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Synthesis of α-Hydroxy-β-amino Acids from Chiral Cyanohydrins

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Abstract: (-)-(*R*,*E*)-2-hydroxy-3-pentenenitrile **1**, obtained by R-oxynitrilase catalyzed addition of HCN to 2-butenal, was shown to be an excellent chiral starting material for the synthesis of α-hydroxy-β-amino acids of high enantiomeric and diastereomeric purity. The synthesis of *N*-benzyl (*S*)-isoserine **7a** and (2*S*,3*S*)-isoallothreonine **7b**, as well as *N*-benzoyl (2*S*,3*S*)-3-phenylisoserine **14** is reported. Copyright © 1996 Elsevier Science Ltd

Introduction

α-Hydroxy-β-amino acids form a class of compounds that has received considerable interest in recent years. This interest partly stems from their abundance in biologically active compounds such as edeine[1], tatumine[2], amastatin[3], bestatin[4], and microginin[5]. In addition, the use of these *iso*-amino acids in the synthesis of pharmacologically active peptides such as protease inhibitors[6] is of considerable interest. Prominent members of this class of compounds are isoserine[7], isothreonine[8], 3-amino-4-cyclohexyl-2-hydroxybutyric acid[9], 3-amino-2-hydroxydecanoic acid[10], 3-amino-2-hydroxy-5-methylhexanoic acid[11,12], 3-amino-2-hydroxy-4-phenylbutyric acid[12,13], and 3-phenylisoserine[14], of which the (2*R*,3*S*)-isomer is the amino acid side chain of taxol[15].

In spite of the many syntheses of nonracemic α-hydroxy-β-amino acids that have been published[7-14,16], alternative methods for preparing these compounds in enantiopure form is still desirable. Several syntheses start from α-amino acids, or the corresponding aldehydes, and rely on a cyanide addition with low stereoselectivity, thus requiring an often cumbersome separation of diastereomers. An approach via enantiomerically pure β-lactams was shown to possess a certain degree of generality[16b]. Another frequently used approach is via enantioselective addition to allylic alcohols or α,β-unsaturated esters[16e].

We have investigated the use of (-)-(*R*,*E*)-2-hydroxy-3-pentenenitrile **1** as a chiral building block for the synthesis of α-hydroxy-β-amino acids. This approach is general in the sense that any halogenide that

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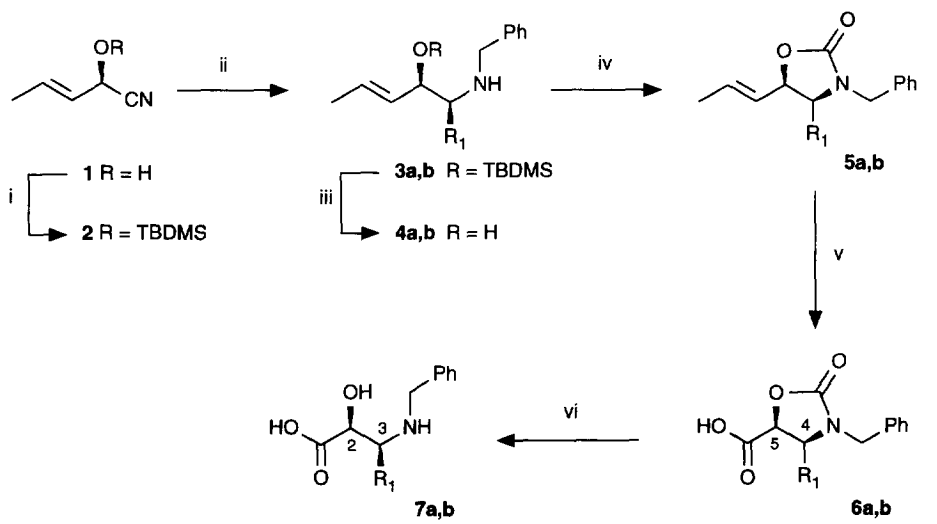
can be converted into a Grignard reagent may be used to introduce the substituent R_1 at the 3 position. In addition, the oxygen bearing stereogenic center retains its stereochemical integrity, and the second stereogenic center can be formed with a high measure of asymmetric induction, by methodology developed earlier in our group[17].

Results and Discussion

(-)-(*R*,*E*)-2-Hydroxy-3-pentenenitrile **1**, readily available in high enantiomeric purity by enzyme catalyzed addition of HCN to 2-butenal[18], is a promising chiral starting material for the preparation of α-hydroxy-ß-amino acids. The nitrile group allows introduction of a wide range of alkyl and aryl substituents with concomitant formation of an amine substituent. The double bond can provide the required carboxylic acid functionality, e.g. by ozonolysis followed by oxidative work-up. This approach was evaluated by the preparation of the two *N*-benzylated amino acids, *N*-benzyl (*S*)-isoserine **7a** and (2*S*,3*S*)-isoallothreonine **7b**.

The alcohol moiety of cyanohydrin **1** was protected as its *tert*-butyldimethylsilyl (TBDMS) ether by reaction with TBDMSCl in DMF. The TBDMS-group was selected for its known[19] superior behaviour, compared with other alcohol-protecting groups, in Grignard addition reactions to cyanohydrins. Additional advantages are the great ease of separation of product and amine used in the transimination step, and the enhanced asymmetric induction when forming a second stereogenic center.

