Pergamon

Tetrahedron Letters, Vol. 35, No. 50, pp. 9455-9458, 1994
Elsevier Science Ltd
Printed in Great Britain
0040-4039/94 $7.00+0.00

0040-4039(94)02046-9

A Novel Macrobicyclic Cryptand Incorporating 3 Endocyclic Hydroxamate Donor Groups

Surinder Singh Chana and Robert Charles Hider*

Department of Pharmacy, King's College London, Manresa Road, London SW3 6LX

Abstract The synthesis of a novel macrobicyclic cryptand and it's formation of a 1:1 complex with both iron(III) and indium(III) is described.

Considerable effort has been devoted to the design of novel chelators for the selective complexation of Fe^{3+}, Ga^{3+}, In^{3+} and Gd^{3+} because of their potential application in the treatment of iron overload disease[1] as NMR contrast agents[2] and for the radioimaging of organs and tumours[3]. Unfortunately, the natural and synthetic siderophore analogs, most of which contain catecholates or hydroxamate donor groups, are not ideal for therapeutic use. Desferrioxamine B for example, lacks oral activity and possesses a short biological half-life. As a consequence there has been a concerted effort to synthesise new classes of chelator molecules for clinical application.

One recent trend has been to synthesise macrobicyclic siderophore analogs incorporating 3 endocyclic catecholate[4] or 2,2 -dihydroxybiphenyl[5] groups for the effective chelation of tribasic cations. The cations are effectively trapped within a cage. Martell *et al* [6] have reported the synthesis of a novel macrobicyclic hydroxamate cryptand which forms a 1:1 stable complex with Fe^{3+}. These workers considered the use of trialkiyamine intermediates, but decided to avoid the use of chains containing more than three carbon atoms because of synthetic difficulties. In this work we describe a synthetic route which overcomes this difficulty by avoiding the involvement of a tripodal intermediate at the capping stage. This new strategy is more versatile than that reported by Martell and co-workers and can be used to functionalise (with for instance, sidearms suitable for protein conjugation) the macrobicyclic ligands. The molecule described in this report possesses 10 methylene units per arm (see Scheme 1).

