Asymmetric Diastereoselective Conjugate Additions of Lithium Amides to Chiral Naphthyloxazolines Leading to Novel β-Amino Acids§

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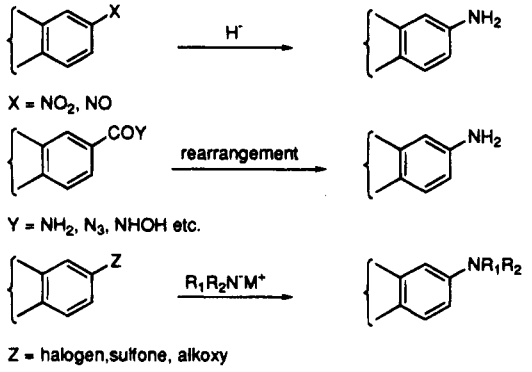
Received July 12, 1995®

The functionalization of the naphthalene ring system by a direct amination–alkylation reaction of chiral nonracemic naphthyloxazolines is described. Chiral 1-naphthyl- and 2-naphthyloxazoline were treated with a variety of lithium amides followed by several different electrophilic quenches. The solvent and additives were varied in order to achieve optimum conditions. The combination of HMPA and THF at −78 °C gave the best yield with excellent stereoselectivity. The present methodology provides a stereospecific synthesis of novel, nonracemic, rigid β-amino acids after hydrolytic removal of the chiral oxazoline.

A number of methods to introduce an amino function into an aromatic ring system exist, and they involve electrophilic substitution by a nitro or nitroso group followed by reduction to the corresponding amine.[1] Additionally, the rearrangement of carboxylic acid derivatives (Hofmann rearrangement,[2] Curtius rearrangement,[3] Lossen rearrangement,[4] and Schmidt rearrangement[5]) and substitution of halogen,[6] sulfone,[7] or alkoxy group[8] by an amino group make up the remainder of the synthetic opportunities.

All of these reactions provide the amino-substituted product with the aromatic ring system intact.[9] Recently, we reported, in a preliminary manner, a direct amination into the naphthalene ring which interrupted the aromaticity and led to the preparation of alicyclic amines in excellent enantioselectivity (Scheme 1).[10] We now describe the details of this direct amination along with mechanistic observations and also present a novel synthesis of a new class of chiral, nonracemic β-amino acids.[11–13]



Addition to Naphthyloxazolines. The approach to the stereoselective formation of carbon–nitrogen bonds involves the diastereoselective 1,4-addition (Scheme 1) of a lithium dialkylamide to chiral nonracemic naphthyloxazolines (**1** or **2**) followed by electrophilic quenching to provide α-amino-β-alkyl-β-oxazolinylnaphthalenes (**3** or **4**). We chose (*S*)-*tert*-leucinol to prepare the starting

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§ Dedicated to Professor Stephen Hanessian on the occasion of his 60th birthday.

® Abstract published in *Advance ACS Abstracts,* November 1, 1995.

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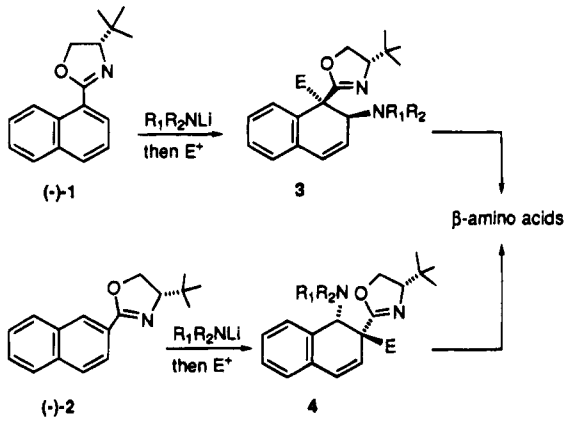
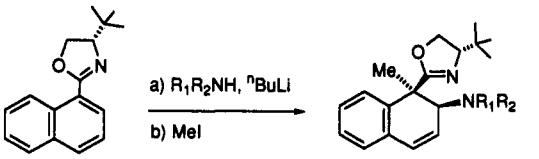
Scheme 1



chiral, nonracemic *tert*-butyloxazoline, since it was already known that the *tert*-butyloxazoline is an excellent auxiliary for asymmetric alkylation reactions.[14] The previously utilized conditions[14] for the diastereoselective addition of an organolithium to *tert*-butylnaphthyloxazoline **1** turned out to be disappointingly poor with lithium methylbutylamide and lithium piperidide, although the observed diastereoselectivity was quite good. In an attempt to improve the yields, a variety of solvents and additives were examined (Table 1). Increasing the polarity of solvent (DME[15] > THF > Et_2O)[16] did indeed increase the yield while maintaining the same level of diastereoselectivity. The addition of TMEDA and PMDETA (*N,N,N′,N′,N″*-pentamethyldiethylenetriamine) had little effect or lowered the yield, whereas DMPU gave acceptable yields. However, when 1 equiv of HMPA (to lithium piperidide) was introduced, the addition to 1-naphthyloxazoline **1** proceeded with high yield and excellent selectivity. It should be noted that a large excess of HMPA (*vs* lithium amide) gave poor selectivity (entry 10), although excess HMPA–lithium amide (up to 1.4 equiv) gave satisfactory results (entry 9).

The procedure using HMPA as an additive in THF was explored using a variety of lithium amides on both

Table 1. Effect of the Solvents and Additives in the Stereoselective Addition of Lithium Amide to 1-Naphthyloxazoline 1



entry[a]	Amine	Solvent	Additive	Product	(%)[b,c]	SM Recovery (%)[b]
1	Me^{n}BuNH	THF	none	**3b**	30	63
2	piperidine	THF	none	**3d**	19	77
3	piperidine	Et_2O	none	**3d**	1.5	91
4	piperidine	DME	none	**3d**	42	51
5	piperidine	THF	TMEDA	**3d**	19	75
6	piperidine	THF	PMDETA	**3d**	24	7
7	piperidine	THF	DMPU	**3d**	86	9.3
8	piperidine	THF	HMPA	**3d**	95	0
9[d]	piperidine	THF	HMPA	**3d**	94	0
10[e]	piperidine	THF	HMPA	**3d**	94[f]	0

a. Unless otherwise noted, all reactions were carried out at -78 °C and allowed to warm to -50 °C using 3 equiv of amine, 3 equiv of ^{n}BuLi, and 3.2 equiv. of iodomethane (see Experimental). If additive was used, 3 equiv. was added. b. Isolated yield. c. Unless otherwise noted, the diastereomeric ratio of every entry was 99 > 1 by GC or ^{1}H-NMR (300 MHz, $CDCl_3$) of crude mixture. d. 1.5 equiv. of amine, 1.4 equiv. of ^{n}BuLi, 1.4 equiv. of HMPA and 1.6 equiv. of iodomethane were used. e. 2.0 equiv. of amine, 2.0 equiv. of ^{n}BuLi, 6.0 equiv. of HMPA and 2.2 equiv. of iodomethane were used. f. The diastereomeric ratio was 76:24.

1-naphthyloxazoline **1** (Table 2) and 2-naphthyloxazoline **2** (Table 3). For acyclic lithium amides (Table 2), the additions gave satisfactory results (entries 1–3), while lithium diethylamide, lithium diallylamide, and lithium diisopropylamide failed to give addition products (entries 4–6).[17] Furthermore, the lithium salt of the primary amine, lithium allylamide, also failed to add to the naphthalene system (entry 7). This was not unexpected, however, since other lithium salts of primary amines have been reported to not undergo Michael additions to α,β-unsaturated carbonyls.[18]

The addition of lithium 2,2-dimethylaziridide did not give addition products, and this may be due to its poor nucleophilic character as well as its bulky nature. We observed some unusual behavior during the course of adding lithium piperidide and trapping the intermediate aza enolate with different electrophiles (Table 2, entries 9–12). The reaction proceeded smoothly and gave excellent yields and good selectivity when reactive electrophiles were introduced, whereas the trap with a relatively unreactive electrophile (entry 12) gave no adduct at all but instead starting material was completely recovered.

