $SiCH_3$), 0.10 (s, 3 H, $SiCH_3$), 0.08 (s, 3 H, $SiCH_3$) ppm. ^{13}C NMR (63 MHz, $CDCl_3$): δ = 173.0 (C), 80.7 (C), 79.6 (CH), 76.9 (CH), 68.6 (CH), 68.5 (CH), 51.8 (OCH_3), 40.5 (CH_2), 26.3 [C(CH_3)$_3$], 25.8 [C(CH_3)$_3$], 18.5 [C(CH_3)$_3$], 18.0 [C(CH_3)$_3$], –2.5 ($SiCH_3$), –2.7 ($SiCH_3$), –4.0 ($SiCH_3$), –4.6 ($SiCH_3$) ppm. IR (film): $\tilde{\nu}$ = 3375 (O–H), 2110 (N≡N), 1757 and 1732 (C=O) cm^{-1}. MS (CI): *m/z* = 461 [M + H – CH_3]$^+$. HRMS: calcd. for $C_{19}H_{39}O_6N_3Si_2$ [M+ H – CH_3]$^+$ 461.2377; found 461.2371.

22b: Beige solid. $[\alpha]_D^{20}$ = –7.4 (*c* = 1.1, $CHCl_3$). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 4.08 (m, 1 H, 5-H), 3.75 (s, 3 H, OCH_3), 3.61 (t, *J* = 10.0 Hz, 1 H, 3-H), 3.36 (m, 2 H, 4-H, 2-H), 2.52 (br. s, 1 H, OH), 2.14 (dd, *J* = 4.8, 13.5 Hz, 1 H, 6-H_{eq}), 1.54 (dd, *J* = 11.8, 13.5 Hz, 1 H, 6-H_{ax}), 0.88 [s, 9 H, C(CH_3)$_3$], 0.87 [s, 9 H, C(CH_3)$_3$], 0.85 [s, 9 H, C(CH_3)$_3$], 0.19 (s, 3 H, $SiCH_3$), 0.13 (s, 3 H, $SiCH_3$), 0.09 (s, 3 H, $SiCH_3$), 0.08 (s, 3 H, $SiCH_3$), 0.06 (s, 6 H, 2×$SiCH_3$) ppm. ^{13}C NMR (63 MHz, $CDCl_3$): δ = 173.1 (C), 80.7 (C), 79.4 (CH), 77.2 (CH), 70.1 (CH), 67.5 (CH), 51.7 (OCH_3), 41.8 (CH_2), 26.2 [C(CH_3)$_3$], 25.8 [C(CH_3)$_3$], 25.7 [2×C(CH_3)$_3$], 18.5 [C(CH_3)$_3$], 18.0 [C(CH_3)$_3$], 18.0 [C(CH_3)$_3$], –2.5 ($SiCH_3$), –2.8 ($SiCH_3$), –4.2 ($SiCH_3$), –4.5 (2×$SiCH_3$), –4.6 ($SiCH_3$) ppm. IR (KBr): $\tilde{\nu}$ = 3481 (O–H), 2110 (N≡N), 1738 (C=O) cm^{-1}. MS (CI): *m/z* = 590 [M + H]$^+$. HRMS: calcd. for $C_{26}H_{56}O_6N_3Si_3$ [M + H]$^+$ 590.3477; found 590.3462.

21c: Colourless oil. $[\alpha]_D^{20}$ = –1.83 (*c* = 1.2, $CHCl_3$). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.61 (m, 4 H, 4×ArH), 7.41 (m, 6 H, 6×ArH), 4.18 (m, 2 H, 4-H, 5-H), 3.84 (d, *J* = 10.0 Hz, 1 H, 2-H), 3.45 (dd, *J* = 2.5 and 10.0 Hz, 1 H, 3-H), 3.43 (s, 3 H, OCH_3), 2.54 (br. s, 1 H, OH), 2.05 (dd, *J* = 11.5 and 13.0 Hz, 1 H, 6-H_{ax}), 1.63 (dd, *J* = 13.0 and 4.5 Hz, 1 H, 6-H_{eq}), 1.07 [s, 9 H, C(CH_3)$_3$], 0.85 [s, 9 H, C(CH_3)$_3$], 0.79 [s, 9 H, C(CH_3)$_3$], 0.13 (s, 3 H, $SiCH_3$), 0.10 (s, 3 H, $SiCH_3$), 0.06 (s, 3 H, $SiCH_3$), –0.23 (s, 3 H, $SiCH_3$) ppm. ^{13}C NMR (63 MHz, $CDCl_3$): δ = 172.7 (C), 135.6 (2×CH), 135.6 (2×CH), 133.2 (C), 132.9 (C), 130.1 (CH), 130.0 (CH), 127.9 (2×CH), 127.8 (2×CH), 80.7 (C), 76.0 (CH), 72.6 (CH), 68.6 (CH), 64.7 (CH), 51.4 (OCH_3), 38.2 (CH_2), 26.9 [C(CH_3)$_3$], 26.3 [C(CH_3)$_3$], 25.7 [C(CH_3)$_3$], 19.1 [C(CH_3)$_3$], 18.5 [C(CH_3)$_3$], 18.0 [C(CH_3)$_3$], –2.5 ($SiCH_3$), –2.8 ($SiCH_3$), –4.0 ($SiCH_3$), –4.8 ($SiCH_3$) ppm. IR (film): $\tilde{\nu}$ = 3510 (O–H), 2104 (N≡N), 1759 (C=O) cm^{-1}. MS (CI) *m/z* = 714 [M + H]$^+$. HRMS: calcd. for $C_{36}H_{60}O_6N_3Si_3$ [M + H]$^+$ 714.3790; found 714.3797.

