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Synthesis of a water-soluble chiral NMR shift reagent: (*S*)-PDTA

Nicola Florini [a,*], Gaëlle F. Arnaud [a], Bálint Kónya [a,b], Claudia Zucchi [a], Gyula Pályi [a]

[a] *Department of Chemistry, University of Modena and Reggio Emilia, via Campi 183, I-41100 Modena, Italy*
[b] *Institute of Chemistry, University of Debrecen, Egytem t. 1, H-5010 Debrecen, Hungary*

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This paper is dedicated to Professor Luciano Caglioti (Roma) on his 75th birthday. The authors are proud to be among his many friends

ABSTRACT

A five-step synthesis of the water-soluble chiral polydentate ligand, (*S*)-PDTA [(*S*)-PDTA = *N*,*N*,*N*′,*N*′-tetrakis[(hydroxycarbonyl)methyl]-(*S*)-1,2-diaminopropane] starting from L-alanine has been worked out, via steps with retention of chirality. Total yield is 50.7% (average of ~88% for each step), while published methods report 33.4% total yield over four steps.

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1. Introduction

Water phase organic reactions assisted or catalyzed by transition metals have attracted increasing interest over the last decade[1] for obvious enviromental[2] reasons, and also because of the particular capacity of water-to-water clusters to build highly organized solvation structures.[3] The latter feature is particularly interesting for asymmetric syntheses since the supramolecular architecture in liquid water serves as a very efficient 'channel' for the transfer of chiral information[4] from a chiral ligand to a prochiral substrate or its transition state.[5] Enantioselective NMR analysis of such reaction mixtures, however meets an important 'technical' difficulty: the fact that water-soluble chiral NMR shift reagents are very rare.[6]

Herein we report an improved synthesis of a chiral water-soluble ligand, *N*,*N*,*N*′,*N*′-tetrakis[(hydroxycarbonyl)methyl]-(*S*)-1,2-diaminiopropane[7] (*S*)-PDTA.

2. Results and discussion

2.1. Preparative experiments

(*S*)-PDTA, its (*R*)-enantiomer as well as the (*R*,*S*)-racemate are known compounds[7–10] [ACS 2008 SciFinder Registry No.: (*S*): 15250-41-6; (*R*): 15456-17-4; (*R*,*S*): 4408-81-5] that are studied for several reasons, but mainly because of their structural and chemical relevance to the related complexon family.[11] (*S*)- or (*R*)-PDTA is the structurally simplest chiral complexon.

The preparation of (*S*)-PDTA was reported starting from (*S*)-1,2-diaminopropane[12–19] in two steps, introducing the (hydroxycarbonyl)methyl-functionalities by ethylbromoacetate and then hydrolyzing the ester groups. (*S*)-1,2-Aminopropane can be made from L-(*S*)-alanine (which is much cheaper) in three steps.[20–22] The overall yield of published procedures starting from L-alanine is only 33.3% (even when we take the unpublished yield of one of these steps as 100%).

We used the reaction sequence as shown in Scheme 1. These improved variants of steps 1–5 provided an overall isolated yield of 50.7% (corresponding to ~88% 'average' yield for each step) and retention of configuration of the 2-(*S*)-carbon in L-(*S*)-alanine.

An earlier publication[7] reports the preparation of enantiopure end product **6** by resolution of its Co(III) complex with crystallization. To avoid this low-yielding and time-consuming operation, we chose the reaction path shown in Scheme 1, where the individual steps do not involve the stereogenic center and thus a quantitative retention of chirality throughout the procedure can be reasonably expected.

Some authors have suggested making the **1** to **3** transformation in one step.[21,22] We found it more advantageous to proceed over the ester **2** followed by a very cautious ammonolysis (steps 1 and 2), in accordance with Ref. 20.

Reduction step 3 was attempted by using $LiAlH_4$,[23] and Zn/HCl (nascent H) but we found problems with the separation of the product. In our hands BH_3 (generated in situ from $NaBH_4$ and I_2) gave the best results (smooth crystallization of the product **4**).

Alkylation step 4 was tested by several variants. After these attempts we found that the correct basicity of K_3PO_4 ($pK_a = 12.4$) was the key element for a high yield of product **5**, which could be isolated in analytically pure form by extraction.

