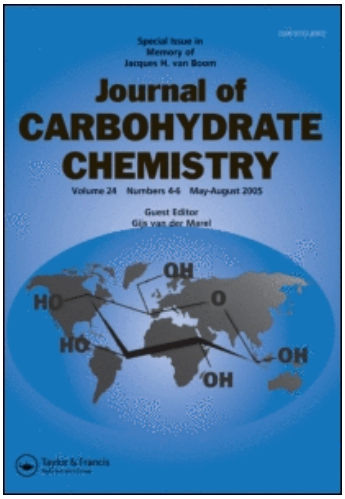

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Synthesis of *p*-Trifluoroacetamidophenylethyl *O*-(2-Acetamido-2-Deoxy-β-D-Galactopyranosyl)-(1→4)-*O*-β-D- Galactopyanosyl-(1→4)-*O*-β-D-Glucopyranoside, Containing the Trisaccharide Portion of the Asialo-GM2 Glycolipid

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SYNTHESIS OF *p*-TRIFLUOROACETAMIDOPHENYLETHYL *O*-(2-ACETAMIDO-2-DEOXY-β-D-GALACTOPYRANOSYL)-(1→4)-*O*-β-D-GALACTOPYANOSYL-(1→4)-*O*-β-D-GLUCOPYRANOSIDE, CONTAINING THE TRISACCHARIDE PORTION OF THE ASIALO-GM2 GLYCOLIPID

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ABSTRACT

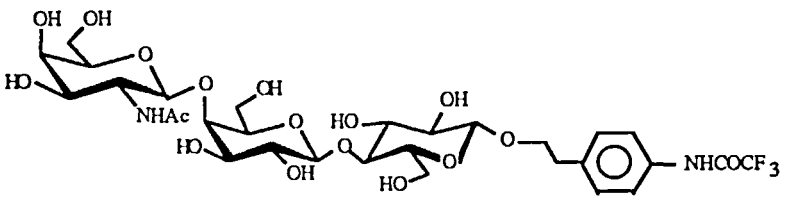
The *p*-trifluoroacetamidophenylethyl β-glycoside 9 of the trisaccharide O-(2-acetamido-2-deoxy-β-D-galactopyranosyl)-(1→4)-*O*-β-D-galactopyranosyl-(1→4)-D-glucopyranose (gangliotriose, asialo-GM2) was synthesised. The key step was coupling of a suitably protected lactose derivative with a galactosamine thioglycoside derivative using sulfuryl chloride/trifluoromethanesulfonic acid activation.

INTRODUCTION

The asialo-GM2 oligosaccharide (gangliotriose, *O*-(2-acetamido-2-deoxy-β-D-galactopyranosyl)-(1→4)-*O*-β-D-galactopyranosyl-(1→4)-D-

glucopyranose) is a common core structure in many gangliosides, such as GM1, GM2, GD1a, GD1b, and GT1b. The simplest glycolipid containing this structure, gangliotriosylceramide (asialo-GM2) has been reported[1] as a mouse tumor-associated cell surface antigen, and was also recently shown to be the minimum structure required for binding to some pathogenic bacteria.[2] It was therefore considered of interest to have access to the trisaccharide portion of this glycolipid for biological experiments.

Syntheses of the free gangliotriose[3] and of the methyl,[4] 8-methoxycarbonyloctyl[5], and ceramide[6] glycosides have been reported, as well as syntheses[6,7,8] of more complicated glycolipids containing this structure. We now report the synthesis of the title trisaccharide glycoside (9) containing the *p*-trifluoroacetamidophenylethyl[9] linker arm. Thioglycosides were used as building blocks, and the key galactosamine to lactose glycosidation was promoted by the sulfuryl chloride-triflic acid[10,11] reagent. The usefulness of this promotor system with 2-phthaloyl thioglycoside donors has not been demonstrated previously.



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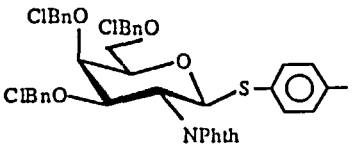
RESULTS AND DISCUSSION

For the synthesis of gangliotriose, a galactosamine plus lactose synthetic strategy, using thioglycoside blocks, was chosen. The starting material used for the galactosaminyl block was 4-methylphenyl 2-azido-

3,4,6-tri-*O*-*p*-chlorobenzyl-2-deoxy-1-thio-β-D-galactopyranoside,[12] because of its availability in bulk quantities in our laboratory. The azido group was transformed into a phthalimido group by successive treatment with hydrogen sulfide/triethylamine, phthalic anhydride, and acetic anhydride. The desired galactosamine block **1** was obtained in 68 % yield.