22c: $[\alpha]_D^{20}$ = +13.2 (*c* = 1.1, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.64 (m, 4 H, 4×ArH), 7.46–7.35 (m, 6 H, 6×ArH), 4.01 (ddd, *J* = 11.6, 8.8, 4.8 Hz, 1 H, 4-H), 3.56 (m, 1 H, 5-H), 3.53 (dd, *J* = 9.2, 10.0 Hz, 1 H, 3-H), 3.42 (s, 3 H, OCH_3), 3.29 (d, *J* = 9.2 Hz, 1 H, 2-H), 2.64 (d, *J* = 1.6 Hz, 1 H, OH), 1.87 (dd, *J* = 13.6, 4.8 Hz, 1 H, 6-H_{eq}), 1.53 (dd, *J* = 13.6, 11.6 Hz, 1 H, 6-H_{ax}), 1.07 [s, 9 H, C(CH_3)$_3$], 0.81 [s, 9 H, C(CH_3)$_3$], 0.79 [s, 9 H, C(CH_3)$_3$], 0.10 (s, 3 H, $SiCH_3$), 0.09 (s, 3 H, $SiCH_3$), 0.03 (s, 3 H, $SiCH_3$), –0.33 (s, 3 H, $SiCH_3$) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.2 (C), 135.7 (2×CH), 135.7 (2×CH), 133.5 (C), 133.0 (C), 130.0 (CH), 129.9 (CH), 127.9 (2×CH), 127.7 (2×CH), 80.5 (C), 79.3 (CH), 77.4 (CH), 71.1 (CH), 67.9 (CH), 51.6 (OCH_3), 41.2 (CH_2), 26.9 [C(CH_3)$_3$], 26.3 [C(CH_3)$_3$], 25.8 [C(CH_3)$_3$], 19.2 [C(CH_3)$_3$], 18.5 [C(CH_3)$_3$], 18.0 [C(CH_3)$_3$], –2.6 ($SiCH_3$), –3.0 ($SiCH_3$), –4.2 ($SiCH_3$), –4.6 ($SiCH_3$) ppm. IR (KBr): $\tilde{\nu}$ = 3496 (O–H), 2108 (N≡N), 1734 (C=O) cm^{-1}. MS (CI): *m/z* (%) = 714 [M + H]$^+$. HRMS: calcd. for $C_{36}H_{60}O_6N_3Si_3$ [M + H]$^+$ 714.3790; found 714.3783.

(1*S*,2*S*,3*R*,4*R*,5*R*)-3-Azido-1,3,4,6-tetrahydroxycyclohexane-1-carboxylic Acid (2): A solution of protected ester **22b** (65 mg, 0.11 mmol) in aqueous TFA (1.0 mL, 50%) was heated at 70 °C for 3 h. The reaction mixture was cooled to room temperature, and the solvent was removed under reduced pressure. A solution of the crude product in water was washed with diethyl ether (3×) and lyophilised. The obtained residue was dissolved in water (1.0 mL), treated with aqueous lithium hydroxide (0.6 mL, 0.5 M) and stirred at room temperature for 11 h. The aqueous solution was treated with Amberlite IR-120 until pH = 6 was reached. The resin was filtered and washed with water. The filtrate and the washings were lyophilised to afford azido acid **2** (25.5 mg, 99%) as a beige solid. $[\alpha]_D^{20}$ = +13.0 (*c* = 1.2, H_2O). ^{1}H NMR (400 MHz, D_2O): δ = 4.00 (m, 1 H, 5-H), 3.90 (t, *J* = 10.0 Hz, 1 H, 4-H), 3.57 (d, *J* = 10.0 Hz, 1 H, 2-H), 3.36 (t, *J* = 9.6 Hz, 1 H, 3-H), 2.28 (dd, *J* = 4.8, 13.6 Hz, 1 H, 6-H_{eq}), 1.63 (dd, *J* = 14.0, 13.6 Hz, 1 H, 6-H_{ax}) ppm. ^{13}C NMR (100 MHz, D_2O): δ = 178.3 (C), 79.7 (CH), 78.7 (CH, 1 C), 71.3 (CH), 69.9 (CH), 41.5 (CH_2) ppm. IR (KBr): $\tilde{\nu}$ = 3398 (O–H), 2119 (N≡N), 1730 (C=O) cm^{-1}. MS (ESI): *m/z* = 256 [M + Na]$^+$. HRMS: calcd. for $C_7H_{11}O_6N_3Na$ [M + Na]$^+$ 256.0540; found 256.0540.

Methyl (1*S*,2*S*,3*R*,4*S*,5*S*)-3-Azido-1,2-bis(*tert*-butyldimethylsilyloxy)-4,5-dihydroxycyclohexane-1-carboxylate (23): A stirred solution of ketone **17** (59 mg, 0.12 mmol) in dry methanol (0.6 mL) was treated at room temperature under an inert gas with sodium borohydride (5 mg, 0.12 mmol). The resulting mixture was stirred for 3 h, acidified with H_2SO_4 (5%) and then diluted with water and ethyl acetate. The organic phase was separated, and the aqueous layer was extracted twice with ethyl acetate. All combined organic extracts were dried (anh. Na_2SO_4), filtered and concentrated under reduced pressure. The obtained residue was purified by flash chromatography, with elution with ethyl acetate/hexane (10:90), to afford diol **23** (47 mg, 83%) as a yellow oil that solidified in the refridgerator, together with some diol **15** (9 mg, 16%). $[\alpha]_D^{20}$ = +16.2 (*c* = 1.0, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.18 (d, *J* = 3.5 Hz, 1 H, 2-H), 3.98 (t, *J* = 4.0 Hz, 1 H, 3-H), 3.91 (m, 1 H, 5-H), 3.77 (m, 1 H, 4-H), 3.71 (s, 3 H, OCH_3), 2.17 (m, 2 H, 6-H), 0.91 [s, 9 H, C(CH_3)$_3$], 0.84 [s, 9 H, C(CH_3)$_3$], 0.14 (s, 3 H, $SiCH_3$), 0.08 (s, 3 H, $SiCH_3$), 0.07 (s, 3 H, $SiCH_3$), 0.04 (s, 3 H, $SiCH_3$)

ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.3 (C), 80.1 (C), 73.4 (CH), 72.4 (CH), 67.5 (CH), 64.9 (CH), 52.1 (CH_3), 36.3 (CH_2), 25.5 [2 × C(CH_3)$_3$], 18.3 [C(CH_3)$_3$], 17.7 [C(CH_3)$_3$], –3.6 ($SiCH_3$), –4.2 ($SiCH_3$), –4.4 ($SiCH_3$), –5.2 ($SiCH_3$) ppm. IR (film): $\tilde{\nu}$ = 3398 (O–H), 2115 (N≡N), 1741 (C=O) cm^{-1}. MS (CI): *m*/*z* = 476 [M + H]$^+$. HRMS: calcd. for $C_{20}H_{42}O_6Si_2N_3$ [M + H]$^+$ 476.2612; found 476.2594.

