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Efficient Stereoselective Preparation of Protected Isodityrosines

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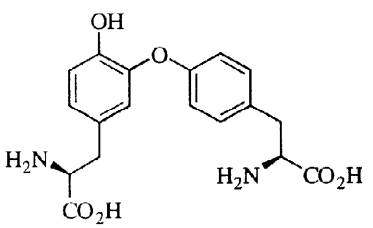
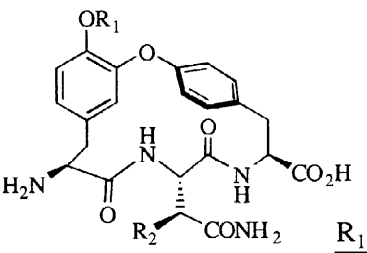
Abstract: A method for stereoselective preparation of isodityrosines with identical and orthogonal protecting groups is reported. The isodityrosines holding identical protecting groups were prepared from isovaniline in a three step procedure, in 50–64 % yield (> 98% ee, 84–96% de). Isodityrosine holding four orthogonal groups was prepared in four steps from isovaniline in 20 % total yield (> 98% ee, 87% de).

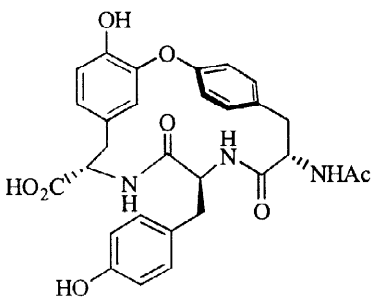
Isodityrosine, which consists of two tyrosine units linked through an unsymmetrical diphenyl ether bond, appears as a common building block in several biologically active natural compounds.[1] One example is the cyclic peptide K-13 which has been shown to be an inhibitor of angotensin I converting enzyme.[2] Other examples of importance are the antitumour active OF4949 I-IV[3] and the antibiotic (+)-piperazinomycin[4] shown in Fig. 1.



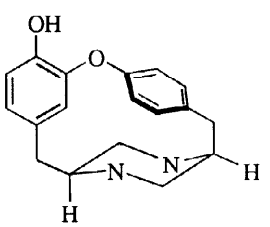
Isodityrosine



	R_1	R_2
OF4949 I	Me	OH
OF4949-II	H	OH
OF4949-III	Me	H
OF4949-IV	H	H



K-13



(+)-Piperazinomycin

Fig.1

Several total syntheses of isodityrosine have been effected,[5] and in connection with the total synthesis of the above isodityrosine-containing antibiotics, the preparation of differentially protected isodityrosine derivatives has been reported.[6] Unfortunately, all these synthesis contain many steps, and a more efficient way to prepare protected isodityrosine is therefore desirable. We hereby report a short, stereoselective synthesis of

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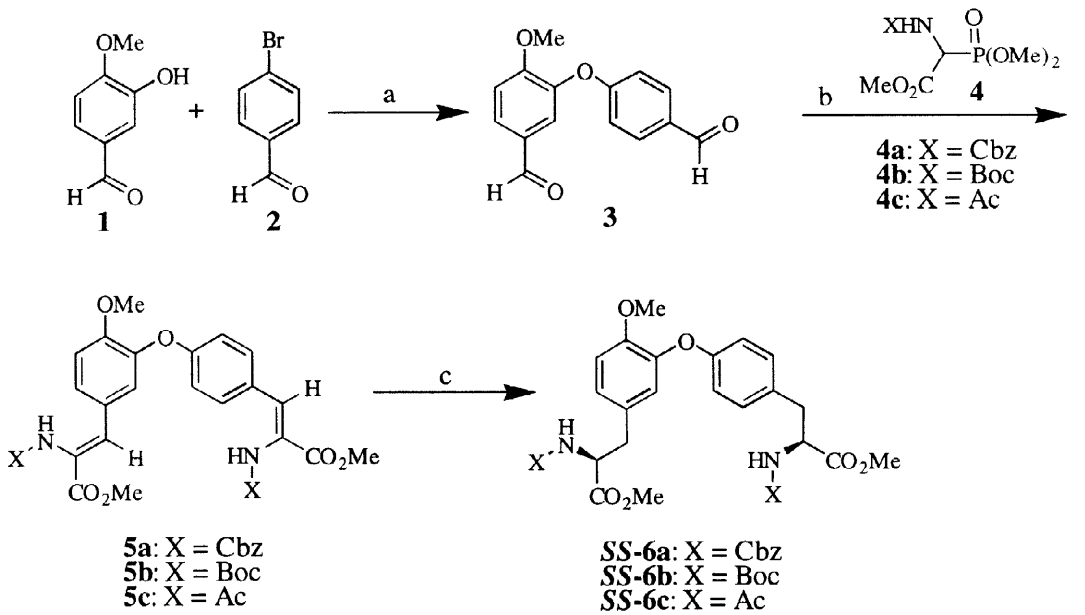
isodityrosine protected with identical, and with orthogonal protecting groups (see Schemes 1 and 2). Both strategies apply asymmetric catalytic hydrogenation of the corresponding unsaturated derivatives, which were synthesised by Horner-Wadsworth-Emmons[7] (HWE) olefination (Scheme 1), or by Heck coupling[8] followed by HWE olefination (Scheme 2). During our work the use of this methodology was reported by Frejd's group in the synthesis of various derivatives of ferrocenylene-bis-alanine,[9] pyridine-2,6-diyl-bis-alanine,[10] phenylene-bis-alanine,[11] and C_3-symmetric phenyltrisalanine.[12]

RESULTS AND DISCUSSION

Isodityrosine with identical protecting groups

Both enantiomers, (*S,S*) and (*R,R*), of the isodityrosines **6a–c** were prepared in a three step synthesis starting from isovaniline **1** (Scheme 1). The Ullmann coupling reaction of **1** with *p*-bromobenzaldehyde **2**, according to Evans and Ellman's general conditions,[6g] afforded the bisaldehyde **3** in 80 % yield. A parallel HWE olefination of both aldehyde groups in **3** with phosphonates **4a-c**[13] and DBU gave the bis(didehydroamino acid) derivatives **5a-c**, respectively.



