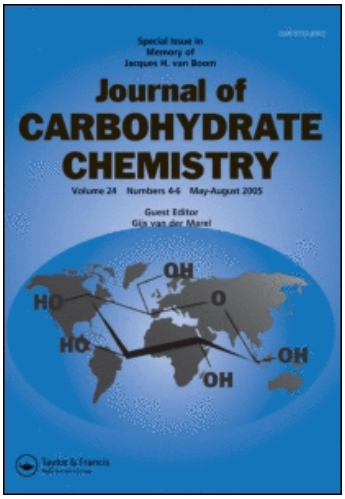

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A FACILE SYNTHESIS OF BENZYL 2-AMINO-3-AZIDO-4-*O*-*p*-METHOXYBENZYL-6-*O*-BENZYL-2,3-DIDEOXY-α-D-GLUCOPYRANOSIDE: A KEY INTERMEDIATE IN THE FORMATION OF A DIDEMNIN B ANALOG

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ABSTRACT

Although the deprotection of amides by hydrazinolysis is a well established method in carbohydrate chemistry, this reaction is dependent upon the nearby substituents. In our facile synthesis of intermediate benzyl 2-amino-3-azido-4-*O*-*p*-methoxybenzyl-6-*O*-benzyl-2,3-dideoxy-α-D-glucopyranoside (**3**), we found that the use of trifluoroacetamides provided a more efficient protection strategy.

INTRODUCTION

The didemnins, a new class of cyclodepsipeptides were isolated in 1981 from a Caribbean tunicate of the family *Didemnidae*.[1] Most didemnins contain a common macrocycle, and differ only in the side chains attached to the backbone through the amino group of threonine. These natural products display a wide spectrum of biological activity including antiviral, antitumor, and immunomodulatory properties.[2,3] Didemnin B (**1**, Figure 1) was tested extensively and showed potent activity in each area.

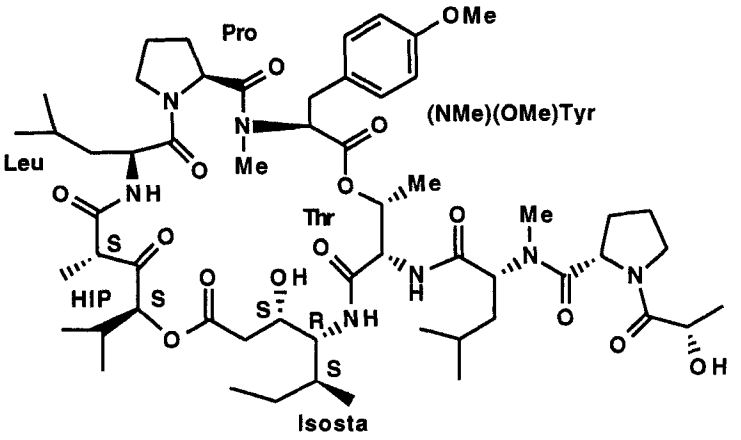

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Figure 1. Structure of didemnin B.

