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# *quart*-Feproline: Synthesis of a Very Rigid [3]Ferrocenophane-Derived Artificial Amino Acid

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Starting from the α-(dimethylamino)[3]ferrocenophane derivative **1**, a short reaction sequence was developed to form a doubly anellated dihydropyrrole derivative **6** containing the ferrocenophane framework. Intermediate **6** was used for the synthesis of the (*R,S,pS*)-enantiomer of the rigid artificial amino acid "*quart*-Feproline".


## Introduction

Nonnatural amino acids are receiving increasing interest. They may introduce hydrolytic stability and/or induce novel structural features to peptide or protein backbones.[1] In addition, a variety of proline derivatives have found interest as active species in organocatalysis.[2] Ferrocene-based amino acids[3] are of importance in the emerging field of bio-organometallic chemistry.[4] In this article we wish to report on the synthesis of an nonnatural amino acid system where the proline structure has become deeply incorporated into a [3]ferrocenophane moiety such that it shares three of its four ring carbon atoms with the rigid metallocenophane framework, to the best of our knowledge the first example of its kind.[5]

## Results and Discussion

Our synthesis starts with racemic (dimethylamino)[3]-ferrocenophane derivative **1** (*trans*/*cis* = 7:1) that is easily available from 1,1′-diacetylferrocene by Mannich reaction followed by catalytic hydrogenation.[6] A directed metallation[7] (*tert*-butyllithium) followed by quenching with 1,2-dibromotetrachloroethane gives the corresponding *ortho*-bromo[3]ferrocenophane derivative **2**. The α-dimethylamino group can be exchanged for the (*S*)-phenylethylamino chiral auxiliary[8] by quaternization (with MeI) followed by exchange with (*S*)-phenylethylamine. This two-step exchange reaction proceeds with overall retention of configuration at the α-position of the [3]ferrocenophane bridge.[9] Simple chromatographic separation furnishes the product (6*R*,9*R*,15*S*,*pR*)-**3**, which was found to be isomerically pure within the limits of $^1$H NMR measurements; the methyl resonances at $\delta$ = 1.23 (d, 7-H) and $\delta$ = 1.29 (d, 16-H) were analyzed for this purpose. In the *trans*-series the three stereogenic units at the [3]ferrocenophane framework are dependent from each other, i.e. for **3** they can only be (*R,R,pR*) or (*S,S,pS*). In order to secure our stereochemical assignment we have isolated the other diastereomer, (6*S*,9*S*,15*S*,*pS*)-**3**, as well. Its characteristic $^1$H NMR methyl signals appear at $\delta$ = 1.05 (7-H) and $\delta$ = 1.24 (16-H), respectively (in [D$_2$]dichloromethane).

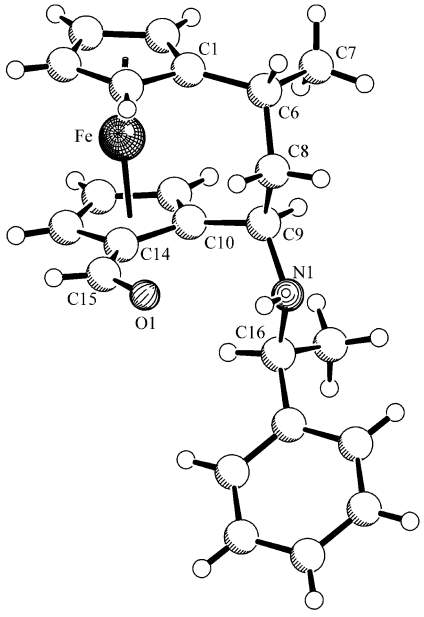


Figure 1. Molecular structure of (6*R*,9*R*,16*S*,*pR*)-**4**. Selected bond lengths and angles for **4**: C1–C6 1.508(2), C6–C7 1.531(2), C6–C8 1.541(2), C8–C9 1.541(2), C9–N1 1.479(2), N1–C16 1.478(2), C14–C15 1.445(2), C15–O1 1.219(2); C1–C6–C7 111.8(1), C1–C6–C8 112.7(1), C7–C6–C8 112.2(1), C6–C8–C9 115.5(1), C8–C9–N1 107.0(1), C9–N1–C16 115.3(1), C14–C15–O1 127.5.

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[‡] X-ray crystal structure analyses.
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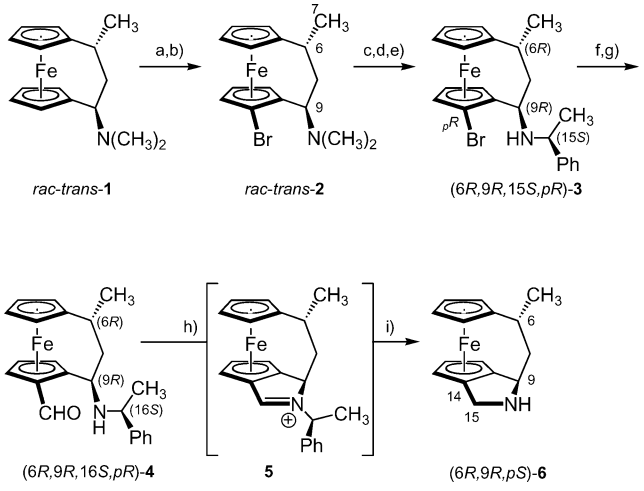
Next the bromine substituent in **3** was exchanged for lithium by treatment with *tert*-butyllithium. Formylation was carried out by subsequent treatment with dimethylformamide to give the aldehyde **4** in 83% yield [$^1H/^{13}C$ NMR: $\delta$ = 9.90/195.8 (–CHO)]. Complex **4** was characterized by X-ray diffraction (single crystals from diethyl ether), which independently confirmed the stereochemistry of the (6*R*,9*R*,16*S*,*pR*) enantiomer of **4** at this stage of the synthesis (see Figure 1).

