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Syntheses of Amino Alcohols and Chiral C_2-Symmetric Bisoxazolines Derived from *O*-Alkylated *R*-4-Hydroxyphenylglycine and *S*-Tyrosine

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Chiral C_2-symmetric bisoxazolines **1b–f** and **2b,c**, derived from 4'-*O*-alkylated *R*-4-hydroxyphenylglycine or *S*-tyrosine, were prepared. As intermediates, a series of chiral amino alcohols possessing substituted phenolic groups was prepared and fully characterized.

INTRODUCTION

Chiral amino alcohols are important synthetic intermediates in asymmetric synthesis, peptide and pharmaceutical chemistry, and resolution of racemic mixtures.[1] They are also useful in the synthesis of peptide aldehydes, which are potent inhibitors of proteases.[2] Additional interest in amino alcohols, as precursors in bisoxazoline ring synthesis, was pushed up by the recent development of this system as C_2-symmetric ligand used in stereodifferentiating reactions.[3a–c]

Recently, amino alcohols possessing the phenolic group were needed in our laboratory as precursors for chiral cavity containing bisoxazolines[4] (Chart 1), designed for enantioselective control of metal-catalyzed reactions.[5a–f] The incorporation of selected recognition elements into simple organometallic catalysts presents an appealing design feature, since additional attractive interactions can in principle reduce conformational degrees of freedom and enhance chiral discrimination in selectivity-determining transition states.[6a–d] It was observed that the defined topology of some organometallic catalytic complexes of monodentate nitrogen ligands[5a] or bidentate C_1-symmetric ligands led to an enhancement of enantioselectivity when topology became restricted by repulsive,[5b–e] or attracting π-π interactions.[5a,f]

We have considered the synthesis of chiral bisoxazoline ligands bearing aromatic arms of variable length and flexibility (Chart 1). The presence of such aromatic units may provide additional attractive and/or repulsive interactions in catalytic complexes with aromatic substrates. For this purpose, such ligands, based on *R*-4-hydroxyphenylglycine and *S*-tyrosine, have been selected. The phenolic hydroxy group remote from the stereogenic centers may be used for additional modification of the ligands by introducing new sterically demanding groups.

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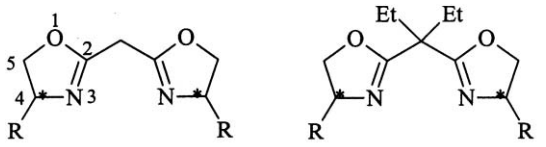


1a R = C_6H_4–OH
1b R = C_6H_4–OBzl
1c R = CH_2–C_6H_4–OBzl
1d R = CH_2–C_6H_4–OMe
1e R = CH_2–C_6H_4–O*t*Bu
1f R = C_6H_4–O*t*Bu

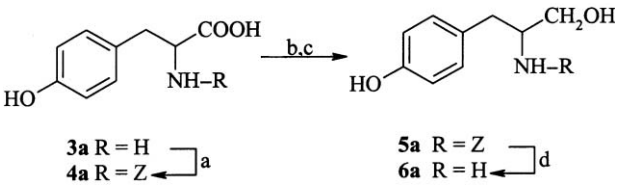
2a R = C_6H_4–OH
2b R = C_6H_4–OBzl
2c R = CH_2–C_6H_4–OBzl

Chart 1.

RESULTS AND DISCUSSION

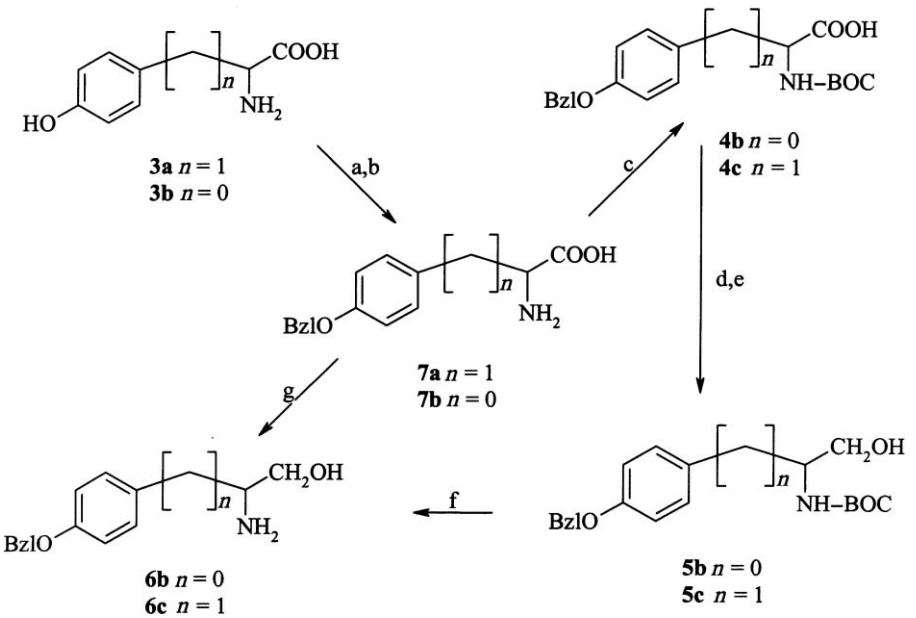
Preparation of Amino Alcohols

Enantiomerically pure amino alcohols are the key intermediates in the synthesis of chiral bisoxazoline ligands. Preparation of the needed amino alcohols was effected by reduction of carboxylic function in the corresponding amino acids, *S*-tyrosine or *R*-4-hydroxyphenylglycine. Direct reduction of *S*-tyrosine **3a** with $NaBH_4/H_2SO_4$ in THF to amino alcohol, as described for phenylglycine,[7] failed due to insufficient solubility of tyrosine in the reaction medium, arising from additional hydroxyl functionality in the starting amino acid. Introduction of an appropriate amino protecting group, *e.g.* benzyloxycarbonyl group (Z), provided the more soluble *N*-protected amino acid **4a**[8] (Scheme 1), which can be successfully reduced with sodium borohydride[9a–d] in methanol *via* mixed anhydride (*N*-methylmorpholine; ethyl chloroformate in tetrahydrofurane) [9a,b] to *N*-protected amino alcohol **5a**. We modified the procedure by removing *N*-methylmorpholine hydrochloride, thereby avoiding formation of the *N*-methylmorpholine-$NaBH_4$ addition product. This modification considerably simplifies isolation of the reduced product. Preparation of amino alcohol **5a** was also reported by reduction of the ester group in ethyl *N*-benzyloxycarbonyl tyrosine using $NaBH_4$/LiI in dry tetrahydrofurane.[10] Hydrogenolytic cleavage of benzyloxycarbonyl group provided *S*-tyrosinol **6a**, which after acetylation (Ac_2O; pyridine) gave the triacetylated product identical to that described.[11]



Scheme 1. Reagents and solvents: a) C_6H_5OCOCl, NaOH, H_2O; b) NMM, $ClCO_2Et$, THF; c) $NaBH_4$, CH_3OH; d) H_2-Pd/C, CH_3OH.

However, the unsubstituted tyrosinol **6a** was found unsuitable for the preparation of bisoxazolines **1a** and **2a** due to its insufficient solubility in nonpolar solvents usually used in the cyclization step. Introduction of the benzyl group into the phenolic group on the side chain of *S*-tyrosine **3a** and also *R*-4-hydroxyphenylglycine **3b** in the first step afforded the soluble benzyl ethers **7a** and **7b** (Scheme 2). They were prepared from Cu^{II}-complexes of **3a** and **3b** by treatment with benzylbromide in alkaline medium[12,13] in 63–73 % and 58–63 % yield, respectively. The recently introduced reduction method, by $NaBH_4$ and iodine in THF, followed by the treatment with KOH[1,14] requires no protection of the amino function. Thus, the direct reduction of *O*-benzyl-*S*-tyrosine **7a** and 4-*O*-benzyloxy-*R*-phenylglycine **7b** gave alcohols **6b** and **6c**,



Scheme 2. Reagents and solvents: a) $CuSO_4$, NaOH, H_2O; b) BzlBr, NaOH, CH_3OH; c) $(BOC)_2O$, NaOH, dioxane-H_2O; d) NMM, $ClCO_2Et$, THF; e) $NaBH_4$, CH_3OH; f) $(CH_3)_3SiCl$, PhOH, CH_2Cl_2, KOH; g) $NaBH_4$, I_2, THF, KOH, H_2O.

both in 66 % yield. In order to overcome the possible racemization in strong alkaline conditions, we also performed reduction of *N*-BOC protected derivatives, *i.e.* *O*-4-benzyloxy-*N*-BOC-*R*-phenylglycine **4b** and *O*-benzyl-*N*-BOC-tyrosine **4c**, which were obtained in 93–98 % and 90 % yield, respectively, by treating **7a** and **7b** with di-*tert*-butyl dicarbonate in dioxane-water.[15] Reduction of the carboxylic group in **4b** and **4c** was performed *via* mixed anhydride (*N*-methylmorpholine, ethyl chloroformate in tetrahydrofurane), and subsequent addition of sodium borohydride in methanol, giving *N*-protected amino alcohols **5b, 5c** in 75–87 % yield.[9a] The variant using *N*-methylmorpholine and isobutyl chloroformate in 1,2-dimethoxyethane described for **4c**[9c] was not efficient in our hands, giving a mixture of products. Another method of reduction of *N*-BOC protected amino acids is based on the reduction of acyl fluorides with $NaBH_4$.[9d]

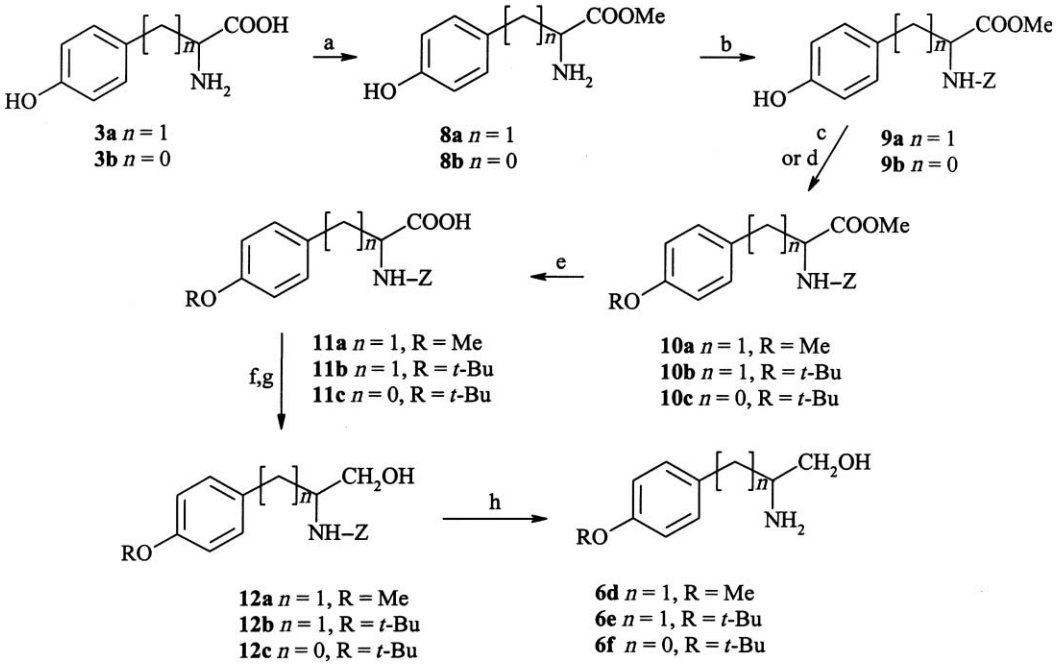
BOC-Deprotection in **5b** and **5c** was attempted at first by the commonly used deprotection procedure (TFA),[16] but this method proved to be unsuccessful, probably due to the reaction of the alcoholic group with acid and partial debenzylation. Next, the attempt of deprotection with an acid ion-exchanger (Amberlyst 15) left the starting material unchanged. The method developed for the solid-phase peptide synthesis[17] with a combined reagent made from trimethylchlorosilane and phenol (4 M solutions in dichloromethane) in a 1:3 ratio was found satisfactory. We adapted the procedure by diminishing the originally used ratio of reactants of 100:1 to only 2.5:1. The yield of both end-products **6b** and **6c** was around 70 %.

The optical activities of end-products **6b,c** (Scheme 2) obtained by pathway **3a,b→7a,b→4b,c→5b,c→6b,c** were identical to those obtained by pathway **3a,b→7a,b →6b,c,** indicating the same optical purity of the obtained products, *i.e*: $[\alpha]_D = -26°$ for **6b** and $[\alpha]_D = -20°$ for **6c**.

