Pergamon

Tetrahedron Letters 40 (1999) 4989–4992

TETRAHEDRON
LETTERS

Synthesis of new triazamacrocycles *N*-functionalised with α-(*S*)-hydroxycarboxylic acid pendant-arms

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Received 10 April 1999; accepted 2 May 1999

Abstract

The synthesis of two new macrocyclic ligands, *N,N′,N″*-tris[2(*S*)-hydroxybutyric acid]-1,4,7-triazacyclononane and *N,N′,N″*-tris[2(*S*)-hydroxybutyric acid]-1,5,9-triazacyclododecane is reported. Each macrocycle bears three L-lactate-like pendant arms. Starting from L-malic acid, the absolute configuration of the α-(*S*)-hydroxy acid was kept along the synthesis leading to pure (*S,S,S*) enantiomers.

Keywords: macrocycles; polyazacycloalkanes; α-hydroxy acids; regiospecificity.

Chelating ligands based on polyazamacrocycles have received considerable attention over the last two decades both in the improvement of the synthetic pathways of the cycle and in the functionalisation of the ring in order to extend the chemical properties.[1,2] *N*-Functionalised triazamacrocycles are particularly attractive compounds for the design of selective ligands for transition metal coordination.[3] Polyazamacrocycles bearing oxido-reducible side arms in association with a transition metal ion offer the possibility of building redox systems able to catalyse chemical reactions. Some examples of such redox molecular assemblies have been recently reported.[4] In connection with a research program regarding the role of oxygen reactive species in biology and the search for superoxide ($O_2^{\cdot-}$) scavengers, we built redox systems able to react with this radical. Some aerobic organisms, such as *Lactobacillus plantarum* which are devoid of enzymatic defences, use chemical systems associating intracellular Mn(II) ions weakly bound to complexing ligands (α-hydroxy acids or phosphate groups) to scavenge the $O_2^{\cdot-}$ radical.[5] For this reason we chose to place L-lactic acid functions at the periphery of polyazamacrocycles. The aim was to test the ability of a system associating several lactate/pyruvate couples to the Mn(II) ion to react with the $O_2^{\cdot-}$ radical.

Since enantiomers of biologically active compounds usually display different physiological activities, our initial choice was to obtain pure enantiomeric compounds. The strategy of the synthesis

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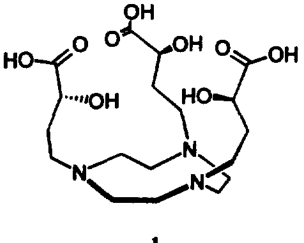
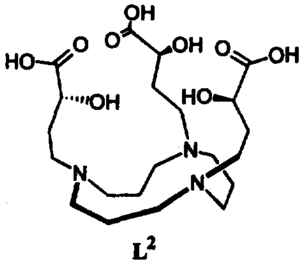
PII: S0040-4039(99)00875-8

was to get (*S*,*S*,*S*) enantiomers by functionalising triazamacrocycles with L-lactate pendant-arms. We report here the synthesis of two new macrocyclic ligands, *N*,*N*′,*N*″-tris[2(*S*)-hydroxybutyric acid]-1,4,7-triazacyclononane **L**^{1} and *N*,*N*′,*N*″-tris[2(*S*)-hydroxybutyric acid]-1,5,9-triazacyclododecane **L**^{2}, each bearing three L-lactate-like pendant-arms.