We also examined the 2-naphthyloxazoline system **2** and found similar behavior, both with regard to yield and stereochemical efficiency (Table 3). Once again, the lithium 2,2-dimethylaziridide or other bulky amine salts (e.g., LiHMDS) failed to add to **2** (entries 2 and 6). We also examined the methoxy-substituted 2-naphthyloxazoline and found that the electron-rich substituent had little or no negative effects on the reaction (entry 7). The stereochemistry of the addition was confirmed by X-ray analysis of the piperidine adduct **4c** which supported the *trans*-tandem addition as described earlier.

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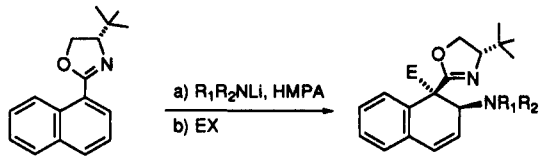
(15) During the preparation of the amide from *n*-butyllithium and a secondary amine, a white precipitate often appeared in DME, and once this occurred, the white precipitate would not redissolve in the reaction mixture even after addition of HMPA and a substrate at −50 to −78 °C. The white precipitate is most likely lithium methoxide, generated by reaction with DME and butyllithium (Fitt, J. J.; Gschwend, H. W. *J. Org. Chem.* **1984**, *49*, 209).

(16) Reichardt, C. *Solvents and Solvent Effects in Organic Chemistry*; 2nd ed.; VCH Publishers: New York, 1988.

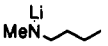
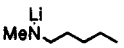
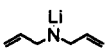
(17) The excess HMPA *vs* lithium diethylamide could give the adduct, although the diastereoselectivity was found to be low.

(18) Davies, S. G.; Ichihara, O. *Tetrahedron: Asymmetry* **1991**, *2*, 183.

Table 2. Addition of Lithium Amides to Naphthyloxazoline1

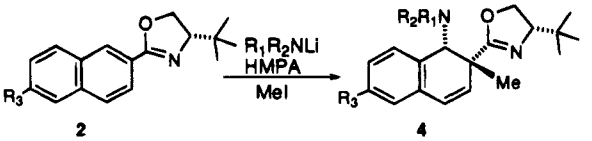


1 3

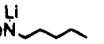
entry	R_1R_2NLi[a]	electrophile (EX)	product	(%)[b]	diastereoratio[c]
1	Me_2NLi	MeI	**3a**	94	98.5 : 1.5[d]
2[g]		MeI	**3b**	93	>99 : 1
3[g]		MeI	**3c**	93	>99 : 1
4		MeI		0[e]	—
5		MeI		0[e]	—
6		MeI		0[e]	—
7		MeI		0[f]	—
8		MeI		0[e]	—
9		MeI	**3d**	95	>99 : 1
10			**3e**	92	>99 : 1
11		$PhCH_2Br$	**3f**	67	>99 : 1
12		$CO(OEt)_2$		0[e]	—
13		MeI	**3g**	96	>99 : 1

a. The lithium amides, except for lithium methylpentylamide, were prepared *in situ* from corresponding amine and ^nBuLi. Lithium methylpentylamide was prepared in situ by the reaction of ^nBuLi and HMPA. b. Isolated yields. c. Ratios determined by GC or ^1H-NMR (300MHz, $CDCl_3$) of crude mixture. d. The minor isomer was determined as 1,6-amino adduct. e. Complete recovery of **1**. f. Multiple product mixture. g. See reference 34.

Table 3. Addition of Lithium Amides to Naphthyloxazoline 2

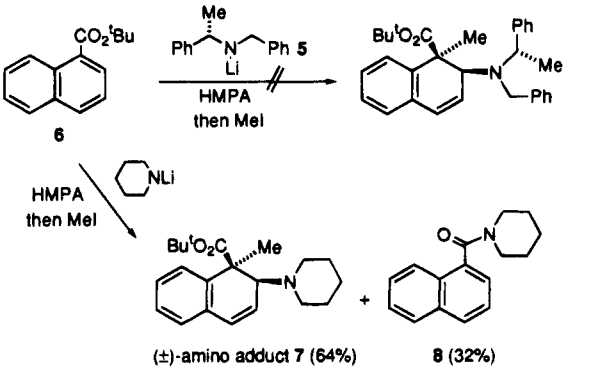


2 4

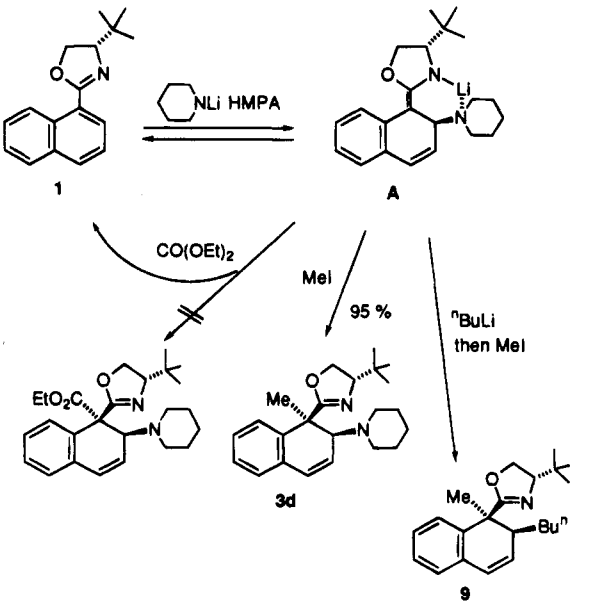
entry	R_1R_2NLi[a]	R_3	product	(%)[b]	diastereoratio[c]
1	Me_2NLi	H	**4a**	91	97.5 : 2.5
2		H		0[d]	—
3		H	**4b**	94	>99 : 1
4		H	**4c**	94	>99 : 1
5		H	**4d**	94	>99 : 1
6	$(TMS)_2NLi$	H		0[d]	—
7		MeO	**4e**	90	>99 : 1

a. The lithium amides, except for lithium methylpentylamide, were prepared *in situ* from corresponding amine and ^nBuLi. Lithium methylpentylamide was prepared in situ by the reaction of ^nBuLi and HMPA. b. Isolated yields. c. Ratio was determined by GC or ^1H-NMR (300MHz, $CDCl_3$) of crude mixture. d. Complete recovery of **2**.

Scheme 2



Scheme 3

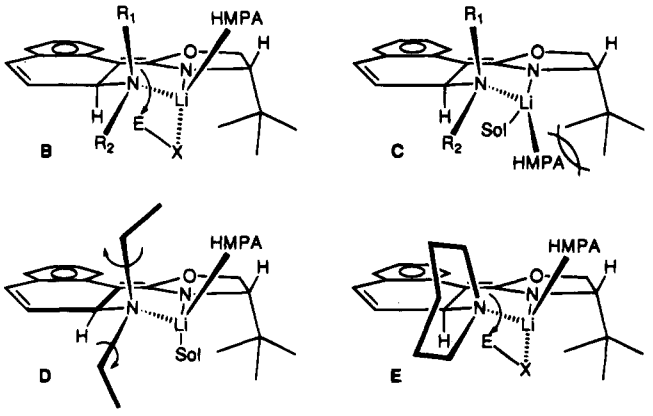


To assess whether the oxazoline moiety was indeed unique in this amide addition, we examined the reaction of chiral lithium amide **5**[19] with the *tert*-butyl naphthalenecarboxylate **6** (Scheme 2). The event ended with complete ester recovery. Furthermore, we investigated the reaction of lithium piperidide with ester **6** which did indeed furnish the *dl*-adduct **7** along with a considerable amount of the amide **8**. These results suggest that it may be possible to reach the chiral amine adduct (e.g., **7**) in satisfactory yield by employing either a chiral ester in **6** or an external chiral auxiliary complexed to **5**. However, reactions such as the formation of **8** could affect the efficiency of the process.

