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Novel metal complex synthons for chiral 4-azaleucine, 2,3-diaminopropanoic acid and its elaboration

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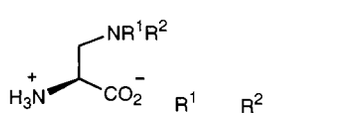
Efficient syntheses of chiral Co(III) complexes with 2,3-diaminopropanoic acid (A_2pr) have been developed. In these complexes, the amino acid zwitterion [$A_2pr(H^+)O^-$] is bound didentate through the carboxylate and N^2-amine groups while the N^3-ammonio group [$pK_a = 7.19(2)$] is unprotected. Syntheses of $\Lambda(+)_{578}$- and $\Delta(-)_{578}$-[$(en)_2Co$-(S-$A_2pr(H^+)O$)]$Cl_3\cdot H_2O$ were effected stereoretentively from the similarly didentate aspartato complexes Λ- and Δ-[$(en)_2Co(S$-Asp(OH)O)]Cl_2 in reaction sequences transforming the unbound β-carboxyl group into an amine by Curtius rearrangement. The absolute configuration of the $\Lambda(+)_{578}$-[$(en)_2Co(S$-Asp(OH)O)]$(ClO_4)_2$ complex was determined by X-ray crystallographic analysis and defined the absolute stereochemistry of diastereoisomers and derived products. Methylation of the N^3-amine group of $\Lambda(+)_{578}$-[$(en)_2Co(S$-$A_2pr(H^+)O$)]$Cl_3\cdot H_2O$ gave the (S)-4-azaleucine complex $\Lambda(+)_{578}$-[$(en)_2Co(S$-$A_2pr(Me_2H^+)O$)]$(C_4F_9SO_3)_3$ from which enantiopure (+)-(S)-2-amino-3-(dimethylamino)propanoic acid dihydrochloride hemihydrate [=(+)-(S)-$A_2pr(Me_2)\cdot 2HCl\cdot 0.5H_2O$] was obtained upon reductive removal of the protecting Co(III) centre. Racemic 4-azaleucine was easily produced by an alternative, but also metal-dependent method and the intermediate *rac*-(p)-[(tren)Co($A_2pr(Me_2H^+)O$)]$Zn_2Cl_7\cdot 3H_2O$ obtained in a simple solid-phase synthesis by selective reduction of achiral (p)-[(tren)Co(2-amino-3-(dimethylamino)acrylyl chloride)]$^{3+}$ ion adsorbed on AG 50W-X2 cation exchange resin. The epimerization rate of the Λ-[$(en)_2Co(S$-A_2prO)]$^{2+}$ complex ion was first-order in [HO^-] [$k_E = 3.8 \times 10^{-2}$ dm^3 mol^{-1} s^{-1}, $I = 1.00$ M ($NaClO_4$), 25 °C] with the diastereoisomer ratio K_C(=[Λ-R]/[Λ-S]) = 0.77(2) at equilibrium in 10 mM NaOH. However, no epimerization was observed after at least 3 hours in 6 M HCl at 45 °C.

The non-proteinogenic 2,3-diaminopropanoic acid (abbreviated: A_2pr; Scheme 1) is an essential component of many



	R^1	R^2
A_2pr	H	H
$A_2pr(ox)$	H	$COCO_2H$
$A_2pr(Me)$	H	Me
$A_2pr(Me_2)$	Me	Me

Scheme 1

natural products, a large number of which possess significant biological activities. The seeds of certain *Acacia* species contain free S-A_2pr, and several formal derivatives of this, all extensions of the N^3-amine group, also appear in higher plants,[1–3] *e.g.* thyrotoxic mimosine which causes loss of hair in growing animals,[4] and the excitotoxins quisqualic acid, (S)-2-amino-3-(oxalylamino)propanoic acid[4,5] [S-$A_2pr(ox)$] and (S)-2-amino-3-(methylamino)propanoic acid [S-$A_2pr(Me)$].[6] $A_2pr(ox)$ is implicated in the pathogenesis of neurolathyrism[5] and S-$A_2pr(Me)$ is present in the seeds of some Cycad palms which correlate with Pacific amyotrophic lateral sclerosis (Guam disease).[7] The toxicity of the latter is potentiated by carbonate, evidently *via* carbamate formation. The bacterial growth inhibitor (S)-2-amino-3-(N,N-dimethylamino)propanoic acid [S-$A_2pr(Me_2)$] produced by *Streptomyces neocaliberis* acts as an antimetabolite for leucine of which it is an isostere ("4-azaleucine").[8] Other microbial metabolites which also include the S-A_2pr unit, comprise the fungal aspergillomarasmin plant toxins[9] and several peptide antibiotics,[10–18] *e.g.* all members of the bleomycin[10,11] and malonomicin[12] families. The S-A_2pr unit constitutes the β-lactam element of the antibiotic nocardicin[13] and monobactam[14] structures. The serine protease (thrombin) inhibitor cyclotheonamide from the marine sponge *Theonella* sp.[15] contains one S-A_2pr unit and members of the tuberactinomycin family[16] incorporate up to three such units; for example, the antitubercular capreomycin.[17] Derived biosynthetically from (S)-serine, the S-A_2pr molecule is a genuine intermediate for the biosyntheses of certain peptides.[12,17,19] However, for derivatives in higher plants biosynthetic pathways involving O-acetyl-(S)-serine as an intermediate have been identified[2] but not pathways involving S-A_2pr. Curiously, the enantiomer, R-A_2pr, is detected in the digestive fluid of silkworm larvae, *Bombyx mori*.[20] So both enantiomers occur in biology and the S isomer at least has important roles to play. For the chemical syntheses of the natural products and analogues, partially protected derivatives of A_2pr are important building blocks. However, the direct synthesis of such derivatives from A_2pr is hampered by overall poor discrimination between the N^2- and N^3-amine groups.[9,21] Thus, in water at 25 °C the dissociable proton of the A_2pr zwitterion is almost equally distributed between the N^3- and N^2-amine groups.[22] By contrast, for the higher homologues, ornithine and lysine, the N^ω-amine is clearly favoured over the N^2-amine group by nearly an order of magnitude.[22] In practice, however, moderate selectivity between the N^2- and N^3-amine groups of A_2pr has been achieved. Thus, reaction with benzyloxycarbonyl chloride occurs preferentially at N^3 in a general procedure,[21,23–28] and similar selectivity was

recently reported for the reaction with the anhydride $(BOC)_2O$.[29] Other traditional avenues[24] to N^3-modified A_2pr derivatives are less direct and require several steps. An early strategy used the labile Cu(II) ion to mask the N^2-amine and carboxylate groups by chelation.[30] In the resulting square planar complex a stable five-membered chelate structure[31] leaves the N^3-amine available for modification in preference to the coordinated N^2-amine group. This masking strategy works well with ornithine and lysine,[30,32,33] and has been used to synthesize albizziine[28] as well as other molecules from A_2pr.[4,24,34] However, the reproducibility of a reported synthesis[4] of $A_2pr(ox)$ by the same method was later disputed.[35] Overall, the Cu(II)-masking strategy for A_2pr appears less reliable[35] and definitely lacks selectivity for acylations.[21]

While electrophiles may vaguely favour the N^3-amine over the N^2-amine group, the important N^2-protected A_2pr synthons are only achieved in multistep syntheses. Major strategies adopted for this purpose include (1) orthogonal protection procedures[9,16,24,26,27,32,36] applied to 2-amino-3-(benzyloxycarbonylamino)propanoic acid (or similar), (2) Hofmann and Curtius rearrangements with N^2-protected asparagine[9,37–39] and aspartic acid,[40] respectively, and (3) reactions involving key intermediates derived from N^2-protected serine. Such intermediates comprise protected 3-azidoalanine,[9,11,41] azetidinones,[42] serine-β-lactones[43] and *N*-tosylaziridine-2-carboxylates.[44] Gabriel syntheses with N^2-protected β-chloroalanine,[38,45] addition reactions to dehydroalanine synthons[46] and other strategies[47] have also been applied.

Elaborating the metal masking strategy, by protecting the carboxyl and N^2-amine groups of A_2pr with the substitution inert Co(III) centre offers significant advantages over the labile Cu(II) centre.[48,49] Chelate polyamine and amino acidato ligands of complexes of Co(III) usually remain undissociated in conditions covering a wide pH range. However, ligands may be readily released (deprotected!) by controlled reduction of the complex ($Co^{III} \rightarrow Co^{II}$) in relatively mild acid conditions.[50] Furthermore, their usually ionic character generally allows reaction and product separation procedures to be conducted in aqueous solution. Moreover, with adequate choice of counter ion (*e.g.* $CF_3SO_3^-$) reactions in other solvents are not precluded.[49] As part of a program to develop and exploit metal complex synthons for amino acid synthesis, this paper reports the syntheses and properties of chiral 2,3-diaminopropanoic acid Co(III) complexes with the A_2pr anion coordinated through the carboxylate and N^2-amine groups. Thus, the pendant N^3-amine group is available for further modification, and this aspect is explored in this publication along with alternative routes to 4-azaleucine derivatives.

