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ORIGINAL ARTICLE

Preparation of L-vancosamine-related glycosyl donors

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An improved practical synthesis of L-vancosamine-related glycosyl donors is described. The key steps include (1) stereoselective addition of methylcerium reagent to oximino ether and (2) stereoselective hydrogenation of exocyclic unsaturated glycoside in the presence of Wilkinson catalyst with C(5) inversion to give L-vancosamine derivatives. Three glycosyl donors were prepared, and their reactivities in the aryl *C*-glycoside formation were compared. Conversion of primary amine and azide to the corresponding *N,N*-dimethyl derivative is also described.
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Keywords: glycosyl donor; L-vancosamine; practical synthesis

INTRODUCTION

L-Vancosamine and its *N*,*N*-dimethyl derivative are found as the sugar constituents of several antibiotics. For example, L-vancosamine[1,2] is included in vancomycin, a glycopeptide antibiotic that is important for the treatment of methicillin-resistant *Staphylococcus aureus*.[3] The *N*,*N*-dimethyl analog occurs as an *O*-glycoside in the nocardicyclin antibiotics[4,5] and as a *C*-glycoside in the pluramycin–hedamycin class antibiotics (Figure 1).[6–8]

Many methods have been recorded for synthesizing the vancosamine derivatives starting either from carbohydrates[9–16] or non-carbohydrates.[17–28] However, most of the methods had problems on practicality; for example, use of toxic reagents or expensive starting materials. Herein, we record a viable method for preparing glycosyl donors of L-vancosamine derivatives.

RESULTS AND DISCUSSION

The route is primarily based on the report by Thang *et al.*,[29] which has been improved[30] in terms of the stereoselectivity, and thus overall efficiency. The starting material was a known ketone **1** [31] derived from commercially available methyl α-D-mannopyranoside, treatment of which with *O*-methyl hydroxylamine hydrochloride

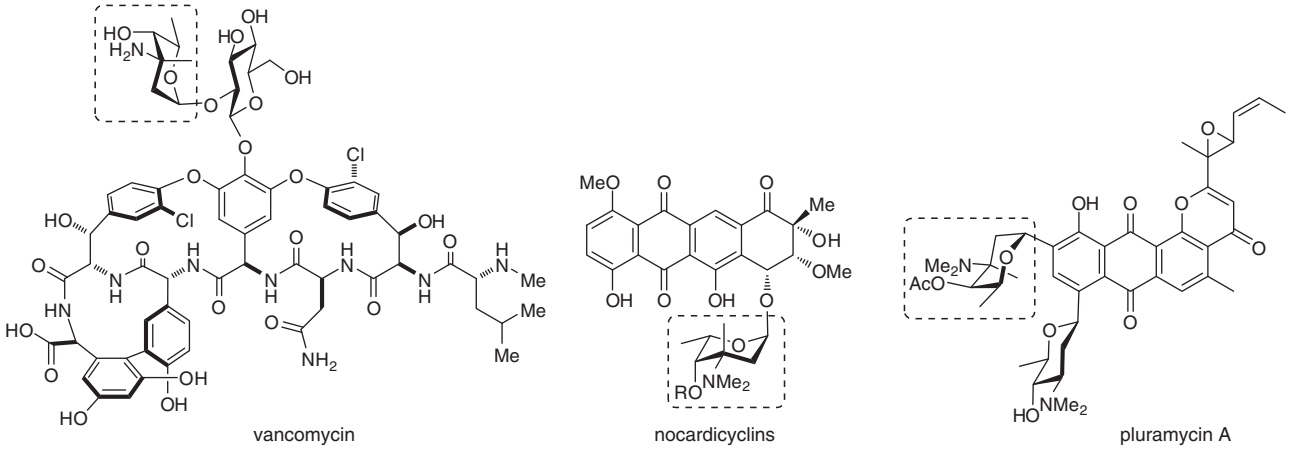

Figure 1 L-Vancosamine in antibiotic structures.

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Dedicated to Professor Kuniaki Tatsuta for his great synthetic expeditions, having conquered 101 peaks, including the 4 major antibiotics.
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(NaOAc, MeOH, room temperature, 6 h) gave oximino ether **2** in 86% yield. Treatment of **2** with the methylcerium species,[32,33] generated by mixing MeLi and anhydrous $CeCl_3$ (tetrahydrofuran (THF), −78 °C→0 °C, 4 h), gave amine **3** as a single product. The stereostructure of **3** was assigned by the NOE experiment as shown in Figure 2. After conversion of amine **3** to trifluoroacetamide **4** [$(CF_3CO)_2O$, pyridine, 4-(dimethylamino)pyridine (DMAP), CH_2Cl_2, 30 min], the N–O bond was cleaved with samarium iodide[34,35] (MeOH, THF, 0 °C, 30 min), giving amide **5** in 95% yield. Recrystallization (EtOAc, hexane) gave nice single crystals of **5** suitable for X-ray analysis, confirming the stereochemical identity (Figure 3 and Scheme 1).

The benzylidene acetal in **5** was cleaved with *N*-bromosuccinimide[36,37] (pyridine, CCl_4, reflux, 4 h) to give bromide **6** in 87% yield. Note that this process should be conducted at low concentration (<30 mM): When performed at higher concentration the yield was not reproducible, and unidentified products were produced presumably by the competing bromination of the trifluoroacetamide in **5**.[38] Recrystallization (Et_2O, hexane) gave nice single crystals of **6** suitable for X-ray analysis (Figure 4), confirming that the benzylidene acetal in **5** was

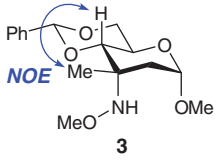


Figure 2 NOE study of amine **3**.

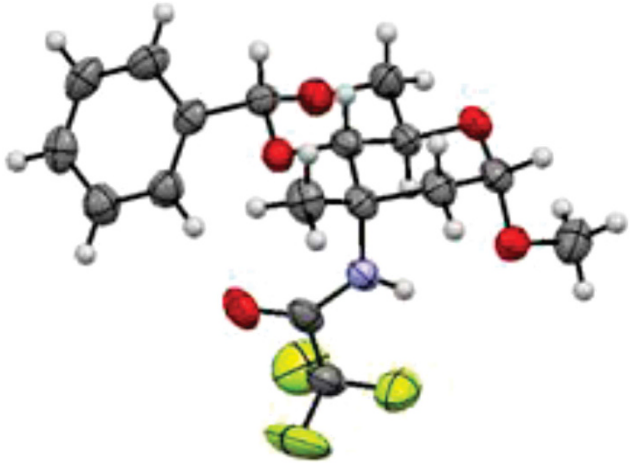


Figure 3 X-ray structure of trifluoroacetamide **5**.

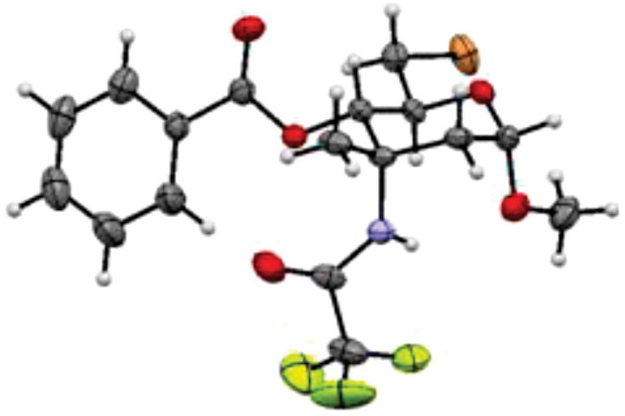
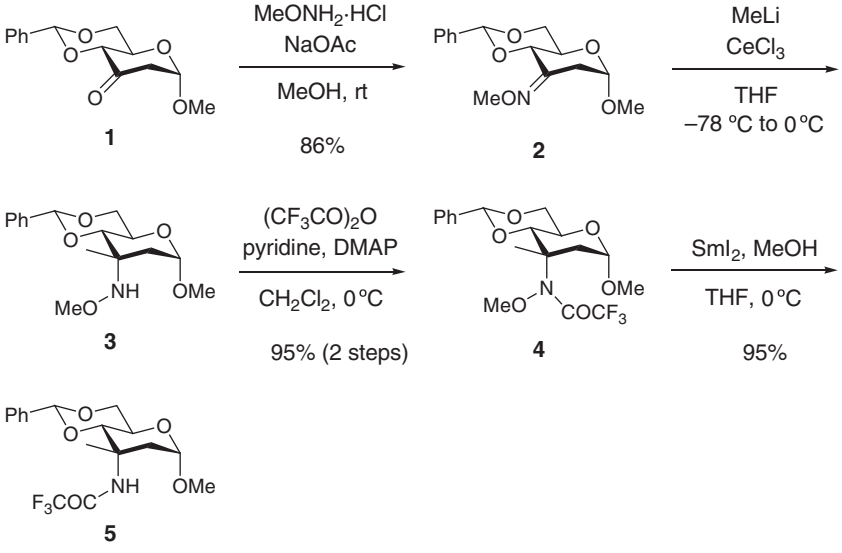


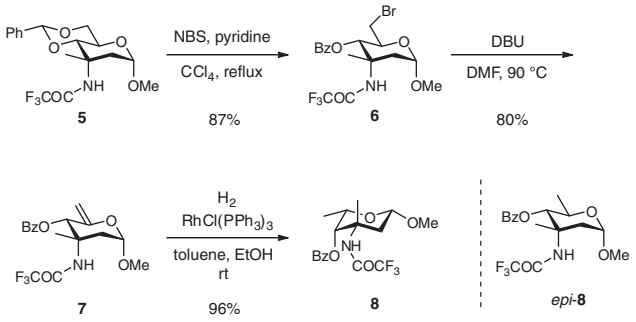
Figure 4 X-ray structure of bromide **6**.