Mechanistic Studies. The results of entries 9 and 12 in Table 2 suggested to us that the addition of lithium dialkylamide was reversible (Scheme 3), and we set out to confirm this. When 1-naphthyloxazoline **1** was treated with lithium piperidide, the aza enolate **A** was presumably formed *in situ* and was readily recognized by its bright yellow color. When **A** was alkylated with iodomethane, we obtained the expected product (**3d**) in 95% yield. However, when **A** was treated with diethyl carbonate, only the starting naphthyloxazoline **1** was recovered along with *N*-carbethoxypiperidine. To confirm the reversibility between the starting naphthyloxazoline and the intermediate **A**, *n*-BuLi was added into the reaction mixture, after **A** had been generated, and the solution was stirred for 2 h prior to addition of the electrophile (MeI). The nonreversible butyl adduct **9**[14] was the sole

product recovered, and we could not detect any trace of piperidine adduct **3d**.[20] It, therefore, appears that the extent of reversibility of **A** to **1** is due to the steric nature of the adduct **A** and the ready driving force to return to the naphthalene aromaticity.

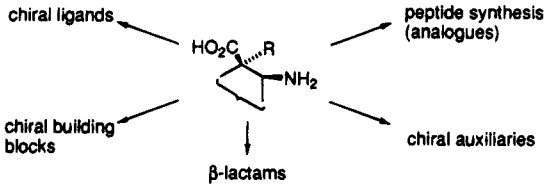
The fact that lithium piperidide adds smoothly while lithium diethylamide fails to give an addition product (Table 2, entry 4 *vs* 9) cannot be due to any major electronic factor[16] (pK_a, nucleophilicity, etc.) and therefore must be due solely to a steric factor. We may consider two configurational aza enolates **B** and **C** which resulted from the addition of lithium amide to the naphthyloxazoline from the β face. The existence of the bulky *tert*-butyl group on the α face should hinder addition from this face. Aza enolate **B** shows HMPA chelating to lithium ion from the β face, while HMPA in aza enolate **C** is chelated to lithium ion from the α face. Because of the bulky interaction in the latter, aza enolate **B** seems to be favored. Using this model, the observed difference in behavior between lithium diethylamide and lithium piperidide may also be rationalized. In the case of lithium diethylamide (**D**), two ethyl groups on the nitrogen can freely rotate and interact with the HMPA, *tert*-butyl, and solvated lithium ion, thus rendering the aza enolate relatively crowded such that the equilibrium favors return to the starting naphthyloxazoline. Furthermore, these bulky alkyl groups may hinder the approach of the electrophile which is known to enter **D** or **E** from the α face. On the other hand, these factors are much less prevelant in the aza enolate containing the piperidine ring (**E**), due to its smaller steric bulk.



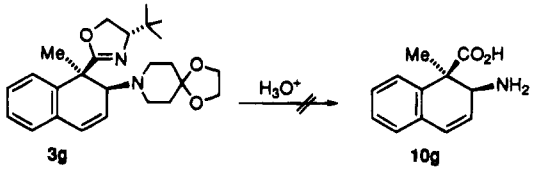
This also explains the successful addition of lithium methylalkylamide (entries 1, 2, and 3 in Table 2). In this case, the steric interaction between the small methyl group and any other alkyl group on the nitrogen should be greatly diminished over that observed with lithium diethylamide because of the lack of the larger alkyl group.

There is another aspect of this process that may be worth mentioning. It is also plausible to consider that all the amines listed in Tables 2 and 3 are, in fact, adding to the naphthalene ring, but due to the bulky nature of the amine in the adduct **B** (or **D**), the entry of the electrophile is prevented. On warming, the amino adduct **A** simply reverses to the naphthalene starting material.

β-Amino Acid Synthesis. The main intent in this study was to synthesize novel β-amino acids, due to their occurrence in natural products,[21,22] as well as their utility as intermediates for preparing β-lactams,[23] therapeutically enhanced peptides,[24] chiral ligands, chiral building blocks, and chiral auxiliaries.



The initial attempt to obtain primary β-amino acids by hydrolyzing the oxazoline **3g** with acid were disappointing, and no trace of the amino acid **10g** could be found.[25] Therefore, a stepwise sequence was designed to carry out the planned transformation which first required the removal of the 1,3-dioxolane in **3g**. This was readily accomplished by using concentrated hydrochloric



acid, below 20 °C (Scheme 4). Surprisingly, when the oxazoline **3g** was exposed to 1 N hydrochloric acid or PPTS (pyridinium *p*-toluenesulfonate), the oxazoline moiety was hydrolyzed to the amino ester **12g** while the ethylene glycol acetal remained intact.

Various conditions were explored to effect the cleavage of the piperidone ring in **11g** and liberate the primary amine to **13g** (Table 4). Optimum results were finally obtained using sodium hydroxide in water and *n*-butylamine (7:3) at 125 °C in a sealed tube (entry 6). The mixed solvent of methanol and *n*-butylamine (entry 5) only produced a trace of product. *n*-Butylamine may be considered to have three important roles in this reaction. First, it was used to dissolve the substrate. Second, it

(19) Davies, S. G.; Ichihara, O.; Walters, I. A. *Synlett* **1993**, 461.

(20) To the best of our knowledge, this is the first example exhibiting the reversible addition of an lithium amide to an α,β-unsaturated system. However, the reversible addition of a simple amine under thermodynamic conditions has been reported: Hawkins, J. M.; Fu, G. C. *J. Org. Chem.* **1986**, *51*, 2820.

(21) Recent reports about natural products continaing the β-amino acid moiety: (a) Rinehart, K. L.; Harada, K.-I.; Namikoshi, M.; Chen, C.; Harvis, C.; Munro, M. H. G.; Blunt, J. W.; Mulligan, P. E.; Beasley, V. R.; Dahlem, A. M.; Carmichael, W. W. *J. Am Chem. Soc.* **1988**, *110*, 8557. (b) Mynderse, J. S.; Hunt, A. H.; Moor, R. E. *J. Nat. Prod.* **1988**, *51*, 1299. (c) Helms, G. L.; Moor, R. E.; Niemczura, W. P.; Patterson, G. M.; Tomer, K. B.; Gross, M. L. *J. Org. Chem.* **1988**, *53*, 1298. (d) Itagaki, F.; Shigemori, H.; Ishibashi, M.; Nakamura, T.; Sasaki, T.; Kobayashi, J. *J. Org. Chem.* **1992**, *57*, 5540. (e) Kosemura, S.; Ogawa, T.; Totsuka, K. *Tetrahedron Lett.* **1993**, *34*, 1291. (f) Onuki, H.; Tachibana, K.; Fusetani, N. *Tetrahedron Lett.* **1993**, *34*, 5609. (g) Sone, H.; Nemoto, T.; Ishiwata, H.; Ojika, M.; Yamada, K. *Tetrahedron Lett.* **1993**, *34*, 8449. (h) Needham, J.; Kelly, M. T.; Ishige, M.; Andersen, R. J. *J. Org. Chem.* **1994**, *59*, 2058.

