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A simple regioselective synthesis of 1,4-bis(*tert*-butoxycarbonylmethyl)-tetraazacyclododecane (cyclen)

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Experimental procedure, synthesis and characterization of compounds **3a**, **5a**, **6a**, **8a**, **9a**.

Copy of ¹H NMR, ¹³C NMR and ESI-MS spectra of **1–8**

Synthesis of (2-Methyl-quinoline) methyl-15-crown-5 (3a). Distilled quinaldine (3.0 g, 20.9 mmol) was added to the solution of H₂O₂(40%) (5.0 g, 40 mmol) and glacial HOAc (20 mL), the mixture was warmed at 55°C for 20 h. Cooled to 0°C, treated with KOH to pH = 10, the yellow solid was filtered and the filtrate was washed with CHCl₃. The yellow solid and the extracted CHCl₃ solution were dissolved in 40 mL benzene, and the water was separated by azeotropism. The benzene solution was filtered and cooled by ice water, adding 10-15 mL water; yellow needle crystal was filtrated as quinaldine *N*-oxide monohydrate. A solution of quinaldine *N*-oxide monohydrate (0.8 g, 4.53 mmol) in dry toluene (30 mL) was heated to 80°C with stirring under Ar, a solution of benzenesulfonyl chloride (2.0 g, 11.3 mmol) dissolved in 10 mL toluene was added in 10 min, after 2h, a red oil separated from the solution, cooled the mixture and treated with 5% aqueous HCl (15 mL). The aqueous phase was diluted by CHCl₃ (200 mL) and 10% aqueous NaOH (15 mL). The yellow aqueous phase was extracted with CHCl₃ (3×150 mL). The combined organic phases were washed by water (2×150 mL) and dried over anhydrous Na₂SO₄. Filtration and concentration afforded the product as a yellow solid 0.61 g (76%). ¹H NMR (400 MHz, CDCl₃): δ 8.08 (1H, d, *J* = 8.5 Hz), 8.03 (1H, d, *J* = 8.5 Hz), 7.72 (1H, d, *J* = 8.1 Hz), 7.66 (1H, dd, *J*¹ = 8.1 Hz, *J*² = 1.4 Hz), 7.50 (1H, d, *J* = 8.5 Hz), 7.46 (1H, dd, *J*¹ = 7.1 Hz, *J*² = 1.1 Hz), 4.79 (1H, s). ¹³C NMR (100 MHz, CDCl₃): δ 158.2 (C), 139.3 (C), 137.5 (CH), 130.1 (CH), 129.3 (CH), 127.7 (CH), 127.5 (C), 127.1 (CH), 120.6 (CH), 47.4 (CH₂); ESIMS: *m/z* 178.5 [M+H]⁺. Anal. Calcd for C₁₀H₈NCl: C, 67.62; H, 4.54; N, 7.88, Found: C, 67.53; H, 4.66; N, 7.64%.

Synthesis of *N*-chloroacetyl-aza-15-crown-5 (5a) Aza-15-crown-5 (300.0 mg, 1.368 mmol) was dissolved in anhydrous dichloromethane (20 mL), triethylamine (207.1 mg, 2.052 mmol) and then chloroacetyl chloride (231.7 mg, 2.052 mmol) was added. The reaction mixture was stirred at room temperature for 1 h. The organic layer was then washed by water (2 × 20 mL), dried by anhydrous Na₂SO₄ and evaporated under reduced pressure. Purification of this material was achieved by column chromatography on aluminium oxide eluting with ethyl acetate: hexane = 5: 6 (v/v). The product was isolated as a colourless oil (279.0 mg, 1.204 mmol). Yield: 88%. ¹H NMR(400 MHz, CDCl₃): δ 4.14 (2H, s), 3.79 (2H, t, *J* = 5.0 Hz), 3.62–3.48 (18H, m); ¹³C NMR(CDCl₃): δ 167.2 (C), 71.6 (CH₂), 70.5 (CH₂), 70.4 (CH₂), 70.3 (CH₂), 70.1 (CH₂), 70.0 (CH₂), 69.4 (CH₂), 68.9 (CH₂), 51.0 (CH₂), 50.1 (CH₂), 41.6 (CH₂). ESI-MS: *m/z* 295.8 [M+H]⁺; Anal. Calcd for C₁₂H₂₂O₅NCl: C, 48.79; H, 7.50; N, 4.73, Found: C, 48.63; H, 7.86; N, 4.48%.