Easily removable *O*-benzyl group makes the prepared products useful precursors of various bisoxazoline derivatives,[4] enabling their further functionalization at phenolic hydroxy group.

Alkyl ethers of phenolic amino alcohols were also prepared from amino acids with appropriate ether linkages, and their subsequent reduction. Before alkylation of the phenolic OH group of tyrosine **3a** and 4-hydroxyphenylglycine **3b**, the carboxylic and amino functions had to be protected. The alkyl derivatives of tyrosinol and 4-hydroxyphenylglycinol were prepared starting from the corresponding *N*-benzyloxycarbonyl protected amino acid methyl ester (Scheme 3). *S*-Tyrosine methyl ester **8a** was prepared[18] starting from *S*-tyrosine (**3a**) and thionyl chloride in methanol, in 99 % yield, as well as *R*-4-hydroxyphenylglycine methyl ester (**8b**) in 98 % yield starting from *R*-4-hydroxyphenylglycine **3b**. The benzyloxycarbonyl protecting group was introduced in 87–89 % yield[19] to give benzyloxycarbonyl-*S*-tyrosine methyl ester (**9a**) and benzyloxycarbonyl-*R*-4-hydroxyphenylglycine methyl ester (**9b**). Tyrosine derivative **9a** was successfully alkylated with methyl iodide in the presence of anh. potassium carbonate in acetone, giving **10a** in quantitative yield.

tert-Butyl group was introduced by acid-catalyzed addition (H_2SO_4), using a large excess of isobutylene in dichloromethane[19] in an autoclave; after three days at room temperature, benzyloxycarbonyl-*O*-*tert*-butyl-*S*-ty-



Scheme 3. Reagents and solvents: a) CH_3OH, $SOCl_2$; b) C_6H_5OCOCl, Na_2CO_3, CH_2Cl_2, H_2O; c) CH_3I, K_2CO_3, acetone; d) $CH_2{=}C(CH_3)_2$, CH_2Cl_2; e) NaOH, dioxane-H_2O; f) NMM, $ClCO_2Et$, THF; g) $NaBH_4$, CH_3OH; h) H_2-Pd/C, CH_3OH.

rosine methyl ester **10b** was obtained in 66 % yield, together with 32 % of recovered **9a**. In the case of phenylglycine analog **10c**, only 34 % of benzyloxycarbonyl-4-*O*-*tert*-butoxy-*R*-phenylglycine methyl ester (**10c**) and 57 % of recovered **9b** were obtained, presumably due to insufficient solubility of **9b** in dichloromethane.

The hydrolysis of methyl esters **10a–c** in dioxane-water 4:1, using 2 M NaOH, and subsequent acidification with 2.5 M H_2SO_4,[20] gave *O*-alkyl-*N*-protected amino acids **11a–c** (94–98 % yield).

Reduction of the carboxylic group in **11a–c** was performed as described previously for compounds **5a–c**. Yields of *O*-alkyl-*N*-protected amino alcohols **12a–c** were 85–90 %. As the minor by-product, the ester obtained from the starting acid and formed alcohol was detected (5 %).

Hydrogenolysis of the benzyloxycarbonyl protecting group was carried out in a Parr hydrogenator overnight, in methanolic solution with 10 % Pd/C as a catalyst, giving the end-products *O*-alkyl amino alcohols **6d–f** in quantitative yield.

Synthesis of *(S)*-2-amino-3-(4-methoxyphenyl)-1-propanol **6d** was previously reported by reduction of *O*-methyl-tyrosine ethyl ester hydrochloride with $LiAlH_4$ in ether-dioxane mixture, in 68 % yield.[21]

Preparation of Bisoxazolines

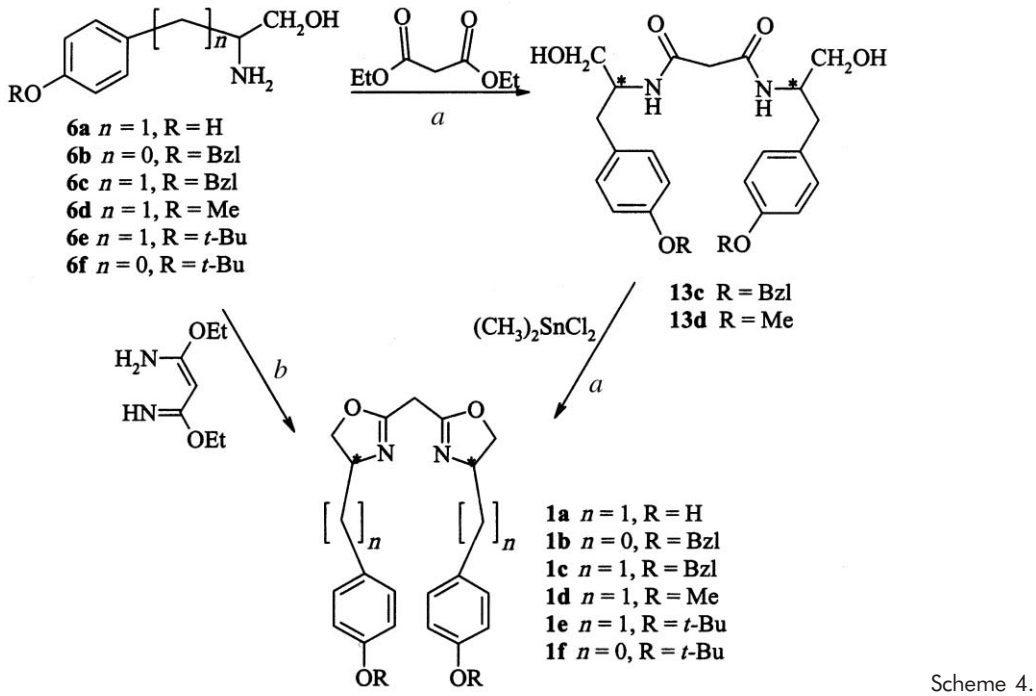
Bisoxazoline ligands derived from *R*-4-hydroxyphenylglycine and *S*-tyrosine belong either to C(2)-methylene derivatives **1a–f** or C(2)-dialkyl methylene derivatives **2a–c** and comprise ligands with elongated »arms« at stereogenic centers possessing aromatic units. They were prepared according to Schemes 4 and 5.

2,2'-Methylene bisoxazolines **1b–f** were obtained by one of the two routes outlined in Scheme 4.

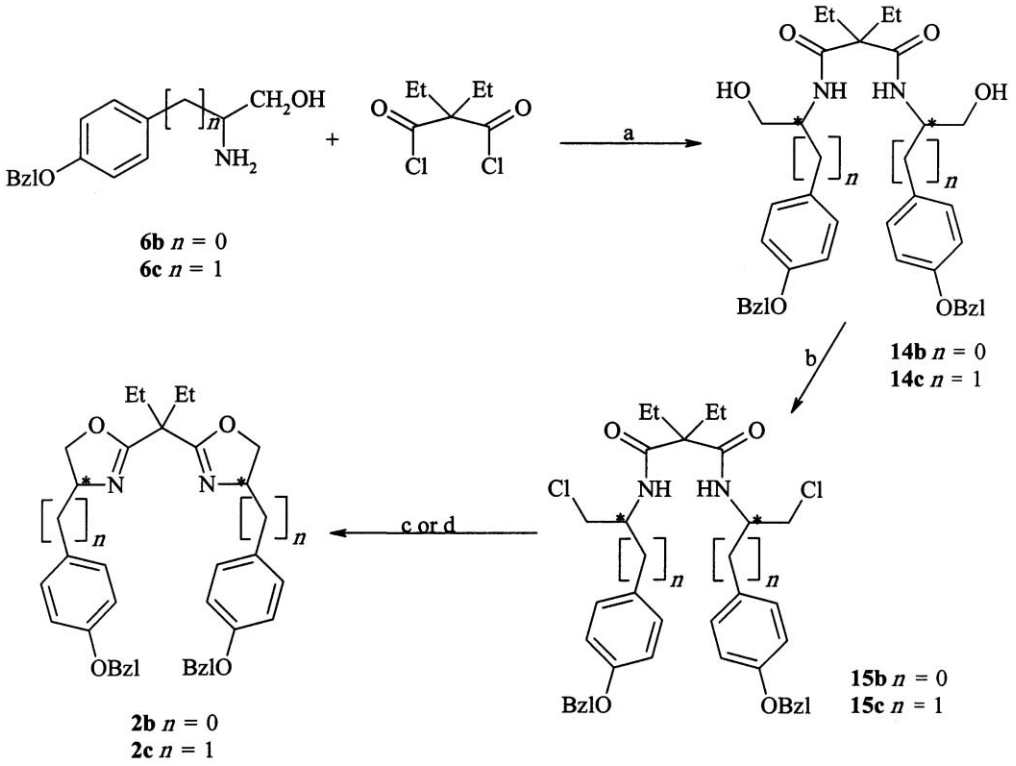
Using the method described by Masamune *et al.*,[22] the 4-*O*-alkylated amino alcohols **6c,d** were reacted with diethyl malonate giving the respective bis(hydroxy)amides **13c,d.** Their activation with dimethyltin dichloride resulted in cyclization into bisoxazolines **1c,d** (route *a*). The reaction proceeded well with *S*-benzyltyrosinol **6c**, giving ligand **1c** in 58 % yield, without isolation of diamide **13c.** *S*-Methyltyrosinol **6d** afforded diamide **13d** in poor yield (23 %) and the isolated diamide cyclized into **1d** in 19 % yield. A better route to bisoxazolines **1b–f** is the method described by Lehn *et al.*[23] Starting amino alcohols **6b–f** are condensed with amino-ethoxy-propen-imidate dihydrochloride in dichloromethane, using triethylamine as the base affording bisoxazolines **1b–f** in moderate to good yields (46–79 %, route *b*). Bisoxazoline **1a** could not be obtained by either of the examined routes due to poor solubility of the starting alcohol **6a**.

Although the structure of methylene-bridged bisoxazolines enables tautomeric forms, ^{1}H NMR spectra did not reveal their appearance.

C(2)-Dialkylated bisoxazolines **2b,c** were obtained in good yields according to Scheme 5. Condensation of **6b,c** with diethylmalonyl dichloride was carried out in the presence of triethylamine in dichloromethane at 0 °C,[24] giving dihydroxy diamides **14b,c** as white solids in high yields (86 % and 78 %, respectively). Diamides were treated with a mixture of triphosgen/triphenylphosphine[25a,b] to afford the corresponding dichlorides **15b,c**, which on heating under basic conditions were cyclized to **2b,c** in 72–92 % yields. The reactions were performed either in methano-



Scheme 4.



Scheme 5. Reagents and solvents: a) Et_3N, CH_2Cl_2; b) $(COCl_2)_3$, PPh_3, CH_2Cl_2; c) NaOH, CH_3OH, reflux; d) Et_3N, toluene, reflux.

lic solution of NaOH[24] or triethylamine in toluene,[26] both giving products of identical optical purity.

The prepared bisoxazolines served as bidentate ligands for metal-catalyzed enantioselective transformations (Cu^I-complex catalyzed cyclopropanation of styrene with ethyl diazoacetic ester and Pd^{II}-complex catalyzed alkylation of 1,3-diphenylprop-2-enyl acetate by dimethylmalonate anion), which will be published separately.

CONCLUSION

Chiral amino alcohols with free and substituted (alkyl, benzyl) phenolic groups have been prepared in high yields, using easily available reagents and mild conditions. They served as precursors for the preparation of either macrocyclic or acyclic chiral C_2-symmetric bisoxazolines, designed as ligands for metal-catalyzed enantioselective transformations.

EXPERIMENTAL

General

Reagents were purchased from Aldrich or Fluka and were used without further purification. All solvents were purified and dried according to standard procedures. TLC was performed on silica gel Merck 60 F_{254} plates and column chromatography was carried out with 230–240 mesh Merck 60 silica gel. ^1H and ^{13}C NMR spectra were recorded on the Varian Gemini 3000 spectrometer with tetramethylsylane as an internal standard at 300 MHz, in $CDCl_3$ unless otherwise stated. Chemical shifts (δ) were given in ppm, J in Hz. IR spectra were taken in KBr pellets on a Perkin Elmer 297 spectrometer, ν given in cm^{-1}. Melting points were determined on a Kofler hot-stage apparatus (Reichert, Wien) or an Electrothermal Melting Point Apparatus 9100 in capillary tubes and were not corrected. Optical rotations were measured on an Optical Activity AA-10 Automatic Polarimeter in a 1 dm cell at 589 nm; concentrations were given in g/100 mL. UV spectra $\lambda_{max.}$ in nm (log ε in mol^{-1} dm^3 cm^{-1}) were run on a Philips PU8700 UV/Vis spectrophotometer, in 96 % EtOH solutions if not stated otherwise. TLC was performed on Merck Kieselgel HF_{254} plates and spots were made visible using a UV lamp (254 nm) or I_2 vapors, in CH_2Cl_2-MeOH 9:1 or 19:1 as developing systems. Flash chromatography was run on Merck Kieselgel 60 (0.040–0.063 mm). Mass spectrum was recorded on an Extrell FTMS 2001-DD Fourier Transform Mass Spectrometer (Madison, WI, USA) equipped with a 3 T superconducting magnet and a Nicolet 1280 Data Station.

