Synthesis of New Analogs of the C-13 Docetaxel Side Chain By Asymmetric Aminohydroxylation

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Keywords: Asymmetric synthesis / Hydroxylation / Natural products / Taxoids

The synthesis of six new β-phenyl isoserines, each bearing an amino or a nitro substituent on the phenyl ring in various positions, is reported. These compounds, analogues of the docetaxel side chain, have been obtained by asymmetric aminohydroxylation of the corresponding cinnamates with excellent regiospecificity and in good enantiomeric excess.

Introduction

Isoserines (α-hydroxy-β-amino acids) are key molecules that can serve as precursors to important bioactive substances such as the anticancer agents paclitaxel (**1a**) and docetaxel (**1b**) (Figure 1).[1]

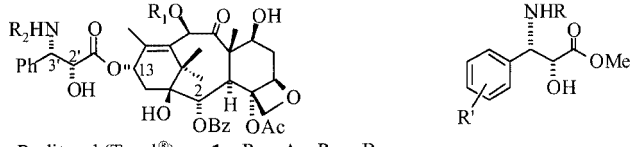

Figure 1. Structures of paclitaxel, docetaxel and β-phenylisoserine

Because of their importance, several efficient methods to synthesize isoserines have been developed. Among them, catalytic asymmetric syntheses, and especially asymmetric epoxidation (AE), dihydroxylation (AD) and aminohydroxylation (AA) have been applied to the synthesis of the paclitaxel side chain.[2] As part of our research on the bioactive conformation of docetaxel, we were interested in the synthesis of macrocyclic taxoids in which position 2 is linked to the C-13 side chain, and therefore in the synthesis of new C-13 side chains **2** (Figure 1) bearing a functional group on the phenyl ring allowing the closure of the macrocycle.

In the taxoid series, the first assay of aminohydroxylation was realized on the *trans*-cinnamic ester of 10-deacetylbaccatin III[3] using the silver(I) salt of *N*-chloro-*tert*-butoxycarboxamide as the nitrogen source, according to Sharpless et al.[4] This led to the discovery of docetaxel (**1b**).[3] The use of dihydroquinine esters improved the yields of hydroxycarbamates and led to a small diastereoisomeric excess (46% *de*) in the desired (2′*R*,3′*S*) compound.[3] Later, Sharpless et al. greatly improved the asymmetric aminohydroxylation of methyl cinnamate by using chloramine T as a nitrogen source and $(DHQ)_2PHAL$[5] as chiral inductor (81% *de*), and showed that *N*-halo-benzylcarbamate and *N*-halo-ethylcarbamate salts lead to more efficient catalytic AA (99% *ee* and 94% *ee* respectively).[6]

We were interested in the synthesis of (2*R*,3*S*)-β-phenylisoserines whose amine was protected by a Boc group and substituted on the phenyl ring at the *ortho*, *meta* or *para* position by a functional group precursor of another amine. Although the synthesis of the corresponding *N*-tosyl-nitrophenylisoserines **3** (Figure 2) has been described in a patent in 1997,[7] our experience of the difficulties to remove this protecting group prompted us to reexamine the direct synthesis of the desired compounds. Only a few other (2*R*,3*S*)-β-phenylisoserines with a nitrogen-substituted phenyl ring have been described, such as, for example, compounds **4**[6,8,9,10] and **5**[11,12] (Figure 2).

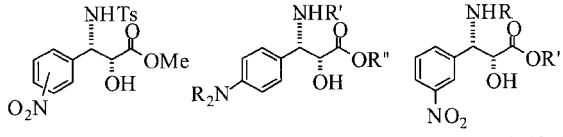

Figure 2. β-Phenylisoserines with a nitrogen-substituted phenyl ring

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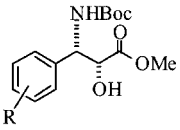
We wish to present here the asymmetric synthesis of new (2*R*,3*S*)-*N*-Boc-β-phenylisoserines **2b**−**e** (Figure 3) bearing a nitrogen atom on the phenyl ring.

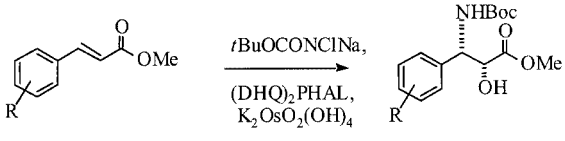


2a R = H
2b R = *p*-NO_2
2c R = *m*-NO_2
2d R = *o*-NO_2
2e R = *p*-$NHCO(CH_2)_3CO_2Bn$

Figure 3. (2*R*,3*S*)-*N*-Boc-β-phenylisoserines

Results and Discussion

Despite the lower enantioselectivity observed with *tert*-BuOCONClNa as the nitrogen donor[13] in the Sharpless aminohydroxylation (78% *ee*), this method was chosen to afford directly the expected docetaxel side chain. In fact, using the same experimental conditions as with methyl *trans*-cinnamate, compound **2a** was obtained in 79% yield and in 80% *ee* as described. A similar procedure was applied to nitrocinnamate derivatives. Although AA has been recently described with cinnamic acid,[11] the reported regioselectivity was not good enough to use the commercially available nitrocinnamic acids directly. After classical esterification, the methyl nitrocinnamates were subjected to asymmetric aminohydroxylation (Scheme 1).