Hydrolysis (deprotection) step 5 could be performed by either acid[18] or the basic[19] treatment. We chose a basic hydrolysis, followed by acid treatment to obtain end product **6** in HCl-salt stabilized form. This method provided a near-quantitative yield (98%) of analytically pure product.

* Corresponding author. Tel.:+39 059 205 5059; fax: +39 059 373 543.
E-mail address: nicola.florini@unimore.it (N. Florini).

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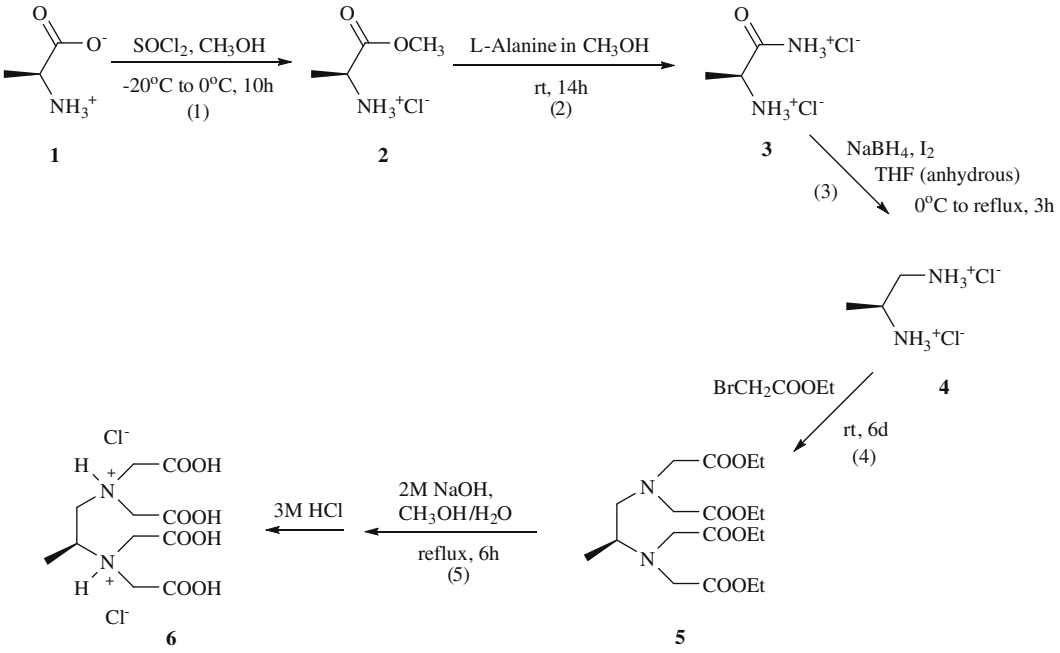

Scheme 1. Reaction sequence used in the synthesis of (*S*)-PDTA from L-alanine.

3. Experimental

Starting compounds were of commercial origin. Anhydrous THF was prepared according to published procedures.[24]

Instrumental measurements were performed with the following devices. *Elemental analysis*: Carlo Erba Analyzer Mod. 1106. The instrument was calibrated with three authentic samples of commercially available compounds (five measurements) of known C, H, and N contents. *Infrared spectra*: JASCO 4200 spectrometer, KBr pellets. *NMR spectra*: Bruker FT-NMR DPX200 and Bruker FT-NMR AVANCE 400. *Polarimeter*: Perkin–Elmer 241 polarimeter, Na-lamp (589 nm).

3.1. Preparation of L-(*S*)-alanine methyl ester hydrochloride 2

L-Alanine, 14.00 g (157.3 mmol) was dissolved in 160 mL methanol in a 500 mL three-necked reaction vessel, equipped with a thermometer and magnetic stirrer. This mixture (suspension) was chilled to −20 °C (ice/NaCl, external). To this suspension, thionyl dichloride, $SOCl_2$, 19.7 g (12.3 mL, 165.2 mmol) was added dropwise, making sure that the temperature of the reaction mixture remained below +5 °C (∼15 min). After the addition of $SOCl_2$, the solution was stirred for an additional 16 h at 0 °C. After this period, the reaction mixture was left to warm to rt and it was concentrated in a rotary evaporator (until it became oily). To the rest, 20 mL of *i*-PrOH and 50 mL of *n*-hexane were added and these solvents were evaporated again under rotary evaporation. This procedure was repeated four times. The dried product was a white crystalline substance. Yield 21.70 g (99.2%). The product was characterized by elemental analyses, IR and NMR spectra, and polarimetry.

