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Synthesis of Chiral α-Substituted *N*-[((2*S*)-2-Hydroxy-2-phenyl)-ethyl]-2-phenylglycine Derivatives by Diastereocontrolled Alkylation of (6 *R*)-2,3,5,6-Tetrahydro-3,6-diaryl-*N*-[(2'*R*)-(2'-methyl)phenyl-methyl]-4*H*-1,4-oxazin-2-ones

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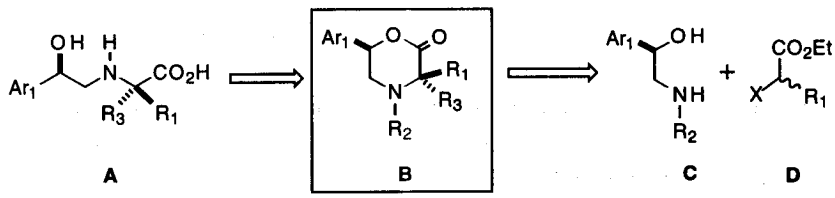
Abstract: The synthesis of α-substituted *N*-[((2*S*)-2-hydroxy-2-phenyl)-ethyl]-2-phenylglycine derivatives is reported. The key step of the sequence is the highly diastereoselective alkylation of (6*R*)-2,3,5,6-tetrahydro-3,6-diaryl-*N*-[(2'*R*)-(2'-methyl)phenylmethyl]-4*H*-1,4-oxazin-2-ones after deprotonation with *t*-BuOK. Opening of the resulting oxazinone with ethanolic KOH, followed by hydrogenolysis of the corresponding *N*-[(2*R*)-(2-methyl)phenylmethyl] compound to furnish the expected 2-phenylglycine derivative, is also described.

Introduction

In order to prepare β-amino-alcohols of type **A**, and as a model, we examined the possibility of synthesizing oxazinones of type **B** with complete control of the chirality at C-3 (*R* configuration was needed). Successive introduction of R_3 and R_1 or vice-versa (R_1 = alkyl, R_3 = aryl, and R_2 = protecting group) was envisioned, with stereochemistry controlled by the phenyl substituent at C-6. Oxazinones **B** should be easily prepared by condensation of **C** with **D**.



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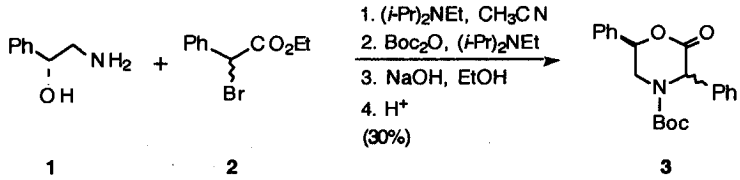
Baldwin[1,2] has reported that double successive dialkylations at C-3 of Williams chiral *N*-*t*-Boc or *N*-Cbz-5,6-diphenyl-1,4-oxazin-2-ones with reactive electrophiles very efficiently afforded chiral α-alkylated non-natural α-amino-acids. In contrast to the chiral glycine anion equivalents of Williams (5,6-diphenyloxazinones[3]) and of Dellaria[4] (5-phenyloxazinones) and Baker[5] (5-benzyloxazinones), oxazinones of type **B** lacked phenyl or benzyl groups at C-5. Nevertheless, we were interested to check if diastereoselection at C-3 could be driven only by the phenyl ring at C-6.

Discussion

Various *N*-protecting groups of oxazinones have been described,[3,4] the *t*-Boc group being the most used in diastereoselective alkylation and/or arylation at C-3 of these rings. Our first attempt was to introduce an alkyl group at C-3 of oxazinones such as **3** according to Dellaria's procedures.[4]

We prepared 3-phenyloxazinone **3** in 30% yield as a mixture of diastereoisomers (*ca.* 3:1) by condensation of **1** and **2**[6] as depicted in Scheme 1, starting from ethyl 2-bromophenylacetate **2**, introduction of the protecting group, hydrolysis of the ethyl ester, and acidic cyclization.

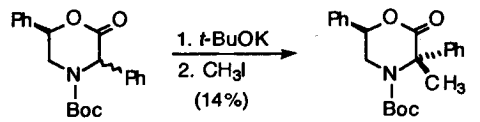
Scheme 1



1 **2** **3**

Methylations of **3** with bases such as NaH, NaHMDS or LDA at low temperature were unsuccessful. Only KHMDS or *t*-BuOK, as described by Schöllkopf[7] for 3-phenyl-5-methoxy-3,6-dihydro-2*H*-1,4-oxazin-2-ones, were useful bases to furnish **4**, albeit with some remaining oxazinone **3** (40 %) (Scheme 2). When the reaction was carried out at higher temperature, no starting material remained but **4** (the only diastereoisomer observed) was obtained in low yield (14%).

Scheme 2

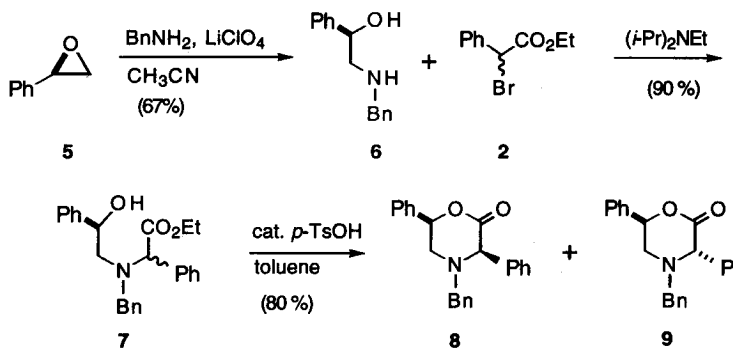


3 **4** (3*R*, 6*R*)

The *N*-benzyl protecting group was studied next, although for Dellaria[4a] in the case of chiral (5*R*)-5-phenyl-*N*-benzyl-2,3,5,6-4*H*-1,4-oxazin-2-one, alkylation with benzyl bromide took place preferentially in a *cis* fashion at C-3 after deprotonation with NaHMDS. Thus, condensation of an excess of benzylamine with (*R*)-

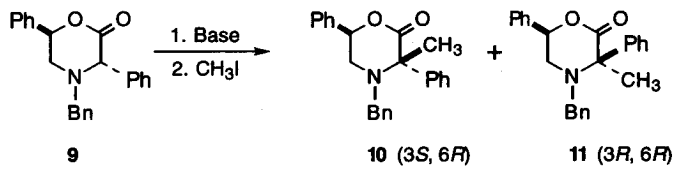
phenyloxirane **5** in the presence of $LiClO_4$ took place preferentially at the β position of the epoxide ring (93:7 ratio), and pure regioisomer **6** was obtained in 69 % yield after recrystallization from isopropanol. It is noteworthy that Crotti[8] obtained, under the same conditions, but with an equimolecular amount of benzylamine relative to **5**, a 40:60 mixture of regioisomers, with predominant α-opening. Condensation of **6** with **2**, followed by lactonisation with a catalytic amount of *p*-toluenesulfonic acid monohydrate in refluxing toluene, furnished oxazinone **8** and **9** (40:60) in 48 % overall yield from **5** (Scheme 3).