6b R = *p*-NO_2
6c R = *m*-NO_2
6d R = *o*-NO_2

2b-d

Scheme 1

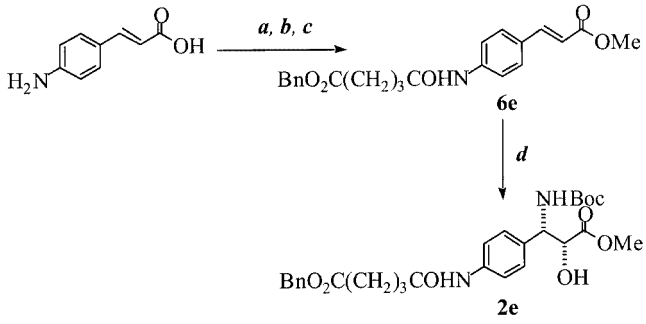
The reactivity of the nitrocinnamates appeared to be dependent on the position of the nitro group (Table 1). The aminohydroxylation of methyl *p*-nitrocinnamate (**6b**) under classical conditions [sodium salt of *tert*-butylcarbamate and a 4 mol % $K_2OsO_2(OH)_4$/5 mol % $(DHQ)_2PHAL$ admixture in *n*PrOH/water at room temperature] gave **2b** with a moderate yield. For methyl *m*-nitrocinnamate (**6c**) the reaction was much slower, and with the *ortho* compound **6d** the expected compound **2d** was not observed. The reaction conditions had to be modified to obtain the desired (2*R*,3*S*)-β-phenylisoserines **2c** and **2d** in higher yield. This was done by addition of the reactants (osmium catalyst and the nitrocinnamate) at 0 °C instead of room temperature and stirring the reaction mixture for 30 min at 0 °C and then at room temperature. The *o*-nitro derivative **2d** appeared to be very sensitive to temperature and had to be kept below 4 °C after purification. This instability could explain why no **2d** has been observed when the AA reaction is performed at room temperature.

Table 1. Results of AA reactions for methyl cinnamate derivatives

Substrate	Product[a]	*ee* (%)[b]	Yield (%)	t (h)
Methyl cinnamate	**2a**	80	79	3
6b	**2b**	86	53	3
6c[c]	**2c**	81	55	6
6d[c]	**2d**	82	38	6
6e	**2e**	79	24	20

[a] Major product of the reaction. [b] Calculated from HPLC analysis. [c] Addition of the reactants at 0 °C.

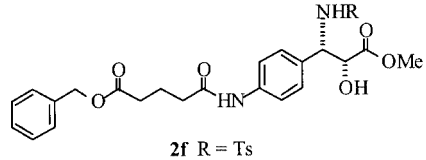
Methyl benzyloxyglutaryl-*p*-aminocinnamate (**6e**) — a precursor of compound **2e** — was obtained from commercially available *p*-aminocinnamic acid in three steps as shown in Scheme 2, and was then subjected to asymmetric aminohydroxylation.



Scheme 2. *a*) AcCl, MeOH; *b*) Glutaric anhydride, K_2CO_3, H_2O/THF; c) BnCl, DMF; *d*) *t*BuOCONHBr, $(DHQ)_2PHAL$, $K_2OsO_2(OH)_4$, LiOH, *t*BuOH

In our hands, the use of the sodium salt of *N*-bromo-*tert*-butoxycarboxamide yielded better results than the sodium salt of *N*-chloro-*tert*-butoxycarboxamide, although compound **2e** was still obtained in poor yield (Table 1).

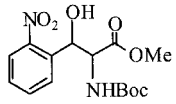
In order to get larger amounts of the desired compound, chloramine T and AcNHBr[14] were assayed as alternative sources of nitrogen donor. *N*-Bromoacetamide did not lead to any improvement of the reaction since **2g** (Figure 4) has previously been obtained in low yield (23%) but with a better enantiomeric excess (98% *ee*). On the other hand the use of chloramine T afforded **2f** (Figure 4) in a satisfactory yield (69%) but with a lower enantiomeric excess (66% *ee*). These results for the AA reaction showed that the nitrogen donor and the nature of the substituent on the phenyl ring (**6e** versus **6b**) are both important for the course of the reaction.



2f R = Ts
2g R = Ac

Figure 4. Structure of compounds **2f** and **2g**

With *para*- or *meta*-substituted cinnamates (**6b** and **6c** respectively), the regioselectivity was good (no regioisomer was generally detectable by ^{1}H NMR spectroscopy) and the moderate yields observed were due to the competitive formation of methyl 2,3-dihydroxy-3-phenylpropionate. Although *ortho* substitution with methyl or methoxy groups did not change the regioselectivity of the AA reaction,[6,13] the presence of a nitro group at this position yielded to non-negligible amount of the regioisomers (2-NHBoc, 3-OH) **2′d** (Figure 5). This difference of reactivity could be explained by the additivity of the electronic and steric effects of the nitro group when located in the *ortho* position.