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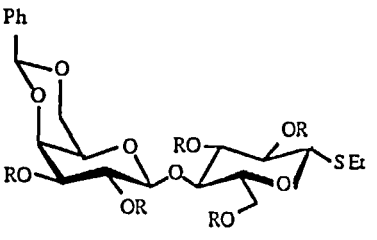


3: R = H

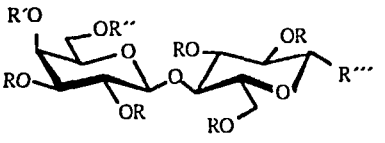
4: R = ClBn

For preparation of the lactosyl block, lactose was converted to its thioethyl 4,6-*O*-benzylidene derivative **3** by a two-step sequence analogous to that used[13] for preparation of the corresponding thiomethyl derivative. Benzylation of **3** with *p*-chlorobenzyl chloride in *N*,*N*-dimethylformamide gave **4** (77 %), which on treatment with sodium cyanoborohydride and hydrogen chloride in tetrahydrofuran-diethyl ether[14] gave the expected 4-OH compound **5** (82%).

At this stage, silver salt glycosidation of **5** with the galactoamine glycosyl halide derived from **1** would have given the protected 1-thioethyl trisaccharide derivative of gangliotriose. However, since a spacer derivative was desired, it was considered a more economical strategy to introduce the spacer arm already at the disaccharide stage.

Since **5** has a non-participating benzyl group in the 2-position, different glycosidation conditions (thioglycoside/sulfuryl chloride-triflic acid, glycosyl bromide/zinc fluoride, bromide or chloride) were examined

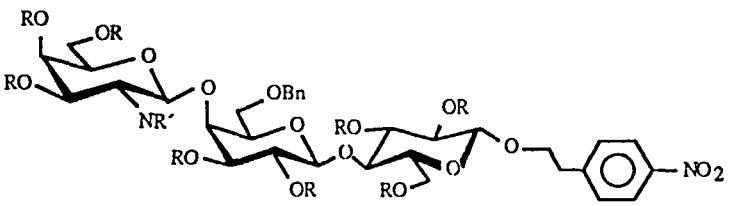
for ability to give a high β/α ratio in glycosidations between 5 and *p*-trifluoroacetamidophenylethanol. The highest ratio β/α was obtained with zinc chloride in dichloromethane,[15] giving a β/α ratio of 5:1. Thus, 5 was treated first with bromine to give the corresponding bromide, and then with *p*-trifluoroacetamidophenylethanol and zinc chloride in dichloromethane. The desired β-glycoside 6 was obtained in 62% yield.



2: R = H R‴ = SEt

5: R = ClBn R′ = H R″ = Bn R‴ = SEt

6: R = ClBn R′ = H R″ = Bn R‴ = O



7: R = ClBn R′ = Phth

8: R = ClBn R′ = HAc

Condensation between the galactosaminyl block **1** and the lactosyl block **6** was performed using sulfuryl chloride-triflic acid[10,11] in acetonitrile. Trisaccharide **7** was obtained in 72 % yield. No α-coupling product was detected. This demonstrates the usefulness of this reagent system, previously developed[10,11] mainly for 1,2-*cis*-glycosidations, also for 1,2-*trans* glycosidations with 2-phthaloyl glycosyl donors. The trisaccharide derivative **7** was treated with hydrazine hydrate, followed by acetic anhydride to give **8** (52 % yield).

In the NMR spectrum of **8** in deuterochloroform, signals from two isomers could be detected. If the NMR solvent was changed to tetrahydrofuran-d_8, only one isomer was observed. The occurence of two resolved isomers in deuterochloroform solution can be explained by slow rotation around the amide bond in the galactosamine residue, caused by amide hydrogen bonds to oxygen in the surrounding *p*-chlorobenzyl ethers. In tetrahydrofuran, rotation is faster, since hydrogen bonding to solvent is possible.

Treatment of **8** with, successively, zinc in acetic acid, trifluoroacetic anhydride in pyridine, and hydrogen/palladium on charcoal gave the target trisaccharide glycoside **9** in 72 % yield. The NMR data of **9** agreed well with those for the corresponding methyl[4] and 8-methoxycarbonyloctyl[5] glycosides.