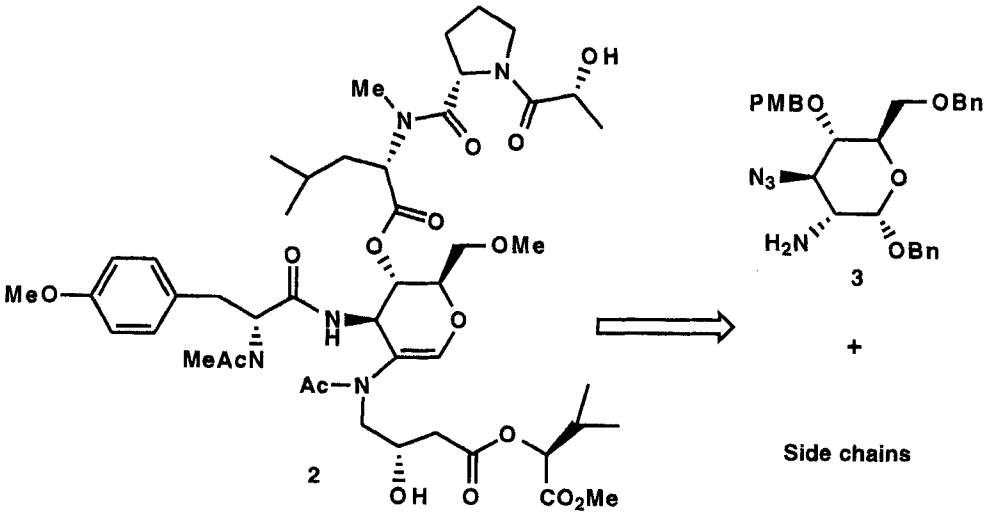
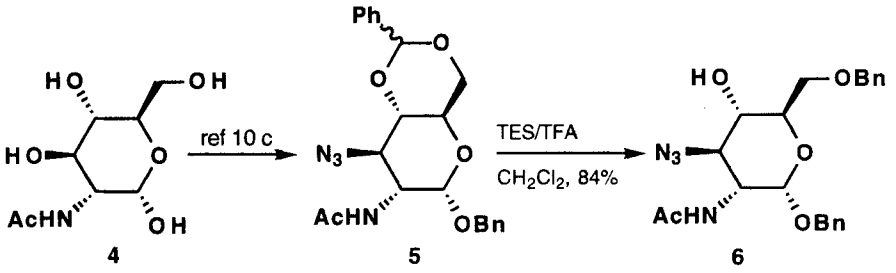


Figure 2. Peptidomimetic of didemnin B based on a diaminoglycal template.



Scheme 1

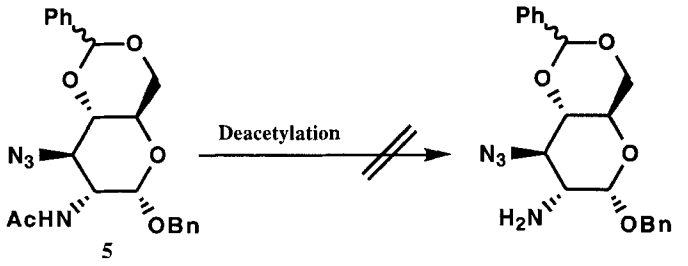
After examining the X-ray crystal structure analysis,[4] NMR studies[5,6] and SARs[7-9] of the didemnins, we designed a peptidomimetic (**2**) of didemnin B using a masked 2-amino-3-azido sugar (**3**) as the precursor (Figure 2).

RESULTS AND DISCUSSION

The synthesis of the sugar precursor **3**, began with *N*-acetyl-α-D-glucosamine **4** (Scheme 1). Using previously developed methodology benzyl 2-acetamido-3-azido-4,6-*O*-benzylidene-2,3-dideoxy-α-D-glucopyranoside (**7**) was synthesized.[10c] At this point, several reagents such as DIBAL,[11] BH_3•$NMe_3/AlCl_3$[12] and sodium cyanoborohydride with various activating reagents (HCl, TFA[13] and $TiCl_4$[14]) were employed to achieve the regioselective opening of the benzylidene acetal. Although the borane trimethylamine complex (solvent THF) was the best reagent,[12] the reproducibility of yields and the regioselectivity were still unsatisfactory. Finally, application of a triethylsilane/trifluoro acetic acid (TES/TFA) reagent system[15] gave predominately one regioisomer, benzyl 2-acetamido-3-azido-4-hydroxy-6-*O*-benzyl-α-D-glucopyranoside (**6**) in 84% yield. After we solved the regioselectivity problem, the next step was to remove the acetyl group to obtain the primary amine needed for coupling to a side chain.

