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SYNTHESIS OF N-METHYL-N-POLYFLUOROALKYL-D-GLUCAMINES AND N-METHYL-(FLUOROUS ACID D-GLUCAMIDES)

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Abstract: The selective *N*-alkylation or *N*-acylation of D-glucamine using (perfluoroalkyl)propyl iodides/mesylates or fluorinated carboxylic acids allowed the synthesis of novel fluorous chiral resolving agents.

Keywords: fluorous, chiral tertiary amines/amides, carbohydrate based amphiphiles, alkylation, acylation.

Living organisms usually synthesize only one of the two enantiomers of chiral molecules, but in the chemical syntheses often racemic compounds are obtained. The biological activity of enantiomers may be different or even opposite, so enantiomeric separations are necessary and inevitable for the pharmaceutical and fine chemical industries. The strict regulations put in place in the 1990's on production and marketing chiral drugs made a policy change of pharmaceutical industry [1].

There is high level of commercial interest in chirality and the incentive to produce optically pure materials (i.e. *single enantiomers*) by methods applicable to at least multigram amounts, and in many cases to hundreds and thousands of tonnes [2].

There are two basic approaches for obtaining chiral compounds: resolution and asymmetric synthesis [3]. Although *crystallization* is the leading technique for *separation of diastereomers* [4], several *non-conventional techniques* are complementary with it or provide the only solutions for special cases [5].

We have disclosed our results on the development of nonconventional optical resolution methods based on the separation of diastereomeric salts or complexes using sulfoxide carboxylic acids as models. Such methods include *salting-out selective extraction* ('SOSE') [6,7] – an early example of today's *enantioselective liquid-liquid extraction* – ('ELLE') [8], *chiroselective transport through liquid membranes* [7], and *heat-facilitated crystallization* ('HFC') [7,9,10]. In

addition, some $(\text{CF}_3)_3\text{CO}$ -substituted fluorous carboxylic acids were synthesized and introduced as new chiral solvating reagents for the determination of enantiomeric ratios of selected amines using ^1H and ^{19}F NMR spectroscopy [11].

Carbohydrate based resolving agents play important role in the production of the single enantiomer of active pharmaceutical ingredients [3]. Thus, (*S*)-(+)- Naproxen was directly resolved from the racemate with high enantiopurity (>95% e.e.) by inclusion crystallization using *N*-octyl-D-(-)-glucamine as the chiral host [12].

The manufacture of *N*-polyhydroxyalkyl amines, such as *N*-methyl D-(-)- glucamine (**2**), has been known for many years, and such materials are available commercially. The fatty acid amide surfactants (**3**) are made by the acylation reaction of the unprotected 2^o amine (**2**) with a fatty acid ester (Scheme 1) [13].

Scheme 1. Manufacturing scheme for the production of fatty acid glucamides.

The title compounds were designed to exploit the unique effects of perfluoroalkyl-groups [14] on the substituted molecules' microscopic [15] and macroscopic [16] properties. Here we disclose the synthesis of fluorous chiral amines **5a-c** and amides **7a-b** as shown by Scheme 2 and Scheme 3, respectively.

In the alkylation reactions fluorous alkyl iodides **4a-c** [17] were reacted with 2 molar excess of *N*-methyl D-glucamine (**2**) and that of K_2CO_3 in boiling acetonitrile for 4h to achieve full conversion of **4a-c** (TLC). Following solvent evaporation the excess of **2** was removed by triturating the crude with water. Then the solid residues were filtered, dried and recrystallized from boiling methanol to afford pure 3^o amines **5a-c** in medium to good yield as white crystals with narrow melting point range. We note, that $\text{C}_8\text{F}_{17}(\text{CH}_2)_3\text{OTs}$ was ineffective for the alkylation of **2** in CH_3CN with refluxing for days, while the corresponding mesylate was effective (Scheme 2 and Experimental).

Scheme 2. Preparation of *N*-methyl-*N*-[3-(perfluoroalkyl)propyl]-*D*-glucamines **5a-c**. (The numbering presented on **5a-c** is used for the assignment of NMR data).