Ring closure to the five-membered nitrogen heterocycle was effected by acid catalyzed condensation. The resulting iminium ion **5** was not isolated but directly subjected to catalytic hydrogenation. This removed the "benzylic" chiral auxiliary from nitrogen and reduced the C=N double bond to directly yield the desired dihydropyrrol moiety doubly anellated with the [3]ferrocenophane framework (see Scheme 1).




Scheme 1. Synthesis of dihydropyrrol (6*R*,9*R*,*pS*)-**6**: a) *t*BuLi, $Et_2O$, 0 °C; b) $Cl_2BrC–CBrCl_2$, $Et_2O$, –78 °C (93%); c) $CH_3I$, $CH_3CN$, room temp.; d) (*S*)-phenylethylamine, $K_2CO_3$, $CH_3CN$; e) chromatographic separation [(6*S*,9*S*,15*S*,*pS*)-**3** 32%, (6*R*,9*R*,15*S*,*pR*)-**3** 36%]; f) *t*BuLi (2 equiv.), THF, –78 °C, g) DMF (83%); h) HOAc, MeOH; i) $H_2$, Pd-C, MeOH/THF (95%).

The hydrochloride salt of complex (6*R*,9*R*,*pS*)-**6** was also characterized by an X-ray crystal structure analysis (see Figure 2).

It is well known that C–H groups adjacent to nitrogen can readily and selectively be deprotonated in a directed metallation reaction via their carbamate derivatives.[10]

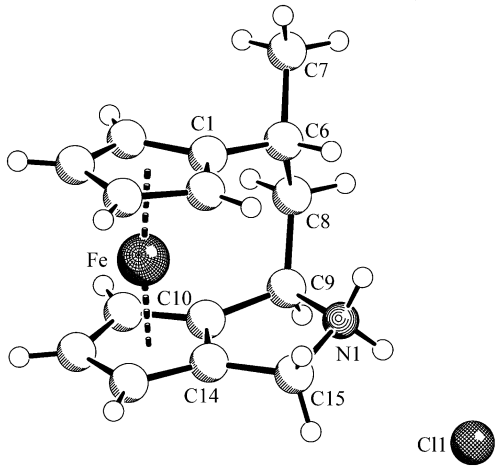
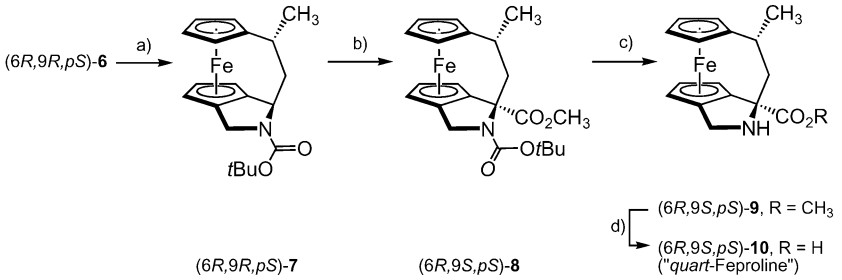



Figure 2. Molecular structure of (6*R*,9*R*,*pS*)-**6**·HCl. Selected bond lengths and angles for **6** [data of the second independent molecule are given in square brackets]: C1–C6 1.509(4) [1.503(4)], C6–C7 1.546(4) [1.533(4)], C6–C8 1.528(5) [1.536(4)], C8–C9 1.536(4) [1.532(4)], C9–N1 1.533(4) [1.539(4)], N1–C15 1.512(4) [1.508(4)], C14–C15 1.485(4) [1.498(4)]; C1–C6–C7 109.8(2) [109.7(2)], C1–C6–C8 114.9(3) [115.3(3)], C7–C6–C8 108.7(3) [109.0(3)], C6–C8–C9 119.0(3) [118.8(3)], C8–C9–N1 112.9(3) [112.9(2)], C9–N1–C15 111.5(2) [112.4(2)], N1–C15–C14 102.9(3) [102.1(2)].

Therefore, we have converted **6** to its *tert*-butoxycarbonyl (Boc) derivative **7**. Subsequent treatment of **7** with *sec*-butyllithium followed by quenching with methyl chloroformate gave the doubly protected "*quart*-Feproline" derivative **8** (see Scheme 2). Compound (6*R*,9*S*,*pS*)-**8** was characterized by X-ray diffraction (see Figure 3).