EXPERIMENTAL

General Procedures. Melting points are corrected. Concentrations were performed at <40 °C (bath). Optical rotations were recorded at 25 °C with a Perkin-Elmer 241 polarimeter. NMR spectra were recorded at 27 °C with a Bruker AM 500 instrument, using TMS as internal standard, unless otherwise stated. The spectra were invariably in agreement with the proposed structures, only selected NMR data are reported. The FAB-MS spectra were recorded with a VG ZAB-SE mass spectrometer. The primary beam consisted of xenon atoms with a maximum energy of 8 keV. The samples were dissolved in thioglycerol and the positive ions were extracted and accelerated over a potential of 10 kV. Thin layer chromatography was performed on silica gel 60 F_{254} (Merck, Darmstadt, FRG) using appropriate

eluant systems. The spots were visualized by UV light and/or by charring with 5 % aqueous sulfuric acid. Silica gel chromatography was performed on Matrex silica Si, 60A, 20-45 μ, (Amicon Corporation, Danvers, MA 01923, U.S.A.). Sulfuryl chloride/ triflic acid reagent[10,11] was made 1 M in toluene containing 10% diethyl ether. Organic solutions were dried with magnesium sulfate. Organic solvents were of pro analysi quality and distilled over appropriate drying agents.

***p*-Methylphenyl 3,4,6-Tri-*O*-*p*-chlorobenzyl-2-deoxy-2-phthalimido-1-thio-β-D-galactopyranoside (1):** Hydrogen sulfide was bubbled into a stirred solution of *p*-methylphenyl 2-azido-3,4,6-tri-*O*-*p*-chlorobenzyl-2-deoxy-1-thio-β-D-galacto-pyranoside[12] (5.00 g) in 1:1 pyridine/ triethylamine (200 mL) at room temperature. The flask was sealed and stirring was continued for 2 h. Then nitrogen was flushed through the solution, and phthalic anhydride (3.0 g) in dichloromethane (100 mL) was added. The mixture was stirred overnight, then acetic anhydride (50 mL) in toluene (100 mL) was added. After 2 h water (50 mL) was added. The organic phase was washed with water, saturated sodium bicarbonate and 1 M sulfuric acid and concentrated. The resulting syrup was purified by column chromatography on silica gel (7/1 toluene/ethyl acetate). Crystallization of appropriate fractions from diethyl ether/ isooctane gave pure (1) (3.89 g, 68%), mp 63-70 °C, $[\alpha]_D$ +70.1° (*c* 1.0, chloroform). NMR data: ^{13}C, δ 21.1 (CH_3Ph), 51.6 (C-2), 68.6, 70.8, 72.5, 72.7, 73.7, 77.3, 77.7 (C-3,4,5,6, 3 x $PhCH_2$), 84.2 (C-1).

Anal. Calcd for $C_{42}H_{36}Cl_3NO_6S$ (789.2 u): C, 63.9; H, 4.6; N, 1.8. Found: C, 63.7; H, 4.6; N, 1.8.

Ethyl 4-*O*-β-D-Galactopyranosyl-1-thio-β-D-glucopyranoside (2): Boron trifluoride etherate (8.5 g, 7.3 mL) was added, at room temperature, to a mixture of β-lactose pentaacetate (50 g), ethanethiol (6.9 g, 822 mL) and dichloromethane (200 mL). After 2 h, TLC detected no more change. The

mixture was washed with aqueous 1M sodium hydroxide (500 mL). The organic layer was concentrated and taken up in methanol (150 mL), then sodium methoxide in methanol (0.5 M, 10 mL) was added and the mixture was stirred overnight at room temperature. The reaction mixture was neutralized with Dowex (50W x 8, H^+), filtered, and concentrated. The solid residue was recrystalliszed from ethanol (300 ml). Pure **2** was obtained (16.4 g, 56%), mp 191-192 °C, $[\alpha]_D$ -33.6 ° (*c* 0.5, ethanol).

Anal. Calcd for $C_{14}H_{26}O_{10}S \times H_2O$ (386.4 u): C, 41.6; H, 7.0. Found: C, 41.8; H, 6.8. A FAB-MS spectrum showed an M+1 ion at m/z 387.