Scheme 3



Crystallization from AcOEt/heptane of the mixture allowed us to obtain oxazinone **9** as a pure single diastereoisomer. Deprotonation of **9** with LDA, LiHMDS, NaHMDS or NaH, followed by addition of an excess of CH_3I resulted in no alkylation but rather in epimerization at C-3 leading to 60 : 40 mixture of **8** and **9**.

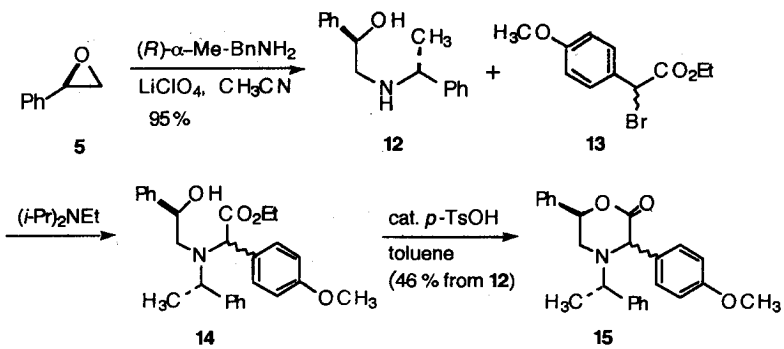
Scheme 4



When *t*-BuOK or KHMDS were used as bases at -75 °C to generate the corresponding enolate, only partial alkylation took place. When the temperature was raised to 0 °C, a mixture of **10** and **11** was obtained (60:40 ratio), but with some **9** remaining (Scheme 4). Finally, the reaction was found to go to completion when the intermediate enolate was brought to 23 °C before the addition of the electrophile. In this case, the mixture of **10** and **11** was obtained in 79 % yield, but still with a very limited diastereoselectivity. In this case de (diastereoisomeric excess) was only 20 % in favor of (3*S*, 6*R*)-isomer **10**. Each diastereoisomer was isolated by reverse phase preparative chromatography and characterized by NMR and X-rays experiments.

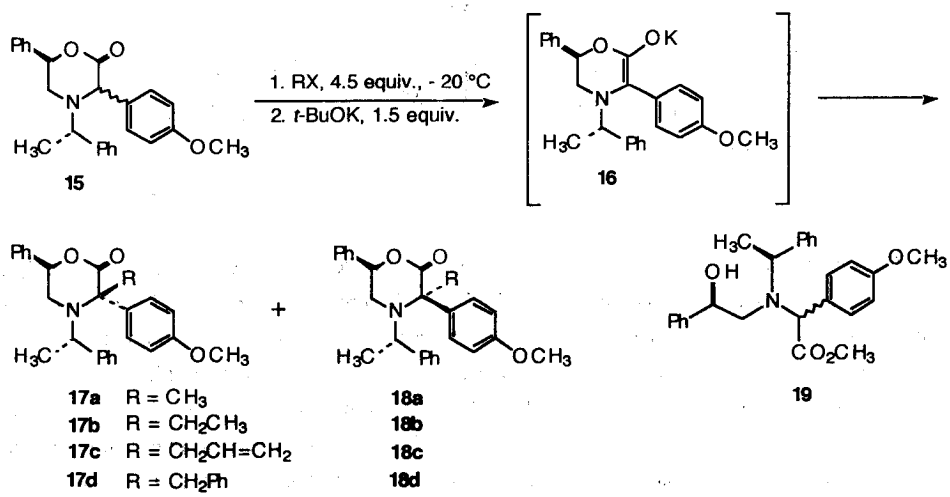
Next, we turned our attention to the same *N*-benzyl-oxazinone **9** with an additional chiral methyl group on the *N*-benzyl position. Our hope was to drive the steroselectivity by adding a new chiral center close to C-3 as well as increasing the steric bulk near this center. We also replaced the 3-phenyl ring with the required 4-methoxyphenyl ring. Thus, we prepared oxazinone **15** in three steps from epoxide **5** and (*R*)-α-methylbenzylamine in 44 % overall yield *via* ethyl 2-bromo-(4-methoxy)phenyl acetate **13**[9] and β-amino-alcohol **14** prepared similarly as for the derivative 7 (Scheme 5).

Scheme 5



When **15** was deprotonated with *t*-BuOK in THF at -20 °C, followed by addition of CH_3I, we observed the formation of diastereoisomers **17a** and **18a** in a 91:9 ratio and in 58 % yield in addition to some ring-opened derivative **19** of the starting oxazinone (Scheme 6).

Scheme 6



When the electrophile was added prior to the addition of *t*-BuOK, we were able to increase the yield to 87 % and in a similar 84 % de. According to this procedure, with each single (3*S*, 6*R*) and (3*R*, 6*R*) diastereoisomer of **15**, we obtained the same diastereoisomeric excess of C-3 methylated oxazinone **17a** and **18a**, thus indicating that the process went through the enolate **16** (Scheme 6). We examined various electrophiles as depicted in Table 1. Increasing the size of the electrophile resulted in an increase in the diastereoisomeric excess, although some other factors such as the type of leaving group (Br vs I) or electronic factors for the last two electrophiles could also contribute to the stereochemical outcome.[10] Recrystallization or silica gel chromatography of the crude mixture allowed us to isolate pure derivatives **17**.

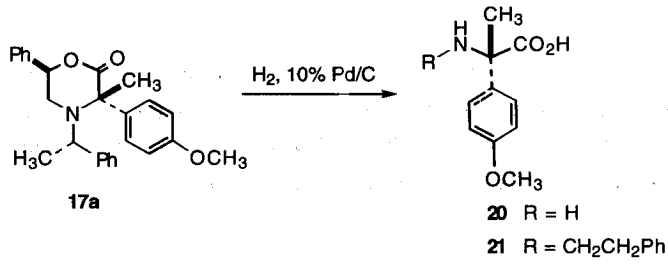
Table 1. Alkylation of oxazinones **15**

Compound	RX	Crude yield[a] (%)	Isolated yield[b] (%)	de[c]
17a	CH_3I	87	74	84
17b	CH_3CH_2I	92	65	98
17c	$CH_2{=}CHCH_2Br$	89	77	100
17d	$PhCH_2Br$		69[d]	94

[a] crude yield for the mixture of **17** + **18**
[b] isolated yield of **17** after recrystallization and/or chromatography
[c] de: diastereoisomeric excess of **17** vs **18** on the crude mixture (as measured by NMR or HPLC)
[d] diastereoisomers could not be separated by chromatography but were quantified by HPLC

We next tried to hydrogenolyze the benzylic protecting group of the nitrogen of oxazinones **17** (Scheme 7). Surprisingly, attempted removal of the α-methyl-benzyl group of oxazinone **17a** with 10% Pd on C in methanol under 1-2 bars gave, in quantitative crude yield, a mixture of the unexpected 2-(4-methoxyphenyl)-2-methylglycine **20** and also the *N*-phenethyl analogue **21** in a 60:40 ratio respectively as seen by NMR. While derivative **21** was likely to arise from the hydrogenolysis of the C-1-C-6 bond of oxazinone derivative **17a**, formation of phenylglycine derivative **20** was not completely understood.