Selective acylation of *N*-methyl *D*-glucamine (**2**) was performed using the mixed-anhydride protocol for the activation of 4,4,5,5,6,6,7,7,8,8,9,9,10,10,11,11,11-heptadecafluoroundecanoic acid (**6a**) to afford the fluorous *D*-glucamide **8a** in acceptable isolated yield (Scheme 3.) This carboxyl-activation protocol has been used by Ben *et al.* [18] for the synthesis of *N*-methyl-*N*-octanoyl-*D*-glucamine (**8b**).

However, the present fluorous amide **8a** gave a massive hydrogel during the aqueous work-up procedure, which was destroyed by the addition of methanol and consecutive boiling to initiate crystallization (Experimental).

We note that the yield of *D*-glucamide **8b** was increased from reported 30% [18] to 79% by the dropwise addition of **2** dissolved in lukewarm methanol to the chilled ether solution of the mixed anhydride **7b** (Experimental).

Scheme 3. Selective *N*-acylation of *N*-methyl-*D*-glucamine **2** with in situ generated mixed anhydrides **7a-b**.

All new compounds were characterized by ^1H NMR, ^{13}C NMR and HRMS spectroscopy (Experimental, Supporting Information). These novel fluorous tertiary amines **5a-c** and amides **8a-b** will be tested in for the optical resolution of selected volatile racemic fluorinated compounds in our laboratory.

Figure 1. The numbering presented on **8a** (major and minor) is used for the assignment of NMR data.

Of note is that the basic *tert* amine unit in **5a-c** seems to accelerate the exchange-processes of the OH protons as their signals merge in the water signal of DMSO- d_6 used as solvent for the NMR measurements, while in the ^1H NMR spectrum of amide **8a** registered in the same solvent, the OH signals are separated as doublets or triplets according to their position in the carbohydrate framework. On the other hand, **8a** was present as a ca. 2:1 mixture of two amide rotamers in the sample subjected to NMR measurements (Figure 1). Due to the pronounced deshielding effect of the carbonyl oxygen the ^1H -NMR chemical shift of *N*-CH $_3$ signal of **8a** (minor) is markedly downfield-shifted relative to that detected for **8a** (major) (3.02 ppm and 2.83 ppm, respectively). Although the fluorinated chain was not assigned in the investigated products, the triplet split of C-3' resonance clearly refers to the direct attachment of a CF $_2$ group.

Experimental

The fluorinated carboxylic acid **6a** was prepared as reported in [19] and [20]. CF $_3$ CH $_2$ OH and fluorinated precursors were purchased from FC Chemicals, while the other reagents and organic solvents from Sigma-Aldrich and Molar Chemicals Kft (Hungary). The ^1H and ^{13}C NMR spectra of all compounds were recorded in DMSO- d_6 solution in 5 mm tubes at RT, on a Bruker DRX- 500 spectrometer at 500 (^1H) and 125 (^{13}C) MHz, with the deuterium signal of the solvent as the lock and TMS as internal standard. The HSQC, HMBC and COSY spectra, which support exact assignment of ^1H - and ^{13}C NMR signals were obtained by using the standard Bruker pulse programs.

Determination of molecular mass and acquisition of the tandem mass spectrum were performed by electrospray ionization mass spectrometry (ESI- MS) on a Bruker Daltonics Esquire 3000 plus (Germany) ion trap mass spectrometer. Melting points were determined on a Boetius micro-melting point apparatus and are uncorrected. The reactions were monitored by TLC (Silica gel 60 F $_{254}$, Merck Darmstadt). Optical rotations were measured on a Polamat A, Zeiss, Jena

polarimeter (concentration *c* is given as g/100 ml).

(2*R*,3*R*,4*R*,5*S*)-6-[(methyl(4,4,5,5,6,6,7,7,8,8,9,9,9-tridecafluorononyl)amino)]-hexane-1,2,3,4,5-pentanol (5a)

The mixture of *N*-methyl-glucamine (**2**, 4.29 g, 22 mmol), 3-(perfluorohexyl)propyl iodide (**4a**, 5.37 g, 11 mmol) and K₂CO₃ (3.04 g, 22 mmol) in acetonitrile (180 ml) was boiled for 4h under vigorous stirring. The solvent was removed in vacuo then the residue was stirred with water (40 ml) for 1h, then filtered, washed with water and dried. The crude product was crystallized from MeOH (16 ml) to yield pure **5a** (3.75 g, 61.5%), as white crystals with mp 91-93 °C.

