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Enantiospecific synthesis of isomers of AES, a new environmentally friendly chelating agent

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Abstract—Three four-step enantiospecific syntheses of different diastereomers of AES, a new biodegradable chelating agent, are described. The stereocenters in each of the isomers are accessible from L- and D-malic and aspartic acids.

1. Introduction

Due to the increasing use of chelating agents, their environmental fate has become an important issue.[1] Approximately 50,000 tons of aminopolycarboxylates such as EDTA and DTPA are used annually; mainly in the textile, detergent and pulp and paper industries.[2] EDTA and DTPA have proven to be practically non-biodegradable in standard tests.[3] For this reason, alternative chelating agents such as the aspartic acid derivatives ethylene diamine disuccinic acid (EDDS) and iminodisuccinic acid (IDS) have become more popular as biodegradable chelating agents, particularly for detergent applications.[4]

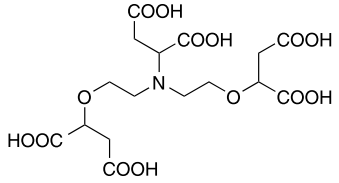
A series of novel diethanolamine derivatives such as aspartic acid ethoxysuccinate (AES) have recently been introduced as chelating agents suitable for pulp and paper applications (Fig. 1).[5] Due to its higher biodegradability, lower nitrogen content and capacity to form inert complexes with iron and manganese ions, AES is a more environmentally friendly alternative to EDTA and DTPA in the pulp and paper industry.[6] A non-selective but industrially viable route to AES via a lanthanum catalyzed Michael addition of diethanolamine to maleate has recently been described.[7] The presence of three stereogenic centers in the AES molecule gives rise to stereoisomerism. When the pseudo-symmetrical nature of the AES molecule is taken into account, one can observe that the (*S*,*S*,*R*) and the (*R*,*S*,*S*) isomers are identical to each other, as are the (*S*,*R*,*R*) and the (*R*,*R*,*S*) isomers. For this reason, there are only six possible isomers of AES, consisting of three pairs of enantiomers (Fig. 2).

Based on previous studies with the EDDS isomers,[8] the different AES isomers are expected to have different biodegradability characteristics. For full characterization of these new chelating agents, we therefore needed access to all AES isomers. Herein, we present a simple and efficient protocol for the enantiospecific synthesis of AES.

2. Results and discussion

The three chiral centers of AES are, in principle, accessible from (*R*)- and (*S*)-isomers of the readily available malic and aspartic acids. Connecting these building blocks to form the AES framework, however, is not straightforward. There are numerous possible side-reactions including the formation of lactams and lactones as well as retro-Michael reactions.

Retrosynthetic analysis of the target molecule reveals two suitable synthetic strategies which use malic and aspartic



AES (1)

Figure 1. Structure of AES (**1**).

Keywords: Aldehydes; Amino acids; Chelating agents; Reductive amination; Stereoisomerism.
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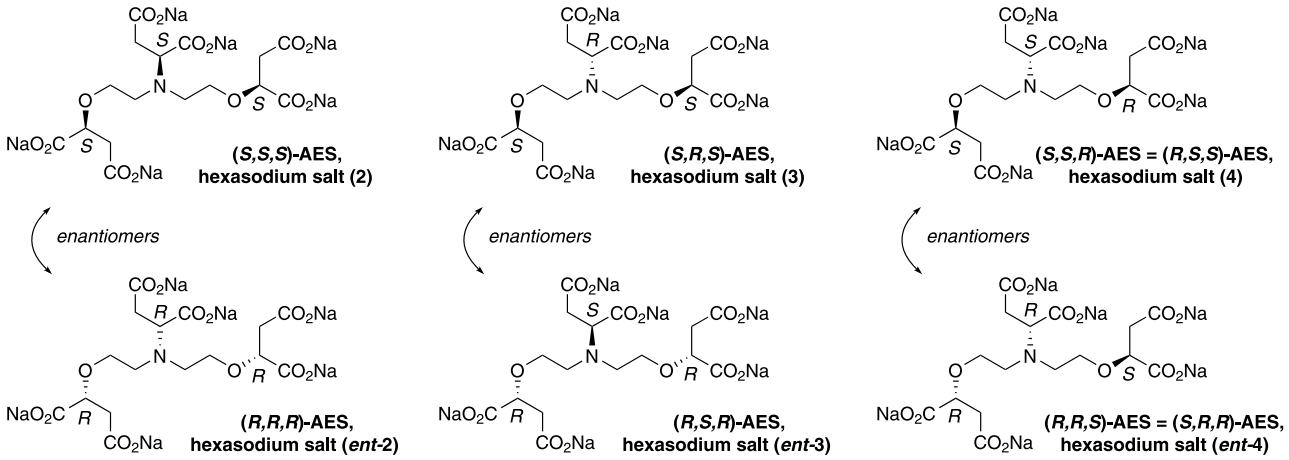
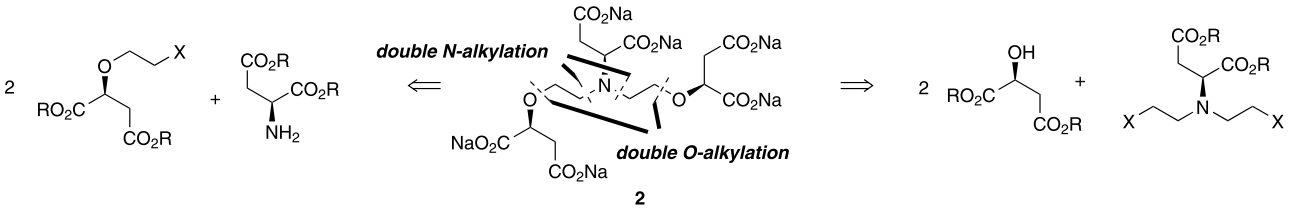