To prepare β-aminoalcohol **3a** (R_1 = H), TBDMS-protected cyanohydrin **2** was subjected to a one-pot DIBAL reduction-transimination-hydride reduction sequence[20] using benzylamine in the transimination step.



a: R_1 = H; **b**: R_1 = Me.

i) TBDMSCl, imidazole. ii) 1. DIBAL or MeMgI; 2. MeOH; 3. benzylamine; 4. $NaBH_4$.
iii) $LiAlH_4$. iv) carbonyldiimidazole. v) 1. O_3; 2. Jones ox. vi) 1. 2N KOH, 60°C; 2. H_3O^+.

Scheme 1: *Preparation of* N-*benzyl* α-*hydroxy*-β-*amino acids.*

To prepare β-aminoalcohol **3b** ($R_1 = CH_3$), protected cyanohydrin **2** was subjected to a similar sequence[17b], using a Grignard addition with MeMgI instead of the DIBAL reduction step.

The *O*-TBDMS protected β-aminoalcohols **3a** and **3b** were obtained in yields of 92% and 96%, respectively. The d.e. of compound **3b** was only 20%, in favor of the *erythro* isomer, when the $NaBH_4$ reduction of the imine was performed at 0°C. This is considerably lower than the results obtained by Brussee *et al.*[17] upon reduction of primary and secondary imines obtained from mandelonitrile. This discrepancy is presumably caused by the decreased size of the propenyl side chain of the cyanohydrin, resulting in a smaller difference between both enantiofaces. However, when reduction of the imine was performed at lower temperature (-78°C) the d.e. of compound **3b** increased to 70%. The crude products **3a** and **3b** were directly deprotected using $LiAlH_4$[17bc,21], converted to their HCl salts, and crystallized. Compound **4a** (e.e. 97%) was obtained in 81% yield, based upon TBDMS-protected cyanohydrin **2**. Compound **4b** was obtained in 56% yield, based upon **2**, as a single diastereomer (^1H NMR). Thus, crystallization had caused a dramatic increase of the d.e. of compound **4b**. The configuration of **4b** was assigned as (2*S*,3*R*), in analogy with earlier results[17].

Prior to ozonolysis, the hydroxy and amino groups had to be protected against oxidation. Both functionalities require a protecting group which is stable under fairly strong acidic conditions, a prerequisite with which the *O*-TBDMS group does not comply. Additionally, the nitrogen has to be protected as an amide to withstand the ozonolysis conditions. These requirements can be met in one step by converting the β-aminoalcohol into an oxazolidinone[22]. Reaction of the β-aminoalcohols **4a** and **4b** with carbonyldiimidazole gave the oxazolidinones **5a** and **5b** in good yields.

Ozonolysis of oxazolidinones **5a** and **5b** at low temperature (-70°C) in the presence of 2 equiv of MeOH, followed by oxidative work-up using an excess of 2M Jones reagent, gave the acids **6a** and **6b**. Acid **6a** (89%) contained traces of its methyl ester. Acid **6b** was obtained quantitatively as a single diastereomer. The H-C(4)/H-C(5) coupling constant of 9.0 Hz in compound **6b** is in agreement with a *cis*-disposition of the oxazolidinone substituents. Since the *trans*-oxazolidinone is the more stable isomer, this is a strong indication that no racemization at C(5) has occurred. For the same reason it may be expected that in the formation of oxazolidinone carboxylic acid **6a** no racemization has occurred, where the driving force for racemization is even smaller.