(1*S*,2*S*,3*R*,4*S*,5*S*)-3-Azido-1,2,4,5-tetrahydroxycyclohexane-1-carboxylic Acid (3a): A solution of ester **23** (78 mg, 0.16 mmol) in aqueous TFA (1.6 mL, 50%) was heated at 70 °C for 4 h. The reaction mixture was cooled to room temperature, and the solvent was removed under reduced pressure. A solution of the crude product in water was washed with diethyl ether (3×) and lyophilised. The obtained residue was dissolved in water (1.5 mL), treated with aqueous lithium hydroxide (0.8 mL, 0.5 M) and stirred at room temperature for 16 h. The aqueous solution was treated with Amberlite IR-120 until pH = 6 was reached. The resin was filtered and washed with water. The filtrate and the washings were lyophilised to afford azido acid **3a** (37 mg, 99%) as a beige solid. $[\alpha]_D^{20}$ = +7.6 (*c* = 1.8, H_2O). ^{1}H NMR (400 MHz, D_2O): δ = 4.03 (m, 4 H, 2-H, 3-H, 4-H, 5-H), 2.11 (m, 2 H, 6-H) ppm. ^{13}C NMR (100 MHz, D_2O): δ = 179.5 (C), 80.2 (C), 75.6 (CH), 74.7 (CH), 70.4 (CH), 66.6 (CH), 38.3 (CH_2) ppm. IR (KBr): $\tilde{\nu}$ = 3400 (O–H), 2119 (N≡N), 1716 (C=O) cm^{-1}. MS (ESI): *m*/*z* = 256 [M + Na]$^+$. HRMS: calcd. for $C_7H_{11}O_6N_3Na$ [M + Na]$^+$ 256.0540; found 256.0535.

(1*S*,2*S*,3*R*,4*S*,5*S*)-3-(*tert*-Butoxycarbonylamino)-1,2,4,5-tetrahydroxycyclohexane-1-carboxylic Acid (3b): The experimental procedure used was as for **1b**. Firstly, the acetyl derivative of **3a** was prepared from acid **3a** (35 mg, 0.15 mmol) with pyridine (0.4 mL) and acetic anhydride (0.4 mL). ^{1}H NMR (250 MHz, CD_3OD): δ = 5.31 (m, 1 H, 2-H), 5.14 (m, 2 H, 4-H, 5-H), 4.28 (m, 1 H, 3-H), 2.60 (dd, *J* = 12.8, 3.5 Hz, 1 H, 6_{eq}-H), 2.28 (m, 1 H, 6_{ax}-H), 2.03 (s, 3 H, CH_3), 2.01 (s, 6 H, 2 × CH_3), 1.96 (s, 3 H, CH_3) ppm. For the reduction step, di-*tert*-butyl dicarbonate (44 mg, 0.20 mmol), platinium(IV) oxide (15 mg) and THF (1.7 mL) were used, whereas for the hydrolysis step, LiOH (1.76 mL) and THF (1.1 mL) were used. Yield: 26 mg, 56%. Amorphous beige solid. $[\alpha]_D^{20}$ = +2.1 (*c* = 1.0, H_2O). ^{1}H NMR (250 MHz, D_2O): δ = 4.14 (m, 1 H, 2-H), 3.88–3.75 (m, 3 H, 3-H, 4-H, 5-H), 2.07 (m, 2 H, 6-H), 1.41 [s, 9 H, (CH_3)$_3$] ppm. ^{13}C NMR (63 MHz, D_2O): δ = 177.8 (C), 158.4 (C), 81.9 (C), 77.9 [C(CH_3)$_3$], 73.2 (CH), 72.0 (CH), 68.0 (CH), 54.6 (CH), 35.8 (CH_2), 28.3 [C(CH_3)$_3$] ppm. IR (KBr): $\tilde{\nu}$ = 3400 (O–H), 1693 (C=O), 1614 (C=O) cm^{-1}. MS (ESI): *m*/*z* = 330 [M + Na]$^+$. HRMS: calcd. for $C_{12}H_{21}O_8NNa$ [M + Na]$^+$ 330.1159; found 330.1150.

