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Synthesis of optically active arylene bis-alanine derivatives carrying orthogonal protecting groups

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Abstract

Derivatives of *para*- and *meta*-phenylene bis-alanine and related biphenyl systems, carrying four orthogonal protecting groups, were synthesised *via* combinations of Heck couplings and asymmetric hydrogenations. The intermediate unsaturated arylalanine derivatives were hydrogenated using [Rh(COD)((*R*,*R*)-DIPAMP)]$^{+}BF_4^{-}$ or [Rh(COD)(Me-DuPHOS)]$^{+}X^{-}$ as catalysts to produce the optically active, protected amino acid derivatives in ≥98% e.e. as analysed by chiral phase HPLC.

Bis-armed, aromatic amino acid substructures occur in several cyclic peptide antibiotics, such as the biphenomycins, ristocetins, teichoplanins and vancomycin.[1] This made us interested in the synthesis of optically active aromatic amino acids, carrying two or more amino acid arms located in various positions on the aromatic ring systems. Such compounds would be useful structural variants in the synthesis of these types of antibiotics. They could also serve as structural units mimicking some of the possible geometries of aromatic–aromatic interactions in peptides.[2] We,[3,4] and Jackson et al.,[5] recently reported the syntheses of some bis-armed amino acids based on ferrocene, and in the present work, the scope has been broadened to include benzene- and biphenyl-based amino acids as well. Similar optically active bis-amino acid derivatives have been reported.[6–9]

It is important to have access to pure stereoisomers of the target bis-armed amino acids. In the present work we demonstrate how this can be accomplished by using asymmetric hydrogenations with cationic Rh(I)–bisphosphine catalysts. The development of new ligands for this important reaction has made it a preferred method for the synthesis of various aromatic amino acids.[10] One of the most general and stereoselective ligand classes so far developed is the DuPHOS family of bisphosphines.[10] Since these ligands were not available when this project was initiated, we started using the DIPAMP ligand.[11] When both enantiomers of Me-DuPHOS became available, we decided to switch to these (the DIPAMP was only available to us as the (*R*,*R*)-enantiomer).

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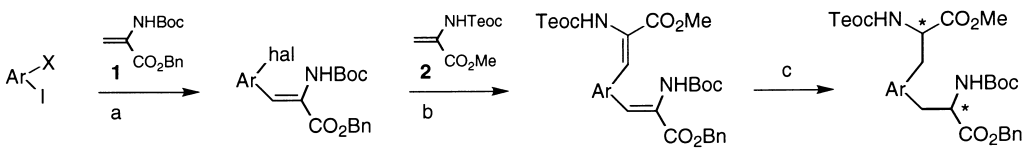
1. Results and discussion

The synthesis of the (*S*,*S*)- and (*R*,*R*)-isomers[12] of the target amino acids start from dihaloaromatics **3**, **4** and **5** (Scheme 1). Since the obtained amino acid derivatives should be useful for peptide synthesis, they must carry suitable orthogonal protecting groups. To this end, the readily available 2-carbamatoacrylates **1** and **2**,[13] which carry the requisite protecting groups, were coupled to the aromatic core in two successive Heck–Jeffery reactions.[14,15] Each of the so-obtained dehydro derivatives **9**, **10** and **11** was then hydrogenated using a [Rh(COD)(bisphosphine)]$^+$X$^-$ catalyst, where bisphosphine=DIPAMP or Me-DuPHOS, and X=BF_4 or OTf. This produced the target amino acid derivatives **12**, **13** and **14** in ≥95% yield and with very good stereoselectivity; e.e.≥98% and d.r.≥90:10. It is worth noting that the presence of two dehydro amino acid functionalities in close proximity in the same molecule does not diminish either the rate or the selectivity of the hydrogenation reaction. This is in contrast to our experience with the related ferrocene systems.[3,4]



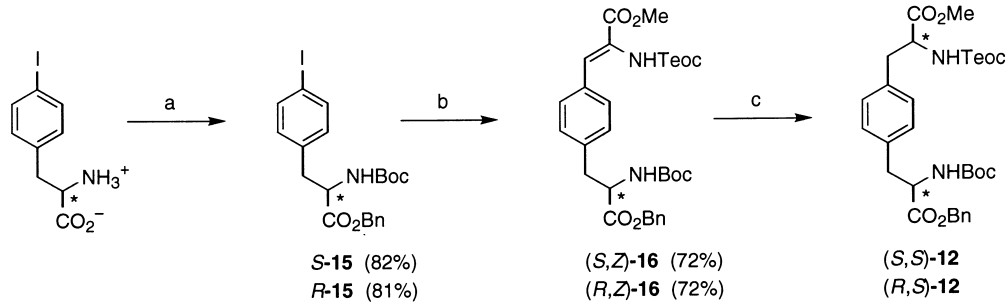
3 Ar = *p*-C_6H_4, X = Br	**6** (52%)[15]	**9** (62%)[15]	(*S*,*S*)-**12**
4 Ar = *m*-C_6H_4, X = Br	**7** (63%)[15]	**10** (77%)	(*S*,*S*)-**13** and (*R*,*R*)-**13**
5 Ar = *p*,*p*'-$(C_6H_4)_2$, X = I	**8** (23%)	**11** (66%)	(*S*,*S*)-**14**