Figure 2. Structures of all AES isomers.

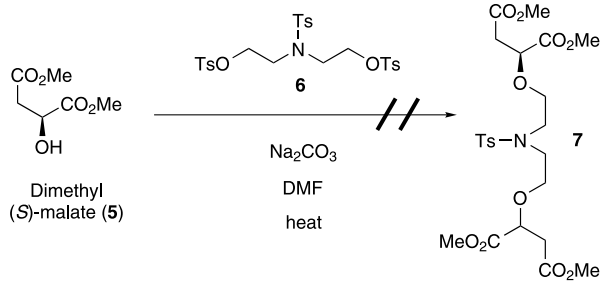


Scheme 1. Retrosynthetic analysis.

acid as starting materials: double *O*-alkylation and double *N*-alkylation (Scheme 1). Of the two disconnections, the double *N*-alkylation strategy appears more attractive since it would, at least in principle, allow the stepwise construction of the molecule by two consecutive *N*-alkylation steps. Thus, the (*S*,*S*,*R*) isomers could also be accessed by this method.

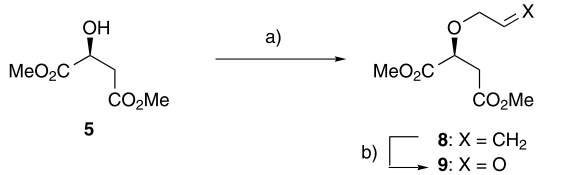
We were also further discouraged from pursuing the *O*-alkylation strategy by our initial attempts at *O*-alkylation of (*S*)-malic acid dialkyl esters with tosylated diethanolamine derivatives (Scheme 2). Instead of the desired *O*-alkylation, the reaction invariably produced the corresponding morpholines derived from the tosylate **6**.

There are several reductive amination methods available which reliably give the monoalkylation product so we decided to use this approach next to perform double *N*-alkylation of the aspartate methyl ester using a suitable malic acid derived aldehyde.[9] This approach would provide easy access to all AES isomers since the final reductive amination could then be performed with either of the enantiomeric aldehydes. However, we recognized that the requisite dialkylation reaction could be a difficult task given the low nucleophilicity of the monoalkylation product.