(1*S*,2*S*,3*S*,4*R*,5*R*)-1,2-Bis(*tert*-butyldimethylsilyloxy)-4,5-*O*-isopropylidenecyclohexane-1,3-carbolactone (25): Dry pyridine (0.41 mL, 5.07 mmol) and then *tert*-butyldimethylsilyloxy trifluorosulfonate (1.0 mL, 4.35 mmol) were added at 0 °C under argon to a stirred solution of the alcohol **13** (500 mg, 1.45 mmol) in dry dichloromethane (4.8 mL). The resulting mixture was stirred at this temperature for 30 min and at room temperature for 4 d. The reaction mixture was diluted successively with dichloromethane and water. The aqueous layer was acidified with HCl (10%), and the organic phase was separated. The aqueous layer was extracted with dichloromethane (2×). All combined organic extracts were dried (anh. Na_2SO_4), filtered and concentrated under reduced pressure. The obtained residue was purified by flash chromatography, with elution with ethyl acetate/hexane (10:90), to afford silyl ether **25** (662 mg, 99%) as a white solid. $[\alpha]_D^{20}$ = +10.5 (*c* = 1.4, $CHCl_3$). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 4.44–4.31 (m, 4 H, 2-H, 3-H, 4-H, 5-H), 2.50 (dd, *J* = 15.3, 7.0 Hz, 1 H, $6\text{-}H_{ax}$), 2.14 (dd, *J* = 15.3, 1.5 Hz, 1 H, $6\text{-}H_{eq}$), 1.50 (s, 3 H, CH_3), 1.28 (s, 3 H, CH_3), 0.87 [s, 18 H, 2 × C(CH_3)$_3$], 0.23 (s, 3 H, $SiCH_3$), 0.15 (s, 3 H, $SiCH_3$), 0.11 (s, 3 H, $SiCH_3$), 0.09 (s, 3 H, $SiCH_3$) ppm. ^{13}C NMR (63 MHz, $CDCl_3$): δ = 176.5 (C), 109.2 (C), 81.8 (CH), 76.6 (C), 73.8 (CH), 72.9 (CH), 71.2 (CH), 39.5 (CH_2), 26.8 (CH_3), 26.0 [C(CH_3)$_3$], 25.6 [C(CH_3)$_3$], 24.0 (CH_3), 18.3 [C(CH_3)$_3$], 18.0 [C(CH_3)$_3$], –2.5 ($SiCH_3$), –3.2 ($SiCH_3$), –4.6 ($SiCH_3$), –5.1 ($SiCH_3$) ppm. IR (KBr): $\tilde{\nu}$ = 1801 (C=O) cm^{-1}. MS (CI): *m*/*z* = 459 [M + H]$^+$. HRMS: calcd. for $C_{22}H_{43}O_6Si_2$ [M + H]$^+$ 459.2598; found 459.2600. $C_{22}H_{42}O_6Si_2$ (458.74): calcd. C 57.60, H 9.23; found C 57.62, H 9.44.

(1*S*,3*R*,4*R*,5*S*,6*S*)-1,6-Bis(*tert*-butyldimethylsilyloxy)-3,4-dihydroxycyclohexane-1,5-carbolactone (26): A solution of isopropylidene acetal **25** (262 mg, 0.57 mmol) in aqueous acetic acid (9.5 mL, 80%) was heated at 65 °C for 3 h. After the mixture had cooled to room temperature, water (2 mL) was added, and the resulting mixture was heated at 65 °C for another 24 h. The mixture was cooled to room temperature, and the solvents were evaporated. The obtained residue was purified by flash chromatography, with elution with ethyl acetate/hexane [(1) 30:70; (2) 50:50] to afford diol **26** (96 mg, 40%), together with a monodesilylated derivative of **26** (59 mg, 34%), both as light yellow solids.

26: $[\alpha]_D^{20}$ = +15.9 (*c* = 1.0, $CHCl_3$). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 4.49 (d, *J* = 5.3 Hz, 1 H, 3-H), 4.33 (s, 1 H, 2-H), 4.21 (m, 1 H, 4-H), 3.93 (m, 1 H, 5-H), 2.89 (d, *J* = 2.5 Hz, 1 H, OH), 2.43 (d, *J* = 6.3 Hz, 1 H, OH), 2.20 (dd, *J* = 12.0, 6.5 Hz, 1 H, $6\text{-}H_{eq}$), 1.89 (t, *J* = 12.0 Hz, 1 H, $6\text{-}H_{ax}$), 0.89 [s, 9 H, C(CH_3)$_3$], 0.88 [s, 9 H, C(CH_3)$_3$], 0.25 (s, 3 H, $SiCH_3$), 0.17 (s, 3 H, $SiCH_3$), 0.12 (s, 3 H, $SiCH_3$), 0.10 (s, 3 H, $SiCH_3$) ppm. ^{13}C NMR (63 MHz, $CDCl_3$): δ = 175.7 (C), 82.4 (CH), 76.8 (C), 75.7 (CH), 67.8 (CH), 65.6 (CH), 38.8 (CH_2), 25.9 [C(CH_3)$_3$], 25.7 [C(CH_3)$_3$], 18.3 [C(CH_3)$_3$], 18.0 [C(CH_3)$_3$], –2.5 ($SiCH_3$), –3.0 ($SiCH_3$), –4.5 ($SiCH_3$), –5.0 ($SiCH_3$) ppm. IR (KBr): $\tilde{\nu}$ = 3501 (O–H), 3453 (O–H), 1791 and 1766 (C=O) cm^{-1}. MS (CI): *m*/*z* = 419 [M + H]$^+$. HRMS: calcd. for $C_{19}H_{39}O_6Si_2$ [M + H]$^+$ 419.2285; found 419.2281. $C_{19}H_{38}O_6Si_2$ (418.67): calcd. C 54.51, H 9.15; found C 54.28, H 9.10.

Sulfate 24: Thionyl chloride (24 μL, 0.33 mmol) was added at 0 °C under argon to a stirred solution of diol **26** (39 mg, 0.09 mmol) and dry triethylamine (52 μL, 0.37 mmol) in dry dichloromethane (1.9 mL). The ice bath was removed, and the resulting solution was stirred at room temperature. After 24 h, the reaction mixture was cooled to 0 °C, and more thionyl chloride (24 μL, 0.33 mmol) and dry triethylamine (52 μL, 0.37 mmol) were added. The resulting mixture was stirred at room temperature for 1 h and was then diluted with dichloromethane and water. The organic phase was separated, and the aqueous layer was extracted with dichloromethane (3×). All the combined organic extracts were dried (anh. Na_2SO_4) and filtered, and the solvents were evaporated. The obtained residue was dissolved in a CCl_4/CH_3CN mixture (1:1, 1.8 mL) and cooled to 0 °C. Aqueous $NaIO_4$ (0.9 mL, 0.4 M) and $RuCl_3 \cdot 3H_2O$ (2 mg, 9.3 μmol) were then added. The resulting reaction mixture was stirred at this temperature for 2 h and was then diluted with diethyl ether and water. The organic phase was separated and successively washed with water, $NaHCO_3$ (sat.) and NaCl (sat.). The organic extract was dried (anh. Na_2SO_4) and filtered, and the solvents were evaporated. The obtained residue was purified by flash chromatography, with elution with ethyl acetate/hexanes (20:80), to yield sulfate **24** (44 mg, 99%) as a white amorphous solid. $[\alpha]_D^{20}$ = +16.2 (*c* = 1.0, $CHCl_3$). ^{1}H NMR (250 MHz, $CDCl_3$): δ = 5.15 (m, 2 H, 4-H, 5-H), 4.66 (dd, *J* = 2.6, 0.9 Hz, 1 H, 3-H), 4.43 (s, 1 H, 2-H), 2.73 (m, 1 H, 6-H), 2.42 (m, 1 H, 6-H), 0.90 [s, 9 H, C(CH_3)$_3$], 0.89 [s, 9 H, C(CH_3)$_3$], 0.27 (s, 3 H, $SiCH_3$), 0.18 (s, 3

