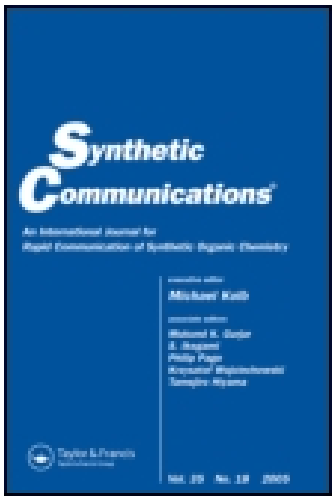

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SYNTHESIS OF NEW CRYPTANDS STARTING FROM TRANS (DIPROTECTED AND DISUBSTITUTED) 1,4,7,10-TETRAAZACYCLODODECANE

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SYNTHESIS OF NEW CRYPTANDS STARTING FROM *TRANS* (DIPROTECTED AND DISUBSTITUTED) 1,4,7,10-TETRAAZACYCLODODECANE

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ABSTRACT

New cryptands are synthesised by aminolysis between 1,7-di(ethylacetate)-4,10-di(tosyl)-1,4,7,10-tetraazacyclododecane and various diamines.

The design and synthesis of new cross-bridged ligands containing a 1,4,7,10-tetraazacyclododecane backbone is of growing interest justified by their remarkable complexing properties with transition elements and heavy metal ions.[1–3] Only a few reports of cryptands based on 1,4,7,10-tetraazacyclododecane (cyclen) have appeared.[4–8] In search of new compounds for applications in magnetic resonance imaging, in purification of water or in molecular recognition, we developed a strategy which can be applied to the preparation of many other cryptands.

The synthesis of the aimed cryptands involves the use of a *trans* (diprotected and disubstituted) 1,4,7,10-tetraazacyclododecane. First of all,

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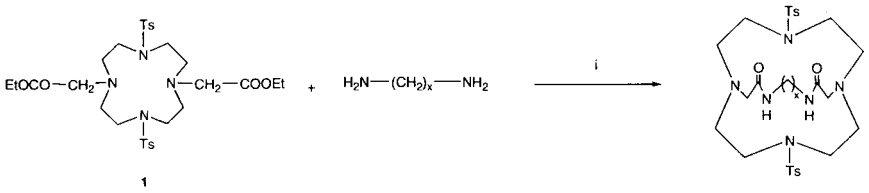
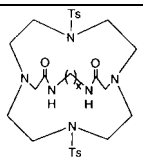


Scheme 1.

Table 1.

Compound		Yield (%)
2	$x=2$	29
3	$x=6$	8
4	$x=12$	4

selective "*trans*" protection of cyclen has been carried out by reaction of cyclen with *p*-toluenesulfonylchloride in pyridine leading exclusively to the 1,7-isomer with a good yield.[9] Then, difunctionalization has been realized by reaction between 1,7-di(tosyl)-1,4,7,10-tetraazacyclododecane with ethyl bromoacetate in presence of sodium carbonate in acetonitrile. The mixture was refluxed during a few hours and then solvent was evaporated. 1,7-di(ethylacetate)-4,10-di(tosyl)-1,4,7,10-tetraazacyclododecane **1** was isolated and purified by liquid chromatography (CH_3OH/H_2O, 80/20) with 63% yield. This strategy has previously been described for the synthesis of the diester derivative of dioxocyclen.[10] Our route to synthesis of the cryptands is shown in Sch. 1 and yields are reported in Table 1. It proceeds from **1** and various diamines (ethylenediamine, hexamethylenediamine and dodecanediamine) in methanol at $T=100^{\circ}C$. A control of the cryptands formation carried out by ^1H NMR spectroscopy in deuterated methanol has shown the necessity of a reaction time of seven days to obtain a complete conversion whatever the diamine used. After evaporation of the solvent, the resulting cryptands were analysed by liquid chromatography (CH_3CN/H_2O, 70/30) coupled mass spectrometry (APCI). The analyses showed up formation of linear and macrocyclic oligomers. Among them the cryptands **2**, **3**, and **4** were isolated in 29, 8 and 4% yields respectively after chromatography.

The introduction of a bridge containing two amide functions allow further functionalization. Moreover, deprotection of tosyl groups could permit a double difunctionalization. On the other hand, different bridges containing other functional groups could be linked to the *trans*(diprotected and difunctionalized) 1,4,7,10-tetraazacyclododecane using this strategy.

EXPERIMENTAL

1: $m/z = 653$ (M^+); ^{1}H NMR (400.13 MHz, $CDCl_3$) δ: 1.27 (6H, t, J 7 Hz, C**H**$_3$(Et)), 2.42 (6H, s, C**H**$_3$(Ts)), 3 (8H, t, J 4.7 Hz, C**H**$_2$N), 3.22 (8H, t, J 4.7 Hz, C**H**$_2$NTs), 3.43 (4H, s, C**H**$_2$COOEt), 4.14 (4H, q, J 7 Hz, C**H**$_2$(Et)), 7.28 (4H, d, J 8 Hz, C**H** ar.), 7.64 (4H, d, J 8 Hz, C**H** ar.).

2: $m/z = 624$ (M^+); ^{1}H NMR (400.13 MHz, $CDCl_3$) δ: [7.29 (1H, d, J 8.4 Hz); 7.35 (3H, d, J 8.4 Hz); 7.64 (4H, d, J 8.4 Hz), C**H** ar.]; [2.41 (1H, s); 2.46 (5H, s), C**H**$_3$(Ts)]; [3.08–3.21 (m), C**H**$_2$NTs]; [2.80–3.02 (m), C**H**$_2$N]; [3.28 (2H, s); 3.43 (2H, s), C**H**$_2$CONH]; [3.55 (4H, s), C**H**$_2$NHCO].

3: $m/z = 680$ (M^+); ^{1}H NMR (400.13 MHz, $CDCl_3$) δ: [7.30 (2H, d, J 8 Hz); 7.33 (2H, d, J 8 Hz); 7.63–7.66 (m), C**H** ar.]; [2.42 (5H, s); 2.44 (1H, s), C**H**$_3$(Ts)]; [3.14 (4H, m); 3.20 (4H, m), C**H**$_2$NTs]; [3.04 (8H, m), C**H**$_2$N]; [3.25–3.31 (8H, m), C**H**$_2$CONH, C**H**$_2$NHCO]; [1.58 (4H, m), C**H**$_2$CH$_2$NHCO]; [1.37–1.44 (4H, m), C**H**$_2$CH$_2$CH$_2$NHCO].

4: $m/z = 764$ (M^+); ^{1}H NMR (400.13 MHz, $CDCl_3$) δ: [7.30 (4H, d, J 8 Hz); 7.61 (4H, d, J 8 Hz), C**H** ar.]; [2.34 (6H, s), C**H**$_3$(Ts)]; [2.7, 2.76, 2.9 (8H, m), C**H**$_2$N]; [3.1–3.3 (16H, m), C**H**$_2$NTs, C**H**$_2$CONH, C**H**$_2$NHCO]; [1.19–1.39 (20H, m), (C**H**$_2$)$_{10}$CH$_2$NHCO].

N. B. The obtained results in mass spectrometry show higher values than those expected, because of deuterium exchange between deuterated methanol and cryptands during aminolysis reaction.

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