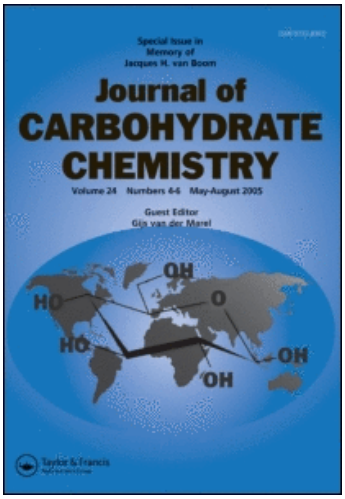

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ANOMERIC *O*-ALKYLATION OF *O*-ACETYL-PROTECTED SUGARS[1]

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ABSTRACT

Anomeric *O*-alkylation of 2,3,4,6-tetra-*O*-acetyl-protected glucose, galactose, and mannose (**1a-c**) and of hepta-*O*-acetyllactose **5** with decyl triflate (**2**) in the presence of NaH as the base and in DME or DEE as solvents afforded directly decyl glycosides **3a-c** and **5**, respectively, in good yields. The anomeric diastereo control is temperature dependent, furnishing at room temperature preferentially the β-anomers. Similarly, reaction of **5** with the triflate **8** of the spacer **7** or with the triflate **10** or nonaflate **11** of 3-*O*-protected sphingosine **9** gave at room temperature mainly β-lactosides **12** and **13**, respectively. Thus, important intermediates for the synthesis of amphiphilic carbohydrate derivatives and for glycoconjugate synthesis are readily accessible.

INTRODUCTION

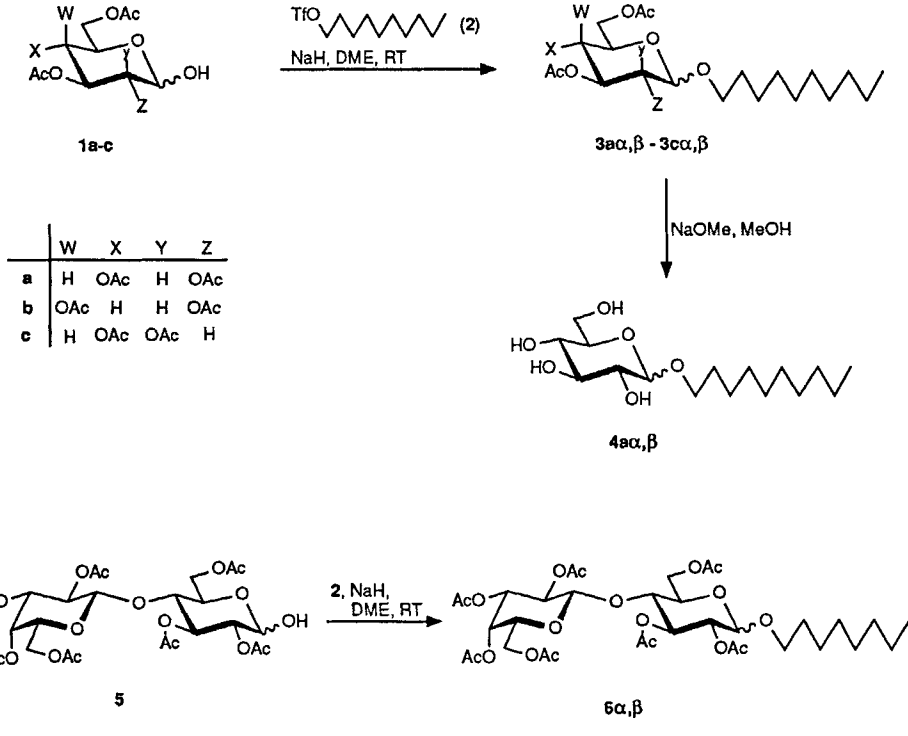
Direct anomeric *O*-alkylation of *O*-benzyl and/or *O*-alkylidene protected sugars in the presence of a base with trifluoromethanesulfonates (TfOR) of various primary and secondary alcohols including sugars as alkylating agents has become a very convenient method for glycoside bond formation.[2-5] Also *O*-unprotected sugars and less reactive alkylating agents have been recently successfully employed in this reaction, furnishing directly and often with high anomeric control the desired glycosidic products.[6,7] Obviously, *O*-acyl protection will strongly diminish the nucleophilicity of anomeric oxide oxygen atoms. Additionally, in the presence of a base, due to alkoxide generation,