Scheme 7



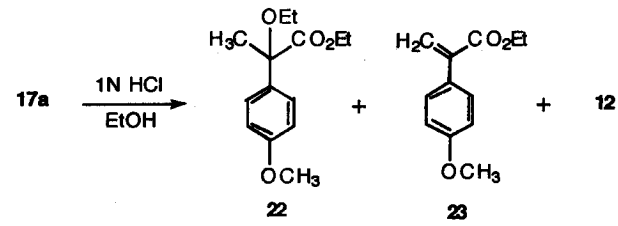
17a

20 R = H

21 R = CH_2CH_2Ph

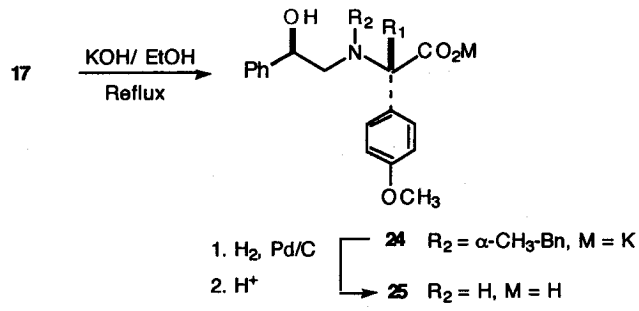
In the other hand, attempts were made to first open the lactone ring and then to deprotect the benzylic group. Several conditions were tried to open oxazinone **17a** such as KCN/MeOH,[11] NH_3/EtOH,[12] *t*-BuOK/BnBr, excess morpholine, benzylmercaptan, or *p*-TsOH/EtOH. Oxazinone **17a** resisted all these conditions. We also tried hydrochloric acid in ethanol,[2] which led to the starting amino-alcohol **12** and derivatives **22** and **23** which, in our hands, could not be separated by chromatography (Scheme 8).

Scheme 8



Acid-catalyzed elimination of the nitrogen substituent attached at C-3 would explain the formation of **23** while nucleophilic attack of ethanol directly at C-3 of the oxazinone is likely the process to generate **22**.[13]
Finally, we were able to cleave oxazinone **17** with alcoholic potassium hydroxyde under reflux to provide *N*-protected derivative **24** as a potassium salt in quantitative yield (Scheme 9).

Scheme 9



Hydrogenolysis of **24** over 10% Pd/C in H_2O under 4 bars furnished the expected 2-phenylglycine derivatives **25** after neutralization with 2N aqueous hydrochloric acid in 91 % yield (Scheme 9). Thus, the overall yield from oxazinone **15** to chiral 2-methyl-2-phenylglycine **25a** was 67 % (Table 2). Under similar conditions, hydrogenolysis of 3-allyl derivative **17c** furnished the 3-propyl derivative **24c** in quantitative yield (Table 2).

Table 2. Preparation of phenylglycine derivatives **25**

Compound	R_2	Isolated yield 24 (%)	Isolated yield 25 (%)
25a	CH_3	100	91[b]
25b	CH_3CH_2	100	nd[c]
25c	$CH_3CH_2CH_2$	100[a]	87[b]

[a] $R_2 = CH_2CH{=}CH_2$
[b] isolated yield from **17**
[c] not done

Conclusion

In this report, we have demonstrated the diastereoselective alkylation of oxazinone **15** in good yield with various electrophiles. Oxazinone **15** was readily prepared in 3 steps from (*R*)-styrene oxide **5** and (*R*)-(+)-α-methylbenzylamine followed by addition of ethyl 2-bromo-(4-methoxyphenyl)acetate **13**. Opening of α-alkylated oxazinones **17** with ethanolic potassium hydroxyde followed by hydrogenolysis furnished the chiral 2-alkyl-2-phenylglycines in 30 % overall yield from **5** for derivative **25a** and **25c**.

Experimental Section

Unless otherwise noted, starting materials were obtained from commercial suppliers and used without further purification. Melting points were taken in a Büchi 510 capillary apparatus and are uncorrected. Elemental analyses were performed by the Bristol-Myers Squibb Analytical Department. ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ or DMSO-d_6 solutions on a Bruker ARX 500 spectrometer at 500 and 50 Mhz respectively. The ^1H chemical shifts are reported in ppm from H_2O as external signal. The ^{13}C chemical shifts are reported in ppm relative to the center line of $CDCl_3$ (77.0 ppm). Infra-red spectra were recorded on a Nicolet FT-IR SXC spectrophotometer. Optical rotations were measured in a 1-dm cell with a Perkin-Elmer model 241 polarimeter. HPLC experiments were performed on Varian 9000 Series or Hewlett-Packard 1050 Series chromatographs. Flash chromatography was done with Merck silica gel 60 70-230 mesh and analytical TLC was performed on Merck glass-backed silica gel 60 plates, 0.25 mm thickness, with a 254-nm fluorescent indicator. All reactions were performed under N_2 pressure unless otherwise stated.

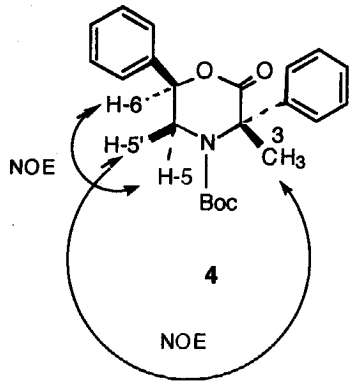
N-tert-Butyloxycarbonyl-(6R)-3,6-diphenyl-2,3,5,6-tetrahydro-4H-1,4-oxazin-2-one 3