N-*Benzyloxycarbonyl*-S-*tyrosine* (***4a***)

To a solution of **3a** (3.624 g, 20 mmol) in 2 M NaOH (10 mL, 20 mmol) cooled in an ice-water bath, 50 % toluene solution of benzyloxycarbonylchloride (6.7 mL, 20 mmol) and 2 M NaOH (10 mL, 20 mmol) were added dropwise during 15 min and stirred at room temperature overnight. After addition of 2 M HCl (10.5 mL, 21 mmol), the product

was extracted into EtOAc and purified by flash-chromatography (CH_2Cl_2-MeOH 30:1 and 15:1) to give the monosubstituted product **4a** (2.850 g, 45 %); m.p. 95–98 °C (lit.[27] m.p. 101 °C, lit.[20] m.p. 92–95 °C) and disubstituted product (1.229 g, 27 %). ^{1}H NMR (acetone-d_6) δ/ppm: 8.3 (bs, 1H, –OH), 7.2 (s, 5H, Ph), 6.9 + 6.6 (2d, H(2') + H(3'), J = 8.1 Hz), 6.2 (d, 1H, –NH–, J = 6.5 Hz), 5.5–5.2 (m, 1H, C(2)H), 5.0 (s, C(4')–OCH_2), 4.6 (m, 1H, OH), 3.0 (m, 2H, C(3)H). ^{13}C NMR ($CDCl_3$) δ/ppm: 175.79 (–**C**OOH), 156.29 (C(4')), 154.96 (–**C**OOBzl), 135.83 (C(1')), 130.43 (C(2')), 128.68 (C(1'')), 128.51 (C(2'')), 128.03 (C(4'')) and (C(3''), 115.62 (C(3')), 67.21 (–O**C**H_2Ph), 54.72 (C(2)), 36.75 (C(3)).

General Procedure for Reduction of N*-protected Amino Acids*

The starting acid **4a–c, 11a–c** (10.0 mmol) was dissolved in dry THF (50 mL), cooled down to –15 ºC, and *N*-methylmorpholine (1.1 mL, 1.015 g, 10.0 mmol) and ethylchloroformiate (0.97 mL, 1.085 g, 10.0 mmol) were added under stirring. The separated *N*-methylmorpholine hydrochloride was filtrated into the cooled flask and washed with dry THF (20 mL). Into the cold filtrate $NaBH_4$ (568 mg, 15.0 mmol) was added at once, and then MeOH (100 mL) was added dropwise, very slowly at the beginning because of vigorous foaming. After completed addition, the solution was stirred in an ice-water bath for 0.5 h and at room temperature for 1 h. The solvents were partially evaporated, some water (100–150 mL) was added and the product was isolated by filtration or extraction into EtOAc (3 × 50 mL). The combined extracts were dried ($MgSO_4$) and evaporated. Alcohols **5a–c, 12a–c** were obtained in 85–90 % yield.

N-*Benzyloxycarbonyl*-S-*tyrosinol (**5a**)*

It was prepared according to the general procedure for reduction of *N*-protected amino acids. Yield: 84.5 %. ^{1}H NMR (acetone-d_6) δ/ppm: 8.2 (bs, 1H, –OH), 7.3–7.1 (m, 5H, Ph), 7.1 + 6.8 (2d, H(2') + H(3'), J = 8.2 Hz), 6.1 (d, 1H, –NH–, J = 7.6 Hz), 5.0 (s, C(4')–OCH_2), 4.0 (t, 1H, C(2)H, J = 5.5 Hz), 2.9 (dd, 1H, C(3)Ha, J = 6.4, 13.7 Hz), 2.7 (dd, 1H, C(3)Hb, J = 7.6, 13.7 Hz). ^{13}C NMR (acetone-d_6) δ/ppm: 156.00 (C(4')) and (–**C**OOBzl), 137.70 (C(1')), 130.39 (C(2')), 129.76 (C(1'')), 128.42 (C(2'')), 127.74 (C(4'')) and (C(3''), 115.12 (C(3')), 65.43 (–O**C**H_2Ph), 63.17 (–CH_2OH), 55.02 (C(2)), 36.21 (C(3)).

General Procedure for Hydrogenolytic Deprotection

Compound **5a, 12a–c** (14 mmol) was dissolved in MeOH (140 mL), the catalyst 10 % Pd/C (500 mg) was added and reduction was performed in a Parr hydrogenator at 0.3 MPa H_2 overnight. The catalyst was removed by filtration through a celite pad, and the filtrate was evaporated to give the crude product in quantitative yield. The product was purified by recrystallization from EtOAc (Me-derivative **6d**) or flash chromatography (eluents CH_2Cl_2-MeOH 25:1 and 10:1) (**6a,** *t*-Bu-derivatives **6e,f**).

S-*Tyrosinol (**6a**)*

It was prepared by the general procedure for hydrogenolytic deprotection. Yield: 95.5 %. ^{1}H NMR (acetone-d_6): 7.1 + 6.7 (2d, H(2') + H(3'), J = 8.35 Hz), 3.8 (t, 1H, C(1)Ha, J = 7.0 Hz), 3.60 (q, 1H, C(2)H, J = 7.2 Hz), 3.3 (t, 1H, C(1)Hb, J = 7.7 Hz). 2.8 (dd, 1H, C(3)Ha, J = 6.3, 13.7 Hz), 2.6 (dd, 1H, C(3)Hb, J = 7.5, 13.7 Hz). ^{13}C NMR (acetone-d_6): 156.33 (C(4')), 130.71 (C(1')), 130.14 (C(2')), 115.52 (C(3')), 70.38 (–CH_2OH), 59.93 (C(2)), 38.41 (C(3)).

N,O,O-*Triacetyl*-S-*tyrosinol.* – It was prepared with Ac_2O in pyridine at room temperature overnight, m.p. 115–118 °C (lit.[10] m.p. 118–119 °C). ^{1}H NMR ($CDCl_3$) δ/ppm: 7.2 + 7.0 (2d, H(2') + H(3'), J = 8.1 Hz), 6.2 (d, 1H, J = 8.1 Hz), 4.4 (dd, 1H, C(2)H, J = 7.0 Hz), 4.0 (d, 2H, C(1)H, J = 5.1 Hz). 2.8 (m, 2H, C(3)H), 2.3, 2.1 and 1.9 (3s, 3 × 3H, –Ac). ^{13}C NMR: 170.84, 169.77 and 169.35 (3 × –COO–), 149.27 (C(4')), 134.58 (C(1')), 129.89 (C(2')), 121.43 (C(3')), 64.44 (–CH_2OH), 49.08 (C(2)), 36.38 (C(3)), 22.80, 20.68 and 20.37 (3 × –OCH_3).

General Procedure for Benzylation of Amino Acids

To a solution of an amino acid, (*S*-tyrosine **3a** or *R*-4-hydroxyphenylglycine **3b**) (50.0 mmol) in 2 M NaOH (25 mL, 50.0 mmol) and a solution of $CuSO_4 \cdot 5H_2O$ (6.24 g, 25.0 mmol) in water (25 mL) were added under stirring at room temperature. The blue precipitate of the Cu-complex separated immediately. After 1 h of reflux, the mixture was allowed to cool down to room temperature, and was dissolved in methanol (180 mL) and 2 M NaOH (25 mL, 50 mmol). Benzylbromide (6.25 mL, 52.5 mmol, 5 % excess) was added, and the mixture was stirred at room temperature overnight. The Cu-complex precipitate was collected, washed with water and MeOH, transferred to an Erlenmeyer flask and stirred with 1 M HCl (100 mL) for 1 h to transform the Cu-complex into hydrochloride. The precipitate was filtered, washed with water (125 mL) and treated with 1 M NH_3 (2 × 100 mL) to remove HCl, again washed with water (125 mL) and acetone (60 mL), and dried.

O-*Benzyl*-S-*tyrosine (**7a**)*

Yield: 73 %; m.p. 216–220 ºC (lit.[12] m. p. 223 ºC). ^{1}H NMR (CF_3COOD) δ/ppm: 7.2–6.9 (m, 9H, Ph), 5.0 (s, C(4')–OCH_2), 4.4 (m, 1H, C(2)H), 3.4–3.1 (m, 2H, C(3)H). ^{13}C NMR (CF_3COOD) δ/ppm: 175.07 (–COOH), 160.32 (C(4')), 137.01 (C(1'')), 133.05 (C(2')), 131.33 (C(1')), 131.08 (C(2'')), 130.65 (C(3'')), 128.17 (C(4'')), 119.32 (C(3')), 74.81 (C(4')–O**C**H_2), 58.00 (C(2)), 36.99 (C(3)).

*4-O-Benzyloxy-R-phenylgycine (**7b**)*

Yield: 67 %; m.p. 214–216 ºC. ^{1}H NMR (CF_3COOD) δ/ppm: 7.2–6.9 (m, 9H, Ph), 5.2 (m, 1H, C(2)H), 5.0 (s, C(4')–OCH_2). ^{13}C NMR (CF_3COOD) δ/ppm: 174.73 (–COOH), 162.63 (C(4')), 137.14 (C(1'')), 131.99 (C(2')), 131.08 (C(1')), 130.99 (C(2'')), 130.16 (C(3'')), 124.48 (C(4'')), 119.28 (C(3')), 74.15 (C(4')–O**C**H_2), 59.98 (C(2)).

General Procedure for BOC-protection of Benzylated Amino Acids

To the crude benzylated amino acid **7a,b** (29.1 mmol) suspended in dioxane-water (2:1, 175 mL), 1 M NaOH (29.1 mL, 29.1 mmol) and $NaHCO_3$ (2.445 g, 29.1 mmol) were added. To the reaction mixture cooled in ice-water, $(BOC)_2O$ (13.0 g, 58.2 mmol) was added and stirred at room temperature overnight. Undissolved material was discarded and the filtrate was partially evaporated (to approx. 150 mL). The aqueous residue was cooled in ice-water, EtOAc (100 mL) was added and the mixture was acidified to pH = 2–3 by addition of 1 M $KHSO_4$ (approx. 50 mL). Layers were separated, the aqueous layer was extracted with EtOAc (2 × 30 mL), combined extracts were washed with water, dried ($MgSO_4$), and evaporated to give the BOC-protected amino acids **4b,c** in 92–98 % yield.

4-O-*Benzyloxy*-N-tert-*butoxycarbonyl*-R-*phenylglycine (**4b**)*

A thick oil. Yield: 92 %. ^{1}H NMR ($CDCl_3$) δ/ppm: 8.7 (bs, 1H, OH), 7.4–7.3 (m, 5 + 2H, Ph + H(3')), 7.0 (d, H(2'), J = 8.2 Hz), 5.5 (dd, J = 6.9; 105.8 Hz, C(2)H), 5.1 (s, C(4')–OCH_2), 1.5 (s, 9H, *t*-Bu). ^{13}C NMR ($CDCl_3$) δ/ppm: 173.56 (–COOH), 158.36 (C(4')), 156.63 (–**C**OO–*t*-Bu), 136.61 (C(1''), 130.36 (C(1')), 128.37 (C(2'')), 128.22 (C(4'')), 127.79 (C(3'')), 127.30 (C(2')), 114.64 (C(3')), 81.42 (–**C**$(CH_3)_3$), 69.83 (C(4')–O**C**H_2), 58.02 (C(2)), 27.84 (–OC(**C**$H_3)_3$).

