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

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INTRODUCTION

Chiral amino alcohols are important synthetic intermediates in asymmetric synthesis, peptide and pharmaceutical chemistry, and resolution of racemic mixtures. They are also useful in the synthesis of peptide aldehydes, which are potent inhibitors of proteases. 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.5a–c

Recently, amino alcohols possessing the phenolic group were needed in our laboratory as precursors for chiral cavity containing bisoxazolines4 (Chart 1), designed for enantioselective control of metal-catalyzed reactions.5a–d 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. It was observed that the defined topology of some organometallic catalytic complexes of monodentate nitrogen ligands5b or bidentate $C_1$-symmetric ligands led to an enhancement of enantioselectivity when topology became restricted by repulsive,5b–c or attracting $\pi-\pi$ 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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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 NaBH4/H2SO4 in THF to amino alcohol, as described for phenylglycine, 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\( \text{8a} \) (Scheme 1), which can be successfully reduced with sodium borohydride in methanol via mixed anhydride (N-methylmorpholine; ethyl chloroformate in tetrahydrofurane) to N-protected amino alcohol 5a. We modified the procedure by removing N-methylmorpholine hydrochloride, thereby avoiding formation of the N-methylmorpholine-NaBH4 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-benzyloxy-carbonyl tyrosine using NaBH4/LiI in dry tetrahydrofurane.\( ^{10} \)

Hydrogenolytic cleavage of benzyloxy-carbonyl group provided S-tyrosinol 6a, which after acetylation (Ac2O; pyridine) gave the triacetylated product identical to that described.\( ^{11} \)

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 CuII-complexes of 3a and 3b by treatment with benzylbromide in alkaline medium in 63–73 % and 58–63 % yield, respectively. The recently introduced reduction method, by NaBH4 and iodine in THF, followed by the treatment with KOH 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,
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. 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. The variant using \( N\)-methylmorpholine and isobutyl chloroformate in 1,2-dimethoxyethane described for 4c 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 \( NaBH_4 \). BOC-Deprotection in 5b and 5c was attempted at first by the commonly used deprotection procedure (TFA), 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 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\( \rightarrow \)7a,b \( \rightarrow \)4b,c \( \rightarrow \)5b,c \( \rightarrow \)6b,c were identical to those obtained by pathway 3a,b \( \rightarrow \)7a,b \( \rightarrow \)6b,c, indicating the same optical purity of the obtained products, i.e.: \( [\alpha]_D = -26^\circ \) for 6b and \( [\alpha]_D = -20^\circ \) for 6c.

Easily removable \( O\)-benzyl group makes the prepared products useful precursors of various bisoxazoline derivatives, 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 \( N\)-benzyloxy carbonyl protected amino acid methyl ester (Scheme 3). \( S\)-Tyrosine methyl ester 8a was prepared 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 benzyloxy carbonyl protecting group was introduced in 87–89% yield to give benzyloxy carbonyl-\( S\)-tyrosine methyl ester (9a) and benzyloxy carbonyl-\( R\)-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 in an autoclave; after three days at room temperature, benzyloxy carbonyl-\( O\)-tert-butyl-\( S\)-ty-
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 benzoylcarbonyl-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 H2SO4 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 benzoylcarbonyl 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 12a–c 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 LiAlH4 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 dimethylthionym chloride 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, 1H 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 triphosgene/triphenylphosphine25a,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.
lic solution of NaOH\textsuperscript{24} or triethylamine in toluene,\textsuperscript{26} both giving products of identical optical purity.

The prepared bisoxazolines served as bidentate ligands for metal-catalyzed enantioselective transformations (Cu\textsuperscript{I}-complex catalyzed cyclopropanation of styrene with ethyl diazoacetate and Pd\textsuperscript{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\textsubscript{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\textsubscript{254} plates and column chromatography was carried out with 230–240 mesh Merck 60 silica gel. \textsuperscript{1}H and \textsuperscript{13}C NMR spectra were recorded on the Varian Gemini 3000 spectrometer with tetramethylsilane as an internal standard at 300 MHz, in CDCl\textsubscript{3} unless otherwise stated. Chemical shifts (\delta) were given in ppm, J in Hz. IR spectra were taken in KBr pellets on a Perkin Elmer 297 spectrometer, \nu given in cm\textsuperscript{-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\textsubscript{max} in nm (log \varepsilon in mol\textsuperscript{-1} dm\textsuperscript{3} cm\textsuperscript{-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\textsubscript{254} plates and spots were made visible using a UV lamp (254 nm) or I\textsubscript{2} vapors, in CH\textsubscript{2}Cl\textsubscript{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 Extrel FTMS 2001-DD Fourier Transform Mass Spectrometer (Madison, WI, USA) equipped with a 3 T superconducting magnet and a Nicolet 1280 Data Station.