To a solution of 9.1 g (66 mmoles) of **1** in 110 mL of CH_3CN were added 14.0 g (58 mmoles) of ethyl 2-bromo-2-phenylacetate **2** prepared according to Isbell's procedure[6] and 7.5 g (58 mmoles) of $(i\text{-Pr})_2NEt$. After being stirred for 4 h, the mixture was concentrated to dryness and the residue was dissolved in 300 mL of CH_2Cl_2. The organic layer was washed three times with water, dried over $MgSO_4$ and concentrated to dryness to provide an amorphous solid which was crystallized from heptane to yield 14.25 g (72%) of the mixture of diastereoisomers of ethyl 2-[*N*-((2*R*)-2-hydroxy-2-phenylethyl)amino]-2-phenylacetate, which was used as it for the next step; mp 90 °C; ^1H NMR (DMSO-d_6), δ 1.15 (2t, 3H), 2.54 (m, 2H), 4.10 (2q, 2H), 4.49 (2s, 1H), 4.64 (m, 1H), 5.36 (2d,1H), 7.31-7.37 (m, 11H). In 100 mL of CH_3CN, 7.0 g (21 mmoles) of the above intermediate, 3.15 g (21 mmoles) of K_2CO_3 and 4.9 g (21 mmoles) of di-*tert*-butyl dicarbonate were mixed together until total dissolution occurred as 7.5 mL of water were added to the mixture. After 24 h at room temperature, the reaction was found to be uncomplete and 3.15 g (21 mmoles) of K_2CO_3 and 4.9 g (21 mmoles) of di-*tert*-butyl dicarbonate were added to the solution, the overall mixture being stirred for 24 additional hours at room temperature. The solution was diluted with 300 mL of EtOAc and washed three times with brine. The organic layer was dried ($MgSO_4$) and concentrated to dryness to provide 14 g of an oil which was chromatographed (95:5 CH_2Cl_2/EtOAc) to afford 1.54 g of the residual unprotected α-amino-ester, 3.00 g (44.4%) of a diastereomeric mixture (54/46) of oxazinone **3**, and 4.40 g (47.5%) of a diastereomeric mixture (93/7) of the *N*-Boc α-amino-ester: ^1H NMR (DMSO-d_6), δ 1.24 (2t, 3H), 1.34 (1s, 9H), 3.21-3.54 (m, 2H), 4.19 (2q, 2H), 4.56 (m, 1H), 4.94 (d, 1H), 5.51 (s, 1H), 7.26-7.41 (m, 10H). The latter compound (4.2 g, 10.5 mmoles) was dissolved in 60 mL of EtOH and 9.9 mL (9.9 mmoles) of aqueous 1N NaOH were added, the resulting mixture being stirred for 2 h at room temperature before it was neutralized with 9.9 mL of 1N HCl. The residue was dissolved in Et_2O, washed twice with 5% $NaHCO_3$, dried ($MgSO_4$) and concentrated to dryness to yield 1.70 g of oxazinone **3** as a 75/25 diastereomeric mixture. The pH of the aqueous layer was adjusted to pH 5 and extracted with Et_2O. This organic layer was dried ($MgSO_4$) and concentrated to dryness to yield an additional 1.5 g (total 86%) of **3** in the same diastereoisomeric ratio; ^1H NMR at 340 °K (DMSO-d_6), δ 1.31 (s, 3H), 1.40 (s, 6H), 3.45 (dd, J= 14.6, 10.9 Hz, 1H), 3.85 (dd, J = 13.6, 8.3 Hz, 0.33H), 4.06 (dd, J = 13.6, 3.0 Hz, 0.33H), 4.35 (dd, J= 14.6, 3.0 Hz, 1H), 5.66 (dd, J= 8.3, 3.0 Hz, 0.34H), 5.78 (m, J= 10.9, 3.0 Hz, 2.3H), 7.39-7.51 (m, 13.5H); Anal. Calcd for $C_{21}H_{23}NO_4$: C, 71.35; H, 5.98; N, 3.96. Found: C, 70.98; H, 6.29; N, 3.62.

N-tert-Butyloxycarbonyl-(3R,6R)-3-methyl-3,6-diphenyl-2,3,5,6-tetrahydro-4H-1,4-oxazin-2-one 4

To a solution of 0.35 g (1 mmole) of **3** in 8 mL of anhydrous THF cooled to -20 °C, was added dropwise through a septum 1.5 mL (1.5 mmoles) of a 1 M solution of *t*-BuOK in THF for 15 min. After the resulting solution was stirred for 1 h at -20 °C, 0.37 mL (6 mmoles) of CH_3I was added rapidly and the mixture was allowed to warm to room temperature for 2 h. After cooling to 0 °C and quenching with 1 mL of aqueous saturated NH_4Cl, the mixture was diluted with Et_2O. The organic layer was decanted, washed twice with brine, dried over $MgSO_4$ and concentrated to dryness to provide 0.2 g of an oil which after chromatography (1:4 EtOAc/heptane) yielded 0.05 g (14%) of compound **4**: IR (NaCl): ν 2977, 2927, 1745, 1692, 1497, 1451, 1389, 1256, 1209, 1161, 1092 cm^{-1}; ^1H NMR (DMSO-$d6$), δ 1.09 (s, 9H), 2.20 (s, 3H), 3.86 (dd, J= 14.1, 9.6 Hz, 1H), 4.29 (dd,J = 14.1, 2.2 Hz, 1H), 5.96 (dd, J = 9.6, 2.2 Hz, 1H), 7.32-7.60 (m, 10H); ^{13}C NMR

(DMSO-d_6), δ 24.23, 27.42, 47.57, 64.27, 78.30, 80.06, 126.06, 126.51, 126.59, 126.86, 127.66, 128.53, 128.83, 136.41, 143.30, 152.79, 171.17; MS (ESP+) *m/z* 368 (MH+), 358, 312, 294, 268, 252, 214, 196, 178, 164. The stereochemistry (3*R*,6*R*) of **4** was confirmed by 2D NOESY experiments (in DMSO-d_6)). A NOE was observed between H-6 and H-5 and also between H-5' and protons H-3.



(1R)-2-(N-Phenylmethylamino)-1-phenylethanol ***6***

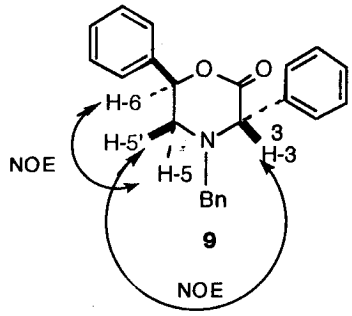
To a solution of 24.0 g (200 mmoles) of (*R*)-(+)-styrene oxide in 120 mL of CH_3CN, were added 107.2 g (1000 mmoles) of benzylamine over 5 min. This mixture was cooled to + 10 °C prior to the portionswise addition of 21.3 g (200 mmoles) of $LiClO_4$ over 10 min. The resulting mixture was stirred for 24 h at room temperature before addition of 1 L of H_2O. The resulting suspension was stirred at 0 °C for 30 min and the white precipitate was collected by filtration, rinsed with 100 mL of water and dried over P_2O_5 to provide a mixture of the desired compound **6** and its regioisomer in a 93:7 ratio. Pure compound **6** was recovered (31.2 g, 68.6%) after the crude material was recrystallized from 200 mL of isopropyl alcohol; mp 111 °C; $[\alpha]^{25}_D$ -54.6°(*c* 1.22, $CHCl_3$); ^{1}H NMR (DMSO-d_6), δ 2.07 (s, 1H), 2.68 (d, J = 6.2 Hz, 2H), 3.77 (d, J = 13.6 Hz, 2H), 4.72 (dd, J = 6.2 Hz, 1H), 5.27 (s, 1H), 7.19-7.42 (m, 10H).