Scheme 1. (a) $Pd(OAc)_2$, $NaHCO_3$, Bu_4NCl, DMF, 85–90°C, 18 h; (b) $Pd(OAc)_2$, $NaHCO_3$, Bu_4NCl, DMF, 85–90°C, 18 h; (c) H_2, [Rh(COD)(bisphosphine)]$^+$X$^-$, MeOH. *List of abbreviations*: Bn=benzyl, Boc=*tert*-butyloxycarbonyl, Cbz=benzyloxycarbonyl, COD=1,5-cyclooctadiene, dppe=1,2-bis(diphenylphosphino)ethane, Teoc=2-(trimethylsilyl)etyloxycarbonyl

The double bond configuration of most of the Heck products was assigned by NOE in the same way as for the ferrocene amino acids published earlier.[4] In all cases examined, the configuration was (*Z*), which also appears to be more thermodynamically stable than (*E*) for these compounds.[16] This is fortunate, since the (*Z*)-isomers are hydrogenated faster and with higher selectivity than the (*E*)-isomers.[10,11]

Having secured the (*S*,*S*) and (*R*,*R*) forms of the requisite bis-armed amino acids, we next turned to the other diastereomer, represented by the (*S*,*R*)-isomer. For the *para* case, we started with commercially available *para*-iodophenylalanine (Scheme 2). Protection of the amino and carboxylate functions, followed by Heck reaction with **2**, gave the mono-olefin **16**. Hydrogenation of (*R*,*Z*)-**16** with [Rh(COD)((*R*,*R*)-DIPAMP)]$^+BF_4^-$ afforded (*R*,*S*)-**12** with high stereoselectivity; d.r.≥90:10, e.e.≥90%.

We were also interested to find out whether the stereoselectivities in the hydrogenations were different for substrates such as **16** (carrying one unsaturated and one saturated arm; Scheme 2) as compared to substrates such as **9** (carrying two unsaturated arms). To this end, we hydrogenated (*S*,*Z*)-**16** with [Rh(COD)((*R*,*R*)-DIPAMP)]$^+BF_4^-$ to afford (*S*,*S*)-**12**. The selectivity was equally high for this reaction as for the hydrogenation of **9** above.



Scheme 2. (a) 1. $(Boc)_2O$, K_2CO_3, dioxane:H_2O 1:1; 2. BnBr, DMF; (b) **2**, $Pd(OAc)_2$, $NaHCO_3$, Bu_4NCl, DMF, 85–90°C, 18 h; (c) H_2, [Rh(COD)((*R*,*R*)-DIPAMP)]$^+BF_4^-$, MeOH

2. Stereochemical analysis[12]

It should be emphasised that the analysis of the stereoisomeric composition of the products is not trivial. HPLC analysis on chiral stationary phases seems to be the method of choice, but although three different phases (Chiralcel OJ, covalent DNBPG and Whelk-O1) were tried, most of our compounds were at the limit of resolution at best, and were not resolved at all at worst. Overall, the best column generally seemed to be the Whelk-O1, but even with this column, it was necessary to change the Teoc protecting group of **13** to Cbz to give **17** (see Experimental), in order to get acceptable separation of the four different stereoisomers.

Compound **12** may be taken as a representative example of the stereochemical analysis. HPLC analysis of (±)-**12**[17] on the (*R*,*R*)-Whelk-O1 column yielded a chromatogram with four poorly resolved peaks; R_t (min)=17.2 (*S*,*S*), 17.7 (*R*,*S*), 18.2 (probably (*S*,*R*)) and 19.3 (probably (*R*,*R*) assuming the same elution order as for (±)-**17**[17]). Co-injection with (*S*,*S*)-**12** resulted in an increase in the height of the first eluted peak (R_t=17.2 min), thus identifying this peak as corresponding to the (*S*,*S*)-isomer. Co-injection with (*R*,*S*)-**12** increased the height of the second eluted peak (R_t=17.7 min), thus identifying this peak as corresponding to the (*R*,*S*) isomer.

Now, HPLC analysis of (*S*,*S*)-**12** on the (*R*,*R*)-Whelk-O1 column gave a single peak, but given the poor resolution of the different stereoisomers, a small amount (≤10%) of the (*S*,*R*) and/or (*R*,*S*) isomers may be present. We therefore concluded that the d.r. was ≥90:10. Since the (*S*,*S*) and (*R*,*R*) isomers were fairly well-resolved (assuming that (*R*,*R*)-**12** corresponded to the last eluted peak), and no trace of the (*R*,*R*) was seen. The e.e. was estimated at ≥98%, assuming a 1% detection limit in this case.

It should also be stressed that for compounds **12** and **14**, the different diastereomers have identical ^1H and ^{13}C NMR spectra. Thus, NMR analysis could not be used to determine the d.r. for these compounds.

3. Conclusion

We have demonstrated that various aromatic, bis-armed amino acids can be synthesised in a few steps and with very good stereoselectivity. By the appropriate route, both the (*S*,*S*)/(*R*,*R*) and the (*S*,*R*)/(*R*,*S*) diastereomer of the *para*-substituted compound **12** could be obtained in ≥98% e.e. Since orthogonal protecting groups are present in the amino acids synthesised, they would be versatile building blocks for a wide range of applications, one of which may be the synthesis of peptide analogues.