\textbf{N-Benzoylcarboxamidem-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 benzoylcarbonylchloride (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

\begin{align*}
\text{BzO} & \quad \text{CH}_2\text{OH} \\
\text{Et}_3\text{N} & \quad \text{Cl} \\
\text{(COCl)}_3 & \quad \text{PPh}_3 \\
\text{BzO} & \quad \text{BzO} \\
\text{2b} & \quad n = 0 \\
\text{2c} & \quad n = 1 \\
\text{6b} & \quad n = 0 \\
\text{6c} & \quad n = 1 \\
\to & \quad \text{Cl} \\
\text{Cl} & \quad \text{Et} \\
\text{OH} & \quad \text{OH} \\
\text{Et} & \quad \text{Et} \\
\text{HO} & \quad \text{NH} \\
\text{NH} & \quad \text{HO} \\
\text{BzO} & \quad \text{OBz} \\
\text{14b} & \quad n = 0 \\
\text{14c} & \quad n = 1 \\
\text{Cl} & \quad \text{Cl} \\
\text{Cl} & \quad \text{Cl} \\
\text{BzO} & \quad \text{BzO} \\
\text{OBz} & \quad \text{OBz} \\
\text{15b} & \quad n = 0 \\
\text{15c} & \quad n = 1 \\
\text{Cl} & \quad \text{Cl} \\
\text{Cl} & \quad \text{Cl} \\
\text{BzO} & \quad \text{BzO} \\
\text{OBz} & \quad \text{OBz} \\
\text{15b} & \quad n = 0 \\
\text{15c} & \quad n = 1 \\
\end{align*}
was extracted into EtOAc and purified by flash-chromatography (CH2Cl2-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.28 m.p. 95–90 °C) and dissubstituted product (1.229 g, 27 %). 1H NMR (acetone-d6): 7.1 + 6.7 (2d, H(2') + H(3')), J = 8.35 Hz), 3.8 (t, 1H, C(1)H), 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). 13C NMR (acetone-d6): 156.33 (C(4')), 130.71 (C(1'))), 130.14 (C(2')), 115.52 (C(3')). 70.38 (–CH2OH), 59.93 (C(2)), 38.41 (C(3)).

**N,O,O-Triacetyl-S-tyrosinol.** It was prepared with Ac2O in pyridine at room temperature overnight, m.p. 115–118 °C (lit.10 m.p. 118–119 °C). 1H NMR (CDCl3) 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). 13C 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 (–CH2OH), 49.08 (C(2)), 36.38 (C(3)), 22.80, 20.68 and 20.37 (3 × –OCH3).

**General Procedure for Benzylaition 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 CuSO4·5H2O (6.24 g, 25.0 mmol) in water (25 mL) were added under stirring. 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 (125 mL) and treated with 1 M HCl (100 mL) to remove HCl, again washed with water (125 mL) and acetone (60 mL), and dried.

**S-Tyrosinol (6a)**

It was prepared by the general procedure for hydrogencolytic deprotection. Yield: 95.5 %. 1H NMR (acetone-d6): 7.3–3.6 (2003) (20 mL). Into the cold filtrate NaBH4 (568 mg, 15.0 mmol) was filtrated into the cooled flask and washed with dry THF (20 mL). The solvent was partially evaporated, some water 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 (MgSO4) and evaporated. Alcohols 5a–c, 12a–c were obtained in 85–90 % yield.

**N-Benzylxy carbonyl-S-tyrosinol (5a)**

It was prepared according to the general procedure for reduction of N-protected amino acids. Yield: 84.5 %. 1H NMR (acetone-d6) 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')–OCH2), 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). 13C NMR (acetone-d6) δ/ppm: 156.00 (C(4')), 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 (–OCH2Ph), 63.17 (–CH2OH), 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 H2 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 CH2Cl2-MeOH 25:1 and 10:1) (6a, t-Bu-derivatives 6e,f).

