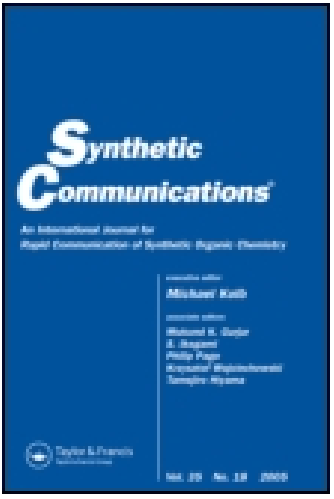


Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

Unequivocal Synthesis of 1,9-Dibenzyl-1,5,9,13-tetracyclohexadecane.

Dominique Fasseur [a] , Sylvie Lacour [b] & Roger Guilard [a b]

[a] Laboratoire de Synthèse et Electrosynthèse Organométalliques (LSEO) , UMR 5632

[b] Laboratoire d'Ingénierie Moléculaire pour la Séparation et l'Application des Gaz (LIMSAG) , UMR 5633 Faculté des Sciences 'Gabriel' 6 boulevard Gabriel, 21000 , Dijon , France

Published online: 21 Aug 2006.

To cite this article: Dominique Fasseur , Sylvie Lacour & Roger Guilard (1998) Unequivocal Synthesis of 1,9-Dibenzyl-1,5,9,13-tetracyclohexadecane., Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 28:2, 285-294, DOI: 10.1080/00397919808005721

To link to this article: http://dx.doi.org/10.1080/00397919808005721

SYNTHETIC COMMUNICATIONS, 28(2), 285-294 (1998)

UNEQUIVOCAL SYNTHESIS OF 1,9-DIBENZYL-1,5,9,13-TETRACYCLOHEXADECANE.

Dominique Fasseur[a], Sylvie Lacour[b] and Roger Guilard*[a, b]

a) Laboratoire de Synthèse et Electrosynthèse Organométalliques (LSEO),UMR 5632

b) Laboratoire d'Ingénierie Moléculaire pour la Séparation et l'Application des Gaz (LIMSAG) UMR 5633 Faculté des Sciences "Gabriel"

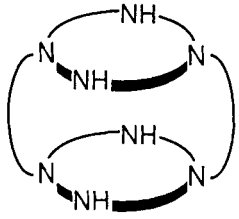
6 boulevard Gabriel 21000 Dijon France

Abstract : Condensation of two *N*-benzylated derivatives **3** and **4** according to the Richman and Atkins's method allows the unequivocal synthesis of 1,9-dibenzyl-1,5,9,13-tetracyclohexadecane (**2**). Preparation of the two precursors **3** and **4** is also described.

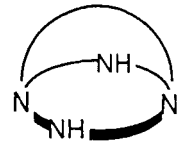
The interest in macropolycyclic ligands is mainly due to their complexation properties which are superior to those of the

*To whom correspondence should be addressed.

macromonocyclic ligands[1-3]. During the two last decades, much research has been devoted to these derivatives. For example, in the series of polyazamacrocycles, the macrotricyclic molecules **I** and the macrobicyclic molecules **II** have been prepared starting from cyclam [4] and cyclen [5-7] ligands.



I

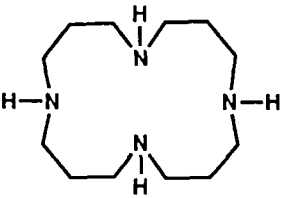


II

For each of these derivatives, the final cyclisation step is carried out using *N*-diprotected or *N*-triprotected azamacrocycles which are prepared by the *N*-alkylation reaction of the unsubstituted macrocycles[4] or by condensation of two *N*-substituted moieties[7].

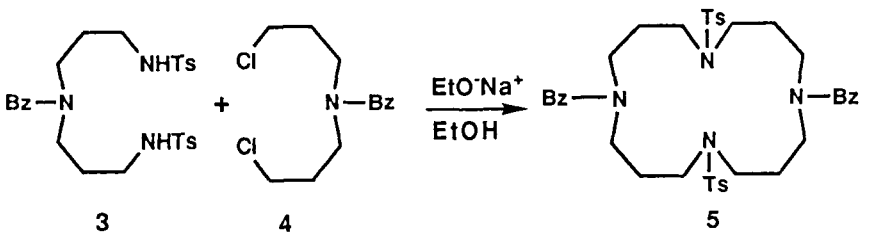
In order to synthesize macrotricyclic ligand **I** containing macrocyclic units having a larger cavity than cyclam and cyclen, we have chosen 1,5,9,13-tetraazacyclohexadecane (**1**) such as macrocyclic skeleton which is a symmetrical tetraazamacrocycle previously described[8,9]. The key problem of the synthesis of **I** and **II** is to protect two nitrogen atoms of the macrocyclic unit before the cyclisation step. Thus, we have chosen to develop an unequivocal synthesis of bis *N*-substituted ligand rather to prepare the latter compound by reacting the free base **1** with protective reagents. Indeed, it is very well known that the latter reaction leads to