Experimental

General

CAUTION! Although no difficulty was experienced with the perchlorate salts described in the following, these should be treated as potentially explosive and handled accordingly.

Dimensions of cation exchange columns (AG 50W-X2 resin, 200–400 mesh; Bio-Rad) are given as diameter × length. Routine evaporation of solvents was carried out at reduced pressure on a Büchi rotary evaporator using a water aspirator (≈20 Torr) and water bath (40 °C). Drying "*in vacuo*" was accomplished over P_4O_{10}. Anhydrous CF_3SO_3H (3M Comp.) was used as supplied and all other chemicals were of reagent grade or better. ^1H and ^{13}C NMR spectra were recorded in D_2O using Bruker HX-270 (modified to 250 MHz) or Varian 400 spectrometers and TPS [TPS = 3-(trimethylsilyl)propanesulfonic acid] and 1,4-dioxane (^{13}C, taking δ 69.14 relative to $SiMe_4$) as internal standards, respectively. In general, signals ascribable to the reference, the $CF_3SO_3^-$ ion, $C_4F_9SO_3^-$ ion, solvents of crystallisation and minor identifiable impurities are not listed. However, the presence of such impurities is reported in the text. Unless otherwise stated absorption, CD and optical rotation data were monitored in water with a Perkin-Elmer UV/VIS Spectrometer Lambda 2, a Jasco J-710 Spectropolarimeter and a Perkin-Elmer Polarimeter 141 (±0.002°, 1 dm quartz cell, 25.0 °C), respectively. Within experimental error all listed values for specific rotations ($[a]_\lambda$, in units of 10^{-1} deg cm^2 g^{-1}) of chiral products were unchanged after further recrystallization of the product, and this was taken as evidence of optical purity. Acid dissociation constants were determined in water at 25.0 °C and I = 1.00 M (NaBr) as described.[51]

Synthesis

Λ-[(en)$_2$Co(*S*-Asp(OH)O)]Cl$_2$·0.5EtOH·1.5H$_2$O and Δ-[(en)$_2$-Co(*S*-Asp(OH)O)]Cl$_2$·0.5EtOH·H$_2$O

L-(*S*)-Aspartic acid (13.3 g, 0.10 mol) was rapidly added to a stirring suspension of $[(en)_2Co(CO_3)]Cl$[52] (27.5 g, 0.10 mol) and activated charcoal (20 g) in water (0.5 l) at *ca.* 40 °C. The temperature was raised to *ca.* 70 °C and the stirred suspension left for 1 h. After addition of crushed ice (0.5 kg) and filtration ("Hyflo" filter aid) the filtrate was sorbed on an AG 50W-X2 column (Na^+ form, 6 × 40 cm). Elution with 0.15 M trisodium citrate revealed a minor leading purple band followed by two major orange bands and a minor yellow band. The first orange eluate {Λ-[(en)$_2$Co(*S*-Asp(O$^-$)O)]$^+$ diastereoisomer} was acidified (pH ≈3) with 12 M HCl and the solution desalted by sorption on an AG 50W-X2 column (7 × 20 cm, H^+ form) followed by washing with water (0.2 l) and 1 M HCl (1 l) before elution with 2 M HCl. The orange eluate was evaporated to almost dryness and the oily residue triturated under ethanol (150 ml) into a suspension of solid material. After addition of diethyl ether (50 ml) the solid of Λ-[(en)$_2$Co(*S*-Asp(OH)O]Cl$_2$·0.5EtOH·1.5H$_2$O (16.7 g, 39%) was collected, washed thoroughly with ethanol, diethyl ether and dried *in vacuo* (Found: Co, 13.8; C, 24.6; H, 6.2; N, 16.1. Calc. for $CoC_9H_{28}N_5O_6Cl_2$: Co, 13.64; C, 25.01; H, 6.53; N, 16.20%); ^{13}C NMR δ 187.0 (*C*OOCo), 177.6 (*C*OOH), 56.4 (α-*C*H), 48.1, 47.5, 47.4, 46.0 (4 × en-*C*H$_2$) and 39.0 (β-*C*H$_2$).

The second orange band (Δ-[(en)$_2$Co(*S*-Asp(O$^-$)O)]$^+$ diastereoisomer) of the original separation was eluted with 1.0 M NaCl and the complex isolated in an identical manner to yield Δ-[(en)$_2$Co(*S*-Asp(OH)O)]Cl$_2$·0.5EtOH·H$_2$O (12.4 g, 30%) (Found: Co, 14.0; C, 25.3; H, 6.3; N, 16.4. Calc. for $CoC_9H_{27}N_5O_{5.5}Cl_2$: Co, 13.93; C, 25.54; H, 6.43; N, 16.55%); ^{13}C NMR δ 186.9 (*C*OOCo), 177.4 (*C*OOH), 55.9 (α-*C*H), 47.8, 47.5, 47.1, 46.4 (4 × en-*C*H$_2$) and 38.9 (β-*C*H$_2$).

Λ(+)$_{578}$-[(en)$_2$Co(*S*-Asp(OH)O)](ClO$_4$)$_2$

To a filtered (0.45 μm Millipore filter) stirred solution of Λ-[(en)$_2$Co(*S*-Asp(OH)O)]Cl$_2$·0.5EtOH·1.5H$_2$O (3.82 g, 8.8 mmol) in water (5 ml) was added NaClO$_4$·H$_2$O (10.0 g) and 3 drops of 70% HClO$_4$. Heating to 60 °C with stirring initiated crystallization, and the mixture was left to cool before the solid product was collected, washed with ethanol, diethyl ether and dried. The product (4.5 g) was recrystallized from hot water (18 ml) by addition of NaClO$_4$·H$_2$O (5.0 g). Slow cooling to 5 °C afforded large orange crystals (4.0 g, 80%) which were collected, washed as above and dried in the air. $[a]_\lambda$ (λ/nm): 432 (578), 726 (546), −760 (436) and −709 (364) (0.08%, in 0.10 M HCl); CD_{max}, $\Delta\varepsilon_{510}$: 0.251 m^2 mol^{-1} (Found: Co, 11.6; C, 18.9; H, 4.1; N, 13.6; Cl, 14.1. Calc. for $CoC_8H_{22}N_5O_{12}Cl_2$: Co, 11.51; C, 18.86; H, 4.35; N, 13.73; Cl, 13.90%); λ_{max}/nm (ε_{max}/m^2 mol^{-1}): 485 (13.0), 347 (14.0) and 212 (24·10^2); ^{13}C NMR δ 187.1 (*C*OOCo), 177.9 (*C*OOH), 56.4 (α-*C*H), 48.1, 47.4 (double int.), 45.8 (4 × en-*C*H$_2$) and 38.9 (β-*C*H$_2$); pK_a = 3.27(2).

Λ-[(en)$_2$Co(*S*-Asp(OEt)O)]Cl$_2$

A stirred suspension of Λ-[(en)$_2$Co(*S*-Asp(OH)O)]Cl$_2$·0.5Et-

OH·1.5H_2O (16.0 g, 36.3 mmol) in ethanol (0.50 l) was cooled to −5 °C (ice/acetone mixture) in a flask fitted with a thermometer, dropping funnel and reflux condenser and a $CaCl_2$ drying tube. With stirring and cooling, thionyl chloride (12.0 ml, 165 mmol) was added dropwise at such a rate (over *ca*. 20 min) that the temperature remained below 0 °C. The mixture was then refluxed for 45 min while the suspended orange solid dissolved and another separated. After cooling to *ca*. 20 °C, diethyl ether (0.15 l) was added dropwise with gentle stirring over 15 min. The separated solid (14.8 g, 95%) was collected, washed with ethanol, diethyl ether and dried *in vacuo* (Found: Co, 14.2; C, 28.8; H, 6.4; N, 16.8; Cl, 17.6. Calc. for $CoC_{10}H_{26}N_5O_4Cl_2$: Co, 14.37; C, 29.28; H, 6.39; N, 17.07; Cl, 17.29%); ^{13}C NMR δ 187.0 (*C*OOCo), 176.1 (*C*OOEt), 65.2 (*C*H_2CH$_3$), 56.5 (α-*C*H), 48.1, 47.5, 47.4, 46.0 (4 × en-*C*H_2), 39.2 (β-*C*H_2) and 15.9 (*C*H_3).

Δ-[(en)$_2$Co(*S*-Asp(OEt)O)]Cl$_2$·0.33EtOH

This isomer was synthesized from Δ-[(en)$_2$Co(*S*-Asp(OH)O)]-Cl$_2$·0.5EtOH·H_2O analogously to the diastereoisomeric salt above (Found: Co, 13.7; C, 29.7; H, 6.4; N, 16.2; Cl, 16.9. Calc. for $CoC_{10.66}H_{28}N_5O_{4.33}Cl_2$: Co, 13.85; C, 30.09; H, 6.63; N, 16.46; Cl, 16.66%); ^{13}C NMR δ 186.9 (*C*OOCo), 175.9 (*C*OOEt), 65.2 (*C*H_2CH$_3$), 55.9 (α-*C*H) 47.8, 47.5, 47.0, 46.4 (4 × en-*C*H_2), 39.0 (β-*C*H_2) and 15.9 (*C*H_3).

