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Efficient Synthesis of the Gadolinium Complex of a New C_2-Symmetric Tetramine

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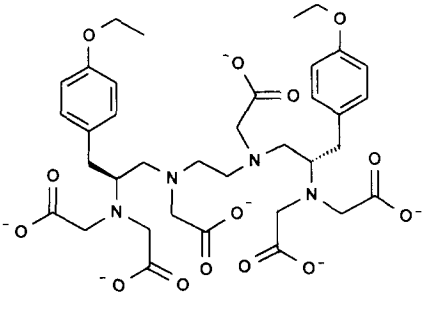
Abstract : A short and efficient synthesis of the substituted tetramines **2a** and **7** and of the gadolinium complex **1** was developed starting from the Cbz-protected amino alcohol **3** . Key steps of the synthesis are the optimized bleach oxidation of enantiopure alcohols and the bridging of the resulting aldehyde molecules by double reductive amination with ethylenediamine. Interesting biological activity of the amines **2a** and **7** was detected.

Polyamines have gained recently much interest because of their potential activity in curring neurodegenerative diseases. The work described here was triggered especially by a patent application[2] recently disclosed from Nakanishi et al. in which spermine derived polyamines are claimed for their interesting biological properties.

Above that these amines could after alkylation with bromo acetic acid lead to chiral ligands with interesting complexation abilities. Metal complexes like **1** which are derived from these chiral amines could have potential applications as in vivo diagnostics[3] or catalysts for asymmetric synthesis[4].



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Scheme 1

Our strategy for the preparation of **1** was to synthesize the corresponding tetramine first and then alkylate it with a bromo acetic acid derivative to the C_2-symmetric hexaacid which is the ligand of the complex **1**. For this reason we had to get the Cbz-protected tetramine **2** in our hands.

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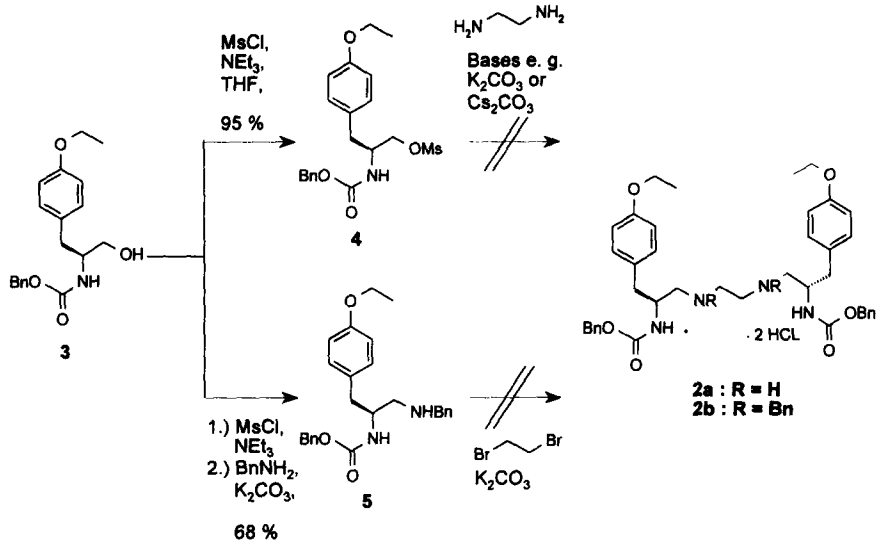
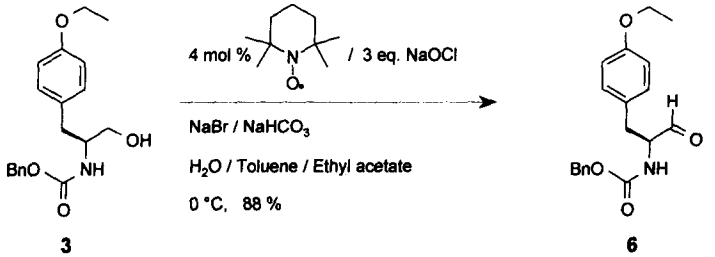
Unfortunately our initial attempts to use the mesylate **4** or the diamine **5** which are both easily available in good yields from the alcohol **3** were not successful. In both cases we got inseparable mixtures of products.