several products (*i. e.* mono- or poly- *N*-protected macrocycles) which are difficult to separate.

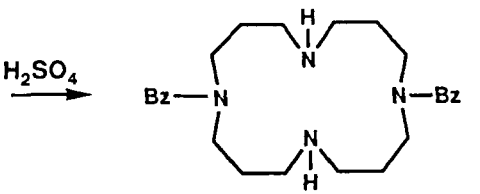


1

We describe in this paper the unequivocal synthesis of 1,9-dibenzyl-1,5,9,13-tetraazacyclohexadecane (**2**) according a Richman and Atkins-like cyclization[10] of two *N*-benzylated moieties **3** and **4.**



3 **4** **5**



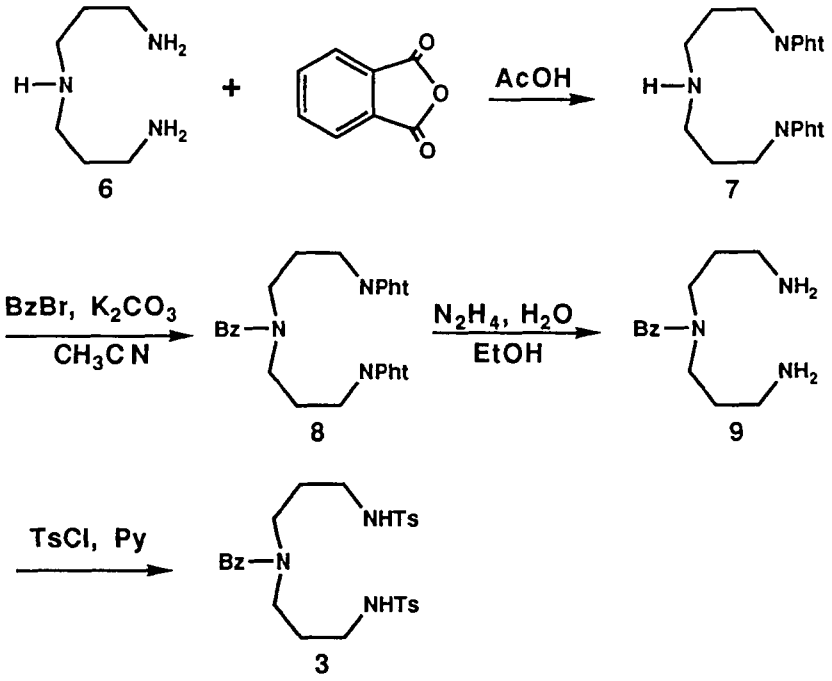
2

Synthesis of compounds **3** and **4.**

Compound **3** was prepared from *N*-(3-Aminopropyl)-1,3-propanediamine (**6**) according a four-step procedure. *N,N'*-(iminopropylene)bisphtalimide (**7**) was obtained by direct reaction of **6** with

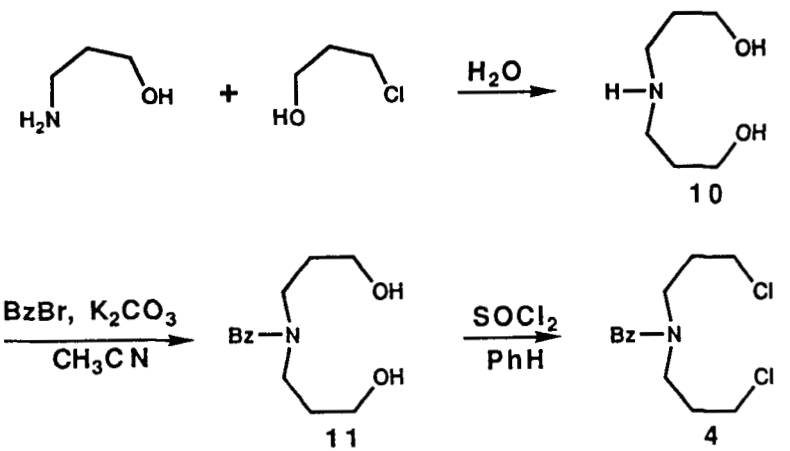
phtalic anhydride[11]. *N*-benzylation of **7** with benzylbromide in presence of K_2CO_3 as base in acetonitrile[12] gave the *N*-benzylated derivative (**8**).The final cleavage of phtalic groups was carried out by hydrazine in ethanol[12] and *N*-benzyl-(3-aminopropyl)-1,3-propanediamine (**9**) was obtained after purification in a 58% yield.