Ethyl 2-[N-Benzyl-N-((2R)-2-hydroxy-2-phenylethyl)]amino-2-phenylacetate ***7***

To a suspension of 30.0 g (132 mmoles) of β-amino-alcohol **6**, in 420 mL of CH_3CN, were successively added 29.61 g (122 mmoles) of α-bromoester **2**[6] and 15.75 g (122 mmoles) of (*i*-Pr)$_2$NEt. After 1 h, total dissolution occurred and the resulting solution was stirred for 4 h before it was concentrated to dryness. The oily residue was dissolved in 1 L of CH_2Cl_2, then washed three times with 250 mL of H_2O dried over $MgSO_4$ and concentrated to dryness. The resulting oil was dissolved at 50 °C in heptane. After removal of insoluble materials, the clear solution was concentrated to dryness to yield 46.5 g (90%) of compound **7** as a mixture of two diastereomers in a 56:44 ratio. This mixture was used as is for the next step: ^{1}H NMR (DMSO-d_6), δ 1.25 (2t, 3H), 2.82 (m, 2H), 3.78 (m, 2H), 4.21 (2q, 2H), 4.57 (dd, 1H), 4.67 (s, 0.56H), 4.76 (s, 0.44H), 4.97 (d, 0.56H), 5.20 (d, 0.44H), 7.23-7.33 (m, 15H); MS (ESP+) *m/z* 390 (MH+), 209, 163, 135, 107, 92, 91.

N-Benzyl-(6R)-3,6-diphenyl-2,3,5,6-tetrahydro-4H-1,4-oxazin-2-one ***8***

To a solution of 15.0 g (38.5 mmoles) of compound **7** in 900 mL of toluene, 0.75 g (3.94 mmoles) of *p*-TsOH.H_2O was added in one portion and the mixture was azeotropically distillated with a Dean-Stark. After distillation at atmospheric pressure of 100 mL of toluene, the mixture was allowed to cool at 40 °C and was concentrated to dryness. The residue was partitioned between 300 mL of EtOAc and 150 mL of H_2O. The organic layer was washed with 150 mL of 0.5N HCl, 250 mL of brine, dried over $MgSO_4$ and concentrated to dryness to give 13.8 g of a yellowish oil yielding, after flash chromatography (3:7 EtOAc/heptane), 11.04 g (83.4%) of the diastereomeric mixture of (3*R*, 6*R*) and (3*S*, 6*R*) isomers **8** and **9**. Isomer **9** could be isolated by crystallization from heptane/EtOAc (15:1); mp 125 °C; $[\alpha]^{25}_D$ +172.6° (*c* 1.5, $CHCl_3$); ^1H NMR (DMSO-d_6), δ 2.81 (dd, 1H), 3.05 (dd, 1H), 3.29 (d, 1H), 3.67 (d, 1H), 4.50 (s, 1H), 5.79 (dd, 1H), 7.26-7.68 (m, 15H); Anal. Calcd for $C_{23}H_{21}NO_2$: C, 80.44; H, 6.16; N, 4.08. Found: C, 80.81; H, 6.16; N, 3.86. The stereochemistry (3*S*,6*R*) of **9** was confirmed by 2D NOESY experiments (in DMSO-d_6)). A NOE was observed between H-5 and H-6 and also between H-5' and H-3.



(3S,6R) and (3R,6R)-N-Benzyl-3-methyl-3,6-diphenyl-2,3,5,6-tetrahydro-4H-1,4-oxazin-2-one ***10*** *and* ***11***

To a solution of 10.00 g (29.1 mmoles) of oxazinone **9** in 280 mL of anhydrous THF cooled to -5 °C, a solution of 4.90 g (43.8 mmoles) of *t*-BuOK in 120 mL of anhydrous THF was added dropwise over 20 min. After the solution was stirred for 1 h at -5 °C, 9.10 mL (20.65 g, 145.5 mmoles) of CH_3I were added rapidly and the resulting suspension was stirred at room temperature for 4.5 h. The reaction was quenched with 30 mL of aqueous saturated NH_4Cl, before 200 mL of Et_2O were added. The organic layer was washed once with 250 mL of 1N aqueous HCl, twice by 200 mL, once by 150 mL of 10% $NaHCO_3$, once with 200 mL of brine, dried ($MgSO_4$) and concentrated to dryness. Flash chromatography of the residue (3:7 EtOAc/heptane) provided 8.15 g (78.3%) of the expected C-3 methylated oxazinone (R_f 0.42) as a mixture of its diastereomers (3*S*, 6*R*) **10** and (3*R*, 6*R*) **11** in a 61/39 ratio. The two diastereomers **10** and **11** could be separated from 1.2 g of the mixture by preparative HPLC (HPLC system: Waters; 22 x 250 Zorbax column; 95:5 heptane/MTBE) and recrystallized from heptane to yield 0.4 g of diastereomer **10**: mp 115 °C, $[\alpha]^{25}_D$ +121.1° (*c* 1.01, $CHCl_3$); IR (KBr), 1729, 1447, 1369, 1219, 1146 cm^{-1}; ^1H NMR (DMSO-d_6), δ 1.93 (s, 3H), 2.85 (dd, *J* = 13.4, 3.5 Hz, 1H), 3.09 (dd, *J* = 13.4, 10.4 Hz, 1H), 3.40 (dd, 2H), 5.82 (dd, *J* = 10.4, 3.5 Hz, 1H), 7.25-7.86 (m, 15H); X-rays, crystal size (mm), 0.15 x 0.33 x 0.50, monoclinic system, space group $P2_1$, a = 6.999 Å, α = 90°, b = 7.7062 Å, β = 94.90°, c = 18.720 Å, γ = 90°, Z = 2, V = 1006.0 $Å^3$, d_x = 1.180 g.cm $^{-3}$, Anal. Calcd for $C_{24}H_{23}NO_2$: C, 80.64; H, 6.49; N, 3.92. Found: C, 80.38; H, 6.49; N, 3.75, and 0.2 g of diastereomer **11**: mp 122 °C; $[\alpha]^{25}_D$ +52.1° (*c* 1.21, $CHCl_3$); IR (KBr), 1732, 1445, 1367, 1206, 1152 cm^{-1}; ^1H NMR (DMSO-d_6),

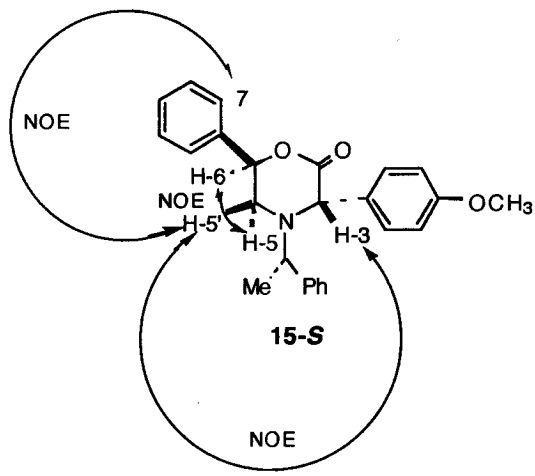
δ 1.91 (s, 3H), 2.87 (dd, J = 13.6, 5.8 Hz, 1H), 3.14 (dd, J = 13.6, 4.2 Hz, 1H), 3.23 (d, J = 14.1 Hz, 1H), 3.71 (d, J = 14.1 Hz, 1H), 5.75 (dd, J = 5.8, 4.2 Hz, 1H), 7.09-7.58 (m, 15H); X-rays, crystal size(mm), 0.12 x 0.32 x 0.35, orthorhombic system, space group $P2_12_12_1$, a = 9.4229 Å, α = 90°, b = 15.825 Å, β = 90°, c = 26.002 Å, γ = 90°, Z = 8, V = 3877.2 $Å^3$, d_x = 1.225 g.cm $^{-3}$; Anal. Calcd for $C_{24}H_{23}NO_2$: C, 80.64; H, 6.49; N, 3.92. Found: C, 80.41; H, 6.20; N, 3.64.

