Highly Regioselective Synthesis of 1,7-Diprotected 1,4,7,10-Tetraazacyclododecane Derivatives

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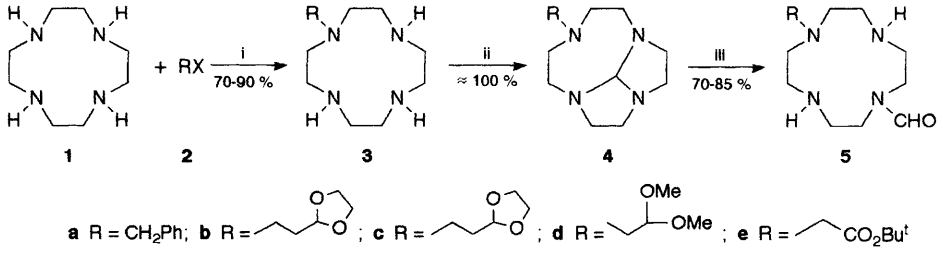
Reaction of dimethylformamide diethyl acetal with monoalkylated 1,4,7,10-tetraazacyclododecane derivatives **3**, followed by hydrolysis of the tricyclic intermediates **4**, selectively affords 1,7-disubstituted tetraazamacrocycles **5**.

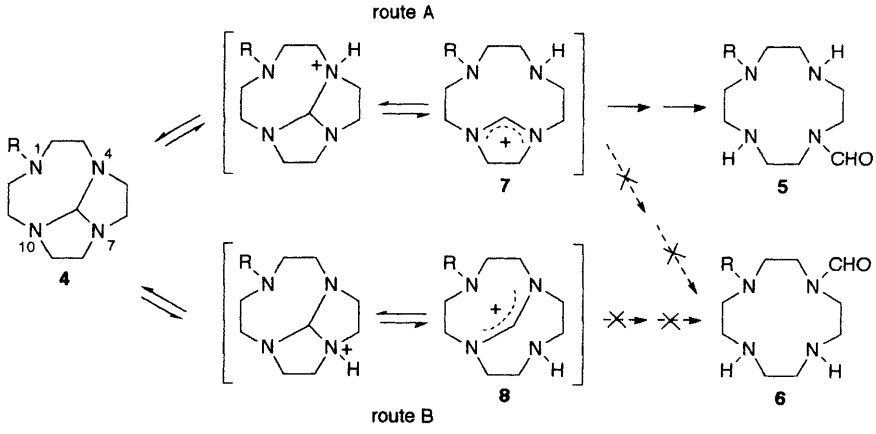
The chemistry of polyazamacrocycles with coordinating side arms, which increase the ligating ability of the macrocycles, has developed quickly over the last decade.[1] Derivatives of 1,4,7,10-tetraazacyclododecane **1** which contain additional donor groups, have been widely investigated owing to the applications found for some of their metal complexes: *e.g.* use of the Gd complex of 1,4,7,10-tetraazacyclododecane-tetraacetic acid (dota) as a contrast agent for *in vivo* magnetic resonance imaging (MRI)[2] and of ^{90}Y complexed dota derivatives attached to monoclonal antibodies in radio-immunotherapy.[3] The literature contains many reports on derivatives of **1** bearing four identical residues on the nitrogen atoms, whereas tetrasubstituted derivatives of **1** containing different coordinating side arms on the nitrogen atoms have received limited attention, probably owing to the difficulties in their synthesis. However, such macrocycles have features deserving attention, *e.g.* Gd complexes of dota analogues bearing branched acetic residues in the 1,4 or 1,7 positions of the ring show different water proton relaxivities, and thus different efficacies as contrast agents for MRI.[4] In order to have easier access to heterosubstituted derivatives of **1**, we have focused our attention on the synthesis of 1,7-disubstituted-1,4,7,10-tetraazacyclododecanes. These compounds can, in principle, be synthesized[5] by classical condensation according to the method of Richman and Atkins.[6] However, the nature of the residues which can be introduced into positions 1 and 7 by this synthetic approach is severely limited by the harsh conditions required in the detosylation step.

Here we report the synthesis of compounds **5a–e** by reaction of monoalkyl derivatives **3a–e** with dimethylformamide diethyl acetal to give tricyclic structures which are subsequently hydrolysed in a regioselective manner. Condensation of polyazamacrocycles with either triethyl orthoformate under acid catalysis[7] or dimethylformamide dimethyl acetal[8] to give orthoamides has previously been described. The introduction of an *N*-formyl group, initially masked as a tricyclic orthoamide, into 1,4,7-triazacyclononane and 1,5,9-triazacyclododecane,[9] and into unsubstituted 1,4,7,10-tetraazacyclododecane[10] was recently reported.

