A New Diastereoselective Synthesis of *anti*-α-Alkyl α-Hydroxy β-Amino Acids

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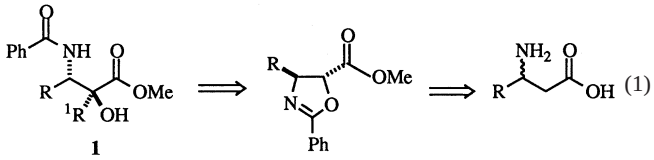
As part of an ongoing project concerning the synthesis of enantiomerically pure α-hydroxy β-amino acids, we have now developed a general strategy allowing the synthesis of *anti*-α-alkyl α-hydroxy β-amino acids. Our procedure involves the intermediate formation of *trans*-oxazolines, which are alkylated at C-5 with good to high diastereoselectivity and then hydrolysed under mildly acidic conditions, affording in quantitative yield the corresponding hydroxy amides. The starting (*R*)-3-amino-3-phenylpropanoic acid and (*S*)-3-aminobutanoic acid were obtained in enantiomerically pure form by selective enzymatic hydrolysis of the corresponding phenylacetylamides with penicillin G acylase.

Introduction

Non-proteinogenic amino acids are currently of interest with regard to the modification of native peptides and the synthesis of peptidomimetics. β-Amino acids, although less abundant than their α analogues, are important components in a variety of biologically interesting compounds.[1] In particular, some biologically active structures contain α-hydroxy β-amino acids. For instance, (2*R*,3*S*)-phenylisoserine is an important component of taxol (paclitaxel), which is the most promising anticancer agent specifically for breast and ovarian cancer.[2]

Many taxol derivatives have been synthesized in the quest for more powerful and less toxic derivatives, the most promising among them being the *N*-Boc derivative (taxotere). Furthermore, 3-*tert*-butyldocetaxel and 9-dihydrodocetaxel have also been shown to be active molecules. The general strategy is to synthesize new molecules possessing an intact ABC skeleton, but bearing simplified or altered side chains at C-13. Interestingly, modification of the 2′-hydroxy group results in analogues with greatly reduced toxicity, thus showing that the presence of a free hydroxy group is important with regard to MTD (microtubule disassembly method) activity and that the stereochemistry is of little consequence. These results further suggest that the 2′-hydroxy group is involved in a binding interaction and/or serves to increase the conformational rigidity of the side chain.[3] On the other hand, recent conformational studies on paclitaxel suggest that the C-13 side chain has a high degree of freedom, and therefore adopts a variety of conformations.[4] Thus, introduction of a methyl group at the C-2′ position should create some additional torsional strain associated with rotation. These analogues are indeed more cytotoxic then the parent paclitaxel and also display increased binding affinity to microtubules.

As part of an ongoing project concerning the synthesis of enantiomerically pure α-hydroxy β-amino acids,[5] we have now developed a general strategy allowing the introduction of an alkyl group in the α position, thereby leading to the synthesis of *anti*-α-alkyl α-hydroxy β-amino acids. Thus, the α-hydroxy β-amino acids **1** have been obtained in enantiomerically pure form starting from β-amino acids through the intermediate formation of a *trans*-oxazoline (Equation 1). While various syntheses of α-alkylated α-amino acids have been described in the literature,[6] few methods for the preparation of *syn*-α-alkyl α-hydroxy β-amino acids have been reported.[4][7] As far as we are aware, no attempts have previously been made to synthesize compounds with structures akin to that of **1**.



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Results and Discussion

A synthetic procedure for α-alkylphenylisoserines was developed starting from (*R*)-3-amino-3-phenylpropanoic acid [(*R*)-**3**]. This compound was readily obtained in racemic form according to a known procedure[8] and was resolved by enzymatic hydrolysis of the corresponding phenylacetylamides **2** with penicillin G acylase (Scheme 1).[9] This approach has been utilized in the past, both by ourselves and by other groups, to obtain both the (*R*) and the (*S*) isomers in pure form and in good quantities.[5a,10] Penicillin G acylase is known to hydrolyse preferentially phenylacetamides of amino acids of the L-series; indeed, the (*R*)-phenylacetamide (*R*)-**2** was completely hydrolysed after 4 h at room temperature in ethanol/phosphate buffer at pH = 7, while the unreacted (*S*)-**2** could be recovered by extraction with ethyl acetate as a 1:1 mixture with phenylacetic acid.

The β-amino acid (*R*)-**3** was then transformed into the corresponding benzamido ester (*R*)-**4**, which in turn was cyclized to the oxazoline **5**, in high yield and with high diastereoselectivity. Following this methodology, the hydroxy

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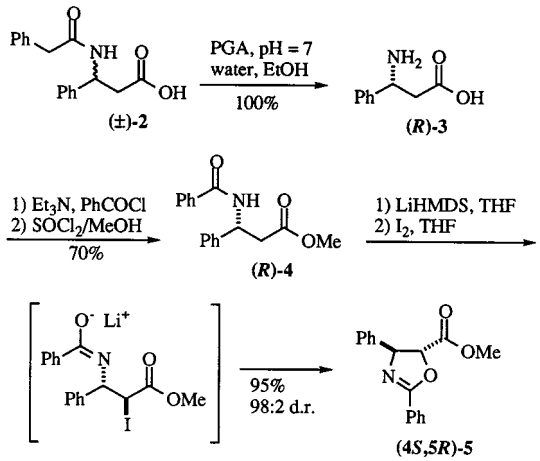
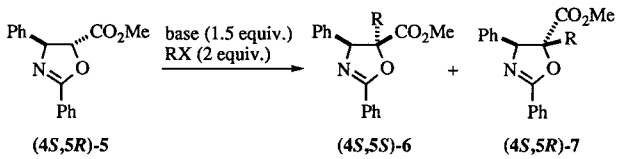
group was introduced in the α position, owing to the intermediate formation of the corresponding α-iodo derivative, which could only be detected when the reaction was performed at −80°C. The oxazoline **5** was obtained in a pure state by flash chromatography of the crude reaction mixture and the *trans* configuration of the heterocycle was established by ^{1}H NMR.



Scheme 1. Synthesis of enantiomerically pure (4*S*,5*R*)-5-(methoxycarbonyl)-2,4-diphenyl-2-oxazoline (**5**) from (±)-3-phenyl-3-[(phenylacetyl)amino]propanoic acid (**2**)

Oxazolines are versatile heterocycles that have found extensive application in organic synthesis and represent a useful means of protecting vicinal hydroxy amino groups. Seebach et al.[11] have reported the facile deprotonation of the activated C-4 position of 4-methoxycarbonyloxazoline with LDA at −78°C, followed by highly stereoselective alkylation of the exocyclic enolate double bond (> 95% ds). However, for the alkylation of dioxolane derivatives, more drastic conditions have proved necessary, leading to poorer diastereoselectivities.



(2)

In our hands, all attempts to alkylate the 5-methoxycarbonyloxazoline **5** at −78°C proved unsuccessful. The introduction of the alkyl group at C-5 thus had to be performed by treatment of the lithium enolate of the oxazoline **5** with alkyl halides at room temperature or at 0°C (Equation 2). In a typical experimental procedure, to a mixture of the oxazoline **5** and the alkyl halide (2 equiv.) in dry THF was added LiHMDS (1.5 equiv.) at room temperature. The mixture was stirred for 5 h, the reaction was then quenched with methanol, and worked up in the standard manner. The crude product was analysed by NMR and GC MS, which showed exclusively the presence of compounds **6** and **7** and unreacted starting material **5**. The results are summarized in Table 1.