Scheme 1. (a) CuO, K_2CO_3, pyr., reflux, 18 h, 80 %; (b) DBU, CH_2Cl_2, rt, 3 h, 73-82 %; (c) {Rh(COD)[(S,S)-Et-DuPHOS]}$^+OTf^-$, 5 atm H_2, rt, MeOH, 1-3 d, 85-97 %.

The *Z*-configurations of **5a-c** were assigned by NOE difference experiments. Didehydroamino acid derivatives with an *E*-configuration have been reported to show NOE effects between the olefinic CH protons and NH protons.[14] No such effects were observed for **5a-c**. Other literature examples of HWE olefination with DBU as base[15] support this assignment. Asymmetric hydrogenation of **5a-c** using Burk's catalytic Rh(I)-(*S,S*)-Et-DuPHOS system[16] afforded **6a-c** in 86, 91 and 97 % yields, respectively (Table 1). The absolute configurations were assigned as *SS* based on the selectivity of the (*S,S*)-Et-DuPHOS ligand.[16] Similarly, the *RR* enantiomers of **6a-c** were prepared from **5a-c** by using (*R,R*)-Et-DuPHOS as chiral ligand in the hydrogenation step.

The stereochemical analyses of **6a-c** were not trivial. For identification purposes all four stereoisomers of **6a-c** were prepared under achiral conditions. Compounds **6a** and **6c** were obtained by hydrogenation of **5a** and **5c** using Wilkinson's catalyst, $Rh(PPh)_3Cl$, while **6b** was obtained from **5b** using 10 % Pd-C as catalyst.

Four different HPLC columns were tested: Chiracel OH, Chiracel OJ, Chiracel AS and Chiralpak AD. The best results were obtained with Chiralpak AD. The *RR* and *SS* enantiomers separated well, as did the *RS* and *SR* enantiomers. Thus, the enantiomeric excess of *RR* and *SS* could be determined directly. However, in all three cases either the *RS* or the *SR* enantiomer overlapped partially with one of the other two isomers. The diastereomeric excess was therefore determined under the assumption that equal amounts of *RS* and *SR* were formed. The results given in Table 1 show that the enantioselectivity obtained was excellent in all cases. No traces of the antipode of the major isomer was observed. The best diastereoselectivity was achieved in preparation of ***SS*-6c** and ***RR*-6c** (X = Ac, de 96 %).

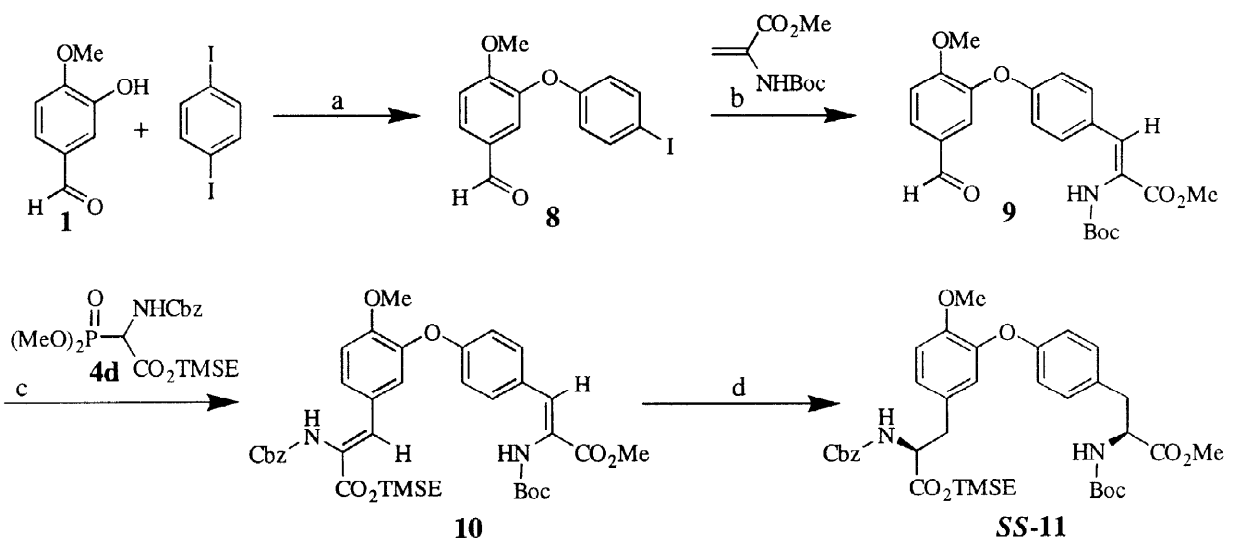
*Table 1. Asymmetric catalytic hydrogenation of bis(didehydroamino acid) derivatives **5a-c**.*

Substrate	Ligand	Product	% Yield	% Stereoselectivity[a]
5a; X = Cbz	(*S,S*)-Et-DuPHOS	***SS*-6a**	86	ee > 98; de 84
5a; X = Cbz	(*R,R*)-Et-DuPHOS	***RR*-6a**	91	ee > 98; de 89
5b; X = Boc	(*S,S*)-Et-DuPHOS	***SS*-6b**	91	ee > 98; de 88
5b; X = Boc	(*R,R*)-Et-DuPHOS	***RR*-6b**	96	ee > 98; de 84
5c; X = Ac	(*S,S*)-Et-DuPHOS	***SS*-6c**	97	ee > 98; de 96
5c; X = Ac	(*R,R*)-Et-DuPHOS	***RR*-6c**	100	ee > 98; de 96

[a]*By HPLC analysis using Chiralpak AD column.*

Isodityrosine with orthogonal protecting groups

A practical procedure for preparation of orthogonally protected isodityrosine was desirable, since such compounds may serve as key intermediates in the synthesis of cyclic peptides like K-13 and OF 4949 I – IV. By extending the parallel strategy shown in Scheme 1 with introduction of the didehydroamino acid derivatives in two consecutive steps the incorporation of four orthogonal protecting groups may be achieved. This strategy was applied to the preparation of ***SS*-11** as shown in Scheme 2.



Scheme 2. (a) CuO, K_2CO_3, pyr., reflux, 24 h, 27 %; (b) $Pd(OAc)_2$, $NaHCO_3$, Bu_4NCl, DMF, 85 °C,20 h, 97 %; (c) DBU, CH_2Cl_2, rt, 2 h, 85 %; (d) {Rh(COD)[(S,S)-Et-DuPHOS]}$^+OTf^-$, 5 atm H_2, MeOH, rt, 3 d, 91 %.