Attack of the *tert*-C–H bond being preferred over attack at a secondary $CH_2$ group by *s*-BuLi in carbamate directed "Hoppe/Beak"-type metallation is rare.[10,11] The actual cause is unclear at present. It may be thermodynamic in origin (maybe a potential increase of the s-character of the C–H bond at the very rigid system) or kinetic (maybe *tert*-C–H activation directed by a specific preferred Boc conformation).

The synthesis was finished by removal of the pair of orthogonal protective groups. Treatment of (6*R*,9*S*,*pS*)-**8** with trifluoroacetic acid removed the Boc group to yield the *quart*-Feproline methyl ester (6*R*,9*S*,*pS*)-**9**. Subsequent saponification with lithium hydroxide eventually gave the free artificial "*quart*-Feproline" amino acid **10** [(6*R*,9*S*,*pS*)-isomer].




Scheme 2. Synthesis of *quart*-Feproline (6*R*,9*S*,*pS*)-**10**: a) $Boc_2O$, $NEt_3$, $CH_2Cl_2$, 0 °C (93%); b) *s*-BuLi, $Et_2O$, –78 °C, then $ClCO_2CH_3$ (60%); c) $CF_3CO_2H$, $CHCl_3$ (66%); d) LiOH, MeOH/$H_2O$ (80%).

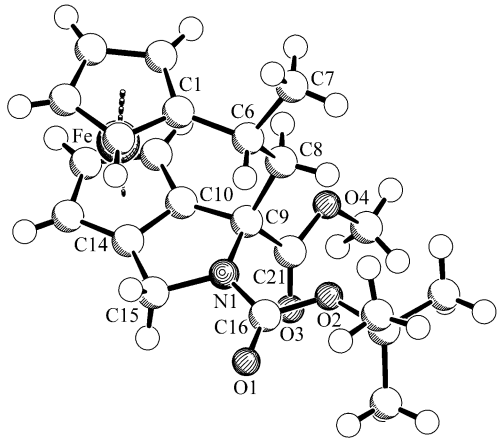



Figure 3. Molecular structure of (6*R*,9*S*,*pS*)-**8**. Selected bond lengths and angles for **8**: C1–C6 1.513(5), C6–C7 1.529(5), C6–C8 1.546(5), C8–C9 1.545(4), C9–N1 1.475(4), C9–C21 1.523(4), N1–C15 1.477(4), C14–C15 1.497(4), N1–C16 1.357(4), C16–O1 1.200(3), C16–O2 1.355(3), C21–O3 1.191(4), C21–O4 1.337(4); C1–C6–C7 111.0(3), C1–C6–C8 112.8(3), C7–C6–C8 109.6(3), C6–C8–C9 115.3(2), C8–C9–N1 113.7(3), C9–N1–C15 115.8(2), N1–C15–C14 010.3(2), C9–N1–C16 124.7(2), N1–C16–O1 124.5(3), N1–C16–O2 109.5(2), O1–C16–O2 126.0(3), C8–C9–C21 112.1(2), N1–C9–C21 110.0(2), C9–C21–O3 125.3(3), C9–C21–O4 111.1(3), O3–C21–O4 123.6(3).

## Conclusions

We have reported on the synthesis of an nonnatural proline analogue as an integral part of a [3]ferrocenophane framework. This was achieved via an unusual carbamate directed lithiation at the new ferrocenopyrrol motif. We are looking forward to learn about the properties of this novel very rigid ferrocene-derived artificial amino acid, for instance as a peptide building block and its potential catalytic features in the future.

## Experimental Section

Compounds **1**,[6b] **2**[8c] and **3**[8b] were prepared in analogy to previously reported procedures (see the Supporting Information).

**(6*R*,9*R*,15*S*,*pR*)-3:** 8.37 g, 19.1 mmol, 32%. $^1$H NMR (599.9 MHz, $CD_2Cl_2$, 298 K): $\delta$ = 7.31 (m, 2 H, 18-H), 7.28 (m, 2 H, 19-H), 7.20 (m, 1 H, 20-H), 4.35, 4.14, 4.00, 3.71 (m, 4×1 H, 2-H–5-H), 4.33, 3.93 (m, 2×1 H, 11-H, 13-H), 4.02 (m, 1 H, 12-H), 3.73 (q, $^3J$ = 6.5 Hz, 1 H, 15-H), 3.54 (dd, $^3J$ = 11.4 Hz, 2.8 Hz, 1 H, 9-H), 2.80 (m, 2 H, 6-H, 8-H$_{ax}$), 2.25 (ddd, $^2J$ = 14.3 Hz, $^3J$ = 4.4 Hz, 2.8 Hz, 1 H, 8-H$_{eq}$), 1.74 (br. s, 1 H, N*H*), 1.29 (d, $^3J$ = 6.5 Hz, 3 H, 16-H), 1.23 (d, $^3J$ = 7.3 Hz, 3 H, 7-H); $^{13}$C{$^1$H} NMR (150.8 MHz, $CD_2Cl_2$, 298 K): $\delta$ = 146.8 (C17), 128.6 (C19), 127.4 (C18), 127.2 (C20), 95.8 (C1), 80.5 (C10), 78.8 (C14), 78.8, 70.8, 69.0, 68.0 (C2 – C5), 72.7, 70.2 (C11, C13), 67.0 (C12), 55.9 (C15), 48.3 (C9), 48.2 (C8), 28.0 (C6), 22.1 (C16), 16.9 (C7). $C_{22}H_{24}BrFeN$ (438.2) requires C 60.30, H 5.52, N 3.20, found C 60.33, H 5.38, N 3.07. MS-ESI; ES$^+$: *m*/*z* = 438.05 (90) [M + H]$^+$, 316.96 (90) [M – NHCH(CH$_3$)C$_6$H$_5$]$^+$; m.p. 97 °C. IR (ATR): $\tilde{\nu}$ = 2964 (m), 2930 (m), 2857 (m), 1494 (m), 1451 (s), 1375 (m), 1327 (m), 1124 (m), 1070 (m), 1027 (m), 901 (m), 787 (s), 762 (s), 701 (vs), 641 (m) cm$^{-1}$. $[\alpha]_D^{20}$ = +161 (*c* = 0.01, acetonitrile). CD $\Delta\varepsilon$/dm$^3$ cm$^{-1}$ mol$^{-1}$ ($\lambda_{max}$ /nm) = +0.04 (452), –0.16 (404), +0.55 (326), –1.31 (283) (*c* = 0.012, acetonitrile).

