An Alternative Synthesis of Cyclic Aza Compounds

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A series of cyclic mono-, di- and poly-aza compounds has been synthesised in moderate to good yields by the reaction of *p*-toluenesulfonamide and either α,ω-ditosylates or α,ω-dichlorides.

Polyazamacrocycles have been a source of considerable interest in recent years, because of their ability to bind various metals[1–3] and anions and, indeed, to catalyse hydrolysis reactions.[4–6] The synthesis of such compounds is normally carried out by the reaction of α,ω-ditosylamides with either α,ω-dihalides or α,ω-ditosylates.[7,8] Although there are many cases where α,ω-diamines are readily available, an alternative method for the synthesis of cyclic di- and poly-azamacrocycles is desirable. We present herein one such alternative method.

Attempts to form ditosylamides by the reaction of toluenesulfonamide with ditosylates or dihalides under basic conditions led to the formation of very small amounts of the desired compounds.[9] The isolated products were either cyclic tosylamides containing only one tosyl group, or mixtures of mono- and di-alkyl tosylamides. Our attempts to prepare 3- oxa-*N*,*N*-ditosylpentane-1,5-diamine from bis(2-chloroethyl) ether (**1a**) resulted in the production of 1-oxa-4-aza-4-tosylcyclohexane (*N*-tosylmorpholine) (**2**) in moderate yield. By adjusting the reaction conditions we were able to improve the yield of *N*-tosylmorpholine to >90% starting from either **1a** or bis(2-tosyloxyethyl) ether (**1b**) (Scheme 1).

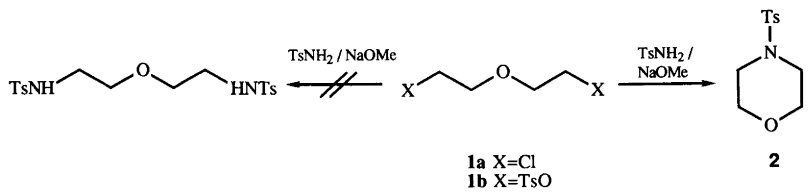
These results prompted us to investigate the possible use of *p*-toluenesulfonamide as a starting material for a general synthesis of cyclic aza compounds. The general method has some similarities with previously reported procedures,[8] but owing to the stepwise manner in which the reactions are carried out, greater control over their outcome is achieved. The method allows for the synthesis of cyclic aza compounds in moderate to good yields, and is sufficiently flexible to allow modification for the synthesis of substituted and unsymmetrical cyclic aza compounds.

Two series of compounds were prepared, one where oxygen was included in the ring, giving rings of 6 to 18 atoms, and one where no oxygen atoms were included giving rings with 8 and 12 atoms.

Results and discussion

Diethylene glycol (**3a**) and triethyleneglycol (**3b**) were monotosylated using *p*-toluenesulfonyl chloride and triethylamine in the presence of 4-dimethylaminopyridine, to give 5-tosyloxy-3-oxapentanol (**4a**) and 8-tosyloxy-3,6-dioxaoctanol (**4b**) in 88 and 70 % yields, respectively. These monotosylates were treated with sodium *p*-toluenesulfonamide, prepared from sodium hydride and *p*-toluenesulfonamide, in DMF to give a mixture of mono- and di-alkylated tosylamides. Compound **4a** gave the di-alkylated product **5a** in 60 % yield and the monoalkylated product **6a** in 38 % yield, whilst **4b** gave the di- and monoalkylated products **5b** and **6b** in 41 and 45 % yields, respectively (Scheme 2). Tosylation of **5a** and **5b** was accomplished using *p*-toluenesulfonyl chloride, triethylamine and 4-dimethylaminopyridine to give **7a** in 75 % yield and **7b** in 97 % yield.