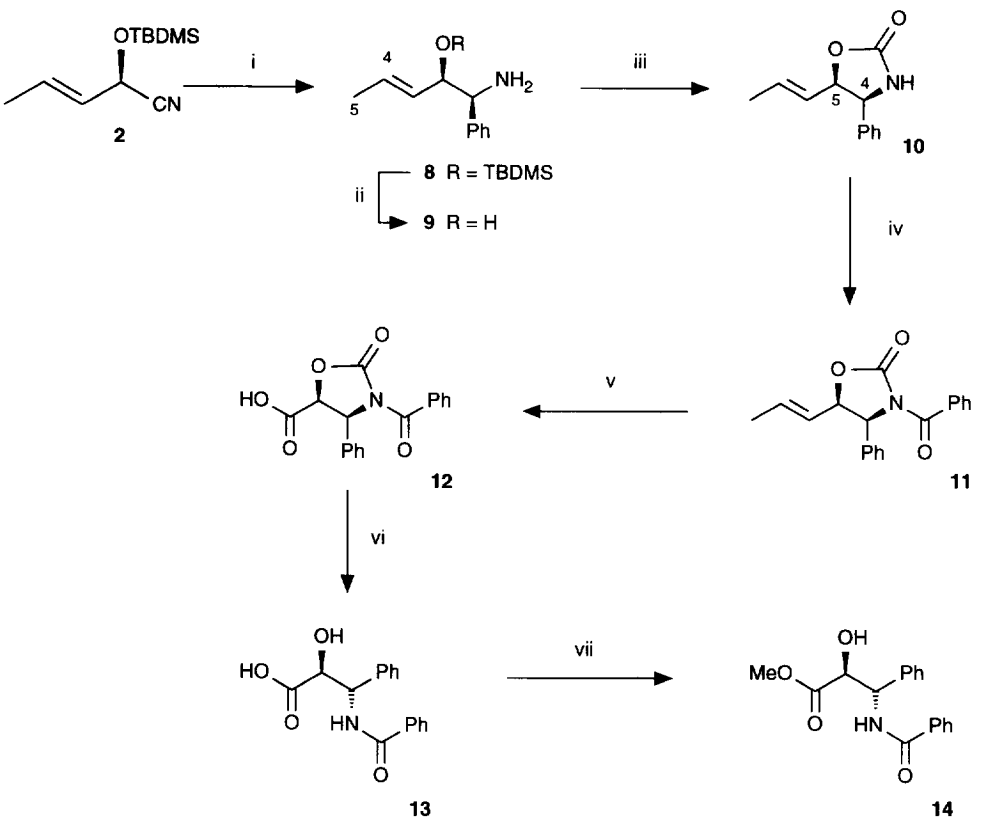
The acids **6a** and **6b** were treated with 2N KOH to hydrolyse the oxazolidinone. Acidification of the reaction mixture, which resulted in *N*-decarboxylation, and purification of the crude products over a DOWEX 50W-X4 ion exchange resin (H^+ form) provided the *N*-benzyl protected amino acids **7a** and **7b**. Both amino acids were isolated as the zwitterion in 90% yield after crystallization. Amino acid **7b** showed only one doublet at 1.28 ppm (CH_3) in the ^1H NMR and no sign of the other diastereomer, indicating that this last step had occurred without racemization. The e.e.'s of amino acids **7a** and **7b** were determined by HPLC, after conversion into the corresponding methyl esters. Both amino acids were found to be enantiomerically pure (e.e. ≥99%) by comparison with racemic samples.

A slightly modified procedure was elaborated for the synthesis of amide containing α-hydroxy ß-amino acids. The amino acid side chain of taxol was chosen as an interesting example of an *N*-acyl substituted amino acid.

In a one-pot procedure, *O*-protected cyanohydrin **2** (e.e. 96%) was reacted with phenyl magnesium bromide to form the metallo imine, which was quenched with MeOH to generate the primary imine. This was reduced *in situ* with an excess of $NaBH_4$, to form the *O*-TBDMS-protected ß-amino alcohol **8** in

quantitative yield (Scheme 2). Reduction at 0°C resulted in an *erythro/threo* ratio of about 4 to 1. In this case reduction at lower temperature (-78°C) did not substantially improve the *erythro/threo* ratio.

The diastereomeric mixture was deprotected using $LiAlH_4$[17bc,21]. The resulting product was converted into its HCl salt and crystallized from EtOAc/hexanes to afford β-aminoalcohol **9** as a white solid in 55% yield. By this crystallization the d.e. increased from 60 to 90% (^{1}H-NMR). The diastereomeric ratio was determined by integrating the signals for the protons at C-5 (*erythro* 1.73 ppm, *threo* 1.54 ppm).



i) 1. PhMgBr; 2. MeOH; 3. $NaBH_4$. ii) $LiAlH_4$. iii) carbonyldiimidazole.
iv) benzoyl chloride. v) 1. O_3; 2. Jones ox. vi) 1. 2N KOH; 2. H_3O^+. vii) CH_2N_2.

Scheme 2: *Synthesis of* N*-benzoyl (2S,3S)-3-phenylisoserine methyl ester.*

β-Aminoalcohol **9** was allowed to react with carbonyldiimidazole to produce oxazolidinone **10**. Purification by chromatography led to removal of the last detectable traces (^{1}H-NMR) of the *threo* isomer. The e.e. of **10** was determined to be over 99% (HPLC).

Oxazolidinones containing an amidic hydrogen gave rise to the formation of unidentified by-products in the ozonolysis reaction. Therefore it was decided to introduce the benzoyl moiety at this stage. Reaction with benzoyl chloride led to quantitative formation of *N*-benzoyl protected oxazolidinone **11**. This compound was subjected to the same ozonolysis/Jones oxidation procedure as described for compounds **5a**

and **5b**, to produce carboxylic acid **12** in essentially quantitative yield. Only one diastereomer was detected by ^{1}H-NMR. The coupling constant observed for the protons at C-4 and C-5 (9.2 Hz) was in agreement with a *cis*-disposition of the substituents at the oxazolidinone ring.

Alkaline hydrolysis of the oxazolidinone ring, followed by acidic work-up, afforded (2*S*,3*S*)-*N*-benzoyl-3-phenylisoserine **13** . Compound **13** was treated with diazomethane to give the corresponding methyl ester **14**, in 82% yield. The e.e. was determined by HPLC to be ≥99%. By ^{1}H-NMR only one diastereomer could be detected, indicating a d.e. ≥ 95%. An analytical sample was crystallized from EtOAc/hexanes. The observed $[\alpha]_D^{20}$ of -28.8 (c = 1, $CHCl_3$) is significantly higher than that reported by Chen *et al.*[14b] {$[\alpha]_D^{20}$ = -23 (c = 1, $CHCl_3$)}. The $[\alpha]_D^{20}$ of + 8.7 (c = 1, MeOH) reported by Davis *et al.*[14a] agrees well with the $[\alpha]_D^{20}$ of +8.5 (c = 1, MeOH) observed by us. The NMR data are in good agreement with those published by Davies et al.[14c] for the *erythro* compound. It should be noted that the naturally occurring side chain of taxol has the (2*R*,3*S*)-configuration (*threo*). It has been reported that taxol equipped with an *erythro* side chain displays a biological activity comparable with that of taxol itself[23]. Based on recent literature reports, it is possible to prepare the *threo*-(2*R*,3*S*)-isomer from **14** by inversion of the oxygen bearing stereogenic center[14b,c]