2'd

Figure 5. Structure of compound **2′d**

The absolute configuration of compound **2a** was assigned as 2*R*,3*S* by comparison with an authentic sample of the methyl ester of the docetaxel side chain. For the other derivatives, the major product of the reaction was assumed to have the same configuration as **2a**. The enantioselectivity was satisfactory for all compounds (about 80% *ee*). Although other methods are known to afford the docetaxel side chain in high enantiomeric excess,[15] this aminohydroxylation reaction afforded the desired analogues in only one step from commercial compounds. Moreover, these derivatives can be easily obtained in 100% *ee* by further crystallization.

In conclusion, we have prepared six new analogues of the docetaxel side chains bearing a nitrogen atom on the phenyl ring in all the positions by AA reaction. Compounds **2b**−**g** have been obtained with good enantiomeric excesses. They are now used in our laboratory for the synthesis of conformationally locked taxoids, the nitrogen atom being the anchoring for the macrocycle formation.

Experimental Section

General: IR spectra were recorded on a Perkin−Elmer Spectrum BX FT-IR apparatus, as films on NaCl or KBr pellets. ^{1}H and ^{13}C NMR spectra were recorded with Bruker AC 250, AM 300 or Jeol 400 instruments. Chemical shifts are given as delta values and are referenced to the residual solvent proton peak of either chloroform (δ = 7.27 ppm) or dimethylsulfoxide (δ = 2.49 ppm). Mass spectra were obtained on an AQA Navigator ThermoQuest®. Optical rotations were measured on a Perkin−Elmer 241 polarimeter. Melting points were obtained with a Büchi B-540 apparatus and are uncorrected. Microanalyses were performed at the ICSN, CNRS, Gif-sur-Yvette, France. Merck silica gel 60 (40−63 μm) was used for flash chromatography. HPLC analyses were carried out on a Waters apparatus equipped with a Chiralcel OD column (25 × 0.46 cm).

General Procedure for AA Reaction with *tert*-BuOCONClNa: *tert*-Butyl carbamate (363 mg, 3.1 mmol) was dissolved in *n*-propyl alcohol (4 mL). To this stirred solution were added freshly prepared solutions of NaOH (122 mg, 3.05 mmol) in water (7.5 mL) and *tert*-butyl hypochlorite (0.35 mL, 3.05 mmol). Then a solution of $(DHQ)_2PHAL$ (40 mg, 0.05 mmol, 5 mol %) in *n*-propyl alcohol (3.5 mL) was added. The vial was then immersed in a room temperature or ice-cold water bath and stirred for a few minutes. The reaction mixture was then treated with the olefin (methyl nitrocinnamate, 207 mg, 1 mmol) and the osmium catalyst [$K_2OsO_2(OH)_4$, 14.7 mg, 0.04 mmol, 4 mol %]. The reaction mixture turned from brown to green and then to yellow at the end of the reaction. The reaction time for each compound is given in Table 1. Ethyl acetate (7 mL) was then added and the phases were separated. The lower aqueous phase was extracted three times with ethyl acetate. The combined organic extracts were washed with water and brine, dried over sodium sulfate and concentrated to dryness. The crude product was purified by flash chromatography (heptane/ethyl acetate, 5:1).

(2*R*,3*S*)-(+)-*N*-(*tert*-butoxycarbonyl)-3-(*p*-nitrophenyl)isoserine Methyl Ester (2b): The reaction was conducted at room temperature for 3 h. Flash chromatography afforded **2b** (178 mg, 52.5%) as a white solid. m.p. 114−115 °C. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 1.42 (s, 9 H, Boc), 3.30 (d, $^3J_{H,H}$ = 2.5 Hz, 1 H, O*H*), 3.87 (s, 3 H, OCH_3), 4.46 (br. s, 1 H, C*H*OH), 5.32 (br. d, $^3J_{H,H}$ = 9.8 Hz, 1 H, C*H*NH), 5.52 (d, $^3J_{H,H}$ = 9.8 Hz, 1 H, N*H*), 7.58 (d, $^3J_{H,H}$ = 9.0 Hz, 2 H, Ph), 8.22 (d, $^3J_{H,H}$ = 9.0 Hz, 2 H, Ph) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 28.4 (*C*H$_3$ Boc), 53.5 (O*C*H$_3$), 55.8 (*C*HNH), 73.1 (*C*HOH), 80.7 [*C*(CH$_3$)$_3$], 123.9, 127.9, 146.8, 147.6 (Ph), 155.1(*C*O-Boc), 172.9 (*C*OOMe) ppm. IR ($CHCl_3$, NaCl): ṽ = 3380 (OH and NH), 1740 (C=O ester), 1720 (C=O carbamate), 1521 (N=O nitro) cm^{-1}. MS (ESI$^+$): *m*/*z* = 363 [M + Na$^+$]. $C_{15}H_{20}N_2O_7$ (340.3): calcd. C 52.94, H 5.92, N 8.23, O 32.91; found C 52.91, H 5.91, N 8.22, O 33.14. HPLC: chiralcel OD, *i*PrOH/hexane (7:93), 1 mL·min^{-1}, 16.5 min (2*S*,3*R*), 19.3 min (2*R*,3*S*), 86% *ee*. $[\alpha]_D^{20}$ = +8.1 (*c* = 1, $CHCl_3$) for the pure enantiomer (2*R*,3*S*).