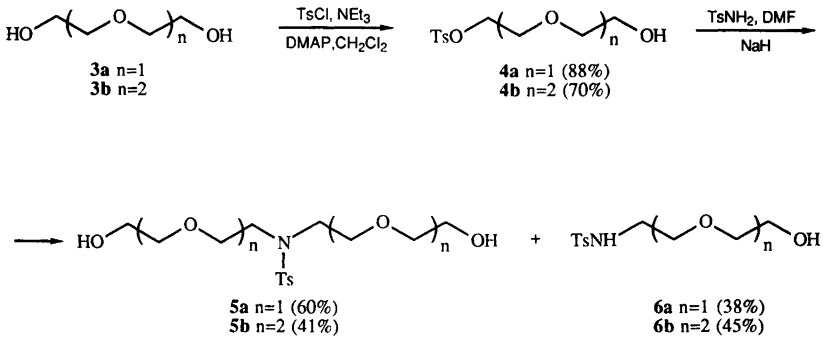
Cyclisation of **7a** and **7b** using *p*-toluenesulfonamide and sodium hydride in DMF led to the isolation of the desired products. Compound **7a** gave 4,10-ditosyl-1,7-dioxa-4,10-diazacyclododecane (**8a**) in 50 % yield and **7b** gave 7,16-ditosyl-1,4,10,13-tetraoxa-7,16-diazacyclooctadecane (**8b**) in 43 % yield (Scheme 3). Removal of the tosyl groups using hydrogen bromide and phenol in acetic acid proceeded smoothly giving 1,7-dioxa-4,10-diazacyclododecane (**9a**) (4,10-diaza-12-crown-4) quantitatively and 1,4,10,13-



1a X=Cl
1b X=TsO

2

Scheme 1.



3a n=1
3b n=2

4a n=1 (88%)
4b n=2 (70%)

5a n=1 (60%)
5b n=2 (41%)

6a n=1 (38%)
6b n=2 (45%)

Scheme 2.

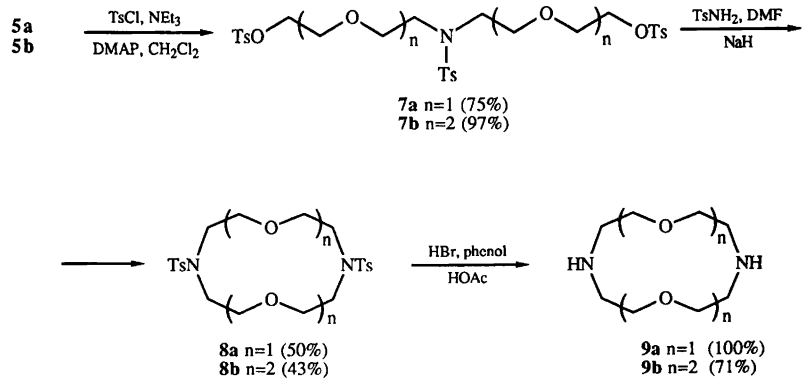
tetraoxa-7,16-diazacyclooctadecane (**9b**) (7,16 diaza-18-crown-6) in 71 % yield, as the dihydrochloride salts.

The cyclisation procedure was also applied to 6,9,12-tritosyl-1,17-ditosyloxy-3,15-dioxa-6,9,12-triazaheptadecane (**10**).[10] The product, 4,10,13,16-tetratosyl-1,7-dioxa-4,10,13,16-tetraazacyclooctadecane (**11**), was isolated in 40 % yield and was detosylated to give 1,7-dioxa-4,10,13,16-tetraazacyclooctadecane (**12**) in 88 % yield (Scheme 4).

