An efficient synthesis of triazolo-carbohydrate mimetics and their conformational analysis†

Hikaru Yanai, Shun Obara and Takeo Taguchi*

Received 6th March 2008, Accepted 14th April 2008
First published as an Advance Article on the web 19th May 2008
DOI: 10.1039/b803924k

A chemical library of 1,2,3-triazole fused carbohydrate mimetics was constructed. To synthesize enantiomerically pure mimetics, we developed a stereo- or diastereodivergent synthetic route from D-glucose, D-mannose and D-galactose as chiral sources. In this synthesis, an $In(OTf)_3$-catalyzed tandem azidation–1,3-dipolar cycloaddition reaction of 1,1-dimethoxyhex-5-yne derivatives with $TMSN_3$ was used as the key step to construct the 4,5,6,7-tetrahydro[1,2,3]triazolo[1,5-*a*]pyridine framework. Additionally, NMR was used to carry out a conformational analysis of the synthesized mimetics, which are of structural interest since they have an *N*,*O*-acetal moiety in place of the anomeric position of normal pyranosides.

Introduction

1,2,3-Triazole derivatives are attracting much attention from medicinal chemists due to their interesting biological properties, such as antibacterial and antitumor activities, and glycosidase inhibition.[1,2] The isolation of triazole-containing compounds from nature has not been reported, therefore, these compounds can only be obtained by chemical synthesis. A number of methodologies to construct 1,2,3-triazole ring systems have already been reported. Among these methodologies, the 1,3-dipolar cycloaddition of organic azides to carbon–carbon multiple bonds, namely the Huisgen reaction, is one of the most important reactions.[3] Recently, Meldal *et al*. and Sharpless *et al.* independently reported that, under mild conditions, Cu(I) complexes catalyze the intermolecular Huisgen reaction of terminal alkynes and organic azides to give 1,4-disubstituted 1,2,3-triazoles with excellent regio- and chemoselectivities.[4,5] However, due to the rapid formation of dimerized products through *intermolecular* cycloaddition, it is essentially difficult to apply Cu(I) catalysts to the *intramolecular* Huisgen reaction.[6] Bicyclic triazoles, which would be prepared by the *intramolecular* Huisgen reaction of ω-azidoalkyne derivatives, are also interesting compounds in medicinal chemistry. For example, Vasella *et al*. and Wong *et al*. reported the synthesis of carbohydrate mimetics having a 4,5,6,7-tetrahydro[1,2,3]triazolo[1,5-*a*]pyridine framework and their inhibition properties against several glycosidases (Fig. 1).[7,8] However, the construction of a bicyclic triazole framework by the *intramolecular* Huisgen type reaction under simple thermal conditions remains a problematic step in these syntheses. Therefore, the development of active catalysis for the intramolecular Huisgen reaction is one of the challenges in synthetic organic chemistry. Recently, we reported that indium(III) triflate [$In(OTf)_3$] nicely catalyzes the tandem azidation–1,3-dipolar cycloaddition reaction of ω,ω-dialkoxyalkyne derivatives with $TMSN_3$ to give alkoxylated bicyclic 1,2,3-triazole products (Scheme 1).[9] In this reaction procedure, the isolation of potentially explosive organic azides was not needed.[10] Additionally, the mild Lewis acidity and chemical stability of $In(OTf)_3$ encouraged us to apply this reaction to more complex substrates.[11] Consequently, we designed triazolo-carbohydrate mimetic **A**, which is not only a potential synthetic intermediate of Vasella's triazolo-mimetics but also a structurally interesting mimic having an *N*,*O*-acetal moiety as an equivalent to the anomeric position in normal pyranosides. Herein we disclose the stereodivergent synthesis of **A** through the tandem azidation–1,3-dipolar cycloaddition reaction of highly oxygenated 1,1-dimethoxyhex-5-yne derivatives with $TMSN_3$.

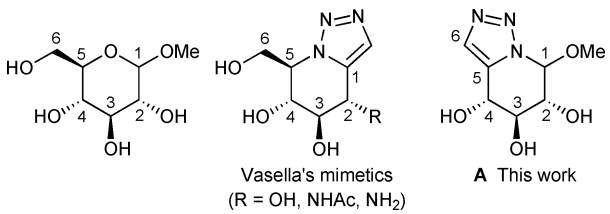
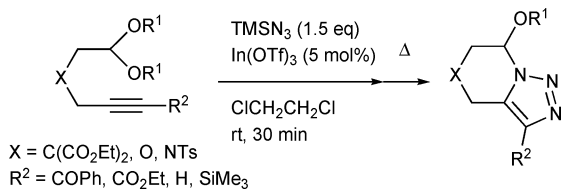


Fig. 1 Structures of D-glucose and triazolo-glucose mimetics.



Scheme 1 $In(OTf)_3$-catalyzed tandem azidation–1,3-dipolar cycloaddition reaction.

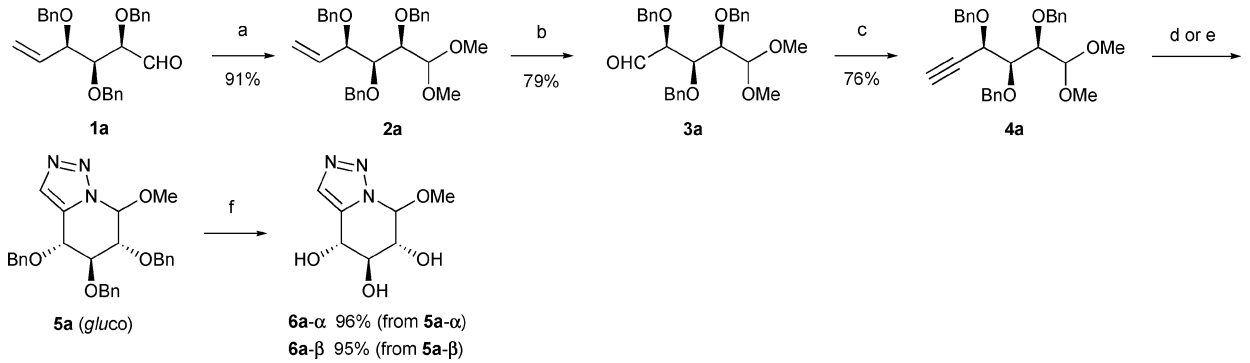
Results and discussion

Stereodivergent synthesis of triazolo-glucose/idose mimetics

Enantiomerically pure 1,1-dimethoxyhex-5-yne derivative **4a** was synthesized in three steps from the chiral building block **1a**, which was easily prepared from D-glucose in multi-gram scale (Scheme 2).[12] That is, under acidic conditions, **1a** was converted

School of Pharmacy, Tokyo University of Pharmacy and Life Sciences, 1432-1 Horinouchi, Hachioji, Tokyo 192-0392, Japan. E-mail: taguchi@ps.toyaku.ac.jp; Fax: +81 42 676 3257; Tel: +81 42 676 3257

† Electronic Supplementary Information (ESI) available: Preparative procedures for **6b**, **6c**, ***ent*-5b** and ***ent*-5c**, and NMR spectra of new compounds.