4. Experimental

NMR spectra were recorded on a Bruker DRX 400 NMR spectrometer in $CDCl_3$. For ^1H experiments, residual $CHCl_3$ at δ 7.27 was used as an internal standard, while the central peak of the $CDCl_3$ triplet at δ 77.23 was used for ^{13}C experiments. Optical rotations were measured on a Perkin–Elmer 241 polarimeter. TLC retention values (TLC R_f) are given in the same solvent as used in the respective column chromatographies unless otherwise stated. Stereochemical analyses were performed using HPLC on a covalent DNBPG column (J. T. Baker Inc., 250×4.6 mm; DNBPG=dinitrobenzoylphenylglycine) or an (*R*,*R*)-Whelk-O1 column (Merck, 250×4.6 mm). Two detectors in tandem were routinely used; one refractive index detector and one ultraviolet detector at 254 nm.

[Rh(COD)((*R*,*R*)-DIPAMP)]$^+BF_4^-$ was a gift from Searle Chemical Corporation, and [Rh(COD)((*S*,*S*)-Me-DuPHOS)]$^+BF_4^-$ and [Rh(COD)((*R*,*R*)-Me-DuPHOS)]$^+OTf^-$ were synthesised according to the published procedure.[10] The DuPHOS ligands are commercially available from Strem. Analytical grade methanol was used in all hydrogenations. The hydrogen gas was of zero grade quality (<2 ppm oxygen). The following compounds were prepared according to literature procedures: **1**[18], **2**[19], **6**[19], **7**[19] and **9**.[19]

4.1. General procedure for the Heck–Jeffery coupling reactions

The aryl halide (1 equiv.), olefin (1.4 equiv.), $Pd(OAc)_2$ (0.03 equiv.), Bu_4NCl (1 equiv.), $NaHCO_3$ (2.5 equiv.) and a few mg of hydroquinone (to avoid polymerisation of the olefin) in DMF (10 mL per mmol of olefin) were heated at 85–90°C for 18 h in a closed screw-capped vial under nitrogen. The reaction mixture was then cooled to room temperature and diluted with EtOAc to 10 times its original volume. The mixture was washed four times with half-saturated brine to remove most of the DMF. After drying with Na_2SO_4 and evaporation of the solvent on a rotary evaporator, the residue was purified using flash chromatography on Matrex (Amicon) silica gel, particle size 35–70 μm.

4.2. General procedure for hydrogenations

The catalyst and the substrate were placed in the hydrogenation vessel, which was then flushed with nitrogen. Methanol, deoxygenated by sonication and purging with nitrogen for 30 min, was then added and the nitrogen was replaced by hydrogen by four successive vacuum–pressurisation cycles. With the DuPHOS-derived catalyst, the pressure was set to 2.7 atm and the reactions were, in general, complete after 1 to 4 hours at r.t. depending on the substrate-to-catalyst ratio. After this time the methanol was removed by evaporation and the residue was dissolved in EtOAc and filtered through a short plug of silica to remove the catalyst. After evaporation of the solvent the pure product was obtained.

4.3. (Z)-4-[2′′-(Benzyloxycarbonyl)-2′′-[(tert-butyloxycarbonyl)amino]ethenyl]-4′-iodo-biphenyl **8**

The coupling reaction was done following the general procedure using 4,4′-diiodobiphenyl (154 mg, 0.380 mmol) and **1**. Chromatography (hexane:EtOAc=2:1) of the crude product gave **8** (49 mg, 23%, TLC R_f=0.31, mp 173–175°C), and the bis-coupled product[19] (57 mg, 22%). ^1H NMR (400 MHz, $CDCl_3$) δ 1.27 (s, 9H), 5.31 (s, 2H), 6.33 (br s, 1H), 7.33–7.48 (m, 8H), 7.54–7.63 (m, 4H), 7.76–7.80 (m, 2H); ^{13}C NMR δ 28.33, 67.73, 81.30, 93.78, 124.71 (br), 127.01, 128.65, 128.83, 129.04, 129.86, 130.58, 133.81, 135.73, 138.15, 139.99, 140.79, 152.82 (br), 165.67; HRMS (FAB+) *m*/*z* calcd for $C_{27}H_{26}INO_4$: 556.0985 [M+H]. Found: 556.0987.

*4.4. (Z′,Z′′)-1-[2′-(Benzyloxycarbonyl)-2′-[(*tert*-butyloxycarbonyl)amino]ethenyl]-3-[2′′-(methoxycarbonyl)-2′′-[[2′′′-(trimethylsilyl)ethyloxycarbonyl]amino]ethenyl]benzene* ***10***