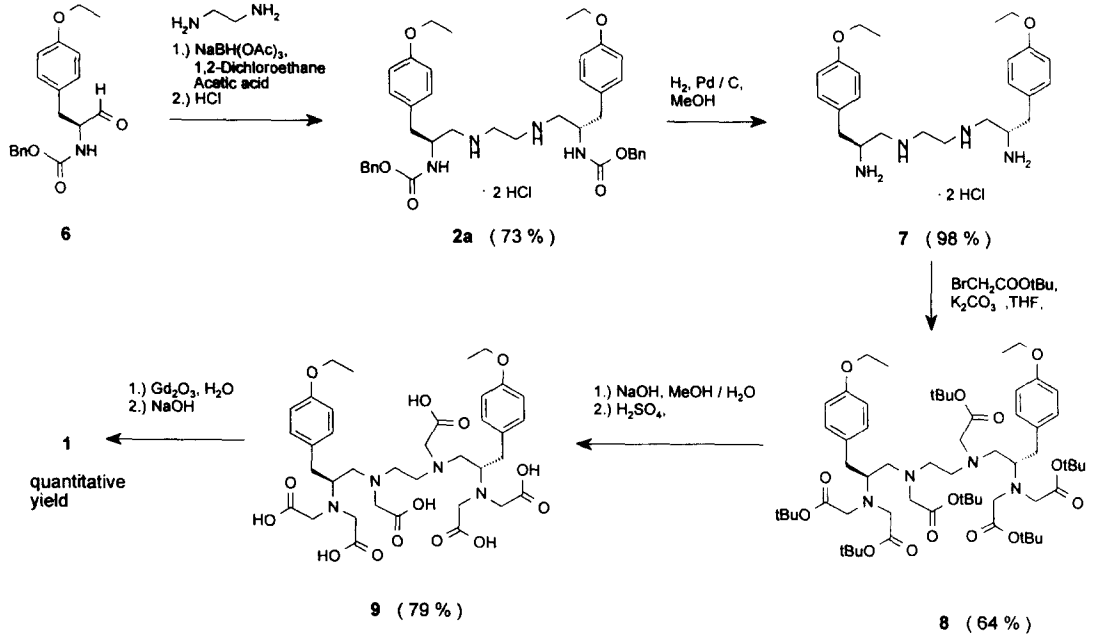
Scheme 2

After those disappointing results we switched to the amino aldehyde **6** as a key intermediate for the preparation of **2**. This aldehyde should also be available from the alcohol **3** by simple oxidation. There are several methods for the oxidation of amino alcohols to the corresponding aldehydes described in the literature e. g. chromium-based oxidants or activated forms of dimethylsulfoxide[5]. For the successful application of this reaction methods it is necessary to use low reaction temperatures and to adhere strictly to the documented reaction conditions in order to avoid racemization. Further unpleasant aspects of this reactions are the toxic side products and the co-production of dimethylsulfide. Therefore we decided to apply a new oxidation method for amino alcohols published recently by Leanna and coworkers[6]. Bleach is used together with a catalytic amount of 2,2,6,6-tetramethyl-1-piperidinyloxy free radical (TEMPO) as a cheap oxidizing agent in a two phase system . After some optimization this mild and simple procedure worked very smoothly and we received 88 % of the CBZ-protected amino aldehyde as a pure white solid which was used without delay in the next step.