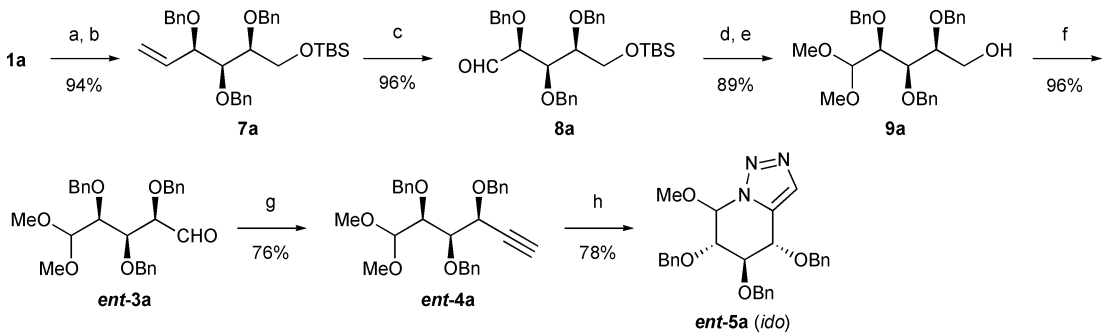
Scheme 2 Synthesis of **6a**. *Reagents and conditions:* (a) $HC(OMe)_3$, *p*TsOH, rt, 6 h, 91%; (b) OsO_4, NMO, acetone–^{t}BuOH–H_2O (20 : 5 : 1), rt, 7 h, then $NaIO_4$, rt, 1 h, 79%; (c) $CH_3COC(N_2)P(O)(OMe)_2$, K_2CO_3, MeOH, rt, 2 h, 76%; (d) $TMSN_3$, $In(OTf)_3$ (5 mol%), $ClCH_2CH_2Cl$, 0 °C, 4 h, then 80 °C, 8 h, 75% (α : β = 1 : 1.2); (e) $TMSN_3$, $In(OTf)_3$ (5 mol%), hexane, 0 °C, 4 h, then 60 °C, 16 h, 82% (α : β = 1.4 : 1); (f) $Pd(OH)_2/C$, H_2 (1 atm.), MeOH, rt, 11 h.

to dimethyl acetal **2a** in 91% yield by reaction with trimethyl orthoformate. Catalytic dihydroxylation of **2a** using an OsO_4–4-methylmorpholine *N*-oxide (NMO) system and an oxidative work-up by $NaIO_4$ provided the 5,5-dimethoxypentanal derivative **3a** in 79% yield. The homologation of **3a** was achieved by Ohira–Bestmann conditions using a $CH_3COC(N_2)P(O)(OMe)_2$–K_2CO_3 system to give the 1,1-dimethoxyhex-5-yne derivative **4a** in 76% yield.[13] In the presence of 5 mol% of $In(OTf)_3$, the reaction of **4a** and 5.0 molar equivalents of $TMSN_3$ in 1,2-dichloroethane at 0 °C for 4 h resulted in the complete consumption of **4a** (by TLC). Without isolation of the α-azido ether intermediate, further heating of the reaction mixture at 80 °C for 8 h gave the tribenzylated *gluco*-mimic **5a** in 75% yield with low β-selectivity (α : β = 1 : 1.2).[14] Interestingly, the reaction of **4a** in hexane instead of 1,2-dichoroethane resulted in a change of diastereoselectivity. That is, in hexane, the tandem azidation–1,3-dipolar cycloaddition reaction of **4a** for 16 h at 60 °C provided the cycloadduct **5a** in 82% yield with α-selectivity (α : β = 1.4 : 1). After chromatographic separation of the anomeric mixture **5a**, **5a**-α and **5a**-β were stirred under a H_2 atmosphere (1 atm.) in the presence of 40 mol% of $Pd(OH)_2$ on carbon for 11 h at room temperature to give **6a**-α and **6a**-β respectively in excellent yield without epimerization at the anomeric position.

As shown in Scheme 3, the latent symmetry of **1a** also enabled us to synthesize an enantiomer of **4a** (***ent*-4a**). $NaBH_4$ reduction of **1a** followed by silylation using the standard procedure produced the silyl ether **7a** in 94% yield over two steps. Catalytic dihydroxylation of **7a** and oxidative work-up gave the aldehyde **8a** in 96% yield, then **8a** was converted to the 5,5-dimethoxypentan-1-ol derivative **9a** in 89% yield over two steps *via* dimethyl acetalization and desilylation by fluoride. According to the preparation of **4a**, the homologation reaction of aldehyde ***ent*-3a**, which was prepared by the Dess–Martin oxidation of **9a**, gave ***ent*-4a**. The tandem azidation–1,3-dipolar cycloaddition reaction of ***ent*-4a** catalyzed by $In(OTf)_3$ gave essentially the same results as in the case of **4a** (78% yield, α : β = 1 : 1.2).

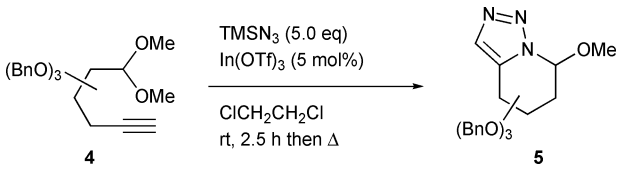
Diastereodivergent synthesis of triazolo-carbohydrate mimetics

Next, we carried out the diastereodivergent synthesis of triazolo-carbohydrate mimetics from D-mannose and D-galactose. Mimetics **4b** and ***ent*-4c**, and **4c** and ***ent*-4b**, were easily prepared from D-mannose and D-galactose respectively, according to the synthetic procedures for **4a** and ***ent*-4a** (see Experimental section). The results of the tandem azidation–1,3-dipolar cycloaddition reaction are summarized in Table 1. Compared to the case of **4a**, the reactions of **4b** and **4c** gave better results. By the reaction of **4b** at 80 °C for 11 h, *manno*-mimic **5b** was obtained in 91% yield as a mixture of anomeric diastereomers in a ratio of 1.2 : 1 (entry 1). Interestingly, the reaction at room temperature for 24 h gave only

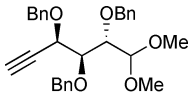
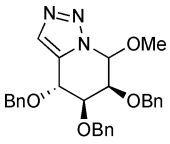
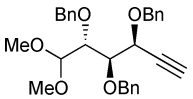
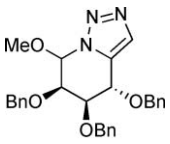
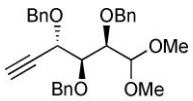
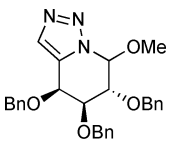
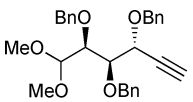
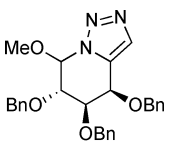


Scheme 3 Synthesis of ***ent*-5a**. *Reagents and conditions:* (a) $NaBH_4$, MeOH, rt, 2 h; (b) TBSCl, imidazole, DMF, rt, 3 h, 94% over 2 steps; (c) OsO_4, NMO, acetone–^{t}BuOH–H_2O (20 : 5 : 1), rt, 6 h, then $NaIO_4$, rt, 1 h, 96%; (d) $HC(OMe)_3$, *p*TsOH, rt, 45 min; (e) TBAF, THF, rt, 8 h, 89% over 2 steps; (f) Dess–Martin periodinane, CH_2Cl_2, rt, 2 h, 96%; (g) $CH_3COC(N_2)P(O)(OMe)_2$, K_2CO_3, MeOH, rt, 2 h; (h) $TMSN_3$, $In(OTf)_3$ (5 mol%), $ClCH_2CH_2Cl$, 0 °C, 4 h, then 80 °C, 8 h, 78% (α : β = 1 : 1.2).