Experimental

Enantiomeric purities were determined by HPLC using a *Chiralcel-OD* column and hexane/*i*-PrOH (H:I) mixtures, specified for each compound. Optical rotations were measured on a *Propol* automatic polarimeter or a *Perkin-Elmer-141* polarimeter. ^{1}H- and ^{13}C-NMR spectra were recorded on a *Jeol-FX-200* instrument; solvents specified for each compound; Internal reference Me_4Si (TSP for D_2O solns.), δ in ppm, *J* in Hz.

(-)-(*R*,*E*)-2-Hydroxy-3-pentenenitrile 1 was prepared on a 200 mmol scale by the procedure described by Zandbergen *et al*[18b], in 85% yield. Anal. data: in agreement with those published; e.e. 96% (HPLC, determined as TBDPS ether, eluent H:I = 99.75:0.25, 1 ml/min, 254 nm).

(+)-(*R*,*E*)-2-[(*tert*-Butyldimethylsilyl)oxy]-3-pentenenitrile 2. The crude cyanohydrin **1** was converted into the TBDMS ether as described in literature[18a]. The crude product was distilled: 30.5 g (72%, based on aldehyde) of **2**. Colorless oil. B.p. 48°C, 0.1 mm Hg. $[\alpha]_D^{20}$ +11.5 (c = 1, $CHCl_3$); e.e. 96% (HPLC). Anal. data: in agreement with those published.

(-)-(2*R*,3*E*)-1-Benzylamino-3-penten-2-ol.HCl 4a. To a cooled soln. (-70°C) of **2** (4.22 g, 20 mmol) in dry Et_2O (160 ml) was added 1M DIBAL in cyclohexane (40 ml, 40 mmol). After stirring at -70°C for 3 h, dry MeOH (60 ml) was added. The cooling bath was removed and benzylamine (8.6 g, 80 mmol) in MeOH (20 ml) added. Stirring was continued for 1 h during which time the temperature was allowed to rise to r.t. The mixture was then cooled with an ice-bath, $NaBH_4$ (1.5 g, 40 mmol) was added in 3 portions, the mixture was stirred for another 2 h, and 1N HCl (250 ml) added. The aq. layer was extracted with Et_2O (2 x 50 ml). The combined org. layers were washed with 2N NaOH (30 ml), dried (K_2CO_3) and the solvent evaporated. The crude product (compound **3a**, 5.62 g, 92%) was dissolved in THF (30 ml) and added dropwise to a suspension of $LiAlH_4$ (0.7 g, 20 mmol) in THF (20 ml) over a 15 min period. After 1.5 h of reflux the mixture was cooled to r.t. and H_2O (0.7 ml) in THF (5 ml), 15% NaOH (0.7 ml), and H_2O (2.1 ml) were sequentially added. After stirring for 2 h the precipitate was filtered off and washed with THF. After evaporation of the solvent the crude product (3.34 g, 95 %) was converted into its HCl

salt and crystallized from EtOAc/hexanes: 3.40 g (81%) of **4a**. White crystals. M.p. 157°C, $[\alpha]_D^{20}$ = -16.4 (c = 1, MeOH). ^{1}H-NMR: (MeOD-d_3) 1.71 (d, 3 H-C(5)), 2.88 ('dd', ABX, J_{AB} = 12.6, J_{AX} = 9.25, 1 H-C(1)), 3.02 ('dd', ABX, J_{AB} = 12.6, J_{BX} = 3.6, 1 H-C(1)), 4.23 (s, PhCH_2), 4.33 (m, H-C(2)), 5.45 (m, H-C(3)), 5.83 (m, H-C(4)), 7.48 (m, Ph). ^{13}C-NMR: (MeOD-d_3) 17.9 (C(5)); 52.0 (Ph*C*H$_2$); 52.8 (C(1)); 68.8 (C(2)); 130.2; 130.3; 130.6; 131.1; 131.1; 132.4 (C_{ipso}).