H, $SiCH_3$), 0.16 (s, 3 H, $SiCH_3$), 0.14 (s, 3 H, $SiCH_3$) ppm. ^{13}C NMR (63 MHz, $CDCl_3$): δ = 173.8 (C), 78.8 (CH), 77.1 (2 × CH), 75.2 (C), 73.3 (CH), 37.9 (CH_2), 25.9 [$C(CH_3)_3$], 25.6 [$C(CH_3)_3$], 18.3 [$C(CH_3)_3$], 18.0 [$C(CH_3)_3$], –2.5 ($SiCH_3$), –3.1 ($SiCH_3$), –4.5 ($SiCH_3$), –5.1 ($SiCH_3$) ppm. IR (KBr): $\tilde{\nu}$ = 1811 (C=O) cm^{-1}. MS (CI): *m*/*z* = 481 $[M + H]^+$. HRMS: calcd. for $C_{19}H_{37}O_8SSi_2$ $[M + H]^+$ 481.1748; found 481.1735. $C_{19}H_{36}O_8SSi_2$ (480.72): calcd. C 47.47, H 7.55; found C 47.56, H 7.73.

(1*S*,3*S*,4*R*,5*S*,6*S*)-3-Azido-1,6-bis(*tert*-butyldimethylsilyloxy)-4-hydroxycyclohexane-1,5-carbolactone (27): A solution of sulfate **24** (335 mg, 0.70 mmol) in dry DMF (17.5 mL) was treated with sodium azide (182 mg, 2.80 mmol) and 15-crown ether (14 μL, 70 μmol), and the resulting mixture was heated at 90 °C for 4 h. After the mixture had cooled to room temperature, the solvent was removed under reduced pressure. The obtained residue was dissolved in THF (35 mL) and aqueous H_2SO_4 (50 μL, 70%) and was then heated at 50 °C for 1 h. After the mixture had cooled to room temperature, powdered $NaHCO_3$ (642 mg) was added, and the resulting mixture was stirred for 20 min. The suspension was filtered through a plug of Celite, and the residue was washed with ethyl acetate. The filtrate and washings were concentrated under reduced pressure. The obtained residue was purified by flash chromatography, with elution with ethyl acetate/hexanes (20:80), to yield azide **27** (269 mg, 87%) as a beige solid. $[\alpha]_D^{20}$ = +31.8 (*c* = 1.1, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$): δ = 4.47 (d, *J* = 4.0 Hz, 1 H, 3-H), 4.30 (s, 1 H, 2-H), 4.27 (br. s, 1 H, 4-H), 3.95 (d, *J* = 5.0 Hz, 1 H, 5-H), 3.20 (br. s, 1 H, OH), 2.34 (dd, *J* = 14.5, 5.5 Hz, 1 H, 6-H_{ax}), 2.14 (d, *J* = 14.5 Hz, 1 H, CH), 0.89 [s, 18 H, 2 × $C(CH_3)_3$], 0.29 (s, 3 H, $SiCH_3$), 0.19 (s, 3 H, $SiCH_3$), 0.12 (s, 3 H, $SiCH_3$), 0.10 (s, 3 H, $SiCH_3$) ppm. ^{13}C NMR (63 MHz, $CDCl_3$): δ = 176.1 (C), 82.9 (CH), 77.2 (C), 76.1 (CH), 68.6 (CH), 60.5 (CH), 37.7 (CH_2), 25.9 [$C(CH_3)_3$], 25.6 [$C(CH_3)_3$], 18.3 [$C(CH_3)_3$], 18.0 [$C(CH_3)_3$], –2.5 ($SiCH_3$), –3.0 ($SiCH_3$), –4.5 ($SiCH_3$),–5.0 ($SiCH_3$) ppm. IR (KBr): $\tilde{\nu}$ = 3396 (O–H), 2122 and 2090 (N≡N), 1760 (C=O) cm^{-1}. MS (CI): *m*/*z* = 444 $[M + H]^+$. HRMS: calcd. for $C_{19}H_{38}O_5N_3Si_2$ $[M + H]^+$ 444.2350; found 444.2350. $C_{19}H_{37}N_3O_5Si_2$ (443.69): calcd. C 51.43, H 8.41, N 9.47; found C 51.63, H 8.72, N 9.23.

(1*S*,3*S*,4*R*,5*S*,6*S*)-3-Azido-1,4,5,6-tetrahydroxycyclohexane-1-carboxylic Acid (4a): A solution of lactone **27** (256 mg, 0.58 mmol) in aqueous TFA (5.8 mL, 50%) was heated at 70 °C for 2 h. The reaction mixture was cooled to room temperature, and the solvent was removed under reduced pressure. The crude product was dissolved in water and washed with diethyl ether (3 ×). The aqueous extract was then lyophilised. The obtained residue was dissolved in water (5.3 mL) and was then treated with aqueous lithium hydroxide (2.9 mL, 0.5 M) and stirred at room temperature for 8 h. The aqueous solution was diluted with water and treated with Amberlite IR-120 until pH = 6 was reached. The resin was filtered and washed with water. The filtrate was lyophilised to afford azido acid **4a** (130 mg, 96%) as a beige solid. $[\alpha]_D^{20}$ = –4.5 (*c* = 1.3, H_2O). ^1H NMR (300 MHz, D_2O): δ = 4.00 (d, *J* = 3.0 Hz, 1 H, 2-H), 3.84 (dd, *J* = 9.6, 3.0 Hz, 1 H, 3-H), 3.71–3.57 (m, 2 H, 4-H, 5-H) and 2.10 (m, 2 H, 6-H) ppm. ^{13}C NMR (75 MHz, D_2O): δ = 177.4 (C), 76.4 (C), 73.7 (CH), 73.4 (CH), 71.7 (CH), 61.1 (CH) and 32.6 (CH_2) ppm. IR (KBr): $\tilde{\nu}$ = 3419 (O–H), 2115 (N≡N) and 1719 (C=O) cm^{-1}. MS (ESI): *m*/*z* = 256 $[M + Na]^+$. HRMS: calcd. for $C_7H_{11}O_6N_3Na$ $[M + Na]^+$ 256.0540; found 256.0528.