Table 1 Hydrogenation of enol ether 7

Run	*Conditions*	*Yield of **8**/%*	*Yield of epi-**8**/%*
1	H_2 (1 atm), 10% Pd/C, MeOH, rt	67	29
2	H_2 (1 atm), Raney Ni, EtOH, rt	—	—
3	H_2 (1 atm), $Pd(OH)_2$, MeOH, rt	75	22
4	Et_3SiH, $AgBF_4$, CH_2Cl_2, rt	—	—
5	H_2 (1 atm), $RhCl(PPh_3)_3$, toluene, EtOH, rt	96	3



Scheme 1 Preparation of trifluoroacetamide **5**.



Scheme 2 Preparation of benzoate **8**.

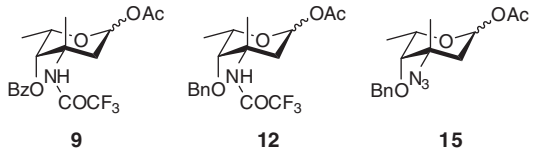
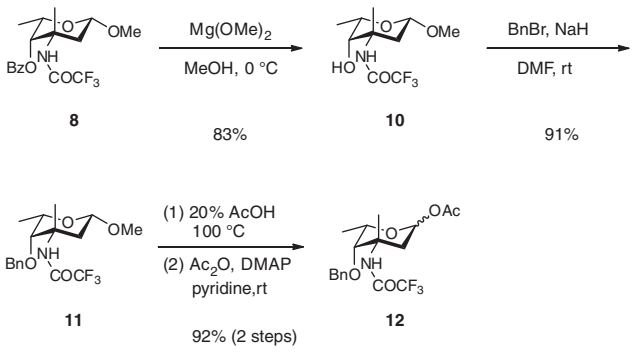
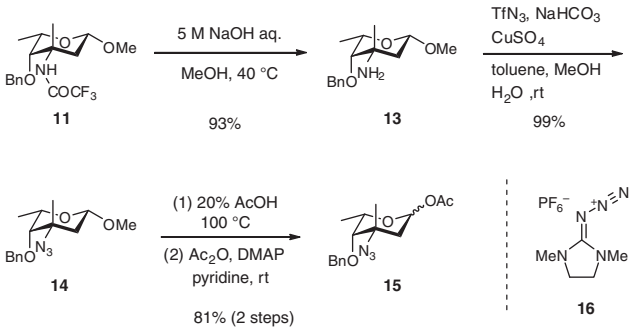


Figure 5 Glycosyl donors **9**, **12** and **15**.



Scheme 3 Preparation of amide acetate **12**.



Scheme 4 Preparation of azide acetate **15**.

regioselectively cleaved. Dehydrobromination of **6** was effected by using 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (*N*,*N*-dimethylformamide (DMF), 90 °C, 4 h) to give enol ether **7** in 80% yield,[39] which was subjected to catalytic hydrogenation of the exocyclic 5,6-double bond.

Our previous protocol[30] using 10% Pd/C (MeOH, room temperature, 12 h) suffered from the low stereoselectivety (<7:3). The main product **8** was produced in 67% yield, and the C(5)-epimer, *epi*-**8** in 29% yield (Table 1, run 1). Although these stereoisomers (**8** and *epi*-**8**) were easily separable by silica-gel chromatography, we sought for a better protocol to improve the stereoselectivity and the yield. In spite of the originally reported protocol,[29] use of Raney Ni as the catalyst gave no hydrogenated products in our hands (run 2). Pearlman's catalyst ($Pd(OH)_2$/C) gave products **8** and *epi*-**8** in a better stereoselectivity (run 3). On the other hand, the combination of triethylsilane with Lewis acids gave no desired compound (run 4). Finally, we found that the hydrogenation of **7** over Wilkinson catalyst[40] (5 mol%, toluene, EtOH, room temperature, 10 h) proceeded in an excellent stereoselectively to give the desired stereoisomer **8** in 96% yield (run 5; Scheme 2).

Having the key intermediate **8** in hand, we prepared three vancosaminyl acetate donors **9**, **12** and **15**, differing in the protection of 3-amino and 4-hydroxy groups (Figure 5). Preparation of 4-*O*-benzoyl donor **9** was previously described,[30] and the routes to amide acetate **12** and azide **15** are outlined in Schemes 3 and 4, respectively.

Scheme 3 shows preparation of amide acetate **12**. The 4-*O*-benzoyl group in **8** was selectively removed by treatment with $Mg(OMe)_2$ (MeOH, 0 °C, 1.5 h) to give the corresponding alcohol **10**,[41] which was protected with a benzyl group (BnBr, NaH, DMF, room temperature, 2 h) to give benzyl ether **11** in 80% yield (two steps). Hydrolysis of **11** in 20% aqueous AcOH (100 °C, 3.5 h)[42] followed by acetylation (Ac_2O, DMAP, pyridine, room temperature, 11 h) gave glycosyl acetate **12** in 92% yield (two steps).

In our synthetic study on the pluramycin-class antibiotics, we needed the glycosyl donors with different protection for the C(3)-amino group. One of the promising donors was azide **15**. After hydrolysis of **11** by 5 M aqueous NaOH (MeOH, 40 °C, 9 h), the resulting free amine **13** was subjected to the diazo-transfer reaction by treatment of TfN_3[43–45] in the presence of $CuSO_4$ (MeOH, H_2O, room temperature, 2.5 h), giving the desired azide **14** in 95% yield (two steps). Recently, Kitamura *et al.*[45] have developed diazo-transfer reagent **16**, which is stable against heat and impact. Indeed, use of **16** for the same conversion (**13**→**14**) proceeded smoothly (DMAP, MeCN, room temperature, 1 h), giving azide **14** in 91% yield. Recrystallization (hexane, EtOAc) gave nice single crystals of **14** amenable for the X-ray analysis (Figure 6). Hydrolysis of **14** (20% aqueous AcOH, 100 °C, 3.5 h) followed by acetylation (Ac_2O, DMAP, pyridine, room temperature, 11 h) gave glycosyl actetate **15** in 81% yield (two steps).

With three glycosyl donors **9**, **12** and **15** in hand, their reactivities were assessed by the aryl *C*-glycosidation with phenol **17** in the presence of 25 mol% of $Sc(OTf)_3$ (Drierite, 1,2-dichloroethane). In the case of C(3)-trifluoroacetamide-substituted acetates **9** and **12**, *C*-glycosides **18** and **19** were obtained in 94% and 88% yield, respectively (runs 1 and 2). However, the azide acetate **15** gave poor result, giving *C*-glycoside **20** in 48% yield (run 3; Table 2).

Finally described is a reliable protocol for converting these amino and azido compounds into the *N*,*N*-dimethyl derivatives. Primary amine **13** was converted to the dimethylamino sugar **21** in excellent yield by treatment with formalin and sodium cyanoborohydride (MeCN, 0 °C, 15 min). Azide **14** could also be converted in one pot to *N*,*N*-dimethylamine **21** (74% yield) by a modified protocol of our previous report[46,47] (PMe_3, CH_2Cl_2, room temperature, 4 h; aq HCHO, $NaBH_3CN$, AcOH, MeCN, room temperature, 1 h; Scheme 5).

In conclusion, an improved synthesis of L-vancosamine donors has been described. Conversion of primary amine and azide to the corresponding *N*,*N*-dimethyl derivative is also described.

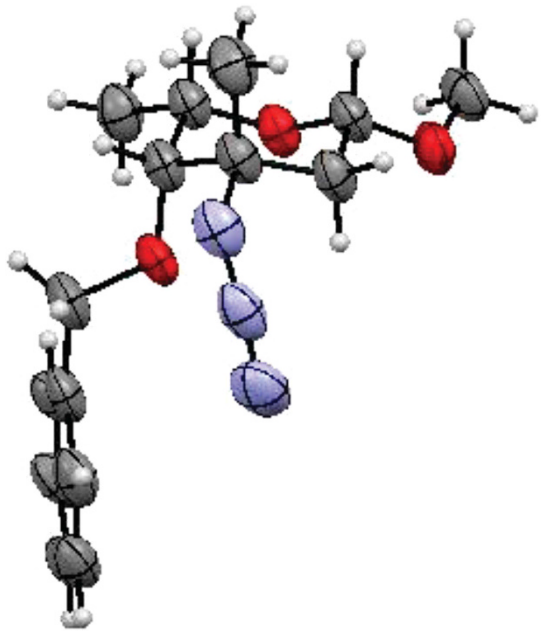
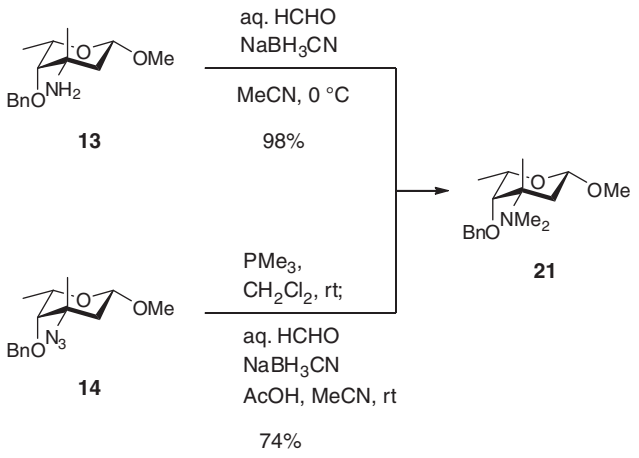
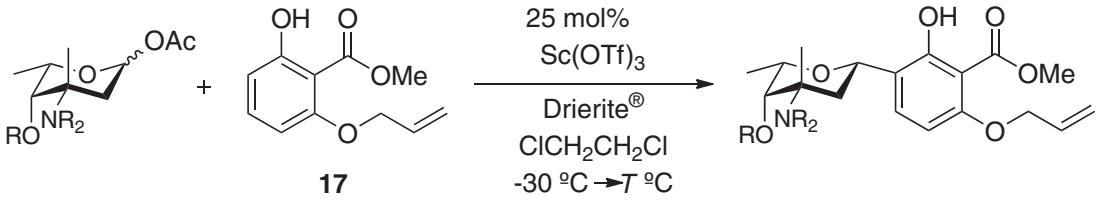