(+)-(2*S*,3*R*,4*E*)-2-Benzylamino-4-hexen-3-ol.HCl 4b. To a soln. of MeMgI (30 mmol) in dry Et_2O (50 ml) was added a soln. of **2** (4.22 g, 20 mmol) in dry Et_2O (30 ml). The mixture was refluxed for 2 h, cooled to 0°C, and MeOH was added dropwise (30 ml) followed by a soln. of benzylamine (8.6 g, 80 mmol) in MeOH (20 ml). The mixture was stirred at r.t. for 1 h, cooled to -78°C, and $NaBH_4$ (0.8 g, 21 mmol) was added. Stirring was continued at -78°C for 3 h, after which 1N HCl (200 ml) was added. The aq. layer was extracted with Et_2O (2 x 50 ml), dried (K_2CO_3), and the solvent evaporated: 6.1 g (96%) of **3b**. Crude **3b** was dissolved in dry THF (25 ml) and added dropwise to a suspension of $LiAlH_4$ (1.4 g, 40 mmol) in THF (25 ml) in a 30 min period. After 1.5 h of reflux the mixture was cooled to r.t. and H_2O (1.4 ml) in THF (20 ml), 15% NaOH soln. (1.4 ml), and H_2O (4.2 ml) were sequentially added. After stirring for 2 h the precipitate was filtered off and washed with THF. The org. layer was dried (K_2CO_3) and the solvent evaporated. The crude product was converted into its HCl salt and crystallized from EtOAc/hexanes: 2.57 g (56%) of **4b**. White solid. M.p. 167-8°C. $[\alpha]_D^{20}$ = +5.8 (c = 1.44, MeOH). ^{1}H-NMR (D_2O + DCl): 1.31 (d, *J* = 6.7, 3 H-C(1)); 1.74 (d, *J* = 6.7, 3 H-C(6)); 3.37 (m, H-C(2)); 4.28 (AB, *J* = 12.8, 1/2 PhCH_2); 4.37 (AB, *J* = 12.8, 1/2 PhCH_2); 4.45 (m, H-C(3)); 5.51 (m, H-C(4)); 5.91 (m, H-C(5)); 7.51 (m, Ph). ^{13}C-NMR (D_2O + DCl): 11.2 (C(1)); 17.8 (C(6)); 49.2 (Ph*C*H$_2$); 57.8 (C(2)); 71.4 (C(3)); 123.0; 127.3; 130.3; 130.5 131.2 (C_{ipso}); 132.2.

(+)-(5*R*)-3-Benzyl-5-(prop-1-enyl)oxazolidin-2-one 5a. To a soln. of **4a** (2.28 g, 10 mmol) in dry CH_2Cl_2 (30 ml) under N_2 at 0°C, carbonyldiimidazole (3.2 g, 20 mmol) was added and the mixture stirred overnight. The mixture was then acidified (pH *ca.* 3) with 0.5N HCl, the aq. layer extracted with CH_2Cl_2 (4 x 25 ml), and the combined org. layers dried ($MgSO_4$) and the solvent evaporated. The crude product was chromatographed (silica gel, EtOAc/light petroleum 1:3): 1.69 g (78 %) of **5a**. Colorless oil. $[\alpha]_D^{20}$ = +55.6 (c = 1, $CHCl_3$); e.e. 97% (HPLC, H:I 95:5). ^{1}H-NMR ($CDCl_3$): 1.72 (d, *J* = 6.4, *Me*CH=CH), 3.10 ('dd', ABX, J_{AB} = 8.7, J_{AX} = 7.6, 1 H-C(1)), 3.49 ('dd', ABX, J_{AB} = J_{BX} = 8.7, 1 H-C(1)), 4.36 (AB, *J* = 14.8, 1/2 PhCH_2), 4.48 (AB, *J* = 14.8, 1/2 PhCH_2), 4.85 (m, H-C(5)), 5.49 (m, MeCH=C*H*), 5.82 (m, MeC*H*=CH), 7.33 (m, Ph). ^{13}C-NMR ($CDCl_3$): 17.4 (*Me*CH=CH); 48.0 (Ph*C*H$_2$); 49.3 (C(4)); 74.1 (C(5)); 127.4; 127.7; 127.9; 128.6; 131.6; 135.6 (C_{ipso}); 157.4 (C(2)).

(+)-(4*S*,5*R*)-3-Benzyl-4-methyl-5-(prop-1-enyl)oxazolidin-2-one 5b. To a soln. of **4b** (2.17 g, 9.0 mmol) in a mixture of dry CH_2Cl_2 (50 ml) and Et_3N (1.3 ml, 9.5 mmol) at 0°C, was added carbonyldiimidazole (2.16 g, 13.5 mmol, 1.5 eq.). The mixture was stirred overnight, the solvent evaporated, and the crude product chromatographed (silica gel, EtOAc/light petroleum 1:4): 1.95 g (93%) of **5b**. Colorless oil. $[\alpha]_D^{20}$ = +15.3 (c = 1, $CHCl_3$). ^{1}H-NMR ($CDCl_3$): 1.07 (d, *J* = 6.7, 4-Me); 1.75 (d, *J* = 6.4, *Me*CH=CH); 3.66 (dq, J_1 = 6.7, J_2 = 8.0, H-C(4)); 4.03 (AB, *J* = 15.4, 1/2 PhCH_2); 4.82 (AB, *J* = 15.4, 1/2 PhCH_2); 4.82 ('dd', J_1 = J_2 = 7.5, H-C(5)); 5.50 (m, MeCH=C*H*); 5.82 (m, MeC*H*=CH); 7.28-7.38 (m, Ph). ^{13}C-NMR ($CDCl_3$): 13.4 (4-Me); 17.5 (*Me*CH=CH); 45.5 (Ph*C*H$_2$); 53.2 (C(4)); 78.2 (C(5)); 123.9; 127.5; 127.7; 128.5; 132.4; 135.9; 157.6 (C(2)).