The Ullmann coupling in step *a* afforded only 27 % yield of **8**. Attempts to improve this yield by changing from *p*-diiodobenzene to *p*-dibromobenzene gave 67 % of the bromo diphenyl ether. Unfortunately, application of this compound in the following step reduced the yield of **9** from 97 %, obtained from **8** under Heck–Jeffery conditions,[17] to only 21 % obtained under the original Heck conditions.[18] Ullmann coupling using *p*-bromoiodobenzene gave a mixture of bromo and iodo biphenyl ethers in a ratio of 58 : 42. The total yield was 43 %. Application of other conditions for the Ullmann[5a,19] and Heck[17,18] coupling reactions did not improve the yields either. The HWE olifination of **9** with **4d** proceeded in 85 % yield. Both of the double bonds in **10** were assumed to have *Z*-configuration by the same arguments as given for **5a-c**. Hydrogenation of **10** in the presence of the Rh(I)-(*S,S*)-Et-DuPHOS catalyst gave ***SS*-11** in 91 % yield. The isomeric composition was determined by HPLC to > 98 % ee and 87 % de. Likewise, hydrogenation with Rh(I)-(*R,R*)-Et-DuPHOS as catalyst afforded ***RR*-11** in 89 % yield (> 98 % ee, 87 % de).

We have hereby shown that the described strategies may be used for the stereoselective preparation of variously protected isodityrosines. The application of these compounds in enantioselective total synthesis will be described elsewhere.

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EXPERIMENTAL

General remarks. Melting points were determined on a Buchi 535 apparatus and are uncorrected. TLC was performed on Merck 5554, Fertigplatten, DC-Alufolien, Kieselgel 60_{254}, using UV light at 254 nm and 5 % alcoholic molybdophosphoric acid for detection. Silica gel for flash chromatography was purchased from Grace-Amicon. Optical rotations were measured with a Perkin Elmer 241 Polarimeter. Enantiomeric and diastereomeric excesses were determined by HPLC analysis, using a Chiralpak AD column (Daicel Chemical Industries, Ltd., 250 x 4.6 mm). ^{1}H (400 MHz) and ^{13}C (100 MHz) NMR spectra were obtained on a JEOL JNM-EX 400 FT spectrometer ($CDCl_3$ as solvent and internal standard). Abbreviations: s, singlet; d, doublet; t, triplet; b, broad; J, coupling constant in Hz. IR spectra were run on a Shimadzu IR-470 spectrophotometer, and only the strongest/structurally most important peaks are listed. The mass spectra were recorded on a AEI MS-902 double focusing mass spectrometer (Nier-Johnson geometry) and a VG QUATTRO connected to a Hewlett Packard 5890 II gas chromatograph, equipped with an unpolar CP-Sil 5CB-MS caillary column (30 m). The ionization potential was 70 eV and the temperature in the ion source was 180 °C. The elemental analyses were performed at the Department of Organic Chemical Technology, Prague, Czech Republic. Compounds **4a-c**[13] and methyl 2-(*tert*-butoxycarbonylamino)acrylate[8d] were synthesised according to literature procedures. Bis(1,5-dicyclooctadiene)rhodium (I) trifluoromethanesulfonate, (*S,S*)-Et-DUPHOS, and (*R,R*)-Et-DUPHOS were purchased from Strem. Tris(triphenylphosphine)rhodium(I) chloride was purchased from Fluka. Tetrahydrofuran (THF) was distilled under nitrogen from Na/benzophenone. Pyridine and methylene chloride were distilled under nitrogen from calcium hydride.

3-(4-Formylphenoxy)-4-methoxybenzaldehyde (**3**). A mixture of isovaniline (**1**) (9.36 g, 61.5mmol), *p*-bromobenzaldehyde (**2**) (13.64g, 73.72 mmol) and potassium carbonate (17.7 g, 128 mmol) in dry pyridine (130 ml) were stirred under N_2 atm and heated to 80 °C. Copper (II) oxide (12.3 g, 155 mmol) was added and the reaction mixture refluxed for 18 hours. After cooling to room temperature the mixture was added CH_2Cl_2 (100 ml) and filtered through Celite. The filter cake was subsequently washed with fresh CH_2Cl_2 (200 ml). The combined organics were concentrated *in vacuo*. The residue was then dissolved in CH_2Cl_2 (400 ml) and washed with aqueous $NaHSO_4$ (1.0 M, 2 x 100 ml) and a mixture of brine (50 ml) and aqueous $NaHCO_3$ (sat, 50 ml).

Drying ($MgSO_4$) and evaporation of the solvents gave a crude product which was purified by flash chromatography (ethyl acetate/pentane, 3:7 to 1:1) to yield 12.59 g (80 %) of **3** as a brownish solid.
Data for **3**. ^{1}H NMR: 3.89 (3H; s); 6.99 and 7.83 (each 2H; AA'BB', J_{AB} = 8.4); 7.15 (1H; d, J = 8.4); 7.62 (1H; d, J = 2.2); 7.77 (1H; dd, J = 8.4, 2.2); 9.87 (1H; s); 9.91 (1H; s). ^{13}C NMR: 56.4, 112.6, 116.7, 122.3, 129.6, 130.5, 131.5, 132.0, 143.9, 156.8, 162.7, 190.1, 190.8. IR (KBr): 1699 (s), 1680 (s). GC-MS *m/z* (% rel. int.): 256 (M^+, 100), 255 (60), 183 (6), 128 (13), 127 (16), 119 (12), 105 (7), 91 (10), 77 (22). Anal. Calc. for $C_{15}H_{12}O_4$: C, 70.31%; H, 4.72. Found: C, 70.02; H, 5.01.