Anal. Calcd for $C_4H_{10}ClNO_2$: C, 34.42; H, 7.22; N, 10.03. Found: C, 34.5; H, 7.9; N, 10.0. Infrared (KBr pellet, cm^{-1}): 3472, m, 3430, m (ν C–NH_3^+); 2985, s (ν NH_3^+); 2825, s (ν CH_3); 1742, s (ν C=O); 1630, w, 1461, m (δ NH_3^+); 1492, s (δ O–CH_3); 1220, s (ν C–O–); 514, s (τ NH_3^+). NMR: ^{1}H NMR (200.13 MHz, D_2O, ppm): 1.56, (d, 3H (CH_3)); 3.85, (s, 3H (OCH_3)); 4.22, (q, 1H (CH)); ^{13}C NMR (50.29 MHz, D_2O, ppm): 15.2 (CH_3); 48.2 (CH); 53.7 (OCH_3); 171.3 (COO). Polarimetry: $[\alpha]_D^{20} = +4.1$ (*c* 9.83, CH_3OH). Lit.: $[\alpha]_D^{25} = +7.0$ (*c* 1.60, CH_3OH).[25]

3.2. Preparation of L-(*S*)-alanylamide 3

L-Alanine methylester HCl, 10.36 g (74.5 mmol), potassium hydroxide, KOH, 4.17 g (74.5 mmol), and 300 mL of 7 M ammonia solution in methanol were mixed together in a one-necked 0.5 L reaction vessel and were stirred for 14 h with magnetic stirrer at rt. After this period the solvent was evaporated with rotary evaporator, and then 50 mL of methanol was added and evaporated again. This last operation was repeated twice. At the end, the last traces of water were eliminated completely by washing the product thrice with 100 mL portions of abs. ethanol and by evaporating the solvent. At the end a white solid was obtained, which was extracted thrice with 50 mL portions of pyridine. The pyridine extract was drawn dry at reduced pressure. The resulting white product was hygroscopic and therefore it was stored over P_40_{10}. Yield: 5.27 g (80.5%).

The product was identified by elemental analysis, IR and NMR spectra, and polarimetry. Anal. Calcd for $C_3H_8N_2O$: C, 40.91; H, 9.09; N, 31.82. Found: C, 41.2; H, 9.3; N, 31.2. Infrared (KBr pellet, cm^{-1}): 3369, s, 3333, s, 3160, m (ν NH_2); 2974, s (ν CH_3); 1697, m (ν C(O)–N); 1647, m, 1578, m (δ C–NH_2). NMR: ^{1}H NMR (200.13 MHz, $CDCl_3$, ppm): 1.32, d, 3H (CH_3); 1.47, s, 2H (NH_2); 3.47, q, 1H (CH); 6.11–7.04, br, 2H (C(O)–NH_2). ^{13}C NMR (50.29 MHz, $CDCl_3$, ppm): 21.6 (CH_3); 50.7 (CH); 179.1 (C(O)NH_2). Polarimetry: $[\alpha]_D^{20} = +10.0$ (*c* 9.33, CH_3OH).

3.3. Preparation of (*S*)-1,2-diaminopropane 2HCl 4

In a three-necked 500 mL reaction vessel the L-(*S*)-alanylamide, 1.87 g (21.25 mmol) was dissolved in 250 mL of anhyd THF under a dry Ar atmosphere. This solution was chilled to 0 °C under magnetic stirring and while stirring was continued sodium tetrahydroborate, $NaBH_4$, 1.85 g (48.87 mmol) was added. In a 250 mL vessel iodine, I_2, 5.398 g (21.25 mmol) was dissolved in 100 mL of anhyd THF, under a dry Ar atmosphere. Then the I_2 solution was slowly added dropwise to the reaction mixture (∼2.5 h). The addition of the I_2 solution resulted in some gas (H_2) evolution and a white precipitate was formed. After the addition of the I_2 solution was completed the reaction mixture was heated (oil bath) to reflux for 3 h, then it was left to cool to rt and the product was filtered, washing it

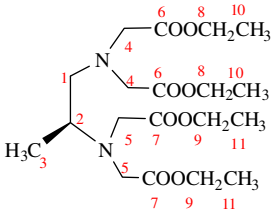

Figure 1. Compound **5** (C numbered for NMR assignments).