(+)-(5*S*)-3-Benzyloxazolidin-2-one-5-carboxylic acid 6a. Through a soln. of **5a** (1.53 g, 7.0 mmol) in CH_2Cl_2 (30 ml) and MeOH (0.57 ml, 14.0 mmol, 2 equiv.) cooled to -70°C, ozone was passed until a blue

color persisted. Stirring was continued for 1 h allowing the temperature to rise to -30°C after which the solution was diluted with acetone (30 ml) and treated with a 2M Jones reagent (21 ml, 42 mmol). The temperature was allowed to rise to r.t. and stirring continued for 3 h, after which the reaction was quenched by the addition of 2-propanol (4 ml). The org. layer was decanted and the inorganic salts were washed with Et_2O (2 x 50 ml). The org. layers were combined and diluted with H_2O (100 ml). The aq. layer was extracted with Et_2O (3 x 50 ml). The combined org. layers were dried (Na_2SO_4), and the solvent evaporated. The crude product (1.38 g, 89%) contained traces of the methyl ester, but was used directly for the next reaction. The crude product can be crystallized from Et_2O. M.p. 115-117°C, $[\alpha]_D^{20}$ = +42.1 (c = 1 acetone). ^{1}H-NMR ($CDCl_3$): 3.54 ('dd', ABX, J_{AB} = 9.3, J_{AX} = 5.7, 1 H-C(4)), 3.71 ('dd', ABX, J_{AB} = 9.3, J_{BX} = 9.8, 1 H-C(4)), 4.34 (AB, J = 14.9, 1/2 CH_2Ph), 4.48 (AB, J = 14.9, 1/2 CH_2Ph), 4.92 ('dd', ABX, J_{AX} = 5.7, J_{BX} = 9.8, 1 H-C(5)), 7.28 (m, Ph), 9.30, (br., COOH). ^{13}C-NMR ($CDCl_3$): 46.8 (PhCH_2); 48.3 (C(4)); 69.6 (C(5)); 128.1; 128.5; 128.9; 130.2; 133.9; 134.8 (C_{ipso}); 157.2 (C(2)); 172.0 (COOH).

(+)-(4*S*,5*S*)-3-Benzyl-4-methyloxazolidin-2-one-5-carboxylic acid 6b was prepared from **5b** (1.65 g, 7.1 mmol) by the procedure as described for **6a**. The crude product was dissolved in 2N NaOH (10 ml), washed with Et_2O (20 ml), the aq. layer acidified (pH ≈ 2) and extracted with Et_2O (4 x 25 ml). The combined org. layers were dried (Na_2SO_4) and the solvent evaporated: 1.70 g (100%) of **6b**. Light yellow solid. The crude product can be crystallized from 2-propanol. M.p. 158-9°C. $[\alpha]_D^{20}$ = +30.8 (c = 2, acetone). ^{1}H-NMR (acetone-d_6): 1.20 (d, J = 6.4, 4-Me); 4.08 (dq, J_1 = 6.4, J_2 = 9.0, H-C(4)); 4.27 (d, AB, J = 15.4, 1/2 PhCH_2); 4.64 (d, AB, J = 15.4, 1/2 PhCH_2); 5.05 (d, J = 9.0, H-C(5)); 7.35 (Ph). ^{13}C-NMR (acetone-d_6): 14.3 (4-Me); 46.1 (PhCH_2); 52.8 (C(4)); 75.1 (C(5)); 128.3 (C-arom); 128.5 (C-arom); 129.4 (C-arom); 137.3 (C_{ipso}); 157.8 (C(2)); 169.0 (COOH).

(-)-(2*S*)-N-Benzylisoserine 7a. A soln. of crude **6a** (1.38 g) in 2N KOH (20 ml) was stirred for 3 h at 60°C, cooled to r.t. and acidified to pH 2 by the addition of 6N HCl (8 ml). The aq. layer was charged on a DOWEX 50W X4 ion exchange resin (H^+ form), washed with H_2O (200 ml), and eluted with 5% NH_4OH. The ninhydrin positive fractions were concentrated and the crude product crystallized from MeOH/H_2O: 1.11 g (91 %). M.p. 210-4°C, $[\alpha]_D^{20}$ = -8.9 (c = 1, 1N HCl). ^{1}H-NMR (D_2O + DCl): 3.33 ('dd', ABX, J_{AB} = 12.9, J_{AX} = 9.3, 1 H-C(3)), 3.55 ('dd', ABX, J_{AB} = 12.9, J_{BX} = 4.1, 1 H-C(3)), 4.38 (s, CH_2Ph), 4.60 ('dd', ABX, J_{AX} = 9.3, J_{BX} = 4.1, 1 H-C(2)), 7.54 (m, Ph). ^{13}C-NMR (D_2O + DCl): 49.8 (PhCH_2); 51.5 (C(3)); 67.7 (C(2)); 129.8 (C-arom); 130.2 (C-arom); 130.4 (C-arom); 130.9 (C_{ipso}); 176.3 (COOH).