acyl migration may play a major role, thus precluding anomeric *O*-alkylation. Because *O*-acetyl groups are frequently used, however particularly prone to acyl migration, anomeric *O*-alkylation of *O*-acetyl protected sugars with primary alkyl triflates as alkylating agents was investigated. Long chain alkyl triflates were employed as alkylating agents, thus hopefully leading to versatile intermediates for the synthesis of carbohydrate based surfactants, of saccharides with spacer arms, and of membrane constituents.

RESULTS AND DISCUSSION

2,3,4,6-Tetra-*O*-acetylglucose, -galactose, and -mannose (**1a-c**, Scheme 1) are readily available from the 1,2,3,4,6-penta-*O*-acetyl derivatives.[8]

Scheme 1



	W	X	Y	Z
a	H	OAc	H	OAc
b	OAc	H	H	OAc
c	H	OAc	OAc	H

Various solvents and bases were investigated for their efficacy in anomeric *O*-alkylation; 1,2-dimethoxyethane (DME) or 1,2-diethoxyethane (DEE) as solvents and sodium hydride (NaH) as base gave the best results.[9] Thus, with **1a,b** and decyl triflate (**2**)[6,10] as

Table 1. Results in the Anomeric *O*-Alkylation of *O*-Acetyl Protected Sugars **1a-c** and **5** with Decyl Triflate (**2**)[a]

Reaction Temp. [°C]	Products (Yield [%], α/β - Ratio)			
	3aα,β	**3b**α,β	**3c**α,β	**6**α,β
- 40	74, 1:3	75, 1:5	70, 20 : 1	72, 1:1
- 20	70, 1:4	70, 1:6	70, 16 : 1	70, 1:3
0	70, 1:5	70, 1:9	65, 10 : 1	70, 1:5
25	70, ≤ 1 : 19	70, ≤ 1:19	65, 1 : 1	65, ≤ 1 : 19

a For details of the reaction procedure, see experimental section

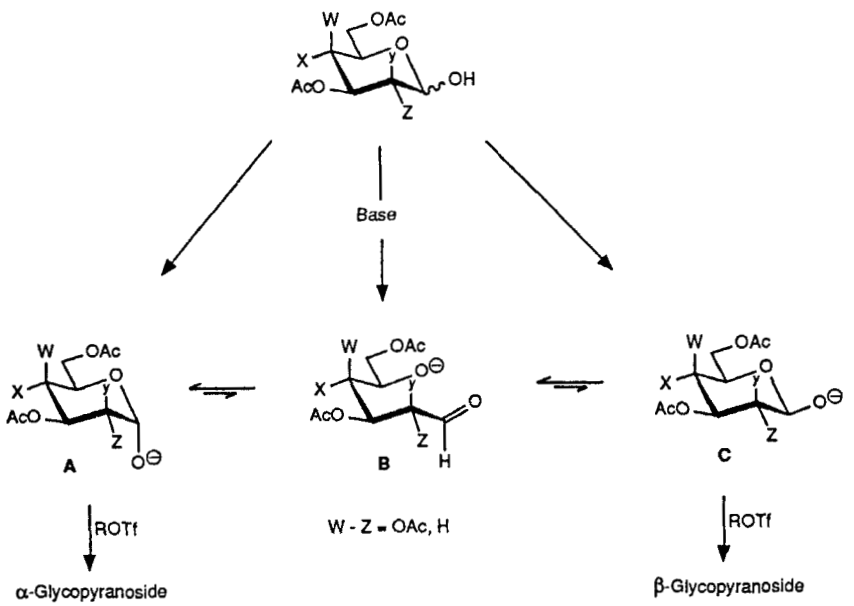
alkylating agent at room temperature the β-isomers **3a**β and **3b**β were obtained with high preference (for yields and α/β-ratios, see Table 1). Acetyl migration did not play a limitation for the yield under these reaction conditions; rather, side reactions of the strong alkylating agent were observed. Similarly, mannose derivative **1c** gave with **2** the corresponding decyl mannoside **3c** in a 1:1 α/β-ratio. The structural assignments of these compounds were based on their ^{1}H NMR data and comparisons with known compounds.[7,11] Also deacetylation of **3a**α and **3a**β with sodium methanolate/methanol was carried out providing known unprotected decyl glucosides **4a**α and **4a**β, respectively, in quantitative yield.[7]