Following the general procedure of coupling using the bromide **7**[19] (0.86 g, 1.99 mmol) and olefin **2**[19] (0.77 g, 3.14 mmol) the product was isolated as a viscous, pale yellow oil, 0.92 g (77%), after flash chromatography using heptane:ethyl acetate (2:1) as eluent (TLC R_f=0.24). NOE experiments confirmed the assigned (*Z*) stereochemistry.[4] ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.02 (s, 9H), 0.87–1.02 (m, 2H), 1.38 (s, 9H), 3.86 (s, 3H), 4.13–4.19 (m, 2H), 5.29 (s, 2H), 6.32 (br s, 2H), 7.26 (s, 2H), 7.34–7.44 (m, 6H) 7.51 (d, 2H, *J*=7.9 Hz), 7.64 (s, 1H); ^{13}C NMR δ −1.33, 17.77, 28.24, 52.93, 64.47, 67.73, 81.35, 125.22, 128.58, 128.64, 128.81, 128.92, 129.48, 130.04, 130.43, 131.41, 134.26, 134.78, 135.62, 152.73 (br), 154.25 (br), 165.51, 165.90; HRMS (FAB+) *m*/*z* calcd for $C_{31}H_{40}N_2O_8Si$: 597.2632 [M+H]. Found: 597.2638.

*4.5. (Z′′,Z′′′)-4-[2′′-(Benzyloxycarbonyl)-2′′-[(*tert*-butyloxycarbonyl)amino]ethenyl]-4′-[2′′′-(methoxycarbonyl)-2′′′-[[2′′′′-(trimethylsilyl)ethyloxycarbonyl]amino]ethenyl]biphenyl* ***11***

The coupling reaction was performed following the general procedure using **8** (0.50 g, 0.90 mmol) and **2** (0.29 g, 1.17 mmol). Purification of the crude product by chromatography (hexane:EtOAc=2:1, TLC R_f=0.25) gave **11** in 74% yield. Recrystallisation from ethyl acetate:hexane afforded the analytically pure compound (0.40 g, 66%, mp 161–162°C). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.03 (s, 9H), 0.92–1.01 (m, 2H), 1.41 (s, 9H), 3.88 (s, 3H), 4.16–4.22 (m, 2H), 5.30 (s, 2H), 6.31 (br s, 2H), 7.34–7.46 (m, 7H), 7.61–7.63 (m, 8H); ^{13}C NMR δ −1.28, 17.79, 28.33, 52.96, 64.53, 67.72, 81.32, 124.55, 127.18, 127.30, 128.64, 128.65, 128.84, 129.94, 130.53, 130.56, 130.82, 133.47, 133.85, 135.74, 140.97, 141.26, 152.84 (br), 154.27 (br), 165.69, 166.07; HRMS (FAB+) *m*/*z* calcd for $C_{37}H_{44}N_2O_8Si$: 672.2867. Found: 672.2861.

*4.6. (2′*S*,2′′*S*)-1-[2′-(Benzyloxycarbonyl)-2′-[(*tert*-butyloxycarbonyl)amino]ethyl]-4-[2′′-(methoxycarbonyl)-2′′-[[2′′′-(trimethylsilyl)ethyloxycarbonyl]amino]ethyl]benzene (*S,S*)-****12****

(a) Hydrogenation of bis-olefin **9**: Bis-olefin **9**[19] (400 mg, 0.670 mmol) was dissolved in methanol (20 mL) and hydrogenated at 2.8 atm at 40°C in the presence of [Rh(COD)((*R*,*R*)-DIPAMP)]$^+BF_4^-$ (10 mg) as catalyst for 4 days. The solvent was then removed in vacuo and the crude mass was passed through a short pad of silica to give the title compound (370 mg, 92%) as a highly viscous liquid using heptane:ethyl acetate (2:1) as an eluent (TLC R_f=0.3); $[\alpha]_D^{22}$ +30 (c 3.7, $CHCl_3$). HPLC analysis (see Stereochemical analysis) on an (*R*,*R*)-Whelk-O1 column (hexane:2-propanol=90:10+0.5% HOAc; 1.0 mL/min) gave a single peak (R_t=16.8 min); d.r.≥90:10; e.e.≥98%. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.03 (s, 9H), 0.95–0.99 (m, 2H), 1.42 (s, 9H), 3.00–3.11 (m, 4H), 3.70 (s, 3H), 4.12–4.17 (m, 2H), 4.58–4.63 (m, 2H), 4.98 (br d, 1H, *J*=8.4 Hz), 5.06 (br d, 1H, *J*=8.4 Hz), 5.10 (d, 1H, *J*=12 Hz), 5.17 (d, 1H, *J*=12 Hz), 6.95–7.00 (m, 4H), 7.30–7.40 (m, 5H); ^{13}C NMR δ −1.30, 17.86, 28.49, 38.02, 38.10, 52.46, 54.56, 54.80, 63.67, 67.30, 80.15, 128.69, 128.79, 129.58, 129.78, 134.70, 134.90, 135.37, 155.25, 156.19, 171.87, 172.35; HRMS (CI-CH_4) *m*/*z* calcd for $C_{31}H_{44}N_2O_8Si$: 601.2945 [M+H]. Found: 601.2929.

(b) Hydrogenation of mono-olefin (*S*,*Z*)-**16**: Olefin (*S*,*Z*)-**16** (198 mg, 0.331 mmol) dissolved in methanol (10 mL) was hydrogenated at 3 atm and at room temperature for 3 days using [Rh(COD)((*R*,*R*)-DIPAMP)]$^+BF_4^-$ (6 mg) as a catalyst. The solvent was removed in vacuo and the crude viscous mass was passed through a short pad of silica using hexane:ethyl acetate (2:1) as eluent to give the title compound

(190 mg, 96%) as a viscous liquid (TLC R_f=0.3); $[\alpha]_D^{22}$ +29 (c 2.7, $CHCl_3$). The NMR and HPLC data were identical with those reported for procedure (a) above.