(+)-(2*S*,3*S*)-*N*-Benzylisoallothreonine 7b was prepared from **6b** (1.25 g, 5.3 mmol) by the procedure as described for **7a**. The crude product was crystallized from MeOH: 1.0 g (90%) of **7b**. White solid. M.p. 252-4°C (dec.). $[\alpha]_D^{20}$ = +5.1 (c = 1, 1N HCl). ^{1}H-NMR (D_2O + DCl): 1.28 (d, J = 6.7, CH_3); 3.79 (dq, J_1 = 6.7, J_2 = 3.1, H-C(3)); 4.30 (s, PhCH_2); 4.72 (d, J = 3.1, H-C(2)): 7.47 (m, Ph). ^{13}C-NMR (D_2O + DCl): 11.1 (C(4)); 49.3 (PhCH_2); 55.7 (C(3)); 69.4 (C(2)); 129.9 (C-arom); 130.2 (C-arom); 130.4 (C-arom); 131.0 (C_{ipso}); 175.0 (COOH).

(+)-(1*S*,2*R*,3*E*)-1-Amino-1-phenyl-3-penten-2-ol.HCl 9. To a soln. of phenyl magnesium bromide (80 mmol) in dry Et_2O (160 ml) under N_2 was added dropwise a soln. of **2** (8.4 g, 40 mmol) in dry Et_2O (60 ml), and the reaction mixture was refluxed for 3 h. After cooling the reaction mixture in an ice-bath, dry MeOH (100 ml) was slowly added. Solid $NaBH_4$ (3 g, 80 mmol) was added in 3 portions and the mixture was stirred for another 2 h, after which H_2O (250 ml) was added followed by 6N HCl (→clear soln.). The aq. layer was extracted with Et_2O (2 x 100 ml). The combined org. layers were washed with 2N NaOH

(200 ml), dried ($MgSO_4$), and the solvent evaporated. The crude product (compound **8**, 11.6 g, 40 mmol, quant.) was dissolved in dry THF (50 ml), and added dropwise to a suspension of $LiAlH_4$ (1.5 g, 40 mmol) in THF (50 ml) in a 30 min. period. After 1.5 h of reflux the mixture was cooled to room temperature and 1.5 ml of H_2O in 11 ml of THF, 1.5 ml of 15 % NaOH, and 4.5 ml of H_2O were sequentially added. After stirring for 2 h the precipitate was filtered off and washed with THF. The filtrate was extracted with 1N HCl (2 x 50 ml). The combined aq. layer was made alkaline (pH 12) by addition of 5N NaOH and extracted with CH_2Cl_2 (6 x 50 ml). The combined CH_2Cl_2 layer was dried (K_2CO_3) and the solvent evaporated. The crude product (7.0 g, 99 %) was converted into its HCl salt and crystallized from EtOAc/hexanes: 4.7 g (55%) of **9**. White solid. M.p. 162-163°C. $[\alpha]_D^{20}$ = +25.2 (c = 1, H_2O); d.e. 90% (by ^{1}H-NMR). ^{1}H-NMR (D_2O + DCl): 1.73 (d, 3 H-C(5)), 4.36 (d, *J* = 7.0, H-C(1)), 4.56 (t, *J* = 7.0, H-C(2)), 5.44 (dd, H-C(3)), 5.92 (m, H-C(4)), 7.50 (m, Ph). ^{13}C-NMR (D_2O + DCl): 18.2 (C(5)); 59.7 (C(1)); 73.9 (C(2)); 128.1; 128.9; 130.1; 130.4; 134.3; 134.4 (C_{ipso}).

(+)-(4*S*,5*R*)-4-Phenyl-5-(prop-1-enyl)oxazolidin-2-one 10. To a soln. of **9** (2.14 g, 10 mmol) in dry CH_2Cl_2 (30 ml) under N_2 at 0°C, Et_3N (1.05 g, 10 mmol), and carbonyldiimidazole (1.6 g, 10 mmol) in CH_2Cl_2 (20 ml) were added and the mixture stirred for 3 h, after which an additional amount of carbonyldiimidazole (1.6 g, 10 mmol) in CH_2Cl_2 (20 ml) was added. Stirring was continued for another 2 h, after which H_2O (50 ml) was added. After stirring for 30 min. the layers were separated and the aq. layer extracted with CH_2Cl_2 (4 x 25 ml). The combined org. layers were dried ($MgSO_4$), and the solvent evaporated. The crude product was chromatographed (silica gel, light petroleum/EtOAc/Et_3N 14:5:1): 1.78 g (88%) of **10**. White solid. M.p. 148°C. $[\alpha]_D^{20}$ = +14.5 (c = 1 MeOH), d.e. ≥ 95%, e.e. ≥ 99% (HPLC, H:I = 90:10). ^{1}H-NMR ($CDCl_3$): 1.54 (d, *J* = 6.2, *Me*CH=CH), 4.88 (dd, MeCH=C*H*), 4.90 (d, *J* = 7.7, H-C(4)), 5.24 (t, *J* = 8.2, H-C(5)), 5.46 (br., NH), 5.78 (m, MeC*H*=CH), 7.17-7.43 (m, Ph). ^{13}C-NMR ($CDCl_3$): 17.5 (*Me*CH=CH); 60.0 (C(4)); 81.9 (C(5)); 124.7; 126.9; 128.4; 128.6; 132.9; 136.8 (C_{ipso}); 159.8 (C(2)).