(2*R*,3*S*)-(+)-*N*-(*tert*-butoxycarbonyl)-3-(*m*-nitrophenyl)isoserine Methyl Ester (2c): The catalyst was added at 0 °C and the reaction mixture was stirred for 30 min at 0 °C and then for 6 h at room temperature. Flash chromatography afforded **2c** (186 mg, 54.8%) as a white solid. m.p. 128−129 °C. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 1.45 (s, 9 H, Boc), 3.24 (d, $^3J_{H,H}$ = 2.7 Hz, 1 H, O*H*), 3.90 (s, 3 H, OCH_3), 4.52 (br. s, 1 H, C*H*OH), 5.32 (br. d, $^3J_{H,H}$ = 9.1 Hz, 1 H, C*H*NH), 5.50 (d, $^3J_{H,H}$ = 9.1 Hz, 1 H, N*H*), 7.52 (t, $^3J_{H,H}$ = 7.9 Hz, 1 H, Ph), 7.72 (d, $^3J_{H,H}$ = 7.6 Hz, 1 H, Ph), 8.15 (d, $^3J_{H,H}$ = 8.1 Hz, 1 H, Ph), 8.28 (s, 1 H, Ph) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 28.3 (*C*H$_3$ Boc), 53.5 (O*C*H$_3$), 55.6 (*C*HNH), 73.2 (*C*HOH), 80.7 [*C*(CH$_3$)$_3$], 122.0, 122.8, 129.6, 133.2, 141.7, 148.5 (Ph), 155.1 (*C*O-Boc), 172.9 (*C*OOMe) ppm. IR ($CHCl_3$, NaCl): ṽ = 3380 (OH and NH), 1740 (C=O ester), 1720 (C=O carbamate), 1530 (N=O nitro) cm^{-1}. MS (ESI$^+$): *m*/*z* = 363 [M + Na$^+$]. $C_{15}H_{20}N_2O_7$ (340.3): calcd. C 52.94, H 5.92, N 8.23, O 32.91; found C 52.83, H 5.98, N 8.18, O 33.01. HPLC: chiralcel OD, *i*PrOH/hexane (7:93), 1 mL·min^{-1}, 18.4 min (2*S*,3*R*), 20.2 min (2*R*,3*S*), 81% *ee*. $[\alpha]_D^{20}$ = +1.6 (*c* = 1.2, $CHCl_3$) for the pure enantiomer (2*R*,3*S*).

(2*R*,3*S*)-(−)-*N*-(*tert*-butoxycarbonyl)-3-(*o*-nitrophenyl)isoserine Methyl Ester (2d): The catalyst was added at 0 °C and the reaction mixture was stirred for 30 min at 0 °C and then for 6 h at room temperature. Flash chromatography afforded a mixture of **2d** and its regioisomer **2′d** (184 mg, 54.1%) as a yellow foam. Further TLC chromatography (CH_2Cl_2/acetone, 97:3) of 43.9 mg of the mixture

afforded **2d** (30.3 mg, 38%) as a yellow foam and **2′d** (12.7 mg, 15.7%).

2d: ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 1.39 (s, 9 H, Boc), 3.64 (s, 1 H, O*H*), 3.90 (s, 3 H, OCH_3), 4.67 (br. s, 1 H, C*H*OH), 5.59 (br. d, $^3J_{H,H}$ = 9.0 Hz, 1 H, C*H*NH), 5.89 (d, $^3J_{H,H}$ = 9.0 Hz, 1 H, N*H*), 7.46 (t, $^3J_{H,H}$ = 8.4 Hz, 1 H, Ph), 7.62 (m, 2 H, Ph), 8.02 (d, $^3J_{H,H}$ = 7.8 Hz, 1 H, Ph) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 28.3 (*C*H$_3$ Boc), 52.1 (O*C*H$_3$), 53.6 (*C*HNH), 72.3 (*C*HOH), 80.4 [*C*(CH$_3$)$_3$], 125.0, 128.6, 129.4, 133.3, 135.3, 148.3 (Ph), 154.8 (*C*O-Boc), 173.5 (*C*OOMe) ppm. IR ($CHCl_3$, NaCl): $\tilde{\nu}$ = 3390 (OH and NH), 1740 (C=O ester), 1709 (C=O carbamate), 1524 (N=O nitro) cm^{-1}. MS (ESI $^+$): *m*/*z* = 363 [M + Na$^+$]. $C_{15}H_{20}N_2O_7$ (340.3): calcd. C 52.94, H 5.92, N 8.23, O 32.91; found C 52.01, H 5.95, N 8.21, O 32.9. HPLC: chiralcel OD, *i*PrOH/hexane (7:93), 1 mL·min^{-1}, 14.1 min (2*S*,3*R*), 21.3 min (2*R*,3*S*), 82% *ee*. $[\alpha]_D^{20}$ = −235 (*c* = 0.2, $CHCl_3$) for the pure enantiomer (2*R*,3*S*).

