COMMUNICATION

ChemComm
www.rsc.org/chemcomm

Assembly of polyamines *via* amino acids from three components using cobalt(III) template methodology

Gilles Laval,[a] William Clegg,[a] Christopher G. Crane,[b] Anders Hammershøi,[c] Alan M. Sargeson[b] and Bernard T. Golding*[a]

[a] *Department of Chemistry, Bedson Building, University of Newcastle upon Tyne, Newcastle upon Tyne, UK NE1 7RU. E-mail: b.t.golding@ncl.ac.uk; Fax: +44(0) 191-222-6929; Tel: +44(0) 191-222-6647*

[b] *Research School of Chemistry, Australian National University, Canberra ACT. 0200, Australia. E-mail: sargeson@rsc.anu.edu.au; Fax: (+612) 61253216; Tel: (+61) 6125-3160*

[c] *Department of Chemistry, University of Copenhagen, Universitetsparken 5, DK-2100 Copenhagen, Denmark. E-mail: anders@kiku.dk; Fax: (+45) 3532-0133; Tel: (+45) 3532-0110*

Received (in Cambridge, UK) 3rd July 2002, Accepted 19th July 2002
First published as an Advance Article on the web 2nd August 2002

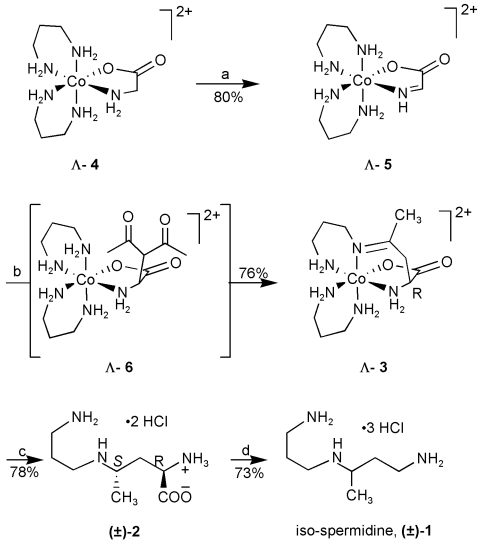
A versatile and efficient template synthesis has been developed to synthesise novel polyamines [*e.g. rac*-N^3-(3-aminopropyl)butane-1,3-diamine, isospermidine 1] *via* amino acids [*e.g.* (2*R*,4*S*/2*S*,4*R*)-N^4-(3-aminopropyl)-2,4-diaminopentanoic acid] using cobalt(III) to assemble the three precursor components in a biomimetic manner.

Spermidine [*N*-(3-aminopropyl)butane-1,4-diamine] and other polyamines are cationic species with a remarkable range of biological activities[1] and potential medical applications.[2,3] A common synthetic approach to polyamines condenses suitably protected fragments, *e.g.* putrescine [butane-1,4-diamine] monoprotected on one nitrogen function, with an *N*-protected 3-aminopropanal.[4] *N*-Protection in polyamine synthesis has generally been achieved using classical methodology, whereby nitrogen functions are blocked with *e.g.* benzyl[5] or benzyloxycarbonyl[6] or trifluoroacetyl groups.[6a]

We have found that a cobalt(III) reagent can be used as a template to assemble three components in a manner analogous to one route of biosynthesis of spermidine[7,8] leading to novel amino acids and polyamines. For example, propane-1,3-diamine, acetylacetone and glycine can be combined to yield (2*R*,4*S*/2*S*,4*R*)-N^4-(3-aminopropyl)-2,4-diaminopentanoic acid ('carboxyisospermidine' **2**), which can be decarboxylated to the triamine N^3-(3-amino-propyl)-butane-1,3-diamine ('isospermidine' **1**). The Schiff base tetradentate cobalt(III) complex **3** constitutes the key intermediate in the synthesis of **2** and **1** (Scheme 1). From the viewpoint of synthetic strategy the cobalt ion serves to mask simultaneously specific nitrogen functions and to provide controlled activation of certain functional groups.