(1R)-2-(N-((1'R)-1'-methylphenylmethyl)amino)-1-phenylethanol **12**

To a solution of 45.7 mL (48.0 g, 0.4 mol) of styrene oxide **5** in 240 mL of CH_3CN, were added 206.5 mL (194.0 g, 1600 mmoles) of (*R*)-(+)-α-methylbenzylamine. Portionwise, 42.76 g (400 mmoles) of $LiClO_4$ were added in 45 minutes to the reaction mixture which was further stirred for 2 days. The resulting suspension was poured into 2.4 L of H_2O and stirred for 1 h. The solid was collected by filtration, rinsed twice with 50 mL of H_2O and dried until constant weight to yield 86.9 g (90 %) of amino-alcool **12**: mp 150.6 °C; $[\alpha]^{25}_D$ +42.8° (*c* 1.00, MeOH); ^{1}H NMR (DMSO-d_6), δ 1.28 (d, J = 6.5 Hz, 3H), 2.02 (m, 1H), 2.44 (dd, J = 11.8, 4.2 Hz, 1H), 2.58 (dd, J = 11.8, 8.4 Hz, 1H), 3.75 (q, J = 6.5 Hz, 1H), 4.59 (ddt, J = 8.4, 4.2, 4.2 Hz, 1H), 5.28 (d, J = 4.2 Hz, 1H), 7.22-7.32 (m, 10H).

(3S, 6R, 1'R) and (3R, 6R, 1'R)-N-(1'-methylphenylmethyl)-3-(4-methoxyphenyl)-6-phenyl-2,3,5,6-tetrahydro-4H-1,4-oxazin-2-one **15**

To a mixture of 34.07 g (124.7 mmoles) of compound **13**[9] and 30.10 g (124.7 mmole) of compound **12** in 600 mL of CH_3CN, 20.9 mL (16.12 g, 124.7 mmoles) of (i-Pr)$_2$NEt were added, the resulting solution being stirred for 18 h at 65 °C. The concentrated residue was dissolved in 600 mL of CH_2Cl_2, washed twice with 180 mL of H_2O, dried ($MgSO_4$) and concentrated to dryness to give 58.30 g of a red oil which was dissolved in 1.75 L of toluene, 2.10 g (11.05 mmoles) of p-TsOH. H_2O were added and the mixture was azeotropically distilled with a Dean-Stark, and then, concentrated to dryness. Chromatography of the residue (1:7 to 1:3 EtOAc/heptane) yielded 31.16 g (64.5%) of pure compound **15-*S*** with the (3*S*) configuration:



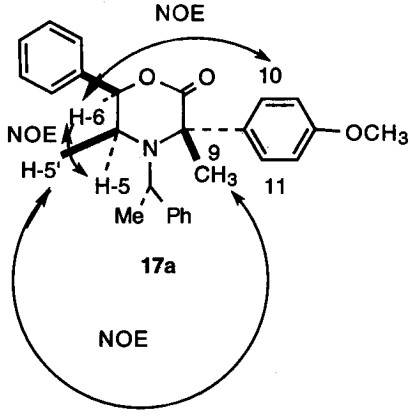
$[\alpha]^{25}_D$ +158.2° (*c* 2.23, $CHCl_3$); ^{1}H NMR (DMSO-d_6), δ 1.38 (d, 3H), 2.34 (dd, 1H), 3.53 (dd, 1H), 3.71 (d, 1H), 3.85 (s, 3H), 4.25 (s, 1H), 5.79 (d, 1H), 7.07-7.44 (m, 14H); ^{13}C NMR (DMSO-d_6), δ 18.9, 49.0, 55.1, 57.6, 65.8, 80.4, 114.0, 126.4, 127.4, 128.1, 128.2, 128.4, 128.5, 129.7, 130.6, 137.5, 159.0, 168.9, and 9.09 g (18.8 % yield) of pure compound **15-*R*** with the (3*R*) configuration: ^{1}H NMR (DMSO-d_6), δ 1.35 (d, 3H), 2.84 (dd, 1H), 3.18 (dd, 1H), 3.71 (d, 1H), 3.76 (s, 3H), 4.72 (s, 1H), 5.78 (m, 1H), 6.94-7.43 (m, 14H). The stereochemistry (3*S*,6*R*) of **15-*S*** was confirmed by 2D NOESY experiments (in DMSO-d_6)). A strong NOE was observed between H-6 and H-5. Correlations were also observed between H-5' and H-3 and also between H-5' and the aromatic protons H-7.

General Procedure for the Diastereoselective Alkylation of Compound ***15***

To a solution of oxazinone **15** (1.0 equiv.) in 25 volumes of dry THF cooled to -22 °C were added rapidly 4.5-11 equiv. of the alkylating agent. To the resulting mixture was slowly added a solution of 1.5 equiv. of *t*-BuOK in 15 to 20 volumes of dry THF. The occurring suspension was stirred for 1 h between -15 °C and -10 °C before being allowed to warm to room temperature and being quenched with aqueous saturated NH_4Cl (1mL aqueous sat. NH_4Cl/mmole **15**). The mixture was diluted with 40 volumes of MTBE. The organic layer was washed with H_2O and brine, dried ($MgSO_4$) and concentrated to dryness. The residue was purified either by crystallization from AcOEt/heptane, or by flash chromatography (EtOAc/heptane) to afford pure **17**.