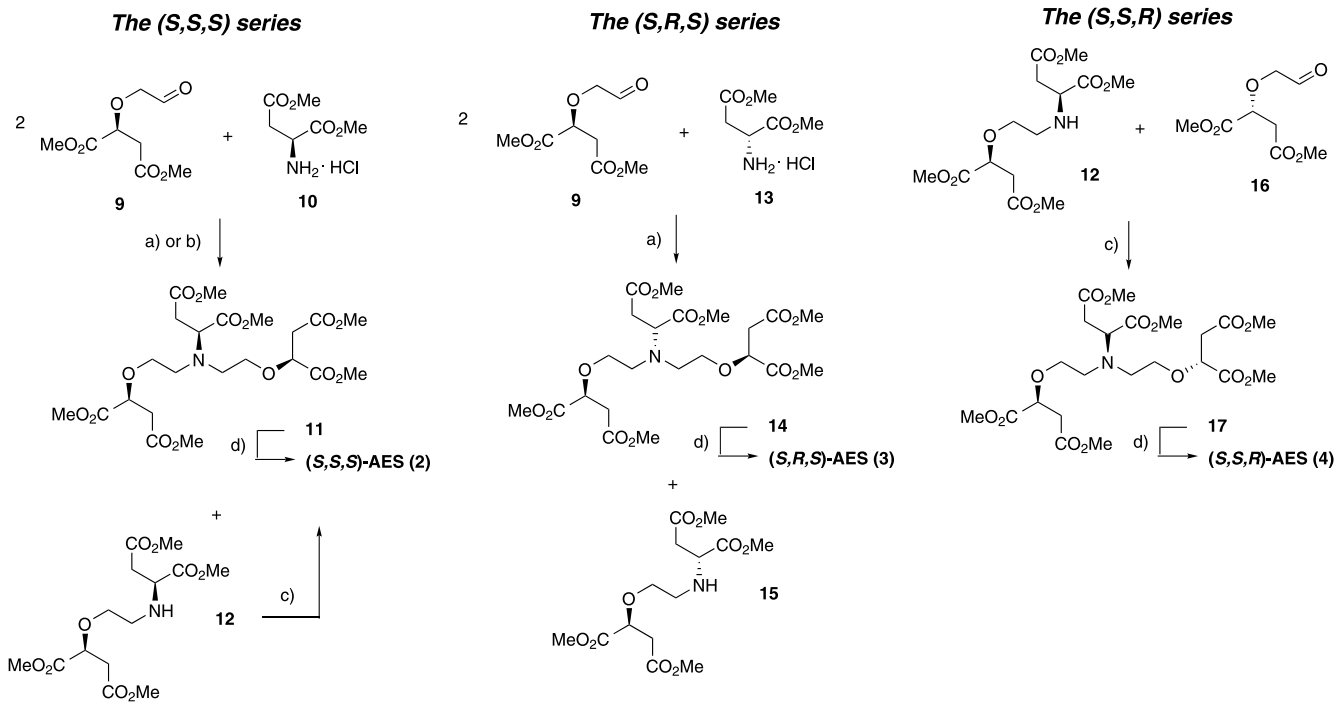


Scheme 2. Initial attempts at *O*-alkylation of dimethyl malate with diethanolamine-derived electrophiles.

For the synthesis of the key aldehyde building block **9** (Scheme 3) and its enantiomer **16** (see Scheme 4), we initially used a procedure adapted from the previous synthesis of **9** by Samuelsson and co-workers.[10] Thus, dimethyl (*S*)- or (*R*)-malate was alkylated with allyl bromide using freshly prepared Ag_2O as the bromide scavenger. We found that the amount of Ag_2O was critical for this transformation since use of more than 20 mol% excess of the reagent led to allylation of the solvent as well. After OsO_4-catalyzed dihydroxylation and subsequent cleavage of the resulting diol with sodium periodate, the aldehyde **9** was obtained in 60–65% overall yield from dimethyl malate. This procedure worked very efficiently on the small scale described by the authors (0.5 mmol). On scaleup, however, several modifications to the procedure were required. The aldehyde **9** is very prone to polymerization and decomposition, particularly when dry. Even traces of acids in deuterated chloroform were enough to completely destroy a batch of aldehyde **9** in a matter of hours! However, when pure, **9** could easily be stored in a freezer in a frozen cyclohexane matrix for several months without decomposition.



Scheme 3. Synthesis of aldehyde **9**. Reagents and conditions: (a) allyl bromide (9 equiv), Ag_2O (1 equiv), toluene, rt, 2 h; (b) OsO_4 (2 mol%), *N*-methylmorpholine-*N*-oxide (NMO, 2 equiv), 3:1 THF/H_2O, 0 °C→rt, 21 h; then $NaIO_4$ (2 equiv), 3:1 THF/H_2O, 80% from **5**.



Scheme 4. Synthesis of AES isomers. Reagents and conditions: (a) aldehyde **9** (2.6 equiv), aspartate **10** or **13** (1 equiv), $NaBH_3CN$ (2.1 equiv), MeOH, 0 °C→rt, 24 h; 40% **11**, 48% **12** or 40% **14**, 42% **15**; (b) aldehyde **9** (3.65 equiv), aspartate **10** (1 equiv), $NaBH_3CN$ (3 equiv), MeOH, 0 °C→rt, 48 h, 80% **11**; (c) aldehyde **9** or **16** (1.1 equiv), amine **12** (1 equiv), $NaBH_3CN$ (1.1–1.5 equiv), formic acid (2 equiv), MeOH, 0 °C→rt, 24 h, 40% **11** or **17** (55% **11**, 59% **17** based on recovered **12**); (d) 1 M aq. NaOH (6.8 equiv), 1:1 MeOH/THF, rt, 18 h, quant.

After considerable experimentation, we found that aldehyde **9** was obtained in 80% overall yield by filtering the crude reaction mixture through silica, concentration in vacuo, addition of brine followed by careful gradient extraction with Et_2O and CH_2Cl_2. The first Et_2O extract had to be purified by filtration through a pad of silica, however, all subsequent extracts gave pure **9** upon concentration! If further purification was needed, **9** could readily be distilled in high vacuum using a Kugelrohr apparatus. With these modifications, multigram amounts of **9** and **16** could readily be prepared.

With the aldehydes **9** and **16** in hand, the reductive amination was explored. Initial experiments using Pd/C catalysis (2.2 equiv of aldehyde, 1 equiv **10**, EtOAc or EtOH solvents) gave complex reaction mixtures with only traces of the desired alkylation products. Very poor conversions were also obtained with sodium triacetoxyborohydride. However, sodium cyanoborohydride gave more satisfactory results. If all the reagents were added at the same time to a cooled mixture of 2.5 equiv of the aldehyde, 1 equiv of amine and 2 equiv of $NaBH_3CN$, substantial decomposition of the aldehyde was observed, even at 0 °C. However, with gradual addition of the amine and the cyanoborohydride over 1.5 h, and with 2 equiv of aldehyde, the monoalkylation product **12** was obtained in 63% yield and the dialkylation product **11** in 23% yield.