Smaller rings not containing oxygen were also synthesised. Commerically available 3-chloro-1-propanol (**13**) reacted with toluenesulfonamide and sodium hydride in DMF to give a mixture of the dialkylated-4-tosyl-4-aza-1,7-heptanediol (**14**) in 61 % yield and the monoalkylated *N*-tosyl-3-amino-1-propanol (**15**) in 15 % yield (Scheme 5). Compound **14** was tosylated to give **16** (65 %) which was cyclised with *p*-toluenesulfonamide and sodium hydride to give 1,5-ditosyl-1,5-diazacyclooctane (**17**) (55 %). This product was detosylated to yield 1,5-diazacyclooctane (**18**) in 86 % yield as the dihydrochloride salt (Scheme 6). 1,7-Diazacyclododecane (**25**) was prepared in an analogous manner starting from 1,5-pentanediol (**19**). Monotosylation proceeded in 77 % yield to give 5-tosyloxy-1-pentanol (**20**), which was used to alkylate *p*-toluenesulfonamide, giving 6-tosyl-6-aza-1,11-undecanediol (**21**) and *N*-tosyl-5-amino-1-pentanol (**22**) in 32 and 30 % yields (Scheme 7). The dialkylated product (**21**) was tosylated in 84 % yield to give 6-tosyl-1,11-tosyloxy-6-azaundecane (**23**). This compound was then cyclised with *p*-toluenesulfonamide to give 1,7-ditosyl-1,7-diazacyclododecane (**24**) in 14 % yield. Detosylation of **24** could be easily carried out to give 1,7-diazacyclododecane (**25**) (80 %) (Scheme 8).

The syntheses presented in this paper are an alternative to other procedures presented in the literature.[9] In most cases the yields are reasonable and the experimental procedures fairly simple. We chose not to use high dilution techniques as template effects can be expected to ensure that cyclisations take place rather than linear addition reactions. A lack of template effects may be responsible for the drop in yield on increasing the non-oxygen-containing ring from 8 atoms to 12, compounds **17** and **24**.

Upon alkylation of *p*-toluenesulfonamide it is apparent that monoalkylated products are readily formed whilst dialkylated products can only be formed when much larger excesses of both base and alkylating agent are used. This observation is consistent with similar alkylation reactions using trifluoroacetamide.[11] As in the case of monoalkyltrifluoroacetamides, the monoalkylated *p*-toluenesulfonamides may be further alkylated allowing for the formation of unsymmetrically disubstituted tosylamides. This method would then give rather easy access to unsymmetrically substituted aza macrocycles.

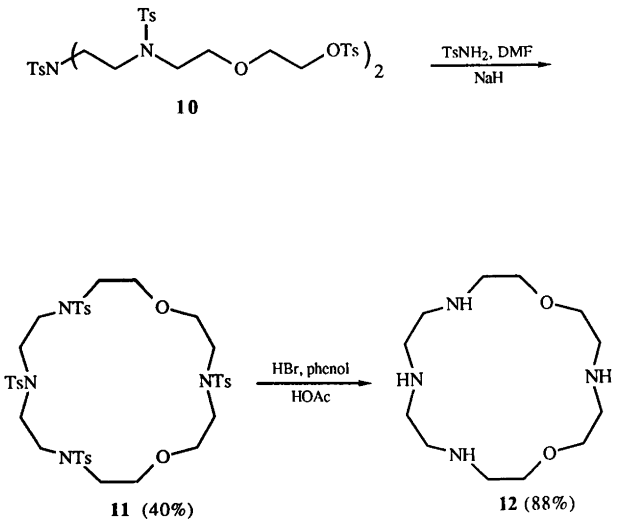


7a n=1 (75%)
7b n=2 (97%)

8a n=1 (50%)
8b n=2 (43%)

9a n=1 (100%)
9b n=2 (71%)

Scheme 3.



Scheme 4.

The compounds presented are interesting for their potential binding properties to cationic, anionic and neutral species, and for their possible use in organic synthesis. Studies of these properties and exploration of further synthetic applications of this method are currently in progress in our laboratory.