Surprisingly, at temperatures as low as -40 °C these reactions could be carried out with even slightly higher yields; the α:β-ratios exhibited increased α-anomer formation (Table 1). This result is in accordance with previous observations for *O*-benzyl protected pyranoses: the anomeric diastereo control is at low temperature mainly governed by the isomer ratio **A**:**C** (Scheme 2); when the reactions are carried out at room temperature, the equilibration **A**⇌**B**⇌**C** becomes fast, thus allowing for other factors to influence anomeric selection.[2-7] In pyranoses generally the enhanced nucleophilicity of the equatorial oxide oxygen atoms (kinetic anomeric effect)[2,12,13] favors reaction with **C**. Side reactions with acyclic intermediate **B**, for instance elimination or alternatively *O*-alkylation at *O*-5, are generally not observed[2-4,6] and also not found in the above described reactions.[9]

Similar reaction of readily available 1-*O*-unprotected lactose **5**[14] with **2** afforded at room temperature practically exclusively the known β-lactoside **6**β,[15] whereas at -40 °C a 1:1-ratio of **6a**,β[15] was obtained (Scheme 1, Table 1). Because attachment of oligosaccharide moieties to proteins and other carriers is important, glycoside bond formation of **5** with the Lemieux spacer **7**[16] via anomeric *O*-alkylation was investigated

(Scheme 3). To this aim, **7** was transformed with Tf_2O in the presence of triethylamine as the base into triflate **8**. Reaction with **5** under the same conditions at room temperature gave preferentially β-lactoside **12** in good yield (75%, β:α > 19:1) as indicated by the ^1H NMR data.