Synthesis of *N*-Chloroacetyl-aza-18-crown-6 (6a) Aza-18-crown-6 (200.0 mg, 0.76 mmol) was dissolved in anhydrous dichloromethane (20 mL), triethylamine (151.9 mg, 1.51 mmol) and then chloroacetyl chloride (128.8 mg, 1.14 mmol) was added. The reaction mixture was stirred at room temperature for 1 h. The organic layer was then washed by water (2×20 mL), dried by anhydrous Na_2SO_4 and evaporated under reduced pressure. Purification of this material was achieved by column chromatography on aluminium oxide eluting with ethyl acetate: hexane = 5: 6 (v/v). The product was isolated as a colourless oil (241.3 mg, 0.71 mmol). Yield: 93%. ^1H NMR(400 MHz, CDCl_3): δ 4.20 (2H, s), 3.72 (2H, t, $J = 5.4$ Hz), 3.62–3.48 (22H, m); ^{13}C NMR(CDCl_3): δ 167.2 (C), 71.2 (CH_2), 70.7 ($3 \times \text{CH}_2$), 70.6 ($2 \times \text{CH}_2$), 70.4 (CH_2), 70.3 (CH_2), 69.6 (CH_2), 69.4 (CH_2), 49.7 (CH_2), 47.4 (CH_2), 41.6 (CH_2). ESI-MS: m/z 339.9 $[\text{M}+\text{H}]^+$; Anal. Calcd for $\text{C}_{14}\text{H}_{26}\text{O}_6\text{NCl}$: C, 49.48; H, 7.71; N, 4.12, Found: C, 49.23; H, 7.96; N, 4.33%.

Synthesis of 2,3,4,6-tetraacetyl-1-(2-bromoethoxyl)-D-glucopyranoside (8a). 1.5 equivalents of 2-bromoethanol (5.6 g, 45 mmol) was added to the solution of the penta-*O*-acetyl *D*-glucopyranose (11.7 g, 30 mmol) in dichloromethane (80 mL). Boron trifluoride etherate (28.5 mL, 225 mmol) was added to the stirred solution at 0°C for 1 h and then at 35°C overnight. The solution was washed with water, aqueous sodium carbonate and saturated aqueous sodium chloride, respectively, dried with magnesium sulfate and evaporated in *vacuo* to give the crude product (12.02 g, 26.4 mmol) as a yellow oil, yield: 88%. Diethyl ether (50 mL) was added and the mixture was placed in a refrigerator overnight during which time a white solid precipitated. The white solid was recrystallized from diethyl ether to yield white needle-like single crystals. mp: $119\text{--}120^\circ\text{C}$. ^1H NMR (300 MHz, CDCl_3): δ 5.22 (1H, t, $J = 10.2$ Hz), 5.08 (1H, t, $J = 10.2$ Hz), 5.02 (1H, t, $J = 10.1$ Hz), 4.57 (1H, d, $J = 7.9$ Hz), 4.26 (1H, dd, $J = 12.2, 5.1$ Hz), 4.20–4.12 (2H, m), 3.86–3.80 (1H, m), 3.78–3.68 (1H, m), 3.46 (2 H, t, $J = 6$ Hz), 2.09 (3H, s), 2.07 (3H, s), 2.03 (3H, s), 2.01 (3H, s); ^{13}C NMR (75 MHz, CDCl_3): δ 170.5 (C), 170.1 (C), 169.3 ($2 \times \text{C}$), 100.9 (CH), 72.5 (CH), 71.8 (CH), 70.9 (CH), 69.7 (CH_2), 68.2 (CH), 61.7 (CH_2), 29.8 (CH_2), 20.6 ($2 \times \text{CH}_2$), 20.5 ($2 \times \text{CH}_2$). FABMS: m/z 455 $[\text{M}+\text{H}]^+$, 477 $[\text{M}+\text{Na}]^+$. Anal. Calcd for $\text{C}_{16}\text{H}_{23}\text{O}_{10}\text{Br}$: C, 42.21; H, 5.09%. Found: C, 42.36; H, 5.34%.

Synthesis of 2-(2-bromoethoxy)methyl-15-crown-5 (9a). 300 mg (1.2 mmol) hydromethyl-15-crown-5 and 75 mg (0.4 mmol) triethylbenzyl ammonium chloride were added to dibromoethane (10 mL) at the same time. An aqueous solution of 50% sodium hydroxide (5 mL) was added and stirred at 60°C