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

Yield: 73 %; m.p. 216–220 °C (lit.12 m.p. 223 °C). 1H NMR (CDCl3) δ/ppm: 7.2–6.9 (m, 9H, Ph), 5.0 (s, C(4')–OCH2), 4.4 (m, 1H, C(2)H), 3.4–3.1 (m, 2H, C(3)H), 2.8 (d, 1H, C(3)Hb, J = 13.2 Hz), 2.5 (dd, 1H, C(3)Ha, J = 8.3 Hz), 2.3–2.1 (3s, 3 × 3H, –Ac). 13C NMR (CDCl3) δ/ppm: 175.07 (–COOH), 162.63 (C(4')), 137.01 (C(1')), 133.05 (C(2')), 131.33 (C(1')'), 131.08 (C(3')'), 128.31 (C(4')'), 119.32 (C(3')'), 74.81 (C(4')–OCH2), 58.00 (C(2)), 36.99 (C(3)).

**4-O-Benzylxy-R-phenylglycine (7b)**

Yield: 67 %; m.p. 214–216 °C. 1H NMR (CDCl3) δ/ppm: 7.2–6.9 (m, 9H, Ph), 5.2 (m, 1H, C(2)H), 5.0 (s, C(4')–OCH2). 13C NMR (CDCl3) 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')–OCH2), 59.98 (C(2)).
General Procedure for BOC-protection of Benzylated Amino Acids

To the crude 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 NaHCO₃ (2.445 g, 29.1 mmol) were added. To the reaction mixture cooled in ice-water, (BOC₂)O (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, extracted with EtOAc (2 × 30 mL), combined extracts were washed with water, dried (MgSO₄), and evaporated to give the BOC-protected amino acids 4b,c in 92–98 % yield.

4-O-Benzoyloxy-N-tert-butoxycarbonyl-R-phenylglycine (4b)

A thick oil. Yield: 92 %. ¹H NMR (CDCl₃) 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')–OCH₂), 1.5 (s, 9H, t-Bu). ¹³C NMR (CDCl₃) δ/ppm: 173.56 (–COOH), 158.36 (C(4')), 156.63 (–COO–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 (–CH(CH₃)₂), 69.83 (C(4'')–OCH₂), 58.02 (C(2'')).

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

Yield: 96 %; m.p. 109–111 °C (lit.28 m.p. 108–109 °C). ¹H NMR (CDCl₃) 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')–OCH₂), 4.6–4.4 (m, 1H, C(2'H)), 3.1 (t, 2H, C(3'H)), 1.4 (s, 9H, t-Bu). ¹³C NMR (CDCl₃) δ/ppm: 176.78 (–COOH), 157.96 (C(4')), 155.37 (–COO–t-Bu), 139.62 (C(1'') and C(1')), 130.40 (C(2'')), 128.50 (C(3'')), 127.89 (C(4'')), 127.42 (C(3'')), 114.88 (C(2'')), 80.13 (–CH(CH₃)₂), 69.84 (C(4'')–OCH₂), 54.20 (C(2'')), 36.75 (C(3'')), 28.06 (–OC(CH₃)₂).

4-O-Benzoxyl-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). ¹H NMR (acetone-d₆) 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 D₂O), 5.2 (s, C(4')–OCH₂), 4.8 (m, 1H, C(2'H)), 3.8 (dd, 2H, –CH₂-OH, J = 5.0 Hz), 3.1 (bs, 1H, –OH), 1.5 (s, 9H, t-Bu). ¹³C NMR (acetone-d₆) δ/ppm: 158.39 (C(4')), 155.87 (–COO–t-Bu), 134.03 (C(1')), 138.32 (C(1'')), 128.77 (C(2'')), 128.37 (C(2'')), 128.08 (C(4'')), 127.89 (C(3'')), 114.79 (C(3'')), 78.19 (–CH(CH₃)₂), 69.78 (C(4'')–OCH₂), 65.81 (C(1'')), 56.66 (C(2'')), 27.95 (–OC(CH₃)₂).

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.29 m.p. 104–106 °C). ¹H NMR (acetone-d₆) 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')–OCH₂), 3.9–3.7 (m, 2H, C(2'H) + OH), 3.5 (dd, 2H, –CH₂-OH, J = 1.5, 4.8 Hz), 2.8 (2dd, 2H, –CH₂–, J = 7.3, 13.4, 42.7 Hz), 1.4 (s, 9H, t-Bu). ¹³C NMR (acetone-d₆) δ/ppm: 157.49 (C(4')), 155.99 (–COO–t-Bu), 138.15 (C(1'')), 131.80 (C(1'')), 130.68 (C(2'')), 128.79 (C(4'')), 128.06 (C(4'')), 127.88 (C(3'')), 114.92 (C(3'')), 78.05 (–CH(CH₃)₂), 69.81 (C(4'')–OCH₂), 63.45 (C(1'')), 54.55 (C(2'')), 36.47 (C(3'')), 27.97 (–OC(CH₃)₂).