Λ(+)$_{578}$-[(en)$_2$Co(*S*-Asp(OEt)O)](ClO$_4$)$_2$·H_2O

Gradual addition of $NaClO_4$·H_2O (4.0 g) to a solution of Λ-[(en)$_2$Co(*S*-Asp(OEt)O)]Cl$_2$ (3.5 g) in water (12 ml) followed by cooling in ice gave a crystalline product which was collected and washed with ethanol, diethyl ether and dried. The product (2.9 g) was recrystallized from hot water (15 ml) by gradual addition of $NaClO_4$·H_2O (3.0 g) and the crystals (2.5 g, 53%) isolated as above; $[\alpha]_\lambda$ (λ/nm): 397 (578), 666 (546), −705 (436), −675 (364) and −1080 (313), (0.06% solute in H_2O used for optical rotation measurement) (Found: Co, 10.7; C, 21.4; H, 5.0; N, 12.6; Cl, 12.6. Calc. for $CoC_{10}H_{28}N_5O_{13}Cl_2$: Co, 10.60; C, 21.59; H, 5.07; N, 12.59; Cl, 12.75%).

Δ(−)$_{578}$-[(en)$_2$Co(*S*-Asp(OEt)O)](ClO$_4$)$_2$·H_2O

This isomer was obtained from Δ-[(en)$_2$Co(*S*-Asp(OEt)O)]-Cl$_2$·0.33EtOH in the same manner as described for the diastereoisomeric salt above; $[\alpha]_\lambda$ (λ/nm): −347 (578), −595 (546), 895 (436), 835 (364) and 1325 (313), (0.06% in H_2O) (Found: Co, 10.7; C, 21.6; H, 4.9; N, 12.7; Cl, 12.8%).

Λ(+)$_{578}$-[(en)$_2$Co(*S*-A$_2$pr(H$^+$)O)]Cl$_3$·H_2O

Λ-[(en)$_2$Co(*S*-Asp(OEt)O)]Cl$_2$ (12.3 g, 30 mmol) was added to a stirring solution of hydrazine monohydrate (1.80 g, 36 mmol) and hydrazine monohydrochloride (2.47 g, 36 mmol) in water (30 ml). The resulting solution was stirred for 3 days in a closed flask. (**WARNING**: The following operations should be carried out in a well ventilated hood as HN_3 may be produced). The reaction mixture was cooled to 0 °C and mixed with a suspension of crushed ice (30 g) and concentrated HCl (16 ml, 0.19 mol). At 0 °C, a solution of $NaNO_2$ (9.00 g, 0.13 mol) in water (40 ml) was added at such a rate (over *ca*. 15 min) so as to keep the temperature below 5 °C. The resulting solution was left at 5 °C for 10 min then rapidly heated to 25 °C and left at this temperature for 10 min before it was poured into vigorously boiling 0.1 M HCl (2.0 l). Boiling was maintained for 20 min then the solution was cooled and sorbed on an AG 50W-X2 column (H^+-form, 7 × 25 cm). After washing with water (2 × 0.1 l), elution with 1.5 M HCl removed a minor orange band {Λ-[(en)$_2$Co(*S*-Asp(OH)O)]$^{2+}$}. The major orange band was eluted with 4 M HCl and evaporated to a viscous oil which was triturated under ethanol (0.1 l) to a crystalline powder (9.2 g). After washing with ethanol, diethyl ether and drying *in vacuo*, the product was recrystallized by dissolution at 70 °C in 20 ml of a saturated (25 °C) aqueous solution of LiCl. The hot solution was filtered and the frit washed with saturated LiCl solution (5 ml). The combined filtrate and washings were heated to 65 °C and boiling methanol (*ca*. 75 ml) was slowly added to initiate crystallization. The resulting suspension was left at *ca*. 20 °C for 3 h, and finally cooled to 0 °C when red crystalline needles separated which were collected, washed with methanol, diethyl ether and dried *in vacuo* (8.0 g, 65%); $[\alpha]_\lambda$ (λ/nm): 563 (578), 963 (546), −1166 (436), −1133 (364) and −1851 (313), (0.06%, in 0.10 M HCl); CD_{max}: $\Delta\varepsilon_{510}$ 0.235 m^2 mol^{-1} (Found: Co, 14.5; C, 20.6; H, 6.1; N, 20.3; Cl, 25.6. Calc. for $CoC_7H_{26}N_6O_3Cl_3$: Co, 14.46; C, 20.64; H, 6.43; N, 20.62; Cl, 26.09%); λ_{max}/nm (ε_{max}/m^2 mol^{-1}): 488 (10.1), 347 (10.9) and 212 (22 × 10^2); ^{13}C NMR δ 184.3 (*C*OOCo), 56.6 (α-*C*H), 48.3, 47.6; 47.4, 46.0 (4 × en-*C*H_2) and 42.9 (β-*C*H_2); ^{1}H NMR (H/D-exchanged amine groups) δ 4.07–4.00 (1 H, m, X part of ABX pattern, α-C*H*), 3.7–3.5 (2 H, m, AB part of ABX pattern, β-CH_2) and 3.0–2.7 (8 H, m, 4 × en-CH_2); pK_a = 7.19(2).

Δ(−)$_{578}$-[(en)$_2$Co(*S*-A$_2$pr(H$^+$)O)]Cl$_3$·H_2O

This isomer was obtained by the same procedure as that described above for the diastereoisomer but using Δ-[(en)$_2$Co-(*S*-Asp(OEt)O)]Cl$_2$·0.33EtOH (12.8 g, 30 mmol) as the starting complex; $[\alpha]_\lambda$ (λ/nm): −534 (578), −824 (546), 1053 (436), 995 (364) and 1649 (313), (0.06%, in 0.10 M HCl); CD_{max}: $\Delta\varepsilon_{515}$ −0.168 m^2 mol^{-1} (Found: Co, 14.4; C, 20.9; H, 6.0; N, 20.2; Cl, 26.0%); λ_{max}/nm (ε_{max}/m^2 mol^{-1}): 488 (10.4), 347 (11.2) and 215 (20 × 10^2); ^{13}C NMR δ 184.4 (*C*OOCo), 55.9 (α-*C*H), 47.8, 47.5, 47.1, 46.6 (4 × en-*C*H_2) and 42.8 (β-*C*H_2); ^{1}H NMR (H/D-exchanged amine groups) δ 4.22–4.16 (1 H, m, X part of ABX pattern, α-C*H*), 3.7–3.5 (2 H, m, AB part of ABX pattern, β-CH_2) and 3.0–2.7 (8 H, m, 4 × en-CH_2); pK_a = 7.18(2).

Λ(+)$_{578}$-[(en)$_2$Co(*S*-A$_2$pr(H$^+$)O)](CF$_3$SO$_3$)$_3$·MeOH

Anhydrous CF_3SO_3H (10 ml) was slowly added to Λ(+)$_{578}$-[(en)$_2$Co(*S*-A$_2$pr(H$^+$)O)]Cl$_3$·H_2O (3.00 g, 7.36 mmol) which dissolved with HCl gas evolution. Degassing was facilitated by applying a vacuum (rotary evaporator) and when gas evolution had ceased the resulting homogeneous solution was slowly poured into vigorously stirred diethyl ether (0.15 l). After 1 h of vigorous stirring, the solid, hygroscopic product was collected, washed with diethyl ether (3 × 25 ml), rapidly sucked almost dry on the filter and briefly dried *in vacuo*. The crude product was recrystallized from boiling methanol (75 ml) with slow cooling to 4 °C. The crystalline needles were collected, washed with ice-cold ethanol (3 × 10 ml), diethyl ether (10 ml) and dried as above (5.4 g, 95%) (Found: C, 17.5; H, 3.5; N, 10.9. Calc. for $CoC_{11}H_{28}N_6O_{12}S_3F_9$: C, 17.33; H, 3.70; N, 11.02%); pK_a = 7.19(2).