**(6*R*,9*R*,16*S*,*pR*)-4:** A mixture prepared from bromoferrocene (6*R*,9*R*,15*S*,*pR*)-**3** (4.40 g, 10.1 mmol) in 20 mL of anhyd THF and *t*BuLi (13.3 mL, 20.2 mmol, 1.5 M in *n*-pentane, 2.0 equiv.) in 30 mL of anhyd THF at –78 °C was added to anhyd DMF (1.7 mL, 22.0 mmol, 1.5 equiv.) in 10 mL of anhyd THF. Aqueous work up and chromatography yielded (6*R*,9*R*,16*S*,*pR*)-**4** (3.20 g, 8.30 mmol, 83%) as a red solid. $^1$H NMR (599.9 MHz, $CD_2Cl_2$, 298 K): $\delta$ = 9.90 (d, *J* = 0.7 Hz, 1 H, H-15), 7.24 (m, 2 H, H-20), 7.23 (m, 2 H, H-19), 7.19 (m, 1 H, 21-H), 4.68, 4.43 (m, 2×1 H, 11-H, 13-H), 4.43 (m, 1 H, 12-H), 4.34, 4.09, 4.09, 3.97 (m, 4×1 H, 2-H–5-H), 3.73 (q, $^3J$ = 6.6 Hz, 16-H), 3.53 (dd, $^3J$ = 11.4 Hz, 3.7 Hz, 9-H), 2.65 (m, 1 H, 6-H), 2.36 (ddd, $^2J$ = 13.7 Hz,$^3J$ = 11.4 Hz, 3.7 Hz, 1 H, 8-H$_{ax}$), 2.27 (ddd, $^2J$ = 13.7 Hz, $^3J$ = 3.7 Hz, 3.4 Hz, 1 H, 8-H$_{eq}$), 1.29 (d, $^3J$ = 6.6 Hz, 3 H, 17-H), 1.19 (d, $^3J$ = 7.2 Hz, 3-H, 7-H); $^{13}$C{$^1$H} NMR (150.8 MHz, $CD_2Cl_2$, 298 K): $\delta$ = 195.8 (C15), 146.9 (C18), 128.5 (C20), 127.1 (C19), 126.9 (C21), 96.0 (C1), 86.9 (C10), 77.7 (C14), 76.9 (C12), 76.0, 72.3 (C11, C13), 71.7, 70.0, 69.4, 69.1 (C2 – C5), 55.9 (C16), 48.0 (C8), 47.8 (C9), 27.5 (C6), 22.9 (C17), 16.9 (C7). $C_{23}H_{25}FeNO_2$ (387.3) requires C 71.33, H 6.51, N 3.62, found C 70.59, H 6.44 N 3.45. MS-ESI; ES$^+$: *m*/*z* = 388.14 (100) [M + H]$^+$, 370.13 (60) [M – H$_2$O]$^+$; m.p. 100 °C. IR (ATR): $\tilde{\nu}$ = 1111–3294 (m), 1111–2975 (m), 2937 (m), 2859 (m), 1668 (vs), 1446 (s), 1359 (m), 1301 (m), 1227 (m), 1131 (m), 1048 (m), 992 (w), 1111–923 (m), 837 (s), 817 (s), 759 (s), 697 (s), 647 (m), 613 (s), 572 (m), 111–552 (m) cm$^{-1}$. $[\alpha]_D^{20}$ = –165 (*c* = 0.01, acetonitrile). CD $\Delta\varepsilon$ /dm$^3$ cm$^{-1}$ mol$^{-1}$ ($\lambda_{max}$ /nm) = –2.38 (461), +1.46 (362), –1.97 (338), +2.21 (300) (*c* = 0.011, acetonitrile).