The racemic bis(propane-1,3-diamine)glycinatocobalt(III) complex **4**[9] was readily oxidised[10] (PBr_3, *N*-bromosuccinimide) to the corresponding glycine-imine complex **5**. The bis(ethane-1,2-diamine) analogue of the cobalt-stabilised imine **5** is known to react at the electrophilic imine carbon with acetylacetone in methanol containing sodium carbonate leading to diastereoisomeric 1:1 adducts.[10] With acetylacetone in aqueous alkaline conditions complex **5** gave the stable Schiff base tetradentate complex **3**, as a single racemic diastereoisomer (Λ,*R*/Δ,*S*). The structure of this complex† was validated by X-ray crystallographic analysis (Fig. 1).

The mechanism of formation of complex **3** involves a nucleophilic addition of the monoanion of acetylacetone to the *Re* face of the activated imine C-atom in complex **5** to give a 1:1 adduct **6**, as shown in Scheme 1. Addition of acetylacetone monoanion to the *Si* face of **5** may be impeded by the adjacent propane-1,3-diamine ligand. Hydroxide-induced intramolecular condensation[11] of one of the acetyl functions of **6** with the nearest apical amino group gives an intermediate imine that loses the other acetyl group (NB alternatively, initial loss of one acetyl followed by intramolecular condensation may occur). One-pot reduction of the imine function and the metal centre,[12]



Scheme 1 *Reagents and conditions*: (a) i. CF_3SO_3H, N_2, rt; ii. NBS, PBr_3, dry DMF, 60 °C; iii. LiBr, 60 °C; (b) $CH_3COCH_2COCH_3$, water, pH 12; (c) i. $NaBH_4$, water, pH 9, rt; ii. pH 5, rt; (d) i. NBS, buffer pH 5, rt; ii. $NiCl_2.6H_2O$, $NaBH_4$, rt. (only the Λ-enantiomer of complexes **3**, **4**, **5** and **6** are shown).

leading from complex **3** to amino acid **2**, was achieved by treatment of the imino complex **3** with sodium borohydride at pH 9 followed by acidification to pH 5. The relative stereochemistry of amino acid **2** was determined as (2*R*,4*S*/2*S*,4*R*) by crystallographic analysis.[13] The reduction of the imine is irreversible and the stereochemical course from **3** to **2** should therefore be determined by the relative energies of the transition state for approach of borohydride to the *Re* and *Si* faces of the imine **3**. Approach to the *Si* face may be more hindered by

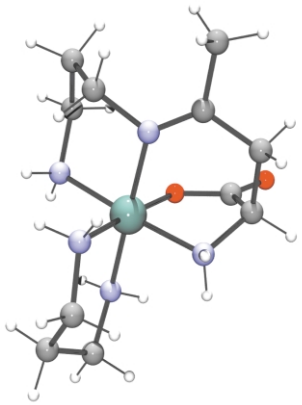
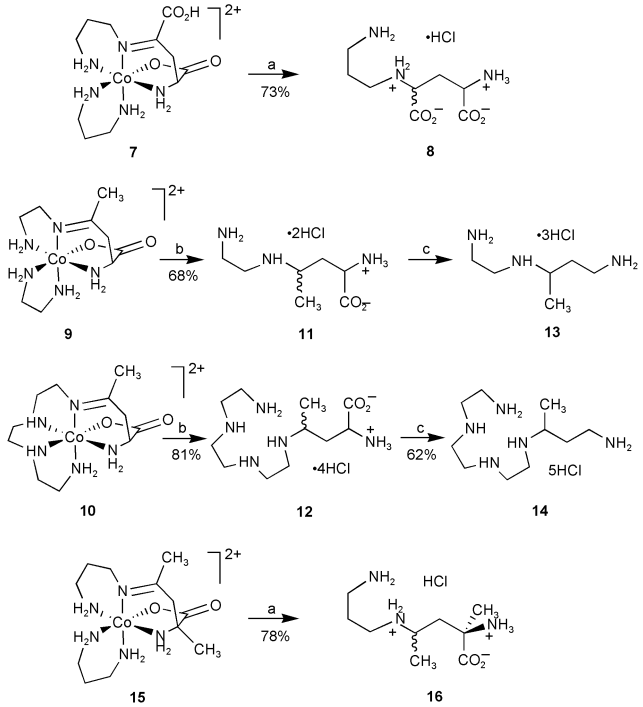


Fig. 1 The dication of complex (Λ,*R*)-**3**, one enantiomer of a pair.