General Procedure for BOC-deprotection

BOC-Protected alcohol 5b,c (8 mmol) was suspended in CH₂Cl₂ (20 mL), and a freshly prepared mixture of trimethylchlorosilane (2.53 mL, 20 mmol) in CH₂Cl₂ (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-Benzoxyl-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 filtered, washed with CH₂Cl₂ and dried: yield 77 %. Hydrochloride (23 mmol) was suspended in CH₂Cl₂ (100 mL) and stirred with 2 M NaOH (23 mL, 60 mmol) overnight. The layers were separated, the aqueous layer was extracted with CH₂Cl₂ (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. 91–96 °C (EtOAc). [α]D = –26 (c = 1.008 g/100 mL, CH₂Cl₂). UV(ETOH) λmax / nm (log ε / mol · l · cm⁻¹): 225 (4.38), 275 (3.41), 282 (3.32). IR(KBr) νmax / cm⁻¹: 3300 (s, OH, NH₂), 1610 and 1580 (m, NH₂), 1250 (s, C–O–C), 1115 (m, –CH₂-OH). ¹H 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')–OCH₂), 3.7–3.5 (m, C(1'H)₂), 4.0 (C(2'H)₂), 2.7 (bs, OH + NH₂). ¹³C 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'')–OCH₂), 67.83 (C(1'')), 56.51 (C(2')).

Anal. Calcd. for C₁₅H₁₇NO₂ (Mₐ = 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 CH₂Cl₂, 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 CH₂Cl₂ (3 × 10 mL). Combined extracts were washed with water, dried (MgSO₄) and evaporated. The product was separated from residual phenol by short column chromatography; eluents CH₃Cl₂-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). [α]D = −20 (c = 1.04 g/100 mL, CHCl₃). IR(KBr) v max /cm⁻¹: 3340 and 3280 (s, OH, NH₂), 1610 and 1580 (m, NH₂), 1235 (C–O–C), 1110 (–CH₂OH). UV(ethanol) λ max /nm (log ε mol⁻¹ dm³ cm⁻¹): 226 (3.88), 277 (2.97). 1H NMR (acetone-d₆) δ/ppm: 7.7–7.3 (m, H(2'') + H(3''), 7.2 + 6.9 (2d, H(2') + H(3'), J = 8.7 Hz), 5.1 (s, C(4')–OCH₂), 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)H₂, J = 6.6, 13.5 Hz), 2.7 (dd, C(3)Hb, J = 7.1, 13.7 Hz). 13C NMR (CDCl₃) 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'')), 115.84 (C(3')), 69.90 (C(4')–OCH₂), 66.12 (C(1)), 54.14 (C(2)), 40.19 (C(3)).

Anal. Calcd for C₁₆H₁₉NO₄ (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 NaBH₄ (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 I₂ (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, 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 heated to reflux for 3 hours and cooled to room temperature overnight. Some undissolved material was removed, the layers were separated, and the aqueous layer was extracted with CH₂Cl₂ (50 mL). The combined extracts were washed with water, dried (MgSO₄) and evaporated. The oily residue was stirred with petroleum ether (100 mL), the product was filtrated and dried: 23.0 g (99 %); m.p. 99 °C. It was used in the next step without any purification.

N-Benzylxocarbonyl-R-4-hydroxyphenylglycine Methyl Ester (9b)

It was prepared as described for compound 9a, starting from 3b, with 98 % yield.

N-Benzoxycarbonyl-S-tyrosine Methyl Ester (9a)

To a solution of 8a (23.2 g, 100 mmol) in water (25 mL) and CH₂Cl₂ (200 mL) cooled down to −10 °C at the same time, solutions of Na₂CO₃ (7.95 g, 75 mmol) in water (30 mL) and 50 % toluenesulphonate solution of C₆H₅OCCO (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 CH₂Cl₂ (50 mL). The combined extracts were washed with water, dried (MgSO₄) 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). 1H NMR (CDCl₃) 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')–OCH₂), 4.6 (dd, 1H, C(2)H, J = 4.9, 12.8 Hz), 3.7 (s, −OCH₃), 3.0 (ddd, 2H, C(3)H, J = 5.6, 14.1, 24.1 Hz). 13C NMR (CDCl₃) δ/ppm: 172.35 (–COOCH₂), 155.88 (C(4')), 155.19 (–COOCH₂), 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 (–OCH₃Ph), 54.80 (C(2)), 52.23 (–OCH₃), 37.19 (C(3)).