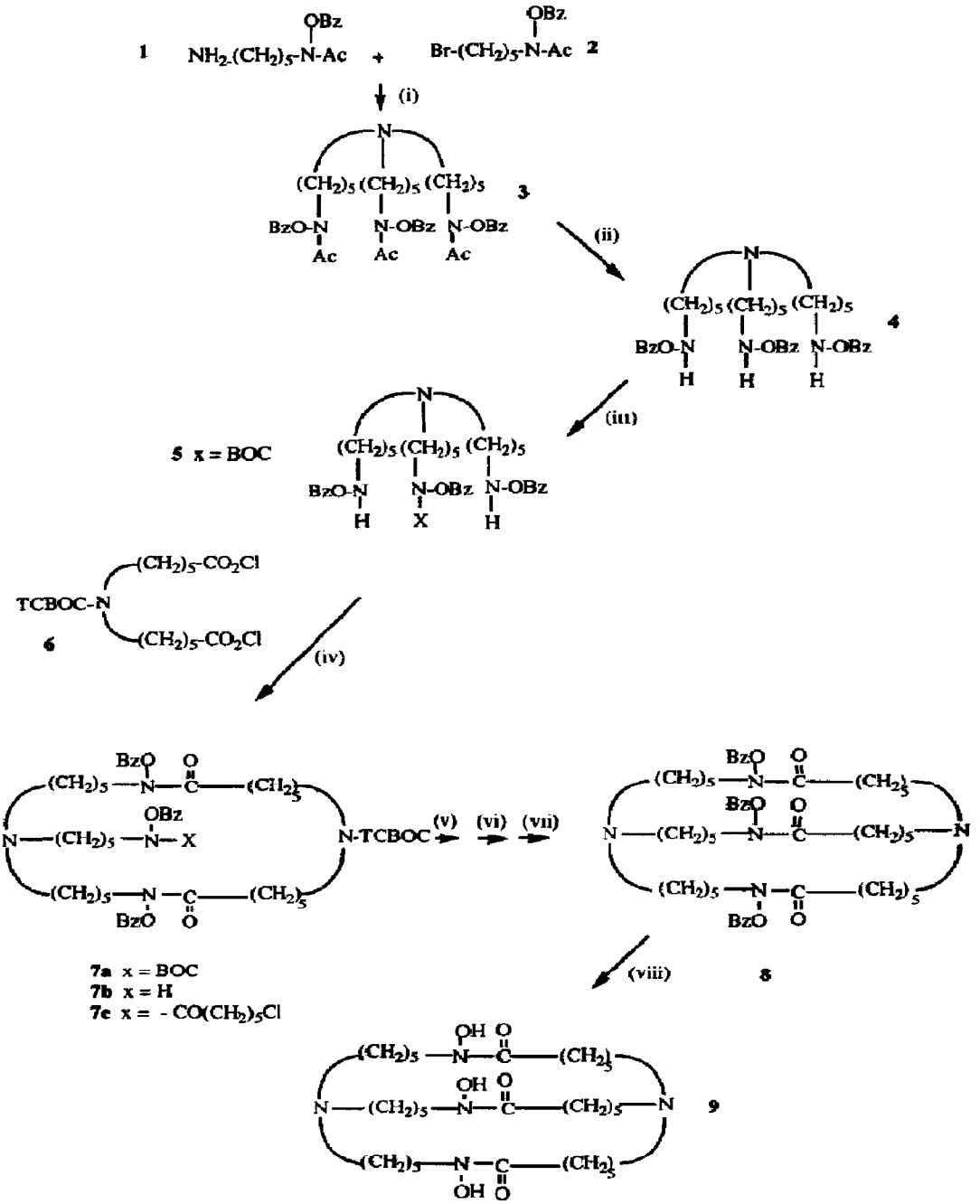
Alkylation of **1** with 2 equiv of **2** in acetonitrile (Dry/reflux/24 h/N_2), afforded the triacetate **3** in 65% yield. ^{1}H NMR ($CDCl_3$) 1.1-1.9 (18H, b, N $CH_2(\underline{CH_2})_3CH_2$N-OBz), 2.1 (9H, s, NCO$\underline{CH_3}$), 2.4-2.8 (6H, t, N$\underline{CH_2}(CH_2)_4$N-OBz), 3.5-3.8 (6H, t, N$(CH_2)_4\underline{CH_2}$N-OBz), 4.8 (6H, s, $C_6H_5\underline{CH_2}$), and 7.35 (15H, s, arom). MS (FAB) $(M+H)^+ = 717$. Deacetylation of **3** was achieved with barium hydroxide in methanol, afforded the triamine **4** in 70% yield. ^{1}H NMR ($CDCl_3$) 1.1-1.9 (18H, b, $NCH_2(\underline{CH_2})_3CH_2$N-OBz), 2.4-3.1 (12H, 2xt, N$\underline{CH_2}(CH_2)_3C\underline{H_2}$N-OBz), 4.7 (6H, s, $C_6H_5\underline{CH_2}$), 5.4-5.8 (3H, b, NH), and 7.35 (15H, s, arom). MS (FAB) $(M+H)^+ = 591$. Selective protection of **4** gave **5** in 32% yield, using di-tert-butyl dicarbonate in acetonitrile. ^{1}H NMR ($CDCl_3$) 1.1-1.9 (27H, m+s, $NCH_2(\underline{CH_2})_3CH_2$N-$\underline{BOC}$), 2.1-2.6 (6H, b, N$\underline{CH_2}(CH_2)_4$N-BOC), 2.7-3.1 (4H, b, N$(CH_2)_4\underline{CH_2}$NH), 3.1-3.6 (2H, t, N$(CH_2)_4\underline{CH_2}$N-BOC), 4.6 (4H, s, $C_6H_5\underline{CH_2}$), 4.7 (2H, s, $C_6H_5\underline{CH_2}$), 5.3-5.5 (2H, b, N$\underline{H}$), and 7.3-7.5 (15H, m, arom). MS (FAB) $(M-2H)^+ = 688$. Condensation of **5** with the diacid chloride **6**[7] under high dilution conditions in benzene gave the macrocycle **7a** in 50% yield. ^{1}H NMR ($CDCl_3$) 1.1-2.0 (45H, b+2xs, $NCH_2(\underline{CH_2})_3CH_2NCOCH\underline{CH_2})_3CH_2$N-$\underline{TCBOC}$, and $NCH_2(\underline{CH_2})_3CH_2$N-$\underline{BOC}$), 2.1-2.7 (6H, m, $N(CH_2)_5NCO\underline{CH_2}(CH_2)_4$N-TCBOC), 2.7-3.0 (6H, b, N-$\underline{CH_2}(CH_2)_4$N-OBz), 3.05-3.5 (4H, b, $NCO(CH_2)_4C\underline{H_2}$N-TCBOC), 3.5-3.8 (6H, t, N$(CH_2)_4C\underline{H_2}$N-OBz), 4.75

