1,4,8,11-Tetraazabicyclo[9.3.1]pentadecanes: Synthesis and Use of a New Strategy for the Selective *cis* -N^4,N^8-Difunctionalization of Cyclam Derivatives

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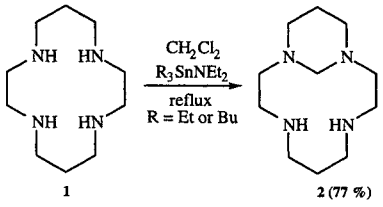
Abstract: A new efficient route to derivatives of 1,4,8,11-tetraazabicyclo[9.3.1]pentadecane **2** and their use in a procedure of selective N^4,N^8-difunctionalization of cyclam is reported.

The tetraazamacrocycloalkanes and particularly 1,4,8,11-tetraazacyclotetradecane **1** (cyclam) are among the most widely studied and useful polyazamacrocycle derivatives due to their remarkable ability to coordinate different metal cations.[1] Many synthetic approaches have been developed to prepare new derivatives of cyclam with pendent substituents attached to N and C atoms of the parent tetraazamacrocycle.[2] The selective functionalization of parent cyclam is one of the most simple and direct ways to these derivatives because the synthesis of cyclam is easy.[3] However, whereas N-mono- and tetrasubstituted cyclams are quite available[4], the preparation of N,N'-disubstituted derivatives is still a problem due to the difficulty encountered in obtaining the corresponding diprotected cyclams.[5] As a part of our interest in the synthesis of new polyazamacrocyclic ligands, we report herein a new efficient route to derivatives of 1,4,8,11-tetraazabicyclo[9.3.1]pentadecane **2** and their use in a procedure of selective N^4,N^8-difunctionalization of cyclam.

In the course of our attempts to prepare tin-substituted derivatives of cyclam we have found that refluxing cyclam with 1 equiv. of diethylaminotrialkylstannane (ethyl or butyl) in dichloromethane surprisingly afforded the novel macrocyclic compound **2** in 77 % isolated yield.



Scheme 1

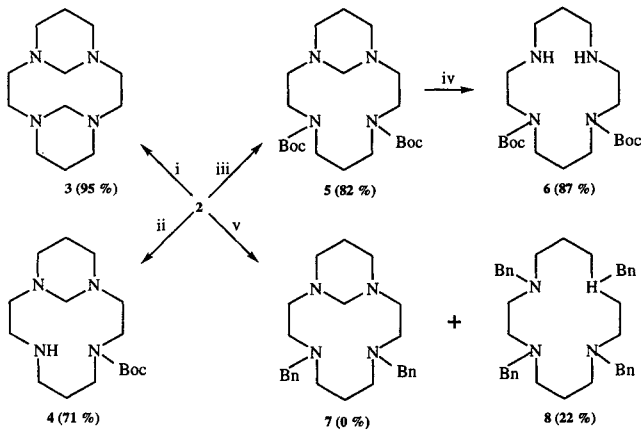
This product containing one hexahydropyrimidine fragment was characterized on the basis of its ^1H and ^{13}C NMR data.[6] The ^{13}C NMR spectrum of **2** exhibits the signal of aminal carbon atom (δ_c 72.66), and six ^{13}C resonance signals (four of which having a double intensity compared to that of the signal of the aminal carbon site) typical of a 4,8-disubstituted cyclam ring. The chemical shifts and coupling constants of aminal protons (δ_{Heq} 3.71 br d, geminal (J=11.4 Hz) and long-range W-plane coupling, δ_{Hax} 3.18 d) are consistent with a hexahydropyrimidine ring adopting an axial, equatorial conformation.[7]

At this stage, any attempt to explain the mechanism of the selective formation of **2** is speculative. However, it is remarkable to note that the reaction of cyclam with CH_2Cl_2 in presence of sodium hydroxide leads to dibridged compound **3** (95 % yield). These data allow us to suggest that tin derivatives act not only as a base (R_3SnNEt_2) but also as a Lewis acid (R_3SnX) coordinated at N^1 and N^{11} atoms.

