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Synthesis of an Unnatural Product -- 4,4' Biaryl Formation as a Macrocyclisation Step

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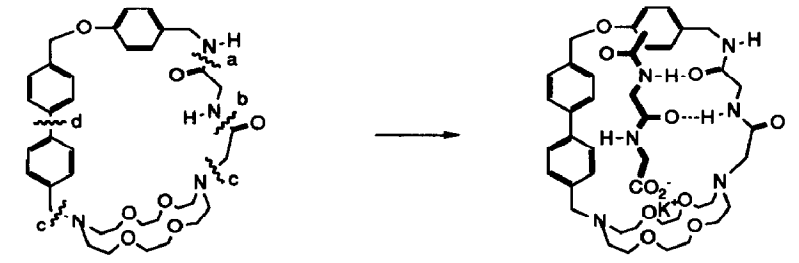
Abstract - A novel macrocycle featuring a crown ether ring, amide functionality and a rigid biaryl unit has been prepared as a potential receptor for small peptidic guests. The synthesis of the macrocyle includes a palladium catalysed biaryl formation as the ring-closing step.

Molecular recognition is of fundamental importance in biological processes, and host-guest chemistry has become a popular area of research for those who wish to examine the nature of these intermolecular interactions. This has led to the development of novel synthetic receptors for a number of biological substrates including nucleotides,[1] carbohydrates,[2] amino acids and derivatives.[3] However, it is not yet possible to design specific hosts for small peptides which can selectively distinguish between various amino acid sequences. We have begun work on an approach to this problem by constructing host molecules, such as **1**, featuring a cavity with a binding site for the terminus (either ammonium or carboxylate[4]) of a peptidic guest, and amide functionality to provide hydrogen bonding with the backbone of the guest, as represented schematically in Figure 1.[5]



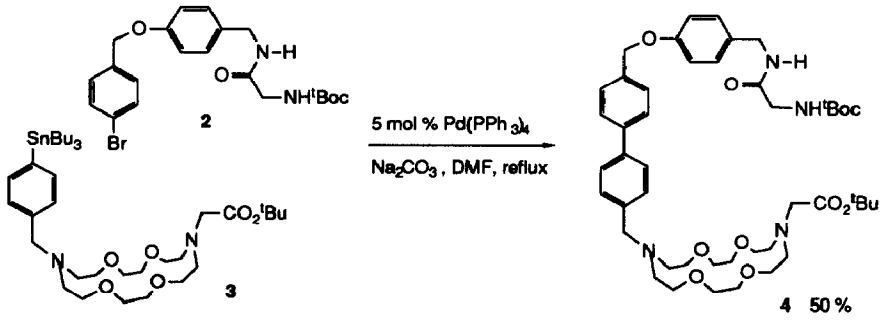
Macrocycle **1** and synthetic disconnections

Possible binding interactions for macrocycle **1** and a dipeptide

Figure 1

Ultimately, considerably more sophisticated receptors will be required for selective binding, but we first set out to develop a convenient synthetic route to the basic macrocyclic structure. In this paper we describe the successful synthesis of macrocycle **1**, which includes a palladium catalysed biaryl formation as the ring-closing step.[6]

In our initial attempts to prepare **1** we have tried to form either of the two amide bonds as the ring closing step (disconnection a or b, fig 1), or to condense 1,10 diaza 18-crown-6 with a bischloride (disconnection c, fig 1). We have had no success using either of these approaches and conclude that the rigid biaryl unit may make ring closure particularly difficult. In the course of our early work we also found that the biaryl unit could be synthesised at a late stage by a palladium catalysed coupling of an aryl bromide and an aryl stannane,[7] and this methodology was perfectly compatible with aza crown and amide functionality. Thus, for example, the coupling of bromide **2** with stannane **3** gave the biaryl derivative **4** in 50% yield.