(6H, s, $C_6H_5C\underline{H}_2$), and 7.35 (15H, s, arom). MS (FAB) $(M)^+$ = 1103. Removal of the BOC group in trifluoroacetic acid gave **7b** in 95% yield. ^1H NMR ($CDCl_3$) 1.1-2.1 (36H, b+s, $NCH_2(\underline{CH}_2)_3CH_2NCOCH_2(\underline{CH}_2)_3CH_2N$-TCBOC), 2.1-2.6 (10H, b, $N\underline{CH}_2(CH_2)_4NCOC\underline{H}_2(CH_2)_4N$-TCBOC), 2.7-3.5 (6H, b, $N(CH_2)_5NCO(CH_2)_4C\underline{H}_2N$-TCBOC, and $N(CH_2)_4C\underline{H}_2N$-H) 3.5-3.8 (4H, t, $N(CH_2)_4C\underline{H}_2N$-OBz, 4.75 (2H, s, $C_6H_5C\underline{H}_2$), 4.85 (4H, s, $C_6H_5C\underline{H}_2$), 5.9-6.0 (1H, b, NH), and 7.3-7.5 (15H, m, arom). MS (FAB) $(M)^+$ = 1003. Acylation of the macrocycle **7b** with 6-chlorohexanoxyl chloride in benzene gave **7c** in 93% yield. ^1H NMR ($CDCl_3$) 1.1-2.0 (42H, m+s, $NCH_2(\underline{CH}_2)_3CH_2NCOCH_2(\underline{CH}_2)_3CH_2N$-TCBOC, and $NCOCH_2(\underline{CH}_2)_3CH_2Cl$), 2.7-3.0 (6H, b, $N\underline{CH}_2(CH_2)_4N$-OBz, 3.05-3.2 (4H, b, $NCO(CH_2)_4C\underline{H}_2N$-TCBOC), 3.5-3.8 (8H, t+b, $N(CH_2)_4C\underline{H}_2NCO(CH_2)_4C\underline{H}_2Cl$), 4.75-4.85 (6H, 2xs, $C_6H_5C\underline{H}_2$), and 7.3-7.5 (15H, m, arom). MS (FAB) $(M)^+$ = 1135. Deprotection of **7c** was accomplished with zinc powder in acetic acid (without isolation of the product). Self-condensation of the deprotected amine under high dilution conditions in acetonitrile gave the macrobicyclic cryptand **8** in 40% yield. ^1H NMR ($CDCl_3$) 1.2-2.0 (36H, m, $NCH_2(\underline{CH}_2)_3CH_2NCOCH_2(\underline{CH}_2)_3CH_2N$), 2.2-3.3 (18H, m, $NC\underline{H}_2(CH_2)_3CH_2NCO$-$C\underline{H}_2(CH_2)_3C\underline{H}_2N$), 3.6-3.8 (6H ,bs, $N(CH_2)_4C\underline{H}_2N$-OBz), 4.8 (6H, s, $C_6H_5C\underline{H}_2$), and 7.35 (15H, s, arom). MS (FAB) $(M+H)^+$ = 896. A number of hydrogenations using several Palladium catalysts were carried out in an attempt to remove the 3 benzyl protecting groups (Pd black/H_2/HCO_2H/MeOH), (10% Pd/C/EtOH/H_2), (10% Pd/C/MeOH/H_2/pH 2), and ($Pd(OH)_2$/H_2/EtOH), but all proved unsuccessful. Finally debenzylation of **8** was achieved in 2 steps, first reacting **8** with dimethylboronbromide[9] in dichloromethane (Dry/Ar), then subjecting the partially debenzylated product to exhaustive hydrogenolysis to give the cryptand (7,20,32-trihydroxy-1,7,14,20,32-pentaazabicyclo [12.12.12] octatriacontane- 8,21,3-trione **9**, in 70% yield. ^1H NMR (CD_3OD) 1.2-2.1 (36H, b, $NCH_2(\underline{CH}_2)_3CH_2NCOCH_2(\underline{CH}_2)_3CH_2N$), 2.45-2.6 (6H, b, $N(CH_2)_5NCOC\underline{H}_2(CH_2)_4N$), 3.0-3.45 (15H, b, $NC\underline{H}_2(CH)_4NCO(CH_2)_4C\underline{H}_2N$, and OH), 3.5-3.85 (6H, b, $N(CH_2)_4C\underline{H}_2N$-OH). MS (FAB) $(M+H)^+$ = 626. Acc MS FAB (High Resolution) $(M+H)^+$ = 654.5178 (-1.3 ppm). $(M)^+$ = 653.5150 (-9.0 ppm).

