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Simplified syntheses of the water-soluble chiral shift reagents Sm-(*R*)-pdta and Sm-(*S*)-pdta

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ABSTRACT

The chiral shift reagents Sm-(*R*)-pdta and Sm-(*S*)-pdta, which are based on (*R*)- or (*S*)-1,2-diaminopropane-*N,N,N′,N′*-tetraacetic acid were synthesized from easily accessible compounds in three simple steps, which makes the method suitable for laboratory-scale production. In addition, a new and efficient method for the preparation of pure anhydrous (*R*)- or (*S*)-1,2-diaminopropane-*N,N,N′,N′*-tetraacetic acid was developed.

Some of the most widely used methods for determining the enantiomeric purity or absolute configuration of chiral compounds are NMR techniques employing chiral shift reagents (CSRs).[1] However, there have only been a few reported water-soluble CSRs to date. Among these, a recently developed complex of propylenediaminetetraacetic acid with samarium (Sm-pdta, **1** and **2**) stands out since it does not cause serious line-broadening in high-field NMR, and can be readily used for determining the absolute configurations of α-amino acids (Fig. 1).[2–5]

Although commercially available in limited quantities, their cost prohibits the use of both complexes in routine laboratory practice. Our need for bulk quantities prompted us to develop a straightforward and cost-effective synthetic route starting from easily accessible compounds, which could be used for expedient laboratory-scale production of these reagents.

Our synthetic approach toward both Sm-(*R*)-pdta and Sm-(*S*)-pdta originated from racemic 1,2-diaminopropane, a commercially available and inexpensive starting material. The first resolution of racemic 1,2-diaminopropane into enantiomers via crystallization of its diastereomeric bitartrate salt was reported in 1895 by Baumann,[6] and was later substantially improved by Dwyer;[7] his method seems to be used in most later works dealing with the resolution of this diamine. Sakie has published an alternative approach employing *N*-*p*-toluenesulfonylphenylglycine as a resolving agent.[8] We decided to utilize the former method because of the common availability of L-tartaric acid. Although Dwyer claimed ten recrystallizations of the diastereomeric salt were necessary to obtain the enantiomeric diamine of satisfactory optical purity and Repta[9] used five recrystallizations, we found[10] that after only one recrystallization the unwanted antipode in either the (*S*)- or (*R*)-diamine sample could not be detected. The bitartrates of (*S*)- or (*R*)-1,2-diaminopropane were converted into crystalline (*R*)- or (*S*)-1,2-diaminopropane dihydrochlorides **3** or **4**, respectively.

The key intermediate, (*R*)- or (*S*)-1,2-diaminopropane-*N,N,N′,N′*-tetraacetic acid (PDTA), has been synthesized traditionally by treatment of dihydrochloride **3** or **4** with chloroacetic acid in strongly alkaline solution for several days at room temperature. However, unlike the racemic compound, isolation of (*R*)- or (*S*)-1,2-diaminopropane-*N,N,N′,N′*-tetraacetic acid is very difficult due to its high solubility in water and strongly chelating nature.[11] Therefore, most published methods describing its purification include laborious desalination,[9,11,12] or even do not attempt to remove the inorganic salts completely.[13] An alternative two-step approach was recently proposed by Florini who synthesized and isolated lipophilic tetraethyl (*R*)-1,2-diaminopropane-*N,N,N′,N′*-tetraacetate, which was subsequently subjected to alkaline hydrolysis and conversion into PDTA dihydrochloride (reported 84% yield over two steps from **4**).[14] However, our efforts to reproduce these results were not successful since we repeatedly obtained only an impure product, while the yield of the target compound was under 50%.