The use of hexahydropyrimidines (obtained by the action of formaldehyde) as N-protected derivatives is very well known in the chemistry of linear polyamines[8] but the reaction of cyclam with formaldehyde leads to dibridged compound **3**.[7c,9] For this reason such a protection has never been used for cyclam derivatives.

The selective synthesis of **2** reported herein allows to obtain N-mono- and N^4,N^8-disubstituted derivatives of cyclam starting from the free base. It is known that free amino groups of linear polyamines can be acylated in the presence of a hexahydropyrimidine protecting fragment.[10] We carried out the transformation of compound **2** to mono- and di(*tert*-butyloxycarbonyl) substituted compounds **4** and **5**. Compound **4**[11] was obtained in 71% yield by treatment of **2** with 1 equiv. of di(*tert*-butyl)dicarbonate (Boc_2O) in dichloromethane. The reaction of **2** with an excess of Boc_2O (4-4.6 equiv.) led to compound **5**[12] (82%) and the rate of this reaction was increased in the presence of 4-dimethylaminopyridine.[13]

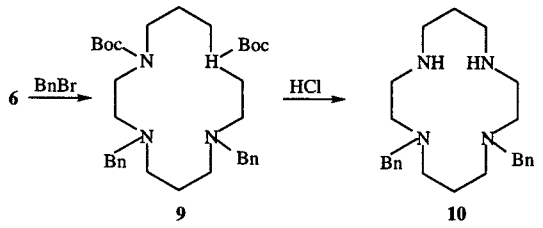
Moreover, we have shown that a Knoevenagel-type reaction used for deprotection in the chemistry of linear polyamines[14] is also an efficient procedure of deprotection in the case of cyclam derivatives. Thus, heating **5** in the presence of malonic acid and pyridine in EtOH provided **6** in 87% yield.[15]



Scheme 2

Reagents and conditions : i) CH_2Cl_2, NaOH, reflux. ii) 1 equiv. of Boc_2O, CH_2Cl_2, rt. iii) 4-4.6 equiv. of Boc_2O, CH_2Cl_2, reflux. iv) malonic acid, pyridine, EtOH, reflux. v) BnBr, Na_2CO_3, CH_2Cl_2, reflux.

However, the aminals do not tolerate the action of electrophiles. For example, we tried to obtain N^4,N^8-dibenzylbicycle **7** by refluxing of **2** with benzyl bromide (2 equiv.) in dichloromethane. Under these conditions a mixture of products was obtained from which tetrabenzylcyclam **8**[16] was separated in 22% yield. However, N^4,N^8-disubstituted cyclams can be obtained from another precursor **6** which is available from **2** (scheme 2, iii and iv). For example, alkylation of **6** with 2 equiv. of benzyl bromide and subsequent deprotection with 4 N HCl led to compound **10**[17] in an overall yield of 72% (Scheme 3).



Scheme 3

It is noteworthy that benzyl is a common protecting group in the chemistry of polyamines. Thus, compound **10** can be used as a starting compound for further transformations even under more drastic conditions than compounds **2** and **6** having more sensitive protecting groups.

In summary, we have developed a new and convenient approach to 1,4,8,11-tetraazabicyclo[9.3.1]pentadecanes and shown the practical utility of compound **2** as a new synthetic entry into N-functionalization of the cyclam ring. A new strategy of preparation for N^4,N^8-disubstituted cyclams based on the use of compounds **4, 6** and **10** is, to the best of our knowledge, the first convenient method of direct selective 4,8-difunctionalization of cyclam. Further applications of this methodology are now under investigation.