2′d: ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 1.27 (s, 9 H, Boc), 3.85 (s, 3 H, OCH_3), 4.94 (d, $^3J_{H,H}$ = 9.2 Hz, 1 H, NH), 5.42 (br. d, $^3J_{H,H}$ = 9.2 Hz, 1 H, C*H*NH), 5.94 (br. s, 1 H, C*H*OH), 7.46 (t, $^3J_{H,H}$ = 7.7 Hz, 1 H, Ph), 7.64 (t, $^3J_{H,H}$ = 7.5 Hz, 1 H, Ph), 7.85 (d, $^3J_{H,H}$ = 7.5 Hz, 1 H, Ph), 8.06 (d, $^3J_{H,H}$ = 8.0 Hz, 1 H, Ph). MS (ESI$^+$): *m*/*z* = 363 [M + Na$^+$]. HPLC: chiralcel OD, *i*PrOH/hexane (7:93), 1 mL·min^{-1}, 16.2 min, 21.3 min.

Benzyloxyglutaryl-*p*-aminocinnamate Methyl Ester (6e)

a) Methyl *p*-Aminocinnamate Hydrochloride: Methanol (20 mL) and acetyl chloride (100 μL) were placed in a round-bottomed flask and stirred for 15 min at 0 °C. Then, the *p*-aminocinnamic acid (500 mg, 2.5 mmol) was added and the mixture was heated to reflux temperature for 3 h. The TLC analysis (CH_2Cl_2/MeOH, 13:1) confirmed the absence of starting material after this time. The reaction mixture was concentrated and the product precipitated out of solution. The mixture was filtered and washed with cold MeOH to afford 465 mg of pure methyl *p*-aminocinnamate hydrochloride (87% yield) as slightly yellow crystals; m.p. 194−196 °C. ^{1}H NMR (400 MHz, CD_3SOCD_3, 25 °C): δ = 3.71 (s, 3 H, OCH_3), 6.58 (d, $^3J_{H,H}$ = 15.7 Hz, C*H*=), 7.31 (d, $^3J_{H,H}$ = 8.4 Hz, 2 H, Ph), 7.61 (d, $^3J_{H,H}$ = 15.7 Hz, 1 H, C*H*=), 7.75 (d, $^3J_{H,H}$ = 8.4 Hz, 2 H, Ph) ppm. ^{13}C NMR (100 MHz, CD_3SOCD_3, 25 °C): δ = 50.0 (O*C*H$_3$), 122.6 (*C*H=), 118.0, 130.2, 132.1, 137.3 (Ph), 144.2 (*C*H=), 167.2 (*C*OOMe) ppm. IR (KBr): $\tilde{\nu}$ = 1716 cm^{-1} (C=O ester). MS (EI$^+$): *m*/*z* = 177 [M$^+$]. $C_{10}H_{12}NO_2$ (178.2): calcd. C 56.21, H 5.66, N 6.55, O 14.97; found C 56.37, H 5.63, N 6.55, O 15.06.

b) Glutaryl-*p*-aminocinnamate Methyl Ester: Methyl *p*-aminocinnamate hydrochloride (500 mg, 2.34 mmol) was dissolved in a mixture H_2O/THF (2:1; 6 mL). Then, solid K_2CO_3 (330 mg) was added until pH 8. The reaction mixture was then stirred for 10 min at room temperature. Glutaric anhydride (1.0 g, 8.76 mmol) was added and the reaction mixture was stirred for 30 min. TLC analysis (CH_2Cl_2/MeOH, 10:1) confirmed the absence of starting material after this time. The reaction mixture was then concentrated and the product precipitated out of solution. The product was isolated by filtration, washed with water and dried under high vacuum to give 578 mg of pure glutaryl-*p*-aminocinnamate methyl ester (85% yield) as a white solid; m.p. 139−141 °C. ^{1}H NMR (400 MHz, CD_3SOCD_3, 25 °C): δ = 1.80 (m, 2 H, -CH_2-), 2.27 (t, $^3J_{H,H}$ = 7.3 Hz, 2 H, -CH_2-CONH), 2.35 (t, $^3J_{H,H}$ = 7.3 Hz, 2 H, -CH_2-COOMe), 3.70 (s, 3 H, OCH_3), 6.49 (d, $^3J_{H,H}$ = 16.1 Hz, C*H*=), 7.57 (d, $^3J_{H,H}$ = 16.1 Hz, 1 H, CH=), 7.65 (s, 4 H, Ph), 10.16 (s, 1 H, -N*H*) ppm. ^{13}C NMR (100 MHz, CD_3SOCD_3, 25 °C): δ = 20.9 (-*C*H$_2$-), 33.5 (-*C*H$_2$-CONH), 36.0 (-*C*H$_2$-COOMe), 51.9 (O*C*H$_3$), 119.5 (*C*H=), 116.3, 129.1, 129.8, 141.9 (Ph), 144.8 (*C*H=), 167.4 (*C*OOMe), 171.7 (-NH*C*O-), 174.8 (-*C*OOH) ppm. IR (KBr): $\tilde{\nu}$ = 3313 cm^{-1} (N−H), 1699 (C=O ester). MS (EI$^+$): *m*/*z* = 291 [M$^+$].