The results presented in Table 1 show that the alkylation reaction generally proceeds with high yield and good diastereoselectivity, favouring the formation of the *cis* diastereoisomer. On increasing the bulkiness of the electrophile, the diastereoselectivity increases markedly. The *cis*/*trans* ratio is identical at 0°C and at room temperature, while yields are higher when the reaction is carried out at room temperature. The methylation reaction proceeds with high yield but poor diastereoselectivity. To improve the diastereoselectivity, the reaction was carried out at higher temperature (entry 2)[12] and using a different base (entry 3). When THF was substituted by toluene, both the yield and the *cis*/*trans* ratio decreased. Furthermore, with DMF a reversal of diastereoselectivity was observed (entry 4).

The configuration of the newly introduced asymmetric centre was determined by means of NOEDIFF experiments, which were performed with the oxazoline **6e** (Figure 1). Furthermore, as a general observation, analysis of the ^{1}H-NMR spectra of all the alkylated products **6** and **7** provides some useful information regarding the stereochemistry of the products. Thus, the methoxy group of the ester is seen to be far more shielded in the *cis* derivatives **6** (δ = 3.15) compared to that in the *trans* derivatives **7** and that in the starting **5** (δ = 3.87), owing to the effect of the neighbouring phenyl group at C-4.

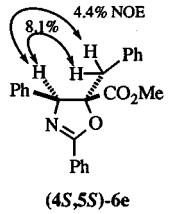


Figure 1. Determination of the configuration at C-4 of oxazolines **6** by means of NOEDIFF experiments performed on oxazoline **6e**

Table 1. Alkylation reactions of oxazoline **5** with various alkylating agents

Entry	R′X	Products	Base	Solvent	*T* [°C]	Yield (%)	*cis*/*trans* ratio
1	MeI	**6a−7a**	LiHMDS	THF	r.t.	94	58:42
2	MeI	**6a−7a**	LiHMDS	THF	66−67	93	66:34
3	MeI	**6a−7a**	NaHMDS	THF	r.t.	50	65:35
4	MeI	**6a−7a**	LiHMDS	DMF	r.t.	55	37:63
5	EtI	**6b−7b**	LiHMDS	THF	r.t.	90	74:26
6	*n*PrI	**6c−7c**	LiHMDS	THF	r.t.	89	87:13
7	Allyl iodide	**6d−7d**	LiHMDS	THF	r.t.	98	92:8
8	Allyl iodide	**6d−7d**	LiHMDS	DMF	r.t.	65	73:27
9	BnBr	**6e−7e**	LiHMDS	THF	r.t.	98	92:8

As the alkylation reaction affords mainly the *cis* derivatives **6**, the oxazolines are preferentially attacked *anti* to the bulky phenyl group, as previously reported by Seebach for the alkylation of the regioisomeric oxazoline (Figure 2).[11] It was observed that the *anti* directing effect stemmed from the C-4 methyl group, regardless of the configuration at C-5.

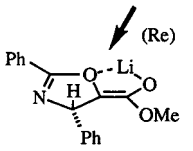
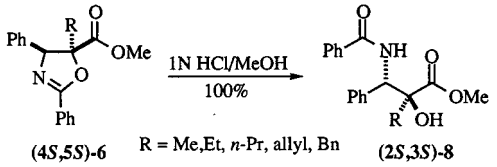


Figure 2. Preferential attack in the alkylation of oxazoline **5**

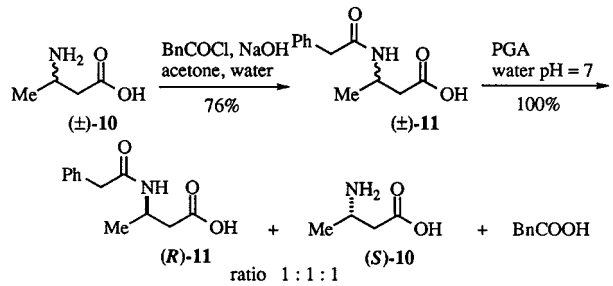
The oxazolines **6** (or a mixture of **6** and **7**) were hydrolysed under mildly acidic conditions by refluxing in 3:1 methanol and 1 N HCl for 7 h. The hydrolysis afforded the hydroxy amides **8** (and, in some cases, the diastereoisomers **9**) in quantitative yield, which were purified by flash chromatography (Scheme 2).



Scheme 2. Hydrolysis of oxazolines **6**

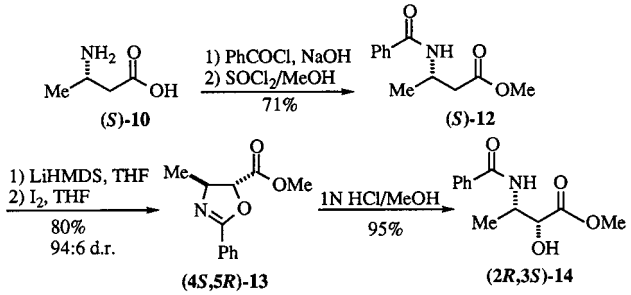
In view of these encouraging results, we extended this method to the preparation of other enantiopure α-alkyl α-hydroxy β-amino acids, in order to test the efficacy of our synthetic method and to prepare some potentially useful new substrates for use as building blocks in the synthesis of novel polypeptides.

Enantiomerically pure (*S*)-3-aminobutanoic acid **10** was obtained by enzymatic resolution of the corresponding racemic phenylacetylamide **11**, which was readily prepared from commercially available racemic 3-aminobutanoic acid [(±)-**10**]. PGA hydrolysis of this substrate proceeded smoothly at pH = 7 in phosphate buffer solution within 6 h at 30°C, and the unreacted (*R*)-**11** could be recovered by extraction with ethyl acetate as a 1:1 mixture with phenylacetic acid (Scheme 3).[10]



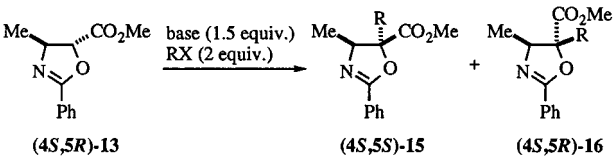
Scheme 3. Kinetic resolution of 3-aminobutanoic acid (±)-**10** with Penicillin G Acylase

The β-amino acid (*S*)-**10** was then transformed into the corresponding amido ester **12**, which in turn was cyclized to the oxazoline **13**. The enolate was obtained by treating the ester **12** with LiHMDS in dry THF at 0°C, and then a solution of iodine in THF was added to the mixture at −78°C (Scheme 4). The product was obtained in 80% yield and with a 94:6 diastereomeric ratio in favour of the *trans* isomer, which was obtained in a pure state by flash chromatography. This simple two-step method allows access to the (4*S*,5*R*)-5-(methoxycarbonyl)-4-methyloxazoline **13**, which is a precursor of *allo*-isothreonine. When the hydrolysis was performed with dilute HCl, the methyl ester **14** of the corresponding benzamido hydroxy compound was obtained in quantitative yield. This route constitutes a short and facile synthesis of this compound, which represents another possible variation in the design of the taxol side-chain.[13]



Scheme 4. Synthesis of methyl (2*R*,3*S*)-3-(benzoylamino)-2-hydroxybutanoate (**14**)

Furthermore, in order to obtain sterically more hindered α-hydroxy β-amino acids, the *trans*-oxazoline **13** was submitted to alkylation by reaction with LiHMDS in the presence of appropriate alkylating agents at room temperature in dry THF (Equation 3). The results are presented in Table 2.