Tosylation of primary amino groups of compound **9** by treatment with tosyl chloride in presence of NaOH[13,14] was unsatisfactory since the compound **3** was obtained in varying yields. Thus, tosylation reaction was carried out by using pyridine as the base[10] leading to ditosylated amine **3** in a 75% yield.



The dichloro derivative **4** was obtained starting from dipropanolamine **10** synthesized by condensation of propanolamine with

chloropropanol[15]. After the *N*-benzylation reaction, the *N*-protected compound **11** was reacted with an excess of thionylchloride in benzene[16] to afford *N*-benzyl-di-(3-chloropropyl)amine (**4**).



Condensation of the two *N*-benzylated precursors **3** and **4** in DMF according to the Richman and Atkins's method[10] yielded after recrystallization ditosylated macrocycle **5** (10%) ; the detosylation reaction was performed in concentrated sulfuric acid at 100°C without cleavage of the benzyl protective group giving the macrocycle **2** in 91% crude yield.

EXPERIMENTAL

All starting materials were commercial derivatives and used without further purification. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ at 200 MHz on a AC 200 Brücker spectrophotometer. Mass spectra were obtained on a KRATOS CONCEPT 321 S spectrometer using EI and FAB ionization modes.

Elemental analyses were performed by the "Service Central de Microanalyses" of CNRS, in Vernaison, France.

N-Benzyl-di(3-chloropropyl)amine (4)

The dichloro derivative was prepared as described in the literature[16].

Diphtaloyldipropylenetriamine (7)

N-(3-Aminopropyl)-1,3-propanediamine (40 mL, 284 mmol) was added to a solution of phtalic anhydride (92 g, 624 mmol) in acetic acid (500 mL). The mixture was refluxed for one hour. The solvent was evaporated and the residue dissolved in 500 mL of absolute ethanol. The solution was stirred under reflux for one hour. After cooling, compound **7** precipitated. The white solid was filtered, washed with ethanol and water and dried, yield 83% ; mp 152°C (EtOH) ; ^{1}H NMR ($CDCl_3$) δ (ppm) : 1.91 (q, 4H), 2.70 (t, 4H), 3.76 (t, 4H), 7.67-7.84 (m, 8H) ; ^{13}C NMR ($CDCl_3$) δ (ppm) : 28.16, 36.13, 46.69, 123.95, 134.63.

Anal. calcd. for $C_{29}H_{27}N_3O_4$, EtOH : C, 65.89 ; H, 6.22 ; N, 9.60 ; O, 18.28. Found : C, 65.87 ; H, 6.22 ; N, 9.60 ; O, 18.66.

N-Benzyldiphtaloyldipropylenetriamine (8)

A suspension of amine **7** (19.5 g, 50 mmol), benzyl bromide (7.5 mL, 63 mmol) and anhydrous potassium carbonate (20 g, 150 mmol) in acetonitrile (150 mL) was refluxed for 12 hours. After cooling, the inorganic salts were filtered and acetonitrile was removed under vacuum. The residue was dissolved in methylene chloride ; the organic phase was washed with water, dried over magnesium sulfate, filtered and evaporated.

Crude product **8** was recrystallized from acetonitrile (20 mL), yield 58%, mp 96°C ; ir (KBr) ν cm^{-1} : 3464 (N-H), 1704 (C=O) ; ^1H NMR ($CDCl_3$) δ (ppm): 1.83 (q, 4H), 2.49 (t, 4H), 3.53 (s, 2H), 3.70 (t, 4H), 7.08-7.63 (m, 13H) ; ^{13}C NMR ($CDCl_3$) δ (ppm): 26.72, 37.01, 51.67, 59.00, 123.78, 127.46, 128.80, 129.59, 132.89, 134.43, 139.93, MS: M, 481.