Table 1 Tandem azidation–1,3-dipolar cycloaddition reactions of 1,1-dimethoxyhex-5-yne **4**

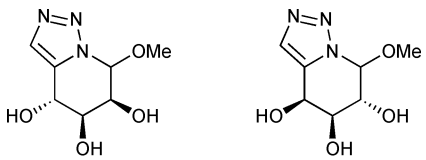


4 **5**

Entry	4	Temp./°C	Time/h	5	Yield[a]	α : β[b]
1	 **4b**	80	12	 **5b** (*manno*)	91	1.2 : 1
2		*rt*	16		26	β-only
3		*rt*	120		39	1 : 1.1
4[c]		60	24		66	1 : 1.1
5	 ***ent*-4b**	80	12	 ***ent*-5b** (*gulo*)	86	1.3 : 1
6	 **4c**	80	8	 **5c** (*galacto*)	90	1 : 1.8
7[c]		60	12		63	1.3 : 1
8	 ***ent*-4c**	80	8	 ***ent*-5c** (*altro*)	89	1 : 2.2

[a] Isolated yield. [b] Based on ^{1}H-NMR. [c] Solvent: hexane.

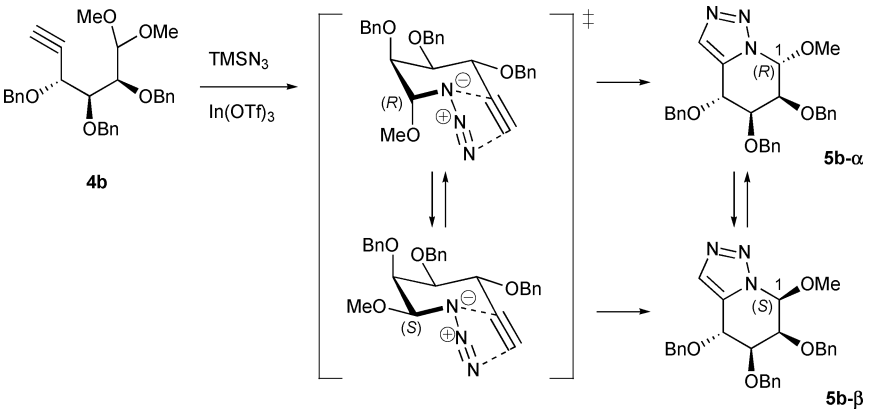
the β-anomer **5b-β** as the sole cycloadduct in 26% yield (entry 2), although a prolonged reaction time (120 h) at room temperature remarkably decreased the β-selectivity (entry 3).[15] In addition, carrying out the reaction in hexane for 24 h at 60 °C resulted in low β-selectivity with a reasonable product yield (66% yield, α : β = 1 : 1.1) (entry 4). Likewise, the reaction of **4c** in 1,2-dichloroethane gave the *galacto*-mimic **5c** in 90% yield with moderate β-selectivity and the reaction in hexane gave **5c** in 63% yield with α-selectivity (entry 6, α : β = 1 : 1.8; entry 7, α : β = 1.3 : 1). *gulo*-Mimic ***ent*-5b** and *altro*-mimic ***ent*-5c** were also obtained in 86% and 89% yield, respectively (entry 5, α : β = 1.3 : 1; entry 8, α : β = 1 : 2.1). Furthermore, *manno*- and *galacto*-cycloadducts **5b** and **5c** were debenzylated by the above hydrogenolysis conditions to give triols **6b** and **6c** in excellent yield without epimerization at the anomeric position (Fig. 2).



6b-α 88% **6b-β** 79% **6c-α** 83% **6c-β** 90%

Fig. 2 Synthesized *manno*- and *galacto*-mimetics.

Concerning the observed diastereoselectivity, we propose the mechanism of tandem azidation–1,3-dipolar cycloaddition reaction. An example with the 1,1-dimethoxyhex-5-yne derivative **4b** is shown in Scheme 4. It was found that the ^{1}H NMR of a crude mixture obtained by the reaction of **4b** with 5.0 molar



Scheme 4 Proposed reaction mechanism.

equivalents of $TMSN_3$ in the presence of 5 mol% of $In(OTf)_3$ at room temperature for 2.5 h, showed the formation of (1*R*)-azido ether and a mixture of (1*S*)-products, consisting of (1*S*)-azido ether and (1*S*)-bicyclic triazole **5b**-β. The ratio of (1*R*)-azido ether to (1*S*)-products was 1.8 : 1. This finding clearly supported the fact that (1*R*)-azido ether is a preferable product in the azidation step, while its intramolecular cycloaddition does not occur at room temperature due to the destabilization of its transition state by the *axial*-methoxy group. On the other hand, the (1*S*)-azido ether smoothly converts to the bicyclic triazole **5b**-β having *S* configuration at the anomeric position.[16] Prolonged reaction at room temperature should result in the epimerization of the initially formed **5b**-β at the anomeric position, catalyzed by $In(OTf)_3$.[9] With the reaction at a higher temperature, both diastereomers of the α-azido ether should stereospecifically convert to the corresponding cycloadduct **5b**, which finally falls into an appropriate ratio of α- and β-isomers *via* an epimerization process after the formation of **5b**-β from (1*S*)-azido ether and **5b**-α from (1*R*)-azido ether.

Conformational analysis of the triazolo-carbohydrate mimetics

Based on NMR studies of triazolo-carbohydrate mimetics **6** in D_2O (600 MHz), their unique conformational behaviors were revealed (Fig. 3). In both anomers of *gluco*-mimetic **6a**, ^3J coupling constants and NOE correlation between H2 and H4 clearly indicated that these mimetics occupy $^2H_3$ conformations: $J_{1,2}$ 3.2, $J_{2,3}$ 10.6, $J_{3,4}$ 7.1 Hz for **6a**-α and $J_{1,2}$ 6.8, $J_{2,3}$ 9.5, $J_{3,4}$ 8.4 Hz for **6a**-β. Furthermore, NOESY spectra of β-*gluco*-mimic **6a**-β also showed a strong correlation between H1 and H3, which supports its $^2H_3$ conformation, and a weak correlation between H1 and H2, although an NOE correlation between H3 and H4 was not observed. Since the H1–H2 correlation cannot be assigned to its $^2H_3$ conformation, we proposed that the β-*gluco*-mimic **6a**-β exists as an equilibrium mixture of the $^2H_3$ conformer and the $^{1,4}B$ conformer.[17] Furthermore, in tribenzyl ether **5a**-β (400 MHz, in $CDCl_3$), small coupling constants, $J_{1,2}$ 4.0, $J_{2,3}$ 6.2 and $J_{3,4}$ 7.4 Hz, and a relatively weak NOE correlation between H1 and H3, compared to a strong NOE correlation between H1 and H2, supported the assignment of the $^{1,4}B$ conformation to this molecule. A similar tendency was also observed in the NMR spectra of *galacto*-mimetic **6c**. That is, the α-anomer occupies the relatively stable $^2H_3$ conformation, while the β-anomer exists as an equilibrium mixture between the $^2H_3$ conformer and the $^{1,4}B$ conformer.[18] Previously, we confirmed that the anomeric effect of the triazolic N–C–O system is notably stronger than that of an O–C–O system such as in 2-methoxytetrahydropyran derivatives.[19] The present conformational behavior of triazolo-carbohydrate mimetics can be attributeted to the anomeric effect of the triazolic N–C–O moiety. In α-anomers, the anomeric effect of the triazolic N–C–O moiety stabilizes the $^2H_3$ conformation. In contrast, this anomeric effect possibly destabilizes the $^2H_3$ conformation of β-anomers to form detectable amounts of $^{1,4}B$ conformers.

