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The synthesis of chiral annulet 1,4,7-triazacyclononanes

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Abstract—Novel and flexible routes for the synthesis of chiral ring annulet 2,6-disubstituted 1,4,7-trimethyl-1,4,7-triazamacrocycles are described. Efficient macrocyclisations were realised provided that chiral analogues of *N*,*N*-bis-[2-(toluene-sulfonyl-amino)ethyl]-toluene-4-sulfonamide were used as the nucleophilic components. Complexes prepared, in situ, from these 2,6-disubstituted 1,4,7-trimethyl-1,4,7-triazamacrocycles and manganese(II) catalysed the asymmetric epoxidation of styrene with hydrogen peroxide.

The azamacrocycle 1,4,7-triazacyclononane **1a** and its *N*-alkylated analogues e.g. **1b** have rich and diverse chelation chemistries. This is because there is an enormous thermodynamic and kinetic stability of the amine–metal fragment regardless of the oxidation state and d^n configuration of the central metal ion.[1] Thus, the metal complexes that have been observed include Mn(II–V), Fe(II), Fe(III), Ru(II–IV and VI), Co(III), Cu(II) and Zn(II). The ability of the triazacyclononanes **1** to stabilise high oxidation states of metal ions, in particular manganese, has led to the development of such complexes as oxidation catalysts. In this context, the epoxidation of unfunctionalised alkenes using hydrogen peroxide as the terminal oxidant is particularly noteworthy. Overcoming the problems of hydrogen peroxide disproportionation by these manganese complexes has resulted in the development of effective stereospecific epoxidation protocols.[2] Enantioselective epoxidations have also been carried out with managanese complexes bearing chiral analogues of **1b**.[3]

Despite this rich array of chemistry, there are few examples of the synthesis of chiral triazacyclononanes where the stereochemistry is directly on the macrocyclic ring. Indeed, at the outset of our studies only triazacyclononanes with one stereocentre on the macrocyclic ring had been recorded.[4] Recently, triazacyclononanes possessing two (at C-2,3[5] and C-2,6[6]) and three stereogenic centres (C-2,5,8)[3b] on the macrocycle have been reported.

As part of a continuing programme of chiral ligand evolution we wished to develop flexible syntheses of chiral analogues of **1** carrying two stereogenic centres on the annulus. The desire was to place the ring stereocentres close to the metal chelation centres (nitrogen) to maximise the transfer of stereochemical information to any chelated metal. In this letter we describe the effective synthesis of such triazacyclononanes possessing C_2 and C_1 symmetry.

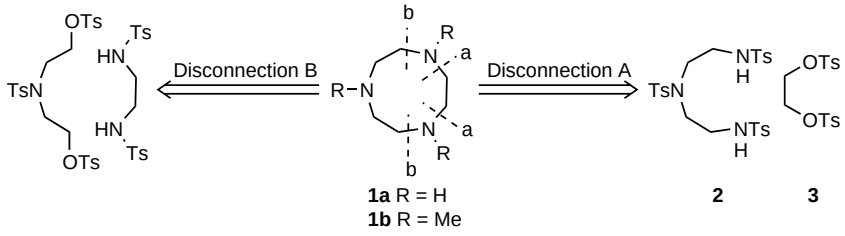

Figure 1. Possible disconnections of macrocycles **1**.

Keywords: asymmetric synthesis; epoxidation; polyamines.

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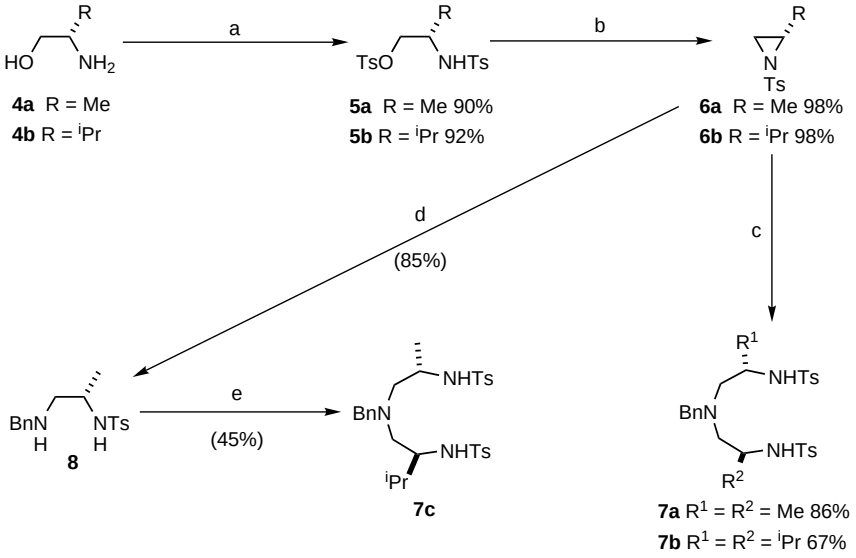
At the outset we were aware that disconnection A (Fig. 1) would be problematic if the analogues of ditosylate **3** used were secondary.[4b,7] Furthermore, using disconnection B (Fig. 1) generally results in low yields in the macrocyclisation step (<30%).[4c,5a] Consequently, our plan was to use disconnection A, but with a chiral analogue of tristosamide **2**.