(3)

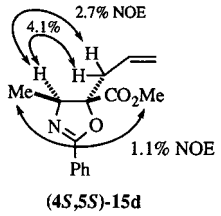
As in the alkylation of the 4-phenyloxazoline **5**, the *cis* derivatives **15** are the preferred products. Furthermore, the yields are good to excellent and the diastereoselectivity is satisfactory in all cases, apart from that of the methylation reaction. The oxazoline **13** was alkylated both as the pure *trans* diastereoisomer and as a *trans/cis* mixture. The results in terms of yield and diastereoselectivity were the same, thus proving that the deprotonation step proceeds equally well in both diastereoisomers, as was observed by Seebach.

The oxazolines **15** and **16** were purified by flash chromatography and the configuration of the newly introduced asymmetric centre was assigned with the aid of NOEDIFF experiments (Figure 3).

The oxazolines **15** were subjected to hydrolysis under mildly acidic conditions by refluxing for 7 h in methanol and 1 N HCl (3:1 ratio). The hydrolysis afforded the hydroxy amides **17** (and, in some cases, the diastereoisomers **18**) in quantitative yield, which were purified by flash chromatography (Scheme 5).

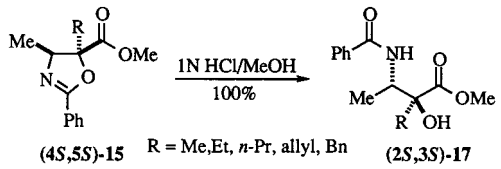
Table 2. Alkylation reactions of oxazoline **13** with various alkylating agents

Entry	R′X	Products	Base	Solvent	Yield (%)	*cis*/*trans* ratio
1	MeI	**15a**−**16a**	LiHMDS	THF	81	52:48
2	EtI	**15b**−**16b**	LiHMDS	THF	80	80:20
3	*n*PrI	**15c**−**16c**	LiHMDS	THF	85	88:12
4	Allyl iodide	**15d**−**16d**	LiHMDS	THF	> 99	98:2
5	BnBr	**15e**−**16e**	LiHMDS	THF	> 99	94:6



(4*S*,5*S*)-15d

Figure 3. Determination of the configuration at C-4 of oxazolines **15** by means of NOEDIFF experiments performed on oxazoline **15d**



(4*S*,5*S*)-15 R = Me,Et, *n*-Pr, allyl, Bn (2*S*,3*S*)-17

Scheme 5. Hydrolysis of oxazolines **15**

Conclusions

To sum up, in this paper we have presented a general method for the preparation of *anti*-α-alkyl α-hydroxy β-amino acids starting from racemic β-amino acids. These highly functionalized molecules are interesting substrates for the modification of native peptides and for the synthesis of peptidomimetics. Furthermore, the α-alkylphenylisoserines can be utilized for the preparation of taxol analogues.

Experimental Section

General: NMR spectra were recorded with a Gemini Varian spectrometer at 300 or 200 MHz (^{1}H NMR) and at 75 MHz (^{13}C NMR). Chemical shifts are reported as δ values relative to the solvent peak of $CHCl_3$, set at δ = 7.27. − Infrared spectra were recorded with an FT-IR NICOLET 205 spectrometer. − Melting points were determined in open capillaries and are uncorrected. − Flash chromatography was performed on Merck silica gel 60 (230−400 mesh). − THF and toluene were distilled from sodium benzophenone ketyl. DMF was distilled from calcium hydride.

(±)-3-Phenyl-3-[(phenylacetyl)amino]propanoic Acid (2): Phenylacetyl chloride (13 mmol, 1.72 mL) in acetone (5 mL) was added dropwise to a stirred solution of (±)-3-amino-3-phenylpropanoic acid (**3**) (10 mmol, 1.65 g) and triethylamine (24 mmol, 3.35 mL) in water (15 mL) and acetone (5 mL) at −5°C. The mixture was stirred for 2 h at −5°C, and then for 3 h at room temperature. After filtering off the precipitate of triethylammonium chloride, the acetone was removed under reduced pressure, and the residue was extracted twice with ethyl acetate. Then, 2 N HCl was added to the aqueous layer until pH = 2 was reached, and the solution was extracted with ethyl acetate. The combined organic extracts were dried with Na_2SO_4 and concentrated to give 2.1 g of compound **2** (75% yield); m.p. 138−140°C (ref.[10d] 134−140°C). − IR (Nujol): $\tilde{\nu}$ = 3278, 1702, 1653 cm^{-1}. − ^{1}H NMR ($CDCl_3$): δ = 2.83 (ABX, 2 H, *J* = 5.8, 6.0, 16.1 Hz), 3.61 (s, 2 H), 5.41 (m, 1 H), 6.53 (d, *J* = 8.5 Hz, 1 H), 7.30 (m, 10 H), 9.20−9.70 (br. s, 1 H). − ^{13}C NMR ($CDCl_3$): δ = 39.4, 43.8, 49.3, 126.1, 127.5, 127.7, 128.8, 129.0, 129.4, 133.7, 139.8, 170.4, 176.0. − $C_{17}H_{17}NO_3$ (283.3): calcd. C 72.07, H 6.05, N 4.94; found C 72.12, H 6.01, N 4.97.

Enzymatic Hydrolysis of 2: PGA immobilized on Eupergit (200 mg) was added to a pH-7 solution of the acid amide **2** (7.5 mmol, 2.12 g) in 1 M phosphate buffer (50 mL) and ethanol (7 mL). The reaction mixture was stirred at room temperature for 4 h. Then, after filtering off the immobilized enzyme, the ethanol was removed under reduced pressure and 2 N HCl was added to the aqueous solution until pH = 3 was reached. The mixture was extracted twice with ethyl acetate, the combined extracts were dried with Na_2SO_4, and concentrated to afford phenylacetic acid and the unhydrolysed amide [1.51 g, 100% yield, 3.75 mmol of (3*S*)-**2** + 3.75 mmol of phenylacetic acid]. Concentration of the aqueous layer gave (*R*)-3-amino-3-phenylpropanoic acid (**3**) as the hydrochloride. The amino acid hydrochloride was used directly in the following step without further purification.