[*a*]₅₇₈ = − 4.03; [*a*]₅₄₆ = − 4.36; [*a*]₄₃₆ = − 6.38; [*a*]₄₀₆ = − 6.71 (*c* = 3.0 DMF)

¹H NMR (DMSO-*d*₆): 3.67 (m, 1H, H-5); 3.58 (m, 1H, H-4); 3.56 (dd, *J*=10.8 Hz and 3.8 Hz, 1H, H-1_A); 3.48 (m, 1H, H-2); 3.43 (dd, *J*=7.6 Hz and 2.0 Hz, 1H, H-3); 3.38 (dd, *J*=10.8 Hz and 5.8 Hz, 1H, H-1_B); 2.44-2.39 (overlapping m's, 3H, H-1' and H-6_A); 2.33 (dd, *J*=13.2 Hz and 6.8 Hz, 1H, H-6_B); 2.20 (m, 2H, H-3'); 2.16 (s, 3H, N-CH₃); 1.63 (qui, *J*=7.9 Hz, 2H, H-2').

¹³C NMR (DMSO-*d*₆) (non-fluorinated carbons: 72.9 (C-3); 72.2 (C-2); 70.9 (C-4); 70.8 (C-5); 64.0 (C-1); 60.7 (C-6); 56.9 (C-1'); 42.6 (N-CH₃); 28.4 (t, *J*=21.2 Hz, C-3'); 18.2 (C-2').

HRMS (ESI) *m/z*: calcd. for C₁₆H₂₂F₁₃NO₅ 555.12904; found 555.12721. Mass error: −3.3 ppm.

(2*R*,3*R*,4*R*,5*S*)-6-[(4,4,5,5,6,6,7,7,8,8,9,9,10,10,11,11,11-heptafluoroundecyl)(methyl)amino]hexane-1,2,3,4,5-pentanol (5b)

Method A:

The mixture of *N*-methyl-glucamine (**2**, 5.85 g, 30 mmol), 3-(perfluorooctyl)propyl iodide (**4b**, 8.85 g, 15 mmol) and K₂CO₃ (4.14 g, 30 mmol) in acetonitrile (300 ml) was boiled for 4h under vigorous stirring. The solvent was removed in vacuo then the residue was stirred with water (50 ml) for 1h, then filtered, washed with water and dried. The crude product was crystallized from MeOH (35 ml) to yield pure **5b** as white crystals (Fw = 655, 6.33 g, 64.5%), mp 103-105°C. Using 30 mmol of **4b** 13.74 g (70%) of **5b** was obtained as white crystals with mp 104-107°C.

[*a*]₅₇₈ = − 3.07; [*a*]₅₄₆ = − 3.41; [*a*]₄₃₆ = − 6.48; [*a*]₄₀₆ = − 6.83 (*c* = 3, DMF).

¹H NMR (DMSO-*d*₆): 3.63 (m, 1H, H-5); 3.54 (m, 1H, H-4); 3.52 (dd, *J*=10.8 Hz and 3.8 Hz, 1H, H-1_A); 3.43 (m, 1H, H-2); 3.36 (dd, *J*=7.6 Hz and 2.0 Hz, 1H, H-3); 3.32 (dd, *J*=10.8 Hz and 5.8 Hz, 1H, H-1_B); 2.42-2.33 (overlapping m's, 3H, H-1' and H-6_A); 2.27 (dd, *J*=13.2 Hz and 6.8 Hz, 1H, H-6_B); 2.16 (m, 2H, H-3'); 2.12 (s, 3H, N-CH₃); 1.58 (qui, *J*=7.9 Hz, 2H, H-2').

¹³C NMR (DMSO-*d*₆) (non-fluorinated carbons: 72.6 (C-3); 71.9 (C-2); 70.7 (C-5); 70.6 (C-4); 63.9 (C-1); 60.6 (C-6); 56.8 (C-1'); 42.6 (N-CH₃); 28.1 (t, *J*=21.5 Hz, C-3'); 18.0 (C-2').