(3S,6R,1'R)-N-(1'-Methylphenylmethyl)-3-(4-methoxyphenyl)-3-methyl-6-phenyl-2,3,5,6-tetrahydro-4H-1,4-oxazin-2-one ***17a***

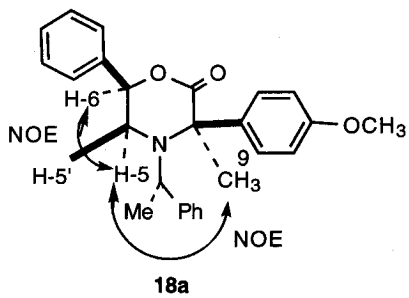
The reaction was performed on 16.26 g (42 mmoles) of **15** in 420 mL of THF with 11.8 mL (189 mmoles) of distillated methyl iodide as the alkylating reagent and in presence of 7.07 g (63 mmoles) of *t*-BuOK in 300 mL of THF. Crystallization from AcOEt/heptane 92:8 (10.3 g) and purification of mother liquors by chromatography with AcOEt/heptane 90:10 (2.36 g) furnished **17a** in 78 % yield; mp 183 °C; $[\alpha]^{25}_D$ +103.6° (*c* 0.95, $CHCl_3$); IR (KBr), 3437, 3065-2822, 2361, 2337, 1720, 1607, 1508, 1268, 1217,1147 cm^{-1};



^{1}H NMR (DMSO-d_6), δ 1.07 (d, 3H), 1.67 (s, 3H), 2.92 (dd, 1H), 3.50 (dd, 1H), 3.78 (d, 1H), 3.84 (s, 3H), 5.79 (dd, 1H), 7.05-7.67 (m, 14H); ^{13}C NMR (DMSO-d_6), δ 18.5, 21.6, 46.1, 55.0, 56.3, 67.8, 81.2, 113.6, 126.2, 126.6, 127.2, 128.1, 128.3, 135.4, 137.9, 144.1, 158.6, 172.4; MS (ESP+) *m/z* 402 (MH+); Anal. Calcd for $C_{26}H_{27}NO_3$: C, 77.78; H, 6.78; N, 3.49. Found: C, 77.30; H, 6.83; N, 3.44. The stereochemistry (3*S*,6*R*) of **17a** was confirmed by 2D NOESY experiments (in DMSO-d_6)). A strong NOE was observed between H-9 and H-5' and also between H-6 and H-5. A correlation was also observed between H-6 and the aromatic protons H-10 and H-11.

(3R,6R,1'R)-N-(1'-Methylphenylmethyl)-3-(4-methoxyphenyl)-3-methyl-6-phenyl-2,3,5,6-tetrahydro-4H-1,4-oxazin-2-one ***18a***

Compound **18a** (1.13 g)was isolated by silica gel chromatography of the concentrated mother liquors of crystallized **17a**: $[\alpha]^{25}_D$ -13.6° (*c* 0.8, $CHCl_3$); ^{1}H NMR (DMSO-d_6), δ 1.45 (d, 3H), 1.90 (s, 3H), 3.04 (d, 1H), 3.48 (d, 1H), 3.74 (s, 3H), 3.89 (d, 1H), 5.79 (m, 1H), 6.79-7.38 (m, 14H); ^{13}C NMR (DMSO-d_6), δ 20.7, 43.8, 53.9, 55.0, 67.8, 79.4, 113.2, 125.5, 125.9, 126.5, 127.5, 127.6, 128.1, 128.3, 134.6, 139.6, 143.5, 172.3; MS (ESP+) *m/z* 402 (MH+). The stereochemistry (3*R*,6*R*) of **18a** was confirmed by 2D NOESY experiments (in DMSO-d_6)). A strong NOE was observed between H-6 and H-5 and also between H-5 and H-9.



18a

(3S,6R,1'R)-N-(1'-Methylphenylmethyl)-3-ethyl-3-(4-methoxyphenyl)-6-phenyl-2,3,5,6-tetrahydro-4H-1,4-oxazin-2-one ***17b***

The reaction was performed with 0.77 g (2 mmoles) of **15**, and 0.72 mL (9 mmoles) of distillated ethyl iodide as the alkylating reagent in 20 mL of THF in presence of 0.337 g (3 mmoles) of *t*-BuOK in 16 mL of THF. Yield 65% after chromatography with AcOEt/heptane 85:15 (crude yield 92%); mp 144 °C; $[\alpha]^{25}_D$ +80.3° (*c* 0.98, $CHCl_3$); IR (KBr), 3435, 1726, 1607, 1506, 1455, 1250 cm^{-1}; ^{1}H NMR (DMSO-d_6), δ 0.63 (t, *J* = 6.9 Hz, 3H), 0.93 (d, *J* = 6.9 Hz, 3H), 2.39 (m, 2H), 3.12 (dd, *J* = 13.6, 6.4 Hz, 1H), 3.66 (dd, *J* = 13.6, 3.9 Hz, 1H), 3.84 (s, 3H), 3.99 (d, *J* = 6.9 Hz, 1H), 5.80 (dd, *J* = 6.4, 3.9 Hz, 1H), 7.03-7.61 (m, 14H); MS (ESP+) *m/z* 416 (MH+), 388, 370, 312, 266, 224, 193, 120; Anal. Calcd for $C_{27}H_{29}NO_3$: C, 78.04; H, 7.03; N, 3.37. Found: C, 77.85; H, 7.19; N, 3.24.

(3S,6R,1'R)-N-(1'-Methylphenylmethyl)-3-(4-methoxyphenyl)-3-(propen-2-yl)-6-phenyl-2,3,5,6-tetrahydro-4H-1,4-oxazin-2-one ***17c***

The reaction was performed with 0.388 g (1 mmole) of **15**, and 0.39 mL (4.5 mmoles) of freshly distillated allyl bromide as the alkylating reagent. Yield 77% after crystallization from AcOEt/ heptane (crude yield 89%); mp 118.2 °C; $[\alpha]^{25}_{D}$ +59.9° (*c* 1.02, $CHCl_3$); IR (KBr), 3442, 3067-2863, 2292, 2049, 1730, 1639, 1606, 1513, 1445, 1254, 1192, 1166, 971, 916, 836 cm^{-1}; ^1H NMR (DMSO-d_6), δ 1.04 (d, J = 6.9 Hz, 3H), 3.13 (dd, 13.6, 7.6 Hz, 3H), 3.64 (dd, 13.6, 3.7 Hz, 1H), 3.85 (s, 3H), 3.96 (dd, J = 6.9 Hz, 1H), 4.80 (d, J = 17.1, 2.1 Hz, 1H), 4.90 (dd, J = 10.2, 2.1 Hz, 1H), 5.41 (dddd, 1H), 7.04-7.65 (m, 14H); Anal. Calcd for $C_{28}H_{29}NO_3$: C, 78.65; H, 6.84; N, 3.27. Found: C, 78.56; H, 6.73; N, 3.08.

(3S,6R,1'R)-N-(1'-Methylphenylmethyl)-3-phenylmethyl-3-(4-methoxyphenyl)-6-phenyl-2,3,5,6-tetrahydro-4H-1,4-oxazin-2-one ***17d***

The reaction was performed with 0.97 (1 mmole) of **15**, and 1.34 mL (11.2 mmoles) of distillated benzyl bromide as the alkylating reagent; Yield 69% after chromatography from AcOEt:heptane 90:10 then 85:15; IR (KBr), 3063-2853, 1725, 1512, 1241, 1178, 1029 cm^{-1}; ^1H NMR (DMSO-d_6), δ 0.98 (d, J = 6.9 Hz, 3H), 2.52 (q, J = 13.7, 7.6 Hz, 1H), 3.34 (d, J = 4.0 Hz, 1H), 3.68 (s, 2H), 3.87 (s, 3H), 4.12 (d, J = 6.9 Hz, 1H), 5.72 (dd, J = 7.6, 4.0 Hz, 1H), 6.58-7.72 (m, 19H).