Better yields of the dialkylation product were obtained with 2.5 equiv of the aldehyde (40% **11**, 48% **12**). A more dramatic improvement in yield was realized when a further portion of the aldehyde (1.3 equiv) was added to the reaction mixture after 24 h. Using this procedure, the yield of the dialkylation product climbed to 80%. However, purification of the product became progressively more difficult with increased amounts of the aldehyde. Thus, it was easier and more reliable to recycle the monoalkylated product **12** and to resubject it to the reaction conditions (in this case, 2 equiv of formic acid was added to the reaction mixture to facilitate the iminium ion formation). The overall yield of the dialkylated product after one cycle was 55%. The corresponding (*S*,*R*,*S*) isomer was synthesized in a similar manner using the (*R*)-aspartic acid dimethyl ester **13** as the starting material (Scheme 4). The hexamethylester **14** was obtained in 40% yield after one cycle, along with 42% of the monoalkylated product **15**.

To access the (*S*,*S*,*R*)-isomer, the (*S*,*S*)-tetraester **12** was treated with the (*R*)-malic acid derived aldehyde **16** (1.1 equiv). The (*S*,*S*,*R*) ester **17** was obtained in 40% yield (59% based on recovered **12**). All the hexamethyl esters were diastereomerically >95% pure according to NMR spectroscopic analysis (the ^1H and ^{13}C NMR signals, although very close, are clearly distinct in all isomers).

Finally, the corresponding sodium salts of the AES isomers were readily obtained in quantitative yields by careful saponification of the products. Here, slow addition of a slight excess of NaOH was necessary to prevent unwanted retro-Michael reactions. Using an excess of NaOH led to the partial loss of one of the malic acid groups as the fumarate. However, no isomerization could be detected in the NMR spectra. The final products were judged to be >95% diastereomerically pure by ^1H and ^{13}C NMR spectroscopy.

The three isomers of AES synthesized herein, the (*S*,*S*,*S*), the (*S*,*R*,*S*) and the (*S*,*S*,*R*) isomers, are each members of the three possible enantiomeric pairs of AES isomers. The remaining

isomers are thus enantiomeric to the ones described herein and accessible through identical procedures.

3. Conclusion

In summary, a concise and versatile synthesis of isomers of AES, a novel biodegradable chelating agent is described. The synthesis is applicable to the asymmetric synthesis of all isomers of AES in pure form and it is amenable to scaleup.

With the pure isomers **2–4** in hand, the differences in biodegradability and capacity as chelating agents can now be fully explored. These studies will be described in detail elsewhere.

4. Experimental

4.1. General methods

All reactions were carried out under an argon atmosphere in flame-dried glassware, unless otherwise noted. Non-aqueous reagents were transferred under argon via syringe or cannula and dried prior to use. THF was distilled from Na/benzophenone. CH_2Cl_2 was distilled over CaH_2. All synthetic intermediates were azeotropically dried with toluene prior to use. Other solvents and reagents were used as obtained from supplier, unless otherwise noted. Analytical TLC was performed using Merck silica gel F254 (230–400 mesh) plates and analyzed by UV light or by staining upon heating with vanillin solution (6 g vanillin, 5 mL conc. H_2SO_4, 3 mL glacial acetic acid, 250 mL EtOH) or with ninhydrin solution (1 g ninhydrin, 100 mL isopropanol, five drops glacial acetic acid). For silica gel chromatography, the flash chromatography technique was used, with Merck silica gel 60 (230–400 mesh) and p.a. grade solvents unless otherwise noted.

The ^1H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$ on a Bruker Avance 400 (^1H 399.98 MHz; ^{13}C 100.59 MHz) spectrometer. The chemical shifts are reported in ppm relative to $CHCl_3$ (δ 7.26) for ^1H NMR and the residual $CDCl_3$ (δ 77.0) for ^{13}C NMR spectra. IR spectra were recorded on a Perkin–Elmer Spectrum One spectrometer. Optical rotations were obtained with a Perkin–Elmer 343 polarimeter. High resolution mass spectrometric data were obtained by the University of Oulu Analytical Services on Micromass LCT spectrometer. The elemental analyses were performed at the Analytical Services of the Department of Chemical Technology, Laboratory of Organic Chemistry.

4.1.1. (*S*)-(2-Oxoethoxy)succinic acid, dimethyl ester 9 and (*R*)-(2-oxoethoxy)succinic acid, dimethyl ester 16. To a solution of dimethyl (*S*)-malate **5** (5.60 g, 34.6 mmol, 1 equiv) in toluene (60 mL) was added allyl bromide (27.0 mL, 312 mmol, 9 equiv) and silver (I) oxide (8.01 g, 34.6 mmol, 1 equiv). After stirring for 2 h 20 min at rt the mixture was filtered through Celite and the solvent was evaporated to give the crude product **8** (6.72 g, 96%) as a pale yellow oil. The crude product was used directly in the next reaction.