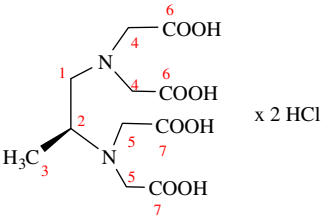

Figure 2. Compound **6** (C numbered for NMR assignments).

with THF. Next the filtrate was dried and 20 mL of methanol was added to it and the mixture solution was left to stand. The next morning HCl gas was bubbled through the reaction mixture for 30 min, which caused the solution to turn yellow and a light yellow precipitate was formed. This precipitate was filtered out by G4 filter, washed with Et_2O, and dried. The product was a yellow powder. Yield: 2.336 g (75.3%) The product was identified by NMR spectroscopy. NMR: ^{1}H NMR (200.13 MHz, DMSO-d_6, ppm): 1.30, (d, 3H, J^3_{HH} 6.85 Hz (CH_3)); 2.98, (dd, $J^2_{\alpha\beta}$ 13.20 Hz, $J^3_{\alpha A}$ 6.20 Hz, H_α (CH_2)); 3.18, (dd, $J^3_{\beta A}$ 5.87 Hz, H_β (CH_2)); 3.54, (sex, $J^3_{H\alpha}$ 6.60 Hz, $J^3_{H\beta}$ 5.87 Hz (CH)); 8.67, s, (NH_3^+). ^{13}C NMR (50.29 MHz, DMSO-D_6, ppm): 16.69 (CH_3); 42.11 (CH_2); 45.41 (CH).

3.4. Preparation of (*S*)-*N*,*N*,*N*′,*N*′-tetrakis[(ethoxy-carbonyl)methyl]-1,2-diaminopropane 5

In a 500 mL one-necked reaction vessel, equipped with an external magnetic stirrer, a suspension of 1,2-diaminopropane dihydrochloride, **4**, 2.51 g (17.09 mmol) and anhyd tripotassium phosphate, K_3PO_4, 36.23 g (170.9 mmol) in 180 mL of acetonitrile (AN) was prepared. To this solution, while stirring at rt ethylbromoacetate, $BrCH_2COOEt$, 38.1 g (341.8 mmol) was added in one portion. Then the reaction mixture was stirred at rt for 6 days. After this period the solvent and most of the excess $BrCH_2COOEt$ were removed by distillation (2 mmHg). To the solid product 180 mL of 3 M aqueous HCl was added, which resulted in the complete dissolution of this solid. The aqueous solution was then extracted twice with 70 mL portions of Et_2O. Then the reaction vessel, with an Allihn condenser, containing the aqueous phase was immersed in an ice/water bath and to the solution solid NaOH was added until a pH of 14 was reached. At this point, the aqueous solution was extracted with 4 × 70 mL portions of Et_2O, the extracts were gathered and dried over anhyd Na_2SO_4, filtered and then the solvent was evaporated in a rotary evaporator. The product was a yellow oil. Yield: 6.146 g (86.0%).

The product was characterized by elemental analyses, infrared and NMR spectroscopy, and polarimetry.