**X-ray Crystal Structure Analysis for (6*R*,9*R*,16*S*,*pR*)-4:** Formula $C_{23}H_{25}FeNO{\cdot}H_2O$, *M* = 405.31, orange crystal 0.45×0.40×0.10 mm, *a* = 7.818(1), *b* = 11.947(1), *c* = 20.940(1) Å, *V* = 1955.8(3) Å$^3$, $\rho_{calcd.}$ = 1.376 g cm$^{-3}$, $\mu$ = 0.789 mm$^{-1}$, empirical absorption correction (0.718 ≤ *T* ≤ 0.925), *Z* = 4, orthorhombic, space group $P2_12_12_1$ (No. 19), $\lambda$ = 0.71073 Å, *T* = 198 K, $\omega$ and $\phi$ scans, 12778 reflections collected (±*h*, ±*k*, ±*l*), [(sin$\theta$)/$\lambda$] = 0.67 Å$^{-1}$, 4617 independent ($R_{int}$ = 0.038) and 4421 observed reflections [$I \geq 2\sigma(I)$], 255 refined parameters, *R* = 0.023, $wR^2$ = 0.060, max. residual electron density 0.23 (–0.32) e Å$^{-3}$, Flack parameter –0.01(1), hydrogen atoms at N1 and O2 from difference fourier maps, others calculated and refined as riding atoms.

**(6*R*,9*R*,*pS*)-6:** 3.00 g of (6*R*,9*R*,16S,*pR*)-**4** (7.75 mmol) dissolved in 50 mL of MeOH were treated with 10 mL of glacial HOAc and stirred for 1 h prior to hydrogenation with Pd–C catalyst (1.3 bar H$_2$, 10% Pd). Removal of the catalyst and aqueous work-up yielded (6*S*,9*S*,*pR*)-**6** as a yellow solid (1.97 g, 7.36 mmol, 95%). $^1$H NMR (599.9 MHz, $CD_2Cl_2$, 298 K): $\delta$ = 4.11, 4.04, 3.94, 3.48 (m, 4×1 H, 2-H–5-H), 4.00 (d, $^3J$ = 5.0 Hz, 1 H, 9-H), 3.97 (m, 2 H, 11-H, 13-H), 3.95 (m, 1 H, 12-H), 3.85 (dd, $^2J$ = 12.2 Hz, $^4J$ = 1.4 Hz, 15-H), 3.75 (d, $^2J$ = 12.2 Hz, 15-H′), 2.65 (dqd, $^3J$ = 12.0 Hz, 7.1 Hz, 3.6 Hz, 1 H, 6-H), 2.25 (ddd, $^2J$ = 13.8 Hz, $^3J$ = 5.0, 3.6 Hz, 1 H, 8-H$_{eq}$), 2.12 (br. s, 1 H, *N*-H), 1.93 (ddd, $^2J$ = 13.8 Hz, $^3J$ = 12.0, 1.5 Hz, 1 H, 8-H$_{eq}$), 1.22 (d, $^3J$ = 7.1 Hz, 3 H, 7-H); $^{13}$C{$^1$H} NMR (150.8 MHz, $CD_2Cl_2$, 298 K): $\delta$ = 95.5 (C10), 95.2 (C14), 90.9 (C1), 76.1, 68.7, 67.8, 64.3 (C2 – C5), 70.8 (C12), 60.7, 60.5 (C11, C13), 52.7 (C9), 50.8 (C8), 47.8 (C15), 23.5 (C6), 22.0 (C7). $C_{15}H_{17}FeN$ (267.2) requires C 67.44, H 6.41, N 5.24, found C 67.40, H 6.29, N 5.10; m.p. 113 °C. IR (ATR): $\tilde{\nu}$ = 3086 (m), 2954 (m), 2921 (m), 2838 (m), 1735 (w), 1637 (s), 1453 (m), 1392 (m), 1333 (m), 1151 (m), 1020 (s), 915 (w), 851 (m), 796 (vs), 723 (m), 661 (m) cm$^{-1}$. $[\alpha]_D^{20}$ = –141 (*c* = 0.04, acetonitrile). CD $\Delta\varepsilon$ / dm$^3$ cm$^{-1}$ mol$^{-1}$ ($\lambda_{max}$ /nm) = –0.53 (464), +0.10 (328), +1.26 (270) (*c* = 0.043, acetonitrile).

**X-ray Crystal Structure Analysis for (6*R*,9*R*,*pS*)-6·HCl:** Formula $C_{15}H_{18}ClFeN$, $M$ = 303.60, yellow crystal 0.30 × 0.25 × 0.06 mm, $a$ = 7.4256(1), $b$ = 11.5087(3), $c$ = 31.7517(6) Å, $V$ = 2713.47(9) Å$^3$, $\rho_{calcd.}$ = 1.486 g cm$^{-3}$, $\mu$ = 1.289 mm$^{-1}$, empirical absorption correction (0.699 ≤ $T$ ≤ 0.927), $Z$ = 8, orthorhombic, space group $P2_12_12_1$ (No. 19), $\lambda$ = 0.71073 Å, $T$ = 198 K, $\omega$ and $\phi$ scans, 20776 reflections collected (±$h$, ±$k$, ±$l$), [(sin$\theta$)/$\lambda$] = 0.67 Å$^{-1}$, 6576 independent ($R_{int}$ = 0.064) and 5077 observed reflections [$I \geq 2\sigma(I)$], 327 refined parameters, $R$ = 0.040, $wR^2$ = 0.095, max. residual electron density 0.39 (–0.37) e Å$^{-3}$, Flack parameter –0.02(1), hydrogen atoms calculated and refined as riding atoms, two almost identical molecules in the asymmetric unit.