c) Benzyloxyglutaryl-*p*-aminocinnamate Methyl Ester (6e): Glutaryl-*p*-aminocinnamate methyl ester (500 mg, 2.04 mmol) was dissolved in methanol (6.02 mL). Then K_2CO_3 solution (20% aq) was added dropwise until pH 8, and the solvents evaporated to dryness. *N,N*-Dimethylformamide (6 mL) and benzyl chloride (0.3 mL, 2.24 mmol) were then added and the resulting mixture was stirred at room temperature under argon overnight. The reaction was monitored by TLC analysis (CH_2Cl_2/MeOH, 18:1); after this time, water (20 mL) and ethyl acetate (20 mL) was added and the phases were separated. The organic phase was dried over Na_2SO_4 and concentrated to dryness to give 622 mg of pure benzyloxyglutaryl-*p*-aminocinnamate methyl ester (95% yield) as a white solid; m.p. 90−92 °C. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 2.04 (m, 2 H, -CH_2-), 2.39 (t, $^3J_{H,H}$ = 7.3 Hz, 2 H, -CH_2-CONH), 2.46 (t, $^3J_{H,H}$ = 6.9 Hz, 2 H, -CH_2-COOBn), 3.77 (s, 3 H, OCH_3), 5.10 (s, 2 H, -OCH_2-Ph) 6.32 (d, $^3J_{H,H}$ = 16.1 Hz, C*H*=), 7.59 (d, $^3J_{H,H}$ = 16.1 Hz, 1 H, CH=),7.34−7.50 (m, 9 H, Ph), 7.80 (s, 1 H, -N*H*) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 20.8 (-*C*H$_2$-), 33.2 (-*C*H$_2$-CONH), 36.4 (-*C*H$_2$-COOMe), 51.7 (O*C*H$_3$), 66.5 (Ph*C*H$_2$-O), 116.7 (*C*H=), 119.8, 129.1, 128.3, 128.4, 129.1, 135.9, 139.9 (Ph), 144.3 (*C*H=), 167.7 (*C*OOMe), 170.8 (-NH*C*O-), 173.2 (-*C*O-OBz) ppm. IR (KBr): $\tilde{\nu}$ = 3350 cm^{-1} (N−H), 1733 (C=O ester). MS (ESI$^+$): *m*/*z* = 404 [M + Na$^+$]. $C_{22}H_{23}NO_5$ (381.4): calcd. C 69.27, H 6.08, N 3.67, O 20.97; found C 69.39, H 6.17, N 3.53, O 21.17.

(2*R*,3*S*)-(+)-*N*-(*tert*-butoxycarbonyl)-3-(benzyloxyglutaryl-*p*-aminophenyl)isoserine Methyl Ester (2e)

Preparation of *N*-Bromo-*tert*-butoxycarboxamide: Oxone® (9.22 g, 15 mmol) was added to a suspension of KBr (1.78 g, 15 mmol) and wet alumina (0.2 mL H_2O/g alumina, 15 g) in a 3:1 mixture of CCl_4 and $CHCl_3$ (60 mL). The mixture was heated at 45 °C for 15 min. A solution of the *tert*-butoxycarboxamide (351 mg, 3 mmol) in a 1:1 mixture of CCl_4 and $CHCl_3$ (15 mL) was then added and the resulting mixture stirred for 60 h at room temperature. The mixture was then filtered and the solution evaporated to dryness. The crude material was purified by flash chromatography on silica gel (petroleum ether/EtOAc, 11:1) to afford pure *N*-bromo-*tert*-butoxycarboxamide (372 mg, 63.5%) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 1.39 [s, 9 H, -C(CH_3)$_3$], 6.5 (s, 1 H, -CON*H*Br) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 28.0 [C(*C*H$_3$)$_3$], 83.3 [*C*(CH$_3$)$_3$], 156.1(*C*ONHBr) ppm. IR (KBr): $\tilde{\nu}$ = 3240 cm^{-1} (N−H), 1701 (C=O), 1248 (C−O).