The corresponding (*R*)-isomer was synthesized according to the method for preparation of **8** described above, with the exception that 1.05 equiv of Ag_2O was used and the reaction time was 5 h. Compound **19** was obtained in quantitative yield. The NMR data of **6** and its enantiomer match those reported in the literature.

To an ice-cold solution of **8** (2.01 g, 9.94 mmol, 1 equiv) and *N*-methylmorpholine *N*-oxide monohydrate (2.26 g, 16.72 mmol, 2 equiv) in THF/H_2O 3:1 (62 mL) was added OsO_4 (2.5 wt% solution in *t*-BuOH, 2.1 mL, 0.167 mmol, 2.0 mol%). The reaction mixture was stirred for 3 h at 0 °C and then allowed to warm to rt, overnight. Solid sodium hydrogen sulfite (2.10 g) was then added and the mixture was stirred for an additional 30 min at rt. The mixture was filtered through a pad of silica (2×20 mL THF rinse) and the solvents were evaporated to give the crude diol intermediate.

The crude diol (9.94 mmol, 1 equiv) was dissolved in THF/H_2O 3:1 (107 mL) and sodium periodate (4.25 g, 19.9 mmol, 2 equiv) was added. The mixture was stirred at rt for 30 min and then filtered through silica (2×20 mL THF rinse). After concentration, brine (100 mL) and Et_2O (100 mL) were added. The layers were separated and the aqueous phase was extracted with Et_2O (2×75 mL).The combined organic layers were dried (Na_2SO_4), filtered and concentrated, and the crude product was purified by dry flash chromatography (4×8 cm silica, EtOAc/hexanes stepwise gradient from 0 to 100% EtOAc, final flush with pure MeOH) to give a first batch, 0.44 g (22%), of the aldehyde. The aqueous layer was further extracted with CH_2Cl_2 (6×100 mL). These extracts were combined, dried (Na_2SO_4) and concentrated to give pure aldehyde **9** (1.27 g, 63%). Total yield of **9** 1.71 g, 84% (80% from **5**). **9**: viscous, colorless oil, $[\alpha]_D^{22}=-62.8$ (*c* 0.9, CH_2Cl_2), lit.[10] $[\alpha]_D^{22}=-44.1$ (*c* 0.5, $CHCl_3$). A reliable comparison of the rotation in $CHCl_3$ could not be made because the aldehyde decomposed relatively easily in dry $CHCl_3$! The NMR spectral data corresponded to those reported in the literature[10] but were best recorded with a trace of added Et_3N.

The aldehyde **9** could be stored in a frozen cyclohexane matrix at −20 °C for several months without appreciable decomposition. If necessary, it could be purified by Kugelrohr distillation (0.1 mmHg, bp 80–90 °C).

The corresponding enantiomeric aldehyde **16** was prepared using the same procedure from dimethyl (*R*)-malate in 61% overall yield. Its NMR spectra were identical to that of **9**. $[\alpha]_D^{22}=+56.8$ (*c*0.8, CH_2Cl_2).

4.1.2. (2*S*,2′*S*′,2″*S*)-{2-[[2′-(1″,2″-Bis-methoxycarbonyl-ethoxy)-ethyl]-(1′,2′-bis-methoxycarbonyl-ethyl)-amino]-ethoxy}-succinic acid hexamethyl ester (11) and (2*S*,2′*S*)-2-[2′-(1′,2′-bis-methoxycarbonyl-ethylamino)-ethoxy]-succinic acid tetramethyl ester (12). To a solution of aldehyde **9** (480 mg, 2.35 mmol, 2.35 equiv) in MeOH (1.8 mL) at 0 °C was added L-aspartic acid dimethyl ester hydrochloride **10** (197.6 mg, 1.00 mmol, 1 equiv) and $NaBH_3CN$ (94.3 mg, 1.50 mmol, 1.5 equiv) in three equal portions at 30 min intervals. After the last addition, the

resulting suspension was allowed to warm to rt over 18 h. The mixture was cooled to 0 °C and more **9** (265 mg, 1.30 mmol, 1.3 equiv) dissolved in MeOH (1.2 mL) was added, followed by $NaBH_3CN$ (94.3 mg, 1.50 mmol, 1.5 equiv). The reaction mixture was allowed to gradually warm to rt over 5 h. After a total reaction time of 48 h, the mixture was filtered and concentrated. The residue was dissolved in CH_2Cl_2 (50 mL) and washed with sat. $NaHCO_3$ (20 mL). The aqueous layer was extracted with CH_2Cl_2 (3×15 mL). The combined organic layers were dried (Na_2SO_4) and concentrated, and the crude product was purified by flash chromatography (silica gel, 85% EtOAc in hexanes+1.5% triethylamine). Yield of **11** 428 mg, 80%. **11:** colorless viscous oil, $[\alpha]_D^{22}=-82.7$ (*c*1.0, CH_2Cl_2); IR (film) 3634, 3462, 2998, 2955, 1737, 1438, 1371, 1279, 1169, 1128, 1002, 849, 782, 674 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 4.29 (dd, $J=5.1$, 7.5 Hz, 2H), 3.96 (t, $J=7.5$ Hz, 1H), 3.77 (s, 6H), 3.70 (s, 9H), 3.67 (td, $J=6.3$, 9.7 Hz, 2H), 3.68 (s, 3H), 3.44 (td, $J=6.2$, 9.5 Hz, 2H), 2.90–2.74 (m, 8H), 2.73 (dd, $J=7.5$, 16.1 Hz, 1H), 2.58 (dd, $J=7.5$, 15.9 Hz, 1H); ^{13}C NMR ($CDCl_3$, 400 MHz) δ 172.6, 171.8, 171.7, 170.5, 75.5, 70.8, 61.6, 52.2, 52.1 (2), 51.9, 51.7, 51.6, 37.6, 35.6; ESI MS calcd for (M^++H) $C_{22}H_{36}NO_{14}$ 538.2136, found 538.2147, $\Delta=2.1$ ppm.