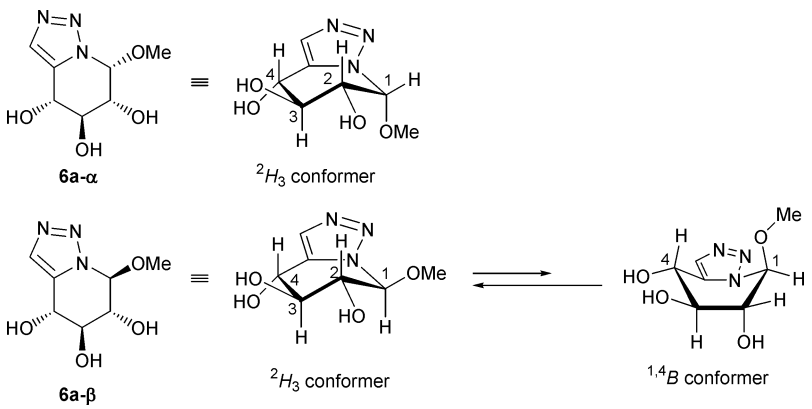


Fig. 3 Conformations of triazolo-glucose mimics **6a**.

Conclusion

We achieved the stereodivergent synthesis of triazole-fused glucose/idose mimetics through a tandem azidation–1,3-dipolar cycloaddition reaction. According to the common synthetic route, a chemical library of triazolo-carbohydrate mimetics with stereochemical diversity was also constructed. Since the present triazolo-carbohydrate mimetics have an sp^3-hybridized anomeric carbon, the existence of the anomeric effect at the triazolic N–C–O system was expected. NMR experiments in D_2O of the present *gluco*- and *galacto*-mimetics showed that the α-anomers occupy the relatively stable $^2H_3$ conformation. In contrast, the β-anomers exist as unstable $^2H_3$ conformers in equilibrium with $^{1,4}B$ conformers.

Experimental

General and materials

$In(OTf)_3$ is commercially available. All reactions were carried out under an argon atmosphere. ^1H and ^{13}C NMR spectra were taken on a Bruker dpx400 spectrometer, and chemical shifts were reported in parts per million (ppm) using $CHCl_3$ (7.26 ppm) in $CDCl_3$ or sodium 3-trimethylsilylpropionate-2,2,3,3-d_4 (TSP) (0.00 ppm) in D_2O for ^1H NMR, and $CDCl_3$ (77.01 ppm) or TSP (0.00 ppm) in D_2O for ^{13}C NMR as an internal standard, respectively. Infrared (IR) spectra were recorded on JASCO FT/IR-620 or JASCO FT/IR-4100 infrared spectrophotometers. Mass spectra (MS) were obtained on a Micromass LCT (ESI-TOF). Medium pressure liquid chromatography (MPLC) was performed using prepacked columns (KUSANO prepacked column Si-10, 40 × 300 mm i. d., silica gel, 50 μm) with a UV detector.

Preparation of triazolo-glucose mimic (6a)

(2*R*,3*S*,4*R*)-2,3,4-Tri(benzyloxy)-1,1-dimethoxyhex-5-ene (2a). (2*R*,3*S*,4*R*)-2,3,4-Tribenzyloxyhex-5-enal **1a** (24 mmol, 10.0 g)[12] was treated with *p*-toluenesulfonic acid monohydrate (*p*TsOH·H_2O, 200 mg, 20 μmol) in trimethyl orthoformate (200 mL) for 45 min at room temperature. The reaction mixture was quenched with saturated $NaHCO_3$ aqueous solution (200 mL), followed by extraction with EtOAc (150 mL × 3). The organic layer was washed with brine (100 mL), dried over $MgSO_4$, and evaporated. The residue was purified by column chromatography on silica gel (hexane–EtOAc = 20 : 1) to give **2a** in 91% yield (10.1 g, 21.8 mmol). Colorless oil. $[\alpha]_D^{25}$ (*c* 1.00, $CHCl_3$) −22.8; IR (neat) *ν* 3031, 2908, 1496, 1454, 1072, 735 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) *δ* 3.25 (3H, s), 3.42 (3H, s), 3.58 (1H, dd, *J* = 6.6, 3.0 Hz), 3.73 (1H, dd, *J* = 7.4, 3.0 Hz), 4.16 (1H, m), 4.41 (1H, *J* = 11.7 Hz), 4.47 (1H, *J* = 6.6 Hz), 4.55 (1H, d, *J* = 11.6 Hz), 4.61 (1H, d, *J* = 11.7 Hz), 4.67 (1H, d, *J* = 11.6 Hz), 4.86 (1H, d, *J* = 11.6 Hz), 4.92 (1H, d, *J* = 11.5 Hz), 5.23 (1H, brd, *J* = 17.6 Hz), 5.25 (1H, dd, *J* = 10.6, 1.8 Hz), 5.77 (1H, ddd, *J* = 17.6, 10.6, 7.7 Hz), 7.25–7.36 (15H, m). ^{13}C NMR (100.6 MHz, $CDCl_3$) *δ* 54.5, 56.1, 70.7, 73.9, 75.0, 78.8, 81.3, 81.9, 105.6, 119.1, 127.29, 127.34, 127.4, 127.8, 127.9, 128.16, 128.18, 128.3, 138.6, 139.0, 139.1. MS (ESI-TOF) *m/z* 485 [M + Na]$^+$. HRMS calcd for $C_{29}H_{34}NaO_5$ [M + Na]$^+$, 485.2304; found: 485.2282.