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References and Notes

1. For some reviews, see: (a) Tsukube, H. *Talanta* **1993**, *40*, 1313. (b) Bencini, A.; Bianchi, A.; Paoletti, P.; Paoli, P. *Coord. Chem. Rev.* **1992**, *120*, 51. (d) Dietrich, B.; Viout, P.; Lehn, J. M. *Macrocyclic Chemistry*; VCH: Weinheim, 1993. (e) Lindoy, L. F. *The Chemistry of Macrocyclic Ligand Complexes*; Cambridge University Press: Cambridge, 1989. (f) McWhinnie, S. L. W. *Annu. Rep. Prog. Chem., Sect. A: Inorg. Chem.* **1993**, *1993*, 303.
2. For some reviews, see: (a) Bradshaw, J. S.; Krakowiak, K. E.; Izatt, R. M. *Aza-Crown Macrocycles*; Wiley: New York, 1993; Vol. 51. (b) Kaden, T. A. *Topics in Current Chemistry* **1984**, *121*, 157
3. (a) Barefield, E. K.; Wagner, F. *Inorg. Chem.* **1973**, *12*, 2435. (b) Chavez, F.; Sherry, A. D. *J. Org. Chem.* **1989**, *54*, 2990.
4. (a) Yaouanc, J.-J.; Le Bris, N.; Le Gall, G.; Clément, J.-C.; Handel, H.; des Abbayes, H. *J. Chem. Soc., Chem. Commun.* **1991**, 206. (b) Brandès, S.; Gros, C.; Denat, F.; Pullumbi, P.; Guilard, R. *Bull. Soc. Chim. Fr.*, **1996**, 133, 65. (c) Ciampolini, M.; Fabbrizzi, L.; Perotti, A.;. Poggi, A.; Seghi, B.; Zanobini, F. *Inorg. Chem.*, **1987**, 26, 3527. (d) Filali, A., Yaouanc, J.-J., Handel, H. *Angew. Chem., Int. Ed. Engl.*, **1991**, 30, 560. (e) Gros, C.; Chollet, H.; Mishra, A. K.; Guilard, R. *Synth. Commun.* **1996**, 26, 35. (f) Wainwright, K. P. *J. Chem. Soc., Dalton Trans.* **1980**, 2117.
5. (a) Boitrel, B.; Andrioletti, B.; Lachkar, M.; Guilard, R. *Tetrahedron Lett.* **1995**, *36*, 4995. (b) Helps, I. M.; Parker, D.; Chapman, J.; Ferguson, G. *J. Chem. Soc., Chem. Commun.* **1988**, 1094.
6. **1,4,8,11-Tetraazabicyclo[9.3.1]pentadecane (2).** To a solution of cyclam **1** (2.8 g, 14 mmol) in 180 mL of dichloromethane, Bu_3SnNEt_2 (5.27 g, 14.5 mmol) was added and the reaction mixture was stirred under reflux while monitoring the disappearance of the starting cyclam by ^{13}C NMR (7 hours). The reaction mixture was evaporated *in vacuo* and the residue was dissolved in 100 ml of acetonitrile and washed with cold hexane (5x20 mL). After evaporation *in vacuo* the residue was crystallized from a mixture of CH_2Cl_2, Et_2O and heptane. Yield: 2.3 g of **2**, 77 %.
2: ^1H NMR (200 MHz, $CDCl_3$): δ (ppm) 1.58-1.93 (m, 4H), 2.35-2.98 (m, 18H), 3.18 (d, J = 11.4 Hz, 1 H), 3.71 (br d, J = 11.4 Hz, 1H). ^{13}C NMR (200 MHz, $CDCl_3$): δ (ppm): 24.51, 25.93, 46.56 (2C), 46.91 (2C), 50.75 (2C), 52.19(2C), 72.66.MS: m/z = 212 (M^+), 207, 197, 182, 168, 154, 140, 126, 113, 99, 84, 83, 70 (100%).