(22) Reviews: (a) Drey, C. N. C. In *Chemistry and Biochemistry of the amino acids*; Barret, G. C., Ed.; Chapman and Hall: New York, 1985; Chapter 3. (b) Griffith, O. W. *Annu. Rev. Biochem.* **1986**, *55*, 855.

(23) Wang, W.-B.; Roskamp, E. J. *J. Am Chem. Soc.* **1993**, *115*, 9417 and references cited therein.

(24) (a) Xie, J.; Soleilhac, J.-M.; Schmidt, C.; Peyroux, J.; Roques, B. P.; Fournié-Zaluski, M.-C. *J. Med. Chem.* **1989**, *32*, 1497. (b) Yamazaki, T.; Zhu, Y.-F.; Probstl, A.; Chadha, R. K.; Goodman, M. *J. Org. Chem.* **1991**, *56*, 6644. (c) Mimoto, T.; Imai, J.; Kisanuki, S.; Enomoto, H.; Hattori, N.; Akaji, K.; Kiso, Y. *Chem. Pharm. Bull.* **1992**, *40*, 2251. (d) Bovy, P. R.; Garland, R. B.; Tjoeng, F. S.; Zupec, M. E.; Zablocki, J. A.; Rico, J. G.; Rogers, T. E.; Lindmark, R. J.; Panzer-Knodle, S. G.; Nicholson, N. S.; Taite, B. B.; Miyano, M.; Feigen, L. P.; Adams, S. P. *J. Cell. Biochem. Suppl. C* **1993**, 308.

(25) The product from **3g** was 2-methyl-1-naphthoic acid. From **4d**, the product was 2-methylnaphthalene.

Scheme 4

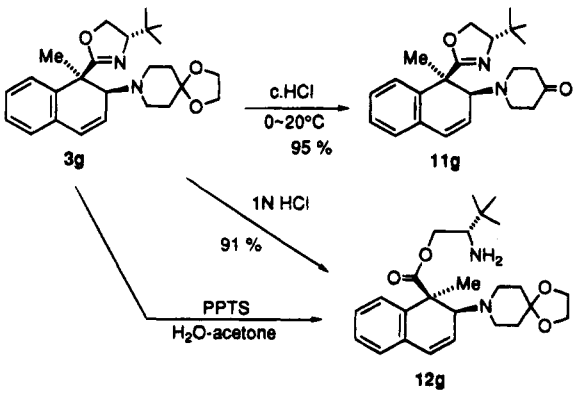
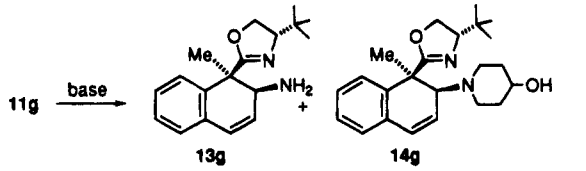


Table 4. Cleavage of Piperidone 11g to Free Amine 13g

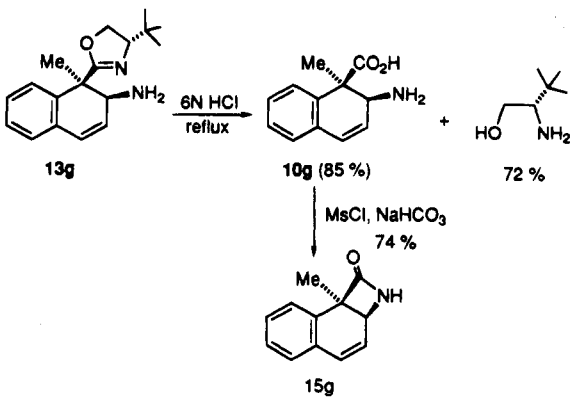


entry	base[a]	conditions solvent	temp.	t. (hours)	yield (%) 13g	14g
1	NaOMe	MeOH	reflux	96	38	0
2	NaOMe	MeOH	160 C[cb]	3	42	0
3	NaOEt	EtOH	reflux	48	10	49
4	NaOEt	EtOH-^{n}BuNH$_2$ (8 : 3)	125 C[cb]	20	trace	86
5	NaOH	MeOH-^{n}BuNH$_2$ (7 : 3)	125 C[cb]	24	trace[c]	0
6	NaOH	H$_2$O-^{n}BuNH$_2$ (7 : 3)	125 C[cb]	12	82	0

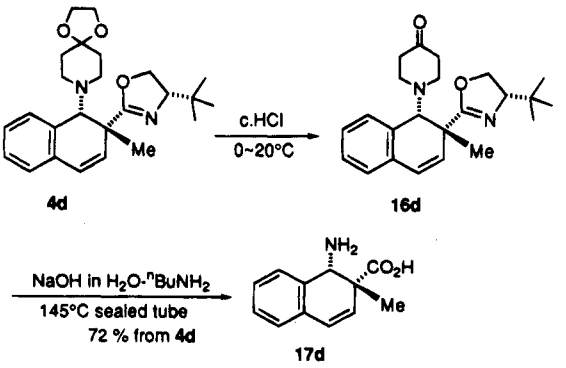
a. About 8 equivalents of base were used against the starting material. b. The reaction was conducted in the sealed tube. c. Starting material was recovered (85 %).

acted as a scavenger to trap the released divinyl ketone which was the coproduct of the desired primary amine (**13g**), forming *N*-*n*-butylpiperidone. To confirm that the reversal of the piperidone ring had occurred, the latter was isolated from the reaction mixture. Third, it acts as a "blanket" to shield the primary amine **13g** from air oxidation. An unusual reduction was also observed during the reaction (entries 3 and 4). In fact, the process was quite efficient, reducing the piperidone **11g** to the piperidinol **14g** in 86% yield. This unusual reduction, although apparently unprecedented using aqueous amines, may in fact have some roots in the Meerwein–Ponndorf–Verley reduction.[26]

Scheme 5



Scheme 6



With the free amino group in **13g** now attainable, the desired β-amino acid **10g** was readily produced by hydrolysis with 6 N HCl. The product was obtained in 85% yield and >99% ee,[27] along with recovery of the chiral auxiliary (Scheme 5). The β-amino acid **10g** was further converted into a corresponding β-lactam **15g**, which reconfirmed that the amino group and the carboxyl group existed *cis* each other.

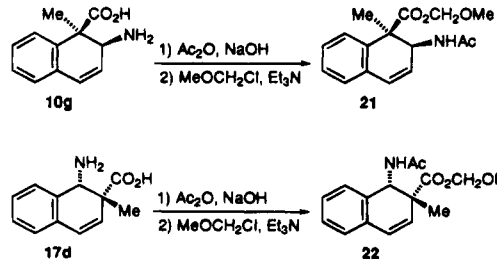
The synthesis of the isomeric primary β-amino acid **17d** from the corresponding amino adduct **4d** was also accomplished by using the procedure described above (Scheme 6).

However, it was of interest and surprising that the hydrolysis of the oxazoline moiety accompanied the cleavage of the piperidone ring to a primary amino group. Thus, the desired β-amino acid **17d** (>99% ee)[25] was obtained directly from the piperidone **16d** at a slightly higher reaction temperature.[28] It should be stated that the cleavage of the oxazoline ring into the corresponding carboxylic acid using a base without any activating step (*i.e.*, MeI, MeOTf, etc.) is very rare. [29]

As shown in Scheme 7, three *N*,*N*-dialkylamino acids **19** (**b,d,e**) were prepared from the corresponding 2-amino-1-oxazolinylnaphthalenes **3** (**b,d,e**) in a two-step sequence.[30] The first step, consisting of two sequential reactions, was carried out in the aqueous medium to give

(26) Kirk, D. N.; Mudd, A. *J. Chem. Soc. C* **1969**, 804.