*4.7. (2′*R,*2′′*S)*-1-[2′-(Benzyloxycarbonyl)-2′-[(*tert*-butyloxycarbonyl)amino]ethyl]-4-[2′′-(methoxycarbonyl)-2′′-[[2′′′-(trimethylsilyl)ethyloxycarbonyl]amino]ethyl]benzene (*R,S*)-**12**

Compound (*R,Z*)-**16** (200 mg, 133 mmol) dissolved in methanol (10 mL) was hydrogenated at 3.1 atm at room temperature for 3 days using [Rh(COD)((*R,R*)-DIPAMP)]$^+BF_4^-$ (6 mg) as catalyst. The solvent was removed in vacuo and the crude mass was passed through a short pad of silica using hexane:ethyl acetate (2:1) as eluent to give 190 mg (95%) of white solid (TLC R_f=0.3); $[\alpha]_D^{22}$ +25 (c 2.7, $CHCl_3$); mp 66–67°C. HPLC analysis (see Stereochemical analysis) on a (*R,R*)-Whelk-O1 column (hexane:2-propanol=90:10+0.5% HOAc; 1.0 mL/min) gave a single peak (R_t=18.3 min); d.r.≥90:10; e.e.≥90%. The NMR data were identical with those of the (*S,S*) isomer, although there is a diastereomeric relationship between these compounds. HRMS (FAB+) *m/z* calcd for $C_{31}H_{44}N_2O_8Si$: 601.2945 [M+H]. Found: 601.2948.

*4.8. (±)-1-[2′-(Benzyloxycarbonyl)-2′-[(*tert*-butyloxycarbonyl)amino]ethyl]-4-[2′′-(methoxycarbonyl)-2′′-[[2′′′-(trimethylsilyl)ethyloxycarbonyl]amino]ethyl]benzene* (±)-**12**

Bis-olefin **9**[19] (30 mg) was dissolved in methanol and hydrogenated at 4 atm at r.t. in the presence of [Rh(COD)(dppe)]$^+BF_4^-$ for 2 days. After work-up, 28 mg of a 1:1:1:1 mixture of stereoisomers of **12** was obtained. HPLC analysis on an (*R,R*)-Whelk-O1 column (hexane:2-propanol=90:10+0.5% HOAc) yielded a chromatogram with four poorly resolved peaks; R_t (min)=17.2 (*S,S*), 17.7 (*R,S*), 18.2 (probably (*S,R*)) and 19.3 (probably (*R,R*); compare with elution order for (±)-**17** below). The NMR data were identical with those of the pure (*S,S*)-isomer, although the product is a 1:1 mixture of diastereomers.

*4.9. (2′*S,*2′′*S)*-1-[2′-(Benzyloxycarbonyl)-2′-[(*tert*-butyloxycarbonyl)amino]ethyl]-3-[2′′-(methoxycarbonyl)-2′′-[[2′′′-(trimethylsilyl)ethyloxycarbonyl]amino]ethyl]benzene (*S,S*)-**13**

A solution of **10** (218 mg, 0.365 mmol) in methanol (3 mL) was hydrogenated in the presence of [Rh(COD)((*S,S*)-Me-DuPHOS)]$^+BF_4^-$ (4 mg) as a catalyst at 2.7 atm and r.t. for 4.5 h. After work-up, (*S,S*)-**13** was obtained as a viscous oil (218 mg, 99%); $[\alpha]_D^{25}$ +23 (c 4.3, $CHCl_3$). However, no separation of the stereoisomers could be obtained on any of the tested HPLC columns: Chiralcel OJ, Covalent DNBPG and (*R,R*)-Whelk-O1, respectively. To be able to analyse the stereoisomeric composition of the product, the Teoc protecting group was exchanged for a Cbz group, since we knew from previous experience that the stereoisomers could then be separated on the (*R,R*)-Whelk-O1 column. After the protecting group change, see (*S,S*)-**17** below, HPLC analysis showed a single peak; d.r.≥90:10; e.e.≥98%. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.02 (s, 9H), 0.93–0.98 (m, 2H), 1.42 (s, 9H), 2.99–3.07 (m, 4H), 3.69 (s, 3H), 4.10–4.15 (m, 2H), 5.01–5.04 (m, 2H), 5.02 (br d, 1H, *J*=8.0 Hz), 5.09–5.19 (m, 3H), 6.83 (s 1H), 6.91 (d, 1H, *J*=7.4 Hz), 6.99 (d, 1H, *J*=7.6 Hz), 7.15 (t, 1H, *J*=7.6 Hz), 7.29–7.38 (m, 5H); ^{13}C NMR δ −1.37, 17.80, 28.43, 38.20, 38.32, 52.42, 54.54, 54.78, 63.58, 67.21, 80.06, 128.01, 128.27, 128.62, 128.64, 128.74, 128.91, 130.58, 135.37, 136.25, 136.33, 155.20, 156.16, 171.75, 172.24; HRMS (FAB+) *m/z* calcd for $C_{31}H_{44}N_2O_8Si$: 601.2945 [M+H]. Found: 601.2963.