7. (a) Barrows, T. H.; Farina, P. R.; Chrzanowski, R. L.; Benkovic, P. A.; Benkovic, S. J. *J. Am. Chem. Soc.* **1976**, *98*, 3678. (b) Fuchs, B.; Ellencweig, A. *Recl. Trav. Chim. Pays-Bas* **1979**, *98*, 326. (c) Alder, R. W.; Heilbronner, E.; Honegger, E.; McEwen, A. B.; Moss, R. E.; Olefirowicz, E.; Petillo, P. A.; Sessions, R. B.; Weisman, G. R.; White, J. M.; Yang, Z.-Z. *J. Am. Chem. Soc.* **1993**, *115*, 6580.
8. For some reviews, see: (a) Bradshaw, J. S.; Krakowiak, K. E.; Izatt, R. M. *Tetrahedron* **1992**, *48*, 4475. (b) Ganem, B. *Acc. Chem. Res.* **1982**, *15*, 290.
9. Gabe, E. J.; Le Page, Y.; Prasad, L.; Weisman, G. R. *Acta Crystallogr.* **1982**, *B38*, 2752.
10. (a) Chantrapromma, K.; Ganem, B. *Tetrahedron Lett.* **1981**, *22*, 23. (b) Dutasta, J.-P.; Gellon, G.; Leuchter, C.; Pierre, J.-L. *J. Org. Chem.* **1988**, *53*, 1817. (c) Ponasik, J. A.; Kassab, D. J.; Ganem, B. *Tetrahedron Lett.* **1996**, *37*, 6041.
11. **1,4,8,11-Tetraazabicyclo[9.3.1.$1^{4,8}$]pentadecane (3).** To a solution of **2** (32 mg, 0.15 mmol) in 5 ml of CH_2Cl_2, 10 mL of 30% aqueous NaOH was added and the reaction mixture was refluxed with vigorous stirring for 8 h. Then, water (10 mL) was added and the organic phase was separated, washed with water (2x5mL) and dried over Na_2SO_4. After evaporation *in vacuo* a pure crystalline product was obtained. Yield: 32 mg of **3**, 95%.
4-*tert*-butyloxycarbonyl-1,4,8,11-tetraazabicyclo [9. 3.1]pentadecane (4). A solution of **2** (106 mg, 0.5 mmol) and di-*tert*-butyl dicarbonate (120 mg, 0.55 mmol) in 15 mL of CH_2Cl_2 was stirred at room temperature for 8 h and then evaporated *in vacuo*. The residue was purified by column chromatography on silica gel (CH_2Cl_2; CH_2Cl_2/MeOH, 5:1). Yield: 111 mg of **4**, 71%.
4: ^{13}C NMR (200 MHz, C_6D_6): δ (ppm): 25.16, 25.56, 28.34(3C), 44.94, 45.30, 45.91, 48.02, 49.81, 50.49, 52.75, 54.35, 73.36, 79.96, 156.86.MS: m/z = 312 (M^+), 297, 282, 268, 239, 211, 157, 140, 125, 113 (100%), 99, 70.
12. **4,8-Bis(*tert*-butyloxycarbonyl)-1,4,8,11-tetraazabicyclo-[9.3.1]pentadecane (5).** A solution of **2** (212 mg, 1 mmol), di-*tert* -butyl dicarbonate (**1.0 g**, 4.59 mmol) and 4-dimethylaminopyridine (56 mg, 0.46 mmol) in 25 mL of CH_2Cl_2 was refluxed with stirring for 2 h and then evaporated *in vacuo*. The residue was purified by column chromatography on silica gel (CH_2Cl_2; CH_2Cl_2/MeOH, 9:1). Yield: 338 mg of **5**, 82%.
5: ^{13}C NMR (200 MHz, $CDCl_3$): δ (ppm): 23.05, 29.17, 29.18(6C), 48.31(2C), 48.81(2C), 54.03 (br s, 2C), 54.91(2C), 72.79, 79.98(2C), 156.48(2C).MS: m/z = 412 (M^+), 357, 312, 299, 281, 254, 239, 207, 182, 157, 139, 111 (100%), 99, 70.
13. (a) Almeida, M. L. S.; Grehn, L.; Ragnarsson, U. *J. Chem. Soc., Perkin Trans. I* **1988**, 1905. (b) Grehn, L.; Ragnarsson, U. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 296. (c) Franzèn, H.; Grehn, L.; Ragnarsson, U. *J. Chem. Soc., Chem. Commun.* **1984**, 1699.