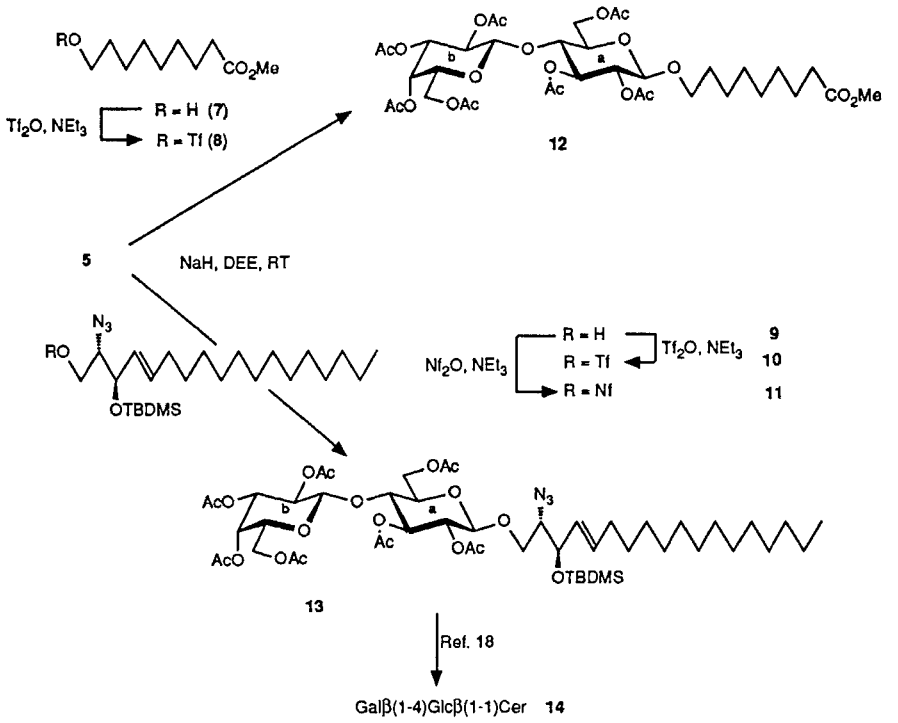
Scheme 2



Because of the importance of lactosyl ceramides in glycosphingolipid synthesis, also the direct connection of **5** with azidosphingosine was of interest. To this aim, known 3-*O*-*tert*-butyldimethylsilyl (TBDMS) protected azidosphingosine **9**[17] was transformed into the triflate **10** and the corresponding nonaflate **11**. Both compounds gave with **5** under the same conditions at room temperature preferentially the desired β-lactoside **13** (β:α ⩾ 19:1), though in lower yield (49% from **10**, 42% from **11**). The structural assignment of **13** was based on the ^1H NMR data and the transformation into lactosyl ceramide **14** employing a known procedure.[18]

In conclusion, anomeric *O*-alkylation of *O*-acetyl protected sugars is a convenient means for the preparation of alkyl glycosides. This method has potential in the synthesis of amphiphilic carbohydrate derivatives and alkyl glycosides possessing functional groups in the alkyl moiety. Ortho-ester formation, often a major side reaction in glycosylations with *O*-acetyl protected glycosyl donors, is not observed here.

Scheme 3



EXPERIMENTAL

General methods. Solvents were purified in the usual way, the petroleum ether (PE) used had a boiling range of 30-70 °C. ^{1}H NMR spectra: Bruker AC-250 Cryospec; internal standard tetramethylsilane (TMS). Flash chromatography: Silica gel 60 (Baker; 0.03-0.06 mm). Thin layer chromatography (TLC): Foil plates, silica gel 60 F_{254} (Merck; layer thickness 0.2 mm). Elementary analyses: Heraeus CHN-O-Rapid.- Optical rotation: Perkin-Elmer polarimeter 241/MS; 1-dm cell.

General Procedure for the Anomeric *O*-Alkylation of 1a-c and 5: 1a-c or **5** (1 mmol) was dissolved in dry DME (20 mL) (for **5** 20 mL of DEE) at room temperature and then NaH (27.5 mg, 1.1 mmol, 96% suspension in paraffin oil) was added. After stirring for 5 min the alkylating agent (1.2 mmol of **2**, **8**, **10**, or **11**) was added and stirring continued for 3 h. For the reactions with **2** at 0 °C, -20 °C, and -40 °C stirring was continued for 15 h. The reaction mixture was filtered through silica and the silica washed with ethyl acetate (EE, 50 mL). The clear solution was washed with saturated

sodium chloride solution (5 x 75 mL), dried with $CaCl_2$, concentrated and then purified by flash chromatography.

Decyl 2,3,4,6-Tetra-*O*-acetyl-α- and -β-D-glucopyranoside (3aα and 3aβ). General procedure; **1a** (348 mg, 1 mmol), **2** (290 mg, 1.2 mmol); flash chromatography (4:1, PE-EE); yield: **3aα** (17.1 mg, 3.5%) and **3aβ** (324.9 mg, 66.5%). The physical data of **3aα,β** were in accordance with published values.[7]

Decyl 2,3,4,6-Tetra-*O*-acetyl-α- and -β-D-galactopyranoside (3bα and 3bβ). General procedure; **1b** (348 mg, 1 mmol), **2** (290 mg, 1.2 mmol); flash chromatography (4:1, PE-EE); yield: **3bα** (16.6 mg, 3.5%) and **3bβ** (322.0 mg, 66.5%). Compounds **3bα,β** are known,[11] however physical data are not reported. **3bα**: Colourless oil; R_F 0.63 (3:2, PE-EE); ^1H NMR (250 MHz, $CDCl_3$): δ 0.88 (dd, 3H, J = 6.2 Hz, CH_3), 1.21-1.43 (m, 14H, 7 CH_2), 1.51-1.63 (m, 2H, O-CH_2-CH_2), 1.98, 2.04, 2.07, 2.14 (4 s, 12H, 4 $COCH_3$), 3.43 (ddd, 1H, J_{gem} = 9.8 Hz, J_{vic} = 6.6 Hz, O-CH_2), 3.68 (ddd, 1H, J_{gem} = 9.8 Hz, J_{vic} = 6.6 Hz, O-CH_2), 4.00-4.30 (m, 3H, H-5, H-6, H-6'), 5.05-5.42 (m, 3H, H-2, H-3, H-1), 5.46 (dd, 1H, $J_{4,5}$ = 1.1 Hz, $J_{3,4}$ = 3.3 Hz, H-4).