Ethyl 4-*O*-(4,6-*O*-Benzylidene-β-D-galactopyranosyl)-1-thio-β-D-glucopyranoside (3): A mixture of **2** (3.00 g) and benzaldehyde (30 mL) was stirred for 1 h at room temperature. Then formic acid (30 mL) was added, and stirring was continued for 25 min. The clear solution was poured into diethyl ether (400 mL) while stirring. After 1 h, the solid was filtered off and dissolved in methanol (50 mL) during heating. After cooling, diethyl ether (25 mL) was added. Crystals of **3** were obtained upon standing overnight (3.09 g, 84%), mp 240-242 °C, $[\alpha]_D$ -49.3° (*c* 1.0, methanol).

Anal. Calcd for $C_{21}H_{30}O_{10}S \times H_2O$ (474.5 u): C, 51.2; H, 6.5. Found: C, 51.8; H, 6.6. A FAB-MS spectrum showed an M+1 ion at m/z 475.

Ethyl 4-*O*-(4,6-*O*-Benzylidene-2,3-di-*O*-*p*-chlorobenzyl-β-D-galacto-pyranosyl)-2,3,6-tri-*O*-*p*-chlorobenzyl-1-thio-β-D-glucopyranoside (4): Treatment of **3** (2.00 g) with *p*-chlorobenzyl chloride (3.0 ml) and sodium hydride (1.4 g) in *N*,*N*-dimethyl formamide (50 ml) at 0 °C under nitrogen for 1 h, plus overnight at room temperature, gave a mixture showing a single spot on TLC (toluene/ ethyl acetate 4/1, Rf 0.39). The mixture was partitioned between toluene and 1M sulfuric acid and water, and the organic layer was concentrated. Crystallization from dichloromethane/ ethyl

acetate/ isooctane gave pure **4** (3.57 g , 77 %), mp 179-183 °C, $[\alpha]_D$ +10.9° (*c* 1.0, chloroform). Anal. Calcd for $C_{56}H_{55}Cl_5O_{10}S \times H_2O$ (1097.4 u): C, 60.3; H, 5.1. Found: C, 60.5; H, 4.9.

Ethyl 4-*O*-(6-*O*-Benzyl-2,3-di-*O*-*p*-chlorobenzyl-β-D-galactopyranosyl)-2,3,6-tri-*O*-*p*-chlorobenzyl-1-thio-β-D-glucopyranoside (5): Diethyl ether saturated with hydrogen chloride was added dropwise to a mixture of compound **4** (100 mg) in tetrahydrofuran (10 mL) containing molecular sieves 3Å (600 mg) and sodium cyanoborohydride (100 mg). After 2 h at room temperature TLC (toluene/ ethyl acetate 4/1, Rf 0.53) showed complete reaction. The mixture was filtered, partitioned between dichloromethane and sodium bicarbonate and the organic layer was washed with water. Pure **5** was obtained after crystallization from ethyl acetate/ isooctane (82 mg, 82 %), mp 137-139 °C, $[\alpha]_D$ +25.6° (*c* 1.0, chloroform). Anal. Calcd for $C_{56}H_{57}Cl_5O_{10}S$ (1099.4 u): C, 61.2; H, 5.2. Found: C, 61.2; H, 5.3.

2-(*p*-Nitrophenyl)ethyl 4-*O*-(6-*O*-Benzyl-2,3-di-*O*-*p*-chlorobenzyl-β-D-galactopyranosyl)-2,3,6-tri-*O*-*p*-chlorobenzyl-β-D-glucopyranoside (6): A solution of **5** (500 mg) in dichloromethane (20 mL) was treated with bromine (50 µL) and molecular sieves 4Å (5.0 g) at 0 °C during stirring. After 30 min TLC (toluene/ ethyl acetate 4/1) indicated that no starting material remained, and excess bromine was destroyed by addition of cyclohexene (100 µL). The mixture was added dropwise to a stirred mixture of 2-(4-nitrophenyl)ethanol (300 mg) and freshly activated[15] zinc chloride (5.0 g) in dichloromethane (10 mL), while maintaining nitrogen atmosphere and 0 °C. After two h the mixture was diluted with dichloromethane, filtered, washed with water and aqueous 1M sulfuric acid, dried and concentrated. The resulting syrup was purified by silica gel chromatography (isooctane/ ethyl acetate 1/1). The first compound eluted was **6** (Rf 0.53, 340 mg, 62%). Next eluted was a compound (Rf 0.49) that was shown to be the α-isomer of