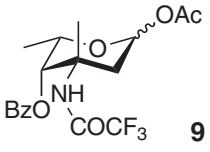
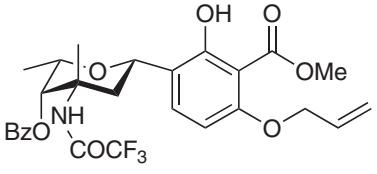
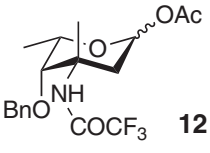
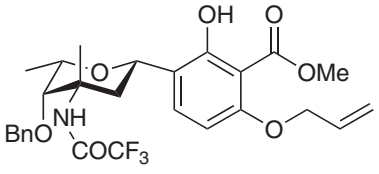
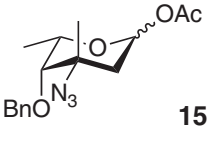
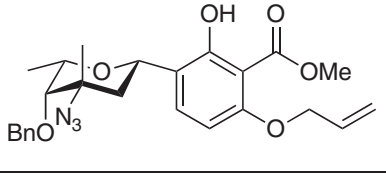
Figure 6 X-ray structure of azide **14**.



Scheme 5 Conversion of amine **13** and azide **14** into *N,N*-dimethylamino derivative **21**.

Table 2 ***C*-Glycosylation with glycosyl acetates**



run	glycosyl donor	*T*/°C	time/h	product	yield/%
1	 **9**	10	7		94 (**18**)
2	 **12**	0	0.5		88 (**19**)
3	 **15**	0	6		48 (**20**)

EXPERIMENTAL PROCEDURE

General

All experiments dealing with air- and moisture-sensitive compounds were conducted under an atmosphere of dry argon. Ethereal solvents (anhydrous; Kanto Chemical Co., Inc., Tokyo, Japan) were used as received. Dichloromethane and 1,2-dichloroethane were distilled successively from P_2O_5 and CaH_2, and stored over 4A molecular sieves. For TLC analysis, Merck precoated plates (Merck, Darmstadt, Gemany) (silica gel 60 F254, Art 5715, 0.25 mm) were used. For flash column chromatography, silica gel 60N (Spherical, neutral, 23–210 μm) from Kanto Chemical was used. Preparative TLC was performed on Merck silica gel 60 PF254 (Art 7747). Determinations of m.p.were performed by using a Yanako MP-500 (Yanako, Kyoto, Japan) instrument. ^{1}H NMR and ^{13}C NMR spectra were measured on a JEOL JNM ECX-500 (JEOL, Tokyo, Japan) (500 MHz), a JEOL JNM AL-400 (400 MHz), a JEOL JNM Lambda-400 (400 MHz) or a JEOL JNM AL-300 (300 MHz) spectrometer, and are reported in p.p.m. using tetramethysilane as an internal standard (tetramethysilane = 0 p.p.m.). ^{1}H NMR spectra data are reported as: (δ shift) ((s = singlet, d = doublet, t = triplet, q = quartet, quin = quintet, m = multiplet, br = broad), (integration) and (J = coupling constant in Hz)). IR spectra were recorded on a Jasco IR-Report 100 (Jasco, Tokyo, Japan) or a Perkin Elmer Spectrum 100 FTIR spectrometer (Perkin Elmer, Waltham, MA, USA). Attenuated total reflectance (ATR) FTIR spectra were recorded on a Perkin Elmer 100 spectrometer. Optical rotations ($[\alpha]_D$) were measured on a Jasco DIP-1000 polarimeter. Elemental analyses were recorded on an Elementar vario MICRO cube analyzer (Elementar, Tokyo, Japan).

O-Methyl methyl 4,6-*O*-benzylidene-2,3-dideoxy-α-D-*erythro*-hexopyranosid-3-ulose oxime (2)

A solution of ketone **1** (52.0 g, 197 mmol), *O*-methylhydroxylamine hydrochloride (29 g, 347 mmol) and NaOAc (29.3 g, 358 mmol) in MeOH (1040 ml) was stirred at room temperature for 6 h. After cooling to 0 °C, the mixture was poured into water (2 l). The precipitates were collected by filtration to provide *O*-methyl oxime **2** (49.5 g, 86%) as white solids, which were used in the next step without further purification. An analytical sample of **2** was obtained by recrystallization from MeOH as colorless needles.

R_f 0.40 (hexane/EtOAc = 7/3); m.p. 209–210 °C (MeOH); $[\alpha]_D^{30}$ +173 (*c* 1.03, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): 2.24 (dd, 1H, J = 4.6, 15.4 Hz), 3.37 (s, 3H), 3.52 (dd, 1H, J = 1.0, 15.4 Hz), 3.83 (dd, 1H, J = 10.0, 10.5 Hz), 3.92 (s, 3H), 4.05 (ddd, 1H, J = 4.9, 9.8, 10.0 Hz), 4.24 (d, 1H, J = 9.8 Hz), 4.31 (dd, 1H, J = 4.9, 10.5 Hz), 4.90 (brd, 1H, J = 4.6 Hz), 5.63 (s, 1H), 7.34–7.39 (m, 3H), 7.51–7.55 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): 30.8, 54.8, 61.9, 64.7, 69.4, 78.1, 98.4, 102.4, 126.5, 128.2, 129.1, 137.0, 148.8; IR (ATR): 3059, 2943, 2866, 1643, 1367, 1124, 1049, 991, 748, 698 cm^{-1}. Anal. calcd for $C_{15}H_{19}NO_5$: C, 61.42; H, 6.53. Found: C, 61.72; H, 6.77.

Methyl 4,6-*O*-benzylidene-2,3-dideoxy-3-*C*-methyl-3-(methoxyamino)-α-D-*ribo*-hexopyranoside (3)

Cerium chloride heptahydrate (36.8 g, 98.8 mmol) was dried under vacuum (0.1 mm Hg) by the Imamoto procedure.[33] The resulting powders were cooled under vacuum, and the flask was flushed with argon. Dry THF (400 ml) was added, and the resulting suspension was stirred vigorously at room temperature for 12 h. The mixture was cooled at –78 °C, to which MeLi (1.09 M in Et_2O, 90 ml, 98.1 mmol) was added dropwise. The yellow suspension was stirred for 1 h, and a solution of *O*-methyl oxime **2** (10.1 g, 34.4 mmol) in THF (100 ml) was added dropwise. After 1 h at –78 °C, the reaction mixture was gradually warmed to 0 °C, and the stirring was continued for 3 h. To the resulting brown suspension saturated aqueous NH_4Cl was added, and the products were extracted with EtOAc (3 ×). The combined organic extracts were successively washed with brine, saturated aqueous $NaHCO_3$ and brine, and then dried (Na_2SO_4). Filtration and concentration *in vacuo* gave amine **3** (11.4 g) as light brown oil, which was used in the next step without further purification. An analytical sample of **3** was obtained by column chromatography (hexane/EtOAc = 7/3) and recrystallization from Et_2O/hexane.

R_f 0.53 (hexane/EtOAc = 7/3); m.p. 87–88 °C (Et_2O/hexane); $[\alpha]_D^{30}$ +105 (*c* 1.02, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): 1.29 (s, 3H), 1.57 (dd, 1H, J = 4.6, 14.9 Hz), 2.36 (dd, 1H, J = 0.6, 14.9 Hz), 3.38 (s, 3H), 3.49 (d, 1H, J = 9.8 Hz), 3.59 (s, 3H), 3.65 (dd, 1H, J = 10.2, 10.2 Hz), 4.16 (ddd, 1H, J = 5.1, 9.8, 10.2 Hz), 4.27 (dd, 1H, J = 5.1, 10.2 Hz), 4.69 (brd, 1H, J = 4.6 Hz), 5.49 (s, 1H), 6.05 (brs, 1H, NH), 7.33–7.39 (m, 3H), 7.46–7.49 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): 23.1, 36.9, 55.3, 56.2, 58.8, 62.5, 69.6, 84.1, 98.5, 102.1, 126.2, 128.1, 128.9, 137.6; IR (ATR): 2968, 2933, 2860, 1456, 1375, 1132, 1082, 1043, 760, 698 cm^{-1}. Anal. calcd for $C_{16}H_{23}NO_5$: C, 62.12; H, 7.49; N, 4.53. Found: C, 62.31; H, 7.69; N, 4.48.