Anal. Calcd for $C_{24}H_{40}O_{10}$: C, 59.00; H, 8.25. Found: C, 59.10; H, 8.15.

3bβ: Colourless oil; R_F 0.55 (3:2, PE-EE); $[\alpha]_D^{20}$ -11.6° (*c* 1.5, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$) δ 0.88 (dd, 3H, J = 6.3 Hz, CH_3) 1.24-1.47 (m, 14H, 7 CH_2), 1.51-1.72 (m, 2H, O-CH_2-CH_2), 1.98, 2.05, 2.06, 2.15 (4 s, 12H, 4 $COCH_3$), 3.45 (ddd, 1H, J_{gem} = 9.6 Hz, J_{vic} = 6.9 Hz, O-CH), 3.8-4.0 (m, 2H, O-CH, H-5), 4.05-4.25 (m, 2H, H-6, H-6'), 4.45 (d, 1H, $J_{1,2}$ = 7.9 Hz, H-1), 5.02 (dd, 1H, $J_{2,3}$ = 10 Hz, $J_{3,4}$ = 3.4 Hz, H-3), 5.21 (dd, 1H, $J_{1,2}$ = 7.9 Hz, $J_{2,3}$ = 10 Hz, H-2), 5.39 (dd, 1H, $J_{3,4}$ = 3.4 Hz, $J_{4,5}$ = 1.0 Hz, H-4).

Anal. Calcd for $C_{24}H_{40}O_{10}$: C, 59.00; H, 8.25. Found: C, 59.03; H, 8.19.

Decyl 2,3,4,6-Tetra-*O*-acetyl-α- and -β-D-mannopyranoside (3cα and 3cβ). General procedure; **1c** (348 mg, 1 mmol), **2** (290 mg, 1.2 mmol); flash chromatography (4:1, PE-EE); yield: **3cα** (156.5 mg, 33%) and **3cβ** (157 mg, 33%). The physical data of **3cα,β** were in accordance with published values.[7]

Decyl *O*-(2,3,4,6-Tetra-*O*-acetyl-β-D-galactopyranosyl)-(1-4)-2,3,6-tri-*O*-acetyl-α- and -β-D-glucopyranoside (6α and 6β). General procedure; **5** (636 mg, 1 mmol), **2** (290 mg, 1.2 mmol); flash chromatography or medium pressure chromatography (7:3, PE-EE); yield: **6α** (25 mg, 3%) and **6β** (479 mg, 62%). The physical data of **6α,β** were in agreement with published values.[15]

8-Methoxycarbonyloct-1-yl Trifluoromethanesulfonate (8). To a solution of **7**[16] (4 g, 19 mmol) in dry dichloromethane (200 mL) was added triethylamine (1.96 g, 19 mmol). The solution was cooled to -10 °C, trifluoromethanesulfonic acid anhydride

(5.35 g, 19 mmol) was added dropwise and stirring continued for 1 h. The reaction mixture was washed with water (3 x 100 mL) and then with saturated NaCl (3 x 100 mL); the organic layer was dried over $MgSO_4$ and then concentrated *in vacuo* to yield pratically pure **8** (5.46 g, 90%) as a colourless oil which was directly used for the anomeric *O*-alkylation reactions. ^1H NMR (250 MHz, $CDCl_3$) δ 1.21-1.49 (m, 8H, 4 CH_2), 1.59-1.68 (m, 2H, CO-CH_2-CH_2), 1.83 (m, 2H, TfO-CH_2-CH_2), 2.31 (m, 2H, $COCH_2$), 3.66 (s, 3H, $COOCH_3$), 4.53 (m, 2H, TfO-CH_2).

