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Synthesis of optically active 1,1′-ferrocenylene-bis-alanine carrying four different protecting groups

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Abstract: The bis-amino acid derivatives (+)-**6** and (+)-**8** were synthesised (>95% ee) in mixtures with the corresponding diastereomers (dr:s 80:20 and 90:10, respectively) *via* asymmetric hydrogenation of the corresponding bis-didehydroamino acid derivatives using [Rh((*R,R*)-DIPAMP)(COD)]BF_4 as catalyst. © 1997 Elsevier Science Ltd

The design and synthesis of aromatic bis-amino acid derivatives has attracted considerable interest mainly due to their presence as subunits in many peptide antibiotics.[1,2] One of the requirements for the action of these antibiotics is most likely the restricted conformational freedom imposed by their cyclic peptide backbone. Moreover, the incorporation of aromatic bis-amino acid derivatives into peptide loops may mimic the peptide structures derived from non-covalent Ar–Ar interactions found in oligopeptides and proteins.[3–6] 1,1′-Ferrocenylene-bis-alanine derivatives possess an interesting feature where the aromatic rings are locked in a face-to-face relationship whilst in proteins the preferred orientations are the displaced–tilted Ar–Ar interactions.[6] In other compounds, however, the face-to-face non-covalent orientation is observed.[7] We earlier reported the synthesis of optically active **8**, using the Heck–Jeffery methodology followed by asymmetric hydrogenation, where the protective groups were identical on both arms.[8] More recently Jackson *et al.* reported a stereospecific synthesis of an analogue of **8** which carries the *NBoc, OMe* protection *via* Pd-catalysed coupling of the corresponding β-iodoalanine-derived organozinc reagent and 1,1′-diiodoferrocene.[9] A more useful derivative for peptide synthesis should carry protecting groups permitting differential deprotection at all four terminals. In this communication, we report the enantioselective synthesis of compound (+)-**6** carrying these features as well as an improved synthesis of (+)-**8**.

The reaction sequence towards (+)-**6** starts with the unselective thioacetalisation of **1** (Scheme 1). After chromatographic removal of the bis-protected derivative **2b** (11%), the monoprotected derivative **2a** was isolated in 40% yield. The free aldehyde function was then condensed with the phosphonylglycine derivative **9** according to Schmidt *et al.*[10,11] to give the protected didehydroamino acid **3**, which was treated with $NCS/AgNO_3$ to liberate the remaining aldehyde moiety. A second condensation reaction, now using the phosphonylglycine derivative **10**, gave the bis-armed unsaturated derivative **5**.

Determination of the configurations of the double bonds in compound **5** was made by NOE differential spectroscopy.[12] Irradiation of the ferrocenylene *ortho* protons (the 2,2′,5,5′-protons together give a triplet at 4.53 ppm) resulted in a 5% enhancement of the NH (broad singlets at 5.80 and 6.24 ppm, respectively) and a 15% enhancement of the vinylic proton signals (singlets at 7.06 and 7.20 ppm, respectively). Irradiation of either of the vinylic protons resulted in a 3% enhancement of the *ortho* proton signals without any detectable enhancement of the NH protons. These results are consistent with a *trans* relationship between the vinylic and NH protons. Thus, the (*Z*) configuration of both didehydroamino acid arms in **5** is strongly indicated.[12]

Fortunately, in asymmetric catalytic hydrogenations using the rhodium/chiral phosphine type of catalyst the (*Z*)-geometry of the precursor olefin usually leads to the highest stereoisomeric purity of

