Synthesis of a new diazacrown ether compound interconnected with an azacrown ether and decorated with a long lipophilic chain

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Supplementary information

Table of Contents:

1. General methods and materials
2. Experimental procedures and characterizations
3. References
4. ¹H and ¹³C NRM of compounds **5-7**, **1** at 295 K

1- General methods and materials :

Reagents were purchased from commercial suppliers and used without further purification. NEt₃ was freshly distilled from KOH, THF from sodium/benzophenone, and

CHCl₃ from P₂O₅. CH₃CN and propionitrile were dried over 3 Å molecular sieves. IR spectra (cm⁻¹) were recorded on either a Bruker Vertex 70 or an Equinox 55 spectrometer. ¹H NMR (400 MHz) and ¹³C NMR (100.6 MHz) spectra were measured with a Bruker Avance (Serie 400). ¹H and ¹³C NMR spectra of compounds **6-7** have been recorded at 295 K but also at 329 K so as to improve their resolutions. They were then compared among themselves to facilitate their interpretations. High resolution MS were measured with an Agilent Technologies 6510 (Q-TOF) Spectrometer using a dual ESI source.

2- Experimental procedures and characterizations

***tert*-Butyl-1,7-diaza-(15-crown-5)-1-carboxylate **2**:**

A solution of 1,7-diaza-15-crown-5 (1.0 g, 4.6 mmol.) and di-*tert*-butyl dicarbonate (1.09 g, 1 equiv.) in CH₃CN (15 mL) was stirred at rt, for 16 h. CH₃CN was then evaporated under reduced pressure. Purification by column chromatography (acetone/NEt₃ 95 :5) afforded the pure monoprotected compound **2** (0.61 g, 42%) as an orange oil. ¹H, ¹³C NMR and HRMS were in agreement with literature.¹

4-[(1-Aza-(15-crown-5)-1-yl)-4 oxo]butyric acid **3:**

A solution of 1-aza-15-crown-5 (1 g, 4.56 mmol.), succinic anhydride (0.91 g, 2 equiv.) and NEt₃ (2.5 mL, 4 equiv.) in CH₃CN (2 mL) was stirred at rt, for 17 h, under Ar. CH₃CN was then evaporated under reduced pressure. The crude product was dissolved in CH₂Cl₂ (20 mL). This organic layer was successively extracted three times with aqueous 1 M HCl and with 20% brine. The combined aqueous layers were extracted twice with CH₂Cl₂ (10 mL). The combined organic layers were then dried over MgSO₄ and evaporated under reduced pressure to afford pure **3** as a yellowish semi-solid (1.3 g, 89%). ¹H, ¹³C NMR and HRMS were in agreement with literature.²

***tert*-Butyl-7[(1-aza(15-crown-5)-1-(1,4-dioxo-but-4-yl)]-1,7-diaza-15-crown-5)-1-carboxylate **5**:**

A solution of **3** (100 mg, 0.31 mmol.) and *N,N*-dicyclohexylcarbodiimide (64 mg, 1 equiv.) in CHCl_3 (0.4 mL) was stirred at rt for 1h. Carbamate **2** (120 mg, 1.5 equiv.) and NEt_3 (128 μL , 3 equiv.) were successively added. The reaction mixture was stirred, at rt, for 17 h. Distilled water (50 μL) was added and the reaction mixture was thoroughly vigorously stirred for 4h. The reaction mixture was then co-evaporated with toluene under reduce pressure. The obtained residue was treated three times with anhydrous toluene and the precipitated urea were discarded. The combined organic layers were evaporated under reduce pressure. Purification by column chromatography (acetone/ NEt_3) afforded pure **5** as an orange oil (75 mg, 39%). ^1H NMR (400 MHz, CDCl_3): 1.44 (s, 9H, 3 CH_3), 2.70 (m, 4H, NCOCH_2), 3.60-3.90 (m, 40H, 6 NCH_2 , 14 OCH_2) ppm. ^{13}C NMR (100.6 MHz, CDCl_3): δ = 28.3 (3C, 3 CH_3), [28.5, 29.1] (2C, NCOCH_2), [47.7, 48.0, 48.2, 48.7, 49.1, 49.3, 49.5, 50.2] (6C, CH_2N), [68.6, 69.1, 69.3, 69.4, 69.5, 70.0, 70.1, 70.4, 70.5, 70.6, 70.9, 71.3, 71.8] (14C, OCH_2), 79.5 (1C, COOC), 155.5 (1C, NCOO), [172.5, 172.7] (2C, NCOCH_2) ppm. IR (KBr): ν = 1111, 1409, 1459, 1637, 1687, 2867, 3400-3550 cm^{-1} . HRMS (ESI-Q-Tof) : calcd for $\text{C}_{29}\text{H}_{53}\text{N}_3\text{NaO}_{11}$ $[\text{M}+\text{Na}]^+$ 642.3572 ; found 642.3574.