(2*S*,3*S*,4*R*)-Tri(benzyloxy)-5,5-dimethoxypentanal (3a). To a solution of 4-methylmorpholine *N*-oxide (NMO, 3.9 g, 34 mmol), *tert*-butyl alcohol (20 mL) and **2a** (9.3 g, 20 mmol) in acetone (640 mL), a solution of OsO_4 in H_2O (0.11 M, 90 mL, 1.7 mmol) was added. After being stirred for 7 h at room temperature, the resultant mixture was treated with $NaIO_4$ (40 g) for 1 h at room temperature. The reaction mixture was filtered through a pad of celite. Afterwards, the filtrate was extracted with EtOAc (100 mL × 3) and the organic layer was washed with brine (100 mL), dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (hexane–EtOAc = 10 : 1) to give aldehyde **3a** (7.36 g, 15.8 mmol) in 79% yield. Colorless oil. $[\alpha]_D^{25}$ (*c* 1.00, $CHCl_3$) +2.48; IR (neat) ν 3031, 2932, 1729, 1455, 1092, 734 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) *δ* 3.29 (3H, s), 3.43 (3H, s), 3.69–3.74 (1H, m), 3.84 (1H, dd, *J* = 5.7, 2.9 Hz), 3.99–4.04 (1H, m), 4.45–4.52 (3H, m), 4.56 (1H, d, *J* = 11.7 Hz), 4.62 (1H, d, *J* = 11.7 Hz), 4.68 (1H, d, *J* = 10.7 Hz), 4.78 (1H, d, *J* = 12.0 Hz), 7.19–7.37 (15H, m), 9.72 (1H, d, *J* = 3.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 54.3, 56.5, 72.9, 73.7, 73.9, 77.3, 79.5, 80.3, 105.4, 127.4, 127.8, 127.9, 127.9, 128.1, 128.3, 128.3, 128.4, 128.4, 137.4, 137.6, 137.9, 200.1; MS (ESI-TOF) *m/z* 487 [M + Na]$^+$; HRMS calcd for $C_{28}H_{32}O_6Na$ [M + Na]$^+$, 487.2097; found, 487.2094.

(2*R*,3*S*,4*R*)-2,3,4-Tri(benzyloxy)-1,1-dimethoxyhex-5-yne (4a). To a solution of **3a** (0.93 g, 2.0 mmol) in MeOH (20 mL), K_2CO_3 (0.83 g, 6.0 mmol) and Ohira–Bestmann reagent (1.34 g, 7.0 mmol) were added. After being stirred for 2 h at room temperature, the reaction mixture was filtered through a pad of celite and the resulting filtrate was concentrated under reduced pressure. Purification of the residue by column chromatography on silica gel (hexane–EtOAc = 10 : 1) followed by MPLC (hexane–EtOAc = 10 : 1) gave **4a** in 76% yield (700.1 mg, 1.52 mmol). Colorless oil. $[\alpha]_D^{25}$ (*c* 1.00, $CHCl_3$) −37.8; IR (neat) *ν* 3282, 3063, 2930, 1454, 1096, 1027, 736, 697 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) *δ* 2.54 (1H, d, *J* = 2.0 Hz), 3.28 (3H, s), 3.48 (3H, s), 3.95 (2H, d, *J* = 7.6 Hz), 4.51–4.63 (3H, m), 4.68 (2H, brd, *J* = 11.1 Hz), 4.89 (1H, d, *J* = 11.5 Hz), 4.90 (1H, d, *J* = 11.1 Hz), 4.99 (1H, d, *J* = 11.1 Hz), 7.23–7.44 (15H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 54.2, 56.3, 71.5, 71.6, 74.9, 75.3, 76.1, 79.2, 80.5, 81.2, 105.5, 127.4, 127.7, 128.1, 128.1, 128.2, 128.2, 128.3, 137.6, 138.6, 138.7; MS (ESI-TOF) *m/z* 483 [M + Na]$^+$; HRMS calcd for $C_{29}H_{32}O_5Na$ [M + Na]$^+$, 483.2147; found, 483.2144.

(4*R*,5*S*,6*R*,7*R*)-4,5,6-Tri(benzyloxy)-7-methoxy-4,5,6,7-tetrahydro[1,2,3]triazolo[1,5-*a*]pyridine (5a-α) and (4*R*,5*S*,6*R*,7*S*)-4,5,6-tri(benzyloxy)-7-methoxy-4,5,6,7-tetrahydro[1,2,3]triazolo[1,5-*a*]-pyridine (5a-β). To a suspension of $In(OTf)_3$ (14.1 mg, 25 μmol) in 1,2-dichloroethane (5.0 mL), $TMSN_3$ (317 μL, 2.5 mmol) and a solution of **4a** (230 mg, 0.50 mmol) in 1,2-dichloroethane (2.0 mL) were added at 0 °C. After being stirred for 4 h at the same temperature, the resulting mixture was heated at 80 °C for 8 h. The reaction mixture was quenched with H_2O, extracted with EtOAc and dried over $MgSO_4$. Evaporation of the organic layer followed by purification by column chromatography on silica gel (hexane–EtOAc = 2 : 1) gave a mixture of anomers. This anomeric mixture was separated by MPLC (hexane–EtOAc = 1 : 1) to give **5a-**β (96.6 mg, 0.205 mmol, 41% yield) and **5a-**α (80.1 mg, 0.170 mmol, 34% yield). **5a-**α was the more polar isomer. White amorphous solid. Mp. 97.9–99.8 °C; $[\alpha]_D^{25}$ (*c* 0.52, $CHCl_3$) −32.4; IR (neat) *ν*

3062, 3030, 2932, 1454, 1363, 1203, 1162, 1096, 739, 698 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.54 (3H, s), 3.75 (1H, dd, $J = 10.1$, 3.2 Hz), 4.50 (1H, dd, $J = 10.1$, 6.9 Hz), 4.73–4.80 (4H, m), 4.87 (1H, d, $J = 11.0$ Hz), 4.91 (1H, d, $J = 12.1$ Hz), 5.12 (1H, d, $J = 11.0$ Hz), 5.56 (1H, d, $J = 3.2$ Hz), 7.29–7.42 (15H, m), 7.52 (1H, s). ^{13}C NMR (100 MHz, $CDCl_3$) δ 58.1, 72.8, 73.5, 73.7, 75.5, 78.1, 79.4, 84.7, 127.9, 128.1, 128.1, 128.2, 128.2, 128.4, 128.5, 128.6, 128.7, 132.6, 133.4, 137.2, 137.2, 138.1; MS (ESI-TOF) m/z 472 $[M + H]^+$; HRMS calcd for $C_{28}H_{30}N_3O_4$ $[M + H]^+$, 472.2236; found, 472.2214. **5a-β** was the less polar isomer. Colorless oil. $[\alpha]_D^{25}$ (c 0.50, $CHCl_3$) −34.6; IR (neat) ν 3062, 3031, 1454, 1359, 1224, 1156, 1090, 739, 698 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.61 (3H, s), 3.83 (1H, dd, $J = 7.4$, 6.2 Hz), 4.02 (1H, dd, $J = 6.2$, 4.0 Hz), 4.69 (1H, d, $J = 11.5$ Hz), 4.73 (1H, d, $J = 11.5$ Hz), 4.75 (1H, d, $J = 11.4$ Hz), 4.79 (1H, d, $J = 11.4$ Hz), 4.81 (1H, d, $J = 7.4$ Hz), 4.83 (1H, d, $J = 11.6$ Hz), 4.88 (1H, d, $J = 11.6$ Hz), 5.60 (1H, d, $J = 4.0$ Hz), 7.29–7.38 (15H, m), 7.60 (1H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 58.5, 73.8, 73.8, 74.0, 74.4, 80.9, 82.5, 88.9, 127.9, 128.0, 128.0, 128.1, 128.1, 128.5, 128.6, 128.6, 130.8, 134.5, 137.1, 137.3, 137.6; MS (ESI-TOF) m/z 472 $[M + H]^+$; HRMS calcd for $C_{28}H_{30}N_3O_4$ $[M + H]^+$, 472.2236; found, 472.2213.