DOI: 10.1039/b206462f

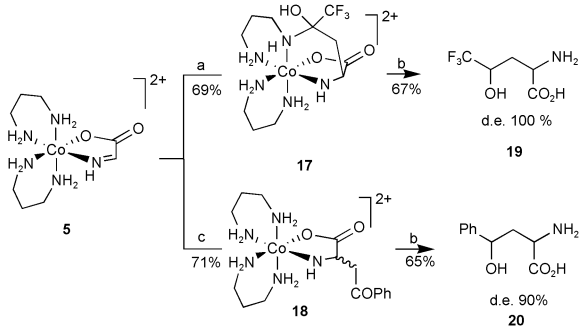
neighbouring H atoms (*e.g.* on the neighbouring methylene group). One-pot decarboxylation *via* the successive treatment of amino acid **2** with *N*-bromosuccinimide[14] and sodium borohydride–nickel dichloride[15] gave the targeted polyamine, isospermidine trihydrochloride **1**.

The versatility of the methodology described has been explored by varying each of the three components. By reacting the glycine-imine complex **5** with methyl pyruvate, an analogous reaction course to that described for acetylacetone was observed leading to the corresponding tetradentate-imine complex **7** (73%, isolated as a carboxylic acid). Reduction of this complex with borohydride gave the novel amino acid *N*-(3-aminopropyl)-2,4-diaminopentanedioic acid **8** (Scheme 2). When 1,2-ethylenediamine and bis(2-aminoethyl)-1,2-diaminoethane were assembled in the manner described above with glycine and acetylacetone, tetradentate-imine complex **9** and hexadentate-imine complex **10** were formed, respectively. Reduction of these complexes with borohydride followed by zinc in acidic aqueous solution afforded the novel amino acids **11** and **12**. Decarboxylation of amino acids **11** and **12** yielded the corresponding polyamines **13** and **14**. Assembling alanine with 1,3-diaminopropane and acetylacetone on the cobalt(III) template furnished tetradentate-imine complex **15**. Reduction of the latter with borohydride afforded N^4-(3-aminopropyl)-2,4-diamino-2-methyl-pentanoic acid **16**.



Scheme 2 *Reagents and conditions*: (a) i. $NaBH_4$, water, pH 9, rt; ii. pH 5, rt; (b) i. $NaBH_4$, water, pH 9, rt; ii. pH 5, rt; iii. zinc dust; (c) i. NBS, buffer pH 5, rt; ii. $NiCl_2{\cdot}6H_2O$, $NaBH_4$, rt (NB all compounds are racemates; the relative stereochemistry of **8**, **11**, **12** and **16** was not yet determined).

With hexafluoroacetylacetone and complex **5**, the intramolecular condensation proceeded only as far as the trifluoromethyl-substituted aminol **17** (Scheme 3), which was isolated in 69% yield. With acetophenone and complex **5**, the condensation stopped at complex **18**, *i.e.* the intramolecular condensation did not occur at all. Reduction of **17** with borohydride gave 2-(3,3,3-trifluoro-2-hydroxypropyl)glycine **19**, whilst reduction of **18** gave 2-(2-hydroxy-2-phenylethyl)-glycine **20**. Full details and other examples of this new route to



Scheme 3 *Reagents and conditions*: (a) $(F_3CCO)_2CH_2$, water, pH 11; (b) $NaBH_4$, water, pH 9 to 1; (c) PhCOMe, water, pH 11 (NB all compounds are racemates; the relative stereochemistry of **17**–**20** has not yet been determined).