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

Compound 9a (6.6 g, 20 mmol) was stirred with anh. K₂CO₃ (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.
1H NMR (CDCl3) 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')−OCH2, J = 2.6 Hz), 4.7 (dd, 1H, C(2)H, J = 5.9, 13.6 Hz), 3.9 and 3.8 (2 x s, −OCH3), 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 CH2Cl2 (17.5–35 mL) and cooled below −15 °C. Isobutylamine (35 mL), previously liquefied by keeping the container in a deep-freezer, and conc. H2SO4 (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 Et3N (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 isobutylamine evaporated. The mixture was diluted with CH2Cl2 (20 mL) and washed with water (3 × 10 mL), dried (MgSO4) and evaporated. The residue was triturated with CH2Cl2 (20 mL) and washed with water (3 × 5 mL), dried (MgSO4) and evaporated to give the product 10a–c in 98–100 % yield.

N-Benzoxycarbonyl-O-methyl-S-tyrosine (11a)

Yield: 94 %; m.p. 112–114 °C. 1H NMR (CDCl3) 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 D2O), 5.1 (d, 2H, C(4')−CH2, J = 5.9 Hz), 4.6 (d, C(2)H, J = 6.2 Hz), 3.8 (s, 3H, −OCH3), 3.2 (dd as t, C(1)Ha, J = 5.3, 14.1 Hz), 3.1 (dd, C(1)Hb, J = 5.3, 14.1 Hz), 1.3 (s, 9H, t-Bu). 13C NMR (CDCl3) δ/ppm: 173.36 (−COOH), 158.74 (C(4')), 156.00 (−COO), 136.03 (C(1')), 130.35 (C(2')), 128.51 (C(2'')), 128.22 (C(4'')), 127.46 (C(1'')), 114.04 (C(3'')), 67.01 (−OCH2Ph), 55.05 (−OCH3), 54.68 (C(2)), 36.67 (C(3)).

N-Benzoxycarbonyl-O-tert-butyl-S-tyrosine (11b)

Yield: 97%; m.p. 70–72 °C. 1H NMR (CDCl3) 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')−OCH3, J = 2.3, 18.5 Hz), 4.6 (m, 1H, C(2)H), 3.1 (dd, 1H, C(2)H, J = 4.4, 9.5 Hz), 3.0 (dd, 1H, C(1)H, J = 7.2, 13.8 Hz), 1.3 (s, 9H, t-Bu). 13C NMR (CDCl3) δ/ppm: 176.01 (−COOH), 156.06 (C(4')), 154.27 (−COO), 136.06 (C(1')), 130.63 (C(2'')), 129.75 (C(2'')), 128.48 (C(2'')), 128.15 (C(4'')), 128.03 (C(3'')), 122.24 (C(3'))., 78.51 (−O(CH3)2), 66.94 (−OCH2Ph), 54.77 (C(2)), 36.81 (C(3)), 28.57 (−OC(CH3)2).

N-Benzoxycarbonyl-O-tert-butoxy-R-phenylglycine (11c)

Yield: 98 %. 1H NMR (CDCl3) 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 D2O disappeared), 5.3 (dd, 1H, C(2)H, J = 7.2, 37.9 Hz), 5.1 (t, C(4')−OCH3, J = 3.3 Hz), 1.3 (s, 9H, t-Bu). 13C NMR (CDCl3) δ/ppm: 175.23 (−COOH), 156.96 (C(4')), 154.87 (−COO), 130.34 (C(1')), 128.48 (C(1'')), 128.31 (C(2'')), 128.14 (C(4'')), 128.70 (C(2'')), 127.49 (C(3'')), 124.23 (C(3')), 66.11 (−OCH2Ph), 54.11 (C(2)), 28.57 (−OC(CH3)2).