*4.10. (2′*R*,2′′*R*)-1-[2′-(Benzyloxycarbonyl)-2′-[(*tert*-butyloxycarbonyl)amino]ethyl]-3-[2′′-(methoxycarbonyl)-2′′-[[2′′′-(trimethylsilyl)ethyloxycarbonyl]amino]ethyl]benzene (*R,R*)-**13***

A solution of **10** (100 mg, 0.168 mmol) in methanol (2 mL) was hydrogenated in the presence of [Rh(COD)((*R*,*R*)-Me-DuPHOS)]$^+$OTf$^-$ (4 mg) as catalyst at 2.7 atm and r.t. for 1.5 h. After work-up, (*S*,*S*)-**13** was obtained as a viscous oil (100 mg, 99%); $[\alpha]_D^{23}$ −26 (c 1.2, $CHCl_3$). After the protecting group change as for (*S*,*S*)-**13** (see (*R*,*R*)-**17** below) HPLC analysis showed a single peak; d.r.≥90% and e.e.≥98%. The NMR data were identical with those of the (*S*,*S*)-isomer. HRMS (FAB+) *m*/*z* calcd for $C_{31}H_{44}N_2O_8Si$: 601.2945 [M+H]. Found: 601.2955.

*4.11. (2′′*S*,2′′′*S*)-4-[2′′-(Benzyloxycarbonyl)-2′′-[(*tert*-butyloxycarbonyl)amino]ethyl]-4′-[2′′′-(methoxycarbonyl)-2′′′-[[2′′′′-(trimethylsilyl)ethyloxycarbonyl]amino]ethyl]biphenyl (*S,S*)-**14***

Bisolefin **11** (200 mg, 0.296 mmol) was dissolved in methanol (10 mL) and THF (5 mL) (the olefin was not very soluble in pure methanol) and hydrogenated at 40°C, 3.5 atm for 89 h in the presence of [Rh(COD)((*R*,*R*)-DIPAMP)]$^+$BF$_4^-$ (8 mg) as a catalyst. The solvent was removed in vacuo and the residue was passed through a short pad of silica using hexane:EtOAc (2:1) as an eluent to give the title compound (195 mg, 97%) as a viscous liquid, which solidified in the freezer; TLC R_f=0.3; $[\alpha]_D^{22}$ +28 (c 1.6, $CHCl_3$); mp 44–46°C. HPLC analysis on a DNBPG column (iPrOH:hexane=10:90, flow rate 1 mL/min) gave a single peak (R_t=14.9 min); d.r.≥90:10; e.e.≥98%. Also note that the NMR data were identical to those of (±)-**14**, see below, implying that NMR cannot be used to measure the diastereomeric ratio for this compound. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.03 (s, 9H), 0.96–1.00 (m, 2H), 1.43 (s, 9H), 3.11–3.18 (m, 4H), 3.75 (s, 3H), 4.14–4.19 (m, 2H), 4.66–4.70 (m, 2H), 5.02 (br d, 1H, *J*=8.0 Hz), 5.10–5.21 (m, 3H), 7.11 (d, 2H, *J*=7.8 Hz), 7.20 (d, 2H, *J*=8.2 Hz), 7.28–7.36 (m, 5H), 7.44 (d, 2H, *J*=8.0 Hz), 7.49 (d, 2H, *J*=8.2 Hz); ^{13}C NMR δ −1.28, 17.91, 28.52, 38.18, 52.54, 54.67, 54.85, 63.71, 67.38, 80.19, 127.29, 127.36, 128.70, 128.79, 128.81, 129.92, 130.02, 135.10, 135.20, 135.39, 139.56, 139.76, 155.30, 156.24, 171.93, 172.38; HRMS (FAB+) *m*/*z* calcd for $C_{37}H_{48}N_2O_8Si$: 676.3180. Found: 676.3192.

*4.12. (±)-4-[2′′-(Benzyloxycarbonyl)-2′′-[(*tert*-butyloxycarbonyl)amino]ethyl]-4′-[2′′′-(methoxycarbonyl)-2′′′-[[2′′′′-(trimethylsilyl)ethyloxycarbonyl]amino]ethyl]biphenyl* (±)-***14***

Bisolefin **11** (100 mg, 0.148 mmol) in EtOH (20 mL) was hydrogenated at 50°C and 4.5 atm in the presence of [Rh(PPh$_3$)$_3$]Cl (25 mg). The solvent was then removed and the crude mixture was passed through a short pad of silica using hexane:ethyl acetate (2:1) as an eluent to give the title compound (68 mg, 67%) as a 1:1:1:1 mixture of stereoisomers; TLC R_f=0.3. HPLC analysis on a DNBPG column (iPrOH:hexane 10:90, flow rate 1 mL/min) yielded a chromatogram with four poorly resolved peaks; R_t (min)=14.9 ((*S*,*S*); assigned by co-injection with (*S*,*S*)-**14**), 15.4 (probably (*R*,*S*) or (*S*,*R*)), 15.6 (probably (*S*,*R*) or (*R*,*S*)) and 16.4 (probably (*R*,*R*); compare with the elution order for (±)-**17**). The NMR data were identical with those of the pure (*S*,*S*)-isomer, although the product was a 1:1 mixture of diastereomers.