An alternative procedure to access both amination products proceeded as follows: to a solution of aldehyde **9** (436 mg, 2.13 mmol, 2.6 equiv) in MeOH (1.8 mL) at 0 °C was added **10** (160 mg, 0.81 mmol, 1 equiv) and $NaBH_3CN$ (107 mg, 1.70 mmol, 2.1 equiv), both in three equal portions at 45 min intervals. The resulting suspension was stirred for 3 h at 0 °C, after which time it was allowed to warm to rt and stirred overnight. The reaction mixture was then treated and purified as described above to afford **11** (152 mg, 35%) and **12** (143 mg, 51%). Resubjection of **12** to the reductive amination conditions with 2 equiv formic acid (see the procedure below) afforded **11** in 40% yield based on **12**, raising the total yield of **11** to 55% (based on **10**).

Compound **12**: colorless oil, $[\alpha]_D^{22}=-47.3$ (*c* 0.7, CH_2Cl_2); IR (film) 3338, 2955, 1739, 1661, 1438, 1367, 1279, 1198, 1171, 1132, 998, 850, 785 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 4.34 (dd, $J=4.8$, 8.1 Hz, 1H), 3.78 (s, 3H), 3.77 (ddd, $J=3.8$, 6.1, 10.4 Hz, 1H), 3.75 (s, 3H), 3.73 (s, 3H), 3.70 (s, 3H), 3.70 (t, $J=5.9$ Hz, 1H), 3.57 (ddd, $J=3.8$, 9.8 Hz, 3.8 Hz, 1H), 2.92–2.70 (m, 3H), 2.76 (dd, $J=6.9$, 15.2 Hz, 2H), 2.67 (dd, $J=6.9$, 16.1 Hz, 1H), 1.87 (s, 1H); ^{13}C NMR ($CDCl_3$, 400 MHz) δ 173.8, 171.8, 171.3, 170.5, 75.3, 70.9, 57.6, 52.2, 52.1, 52.0, 51.8, 47.2, 37.7, 37.6; ESI MS calcd for (M^++Na) $C_{14}H_{23}NO_9Na$ 372.1271, found 372.1264, $\Delta=1.7$ ppm.

4.1.3. (2*S*,2′*R*,2″*S*)-{2-[[2′-(1″,2″-Bis-methoxycarbonyl-ethoxy)-ethyl]-(1′,2′-bis-methoxycarbonyl-ethyl)-amino]-ethoxy}-succinic acid hexamethyl ester (14) and (2*S*,2′*R*)-2-[2′-(1′,2′-bis-methoxycarbonyl-ethylamino)-ethoxy]-succinic acid tetramethyl ester (15). The hexamethyl ester **14** was synthesized as described above for **11** and **12**. Yield of **14**: 40% and **15**: 42%. **14**: colorless viscous oil, $[\alpha]_D^{22}=+1.8$ (*c* 0.6, CH_2Cl_2); IR (film) 3634, 3465, 3000, 2955, 1737, 1438, 1370, 1276, 1170, 1128, 1002, 850, 782 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 4.28 (dd, $J=5.3$, 7.3 Hz, 2H), 3.94 (t, $J=7.4$ Hz, 1H), 3.76 (s, 6H), 3.71 (s, 3H), 3.70 (s, 6H), 3.68 (s, 3H), 3.66 (td, $J=6.0$, 9.8 Hz, 2H), 3.44 (td, $J=6.4$, 9.6 Hz, 2H), 2.89–2.74 (m, 8H), 2.73 (dd, $J=7.4$, 16.0 Hz, 1H), 2.59 (dd, $J=7.4$, 16.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 400 MHz) δ 172.6, 171.8, 171.7, 170.5, 75.5, 70.6, 61.4, 52.14, 52.12 (2), 51.9, 51.7, 51.6, 37.6, 35.7; ESI MS calcd for (M^++H) $C_{22}H_{36}NO_{14}$ 538.2169, found 538.2136, $\Delta=6.1$ ppm. **15**: colorless oil, $[\alpha]_D^{22}=-25.6$ (*c*0.9, CH_2Cl_2); IR (film) 3419, 2956, 1739, 1646, 1439, 1368, 1279, 1198, 1172, 1133, 1044, 999, 857, 784 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 4.29 (dd, $J=4.8$, 8.1 Hz, 1H), 3.77 (ddd, $J=4.2$, 5.5, 9.5 Hz, 1H), 3.74 (s, 3H), 3.71 (s, 3H), 3.69 (s, 3H), 3.66 (s, 3H), 3.66 (t, $J=6.5$ Hz, 1H), 3.52 (ddd, $J=3.8$, 7.5, 9.7 Hz, 1H), 2.90–2.63 (m, 5H), 2.64 (dd, $J=6.5$, 16.0 Hz, 1H), 2.05 (s, 1H); ^{13}C NMR ($CDCl_3$, 400 MHz) δ 173.7, 171.7, 171.3, 170.5, 75.4, 71.0, 57.6, 52.1, 52.0, 51.9, 51.7, 47.3, 37.7, 37.6; ESI MS calcd for (M^++H) $C_{14}H_{24}NO_9$ 350.1451, found 350.1443, $\Delta=2.4$ ppm.