HRMS (ESI) m/z : calcd. for $C_{18}H_{22}F_{17}NO_5$ 655.12265; found 655.12024. Mass error: -3.7 ppm.

Method B:

A mixture of 3-(perfluorooctyl)propyl mesylate (0.56 g, 1.0 mmol), *N*-methyl-glucamine (**2**, 0.39 g, 2 mmol) and K_2CO_3 (0.28 g, 2 mmol) in acetonitrile (10 mL) eddig a ml kis 1 volt was stirred and heated at 70°C temperature for 24 h in a sealed vile. Then the solvent was removed by evaporation in vacuum using a rotavap. The solid residue was treated with water (15 ml) and filtered. The crude product was filtered by suction and dried to afford 0.40 g (62%) white crystals with mp 102-104 °C.

HRMS (ESI) m/z : calcd. for $C_{18}H_{22}F_{17}NO_5$ 655.12265; found 655.12028. Mass error: -3.6 ppm.

(2R,3R,4R,5S)-6-[[4,4,5,5,6,6,7,7,8,8,9,9,10,11,11,11-hexadecafluoro-10-(trifluoromethyl)undecyl](methylamino)hexane-1,2,3,4,5-pentaol (5c)

The mixture of *N*-methyl-glucamine (**2**, 7.0 g, 36 mmol), 3-(*iso*-perfluorononyl)propyl iodide (**4c**, 11.6 g, 18 mmol) and K_2CO_3 (4.98 g, 36 mmol) in acetonitrile (350 ml) was boiled for 4h under vigorous stirring. The solvent was removed in vacuo then the residue was stirred with water (60 ml) for 1h. To this aqueous suspension MeOH (130 ml) was added and the mixture was heated to give a clear solution. After cooling the precipitate was filtered, dried and crystallized from MeOH (45 ml) to yield pure **5c** (6.1 g, 48%); mp 86-91°C.

$[a]_{578} = -3.07$; $[a]_{546} = -3.41$; $[a]_{436} = -6.48$; $[a]_{406} = -6.83$. ($c = 1$, CF_3CH_2OH).

1H NMR (DMSO- d_6): 3.67 (m, 1H, H-5); 3.58 (m, 1H, H-4); 3.56 (dd, $J=10.8$ Hz and 3.8 Hz, 1H, H-1_A); 3.47 (m, 1H, H-2); 3.40 (dd, $J=7.6$ Hz and 2.0 Hz, 1H, H-3); 3.35 (dd, $J=10.8$ Hz and 5.8 Hz, 1H, H-1_B); 2.46-2.37 (overlapping m's, 3H, H-1' and H-6_A); 2.31 (dd, $J=13.2$ Hz and 6.8 Hz, 1H, H-6_B); 2.17 (m, 2H, H-3'); 2.15 (s, 3H, N-CH₃); 1.62 (qui, $J=7.9$ Hz, 2H, H-2').

^{13}C NMR (DMSO- d_6) (non-fluorinated carbons: 72.7 (C-3); 71.9 (C-2); 70.7 (C-4); 70.6 (C-5); 63.9 (C-1); 60.6 (C-6); 56.8 (C-1'); 42.6 (N-CH₃); 28.1 (t, $J=21.5$ Hz, C-3'); 18.0 (C-2').

HRMS (ESI) m/z : calcd. for $C_{19}H_{22}F_{19}NO_5$ 705.11946; found 705.11733. Mass error: -3.0 ppm.

4,4,5,5,6,6,7,7,8,8,9,9,10,10,11,11,11-heptadecafluoro-N-methyl-N-[(2S,3R,4R,5R)-2,3,4,5,6-pentahydroxyhexyl]undecanamide (8a)

The solution of 3-perfluorooctyl-propanoic acid **6a** (4.92 g, 10 mmol) in diethyl ether (20 ml) was cooled to 0 °C and isobutyl chloroformate (1.37 g, 10 mmol) was added. After stirring for 10 min *N*-methyl-morpholin (1.01 g, 10 mmol) was added and stirred for another 10 min. The precipitated hydrochloride salt was removed by filtration, then to the filtrate a warm solution (50°C) of *N*-methylglucamine (0.88 g, 4.5 mmol) in MeOH (30 ml) was dropped during 10 min.