6. Analysis by NMR and weight showed the ratio of α:β in the product mixture to be 1:5. Crystals of **6** were obtained from diethyl ether/ isooctane, mp 110-112 °C, $[\alpha]_D$ +22.8 ° (*c* 1.0, chloroform). NMR data: ^{13}C, δ 36.0 ($PhCH_2CH_2$), 66.0 (C-4'), 68.1, 68.4 (C-6, C-6'), 69.4 ($PhCH_2CH_2$), 71.2, 72.4, 72.6, 73.6, 73.8, 74.39, 74.44, 75.0, (6 xPhCH2, C-5, C-5'), 76.4 (C-4), 79.3 (C-2'), 81.2, 81.5 (C-2, C-3), 82.6 (C-3), 102.4 (C-1'), 103.4 (C-1); ^1H, δ 2.41 (OH), 3.01 (m, $PhCH_2CH_2$), 3.53 (dd, $J_{1',2'}$ 7.9, $J_{2',3'}$ 9.3 Hz, H-2'), 3.76 (m, $PhCH_2CH_2$), 3.91 (dd, H-4), 4.04 (m, H-4'), 4.18 (m, $PhCH_2CH_2$), 4.35 (d, $J_{1,2}$ 7.7 Hz, H-1), 4.36 (d, $J_{1',2'}$ 7.9 Hz, H-1'). Anal. Calcd for $C_{62}H_{60}Cl_5NO_{13} \times H_2O$ (1204.4 u): C, 60.9; H, 5.1. Found: C, 61.0; H, 4.9.

2-(*p*-Nitrophenyl)ethyl 4-*O*-(3,4,6-Tri-*O*-*p*-chlorobenzyl-2-deoxy-2-phthalimido-β-D-galactopyranosyl)-4-*O*-(6-*O*-benzyl-2,3-di-*O*-*p*-chlorobenzyl-β-D-galactopyranosyl)-2,3,6-tri-*O*-*p*-chlorobenzyl-β-D-glucopyranoside (7): Sulfuryl chloride-triflic acid reagent (366 μL, 2 eq) was added, during stirring under nitrogen, to a cooled (-20 °C) solution of disaccharide **6** (213 mg, 1 eq) and thioglycoside **1** (218 mg, 1.5 eq) in dry acetonitrile (15.0 mL) containing molecular sieves 3Å (1.0 g). The mixture was stirred for 30 min, during which the temperature was allowed to rise to 0 °C. Then pyridine (300 μL) was added and the mixture was stirred for another hour at room temperature. The mixture was filtered, partitioned between ethyl acetate and aqueous sodium bicarbonate, dried and concentrated. After silica gel chromatography in toluene/ ethyl acetate 7/1 **7** (237 mg , 72%) was obtained. $[\alpha]_D$ +44° (*c* 1.0, chloroform). NMR data: ^{13}C, δ 36.0 ($PhCH_2CH_2$), 53.3 (C-2''), 68.10, 68.12, 68.2 (C-6, C-6', C-6''), 69.3 ($PhCH_2CH_2$), 71.1, 71.5, 71.8, 72.4, 72.7, 74.90, 72.92, 73.1, 73.8, 73.9, 74.0, 74.7, 75.1, 75.2 (9 x PhCH2, C-5, C-4', C-5', C-4'', C-5''), 76.60, 76.62 (C4, C-3''), 79.9 (C-2'), 80.9 (C-3'), 81.2 (C-2), 82.4 (C-3), 100.0 (C-1''), 102.0 (C-1'), 103.4 (C-1); ^1H, δ 2.99 (m, $PhCH_2CH_2$), 3.21 (m, H-5), 3.26 (dd, $J_{1,2}$ 7.8, $J_{2,3}$ 9.4 Hz, H-2), 3.73 (m, $PhCH_2CH_2$), 4.05 (d, $J_{1,2}$ 7.1 Hz, H-

1'), 4.08 (d, $J_{3,4}$ 2.9 Hz, H-4"), 4.13 (m, $PhCH_2CH_2$), 4.32 (d, $J_{1,2}$ 7.8 Hz, H-1), 4.57 (dd, H-3"), 4.73 (dd, H-2"), 5.11 (d, $J_{1,2}$ 8.4 Hz, H-1").