Methyl 4,6-*O*-benzylidene-2,3-dideoxy-3-(*N*-methoxytrifluoroacetamido)-3-*C*-methyl-α-D-*ribo*-hexopyranoside (4)

To a solution of the crude amine **3** (11.4 g), pyridine (5.9 ml, 73 mmol) and DMAP (0.20 g, 1.6 mmol) in CH_2Cl_2 (100 ml), trifluoroacetic anhydride (10.2 ml, 73.4 mmol) was added dropwise at 0 °C. The mixture was stirred at 0 °C for 0.5 h, and quenched with water and then 1 M HCl. The products were extracted with CH_2Cl_2 (3 ×). The combined organic extracts were successively washed with brine, saturated aqueous $NaHCO_3$ and brine, and then dried (Na_2SO_4), filtered and concentrated. The residue was triturated with (hexane/EtOAc = 9/1) to give trifluoroacetamide **4** (10.9 g) as white solids. The mother liquer was concentrated, and the residue was purified by column chromatography (hexane/EtOAc = 9/1) to give 2.34 g of **4**. The combined yield of these materials was 95% in two steps. An analytical sample of **4** was obtained by recrystallization from Et_2O/hexane as colorless prisms.

R_f 0.52 (hexane/EtOAc = 7/3); m.p. 119–120 °C (Et_2O/hexane); $[\alpha]_D^{28}$ +138 (*c* 1.06, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): 1.53 (s, 3H), 1.65 (dd, 1H, J = 3.7, 15.4 Hz), 3.27 (s, 3H), 3.48 (dd, 1H, J = 1.0, 15.4 Hz), 3.61–3.69 (m, 2H), 3.81 (s, 3H), 4.36 (dd, 1H, J = 5.6, 10.7 Hz), 4.54 (ddd, 1H, J = 5.6, 10.0, 10.0 Hz), 4.63 (brd, 1H, J = 3.7 Hz), 5.53 (s, 1H), 7.37–7.41 (m, 3H), 7.49–7.52 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): 24.1, 35.4, 54.7, 59.9, 63.4, 68.5, 69.8, 85.7, 97.8, 102.8, 116.2 (q, J_{CF} = 289 Hz), 126.1, 128.2, 129.1, 137.3, 157.5 (q, J_{CF} = 37 Hz); IR (ATR): 2950, 2837, 1701, 1379, 1203, 1153, 1115, 1066, 903, 746, 700 cm^{-1}. Anal. calcd for $C_{18}H_{22}F_3NO_6$: C, 53.33; H, 5.47; N, 3.46. Found: C, 53.11; H, 5.77; N, 3.45.

Methyl 4,6-*O*-benzylidene-2,3-dideoxy-3-*C*-methyl-3-trifluoroacetamido-α-D-*ribo*-hexopyranoside (5)

To a solution of trifluoroacetamide **4** (6.99 g, 17.3 mmol) in MeOH (30 ml), SmI_2 (prepared from Sm (10.2 g, 68.1 mmol) and 1,2-diiodoethane (17 g, 60.5 mmol) in THF (600 ml))[35] was added at 0 °C. After stirring for 0.5 h, the reaction was quenched by the addition of 2 M HCl, and the products extracted with EtOAc (3 ×). The combined extracts were successively washed with saturated aqueous $NaHCO_3$, 10% aqueous $Na_2S_2O_3$ and brine, and then dried (Na_2SO_4). After filtration and concentration *in vacuo*, the crude residue was purified by column chromatography (hexane/EtOAc = 75/25) to give amide **5** (6.13 g, 95%) as white solids. An analytical sample of **5** was obtained by crystallization from EtOAc/hexane as colorless prisms.

R_f 0.43 (hexane/EtOAc = 7/3); m.p. 120–121 °C (EtOAc/hexane); $[\alpha]_D^{25}$ +73 (*c* 1.01, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): 1.58 (s, 3H), 1.70 (dd, 1H, J = 3.9, 15.1 Hz), 2.99 (dd, 1H, J = 0.5, 15.1 Hz), 3.33 (s, 3H), 3.51 (d, 1H, J = 9.8 Hz), 3.76 (dd, 1H, J = 10.0, 10.4 Hz), 3.95 (ddd, 1H, J = 4.9, 9.8, 10.0 Hz), 4.30 (dd, 1H, J = 4.9, 10.4 Hz), 4.71 (brd, 1H, J = 3.9 Hz), 5.61 (s, 1H), 7.14 (brs, 1H, NH), 7.34–7.41 (m, 3H), 7.45–7.48 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): 22.9, 37.2, 53.5, 55.1, 59.6, 69.0, 82.9, 98.1, 101.9, 115.6 (q, J_{CF} = 291 Hz), 125.9, 128.3, 129.1, 136.8, 156.4 (q, J_{CF} = 36 Hz); IR (ATR): 3346, 3066, 2939, 2841, 1736, 1545, 1379, 1213, 1159, 1047, 903, 752, 698 cm^{-1}. Anal. calcd for $C_{17}H_{20}F_3NO_5$: C, 54.40; H, 5.37; N, 3.73. Found: C, 54.16; H, 5.66; N, 3.77. Crystallographic data: $C_{17}H_{20}F_3NO_5$, MW = 375.34 Da, 0.30 × 0.30 × 0.10 mm, orthorhombic, space group P = 212 121, Z = 4, T = 173(2) K, a = 9.6053(5), b = 12.3369(6), c = 15.1350(7) Å, V = 1793.49(14) Å^3, λ(Mo Kα) = 0.71075 Å, μ = 0.121 mm^{-1}. Intensity data were collected on Rigaku R-AXIS Rapid IP area detector system (Rigaku, Tokyo, Japan). The structure was solved by direct methods and refined by the full-matrix least-squares on F^2

(SHELXL-97 (Sheldrick, 1997)). A total of 17 480 reflections were measured and 4058 were found to be independent. Final $R1 = 0.0386$, $wR2 = 0.0967$ (3356 references; $I > 2\sigma(I)$), and goodness of fit (GOF) = 1.098 (for all data, $R1 = 0.0474$, $wR2 = 0.1021$).

Methyl 4-*O*-benzoyl-6-bromo-2,3,6-trideoxy-3-*C*-methyl-3-trifluoroacetamido-α-D-ribo-hexopyranoside (6)

To a mixture of trifluoroacetamide **5** (10.0 g, 26.7 mmol) in dry carbon tetrachloride (900 ml), *N*-bromosuccinimide (5.72 g, 32.1 mmol) and pyridine (5 ml, 61.8 mmol) were added. The mixture was heated under reflux for 4 h under normal room light illumination. Solvents were removed *in vacuo* to some extent, and the residue was dissolved in CH_2Cl_2 and washed successively with 5% aqueous $NaHSO_3$, saturated aqueous $NaHCO_3$ and brine, and then dried (Na_2SO_4). After filtration and concentration *in vacuo*, the residue was purified by column chromatography (hexane/EtOAc = 9/1) to give bromide **6** (10.5 g, 87%) as white solids. Recrystallization from Et_2O/hexane gave **6** as colorless prisms.

R_f 0.65 (hexane/EtOAc = 7/3); m.p. 118–119 °C (Et_2O/hexane); $[\alpha]_D^{29}$ −14 (*c* 1.02, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz): 1.68 (s, 3H), 1.94 (dd, 1H, $J = 3.8$, 15.1 Hz), 2.29 (d, 1H, $J = 15.1$ Hz), 3.41–3.51 (m, 2H), 3.52 (s, 3H), 4.10 (ddd, 1H, $J = 2.7$, 7.7, 10.2 Hz), 4.94 (d, 1H, $J = 3.8$ Hz), 5.12 (d, 1H, $J = 10.2$ Hz), 7.45–7.49 (m, 2H), 7.58–7.62 (m, 1H), 8.00–8.02 (m, 2H), 8.24 (brs, 1H, NH); ^{13}C NMR ($CDCl_3$, 100 MHz): 23.3, 32.1, 40.8, 55.5, 56.4, 67.1, 74.8, 97.7, 115.8 (q, $J_{CF} = 291$ Hz), 128.5, 130.1, 133.6, 156.1 (q, $J_{CF} = 36$ Hz), 165.7; IR (ATR): 3334, 3072, 2943, 2841, 1739, 1558, 1450, 1263, 1217, 1178, 1045, 960, 877, 710 cm^{-1}. Anal. calcd for $C_{17}H_{19}BrF_3NO_5$: C, 44.95; H, 4.22; N, 3.08. Found: C, 44.73; H, 4.51; N, 3.01. Crystallographic data: $C_{17}H_{19}BrF_3NO_5$, MW = 454.24 Da, 0.60 × 0.30 × 0.20 mm, monoclinic, space group $P = 21$, $Z = 2$, $T = 168(2)$ K, $a = 10.2351(6)$, $b = 7.6213(5)$, $c = 13.1952(7)$ Å, $V = 967.64(10)$ Å^3, λ(Mo Kα) = 0.71075 Å, $\mu = 2.179$ mm^{-1}. Intensity data were collected on Rigaku R-AXIS Rapid IP area detector system. The structure was solved by direct methods and refined by the full-matrix least-squares on F^2 (SHELXL-97). A total of 9422 reflections were measured and 4368 were independent. Final $R1 = 0.0340$, $wR2 = 0.0774$ (3810 references; $I > 2\sigma(I)$), and GOF = 1.069 (for all data, $R1 = 0.0432$, $wR2 = 0.0850$).