Monoalkylation of **1** with alkyl halides **2** (Scheme 1) was



Scheme 1 *Reagents and conditions*: i, MeCN, reflux, 2–24 h; ii, $Me_2NCH(OEt)_2$, benzene, reflux, 2–4 h; iii, EtOH–H_2O, room temp., 2 h



Scheme 2

achieved in good yield by using a large excess of **1** (5–10 mol equiv.).† The precipitation of most of unreacted **1** on cooling the reaction mixture and the easy purification (usually by crystallization) of monoalkyl derivatives **3** make this procedure very useful for large-scale preparations. Reaction of compounds **3** with dimethylformamide diethyl acetal quantitatively yielded tricyclic orthoamides **4**, whose hydrolysis in EtOH–H_2O gave 1,7-disubstituted-1,4,7,10-tetraazacyclododecanes **5** in fair to good yields. The structure of compounds **5** was unequivocally assigned by 2D NMR, CH-COSY and INADEQUATE[11] experiments. Owing to the high symmetry and to the presence of the nitrogen atoms, which break the continuity of the carbon skeleton in compounds **5**, both CH-COSY and INADEQUATE experiments are necessary to discriminate between the ring carbons in positions related by the symmetry of the unsubstituted ring system.

The mechanism possibly involved in the ring opening of **4** is shown in Scheme 2 and accordingly the reaction product should be a mixture of **5** and **6**. However, the conversion of tricycles **4** into formyl derivatives **5** appears to be highly regioselective since only traces of isomeric products were detected by gas chromatography–mass-spectrometry in the reaction mixtures. This means that cleavage of the $C_{methine}$–N(7) bond and formation of **8** according to route B in Scheme 2 does not occur. The strain introduced into the structure of **8** by the short bridge between N(4) and N(10) possibly prevents the formation of this intermediate. It is noteworthy that the opening of the five-membered ring in **7** also occurs in a regioselective manner (Scheme 2; route A). This selectivity is at present without explanation.

The formyl group is easy to remove from 1,4,7,10-tetraazacyclododecane rings under aqueous acidic conditions.[10] Furthermore under the same conditions the 2-(1,3-dioxolan-2-yl)ethyl group contained in **2b** and **5b** is also removed, probably *via* retro-Michael reaction on the initially deprotected aldehyde. This residue is to be regarded as a promising protecting group[12] for secondary amines, owing to its easy removal under acidic conditions; *e.g.* compound **2b** was dealkylated back to **1** at room temperature in H_2O (pH 1) in 5–10 min.

Derivatives **5** are useful intermediates for the synthesis of substituted 1,4,7,10-tetraazacyclododecane rings bearing side arms of a different nature on the nitrogen atoms. Depending on the choice of the first group introduced by monoalkylation, it is possible to obtain very versatile intermediates with two protecting groups that are removable either at the same time or in two separate steps.

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† Satisfactory C, H, N analyses were obtained for all new compounds. ^1H NMR, ^{13}C NMR and mass spectra are consistent with the reported structures.

References

1 P. V. Bernhardt and G. A. Lawrance, *Coord. Chem. Rev.*, 1990, **104**, 297.
2 M. Magerstädt, O. A. Gansow, M. W. Brechbiel, D. Colcher, L. Baltzer, R. H. Knop, M. E. Girton and M. Naegele, *Magn. Reson. Med.*, 1986, **3**, 808.
3 D. Parker, *Chem. Soc. Rev.*, 1990, **19**, 271; S. V. Deshpande, S. J. DeNardo, D. L. Kukis, M. K. Moi, M. J. McCall, G. L. DeNardo and C. F. Meares, *J. Nucl. Med.*, 1990, **31**, 473.
4 S. Aime, M. Botta, G. Ermondi, F. Fedeli and F. Uggeri, *Inorg. Chem.*, in the press.
5 T. A. Kaden, *Top. Curr. Chem.*, 1984, **121**, 154.
6 J. E. Richman and T. J. Atkins, *J. Am. Chem. Soc.*, 1974, **96**, 2268; T. J. Atkins, J. E. Richman and W. F. Oettle, *Org. Synth.*, 1978, **58**, 86.
7 J. M. Erhardt, E. R. Grover and J. D. Wuest, *J. Am. Chem. Soc.*, 1980, **102**, 6365.
8 T. J. Atkins, *J. Am. Chem. Soc.*, 1980, **102**, 6364; US Pat. 4085106 and 4130715, 1978.
9 G. R. Weisman, D. J. Vachon, V. B. Johnson and D. A. Gronbeck, *J. Chem. Soc., Chem. Commun.*, 1987, 886.
10 M. F. Tweedle, G. T. Gaughan and J. J. Hagan, Eur. Pat. Appl. EP 232751, 1987.
11 A. Bax, *J. Am. Chem. Soc.*, 1980, **102**, 4849.
12 D. C. Lathbury, P. J. Parsons and I. Pinto, *J. Chem. Soc., Chem. Commun.*, 1988, 81.