(+)-(4*S*,5*R*)-3-Benzoyl-4-phenyl-5-(prop-1-enyl)oxazolidin-2-one 11. To a soln. of **10** (1.73 g, 8.5 mmol) in CH_2Cl_2 (20 ml) at 0°C were added Et_3N (1.4 ml), benzoyl chloride (1.4 ml) and a catalytic amount of DMAP sequentially. After stirring overnight at r.t. 1M K_2CO_3 (10 ml) was added and stirring continued for 1 h. The aq. layer was extracted with CH_2Cl_2 (4 x 50 ml). The combined org. layers were dried ($MgSO_4$), and the solvent evaporated. The crude product was chromatographed (silica gel, EtOAc/light petroleum 1:4): 2.53 g (97%) of **11**. White solid. M.p. 134-135°C. $[\alpha]_D^{20}$ = +21.2 (c = 1 MeOH), d.e. ≥ 95%. ^{1}H-NMR ($CDCl_3$): 1.59 (d, *J* = 6.7, *Me*CH=CH), 4.91 (m, MeCH=C*H*), 5.27 (t, *J* = 8.2, H-C(5)), 5.59 (d, *J* = 7.7, H-C(4)), 5.90 (m, MeC*H*=CH), 7.21-7.67 (m, 10 H-arom). ^{13}C-NMR ($CDCl_3$): 17.5 (*Me*CH=CH); 62.3 (C(4)); 79.8 (C(5)); 123.5; 126.5; 127.7; 128.4; 128.6; 128.7; 132.0; 132.9 (C_{ipso}); 134.4; 135.0 (C_{ipso}); 153.1 (C(2)); 168.8 (Ph*C*=O).

(+)-(4*S*,5*S*)-3-Benzoyl-4-phenyloxazolidin-2-one-5-carboxylic acid 12. Through a soln. of **11** (2.53 g, 8.2 mmol) in CH_2Cl_2 (40 ml) and MeOH (0.66 ml, 16.4 mmol, 2 equiv.) cooled to -70°C, ozone was passed until a blue color persisted. Stirring was continued for 1 h allowing the temperature to rise to -30°C after which the solution was diluted with acetone (40 ml) and treated with 2M Jones reagens (25 ml, 50 mmol). The temperature was allowed to rise to r.t. and stirring continued for 3 h, after which the reaction was quenched by the addition of 2-propanol (4 ml). The org. layer was decanted and the inorganic salts were washed with Et_2O (2 x 50 ml). The org. layers were combined and diluted with H_2O (100 ml). The aq. layer was extracted with Et_2O (3 x 50 ml). The combined org. layers were dried (Na_2SO_4), and the solvent

evaporated. The crude product (2.64 g) contained traces of the methyl ester, but was used directly for the next reaction. The crude product can be crystallized from 2-propanol. White solid. M.p. 153°C. $[\alpha]_D^{20}$ = +95.5 (c = 1 acetone), d.e. ≥ 95. ^{1}H-NMR (acetone-d_6): 5.59 (d, *J* = 9.2, H-C(4)), 6.07 (d, *J* = 9.2, H-C(5)), 7.31-7.76 (m, 10 H-arom). ^{13}C-NMR (acetone-d_6): 61.5 (C(4)); 76.3 (C(5)); 127.4; 128.8; 129.4; 129.5; 130.0; 133.3; 134.3 (C_{ipso}); 135.4 (C_{ipso}); 153.6 (C(2)); 167.7 (C=O); 169.4 (C=O).

(-)-(2*S*,3*S*)-Methyl *N*-Benzoyl-3-phenylisoserine 14. A solution of crude **12** (2.64 g) in 2N KOH (40 ml) was stirred for 3 h at 60°C, cooled to r.t. and acidified to pH 2 by the addition of 6N HCl (15 ml). The aq. layer was extracted with THF/CH_2Cl_2 (4:1 v/v, 5 x 50 ml). The combined org. layer was dried (Na_2SO_4) and the solvent evaporated. The crude product (compound **13**) was treated with diazomethane to obtain the methyl ester after chromatography (silica gel, EtOAc/light petroleum 1:2): 2.0 g (82 % based on **11**) of **14**. M.p. 155-156°C. (lit.[14a,c]) $[\alpha]_D^{20}$ = -28.8 (c = 1, $CHCl_3$) (lit.[14b] $[\alpha]_D^{20}$ = -23 (c = 1, $CHCl_3$)) $[\alpha]_D^{20}$ = +8.5 (c = 1, MeOH) (lit.[14a] $[\alpha]_D^{20}$ = +8.7 (c = 1, MeOH)). ^{1}H-NMR ($CDCl_3$): 3.08 (d, *J* = 6.6, OH), 3.73 (s, MeO), 4.71 (dd, J_1 = 3.5, J_2 = 6.6, 1 H-C(2)), 5.62 (dd, J_1 = 3.5, J_2 = 8.7, 1 H-C(3)), 7.14 (d, *J* = 8.7, NH), 7.25-7.52 (m, 8H-arom), 7.81 (d, *J* = 7.9, 2 H-arom). ^{13}C-NMR ($CDCl_3$): 52.5 (MeO); 55.5 (C(4)); 72.9 (C(5)); 127.0; 127.4; 128.2; 128.4; 131.6; 133.9 (C_{ipso}); 136.5 (C_{ipso}); 166.7 (PhC=O); 172.1 (C(1)). NMR data are in agreement with those published in the literature[14b].

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