Methyl 4-*O*-benzoyl-2,3,6-trideoxy-3-*C*-methyl-3-trifluoroacetamido-α-D-*erythro*-hex-5-enopyranoside (7)

To a solution of bromide **6** (19.7 g, 43.3 mmol) in DMF (220 ml), DBU (12.2 ml, 86.5 mmol) was added. The mixture was heated to 90 °C for 4 h. After cooling to room temperature, the mixture was quenched with 10% aqueous $KHSO_4$. The products were extracted with EtOAc (3 ×), and the combined extracts were washed with saturated aqueous $NaHCO_3$ and brine, and then dried (Na_2SO_4). After filtration and concentration *in vacuo*, the residue was purified by column chromatography (hexane/EtOAc = 9/1) to give enol ether **7** (13 g, 80%) as white solids. Recrystallization from Et_2O/hexane gave **7** as colorless prisms.

R_f 0.61 (hexane/EtOAc = 7/3); m.p. 117–118 °C (Et_2O/hexane); $[\alpha]_D^{28}$ +29 (*c* 0.92, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz): 1.69 (s, 3H), 2.07 (dd, 1H, $J = 4.0$, 14.9 Hz), 2.53 (dd, 1H, $J = 1.0$, 14.9 Hz), 3.48 (s, 3H), 4.69 (dd, 1H, $J = 1.7$, 1.7 Hz), 4.85 (dd, 1H, $J = 1.7$, 1.7 Hz), 4.96 (brd, 1H, $J = 4.0$ Hz), 5.55 (dd, 1H, $J = 1.7$, 1.7 Hz), 7.48–7.52 (m, 2H), 7.60–7.64 (m, 1H), 7.77 (brs, 1H, NH), 8.09–8.11 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): 22.7, 39.3, 55.5, 56.7, 74.2, 98.0, 99.4, 115.8 (q, $J_{CF} = 291$ Hz), 128.6, 128.7, 130.0, 133.6, 150.0, 156.5 (q, $J_{CF} = 36$ Hz), 165.3; IR (ATR): 3332, 3072, 2941, 2843, 1736, 1662, 1560, 1452, 1267, 1215, 1161, 1113, 1045, 987, 870, 712, 677 cm^{-1}. Anal. calcd for $C_{17}H_{18}F_3NO_5$: C, 54.69; H, 4.86; N, 3.75. Found: C, 54.93; H, 5.12; N, 3.90.

Methyl 4-*O*-benzoyl-2,3,6-trideoxy-3-*C*-methyl-3-trifluoroacetamido-β-L-*lyxo*-hexopyranoside (8)

A mixture of enol ether **7** (10.3 g, 27.6 mmol) and $RhCl(PPh_3)_3$ (1.20 g, 1.30 mmol) in toluene (250 ml) and EtOH (25 ml) was stirred under a hydrogen atmosphere (balloon) at room temperature for 10 h. After filtration through a Cerite pad followed by concentration *in vacuo*, purification by column chromatography (hexane/EtOAc = 9/1 → 7/3) gave benzoate **8** (9.94 g, 96%) as a colorless syrup and the stereoisomer *epi*-**8** (0.31 g, 3%) as white solids.

R_f 0.37 (hexane/EtOAc = 7/3); $[\alpha]_D^{29}$ +15 (*c* 1.05, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz): 1.29 (d, 3H, $J = 6.3$ Hz), 1.74 (s, 3H), 1.93 (dd, 1H, $J = 9.5$, 15.1 Hz), 2.45 (dd, 1H, $J = 2.2$, 15.1 Hz), 3.56 (s, 3H), 4.03 (dq, 1H, $J = 1.0$, 6.3 Hz), 4.63 (dd, 1H, $J = 2.2$, 9.5 Hz), 5.14 (brs, 1H), 6.79 (brs, 1H, NH), 7.45–7.49 (m, 2H), 7.59–7.64 (m, 1H), 8.11–8.13 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): 17.3, 21.4, 37.1, 56.7, 57.1, 68.2, 73.4, 99.4, 115.2 (q, $J_{CF} = 291$ Hz), 128.5, 128.6, 130.0, 133.8, 156.1 (q, $J_{CF} = 37$ Hz), 167.3; IR (neat): 3336, 3074, 2989, 2846, 1728, 1556, 1452, 1271, 1203, 1070, 739, 714 cm^{-1}. Anal. calcd for $C_{17}H_{20}F_3NO_5$: C, 54.40; H, 5.37; N, 3.73. Found: C, 54.34; H, 5.58; N, 3.57.

Methyl 4-*O*-benzoyl-2,3,6-trideoxy-3-*C*-methyl-3-trifluoroacetamido-α-D-*ribo*-hexopyranoside (*epi*-8)

R_f 0.60 (hexane/EtOAc = 7/3); m.p. 104–105 °C (colorless plates from MeOH); $[\alpha]_D^{20}$ –6.4 (*c* 0.89, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz): 1.22 (d, 3H, $J = 6.0$ Hz), 1.65 (s, 3H), 1.89 (dd, 1H, $J = 4.1$, 15.1 Hz), 2.28 (brd, 1H, $J = 15.1$ Hz), 3.44 (s, 3H), 4.03 (dq, 1H, $J = 10.1$, 6.0 Hz), 4.83 (brd, 1H, $J = 4.1$ Hz), 4.98 (d, 1H, $J = 10.1$ Hz), 7.26–7.47 (m, 2H), 7.56–7.59 (m, 1H), 8.00–8.02 (m, 2H), 8.26 (brs, 1H, NH); ^{13}C NMR ($CDCl_3$, 100 MHz): 17.5, 23.3, 40.9, 55.2, 56.3, 63.1, 77.5, 97.7, 116.0 (q, $J_{CF} = 295$ Hz), 128.4, 129.1, 130.0, 130.1, 156.1 (q, $J_{CF} = 36$ Hz), 166.1; IR (ATR): 3348, 2937, 1737, 1715, 1583, 1556, 1450, 1323, 1266, 1216, 1181, 1128, 1027, 993, 963, 879, 708 cm^{-1}. Anal. calcd for $C_{17}H_{20}F_3NO_5$: C, 54.40; H, 5.37; N, 3.73. Found: C, 54.18; H, 5.13; N, 3.44.

4-*O*-Benzoyl-2,3,6-trideoxy-3-*C*-methyl-3-trifluoroacetamido-α,β-L-*lyxo*-hexopyranosyl acetate (9)

Benzoate **8** (756 mg, 2 mmol) was dissolved in 20% aqueous AcOH (40 ml), and the mixture was heated under reflux for 3.5 h. After cooling to 0 °C, the mixture was basified by saturated aqueous $NaHCO_3$. After extraction (EtOAc, 3 ×), the combined organic extracts were washed with brine and then dried (Na_2SO_4). After filtration and evaporation *in vacuo*, the residue was dissolved in pyridine (8 ml), to which was added Ac_2O (2 ml), and DMAP (6 mg) at 0 °C. After 11 h at room temperature, the reaction was quenched by 1 M HCl. After extraction (EtOAc, 3 ×), the combined organic extracts were sequentially washed with brine, saturated aqueous $NaHCO_3$ and brine, and then dried (Na_2SO_4). After filtration and concentration *in vacuo*, purification with column chromatography (hexane/EtOAc = 6/4) gave acetate **9** (715 mg, 88%, $\alpha/\beta = 1/5$) as white solids. Recrystallization from CH_2Cl_2/hexane gave **9** as white powders.

R_f 0.45 (hexane/EtOAc = 6/4); m.p. 168–169 °C (CH_2Cl_2/hexane); ^1H NMR ($CDCl_3$, 400 MHz) for the β-anomer: 1.29 (d, 3H, $J = 6.3$ Hz), 1.77 (s, 3H), 2.10 (dd, 1H, $J = 10.3$, 12.6 Hz), 2.15 (s, 3H), 2.61 (dd, 1H, $J = 2.7$, 12.6 Hz), 4.17 (dq, 1H, $J = 1.0$, 6.3 Hz), 5.03 (brs, 1H), 5.96 (dd, 1H, $J = 2.7$, 10.3 Hz), 6.99 (brs, 1H, NH), 7.48–7.67 (m, 3H), 8.13–8.16 (m, 2H); for the selected α-anomer: 1.25 (d, 3H, $J = 6.9$ Hz), 4.38 (q, 1H, $J = 6.9$ Hz), 5.07 (brs, 1H), 6.34 (brd, 1H, $J = 4.0$ Hz), 7.10 (brs, 1H, NH); ^{13}C NMR ($CDCl_3$, 100 MHz): 17.2, 21.0, 21.2, 35.3, 57.2, 69.1, 73.4, 90.6, 115.2 (q, $J_{CF} = 290$ Hz), 128.3, 128.7, 130.0, 134.1, 156.3 (q, $J_{CF} = 37$ Hz), 167.7, 169.1; IR (ATR): 3334, 3076, 2989, 1728, 1556, 1452, 1273, 1161, 1049, 908, 758, 715 cm^{-1}. Anal. calcd for $C_{18}H_{20}F_3NO_6$: C, 53.60; H, 5.00; N, 3.47. Found: C, 53.39; H, 5.25; N, 3.37.