Experimental

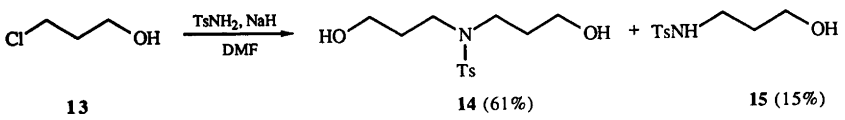
^{1}H and ^{13}C NMR spectra were recorded on a Jeol 90Q spectrometer at 89.5 MHz and 22.5 MHz respectively, unless otherwise stated. Chloroform, $\delta = 7.26$, or methanol, $\delta = 3.35$, were used as internal references in ^{1}H NMR spectra. Chloroform, $\delta = 77$, or methanol, $\delta = 49.8$, were used as references in ^{13}C NMR spectra. TLC was performed using silica gel plates (F_{254}, Merck) and the spots were detected with either UV light or ninhydrin. Column chromatography was performed on silica gel 60 (0.040–0.063 mm, Merck). The elemental analyses were performed by Mikro Kemi AB, Uppsala, Sweden. Melting points are uncorrected. Triethylamine and *N,N*-dimethylformamide were dried and distilled from calcium hydride. Triethylene glycol and diethylene glycol were dried using calcium chloride and distilled. All other commercial chemicals were used without further purification.

The syntheses were carried out using the general procedures described below, the R_f values given are approximate for each series of compounds. Details for each compound, including choice of method, yields and physical data are shown in Table 1, satisfactory elementary analyses were obtained for all new compounds. Mass and ^{13}C NMR data are available from the authors.

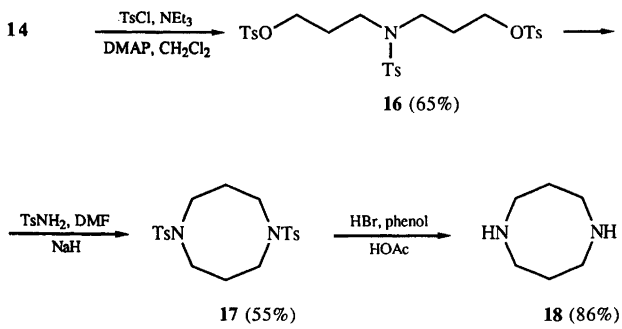
General procedure 1 (monotosylation). 4-Toluenesulfonyl chloride (1 equiv.) in dichloromethane (4 ml mmol^{-1}) was added to a well stirred ice-cooled solution of the diol (4 equiv.), triethylamine (4 equiv.) and 4-dimethylaminopyridine (0.05 equiv.) in dichloromethane (4 ml mmol^{-1}) over a 2 h period. When the addition was complete, the solution was warmed to room temperature and stirred for another 2 h and then washed, first with saturated sodium hydrogen carbonate solution then citric acid solution. The combined organic layers were dried (sodium sulfate) and evaporated. The residue was purified by flash chromatography (silica; dichloromethane–ethanol 0–5 %) and the products isolated as colourless oils.

General procedure 2 (dialkylation). 4-Toluenesulfonamide (1 equiv.) was dissolved in *N,N*-dimethylformamide (6 ml mmol^{-1}) under a nitrogen atmosphere. Sodium hydride (1.2 equiv.) was added and the mixture stirred at 80 °C for 30 min. The suitably functionalised alkane (tosylate or chloride) (1 equiv.) was dissolved in *N,N*-dimethylformamide (2 ml mmol^{-1}) and added to the heated solution over a 10 min period. The mixture was stirred at 80 °C for 1 h. Addition of sodium hydride and the alkylating agent was repeated twice more, to give a total of 3.6 equiv. sodium hydride and 3.0 equiv. alkylating agent. The mixture was stirred at 80 °C under a nitrogen atmosphere overnight. The reaction was monitored by TLC (5 % ethanol in dichloromethane R_f 0.2). The reaction mixture was cooled to room temperature and partitioned between saturated sodium hydrogen carbonate and dichloromethane, and the aqueous phase was extracted several times with dichloromethane. The combined organic layers were dried (sodium sulfate) and evaporated under vacuum. The residue was purified by flash chromatography (silica; dichloromethane–ethanol 0–8 %).

General procedure 3 (tosylation). The diol (1 equiv.), triethylamine (6 equiv.) and 4-dimethylaminopyridine (0.01 equiv.) were mixed in dichloromethane (10 ml mmol^{-1} diol) and cooled to 0 °C. To this solution was added



Scheme 5.