(27) The enantiomeric excesses of the amino acids **10g** and **17d** were determined as follows: **10g** and **17d** were converted into the corresponding amido esters **21** and **22**, respectively, and subjected to HPLC on a Chiralcel OD column. See the Experimental Section. The corresponding racemic **21** and **22** were synthesized from 1-(4′, 4′-dimethyloxazolin-2′-yl)naphthalene and 2-(4′, 4′-dimethyloxazolin-2′-yl)naphthalene, respectively, and analyzed under the same conditions.

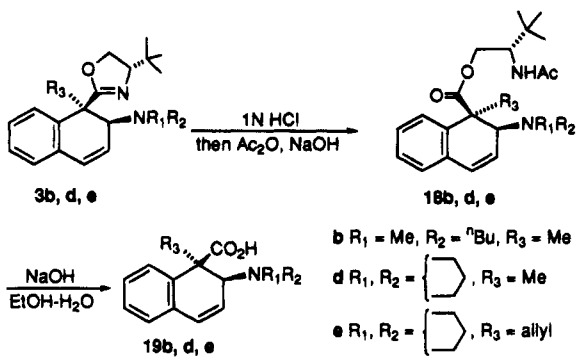


(28) It should be noted that these conditions erode glassware.

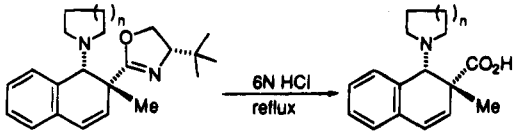
(29) We also examined these conditions with 1-(4′,4′-dimethyloxazolin-2′-yl)naphthalene and 2-(4′, 4′-dimethyloxazolin-2′-yl)naphthalene to ascertain if this was a general reaction for the cleavage of the oxazoline. As it turned out, we obtained 1-naphthoic acid and 2-naphthoic acid in excellent yields, respectively. We are pursuing this hydrolytic method with other oxazolines to determine the breadth of its scope.

(30) The other hydrolysis conditions (6 N HCl reflux) to obtain the *N*,*N*-dialkylamino acid were also examined but failed to give any product, presumably due to the steric hindrance of dialkylamino group.

Scheme 7



Scheme 8



the *N*-acetyl esters **18** in excellent yields.[31] The latter were then hydrolyzed with NaOH in ethanol to the final products **19** (**b,d,e**). On the other hand, *N,N*-dialkylamino acids **20** (**b,c**) derived from 1-amino-2-oxazolinylnaphthalenes **4** were synthesized in excellent yields by being heated to reflux with 6 N hydrochloric acid (Scheme 8).[32] These novel amino acids were converted into their corresponding methoxymethyl esters to determine the enantiomeric excess (ee). HPLC analysis indicated that ee values were higher than 99%.[33]

In summary, this process for functionalizing the aromatic ring system by direct amination–alkylation in an enantioselective sense and the syntheses of the enantiomericaly pure β-amino acids has been shown to be highly efficient. During the development of this methodology, an example of the reversible addition of lithium amide to naphthyloxazoline was clearly indicated, and the application to introduction of a primary amine, using the reversal of a piperidone ring system, has been demonstrated.

Experimental Section

General. Microanalyses were performed by Atlantic Microlab, Inc., Norcross, GA, or on a Yanaco CHN CORDER MT-5. Thin layer chromatography was performed on E. Merk and Co. aluminum sheets (0.20 mm) precoated with silica gel. Silica gel for flash chromatography was purchased from Amicon (200–450 mesh). TMEDA and PMDETA were purchased from Aldrich and dried over CaH_2, distilled under an atmosphere of argon, and stored over 4A molecular sieves. HMPA and DMPU were purchased from Aldrich, dried over CaH_2, distilled under reduced pressure (2 mmHg), and stored over 13X molecular sieves in a dark place. All secondary amines except for dimethylamine were converted into lithium amides and dried over 4A molecular sieves. Dimethylamine was purchased from Aldrich as a 2 M solution in anhydrous THF and used without further purification. *J* values are given in hertz.

Chiral Naphthyloxazolines 1 and 2. A typical procedure for **1** is given, which is identical with the procedure for **2**.

2-(1′-Naphthyl)-4-(*S*)-*tert*-butyloxazoline (1). To a solution of 1-naphthoic acid (10.0 g, 58 mmol) in dichloromethane (120 mL) at rt were added oxalyl chloride (11.0 g, 87 mmol) and DMF (3 drops). After stirring at room temperature for 2 h, the mixture was concentrated to remove excess oxalyl chloride, reddisolved in dichloromethane (200 mL), cooled to 0 °C, and treated with a solution of Et_3N (7.0 g, 69.6 mmol) and *l*-*tert*-leucinol (7.5 g, 63.9 mmol) in dichloromethane (15 mL). The mixture was allowed to warm to rt and stirred overnight. The resulting solution was poured into a 2% $NaHCO_3$ aqueous solution and extracted with dichloromethane (3×). The organic layer was dried over $MgSO_4$ and the solvent removed under reduced pressure. The resulting oil was dissolved in dichloromethane (260 mL), treated with thionyl chloride (13.8 g, 116 mmol) at room temperature, and stirred overnight. The mixture was concentrated to remove excess thionyl chloride, diluted with acetonitrile (250 mL), treated with an aqueous potassium carbonate solution (50 g in 200 mL of H_2O), refluxed for 5 h, and concentrated to remove acetonitrile. The resulting heterogeneous mixture was extracted with ether, washed with brine, dried over $MgSO_4$, and concentrated. Flash chromatography (10% EtOAc/hexane) gave 2-(1′-naphthyl)-4-(*S*)-*tert*-butyloxazoline (**1**) (13.2 g, 90%) as a clear oil; $[\alpha]_D$ −95.3° (*c* 1.15, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) 1.05 (s, 9H), 4.15–4.33 (m, 2H), 4.34–4.42 (m, 1H), 7.44–7.63 (m, 3H), 7.86 (d, *J* = 7.8, 1H), 7.93 (d, *J* = 8.2, 1H), 8.07 (dd, *J* = 7.2, 1.3, 1H), 9.17 (d, *J* = 8.7, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) 26.0 (q, 3C), 34.1 (s), 67.7 (t), 77.1 (d), 124.6 (d), 124.8 (s), 126.0 (d), 126.5 (d), 127.2 (d), 128.4 (d), 128.8 (d), 131.3 (s), 131.7 (d), 133.7 (s), 163.1 (s); IR (thin film) 2954, 1644, 1590, 1511, 1123, 999, 776 cm^{-1}; *m/z* 253 (M^+), 196, 168, 141. Anal. Calcd for $C_{17}H_{19}NO$: C, 80.60; H, 7.56; N, 5.53. Found: C, 80.79; H, 7.70; N, 5.59.

2-(2′-Naphthyl)-4-(*S*)-*tert*-butyloxazoline (2). This was prepared (82%) from 2-naphthoic acid by the procedure described for **1**. **2**: white solid (mp 96.4–97.3 °C); $[\alpha]_D$ −89.8° (*c* 1.00, $CHCl_3$); ^1H NMR (270 MHz, $CDCl_3$) 0.98 (s, 9H), 4.09 (dd, *J* = 10.2, 7.6, 1H), 4.27 (t, *J* = 8.6, 1H), 4.38 (dd, *J* = 9.9, 8.6, 1H), 7.49 (m, 2H), 7.78–7.93 (m, 3H), 8.07 (dd, *J* = 8.6, 1.3, 1H), 8.44 (bs, 1H); ^{13}C NMR (68 MHz, $CDCl_3$) 25.8 (q, 3C), 34.0 (s), 68.7 (t), 76.2 (d), 125.0 (d), 125.2 (s), 126.4 (d), 127.3 (d), 127.7 (d), 127.9 (d), 128.5 (d), 128.8 (d), 132.6 (s), 134.6 (s), 163.2 (s); IR (KBr) 3060, 2950, 1650, 1542, 1362 cm^{-1}; *m/z* 253 (M^+), 196, 168, 141. Anal. Calcd for $C_{17}H_{19}NO$: C, 80.60; H, 7.56; N, 5.53. Found: C, 80.58; H, 7.64; N, 5.59.