Preparation of the bis(didehydroamino acid) derivatives ***5a-c***: **(Z,Z)-4-{5-[2-[(Benzyloxycarbonyl)amino]-2-(methoxycarbonyl)ethenyl]-2-methoxyphenoxy}-1-{2-[(benzyloxycarbonyl)amino]-2-(methoxycarbonyl)-ethenyl}-benzene** (**5a**). A solution of bisaldehyde **3** (422.8 mg, 1.65 mmol) and **4a** (1.24 g, 3.75 mmol)[13] in dry CH_2Cl_2 (10 ml) under nitrogen atm was added DBU (0.515 ml, 3.45 mmol) and stirred at room temperature for 1.5 h. The reaction mixture was poured into ethyl acetate (100 ml) and washed with aqueous HCl (1.0 M, 50 ml), water (50 ml), aqueous $NaHCO_3$ (sat, 50 ml) and brine (50 ml), dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was purified by flash chromatography (ethyl acetate/pentane, 4:5) to yield 800.7 mg (73 %) of **5a** as a white solidified foam.
Data for **5a**. ^{1}H NMR: 3.78 (6H; bs); 3.83 (3H; s); 5.04 (2H; s); 5.12 (2H; s); 6.84 and 7.44 (each 2H; AA'BB', J_{AB} = 8.8); 6.95 (1H; d, J = 8.8); 7.25 (2H; s); 7.30 (10H; s); 7.34 (1H; d, J = 2.2); 7.36 (1H; d, J = 2.2). ^{1}H NMR (DMSO-d_6): 3.71 (6H; bs); 3.77 (3H; s); 5.01-5.11 (4H; m), 6.82 (2H; d, J = 6.2); 7.23-7.40 (13H; m); 7.56 (1H; s); 7.59-7.67 (3H; m); 9.10 (1H; s); 9.12 (1H; s). ^{13}C NMR (DMSO-d_6, 50 °C): 52.6, 56.6, 66.5, 114.0, 116.2, 124.1, 124.8, 124.9, 127.2, 127.9, 128.0, 128.1, 128.3, 128.4, 128.5, 128.8, 129.0, 129.7, 132.5, 137.4, 143.0, 153.2, 155.1, 155.2, 159.3, 166.2, 166.3. IR (KBr): 3300 (b), 1715 (bs).
MS *m/z* (% rel. int.): 666 (M^+, < 1), 558 (5), 450 (15), 363 (10), 261 (5), 205 (15), 173 (5), 130 (7), 115 (10), 108 (30), 91 (100). Anal. Calc. for $C_{37}H_{34}N_2O_{10}$: C, 66.66%; H, 5.14; N, 4.20. Found: C, 66.63; H, 5.18; N, 4.11.

(Z,Z)-4-{5-[2-[(*tert*-Butyloxycarbonyl)amino]-2-(methoxycarbonyl)ethenyl]-2-methoxyphenoxy}-1-{2-[(*tert*-butyloxycarbonyl)amino]-2-(methoxycarbonyl)ethenyl}-benzene (**5b**). Treatment of **4b** (1.19 g, 4.02 mmol)[13] with **3** (385.6 mg, 1.52 mmol) according to the procedure given for preparation of **5a** afforded, after stirring at room temperature over night, an oil, which was purified by flash chromatography (ethyl acetate/pentane, 2:3). This gave 738.6 mg (82 %) of **5b** as a pale yellow solidified foam.
Data for **5b**. ^{1}H NMR (DMSO-d_6, 60 °C): 1.32 (9H; s); 1.37 (9H; s); 3.72 (3H; s); 3.73 (3H; s); 3.78 (3H; s), 6.86 and 7.62 (each 2H; AA'BB', J_{AB} = 8.8); 7.15 (1H; bs); 7.17 (1H; bs); 7.22 (1H; d, J = 8.4); 7.49 (1H; bs); 7.52 (1H; bd, J = 8.4); 8.34 (2H; bs). ^{13}C NMR (DMSO-d_6, 50 °C): 28.5, 28.6, 52.5 (two peaks), 56.5, 79.6 (two peaks), 114.0, 116.3, 123.8, 125.5, 127.7, 128.3, 129.4, 132.3, 143.2, 153.0,154.3 (two peaks), 159.1, 166.5, 166.6. IR (KBr): 3340, 1715 (bs). MS *m/z* (% rel. int.): 598 (M^+, 1), 524 (1), 498 (5), 450 (5), 424 (40), 398 (100), 278 (7), 251 (17), 236 (20), 192 (15), 132 (25), 117 (13), 89 (17). Anal. Calc. for $C_{31}H_{38}N_2O_{10}$: C, 62.20 %; H, 6.40; N, 4.68. Found: C, 61.96; H, 6.68; N, 4.40.

(Z,Z)-4-{5-[2-[(Acetyl)amino]-2-(methoxycarbonyl)ethenyl]-2-methoxyphenoxy}-1-{2-[(acetyl)amino]-2-(methoxycarbonyl)ethenyl}benzene (**5c**). Treatment of **4c** (1.47 g, 6.15 mmol)[13] with **3** (662.0 mg, 2.59 mmol) according to the procedure given for preparation of **5a** afforded, after stirring at room temperature over night, a crude crystalline material. Recrystallization from ethyl acetate afforded 1.02 g (82 %) of **5c** as a white crystalline material.
Data for **5c**. Mp 230 – 232 °C (decomposed). ^{1}H NMR (DMSO-d_6): 1.88 (3H; s); 1.98 (3H; s); 3.68 (3H; s); 3.69 (3H; s); 3.78 (3H; s); 6.90 and 7.63 (each 2H; AA'BB', J_{AB} = 8.8); 7.19 (1H; s); 7.20 (1H; s); 7.25 (1H; d,

J = 8.4); 7.43 (1H; d, J = 2.2); 7.55 (1H; dd, J = 8.4, 2.2); 9.52 (1H; s), 9.56 (1H; s). ^{13}C NMR (DMSO-d_6): 22.9, 23.0, 52.6, 52.7, 56.5, 113.9, 116.6, 123.4, 125.5, 125.6, 127.2, 128.2, 129.2, 131.6, 131.7, 132.4, 143.1, 152.8, 158.9, 166.1, 166.2, 169.7, 169.9. IR (KBr): 3250 (s), 1750 (s), 1665 (s). MS *m/z* (% rel. int.): 482 (M^+, 30), 450 (70), 440 (50), 418 (50), 408 (90), 398 (30), 348 (100), 278 (85), 251 (90), 236 (85), 173 (40), 132 (55). Anal Calc. for $C_{25}H_{26}N_2O_8$: C, 62.23%; H, 5.43; N, 5.81. Found: C, 62.06; H, 5.38; N, 5.82.