**(6*R*,9*R*,*pS*)-7:** Carbamate (6*R*,9*R*,*pS*)-**7** (yellow oil, 1.36 g, 3.70 mmol, 98%) was obtained from treatment of dihydropyrrol (6*R*,9*R*,*pS*)-**6** (1.00 g, 3.74 mmol) in $CH_2Cl_2$ (20 mL) with $NEt_3$ (620 µL, 4.49 mmol, 1.2 equiv.) and $Boc_2O$ (830 mg, 3.80 mmol, 1.0 equiv.) at 0 °C. $^1$H NMR (599.9 MHz, $CD_2Cl_2$, 298 K, two rotamers in a 3:2 ratio, resonances of major rotamer given): $\delta$ = 4.43 (d, $^3J$ = 5.1 Hz, 1 H, 9-H), 4.31 (dd, $^2J$ = 12.9 Hz, $^4J$ = 1.3 Hz, 1 H, 15-H), 4.19 (d, $^2J$ = 12.9 Hz, 1 H, 15-H′), 4.15, 4.10, 3.98, 3.48 (m, 4 × 1 H, 2-H/5-H), 4.10, 4.06, 3.98 (m, 3 ×H, 11-H–13-H), 2.76 (ddd, $^2J$ = 13.7 Hz, $^3J$ = 5.1 Hz, 2.9 Hz, 1 H, 8-H$_{eq}$), 2.28 (dqd, $^3J$ = 12.2 Hz, 7.0 Hz, 2.9 Hz, 1 H, 6-H), 1.91 (ddd, $^2J$ = 13.7 Hz, $^3J$ = 12.2 Hz, 1.0 Hz, 1 H, 8-H$_{ax}$), 1.51 (s, 9 H, 18-H), 1.23 (d, $^3J$ = 7.0 Hz, 3 H, 7-H); $^{13}$C{$^1$H} NMR (150.8 MHz, $CD_2Cl_2$, 298 K): $\delta$ = 154.9 (C16), 92.3 (C10), 90.9 (C1), 88.8 (C14), 79.7 (C17), 76.7, 69.2, 68.3, 64.7 (C2 – C5), 70.3, 61.3, 61.1 (C11 – C13), 54.5 (C9), 49.8 (C15), 49.1 (C8), 28.7 (C18), 24.4 (C6), 22.0 (C7). $C_{20}H_{25}FeNO_2$ (367.3) requires C 65.41, H 6.86, N 3.81, found C 65.43, H 6.86, N 3.75. MS-ESI; ES$^+$: $m/z$ (%) = 390.1124 (100) [M + Na]$^+$, 757.2347 [2M + Na]$^+$, 1124.3553 [3M + Na]$^+$; m.p. 61 °C. IR (ATR): $\tilde{\nu}$ = 3091 (w), 2962 (m), 2926 (m), 2870 (m), 1689 (vs), 1474 (m), 1455 (m), 1411 (m), 1375 (s), 1326 (m), 1249 (m), 1172 (m), 1103 (s), 1027 (m), 997 (m), 916 (m), 866 (m), 799 (m), 768 (m), 615 (m) cm$^{-1}$. $[\alpha]_D^{20}$ = –102 ($c$ = 0.02, acetonitrile). CD $\Delta\varepsilon$ / dm$^3$ cm$^{-1}$ mol$^{-1}$ ($\lambda_{max}$ /nm) = –0.57 (462), +0.12 (328), +2.29 (269) ($c$ = 0.016, acetonitrile).