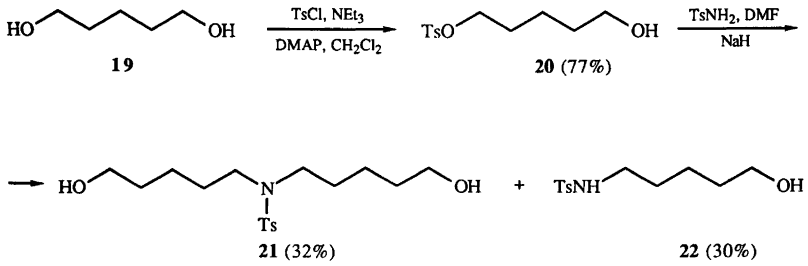


Scheme 6.

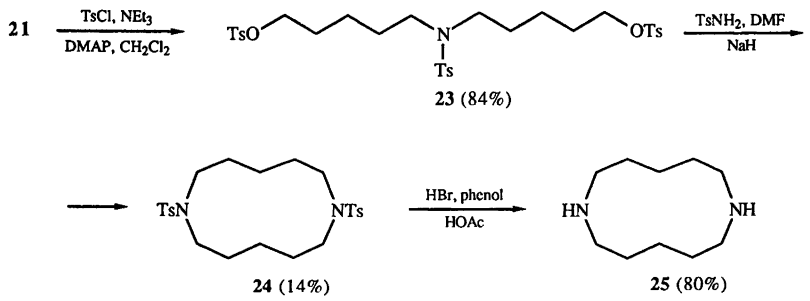
4-toluenesulfonyl chloride (3 equiv.) in dichloromethane (2 ml $mmol^{-1}$) over a 1–2 h period. When the addition was complete, the solution was warmed to room temperature. After 2 h of stirring, the reaction was complete, as judged by TLC (4% ethanol in dichloromethane, R_f 0.8). The solution was washed with saturated sodium hydrogencarbonate and the aqueous phase extracted with dichloromethane. The combined organic layers were dried (sodium sulfate) and evaporated. The residue was purified by flash chromatography (silica; dichloromethane–ethanol 0–4%).

General procedure 4 (cyclisation). 4-Toluenesulfonamide (1 equiv.) was dissolved in *N,N*-dimethylformamide (40 ml $mmol^{-1}$) under a nitrogen atmosphere. Sodium hydride (2.2 equiv.) was added in one portion. This mixture was heated to 80°C and stirred for 2.5 h. The ditosylate (1 equiv.) was dissolved in *N,N*-dimethylformamide (3 ml $mmol^{-1}$) and added to the heated mixture over a 6 h period, using a syringe pump. This mixture was stirred at 80°C under a nitrogen atmosphere for 24 h. The reaction was monitored by TLC. (4% ethanol in dichloromethane, R_f 0.7). The mixture was cooled to room temperature and extracted between saturated sodium hydrogencarbonate and dichloromethane. The combined organic layers were dried (sodium sulfate) and evaporated. The crystalline residue was purified by flash chromatography (silica; dichloromethane–ethanol 0–5%). The isolated products were recrystallised from dichloromethane–ethanol.

General procedure 5 (detosylation). The cyclic tosylamide (1 equiv.) and phenol (3 equiv. per tosyl group) were dissolved in 33% hydrogen bromide in acetic acid (30 ml $mmol^{-1}$) and heated to 80°C. This solution was stirred for 60 h, then cooled to room temperature and the solvent evaporated. The remaining acetic acid was removed by twice adding ethanol and evaporating. The black oily residue was extracted between distilled water and dichloromethane. The aqueous phase was evaporated to give crystals which were dissolved in water and passed twice through an anion-exchange column (Dowex 1×8; hydroxide form) to give white crystals. These crystals were dissolved in diethyl ether and precipitation with diethyl ether saturated in hydrogen chloride gave the hydrochloride salt.



Scheme 7.



Scheme 8.