14. (a) Tice, C. M.; Ganem, B. *J. Org. Chem.* **1983**, *48*, 2106. (b) Nagarajan, S.; Ganem, B. *J. Org. Chem.* **1985**, *50*, 5735.

15. Direct treatment of cyclam with 1.8 equiv. of Boc_2O leads to a complex mixture of tri-and di-protected compounds which is difficult to separate. Compound **6** is obtained from this mixture in 25% yield.[5a]

16. Tsukube, H. *J. Chem. Soc., Chem. Commun.* **1983**, 970.

17. **4,8-Bis(*tert*-butyloxycarbonyl)-1,4,8,11-tetraazacyclotetradecane (6).** The macrocycle **5** (165 mg, 0.4 mmol) was dissolved in absolute ethanol (20 mL) and then malonic acid (161 mg, 1.55 mmol) and dry pyridine (93 mg, 1.2 mmol) were added. The reaction mixture was refluxed for 10 h, cooled and concentrated *in vacuo*. The residue was taken up in water (20 mL), washed with CH_2Cl_2 (2x5 mL), basified to pH 12 by adding aqueous solution of NaOH and extracted with CH_2Cl_2 (4x10 mL). The combined organic layers were dried over Na_2SO_4. Evaporation of the solvent afforded 139 mg (87%) of **6** as colorless oil which has been used without further purification.

1,11-Bis(*tert*-butyloxycarbonyl)-4,8-di(benzyl)-1,4,8,11-tetraazacyclotetradecane (9). To a solution of **6** (200 mg, 0.5 mmol) in 5 mL of CH_2Cl_2 was added anhydrous Na_2CO_3 (812 mg, 7 mmol) and then a solution of benzyl bromide (188 mg, 1.1 mmol) in 5 mL of CH_2Cl_2. The reaction mixture was refluxed for 3 h and, after addition of water (15 mL) the reaction mixture was stirred for an additional 15 min. The organic phase was separated and the water layer was extracted with CH_2Cl_2 (5x5 mL). The combined extracts were dried over Na_2SO_4, evaporated *in vacuo* and purified by column chromatography on silica gel (CH_2Cl_2/MeOH, 9:1). Yield: 214 mg of **9**, 74%.

4,8-Bis(benzyl)-1,4,8,11-tetraazacyclotetradecane (10). A suspension of **9** (230 mg, 0.4 mmol) in 10 mL of 4 M HCl was refluxed for 1 h. After cooling and addition of aqueous solution of NaOH (pH = 12) the reaction mixture was extracted with CH_2Cl_2 (4x10 mL). The combined organic layers were dried over Na_2SO_4. Evaporation of this solution *in vacuo* led to pure white crystalline product. Yield: 147 mg of **10**, 98%.

10: ^1H NMR (200 MHz, $CDCl_3$): δ (ppm): 1.71 (m, 4H), 2.41 (m, 4 H), 2.51 (m, 6H), 2.69 (m, 8H), 3.49 (m, 4H), 7.21 (m, 10H). ^{13}C NMR (200 MHz, $CDCl_3$): δ (ppm): 27.49, 28.90, 48.27(2C), 49.49(2C), 51.32(2C), 54.41(2C), 59.89(2C), 127.52(2C), 128.86(4C), 129.65(4C), 140.32(2C). MS: m/z = 380 (M^+), 293, 281, 267, 220, 203, 173, 160, 134(100%), 118, 99, 91, 70.