A considerable amount of time was spent investigating conditions suitable for the deprotection of the 2-amino functionality of compounds **5** and **6** (Table). Initially, we tried the deacetylation of benzyl 2-acetamido-3-azido-4-hydroxy-6-*O*-benzyl-2-deoxy-α-D-glucopyranoside (**6**). However, after failing to achieve the desired transformation we turned our attention to the more rigid intermediate **5**. At first, acid hydrolysis[16] was tried at various temperatures and concentrations; at higher concentrations protective groups were destroyed. Basic hydrolysis with different bases (NaOH,[17] LiOH, $Ba(OH)_2$[18]) did not

Table. Unsuccessful Attempts to Deacetylate Azido Sugar **5.**



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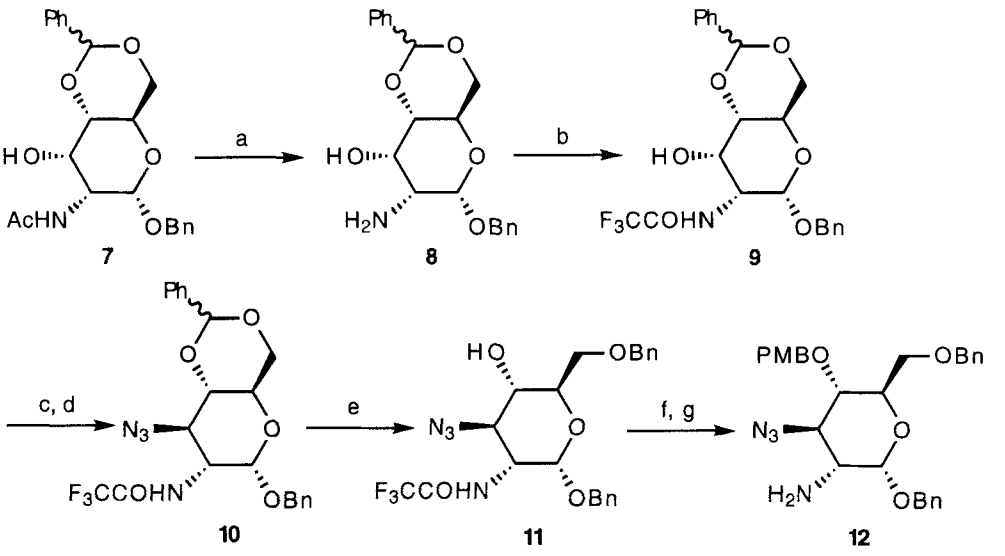
Trial	Reagents	Conditions	Results
1[a]	1N - 6 N HCl	RT - reflux	no reaction
2[a]	2 N - 10 N LiOH	RT - reflux	no reaction
3[b]	$NH_2NH_2.H_2O$	130 °C, sealed tube	mixtures
4[c]	$(Boc)_2O$, TEA, DMAP LiOH, MeOH	RT	15% yield
5[d]	$Et_3O^+BF_4^-$ Hydrolysis	RT	no reaction

a. Reactions were at 1N, 2N and 6N of HCl during acidic hydrolysis; 2N, 5N and 10N of LiOH solutions were used in basic hydrolysis. All reactions were refluxed only after no change was detected by TLC at rt. b. Commercially available hydrazine monohydrate (90% in H_2O) was used. c. The *N-t*-Boc intermediate was purified before hydrolysis. d. An *O*-ethyl acetamidium tetrafluoroborate derivative was isolated in poor yields.

accomplish the desired transformation. We then attempted hydrazinolysis using hydrazine monohydrate. It was observed by Fujinaga that hydrazine hydrate[18] is more efficient than anhydrous hydrazine in deacetylations. However, treatment with hydrazine monohydrate from mild to vigorous conditions gave only unidentifiable mixtures.

At this point, we attempted to increase the nucleophilicity of the amide carbonyl. A mild two-step method for the hydrolysis/methanolysis of secondary amides developed by Grieco was tried.[19] The amide functionality was converted to a *N-t*-Boc derivative which upon reaction with lithium hydroxide or methanolysis gave only a 15% overall yield of the desired compound. The reason for the low yield was partly due to the poor conversion of the acetamide to its Boc derivative.



a. 85% $NH_2NH_2 \cdot H_2O$, sealed tube, 130 °C, quant; b. TFAA, TEA, CH_2Cl_2, 95%; c. MsCl, pyr, 0 °C, 89%; d. NaN_3, DMF, $(n\text{-}Bu)_4N^+HSO_4^-$, 80 °C, 52%; e. TES, TFA, CH_2Cl_2, 78%; f. PMBBr, NaH, THF, 86%; g. K_2CO_3, aq MeOH, reflux, 92%; or KOH, aq MeOH, reflux, 78%.