Catalytic hydrogenation of bis(didehydroamino acid) derivatives ***5a–c*** and ***10*** *under achiral conditions. References for HPLC analysis.* (i) Hydrogenation of bis(didehydroamino acid) derivatives **5a**, **5c** and **10**: A solution of the bis(didehydroamino acid) derivative (0.2 mmol) in degassed methanol (15 ml) was hydrogenated at 5 atm and 25 °C for 3 days using using $Rh(PPh_3)_3Cl$ (0.05 mmol) as catalyst. The reaction mixture was concentrated *in vacuo* and the residue purified by flash chromatography affording mixtures of four stereoisomers of **6a**, **6c** and **11** in 67, 84 and 58 % yields, respectively. The stereochemical compositions were in all three cases ca 1 : 1 : 1 : 1. (ii) The bis(didehydroamino acid) derivative **5b** (X = Boc; 143.6 mg, 0.2 mmol), dissolved in methanol (15 ml), was hydrogenated with 10 % Pd-C (50 mg) at 25 °C and atmospheric pressure over night. The mixture was filtered through Celite and the filter cake washed with methanol.
The combined organics were concentrated *in vacuo* to furnish a mixture of all four stereoisomers (ca 1:1:1:1) of **6b** in quantitative yield.

General procedure for asymmetric hydrogenation of the bis(didehydroamino acid) derivatives ***5a–c*** *and* ***10***.
A reaction vessel for a Parr hydrogenation apparatus was charged with the bis(didehydroamino acid) derivative (0.2 – 0.4 mmol) and bis[1,5-cyclooctadiene]Rhodium trifluoromethane sulfonate (5-15 mg). The vessel was evacuated and filled with argon 3 times before degassed methanol (10-15 ml) (degassed under vacuum at - 78 °C) and a solution of Et-DuPHOS (2-3 mg/ml, 1.1 mol eq. relative Rh) in degassed methanol were added. The vessel was connected to the Parr apparatus and shaken under hydrogen (5 atm) for 3 days. Compound **5c** (X = Ac) needed only 24 h. The reaction mixture was concentrated *in vacuo* and the residue purified by flash chromatography.

(*S*)-*N*-[(Phenylmethoxy)carbonyl]-*O*-[5-[2-[[(phenylmethoxy)carbonyl]amino]-2-(methoxycarbonyl)-ethyl]-2-methoxyphenyl]-L-tyrosine Methyl Ester (*SS*-6a). Asymmetric hydrogenation of **5a** (266.4 mg, 0.400 mmol) in the presence of Rh(I)-(*S*,*S*)-Et-DuPHOS according to the general procedure described above afforded after flash chromatography (ethyl acetate/pentane, 4:5) 231.2 mg (86 % yield) of ***SS*-6a** as a white solidified foam.
Data for ***SS*-6a**. $[\alpha]_D^{22}$ +48.8 (c = 1.06, CH_2Cl_2). HPLC analysis (EtOH; 0.7 ml/min): ee >98 %; de 84 %. ^{1}H NMR: 2.94-3.09 (4H; m); 3.62 (3H; s); 3.70 (3H; s); 3.79 (3H; s); 4.56-4.63 (2H; m); 5.06-5.10 (4H; m); 5.19 (1H; bs); 5.21 (1H; bs); 6.67 (1H; d, J = 1.4); 6.79 and 6.97 (each 2H; AA'BB', J_{AB} = 8.4); 6.85 (1H; dd, J = 8.4, 1.4); 6.88 (1H; d, J = 8.4); 7.28 -7.36 (10H; m). The NH-peaks at 5.19 and 5.21 were reduced to 50 % intensity upon addition of D_2O after two days. ^{13}C NMR: 37.5, 52.37, 52.41, 56.1, 67.1, 112.9, 117.2, 122.0, 125.7, 128.1, 128.2, 128.3, 128.6, 129.7, 130.5, 136.3, 144.8, 150.6, 155.6, 156.7, 157.1, 171.8, 172.0. IR (KBr): 3350 (b), 1715 (bs). MS *m/z* (% rel. int.): 562 (M^+- BnO, < 1), 411 (5), 368 (4), 340 (35), 297 (10), 211 (10), 107 (45), 91 (100), 79 (30). Anal Calc. for $C_{37}H_{38}N_2O_{10}$: C, 66.26%; H, 5.71; N, 4.18. Found: C, 66.34; H, 5.74; N, 4.21.

(*R*)-*N*-[(Phenylmethoxy)carbonyl]-*O*-[5-[2-[[(phenylmethoxy)carbonyl]amino]-2-(methoxycarbonyl)-ethyl]-2-methoxyphenyl]-D-tyrosine Methyl Ester (*RR*-6a). Asymmetric hydrogenation of **5a** (151.7 mg, 0.228 mmol) in the presence of Rh(I)-(*R*,*R*)-Et-DuPHOS according to the general procedure described above afforded 138.9 mg (91 % yield) of ***RR*-6a** as a white solidified foam.

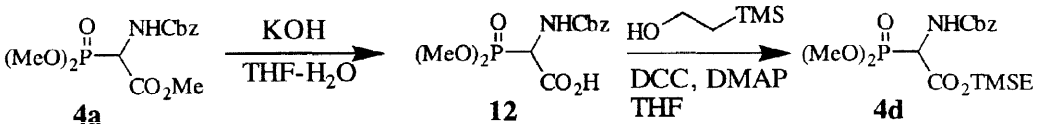
Data for ***RR*-6a**. $[\alpha]_D^{21}$ -50.0 (c = 1.07, CH_2Cl_2). HPLC analysis (EtOH; 0.7 ml/min): ee >98 %; de 89 %.