2-(6′-Methoxy-2′-naphthyl)-4-(*S*)-*tert*-butyloxazoline (2, R_3 = MeO, Table 3). This was prepared (86%) from 6-methoxy-2-naphthoic acid by the procedure described for **1**. **2** (R_3 = **MeO**): white solid (mp 138.2–139.3 °C); ^1H NMR (300 MHz, $CDCl_3$) 0.97 (s, 9H), 3.89 (s, 3H), 4.07 (dd, *J* = 10.0, 7.6, 1H), 4.26 (t, *J* = 7.7, 1H), 4.36 (dd, *J* = 10.0, 8.7, 1H), 7.11 (bs, 1H), 7.15 (dd, *J* = 8.9, 2.5, 1H), 7.72 (d, *J* = 8.6, 1H), 7.78 (d, *J* = 8.9, 1H), 8.02 (dd, *J* = 8.6, 1.5, 1H), 8.35 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) 25.9 (q, 3C), 34.0 (s), 55.2 (q), 68.6 (t), 76.2 (d), 105.7 (d), 119.3 (d), 123.1 (s), 125.6 (d), 126.7 (d), 128.0 (s), 128.3 (d), 130.3 (d), 136.0 (s), 158.8 (s), 163.3 (s); IR (thin film) 2956, 2902, 1648, 1627, 1486, 1352, 1204, 1076, 911 cm^{-1}; *m/z* 283 (M^+), 226, 198, 171, 140.

Addition of Lithium Methylbutylamide to 2-(1′-Naphthyl)-4-(*S*)-*tert*-butyloxazoline (1) in the Absence of HMPA. To a stirred, cooled (−5 °C) solution of methylbutylamine (103 mg, 1.18 mmol) in THF (8 mL) was added *n*-butyllithium (2.44 M of hexane solution, 0.48 mL, 1.18 mmol). After stirring for 50 min at −5 °C, the mixture was cooled to −78 °C and treated with naphthyloxazoline (100 mg, 395 μmol) in THF (0.4 mL). The resulting yellow solution was maintained at −78 °C for 1 h, allowed to warm to −50 °C gradually, then recooled to −78 °C and treated with iodomethane (167 mg, 1.18 mmol). After stirring for 20 min at −78 °C, the mixture was allowed to warm to −25 °C over 3 h. The resulting solution was poured into water and extracted with ethyl acetae. The organic layer was washed with water and brine, dried over $MgSO_4$, and concentrated. Flash chromatography (hexane:ethyl acetate:dichloromethane 10:1:3,

(31) See the Experimental Section.

(32) It is of interest to note that the existence of a cosolvent (EtOH, MeOH, THF, etc.) completely prevented the hydrolysis of **4** even when it was conducted at temperatures higher than 100 °C.

(33) The corresponding racemic *tert*-amino acids were synthesized from 1-(4′,4′-dimethyloxazolin-2′-yl)naphthalene and 2-(4′,4′-dimethyloxazolin-2′-yl)naphthalene, respectively, and analyzed by HPLC on a Chiralcel OD column under the same conditions.

then hexane:ethyl acetate 1:1) gave starting oxazoline **1** (63 mg, 63%) and adduct **3b (R_1 = *n*-Bu, R_2 = E = Me)** (42 mg, 30%) as a clear oil: $[\alpha]_D$ +517.1° (*c* 1.41, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) 0.84 (t, *J* = 7.2, 3H), 0.96 (s, 9H), 1.14–1.40 (m, 4H), 1.46 (s, 3H), 1.93 (s, 3H), 2.34–2.57 (m, 2H), 3.40 (d, *J* = 5.3, 1H), 3.85 (dd, *J* = 9.4, 7.5, 1H), 4.06–4.18 (m, 2H), 5.83 (dd, *J* = 9.8, 5.3, 1H), 6.65 (d, *J* = 9.9, 1H), 7.06 (m, 1H), 7.14 (m, 2H), 7.23 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) 14.0 (q), 20.2 (t), 26.0 (q, 3C), 29.2 (q), 30.7 (t), 33.7 (s), 36.0 (q), 45.8 (s), 55.5 (t), 67.3 (t), 68.4 (t), 75.4 (d), 122.4 (d), 126.3 (d), 127.1 (d), 127.3 (d), 127.4 (d), 128.8 (d), 131.3 (s), 139.1 (s), 170.1 (s); IR (thin film) 2955, 2797, 1654, 1478, 1364, 1208, 1057 cm^{-1}; *m/z* 354 (M^+), 297, 269, 254, 141; HRMS calcd for $C_{23}H_{34}N_2O$ 354.2671, found 354.2669.

Addition of Lithium Piperidide to 2-(1′-Naphthyl)-4-(*S*)-*tert*-butyloxazoline (1) in the Absence of HMPA. To a stirred, cooled (−5 °C) solution of piperidine (100 mg, 1.18 mmol) in THF (9 mL) was added *n*-butyllithium (2.44 M of hexane solution, 0.48 mL, 1.18 mmol). After stirring for 50 min at −5 °C, the mixture was cooled to −78 °C and treated with naphthyloxazoline (100 mg, 395 μmol) in THF (0.4 mL). The resulting yellow solution was maintained at −78 °C for 1 h, allowed to warm to −50 °C gradually, then recooled to −78 °C, and treated with iodomethane (167 mg, 1.18 mmol). After stirring for 20 min at −78 °C, the mixture was allowed to warm to −25 °C over 3 h. The resulting solution was poured into water and extracted with ethyl acetate. The organic layer was washed with water and brine, dried over $MgSO_4$, and concentrated. Flash chromatography (hexane:ethyl acetate:dichloromethane 10:1:3, then hexane:ethyl acetate 1:1) gave starting oxazoline (77 mg, 77%) and the adduct **3d (R_1, R_2 = pentamethylene, E = Me)** (26 mg, 19%) as a white solid (mp 87.9–88.8 °C): $[\alpha]_D$ +561.1° (*c* 1.01, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) 0.98 (s, 9H), 1.18–1.38 (m, 6H), 1.48 (s, 3H), 2.30–2.55 (m, 4H), 3.29 (d, *J* = 5.3, 1H), 3.88 (t, *J* = 8.2, 1H), 4.22 (d, *J* = 8.1, 2H), 5.89 (dd, *J* = 9.9, 5.4, 1H), 6.64 (d, *J* = 9.9, 1H), 7.00–7.18 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) 24.5 (t), 25.9 (q, 3C), 27.0 (t, 2C), 29.7 (q), 33.7 (s), 46.1 (s), 50.3 (t, 2C), 68.7 (t), 69.1 (d), 75.1 (d), 122.7 (d), 126.3 (d), 127.18 (d), 127.25 (d), 127.4 (d), 128.7 (d), 131.2 (s), 139.2 (s), 170.6 (s); IR (thin film) 2931, 2802, 1656, 1478, 1365, 802 cm^{-1}; *m/z* 352 (M^+), 295, 269, 254. Anal. Calcd for $C_{23}H_{32}N_2O$: C, 78.36; H, 9.15. Found: C, 78.43; H, 9.18.