The 1:1 Fe complex of the cryptand was prepared by dissolving the ligand (9.6 mg, 1.53 x 10^{-5} mol), in water (5 ml), and adding a stoichiometric amount of atomic absorption standard iron. This gave a deep red solution (pH = 1.5). The pH of this solution was raised to 4 with slow addition of 0.5N KOH, and stirred at this pH for 1h. The pH was then raised to 7 and maintained at 25°C for 24 h. The mixture was concentrated to dryness to yield a red solid which was extracted into ethanol. The resulting mixture was filtered through celite and the filtrate concentrated to dryness to afford a red solid. Chromatography on LH-20 Sephadex (300 cm x 1.5 cm), equilibrated with 70:30 (by vol) methanol: dichloromethane resulted with the elution of an orange band, which on concentration to dryness gave a dark red solid (3.4 mgs) in 33% yield. This was characterised by mass spec (FAB) $(M+Fe+H)^+$ = 679 . A solution of this complex has a λ max at 418 nm, which is similar to that of ferrioxamine. The 1:1 Indium(III) complex of the cryptand was prepared in a similar manner to that of the iron complex to afford a white solid. MS (FAB) $(M + In)^+$ = 737.

The measurement of the affinity of 7,21,32-trihydroxy-1,7,14,21,32,pentaazabicyclo [12.12.12] octatriacontane-8,20-33-trione **9** for iron(III) and indium(III) is under investigation. The synthesis of a series of cryptands with differing cavity size is currently in progress.

Scheme 1. The route to the synthesis of the macrobicylic cryptand **9**



(i) K_2CO_3/CH_3CN/24 Hrs/reflux, (ii) $Ba(OH)_2.8H_2O$/MeOH/stir/72 Hrs, (iii) $(BOC)_2O/CH_3CN$ (iv) C_6H_6/Py/5°C/N_2 (high dilution conditions), (v) TFA/stir, (vi) C_6H_6/py/N_2, (vii) a) Zn/HOAc, b) CH_3CN/Na_2CO_3/NaI/N_2/reflux/72 Hrs (high dilution conditions), (viii) a) $(Me)_2B$-Br/DCE/0°C/ Ar, b) $Pd(OH)_2/H_2$/EtOH.

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ACKNOWLEDGEMENTS

The authors would like to thank the Cancer Research Campaign who have supported this work (Grant number SP 1996/0201). The authors would also like to thank ULIRS at King's College, Strand, for their fast atom bombardment mass spectral analysis.

(*Received in UK* 16 *September* 1994; *revised* 13 *October* 1994; *accepted* 14 *October* 1994)