Scheme 2

The reaction in the absence of TEA did not improve the yields.[20] Application of a two-step one pot hydrolysis using Meerwein's reagent triethyloxonium tetrafluoroborate[21] was also unsuccessful in achieving the desired transformation. As a final resort, we tried the hydrazinolysis of benzyl 2-acetamido-4,6-*O*-benzylidene-2-deoxy-α-D-glucopyranoside (**7**), a precursor of azido sugar **6**. Treatment of compound **7** with 90% hydrazine monohydrate in H_2O, at 130 °C and in a sealed tube cleanly removed the acetyl group (**8**, Scheme 2). These results are consistent with Fujinaga's observation that *N*-deacetylations in carbohydrates were dependent on the C-3 substitution pattern. Furthermore, no loss of any protective groups such as benzylidene acetal or benzyl was detected under these conditions.

Gross and co-workers[10a] have achieved this transformation of the epimer of **7** by treatment of potassium hydroxide in ethanol at 110 °C whereas zu Reckendorf and co-workers[10b,d] accomplished acetamide hydrolysis of benzyl 2-acetamido-4,6-*O*-benzylidene-3-amino-2,3-dideoxy-α-D-glucopyranoside in 74% yield. However, our reaction is higher yielding and requires no work up or purification. After the deacetylation was accomplished, the resulting amine was protected with a more labile trifluoroacetyl

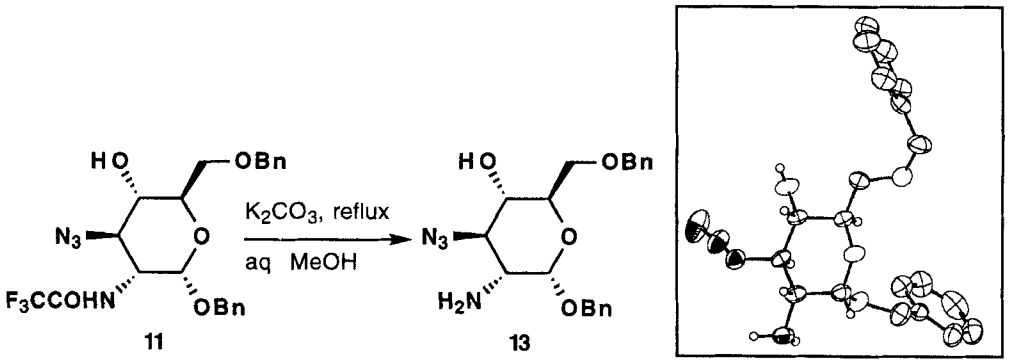


Figure 3. ORTEP drawing of **13** showing the stereochemistry and the regioselective opening of the benzylidene acetal.

group (**9**, Scheme 2). The hydroxyl group was mesylated and the displacement of the mesylate with sodium azide led to the azido sugar **10**. At elevated temperatures this reaction led to a partial loss of trifluoroacetyl group. Application of TES/TFA conditions to **10** gave the desired regioisomer **11** in 78% yield.[15] After protection of the 4-hydroxyl group with *p*-methoxybenzyl bromide, the deprotection of the trifluoroacetyl amide was examined. Potassium hydroxide in aqueous methanol at refluxing temperatures gave the desired compound (**3**) along with an unidentified side product. However, the use of potassium carbonate in aqueous methanol at reflux, although slower, gave only the desired product in 92% yield to complete the synthesis of the masked diamino sugar intermediate **3**. The regioselective opening and stereochemistry at C-3 was confirmed by an X-ray crystal structure of compound **13** (Figure 3).[22]

In conclusion, we have accomplished a facile synthesis of benzyl 2-amino-3-azido-4-*O*-*p*-methoxybenzyl-6-*O*-benzyl-2,3-dideoxy-α-D-glucopyranoside (**3**). Although there are many classical methods for amide hydrolysis, not many of them are successful in carbohydrates, especially acetamide hydrolysis. We have confirmed that the *N*-deacetylation in carbohydrates is dependent on the C-3 substituent. Hydrazinolysis offers the best alternative. Furthermore, sensitive protecting groups such as acetals and benzyl groups are stable to these conditions. Finally, trifluoroacetyl protection of an amino functionality proves to be a better alternative to acetyl protection for carbohydrates, although the yields in some reactions are only moderate. Presently, coupling of the side chains with the sugar template is being investigated.