Λ(+)$_{578}$-[(en)$_2$Co(*S*-A$_2$pr(Me$_2$H$^+$)O)](C$_4$F$_9$SO$_3$)$_3$

In a well ventilated hood, Λ(+)$_{578}$-[(en)$_2$Co(*S*-A$_2$pr(H$^+$)O)]-Cl$_3$·H_2O (2.05 g, 5.0 mmol) was dissolved in a solution of glacial acetic acid (3.0 g, 20 mmol) and sodium acetate trihydrate (6.8 g, 50 mmol) in water (30 ml) followed by addition of aqueous 37% formaldehyde (6.5 ml, 87 mmol). To the vigorously stirring solution was slowly added (over 30 min) a solution of $NaBH_3CN$ (1.25 g, 20 mmol) in water (20 ml). The resulting solution was left with stirring for 30 min before it was diluted with water (0.5 l) and passed down a column of AG 50W-X2 resin (6 × 15 cm). The column was thoroughly washed with water (1 l) and 1 M HCl before the single orange band was eluted with a gradient of 1–3 M HCl. The eluate was concentrated to dryness and the solid residue dissolved in water (75 ml). A solution of potassium nonafluorobutanesulfonate (6.00 g, 17.5 mmol) in almost boiling water (50 ml) was slowly added to

the vigorously stirring solution to crystallize the complex nonafluorobutanesulfonate ("nonaflate") salt. After cooling in ice and stirring for 1 h the solid product was collected, washed with iced water (3 × 30 ml) and dried at 50 °C (5.53 g, 92%) (Found: C, 20.6; H, 2.3; N, 7.1. Calc. for $CoC_{21}H_{28}N_6O_{11}F_{27}S_3$: C, 20.87; H, 2.34; N, 6.95%); ^{13}C NMR (d_6-DMSO, δ 39.6 rel. to TMS): δ 180.1 (*C*OOCo), 58.2 (β-*C*H$_2$), 51.5 (α-*C*H), 45.5, 44.7 (double int.), 43.1 (4 × en-*C*H$_2$), 44.1 and 42.3 [N(*C*H$_3$)$_2$].

(+)-(*S*)-A$_2$pr(Me$_2$)·2HCl·0.5H$_2$O

To a vigorously stirring solution of $\Lambda(+)_{578}$-[(en)$_2$Co(*S*-A$_2$pr-(Me$_2$H$^+$)O)](C$_4$F$_9$SO$_3$)$_3$ (6.10 g, 5.0 mmol) in 50% ethanol (0.6 l) was added 1.0 M HCl (20 ml, 20 mmol) and zinc dust (1.0 g, 15 mmol) in this order. After 25 min of stirring, unreacted zinc was removed by filtration and the faintly pink filtrate was passed down a column of AG 50W-X2 resin (H$^+$-form, 6 × 15 cm) leaving a faint band at the top above a narrower pink band. After washing with cold water (1 l), elution was accomplished with 0.72 M NH$_3$. All column effluent passed through a 1-dm quartz cell placed in a polarimeter with continuous monitoring at 589 nm. After an optically inactive eluate fraction (0.95 l; $a \pm 0.002°$) an optically active fraction (0.2 l; α_{max} −0.3°) was collected and concentrated to *ca*. 0.1 l by rotary evaporation (40 °C). The concentrated solution was cooled by addition of crushed ice (*ca*. 50 g) before it was acidified to pH ≈ 1 with 2 M HCl (20 ml) and the solution passed down an AG 50W-X2 column (H$^+$-form, 6 × 10 cm). After washing with cold water (1 l) the barely visible band was eluted with HCl while the effluent optical rotation was monitored as described above. Following optically inactive eluate fractions of 0.65 l (eluent: 0.5 M HCl) and 0.50 l (eluent: 1.0 M HCl) had passed, an active fraction (0.6 l; eluent: 2.0 M HCl; α_{max} +0.14°) was collected and evaporated to a viscous oil. The residue was dissolved in water (0.1 l) and the solution evaporated to dryness. This process was repeated (0.05 l) leading to a crystalline residue which was dissolved in water (2.5 ml), filtered (0.45 μm Millipore filter) and the filtrate mixed with a similarly filtered saturated solution of LiCl in ethanol (30 ml). Crystal formation was induced in a 0.5 ml sample of the solution by adding ethanol (0.5 ml) and cooling in ice. This seeding mixture was then added to the original solution which was left for 2 days at 4 °C. Finally, colourless needles were collected, washed with cold ethanol (2 × 3 ml) followed by diethyl ether and dried *in vacuo*. Additional crystals separated from the filtrates (0.63 g, 59%, overall); $[a]_\lambda$ (λ/nm): 23 (589), 26 (578), 29.5 (546), 48.5 (436), 74.5 (364) and 110 (313), (0.5%, in 0.10 M HCl) (Found: C, 28.1; H, 6.9; N, 13.1. Calc. for $C_5H_{15}N_2O_{2.5}Cl_2$: C, 28.05; H, 7.06; N, 13.08%); ^{13}C NMR (0.5 M DCl) δ 171 (*C*OO), 58 (β-*C*H$_2$), 50 (α-*C*H), 48 and 46 [N(*C*H$_3$)$_2$]; pK_a = 6.58(2), 9.54(3).

(p)-[(tren)Co(GlyO)]Cl$_2$·2.5H$_2$O

Tris(2-aminoethyl)amine (22.5 ml, 150 mmol) and activated charcoal (2.0 g) were added to a solution of CoCl$_2$·6H$_2$O (30.2 g, 127 mmol) and glycine (10.0 g, 133 mmol) in water (230 ml). The resulting mixture was aerated for 20 h before the charcoal was removed by filtration ("Hyflo" filter aid) and the diluted filtrate (4 l) adsorbed on a column of AG 50W-X2 resin (13 × 10 cm). After washing with water (1 l) and 0.5 M HCl (0.5 l) a single orange band was eluted with 3 M HCl and the eluate evaporated to dryness. The solid residue was taken up in water (100 ml) followed by addition of LiCl (4.0 g) and ethanol (220 ml, in portions). After standing overnight at 5 °C for crystallization to commence a further 100 ml of ethanol was added to the mixture. This was again left overnight at 5 °C before the orange crystals were collected, washed with ethanol and diethyl ether, and dried in the air (30.7 g, 61%) (Found: Co, 14.4; C, 24.2; H, 6.9; N, 17.4; Cl, 17.9. Calc. for $CoC_8H_{27}N_5O_{4.5}Cl_2$: Co, 14.91; C, 24.32; H, 6.89; N, 17.72; Cl, 17.94%); λ_{max}/nm (ε_{max}/m^2 mol^{-1}): 472 (10.8) and 343 (10.3); ^{13}C NMR δ 187.0 (*C*OO), 64.3 (double int.), 61.5 [N(*C*H$_2$-)$_3$], 48.1 (double int.), 47.4 (3 × NH$_2$*C*H$_2$) and 49.3 (Gly-*C*H$_2$).

(p)-[(tren)Co(GlyO)](CF$_3$SO$_3$)$_2$

Anhydrous CF$_3$SO$_3$H (55 ml) was slowly added to (p)-[(tren)-Co(GlyO)]Cl$_2$·2.5H$_2$O (25 g, 63 mmol) in an evaporation flask. The complex gradually dissolved with evolution of HCl, and this process was facilitated by applying a vacuum (rotary evaporator). After the gas evolution, the resulting homogeneous solution was slowly poured into vigorously stirred diethyl ether (0.4 l). After 30 min of stirring a solid, hygroscopic product was collected, washed with diethyl ether, dried on the filter and then *in vacuo*. The solid was again stirred vigorously with absolute ethanol (0.15 l) at *ca*. 50 °C for 15 min before the product was collected, washed with absolute ethanol, diethyl ether and dried *in vacuo* (32.2 g, 88%) (Found: C, 21.1; H, 4.0; N, 11.5. Calc. for $CoC_{10}H_{22}N_5O_8S_2F_6$: C, 20.80; H, 3.84; N, 12.13%). The ^{13}C NMR spectrum was compatible with that of the chloride salt (above) but revealed a small impurity of ethanol.

Rac-(p)-[(tren)Co(A$_2$pr(Me$_2$H$^+$)O)]Zn$_2$Cl$_7$·3H$_2$O

Phosphoryl trichloride (12 ml, 0.10 mol) was added dropwise to a cooled (ice/salt bath) stirred solution of (p)-[(tren)Co-(GlyO)](CF$_3$SO$_3$)$_2$ (3.5 g, 6.0 mmol) in dry DMF (30 ml) at such a rate (over 40 min) that the temperature remained below −3 °C. Without cooling, stirring was continued for 2 h before the reaction mixture was poured into ice water (0.4 l) and the resulting solution adsorbed on a column of AG 50W-X2 resin (H$^+$ form, 5 × 9 cm). After washing with water (0.5 l), minor coloured byproducts (1+ and 2+ charge) were eluted with 0.5–1.0 M HCl leaving a major orange band (3+ charge) at the column top. After washing with 1 M NaCl (0.3 l) and water, the resin containing this band was suspended in 0.2 M NaHCO$_3$ (60 ml) and solid NaBH$_4$ (0.3 g) was added in portions over 30 s with vigorous stirring, which was continued for another 60 s before the resin was rapidly washed with water on a glass filter (vacuum filtration). The resin was transferred to the top of a column of the same resin type (Na$^+$ form, 5 × 4 cm). Elution with 1–2 M HCl removed a minor orange band followed by a major orange band (3+ charge). The eluate of the latter was evaporated to dryness, the residue dissolved in water (1.0 ml) and the product crystallized by addition of 1.5 M ZnCl$_2$, 3 M HCl (2 ml) followed by cooling to 5 °C. The orange crystals were isolated, washed with ethanol and diethyl ether and dried in the air (1.1 g, 25%) (Found: Co, 7.6; C, 17.5; H, 4.6; N, 10.9; Cl, 32.4. Calc. for $CoC_{11}H_{36}N_6O_5Zn_2Cl_7$: Co, 7.65; C, 17.15; H, 4.71; N, 10.91; Cl, 32.22%). ^{13}C NMR (2 M DCl) δ 183.7 (*C*OO), 64.5, 64.4, 61.8 (N(*C*H$_2$-)$_3$), 60.5 (β-*C*H$_2$), 54.6 (α-*C*H), 47.9, 47.8, 47.3 (3 × NH$_2$*C*H$_2$) and 45.5 [N(*C*H$_3$)$_2$].