(1*S*,2*S*,3*S*,4*R*,5*S*)-5-(*tert*-Butoxycarbonylamino)-1,2,3,4-tetrahydroxycyclohexane-1-carboxylic Acid (4b): The experimental procedure used was as for **1b**, with use of acid **4a** (33 mg, 0.14 mmol), pyridine (0.4 mL) and acetic anhydride (0.4 mL) for the preparation of acetyl derivative of **4a**, di-*tert*-butyl dicarbonate (39 mg, 0.18 mmol), platinium(IV) oxide (14 mg) and THF (1.6 mL) for the reduction step and LiOH (2.1 mL) and THF (1.3 mL) for the hydrolysis step. Yield: 27 mg, 63%. Amorphous beige solid. $[\alpha]_D^{20}$ = +13.2 (*c* = 1.4, H_2O). ^1H NMR (400 MHz, D_2O): δ = 3.85 (m, 2 H, 2-H, 4-H), 3.70–3.61 (m, 2 H, 3-H, 5-H), 2.10–2.03 (m, 1 H, 6-H_{ax}) 1.84 (dd, *J* = 12.4 and 3.2 Hz, 1 H, 6-H_{eq}) and 1.46 [s, 9 H, $C(CH_3)_3$] ppm. ^{13}C NMR (100 MHz, D_2O): δ = 182.9 (C), 160.9 (C), 84.0 (C), 78.5 [$C(CH_3)_3$], 76.5 (CH), 75.4 (CH), 75.0 (CH), 53.2 (CH), 37.5 (CH_2) and 30.7 [$C(CH_3)_3$] ppm. IR (KBr): $\tilde{\nu}$ = 3390 (O–H), 1687 (C=O), 1614 (C=O) cm^{-1}. MS (ESI): *m*/*z* = 330 $[M + Na]^+$. HRMS: calcd. for $C_{12}H_{21}O_8NNa$ $[M + Na]^+$ 330.1159; found 330.1155.

(1*S*,2*S*,3*S*,4*R*,5*S*)-1,2,4,5-Tetrahydroxy-3-(4-phenoxymethyl-1*H*-1,2,3-triazol-1-yl)cyclohexane-1-carboxylic Acid (5): A solution of acid **2** (25 mg, 0.11 mmol) in dry pyridine (0.4 mL) was treated under argon at 0 °C with acetic anhydride (0.4 mL). The ice bath was removed, and the resulting mixture was stirred at room temperature for 17 h. The solvents were removed under reduced pressure by successive addition of toluene and acetonitrile and subsequent concentration. Drying under vacuum afforded the acetyl-protected azide **28** (41 mg, 93%) as a colourless oil. ^1H NMR (250 MHz, CD_3OD): δ = 5.53 (m, 1 H, 5-H), 5.23 (d, *J* = 10.8 Hz, 1 H, 2-H), 5.07 (t, *J* = 10.8 Hz, 1 H, 4-H), 4.00 (m, 1 H, 3-H), 3.07 (dd, *J* = 13.0, 5.3 Hz, 1 H, 6-H_{eq}) and 2.06–1.74 (m, 13 H, 4 × CH_3, 6-H_{ax}) ppm. Freshly prepared aqueous sodium ascorbate solution (8 μL, 1.0 M), followed by aqueous copper(II) sulfate solution (3.3 μL, 0.32 M), were added to a solution of the previously obtained azide **28** (31 mg, 0.077 mmol) and phenyl propargyl ether (10 μL, 0.077 mmol) in a *t*BuOH/water mixture (1:1, 0.4 mL). The resulting heterogeneous mixture was stirred vigorously for 36 h and was then diluted with water and ethyl acetate. The organic layer was separated, and the aqueous phase was extracted twice with ethyl acetate. All the combined organic extracts were dried (anh. Na_2SO_4) and filtered, and the solvents were evaporated. The obtained residue was dissolved in THF (0.8 mL) and was then treated with aqueous lithium hydroxide (1.2 mL, 0.5 M) and stirred at room temperature for 30 min. THF was removed under reduced pressure, and the aqueous solution was then diluted with water and ethyl acetate. The aqueous layer was separated and washed with ethyl acetate (3 ×). The aqueous extract was treated with Amberlite IR-120 until pH = 6 was reached. The resin was filtered and washed with water. The filtrate and the washings were lyophilised and purified by HPLC, performed on a semipreparative Merck LiChroCART RP-18 column (10 μm, 250 × 10 mm) with a gradient 0–50% B (35 min) at a flow rate of 5 mL min^{-1}. The eluents for this column were: (A) water with 0.1% TFA and (B) acetonitrile with 0.1% TFA. t_R = 20 min. Yield: 9.8 mg (35%). Amorphous white solid. ^1H NMR (250 MHz, D_2O): δ = 8.15 (s, 1 H, 5′-H), 7.36 (m, 2 H, 2 × ArH), 7.05 (m, 3 H, 3 × ArH), 5.26 (s, 2 H, CH_2OPh), 4.94 (dd, *J* = 10.3, 11.0 Hz, 1 H, 3-H), 4.15 (d, *J* = 11.0 Hz, 1 H, 2-H), 4.09 (m, 1 H, 5-H), 3.96 (dd, *J* = 10.3, 9.3 Hz, 1 H, 4-H), 2.36 (dd, *J* = 13.5, 4.5 Hz, 1 H, 6-H_{eq}), 1.81 (dd, *J* = 11.8, 13.5 Hz, 1 H, 6-H_{ax}) ppm. ^{13}C NMR (63 MHz, D_2O): δ = 175.8 (C), 157.9 (C), 143.9 (C), 130.5 (2 × CH), 126.4 (CH), 122.7 (CH), 116.0 (2 × CH), 77.0 (C), 76.4 (CH), 75.5 (CH), 69.2 (CH), 67.4 (CH), 61.8 (OCH_2), 39.2 (CH_2) ppm. IR (KBr): $\tilde{\nu}$ = 3398 (O–H), 1726 (C=O) cm^{-1}. MS (ESI): *m*/*z* = 366 $[M + H]^+$. HRMS: calcd. for $C_{16}H_{20}O_7N_3$ $[M + H]^+$ 366.1296; found 366.1307. $C_{16}H_{19}N_3O_7 \cdot 3/4H_2O$ (378.85): calcd. C 50.73, H 5.45, N 11.09; found C 50.89, H 5.32, N 11.18.