EXPERIMENTAL

General methods: All manipulations were conducted under an inert atmosphere (argon or nitrogen). All solvents were reagent grade. Anhydrous tetrahydrofuran (THF) was distilled from sodium/benzophenone. Dichloromethane (CH_2Cl_2) was distilled from calcium hydride (CaH_2). Organic acids and bases were reagent grade. All other reagents were commercial compounds of the highest purity available. Analytical thin-layer chromatography (TLC) was performed on Merck silica gel (60 F-254), plates (0.25 mm), precoated with a fluorescent indicator (0.50 mm plates were used for preparatory thin-layer chromatography). Visualization was effected with ultraviolet light, phosphomolybdic acid reagent (7% w/v) in absolute ethanol, and anisaldehyde reagent (5% v/v) in absolute ethanol containing 5% sulfuric acid and 1% acetic acid. Flash column chromatography was carried out on Merck silica gel 60 particle size (0.040-0.063 mm). Proton and carbon magnetic resonance spectra (^1H, ^{13}C NMR) were recorded on a Bruker AM-500 (500 MHz) Fourier transform spectrometer using $CDCl_3$ as the solvent. Chemical shifts were measured in parts per million (δ) relative to tetramethylsilane (TMS-0 ppm) or $CHCl_3$ as an internal reference (7.26 ppm for ^1H and 77.0 ppm for ^{13}C). Coupling constants (J values) are in Hertz (Hz). Multiplicities are designated as singlet (s), broad singlet (bs), doublet (d), doublet of doublets (dd), doublet of doublet of doublets (ddd), doublet of triplets (dt), doublet of quartets (dq), triplet (t), triplet of doublets (td), quartet (q), and multiplet (m). Infrared spectra (IR) were obtained on a Perkin-Elmer Model 281-B or Perkin-Elmer Model 781 spectrometers. Oils were analyzed as neat films between sodium chloride plates. Absorptions are reported in wave numbers (cm^{-1}), and their intensities are designated as strong (s), medium (m), or weak (w). The spectra are calibrated against the 1601 cm^{-1} band of a polystyrene film, and only the most prominent or characteristic absorptions are noted. Optical rotations (in degrees, °) were recorded on a Perkin-Elmer Model 241 polarimeter at the sodium D line. High resolution mass spectra (HRMS) were obtained on either a VG 70-70HS [a high resolution double focusing mass spectrometer using ammonia Chemical Ionization (CI) or Electron Impact (EI)] or a ZAB-E [using Fast Atom Bombardment (FAB), CI or EI]. The mass spectrometer was interfaced to VG/DEC 11-73 data systems.

Benzyl 2-Acetamido-3-azido-6-*O*-benzyl-2,3-dideoxy-α-D-glucopyranoside (6). Compound **5** (0.10 g, 0.0.24 mmol) was dissolved in 3 mL of methylene chloride and the solution cooled to 0 °C. To this mixture was added trifluoroacetic acid (0.092 mL, 0.69 mmol) and triethylsilane (0.19 mL, 0.69 mmol) successively. The reaction mixture was slowly warmed to room temperature and stirred for 24 h. The reaction mixture was diluted with ether (20 mL) and washed with 5% HCl, 5%