The lithium piperidide addition was repeated under various condition as described in Table 1. For reactions in the presence of an additive, the additive was added to the cold (−78 °C) solution of lithium piperidide before 1-naphthyloxazoline **1** was added.

General Procedure for the Addition of Lithium Amide to Naphthyloxazoline 1 or 2 Followed by Subsequent Reaction with Electrophile (Tables 2 and 3). To a stirred, cooled (−5 °C) solution of dialkylamine (1.26 mmol) in THF (9 mL) was added *n*-butyllithium (2.44 M of hexane solution, 1.18 mmol). After stirring for 45 min at −5 °C, the mixture was cooled to −78 °C, treated with HMPA (211 mg, 1.18 mmol), stirred to dissolve HMPA for 5 min, and treated with naphthyloxazoline **1** or **2** (200 mg, 0.79 mmol) in THF (0.5 mL). The resulting yellow solution was maintained at −78 °C for 1 h, allowed to warm to −50 °C gradually, then recooled to −78 °C, and treated with electrophile (1.34 mmol). After stirring for 20 min at −78 °C, the mixture was allowed to warm to −20 °C over 3 h. The resulting solution was poured into water and extracted with ethyl acetate. The organic layer was washed with water (2×) and brine, dried over $MgSO_4$, and concentrated. Flash chromatography (hexane:ethyl acetate: dichloromethane, then hexane:ethyl acetate) gave adducts, shown in Tables 2 and 3.

Adduct 3a (R_1 = R_2 = E = Me): a clear oil; ^1H NMR (300 MHz, $CDCl_3$) 0.94 (s, 9H), 1.46 (s, 3H), 2.11 (s, 6H), 3.37 (d, *J* = 5.3, 1H), 3.89 (dd, *J* = 9.9, 7.4, 1H), 4.07–4.20 (m, 2H), 5.86 (dd, *J* = 9.9, 5.3, 1H), 6.68 (d, *J* = 9.8, 1H), 7.04 (m, 1H), 7.14 (m, 2H), 7.33 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) 25.9 (q, 3C), 29.0 (q), 33.6 (s), 41.1 (q, 2C), 45.7 (s), 66.9 (d), 68.2 (t), 75.5 (d), 121.3 (d), 126.3 (d), 127.1 (d), 127.4 (d), 127.6 (d), 129.3 (d), 131.1 (s), 139.0 (s), 169.6 (s); IR (thin film) 1666 cm^{-1}; *m/z* 312 (M^+), 268, 254, 185; HRMS calcd for $C_{20}H_{28}N_2O$ 312.2202, found 312.2197.

Adduct 3e (R_1, R_2 = pentamethylene, E = allyl): a clear oil; $[\alpha]_D$ +441.7° (*c* 1.20, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) 0.98 (s, 9H), 1.18–1.40 (m, 6H), 2.33–2.55 (m, 5H), 2.84 (dd, *J* = 13.4, 7.1, 1H), 3.30 (d, *J* = 5.4, 1H), 3.89 (dd, *J* = 9.9, 6.5, 1H), 4.14–4.27 (m, 2H), 4.71 (dt, *J* = 17.1, 1.1, 1H), 4.81 (dd, *J* = 10.1, 2.3, 1H), 5.47–5.64 (m, 1H), 5.88 (dd, *J* = 9.9, 5.4, 1H), 6.63 (d, *J* = 9.9, 1H), 6.99–7.15 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) 24.4 (t), 26.0 (q, 3C), 26.9 (t,2C), 33.8 (s), 44.0 (t), 50.1 (s), 50.5 (t, 2C), 68.4 (t), 69.0 (d), 75.4 (d), 117.7 (t), 122.8 (d), 126.3 (d), 126.5 (d), 127.0 (d), 129.0 (d), 129.6 (d), 131.6 (s), 134.7 (d), 135.4 (s), 169.0 (s); IR (thin film) 1654 cm^{-1}; *m/z* 378 (M^+), 337, 294, 254, 167; HRMS calcd for $C_{25}H_{34}N_2O$ 378.2671, found 378.2675.

Adduct 3f (R_1, R_2 = pentamethylene, E = benzyl): a clear oil; $[\alpha]_D$ +398.8° (*c* 1.30, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) 0.98 (s, 9H), 1.20–1.45 (m, 6H), 2.37–2.58 (m, 4H), 3.04 (d, *J* = 12.8, 1H), 3.44 (d, *J* = 5.5, 1H), 3.48 (d, *J* = 12.8, 1H), 3.94 (dd, *J* = 10.5, 6.6, 1H), 4.11 (dd, *J* = 8.4, 6.7, 1H), 4.25 (dd, *J* = 10.4, 8.4, 1H), 5.90 (dd, *J* = 9.8, 5.5, 1H), 6.44 (d, *J* = 7.8, 1H), 6.53–6.60 (m, 2H), 6.64 (d, *J* = 9.9, 1H), 6.84 (td, *J* = 7.5, 1.8, 1H), 6.89–7.15 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) 24.4 (t), 26.1 (q, 3C), 26.9 (t, 2C), 33.8 (s), 44.1 (t), 50.6 (t, 2C), 52.1 (s), 68.3 (t), 69.4 (d), 75.9 (d), 122.8 (d), 125.8 (d), 126.1 (d), 126.5 (d), 126.7 (d, 2C), 126.8 (d), 129.1 (d), 130.4 (d), 131.6 (d, 2C), 131.9 (s), 134.8 (s), 137.4 (s), 169.0 (s); IR (thin film) 1651 cm^{-1}; *m/z* 428 (M^+), 337, 274, 254, 196; HRMS calcd for $C_{29}H_{36}N_2O$ 428.2828, found 428.2819.

Adduct 3g (R_1, R_2 = 3-ethylenedioxapentamethylene, E = Me): a white solid (mp 125.7–126.0 °C); $[\alpha]_D$ +513.0° (*c* 2.80, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) 0.98 (s, 9H), 1.48 (s, 3H), 1.50 (m, 4H), 2.42–2.70 (m, 4H), 3.38 (d, *J* = 5.3, 1H), 3.84 (s, 4H), 3.88 (t, *J* = 8.1, 1H), 4.20 (d, *J* = 8.1, 1H), 5.90 (dd, *J* = 9.9, 5.4, 1H), 6.64 (d, *J* = 9.9, 1H), 7.00–7.18 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) 25.9 (q, 3C), 29.7 (q), 33.7 (s), 35.7 (t, 2C), 46.0 (s), 47.0 (t, 2C), 64.0 (t, 2C), 68.0 (d), 68.7 (t), 75.2 (d), 107.3 (s), 122.2 (d), 126.4 (d, 2C), 127.3 (d), 129.0 (d), 131.0 (s), 138.9 (s), 170.4 (s); IR (thin film) 1656 cm^{-1}; *m/z* 410 (M^+), 353, 309, 269, 254; HRMS calcd for $C_{25}H_{34}N_2O_3$ 410.2569, found 410.2546. Anal. Calcd for $C_{25}H_{34}N_2O_3$: C, 73.14; H, 8.35. Found: C, 73.01; H, 8.38.

Adduct 4a (R_1 = R_2 = E = Me): a clear oil; $[\alpha]_D$ +145.8° (*c* 1.17, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) 0.90 (s, 9H), 1.17 (s, 3H), 2.03 (s, 6H), 3.66 (s, 1H), 3.86 (dd, *J* = 9.8, 8.6, 1H), 4.07 (t, *J* = 8.4, 1H), 4.21 (dd, *J* = 9.9, 8.3, 1H), 6.35 (d, *J* = 9.8, 1H), 6.48 (dd, *J* = 9.8, 0.9, 1H), 7.02–7.12 (m, 2H), 7.16–7.27 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) 24.0 (q), 25.9 (q, 3C), 33.5 (s), 41.7 (q, 2C), 43.4 (s), 67.6 (d),68.5 (t), 75.8 (d), 124.4 (d), 126.1 (d), 127.6 (d), 128.1 (s), 129.9 (d), 133.3 (s), 133.7 (d), 170.0 (s); IR (thin film) 1668 cm^{-1}; *m/z* 312 (M^+), 297, 268, 254.