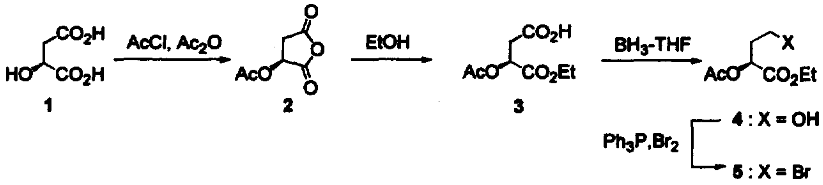


L^1



L^2

The general synthetic procedure included: (i) the preparation of synthon **5**, paying particular attention to obtaining optically pure material; and (ii) the functionalisation of the cycloamines, 1,4,7-triazacyclononane **6** and 1,5,9-triazacyclododecane **7**. Cyclic amines **6** and **7** are commercially available, and their synthesis is also well described in the literature.[6] For the preparation of the pendant arms, a synthetic pathway providing the *S* enantiomer of **5** was investigated. We started from commercially available L-malic acid **1**, which had an *S* absolute configuration, and kept it during synthesis (Scheme 1).

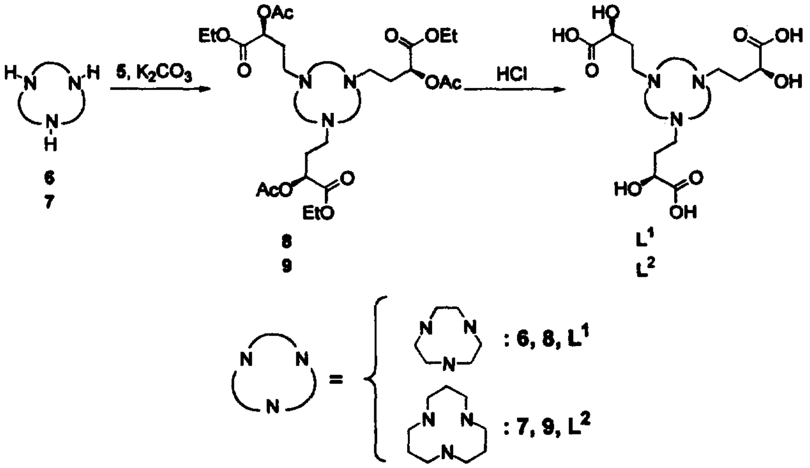


Scheme 1.

The key step of this synthesis was the selective protection of both the hydroxyl and carboxylic acid α to the hydroxyl functions, i.e., protection of the part mimicking L-lactic acid. This was achieved by a two-step reaction.[7] First, treatment of L-malic acid **1** with a mixture of acetyl chloride and acetic anhydride provided 2-(*S*)-acetoxysuccinic anhydride **2**. Then, the anhydride was opened with absolute ethanol to give the regioisomer ethyl 2-(*S*)-acetoxy-3-carboxypropionate **3** in quantitative yield. We checked the regiospecificity of anhydride opening by investigating the structure of the single compound of the reaction. This was achieved using a combination of two NMR experiments with observation of long-range coupling. The process was the following: each carbon signal was first assigned without ambiguity by a Heteronuclear Multiple Bond Connectivity (HMBC) experiment. Then, the structure was finally resolved by recording a proton-coupled ^{13}C (using gated decoupling) spectrum. The carbon signal attributed to the carboxylic acid function, recorded with proton-coupled ^{13}C, splits into a double triplet with coupling constants $^3J_{CH}$ of 5.3 and $^2J_{CH}$ of 6.9 Hz. This multiplicity confirms that the analysed product corresponds to product **3**. To our knowledge, this was the first analytical confirmation of the regiospecificity of the reaction reported in the literature.[8]

The carboxylic acid function can then be transformed into a good leaving-group allowing substitution by amine. Thus, carboxylic acid of **3** was selectively reduced by borane in tetrahydrofuran to provide ethyl 2-(*S*)-acetoxy-4-hydroxybutyrate **4** in 70% yield as a colourless oil. The reaction was carried out at 0°C. At this temperature, ester functions were not affected by reduction.[9] Finally, classic bromination of the alcohol with triphenylphosphine dibromide gave ethyl 4-bromo-2-(*S*)-acetoxybutyrate **5** with a 75% yield.