O-*Benzyl*-N-tert-*butoxycarbonyl*-S-*tyrosine (**4c**)*

Yield: 96 %; m.p. 109–111 °C (lit.[28] m.p. 108–109 °C). ^{1}H NMR ($CDCl_3$) δ/ppm: 10.9 (bs, 1H, OH), 7.4–7.3 (m, 5H, Ph), 7.1 + 6.9 (2d, H(2') + H(3'), J = 8.2 Hz), 5.0 (s, C(4')–OCH_2), 4.6–4.4 (m, 1H, C(2)H), 3.1 (t, 2H, C(3)H), 1.4 (s, 9H, *t*-Bu). ^{13}C NMR ($CDCl_3$) δ/ppm: 176.78 (–COOH), 157.96 (C(4')), 155.37 (–**C**OO-*t*-Bu), 136.92 (C(1'') and (C(1')), 130.40 (C(2')), 128.52 (C(2'')), 127.89 (C(4'')), 127.42 (C(3'')), 114.88 (C(3')), 80.13 (–**C**$(CH_3)_3$), 69.84 (C(4')–O**C**H_2), 54.20 (C(2)), 36.75 (C(3)), 28.06 (–OC(**C**$H_3)_3$).

4-O-*Benzyloxy*-N-tert-*butoxycarbonyl*-R-*phenylglycinol (**5b**)*

It was prepared according to the general procedure for reduction of *N*-protected amino acids. Yield: 75 %; m.p. 128–130 °C (EtOAc). ^{1}H NMR (acetone-d_6) δ/ppm: 7.6–7.5 (m, 5H, Ph), 7.4 + 7.0 (2d, H(2') + H(3'), J = 8.7 Hz), 6.4 (bs, 1H, –NH, disappears with D_2O), 5.2 (s, C(4')–OCH_2), 4.8 (m, 1H, C(2)H)), 3.8 (dd, 2H, –C**H**$_2$OH, J = 5.0 Hz), 3.1 (bs, 1H, –OH), 1.5 (s, 9H, *t*-Bu). ^{13}C NMR (acetone-d_6) δ/ppm: 158.39 (C(4')), 155.87 (–**C**OO-*t*-Bu), 138.03 (C(1')), 134.32 (C(1'')), 128.77 (C(2')), 128.37 (C(2'')), 128.08 (C(4'')), 127.89 (C(3'')), 114.79 (C(3')), 78.19 (–**C**$(CH_3)_3$), 69.78 (C(4')–O**C**H_2), 65.81 (C(1)), 56.66 (C(2)), 27.95 (–OC(**C**$H_3)_3$).

O-*Benzyl*-N-tert-*butoxycarbonyl*-S-*tyrosinol (**5c**)*

It was prepared according to the general procedure for reduction of *N*-protected amino acids. Yield: 77 %; m.p. 110–112 °C (lit.[9c] m.p. 104–106 °C). ^{1}H NMR (acetone-d_6) δ/ppm: 7.5–7.3 (m, 5H, Ph), 7.2 + 6.9 (2d, H(2') + H(3'), J = 8.5 Hz), 5.7 (d, 1H, –NH, J = 7.3 Hz), 5.1 (s, C(4')–OCH_2), 3.9–3.7 (m, 2H, C(2)H+–OH)), 3.5 (dd, 2H, –C**H**$_2$OH, J = 1.5, 4.8 Hz), 2.8 (ddd. 2H, –CH_2–, J = 7.3, 13.4, 42.7 Hz), 1.4 (s, 9H, *t*-Bu). ^{13}C NMR (acetone-d_6) δ/ppm: 157.49 (C(4')), 155.99 (–**C**OO-*t*-Bu), 138.15 (C(1')), 131.80 (C(1'')), 130.68 (C(2')), 128.79 (C(2'')), 128.06 (C(4'')), 127.88 (C(3''), 114.92 (C(3')), 78.05 (–**C**$(CH_3)_3$), 69.81 (C(4')–O**C**H_2), 63.45 (C(1)), 54.55 (C(2)), 36.47 (C(3)), 27.97 (–OC(**C**$H_3)_3$).

General Procedure for BOC-deprotection

BOC-Protected alcohol **5b,c** (8 mmol) was suspended in CH_2Cl_2 (20 mL), and a freshly prepared mixture of trimethylchlorosilane (2.53 mL, 20 mmol) in CH_2Cl_2 (2.47 mL) (4 M solution) and phenol (5.647 g, 60 mmol) (4 M solution) was added under stirring at room temperature. The bubbles of gaseous by-products evolved during 1 h. After that moment, the procedure for PhG and Tyr derivatives differed.

4-O-*Benzyloxy*-R-*phenylglycinol (**6b**)*

The white precipitate of deprotected amino alcohol hydrochloride began to separate; sometimes it was necessary to add some petroleum ether (25 mL) to provoke the separation of hydrochloride. The next day the precipitate was filtrated, washed with CH_2Cl_2 and dried: yield 77 %. Hydrochloride (23 mmol) was suspended in CH_2Cl_2 (100 mL) and stirred with 2 M NaOH (23 mL, 46 mmol) overnight. The layers were separated, the aqueous layer was extracted with CH_2Cl_2 (2 × 50 mL), combined extracts were washed with water, dried and evaporated to give the product **6b** in 91% yield. For analytical purposes it was recrystallized from EtOAc-petroleum ether, m.p. 94–96 °C (EtOAc). $[a]_D$ = –26 (c = 1.008 g/100 mL, CH_2Cl_2). UV(EtOH) λ_{max} / nm (log ε / mol^{-1} dm^3 cm^{-1}): 225 (4.38), 275 (3.41), 282 (3.32). IR(KBr) ν_{max} / cm^{-1}: 3300 (s, OH, NH_2), 1610 and 1580 (m, NH_2), 1250 (s, C–O–C), 1115 (m, –CH_2OH). ^{1}H NMR δ/ppm: 7.4–7.3 (m, H(2''), H(3'') + H(4'')), 7.2 + 6.9 (2d, H(2') + H(3'), J = 9.0 Hz), 5.0 (s, C(4')–O**C**$\mathbf{H_2}$), 3.7–3.5 (m, C(1)H_2), 4.0 (C(2)H), 2.7 (bs, OH + NH_2). ^{13}C NMR δ/ppm: 58.17 (C(4')), 136.90 (C(1'')), 134.91 (C(1')), 128.55 (C(2')), 127.94 (C(2'')), 127.55 (C(4'')), 127.40 (C(3'')), 114.87 (C(3')), 69.87 (C(4')–O**C**H_2), 67.83 (C(1)), 56.51 (C(2)).

Anal. Calcd. for $C_{15}H_{17}NO_2$ (M_r = 243.31): C 74.05, H 7.04, N 5.76%; found: C 74.01, H 6.89, N 5.65%.

O-*Benzyl*-S-*tyrosinol (**6c**)*

To the formed hydrochloride, dissolved in CH_2Cl_2, 2 M NaOH (40 mL, 8.0 mmol) was added with stirring and cooling, and the mixture was vigorously stirred at room temperature overnight. The layers were separated, the aque-

ous layer was extracted three more times with CH_2Cl_2 (3 × 10 mL). Combined extracts were washed with water, dried ($MgSO_4$) and evaporated. The product was separated from residual phenol by short column chromatography; eluents CH_2Cl_2-MeOH 25:1, 10:1 and 5:1. Fractions containing the product were evaporated to give **6c** (yield 91 %). For analytical purposes it was recrystallized from EtOAc, m.p. 102–104 °C (EtOAc). $[\alpha]_D = -20$ (c = 1.04 g/100 mL, $CHCl_3$). IR(KBr) ν_{max} / cm^{-1}: 3340 and 3280 (s, OH, NH_2), 1610 and 1580 (m, NH_2), 1235 (C–O–C), 1110 (–CH_2OH). UV(EtOH) λ_{max} / nm (log ε / mol^{-1} dm^3 cm^{-1}): 226 (3.88), 277 (2.97). ^{1}H NMR (acetone-d_6) δ/ppm: 7.5–7.3 (m, H(2'') + H(3'') + H(4'')), 7.2 + 6.9 (2d, H(2') + H(3'), J = 8.7 Hz), 5.1 (s, C(4')–OCH_2), 3.8 (dd as t, C(1)Ha, J = 7.4 Hz), 3.3 (dd as t, C(1)Hb), J = 7.7 Hz), 3.6 (q, C(2)H, J = 7.7 Hz), 2.8 (dd, C(3)Ha, J = 6.6, 13.5 Hz), 2.7 (dd, C(3)Hb, J = 7.1, 13.7 Hz). ^{13}C NMR ($CDCl_3$) δ/ppm: 157.46 (C(4')), 137.03 (C(1'')), 130.88 (C(1')), 130.12 (C(2')), 128.55 (C(2'')), 127.92 (C(4'')), 127.43 (C(3'')), 114.88 (C(3')), 69.90 (C(4')–O**C**H_2), 66.12 (C(1)), 54.14 (C(2)), 40.19 (C(3)).

Anal. Calcd. for $C_{16}H_{19}NO_2$ (M_r = 257.33): C 74.68, H 7.44, N 5.44 %; found: C 74.57, H 7.35, N 5.37 %.

General Procedure for Reduction of Benzylated Amino Acids

To the suspension of $NaBH_4$ (2.725 g, 30 mmol) in dry THF (79 mL), amino acid **7a,b** (30 mmol) was added in one portion with stirring (evolution of gas bubbles). Argon was introduced into the flask and the mixture was cooled to 0 °C. The solution of I_2 (7.614 g, 30 mmol) in dry THF (20 mL) was added dropwise very slowly, because of vigorous hydrogen evolution. After addition of iodine was completed and gas evolution had ceased, the solution was allowed to reach room temperature. Then the reaction mixture was heated to reflux for 3 hours and cooled to room temperature. Some methanol (15 mL) was added dropwise cautiously, with rapid stirring, until the mixture became clear (vigorous gas evolution). After stirring for 0.5 h, the solvents were evaporated leaving a pasty residue, which was dissolved in 20 % (mass fraction) KOH (59 mL). The mixture was stirred at room temperature for 3–4 h and extracted with CH_2Cl_2 (3 × 75 mL). The combined organic extracts were washed with water, dried ($MgSO_4$) and evaporated to give the crude product, which was purified by flash chromatography (CH_2Cl_2-MeOH 30:1 to 5:1) and recrystallization from EtOAc or EtOAc-petroleum ether.

Benzyl-tyrosinol **6c** was obtained in 66 % yield, while benzyloxy-phenylglycinol **6b** was obtained in 86 % crude yield (after chromatographic purification and recrystallization the yield was 65 %), with the same spectroscopic data and $[\alpha]_D$ as obtained by a previous method, *i.e.* **6b**: $[\alpha]_D$ = –26 (c = 1.01 g/100 mL, CH_2Cl_2) and **6c**: $[\alpha]_D$ = –20 (c = 1.02 g/100 mL, $CHCl_3$).

S-*Tyrosine Methyl Ester Hydrochloride (**8a**)*

$SOCl_2$ (8.0 mL, 13.09 g, 110 mmol) was added dropwise into dry MeOH (70 mL), cooled to –20 °C followed by addition of **3a** (18.2 g, 100 mmol). The clear solution was stirred 0.5 h in an ice-water bath, 2.5 h at room temperature and 0.5 h at reflux. The solvent was evaporated, the residue was slurried in ether (60 mL) and filtrated, washed with ether (4 × 15 mL) and air-dried: 23.0 g (99 %); m.p. 190–192 °C (lit.[18] m.p. 190 °C).

R-*4-Hydroxyphenylglycine Methyl Ester Hydrochloride (**8b**)*

It was prepared as described for compound **8a**, starting from **3b**, with 98 % yield.

N-*Benzyloxycarbonyl*-S-*tyrosine Methyl Ester (**9a**)*

To a solution of **8a** (23.2 g, 100 mmol) in water (25 mL) and CH_2Cl_2 (200 mL) cooled down to –10 °C at the same time, solutions of Na_2CO_3 (7.95 g, 75 mmol) in water (30 mL) and 50 % toluene solution of C_6H_5OCOCl (35.2 mL, 17.9 g, 105 mmol) were added dropwise during 15 min. Stirring was continued for 0.5 h in an ice-water bath and at room temperature overnight. Some undissolved material was removed, the layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (50 mL). The combined extracts were washed with water, dried ($MgSO_4$) and evaporated. The oily residue was stirred with petroleum ether (100 mL), the product was filtrated and dried: 30.0 g (91 %) of **9a**; m.p. 87–90 °C (lit.[19] m.p. 92–93 °C). ^{1}H NMR ($CDCl_3$) δ/ppm: 7.3 (s, 5H, Ph), 6.9 + 6.7 (2d, H(2') + H(3'), J = 8.2 Hz), 5.3 (d, 1H, –NH–, J = 8.2 Hz), 5.1 (s, C(4')–OCH_2), 4.6 (dd, 1H, C(2)H, J = 4.9, 12.8 Hz), 3.7 (s, –OCH_3), 3.0 (ddd, 2H, C(3)H, J = 5.6, 14.1, 24.1 Hz). ^{13}C NMR ($CDCl_3$) δ/ppm: 172.35 (–**C**$OOCH_3$), 155.88 (C(4')), 155.19 (–**C**OOBzl), 136.01 (C(1')), 130.29 (C(2')), 128.49 (C(2'')), 128.19 (C(3'')), 128.03 (C(4'')), 127.05 (C(1'')), 115.50 (C(3')), 66.98 (–O**C**H_2Ph), 54.80 (C(2)), 52.23 (–OCH_3), 37.19 (C(3)).