(*S*)-*N*-[*tert*-Butyloxycarbonyl]-*O*-[5-[2-[(*tert*-butyloxycarbonyl)amino]-2-(methoxycarbonyl)ethyl]-2-methoxyphenyl]-L-tyrosine Methyl Ester (*SS*-6b). Asymmetric hydrogenation of **5b** (221.5 mg, 0.400 mmol) in the presence of Rh(I)-(*S*,*S*)-Et-DuPHOS according to the general procedure described above afforded after flash chromatography (ethyl acetate/pentane, 2:3) 221.5 mg (91 % yield) of ***SS*-6b** as a white solidified foam.
Data for ***SS*-6b**. $[\alpha]_D^{23}$ +53.2 (c = 1.20, CH_2Cl_2). HPLC analysis (2-propanol/*n*-hexane, 1:1; 0.5 ml/min): ee >98 %; de 88 %. ^{1}H NMR: 1.40 (9H; s); 1.41 (9H; s); 2.91-3.07 (4H; m); 3.63 (3H; s); 3.70 (3H; s); 3.80 (3H; s); 4.49-4.56 (2H; m); 4.95 (2H; bs), 6.70 (1H; d, J = 1.8); 6.83 and 7.03 (each 2H; AA'BB', J_{AB} = 8.4); 6.87 (1H; dd, J = 8.1, 1.8); 6.91 (1H; d, J = 8.2). ^{13}C NMR: 28.4, 32.5, 37.6, 52.2, 52.3, 54.48, 54.55, 56.1, 79.99, 80.01, 112.9, 117.2, 122.1, 125.7, 128.9, 130.0, 130.5, 144.8, 150.6, 155.06, 155.16,157.1, 172.2, 172.4. IR (KBr): 3350 (b), 1750 (s), 1710 (s). MS *m/z* (% rel. int.): 546 (M^+- C_3H_8, < 1), 485 (10), 368 (12), 358 (70), 340 (20), 314 (20), 297 (50), 254 (15), 227 (18), 211 (27), 90 (26), 57 (100). Anal. Calc. for $C_{31}H_{42}N_2O_{10}$: C, 61.78%; H, 7.02; N, 4.65. Found: C, 61.51; H, 6.84; N, 4.40.

(*R*)-*N*-[*tert*-Butyloxycarbonyl]-*O*-[5-[2-[(*tert*-butyloxycarbonyl)amino]-2-(methoxycarbonyl)ethyl]-2-methoxyphenyl]-D-tyrosine Methyl Ester (*RR*-6b). Asymmetric hydrogenation of **5b** (150.1 mg, 0.251 mmol) in the presence of Rh(I)-(*R*,*R*)-Et-DuPHOS according to the general procedure described above afforded 144.5 mg (96 % yield) of ***RR*-6b** as a white solidified foam.
Data for ***RR*-6b**. $[\alpha]_D^{21}$ -51.4 (c = 1.02, CH_2Cl_2). HPLC analysis (2-propanol/*n*-hexane, 1:1; 0.5 ml/min): ee >98 %; de 84 %.

(*S*)-*N*-Acetyl-*O*-[5-[2-[(acetyl)amino]-2-(methoxycarbonyl)ethyl]-2-methoxyphenyl]-L-tyrosine Methyl Ester (*SS*-6c). Asymmetric hydrogenation of **5c** (192.8 mg, 0.400 mmol) in the presence of Rh(I)-(*S*,*S*)-Et-DuPHOS according to the general procedure described above afforded after flash chromatography (acetone) 190.0 mg (97 % yield) of ***SS*-6c** as a white solid.
Data for ***SS*-6c**. Mp 155.5 – 156.5 °C. $[\alpha]_D^{20}$ +97.9 (c = 1.01, CH_2Cl_2). HPLC analysis (EtOH/*n*-hexane, 55:45; 0.4 ml/min): ee >98 %; de 96 %. ^{1}H NMR: 1.96 (3H; s); 2.00 (3H; s); 2.94-3.13 (4H; m); 3.64 (3H; s); 3.71 (3H; s); 3.81 (3H; s), 4.76-4.86 (2H; m); 6.02 (1H; bd, J = 7.3); 6.11 (1H; bd, J = 6.2); 6.64 (1H; d, J =2.2); 6.82 and 7.01 (each 2H; AA'BB', J_{AB} = 8.4); 6.84 (1H; dd, J = 8.4, 2.2); 6.90 (1H; d, J = 8.4). The NH-signals at 6.02 and 6.11 disappeared upon addition of D_2O, and the multiplets at 4.76-4.86 ppm collapsed into two triplets: 4.78 (1H; t, J = 5.7); 4.83 (1H; t, J = 5.7). ^{13}C NMR: 23.14, 23.16, 37.0, 37.1, 52.4, 52.5, 53.3, 53.4, 56.1, 112.9, 117.5, 121.7, 125.5, 128.7, 130.1, 130.5, 145.0, 150.5, 157.0, 169.7, 169.9, 171.9 172.0. IR (KBr): 3300 (s), 1750 (s), 1655 (s). MS *m/z* (% rel. int.): 486 (M^+, 25), 455 (5), 427 (25), 368 (100), 356 (50), 297 (50), 211 (20), 90 (20), 88 (45). Anal. Calc. for $C_{25}H_{30}N_2O_8$: C, 61.72%; H, 6.22; N, 5.76. Found: C, 61.99; H, 5.95; N, 5.71.

(*R*)-*N*-Acetyl-*O*-[5-[2-[(acetyl)amino]-2-(methoxycarbonyl)ethyl]-2-methoxyphenyl]-D-tyrosine Methyl Ester (*RR*-6c). Asymmetric hydrogenation of **5c** (150 mg, 0.311 mmol) in the presence of Rh(I)-(*R*,*R*)-Et-DuPHOS according to the general procedure described above afforded 155.5 mg (100 % yield) of ***RR*-6c** as a white solid.
Data for ***RR*-6c**. $[\alpha]_D^{23}$ -91.7 (c = 1.00, CH_2Cl_2). HPLC analysis (EtOH/*n*-hexane, 55:45; 0.4 ml/min): ee >98 %; de 96 %.



4a 12 4d

Scheme 3. Synthesis of ***4d.***

2-Benzyloxycarbonylamino-2-(dimethoxyphosphinyl)acetic acid (12). Compound **4a**[13] (5.12 g, 15.45mmol) was dissolved in THF (30 ml) and aqueous KOH (2.0 M, 15 ml) added. After stirring for 30 min at room temperature the reaction mixture was poured into ethyl acetate (100 ml) and washed with a mixture of aqueous HCl (37 %, 9 ml) and brine (100 ml). The aqueous layer was extracted with ethyl acetate (2 x 50 ml). The combined organics were dried ($MgSO_4$) and the solvents evaporated to yield 4.65 g (95%) of the free acid **12** as a viscous oil.