Rac-A$_2$pr(Me$_2$)·2HCl·H$_2$O

To a solution of *rac*-(p)-[(tren)Co(A$_2$pr(Me$_2$H$^+$)O)]Zn$_2$Cl$_7$·3H$_2$O (4.72 g, 6.13 mmol) in water (0.5 l) was added 1.0 M HCl (25 ml, 25 mmol) and zinc dust (1.3 g, 20 mmol). After 15 min of stirring, unreacted zinc was removed by filtration and the faintly pink filtrate was passed down a column of AG 50W-X2 resin (H$^+$-form, 7 × 14 cm) leaving a faint band at the top above a narrower pink band. After washing with cold water (1 l), elution was accomplished with ice-cold 0.7 M NH$_3$. All column effluent passed through a 1.00 cm quartz flow cell placed in a Zeiss Spekol 1200 spectrophotometer with monitoring at 200 nm. After *ca*. 1.0 l of essentially non-absorbing eluate had passed, the absorbing eluate fraction (≈0.25 l) was collected and concentrated to *ca*. 0.15 l. The concentrated and cooled solution was acidified to pH ≈ 1 with 2 M HCl (25 ml) and the resulting solution passed down an AG 50W-X2 column (H$^+$-form, 7 × 14 cm). After washing with cold water (1 l) the

adsorbed, barely visible band was eluted with HCl while the effluent absorption was monitored as described above. After essentially non-absorbing eluate fractions of 0.65 l (eluent: 0.5 M HCl), 0.55 l (eluent: 1.0 M HCl) and 0.25 l (eluent: 2 M HCl) had passed, an absorbing fraction (0.35 l; eluent: 2.0 M HCl) was collected and evaporated to dryness. The residue was dissolved in water (0.1 l) and the solution re-evaporated to dryness before it was dissolved in water (3.0 ml), filtered (0.45 μm Millipore filter) and the filtrate mixed with a similarly filtered saturated solution of LiCl in ethanol (35 ml). The mixture was left for 3 h at 4 °C to separate colourless needles which were collected, washed with cold ethanol, diethyl ether and dried *in vacuo* (0.90 g, 66%) (Found: C, 27.2; H, 7.1; N, 12.5. Calc. for $C_5H_{16}N_2O_3Cl_2$: C, 26.92; H, 7.22; N, 12.56%); ^{1}H NMR (0.5 M DCl) δ 3.08 [6 H, s, N(CH_3)$_2$], 3.62 [1 H, dd, J 13.6 and 4.7, β-CH(1)H(2)], 3.88 [1 H, dd, J 13.6 and 9.3, β-CH(1)H(2)], 4.62 (1 H, dd, J 9.3 and 4.7, α-CH); ^{13}C NMR (0.5 M DCl) δ 171 (COO), 58 (β-CH$_2$), 50 (α-CH), 48 and 46 [N(CH$_3$)$_2$].

Epimerization kinetics and equilibration experiments

Qualitative experiments involving product analysis by ion exchange chromatography (Pharmacia FPLC equipment, Mono-S column, linear gradient (6.6 mM→0.167 M) Na_2-Hcitrate–Na_3citrate 1 : 1 buffer eluent, detector λ: 280 nm) indicated the ester hydrolysis of $\Lambda(+)_{578}$-[(en)$_2$Co(*S*-Asp(OEt)O)]-$(ClO_4)_2\cdot H_2O$ in 0.1 M NaOH to be over in <90 s forming the Λ-[(en)$_2$Co(*S*-Asp(O^-)O)]$^+$ complex which subsequently epimerised at the α-C atom on a slower timescale. The epimerization reaction was followed polarimetrically (Perkin-Elmer P-22 spectropolarimeter; 1 dm quartz cell, λ = 420 nm, $\Delta\alpha \approx 0.06°$, 25.0 °C) for freshly made solutions of $\Lambda(+)_{578}$-[(en)$_2$Co(*S*-Asp(OEt)O)]$(ClO_4)_2\cdot H_2O$ (1.0 mM) in different concentrations of NaOH, I = 1.00 M ($NaClO_4$). Plots of $\log(\alpha_\infty - \alpha_t)$ *versus* time were linear over at least three half-lives and gave observed rate constants [$10^4 k_{obs}/s^{-1}$ ([HO^-]/M): 0.95 (0.020), 2.9 (0.050), 6.5 (0.10), 12.5 (0.20)] which established a first-order dependence on [HO^-] and the second-order rate constant, $k_E = 0.6 \times 10^{-2}$ dm^3 mol^{-1} s^{-1}.

Likewise, the rotational change (λ = 435 nm, $\Delta\alpha \approx 0.06°$) of solutions of $\Lambda(+)_{578}$-[(en)$_2$Co(*S*-A_2pr(H^+O)O)]$Cl_3\cdot H_2O$ (1.0 mM) in the same conditions established a first-order dependence on [HO^-] [$10^3 k_{obs}/s^{-1}$ ([HO^-]/M): 0.80 (0.020), 1.9 (0.050), 4.0 (0.10), 7.6 (0.20)] with $k_E = 3.8 \times 10^{-2}$ M^{-1} s^{-1}. The epimer distribution of the [(en)$_2$Co(A_2prO)]$^{2+}$ complexes at equilibrium in 0.1 M NaOH was determined by the method of Buckingham *et al.*[53] Equilibrium was approached from both sides employing $\Lambda(+)_{578}$- and $\Delta(-)_{578}$-[(en)$_2$Co(*S*-A_2pr(H^+O)O)]$Cl_3\cdot H_2O$, respectively. The complex (*ca.* 85 mg) was dissolved in 50 ml 0.10 M NaOH, 0.90 M $NaClO_4$ and held at 25 °C for 10 h before acidification with excess 2 M HCl, dilution with water and sorption on AG 50W-X2 resin (2.5 × 4 cm). After elution with 3–4 M HCl the total band was evaporated and the residue then dissolved in D_2O and taken to dryness (2×). In order to effect H^+/D^+ exchange of all amine protons a solution of the residue in D_2O (0.5 ml) was mixed with 1 M Na_2CO_3 (in D_2O, 50 μl) and acidified after 60 s by addition of 12 M DCl (50 μl). The ^{1}H and ^{13}C NMR spectra of the resulting solutions were compatible with diastereoisomeric mixtures of the starting complexes and the isomer distributions were determined from integrations of the separate α-CH signal sets in the ^{1}H NMR spectra.

Crystallography

An orange crystal from a batch of $\Lambda(+)_{578}$-[(en)$_2$Co(*S*-Asp(OH)O)]$(ClO_4)_2$ crystals was cleaved and one half was glued on the end of a quartz fibre and transferred to the diffractometer. An X-ray powder diffraction pattern (STOE STADI P Instrument, quartz-crystal-monochromated Cu-Kα radiation) of other crystals from the same batch confirmed the selected crystal specimen to be representative of its batch of origin.

Crystal data. $CoC_8H_{22}N_5O_{12}Cl_2$, M = 510.07, orthorhombic, a = 8.811(1), b = 11.843(2), c = 17.788(3) Å, U = 1856.2(8) Å^3 [by least-squares refinement of diffractometer setting angles for 25 automatically centered reflections with 39° < 2θ < 44°, λ = 0.70930 Å, T = 297(2) K], space group $P2_12_12_1$ (no. 19), D_c (Z = 4) = 1.83, F(000) = 1048, μ(Mo-Kα) = 12.8 cm^{-1}, specimen 0.30 × 0.19 × 0.15 mm.

Data collection and processing. Philips PW 1100/20 diffractometer, graphite-monochromated Mo-Kα radiation (λ = 0.71069 Å), θ–2θ scans with θ scan width (0.95 + 0.346tanθ)°, 2441 unique reflections ($4 \le 2\theta \le 50°$ $0 \le h \le 11$, $0 \le k \le 15$, $0 \le l \le 23$) giving 2168 observed with $I \geqslant 3\sigma(I)$. Data corrected for crystal decay (*ca.* 2%)[54] and absorption,[55,56] $A^*_{min,max}$ = 1.17, 1.19.

Structure solution and refinement. Direct methods[57] led to location of all non-hydrogen atoms. Refinement with anisotropic displacement factors yielded R = 0.044, R_w = 0.054. Refinement of a model with coordinates transformed by ($-x$, $-y$, $-z$) yielded R = 0.054, R_w = 0.061, indicating that the original model corresponds to the absolute configuration of the crystal. All hydrogen atoms were observed in a difference electron density map. Coordinates for H(38) were taken from this map while the remainder of the H atoms were included at their calculated positions [r_{C-H} 0.95 Å, r_{N-H} 0.85 Å, U_{iso}(H) = 0.05] and their coordinates recalculated periodically during the refinement. Full-matrix least-squares refinement[55] was on $\Sigma w(|F_o| - |F_c|)^2$ including all non-H atoms (anisotropic) with the weighting scheme $w^{-1} = [\sigma(F_o)^2 + 0.0004(F_o)^2]$. Final R = 0.028, R_w = 0.035, $S[F^2]$ = 1.26 for 253 refined parameters. Features in final ΔF synthesis were all <0.4 e Å^{-3}.