2-hydroxyalkyl-substituted glycines will be reported elsewhere.

In conclusion, using the cobalt template syntheses detailed above, novel amino acids and polyamine derivatives have been obtained in a few steps, starting from readily available cobalt complexes. Application of the methodology described to the synthesis of single enantiomers of amino acids and polyamines is under investigation.

This work was supported by grants from the EPSRC and ANU.

Notes and references

† *Crystal data* for **3**: $[Co(C_{11}H_{26}N_5O_2)]Cl_2.H_2O$, M = 408.2, orthorhombic, space group *Pbca*, a = 8.3623(4), b = 13.7158(7), c = 30.2033(15) Å, U = 3464.2(3) Å^3, Z = 8, D_c = 1.565 g cm^{-3}, μ = 1.32 mm^{-1} (Mo-Kα radiation, λ = 0.71073 Å), T = 160 K, $R(F^2 > 2\sigma F)$ = 0.039, $R_w(F^2$, all data) = 0.090, with 4172 unique reflections and 207 refined parameters. CCDC reference number 168722. See http://www.rsc.org/suppdata/cc/b2/b206462f/ for crystallographic data in CIF or other electronic format.

1 T. Thomas and T. J. Thomas, *Cell. Mol. Life Sci.*, 2001, **58**, 244.
2 B. L. Varnado, C. J. Voci, L. M. Meyer and J. K. Coward, *Bioorg. Chem.*, 2000, **28**, 395.
3 S. A. Gamage, J. A. Spicer, G. J. Finlay, A. J. Stewart, P. Charlton, B. C. Baguley and W. A. Denny, *J. Med. Chem.*, 2001, **44**, 1407.
4 See *e.g.*: J. Boukouvalas, B. T. Golding, R. W. McCabe and P. K. Slaich, *Angew. Chem.*, 1983, **93**, 646–647; *Angew. Chem., Int. Ed. Engl.*, 1983, **22**, 618.
5 R. J. Bergeron, K. A. McGovern, M. A. Channing and P. S. Burton, *J. Org. Chem.*, 1980, **45**, 1589.
6 (*a*) B. T. Golding, A. Mitchinson, W. Clegg, M. R. J. Elsegood and R. J. Griffin, *J. Chem. Soc., Perkin Trans. 1*, 1999, 349; (*b*) S. C. Yorke, J. W. Blunt, M. H. Munro, J. C. Cook and K. L. Rinehart, *Aust. J. Chem.*, 1986, **39**, 447.
7 D. M. L. Morgan, *Mol. Biotech.*, 1999, **11**, 229 and references therein.
8 G. H. Tait, *Biochem. Soc. Trans.*, 1985, **13**, 316 (we thank Dr T. A. Smith for bringing this work to our attention).
9 Complex **4** was prepared from $[Co(tn)_2Cl_2]Cl$ (D. R. Stranks, S. F. Lincoln and I. R. Jonesson, *Aust. J. Chem.*, 1970, **23**, 2267 following a procedure adapted from: Y. Kojima, *Bull. Chem. Soc. Jpn.*, 1975, **48**, 2033.
10 L. Bendahl, A. Hammershøi, D. K. Jensen, E. Kaifer, A. M. Sargeson and A. C. Willis, *Chem. Commun.*, 1996, 1649.
11 L. M. Engelhardt, A. R. Gainsford, G. J. Gainsford, B. T. Golding, J. MacB. Harrowfield, A. J. Herlt, A. M. Sargeson and A. H. White, *Inorg. Chem.*, 1988, **27**, 4551.
12 K. J. Drok, J. MacB. Harrowfield, S. J. McNiven, A. M. Sargeson, B. W. Skelton and A. H. White, *Aust. J. Chem.*, 1993, **46**, 1557.
13 G. Laval, W. Clegg and B. T. Golding, unpublished work.
14 G. Gopalakrishnan and J. L. Hogg, *J. Org. Chem.*, 1985, **50**, 1206.
15 T. Satoh and S. Suzuki, *Tetrahedron Lett.*, 1969, **52**, 4555.