For coupling **5** to polyazamacrocycles **6** or **7** (Scheme 2), the cyclic triamines were first treated with base in non-protic polar solvent and the mixture was allowed to react with **5** to afford *N,N′,N″*-tris[2(*S*)-acetoxy-butyrate ethyl ester]-1,4,7-triazacyclononane **8** or *N,N′,N″*-tris[2(*S*)-acetoxy-butyrate ethyl ester]-1,5,9-triazacyclododecane **9**, respectively; yields were dependent on the base and solvent used. The highest yields, 48% for **8** and 54% for **9** after chromatographic purification, were obtained with K_2CO_3 as base in DMF at room temperature.[10] Compounds **8** and **9** were characterised by mass spectrometry and NMR spectroscopy.[11] The ^{13}C and ^{1}H NMR spectra are in agreement with the symmetric structure of both compounds. Finally, both ethyl and acetyl ester functions were hydrolysed under acidic conditions to give *N,N′,N″*-tris[2(*S*)-hydroxybutyric acid]-1,4,7-triazacyclononane L^1 and *N,N′,N″*-tris[2(*S*)-hydroxybutyric acid]-1,5,9-triazacyclododecane L^2 as polyhydrochloride salts.[12] The structural characterisation and purity of each ligand were checked by satisfying high resolution mass spectrometry (HRMS) results and clean ^{1}H and ^{13}C NMR spectra since both ligands were too hygroscopic to make satisfying microanalysis.[13]



Scheme 2.

The synthetic approach presented here could be applied to the synthesis of macrocycles bearing other α-hydroxy or α-keto-carboxylic groups and obtained as pure enantiomers. The chemistry and electrochemistry of the manganese species obtained with these new ligands are under investigation.

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8. Until now, the regiospecificity of the reaction had only been testified by the chemical reactivity of compound **3** in selective reductions: Horn, Pretorius, *J. Chem. Soc.* **1954**, 1460.
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10. General procedure for the preparation of compounds **8** and **9**: to a suspension of triazacycloalkane **6** or **7** (3.9 mmol) and K_2CO_3 (2.40 g, 17.5 mmol) in anhydrous DMF (10 ml) was added dropwise bromide **5** (3.23 g, 12.9 mmol) in anhydrous

DMF (5 ml) with stirring under N_2. The reaction mixture was stirred at room temperature for 8 h and then taken up into ethyl ether (100 ml). The solution was filtered and the solvents evaporated off under reduced pressure. The residue was chromatographed on a silica gel column eluted with CH_2Cl_2:MeOH (95:5, v/v) to afford pure product as a pale yellow oil.