Methyl (3*R*)-3-(Benzoylamino)-3-phenylpropanoate (4): Benzoyl chloride (4.88 mmol, 0.57 mL) in acetone (5 mL) was added dropwise to a stirred solution of the recovered (*R*)-3-amino-3-phenylpropanoic acid hydrochloride (**2**; 3.75 mmol, 0.62 g) and triethylamine (13 mmol, 1.81 mL) in water (15 mL) and acetone (5 mL) at −5°C. The mixture was stirred for 2 h at −5°C, and for 3 h at room temperature. After filtering off the precipitate of triethylammonium chloride, the acetone was removed under reduced pressure and the residue was extracted twice with ethyl acetate. Then, 2 N HCl was added to the aqueous layer until pH = 2 was reached, and the solution was extracted with ethyl acetate. The combined extracts were dried with Na_2SO_4 and concentrated to give 0.75 g of the *N*-benzoyl derivative. Meanwhile, a solution of $SOCl_2$ (5.6 mmol, 0.4 mL) in methanol (50 mL) was stirred for 2 h at −15°C, and then to this the aforementioned benzamide was added in one portion. The mixture was gradually allowed to warm to room temperature overnight, and was then concentrated under reduced pressure. Compound **4** was obtained in 67% overall yield (0.71 g, 2.5 mmol) after flash chromatography (cyclohexane/ethyl acetate, 6:4, as eluent); m.p. 108−112°C; $[\alpha]_D$ = −17.9 (*c* = 4.52, $CHCl_3$). − IR (Nujol): $\tilde{\nu}$ = 3358, 1720, 1649 cm^{-1}. − ^{1}H NMR ($CDCl_3$): δ = 3.00 (ABX, *J* = 5.5, 5.7, 15.9 Hz, 2 H), 3.63 (s, 3 H), 5.65 (ddd, *J* = 5.5, 5.7, 8.4 Hz, 1 H), 7.25 (m, 10 H), 7.82 (d, *J* = 8.4 Hz, 1 H). − ^{13}C NMR ($CDCl_3$): δ = 39.6, 49.7, 51.8, 126.2, 127.0, 127.6, 128.5, 128.6, 131.5, 134.1, 140.5, 166.5, 172.0. − $C_{17}H_{17}NO_3$ (283.3): calcd. C 72.07, H 6.05, N 4.94; found C 72.03, H 6.03, N 4.90.

(4*S*,5*R*)-5-(Methoxycarbonyl)-2,4-diphenyl-2-oxazoline (5): To a stirred solution of ester **4** (2.5 mmol, 0.7 g) in dry THF (10 mL)

at 0°C under argon, LiHMDS (5.5 mmol, 5.5 mL, 1 M solution in THF) was added in one portion. After 1 h, the mixture was cooled to −60°C and a solution of iodine (6 mmol, 1.52 g) in THF (5 mL) was added dropwise. The reaction was quenched after 1 h with saturated aqueous NH_4Cl solution (10 mL), and the solvent was removed under reduced pressure. The residue was dissolved in ethyl acetate and washed twice with a $Na_2S_2O_3$ solution. The organic layer was dried with Na_2SO_4 and concentrated. Compound **5** was obtained as an oil in 93% yield (0.65 g, 2.32 mmol) after flash chromatography on silica gel (cyclohexane/ethyl acetate, 9:1, as eluent); $[\alpha]_D = +14.0$ ($c = 0.8$, $CHCl_3$) [ref.[14] +13.0 ($c = 1$, $CHCl_3$)]. − IR (film): $\tilde{\nu} = 1760, 1655\ cm^{-1}$. − ^1H NMR ($CDCl_3$): δ = 3.87 (s, 3 H), 4.93 (d, $J = 6.5$ Hz, 1 H), 5.47 (d, $J = 6.5$ Hz, 1 H), 7.40 (m, 10 H). − ^{13}C NMR ($CDCl_3$): δ = 52.6, 74.5, 83.0, 126.3, 126.4, 126.6, 128.3, 128.6, 128.7, 131.8, 141.0, 163.8, 170.4. − $C_{17}H_{15}NO_3$ (281.3): calcd. C 72.58, H 5.37, N 4.98; found C 72.55, H 5.38, N 4.96.

General Procedure for the Alkylation of Oxazoline 5: In a typical experiment, LiHMDS (1.5 equiv., 1.04 mmol, 1 M solution in THF, 1.04 mL) was added under argon at room temperature to a stirred solution of oxazoline **5** (0.7 mmol, 200 mg) and the alkylating agent (2 equiv., 1.4 mmol) in a dry solvent (15 mL). The mixture was stirred for 5 h, MeOH (1 mL) was then added, the THF was removed under reduced pressure, and replaced with ethyl acetate (20 mL). The organic layer was washed twice with water (20 mL), dried with Na_2SO_4, and concentrated under reduced pressure. Products **6** and **7** were obtained as a mixture after flash chromatography (cyclohexane/ethyl acetate, 9:1, as eluent).

6a + 7a: IR (Nujol): $\tilde{\nu} = 1743, 1652\ cm^{-1}$. − $C_{18}H_{17}NO_3$ (295.3): calcd. C 73.20, H 5.80, N 4.74; found C 73.18, H 5.80, N 4.70. − **6a:** ^1H NMR ($CDCl_3$): δ = 1.87 (s, 3 H), 3.16 (s, 3 H), 5.23 (s, 1 H), 7.40 (m, 8 H), 8.15 (m, 2 H). − ^{13}C NMR ($CDCl_3$): δ = 20.4, 51.8, 52.9, 80.7, 124.5, 126.5, 126.6, 127.4, 127.8, 128.0, 128.1, 128.5, 128.6, 131.9, 137.0, 164.1, 169.8. − **7a:** ^1H NMR ($CDCl_3$): δ = 1.18 (s, 3 H), 3.87 (s, 3 H), 5.60 (s, 1 H), 7.40 (m, 8 H), 8.15 (m, 2 H). − ^{13}C NMR ($CDCl_3$): δ = 24.4, 51.8, 53.0, 80.7, 124.5, 126.5, 126.6, 127.4, 127.8, 128.0, 128.1, 128.5, 128.6, 131.9, 137.0, 164.1, 169.8.

6b + 7b: IR (Nujol): $\tilde{\nu} = 1743, 1659\ cm^{-1}$. − $C_{19}H_{19}NO_3$ (309.4): calcd. C 73.77, H 6.19, N 4.53; found C 73.75, H 6.21, N 4.53. − **6b:** ^1H NMR ($CDCl_3$): δ = 1.09 (t, $J = 7.3$ Hz, 3 H), 2.09 (dq, $J = 7.3$, 14.4 Hz, 1 H), 2.34 (dq, $J = 7.3$, 14.4 Hz, 1 H), 3.15 (s, 3 H), 5.21 (s, 1 H), 7.60 (m, 8 H), 8.15 (m, 2 H). − ^{13}C NMR ($CDCl_3$): δ = 8.3, 31.5, 51.6, 79.3, 93.2, 127.6, 127.9, 128.0, 128.2, 128.5, 128.7, 131.8, 137.7, 164.2, 169.9. − **7b:** ^1H NMR ($CDCl_3$): δ = 0.90 (t, $J = 7.3$ Hz, 3 H), 1.25 (dq, $J = 7.3$, 14.4 Hz, 1 H), 1.55 (dq, $J = 7.3$, 14.4 Hz, 1 H), 3.90 (s, 3 H), 5.54 (s, 1 H), 7.60 (m, 8 H), 8.15 (m, 2 H). − ^{13}C NMR ($CDCl_3$): δ = 8.9, 27.8, 52.8, 79.3, 93.2, 127.6, 127.9, 128.0, 128.2, 128.5, 128.7, 131.8, 137.7, 164.2, 169.9.