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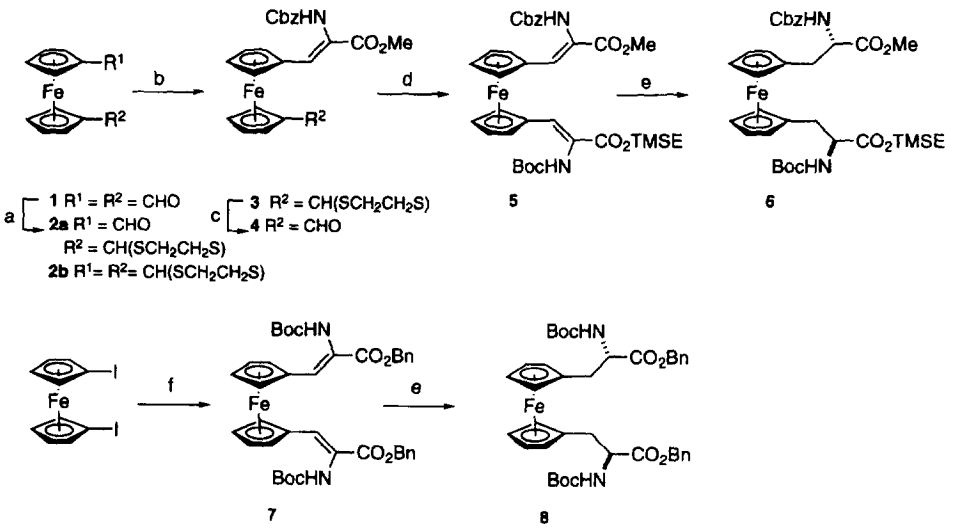

Scheme 1. [a]$BF_3 \cdot Et_2O$ followed by removal of the bis-protected derivative by chromatography; [b]TMG, $(MeO)_2P(O)CH(NHCbz)CO_2Me$ (**9**), [c]NCS/$AgNO_3$; [d]TMG, $(MeO)_2P(O)CH(NHBoc)CO_2TMSE$ (**10**); [e]H_2, 4 atm, 40°C, MeOH, [Rh((*R,R*)-DIPAMP)(COD)]BF_4; [f]$Pd(OAc)_2$, Bu_4NCl, $NaHCO_3$, DMF, $CH_2{=}C(NHBoc)CO_2Bn$ (**11**). List of abbreviations: COD=1,5-cyclooctadiene, DIPAMP=1,2-bis[(*o*-methoxyphenyl)phenylphosphino]ethane, PROPHOS=1,2-bis(diphenylphosphino)propane, DPPE=1,2-bis(diphenylphosphino)ethane, TMSE=2-trimethylsilylethyl, TMG=1,1,3,3-tetramethylguanidine, NBD=norbornadiene.

the product.[13] Thus, hydrogenation of **5** using the [Rh((*R,R*)-DIPAMP)(COD)]BF_4 catalyst resulted in a high yield and high ee (see below) of the bis-amino acid derivative **6** carrying four different protecting groups.

The pairwise protected derivative **7** as well as its corresponding bis-ethyl ester were previously hydrogenated using [Rh((*R*)-PROPHOS)(NBD)]ClO_4 as catalyst.[8] This resulted in a dr of only 62:38 and an ee of 85% for the saturated bis-ethyl ester as analysed by HPLC using a Chiralcel OJ column. Unfortunately, this column did not separate the stereoisomers of **8**. A better hydrogenation catalyst and a better chiral column for diastereomeric and enantiomeric separations were obviously needed.

Two assumptions have been made in the analysis of the results of the asymmetric hydrogenations: the DIPAMP catalyst has a general (*S*)-selectivity, and the two arms of **5** and **7** were hydrogenated independently so that the configuration of one arm has little or no effect on the reaction at the other arm. From this (+)-**6** and (+)-**8** were assigned (*S,S*) absolute configurations.[14]

Furthermore, hydrogenation of **5** using the Rh(DIPAMP) catalyst resulted in a dr of 80:20 and an ee of >95% for the diastereomer of **6** ((+)-form) having the largest α-value as analysed on the (*R,R*)-Whelk-O1 chiral HPLC column. The second and minor diastereomer was formed with essentially 0% ee (a 90:10 stereoselectivity in the hydrogenation of each olefinic unit would lead to approximately these numbers).