(1*S*,2*S*,3*S*,4*R*,5*S*)-1,2,3,4-Tetrahydroxy-5-[4-(phenoxymethyl)-1*H*-1,2,3-triazol-1-yl]cyclohexane-1-carboxylic Acid (6): The experimental procedure used was as for **5**. Firstly, acetyl-protected azide **29**

(43 mg, 0.18 mmol) was prepared as **28** with pyridine (0.4 mL), and acetic anhydride (0.4 mL). Yield of **29**: 72 mg (99%) of a colourless oil. ^{1}H NMR (250 MHz, CD_3OD): δ = 5.38 (br. s, 1 H, 2-H), 5.13–5.02 (m, 2 H, 3-H, 4-H), 3.66 (m, 1 H, 5-H), 2.57 (dd, J = 14.8, 4.5 Hz, 1 H, 6-H_{eq}), 2.09 (dd, J = 14.8, 13.5 Hz, 1 H, 6-H_{ax}), 2.00 (s, 3 H, CH_3), 1.93 (s, 6 H, 2 × CH_3), 1.78 (s, 3 H, CH_3) ppm. Secondly, triazole **6** was prepared in the same way as triazole **5**, with azide **29** (18 mg, 0.046 mmol), phenyl propargyl ether (6 μL, 0.046 mmol), *t*BuOH/water (0.2 mL), aqueous sodium ascorbate (5 μL, 1.0 M) and aqueous copper(II) sulfate (2 μL, 0.32 M). For the hydrolysis step, LiOH (0.72 mL) and THF (0.45 mL) were used. Yield of **6**: 10 mg (60%). Amorphous beige solid. ^{1}H NMR (250 MHz, D_2O): δ = 8.15 (s, 1 H, 5′-H), 7.34 (m, 2 H, 2 × ArH), 7.04 (m, 3 H, 3 × ArH), 5.23 (s, 2 H, CH_2OPh), 4.80–4.64 (m, 1 H, 5-H), 4.07 (m, 2 H, 2-H, 4-H), 3.94 (dd, J = 9.8, 3.0 Hz, 1 H, 3-H), 2.73 (t, J = 14.0 Hz, 1 H, 6-H_{ax}), 2.20 (ddd, J = 14.0, 4.3, 1.3 Hz, 1 H, 6-H_{eq}) ppm. ^{13}C NMR (63 MHz, D_2O): δ = 176.1 (C), 157.9 (C), 130.5 (1 C, 2 × CH), 125.3 (CH), 122.7 (CH), 116.0 (2 × CH), 76.3 (C), 73.3 (CH), 72.5 (CH), 71.9 (CH), 61.8 (CH_2), 61.3 (CH), 33.4 (CH_2) ppm. IR (KBr): $\tilde{\nu}$ = 3410 (O–H), 1732 (C=O) cm^{-1}. MS (CI): m/z = 366 $[M + H]^+$. HRMS: calcd. for $C_{16}H_{20}O_7N_3$ $[M + H]^+$ 366.1301; found 366.1301.

Supporting Information (see footnote on the first page of this article): Copies of ^{1}H NMR, ^{13}C NMR and DEPT spectra of all the reported compounds.

Acknowledgments

This work was supported by the Xunta de Galicia (under projects PGIDT07PXIB209080PR and GRC2006/132) and by the Ministerio de Educación y Cultura (SAF2007-63533). V. F. V. P. thanks the Portuguese Fundação para a Ciência e a Tecnologia for an FCT scholarship.

[1] a) M. Ordóñez, C. Cativiela, *Tetrahedron: Asymmetry* **2007**, *18*, 3–99; b) C. Cativiela, M. D. Díaz de Villegas, *Tetrahedron: Asymmetry* **1998**, *9*, 3517–3599; c) C. Cativiela, M. D. Díaz de Villegas, *Tetrahedron: Asymmetry* **2000**, *11*, 645–732; d) K.-H. Park, M. J. Kurth, *Tetrahedron* **2002**, *58*, 8629–8659; e) M. D. P. Risseeuw, M. Overhand, G. W. J. Fleet, M. I. Simone, *Tetrahedron: Asymmetry* **2007**, *18*, 2001–2010.

[2] a) S. Ogawa in *Carbohydrates in Drug Design* (Eds.: Z. J. Witczak, K. A. Nieforth), Dekker, New York, **1997**, p. 433; b) S. Ogawa, *Carbohydrate Mimics: Concepts and Methods* (Ed.: Y. Chapteur), Wiley-VCH, Weinheim, **1998**; c) E. Truscheit, W. Frommer, B. Junge, L. Müller, D. D. Schmidt, W. Wingender, *Angew. Chem.* **1981**, *93*, 738–755.