Table 1. Experimental data for compounds **2–25**.

Product	Starting material	Method	Yield (%)	M.p./ °C	^{1}H NMR δ (ppm)
2	**1a**	4	91	160[b]	7.64 (2 H, m), 7.33 (2 H, m), 3.73 (4 H, t, *J* = 4.7 Hz)
2	**1b**	4	95	160[b]	2.98 (4 H, t, *J* = 4.7 Hz), 2.44 (3 H, s)
4a	**3a**	1	88	[a]	7.26–7.82 (4 H, m, arom), 4.12–4.22 (2 H, m), 3.44–3.72 (6 H, m), 2.43 (3 H, s), 2.24 (1 H, s)
4b	**3b**	1	70	[a]	7.26–7.82 (4 H, arom), 4.08–4.20 (2 H, m), 3.51–3.75 (10 H, m), 2.50 (1 H, s), 2.42 (3 H, s)
5a	**4a**	2	60	[a]	7.24–7.72 (4 H, m, arom), 3.47–3.73 (12 H, m), 3.33 (4 H, t, *J* = 4.8 Hz), 3.14 (2 H, s), 2.40 (3 H, s)[15]
6a	**4a**	2	38	[a]	7.23–7.79 (4 H, m, arom), 5.82 (1 H, br s), 3.43–3.66 (6 H, m), 3.13–3.19 (2 H, m), 2.40 (3 H, s)[15]
5b	**4b**	2	41	[a]	7.23–7.73 (4 H, arom), 3.36–3.73 (26 H, m), 2.41 (3 H, s)
6b	**4b**	2	45	[a]	7.24–7.78 (4 H, arom), 5.80 (1 H, br s), 3.46–3.67 (12 H, m), 2.41 (3 H, s)
7a	**5a**	3	75	[a]	7.24–7.83 (12 H, m, arom), 4.04–4.14 (4 H, m), 3.48–3.62 (8 H, m), 3.21–3.35 (4 H, m), 2.43 (9 H, s)
7b	**5b**	3	97	[a]	7.26–7.83 (12 H, arom), 4.08–4.19 (4 H, m), 3.34–3.70 (20 H, m), 2.43 (6 H, s), 2.40 (3 H, s)
8a	**7a**	4	50	203[c]	[h]
8b	**7b**	4	43	163–165[d]	[h]
9a	**8a**	5	100	82–84[e]	[i]
9b	**8b**	5	71	116[f]	[i]
11	**10**	4	40	72–75	7.22–7.82 (16 H, arom), 3.52–3.56 (8 H, m), 3.22–3.42 (16 H, m), 2.42 (12 H, s)
12	**11**	5	88	275–278	3.68 (8 H, t, *J* = 4.6 Hz), 2.77–2.88 (16 H, m)
14	**13**	2	61	[a]	7.26–7.74 (4 H, arom), 3.72 (4 H, t, *J* = 5.7 Hz), 3.25 (4 H, t, *J* = 6.8 Hz), 2.45 (2 H, br s), 2.42 (3 H, s), 1.76 (4 H, tt, *J* = 6.8 and 5.7 Hz)
15	**13**	2	15	[a]	7.26–7.70 (4 H, arom), 3.72 (2 H, t, *J* = 5.5 Hz), 3.52 (2 H, br s), 3.08 (2 H, t, *J* = 6.1 Hz), 2.41 (3 H, s), 1.69 (2 H, tt, *J* = 6.1 and 5.5 Hz)
16	**14**	3	65	[a]	7.26–7.82 (12 H, arom), 4.02 (4 H, t, *J* = 6.0 Hz), 3.08 (4 H, t, *J* = 6.2 Hz), 2.45 (9 H, s), 1.87 (4 H, m)
17	**16**	4	55	214–215	7.26–7.72 (8 H, arom), 3.33 (8 H, t, *J* = 5.9 Hz), 2.42 (6 H, s), 2.03 (4 H, quintet, *J* = 5.9 Hz)
18	**17**	5	86	244–245	4.82 (8 H, s), 3.41 (4 H, m), 2.73 (2 H, br s)
20	**19**	1	77	[a]	7.24–7.79 (4 H, arom), 3.99 (2 H, t, *J* = 6.1 Hz), 3.55 (2 H, t, *J* = 6.1 Hz), 2.41 (3 H, s), 1.39–1.72 (7 H, m)
21	**20**	2	32	[a]	7.24–7.72 (4 H, arom), 3.61 (4 H, m), 3.17 (4 H, m), 2.41 (3 H, s), 1.15–1.56 (14 H, m)
22	**20**	2	30	[a]	7.23–7.77 (4 H, arom), 5.08 (1 H, br s), 3.62 (2 H, br s), 2.86 (2 H, br s), 2.40 (3 H, s), 2.09 (1 H, br s), 1.39–1.65 (6 H, m)
23	**21**	3	84	[a]	7.26–7.82 (12 H, arom), 3.98 (4 H, t, *J* = 6.1 Hz), 3.00 (4 H, t, *J* = 6.5 Hz), 2.44 (6 H, s), 2.41 (3 H, s), 1.25–1.73 (12 H, m)
24	**23**	4	14	238[g]	[j]
25	**24**	5	80	206–209	2.91 (8 H, m), 1.75 (12 H, m)