Analysis of the stereoisomeric composition of **8** (prepared as for (+)-**6**) on the same column did not allow a definite conclusion of whether the minor, last eluted component was the *meso*-form or one of the enantiomers. This was due to the fact that the last two peaks in the chromatogram of (±)-**8**[15] were of similar size but not well resolved. The first peak in the chromatogram of (±)-**8** corresponded to the first, major peak in the chromatogram of (+)-**8**. When (+)-**8** and a small amount of (±)-**8** where co-injected, a slight hump on the tail of the minor peak was observed. This indicated that in the chromatogram of (+)-**8** the minor peak corresponded to the middle peak of (±)-**8** and thus was the *meso*-form.

From this analysis the dr was 90:10 and the ee was >95% (a 95:5 stereoselectivity in the

hydrogenation of each olefinic unit would lead to approximately this dr and >99% ee). Thus, asymmetric hydrogenations of doubly unsaturated amino acid derivatives such as **5** and **7** gave stereoselectivities in the same range as those of bis-didehydropeptides.[16,17]

In conclusion we have shown that it is possible to prepare (+)-**6** and (+)-**8** in stereoisomeric purities high enough to be of synthetic value. These derivatives carry different protecting groups which may be removed selectively to make possible the selective attachment of various chains or loops. Development along these lines will be reported in due course.

Experimental

TLC analyses were performed on silica gel plates (Merck, 0.25 mm Kieselgel 60 F_{254}) and for column chromatography Matrex™ (35–70 μm) silica gel was used. For stereoisomer determinations a Merck (*R,R*)-Whelk-O1 HPLC column was used. Melting points are uncorrected. ^1H and ^{13}C NMR spectra were recorded at 300 and 75.43 MHz, respectively, unless otherwise stated. The chemical shifts were measured with reference to $CHCl_3$ (7.26 ppm). Solvents were removed on a rotary evaporator. The following starting materials were prepared according to literature procedures: **9**,[11] **10**,[18] **11**,[19] 1,1'-diformylferrocene **1**[20,21] and 1,1'-diiodoferrocene.[22]

1-[2-(1,3-Dithiolanyl)]-1'-formylferrocene 2a

A solution of $BF_3 \cdot Et_2O$ (0.6 mL) in dry CH_2Cl_2 (5 mL) was added dropwise to an ice-cold solution of **1** (548 mg, 2.26 mmol) and ethanedithiol (320 mg, 3.40 mmol) in CH_2Cl_2 (15 mL) followed by stirring for 5 h at 0°C. The mixture was then successively washed with 5% aqueous $NaHCO_3$ (2×10 mL), water (10 mL), and brine (10 mL) and was then concentrated. Chromatography of the black viscous residue (SiO_2, heptane:EtOAc 5:1) afforded **2a** (285 mg, 40%; R_f=0.15 heptane:EtOAc 5:1) and the corresponding bis-protected compound **2b** (101 mg, 11%; R_f=0.36 heptane:EtOAc 5:1).

For **2a**: mp 52–54°C; ^1H NMR ($CDCl_3$) δ 3.17–3.32 (m, 4 H), 4.21 (t, 2 H, J=1.8 Hz), 4.33 (t, 2 H, J=1.8 Hz), 4.57 (t, 2 H, J=1.8 Hz), 4.75 (t, 2 H, J=1.8 Hz), 5.38 (s, 1 H), 9.92 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 39.84, 51.79, 68.98, 69.97, 70.60, 74.29, 79.90, 91.29, 193.46; Anal. Calcd for $C_{14}H_{14}FeOS_2$: C, 52.84; H, 4.43. Found: C, 53.20; H, 4.30.

For *1,1'-bis[2-(1,3-dithiolanyl)]ferrocene* (**2b**): mp 128°C; ^1H NMR ($CDCl_3$) δ 3.23–3.41 (m, 8 H), 4.22 (s, 4 H), 4.33 (s, 4 H), 5.63 (s, 2 H); ^{13}C NMR ($CDCl_3$) δ 39.66, 52.62, 68.52, 69.49, 89.53. HRMS (CI; CH_4) *m/z* calcd for $C_{16}H_{18}FeS_4$: 393.9641. Found: 393.9638.