6c (major isomer): $[\alpha]_D = -8.1$ ($c = 0.2$, $CHCl_3$). − IR (Nujol): $\tilde{\nu} = 1736, 1652\ cm^{-1}$. − ^1H NMR ($CDCl_3$): δ = 1.00 (t, $J = 7.2$ Hz, 3 H), 1.40 (m, 2 H), 2.01 (ddd, $J = 4.8$, 11.4, 14.0 Hz, 1 H), 2.30 (ddd, $J = 4.8$, 11.5, 14.0 Hz, 1 H), 3.14 (s, 3 H), 5.21 (s, 1 H), 7.50 (m, 8 H), 8.12 (m, 2 H). − ^{13}C NMR ($CDCl_3$): δ = 14.1, 17.5, 40.6, 51.6, 79.8, 92.7, 127.6, 128.0, 128.1, 128.7, 131.8, 137.7, 164.1, 170.0. − $C_{20}H_{21}NO_3$ (323.4): calcd. C 74.28, H 6.55, N 4.33; found C 74.25, H 6.50, N 4.37.

6d (major isomer): $[\alpha]_D = -41.7$ ($c = 0.1$ $CHCl_3$). − IR (Nujol): $\tilde{\nu} = 1750, 1659\ cm^{-1}$. − ^1H NMR ($CDCl_3$): δ = 2.82 (dd, $J = 7.0$, 14.4 Hz, 1 H), 3.03 (dd, $J = 7.0$, 14.4 Hz, 1 H), 3.16 (s, 3 H), 5.28 (m, 3 H), 5.90 (m, 1 H), 7.40 (m, 8 H), 8.15 (m, 2 H). − ^{13}C NMR ($CDCl_3$): δ = 42.0, 51.7, 78.7, 91.7, 102.4, 120.3, 127.6, 128.0, 128.1, 128.4, 128.7, 130.1, 131.8, 137.5, 164.0, 169.5. − $C_{20}H_{19}NO_3$ (321.3): calcd. C 74.75, H 5.96, N 4.36; found C 74.77, H 5.96, N 4.37.

6e (major isomer): $[\alpha]_D = -22.3$ ($c = 0.1$, $CHCl_3$). − IR (Nujol): $\tilde{\nu} = 1744, 1656\ cm^{-1}$. − ^1H NMR ($CDCl_3$): δ = 3.13 (s, 3 H), 3.35 (d, $J = 14.2$ Hz, 1 H), 3.63 (d, $J = 14.2$ Hz, 1 H), 5.35 (s, 1 H), 7.40 (m, 13 H), 8.15 (m, 2 H). − ^{13}C NMR ($CDCl_3$): δ = 43.5, 51.7, 79.3, 92.6, 127.2, 127.7, 127.9, 128.1, 128.2, 128.3, 128.5, 128.7, 129.8, 130.4, 131.9, 134.9, 137.3, 164.0, 169.2. − $C_{24}H_{21}NO_3$ (371.4): calcd. C 77.61, H 5.70, N 3.77; found C 77.65, H 5.71, N 3.80.

General Procedure for the Hydrolysis of Oxazolines. − Synthesis of Hydroxy Amido Esters 8: A solution of oxazolines **6** and **7** (0.5 mmol) in methanol (6 mL) and 1 N HCl (2 mL) was refluxed for 7 h. After removal of the solvent under reduced pressure, the residue was dissolved in ethyl acetate (15 mL), and washed twice with water (15 mL). The organic layer was dried with Na_2SO_4 and concentrated. The hydroxy amido esters **8** and **9** were obtained in quantitative yield and separated by flash chromatography (cyclohexane/ethyl acetate, 7:3, as eluent).

8a + 9a: IR (Nujol): $\tilde{\nu} = 3374, 1736, 1645\ cm^{-1}$. − $C_{18}H_{19}NO_4$ (313.4): calcd. C 68.71, H 6.11, N 4.47; found C 68.69, H 6.15, N 4.48. − **8a:** ^1H NMR ($CDCl_3$): δ = 1.62 (s, 3 H), 3.67 (s, 3 H), 5.49 (d, $J = 9.4$ Hz, 1 H), 7.50 (m, 11 H). − ^{13}C NMR ($CDCl_3$): δ = 24.1, 52.9, 58.4, 77.2, 127.0, 127.5, 128.2, 128.4, 128.8, 131.6, 134.3, 138.0, 166.9, 175.1. − **9a:** ^1H NMR ($CDCl_3$): δ = 1.31 (s, 3 H), 3.84 (s, 3 H), 5.49 (d, $J = 9.4$ Hz, 1 H), 7.50 (m, 11 H). − ^{13}C NMR ($CDCl_3$): δ = 23.9, 53.6, 58.4, 77.2, 127.0, 127.5, 128.2, 128.4, 128.8, 131.1, 134.3, 138.0, 166.3, 175.1.

8b: M.p. 135°C; $[\alpha]_D = +3.3$ ($c = 0.4$, $CHCl_3$). − IR (Nujol): $\tilde{\nu} = 3515, 3374, 1729, 1652\ cm^{-1}$. − ^1H NMR ($CDCl_3$): δ = 0.87 (t, $J = 7.5$ Hz, 3 H), 2.02 (q, $J = 7.5$ Hz, 2 H), 3.45 (s, 1 H), 3.65 (s, 3 H), 5.48 (d, $J = 9.4$ Hz, 2 H), 7.40 (m, 11 H). − ^{13}C NMR ($CDCl_3$): δ = 8.0, 52.8, 53.4, 58.4, 81.1, 127.0, 127.6, 128.2, 128.4, 128.6, 131.6, 138.2, 166.7, 169.5. − $C_{19}H_{21}NO_4$ (327.4): calcd. C 69.71, H 6.47, N 4.28; found C 69.69, H 6.45, N 4.26.

8c: M.p. 153°C; $[\alpha]_D = -1.9$ ($c = 0.2$, $CHCl_3$). − IR (Nujol): $\tilde{\nu} = 3380, 1729, 1562\ cm^{-1}$. − ^1H NMR ($CDCl_3$): δ = 0.92 (t, $J = 6.6$ Hz, 3 H), 1.35 (m, 2 H), 1.96 (m, 2 H), 3.45 (s, 1 H), 3.64 (s, 3 H), 5.46 (d, $J = 9.3$ Hz, 1 H), 7.18 (d, $J = 9.3$ Hz, 1 H), 7.50 (m, 10 H). − ^{13}C NMR ($CDCl_3$): δ = 14.1, 17.1, 38.8, 52.7, 58.5, 80.6, 127.0, 127.6, 128.1, 128.3, 128.4, 128.6, 131.6, 134.3, 138.2, 166.6, 174.5. − $C_{20}H_{23}NO_4$ (341.4): calcd. C 70.36, H 6.79, N 4.10; found C 70.37, H 6.82, N 4.10.