Our synthesis of chiral triazacyclononanes began with alaninol **4a** and valinol **4b** which were converted into the tosylates **5a** and **5b** and hence the chiral tosyl aziridines **6a**[8] and **6b**.[9] Ring opening[9a,10] of the chiral tosyl aziridines **6a** and **6b** with 0.5 equiv. of benzylamine in methanol afforded the C_2 symmetric bistosamides **7a** and **7b**, respectively. Alternatively, ring opening of chiral tosyl aziridine **6a** with excess benzylamine afforded the amino tosamide **8**. Subsequent, ring opening of aziridine **6b** with amino tosamide **8** gave the C_1 symmetric bistosamide **7c** (Scheme 1).

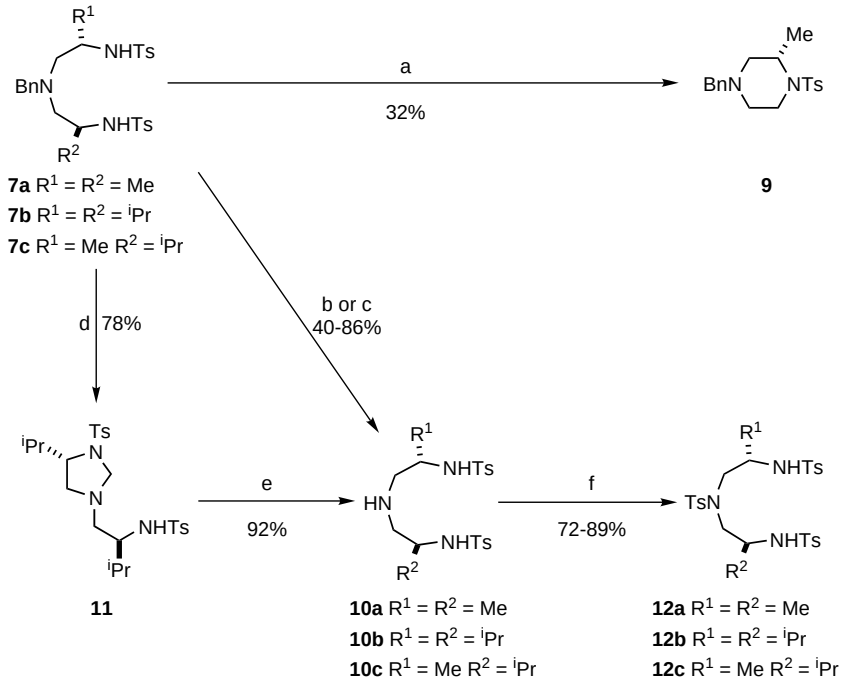
Armed with the bistosamides **7a–c**, the Richman–Atkins cyclisation was attempted.[11] However, under standard Richman–Atkins conditions with bistosamide **7a** and ditosylate **3** no reaction took place, while with more forcing conditions (120°C) the chiral piperazine **9** resulted (Scheme 2). The formation of piperazine **9** is a result of nucleophilic attack of the central benzylic amine on an electrophilic tosylate from ethylene glycol ditosylate **3** followed by expulsion of a C-3 tosamide unit either prior to or during cyclisation. Clearly, the nucleophilicity of the central benzylic amine in **7** needed to be lowered for successful Richman–Atkins cyclisations. Accordingly, hydrogenolytic removal of the benzyl group from **7a** and **7b** was achieved using palladium hydroxide to afford the free amines **10a** and **10b**[9a] in 86 and 71% yields, respectively. On the other hand, debenzylation of **7c** was unsuccessful using palladium hydroxide, probably because of the insolubility of **7c** in methanol. However, debenzylation of **7c** was achieved using palladium on charcoal with acetic acid as the solvent, this afforded the required amine **10c** in 40% yield. Indeed, solubility problems were severe in the large scale (ca. 1 g) palladium hydroxide debenzylation of **7b**. In this case, addition of dichloromethane as a co-solvent resulted in the efficient formation of the novel imidazolidine **11**. Subsequent hydrolysis in refluxing 3N hydrochloric acid afforded the required amine **10b**. The free amines **10a–c** were uneventfully converted into the tristosamides **12a–c** using tosyl chloride in pyridine.