(Z)-1-[2-[(Benzyloxycarbonyl)amino]-2-(methoxycarbonyl)ethenyl]-1'-[2-(1,3-dithiolanyl)]-ferrocene 3

A solution of **2a** (385 mg, 1.20 mmol) in dry THF (5 mL) was added to a solution of **9** (485 mg, 1.46 mmol) and TMG (170 mg, 1.46 mmol) in dry THF (5 mL) at −70°C. The mixture was allowed to reach room temperature overnight and was stirred at room temperature for another 24 h. It was then diluted with EtOAc (100 ml), washed with water (2×20 ml) and brine (20 ml). Removal of the solvent at reduced pressure after drying with Na_2SO_4 gave a viscous mass, which was chromatographed (SiO_2, heptane:EtOAc 2.5:1). After chromatography the fractions containing **3** were concentrated and the residue was dissolved in EtOAc followed by addition of heptane until a small amount of a white precipitate appeared, which was removed by filtration. The filtrate was concentrated to give **3** (382 mg, 61%; R_f=0.24 heptane:EtOAc 2:1) as a red solid; mp 104–105°C.

^1H NMR ($CDCl_3$) δ 3.17–3.36 (m, 4 H), 3.75 (s, 3 H), 4.13 (t, 2 H, J=1.8 Hz), 4.25 (t, 2 H, J=1.8 Hz), 4.43 (t, 2 H, J=1.8 Hz), 4.55 (s, 2 H), 5.16 (s, 2 H), 5.44 (s, 1 H), 6.16 (br. s, 1 H), 7.27–7.35 (m, 6 H); ^{13}C NMR ($CDCl_3$) δ 39.57, 52.10, 52.17, 67.18, 68.83, 70.04, 71.47, 72.05, 76.61, 90.29, 121.19, 128.03, 128.14, 128.36, 135.45, 136.12, 154.18, 165.45; Anal. Calcd for $C_{25}H_{25}FeNO_4S_2$: C, 57.37; H, 4.81; N, 2.68. Found: C, 57.40; H, 4.90; N, 2.70.

(Z)-1-[2-[(Benzyloxycarbonyl)amino]-2-(methoxycarbonyl)ethenyl]-1'-formylferrocene **4**

A solution of **3** (360 mg, 0.688 mmol) in a mixture of acetone (1.5 mL) and CH_3CN (4.5 mL) was rapidly added to a well-stirred solution of *N*-chlorosuccinimide (368 mg, 2.75 mmol) and $AgNO_3$ (525 mg, 3.09 mmol) in CH_3CN/H_2O (10 mL; 80/20) at 0°C. The reaction mixture was stirred at 0°C for 30 min followed by sequential addition of saturated Na_2SO_3 (5 mL), saturated Na_2CO_3 (5 mL) and brine (5 mL) at 1 min intervals. Then dichloromethane:hexane (1:1, 50 mL) was added. The resulting mixture was stirred for 5 min, filtered through Hyflo Supercel and the filter cake was washed with dichloromethane:hexane (1:1; 50 mL). The water phase was separated from the combined filtrate and the organic phase was dried (Na_2SO_4), concentrated and the residue was chromatographed (SiO_2, heptane:EtOAc 1:1) to afford **4** (225 mg, 72%; R_f=0.24 heptane:EtOAc 1:1) as a dark red viscous mass; ^1H NMR ($CDCl_3$) δ 3.76 (s, 3 H), 4.43–4.72 (m, 8 H), 5.16 (m, 2 H), 6.44 (br s, 1 H), 7.18–7.35 (m, 6 H), 9.85 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 52.25, 67.11, 70.82, 71.70, 71.94, 74.49, 76.59, 79.77, 122.49, 127.84, 127.97, 128.30, 133.86, 136.03, 154.26, 165.24, 193.45; Anal. Calcd for $C_{23}H_{21}FeNO_5$: C, 61.76; H, 4.73; N, 3.13. Found: C, 61.90; H, 4.90; N, 3.10.