$NaHCO_3$ and saturated NaCl solutions. The organic layer was dried (Na_2SO_4), filtered and concentrated. The resulting crude oil was purified by column chromatography eluting with EtOAc/petroleum ether (30:70). The pure compound (0.098 g, 84%) was obtained as a white foam. mp 195 °C, $[\alpha]_D^{25}$ +70.09 (*c* 0.58, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$) δ 1.90 (s, 3H), 3.20-3.30 (bs, 1H), 3.55-3.85 (m, 5H), 4.13-4.17 (m, 1H), 4.44-4.75 (m, 4H), 4.79 (d, J=2.2 Hz, 1H), 5.73 (d, J=9.7 Hz, 1H), 7.16-7.28 (m, 10H); ^{13}C NMR (250 MHz, $CDCl_3$) δ 23.19, 51.03, 61.59, 69.82, 69.99, 71.29, 73.71, 76.48, 76.99, 77.59, 96.41, 127.70, 127.87, 128.13, 128.26, 128.46, 128.61, 136.76, 137.49, 170.03; IR ($CHCl_3$) 3302 (br), 2925 (m), 2103 (s), 1649 (s), 1547 (s), 1513 (s), 1367 (m), 1251 (s), 1059 (s) cm^{-1}; HRMS *m/z* calcd for $C_{22}H_{27}N_4O_5$, 427.1981 (M+H). Found: 427.1984.

Benzyl 2-Amino-4,6-*O*-benzylidene-2-deoxy-α-D-glucopyranoside (8). Benzyl 2-acetamido-4,6-*O*-benzylidene-α-D-glucopyranoside (1.00 g, 0.025 mmol) was placed in a sealed tube and 60 mL of hydrazine monohydrate/H_2O (90:10) was added. The sealed tube was heated to 130 °C for 12 h. After this time the reaction was cooled to 0 °C and the crystals formed were collected (0.88 g, 99%). R_f 0.78 MeOH/$CHCl_3$ (10:90), mp 173 °C (decomp), $[\alpha]_D^{25}$ +128.5 (*c* 0.20, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 1.40-1.80 (bs, 2H), 2.31 (s, 1H), 3.11 (d, J=7.4 Hz, 1H), 3.51-3.56 (m, 2H), 3.86 (bs, 1H), 4.19-4.22 (m, 3H), 4.47 (d, J=12.2 Hz, 1H), 4.61 (s, 1H), 5.39 (s, 1H), 7.00-7.21 (m, 10H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 53.18, 57.97, 69.57, 70.01, 71.00, 80.01, 100.53, 102.01, 126.85, 127.81, 127.94, 128.00, 128.20, 128.31, 128.66, 129.01; IR (C_6D_6) 3013 (s), 2935 (w), 2868 (w), 1455 (w), 1379 (w), 1219 (s), 1121 (s), 1104 (s), 1054 (s), 1018 (s), 768 (s), 699 (s) cm^{-1}; HRMS *m/z* calcd for $C_{20}H_{24}NO_5$, 358.1604 (M+H). Found: 358.1617.

Benzyl 2-Trifluoroacetamido-4,6-*O*-benzylidene-2-deoxy-α-D-glucopyranoside (9). Compound **8** (0.64 g, 1.79 mmol) dissolved in methylene chloride (20 mL), was treated with triethylamine (0.24 mL, 5.37 mmol) and trifluoroacetic anhydride (0.26 mL, 1.79 mmol). The reaction mixture was stirred 12 h and diluted with 50 mL of chloroform. The organic layer was washed with 5% HCl, 5% $NaHCO_3$ and saturated NaCl solutions sequentially. The organic layer was dried (Na_2SO_4), filtered and concentrated. The resulting crude oil was purified by column chromatography eluting with $CHCl_3$. Pure **9** (0.81 g, 95%) was obtained as a white foam. R_f 0.78 MeOH/$CHCl_3$ (10:90), mp 130 °C (decomp), $[\alpha]_D^{25}$ +71.5 (*c* 0.20, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 2.67 (bs, 1H), 3.62-3.63 (m, 1H), 3.73-3.77 (t, J=10.2 Hz, 1H), 4.20-4.32 (m, 4H), 4.54 and 4.76 (AB, J=12.1 Hz, 2H), 4.93 (d, J=3.4 Hz, 1H), 5.60 (s, 1H), 7.06 (d, J=7.9 Hz, 1H), 7.24-7.49 (m, 10H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 49.67, 57.58, 67.19, 68.94, 70.39, 78.01, 95.65, 101.90, 115.67 (q, 287.43), 126.17, 128.08,

128.33, 128.40, 128.70, 128.30, 136.22, 136.88, 156.68 (q, 37.58); IR ($CHCl_3$) 3287 (br), 2863 (w), 2359 (m), 1709 (s), 1548 (m), 1210 (s), 1179 (s), 1120 (s) cm^{-1}; HRMS *m/z* calcd for $C_{22}H_{22}NO_6F_3$, 453.1399. Found: 453.1408.