Data for **12**. ^{1}H NMR: 3.75 (3H; d, J = 11.0); 3.84 (3H; J = 11.0); 5.00 (1H; dd, J = 22.7, 9.16); 5.07-5.17 (2H; m); 6.01 (1H; d, J = 6.1); 7.30-7.34 (5H; m); 10.51 (1H; bs). ^{13}C NMR: 52.1 (d, J = 150), 54.6 (d, J = 6.1), 54.9 (d, J = 6.1), 67.7, 128.2, 128.4, 128.6, 135.9, 155.8 (d, J = 6.1), 167.6.

2-(Trimethylsilyl)ethyl 2-(benzyloxycarbonyl)amino-2-(dimethoxyphosphinyl)acetate (4d). The carboxylic acid **12** (244.1 mg, 0.769 mmol) was dissolved in dry THF (3 ml) under nitrogen and 2-trimethylsilylethanol (0.154 ml, 1.07 mmol) added. A solution of DCC (258.0 mg, 1.25 mmol) and DMAP (12 mg, 0.10 mmol) in THF (3 ml) was added and the reaction mixture was stirred for 3 days at room temperature. A solid material was filtered off and washed with ether. The filtrate was concentrated and purified by flash chromatography (ethyl acetate/pentane, 3:2) to yield 255.1 mg (79 %) of **4d** as a viscous oil. The oil was precipitated as a white powder by stirring in pentane over night.

Data for **4d**. Mp 52.0 – 52.5 °C. ^{1}H NMR: 0.03 (9H; s); 1.02-1.07 (2H; m); 3.78 (3H; d, J = 11.0); 3.81 (3H; d, J = 11.0); 4.27-4.33 (2H; m); 4.88 (1H; dd, J = 9.2, 22.0); 5.08-5.17 (2H; m); 5.58 (1H; d, J = 9.2), 7.33-7.36 (5H; m). ^{13}C NMR: -1.51, 17.4, 52.3 (d, J = 148), 54.0 (d, J = 6), 54.1 (d, J = 6), 65.3, 67.7, 128.2, 128.4, 128.6, 135.9, 166.8. IR (neat): 3250 (b), 1720 (s). Anal. Calc. for $C_{17}H_{28}N_1O_7Si_1P_1$: C, 48.92%; H, 6.76; N, 3.36. Found: C, 49.20; H, 6.60; N, 3.62.

3-(4-Iodophenoxy)-4-methoxybenzaldehyde (8). A mixture of isovaniline (**1**) (500 mg, 3.31 mmol), 1,4-diiodobenzene (**7**) (3.27 g, 9.92 mmol) and potassium carbonate (950 mg, 6.87 mmol) in dry pyridine (20 ml) was stirred under N_2 atm and heated to 80 °C. Copper(II) oxide (650 mg, 8.17 mmol) was added and the reaction mixture refluxed for 24 h. After cooling to room temperature the mixture was added CH_2Cl_2 (25 ml) and filtered through Celite. The filter cake was subsequently washed with CH_2Cl_2 (50 ml). The combined organics were concentrated *in vacuo*. The residue was then dissolved in CH_2Cl_2 (200 ml) and washed with aqueous $NaHSO_4$ (1.0 M, 2 x 60 ml), brine (50 ml), aqueous $NaHCO_3$ (sat, 50 ml) and brine (50 ml). Drying ($MgSO_4$) and evaporation of the solvents gave a crude product which was purified by flash chromatography (ethyl acetate/pentane, 1:4) to yield 310 mg (27 %) of **8** as a white solid.

Data for **8**. Mp 101 – 103 °C. ^{1}H NMR: 3.92 (3H; s); 6.72 and 7.60 (each 2H; AA'BB', J_{AB} = 8.7); 7.10 (1H; d, J = 8.4); 7.46 (1H; d, J = 2.0); 7.68 (1H; dd, J = 8.4, 2.0); 9.82 (1H; s). ^{13}C NMR: 56.3, 112.3, 119.9, 120.3, 128.7, 130.3, 138.7, 139.4, 145.5, 156.4, 157.1, 190.2. IR (KBr): 1675 (s). GC-MS *m/z* (% rel. int.): 355 (10), 354 (M^+, 100), 353 (10), 219 (15), 211 (20), 183 (15), 127 (30), 79 (30), 76 (70). Anal. Calc. for $C_{14}H_{11}I_1O_3$: C, 47.48%; H, 3.13. Found: C, 47.30; H, 3.34.

(*Z*)-4-(5-Formyl-2-methoxyphenoxy)-1-{2-[(*tert*-butyloxycarbonyl)amino]-2-(methoxycarbonyl)ethenyl}-benzene (9). A Schlenk-tube was charged with iodoaldehyde **8** (641.0 mg,1.81 mmol), palladium(II) diacetate

(20.7 mg, 0.09 mmol), tetrabutylammonium chloride (528.0 mg, 1.86 mmol) and $NaHCO_3$ (399.0 mg, 4.75 mmol) before being evacuated and filled with nitrogen. A solution of methyl 2-(*tert*-butoxycarbonylamino)-acrylate[8d] (520.0 mg, 2.58 mmol) in DMF (25 ml) was added before the tube was closed and heated at 85 °C for 20 hours. The reaction mixture was then dissolved in CH_2Cl_2 (100 ml) and washed with water (30 ml). The aqueous layer was extracted with CH_2Cl_2 (30 ml), and the combined organics dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by flash chromatography (ethyl acetate/pentane, 1:1) to afford 754.3 mg (97%) of **9** as a white solidified foam.

Data for **9**. ^{1}H NMR: 1.40 (9H; bs); 3.83 (3H; s); 3.91 (3H; s); 6.91 and 7.52 (each 2H; AA'BB', J_{AB} = 8.6); 7.11 (1H; d, J = 8.4); 7.25 (1H; s); 7.53 (1H; d, J = 2.0); 7.71 (1H; dd, J = 8.4, 2.0); 9.83 (1H; s).
^{13}C NMR: 14.3, 28.2, 52.6, 56.3, 60.5,80.1, 112.4, 177.2, 121.1, 128.7, 129.1, 130.2, 130.4, 131.7, 145.1, 156.7, 158.0, 166.2, 190.2. IR (KBr): 3340 (b), 1690 (s). MS *m/z* (% rel. int.): 428 (21), 427 (M^+, 80), 413 (6), 354 (16), 353 (21), 340 (10), 329 (19), 328 (100), 327 (100).). Anal. Calc. for $C_{23}H_{25}N_1O_7$: C, 64.63%; H, 5.90; N, 3.28. Found: C, 64.81; H, 6.07; N, 3.15.