(4*R*,5*S*,6*R*,7*R*)-4,5,6-Trihydroxy-7-methoxy-4,5,6,7-tetrahydro-[1,2,3]triazolo[1,5-*a*]pyridine (6a-α). To a suspension of 20% $Pd(OH)_2$ on carbon (50 mg) in MeOH (1.0 mL), a solution of **5a-**α (33.1 mg, 70 μmol) in MeOH (2.0 mL) was added. After being stirred at room temperature for 11 h under a H_2 atmosphere (1 atm.), the reaction mixture was filtered. The filtrate was concentrated under reduced pressure, and purified by column chromatography on silica gel ($CHCl_3$–MeOH = 10 : 1) to give **6a-**α (13.8 mg, 68.8 μmol) in 96% yield. Colorless oil. $[\alpha]_D^{25}$ (c 1.00, CH_3OH) +71.5; IR (neat) ν 3031, 2908, 1496, 1454, 1072, 735 cm^{-1}; ^1H NMR (400 MHz, D_2O) δ 3.65 (3H, s), 4.07–4.12 (1H, m), 4.14 (1H, dd, $J = 10.6$, 7.1 Hz), 4.82 (1H, d, $J = 7.1$ Hz), 5.90 (1H, d, $J = 3.2$ Hz), 7.90 (1H, s); ^{13}C NMR (100 MHz, D_2O) δ 60.5, 68.4, 71.1, 73.5, 88.6, 134.2, 138.3; MS (ESI-TOF) m/z 202 $[M + H]^+$; HRMS calcd for $C_7H_{12}N_3O_4$ $[M + H]^+$, 202.0828; found, 202.0821.

(4*R*,5*S*,6*R*,7*S*)-4,5,6-Trihydroxy-7-methoxy-4,5,6,7-tetrahydro-[1,2,3]triazolo[1,5-*a*]pyridine (6a-β). This compound was prepared according to the synthesis of **6a-**α and obtained in 95% yield (12.2 mg, 60.6 μmol) by the reaction of **5a-**β (30.1 mg, 64 μmol), $Pd(OH)_2$ on carbon (20 w/w%, 50 mg) and H_2 (1 atm.) in MeOH (2.5 mL). Colorless oil. $[\alpha]_D^{25}$ (c 0.50, CH_3OH) −26.6; IR (neat) ν 3031, 2908, 1496, 1454, 1072, 735 cm^{-1}; ^1H NMR (400 MHz, D_2O) δ 3.83 (3H, s), 3.85 (1H, dd, $J = 9.5$, 8.4 Hz), 4.09 (1H, dd, $J = 9.5$, 6.8 Hz), 4.89 (1H, d, $J = 6.8$ Hz), 5.67 (1H, d, $J = 6.8$ Hz), 7.87 (1H, s); ^{13}C NMR (100 MHz, D_2O) δ 60.9, 67.9, 73.6, 75.6, 92.5, 133.2, 139.0; ESI-MS (m/z) 202 $[M + H]^+$; HRMS calcd for $C_7H_{12}N_3O_4$ $[M + H]^+$, 202.0828; found, 202.0821.

Preparation of triazolo-idose mimic (*ent*-5a)

***tert*-Butyl(dimethyl){[(2*S*,3*S*,4*R*)-2,3,4-tri(benzyloxy)hex-5-enyl]-oxy}silane (7a).** To a solution of (2*S*,3*S*,4*R*)-2,3,4-tris-(benzyloxy)hex-5-en-1-ol (2.1 g, 5.0 mmol),[20] which was prepared by $NaBH_4$ reduction of **1a**, and imidazole (510 mg, 7.5 mmol) in DMF (5 mL), *tert*-butylchlorodimethylsilane (905 mg, 6.0 mmol) was added at 0 °C. After being stirred at room temperature for 3 h, the reaction mixture was quenched with H_2O (25 mL) and extracted with hexane (25 mL × 3). The combined organic layer was dried over $MgSO_4$ and evaporated. The residue was purified by column chromatography on silica gel (hexane–EtOAc = 50 : 1) to give the TBS ether **7a** in 94% yield (2.76 g, 4.70 mmol). Colorless oil. $[\alpha]_D^{25}$ (c 1.01, $CHCl_3$) −7.96; IR (neat) ν 3031, 2928, 2856, 1455, 1254, 1092, 1028, 837, 733, 697 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.00 (6H, s), 0.88 (9H, s), 3.61–3.75 (4H, m), 4.16 (1H, t, $J = 6.6$ Hz), 4.41 (1H, d, $J = 11.5$ Hz), 4.56 (1H, d, $J = 11.7$ Hz), 4.63 (1H, d, $J = 11.7$ Hz), 4.71 (2H, d, $J = 11.8$ Hz), 4.83 (1H, d, $J = 11.5$ Hz), 5.25 (1H, brd, $J = 14.7$ Hz), 5.28 (1H, brd, $J = 8.0$ Hz), 5.77–5.89 (1H, m), 7.23–7.38 (15H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ −5.5, 18.1, 25.9, 62.7, 70.7, 73.0, 75.1, 80.0, 81.1, 81.5, 118.6, 127.4, 127.4, 127.8, 128.0, 128.1, 128.2, 128.2, 128.4, 135.7, 138.5, 138.8, 138.9; MS (ESI-TOF) m/z 555 $[M + Na]^+$; HRMS calcd for $C_{33}H_{44}NaO_4Si$ $[M + Na]^+$, 555.2907; found, 555.2884.

(2*S*,3*R*,4*S*)-2,3,4-Tri(benzyloxy)-5-{[*tert*-butyl(dimethyl)silyl]-oxy}pentanal (8a). Aldehyde **8a** was obtained in 96% yield (2.30 g, 4.30 mmol) by the reaction of **7a** (2.4 g, 4.5 mmol), OsO_4 (0.11 M in H_2O, 4.0 mL, 0.44 mmol) and NMO (1.4 g, 12 mmol) in a mixture of acetone (65 mL), H_2O (15 mL) and *tert*-butyl alcohol (2 mL) for 6 h at room temperature, followed by treatment of the reaction mixture with $NaIO_4$ (10 g) for 1 h at the same temperature. Colorless oil. $[\alpha]_D^{25}$ (c 1.03, $CHCl_3$) −11.1; IR (neat) ν 3031, 2952, 2857, 1731, 1455, 1255, 1092, 1028, 838, 735, 697 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.00 (6H, s), 0.89 (9H, s), 3.55–3.61 (1H, m), 3.67–3.77 (2H, m), 3.92 (1H, dd, $J = 5.4$, 1.6 Hz), 3.98–4.03 (1H, m), 4.47–4.55 (3H, m), 4.59 (1H, d, $J = 11.8$ Hz), 4.67 (1H, d, $J = 11.8$ Hz), 4.79 (1H, d, $J = 12.0$ Hz), 7.23–7.38 (15H, m), 9.73 (1H, d, $J = 1.6$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ −5.5, −5.5, 18.1, 25.8, 61.6, 72.9, 73.1, 74.1, 78.2, 78.7, 81.2, 127.7, 128.0, 128.2, 128.4, 128.4, 137.3, 137.7, 138.0, 200.7; MS (ESI-TOF) m/z 557 $[M + Na]^+$; HRMS calcd for $C_{32}H_{42}NaO_5Si$ $[M + Na]^+$, 557.2699; found, 557.2687.