N-*Benzyloxycarbonyl*-R-*4-hydroxyphenylglycine Methyl Ester (**9b**)*

It was prepared as described for **20**, with 87 % yield; m.p. 107–110 °C. ^{1}H NMR ($CDCl_3$) δ/ppm: 7.3 (m, 5H, Ph), 7.2 + 6.7 (2d, H(2') + H(3'), J = 8.5 Hz), 5.9 (d, 1H, –NH–, J = 6.9 Hz, disappeared with D_2O), 5.3 (d, C(2)H, J = 6.7 Hz, with D_2O changed to s), 5.1 (d, C(4')–OCH_2, J = 4.4 Hz), 3.7 (s, 3H, –OCH_3). ^{13}C NMR ($CDCl_3$) δ/ppm: 171.69 (–**C**$OOCH_3$), 156.39 (C(4')), 155.60 (–**C**OOBzl), 135.86 (C(1')), 128.51 (C(1'')), 128.42 (C(2')), 128.25 (C(2'')), 128.12 (C(3''), 127.94 (C(4'')), 115.84 (C(3')), 67.17 (–O**C**H_2Ph), 57.23 (C(2)), 52.68 (–OCH_3).

N-*Benzyloxycarbonyl*-O-*methyl*-S-*tyrosine Methyl Ester (**10a**)*

Compound **9a** (6.6 g, 20 mmol) was stirred with anh. K_2CO_3 (13.82 g, 100 mmol) in acetone (90 mL) for 1 h, methyl iodide (12.5 mL, 28.4 g, 100 mmol) was added and heated to reflux for 2 h. Inorganic salts were removed; and the filtrate was evaporated to give the product **10a** (6.80 g, 99 %). It was used in the next step without any purification.

^{1}H NMR ($CDCl_3$) δ/ppm: 7.5 (s, 5H, Ph), 7.1 + 6.9 (2d, H(2') + H(3'), J = 8.5 Hz), 5.3 (d, 1H, –NH–, J = 8.2 Hz), 5.2 (d, 2H, C(4')–OCH_2, J = 2.6 Hz), 4.7 (dd, 1H, C(2)H, J = 5.9, 13.6 Hz), 3.9 and 3.8 (2 × s, –OCH_3), 3.2 (dd as t, 2H, C(3)H, J = 5.1 Hz).

General Procedure for tert-*Butyl Introduction*

Compound **9a,b** (17.5 mmol) was dissolved in CH_2Cl_2 (17.5–35 mL) and cooled below –15 °C. Isobutylene (35 mL), previously liquefied by keeping the container in a deep-freezer, and conc. H_2SO_4 (0.175 mL, 309 mg, 3.15 mmol) were added under stirring. The reaction flask was transferred into an autoclave and tightly closed. It was stirred at room temperature for three days. The autoclave was cooled in a deep-freezer, opened, and Et_3N (0.88 mL, 638 mg, 6.30 mmol) was added to the reaction mixture. The reaction mixture was then allowed to reach the room temperature, which took about 1 h. During that time, the excess of isobutylene evaporated. The mixture was diluted with CH_2Cl_2 (20 mL) and washed with water (3 × 10 mL), dried ($MgSO_4$) and evaporated. The residue was triturated with hot petroleum ether (4 × 30 mL). The unreacted starting material remained undissolved (32 % of **9a** and 57 % **9b**), while evaporation of petroleum ether extracts gave the crude products **10b** (66 %) and **10c** (34 %).

N-*Benzyloxycarbonyl*-O-tert-*butyl*-S-*tyrosine Methyl Ester (**10b**)*

M.p. 46–49 °C (lit.[19] m.p. 51–53.5 °C). ^{1}H NMR ($CDCl_3$) δ/ppm: 7.3 (s, 5H, Ph), 7.0 + 6.9 (2d, H(2') + H(3'), J = 8.5 Hz), 5.2 (d, 1H, –NH–, J = 7.9 Hz), 5.1 (s, C(4')–OCH_2), 4.6 (dd, 1H, C(2)H, J = 5.9, 13.8 Hz), 3.7 (s, –OCH_3), 3.1 (d, 2H, C(3)H, J = 4.1 Hz), 1.3 (s, 9H, *t*-Bu). ^{13}C NMR ($CDCl_3$) δ/ppm: 172.06 (–**C**$OOCH_3$), 155.63 (C(4')), 155.37, (–**C**OOBzl), 136.18 (C(1')), 130.32 (C(1'')), 129.65 (C(2')), 128.48 (C(2'')), 128.15 (C(4'')), 128.06 (C(3'')), 124.17 (C(3')), 78.31 (–**C**$(CH_3)_3$), 66.83 (–O**C**H_2Ph), 54.69 (C(2)), 52.06 (–OCH_3), 37.39 (C(3)), 28.60 (–OC(**C**$H_3)_3$).

N-*Benzyloxycarbonyl-4*-O-tert-*butoxy*-R-*phenylglycine Methyl Ester (**10c**)*

M.p. 110–112 °C. ^{1}H NMR ($CDCl_3$) δ/ppm: 7.3 (m, 5H, Ph), 7.2 + 7.0 (2d, H(2') + H(3'), J = 8.5Hz), 5.8 (d, 1H, –NH–, J = 6.9 Hz, disappeared with D_2O), 5.3 (d, C(2)H, J = 7.4 Hz, with D_2O changed to s), 5.1 (s, C(4')–OCH_2), 3.7 (s, 3H, –OCH_3), 1.3 (s, 9H, *t*-Bu). ^{13}C NMR ($CDCl_3$) δ/ppm: 171.50 (–**C**$OOCH_3$), 155.82 (C(4')), 155.37 (–**C**OOBzl), 136.09 (C(1')), 130.91 (C(1'')), 128.45 (C(2'') and (C(4'')), 128.12 (C(3''), 127.69 (C(2')), 124.14 (C(3')), 78.61 (–**C**$(CH_3)_3$), 66.94 (–O**C**H_2Ph), 57.22 (C(2)), 28.58 (–OC(**C**$H_3)_3$).

General Procedure for Hydrolysis

To a solution of methyl ester **10a–c** (6.731 mmol) in dioxane-water 4:1 (15 mL), 2 M NaOH (6.73 mL, 13.46 mmol) was added and stirred at room temperature for 0.5–1 h. The reaction mixture was partially evaporated, some water (10 mL) and EtOAc (25 mL) were added, cooled in an ice-water bath and acidified to pH = 2 with 2.5 M H_2SO_4, under stirring. The layers were separated, the aqueous layer was extracted with EtOAc (2 × 25 mL). Combined extracts were washed with water (3 × 5 mL), dried ($MgSO_4$) and evaporated to give the product **11a–c** in 98–100 % yield.

N-*Benzyloxycarbonyl*-O-*methyl*-S-*tyrosine (**11a**)*

Yield: 94 %; m.p. 112–114 °C. ^{1}H NMR ($CDCl_3$) δ/ppm: 9.6 (bs, –OH), 7.3 (m, 5H, Ph), 7.1 + 6.8 (2d, H(2') + H(3'), J = 8.2 Hz), 5.3 (d, 1H, –NH–, J = 8.0 Hz, disappeared with D_2O), 5.1 (d, 2H, C(4')–CH_2, J = 5.9 Hz), 4.6 (d, C(2)H, J = 6.2 Hz), 3.8 (s, 3H, –OCH_3), 3.2 (dd, C(1)Ha, J = 5.3, 14.1 Hz), 3.1 (dd, C(1)Hb, J = 5.3, 14.1 Hz). ^{13}C NMR ($CDCl_3$) δ/ppm: 176.36 (–COOH), 158.74 (C(4')), 156.00 (–**C**OOBzl), 136.09 (C(1')), 130.35 (C(2')), 128.51 (C(2'')), 128.22 (C(4'')), 128.09 (C(3''), 127.46 (C(1''), 114.04 (C(3')), 67.01 (–O**C**H_2Ph), 55.05 (–OCH_3), 54.68 (C(2)), 36.67 (C(3)).

N-*Benzyloxycarbonyl*-O-tert-*butyl*-S-*tyrosine (**11b**)*

Yield: 97%; m.p. 70–72 °C. ^{1}H NMR ($CDCl_3$) δ/ppm: 9.7 (bs, –OH), 7.3 (m, 5H, Ph), 7.0 + 6.9 (2d, H(2') + H(3'), J = 8.2 Hz), 5.4 (d, 1H, –NH–, J = 7.7 Hz), 5.0 (dd, C(4')–OCH_2), J = 2.3, 18,5 Hz), 4.6 (m, 1H, C(2)H), 3.1 (dd, 1H, C(1)Ha, J = 4.4, 9.5 Hz), 3.0 (dd, 1H, C(1)Hb, J = 7.2, 13.8 Hz), 1.3 (s, 9H, *t*-Bu). ^{13}C NMR ($CDCl_3$) δ/ppm: 176.01 (COOH), 156.06 (C(4')), 154.27 (–**C**OOBzl), 136.06 (C(1')), 130.63 (C(1'')), 129.75 (C(2')), 128.48 (C(2'')), 128.15 (C(4'')), 128.03 (C(3'')), 124.22 (C(3')), 78.51 (–**C**$(CH_3)_3$), 66.94 (–O**C**H_2Ph), 54.77 (C(2)), 36.81 (C(3)), 28.57 (–OC(**C**$H_3)_3$).

N-*Benzyloxycarbonyl-4*-O-tert-*butoxy-R-phenylglycine (**11c**)*

Yield: 98 %. ^{1}H NMR ($CDCl_3$) δ/ppm: 10.3 (bs, –OH), 7.3 (m, 5H, Ph), 7.3 + 7.0 (2d, H(2') + H(3'), J = 8.2 Hz), 5.8 (d, 1H, –NH–, J = 7.2 Hz, with D_2O disappeared), 5.3 (dd, 1H, C(2)H) J = 7.2, 37.9 Hz), 5.1 (d, C(4')–OCH_2, J = 3.3 Hz), 1.3 (s, 9H, *t*-Bu). ^{13}C NMR ($CDCl_3$) δ/ppm: 175.23 (COOH), 156.96 (C(4')), 155.48 (–**C**OOBzl), 130.34 (C(1')), 128.48 (C(1'')), 128.31 (C(2'')), 128.14 (C(4'')), 127.80 (C(2')), 127.49 (C(3'')), 124.23 (C(3')), 66.11 (–O**C**H_2Ph), 54.11 (C(2)), 28.57 (–OC(**C**$H_3)_3$).

N-*Benzyloxycarbonyl*-O-*methyl*-S-*tyrosinol (**12a**)*

It was prepared according to the general procedure for reduction of *N*-protected amino acids. M.p. 94–97 °C. ^{1}H NMR ($CDCl_3$) δ/ppm: 7.3 (m, 5H, Ph), 7.1 + 6.8 (2d, H(2') + H(3'), J = 8.2 Hz), 5.1 (s, C(4')–OCH_2), 5.0 (bs, 1H, –NH), 3.9 (m, 1H, C(2)H), 3.8(s, 3H, –CH_3), 3.7–3.6 (m, 2H, C(1)H), 2.8 (d, 2H, C(3)H, J = 6.7 Hz), 2.4 (bs, –OH). ^{13}C NMR ($CDCl_3$) δ/ppm: 158.33 (C(4')), 156.53 (–**C**OOBzl), 136.30 (C(1')), 130.18 (C(2')), 129.45 (C(1'')), 128.48 (C(2'')), 128.11 (C(4'')), 128.02 (C(3'')), 113.93 (C(3')), 66.66 (–O**C**H_2Ph), 63.78 (CH_2OH), 55.05 (–OCH_3), 54.05 (C(2)), 36.18 (C(3)).