Benzyl 2-Trifluoroacetamido-3-azido-4,6-*O*-benzylidene-2,3-dideoxy-α-D-glucopyranoside (10): Compound **9** (0.17 g, 0.38 mmol) dissolved in pyridine (10 mL) and the solution cooled to 0 °C. To this solution was added mesyl chloride (0.035 mL, 0.45 mmol) and the reaction mixture was stirred overnight. After the reaction was complete, it was diluted with 30 mL of chloroform and extracted with saturated copper sulfate (4 x 20 mL). The organic layer was collected and washed with H_2O (20 mL) and saturated NaCl (10 mL). The organic layer was dried (Na_2SO_4), filtered and concentrated. The resulting crude oil was purified by column chromatography eluting with chloroform. Pure **10** (0.17 g, 89%) was obtained as a white foam. The pure mesylate (0.11 g, 0.20 mmol) was dissolved in 10 mL of distilled DMF. Sodium azide (0.07 g, 1.02 mmol) and tetrabutylammonium hydrogen sulfate (7 mg) were added to this mixture and stirred at 80 °C for 36 h. After the reaction was complete, it was cooled to room temperature and poured into cold water. The precipitate was collected and recrystallized from ethanol (0.05 g, 52% yield). R_f 0.78 MeOH/$CHCl_3$ (10:90), mp 239 °C (decomp), $[\alpha]_D^{25}$ +88.5 (*c* 0.20, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 3.45 (t, J=9.3 Hz, 1H), 3.59 (t, J=10 Hz, 1H), 3.84-3.92 (m, 2H), 4.06-4.08 (m, 1H), 4.14-4.17 (m, 1H), 4.29 and 4.54 (AB, J=12 Hz, 2H), 4.80 (s, 1H), 5.41 (s, 1H), 7.19-7.7.27 (m, 10H), 7.49 (d, J=7.32 Hz, 1H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 49.03, 52.20, 59.52, 62.98, 68.43, 69.88, 80.36, 95.74, 101.17, 125.76, 127.35, 127.55, 127.74, 128.01, 128.03, 128.21, 128.44, 128.82, 136.12, 136.68; IR ($CHCl_3$) 3010 (s), 2111 (s), 1732 (s), 1531 (m), 122 (s), 1165 (m), 1043 (m) cm^{-1}; HRMS *m/z* calcd for $C_{22}H_{22}N_4O_5F_3$, 479.1542 (M+H). Found: 479.1560.

Benzyl 2-Trifluoroacetamido-3-azido-6-*O*-benzyl-2,3-dideoxy-α-D-glucopyranoside (11): Compound **10** (0.07 g, 0.14 mmol) was dissolved in 3 mL of methylene chloride and the solution cooled to 0 °C. To this solution were added trifluoroacetic acid (0.054 mL, 0.69 mmol) and triethylsilane (0.11 mL, 0.69 mmol) successively. The reaction mixture was slowly warmed to room temperature and stirred for 24 h. The reaction mixture was diluted with ether (20 mL) and washed with 5% HCl, 5% $NaHCO_3$ and saturated NaCl solutions sequentially. The organic layer was dried (Na_2SO_4), filtered and concentrated. The resulting crude oil was purified by column chromatography eluting with EtOAc/petroleum ether (30:70). The pure compound (0.055 g, 78%) was obtained as a white foam. R_f 0.78 MeOH/$CHCl_3$ (10:90), m.p. 160 °C (decomp), $[\alpha]_D^{25}$ +60.9 (*c* 0.20, $CHCi_3$); mp 159-161 °C; ^1H NMR (500 MHz, $CDCl_3$) δ 2.84-2.88 (bs, 1H), 3.70-3.79 (m, 4H), 3.81-4.01 (m, 4.54-4.56, 4H), 4.79 (AB,