(2S,1'R,2"R)-2-[N,N-(1'-methylphenylmethyl)-[1"-(2"-hydroxy-2"-phenyl)ethyl]amino]-2-(4'-methoxyphenyl) propionate Potassium salt ***24a***

To a suspension of 5.05 g (12.6 mmoles) of **17a** in 60 mL of absolute EtOH was added 0.83 g (12.6 mmoles) of 85% solid KOH dissolved in 15 mL of EtOH. After 2 hours of reflux, cooling, and concentration to dryness gave a residue which was taken up twice in fresh EtOH which was further crystallized out from acetone to furnish 5.75 g of **24a** as a white powder; Yield 100% ; ^1H NMR (DMSO-d_6), δ 1.30 (d, J = 7.2 Hz, 3H), 1.38 (s, 3H), 2.46 (dd, J = 14.3, 11.1 Hz, 1H), 2.55 (dd, J = 14.3, 3.2 Hz, 1H), 3.79 (s, 3H), 3.81 (d, J = 7.2 Hz, 1H), 4.63 (dd, J = 11.1, 3.2 Hz, 1H), 6.86-6.88 (d, 2H), 7.16-7.35 (m, 10H), 7.76-7.78 (d, 2H), 8.84 (d, 1H); MS (ESP+) *m/z* 459 (MH+), 421, 243, 217, 179, 165, 138, 120, 105, 39; MS (ESP-): 418 ($RCOO^-$), 374 (R^-).

(2S,1'R,2"R)-2-[N,N-(1'-Methylphenylmethyl)-[1"-(2"-hydroxy-2"-phenyl)ethyl]amino]-2-(4'-methoxyphenyl) butanoate Potassium salt ***24b***

Using the same methodology compound **24b** was obtained in 100% yield (0.16 g scale); ^1H NMR (DMSO-d_6), δ 0.39 (t, 3H), 1.31 (d, 3H), 2.00 (m, 1H), 2.54-3.01 (m, 4H), 3.77 (s, 3H), 4.71 (dd, 1H), 6.82-7.88 (m, 13H), 8.60 (s, 1H).

(2S,1'R,2"R)-2-[N,N-(1'-methylphenylmethyl)-[1"-(2"-hydroxy-2"-phenyl)ethyl]amino]-2-(4'-methoxyphenyl) pent-4-enoate Potassium salt ***24c***

Using the same methodology as for 24a, the reaction took place in 100% yield (0.8 g scale); ^1H NMR (DMSO-d_6), δ 1.29 (d, 3H), 2.77 (m, 3H), 3.78 (s, 3H), 3.87 (d, 2H), 4.40 (m, 1H), 4.62 (d, 1H), 5.57 (m, 1H), 6.86 (d, 2H), 7.15-7.37 (m, 10H), 7.81 (d, 2H), 9.35 (d, 1H).

General procedure for the hydrogenolysis of compounds ***24*** *into compounds* ***25***

To an aqueous solution of 1 equiv. of potassium salt **24** , was added 10% Pd/C (25% w/w) and hydrogenolysis was performed under 4 bars for 2 h. Solid materials were dissolved with MeOH and the palladium catalyst removed by filtration. The solvent was concentrated and the basic solution was brought to pH 7.0 with 2N aqueous HCl to afford a white precipitate which was collected by filtration, rinsed with heptane to yield compounds **25** as single diastereomers.

(2S, 2'R)-2-[N-(1'-(2'-hydroxy-2'-phenylethyl)amino]-2-(4'-methoxyphenyl)propionic acid ***25a***

To an aqueous solution of 6.38 g (13.3 mmoles) of **24a** in 110 mL of H_2O was added 1.5 g of 10% Pd on C. Under stirring, the resulting suspension was stirred under 4 bars for 3 h. The resulting white suspension was taken up with 250 mL of MeOH. The catalyst was filtered off over a celite pad and the filtrate was concentrated under vacuum to *ca* 100 mL. The resulting basic solution was ice-cooled and neutralized to pH 7 with aqueous 2N HCl. The solid was filtered, washed with water followed by heptane and dried under vacuum at 55 °C to furnish 4.01 g of **25a** as a white solid. Yield 91% (6.4 g scale): mp 238 °C; $[\alpha]^{25}_D$ +84.5° (*c* 0.52, 1:1 MeOH/1N HCl); IR (KBr), 3500-2700, 3364, 1584, 1516, 1494, 1390, 1257, 1190 cm^{-1}; ^1H NMR (DMSO-d_6), δ 1.65 (s, 3H), 2.53 (dd, J = 11.8, 9.8 Hz, 1H), 2.60 (dd, J = 11.8, 2.9 Hz, 1H), 3.33 (m, 1H), 3.77 (s, 3H), 4.77 (dd, J = 9.8, 2.9 Hz, 1H), 6.92 (d, 2H), 7.26-7.42 (m, 5H), 7.43 (d, 2H), 8.20 (m, 1H); MS (ESP-)*m/z* 314 (MH-), 270, (M-COOH), MS/MS daughters 270, 192, 174, 107, 77, 56; Anal. Calcd for $C_{18}H_{21}NO_4$: C, 68.55; H, 6.71; N, 4.44. Found: C, 68.45; H, 6.72; N, 4.27.

(2S, 2'R)-2-[N-(1'-(2'-hydroxy-2'-phenylethyl)amino]-2-(4'-methoxyphenyl)pentanoic acid ***25c***

Under similar conditions, compound **24c** was hydrogenolyzed and precipitated with 2N aqueous HCl in 87% yield (0.5 g scale) to provide **25c** as a white solid; mp 256 °C; $[\alpha]^{25}_D$ +52.4° (*c* 0.54, 1:1 MeOH/1N HCl); ^1H NMR (DMSO-d_6), δ 0.86 (t, 3H), 1.87 (m, 2H), 1.96 (m, 2H), 2.52 (dd, 2H), 3.39 (m, 3H, exchange D_2O), 3.76 (s, 3H), 6.87-7.40 (m, 9H); MS (ESP+)*m/z* 344 (MH+), 207, MS/MS daughters 207, 165, 161, 137, 121, 98; Anal. Calcd for $C_{20}H_{25}NO_4$: C, 69.95; H, 7.34; N, 4.08; Found: C, 69.85; H, 7.23; N, 3.96.

Acknowledgement

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Acronyms used in this report:

Boc: tert-butoxycarbonyl
BnBr: benzyl bromide
$BnNH_2$: benzylamine
Cbz: benzyloxycarbonyl
DMAP: 4-dimethylaminopyridine
KHMDS: hexamethylsilylazane potassium salt
LDA: diisopropylamide lithium salt
LIHMDS: hexamethylsilylazane lithium salt
MTBE: methyltert-butyl ether
NaHMDS: hexamethylsilylazane sodium salt
TEA: triethylamine
p-TsOH: 4-toluenesulfonic acid

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