Anal. calcd. for $C_{29}H_{27}N_3O_4$: C, 72.33 ; H, 5.65 ; N, 8.72 ; O,13.29. Found : C, 71.61; H, 5.68 ; N, 8.71 ; O, 14.00.

4-Benzyl-4-aza-1,7-heptanediamine (9)

A solution of compound **8** (13.8 g, 28 mmol), hydrate hydrazine (15 mL, 280 mmol) in absolute ethanol (200 mL) was mechanically stirred at reflux for two hours. The mixture was maintained at 0°C overnight and the white solid was filtered and washed with ethanol. The solvent was removed under vacuum and the compound was obtained as a yellow hygroscopic oil, yield 85% ; ir (KBr) ν cm^{-1} : 1699 (C=O) ; ^1H NMR ($CDCl_3$) δ (ppm) : 1.58 (q, 4H) ; 2.40 (t, 4H) ; 2.60 (s, 4H) ; 2.68 (t, 4H) ; 3.46 (s, 2H) ; 7.21 (m, 5H) ; ^{13}C NMR ($CDCl_3$) δ (ppm): 30.93 ; 40.78 ; 51.94 ; 59.35 ; 127.49; 128.82; 129.44 ; 140.28.

1,7-Ditosyl-4-benzyl-4-aza-1,7-heptadiamine (3)

p-Toluenesulfonylchloride (3.4 g, 180 mmol) was dissolved in pyridine (9 mL) at 50°C. A solution of amine **9** (2 g, 9 mmol) in pyridine (1.4 mL) was added slowly at 50°C. The solution was stirred for 30 minutes, cooled and poured on water (5 mL). The mixture was stirred overnight, cooled in an ice-bath and filtered. The solvent was removed under vacuum and the residue dissolved in methylene chloride. The organic phase was washed

with water, dried over magnesium sulfate, filtered and evaporated. Crude product **3** was obtained in 58% yield ; ^{1}H NMR ($CDCl_3$) δ (ppm) : 1.63 (q, 4H) ; 2.41 (m, 10H) ; 2.91 (t, 4H) ; 3.41 (s, 2H) ; 7.14-7.96 (m, 13H) ; ^{13}C NMR ($CDCl_3$) δ (ppm): 22.18 ; 26.01 ; 42.27 ; 51.91 ; 58.94 ; 127.78 ; 128.69 ; 129.36 ; 130.35 ; 136.74 ; 137.55 ; 143.85 ; 150.40 .MS: M+1, 529.

1,9-Dibenzyl-5,13-ditosyl-1,5,9,13-tetraazacyclododecane (5)

Sodium (2.13 g, 90 mmol) was dissolved in absolute ethanol (100 mL) ; this solution was added dropwise under inert atmosphere to the compound **3** (12.43 g, 23 mmol) in absolute ethanol (100 mL). The solution was stirred at room temperature and the solvent removed under vacuum. The disodium salt was dissolved in dried DMF (300 mL) and a solution of the dichloride derivative **4** (10 g, 38 mmol) in DMF (150 mL) was added at 90°C under N_2. The reaction mixture was stirred overnight. After cooling, the solvent was removed under vacuum and water was added. Product was extracted with methylene chloride and organic phase was dried over magnesium sulfate. After filtration, the solvent was evaporated and the residue chromatographed (SiO_2, CH_2Cl_2/MeOH ; 99:1). After recristallization from CH_2Cl_2/heptane, the aimed compound was obtained in a 10% yield, mp 135°C ; ^{1}H NMR ($CDCl_3$) δ (ppm) : 1.68 (q, 8H) ; 2.39 (t, 8H) ; 2.40 (s, 6H) ; 3.05 (t, 8H) ; 3.47 (s, 4H) ; 7.23-7.60 (m, 18H) ; ^{13}C NMR ($CDCl_3$) δ (ppm) : 22.14, 27.83, 47.57, 52.12, 60.52, 127.79, 128.90, 129.57, 130.29, 137.19, 140.05, 143.73. MS: M-91, 625.

Anal. calcd. for $C_{40}H_{52}N_4O_4S_2$: C, 67.00 ; H, 7.31 ; N, 7.81 ; O, 8.82 ; S, 8.94. Found : C, 67.13 ; H, 7.31 ; N, 7.87 ; O, 8.78 ; S, 9.07 .