[3] a) A. Dondoni, *Chem. Asian J.* **2007**, *2*, 700–708; b) W. H. Binder, R. Sachsenhofer, *Macromol. Rapid Commun.* **2007**, *28*, 15–54; c) F. Santoyo-González, F. Hernández-Mateo, "Azide-alkyne 1,3-dipolar cycloadditions: a valuable tool in carbohydrate chemistry", in *Topics in Heterocyclic Chemistry* (Series Ed.: R. R. Gupta), Springer Verlag, Heidelberg, **2007**, vol. 7 (*Heterocycles from Carbohydrate Precursors*), pp. 133–177; d) J. E. Moses, A. D. Moorhouse, *Chem. Soc. Rev.* **2007**, *36*, 1249–1262.

[4] R. Huisgen, G. Szeimies, L. Möbius, *Chem. Ber.* **1967**, *100*, 2494–2507.

[5] a) H. C. Kolb, M. G. Finn, K. B. Sharpless, *Angew. Chem. Int. Ed.* **2001**, *40*, 2004–2021; b) V. V. Rostovtsev, L. G. Green, V. V. Fokin, K. B. Sharpless, *Angew. Chem. Int. Ed.* **2002**, *41*, 2596–2599.

[6] For examples, see: a) P. Wu, M. Malkoch, J. N. Hunt, R. Vestberg, E. Kaltgrad, M. G. Finn, V. V. Fokin, K. B. Sharpless, C. J. Hawker, *Chem. Commun.* **2005**, 5775–5777; b) E. Fernández-Megía, J. Correa, I. Rodríguez-Meizoso, R. Riguera, *Macromolecules* **2006**, *39*, 2113–2120; c) E. Fernández-Megía, J. Correa, R. Riguera, *Biomacromolecules* **2006**, *7*, 3104–3111; d) I. Deguise, D. Lagnoux, R. Roy, *New J. Chem.* **2007**, *31*, 1321–1331; e) M. Ortega-Muñoz, J. López-Jaramillo, F. Hernández-Mateo, F. Santoyo-González, *Adv. Synth. Catal.* **2006**, *348*, 2410–2420; f) M. Touaibia, A. Wellens, T. C. Shiao, Q. Wang, S. Sirois, J. Bouckaert, R. Roy, *ChemMedChem* **2007**, *2*, 1190–1201; g) J. R. Thomas, X. Liu, P. J. Hergenrother, *J. Am. Chem. Soc.* **2005**, *127*, 12434–12435; h) S. Quader, S. E. Boyd, I. D. Jenkins, T. A. Houston, *J. Org. Chem.* **2007**, *72*, 1962–1979; i) C. W. Tornøe, C. Christensen, M. Meldal, *J. Org. Chem.* **2002**, *67*, 3057–3064; j) C. W. Tornøe, S. J. Sanderson, J. C. Mottram, G. H. Coombs, M. Meldal, *J. Comb. Chem.* **2004**, *6*, 312–324.

[7] J. C. Rohloff, K. M. Kent, M. J. Postich, M. W. Becker, H. H. Chapman, D. E. Kelly, W. Lew, M. S. Louie, L. R. McGee, E. J. Prisbe, L. M. Schultze, R. H. Yu, L. Zhang, *J. Org. Chem.* **1998**, *63*, 4545–4550.

[8] Geometry optimizations and energy calculations were performed with the Gaussian 03W[9] program with the semiempirical AM1 method.

[9] M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, J. A. Montgomery, T. Vreven, K. N. Kudin, J. C. Burant, J. M. Millam, S. S. Iyengar, J. Tomasi, V. Barone, B. Mennucci, M. Cossi, G. Scalmani, N. Rega, G. A. Petersson, H. Nakatsuji, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, M. Klene, X. Li, J. E. Knox, H. P. Hratchian, J. B. Cross, V. Bakken, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, P. Y. Ayala, K. Morokuma, G. A. Voth, P. Salvador, J. J. Dannenberg, V. G. Zakrzewski, S. Dapprich, A. D. Daniels, M. C. Strain, O. Farkas, D. K. Malick, A. D. Rabuck, K. Raghavachari, J. B. Foresman, J. V. Ortiz, Q. Cui, A. G. Baboul, S. Clifford, J. Cioslowski, B. B. Stefanov, G. Liu, A. Liashenko, P. Piskorz, I. Komaromi, R. L. Martin, D. J. Fox, T. Keith, M. A. Al-Laham, C. Y. Peng, A. Nanayakkara, M. Challacombe, P. M. W. Gill, B. Johnson, W. Chen, M. W. Wong, C. González, J. A. Pople, *Gaussian 03*, Revision C.02, Gaussian, Inc., Wallingford CT, **2004**.

[10] a) B. M. Kim, K. B. Sharpless, *Tetrahedron Lett.* **1989**, *30*, 655–658; b) Y. Gao, K. B. Sharpless, *J. Am. Chem. Soc.* **1988**, *110*, 7538–7539.

[11] S. David, A. Thieffry, *J. Chem. Soc. Perkin Trans. 1* **1979**, 1568–1572.

[12] X. Kong, T. B. Grindley, *J. Carbohydr. Chem.* **1993**, *12*, 557–571.

[13] P. Söderman, G. Widmalm, *Carbohydr. Res.* **1999**, *316*, 184–186.

[14] For examples, see: a) A. Bernardi, D. Arosio, L. Manzini, F. Micheli, A. Pasquqrello, P. Seneci, *J. Org. Chem.* **2001**, *66*, 6209–6216; b) H.-M. Liu, Y. Sato, Y. Tsuda, *Chem. Pharm. Bull.* **1993**, *41*, 491–501; c) Y. Tsuda, N. Matsuhira, K. Kanemitsu, *Chem. Pharm. Bull.* **1985**, *33*, 4095–4097.

[15] a) A. Delgado, *Eur. J. Org. Chem.*, in press; b) S. Ogawa, M. Kanto, Y. Suzuki, *Mini-Rev. Med. Chem.* **2007**, *7*, 679–691; c) S. Ogawa, M. Kanto, *J. Nat. Prod.* **2007**, *70*, 493–497.

Received: May 16, 2008
Published Online: July 11, 2008