J=11.9 Hz, 1H), 5.00 (s, 1H), 5.10 (d, J=6.0 Hz, 1H), 7.27-7.38 (m, 10H), 8.67 (s, 1H), ; ^{13}C NMR (500 MHz, $CDCl_3$) δ 53.43, 64.48, 69.87, 70.18, 71.32, 72.77, 73.83, 96.07, 128.14, 128.19, 128.58, 128.73, 129.02, 129.10, 129.16, 138.35, 138.73; IR ($CHCl_3$) 3447 (m), 3290 (m), 2102 (s), 1698 (s), 1559 (m), 1182 (s), 1063 (m) cm^{-1}; HRMS *m/z* calcd for $C_{22}H_{27}N_5O_5F_3$, 498.1964 (M+NH_4). Found: 498.1956.

Benzyl 2-Amino-3-azido-4-*O*-*p*-methoxybenzyl-6-*O*-benzyl-2,3-dideoxy-α-D-glucopyranoside (3): Compound **11** (0.098 g, 0.21 mmol) was dissolved in THF and the solution was treated with sodium hydride (0.041 g, 1.05 mmol) and *p*-methoxybenzyl bromide (0.082 g, 4.08 mmol). The reaction mixture was stirred for 6 h and then diluted with ether. The excess sodium hydride was quenched by dropwise addition of water. The organic layer was washed with 10% HCl, 5% $NaHCO_3$ and brine sequentially. The ether layer was dried over Na_2SO_4 and concentrated. Purification by column chromatography eluting with $CHCl_3$ provided the desired compound (0.1054 g, 86%). This fully protected compound (0.088 g, 0.15 mmol) was dissolved in 4 mL of a THF:MeOH:H_2O (2:1:1) solvent mixture and potassium carbonate (0.21 g, 1.5 mmol) was added. The reaction mixture was refluxed for 48 h, after which time it was cooled to room temperature and concentrated under reduced pressure. The aqueous layer was extracted with chloroform. The organic layer dried (Na_2SO_4), filtered and concentrated. The crude product was purified by column chromatography eluting with MeOH/$CHCl_3$(NH_3) (20:80). Pure compound (0.071 g, 92%) was obtained as an semi-solid. R_f 0.78 MeOH/$CHCl_3$ (10:90), $[\alpha]_D^{25}$ +65.3 (*c* 0.20, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 1.37 (bs, 2H), 2.25-2.57 (m, 1H), 3.41-3.44 (m, 2H), 3.48 and 3.51 (dd, J=1.7, 1.8 Hz, 1H), 3.62 (s, 3H), 3.62-3.70 (m, 2H), 4.31 and 4.37 (AB, J=10.2 Hz, 2H), 4.41 and 4.55 (AB, J=12.1 Hz, 2H), 4.70-4.59 (m, 2H), 4.80 (d, J=3.3 Hz, 1H), 6.71 and 7.03 ($[AX]_2$, J=6.7 Hz, 4H), 7.15-7.26 (m, 10H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 54.77, 54.97, 68.14, 68.81, 69.46, 70.61, 73.41, 74.15, 76.77, 98.43, 113.65, 127.59, 127.69, 127.80, 127.83, 127.99, 128.23, 128.80, 128.99, 129.46, 129.78, 137.01, 137.63, 159.26; HRMS *m/z* calcd for $C_{28}H_{33}N_4O_5$, 505.2450 (M+H). Found: 505.2446.

ACKNOWLEDGMENTS

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22. The X-ray structure of compound **13** has been submitted for publication to *Acta Crystallogr., Section C*. Suitable crystals were obtained using vapor diffusion techniques with ethyl acetate/hexane as the solvent pair under nitrogen atmosphere. X-ray intensity data were collected on a Rigaku R-AXIS-IIc area detector employing graphite-monochromated Mo-K_α radiation (λ=0.71069 Å). The structure was solved and refined using the Molecular Structure Corporation teXsan package on a Silicon Graphics R4000 computer.