CCDC reference number 186/1269.

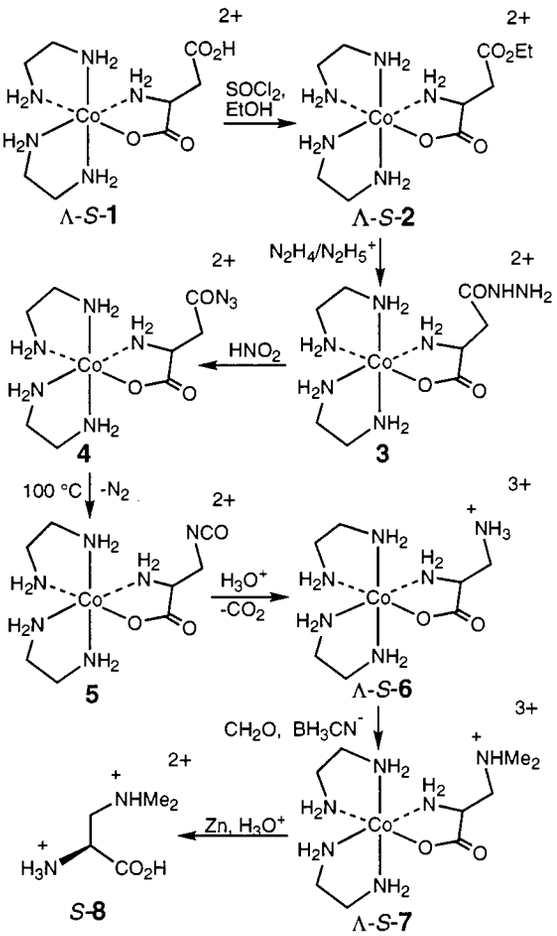
Results and discussion

Syntheses

Diaminopropanoic acid anion (A_2prO^-) was synthesized on a metal template by a single route and 4-azaleucine anion [$A_2pr(Me_2)O^-$] by two different routes, one yielding a chiral product the other racemic. In both instances the amino acid anion is bound in a didentate manner to the carboxylate and N^2-amine groups while the N^3-amine group is uncoordinated.

With bis(ethane-1,2-diamine)cobalt(III) complexes ("(en)$_2$Co^{III}"), selective N^2,O^1-coordination of potentially tridentate[58] amino acidates such as lysine[59] and aspartic acid[60] is often achieved in direct substitution reactions involving the amino acid anion and the diaqua complex or the amino acid and the aquahydroxo complex. However, attempts at reacting *S*-A_2pr with [(en)$_2$Co(OH_2)(OH)]$^{2+}$ only led to multiple products and very little, if any, of the desired products (**6**). Therefore, a synthetic strategy leading to the (*S*)-2,3-diaminopropanoato-N^2,O^1 complexes was developed using a selectively coordinated chiral amino acid precursor. For this purpose, the readily produced aspartato-N^2,O^1 complex diastereoisomers, Λ- and Δ-[(en)$_2$-Co(*S*-Asp(OH)O)]$^{2+}$ (**1**), were chosen. In these molecules, the (*S*)-aspartate ion is coordinated in the desired didentate fashion leaving the unprotected β-carboxyl group available for chemical manipulation. The conversion of this to an amine group was effected through a reaction sequence which initially generated the acyl azide (**4**) then *via* a Curtius rearrangement the isocyanate (**5**) and finally hydrolysis to give the end product (**6**) (Scheme 2).

The chiral aspartato complexes were synthesized essentially as before from [(en)$_2$Co(CO_3)]Cl and (*S*)-aspartic acid with a



Scheme 2

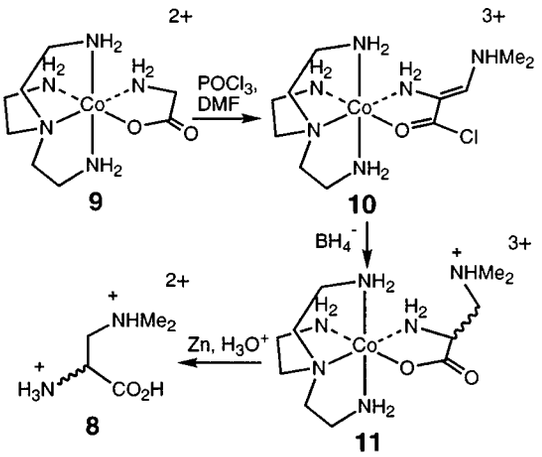
charcoal catalyst in aqueous suspension,[60] but the earlier separation and isolation procedures were improved. Thus, the Λ- and Δ-$[(en)_2Co(S\text{-}Asp(O^-)O)]^+$ cations were efficiently separated using trisodium citrate eluent on AG 50W-X2 resin and each diastereoisomer (acid form) was isolated as its dichloride salt in order to avoid the potentially hazardous perchlorate salts used earlier.[60] However, the perchlorate salt $\Lambda(+)_{578}$-$[(en)_2Co(S\text{-}Asp(OH)O)](ClO_4)_2$ was also isolated for characterization purposes and its absolute stereochemistry was established by X-ray crystallographic analysis. The isolated chloride salts, Λ- and Δ-$[(en)_2Co(S\text{-}Asp(OH)O)]Cl_2$, were diastereoisomerically pure but also contained some ethanol and water of crystallisation and, occasionally, slight amounts of the derivative monoethyl ester complexes. The latter arise from a subsequent esterification step (Scheme 2, **1**→**2**) which, in turn, was carried out more efficiently and stereoretentively for each diastereoisomer by refluxing them in ethanol with thionyl chloride. The resultant monoethylaspartato complex (**2**) chloride salts each precipitated directly from the reaction mixture. The ideally crystalline perchlorate salts were also isolated in small quantities for characterization purposes. In a series of reaction steps (**2**→→**6**), each monoethylaspartato complex diastereoisomer was converted to the derivative 2,3-diaminopropanoato complex in over 70% yield. These steps were conducted in water as a one-pot synthesis, and, therefore, the putative intermediates **3**–**5** are inferred from the proposed organic reaction sequence. This comprises hydrazinolysis of the ethyl ester complex (**2**), oxidation of the hydrazide (**3**) with nitrous acid to the acyl azide (**4**) followed by the Curtius rearrangement in boiling 0.1 M HCl to give the isocyanate (**5**) and subsequent hydrolysis to the carbamate and thence to the amine (**6**).

Related didentate α-amino acidato complexes are generally prone to base-catalyzed epimerization at the α-carbon centre.[53] However, such a process was effectively suppressed during the hydrazinolysis step by conducting the reaction in a hydrazine/hydrazinium chloride buffer (pH 8.2), thus avoiding the higher pH of aqueous hydrazine alone. At the lower pH, the epimerization half-life for the aspartato complex would be on the order of two years (*vide infra*) and the half lives for the derivative ester (**2**) and hydrazide (**3**) complexes would not be expected to be much different. During the nitrous acid oxidation step (Scheme 2, **3**→**4**), unreacted hydrazine in solution would also be consumed (→N_2) in parallel with the metal complex hydrazide (**3**), and an overall 50% excess of nitrous acid (aqueous HCl + solid $NaNO_2$) proved necessary for optimal yields. Moreover, it appeared critical that the Curtius rearrangement step (Scheme 2, **4**→**5**) be conducted in a vigorously boiling solution. At lower temperatures, yields of **6** were lower and the aspartato complex (**1**) became increasingly dominant as a byproduct. Obviously, hydrolysis and rearrangement are competing reactions available to the acyl azide (**4**) but, generally, rearrangement dominates at higher temperatures (>80 °C).[61]

As an alternative to the Curtius rearrangement strategy adopted here with the aspartato complexes the Hofmann rearrangement may be applied to the related asparaginato complexes, $[(en)_2Co(AsnO)]^{2+}$.[62] However, the classical method employing bromine in aqueous base was not effective at generating coordinated 2,3-diaminopropanoic acid. In these conditions only epimerization at the α-carbon centre and hydrolysis of the amide functionality of the starting Λ-$[(en)_2Co(S\text{-}AsnO)]^{2+}$ complex to yield the epimerized aspartato complex, Λ-$[(en)_2Co(R,S\text{-}Asp(O^-)O)]^+$, were observed.[63] However, moderate yields of Λ-$[(en)_2Co(S\text{-}A_2pr(H^+)O]^{3+}$ were achieved in an acidic water–acetonitrile solution of the asparaginato complex triflate salt Λ-$[(en)_2Co(S\text{-}AsnO)](O_3SCF_3)_2$ using $PhI(OAc)_2$[64] as the oxidant.[63]