Methyl 2,3,6-trideoxy-3-*C*-methyl-3-trifluoroacetamido-β-L-*lyxo*-hexopyranoside (10)

To a solution of $Mg(OMe)_2$ in MeOH (prepared from magnesium (1.12 g, 46 mmol) and MeOH (230 ml)), a solution of benzoate **8** (6.24 g, 16.6 mmol) in MeOH (100 ml) was added at 0 °C. After stirring for 1.5 h, the mixture was acidified by carefully adding aqueous 2 M HCl, and MeOH was removed under reduced pressure. The products were extracted with EtOAc (5 ×), and the combined organic extracts were washed with brine and then dried (Na_2SO_4). After filtration, solvents were evaporated *in vacuo*, and purification by column chromatography (hexane/EtOAc = 8/2) gave alcohol **10** (3.75 g, 83%) as white solids. Recrystallization from Et_2O gave **10** as colorless plates.

R_f 0.35 (hexane/EtOAc = 7/3); m.p. 104–106 °C (Et_2O); $[\alpha]_D^{24}$ +56 (*c* 1.1, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz): 1.33 (d, 3H, $J = 6.4$ Hz), 1.61 (s, 3H), 1.62 (dd, 1H, $J = 9.2$, 14.0 Hz), 2.30 (d, 1H, $J = 10.4$ Hz), 2.46 (dd, 1H, $J = 2.0$,

14.0 Hz), 3.24 (d, 1H, $J=10.4$ Hz), 3.49 (s, 3H), 3.88 (q, 1H, $J=6.4$ Hz), 4.43 (dd, 1H, $J=2.0$, 9.2 Hz), 7.06 (s, 1H, NH); ^{13}C NMR ($CDCl_3$, 100 MHz): 17.0, 20.3, 36.4, 56.6, 56.7, 68.5, 72.3, 100.0, 115.5 (q, $J_{CF}=287$ Hz), 156.2 (q, $J_{CF}=35$ Hz); IR (ATR): 3380, 2986, 2950, 1719, 1549, 1463, 1448, 1394, 1332, 1259, 1187, 1164, 1145, 1122, 1104, 1070, 1006 cm^{-1}. Anal. calcd for $C_{10}H_{16}F_3NO_4$: C, 44.28; H, 5.95; N, 5.16. Found: C, 44.50; H, 6.02; N, 4.86.

Methyl 4-*O*-benzyl-2,3,6-trideoxy-3-*C*-methyl-3-trifluoroacetamido-β-L-*lyxo*-hexopyranoside (11)

To a mixture of NaH (63% dispersion in oil, 1.8 g, 48 mmol) in DMF (50 ml), a solution of alcohol **10** (3.75 g, 13.8 mmol) in DMF (20 ml) was added. After stirring for 2 h, benzyl bromide (5.66 g, 33.1 mmol) was added, and the mixture was allowed to warm to room temperature. After stirring for 2 h, water and Et_2NH were successively added at 0 °C. After 0.5 h, aqueous 2 M HCl was added, and the products were extracted with Et_2O (3 ×). Combined organic extracts were washed successively with brine, saturated aqueous $NaHCO_3$ and brine, and then dried (Na_2SO_4). After filtration and concentration *in vacuo*, the residue was purified by column chromatography (hexane/EtOAc = 8/2) to give benzyl ether **11** (4.52 g, 91%) as a colorless oil.

R_f 0.45 (hexane/EtOAc = 7/3); $[\alpha]_D^{29}$ −30 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): 1.40 (d, 3H, $J=6.4$ Hz), 1.64 (s, 3H), 1.80 (dd, 1H, $J=9.2$, 12.4 Hz), 2.05 (dd, 1H, $J=2.4$, 12.4 Hz), 3.44 (s, 1H), 3.49 (s, 3H), 3.86 (q, 1H, $J=6.4$ Hz), 4.48 (dd, 1H, $J=2.4$, 9.2 Hz), 4.50 (d, 1H, $J=11.2$ Hz), 4.81 (d, 1H, $J=11.2$ Hz), 6.42 (brs, 1H, NH), 7.29–7.38 (m, 5H); ^{13}C NMR ($CDCl_3$, 100 MHz): 17.6, 21.3, 37.5, 56.2, 56.8, 69.2, 75.9, 79.2, 99.0, 115.2 (q, $J_{CF}=287$ Hz), 127.7, 127.9, 128.4, 137.0, 156.1 (q, $J_{CF}=36$ Hz) cm^{-1}; IR (ATR): 3326, 3091, 3068, 2989, 2938, 2877, 1723, 1553, 1520, 1498, 1454, 1397, 1371, 1355, 1278, 1258, 1171, 1128, 1111, 1071, 1028, 1016 cm^{-1}. Anal. calcd for $C_{17}H_{22}F_3NO_4$: C, 57.55; H, 5.27; N, 2.82. Found: C, 57.71; H, 5.31; N, 2.58.

4-*O*-Benzyl-2,3,6-trideoxy-3-*C*-methyl-3-trifluoroacetamido-α,β-L-*lyxo*-hexopyranosyl acetate (12)

Benzyl ether **11** (1.50 g, 4.15 mmol) was dissolved in 20% aqueous AcOH (200 ml, 0.68 mol), and the mixture was heated under reflux for 3.5 h. After cooling to 0 °C, the mixture was basified by adding KOH (3 M, 220 ml, 0.66 mol) and saturated aqueous $NaHCO_3$. After extraction with EtOAc (3 ×), the combined organic extracts were washed with brine and then dried (Na_2SO_4). After filtration, solvents were removed *in vacuo*. The residue was dissolved in pyridine (5 ml), to which was added Ac_2O (1 ml) and DMAP (10 mg) at 0 °C. After 1.5 h, the reaction was quenched by adding 1 M HCl. The products were extracted with EtOAc (3 ×), the combined organic extracts were washed successively with brine, saturated aqueous $NaHCO_3$ and brine, and then dried (Na_2SO_4). After filtration and concentration *in vacuo*, purification with column chromatography (hexane/EtOAc = 8/2) gave acetate **12** (1.48 g, 92%; $\alpha/\beta=45/55$) as a colorless gummy syrup.

R_f 0.32 (hexane/EtOAc = 7/3); ^{1}H NMR ($CDCl_3$, 400 MHz) for the β-anomer: 1.41 (d, 3H, $J=6.6$ Hz), 1.66 (s, 3H), 2.04 (dd, 1H, $J=9.0$, 12.4 Hz), 2.08 (s, 3H), 2.11 (dd, 1H, $J=2.9$, 12.4 Hz), 3.45 (s, 1H), 4.02 (q, 1H, $J=6.6$ Hz), 4.51 (d, 1H $J=11.7$ Hz), 4.83 (d, 1H, $J=11.7$ Hz), 5.84 (dd, 1H $J=2.9$, 9.0 Hz), 6.51 (s, 1H, NH), 7.33–7.39 (m, 5H); for the selected α-anomer: 1.39 (d, 3H, $J=6.6$ Hz), 6.17 (dd, 1H, $J=1.6$, 3.6 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) for the α- and β-mixture: 17.6 (2 ×), 21.0, 21.2, 21.4, 22.8, 34.1, 35.9, 54.9, 56.4, 66.5, 70.2, 76.0, 76.1, 79.0, 79.8, 90.5, 90.9, 115.3 (q, $J_{CF}=291$Hz), 128.0, 128.1, 128.4 (2 ×), 128.7, 128.8, 136.8, 156.4 (q, $J_{CF}=37$ Hz), 169.2 (2 ×); IR (neat): 3338, 3092, 3068, 3033, 2988, 2939, 2920, 2883, 1754, 1723, 1556, 1521, 1498, 1455, 1386, 1370, 1355, 1312, 1232, 1201, 1187, 1162, 1130, 1107, 1085, 1049, 1007 cm^{-1}. Anal. calcd for $C_{18}H_{22}F_3NO_5$: C, 55.53; H, 5.70; N, 3.60. Found: C, 55.83; H, 5.47; N, 3.42.

Methyl 4-*O*-benzyl-2,3,6-trideoxy-3-*C*-methyl-3-amino-β-L-*lyxo*-hexopyranoside (13)

To a solution of amide **11** (4.69 g, 13 mmol) in MeOH (55 ml), 5 M NaOH (14 ml, 60 mmol) was added and the reaction mixture was stirred at room temperature for 9 h. The reaction mixture was concentrated *in vacuo* to some extent, was diluted with H_2O and EtOAc, and the was extracted with EtOAc (5 ×). The combined organic extracts were washed with brine and then dried (Na_2SO_4), and concentration *in vacuo* gave amine **13** (3.22 g, 93%) as a colorless oil.

R_f 0.24 ($CHCl_3$/MeOH = 9/1); $[\alpha]_D^{20}$ +2.5 (*c* 1.66, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz): 1.17 (s, 3H), 1.32 (d, 3H, $J=6.6$ Hz), 1.55 (dd, 1H, $J=2.5$, 12.8 Hz), 1.68 (dd, 1H, $J=9.7$, 12.8 Hz), 2.08–2.25 (brs, 2H, NH), 2.89 (s, 1H), 3.47 (s, 3H), 3.76 (q, 1H, $J=6.6$ Hz), 4.39 (dd, 1H, $J=2.5$, 9.7 Hz), 4.68 (d, 1H, $J=15.2$ Hz), 4.77 (d, 1H, $J=15.2$ Hz), 7.25–7.40 (m, 5H); ^{13}C NMR ($CDCl_3$, 125 MHz): 17.5, 24.9, 42.2, 52.4, 56.3, 69.8, 83.9, 100.5, 127.6, 127.8, 128.2, 128.3, 138.2 cm^{-1}; IR (neat): 3361, 2929, 1722, 1586, 1497, 1455, 1392, 1224, 1164, 1070, 1011, 965, 876, 755, 704 cm^{-1}. Anal. calcd for $C_{15}H_{23}NO_3$: C, 67.90; H, 8.74; N, 5.28. Found: C, 67.83; H, 9.03; N, 5.01.