N-Benzoxycarbonyl-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. 1H NMR (CDCl3) 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')−OCH3), 5.0 (bs, 1H, −NH−, 3.9 (m, 1H, C(2)H), 3.8(s, 3H, −CH3), 3.7–3.6 (m, 2H, C(1)H), 2.8 (d, 2H, C(3)H, J = 6.7 Hz), 2.4 (bs, −OH). 13C NMR (CDCl3) δ/ppm: 158.33 (C(4')), 156.53 (−COO), 136.30 (C(1')), 130.18 (C(2'')), 129.45 (C(4'')), 128.48 (C(2'')), 128.11 (C(4'')), 128.02 (C(3'')), 113.93 (C(3')), 66.66 (−OCH2Ph), 63.78 (CH2OH), 55.05 (−OCH3), 54.05 (C(2)), 36.18 (C(3)).
N-Benzoylcarbonyl-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$_3$), 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 (2d, 2H, C(3)H, J = 6.9 Hz), 2.2 (bs, –OH), 1.3 (s, 9H, –Bu). $^{13}$C NMR (CDCl$_3$) δ/ppm: 155.54 (C(4')), 135.37 (C(1')), 127.20 (C(2')), 124.08 (C(3')), 78.21 (–O(CH$_3$)), 65.67 (C(1)), 54.03 (C(2)), 39.53 (C(3)), 28.53 (–OC(CH$_3$)). 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-Butyloxy-R-phenylglycinol (6f)

It was prepared according to the general procedure for hydrogenolysis deprotection. Yield: 87.5 %; m.p. 62–66 °C. [α]$_D$ = −17 (c = 0.99 g/100 mL, CH$_2$Cl$_2$). UV(EtOH) λ$_{max}$/nm (log ε / mol$^{-1}$ dm$^3$ cm$^{-1}$): 221 (4.07), 267 (2.85), 273 (2.84). IR(KBr) v$_{max}$/cm$^{-1}$: 3300 (OH, NH$_2$), 2980 (s, OCH$_2$), 1610 (m) and 1580 (s, NH$_2$), 1325 (s, C–O–C), 1040 (s, –CH$_2$OH). $^1$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, OCH$_3$). $^{13}$C NMR (CDCl$_3$) δ/ppm: 154.91 (C(4')), 135.37 (C(1')), 127.20 (C(2')), 124.08 (C(3')), 78.21 (–OC(CH$_3$)), 66.67 (C(1)), 65.66 (C(2)), 28.55 (–OC(CH$_3$)).

Anal. Calcd. for C$_{12}$H$_{21}$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$_2$SnCl$_2$ (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$_2$Cl$_2$, the organic layer was washed with water, concentrated and purified by flash chromatography.

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

Starting from S-benzyltyrosinol 6e (2.06 g, 8.0 mmol) and diethylmalonate (0.64 g, 4.0 mmol) in the presence of Me$_2$SnCl$_2$ (88.0 mg, 0.44 mmol), after purification of the residue (2.4 g) by flash chromatography using CH$_2$Cl$_2$–MeOH (3:1, 1.26 g (58 %) of the white product 1e was obtained. Analytical sample was obtained upon recrystallization 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) v$_{max}$/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')–OCH$_3$), 4.4–4.3 (m, 2H, H(5a)), 4.0 (dd as t, 2H, H(5a), J = 9.0, 9.0 Hz), 3.7 (d, 2H, C(4')–Cl). $^{13}$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')–OCH$_3$), 39.19 (C(3')).

O-tet-Butyl-S-tyrosinol (6e)

It was prepared according to general procedure for hydrogenolytic deprotection. Yield: 96 %; m.p. 38–40 °C. $[α]_D$ = −12 (c = 1.015 g/100 mL, CH$_2$Cl$_2$). UV(EtOH) λ$_{max}$/nm (log ε / mol$^{-1}$ dm$^3$ cm$^{-1}$): 222 (3.65), 269 (2.70), 275 (2.69). IR(KBr) v$_{max}$/cm$^{-1}$: 3300 (s, OH, NH$_2$), 2980 (s, OCH$_2$), 1610 and 1550 (m, NH$_2$), 1235 (s, ether), 1160 (s, –CH$_2$OH). $^1$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 (2s, OH + NH$_2$), 2.5 (d, 3C(3)Hb, J = 8.5, 13.6 Hz), 1.3 (s, OCH$_3$). $^{13}$C NMR (CDCl$_3$) δ/ppm: 153.84 (C(4'')), 133.20 (C(1'')), 129.51 (C(2'')), 124.25 (C(3'')), 78.21 (–OC(CH$_3$)), 65.67 (C(1)), 54.03 (C(2')), 39.53 (C(3')), 28.53 (–OC(CH$_3$)).

SYNTHESSES OF CHIRAL C2-SYMMETRIC BISOXAZOLINES

(C(5)), 69.86 (C(4’)-OCH3), 67.43 (C(4)), 40.38 (C(4’)-CH2), 28.17 (C(2’)-CH2).