2-(*p*-Nitrophenyl)ethyl 4-*O*-(3,4,6-Tri-*O*-*p*-chlorobenzyl-2-acetamido-2-deoxy-β-D-galactopyranosyl)-4-*O*-(6-*O*-benzyl-2,3-di-*O*-*p*-chlorobenzyl-β-D-galactopyranosyl)-2,3,6-tri-*O*-*p*-chlorobenzyl-β-D-glucopyranoside (8): Hydrazine hydrate (1.0 mL) was added to a stirred solution of trisaccharide 7 (117 mg) in toluene/ 95% ethanol, (1:3, 4 mL). The mixture was refluxed overnight, cooled and concentrated to dryness. The residue was treated with acetic anhydride/ pyridine (1:1, 3 mL) for 30 min at room temperature. The material was concentrated and chromatographed on silica gel in toluene/ethyl acetate (4/1). Appropriate fractions (Rf 0.35) were pooled and concentrated to give amorphous 8 (94 mg, 84 %), $[\alpha]_D$ +33.2° (*c* 1.0, chloroform). NMR data (THF-d_8): ^{13}C, δ 34.1 ($PhCH_2CH_2$), 53.3 (C-2"), 99.3, 101.0, 101.7 (C-1, C-1', C-1"); 1H, δ 4.42 (d, $J_{1,2}$ 7.8 Hz, H-1), 4.45 (d, $J_{1,2}$ 7.5 Hz, H-1'), 5.12 (d, $J_{1,2}$ 8.3 Hz, H-1").

2-(*p*-Trifluoroacetamidophenyl)ethyl *O*-(2-Acetamido-2-deoxy-β-D-galactopyranosyl)-(1→4)-*O*-β-D-galactopyranosyl-(1→4)-*O*-β-D-glucopyranoside (9): Zinc dust (300 mg) was added to a mixture of 8 (165 mg) in tetrahydrofuran (6.0 mL), acetic acid (3.0 mL) and water (0.3 mL) and the mixture was stirred at 0 °C under nitrogen. Then a solution of $CuSO_4 \times 5$ H_2O (100 mg/mL, 0.6 mL) was added. After 30 min TLC (n-heptane: ethyl acetate 1:1) showed complete reaction. The mixture was filtered, diluted with dichloromethane, the organic layer was washed with water and saturated sodium bicarbonate, dried and concentrated. The residue was dissolved in dichloromethane (9.0 mL). The solution was cooled to -20 °C and pyridine (150 µL) and trifluoroacetic anhydride (60 µL) were added. After 10 min TLC (n-heptane: ethyl acetate 1:1) showed complete reaction. The mixture was concentrated to dryness and dissolved in ethyl acetate: ethanol:

Table 1: NMR data, δ_H (upper value), δ_C (lower value) and J (in parenthesis) for compound 9 in deuterium oxide solution (ND= not determined, acetone $\delta_H = 2.225$; $\delta_C = 32.1$).

	Glc	Gal	GalNAc	aglycon
1	4.49 (8.0) 102.9	4.43 (7.9) 103.8	4.62 (8.5) 103.6	
2	3.27 (9.2) 73.6	3.41 (10.0) 71.9	3.90 (10.9) 53.5	
3	3.64 (8.2) 75.2	3.76 (2.9) 72.3	3.73 (3.2) 71.8	
4	3.59 (8.3) 79.3	4.09 (0.5) 77.0	3.91 (0.9) 68.7	
5	3.55 (ND) 75.6	3.71 (ND) 75.2	3.65 (ND) 75.7	
6	ND 60.0	ND 61.5	ND 61.9	
CH_3CO			2.06 23.2	
CH_3CO			175.7	
CF_3CO				116.7 (286)
CF_3CO				157.8 (38)
CH_2CH_2Ph				3.93/4.15 71.5
CH_2CH_2Ph				2.98 35.6

acetic acid: water 4:2:1:1 (8.0 mL) containing sodium acetate (150 mg) and hydrogenolyzed over Pd/C (10%, 150 mg) at atmospheric pressure for 8 h. Complete debenzylation was indicated by TLC (ethyl acetate/ methanol/ acetic acid/ water, 12/3/3/2, Rf 0.15). Purification by C-18 chromatography as described before[11] gave 9 (51 mg, 72%), $[\alpha]_D$ -5.0° (*c* 1.0, water).

Anal. Calcd for $C_{30}H_{43}N_2O_{17}F_3$ (760.7) x H_2O: C, 46.3; H, 5.8; N, 3.6. Found: C, 46.5; H, 6.5; N, 2.8. A FAB-MS spectrum showed an M+Na ion at m/z 783.

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