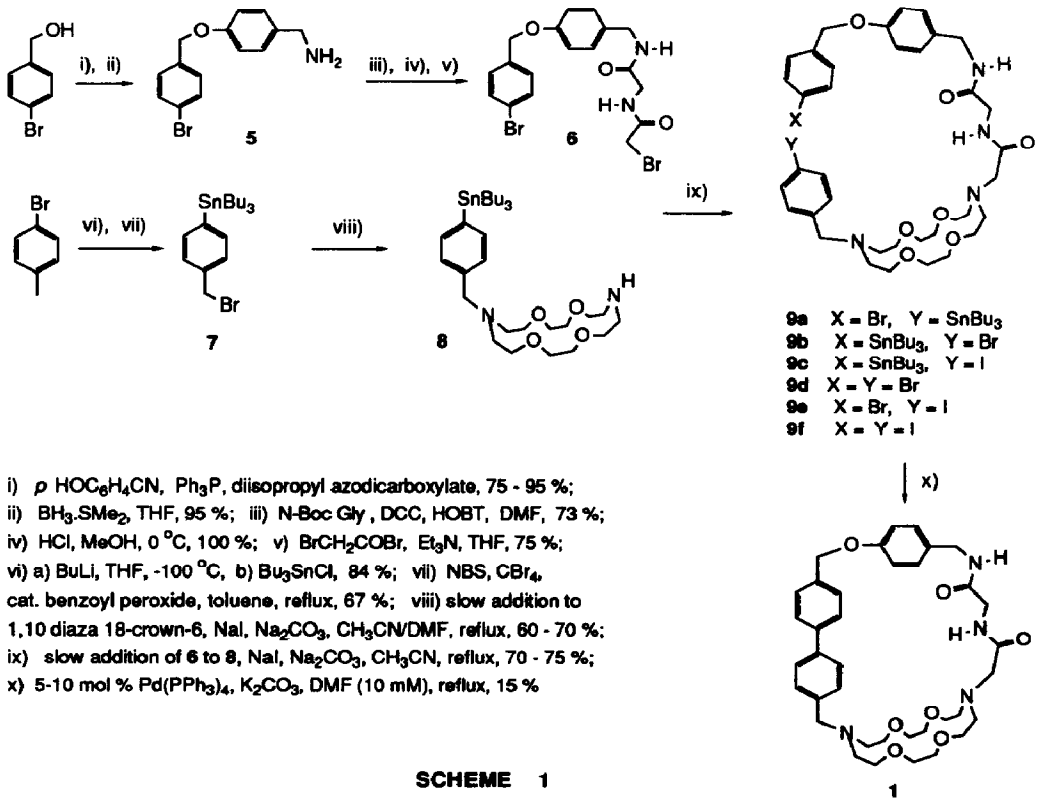


We have therefore investigated the possibility of using an intramolecular biaryl coupling of relatively flexible precursors such as **9a** to form the macrocyclic product (disconnection d, fig 1).

Synthesis of **9a** is shown in Scheme 1. The bromide **6** was prepared by coupling of 4-cyanophenol to 4-bromobenzyl alcohol using Mitsunobu conditions,[8] reduction of the nitrile to give amine **5**, coupling with N-Boc glycine, removal of the Boc protecting group, and finally reaction with bromo acetylbromide. The bromide **7** was prepared in two steps from 4-bromotoluene, using a modification of a literature route to the corresponding bromomethylaryl silane,[9] by transmetallation of the bromide and quenching with Bu_3SnCl, followed by bromination of the methyl group. Sequential alkylation of 1,10 diaza 18-crown-6[10] with first, bromide **7**, and then with **6**, yielded the cyclisation precursor **9a**. Both steps went in reasonable yield when the alkylating agent was added, *via* a syringe pump, to a refluxing solution of the diaza crown in acetonitrile, and in the presence of NaI and Na_2CO_3. Purification of the diaza crown derivatives was achieved using column chromatography on silica gel with a NH_4OH/MeOH /CH_2Cl_2 mixture as eluent.

For the key cyclisation step, best results were obtained using $Pd(PPh_3)_4$ and K_2CO_3 (or Na_2CO_3) in refluxing DMF, yielding the cyclised product **1** in 15 % yield.[11] Using routes similar to that for the synthesis of **9a**, we have also prepared the bromostannane **9b**, the iodostannane **9c**, the dibromide **9d**, bromoiodide **9e**,

and the diiodide **9f**. Attempts to cyclise **9b** or **9c**, under identical conditions for the cyclisation of **9a**, also gave macrocycle **1**, but never in yields exceeding 10 %. Cyclisation of **9d**, **9e** or **9f** using Ullmann conditions[6b] (CuI or CuBr, Zn dust, anisole, reflux) or $(Me_3Sn)_2$ or $(Bu_3Sn)_2$ with $Pd(OAc)_2$/20 mol % Ph_3P, as devised by Grigg,[12] only ever gave macrocycle **1**, in < 5 % yield.