The mixture was stirred for a night at room temperature, then the solvent was removed in vacuo. The residue was triturated with diethyl ether, and the crystals were filtered with suction and dried to give (2.6 g) crude. The crude product was crystallized from MeOH (10 ml) to yield pure **8a** 1.04 g (35%), mp 95-210 °C. This unique melting behaviour could be the result of changes in the structure of the H-bonded network in the solid state upon heating. It is worth to note that in solution (DMSO- d_6) the existence of two distinct rotamers are identified by NMR (cf. Supporting Information).

^1H NMR (DMSO- d_6): the most diagnostic and unambiguous assignments without providing intensity for **8a** (major): 4.94 (d, $J=5.0$ Hz, 5-OH); 4.34 (t, $J=5.5$ Hz, 1-OH); 3.77 (m, H-5); 3.56 (m, H-1_A); 3.37 (m, H-1_B); 3.42-3.27 (overlapping m's, H-6_A and H-6_B in the major and minor components); 2.83 (s, N-CH₃); 2.62 (m, H-3').

^{13}C NMR (DMSO- d_6) the most diagnostic and unambiguous assignments of the non-fluorinated carbons intensity for **8a** (major): 170.16 (C-1'); 70.5 (C-5); 63.78 (C-1); 52.3 (C-6); 34.1 (N-CH₃); 26.5 (t, $J=21.3$ Hz, C-3'); 23.8 (C-2').

^1H -NMR (DMSO- d_6): the most diagnostic and unambiguous assignments without providing intensity for **8a** (minor): 4.69 (d, $J=5.0$ Hz, 5-OH); 4.30 (t, $J=5.5$ Hz, 1-OH); 3.42-3.27 (overlapping m's, H-6_A and H-6_B in the major and minor components); 3.02 (s, N-CH₃); 2.80 (m, H-2').

^{13}C -NMR (DMSO- d_6) the most diagnostic and unambiguous assignments of the non-fluorinated carbons intensity for **8a** (minor): 170.06 (C-1'); 71.5 (C-5); 63.75 (C-1); 51.6 (C-6); 36.9 (N-CH₃); 26.3 (t, $J=21.9$ Hz, C-3'); 24.2 (C-2'). **HRMS** (ESI) m/z : calcd. for C₁₈H₂₀F₁₇NO₆ 669.10192; found 669.10150. Mass error: -6.0 ppm.

HRMS (ESI) m/z : calcd. for C₁₈H₂₀F₁₇NO₆ 669.10192; found 669.10150. Mass error: -6.0 ppm.

N-methyl-N-((2S,3R,4R,5R)-2,3,4,5,6-pentahydroxyhexyl)octanamide (8b)

To the ice-cold solution of octanoic acid (2.88 g, 20 mmol) in ether (30 ml) ClCOOiBu (2.73g, 20 mmol) was added and the mixture stirred for 10 min. After the addition of *N*-methylmorpholine (2.02 g, 20 mmol) the precipitated hydrochloride salt was removed by filtration. The filtrate was cooled with ice while a solution of *N*-methyl-glucamine (1.75 g, 9 mmol) in lukewarm (40-50 °C) ether (60 ml) was added drop-by-drop. Then the mixture was allowed to warm up to room temperature and kept there overnight. The solvent was evaporated and the residual oil was treated with a small volume of ether and scrubbed to initiate crystallization. Filtration gave 2.60 g (81%) solid, which on recrystallization from acetonitrile (10

ml) gave 2.28 g (79%) white crystals with mp = 84-85 °C.

MS (EI) *m/z*: calcd for C₁₅H₃₁NO₆ 321.2; observed 322.4 (M+H)⁺.

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SUPPORTING INFORMATION

**SYNTHESIS OF *N*-METHYL-*N*-POLYFLUOROALKYL-D-GLUCAMINES
AND *N*-METHYL- (FLUOROUS ACID D-GLUCAMIDES)**

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^{13}C NMR of 5b

HSQC of 5b

^{13}C NMR of 8a

HSQC of 8a