8d: M.p. 157°C; $[\alpha]_D = -33.0$ ($c = 0.2$, $CHCl_3$). − IR (Nujol): $\tilde{\nu} = 3416, 1750, 1659\ cm^{-1}$. − ^1H NMR ($CDCl_3$): δ = 2.76 (m, 2 H), 3.47 (s, 1 H), 3.64 (s, 3 H), 5.14 (m, 2 H), 5.53 (d, $J = 9.5$ Hz, 1 H), 5.74 (m, 1 H), 7.16 (d, $J = 9.5$ Hz, 1 H), 7.40 (m, 10 H). − ^{13}C NMR ($CDCl_3$): δ = 41.4, 52.8, 58.0, 80.6, 119.4, 127.1, 127.7, 128.2, 128.4, 128.6, 131.7, 134.3, 137.9, 166.7, 173.8. − $C_{20}H_{21}NO_4$ (339.4): calcd. C 70.78, H 6.24, N 4.13; found C 70.78, H 6.20, N 4.09.

8e: M.p. 185°C; $[\alpha]_D = -11.0$ ($c = 0.1$, $CHCl_3$). − IR (Nujol): $\tilde{\nu} = 3508, 3388, 1729, 1652\ cm^{-1}$. − ^1H NMR ($CDCl_3$): δ = 3.29 (s, 2 H), 3.38 (s, 1 H), 3.57 (s, 3 H), 5.68 (d, $J = 9.6$ Hz, 1 H), 7.37 (m, 15 H), 7.95 (m, 1 H). − ^{13}C NMR ($CDCl_3$): δ = 43.1, 52.5, 58.3, 81.1, 127.0, 127.8, 128.1, 128.3, 128.8, 128.9, 131.7, 134.3, 135.3, 138.0, 166.8, 173.3. − $C_{24}H_{23}NO_4$ (389.5): calcd. C 74.02, H 5.95, N 3.60; found C 73.98, H 5.94, N 3.63.

(±)-3-[(Phenylacetyl)amino]butanoic Acid (11): Phenylacetyl chloride (12 mmol, 1.59 mL) in acetone (10 mL) was added dropwise to a stirred solution of (±)-3-aminobutanoic acid (**10**; 10 mmol, 1.03 g) and NaOH (20 mmol, 0.8 g) in water (30 mL) at 0°C. The mixture was stirred for 1 h at room temperature, the acetone was then removed under reduced pressure, and the residue was extracted twice with ethyl acetate. Then, 2 N HCl was added to the aqueous layer until pH = 1 was reached, and the solution was extracted with ethyl acetate. The combined extracts were dried with Na_2SO_4 and concentrated to give 1.68 g of compound **11** (76% yield) after flash chromatography (cyclohexane/ethyl acetate, 7:3, as eluent); m.p. 106°C. − IR (Nujol): $\tilde{\nu}$ = 3302, 1708, 1686 cm^{-1}. − ^1H NMR ($CDCl_3$): δ = 1.20 (d, *J* = 6.8 Hz, 3 H), 2.54 (ABX, *J* = 5.2, 5.3, 16.0 Hz, 2 H), 3.58 (s, 2 H), 4.35 (m, 1 H), 5.91 (d, *J* = 6.9 Hz, 1 H), 7.30 (m, 5 H). − ^{13}C NMR ($CDCl_3$): δ = 19.9, 39.7, 42.2, 43.8, 127.3, 129.0, 129.4, 134.6, 136.4, 165.0, 170.9. − $C_{12}H_{15}NO_3$ (221.3): calcd. C 65.14, H 6.83, N 6.33; found C 65.10, H 6.88, N 6.30.

Enzymatic Hydrolysis of 11: PGA immobilized on Eupergit (100 mg) was added to a pH-7 solution of the acid amide **11** (4.5 mmol, 1.0 g) in 0.1 M phosphate buffer (100 mL). The reaction mixture was stirred at room temperature for 6 h. Then, after filtering off the immobilized enzyme, 2 N HCl was added to the aqueous solution until pH = 3 was reached. The mixture was extracted twice with ethyl acetate, and the combined extracts were dried with Na_2SO_4 and concentrated to afford phenylacetic acid and the unhydrolysed amide [0.5 g, 100% yield, 2.25 mmol of (3*R*)-**11** + 2.25 mmol of phenylacetic acid]. Concentration of the aqueous layer gave (*S*)-3-aminobutanoic acid (**10**) as its hydrochloride. The amino acid hydrochloride was used directly in the following step without further purification.

Methyl (3*S*)-3-(Benzoylamino)butanoate (12): Benzoyl chloride (2.7 mmol, 0.32 mL) in acetone (5 mL) was added dropwise to a stirred solution of the recovered (*S*)-3-aminobutanoic acid hydrochloride (**10**; 2.25 mmol, 0.23 g) and NaOH (6.75 mmol, 0.27 g) in water (10 mL) and acetone (5 mL) at 0°C. The mixture was stirred for 1 h at room temperature, the acetone was then removed under reduced pressure, and the residue was extracted twice with ethyl acetate. Then, 2 N HCl was added to the aqueous layer until pH = 2 was reached, and the solution was extracted with ethyl acetate. The combined extracts were dried with Na_2SO_4 and concentrated to give 0.40 g of the *N*-benzoyl derivative. Meanwhile, a solution of $SOCl_2$ (3.84 mmol, 0.28 mL) in methanol (20 mL) was stirred for 2 h at −15°C, and then to this the aforementioned benzamide was added in one portion. The mixture was gradually allowed to warm to room temperature overnight and then concentrated under reduced pressure. Compound **12** was obtained in 71% overall yield (0.71 g, 2.5 mmol) after flash chromatography (cyclohexane/ethyl acetate, 7:3, as eluent); m.p. 98°C; $[\alpha]_D$ = −42.3 (*c* = 0.3, $CHCl_3$). − IR (Nujol): $\tilde{\nu}$ = 3296, 1729, 1652 cm^{-1}. − ^1H NMR ($CDCl_3$): δ = 1.18 (d, *J* = 6.8 Hz, 3 H), 2.51 (d, *J* = 5.5 Hz, 2 H), 3.57 (s, 3 H), 4.33 (m, 1 H), 5.98 (d, *J* = 7.0 Hz, 1 H), 7.30 (m, 5 H). − ^{13}C NMR ($CDCl_3$): δ = 19.4, 39.6, 41.8, 42.8, 50.9, 126.3, 128.0, 128.6, 134.9, 169.9, 171.1. − $C_{12}H_{15}NO_3$ (221.3): calcd. C 65.14, H 6.83, N 6.33; found C 65.10, H 6.81, N 6.35.

(4*S*,5*R*)-5-(Methoxycarbonyl)-4-methyl-2-phenyl-2-oxazoline (13): To a stirred solution of ester **12** (1.6 mmol, 0.38 g) in dry THF (35 mL) at 0°C under argon, LiHMDS (3.5 mmol, 3.5 mL, 1 M solution in THF) was added in one portion. After 1 h, the mixture was cooled to −78°C and a solution of iodine (3.3 mmol, 0.82 g) in THF (5 mL) was added dropwise. After 1 h at −78°C, the reaction was quenched with saturated aqueous NH_4Cl solution (10 mL), and the solvent was removed under reduced pressure. The residue was dissolved in ethyl acetate and washed twice with $Na_2S_2O_3$ solution. The organic layer was dried with Na_2SO_4 and concentrated. Compound **13** was obtained as an oil in 80% yield (0.65 g, 2.32 mmol) after flash chromatography on silica gel (cyclohexane/ethyl acetate, 9:1, as eluent); $[\alpha]_D$ = +43.5 (*c* = 0.4, $CHCl_3$). − IR (film): $\tilde{\nu}$ = 1760, 1656 cm^{-1}. − ^1H NMR ($CDCl_3$): δ = 1.48 (d, *J* = 6.8 Hz, 3 H), 3.80 (s, 3 H), 4.39 (quint, *J* = 6.8 Hz, 1 H), 4.61 (d, *J* = 6.8 Hz, 1 H), 7.42 (m, 5 H). − ^{13}C NMR ($CDCl_3$): δ = 21.8, 52.4, 67.4, 82.2, 126.9, 127.3, 128.3, 128.7, 131.3, 131.5, 134.0, 162.5, 170.7. − $C_{12}H_{13}NO_3$ (219.2): calcd. C 65.74, H 5.98, N 6.39; found C 65.77, H 6.01, N 6.40.