Anal. Calcd for $C_{19}H_{34}N_2O_8$: C, 54.55; H, 8.13; N, 6.70. Found: C, 54.0; H, 7.8; N, 6.9. Infrared: (KBr pellet, cm^{-1}): 2981, s, 2875, s, (ν C–NH–); 1745, s, (ν C=O); 1466, m, 1447, m, (ω C–NH–); 1370, s, (δ C–NH–); 1190, s, (ν –O–CH_3). NMR (assigned with ref. to Fig. 1): ^{1}H NMR (200.13 MHz, $CDCl_3$, ppm): 1.27, (d, 3H, J^3_{HH} 7.10 Hz, ($C^{(3)}H_3$)); 1.30, (t, 12H, J^3_{HH} 7.30 Hz, ($C^{(10+11)}H_3$)); 2.57, (dd, 1H, (H_α $C^{(1)}H_2$)); 2.95, (dd, 1H, J^3_{HH} 6.46 Hz, $J^2_{\alpha\beta}$ 13.50 Hz (H_β $C^{(1)}H_2$)); 3.11, (sex, 1H, J^3_{HH} 6.65 Hz ($C^{(2)}H$)); 3.59, (s, 4H ($NC^{(5)}H_2$)); 3.63, (s, 4H ($NC^{(4)}H_2$)); 4.17, (q, 8H, J^3_{HH} 7.26 Hz ($OC^{(8+9)}H_2$)). ^{13}C NMR (50.29 MHz, $CDCl_3$, ppm): 14.86 ($OCH_2C^{(10+11)}H_3$); 15.37 ($C^{(3)}H_3$); 52.53 ($C^{(5)}H_2$–N); 55.55 ($C^{(4)}H_2$–N); 56.28 ($C^{(2)}H$); 58.48 ($C^{(1)}H_2$); 60.42 (O–$C^{(9)}H_2$); 60.35 (O–$C^{(8)}H_2$); 171.3 ($C^{(6)}$=O); 172.1 ($C^{(7)}$=O). Polarimetry: $[\alpha]_D^{20} = +1.4$ (*c* 8.53, $CHCl_3$).

3.5. Preparation of (*S*)-*N*,*N*,*N*′,*N*′-tetrakis[(hydroxy-carbonyl)-methyl]-1,2-diamino-propane dihydrochloride 6

(*S*)-*N*,*N*,*N*′,*N*′-Tetrakis[(ethoxycarbonyl)-methyl]-1,2-diamino-propane, 5.46 g (13.1 mmol), was suspended in 30 mL of methanol and 120 mL of aqueous 2 M NaOH in a 250 mL one-necked reaction vessel and heated in oil bath to reflux for 6 h. After this period the solvents were evaporated by rotary evaporator and then 150 mL of 3 M aqueous HCl was added. After this treatment the solvent was again stripped off by rotary evaporator. The rest was washed thrice with 30 mL of *i*-PrOH and then filtered cold (0 °C), first on a Bückner funnel and then filtered on Celite and washed with 30 mL portions of cold (0 °C) *i*-PrOH. A white, solid product was obtained. Yield: 4.824 g (98.0%). The product was characterized by melting point, elemental analysis, and NMR and UV/CD spectroscopy. Melting point: 238 °C (dec). Anal. Calcd for $C_{11}H_{20}Cl_2N_2O_8$·1 *i*-PrOH, $C_{14}H_{28}Cl_2N_2O_9$: C, 38.28; H, 6.43; N, 6.38. Found: C, 38.6; H, 7.3; N, 6.2 NMR: ^{1}H NMR (400.13 MHz, H_2O/D_2O (3:1), pH 10 buffer NH_4OH/NH_4Cl, ppm): 1.28, (d, 3H, J^3_{HH} 6.95 Hz ($C^{(3)}H_3$)); 2.86, (dd, 1H, $J^3_{A\alpha}$ 10.6 Hz, (H_α $C^{(1)}H_2$)); 2.96, (dd, 1H $J^3_{A\beta}$ 4.28 Hz, (H_β $C^{(1)}H_2$)); 3.35–3.72, (m, 10H ($C^{(4,5)}H_2$, $C^{(2)}H$)). ^{13}C NMR (100.63 MHz, H_2O/D_2O (3:1) pH 10 buffer NH_4OH/NH_4Cl, ppm): 10.9 ($C^{(3)}H_3$); 54.2 ($C^{(5)}H_2$); 55.5 ($C^{(2)}H$); 56.5 ($C^{(1)}H_2$); 58.2 ($C^{(4)}H_2$); 174.9 ($C^{(6)}$=O); 177.6 ($C^{(7)}$=O). Polarimetry: $[\alpha]_D^{20} = +24.7$ (*c* 25.20, CH_3OH). Lit.: +47.0 (without additional details)[7] (Fig. 2).

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