[(1-Aza-(15-crown-5)-1-(1,4-dioxabut-4-yl)]-1,7-diaza-(15-crown-5)hydrochloride **6:**

Carboxylate **5** (290 mg, 0.47 mmol.) was dissolved in an anhydrous solution of 1.5 M HCl in Et_2O (1 mL, 5 equiv.). The reaction mixture was stirred, at rt, for 18 h. After evaporation of Et_2O , the pure hydrochloride **6** was recovered as yellow crystals (260 mg, 100%). ^1H NMR (400 MHz, CDCl_3): 2.61 (m, 4H, NCOCH_2), 3.0-3.33 (m, 6H, 3 NCH_2), 3.33-4.0 (m, 34H, 3 NCH_2 , 14 OCH_2), 9.08 (s, 1H, NH_2Cl), 9.25 (s, 1H, NH_2Cl) ppm. ^{13}C NMR (100.6 MHz, CDCl_3): δ = [27.9, 28.0] (2C, CH_2CON), [47.2, 47.5, 47.8, 48.4, 49.0, 49.2, 49.6, 50.0, 50.1] (4C, CH_2NCO), [65.6, 65.9] (2C, $\text{CH}_2\text{NH}_2\text{Cl}$), [67.9, 68.6, 69.1, 69.3, 69.7, 69.8, 69.9, 70.0, 70.5, 71.0] (14C, CH_2O), [172.2, 172.7] (2C, NCOCH_2) ppm. IR

(KBr): $\nu = 748, 1115, 1355, 1445, 1518, 1579, 1636, 3100\text{-}2500\text{ cm}^{-1}$. HRMS (ESI-Q-Tof) : calcd for $\text{C}_{24}\text{H}_{46}\text{N}_3\text{O}_9$ $[\text{M}+\text{H}]^+$ 520.3229 ; found 520.3243.

{7-[1-Aza-(15-crown-5)-1-(1,4-dioxo-but-4-yl)]-1-docosyl}-1,7-diaza-(15-crown-5) 7 :

A solution of **6** (245 mg, 0.44 mmol.), bromodocosane (172 mg, 1 equiv.) and Na_2CO_3 (94 mg, 2 equiv.) in propionitrile (25 mL) was stirred, at 100°C , for 22 h. Propionitrile was evaporated under reduced pressure. Purification by column chromatography (acetone/ NEt_3 95 :5) afforded the pure **7** compound (120 mg, 33%) as a yellow oil. ^1H NMR (400 MHz, CDCl_3): 0.88 (t, $^3J = 6.8\text{ Hz}$, 3H, CH_3), 1.25 (bs, 38H, $\text{CH}_2(3\text{-}21)$), 1.35-1.50 (m, 2H, $\text{CH}_2(2)$), 2.45 (bt, 2H, $^3J = 6.8\text{ Hz}$, $\text{NCH}_2(1)$), 2.65-2.83 (m, 4H, NCOCH_2), 2.65-2.83 (m, 4H, NCH_2), 3.50-3.85 (m, 36H, 28 OCH_2 , 8 NCH_2) ppm. ^{13}C NMR (100.6 MHz, CDCl_3): $\delta = 14.1$ (C(22)), 22.7 (C(21)), 27.4 (C(3)), 28.4 (C(2)), [29.3, 29.6, 29.7, 30.9, 31.9] (16C, C(4-19)), [48.8, 49.4, 49.7, 50.3] (4C, CH_2NCO), [53.9, 54.4] (2C, NCH_2), 56.8 ($\text{NC}(1)$), [69.0, 69.4, 69.6, 70.1, 70.3, 70.5, 70.7, 71.5] (14C, OCH_2), 172.4, 172.5 (2C, NCO) ppm. IR (KBr): $\nu = 720, 1119, 1293, 1355, 1467, 1642\text{ cm}^{-1}$. HRMS (ESI-Q-Tof) : calcd for $\text{C}_{46}\text{H}_{89}\text{N}_3\text{NaO}_9$ $[\text{M}+\text{Na}]^+$ 850.6491 ; found 850.6494.

{7-[1-Aza-(15-crown-5)-1-(butyl-4-yl)]-1-docosyl}-1,7-diaza-(15-crown-5) 1:

A suspension of **7** (563 mg, 0.68 mmol.) and LiAlH_4 (100 mg, 4 equiv.) in THF (18 mL) was stirred for 18h. To the reaction mixture, Na_2SO_4 , 10 H_2O (1.5 g) was added portionwise and then an aqueous 1M NaOH (0.5 mL) solution. AcOEt (10 mL) was added and the mixture was vigorously stirred for 20 h before extraction. The recovered organic layer was centrifugated. This procedure was repeated three times. The organic layers were combined and the solvents were evaporated under reduced pressure. The crude product was then dissolved in an anhydrous solution of Et_2O . 5M HCl in Et_2O was thoroughly added. The pure trihydrochloride **1** crystallized and was recovered by filtration (431 mg, 70%). ^1H NMR (400 MHz, CDCl_3): 0.84 (t, $^3J = 6.8\text{ Hz}$, 3H, CH_3), 1.26 (bs, 42H, $\text{CH}_2(3\text{-}21)$, NCH_2CH_2),

1.50-2.0 (m, 2H, CH₂(2)), 2.80-5.0 (m, 46H, 18 NCH₂, 28 OCH₂), 8.95-9.15 (m, 1H, NHCl), 9.82 (s, 1H, NHCl), 10.37 (s, 1H, NHCl) ppm. ¹³C NMR (100.6 MHz, CDCl₃): δ = 14.02 (C(22)), 21.7 (C(21)), 25.8 (C(3)), 26.7 (C(2)), [28.9, 29.2, 29.3, 29.4, 29.5, 29.5, 29.6] (18C, C(4-19), CCH₂N), 30.9 (C(20)), [47.4, 47.5, 47.7, 52.2, 53.0, 53.4, 54.1, 54.5] (9C, NCH₂), [63.9, 64.1, 65.0, 65.6, 66.0, 69.0, 69.1, 69.5, 69.7, 69.9, 70.1, 70.3, 70.5] (14C, OCH₂) ppm. IR (KBr): ν = 721, 1100, 1125, 1467, 1640, 3390 cm⁻¹. HRMS (ESI-Q-Tof): calcd for C₄₆H₉₃N₃NaO₂ [M+Na]⁺ 822.6906; found 822.6916.

3- References

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4- ¹H and ¹³C NMR at 295 K