Methyl (2*R*,3*S*)-3-(Benzoylamino)-2-hydroxybutanoate (14): A solution of oxazoline **13** (1 mmol, 0.22 g) in methanol (15 mL) and 1 N HCl (5 mL) was refluxed for 4 h. After removal of the solvent under reduced pressure, the residue was dissolved in CH_2Cl_2 and washed twice with water. The organic layer was dried with Na_2SO_4 and concentrated. Compound **14** was obtained in a pure state as a waxy solid in 95% yield (0.23 g) after flash chromatography on silica gel (cyclohexane/ethyl acetate, 8:2, as eluent); $[\alpha]_D$ = −21.8 (*c* = 0.8, $CHCl_3$). − IR (film): $\tilde{\nu}$ = 3354, 1743, 1642 cm^{-1}. − ^1H NMR ($CDCl_3$): δ = 1.36 (d, *J* = 6.6 Hz, 3 H), 3.65 (br. s, 1 H), 3.77 (s, 3 H), 4.23 (d, *J* = 1.6 Hz, 1 H), 4.70 (m, 1 H), 6.53 (d, *J* = 8.6 Hz, 1 H), 7.45 (m, 5 H). − ^{13}C NMR ($CDCl_3$): δ = 17.7, 47.6, 52.9, 73.1, 126.9, 128.5, 131.5, 134.3, 167.0, 173.8. − $C_{12}H_{15}NO_4$ (237.3): calcd. C 60.75, H 6.37, N 5.90; found C 60.78, H 6.38, N 5.92.

General Procedure for the Alkylation of Oxazoline 13: The alkylation was carried out analogously to that of oxazoline **5**.

15a + 16a: IR (Nujol): $\tilde{\nu}$ = 1743, 1652 cm^{-1}. − $C_{13}H_{15}NO_3$ (233.3): calcd. C 66.94, H 6.48, N 6.00; found C 66.97, H 6.50, N 5.95. − **15a:** ^1H NMR ($CDCl_3$): δ = 1.27 (d, *J* = 6.9 Hz, 3 H), 1.70 (s, 3 H), 3.80 (s, 3 H), 4.18 (q, *J* = 6.9 Hz, 1 H), 7.50 (m, 3 H), 7.95 (m, 2 H). − ^{13}C NMR ($CDCl_3$): δ = 16.4, 17.4, 52.7, 72.1, 87.8, 127.5, 128.3, 131.5, 171.4, 180.1. − **16a:** ^1H NMR ($CDCl_3$): δ = 1.34 (d, *J* = 7.1 Hz, 3 H), 1.57 (s, 3 H), 3.77 (s, 3 H), 4.46 (q, *J* = 7.1 Hz, 1 H), 7.50 (m, 3 H), 7.95 (m, 2 H). − ^{13}C NMR ($CDCl_3$): δ = 17.4, 18.0, 52.2, 68.0, 90.3, 127.5, 128.3, 131.5, 171.4, 180.1.

15b + 16b: IR (Nujol): $\tilde{\nu}$ = 1736, 1659 cm^{-1}. − $C_{14}H_{17}NO_3$ (247.3): calcd. C 68.00, H 6.93, N 5.66; found C 68.03, H 6.95, N 5.70. − **15b:** ^1H NMR ($CDCl_3$): δ = 1.03 (t, *J* = 7.3 Hz, 3 H), 1.26 (d, *J* = 6.9 Hz, 3 H), 1.89 (dq, *J* = 7.3, 14.4 Hz, 1 H), 2.15 (dq, *J* = 7.3, 14.4 Hz, 1 H), 3.79 (s, 3 H), 4.19 (q, *J* = 6.9 Hz, 1 H), 7.50 (m, 3 H), 8.12 (m, 2 H). − ^{13}C NMR ($CDCl_3$): δ = 8.2, 17.6, 22.0, 52.1, 70.2, 82.3, 127.2, 128.4, 131.7, 162.6, 170.8. − **16b:** ^1H NMR ($CDCl_3$): δ = 1.35 (t, *J* = 7.3 Hz, 3 H), 1.48 (d, *J* = 6.9 Hz, 3 H), 1.95 (m, 2 H), 3.81 (s, 3 H), 4.40 (q, *J* = 6.9 Hz, 1 H), 7.50 (m, 3 H), 8.12 (m, 2 H). − ^{13}C NMR ($CDCl_3$): δ = 8.8, 16.0, 23.8, 52.6, 67.4, 82.3, 127.2, 128.4, 131.7, 162.6, 170.8.

15c (major isomer): $[\alpha]_D$ = −87.4 (*c* = 0.4, $CHCl_3$). − IR (Nujol): $\tilde{\nu}$ = 1743, 1659 cm^{-1}. − ^1H NMR ($CDCl_3$): δ = 0.94 (t, *J* = 7.3 Hz, 3 H), 1.24 (d, *J* = 7.0 Hz, 3 H), 1.79 (m, 2 H), 2.11 (m, 2 H), 3.77 (s, 3 H), 4.15 (q, *J* = 7.0 Hz, 1 H), 7.61 (m, 5 H). − ^{13}C NMR ($CDCl_3$): δ = 8.1, 16.5, 21.3, 28.9, 52.9, 71.3, 84.1, 127.0, 127.4, 128.2, 131.6, 168.4, 178.5. − $C_{15}H_{19}NO_3$ (261.3): calcd. C 68.94, H 7.33, N 5.36; found C 68.97, H 7.34, N 5.36.

15d (major isomer): $[\alpha]_D$ = −212.5 (*c* = 0.1, $CHCl_3$). − IR (Nujol): $\tilde{\nu}$ = 1750, 1666 cm^{-1}. − ^1H NMR ($CDCl_3$): δ = 1.26 (d, *J* = 6.9 Hz, 3 H), 2.63 (dd, *J* = 7.8, 14.8 Hz, 1 H), 2.85 (dd, *J* = 7.8, 14.8 Hz, 1 H), 3.78 (s, 3 H), 4.24 (q, *J* = 6.9 Hz, 1 H), 5.20 (m, 2 H),

5.81 (m, 1 H), 7.46 (m, 3 H), 7.98 (m, 2 H). − ^{13}C NMR ($CDCl_3$): δ = 17.5, 41.5, 52.1, 70.1, 90.2, 119.9, 127.4, 128.3, 128.4, 131.1, 131.5, 162.2, 170.6. − $C_{15}H_{17}NO_3$ (259.3): calcd. C 69.48, H 6.61, N 5.40; found C 69.48, H 6.62, N 5.36.