**(6*R*,9*S*,*pS*)-8 ("Boc-*quart*-Feproline-OMe"):** 1.11 g of (6*R*,9*R*,*pS*)-**7** (3.28 mmol) dissolved in 33 mL of anhyd $Et_2O$ were subsequently treated with *s*BuLi (2.8 mL of a 1.3 M solution in cHex, 3.6 mmol, 1.1 equiv.) and after 30 min with $ClCO_2Me$ (279 µL, 3.61 mmol, 1.1 equiv.) at –78 °C to give (6*R*,9*S*,*pS*)-**8** (837 mg, 1.97 mmol, 60%) as an orange solid after chromatography. $^1$H NMR (599.9 MHz, $CD_2Cl_2$, 298 K, two rotamers in a 2:1 ratio, resonances of major rotamer given): $\delta$ = 4.40 (d, $^2J$ = 12.7 Hz, 1 H, 15-H), 4.31 (d, $^2J$ = 12.7 Hz, 1 H, 15-H′), 4.22, 4.15, 4.02, 3.58 (m, 4 × 1 H, 2-H–5-H), 4.16, 4.15, 3.99 (m, 3 × 1 H, 11-H–13-H), 3.65 (s, 3 H, 20-H), 2.85 (dd, $^2J$ = 13.8 Hz, $^3J$ = 2.8 Hz, 1 H, 8-H$_{eq}$), 2.49 (dd, $^2J$ = 13.8 Hz, $^3J$ = 12.2 Hz, 1 H, 8-H$_{ax}$), 2.35 (dqd, $^3J$ = 12.2 Hz, 7.0 Hz, 2.8 Hz, 1 H, 6-H), 1.46 (s, 9 H, 18-H), 1.27 (d, $^3J$ = 7.0 Hz, 3 H, 7-H); $^{13}$C{$^1$H} NMR (150.8 MHz, $CD_2Cl_2$, 298 K): $\delta$ = 173.9 (C19), 154.1 (C16), 92.9 (C10), 92.2 (C1), 88.0 (C14), 80.4 (C17), 76.8, 69.3, 68.9, 65.1 (C2 – C5), 70.5, 62.1, 61.4 (C11 – C13), 66.6 (C9), 52.7 (C20), 51.4 (C8), 49.7 (C15), 28.5 (C18), 26.7 (C6), 21.7 (C7). $C_{22}H_{27}FeNO_4$ (425.3) requires C 62.13, H 6.40, N 3.29, found C 62.45, H 6.34, N 3.20. IR (ATR): $\tilde{\nu}$ = 3101 (w), 2970 (m), 2927 (m), 2870 (m), 1743 (s), 1696 (vs), 1453 (m), 1409 (m), 1363 (s), 1326 (m), 1244 (s), 1164 (s), 1113 (m), 1070 (m), 987 (m), 917 (m), 865 (m), 801 (m) cm$^{-1}$. $[\alpha]_D^{20}$ = –33 ($c$ = 0.11, dichloromethane). CD $\Delta\varepsilon$ /dm$^3$ cm$^{-1}$ mol$^{-1}$ ($\lambda_{max}$ /nm) = –0.12 (459), +0.32 (311), +0.78 (268) ($c$ = 0.006, dichloromethane).

**X-ray Crystal Structure Analysis for (6*R*,9*S*,*pS*)-8:** Formula $C_{22}H_{27}FeNO_4$, $M$ = 425.30, orange crystal 0.30 × 0.20 × 0.15 mm, $a$ = 7.401(1), $b$ = 13.006(1), $c$ = 10.401(1) Å, $\beta$ = 97.69(1)°, $V$ = 992.2(2) Å$^3$, $\rho_{calcd.}$ = 1.424 g cm$^{-3}$, $\mu$ = 0.788 mm$^{-1}$, empirical absorption correction (0.798 ≤ $T$ ≤ 0.891), $Z$ = 2, monoclinic, space group $P2_1$ (No. 4), $\lambda$ = 0.71073 Å, $T$ = 223 K, $\omega$ and $\phi$ scans, 6593 reflections collected (±$h$, ±$k$, ±$l$), [(sin$\theta$)/$\lambda$] = 0.66 Å$^{-1}$, 4021 independent ($R_{int}$ = 0.040) and 3137 observed reflections [$I \geq 2\sigma(I)$], 258 refined parameters, $R$ = 0.041, $wR^2$ = 0.093, max. residual electron density 0.27 (–0.38) e Å$^{-3}$, Flack parameter –0.04(2), hydrogen atoms calculated and refined as riding atoms.

CCDC-676498 [for (6*R*,9*R*,16*S*,*pR*)-**4**], -676499 [for (6*R*,9*S*,*pR*)-**8**], -676500 [for (6*R*,9*R*,*pS*)-**6**·HCl] contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

**(6*R*,9*S*,*pS*)-9 ("H-*quart*-Feproline-OMe"):** The *N*-Boc-protected amino methyl ester (6*R*,9*S*,*pS*)-**8** (1.00 g, 2.35 mmol in 3 mL of $CH_2Cl_2$) was added to a 3:1 mixture of $CHCl_3$ and trifluoro acetic acid (20 mL) at 0 °C. After 1 h at 0 °C and 45 min at room temp. the mixture was poured into methanolic $NEt_3$ at 0 °C and stirred vigorously for 10 min, then 10 mL of sat. aq. $Na_2S_2O_3$ were added. Work-up and chromatography gave the methyl ester of (6*R*,9*S*,*pS*)-*quart*-Feproline (6*R*,9*S*,*pS*)-**9** (480 mg, 1.54 mmol, 66%). $^1$H NMR (599.9 MHz, $CD_2Cl_2$, 298 K): $\delta$ = 4.19, 4.00 (m, 2 × 1 H, 11-H, 13-H), 4.15, 4.11, 3.98, 3.59 (m, 4 × 1 H, 2-H–5-H), 3.97 (m, 1 H, 12-H), 3.88 (d, $^2J$ = 11.8 Hz, 1 H, 15-H), 3.84 (d, $^2J$ = 11.8 Hz, 1 H, 15-H′), 3.70 (s, 3 H, 17-H), 3.07 (br. s, 1 H, N-*H*), 2.85 (dqd, $^3J$ = 12.0 Hz, 7.1 Hz, 3.6 Hz, 1 H, 6-H), 2.42 (dd, $^2J$ = 13.6 Hz, $^3J$ = 12.0 Hz, 1 H, 8-H$_{ax}$), 2.13 (dd, $^2J$ = 13.6 Hz, $^3J$ = 3.6 Hz, 1 H, 8-H$_{eq}$), 1.22 (d, $^3J$ = 7.1 Hz, 3 H, 7-H); $^{13}$C{$^1$H} NMR (150.8 MHz, $CD_2Cl_2$, 298 K) d = 177.4 (C16), 93.9 (C14), 93.4 (C10), 91.7 (C1), 76.4, 68.9, 68.2, 64.5 (C2 – C5), 71.0 (C12), 65.5 (C9), 61.8, 60.9 (C11, C13), 54.2 (C8), 52.8 (C17), 47.3 (C15), 25.7 (C6), 21.5 (C7); exact mass (ESI-HRMS) calculated for $C_{17}H_{19}FeHNO_2$ ([M + H]$^+$) 326.0838, found 326.0841. IR (ATR): $\tilde{\nu}$ = 3389 (w), 3088 (w), 2954 (m), 2924 (m), 2833 (m), 1728 (vs), 1450 (m), 1372 (w), 1313 (w), 1233 (vs), 1119 (m), 1047 (m), 1023 (m), 889 (m), 801 (s), 621 (s) cm$^{-1}$. $[\alpha]_D^{20}$ = –57 ($c$ = 0.07, dichloromethane). CD $\Delta\varepsilon$ / dm$^3$ cm$^{-1}$ mol$^{-1}$ ($\lambda_{max}$ /nm) = +0.50 (488), +0.39 (339), –0.67 (268) ($c$ = 0.002, dichloromethane).