*(Z,Z)-1-[2-[(Benzyloxycarbonyl)amino]-2-(methoxycarbonyl)ethenyl]-1'-[2-[(*tert*-butoxycarbonyl)-amino]-2-[2-(trimethylsilyl)ethoxycarbonyl]ethenyl]ferrocene* **5**

A solution of compound **4** (175 mg, 0.39 mmol) in THF (3 mL) was added to a solution of **10** (192 mg, 0.50 mmol) and TMG (58 mg, 0.50 mmol) in THF (3 mL) at −70°C under a nitrogen atmosphere. The mixture was stirred at −70°C for 5 h, and then allowed to reach room temperature overnight after which stirring was continued for another 36 h. The solvent and volatiles were removed at reduced pressure, EtOAc (30 mL) was added and the organic layer was washed with water (10 mL), and brine (10 mL), and dried (Na_2SO_4). Evaporation of the solvent gave a residue which was purified by chromatography (SiO_2, heptane:EtOAc 3:1) to furnish **5** (190 mg, 69%; R_f=0.17 heptane:EtOAc 3:1) as dark red crystals; mp 78–80°C; ^1H NMR (400 MHz, +50°C, $CDCl_3$) δ 0.08 (s,9 H), 1.06–1.11 (m, 2 H), 1.46 (s, 9 H), 3.77 (s, 3 H), 4.27–4.32 (m, 2 H), 4.35 (t, 2 H, J=2 Hz), 4.37 (t, 2 H,J=2 Hz), 4.53 (t, 4 H, J=2 Hz), 5.16 (s, 2 H), 5.80 (br s, 1 H), 6.24 (br s, 1 H), 7.06 (s, 1 H), 7.20 (s, 1 H), 7.29–7.36 (m, 5 H); ^{13}C NMR (100 MHz, +50°C, $CDCl_3$) δ −1.26, 17.73, 28.51, 52.41, 63.83, 67.47, 72.00, 72.18, 72.44, 78.03, 78.62, 80.77, 122.33, 123.22, 128.28, 128.38, 128.65, 133.14, 135.12, 136.74, 153.74, 154.64, 165.62, 165.76; HRMS (FAB^+) *m/z* calcd for $C_{35}H_{44}FeN_2O_8Si$: 704.2216. Found: 704.2206.

It should be noted that compound **5** is not stable in solution in the presence of air. The ^1H-{^1H} NOE experiments were performed at +50°C using a 5 sec irradiation time.

*(+)-(S,S)-1-[2-[(Benzyloxycarbonyl)amino]-2-(methoxycarbonyl)ethyl]-1'-[2-[(*tert*-butoxycarbonyl)-amino]-2-[2-(trimethylsilyl)ethoxycarbonyl]ethyl]ferrocene (+)-***6**

Compound **5** (60 mg, 0.085 mmol) and [Rh((*R,R*)-DIPAMP)(COD)]BF_4 (7 mg, 0.01 mmol) were combined in degassed MeOH (5 mL) and hydrogenated at 60 psi/45°C for 60 h, after which TLC analysis of the reaction mixture showed complete consumption of the starting material. The solvent was removed at reduced pressure and the residue was chromatographed (SiO_2, heptane:EtOAc 3:1) to give **6** (51 mg; 85%; R_f=0.23 heptane:EtOAc 3:1) as a red viscous mass; $[\alpha]_D^{22}$+21 (c 2.0, $CHCl_3$). HPLC analysis on an (*R,R*)-Whelk-O1 column (flow rate 1.0 mL/min, hexane:iPrOH 19:1+0.5% of HOAc) revealed three peaks with retention times min/(areas) 62/(80), 66/(10) and 76/(10). Comparison with the chromatogram of the racemic diastereomeric mixture (±)-**6** (see below), in combination with the assumptions of (*S*)-selectivity and arm independence of the catalyst as mentioned, resulted in the following assignments. For statistical reasons the minor diastereomer was expected to have a very low ee. Indeed, the peaks from the analysis of (+)-**6** at 66 and 76 min have similar areas and are therefore assigned to this minor diastereomer. These two peaks are also present as the "inner" peaks of (±)-**6**. The remaining two "outer peaks" of (±)-**6** must therefore correspond to the major diastereomer of

(+)-**6**. Since only one of these peaks is present in the analysis of (+)-**6** the ee must be >95% while the areas yield a dr of 80:20.