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

From aminoalcohol 3d (340 mg, 1.87 mmol) and diethylmalonate (160 mg, 1.52 ml, 1.00 mmol) in dry xylene (15 mL), 95 mg (23 %) of diamide 13d was obtained as white crystals from CH2Cl2-ether. From the isolated diamide 13d (147 mg, 0.34 mmol) and Me2SnCl2 (11 mg, 0.05 mmol) under reflux in xylene (15 mL), pure 1d was obtained as colorless oil (17 mg, 19 %) after flash chromatography (CH2Cl2-MeOH, 96:4) and bulb to bulb distillation. The obtained oil slowly crystallized in refrigerator. 1H NMR (CDCl3) 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’)-CH2), 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). 13C NMR (CDCl3) 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’)-OCH3), 40.35 (C(4’)-CH2), 28.15 (C(2’)-CH2).

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

To a solution of amino alcohol 6b–f (2.0 mmol) in dry CH2Cl2 (21.3 mL), under argon, cooled in an ice-water bath, 3-amino-3-ethoxyprop-2-en-imate dihydrochloride (231 mg, 1.00 mmol) and Et3N (0.56 mL, 405 mg, 4.0 mmol) were added. The reaction mixture was stirred at room temperature overnight. Precipitated NH4Cl was removed, the filtrate was evaporated, and the residue was purified by preparative TLC (CH2Cl2-MeOH 19:1) or flash chromatography (first CH2Cl2-MeOH 40:1 then 20:1) to obtain bisoxazoline product.

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

Yield: 63 %; m.p. 132–134 °C. [α]D = +53 (c = 1.01 g/100 mL, CH2Cl2). UV(50% EtOH) λmax/λnm (log ε/mol–1 dm3 cm–1): 283 (3.70), 227 (4.30). IR(KBr) νmax/cm–1: 1660 (s, O-C=O). 1H NMR (CDCl3) δ/ppm: 7.4–7.3 (m, 10H, H(2’)+ H(3’)+ H(4’)+ 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’)-CH2). 13C NMR (CDCl3) δ/ppm: 162.72 (C(2’)), 158.23 (C(4’)), 136.87 (C(1’)), 134.43 (C(1’’)), 124.88 (C(2’’)), 127.86 (C(3’’)), 127.77 (C(2’’’)), 127.37 (C(4’’’)), 114.95 (C(5’’’)), 75.22 (C(5)), 69.83 (C(4’)-OCH3), 69.03 (C(4’)), 28.15 (C(2’)-CH2).

Anal. Calcd. for C35H34N2O4 (M = 584.72); C 77.09, H 6.85, N 7.32 %; found: C 77.29, H 6.81, N 7.17 %.

2,2'-Methylenebis(4S)-4-(4-benzyloxy)phenyl-4,5-dihydro-1,3-oxazole (1e)

Colorless oil, yield: 79 %, [α]D = +36 (c = 1.05 g/100 mL, CH2Cl2). UV(50% EtOH) λmax/λnm (log ε/mol–1 dm3 cm–1): 279 (3.81), 221 (4.19). IR(KBr) νmax/cm–1: 1660 (s, O-C=O). 1H NMR (CDCl3) 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’)-CH2), 3.1 (dd, 2H, C(4’)-CHa), J = 13.8, 8.5 Hz), 2.6 (dd, 2H, C(4’)-CHb, J = 13.8, 8.5 Hz), 1.3 (s, 18H, C(4’)-OC(CH3)3), 13C NMR (CDCl3) 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’)-OC(CH3)3), 72.12 (C(5)), 67.27 (C(4’)), 40.56 (C(4’)-CH2), 28.57 (C(4’)-OC(CH3)3), 28.09 (C(2’)-CH2).

Anal. Calcd. for C29H26N2O4 (M = 478.63); C 72.77, H 8.00, N 5.85 %; found: C 72.75, H 8.06, N 5.82 %.

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

Colorless oil, yield: 60 %. [α]D = +33 (c = 0.96 g/100 mL, CH2Cl2). IR(KBr) νmax/cm–1: 1660 (s, O-C=O); UV(50% EtOH) λmax/λnm (log ε/mol–1 dm3 cm–1): 283 (3.64), 220 (3.88). 1H 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’)-CH2), 1.3 (s, 18H, C(4’)-OC(CH3)3), 13C NMR (CDCl3) 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’)-OC(CH3)3), 75.47 (C(5)), 69.13 (C(4’)), 28.55 (C(4’)-OC(CH3)3), 28.17 (C(2’)-CH2).

Anal. Calcd. for C27H24N2O4 (M = 450.58); C 71.97, H 7.61, N 6.22 %; found: C 72.08, H 7.58, N 6.10 %.