Preparation of TfN_3 in toluene[44]. To a mixture of NaN_3 (5.92 g, 91.1 mmol) in toluene (15 ml) and H_2O (15 ml), Tf_2O (7.76 ml, 45.5 mmol) was added at 0 °C; the mixture was stirred at 10 °C for 2 h. The reaction mixture was quenched by the addition of saturated aqueous $NaHCO_3$, and the mixture was extracted by toluene (10 ml 2 ×) to give a toluene solution of TfN_3, which was used in the subsequent diazo-transfer reaction. (warning: TfN_3 has an explosive nature and requires very careful treatment.)

Methyl 4-*O*-benzyl-2,3,6-trideoxy-3-*C*-methyl-3-azido-β-L-*lyxo*-hexopyranoside (14)

To a suspension of a mixture of amine **13** (3.22 g, 12.2 mmol), $CuSO_4$ (208 mg, 1.30 mmol), $NaHCO_3$ (5.44 g, 64.8 mmol) in MeOH (28 ml) and H_2O (7 ml), a freshly prepared TfN_3 solution (28 ml) was added at 0 °C. After stirring for 2.5 h at room temperature, the mixture was diluted with H_2O and EtOAc, and the products extracted with EtOAc (3 ×). The combined organic extracts were washed with brine, and it was then dried (Na_2SO_4) and concentrated *in vacuo*. The residue was purified by flash column chromatography (hexane/EtOAc = 85/15) to give azide **14** (3.51 g, 99%) as white solids. Recrystallization from MeOH gave **14** as colorless needles.

R_f 0.45 (hexane/EtOAc = 4/1); m.p. 108–110 °C (MeOH); $[\alpha]_D^{28}$ +54.9 (*c* 1.07, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz): 1.19 (d, 3H, $J=6.3$ Hz), 1.30 (s, 3H), 1.77 (dd, 1H, $J=2.3$, 12.6 Hz), 2.11 (dd, 1H, $J=9.2$, 12.6 Hz), 3.01 (s, 1H), 3.48 (s, 3H), 3.67 (q, 1H, $J=6.3$ Hz), 4.45 (dd, 1H, $J=2.3$, 9.2 Hz), 4.57 (d, 1H, $J=11.5$ Hz), 4.92 (d, 1H, $J=11.5$ Hz), 7.28–7.37 (m, 3H), 7.39–7.43 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz): 17.1, 23.3, 36.1, 56.4, 62.8, 69.8, 75.8, 81.1, 99.8, 128.0, 128.3, 128.7, 137.5; IR (ATR): 2866, 2097, 1458, 1390, 1352, 1252, 1156, 1116, 1062, 1010, 977, 876, 813, 764, 697 cm^{-1}. Anal. calcd for $C_{15}H_{21}N_3O_3$: C, 61.84; H, 7.27; N, 14.42. Found: C, 61.98; H, 7.11; N, 14.31. Crystallographic data: $C_{15}H_{21}N_3O_3$, MW = 291.35 Da, 0.20 × 0.15 × 0.15 mm, orthorhombic, space group $P=212121$, $Z=4$, $T=173(2)$ K, $a=10.5718(13)$, $b=11.5146(11)$, $c=12.8642(14)$ Å, $V=1566(3)$ Å^3, λ(Cu Kα) = 1.54187 Å, $\mu=0.713$ mm^{-1}. Intensity data were collected on Rigaku VariMax Rapid-II IP area detector system. The structure was solved by direct methods and refined by the full-matrix least-squares on F^2 (SHELXL-97). A total of 17 995 reflections were measured, and 2852 were found to be independent. Final $R1=0.0452$, $wR2=0.1124$ (2399 references; $I>2\sigma(I)$), and GOF = 1.018 (for all data, $R1=0.0513$, $wR2=0.1168$).

*Alternative synthesis of **14** by using reagent **16**.* To a solution of amine **13** (34.3 mg, 0.13 mmol) and DMAP (47.1 mg, 0.39 mmol) in MeCN (1.3 ml), **16** (45.2 mg, 0.16 mmol) was added at 0 °C. After stirring for 1 h at room temperature, the reaction was quenched with saturated aqueous $NaHCO_3$ at 0 °C, and the products were extracted with EtOAc (3 ×). The combined organic extracts were successively washed with H_2O and brine, and then dried (Na_2SO_4). After filtration and concentration *in vacuo*, the crude residue was purified by preparative TLC (hexane/EtOAc = 8/2) to give azide **14** (34.3 mg, 91%) as white solids.

4-*O*-Benzyl-2,3,6-trideoxy-3-*C*-methyl-3-azido-α,β-L-*lyxo*-hexopyranosyl acetate (15)

Azide **14** (4.06 g, 13.9 mmol) was dissolved in 20% aqueous AcOH (250 ml), and the mixture was heated under reflux for 3.5 h. After cooling to 0 °C, the mixture was basified by adding KOH (46 g) and saturated aqueous $NaHCO_3$. After extraction (AcOEt, 3 ×), the combined organic extracts were washed

with brine and then dried (Na_2SO_4). After filtration and evaporation *in vacuo*, the residue was dissolved in pyridine (65 ml), to which was added Ac_2O (17 ml), and 4-DMAP (18 mg) at 0 °C. After 11 h at room temperature, the reaction was quenched by 1 M HCl. After extraction (EtOAc, 3 ×), the combined organic extracts were sequentially washed with brine, saturated aqueous $NaHCO_3$ and brine, and then dried (Na_2SO_4). After filtration and concentration *in vacuo*, purification with column chromatography (hexane/EtOAc = 8/2) gave azide acetate **15** (3.63 g, 81%; $\alpha/\beta = 1/2.5$) as a colorless gummy syrup.

R_f 0.39 (hexane/EtOAc = 4/1) for the β-anomer, R_f 0.44 (hexane/EtOAc = 4/1) for the α-anomer; ^{1}H NMR ($CDCl_3$, 500 MHz) for the β-anomer: 1.19 (d, 3H, $J = 6.4$ Hz), 1.35 (s, 3H), 1.79 (dd, 1H, $J = 2.3$, 12.4 Hz), 2.10 (s, 3H), 2.29 (dd, 1H, $J = 9.6$, 12.4 Hz), 3.04 (s, 1H), 3.82 (dq, 1H, $J = 1.4$, 6.4 Hz), 4.59 (d, 1H $J = 11.0$ Hz), 4.92 (d, 1H, $J = 11.0$ Hz), 5.80 (dd, 1H $J = 2.3$, 9.6 Hz), 7.28–7.43 (m, 5H); for the selected α-anomer: 1.79 (dd, 1H, $J = 1.4$, 13.7 Hz), 2.42 (dd, 1H, $J = 4,2$, 13.7 Hz), 3.17 (s, 1H), 4.10 (dq, 1H, $J = 1.4$, 6.4 Hz), 6.24 (dd, 1H, $J = 1.4$, 4.2 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) for the α- and β-mixture: 17.1 (2 ×), 21.1, 21.2, 23.0, 24.2, 33.4, 34.8, 61.0, 62.4, 67.5, 70.8, 75.6, 75.7, 80.6, 81.0, 91.2, 91.5, 127.9, 128.3 (2 ×), 128.4, 128.6, 137.5, 137.6, 169.1, 169.3; IR (neat): 2982, 2938, 2099, 1750, 1455, 1368, 1235, 1208, 1168, 1143, 1103, 1048, 1003, 917, 756, 700, 598, 531 cm^{-1}. Anal. calcd for $C_{16}H_{21}N_3O_4$: C, 60.17; H, 6.63; N, 13.16. Found: C, 60.20; H, 6.36; N, 12.96.

Typical procedure for C-glycosylation reaction. To a mixture of $Sc(OTf)_3$ (612 mg, 1.24 mmol), phenol **17** (2.02 g, 9.70 mmol) and powdered Drierite (8.16 g) in 1,2-dichloroethane (40 ml), acetate **12** (2.23 g, 5.73 mol) in 1,2-dichloroethane (10 ml) was added at –30 °C. After gradual warming to 0 °C, the mixture was quenched with saturated aqueous $NaHCO_3$ at 0 °C. After filtration through a Celite pad, the products were extracted with CH_2Cl_2 (3 ×). The combined organic extracts were washed with brine and then dried (Na_2SO_4). After filtration, solvents were removed *in vacuo*, and the residue was purified by column chromatography (hexane/EtOAc = 95/5 → 8/2) to give *C*-glycoside **19** (2.72 g, 88%) as a colorless oil.