(2*S*,3*R*,4*E*)-2-Azido-3-*tert*-butyldimethylsilyloxy-4-octadecen-1-yl Trifluoromethanesulfonate (10). To a solution of **9**[17] (1.82 g, 4.2 mmol) in dry dichloromethane (25 mL) was added at -40 °C triethylamine (455 mg, 4.5 mmol) and trifluoromethanesulfonic acid anhydride (1.26 g, 4.5 mmol). After 2 h the reaction mixture was washed with saturated NaCl solution (3 x 25 mL), the organic layer was dried with $MgSO_4$ and concentrated *in vacuo* and the residue purified by flash chromatography (98:2, PE-EE) to yield **10** (2.81 g, 91%) as a colourless oil. R_F 0.70 (9:1, PE-EE); $[\alpha]_D^{20}$ -36° (*c* 10, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$) δ 0.04 (s, 3H, $SiCH_3$), 0.08 (s, 3H, $SiCH_3$), 0.71-0.93 (m, 12H, 4 CH_3), 1.18-1.51 (m, 22H, 11 CH_2), 2.01-2.23 (m, 2 H, C=CH-CH_2), 3.59-3.71 (m, 1H, H-2), 4.19 (dd, 1H, $J_{2,3}$ = 5.8 Hz, $J_{3,4}$ = 7.5 Hz, H-3), 4.40 (dd, 1H, $J_{1,1'}$ = 10.4 Hz, $J_{1,2}$ = 7.6 Hz, H-1), 4.59 (dd, 1H, $J_{1,1'}$ = 10.4 Hz, $J_{1',2}$ = 3.4 Hz, H-1'), 5.42 (dd, 1H, $J_{3,4}$ = 7.5 Hz, $J_{4,5}$ = 15.5 Hz, H-4), 5.70-5.82 (m, 1H, H-5).

Anal. Calcd for $C_{25}H_{48}F_3N_3O_4SSi$: C, 52.51; H, 8.46; N, 7.35. Found: C, 52.16; H, 8.67; N, 7.00.

(2*S*,3*R*,4*E*)-2-Azido-3-*tert*-butyldimethylsilyloxy-4-octadecen-1-yl Nonafluorobutanesulfonate (11). **9** (0.8 g, 19 mmol), triethylamine (188 mg, 2.2 mmol), and nonafluorobutanesulfonic acid anhydride[19] (1.22 g, 2.24 mmol) were transformed into **11** as described for **10**. Flash chromatography (19:1, PE-EE) of the crude product afforded 373 mg (28%) **11** as a colourless oil which was immediately used in the next step. R_F = 0.27 (PE); $[\alpha]_D^{20}$ -31° (*c* 1, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$) δ 0.04 (s, 3H, $SiCH_3$), 0.08 (s, 3H, $SiCH_3$), 0.71-0.93 (m, 12H, 4 CH_3), 1.18-1.51 (m, 22H, 11 CH_2), 2.01-2.23 (m, 2H, C=CH-CH_2), 3.59-3.71 (m, 1H, H-2), 4.19 (dd, 1H, $J_{2,3}$ = 5.5 Hz, $J_{3,4}$ = 7.5 Hz, H-3), 4.44 (dd, 1H, $J_{1,2}$ = 7.6 Hz, $J_{1,1'}$ = 10.5 Hz, H-1), 4.62 (dd, 1H, $J_{1',2}$ = 3.5 Hz, $J_{1,1'}$ = 10.5 Hz, H-1'), 5.42 (dd, 1H, $J_{3,4}$ = 7.5 Hz, $J_{4,5}$ = 15.5 Hz, H-4), 5.70-5.82 (m, 1H, H-5).

8-Methoxycarbonyloct-1-yl *O*-(2,3,4,6-Tetra-*O*-acetyl-β-D-galactopyranosyl)-(1-4)-2,3,6-tri-*O*-acetyl-β-D-glucopyranoside (12). General procedure; **5** (636 mg, 1 mmol), **8** (348 mg, 1.2 mmol); flash chromatography (1:1, PE-EE) of the crude product