4.2. General procedure for reductive amination of 12 with formic acid

A solution of aldehyde **16** (584 mg, 2.86 mmol, 1.1 equiv) and tetramethylester **12** (900 mg, 2.58 mmol, 1 equiv) in MeOH (5.0 mL) was cooled to 0 °C. $NaBH_3CN$ (180 mg, 2.86 mmol, 1.1 equiv) and formic acid (0.19 mL, 5.0 mmol, 2 equiv) were added at 0 °C in one portion. The suspension was stirred for 3 h, after which time it was allowed to warm to rt and stirred overnight. The reaction mixture was concentrated and the residue was partitioned between CH_2Cl_2 (50 mL) and sat. $NaHCO_3$ (30 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3×30 mL). The combined organic layers were dried (Na_2SO_4), concentrated, and the crude product was purified by flash chromatography (85% EtOAc in hexane + 1–1.5% triethylamine) to give **17** (550 mg, 40%) and recovered **12** (170 mg, 19%).

This procedure was also used for the conversion of the reductive amination product **12** into **11**.

4.2.1. (2*S*,2″*S*,2″*R*)-{2-[[2′-(1″,2″-Bis-methoxycarbonyl-ethoxy)-ethyl]-(1′,2′-bis-methoxycarbonyl-ethyl)-amino]-ethoxy}-succinic acid hexamethyl ester (17). Pale yellow oil, $[\alpha]_D^{22}=-27.61$ (*c* 0.7, CH_2Cl_2); IR (film) 3456, 3155, 3002, 2955, 1736, 1438, 1370, 1280, 1171, 1129, 1002, 909, 732 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 4.29 (dd, $J=3.0$, 5.0 Hz, 1H), 4.27 (dd, $J=3.0$, 5.0 Hz, 1H), 3.94 (t, $J=7.5$ Hz, 1H), 3.76 (s, 6H), 3.71 (s, 3H), 3.70 (s, 6H), 3.67 (s, 3H), 3.71–3.63 (m, 2H), 3.46–3.40 (m, 2H), 2.90–2.73 (m, 8H), 2.72 (dd, $J=7.6$, 16.2 Hz, 1H), 2.58 (dd, $J=7.3$, 15.9 Hz, 1H); ^{13}C NMR ($CDCl_3$, 400 MHz) δ 172.6, 171.8, 171.7, 171.6, 170.5, 75.5, 70.8, 70.6, 61.5, 52.2, 52.1 (2), 51.9, 51.6, 51.5, 37.6, 35.6; ESI MS calcd for (M^++Na) $C_{22}H_{35}NO_{14}Na$ 560.1955, found 560.1951, $\Delta=0.8$ ppm.

4.3. General procedure for saponification of the hexamethyl esters

To a solution of hexamethyl ester **11** (133 mg, 0.25 mmol, 1 equiv) in 1:1 MeOH/THF-solution (1.2 mL) was added 1 M NaOH (1.70 mL, 1.70 mmol, 6.8 equiv). The mixture

was stirred at rt for 18 h and then concentrated to give crude **2** as a tan solid. The excess NaOH was removed by precipitation of the product from H_2O (0.5 mL) by adding ethanol (2 mL), affording **2** (153 mg, quant., calculated as $C_{16}H_{17}NO_{14}Na_6 \cdot H_2O \cdot (C_2H_5OH)_{0.5}$) as a white solid.

The same procedure was used for the synthesis of **3** and **4**, starting from **14** and **17**, respectively.