for about 12 h. After cooling, dichloromethane (10 mL) and H₂O (10 mL) were added and collected separately after extraction. The aqueous phase was further extracted with dichloromethane (3×10 mL), the combined organic fractions were evaporated to give the crude product as a yellow oil, which was purified by column chromatography on aluminum oxide (neutral, 70–230 mesh) with ethyl acetate: hexane=7:3 as eluent. Yield: 67% as a pale viscous oil. ¹H NMR (400 MHz, CDCl₃): δ 3.86–3.54 (23H, m), 3.44 (2H, t, *J* = 6.1 Hz); ¹³C NMR (100 MHz, CDCl₃): δ 78.7 (CH), 71.6 (CH₂), 71.4 (CH₂), 71.2 (CH₂), 71.1 (CH₂), 70.9 (CH₂), 70.8 (CH₂), 70.7 (CH₂), 70.6 (CH₂), 70.5 (CH₂), 70.4 (CH₂), 70.3 (CH₂), 30.5 (CH₂). ESI-MS: *m/z* 357.5 [M+H]⁺, 379.5 [M+Na]⁺. Anal. Calcd for C₁₃H₂₅O₆Br: C, 43.71; H, 7.05. Found: C, 43.56; H, 7.35%.

1
¹H NMR, 400 MHz, CDCl₃)

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 DS 0
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 FIDRES 0.256020 Hz
 AQ 1.9530228 sec
 RG 18
 DW 119.200 usec
 DE 4.50 usec
 TE 300.0 K
 D1 2.0000000 sec

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F2 - Processing parameters
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 GB 0
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 F1 3001.30 Hz
 F2P -0.500 ppm
 F2 -150.07 Hz
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 HZCM 157.56825 Hz/cm

1
¹³C NMR, 100 MHz, CDCl₃

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Time 21.36

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TD 32768

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d12 0.00000000 sec

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PL1 -5.00 dB

SFO1 100.6232033 MHz

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PL2 120.00 dB

PL12 14.00 dB

PL13 14.00 dB

SFO2 400.1315005 MHz

F2 - Processing parameters

SI 32768

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WDW EM

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LB 1.00 Hz

GB 0

PC 0.70

1D NMR plot parameters

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CY 25.17 cm

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F2P -10.000 ppm

F2 -1005.13 Hz

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HZCM 925.63757 Hz/cm

06/07/02 10:54:35

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(¹H NMR, 400 MHz, CDCl₃)

07/22/02 09:29:18

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(ESIMS, in MeOH)

(^1H NMR, 400 MHz, CDCl_3)

4
(¹H NMR, 400 MHz, CDCl₃)

07/27/02 10:36:12

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 PROCNO 1

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 SWH 25125.628 Hz
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 AQ 0.6521332 sec
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***** CHANNEL f2 *****

NUC2 1H
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F2 - Processing parameters

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1D NMR plot parameters

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 F2 -10.000 ppm
 F2 -1006.13 Hz
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 NDCN 975.63745 Hz/cm

170.876
 170.627
 169.866

81.000
 77.459
 77.141
 76.829
 71.601
 70.521
 70.416
 70.339
 70.094
 69.868
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 28.023

07/15/02 03:12:23

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T: + p ms

7

(¹H NMR, 400 MHz, CDCl₃)

¹³C NMR 100 MHz CDCl₃

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PROCNO 1

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Time 14.29

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PULPROG zgpg30
TD 32768
TO 32768

SOLVENT CDCl₃
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DS 2

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FIDRES 0.10655 Hz
AQ 0.707655 sec

RG 6102
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TE 300.0 K

DE 18.00 usec
TE 300.0 K
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C11 0.03000000 sec
C12 0.00000000 sec

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SFO1 100.625000 MHz
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P2 99.00 usec
PL2 -4.00 dB

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PL13 14.00 dB
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F2 - Processing parameters
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LB 1.00 Hz

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PC 0.70

1D NMR plot parameters
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CY 11.51 cm

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F1 22134.81 Hz
F2P -10.000 000

F2 -1046.13 Hz
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N204 925.83751 167/cm

07/15/02 03:19:43

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T: + p ms

Current Data Parameters
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EXPNO 5
PROCNO 1

F2 - Acquisition Parameters

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Time 11.04

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PULPROG zgpg30

TD 65536

SOLVENT CDCl3

NS 566

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SWH 25125.625 Hz

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BT 0.0000000 sec

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PL1 -5.00 dB

SFO1 100.6237654 MHz

***** CHANNEL f2 *****

CPDPRG2 waltz16

NUC2 1H

PCPD2 80.00 usec

PL2 -4.00 dB

PL12 15.00 dB

PL15 14.00 dB

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WDW EN

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L3 1.00 Hz

GB 0

PC 0.70

1D NMR plot parameters

AX 25.00 cm

CY 11.23 cm

F1P 200.000 cm

F1 23134.61 Hz

F2P -10.000 cm

F2 -1005.13 Hz

PPMCH 9.20000 ppm/cm

HZCM 925.63745 Hz/cm

(¹³C NMR, 100 MHz, CDCl₃)

06/03/02 10:29:11

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