15e (major isomer): $[\alpha]_D$ = +167.0 (*c* = 0.2, $CHCl_3$). − IR (Nujol): $\tilde{\nu}$ = 1735, 1651 cm^{-1}. − ^{1}H NMR ($CDCl_3$): δ = 1.30 (d, *J* = 7.0 Hz, 3 H), 3.16 (d, *J* = 14.3 Hz, 1 H), 3.44 (d, *J* = 14.3 Hz, 1 H), 3.72 (s, 3 H), 4.32 (q, *J* = 7.0 Hz, 1 H), 7.45 (m, 8 H), 7.97 (m, 2 H). − ^{13}C NMR ($CDCl_3$): δ = 17.5, 43.0, 52.2, 70.4, 91.2, 127.1, 128.3, 128.4, 130.0, 130.3, 131.8, 135.0, 162.3, 170.2. − $C_{19}H_{19}NO_3$ (309.1): calcd. C 73.75, H 6.19, N 4.53; found C 73.61, H 6.15, N 4.58.

General Procedure for the Hydrolysis of Oxazolines. − Synthesis of Hydroxy Amido Esters 17: The hydrolysis was performed analogously to that of oxazolines **6** and **7**.

17a + 18a: IR (Nujol): $\tilde{\nu}$ = 3360, 1743, 1638 cm^{-1}. − $C_{13}H_{17}NO_4$ (251.3): calcd. C 62.14, H 6.82, N 5.57; found C 62.10, H 6.80, N 5.60. − **17a:** ^{1}H NMR (C_6D_6): δ = 1.01 (d, *J* = 7.0 Hz, 3 H), 1.38 (s, 3 H), 3.18 (s, 3 H), 4.83 (dq, *J* = 7.0, 10.0 Hz, 1 H), 6.33 (d, *J* = 10.0 Hz, 1 H), 7.50 (m, 3 H), 7.88 (m, 2 H). − ^{13}C NMR ($CDCl_3$): δ = 16.1, 23.7, 30.3, 50.3, 53.2, 77.2, 126.8, 127.0, 128.0, 128.6, 131.5, 131.6, 134.5, 167.1, 176.2. − **18a:** ^{1}H NMR (C_6D_6): δ = 1.13 (d, *J* = 7.0 Hz, 3 H), 1.22 (s, 3 H), 3.30 (s, 3 H), 4.84 (dq, *J* = 7.0, 9.1 Hz, 1 H), 6.38 (d, *J* = 9.1 Hz, 1 H), 7.50 (m, 3 H), 7.88 (m, 2 H). − ^{13}C NMR ($CDCl_3$): δ = 16.2, 22.7, 31.9, 50.5, 53.2, 77.7, 126.8, 127.0, 128.0, 128.6, 131.5, 131.6, 134.5, 167.1, 176.2.

17b: $[\alpha]_D$ = −19.4 (*c* = 0.3, $CHCl_3$). − IR (film): $\tilde{\nu}$ = 3522, 3353, 1729, 1638 cm^{-1}. − ^{1}H NMR ($CDCl_3$): δ = 0.82 (t, *J* = 7.1 Hz, 3 H), 1.11 (d, *J* = 6.7 Hz, 3 H), 1.81 (q, *J* = 7.1 Hz, 2 H), 3.41 (s, 1 H), 3.86 (s, 3 H), 4.59 (dq, *J* = 6.4, 9.1 Hz, 1 H), 6.41 (d, *J* = 9.1 Hz, 1 H), 7.46 (m, 3 H), 7.78 (m, 2 H). − ^{13}C NMR ($CDCl_3$): δ = 7.8, 16.3, 29.3, 50.1, 53.1, 80.3, 126.9, 127.1, 128.6, 131.5, 134.4, 134.6, 166.9, 175.6. − $C_{14}H_{19}NO_4$ (265.3): calcd. C 68.38, H 7.22, N 5.28; found C 68.40, H 7.25, N 5.25.

17c: M.p. 99−101°C; $[\alpha]_D$ = −28.3 (*c* = 0.2, $CHCl_3$). − IR (film): $\tilde{\nu}$ = 3543, 3367, 1729, 1645 cm^{-1}. − ^{1}H NMR ($CDCl_3$): δ = 0.87 (t, *J* = 6.8 Hz, 3 H), 1.00 (d, *J* = 6.6 Hz, 3 H), 1.40 (m, 2 H), 1.77 (m, 2 H), 3.75 (s, 1 H), 3.85 (s, 3 H), 4.58 (dq, *J* = 6.6, 9.7 Hz, 1 H), 6.42 (d, *J* = 9.7 Hz, 1 H), 7.45 (m, 3 H), 7.85 (m, 2 H). − ^{13}C NMR ($CDCl_3$): δ = 14.1, 16.2, 16.9, 38.4, 50.3, 53.1, 79.7, 126.9, 127.0, 128.4, 128.6, 128.9, 129.0, 131.6, 134.4, 166.9, 175.8. − $C_{15}H_{21}NO_4$ (279.3): calcd. C 64.50, H 7.58, N 5.01; found C 64.54, H 7.59, N 5.04.

17d: M.p. 95°C; $[\alpha]_D$ = +13.7 (*c* = 0.2, $CHCl_3$). − IR (film): $\tilde{\nu}$ = 3529, 3339, 1736, 1645 cm^{-1}. − ^{1}H NMR ($CDCl_3$): δ = 1.13 (d, *J* = 6.7 Hz, 3 H), 2.55 (m, 2 H), 3.47 (br. s, 1 H), 3.83 (s, 3 H), 4.65 (dq, *J* = 6.7, 9.7 Hz, 1 H), 5.15 (m, 2 H), 5.70 (m, 1 H), 6.47 (d, *J* = 9.7 Hz, 1 H), 7.45 (m, 3 H), 7.82 (m, 2 H). − ^{13}C NMR ($CDCl_3$): δ = 16.3, 41.2, 50.0, 52.3, 80.0, 119.2, 126.9, 127.0, 128.6, 131.5, 131.9, 134.6, 167.0, 175.0. − $C_{15}H_{19}NO_4$ (277.3): calcd. C 64.97, H 6.91, N 5.05; found C 65.01, H 6.89, N 5.04.

17e: M.p. 133°C; $[\alpha]_D$ = +3.3 (*c* = 0.5, $CHCl_3$). − IR (film): $\tilde{\nu}$ = 3521, 3381, 1715, 1638 cm^{-1}. − ^{1}H NMR ($CDCl_3$): δ = 1.50 (d, *J* = 6.6 Hz, 3 H), 3.10 (m, 2 H), 3.33 (s, 1 H), 3.77 (s, 3 H), 4.79 (dq, *J* = 6.6, 9.7 Hz, 1 H), 6.65 (d, *J* = 9.7 Hz, 1 H), 7.50 (m, 8 H), 7.88 (m, 2 H). − ^{13}C NMR ($CDCl_3$): δ = 16.4, 42.8, 50.2, 52.9, 80.5, 127.0, 128.3, 128.7, 129.9, 131.7, 134.4, 135.5, 167.0, 174.5. − $C_{19}H_{21}NO_4$ (327.2): calcd. C 69.69, H 6.47, N 4.28; found C 69.59, H 6.41, N 4.31.

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