11. Selected data: **8**: ^{1}H NMR (300 MHz, $CDCl_3$) δ_H=5.05 (3H, dd, ^3J=7.7 and 5.1 Hz, $C\mathit{H}$), 4.19 (6H, q, ^3J=7.1 Hz, $OC\mathit{H}_2CH_3$), 3.10 (12H, br s, $NC\mathit{H}_2$ ring), 2.88 (6H, br t, ^3J=7.3 Hz, $NC\mathit{H}_2$ arm), 2.14 (9H, s, $COC\mathit{H}_3$), 2.08 (6H, m, $NCH_2C\mathit{H}_2$ arm), 1.27 (9H, t, ^3J=7.1 Hz, $OCH_2C\mathit{H}_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C=170.4, 169.6 ($\mathit{C}O_2Et$, $\mathit{C}OCH_3$), 69.9 ($\mathit{C}H$), 61.9 ($O\mathit{C}H_2CH_3$), 53.0 ($N\mathit{C}H_2$ ring), 52.6 ($N\mathit{C}H_2$ arm), 27.8 ($NCH_2\mathit{C}H_2$ arm), 20.7 ($CO\mathit{C}H_3$), 14.2 ($OCH_2\mathit{C}H_3$); MS (CI/NH_3) *m/z*=646 (100%, $[M+H]^+$). **9**: ^{1}H NMR (300 MHz, $CDCl_3$) δ_H=4.95 (3H, dd, ^3J=7.7 and 5.1 Hz, $C\mathit{H}$), 4.12 (6H, q, ^3J=7.1 Hz, $OC\mathit{H}_2CH_3$), 2.57 (18H, br, $NC\mathit{H}_2$ arm and ring), 2.04 (9H, s, $COC\mathit{H}_3$), 2.01 (6H, br, $NCH_2C\mathit{H}_2$ arm), 1.66 (6H, br, $C\mathit{H}_2$ ring) 1.19 (9H, t, ^3J=7.1 Hz, $OCH_2C\mathit{H}_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C=170.7, 170.0 ($\mathit{C}O_2Et$, $\mathit{C}OCH_3$), 70.5 ($\mathit{C}H$), 62.2 ($O\mathit{C}H_2CH_3$), 49.6 ($N\mathit{C}H_2$ ring), 49.0 ($N\mathit{C}H_2$ arm), 27.7 ($NCH_2\mathit{C}H_2$ arm), 20.7 ($CO\mathit{C}H_3$), 16.0 ($\mathit{C}H_2$ ring), 14.2 ($OCH_2\mathit{C}H_3$); MS (CI/NH_3) *m/z*=688 (100%, $[M+H]^+$).
12. General procedure for the preparation of compounds $\mathbf{L}^1$ and $\mathbf{L}^2$: compound **8** or **9** was treated with an HCl solution (3 M, 7 ml) for 2 h at 100°C. Then, the solvent was evaporated and the salt formed washed several times with dry acetone under nitrogen to afford the product as a white hygroscopic solid (80% yield) which was stable when stored under nitrogen.
13. Selected data: $\mathbf{L}^1$: $[\alpha]_D^{25}=-8.5\pm0.5$ (*c* 0.16 in H_2O); ^{1}H NMR (300 MHz, D_2O, pD=1.11) δ_H=4.47 (3H, dd, ^3J=6.9 and 3.6 Hz, $C\mathit{H}$), 3.46 (12H, br, $NC\mathit{H}_2$ ring), 3.34 (6H, br t, $NC\mathit{H}_2$ arm), 2.35 (3H, m, $NCH_2C\mathit{H}H$ arm), 2.15 (3H, m, $NCH_2CH\mathit{H}$ arm); ^{13}C NMR (75 MHz, D_2O, pD=1.11) δ_C=178.5 ($\mathit{C}O$), 70.4 ($\mathit{C}H$), 55.9 ($N\mathit{C}H_2$ ring), 51.6 ($N\mathit{C}H_2$ arm), 29.8 ($NCH_2\mathit{C}H_2$ arm); MS (FAB): calculated mass for $C_{18}H_{34}N_3O_9$ $[(M+H)^+]$: 436.2295. Found: 436.2311. $\mathbf{L}^2$: $[\alpha]_D^{25}=-14.5\pm0.5$ (*c* 0.20 in H_2O); ^{1}H NMR (300 MHz, D_2O, pD=1.02) δ_H=4.41 (3H, dd, ^3J=4.5 and 3.0 Hz, $C\mathit{H}$), 3.40 (18H, br, $NC\mathit{H}_2$ ring and $NC\mathit{H}_2$ arm), 2.28 (9H, br m, CH_2 ring and $NCH_2C\mathit{H}H$ arm), 2.12 (3H, m, $NCH_2CH\mathit{H}$ arm); ^{13}C NMR (75 MHz, D_2O, pD=1.02) δ_C=176.9 ($\mathit{C}O$), 69.6 ($\mathit{C}H$), 53.2 ($N\mathit{C}H_2$ ring), 49.3 ($N\mathit{C}H_2$ arm), 27.9 ($NCH_2\mathit{C}H_2$ arm), 18.3 ($\mathit{C}H_2$ ring); MS (electrospray): calculated mass for $C_{21}H_{38}N_3O_9$ $[(M-H)^-]$: 476.5. Found: 476.3.