***tert*-Butyl(dimethyl){[(2*S*,3*R*,4*S*)-2,3,4-tri(benzyloxy)-5,5-dimethoxypentyl]oxy}silane.** This compound was obtained in 100% yield (3.90 g, 3.89 mmol) by the reaction of **8a** (2.1 g, 3.9 mmol) and $HC(OMe)_3$ (10 mL) in the presence of pTsOH·H_2O (100 mg) for 45 min at room temperature. Colorless oil. $[\alpha]_D^{25}$ (c 1.00, $CHCl_3$) +7.20; IR (neat) ν 3031, 2929, 2856, 1454, 1254, 1090, 1028, 836, 733, 697 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.00 (6H, s), 0.88 (9H, s), 3.26 (3H, s), 3.43 (3H, s), 3.58 (1H, dd, $J = 10.9$, 5,5 Hz), 3.68–3.74 (2H, m), 3.75–3.81 (1H, m), 3.83–3.88 (1H, m), 4.45 (1H, d, $J = 6.2$ Hz), 4.63 (1H, d, $J = 11.7$ Hz), 4.65 (1H, d, $J = 11.4$ Hz), 4.66 (1H, d, $J = 11.7$ Hz), 4.73 (2H, d, $J = 11.7$ Hz), 4.87 (1H, d, $J = 11.5$ Hz), 7.21–7.39 (15H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ −5.4, 18.2, 25.9, 54.2, 55.9, 63.4, 72.9, 74.0, 74.6, 78.2, 78.3, 80.4, 105.5, 127.3, 127.4, 127.4, 127.9, 128.1, 128.1, 128.3, 138.7, 138.8, 138.9; MS (ESI-TOF) m/z 603 $[M + Na]^+$; HRMS calcd for $C_{34}H_{48}NaO_6Si$ $[M + Na]^+$, 603.3118; found, 603.3132.

(2*S*,3*R*,4*S*)-2,3,4-Tri(benzyloxy)-5,5-dimethoxypentan-1-ol (9a). To a solution of *tert*-butyl(dimethyl){[(2*S*,3*R*,4*S*)-2,3,4-tris-(benzyloxy)-5,5-dimethoxypentyl]oxy}silane (3.9 g, 3.9 mmol) in THF (5.0 mL), tetrabutylammonium fluoride (TBAF, 1.0 M in

THF, 7.5 mL, 7.5 mmol) was added. After being stirred for 8 h at room temperature, the reaction mixture was evaporated. The residue was dissolved in H_2O (20 mL) and extracted with EtOAc (20 mL × 3). The organic layer was washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. Chromatographic purification of the resulting residue on silica gel (hexane–EtOAc = 3 : 1) gave alcohol **7a** in 89% yield (1.66 g, 3.47 mmol). Colorless oil. $[\alpha]_D^{25}$ (*c* 1.00, $CHCl_3$) −0.03; IR (neat) *ν* 3460, 3030, 2933, 1454, 1070, 1028, 735, 698 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) *δ* 2.13 (1H, brs, OH), 3.31 (3H, s), 3.43–3.52 (1H, m), 3.50 (3H, s), 3.65–3.72 (2H, m), 3.73–3.79 (1H, m), 3.88–3.93 (1H, m), 4.57 (1H, d, $J = 6.3$ Hz), 4.61–4.73 (4H, m), 4.81 (1H, d, $J = 11.4$ Hz), 4.93 (1H, d, $J = 11.4$ Hz), 7.26–7.43 (15H, m); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 54.2 56.0, 61.7, 72.8, 73.7, 74.6, 77.6, 78.4, 79.5, 105.3, 127.6, 127.7, 127.9, 128.2, 128.4, 138.3, 138.3, 138.4; MS (ESI-TOF) *m/z* 489 $[M + Na]^+$; HRMS calcd for $C_{28}H_{34}NaO_6$ $[M + Na]^+$, 489.2253; found: 489.2259.

(2*R*,3*R*,4*S*)-2,3,4-Tri(benzyloxy)-5,5-dimethoxypentanal (*ent*-3a). To a solution of **9a** (1.4 g, 3.0 mmol) in CH_2Cl_2, Dess-Martin periodinane (DMP, 1.87 g, 4.5 mmol) was added. After being stirred for 2 h at room temperature, the reaction mixture was treated with pentane (15 mL) and filtered through a pad of celite. The filtrate was concentrated under reduced pressure. Purification of the residue by column chromatography on silica gel (hexane–EtOAc = 5 : 1) gave the 5,5-dimethoxypentanal derivative ***ent*-3a** in 96% yield (1.34 g, 2.88 mmol). The physical data of ***ent*-3a** were coincident with those of **3a**, except for the specific optical rotation: $[\alpha]_D^{25}$ (*c* 1.10, $CHCl_3$) −2.46.

(2*S*,3*R*,4*S*)-2,3,4-Tri(benzyloxy)-1,1-dimethoxyhex-5-yne (*ent*-4a). This compound was prepared from ***ent*-3a** under the same conditions as in the case of **4a**. The physical data of ***ent*-4a** were coincident with those of **4a**, except for the specific optical rotation: $[\alpha]_D^{25}$ (*c* 1.06, $CHCl_3$) +39.6.

(4*S*,5*R*,6*S*,7*S*)-4,5,6-Tri(benzyloxy)-7-methoxy-4,5,6,7-tetrahydro[1,2,3]triazolo[1,5-*a*]pyridine (*ent*-5a-α) and (4*S*,5*R*,6*S*,7*R*)-4,5,6-tri(benzyloxy)-7-methoxy-4,5,6,7-tetrahydro[1,2,3]triazolo-[1,5-*a*]pyridine (*ent*-5a-β). These compounds were prepared according to the synthetic procedure for **5a** and obtained in 78% yield (***ent*-5a-**α 70.7 mg, 0.15 mmol, 30% yield; ***ent*-5a-**β 113.2 mg, 0.24 mmol, 48% yield) by the reaction of ***ent*-4a** (230.1 mg, 0.50 mmol) and $TMSN_3$ (317 μL, 2.5 mmol) in the presence of $In(OTf)_3$ (13.9 mg, 25 μmol) in 1,2-dichloroethane (7.0 mL). The physical data of ***ent*-5a-**α were coincident with those of **5a-**α, except for the specific optical rotation: $[\alpha]_D^{25}$ (*c* 0.49, $CHCl_3$) +32.1. The physical data of ***ent*-5a-**β were also coincident with those of **5a-**β, except for the specific optical rotation: $[\alpha]_D^{25}$ (*c* 0.50, $CHCl_3$) +34.1.