Lithium hydroxide (43 mg, 1.02 mmol) and $K_2OsO_2(OH)_4$ (14.7 mg, 0.04 mmol, 4 mol %) were dissolved in water (9 mL) with stirring. To this solution were added *t*BuOH (6 mL) and $(DHQ)_2PHAL$ (39 mg, 0.05 mmol, 5 mol %). The mixture was stirred for 10 min and the flask was cooled to between 0 and 5 °C. Benzyloxyglutaryl-*p*-aminocinnamate methyl ester **6e** (381 mg, 1 mmol) was then added followed by *t*BuOCONHBr (216.7 mg, 1.1 mmol). The color of the reaction changed immediately from yellow to green and then back to yellow at the end of the reaction. The reaction mixture was stirred at 0−5 °C until the reaction was complete. The reaction was quenched with sodium sulfite (0.5 g) and stirred for 30 min at room temperature. The aqueous phase was separated and extracted with ethyl acetate. The combined organic phases were dried over sodium sulfate and concentrated. The crude product was purified by flash chromatography (EtOAc/diethyl ether, 1:1) to afford **2e** (122.8 mg, 24%) as a white solid. Three

recrystallizations from hexane afforded the pure enantiomer (2*R*,3*S*); m.p. 132−133 °C. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 1.37 (s, 9 H, Boc), 1.95−2.00 (m, 2 H, CH_2), 2.32−2.41 (m, 4 H, CH_2), 3.67 (s, 1 H, O*H*), 3.75 (s, 3 H, OCH_3), 4.38 (br. s, 1 H, C*H*OH), 5.07 (s, 2 H, CH_2Ph), 5.10 (br. d, $^3J_{H,H}$ = 8.4 Hz, 1 H, C*H*NH), 5.49 (d, $^3J_{H,H}$ = 8.4 Hz, 1 H, N*H*), 7.12−7.34 (m, 9 H, Ph), 8.16 (s, 1 H, Ph-N*H*CO) ppm. ^{13}C NMR (100 MHz, $CDCl_3$,25 °C): δ = 20.8 (*C*H_2), 28.3 (*C*H_3 Boc), 33.3 (*C*H_2), 36.2 (*C*H_2), 53.0 (O*C*H_3), 55.9 (*C*HNH), 66.4 (*C*H_2Ph), 73.2 (*C*HOH), 80.1(*C*-Me_3), 119.9, 122.0, 126.6, 127.3, 128.4, 128.7, 137.5 (Ph), 155.4 (*C*O-Boc), 171.1, 173.1, 173.3 (*C*OOMe and *C*ONH) ppm. IR (KBr): ṽ = 3353 cm^{-1}, 2937, 1738, 1678, 1622, 1601, 1516, 1415. MS (L-SIMS$^+$): *m*/*z* = 537 [M + Na^+] $C_{27}H_{34}N_2O_8$ (514.2): calcd. C 63.02, H 6.66, N 5.44, O 24.87; found C 62.99, H 6.82, N 5.52, O 24.99. HPLC: chiralcel OD, *i*PrOH/hexane (2:98), 0.05 mL/min: 39.4 min (2*R*,3*S*), 21.3 (2*S*,3*R*) 79.4% *ee*. $[\alpha]_D^{20}$ = +4.5 (*c* = 10, EtOH) for the pure enantiomer (2*R*,3*S*).

(2*R*,3*S*)-(+)-*N*-tosyl-3-(benzyloxyglutaryl-*p*-aminophenyl)isoserine Methyl Ester (2f): In a 100 mL round-bottomed flask a solution of $(DHQ)_2PHAL$ (35.7 mg, 0.045 mmol), *t*BuOH (3.24 mL) and water (3.24 mL) was prepared. The flask was immersed in a water bath at room temperature. To this homogeneous solution was added, in order, chloramine-T (1.46 g, 5.59 mmol), the olefin (340 mg, 0.89 mmol) and $K_2OsO_2(OH)_4$ (13.5 g, 0.036 mmol). As the reaction proceeded the color changed from yellow to green in 15 min and then back to yellow corresponding to the disappearance of the olefin. The flask was then immersed in an ice bath for 20 min. To this cold, stirred solution the remainder of chloramine-T (0.366 g, 1.39 mmol) and a second portion of the olefin (170 mg, 0.45 mmol) were added. The ice bath was replaced by a water bath at room temperature, the last olefin was consumed changing color from yellow to green and back to yellow. The resulting mixture was cooled back to 0 °C for over 15 min and a final portion of olefin (170 mg, 0.45 mmol) was added. The reaction mixture was then allowed to stand at room temperature. Essentially all the product precipitated out of the solution and was isolated by filtration, washed twice with cold portions of *t*BuOH/H_2O (1:1) and dried under high vacuum to afford **2f** (699 mg, 69%) as a colorless solid; m.p. 115−117 °C. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 2.03−2.08 (m, 2 H, CH_2), 2.30−2.49 (m, 7 H, CH_2 and CH_3-Ts), 3.41 (s, 1 H, O*H*), 3.70 (s, 3 H, OCH_3), 4.32 (br. s, 1 H, C*H*OH), 4.81 (d, $^3J_{H,H}$ = 9.2 Hz, 1 H, C*H*NHTs), 5.14 (s, 2 H, CH_2Ph), 5.79 (d, $^3J_{H,H}$ = 9.2 Hz, 1 H, N*H*), 7.08−7.56 (m, 14 H, Ph and N*H*CO), 8.16 (s, 1 H, Ph-N*H*CO) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 20.9 (*C*H_2), 21.5 (*C*H_3-Ts), 33.2 (*C*H_2), 36.4 (*C*H_2), 53.2 (O*C*H_3), 58.7 (*C*HNH), 66.5 (*C*H_2Ph), 74.3 (*C*HOH), 119.7−143.4 (Ph), 170.7, 172.9, 173.3 (*C*OOMe and *C*ONH) ppm. IR (KBr): ṽ = 3452 cm^{-1}, 3300, 1734, 1662, 1602, 1525. HPLC: chiralcel OD, *i*PrOH/hexane (2:98), 0.05 mL/min: 65.4 min (2*R*,*3S*), 93.2 min (2*S*,3*R*), 65.7% *ee*. $[\alpha]_D^{20}$ = +19.3 (*c* = 0.01, EtOH) for the pure enantiomer (2*R*,3*S*).