The A_2prO^- complexes (**6**) each qualify as chiral synthons for the production of N^3-modified derivatives of A_2pr. While the N^2-amine and carboxylate groups in **6** are protected by the robust Co(III) centre, only the pendant N^3-amine function is available for modification. After modification, the resultant amino acid ligand may be liberated from the metal centre by reduction to the substitutionally labile Co(II) oxidation state. The feasibility of this strategy was here illustrated by the synthesis of optically pure (+)-(*S*)-2-amino-3-(dimethylamino)-propanoic acid [(+)-*S*-$A_2pr(Me_2)$] (**8**) from Λ-*S*-**6**. Alkylation of the primary N^3-amine of Λ-*S*-**6** with formaldehyde and $NaBH_3CN$ in aqueous acetic acid/acetate buffer[65] afforded the dimethylated derivative (**7**) in high yield. Reduction of this complex with zinc dust in acid and chromatographic separation of the liberated ligands led to isolation of the enantiopure free amino acid (**8**) dihydrochloride. This has been obtained before, also in a metal-aided synthesis, but less enantiopure.[66]

An alternative and simpler, albeit achiral strategy for synthesis of $A_2pr(Me_2)O^-$ is provided by Co(III) complexes containing chelated 3-(dimethylamino)-2-aminoacrylyl chloride (**10**, Scheme 3).[49,67] Clearly, reduction of the acrylyl olefinic bond and hydrolysis of the acyl chloride of **10** should give the $A_2pr(Me_2)O^-$ complex (**11**). The remarkably stable 3-(dimethylamino)-2-aminoacrylyl chloride cobalt(III) complex (**10**) is the major product[67] from the reaction of the glycinato complex, $[(tren)Co(GlyO)]^{2+}$, with phosphoryl trichloride and DMF (Vilsmeier–Haack reaction). Due to the inequivalence of the two coordination sites spanned by the unsymmetrical amino acidate ligand in the $[(tren)Co(GlyO)]^{2+}$ complex, two stereoisomers can be formed[68] and the Vilsmeier–Haack reaction has been carried out with both isomers, separately.[67] The isomers were denoted "t" or "p" when the ligating group *trans* to the carboxylate group is the tertiary amine or a primary amine, respectively, and this terminology is extended to derivatives.[67] Here, the (p)-$[(tren)Co(GlyO)]^{2+}$ complex (**9**) was obtained by simple aeration of an aqueous solution of $CoCl_2{\cdot}6H_2O$, tris(2-aminoethyl)amine (tren) and glycine in the presence of activated charcoal. No trace of the t isomer was obtained and,



Scheme 3

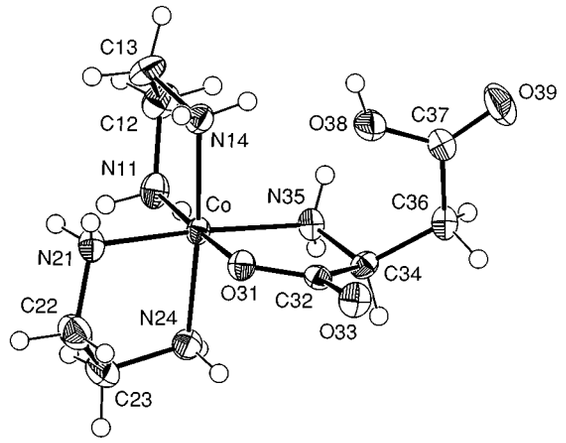


Fig. 1 Molecular structure of the $\Lambda(+)_{578}$-$[(en)_2Co(S\text{-}Asp(OH)O)]^{2+}$ cation.

compared with earlier strategies[67,69] this method represents a superior route to the p isomer, exclusively. It is almost an axiom that equilibration between stereoisomers of this type of Co(III) complex is catalyzed by activated charcoal.[70] The present result thus provides an experimental confirmation that the p isomer is the more stable in accord with earlier suggestions based on structural evidence and strain-energy minimization calculations.[68]

The reaction of **9** leading to the kinetically stable 3-(dimethylamino)-2-aminoacrylyl chloride cobalt(III) complex in DMF with phosphoryl trichloride has been discussed previously and the identity of the product **10**, established by an X-ray crystallographic analysis.[67] Remarkably, the delocalized acid chloride ligand is slow to hydrolyse both by loss of Cl^- and by demasking the formyl group. This raises the possibility of other reactions being competitive and specifically reduction. In this study, the ligand reduction step to produce **11** was conveniently performed as a "solid-phase" synthesis with the reactant complex still adsorbed on the ion exchange resin using $NaBH_4$ as reductant. This procedure enabled rapid removal of excess reductant in solution and thereby served to minimize loss of complex due to competing, but slower, reduction of the Co(III) ion to the Co(II) state. Liberation of the racemic amino acid, $A_2pr(Me_2)$, from **11** was achieved essentially as described above for $\Lambda(+)_{578}$-$[(en)_2Co(S\text{-}A_2pr(Me_2H^+)O)](C_4F_9SO_3)_3$ (**7**). Not surprisingly, the chiral and racemic products gave identical NMR spectra.

The effective mirror-plane symmetry of the $[(tren)Co(GlyO)]^{2+}$ complex isomers precludes their use for asymmetric synthesis along the lines just described (Scheme 3). However, the tris(didentate) $[(en)_2Co(GlyO)]^{2+}$ complex ion would qualify as a chiral substitute for the achiral $[(tren)Co(GlyO)]^{2+}$ complex in such a synthesis. With Λ-$[(en)_2Co(GlyO)](CF_3SO_3)_2$[49] as starting material, the same reaction sequence as that described for the $[(tren)Co(GlyO)]^{2+}$ complex (Scheme 3, **9**→**11**) was performed.[63] The ^{13}C NMR spectrum of the resulting product revealed this to be a mixture of the $[(en)_2Co(A_2pr(Me_2H^+)O)]^{3+}$ complex diastereoisomers, Λ-*S* and Λ-*R* in comparable proportions, testifying to the effective lack of stereospecificity in the reduction step. Separation of the diastereoisomers would also provide a convenient route to each amino acid enantiomer, however, only a partial separation has been achieved to date.[63]

Relative stabilities of diastereoisomers and epimerization kinetics

The poor selectivity observed in the reduction step of the $(en)_2Co^{III}$ analogue of **11** has a parallel in the results of thermodynamic studies of related systems. The level of asymmetric influence exerted by the chiral *cis*-$(en)_2Co^{III}$ backbone on chelated chiral amino acid anions is manifest in diastereoisomer ratios of no greater than 2 at equilibrium in H_2O.[53,71] For the $[(en)_2Co(S\text{-}A_2prO)]^{2+}$ complex system the concentration equilibrium constant $K_C = [\Delta\text{-}S,\Lambda\text{-}R]/[\Delta\text{-}R,\Lambda\text{-}S]$ in 0.010 M NaOH, $I = 1.0$ M ($NaClO_4$) at 25 °C was here determined as 0.77(2), indicating the (Δ-*R*,Λ-*S*) diastereoisomer to be the more stable. The same preference is displayed by the related $[(en)_2Co(AspO)]^+$ ($K_C = 0.67$) and $[(en)_2Co(GluO)]^+$ ($K_C = 0.85$) complexes in 0.05 M NaOH, $I = 1.0$ M (NaCl), whereas the relative stability is reversed for the $[(en)_2Co(ValO)]^{2+}$ ($K_C = 1.9$) and $[(en)_2Co(PheO)]^{2+}$ ($K_C = 1.2$; 0.01 M NaOH) complexes in otherwise identical conditions.[53] Thus, the trend appears to be that the (Δ-*R*,Λ-*S*) diastereoisomer is favoured when the amino acid side chain functional group is an H-bond acceptor whereas the opposite diastereoisomer is preferred in the case of a bulky apolar side chain. However, the K_C values all reflect small energy differences between isomers. In some related reactions where the specificity is established by a kinetic path much higher ratios have been observed.[72]

Estimates of the resistance to racemization (or epimerization) of precursors, intermediates and products are critical in asymmetric synthesis. A metal centre generally enhances the α-carbon acidity of chelated amino acids. For chelated amino acidates in $(en)_2Co^{III}$ systems, proton exchange and epimerization at the α-carbon centre have been demonstrated to be coupled processes, both HO^--catalyzed (first-order dependence), and their kinetics rationalized in terms of a common delocalised carbanion intermediate.[53,71] For Δ-$[(en)_2Co(S\text{-}Asp(O^-)O)]^+$, Buckingham *et al.*[53] obtained a second-order epimerization rate constant of $k_E = 1.6 \times 10^{-2}$ dm^3 mol^{-1} s^{-1} ($I = 0.1$ M (NaCl), 25 °C). In the present study, the epimerization rates of the Λ-$[(en)_2Co(S\text{-}Asp(O^-)O)]^+$ and Λ-$[(en)_2Co(S\text{-}A_2prO)]^{2+}$ complex ions were likewise first order in hydroxide with second-order rate constants of $k_E = 0.6 \times 10^{-2}$ dm^3 mol^{-1} s^{-1} and 3.8×10^{-2} dm^3 mol^{-1} s^{-1} [$I = 1.0$ M ($NaClO_4$), 25 °C], respectively. The slower rate of the aspartato complex at higher ionic strength is consistent with the earlier results[53] and the same mechanism undoubtedly holds.