N-*Benzyloxycarbonyl*-O-tert-*butyl*-S-*tyrosinol* ***(12b)***

It was prepared according to the general procedure for reduction of *N*-protected amino acids; oil. ^{1}H NMR ($CDCl_3$) δ/ppm: 7.3 (m, 5H, Ph), 7.1 + 6.9 (2d, H(2') + H(3'), J = 8.2 Hz), 5.1 (s, C(4')–OCH_2), 5.0 (s, 1H, –NH–), 3.9 (m, 1H, C(2)H), 3.7 (dd, 1H, C(1)Ha, J = 3.9, 11.5 Hz), 3.5 (dd, 1H, C(1)Hb, J = 4.6, 10.4 Hz), 2.8 (d, 2H, C(3)H, J = 6.9 Hz), 2.2 (bs, –OH), 1.3 (s, 9H, *t*-Bu). ^{13}C NMR ($CDCl_3$) δ/ppm: 155.54 (C(4')), 154.00 (–**C**OOBzl), 136.30 (C(1')), 132.30 (C(1'')), 129.62 (C(2')), 128.51 (C(2'')), 128.12 (C(4'')), 128.03 (C(3''), 124.26 (C(3')), 78.27 (–**C**$(CH_3)_3$), 66.71 (–O**C**H_2Ph), 63.80 (CH_2OH), 54.00 (C(2)), 36.44 (C(3)), 28.61 (–OC(**C**$H_3)_3$).

N-*Benzyloxycarbonyl-4*-O-tert-*butoxy*-R-*phenylglycinol* ***(12c)***

It was prepared according to the general procedure for reduction of *N*-protected amino acids. ^{1}H NMR ($CDCl_3$) δ/ppm: 7.3 (m, 5H, Ph), 7.2 + 6.9 (2d, H(2') + H(3'), J = 8.2 Hz), 5.6 (d, 1H, –NH–, J = 4.1 Hz), 5.1 (d, C(4')–OCH_2, J = 2.3 Hz), 4.8 (m, 1H, C(2)H), 3.8 (m, 2H, C(1)H), 2.5 (bs, 1H, –OH), 1.3 (s, 9H, *t*-Bu). ^{13}C NMR ($CDCl_3$) δ/ppm: 156.49 (C(4')), 154.94 (–**C**OOBzl), 136.21 (C(1')), 133.74 (C(1'')), 128.45 (C(2'') and (C(4'')), 128.11 (C(3''), 127.06 (C(2')), 124.19 (C(3')), 78.48 (–**C**$(CH_3)_3$), 66.83 (–O**C**H_2Ph), 66.20 (CH_2OH), 56.46 (C(2)), 28.57 (–OC(**C**$H_3)_3$).

O-*Methyl*-S-*tyrosinol* ***(6d)***

It was prepared according to the general procedure for hydrogenolytic deprotection. Yield: 100 %; m.p. 93–95 °C (EtOAc) (lit.[21] m.p. 99–100 °C). $[a]_D$ = –15 (c = 0.99 g/100 mL, CH_2Cl_2) (lit.[21] $[a]_D$ = –22 (c = 0.17 g/100 mL, 1M HCl)). UV(EtOH) λ_{max} / nm (log ε / mol^{-1} dm^3 cm^{-1}): 225 (3.83), 2785 (3.08), 284 (3.00). IR(KBr) ν_{max} / cm^{-1}: 3340 and 3180 (OH, NH_2), 1600 and 1580 (s, NH_2), 1250 (s, ether), 1180 (s, –CH_2OH). ^{1}H NMR ($CDCl_3$) δ/ppm: 7.1 + 6.8 (2d, H(2') + H(3'), J = 8.5 Hz), 3.8 (s, OCH_3), 3.6 (dd, C(1)Ha, J = 3.6, 10.8 Hz), 3.4 (dd, C(1)Hb, J = 7.2, 10.8 Hz), 3.1 (m, C(2)H), 2.75–2.7 (m, C(3)Ha + OH + NH_2), 2.45 (dd, C(3)Hb, J = 8.5, 13.6 Hz). ^{13}C NMR ($CDCl_3$) δ/ppm: 158.08 (C(4')), 130.40(C(1')), 129.98 (C(2')), 113.79 (C(3')), 65.54 (C(1)), 54.96 (C(2)), 54.03 (C(4')–O**C**H_3), 39.19 (C(3)).

O-tert-*Butyl*-S-*tyrosinol* ***(6e)***

It was prepared according to general procedure for hydrogenolytic deprotection. Yield: 96 %; m.p. 38–40 °C. $[\alpha]_D$ = –12 (c = 1.015 g/100 mL, CH_2Cl_2). UV(EtOH) λ_{max} / nm (log ε / mol^{-1} dm^3 cm^{-1}): 222 (3.65), 269 (2.70), 275 (2.69). IR(KBr ν_{max} / cm^{-1}: 3300 (s, OH, NH_2), 2980 (s, OCH_2), 1610 and 1550 (m, NH_2), 1235 (s, ether), 1160 (s, –CH_2OH). ^{1}H NMR ($CDCl_3$) δ/ppm: 7.1 + 6.9 (2d, H(2') + H(3'), J = 8.5 Hz), 3.64 (dd, C(1)Ha, J = 3.6, 10.8 Hz), 3.60 (dd, C(1)Hb, J = 7.4, 10.8 Hz), 3.1 (sept. C(2)H, J = 3.6 Hz), 2.7 (dd, C(3)Ha, J = 5.4, 13.6 Hz), 2.6 (s, OH + NH_2), 2.5 (dd, C(3)Hb, J = 8.5, 13.6 Hz), 1.3 (s, OC(CH_3)). ^{13}C NMR ($CDCl_3$) δ/ppm: 153.84 (C(4')), 133.20 (C(1')), 129.51 (C(2')), 124.25 (C(3')), 78.21 (–O**C**(CH_3)), 65.67 (C(1)), 54.03 (C(2)), 39.53 (C(3)), 28.53 (–OC(**C**H_3)). Analyzed as *N,O*-diacetyl derivative.

Anal. Calcd. for $C_{17}H_{25}NO_4$ (M_r = 307.39): C 66.43, H 8.20, N 4.56 %; found: C 66.24, H 8.35, N 4.70 %.

4-O-tert-*Butoxy*-R-*phenylglycinol* ***(6f)***

It was prepared according to the general procedure for hydrogenolytic deprotection. Yield: 87.5 %; m.p. 62–66 °C. $[\alpha]_D$ = –17 (c = 0.99 g/100 mL, CH_2Cl_2). UV(EtOH) λ_{max} / nm (log ε / mol^{-1} dm^3 cm^{-1}): 221 (4.07), 267 (2.85), 273 (2.84). IR(KBr ν_{max} / cm^{-1}: 3300 (s, OH, NH_2), 2980 (s, OCH_2), 1610 (m) and 1580 (s, NH_2), 1235 (s, C–O–C), 1040 (s, –CH_2OH). ^{1}H NMR ($CDCl_3$) δ/ppm: 7.2 + 6.9 (2d, H(2') + H(3'), J = 8.5 Hz), 4.0 (m, C(1)Ha + OH + NH_2)), 3.7–3.6 (m, C(1)Hb + C(2)H), 1.3 (s, OC(CH_3)). ^{13}C NMR ($CDCl_3$) δ/ppm: 154.91 (C(4')), 135.37 (C(1')), 127.20 (C(2')), 124.08 (C(3')), 78.38 (–O**C**(CH_3)), 66.67 (C(1)), 56.66 (C(2)), 28.55 (–OC(**C**H_3)).

Anal. Calcd. for $C_{12}H_{19}NO_2$ (M_r = 209.29): C 68.87, H 9.15, N 6.69 %; found: C 68.67, H 8.93, N 6.61 %.

Preparation of Bisoxazolines According to Scheme 4, Route a – *General Procedure*

Starting from alcohols **6c,d** and diethylmalonate (r = 1.0:1.2), on heating in anhydrous xylene (*ca*. 10 mL/mmol of alcohol) for 20 h, intermediary diamides **13c,d** were formed. To this solution, Me_2SnCl_2 (0.01 mol/2.0 mol of starting alcohol) was added and the mixture was heated under reflux for additional 24 h in a Dean-Stark apparatus (only in the case of **1d** intermediary **13d** was isolated). Xylene was then evaporated, the residue was dissolved in CH_2Cl_2, the organic layer was washed with water, concentrated and purified by flash chromatography.

*2,2'-Methylenebis(4*S*)-4-(4-benzyloxy)benzyl-4,5-dihydro-1,3-oxazole* ***(1c)***

Starting from *S*-benzyltyrosinol **6c** (2.06 g, 8.0 mmol) and diethylmalonate (0.64 g, 4.0 mmol) in the presence of Me_2SnCl_2 (88.0 mg, 0.04 mmol), after purification of the residue (2.4 g) by flash chromatography using CH_2Cl_2-MeOH (33:1), 1.26 g (58 %) of the white product **1c** was obtained. Analytical sample was obtained upon recrystallyzation from MeOH (834 mg); m.p. 103–105 °C. UV(MeOH) λ_{max} / nm (log ε / dm^3 mol^{-1} cm^{-1}): 278 (3.93), 226 (4.49), 208 (4.58). IR (KBr) ν_{max} / cm^{-1}: 1665 (s, O–C=N). ^{1}H NMR ($CDCl_3$) δ/ppm: 7.4–7.3 (m, 10H, H(2''), H(3'') + H(4'')), 7.1 (d, 4H, H(2'), J = 9.0 Hz), 6.9 (d, 4H, H(3'), J = 9.0 Hz), 5.0 (s, 4H, C(4')–OC**H**$_2$), 4.4–4.3 (m, 2H, H(4)), 4.2 (dd as t, 2H, H(5a), J = 9.0 Hz), 4.0 (dd as t, 2H, H(5b), J = 9.0 Hz), 3.3 (s, 2H, C(2)–C**H**$_2$), 3.0 (dd, 2H, C(4)–CHa, J = 14.0, 5.0 Hz), 2.6 (dd,, 2H, C(4)–CHb, J = 14.0, 8.0 Hz). ^{13}C NMR ($CDCl_3$) δ/ppm: 162.03 (C(2)), 157.51 (C(4')), 137.03 (C(1'')), 130.18 (C(2')), 130.00 (C(1')), 128.54, 127.89, 127.45 (C(2''), C(3'') and C(4'')), 114.81 (C(3')), 72.07

(C(5)), 69.86 (C(4')–O**C**H_2), 67.43 (C(4)), 40.38 (C(4)–**C**H_2), 28.17 (C(2)–**C**H_2).

Anal. Calcd. for $C_{35}H_{34}N_2O_4$ (M_r = 546.67): $[M+H]^+$ = 547.259134, found: $[M+H]^+$ = 547.251533.

*2,2'-Methylenebis(4*S*)-4-(4-methoxy)benzyl-4,5-dihydro-1,3-oxazole (**1d**)*

From aminoalcohol **3d** (340 mg, 1.87 mmol) and diethylmalonate (160 mg, 152 ml, 1.0 mmol) in dry xylene (15 mL), 95 mg (23 %) of diamide **13d** was obtained as white crystals from CH_2Cl_2-ether. From the isolated diamide **13d** (147 mg, 0.34 mmol) and Me_2SnCl_2 (11 mg, 0.05 mmol) under reflux in xylene (15 mL), pure **1d** was obtained as colorless oil (17 mg, 19 %) after purification by flash chromatography (CH_2Cl_2-MeOH, 96:4) and bulb to bulb distillation. The obtained oil slowly crystallized in refrigerator. ^{1}H NMR ($CDCl_3$) δ/ppm: 7.1 (d, 4H, H(2'), J = 9.0 Hz), 6.9 (d, 4H, H(3'), J = 9.0 Hz), 4.5–4.4 (m, 2H, H(4)), 4.3 (dd as t, 2H, H(5a), J = 9.0 Hz), 4.1 (dd as t, 2H, H(5b J = 9.0 Hz), 3.8 (s, 6H, C(4')–OCH3), 3.4 (s, 2H, C(2)–C**H$_2$**), 3.1 (dd, 2H, C(4)–Cha, J = 14.0, 5.0 Hz), 2.7 (dd, 2H, C(4)–CHb, J = 14.0, 8.0 Hz). ^{13}C NMR ($CDCl_3$) δ/ppm: 162.02 (C(2)), 158.29 (C(4')), 130.15 (C(2')), 129.69 (C(1')), 113.85 (C(3')), 72.05 (C(5)), 67.46 (C(4)), 55.05 (C(4')–O**C**H_3), 40.35 (C(4)–**C**H_2), 28.15 (C(2)–**C**H_2).