Scheme 3

With the aldehyde **6** in our hands we next checked the bridging of two aldehyde molecules with ethylenediamine via reductive amination. Though there is a latent danger of racemization in this step we were optimistic because Ho et al. had shown that it is possible to use peptide aldehydes in reductive aminations without producing larger amounts of the other diastereomer[7]. Furthermore Chandrakumar had reported the use of of a t-butyl protected N-Boc-tyrosine aldehyde in a reductive amination without racemisation[8]. In the beginning the classical reaction conditions for this transformation described by Borch[9] with sodium cyanoborohydride as the reducing agent failed. The problems connected with this reaction could be overcome by using sodium trisacetoxyborohydride in dichloroethane[10]. Addition of a small amount of acetic acid accelerated the reaction. After the usual workup procedure the precipitation with HCl from methyl t-butyl ether gave the pure dihydrochloride **2a** as a stereochemical homogeneous white solid in remarkable 73 % yield[11].



6 **2a** (73 %) **7** (98 %) **8** (64 %) **9** (79 %) **1**

Scheme 4

The following hydrogenolysis of the Cbz-protecting groups was performed at 60 °C and 10 bar hydrogen pressure over Pd / C and worked very cleanly. A 98 % yield of the tetramine dihydrochloride **7** was received after filtration of the catalyst and evaporation of the solvent.

As one might expect the planned alkylation step of the tetramine **7** with 2-bromo acetic acid tert.-butyl ester was more difficult to achieve. The molecule contains four nitrogen atoms which have to be alkylated thoroughly but an overalkylation to the corresponding ammonium salts has to be avoided. After some optimization the method of choice was to use a slight excess of the alkylating reagent (1.2 mol eq. per nitrogen) in THF with potassium carbonate as the base. The crude product was purified by reversed phase chromatography and a 64 % yield of **8** was obtained.

Saponification of the hexaester **8** with sodium hydroxide, acidification with H_2SO_4 and crystallization from water gave the hexaacid **9** in 79 % yield. In the final step an aqueous solution of the hexaacid and

gadoliniumoxide was refluxed for two hours. Neutralization with NaOH and lyophilysation gave a quantitative yield of the gadolinium complex **1** as a white solid.

Some of the compounds described in this paper showed interesting pharmacological activities. The tetramines **2a** and **7** were especially active as b-NO-Synthase- and e-NO-Synthase-Inhibitors with IC_{50}-values ranging from 4 μM to 24 μM.

In summary we were able to make the new C_2-symmetric hexaacid **9** and the corresponding gadolinium complex **1** available in the multigram scale. The preparation of complexes of **9** with other metals and their potential as new catalytic systems is currently under study in our laboratory.

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References and Notes

1 Undergraduate research fellow (Dez. 1996 - Jan. 1997).

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11 Reaction procedure for the preparation of **2a** : To freshly prepared aldehyde **6** (0.5 g; 1.53 mmol) in 1,2-dichloroethane (5 ml) is added under nitrogen atmosphere 1,2-diamino-ethane (51 μl; 0.76 mmol) and sodium tris(acetoxy) borohydride (486 mg; 2.3 mmol). Acetic acid (43 μl; 0.76 mmol) is added dropwise to the stirred reaction mixture. After 2.5 h the mixture is diluted with ethylacetate (30 ml) and a saturated solution of sodium hydrogencarbonate is added. The phases are separated and the aqueous phase is extracted with ethylacetate (30 ml). The combined organic phases are washed with water and dried over sodium sulfate. Evaporation of the solvent yields a yellow oil which is dissolved in methyl t-butyl ether (2.6 ml) and methanol (1.5 ml). At 10 °C conc. HCl (0.3 ml) is added dropwise. The precipitated product is filtered off and dried. Yield : 418.4 mg (0.55 mmol; 73 %) of **2a** as a white solid.$[\alpha]_D^{25}$: + 32.2 °(c = 1, CH_3CN), mp = 210 °C (decomp.). ^1H NMR (300 MHz, CD_3OD) : δ = 1.39 (t, J = 6.5 Hz, 6H), 2.8 (m, 4H), 3.21 (m, 4H), 3.45 (m, 4H), 3.98 (q, J = 6.5 Hz, 4H), 4.12 (m, 2H), 5.12 (m, 8H), 6.82 (d, J = 9 Hz, 4H), 7.13 (d, J = 9 Hz, 4H), 7.28 (m, 10H).