Having removed the nucleophilic amine functionality in **7a–c** by conversion into the tosamides **12a–c**, we were in a position to investigate the Richman–Atkins cyclisations. As such, tosamides **12a–c** smoothly underwent Richman–Atkins cyclisation to afford the novel triazacyclononanes **13a–c** (Scheme 3). Detosylation of the triazacyclononanes **13a–c** was most effectively carried out using lithium in ammonia reduction which provided the free amino triazacyclononanes **14a–c**. In the case of amino triazacyclononane **14a**, the isolated yield was only 13% and was a function of the water solubility. Simply taking the crude aqueous mixture and subjecting it to Eschweiler–Clarke[12] methylation gave the required unique trimethyl triazacyclononane **15a** in 46% over two steps. Water solubility was not a problem in the case of the triazacyclononanes **14b** and **14c**, these could be efficiently isolated after the lithium–ammonia reduction. In these cases subsequent Eschweiler–Clarke *N*-methylation afforded the novel trimethyl triazacyclononanes **15a** and **15b**.

The catalytic activity of the chiral trimethyl triazamacrocycles **15** in the hydrogen peroxide epoxidation of alkenes was investigated using in situ protocols. These procedures utilised 0.16–0.2 mol% of the triazacyclononanes **15** and 0.1–0.13 mol% of manganese(II)



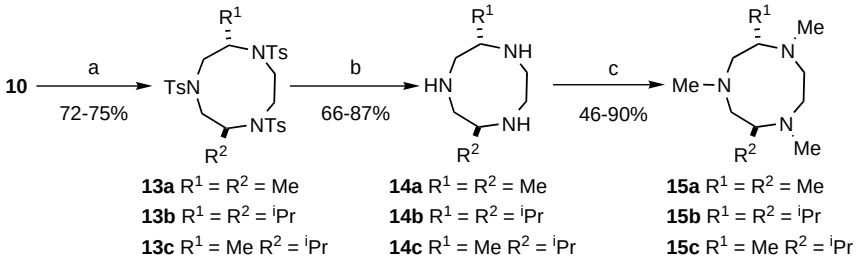
Scheme 1. *Reagents and conditions*: (a) 2 equiv. TsCl, pyr.; (b) NaH, THF; (c) 0.5 equiv. $BnNH_2$, MeOH, rt; (d) **6a**, excess $BnNH_2$, MeOH, rt; (e) **6b**, MeOH; rt.



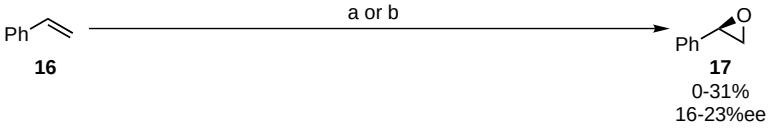
Scheme 2. *Reagents and conditions*: (a) (i) NaH, THF, Δ; (ii) $(CH_2OTs)_2$, DMF, 120°C; (b) $Pd(OH)_2$, H_2, MeOH; (c) Pd–C, H_2, AcOH; (d) $Pd(OH)_2$, H_2, MeOH–CH_2Cl_2; (e) 3N HCl, Δ; (f) TsCl, pyr.

ions with, or without, an ascorbate co-ligand. Using 2,6-dimethyl macrocycle **15a** failed to give any epoxidation while the use of the diispropyl macrocycle **15b** afforded (*R*)-styrene epoxide **17** in 31% yield and 16% ee. In the case of macrocycle **15c**, (*R*)-styrene epoxide **17** was obtained in 15% yield and 23% ee (Scheme 4).

In summary, we have developed novel and flexible routes for the synthesis of C_2 and C_1 symmetric 1,4,7-trimethyl-1,4,7-triazamacrocycles **15a**–**c** where the stereochemical information resides directly on the macrocyclic ring. The key development for effective and efficient Richman–Atkins cyclisations involved the use of the tristosamides **12a**–**c** as the nucleophilic components in the cyclisation. Failure to use tristosamides **12a**–**c** led to no macrocyclisation or to low yields. The tristosamides **12a**–**c** were readily prepared by the ring opening of chiral tosyl aziridines **6a** and **6b** with benzylamine followed by appropriate functional group interchanges. The azamacrocyles **15a**–**c** were used as ligands in the enantioselective epoxidation of styrene **16**, which yielded (*R*)-styrene oxide **17** in up to 23% ee.



Scheme 3. *Reagents and conditions*: (a) (i) NaH, THF, Δ; (ii) $(CH_2OTs)_2$, DMF, 80°C; (b) Li–NH_3, EtOH; (c) HCO_2H, formaldehyde, Δ.



Scheme 4. *Reagents and conditions*: (a) 0.16 mol% of **15a** or **15b**, 0.1 mol% of aq. $Mn(OAc)_2$, 0.21 mol% of aq. sodium ascorbate, 0.05 mol% of aq. ascorbic acid, 2 equiv. H_2O_2, CH_3CN, CH_3COCH_3; (b) 0.2 mol% of **15c**, 0.13 mol% of aq. $MnSO_4$, 2 equiv. H_2O_2, CH_3CN, CH_3COCH_3.

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