SCHEME 1

We recently reported on the use of negative ion FAB mass spectrometry to demonstrate binding of the mono potassium salts of various dicarboxylic acids with a receptor related to **1**.[13] Using the same technique we have found that in the absence of any guest, no signal corresponding to macrocycle **1** is observed in the negative ion FAB MS. However, in the presence of the potassium carboxylate salts of N-acetyl glycine or N-acetyl β-alanine, peaks corresponding to macrocycle **1**, M^-, are observed. In addition, in the case of the potassium carboxylate salt of N-acetyl β-alanine, peaks corresponding to (macrocycle + carboxylate anion + K^+)$^-$ and to (macrocycle + carboxylate anion)$^-$ are observed. Under identical conditions, in the presence of the potassium carboxylate salts of N-^{t}Boc glycine and N-^{t}Boc β-alanine, no peaks corresponding to the macrocycle, or complexes of it, could be detected. Taken together this suggests that the N-acetyl substrates are bound within the macrocycle while the bulkier N-^{t}Boc substrates are not. Further studies on the binding properties of **1** are

now underway and will be reported in full in due course.

Acknowledgements

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4. a) For a review of crown ether binding see R. M. Izatt, K. Pawlak, J. S. Bradshaw and R. L. Bruening, *Chem. Rev.*, 1991, **91**, 1721. b) For crown ether binding of potassium carboxylates, see Flack, S. S.; Chaumette, J.-L.; Kilburn, J. D.; Langley, G. J.; Webster, M. *J. Chem. Soc., Chem. Commun.*, **1993**, 399 and ref 3e.

5. The binding interactions depicted in Fig 1 are only schematic, but we have carried out extensive molecular modelling of macrocycle 1 and related molecules. A number of trial conformations were generated using the Distance Geometry Program DGEOM (© 1990 E I Dupont de Nemours and Co) and energy minimised using CHARMm (ver 2.1) distributed by Molecular Simulations Inc. The low energy conformations so generated all possessed well-defined cavities suitable for the proposed mode of binding.

6. For a review of intramolecular biaryl formation see a) Bringmann, G.; Walter, R.; Weirich, R. *Angew. Chem., Int. Ed. Engl.*, **1990**, *29*, 977; b) Sainsbury, M. *Tetrahedron*, **1980**, *36*, 3327. While biaryl formation as a ring forming step is well documented in the literature, typically using Ullmann conditions or a free radical pathway, these are generally for constrained systems, or for the formation of small to medium rings with a 2, 2' biaryl unit being produced. As far as we are aware, macrocyclisation to produce a 4,4' biaryl unit has not been previously reported.

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10. 1,10 Diaza 18-crown-6 was prepared according to the method of Gatto, V. J.; Miller, S. R.; Gokel, G. W. *Org. Synth.*, 1990, **68**, 227.

11. Data for 1: δH (270 MHz, $CDCl_3$), 8.47 (1 H, t, J = 6 Hz, NH), 7.59 (2 H, d, J = 8 Hz, ArH), 7.48 (2 H, d, J = 8 Hz, ArH), 7.45 (1 H, partly obscured, NH) 7.42 (2 H, d, J = 8 Hz, ArH), 7.21 (2 H, d, J = 8 Hz, ArH), 7.18 (2 H, d, J = 8 Hz, ArH), 6.91 (2 H, d, J = 8 Hz, ArH), 5.08 (2 H, s, $ArCH_2OAr$), 4.35 (2 H, d, J = 5 Hz, $ArCH_2NH$), 4.00 (2 H, d, J = 7 Hz, $NHCH_2CO$), 3.57 (2 H, s, $ArCH_2N(CH_2CH_2O)_2$), 3.62- 3.41(16 H, m, $CH_2OCH_2CH_2OCH_2$), 3.21 (2 H, s, $(OCH_2CH_2)_2NCH_2CO$), 2.73 (4 H, t, J = 5 Hz, $N(CH_2CH_2O)_2$), 2.66 (4 H, t, J = 5 Hz, $N(CH_2CH_2O)_2$); m / z (FAB), 683 ($(M + Na)^+$, 18%), 661 ($(M + H)^+$, 25%), 307 (15), 180 (20), 154 (100).

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