**(6*R*,9*S*,*pS*)-10 ("*quart*-Feproline"):** 450 mg (1.38 mmol) of (6*R*,9*S*,*pS*)-**9** were treated with LiOH (150 mg, 6.25 mmol, 4.5 equiv.) in MeOH/$H_2O$ (11 mL, 10:1) at 0 °C and stirred for 2 h. Repetitive aceotropic removal of water from toluene (3 × 30 mL) and filtration through a short plug of silica (MeOH) gave the lithium salt of (6*R*,9*S*,*pS*)-**10** (360 mg, 1.13 mmol, 82%). **(6*R*,9*S*,*pS*)-10 Li-carboxylate:** $^1$H NMR (599.9 MHz, [D$_4$]methanol, 298 K): $\delta$ = 4.23, 3.92, 3.90 (m, 3 × 1 H, 11-H–13-H), 4.17, 4.11, 3.94, 3.50 (m, 4 × 1 H, 2-H–5-H), 3.86 (d, $^2J$ = 12.7 Hz, 1 H, 15-H$_{endo}$), 3.81 (d, $^2J$ = 12.7 Hz, 1 H, 15-H$_{exo}$), 2.71 (dd, $^2J$ = 13.9 Hz, $^3J$ = 12.4 Hz, 1 H, 8-H$_{ax}$), 2.56 (ddd, $^3J$ = 12.4 Hz, 7.0 Hz, 3.1 Hz, 1 H, 6-H), 2.12 (dd, $^2J$ = 13.9 Hz, $^3J$ = 3.1 Hz, 1 H, 8-H$_{eq}$), 1.22 (d, $^3J$ = 7.0 Hz, 3 H, 7-H); $^{13}$C{$^1$H} NMR (150.8 MHz, [D$_4$]methanol, 298 K): $\delta$ = 182.3 (C16), 98.6 (C10), 94.8 (C14), 91.9 (C1), 76.9, 69.7, 68.8, 65.1 (C2 – C5), 71.6, 62.5, 60.8 (C11 – C13), 68.4 (C9), 56.0 (C8), 47.9 (C15), 27.3 (C6), 22.7 (C7); exact mass (ESI-HRMS) calculated for $C_{16}H_{17}FeLiNO_2$ ([M + Li]$^+$) 318.0769, found 318.0767, calculated for $C_{16}H_{17}FeNNaO_2$ ([M + Na]$^+$) 334.0506, found 334.0501. IR (ATR): $\tilde{\nu}$ = 3570 (m), 3079 (w), 2960 (w), 2867 (w), 2632 (m), 1592 (m), 1416 (vs), 1207 (w), 1104 (w), 995 (w), 859 (s), 736 (w), 695 (w) cm$^{-1}$. $[\alpha]_D^{20}$ = –18 ($c$ = 0.82, methanol). CD $\Delta\varepsilon$ /dm$^3$ cm$^{-1}$ mol$^{-1}$ ($\lambda_{max}$ /nm) = +0.23 (468), –0.04 (345), –0.52 (272) ($c$ = 0.021, methanol). Neutralization was per-

formed by adding a stoichiometric amount of solid dimethylammonium chloride and a few drops of methanol to a stirred suspension of the lithium carboxylate in dichloromethane. The mixture was stirred for 1 h and then evaporated to dryness. The residue was taken up in dichloromethane and filtered. Removal of the solvent provided the neutral amino acid (6*R*,9*S*,*pS*)-**10**.

**Supporting Information** (see also the footnote on the first page of this article): Detailed experimental procedures, NMR spectra, 2D- and VT-NMR data.

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