Preparation of Bisoxazolines According to Scheme 4, Route b *– General Procedure*

To a solution of amino alcohol **6b–f** (2.0 mmol) in dry CH_2Cl_2 (21.3 mL), under argon, cooled in an ice-water bath, 3-amino-3-ethoxyprop-2-en-imidate dihydrochloride (231 mg, 1.0 mmol) and Et_3N (0.56 mL, 405 mg, 4.0 mmol) were added. The reaction mixture was stirred at room temperature overnight. Precipitated NH_4Cl was removed, the filtrate was evaporated, and the residue was purified by preparative TLC (CH_2Cl_2-MeOH 19:1) or flash chromatography (first CH_2Cl_2-MeOH 40:1 then 20:1) to obtain bisoxazoline product.

*2,2'-Methylenebis(4*R*)-4-(4-benzyloxy)phenyl-4,5-dihydro-1,3-oxazole (**1b**)*

Yield: 63 %; m.p. 132–134 °C. $[\alpha]_D$ = +53 (c = 1.01 g/100 mL, CH_2Cl_2). UV(EtOH) λ_{max} / nm (log ε / mol^{-1} dm^3 cm^{-1}): 283 (3.70), 227 (4.30). IR(KBr) ν_{max} / cm^{-1}: 1660 (s, O–C=N). ^{1}H NMR ($CDCl_3$) δ/ppm: 7.4–7.3 (m, 10H, H(2'') + H(3'') + H(4'')), 7.2 (d, 4H, H(2'), J = 8.7 Hz), 6.9 (d, 4H, H(3'), J = 8.7 Hz), 5.2 (t, 2H, H(4), J = 8.5 Hz), 5.0 (s, 4H, C(4')–OCH2), 4.6 (dd as t, 2H, H(5a), J = 8.5 Hz), 4.1 (dd as t, 2H, H(5b), J = 8.5 Hz), 3.5 (s, 2H, C(2)–CH_2), ^{13}C NMR ($CDCl_3$) δ/ppm: 162.75 (C(2)), 158.23 (C(4')), 136.87 (C(1')), 134.43 (C(1'')), 128.48 (C(2'')), 127.86 (C(3'')), 127.77 (C(2')), 127.37 (C(4'')), 114.95 (C(3')), 75.22 (C(5)), 69.83 (C(4')–O**C**H_2), 69.03 (C(4)), 28.15 (C(2)–**C**H_2).

Anal. Calcd. for $C_{33}H_{30}N_2O_4$ (M_r = 518.61): C 76.43, H 5.83, N 5.40 %; found: C 76.62, H 5.71, N 5.39 %.

*2,2'-Methylenebis(4*S*)-4-(4-benzyloxy)benzyl-4,5-dihydro-1,3-oxazole (**1c**)*

Yield: 46 %; m.p. = 103–105 °C (MeOH). $[\alpha]_D$ = –38 (c = 1.10 g/100 mL, CH_2Cl_2). NMR and IR spectra correspond to the spectra of **1c** obtained according to route *a* (in Scheme 4). UV(EtOH) λ_{max} / nm (log ε / mol^{-1} dm^3 cm^{-1}): 278 (4.05), 226 (4.52).

Anal. Calcd. for $C_{35}H_{34}N_2O_4$ (M_r = 546.66): C 76.90, H.6.27, N 5.12 %; found: C 77.01, H 6.30, N 5.27 %.

*2,2'-Methylenebis(4*S*)-4-(4-methoxy)benzyl-4,5-dihydro-1,3-oxazole (**1d**)*

Yield: 55%; m.p. 112–114 °C (MeOH). $[\alpha]_D$ = -49 (c = 0.94 g/100 mL, CH_2Cl_2). NMR and IR spectra correspond to the spectra of **1d** obtained according to route *a* in Scheme 4. UV(EtOH) λ_{max} / nm (log ε / mol^{-1} dm^3 cm^{-1}): 278 (3.86), 225 (4.16).

Anal. Calcd. for $C_{22}H_{26}N_2O_4$ (M_r = 394.46): C 69.09, H 6.85, N 7.32 %; found: C 69.27, H 6.81, N 7.17 %.

*2,2'-Methylenebis(4*S*)-4-(4-tert-butoxy)benzyl-4,5-dihydro-1,3-oxazole (**1e**)*

Colorless oil, yield: 79 %. $[\alpha]_D$ = –36 (c = 1.05 g/100 mL, CH_2Cl_2). UV(EtOH) λ_{max} / nm (log ε / mol^{-1} dm^3 cm^{-1}): 279 (3.81), 221 (4.19). IR(KBr) ν_{max} / cm^{-1}: 1660 (s, O–C=N). ^{1}H NMR ($CDCl_3$) δ/ppm: 7.1 (d, 4H, H(2'), J = 8.5 Hz), 6.9 (d, 4H, H(3'), J = 8.5 Hz), 4.4 (m, 2H, H(4)), 4.2 (t, H(5a), J = 8.7 Hz), 4.0 (t, H(5b), J = 8.2 Hz), 3.3 (s, 2H, C(2)–CH_2), 3.1 (dd, 2H, C(4)–CHa, J = 13.8, 5.4 Hz), 2.6 (dd, 2H, C(4)–CHb, J = 13.8, 8.5 Hz), 1.3 (s, 18H, C(4')–OC$(CH_3)_3$). ^{13}C NMR ($CDCl_3$) δ/ppm: 162.06 (C(2)), 153.88 (C(4')), 132.48 (C(1')), 129.51 (C(2')), 124.11 (C(3')), 78.10 (C(4')–O**C**$(CH_3)_3$), 72.12 (C(5)), 67.27 (C(4)), 40.56 (C(4)–**C**H_2), 28.57 (C(4')–OC(**C**$H_3)_3$), 28.09 (C(2)–**C**H_2).

Anal. Calcd. for $C_{29}H_{38}N_2O_4$ (M_r = 478.63): C 72.77, H 8.00, N 5.85 %; found: C 72.75, H 8.06, N 5.82 %.

*2,2'-Methylenebis(4*R*)-4-(4-tert-butoxy)phenyl-4,5-dihydro-1,3-oxazole (**1f**)*

Colorless oil, yield: 60 %. $[\alpha]_D$ = +33 (c = 0.96 g/100 mL, CH_2Cl_2). IR(KBr) ν_{max} / cm^{-1}: 1660 (s, O–C=N); UV(EtOH) λ_{max} / nm (log ε / mol^{-1} dm^3 cm^{-1}): 283 (3.64), 220 (3.88). ^{1}H NMR: 7.2 (d, 4H, H(2'), J = 8.5 Hz), 6.9 (d, 4H, H(3'), J = 8.5 Hz,), 5.2 (dd as t, 2H, H(4), J = 8.7 Hz), 4.7 (dd, 2H, H(5a), J = 10.0, 8.7 Hz,), 4.2 (t, 2H, H(5b), J = 8.2 Hz,), 3.6 (s, 2H, C(2)–CH_2), 1.3 (s, 18H, C(4')–OC$(CH_3)_3$). ^{13}C NMR ($CDCl_3$) δ/ppm: 162.85 (C(2)), 154.79 (C(4')), 136.75 (C(1')), 127.14 (C(2')), 124.34 (C(3')), 78.33 (C(4')–O**C**$(CH_3)_3$), 75.47 (C(5)), 69.13 (C(4)), 28.55 (C(4')–OC(**C**$H_3)_3$), 28.17 (C(2)–**C**H_2).

Anal. Calcd. for $C_{27}H_{34}N_2O_4$ (M_r = 450.58): C 71.97, H 7.61, N 6.22 %; found: C 72.08, H 7.58, N 6.10 %.

N*1,*N*3-di{(1*R*)-1-[4-(benzyloxy)phenyl]-2-hydroxyethyl}-2,2-diethylmalonamide (**14b**)*

To a solution of amino alcohol **6b** (5.84 g, 24 mmol) and distilled Et_3N (8.4 mL, 60 mmol) in dry CH_2Cl_2 (60 mL) cooled to 0 °C, a solution of diethylmalonyl dichloride (2.2 mL, 13.2 mmol) in CH_2Cl_2 (6.0 mL) was added. The reaction mixture was allowed to warm to room temperature and was stirred for another 1 h. Crystalline product was separated by filtration, carefully washed with chloroform in order to remove $Et_3N \cdot HCl$, and 4.25 g (58 %) of **14b** was obtained, m.p. 177–179 °C. Mother liquor was poured into a saturated aqueous NH_4Cl solution (100 mL). The organic layer was removed and the aqueous phase was extracted with CH_2Cl_2. Combined organic layers were successively washed with 1 M HCl, saturated aqueous $NaHCO_3$, and brine, dried (Na_2SO_4), filtered, and concentrated to afford additional 2.02 g (28 %) of the product. Total yield: 6.27 g, (86 %). Analytical sample was obtained by recrystallization from MeOH, m.p. 179–180 °C. $[\alpha]_D = -74$ (c = 0.50 g/100 mL, MeOH). IR(KBr) ν_{max} / cm^{-1}: 3330 (s, NH and OH), 1660 (s, CONH, amide I), 1615 (m) and 1510 (s, CONH, amide II). ^{1}H NMR ($CDCl_3$) δ/ppm: 8.8 (d, J = 8.0 Hz, 2H, NH), 7.5–7.3 (m, 10H, H(2''), H(3'') + H(4'')), 7.2 (d, 4H, H(2'), J = 8.5 Hz), 6.9 (d, 4H, H(3'), J = 8.5 Hz,), 5.1 (s, 4H, C(4')–OC**H**$_2$), 4.8–4.9 (m, 4H, H(1) + OH), 3.6–3.5 (m, 4H, H(2)), 1.9 (q, 4H, CO–C–C**H**$_2$, J = 7.0 Hz,), 0.6 (t, 6H, CO–C–CH$_2$–C**H**$_3$, J = 7.0 Hz,). ^{13}C NMR ($CDCl_3$) δ/ppm: 172.79 (CO), 157.56 (C(4')), 137.46 (C(1'')), 133.73 (C(1')), 128.70, 128.24, 128.07, 127.93 (C(2'), C(2''), C(3'') and C(4'')), 114.55 (C(3')), 69.32 (C(4')–O**C**H$_2$), 64.70 (C(2)), 57.58 (CO–**C**), 54.72 (C(1)), 29.34 (CO–C–**C**H$_2$), 9.31 (CO–C–CH$_2$–**C**H$_3$).

Anal. Calcd. for $C_{37}H_{42}N_2O_6$ (M_r = 610.72): C 72.76, H 6.93, N 4.59 %; found: C 72.72, H 6.79, N 4.66 %.

N*1,*N*3-di{(1*S*)-1-[4-(benzyloxy)benzyl]-2-hydroxyethyl}-2,2-diethylmalonamide (**14c**)*

Using the procedure described for **14b,** starting from amino alcohol **6c** (4.12 g, 16 mmol), Et_3N (5.6 mL, 40 mmol), CH_2Cl_2 (40 mL) and diethylmalonyl dichloride (1.5 mL, 8.8 mmol) in CH_2Cl_2 (4.0 mL), the reaction mixture was obtained, which was diluted with CH_2Cl_2 (40 mL). The procedure described for mother liquor of **14b** yielded 4 g (78 %) of **14c**, as the solid colorless residue, on recrystallization from ether, m.p. 117–118 °C. $[\alpha]_D = -26$ (c = 1.00 g/100 mL, CH_3OH). IR(KBr) ν_{max} / cm^{-1}: 3330 (m, br, NH and OH), 1655 (m, CONH, amide I), 1615 (m) and 1515 (s, CONH, amide II). ^{1}H NMR ($CDCl_3$) δ/ppm: 7.4–7.3 (m, 10H, H(2''), H(3'') + H(4'')), 7.1 (d, 4H, H(2'), J = 8.5 Hz), 6.9 (d, 4H, H(3'), J = 8.5 Hz), 6.7 (d, 2H, NH, J = 8.0 Hz), 5.0 (s, 4H, C(4')–OC**H**$_2$), 4.2 (br s, 2H, H(1)), 3.7 (dd, 2H, H(2a), J = 11.0, 3.5 Hz), 3.5 (dd, 2H, H(2b), J = 11.0, 6.0 Hz), 2.8 (dd, 2H, C(1)–CHa, J = 14.0, 6.0 Hz), 2.6 (dd, 2H, C(1)–CHb J = 14.0, 9.0 Hz), 1.7–1.6 (m, 4H, CO–C–C**H**$_2$,), 0.5 (t, 6H, CO–C–CH$_2$–C**H**$_3$, J = 7.0 Hz). ^{13}C NMR ($CDCl_3$) δ/ppm: 173.36 (CO), 157.59 (C(4')), 136.93 (C(1'')), 130.00, 129.75 (C(1') and C(2')), 128.49, 127.85, 127.32 (C(2''), C(3'') and C(4'')), 114.91 (C(3')), 69.83 (C(4')–O**C**H2), 64.35 (C(2)), 58.05 (CO–**C**), 52.73 (C(1)), 35.86 (C(1)–**C**H$_2$), 26.49 (CO–C–**C**H$_2$), 8.00 (CO–C–CH$_2$–**C**H$_2$).