[a]Product isolated as an oil. [b]Literature value[9] 160 °C. [c]Literature value[12] 203–204 °C. [d]Literature value[12] 163–165 °C. [e]Literature value[12,13] 82–84 °C, 83–84 °C. [f]Literature value[12,13] 115–116 °C. [g]Literature value[14] 242–244 °C. [h]Ref. 12. [i]Refs. 12 and 13. [j]Ref. 14.

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References

1. Comarond, J., Plumeré, P., Lehn, J.-M., Agnus, Y., Louis, R., Weiss, R., Kahn, O. and Morgenstern-Badarau, I. *J. Am. Chem. Soc. 104* (1982) 6330.
2. Drumhiller, J. A., Montavon, F., Lehn, J.-M. and Taylor, R. W. *Inorg. Chem. 25* (1986) 3751.
3. Amble, E. and Dale, J. *Acta Chem. Scand., Ser. B33* (1979) 698.
4. Hosseini, M. W. and Lehn, J.-M. *J. Am. Chem. Soc. 109* (1987) 7047.
5. Blackburn, G. M., Thatcher, G. R. J., Hosseini, M. W. and Lehn, J.-M. *Tetrahedron Lett. 28* (1987) 2779.
6. Hosseini, M. W., Lehn, J.-M., Maggiora, L., Mertes, K. B. and Mertes, M. P. *J. Am. Chem. Soc. 109* (1987) 537.
7. Gokel, G. W., Dishong, D. M., Schultz, R. A. and Gatto, V. J. *Synthesis* (1982) 997.
8. Krakowiak, K. E., Bradshaw, J. S. and Zamecka-Krakowiak, D. J. *Chem. Rev. 89* (1989) 929.
9. Raßhofer, W. and Vögtle, F. *Liebigs Ann. Chem.* (1978) 552.
10. Hosseini, M. W., Lehn, J. M., Duff, S. R., Gu, K. and Mertes, M. P. *J. Org. Chem. 52* (1987) 1662.
11. Harland, P. A., Hodge, P., Maughan, W. and Wildsmith, E. *Synthesis* (1984) 941.
12. Bogatsky, A. V., Lukyanenko, N. G., Basok, S. S. and Ostrovskaya, L. K. *Synthesis* (1984) 138.
13. Dietrich, B., Lehn, J. M., Sauvage, J. P. and Blanzat, J. *Tetrahedron 29* (1973) 1629.
14. Vriesema, B. K., Buter, J. and Kellogg, R. M. *J. Org. Chem. 49* (1984) 110.
15. Anelli, P. L., Montanari, F., Quici, S., Ciani, G. and Sironi, A. *J. Org. Chem. 53* (1988) 5292.

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