*4.13. (*S*)-1-[2′-(Benzyloxycarbonyl)-2′-[(*tert*-butyloxycarbonyl)amino]ethyl]-4-iodobenzene (*S*)-**15***

A mixture of (*S*)-*para*-iodophenylalanine (1.00 g, 3.43 mmol), Boc_2O (825 mg, 3.78 mmol) and $KHCO_3$ (344 mg, 3.43 mmol) in 1:1 dioxane:water (28 mL) was stirred overnight at room temperature. The solvent was then co-evaporated with toluene and the residual off-white viscous mass was dissolved

in dry DMF (10 mL) and then BnBr (646 mg, 3.78 mmol) was added. The mixture was heated at 60°C for 8 h and then cooled to 5°C. Water (100 mL) was added and the crude product was obtained after extractive work-up and evaporation of the solvent. The crude product was dissolved in hexane–EtOAc and kept in the freezer overnight. A solid separated which was collected by filtration (815 mg). Another 515 mg of product was obtained by chromatography of the filtrate using hexane:EtOAc (3:1) as eluent. Total yield 1.33 g (82%, TLC R_f=0.40); $[\alpha]_D^{22}$ −10.9 (c 0.92, EtOH 99%); mp 109–110°C. HPLC analysis ((*R*,*R*)-Whelk-O1, hexane:2-propanol (98:2), flow rate 1 mL/min) showed one single peak at R_t=11.3 min. Co-injection of both enantiomers gave two peaks at 11.3 and 11.6 min, respectively. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.43 (s, 9H), 2.96–3.06 (m, 2H), 4.58–4.63 (m, 1H), 4.99 (br d, 1H, *J*=7.4 Hz), 5.09 (d, 1H, *J*=12 Hz), 5.18 (d, 1H, *J*=12 Hz), 6.75–6.78 (m, 2H), 7.27–7.30 (m, 2H), 7.36–7.40 (m, 3H), 7.52–7.55 (m, 2H); ^{13}C NMR ($CDCl_3$, 20 MHz) δ 28.49, 38.09, 54.44, 67.45, 80.29, 92.68, 128.81, 128.87, 131.57, 135.23, 135.76, 137.75, 155.18, 171.61; HRMS (FAB+) *m*/*z* calcd for $C_{21}H_{24}INO_4$: 482.0828 [M+H]. Found: 482.0832.

*4.14. (*R*)-1-[2′-(Benzyloxycarbonyl)-2′-[(*tert*-butyloxycarbonyl)amino]ethyl]-4-iodobenzene (*R*)-**15***

This compound was prepared from (*R*)-*para*-iodophenylalanine following the procedure for the (*S*)-isomer and was obtained in 81% yield; $[\alpha]_D^{22}$ +10.7 (c 0.94, EtOH 95%). HPLC analysis ((*R*,*R*)-Whelk-O1, hexane:2-propanol (98:2), flow rate 1 mL/min) showed one single peak at R_t=11.6 min. Co-injection of both enantiomers gave two peaks at 11.3 and 11.6 min respectively. The NMR data and melting point were identical with those of the (*S*)-isomer. HRMS (FAB+) *m*/*z* calcd for $C_{21}H_{24}INO_4$: 482.0828 [M+H]. Found: 482.0842.

*4.15. (2′*S*,1′′*Z*)-1-[2′-(Benzyloxycarbonyl)-2′-[(*tert*-butyloxycarbonyl)amino]ethyl]-4-[2′′-(methoxycarbonyl)-2′′-[[2′′′-(trimethylsilyl)ethyloxycarbonyl]amino]ethenyl]benzene (*S,Z*)-**16***

The general procedure of coupling was followed using (*S*)-**15** (721 mg, 1.50 mmol) and **2** (542 mg, 2.21 mmol). After standard work-up the crude material was chromatographed (hexane:ethyl acetate=2:1) to give the product (645 mg, 72% yield) as a colourless viscous liquid which solidified in the freezer (TLC R_f=0.24); $[\alpha]_D^{22}$ −2.9 (c 2.6, $CHCl_3$); mp 43°C. HPLC analysis on the chiral DNBPG column gave only one peak (iPrOH:hexane (10:90), flow rate 1 mL/min, R_t=15.9 min). Co-injection of the (*S*)- and (*R*)-forms gave two peaks at R_t=15.9 min and 16.6 min, respectively. NOE experiments confirmed the assigned (*Z*) stereochemistry.[4] ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.03 (s, 9H), 0.90–1.04 (m, 2H), 1.42 (s, 9H), 3.03–3.14 (m, 2H), 3.86 (s, 3H), 4.17–4.21 (m, 2H), 4.62–4.66 (m, 1H), 5.02 (d, 1H, *J*=8.2 Hz), 5.10 (d, 1H, *J*=12.2 Hz), 5.18 (d, 1H, *J*=12.2 Hz), 6.19 (br s, 1H), 7.02–7.05 (m, 2H), 7.26–7.41 (m, 8H); ^{13}C NMR δ −1.31, 17.76, 28.47, 38.33, 52.85, 54.44, 64.42, 67.38, 80.23, 124.55, 128.74, 128.80, 128.82, 129.84, 130.14, 131.23, 132.57, 135.27, 137.74, 154.45, 155.21, 166.05, 171.69; HRMS (FAB+) *m*/*z* calcd for $C_{31}H_{42}N_2O_8Si$: 599.2789 [M+H]. Found: 599.2783.