(*Z,Z*)-4-{5-[2-[(Benzyloxycarbonyl)amino]-2-(methoxycarbonyl)ethenyl]-2-methoxy-phenoxy}-1-{2-[(*tert*-butyloxycarbonyl)amino]-2-[[(trimethylsilyl)ethoxy]carbonyl]-ethenyl}benzene (10). The aldehyde **9** (305.6 mg, 0.716 mmol) and **4d** (393.0 mg, 0.942 mmol) were dissolved in dry CH_2Cl_2 (5 ml) under nitrogen and added DBU (0.126 ml, 0.843 mmol). The reaction mixture was stirred for two hours at room temperature, and then concentrated *in vacuo*. The residue was purified by flash chromatography (ethyl acetate/pentane, 3:7) to yield 434.9 mg (85 %) of **10** as a pale yellow solidified foam.

Data for **10**. ^{1}H NMR ($CDCl_3$, 40 °C): 0.04 (9H; s); 1.01 (1H; d, J = 8.4); 1.04 (1H; d, J = 8.6); 1.40 (9H; s); 3.81 (3H; s); 3.82 (3H; s); 4.26 (1H; d, J = 8.6); 4.29 (1H; d, J = 8.4); 5.06 (2H; s); 6.08 (1H; s); 6.29 (1H; s), 6.87 and 7.47 (each 2H; AA'BB', J_{AB} = 8.8); 6.93 (1H; d, J = 8.6); 7.20 - 7.36 (9H; m). ^{13}C NMR ($CDCl_3$, 40 °C): -1.4, 17.5, 28.2, 52.4, 56.0, 64.1, 67.5, 80.9, 112.7, 116.9, 122.9, 123.3, 127.3, 127.9, 128.1, 128.2, 128.3, 128.5, 128.55, 128.6, 130.5, 130.9, 131.6, 136.1, 144.1, 152.5, 158.6, 165.4, 166.2. IR (KBr): 3300 (b), 1710 (s). MS *m/z* (% rel. int.): 718 (M^+, 2), 620 (5), 619 (12), 618 (34), 547 (6), 511 (9), 510 (32), 482 (9), 410 (4), 251 (4), 192 (8), 132 (5), 108 (36), 107 (26), 91 (54), 79 (31), 77 (18), 75 (13), 74 (9), 73 (100). Anal. Calc. for $C_{38}H_{46}N_2O_{10}Si$: C, 63.49%; H, 6.45; N, 3.90. Found: C, 63.31; H, 6.25; N, 3.68.

(*S*)-*N*-[*tert*-Butyloxycarbonyl]-*O*-[5-[2-[[(phenylmethoxy)carbonyl]amino]-2-[[2-(trimethylsilyl)ethoxy]-carbonyl]ethyl]-2-methoxyphenyl]-L-tyrosine Methyl Ester (*SS*-11). Asymmetric hydrogenation of **10** (162.8 mg, 0.226 mmol) in the presence of Rh(I)-(*S,S*)-Et-DuPHOS according to the general procedure described above afforded after flash chromatography (ethyl acetate/pentane, 4:6) 148.5 mg (91% yield) of ***SS*-11** as a white solidified foam.

Data for ***SS*-11**. $[\alpha]_D^{22}$ +35.3 (c = 1.18, CH_2Cl_2). HPLC analysis (EtOH; 0.7 ml/min): ee >98 %; de 87 %. ^{1}H NMR: 0.01 (9H; s); 0.89 - 0.96 (2H; m); 1.41 (9H; s), 2.93 - 3.07 (4H; m), 3.69 (3H; s); 3.79 (3H; s); 4.06 - 4.21 (2H; m); 4.51 - 4.56 (2H; m); 4.94 (1H; d, J = 7.7); 5.07 (2H; bs); 5.20 (1H; d, J = 8.1); 6.74 (1H; bs); 6.80 and 6.99 (each 2H; AA'BB', J_{AB} = 8.4); 6.87 (2H; s); 7.29 - 7.37 (5H; m). ^{13}C NMR: -1.5, 17.4, 28.4, 37.5, 37.6, 52.3, 54.5, 55.0, 56.1, 64.0, 67.0, 80.0, 112.9, 117.0, 122.5, 125.8, 128.1, 128.2, 128.6, 128.8, 129.9, 130.4, 136.4, 144.6, 150.7, 155.2, 155.6, 157.2, 171.5, 172.4. IR (KBr): 3400 (s), 1710 (bs). MS *m/z* (% rel. int.): 722 (M^+, 1), 623 (4), 622 (8), 605 (4), 572 (7), 571 (16), 535 (10), 534 (20), 516 (9), 515 (28), 472 (5), 454 (10), 427 (6), 426 (19), 416 (8), 384 (6), 383 (15), 359 (5), 358 (14), 356 (6), 355 (6), 354 (6), 340 (8), 326 (5), 297 (8), 283 (6), 254 (11), 227 (11), 211 (11), 108 (13), 107 (15), 92 (9), 91 (100). Anal. Calc. for $C_{38}H_{50}N_2O_{10}Si$: C, 63.14%; H, 6.97; N, 3.88. Found: C, 63.41; H, 6.74; N, 3.81.

(*R*)-*N*-[*tert*-Butyloxycarbonyl]-*O*-[5-[2-[[(phenylmethoxy)carbonyl]amino]-2-[[2-(trimethylsilyl)ethoxy]-carbonyl]ethyl]-2-methoxyphenyl]-D-tyrosine Methyl Ester (*RR*-11). Asymmetric hydrogenation of **10** (208.1 mg, 0.299 mmol) in the presence of Rh(I)-(*R,R*)-Et-DuPHOS according to the general procedure described above afforded 185.5 mg (89 % yield) of ***RR*-11** as a white solidified foam.
Data for ***RR*-11**. $[\alpha]_D^{23}$ -33.3 (c = 1.01, CH_2Cl_2). HPLC analysis (EtOH; 0.7 ml/min): ee >98 %; de 87 %.

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