Methyl 2-hydroxy-3-(4-*O*-benzoyl-2,3,6-trideoxy-3-*C*-methyl-3-trifluoroacetamido-β-L-*lyxo*-hexopyranosyl)-6-(prop-2-ene-1-yloxy)benzoate (18)

Colorless plates, 94%; R_f 0.40 (hexane/EtOAc = 3/1); m.p. 71–73 °C (EtOH/hexane); $[\alpha]_D^{22}$ –65 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): 1.29 (d, 3H, $J = 6.0$ Hz), 1.88 (s, 3H), 1.95 (dd, 1H, $J = 11.6$, 12.4 Hz), 2.58 (dd, 1H, $J = 2.0$, 12.4 Hz), 3.97 (s, 3H), 4.17 (q, 1H, $J = 6.0$ Hz), 4.58–4.59 (m, 2H), 5.10 (dd, 1H, $J = 2.0$, 11.6 Hz), 5.21 (s, 1H), 5.31 (dd, 1H, $J = 0.8$, 10.8 Hz), 5.51 (dd, 1H, $J = 0.8$, 17.2 Hz), 6.06 (ddt, 1H, $J = 10.8$, 17.2, 4.8 Hz), 6.49 (d, 1H, $J = 8.8$ Hz), 6.74 (s, 1H, NH), 7.48–7.52 (m, 2H), 7.61–7.65 (m, 1H), 7.62 (d, 1H, $J = 8.8$ Hz), 8.13–8.15 (m, 2H), 11.8 (s, 1H, OH); ^{13}C NMR ($CDCl_3$, 125 MHz): 18.1, 20.6, 37.7, 52.5, 57.1, 69.5, 69.6, 70.8, 103.2, 103.7 (q, $J_{CF} = 271$ Hz), 113.8, 116.9, 121.9, 128.6, 128.9, 129.8, 132.1, 132.5, 133.7, 156.0 (q, $J_{CF} = 36$ Hz), 159.0, 159.3, 167.3, 171.5; IR (neat): 3340, 2980, 2950, 1720, 1650, 1615, 1550 cm^{-1}. Anal. calcd for $C_{27}H_{28}F_3NO_8$: C, 58.80; H, 5.12; N, 2.54. Found: C, 58.59; H, 4.89; N, 2.24.

Methyl 2-hydroxy-3-(4-*O*-benzyl-2,3,6-trideoxy-3-*C*-methyl-3-trifluoroacetamido-β-L-*lyxo*-hexopyranosyl)-6-(prop-2-ene-1-yloxy)benzoate (19)

Colorless oil, 88%; R_f 0.60 (hexane/EtOAc = 7/3); $[\alpha]_D^{25}$ –72 (*c* 1.3, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): 1.40 (d, 3H, $J = 6.4$ Hz), 1.77 (dd, 1H, $J = 11.6$, 12.4 Hz), 1.79 (s, 3H), 2.13 (dd, 1H, $J = 2.0$, 12.4 Hz), 3.58 (s, 1H), 3.95 (s, 3H), 4.00 (q, 1H, $J = 6.4$ Hz), 4.53–4.55 (m, 2H), 4.56 (d, 1H, $J = 11.6$ Hz), 4.82 (d, 1H, $J = 11.6$ Hz), 4.94 (dd, 1H, $J = 2.0$, 11.6 Hz), 5.29 (dd, 1H, $J = 1.6$, 10.8 Hz), 5.49 (dd, 1H, $J = 1.6$, 17.2 Hz), 6.03 (ddt, 1H, $J = 10.8$, 17.2, 4.4 Hz), 6.37 (s, 1H, NH), 6.42 (d, 1H, $J = 8.8$ Hz), 7.30–7.40 (m, 5H), 7.54 (d, 1H, $J = 8.8$ Hz), 11.60 (s, 1H, OH); ^{13}C NMR ($CDCl_3$, 100 MHz): 18.5, 20.6, 38.5, 52.4, 56.9, 69.4, 69.4, 72.1, 75.9, 79.6, 103.3, 103.5, 115.4 (q, $J_{CF} = 287$ Hz), 116.8, 122.0, 127.6, 127.9, 128.5, 132.1, 132.5, 137.5, 156.2 (q, $J_{CF} = 35$ Hz), 158.7, 159.0, 171.3; IR (neat): 3330, 2920, 1718, 1648, 1616, 1436, 1352, 1298, 1198, 1156, 1080 cm^{-1}. Anal. calcd for $C_{27}H_{30}F_3NO_7$: C, 60.33; H, 5.63; N, 2.61. Found: C, 60.12; H, 5.38; N, 2.39.

Methyl 2-hydroxy-3-(4-*O*-benzyl-2,3,6-trideoxy-3-*C*-methyl-3-azido-β-L-*lyxo*-hexopyranosyl)-6-(prop-2-ene-1-yloxy)benzoate (20)

Colorless oil, 48%; R_f 0.51 (hexane/EtOAc = 4/1); $[\alpha]_D^{20}$ –76 (*c* 1.15, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz): 1.23 (d, 3H, $J = 6.3$ Hz), 1.45 (s, 3H), 1.88 (brd, 1H, $J = 12.6$ Hz), 2.12 (dd, 1H, $J = 11.5$, 12.6 Hz), 3.08 (s, 1H), 3.84 (q, 1H, $J = 6.3$ Hz), 3.94 (s, 3H), 4.53–4.55 (m, 2H), 4.61 (d, 1H, $J = 10.9$ Hz), 4.90 (brd, 1H, $J = 11.5$ Hz), 4.96 (d, 1H, $J = 10.9$ Hz), 5.28 (dd, 1H, $J = 1.2$, 10.9 Hz), 5.49 (dd, 1H, $J = 1.2$, 17.2 Hz), 6.02 (ddt, 1H, $J = 10.9$, 17.2, 5.8 Hz), 6.43 (d, 1H, $J = 8.6$ Hz), 7.26–7.46 (m, 5H), 7.58 (d, 1H, $J = 8.6$ Hz), 11.66 (s, 1H, OH); ^{13}C NMR ($CDCl_3$, 125 MHz): 17.9, 22.5, 36.6, 52.3, 62.8, 69.4, 69.8, 72.4, 75.6, 81.8, 103.2, 103.7, 116.8, 122.3, 127.6, 128.2, 128.3, 132.5, 132.7, 138.1, 158.8, 159.1, 171.6; IR (neat): 2891, 2101, 1736, 1654, 1618, 1439, 1357, 1301, 1259, 1206, 1151, 1084, 984, 812, 755, 697, 664, 548 cm^{-1}. Anal. calcd for $C_{25}H_{29}N_3O_6$: C, 64.23; H, 6.25; N, 8.99. Found: C, 64.07; H, 6.38; N, 9.25.

Methyl 4-*O*-benzyl-2,3,6-trideoxy-3-*C*-methyl-3-dimethylamino-β-L-*lyxo*-hexopyranoside (21)

To a solution of amine **13** (76.0 mg, 0.29 mmol) in MeCN (4 ml), formalin (37%, 0.64 ml, 8.6 mmol) and $NaBH_3CN$ (138 mg, 2.19 mmol) were added at 0 °C. After stirring for 15 min, the reaction was quenched with 2 M aqueous NaOH. After extraction (CH_2Cl_2, 6 ×), the combined organic extracts were successively washed with water and brine, and then dried (Na_2SO_4). Filtration and concentration *in vacuo* gave dimethylamine **21** (82.4 mg, 98%) as a colorless oil. An analytical sample of **12** was obtained by preparative TLC (hexane/EtOAc/NEt_3 = 6/4/0.5) as a colorless oil.

R_f 0.65 (hexane/EtOAc/NEt_3 = 6/4/1); $[\alpha]_D^{28}$ + 44 (*c* 0.91, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz): 0.98 (s, 3H), 1.25 (d, 3H, $J = 6.3$ Hz), 1.65 (dd, 1H, $J = 2.3$, 11.5 Hz), 1.91 (dd, 1H, $J = 9.8$, 11.5 Hz), 2.25 (s, 6H), 3.11 (s, 1H), 3.50 (s, 3H), 3.66 (q, 1H, $J = 6.3$ Hz), 4.51 (dd, 1H, $J = 2.3$, 9.8 Hz), 4.64 (d, 1H, $J = 11.5$ Hz), 4.96 (d, 1H, $J = 11.5$ Hz), 7.23–7.32 (m, 3H), 7.41–7.46 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz): 14.0, 18.1, 37.1, 37.8, 56.3, 59.4, 70.0, 74.4, 78.7, 100.7, 127.1, 127.8, 128, 139.3; IR (neat): 2982, 2882, 1453, 1391, 1335, 1256, 1207, 1131, 1072, 1014, 965, 884, 736, 700, 592 cm^{-1}. Anal. calcd for $C_{17}H_{27}NO_3$: C, 69.59; H, 9.28; N, 4.77. Found: C, 69.49; H, 9.15; N, 4.57.

*One-pot conversion of azide **14** to dimethylamine **21**.* To a solution of azide **14** (25.3 mg, 86.8 μmol) in CH_2Cl_2 (1.7 ml), PMe_3 (1 M in toluene, 0.26 ml, 0.26 mmol) was added at room temperature. After stirring for 4 h, the solvent was removed *in vacuo*, and the residue was dissolved in MeCN (1.7 ml). Formalin (37%, 210 μl, 2.8 mmol) was added at room temperature, and the mixture was stirred for 30 min. The pH was adjusted to pH 4 with AcOH and $NaBH_3CN$ (27 mg, 0.43 mmol) was added at room temperature. After stirring for 1 h, the reaction was quenched with saturated aqueous $NaHCO_3$ at 0 °C. After extraction with EtOAc (3 ×), the combined organic extracts were washed with brine and then dried (Na_2SO_4). After filtration, solvents were removed *in vacuo*, and the residue was purified by preparative TLC (hexane/EtOAc/NEt_3 = 6/4/0.5) to give dimethylamine **21** (18.9 mg, 74%) as a colorless oil.

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