*4.16. (2′*R*,1′′*Z*)-1-[2′-(Benzyloxycarbonyl)-2′-[(*tert*-butyloxycarbonyl)amino]ethyl]-4-[2′′-(methoxycarbonyl)-2′′-[[2′′′-(trimethylsilyl)ethyloxycarbonyl]amino]ethenyl]benzene (*R,Z*)-**16***

The general procedure of coupling was followed using (*R*)-**15** (625 mg, 1.30 mmol) and **2** (447 mg, 1.82 mmol). Chromatography of the crude product using hexane:ethyl acetate (2:1) as eluent gave the title compound (560 mg, 72% yield) as a viscous liquid (TLC R_f=0.24); $[\alpha]_D^{22}$ +3.0 (c 2.9, $CHCl_3$). HPLC analysis on the chiral DNBPG column gave only one peak (iPrOH:hexane (10:90), flow rate 1

mL/min, R_t=16.6 min). Co-injection of the (*S*)- and (*R*)-forms gave two peaks at R_t=15.9 min and 16.6 min, respectively. The NMR data were identical with those of the (*S*)-isomer. HRMS (FAB+) *m*/*z* calcd for $C_{31}H_{42}N_2O_8Si$: 599.2789 [M+H]. Found: 599.2780.

*4.17. (2′*S*,2′′*S*)-1-[2′-(Benzyloxycarbonyl)-2′-[(*tert*-butyloxycarbonyl)amino]ethyl]-3-[2′′-(methoxycarbonyl)-2′′-[(benzyloxycarbonyl)amino]ethyl]benzene (*S,S*)-**17***

A solution of (*S*,*S*)-**13** (80 mg, 0.13 mmol) and Bu_4NF (90 mg, 0.34 mmol) in THF (1 mL) was stirred under N_2 for 1 h at r.t. After this time, water (1 mL) was added, and the pH was adjusted to ~6 with HOAc (3 drops). After 5 min, Et_3N was added to pH~10 (*ca* 100 μL) and then benzyl chloroformate (4 drops, *ca* 50 μL) was added, after which the reaction mixture was stirred overnight. EtOAc (5 ml) was then added and the organic phase was washed with half-saturated brine (3×5 mL), dried over Na_2SO_4 and filtered through a short silica plug to yield a crude product (74 mg). An analytically pure product could be obtained by preparative HPLC on a normal-phase silica column using heptane:EtOAc (4:1) as an eluent. In this way, 22 mg (29%) of pure (*S*,*S*)-**17** was obtained, $[\alpha]_D^{25}$ +24 (c 1.1, $CHCl_3$). HPLC analysis of (±)-**17**[20] on a (*R*,*R*)-Whelk-O1 column (hexane:2-propanol=80:20+0.25% HOAc) resulted in a chromatogram with four poorly resolved peaks; R_t (min)=14.4 (*S*,*S*), 15.1 ((*R*,*S*) or (*S*,*R*)), 15.6 ((*S*,*R*) or (*R*,*S*)) and 16.4 (*R*,*R*); assignment by co-injection of known stereoisomers. Under the same conditions, analysis of (*S*,*S*)-**17** yielded a single peak (R_t=13.9 min); d.r.≥90% and e.e.≥98%. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.42 (s, 9H), 2.97–3.09 (m, 4H), 3.71 (s, 3H), 4.59–4.66 (m, 2H), 4.99 (br d, 1H, *J*=8.6 Hz), 5.07–5.19 (m, 4H), 5.23 (br d, 1H, *J*=7.9 Hz), 6.80 (s, 1H), 6.90–6.98 (m, 2H), 7.14 (t, 1H, *J*=7.5), 7.28–7.38 (m, 10H); ^{13}C NMR δ 28.48, 38.23, 38.32, 52.55, 54.58, 54.97, 67.17, 67.29, 80.17, 128.09, 128.34, 128.37, 128.68, 128.71, 128.80, 128.99, 130.63, 135.42, 136.13, 136.42, 155.27, 155.82, 171.80, 172.09; HRMS (FAB+) *m*/*z* calcd for $C_{33}H_{38}N_2O_8$: 591.2706 [M+H]. Found: 591.2711.

*4.18. (2′*R*,2′′*R*)-1-[2′-(Benzyloxycarbonyl)-2′-[(*tert*-butyloxycarbonyl)amino]ethyl]-3-[2′′-(methoxycarbonyl)-2′′-[(benzyloxycarbonyl)amino]ethyl]benzene (*R,R*)-**17***

The preparation of the title compound from (*R*,*R*)-**13** was analogous to the procedure above for the (*S*,*S*) isomer. HPLC analysis of this compound as for (*S*,*S*)-**17** gave a single peak (R_t=16.4 min); d.r.≥90% and e.e.≥98%.

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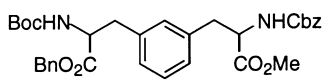

(±)-**17**