1,9-Dibenzyl-1,5,9,13-tetraazacyclododecane (2)

Tetraazamacrocycle **5** (2 g, 2.8 mmol) was stirred in concentrated sulfuric acid (7.4 mL) at 90°C for 24 hours. Absolute ethanol (46 mL) and dried ether (46 mL) were slowly added on the cooled reaction mixture. The protonated macrocycle sulfate was precipitated, filtered and washed with ether and ethanol. The salt was dissolved in water and neutralized by adding 8M NaOH (100 mL). The product was extracted with methylene chloride and the organic phase was separated, dried over magnesium sulfate, filtered, and evaporated. The dibenzylated tetraazamacrocycle **2** was obtained as a yellow hygroscopic oil, yield 91%, ^{1}H NMR ($CDCl_3$) δ (ppm) : 1.67 (q, 8H) ; 2.44 (t, 8H) ; 2.68 (t, 8H) ; 3.48 (s, 4H) ; 7.22-7.29 (m, 10H) ; ^{13}C NMR ($CDCl_3$) δ (ppm) : 28.28 ; 48.64 ; 52.06 ; 59.93 ; 127.43 ; 128.79 ; 129.64.

REFERENCES

[1] Lehn, J. M. *Pure Appl. Chem.*, **1980,** *52,* 2441.

[2] Izatt, R. M., Pawlak, K., Bradshaw, J. S. and Bruening, R. L. *Chem. Rev.*, **1991,** 1721.

[3] Lehn, J. M., Pine, S. H., Watanabe, E and Willard, A. K. *J. Am. Chem. Soc.*, **1978,** *100,* 3604.

[4] Lachkar, M., Andrioletti, B., Boitrel, B., Guilard, R. and Atmani, A. *New. J. Chem.*, **1995,** *19,* 777.

[5] a) Bencini, A., Bianchi, A., Borselli, A., Ciampolini, M., Garcia-Espana, E., Dapporto, P., Micheloni, M., Paoli, P., Ramirez, J. A. and Valtancoli, B. *Inorg. Chem.*, **1989,** *28,* 4279 .

b) Bencini, A., Bianchi, A., Bazzicalupi, C., Ciampolini, M., Dapporto, P., Fusi, V., Micheloni, M., Nardi, N., Paoli, P. and Valtancoli, B. *J. Chem. Soc., Perkin Trans II,* **1993,** 115 .

c) Bencini, A., Bianchi, A., Bazzicalupi, C., Ciampolini, M., Dapporto, P., Fusi, V., Micheloni, M., Nardi, N., Paoli, P. and Valtancoli, B. *J. Chem. Soc., Perkin Trans II,* **1993,** 715 .

[6] Brandès, S., Cocolios, P. and Guilard, R. *C. R. Acad. Sci. Paris,* **1996,** *t.322,* Série II b, 827 .

[7] Ciampolini, M., Micheloni, M., Nardi, N., Paoletti, P., Dapporto, P. and Zanobini, F. *J. Chem. Soc., Dalton Trans* , **1984,** 1357 .

[8] Koyama, H. and Yoshino, T. *Bull. Chem. Soc. Jpn.*, **1972,** *45,* 481.

[9] Smith, W. L., Ekstrand, J. D. and Raymond, K. N. *J. Am. Chem. Soc.*, **1978,** *100,* 3539.

[10] Atkins, T. J., Richman, J. E. and Oettle, W. F. *Org. Synth.*, **1978,** *58,* 86.

[11] Chiu Yuen, N. G., Motekaitis, R. J. and Martell, A. E. *Inorg. Chem.*, **1979,** *18,* 2982.

[12] Anelli, P. R., Lunazzi, L., Montanari, F. and Quici, S., *J. Org. Chem.*, **1984,** *49,* 4197.

[13] Gruenman, V., Hoffer, M., O'Brien, J. P., Rachlin, A. I. and Zbinden, G. *U. S. Patent* ,**1968,** 3,382 260 .

[14] Pilichowski, J. F., Lehn, J. M. and Sauvage, J. P. *Tetrahedron,* **1985** ,*41,* 1959.

[15] Jones, E. R. H. and Wilson, W. J. *J. Chem. Soc.*, **1949,** 547 .

[16] Granier, C. and Guilard, R. *Tetrahedron,* **1995,** *51,* 1197.

(Received in The Netherlands 11 August 1997)