Anal. Calcd. for $C_{39}H_{46}N_2O_6$ (M_r = 638.75): C 73.33, H 7.25, N 4.39 %; found: C 73.28, H 7.25, N 4.46 %.

N*1,*N*3-di{(1*R*)1-[4-(benzyloxy)phenyl]-2-chloroethyl}-2,2-diethylmalonamide (**15b**)*

To a stirred solution of triphenylphosphine (1.67 g, 6.37 mmol) in dry CH_2Cl_2 (20 mL) at 0 °C, triphosgene (0.59 g, 2.125 mmol) was added portionwise over a period of 5 min. After vigorous gas evolution had subsided, the mixture was stirred for another 5 min, and then the solution of diamide **14b** (1.53 g, 2.5 mmol) in dry CH_2Cl_2 (60 mL) was added dropwise and the mixture was stirred for 1 h. at room temperature. The reaction mixture was washed with water, the organic phase was dried (Na_2SO_4), filtered, and concentrated. Purification of the residue (3.54 g) by flash chromatography on 70 g silica gel using CH_2Cl_2-MeOH (99:1) provided 1.33 g (82 %) of the white product; m.p. 146–148 °C (CH_2Cl_2-ether). $[\alpha]_D = -3.1$ (c = 1.00 g/100 mL, CH_2Cl_2). IR(KBr) ν_{max} / cm^{-1}: 3305 (m, br, NH and OH), 1665 (s) and 1635 (s, CONH, amide I), 1615 (s) and 1510 (s, CONH, amide II). ^{1}H NMR ($CDCl_3$) δ/ppm: 7.9 (d, 2H, NH, J = 8.0 Hz), 7.4–7.3 (m, 10H, H(2'') + H(3'') + H(4'')), 7.2 (d, J = 8.0 Hz), 6.9 (d, 4H, H(3'), J = 8.0 Hz), 5.4–5.3 (m, 2H, H(1)), 5.0 (s, 4H, C(4')–OC**H**$_2$), 3.9–3.7 (m, 4H, H(2)), 2.0 (q, 4H, CO–C–C**H**$_2$, J = 7.0 Hz), 0.9 (t, J = 7.0 Hz, 6H, CO–C–CH$_2$–C**H**$_3$). ^{13}C NMR ($CDCl_3$) δ/ppm: 172.70 (CO), 158.56 (C(4')), 136.70 (C(1'')), 130.77 (C(1')), 128.54, 127.97, 127.42 (C(2''), C(3'') and C(4'')), 127.72 (C(2')), 114.99 (C(3')), 69.86 (C(4')–O**C**H2), 58.11 (CO–**C**), 53.36 (C(1)), 47.37 (C(2)), 30.50 (CO–C–**C**H$_2$), 9.16 (CO–C–CH$_2$–**C**H$_3$).

Anal. Calcd. for $C_{37}H_{40}N_2O_4Cl_2$ (M_r = 647.62): C 68.62, H 6.23, N 4.33 %; found: C 68.72, H 6,47, N 4.26 %.

N*1,*N*3-di{(1*S*)-1-[4-(benzyloxy)benzyl]-2-chloroethyl}-2,2-diethylmalonamide (**15c**)*

Following the procedure described for **15b,** starting from triphenylphosphine (1.67 g, 6.37 mmol) in dry CH_2Cl_2 (10 mL), triphosgene (0.64 g, 2.125 mmol) and diamide **14c** (1.72 g, 2.7 mmol) in dry CH_2Cl_2 (20 mL), 1.62 g (89 %) of the white product **15c** was obtained, m.p. 124–126 °C (EtOH). $[\alpha]_D = -26$ (c = 1.00 g/100 mL, $CHCl_3$). IR(KBr) ν_{max} / cm^{-1}: 3305 (s, br, NH and OH), 1635 (s, br, CONH, amide I), 1580 (m) and 1510 (s, CONH, amide II). ^{1}H NMR ($CDCl_3$) δ/ppm: 7.4–7.3 (m, 12H, NH, H(2'') + H(3'') + H(4'')), 7.1 (d, 4H, H(2'), J = 9.0 Hz), 6.9 (d, 4H, H(3'), J = 9.0 Hz), 5.0 (s, 4H C(4')–OC**H**$_2$), 4.5–4.4 (m, 2H, H(1)), 3.6 (dd, 2H, H(2a), J = 11.0, 4.0 Hz), 3.5 (dd, 2H, H(2b), J = 11.0, 4.0 Hz), 2.8–2.7 (m, 4H, C(1)–CH$_2$) 1.8–1.7 (m, 4H, CO–C–C**H**$_2$), 0.7 (t, 6H, CO–C–CH$_2$–C**H**$_3$, J = 7.0 Hz). ^{13}C NMR ($CDCl_3$) δ/ppm: 172.58 (CO), 157.80 (C(4')), 136.93 (C(1'')), 130.15 (C(2')), 129.06 (C(1')), 128.52, 127.91, 127.37 (C(2''), C(3'') and C(4'')), 115.02 (C(3')), 69.86 (C(4')–O**C**H$_2$), 57.91 (CO–**C**), 50.79 (C(1)), 46.45

(C(2)), 36.43 (C(1)–**C**H_2)), 30.50 (CO–C–**C**H_2), 9.16 (CO–C–CH_2–**C**H_3).

Anal. Calcd. for $C_{39}H_{44}N_2O_4Cl_2$ (M_r = 675.67): C 69.32, H 6.56, N 4.15 %; found: C 69.46, H 6.52, N 4.22 %.

*2,2'-(1-Ethylpropylidene)bis[(4*R*)-4-(4-benzyloxy)phenyl-4,5-dihydro-1,3 oxazole] (**2b**)*

Method A. – A solution of dichlorodiamide **15b** (129.5 mg, 0.2 mmol) in methanolic NaOH (0.5 M, 2 mL) was refluxed for 3 h. The reaction mixture was evaporated, the residue was extracted with CH_2Cl_2, washed with water, the organic phase was dried (Na_2SO_4), filtered, and concentrated. The mixture was purified by flash chromatography on 15 g silica gel using CH_2Cl_2-MeOH (98:2) to afford 89 mg (77 %) of product **2b**; m.p. 116–117 °C (diisopropylether). $[\alpha]_D$ = +168.3 (c = 1.00 g/100 mL, CH_2Cl_2).

Method B. – To the solution of dichlorodiamide **15b** (129.5 mg, 0.2 mmol) in dry toluene (3.5 mL), Et_3N (0.25 mL) was added and the mixture was refluxed for 18 h. After cooling to room temperature, ethyl acetate (5.0 mL) was added and the resulting mixture was washed with a saturated solution of $NaHCO_3$. The organic layer was separated, and the aqueous layer was washed with ethyl acetate (3 × 5 mL). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4 and the solvent was removed under reduced pressure. Purification of the residue (107 mg) by flash chromatography on 15 g silica gel using CH_2Cl_2-MeOH (98:2) provided 81.9 mg (71 %) of **2b**; m.p. 116–117 °C (diisopropylether). $[\alpha]_D$ = +169.6 (c = 1.00 g/100 mL, CH_2Cl_2). IR(KBr) ν_{max} / cm^{-1}: 1655 (s, O–C=N). UV(MeOH) λ_{max}/nm (log ε / mol^{-1} dm^3 cm^{-1}): 283 (2.49), 276 (3.56), 226 (4.43), 213 (4.42). ^{1}H NMR ($CDCl_3$) δ/ppm: 7.4–7.3 (m, 10H, H(2''), H(3'') + H(4'')), 7.2 (d, 4H, H(2'), J = 9.0 Hz), 6.9 (d, 4H, H(3'), J = 9.0 Hz), 5.2 (t, 2H, H(4), J = 8.0 Hz), 5.0 (s, 4H, C(4')–OC**H**$_2$), 4.6 (dd as t, 2H, H(5a), J = 8.0 Hz), 4.1 (dd as t, 2H, H(5b), J = 8.0 Hz), 2.2–2.0 (m, 4H, C(2)–C–C**H**$_2$), 0.9 (t, 6H, C(2)–C–CH_2–C**H**$_3$, J = 8.0 Hz). ^{13}C NMR ($CDCl_3$) δ/ppm: 168.64 (C(2)), 158.25 (C(4')), 136.98 (C(1'')), 134.87 (C(1')), 127.89 (C(2')), 128.52, 127.40 (C(2''), and C(3'')) 127.89 C(4'')), 114.96 (C(3')), 74.88 (C(5)), 69.87 (C(4')–O**C**H_2), 68.93 (C(4)), 46.74 (C(2)–**C**), 25.34 (C(2)–C–**C**H_2), 8.28 (C(2)–C–CH_2–**C**H_3).

Anal. Calcd. for $C_{37}H_{38}N_2O_4$ (M_r = 574.69): C 77.32, H 6.66, N 4.87 %; found: C 77.35, H 6.49, N 4.89 %.

*2,2'-(1-Ethylpropylidene)bis[(4*S*)-4-(4-benzyloxy)benzyl-4,5-dihydro-1,3-oxazole] (**2c**)*

Following method A, 192 mg (80 %) of **2c** as colourless oil was obtained from dichlorodiamide **15c** (270 mg, 0.4 mmol) in methanolic NaOH (0.5 M, 4 mL). $[\alpha]_D$ = –47.3 (c = 0.91 g/100 mL, CH_2Cl_2).

Using method B, from dichlorodiamide **15c** (270 mg, 0.4 mmol) in dry toluene (10 mL) and Et_3N (0.7 mL), 222 mg (92 %) of **2c** was obtained. $[\alpha]_D$ = –44.9 (c = 1.00 g/100 mL, CH_2Cl_2). UV(MeOH) λ_{max}/nm (log ε / mol^{-1} dm^3 cm^{-1}): 283 (2.49), 276 (3.57), 236 (Abs>3). IR(KBr) ν_{max} / cm^{-1}: 1650 (s, O–C=N). ^{1}H NMR ($CDCl_3$) δ/ppm: 7.4–7.3 (m, 10H, H(2'') + H(3'') + H(4'')), 7.1 (d, 4H, H(2'), J = 9.0 Hz), 6.9 (d, 4H, H(3'), J = 9.0 Hz), 5.0 (s, 4H, C(4')–OC**H**$_2$), 4.4–4.3 (m, 2H, H(4)), 4.1 (dd as t, 2H, H(5a), J = 9.0 Hz,, 3.9 (dd as t, 2H, H(5b), J = 9.0 Hz), 3.1 (dd, 2H, C(4)–CHa, J = 14.0, 5.0 Hz), 2.6 (dd, 2H, C(4)–CHb, J = 14.0, 9.0 Hz), 1.9 (q, 4H, C(2)–C–C**H**$_2$, J = 7.0 Hz), 0.8 (t, 6H, C(2)–C–CH_2–C**H**$_3$, J = 7.0 Hz). ^{13}C NMR ($CDCl_3$) δ/ppm: 167.78 (C(2)), 157.43 (C(4')), 136.99 (C(1'')), 130.24 (C(2')), 130.11 (C(1')), 128.48, 127.35, (C(2''), and C(3'')), 127.83 C(4'')), 114.73 (C(3')), 71.39 (C(5)), 69.78 (C(4')–O**C**H_2), 67.17 (C(4)), 40.50 (C(4)–**C**H_2), 46.33 (C(2)–**C**), 25.09 (C(2)–C–**C**H_2), 8.02 (C(2)–C–CH_2–**C**H_3).

Anal. Calcd. for $C_{39}H_{42}N_2O_4$ (M_r = 602.74): C 77.71, H 7.02, N 4.65 %; found: C 77.61, H 7.12, N 4.54 %.

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SAŽETAK

Sinteze aminoalkohola i kiralnih C_2-simetričnih bisoksazolina izvedenih od *O*-alkiliranih *R*-4-hidroksifenilglicina i *S*-tirozinola

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Pripravljena je serija kiralnih C_2-simetričnih bisoksazolina **1b–1f** i **2b,c**, izvedenih od 4'-*O*-alkiliranih *R*-4-hidroksifenilglicina ili *S*-tirozina. Kao intermedijari pripravljeni su i karakterizirani aminoalkoholi sa supstituiranom fenolnom skupinom.