Notes and References

1 (*a*) W.-Q. Fan, A. R. Katritzky, 1,2,3-Triazoles, In *Comprehensive Heterocyclic Chemistry II*, ed. A. R. Katritzky, C. W. Rees, E. F. and V. Scriven, Elsevier, Oxford, 1996, vol. 4, 1–126, pp. 905–1006; (*b*) M. Whiting, J. Muldoon, Y.-C. Lin, S. M. Silverman, W. Lindstrom, A. J. Olson, H. C. Kolb, M. G. Finn, K. B. Sharpless, J. H. Elder and V. V. Fokin, *Angew. Chem., Int. Ed.*, 2006, **45**, 1435–1439; (*c*) Y. Bourne, H. C. Kolb, Z. Radić, K. B. Sharpless, P. Taylor and P. Marchot, *Proc. Natl. Acad. Sci. U. S. A.*, 2004, **101**, 1449–1454; (*d*) W. G. Lewis, L. G. Green, F. Grynszpan, Z. Radić, P. R. Carlier, P. Taylor, M. G. Finn and K. B. Sharpless, *Angew. Chem., Int. Ed.*, 2002, **41**, 1053–1057.

2 (*a*) R. Alvarez, S. Velazquez, A. San-Felix, S. Aquaro, E. de Clercq, C.-F. Perno, A. Karlsson, J. Balzarini and M. J. Camarasa, *J. Med. Chem.*, 1994, **37**, 4185–4194; (*b*) M. J. Genin, D. A. Allwine, D. J. Anderson, M. R. Barbachyn, D. E. Emmert, S. A. Garmon, D. R. Graber, K. C. Grega, J. B. Hester, D. K. Hutchinson, J. Morris, R. J. Reischer, C. W. Ford, G. E. Zurenko, J. C. Hamel, R. D. Schaadt, D. Stapert and B. H. Yagi, *J. Med. Chem.*, 2000, **43**, 953–970; (*c*) L. S. Kallander, Q. Lu, W. Chen, T. Tomaszek, G. Yang, D. Tew, T. D. Meek, G. A. Hofmann, C. K. Schulz-Pritchard, W. W. Smith, C. A. Janson, M. D. Ryan, G.-F. Zhang, K. O. Johanson, R. B. Kirkpatrick, T. F. Ho, P. W. Fisher, M. R. Mattern, R. K. Johnson, M. J. Hansbury, J. D. Winkler, K. W. Ward, D. F. Veber and S. K. Thompson, *J. Med. Chem.*, 2005, **48**, 5644–5647; (*d*) M. S. Costa, N. Boechat, E. A. Rangel, F. C. da Silva, A. M. T. de Souza, C. R. Rodrigues, H. C. Castro, I. N. Junior, M. C. S. Lourenço, S. M. S. V. Wardell and V. F. Ferreira, *Bioorg. Med. Chem.*, 2006, **14**, 8644–8653; (*e*) V. D. Bock, D. Speijer, H. Hiemstra and J. H. van Maarseveen, *Org. Biomol. Chem.*, 2007, **5**, 971–975.

3 R. Huisgen, 1,3-Dipolar Cycloadditions, in *1,3-Dipolar Cycloaddition Chemistry*, ed. A. Padwa, Wiley, New York, 1984, vol. 1, pp. 1–176.

4 (*a*) V. V. Rostovtsev, L. G. Green, V. V. Fokin and K. B. Sharpless, *Angew. Chem., Int. Ed.*, 2002, **41**, 2596–2599; (*b*) V. O. Rodionov, V. V. Fokin and M. G. Finn, *Angew. Chem., Int. Ed.*, 2005, **44**, 2210–2215; (*c*) C. W. Tornøe, C. Christensen and M. Meldal, *J. Org. Chem.*, 2002, **67**, 3057–3064.

5 (*a*) H. C. Kolb, M. G. Finn and K. B. Sharpless, *Angew. Chem., Int. Ed.*, 2001, **40**, 2004–2021; (*b*) K. C. Kolb and K. B. Sharpless, *Drug Discovery Today*, 2003, **8**, 1128–1137; (*c*) Y. L. Angell and K. Burgess, *Chem. Soc. Rev.*, 2007, **36**, 1674–1689.

6 (*a*) J. F. Billing and U. J. Nilsson, *J. Org. Chem.*, 2005, **70**, 4847–4850; (*b*) A. Ray, K. Manoj, M. M. Bhadbhade, R. Mukhopadhyay and A. Bhattacharjya, *Tetrahedron Lett.*, 2006, **47**, 2775–2778; (*c*) S. Chandrasekhar, C. L. Rao, C. Nagesh, C. R. Reddy and B. Sridhar, *Tetrahedron Lett.*, 2007, **48**, 5869–5872.

7 (*a*) T. D. Heightman, M. Locatelli and A. Vasella, *Helv. Chim. Acta*, 1996, **79**, 2190–2200; (*b*) N. Panday, M. Meyyappan and A. Vasella, *Helv. Chim. Acta*, 2000, **83**, 513–538; (*c*) N. Panday and A. Vasella, *Helv. Chim. Acta*, 2000, **83**, 1205–1208.

8 (*a*) T. Flessner and C.-H. Wong, *Tetrahedron Lett.*, 2000, **41**, 7805–7808; (*b*) M. L. Mitchell, F. Tian, L. V. Lee and C.-H. Wong, *Angew. Chem., Int. Ed.*, 2002, **41**, 3041–3044.

9 H. Yanai and T. Taguchi, *Tetrahedron Lett.*, 2005, **46**, 8639–8643.

10 For an intramolecular cycloaddition of azidoalkyne derivatives derived from monosaccharides under thermal conditions, see: F. Dolhem, F. Tahli, C. Lièvre and G. Demailly, *Eur. J. Org. Chem.*, 2005, 5019–5023.

11 H. Yanai, S. Saito and T. Taguchi, *Tetrahedron*, 2005, **61**, 7087–7093.

12 M. Kleban, U. Kautz, J. Greul, P. Hilgers, R. Kugler, H.-Q. Dong and V. Jaeger, *Synthesis*, 2000, 1027–1033.

13 S. Ohira, *Synth. Commun.*, 1989, **19**, 561–564.

14 Under simply thermal conditions, the intramolecular cycloaddition of the isolated α-azido ether needed a prolonged reaction time (24 h) for the complete consumption of the α-azido ether (**5a** 77%, α : β = 1.4 : 1). This finding indicates that $In(OTf)_3$ accelerates the reaction rate of the cycloaddition step.

15 The formation of cycloadduct at room temperature was observed only in the reaction of **4b**.

16 C. Herdeis and J. Telser, *Eur. J. Org. Chem.*, 1999, 1407–1414.

17 For an example of the detection of an equilibrium between boat and chair conformers by NOESY spectra see: T. Sakakibara, T. Suganuma and Y. Kajihara, *Chem. Commun.*, 2007, 3568–3570.

18 NOESY spectra of both α-*manno*-mimetic **6b-**α and β-*manno*-mimetic **6b-**β showed weak H3–H4 correlations. This finding strongly indicates the low stability of these $^2H_3$ conformers.

19 H. Yanai, Y. Dobashi, M. Nakayashiki, and T. Taguchi, unpublished result.

20 J. Désiré and J. Prandi, *Eur. J. Org. Chem.*, 2000, 3075–3084.