4.3.1. (2*S*,2′*S*,2″*S*)-2-{2′-[[2′-(1″,2″-Dicarboxy-ethoxy)-ethyl]-(1′,2′-dicarboxy-ethyl)-amino]-ethoxy}-succinic acid, hexasodium salt (2). White powder, melting range 340–385 °C (dec.), $[\alpha]_D^{22} = -13.7$ (*c* 0.5, H_2O); IR (KBr) 3429, 2967, 1591, 1409, 1308, 1196, 1107, 881, 686 cm^{-1}; ^1H NMR (D_2O, 400 MHz) δ 4.11 (dd, $J=3.2$, 9.6 Hz, 2H), 3.67–3.51 (m, 5H), 2.90–2.76 (m, 4H), 2.64–2.34 (m, 8H); ^{13}C NMR (D_2O, 400 MHz) δ 180.1, 179.4, 79.3, 67.4, 64.4, 50.9, 41.5, 37.3; ESI MS calcd for ($M^+ - Na$) $C_{16}H_{17}NO_{14}Na_5$ 562.0138, found 562.0117, $\Delta = 3.6$ ppm. Anal. calcd for $C_{16}H_{17}NO_{14}Na_6 \cdot H_2O \cdot (C_2H_5OH)_{0.5}$: C, 32.60; H, 3.54; N, 2.24. Found: C, 32.27; H, 3.24; N, 1.95.

4.3.2. (2*S*,2′*R*,2″*S*)-2-{2′-[[2′-(1″,2″-Dicarboxy-ethoxy)-ethyl]-(1′,2′-dicarboxy-ethyl)-amino]-ethoxy}-succinic acid, hexasodium salt (3). White powder, melting range 320–370 °C (dec.), $[\alpha]_D^{22} = -2.8$ (*c* 0.8, H_2O); IR (KBr) 3419, 2180, 1586, 1409, 1308, 1197, 1108, 877 cm^{-1}; ^1H NMR (D_2O, 400 MHz) δ 4.06 (dd, $J=3.4$, 9.2 Hz, 2H), 3.70 (dd, $J=5.5$, 8.1 Hz, 1H), 3.64 (ddd, $J=5.0$, 8.7, 9.7 Hz, 2H), 3.78–3.42 (m, 2H), 2.77–2.52 (m, 9H), 2.61 (dd, $J=3.4$, 15.4 Hz, 2H), 2.46 (dd, $J=9.2$ Hz, 15.4 Hz, 2H), 2.38 (ddd, $J=5.4$, 9.8, 15.3 Hz, 1H); ^{13}C NMR (D_2O, 400 MHz) δ 180.1, 179.4, 79.1, 67.2, 63.8, 50.7, 41.5, 35.2; ESI MS calcd for ($M^+ + H$) $C_{16}H_{18}NO_{14}Na_6$ 586.0113, found 586.0095, $\Delta = 3.2$ ppm. Anal. calcd for $C_{16}H_{17}NO_{14}Na_6 \cdot H_2O \cdot (C_2H_5OH)_{0.5}$: C, 32.60; H, 3.54; N, 2.24. Found: C, 32.52; H, 3.39; N, 2.07.

4.3.3. (2*S*,2′*S*,2″*R*)-2-{2′-[[2′-(1″,2″-Dicarboxy-ethoxy)-ethyl]-(1′,2′-dicarboxy-ethyl)-amino]-ethoxy}-succinic acid, hexasodium salt (4). White powder, melting range 300–310 °C (dec.), $[\alpha]_D^{22} = -9.7$ (*c* 0.7, H_2O); IR (KBr) 3434, 2970, 1603, 1385, 1307, 1193, 1105, 880, 683 cm^{-1}; ^1H NMR (D_2O, 400 MHz) δ 4.08 (dd, $J=3.5$, 6.0 Hz, 1H), 4.06 (dd, $J=3.6$, 5.9 Hz, 1H), 3.65 (dd, $J=5.6$, 8.5 Hz, 1H), 3.63–3.59 (m, 1H), 6.31 (t, $J=6.3$ Hz, 2H), 3.46 (td, $J=5.7$, 1.0 Hz, 1H), 2.82–2.69 (m, 4H), 2.58 (dd, $J=4.4$, 15.2 Hz, 1H), 2.57 (dd, $J=6.5$, 15.3 Hz, 1H), 2.57 (dd, $J=6.2$, 15.4 Hz, 1H), 2.44 (dd, $J=9.7$, 15.2 Hz, 1H), 2.44 (dd, $J=9.6$, 15.3 Hz, 1H), 2.40 (dd, $J=5.9$, 15.5 Hz, 1H); ^{13}C NMR (D_2O, 400 MHz) δ 180.8, 180.2, 180.1, 179.8, 179.4, 179.3, 79.3, 79.2, 67.5, 67.1, 63.9, 50.7, 50.6, 41.6, 41.5, 36.3; ESI MS calcd for ($M^+ + H$) $C_{16}H_{18}NO_{14}Na_6$ 586.0113, found 586.0123, $\Delta = 1.7$ ppm. Anal. calcd for $C_{16}H_{17}NO_{14}Na_6 \cdot (H_2O)_{2.5} \cdot (C_2H_5OH)_{0.5}$: C, 31.25; H, 3.86; N, 2.14. Found: C, 31.05; H, 3.74; N, 2.02.

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