The A_2pr amino acid has been reported to undergo racemization in refluxing 6 M HCl (86% loss of optical rotation after 20 h).[73] However, no sign of epimerization was observed with any $[(en)_2Co(A_2pr(H^+)O)]^{3+}$ complex isomer in up to 6 M HCl at 45 °C for at least 3 hours. Such a process would have been readily detected from the ^{13}C NMR spectra given the characteristic chemical shift patterns of each diastereoisomer.

Structure of $\Lambda(+)_{578}$-$[(en)_2Co(S\text{-}Asp(OH)O)](ClO_4)_2$

The molecular structure and numbering scheme for the $\Lambda(+)_{578}$-$[(en)_2Co(S\text{-}Asp(OH)O)]^{2+}$ cation is illustrated in Fig. 1 with selected bond distances and angles detailed in Table 1. The cobalt atom adopts a distorted octahedral coordination with

Table 1 Selected interatomic distances (Å) and bond angles (°) for Λ-(+)$_{578}$-[(en)$_2$Co(*S*-Asp(OH)O)](ClO$_4$)$_2$

Co–N11	1.956(3)	C22–C23	1.519(6)
Co–N14	1.945(3)	C23–N24	1.492(5)
Co–N21	1.961(3)	O31–C32	1.280(4)
Co–N24	1.975(3)	C32–O33	1.235(4)
Co–O31	1.900(2)	C32–C34	1.527(5)
Co–N35	1.967(3)	C34–N35	1.490(4)
N11–C12	1.492(5)	C34–C36	1.523(5)
C12–C13	1.512(6)	C36–C37	1.501(5)
C13–N14	1.483(5)	C37–O38	1.311(5)
N21–C22	1.477(5)	C37–O39	1.205(5)
N11–Co–N14	86.1(2)	N14–Co–N35	91.5(1)
N11–Co–N21	94.0(1)	N21–Co–N24	85.1(1)
N11–Co–N24	92.5(1)	N21–Co–O31	86.6(1)
N11–Co–O31	177.6(1)	N21–Co–N35	172.0(1)
N11–Co–N35	93.9(1)	N24–Co–O31	89.9(1)
N14–Co–N21	90.2(1)	N24–Co–N35	93.3(1)
N14–Co–N24	175.1(1)	O31–Co–N35	85.6(1)
N14–Co–O31	91.5(1)		

two ethane-1,2-diamine ligands and the (*S*)-aspartate ligand all bound didentate, for the latter through the α-carboxylate and amine groups. From the crystallographic analysis and the known configuration of the (*S*)-aspartate ligand the absolute configuration of the complex ion is unambiguously assigned as Λ. This substantiates the earlier assignment based solely on solution CD-spectral correlation[60] with the homologous glutamato complex, $\Lambda(+)_{495}$-[(en)$_2$Co(*S*-Glu(O$^-$)O)]ClO$_4$.[74] This complex ion displays intramolecular H-bonding between the amine group of one ethane-1,2-diamine ligand and one oxygen atom of the side chain γ-carboxylate group [d(N · · · O) = 2.8 Å] in the crystal. A similar interaction also applies between the coordinated N(14) amine and the hydroxyl oxygen atom [O(38)] of the β-carboxyl group in the present structure, d[N(14) · · · O(38)] = 3.086(4) Å. However, the aspartato β-carboxyl group is neutral whereas the glutamato γ-carboxylate group is ionized and the shorter H-bonding distance for the latter is consistent with the expected stronger interaction. Contrasting these examples, the neutral carboxamide side chain of the related asparaginato complex, Λ-[(en)$_2$Co(*S*-AsnO)]I$_{1.6}$(NO$_3$)$_{0.4}$, is conformationally extended in the crystal.[62]

Acid properties

In the $\Lambda(+)_{578}$-[(en)$_2$Co(*S*-Asp(OH)O)](ClO$_4$)$_2$ complex [pK_a = 3.27(2), I = 1.0 M (NaBr), 25 °C] the β-carboxyl group of the aspartato ligand is more acidic than in free aspartic acid [pK_1 = 3.7, I = 1.0 M (NaNO$_3$), 25 °C][75] or the typical peptide aspartyl unit (pK ≈ 4.5).[76] The complex ionic charge (2+) and the stabilizing effect of intramolecular H-bonding from a coordinated amine to the anionic β-carboxylate group are likely factors contributing to the enhanced acidity in the complex. The acidities of the N^3-ammonium groups of the Λ- and Δ-[(en)$_2$Co(*S*-A$_2$pr(H$^+$)O)]Cl$_3$·H$_2$O diastereoisomers [pK_a, Λ = 7.19(2), Δ = 7.18(2); I = 1.0 M (NaBr), 25.0 °C] are close to the microscopic dissociation constant reported for the N^3-ammonium group of free 2,3-diammoniopropanoate cation [$^-$O$_2$CCH(NH$_3^+$)CH$_2$NH$_3^+$ ↔ $^-$O$_2$CCH(NH$_3^+$)CH$_2$NH$_2$ + H$^+$: pK = 7.0, I = 0.2–0.4 M, 25 °C][22] and greater than in a peptide (pK ≈ 8.0).[77] Thus, for AspOH and A$_2$pr(H$^+$)OH the side chain acid properties appear almost unaffected by the formal replacement of one N^2-ammonio group proton with the (en)$_2$Co^{III} moiety in the N^2,O^1-chelate structure. Attempts at obtaining reliable titration data for the poorly soluble $\Lambda(+)_{578}$-[(en)$_2$Co(*S*-A$_2$pr(Me$_2$H$^+$)O)](C$_4$F$_9$SO$_3$)$_3$ complex failed. The macroscopic ionisation constants of *S*-A$_2$pr(Me$_2$H$^+$) [pK_1 = 6.58(2), pK_2 = 9.54(3), I = 1.0 M (NaBr), 25 °C] are close to those of A$_2$pr(H$^+$) [pK_1 = 6.67, pK_2 = 9.62, I = 0.1 M, 25 °C].[78]

Conclusion

From the synthetic sequence outlined in Scheme 2 it is evident that the absolute configuration of the product amino acid (**8**) derives directly from the chiral aspartic acid employed in the synthesis of the starting complex **1**. As a consequence of the additional stereogenic centre in the octahedral tris(didentate) coordination mode of this complex, initial separation of the Δ-*S*-**1** and Λ-*S*-**1** isomers was required in order to have isomerically pure reactants. This could be viewed as a superfluous and complicating factor for the asymmetric synthesis of the amino acid products. However, the stereogenic centre of the (en)$_2$Co^{III} backbone was important for developing the major part of the chemistry reported in this paper. In the complexes **1**, **2**, **6** and **7**, even a slight inversion at the amino acid α-carbon centre during the course of reactions (**1**→**7**) would reveal itself in the NMR spectra of products by the appearance of additional signals due to the diastereoisomers. In this way, the stereogenic (en)$_2$Co^{III} backbone served as a sensitive indicator ("built-in chiral shift reagent") being more sensitive than would assessments of enantiopurity based on the measurement of optical properties alone. Once, the synthetic strategy was optimized, particularly with respect to avoiding inversion at the α-carbon centre, a high yield of *S*-A$_2$pr(Me$_2$H$^+$) was achieved starting with the Δ,Λ-[(en)$_2$Co(*S*-Asp(OH)O)]$^{2+}$ diastereoisomeric mixture.[79] Clearly, the parallel chemistry using a chiral but non-diastereoisomeric complex such as (p)-[(tren)Co(*S*-AspO)]$^{2+}$ may now be carried out, and this aspect is being investigated.

The paper demonstrates simple methods for generating chiral and racemic 2,3-diaminopropanoic acid and its near relative 4-azaleucine. The template metal ion functions as both an activating and protecting group. In the Vilsmeier–Haack chemistry to generate **10** (Scheme 3) it activates the chelated acid chloride methylene group to loss of H$^+$ and to attack by the electrophile while protecting the amine site.[67] Stabilization of the adduct is also remarkably high, enough to allow reduction by BH$_4^-$ to 4-azaleucine (**11**). To date reductions of such imine-like carbon centres have not been very stereoselective but it should be possible to achieve that and research is continuing in this area. In the rearrangement chemistry to give the 2,3-diaminopropanoic acid (Scheme 2) the metal simply functions as an effective protecting group for both the α-amine and carboxyl sites allowing the β-carboxyl to be manipulated. Resolution of chiral amino acids as their complexes is usually a relatively simple process using ion exchange chromatography and a chiral eluant. Also, it is possible to epimerise at the α-carbon atom with HO$^-$ in aqueous solution so that one or other chirality can be obtained in high yield. These aspects of easy and simultaneous addition of a protecting and activating metal complex fragment and its simple quantitative removal have been overlooked by organic chemists as a relatively general synthetic strategy.

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