^{1}H NMR ($CDCl_3$) δ −0.02 (s, 9 H), 0.96 (t, 2 H, *J*=8.7 Hz), 1.41 (s, 9 H), 2.80 (dd, 4 H, *J*=5.1 and 14.4 Hz), 3.68 (s, 3 H), 3.86–4.00 (m, 8 H), 4.17 (t, 2 H, *J*=8.7 Hz), 4.32–4.47 (m, 2 H), 4.98 (d, 1 H, *J*=8.1 Hz), 5.08 (s, 2 H), 5.23 (d, 1 H, *J*=7.8 Hz), 7.33 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ −1.53, 17.35, 28.31, 32.76, 52.26, 54.48, 54.79, 63.64, 66.90, 68.90, 68.95, 69.05, 69.74, 69.80, 79.71, 81.86, 82.43, 128.06, 128.13, 128.47, 136.22, 155.01, 155.53, 171.85, 171.87; Anal. Calcd for $C_{35}H_{48}FeN_2O_8Si$: C, 59.32; H, 6.83; N, 3.95. Found: C, 59.23; H, 6.57; N, 3.80.

*1-[2-[(Benzyloxycarbonyl)amino]-2-(methoxycarbonyl)ethyl]-1'-[2-[(*tert*-butoxycarbonyl)amino]-2-[2-(trimethylsilyl)ethoxycarbonyl]ethyl]ferrocene (±)-6*

Hydrogenation of **5** (50 mg, 0.068 mmol) was carried out as above but with [Rh(DPPE)(COD)]BF_4 (7 mg, 0.01mmol) as catalyst to give (±)-**6** (50 mg, 100%). HPLC analysis as for (+)-**6** above showed four peaks with retention times min/(areas): 63/(1), 67/(1),76/(1) and 80/(1). The ^{1}H NMR data in $CDCl_3$ of (±)-**6** were identical to those of (+)-**6** even though (±)-**6** is a diastereomeric mixture.

*(+)-(S,S)-1,1'-bis[(2-Benzyloxycarbonyl)-2-[(*tert*-butoxycarbonyl)amino]ethyl]ferrocene (+)-8*

The hydrogenation of **7**[8] was performed as for (+)-**6**. After chromatography (SiO_2, heptane:EtOAc 3:1) the product showed NMR data identical with those described;[19] $[\alpha]_D^{22}$+25 (c 0.75, $CHCl_3$). An earlier reported value for a stereoisomerically less pure preparation was $[\alpha]_D^{22}$+17.[8] HPLC analysis as for (+)-**6** above revealed two peaks with retention times min/(area) 42/(90) and 47/(10) indicating *ca* 90:10 dr (the (+)-form is dominating) and >95% ee (no shoulder on the last peak could be detected). A 95:5 stereoselectivity in the hydrogenation of each olefinic unit would lead to approximately this dr and >99% ee. Comparison of retention times was made with (±)-**8** (see below). Anal. Calcd for $C_{40}H_{48}FeN_2O_8$: C, 64.87; H, 6.53; N, 3.78. Found: C, 64.85; H, 6.40; N, 3.65.

*1,1'-bis[(2-Benzyloxycarbonyl)-2-[(*tert*-butoxycarbonyl)amino]ethyl]ferrocene (±)-8.*

The hydrogenation of **7** was performed as for (±)-6. After chromatography as for (+)-**8** the product showed NMR data identical with those described.[19] HPLC analysis as for (+)-**6** above revealed three peaks with retention times 43, 47 and 48 min with estimated areas 1, 2 and 1, respectively. The two last peaks were not well resolved (shoulder).

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