(2*R*,3*S*)-(+)-*N*-acetyl-3-(benzyloxyglutaryl-*p*-aminophenyl)isoserine Methyl Ester (2g): The procedure was the same as for compound **2e** but with *N*-bromoacetamide as the nitrogen donor. The reaction was conducted at 0−5 °C for 20 h. Flash chromatography afforded **2g** (85 mg, 23%) as a white solid; m.p. 142−145 °C. ^{1}H NMR (400 MHz, $CDCl_3$,25 °C): δ = 1.99 (s, 3 H, Ac), 2.07−2.01 (m, 2 H, CH_2), 2.35−2.48 (m, 4 H, CH_2), 3.73 (s, 1 H, O*H*), 3.81 (s, 3 H, OCH_3), 4.40 (d, $^3J_{H,H}$ = 1.8 Hz, 1 H, C*H*OH), 5.11 (s, 2 H, CH_2Ph), 5.44 (br. d, $^3J_{H,H}$ = 8.8 Hz, 1 H, C*H*NH), 6.39 (d, $^3J_{H,H}$ = 9.2 Hz, 1 H, 3-N*H*), 7.22−7.42 (m, 9 H, Ph), 7.56 (s, 1 H, Ph-N*H*CO) ppm. IR (KBr): ṽ = 3326 cm^{-1}, 3124, 2956, 1734, 1655, 1603, 1527. MS (L-SIMS$^+$): *m*/*z* = 479 [M+ Na^+]. HPLC: chiralcel OD, *i*PrOH/hexane (20:80), 0.5 mL/min: 84.7 min (2*R*,3*S*), 73.3 min (2*S*,3*R*), 98% *ee*. $[\alpha]_D^{20}$ = +12.7 (*c* = 10, EtOH) for the pure enantiomer (2*R*,3*S*).

Acknowledgments

This work was supported by the agreement France-Mexico ECOS-ANUIES (M97-E02). S. Montiel acknowledges the fellowship awarded by SEP-ANUIES (México) to carry out a part of her PhD studies in the ICSN-CNRS, France. V. Cervantes acknowledges the fellowship awarded by CONACYT (México) to carry out his PhD.

[1] D. Guénard, F. Guéritte-Voegelein, F. Lavelle, *Current Pharmaceutical Design* **1995**, *1*, 95−112.
[2] For a review, see: I. Ojima, S. Lin, T. Wang, *Current Med. Chem.* **1999**, *6*, 927−954.
[3] L. Mangatal, M.-T. Adeline, D. Guénard, F. Guéritte-Voegelein, P. Potier, *Tetrahedron* **1989**, *45*, 4177−4190.
[4] E. Herranz, S. A. Biller, K. B. Sharpless, *J. Am. Chem. Soc.* **1978**, *100*, 3596−3598.
[5] G. Li, H.-T. Chang, K. B. Sharpless, *Angew. Chem.* **1996**, *108*, 449−452; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 451−454.
[6] G. Li, H. H. Angert, K. B. Sharpless, *Angew. Chem.* **1996**, *108*, 2995−2999; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 2813−2817.
[7] K. B. Sharpless, G. Li, H.-T. Chang, PCT Int. Appl. **1997**, WO 1997-US8593, 1997−05−21.
[8] J.-D. Bourzat, A. Commerçon, *Tetrahedron Lett.* **1993**, *34*, 6049−6052.
[9] C. E. Song, C. R. Oh, S. W. Lee, S. Lee, L. Canali, D. C. Sherrington, *Chem. Commun.* **1998**, 2435−2436.
[10] N. S. Barta, D. R. Sidler, K. B. Somerville, S. A. Weissman, R. D. Larsen, P. J. Reider, *Org. Lett.* **2000**, *2*, 2821−2824.
[11] K. L. Reddy, K. R. Dress, K. B. Sharpless, *Tetrahedron Lett.* **1998**, *39*, 3667−3670.
[12] V. V Fokin, K. B. Sharpless, *Angew. Chem.* **2001**, *113*, 3563−3565; *Angew. Chem. Int. Ed.* **2001**, *40*, 3455−3457.
[13] See ref. 8 of ref.[6]
[14] M. Bruncko, G. Schingloff, K. B. Sharpless, *Angew. Chem.* **1997**, *109*, 1580−1583; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 1483−1486.
[15] T. Boge, G. I. Georg, in *Enantioselective Synthesis of β-Amino Acids* (Ed.: E. Juaristi), Wiley-VCH: New York, **1997**, pp 1−43.

Received March 8, 2002
[O02125]