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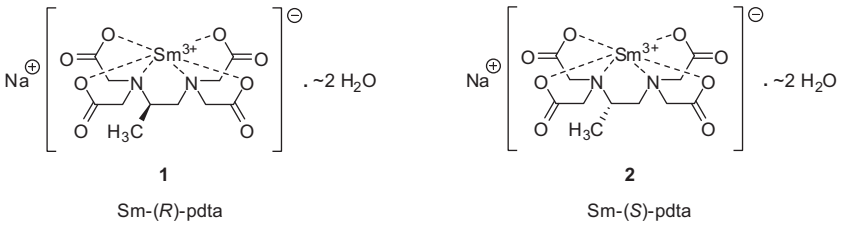
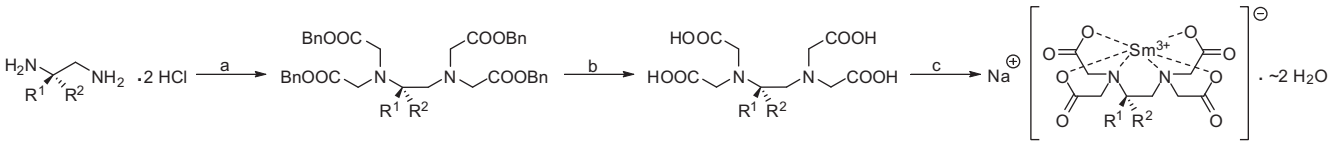


Figure 1.



Scheme 1. Reagents, conditions and yields: (a) $BrCH_2COOBn$, K_3PO_4 in MeCN, 7 d, rt; (b) 10% Pd/C, H_2, EtOAc–MeOH, 12 h, 15 psi, 56% for **7** (over two steps), 63% for **8** (over two steps); (c) Sm_2O_3, H_2O, reflux, 1.5 h, then NaOH, 94% for **1**, 88% for **2**.

Taking all the previous work into consideration, it was obvious that the most convenient route to pure PDTA in salt-free form should start with the synthesis and isolation of its lipophilic derivative, which would be subsequently deprotected by non-ionic reagents, preferably in an organic solvent. Thus, we decided to prepare the tetrabenzyl ester of PDTA, which would be subjected to hydrogenolysis in the next step to afford the desired free tetra-acid.

Alkylation of (*R*)- or (*S*)-1,2-diaminopropane was accomplished with benzyl bromoacetate in an acetonitrile-K_3PO_4 system, as previously reported[14] for the ethyl analogue. The requisite amount of benzyl bromoacetate was successfully reduced during reaction optimization from the original 20 equivalents per equivalent of **3** or **4** to 6 equivalents. Isolation of the crude product by chromatography on silica afforded tetrabenzyl ester **5** or **6** in an impure form (as confirmed by elemental analysis); nevertheless, we later found that these impurities did not affect the next reaction step. Moreover, they were completely removed with the mother liquors during crystallization of **7** or **8**, so no additional purification of **5** or **6** was necessary.

Deprotection of the tetrabenzyl esters was carried out by hydrogenolysis (at 15 psi) with 10% Pd/C catalyst. We decided to purify the resulting crude tetra-acid **7** or **8** by crystallization. After examining several solvents and solvent mixtures without success, we eventually found the methanol–water system to be highly efficient; crystallization of crude (*R*)- or (*S*)-PDTA from 9:1 MeOH–H_2O at 70 °C afforded, after 12 h at 4 °C, colorless needles of tetra-acid **7** or **8**. The product was obtained in an anhydrous form, >98% purity and in yields up to 63% over two steps from dihydrochlorides **3** or **4**.

Final conversion into the desired samarium complex **1** or **2** was accomplished according to the published procedures,[2,15,16] by refluxing samarium(III) oxide with an aqueous solution of (*R*)- or (*S*)-PDTA followed by adding sodium hydroxide. The amount of impurities was low enough to allow isolation of both complexes by direct lyophilization of the reaction mixture without any additional purification (Scheme 1).

In conclusion, the chiral shift reagents Sm-(*R*)-pdta and Sm-(*S*)-pdta were synthesized in three steps from inexpensive starting materials in good yields, which should make this reaction sequence useful for laboratory-scale production of both reagents. In addition, we have developed a new method for the preparation of pure anhydrous (*R*)-PDTA and (*S*)-PDTA from (*R*)- or (*S*)-1,2-diaminopropane, which is straightforward and devoid of laborious purification and deionization of these highly polar and chelating compounds.

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Supplementary data

Supplementary data (experimental procedures and spectroscopic characterization) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.09.009.

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