which contained traces of the α-anomer (< 5%) gave 605 mg (75%) **12** as a colourless oil. R_F 0.25 (1:1, PE-EE); $[\alpha]_D^{20}$ -3.0° (*c* 1, $CHCl_3$) ^1H NMR (250 MHz, $CDCl_3$) δ 1.21-1.41 (m, 8H, 4 CH_2), 1.50-1.59 (m, 4H, O-CH_2-CH_2, CH_2-CH_2-COOMe), 1.96, 2.03, 2.04, 2.04, 2.06, 2.11, 2.15 (7 s, 21H, 7 $COCH_3$), 2.27-2.34 (m, 2H, CH_2-COOMe), 3.67 (s, 3H, OCH_3), 3.34-4.2 (m, 7H), 4.40-4.51 (m, 1H), 4.43 (d, 1H, $J_{1a,2a}$ = 7.9 Hz, H-1a), 4.48 (d, 1H, $J_{1b,2b}$ = 7.9 Hz, H-1b), 4.88 (dd, 1H, $J_{1a,2a}$ = 7.9 Hz, $J_{2a,3a}$ = 9.5 Hz, H-2a), 4.95 (dd, 1H, $J_{3b,4b}$ = 3.3 Hz, $J_{2b,3b}$ = 10.5 Hz, H-3b), 5.11 (dd, 1H, $J_{1b,2b}$ = 7.9 Hz, $J_{2b,3b}$ = 10.5 Hz, H-2b), 5.20 (dd, 1H, $J_{2a,3a}$ = 9.5 Hz, $J_{3a,4a}$ = 9.5 Hz, H-3a), 5.36 (dd, 1H, $J_{3b,4b}$ = 3.3 Hz, $J_{4b,5b}$ < 1 Hz, H-4b).

Anal. Calcd for $C_{36}H_{54}O_{20}$: C, 53.59; H, 6.75. Found: C, 53.15; H, 6.82.

(2*S*,3*R*,4*E*)-2-Azido-3-*tert*-butyldimethylsilyloxy-4-octadecen-1-yl *O*-(2,3,4,6-Tetra-*O*-acetyl-β-D-galactopyranosyl)-(1-4)-2,3,6-tri-*O*-acetyl-β-D-glucopyranoside (13). (a) From **10**: General procedure; **5** (636 mg, 1 mmol), **10** (686 mg, 1.2 mmol); flash chromatography (3:2, PE-EE) of the crude product which contained traces of the α-anomer (≤ 5%) gave 519 mg (49%) **13** as a colourless oil. R_F 0.38 (3:2, PE-EE); $[\alpha]_D^{20}$ -10.5° (*c* 1, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$) δ 0.02 (s, 3H, $SiCH_3$), 0.05 (s, 3H, $SiCH_3$), 0.81-1.02 (m, 12H, 4 CH_3), 1.12-1.51 (m, 22H, 11 CH_2), 1.98-2.23 (m, 2H, C=CH-CH_2), 1.96, 2.04, 2.04, 2.06, 2.06, 2.11, 2.15 (7 s, 21H, 7 $COCH_3$), 3.30-4.21 (m, 10H), 4.40-4.52 (m, 1H), 4.48 (d, 1H, $J_{1a,2a}$ = 7.8 Hz, H-1a), 4.49 (d, 1H, $J_{1b,2b}$ = 7.7 Hz, H-1b), 4.91 (dd, $J_{1a,2a}$ = 7.8 Hz, $J_{2a,3a}$ = 9.4 Hz, H-2a), 4.95 (dd, 1H, $J_{2b,3b}$ = 10.4 Hz, $J_{3b,4b}$ = 3.4 Hz, H-3b), 5.11 (dd, 1H, $J_{1b,2b}$ = 7.7 Hz, $J_{2b,3b}$ = 10.4 Hz, H-2b), 5.19 (dd, 1H, $J_{2a,3a}$ = 9.4 Hz, $J_{3a,4a}$ = 9.2 Hz, H-3a), 5.35 (dd, 1H, $J_{3b,4b}$ = 3.4 Hz, $J_{4b,5b}$ < 1 Hz, H-4b), 5.30-5.45 (m, 1H, C*H*=CH-CH_2), 5.55-5.73 (m, 1H, C=C*H*-CH_2).

Anal. Calcd for $C_{50}H_{83}N_3O_{19}Si$: C, 56.75; H, 7.91; N, 3.97. Found: C, 56.76; H, 7.84; N, 3.98.

(b) From **11**: General procedure; **5** (636 mg, 1 mmol), **11** (868 mg, 1.2 mmol); work up as described above gave 445 mg (42%) **13** which had the same physical data.

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