N1,N3-di[(1R)-1-[4-(benzoxyl)phenyl]-2-hydroxy-ethyl]-2,2-diethylmalonamide (14b)

To a solution of amino alcohol 6b (5.84 g, 24 mmol) and distilled Et3N (8.4 mL, 60 mmol) in dry CH2Cl2 (60 mL) cooled to 0 °C, a solution of diethylmalonyl dichloride (2.2 mL, 13.2 mmol) in CH2Cl2 (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 Et3N⋅HCl, and 4.25 g (58 %) of 14b was obtained, m.p. 177–179 °C. Mother liquor was poured into a saturated aqueous NaHCO3 solution (100 mL). The organic layer was removed and the aqueous phase was washed with 1 M HCl, saturated aqueous NaHCO3, and brine, dried (Na2SO4), filtered, and concentrated to afford additional (78 %) of 14b.

Using the procedure described for 14b, starting from amino alcohol 6c (4.12 g, 16 mmol), Et3N (5.6 mL, 40 mmol), CH2Cl2 (40 mL) and diethylmalonyl dichloride (1.5 mL, 8.8 mmol) in CH2Cl2 (4.0 mL), the reaction mixture was washed with CH2Cl2. Combined organic layers were successively dried (Na2SO4), filtered, and concentrated. To a solution of amino alcohol 14c (5.84 g, 24 mmol) and distilled Et3N (8.4 mL, 60 mmol) in dry CH2Cl2 (60 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 allowed to warm to room temperature and the reaction mixture was washed with water, the organic phase was dried (Na2SO4), filtered, and concentrated.

N1,N3-di[(1S)-1-[4-(benzoxyl)benzyl]-2-hydroxy-ethyl]-2,2-diethylmalonamide (14e)

Following the procedure described for 15b, starting from triphenylphosphine (1.67 g, 6.37 mmol) in dry CH2Cl2 (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 allowed to warm to room temperature, and the reaction mixture was washed with water, the organic phase was dried (Na2SO4), filtered, and concentrated.
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(C(2)), 36.43 (C(1)–CH2)), 30.50 (CO–C–CH2), 9.16 (CO– C–CH2–CH3).

**Anal. Calcd. for C39H42N4O4Cl2 (Mf = 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(4R)-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 CH2Cl2, washed with water, the organic phase was dried (Na2SO4), filtered, and concentrated. The mixture was purified by flash chromatography on 15 g silica gel using CH2Cl2-MeOH (98:2) to afford 89 mg (77 %) of product 2b, m.p. 116–117 °C (diisopropylether). [α]D = +168.3 (c = 1.00 g/100 mL, CH2Cl2).

**Method B.** – To the solution of dichlorodiamide 15b (129.5 mg, 0.2 mmol) in dry toluene (3.5 mL), Et3N (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 NaHCO3. The organic layer was separated, and the aqueous layer was washed with ethyl acetate (3 x 5 mL). The combined organic layers were washed with brine (10 mL), dried over Na2SO4 and the solvent was removed under reduced pressure. Purification of the residue (107 mg) by flash chromatography on 15 g silica gel using CH2Cl2-MeOH (98:2) provided 81.9 mg (71 %) of 2b; m.p. 116–117 °C (diisopropylether). [α]D = +169.6 (c = 1.00 g/100 mL, CH2Cl2). IR(KBr) νmax/cm–1: 283 (2.49), 276 (3.56), 226 (4.43), 213 (4.42). 1H NMR (CDCl3) 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′)–OCH3), 4.6 (dd as t, 2H, H(5a), J = 8.0 Hz), 4.1 (dd as t, 2H, H(5b), J = 9.0 Hz), 3.1 (dd, 2H, C(4)–CH2, J = 14.0, 5.0 Hz), 2.6 (dd, 2H, C(4)–CH2, J = 14.0, 9.0 Hz). 13C NMR (CDCl3) δ/ppm: 167.78 (C(2)), 157.43 (C(3′)), 136.99 (C(1′)), 130.24 (C(2′)), 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′)–OCH3), 67.17 (C(4)), 40.50 (C(4)–CH2), 46.33 (C(2)–C), 25.09 (C(2)–C–CH2), 8.02 (C(2)–C–CH2–CH3).

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**REFERENCES**


Sinteza aminoalkohola i kiralnih C₂-simetričnih bisoksazolina izvedenih od O-alkiliranih R-4-hidroksifenilglicina i S-tirozinola

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Pripravljena je serija kiralnih C₂-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.