Adduct 4b (R_1, R_2 = tetramethylene, E = Me): a clear oil; $[\alpha]_D$ +172.4° (*c* 1.27, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) 0.92 (s, 9H), 1.16 (s, 3H), 1.41 (bs, 4H), 2.16 (bs, 2H), 2.59 (bs, 2H), 3.84 (t, *J* = 9.3, 1H), 3.98 (s, 1H), 4.03 (t, *J* = 8.6, 1H), 4.21 (bt, *J* = 8.9, 1H), 6.36 (d, *J* = 9.8, 1H), 6.50 (dd, *J* = 9.8, 0.8, 1H), 6.98–7.28 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) 23.0 (t, 2C), 23.7 (q), 26.0 (q, 3C), 33.3 (s), 43.3 (s), 48.2 (t, 2C), 63.8 (d), 68.6 (t), 75.8 (d), 124.3 (d), 125.8 (d), 126.4 (d), 127.6 (d), 128.2 (s), 130.2 (d), 133.6 (s, d, 2C), 170.4 (s); IR (thin film) 1667 cm^{-1}; *m/z* 338 (M^+), 281, 268, 254. Anal. Calcd for $C_{22}H_{30}N_2O$: C, 78.06; H, 8.93. Found: C, 77.98; H, 8.92.

Adduct 4c (R_1, R_2 = pentamethylene, E = Me): a white solid (mp 124.0–125.0 °C); $[\alpha]_D$ +138.3° (*c* 2.12, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) 0.95 (s, 9H), 1.14 (m, 2H), 1.20 (s, 3H), 1.21–1.47 (m, 4H), 2.08 (m, 2H), 2.66 (m, 2H), 3.63 (s, 1H), 3.86 (t, *J* = 9.6, 1H), 4.06 (t, *J* = 8.5, 1H), 4.24 (dd, *J* = 9.7, 8.3, 1H), 6.34 (d, *J* = 9.8, 1H), 6.46 (d, *J* = 9.8, 1H), 7.03–7.14 (m, 2H), 7.16–7.25 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) 24.2 (t), 24.9 (q), 26.3 (q, 3C), 26.5 (t, 2C), 33.3 (s), 43.7 (s), 50.9 (t, 2C), 68.6 (t), 70.0 (d), 75.8 (d), 125.0 (d), 126.2 (d), 126.6 (d), 127.5 (d), 129.9 (s, d, 2C), 133.2 (s), 170.7 (s); IR (thin film) 1664 cm^{-1}; *m/z* 352 (M^+), 295, 254, 167. Anal. Calcd for $C_{23}H_{32}N_2O$: C, 78.36; H, 9.15. Found: C, 78.42; H, 9.16.

Adduct 4d (R_1, R_2 = 3-ethylenedioxapentamethylene, E = Me): a white solid (mp 154.5–155.0 °C); $[\alpha]_D$ +135.9° (*c* 1.25, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) 0.94 (s, 9H), 1.21 (s, 3H), 1.52 (m, 4H), 2.22 (m, 2H), 2.80 (m, 2H), 3.72 (bs, 1H), 3.79 (m, 4H), 3.85 (dd, *J* = 9.8, 8.7, 1H), 4.06 (t, *J* = 8.4, 1H), 4.23 (dd, *J* = 9.8, 8.5, 1H), 6.35 (d, *J* = 9.8, 1H), 6.42 (bd, *J* = 9.8, 1H), 7.02–7.13 (m, 2H), 7.15–7.24(m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) 24.9 (q), 26.2 (q, 3C), 33.4 (s), 35.5 (t, 2C), 43.8 (s), 47.9 (t, 2C), 64.0 (t, 2C), 68.7 (t), 69.2 (d), 75.8 (d), 107.0 (s), 125.2 (d), 126.4 (d), 127.1 (d), 127.7 (d), 129.6 (s), 129.8 (d), 132.9 (s), 133.5 (d), 170.7 (s); IR (thin film) 1666, cm^{-1}; *m/z* 410 (M^+), 354, 270, 254. Anal. Calcd for $C_{25}H_{34}N_2O_3$: C, 73.14; H, 8.35. Found: C, 73.04; H, 8.36.

Addition of Lithium Methylpentylamide[34] Prepared from HMPA to 2-(1′-Naphthyl)-4-(*S*)-*tert*-butyloxazoline (1). To a stirred, cooled (−5 °C) solution of *n*-butyllithium (2.44 M of hexane solution, 0.97 mL, 2.37 mmol) in THF (14 mL) was added HMPA (425 mg, 2.37 mmol). After stirring for 10 min at −5 °C, the mixture was cooled to −78 °C, and treated with naphthyloxazoline (200 mg, 789 μmol) in THF (0.5 mL). The resulting yellow solution was maintained at −78 °C for 1 h, allowed to warm to −50 °C gradually, then re-cooled to −78 °C and treated with iodomethane (336 mg, 2.37 mmol). After stirring for 20 min at −78 °C, the mixture was allowed to warm to −25 °C over 3 h. The resulting solution was poured into water and extracted with ethyl acetae. The organic layer was washed with water and brine, dried over $MgSO_4$, and concentrated. Flash chromatography (hexane:ethyl acetate:dichloromethane 10:1:3, then hexane:ethyl acetate 1:1) gave the adduct **3c (R_1 = pentyl, R_2 = E = Me)** (270 mg, 93%) as a clear oil: $[\alpha]_D$ +465.1° (*c* 2.49, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) 0.85 (t, *J* = 7.1, 3H), 0.96 (s, 9H), 1.12–1.46 (m, 6H), 1.92 (s, 3H), 2.36–2.56 (m,2 H), 3.40 (d, *J* = 5.3, 1H), 3.86 (dd, *J* = 9.4, 7.6, 1H), 4.05–4.19 (m, 2H), 5.82 (dd, *J* = 9.8, 5.3, 1H), 6.65 (d, *J* = 9.8, 1H), 7.05 (dd, *J* = 4.8, 2.4, 1H), 7.09–7.25 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) 14.1 (q), 22.6 (t), 26.0 (q, 3C), 28.2 (t), 29.3 (q), 33.7 (s), 35.9 (q), 45.8 (s), 55.8 (t), 67.3 (d), 68.4 (t), 75.4 (d), 122.4 (d), 126.3 (d), 127.1 (d), 127.3 (d), 127.4 (d), 128.8 (d), 131.3 (s), 139.1 (s), 170.1 (s); IR (thin film) 1655 cm^{-1}; *m/z* 368 (M^+), 311, 297, 254, 184; HRMS calcd for $C_{24}H_{36}N_2O$ 368.2828, found 368.2855.

Adduct 4e (R_1 = Pentyl, R_2 = E = Me, R_3 = MeO). This was prepared from 2-(6′-methoxy-2′-naphthyl)-4-(*S*)-*tert*-butyloxazoline (**2**, R_3 = MeO, Table 3) by the procedure described for **3c**. **Adduct 4e:** white solid (mp 105.6–106.8 °C); $[\alpha]_D$ +136.5° (*c* 1.35, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) 0.87 (t, *J* = 7.1, 3H), 0.90 (s, 9H), 1.17 (s, 3H), 1.16–1.42 (m, 6H), 1.85 (s, 3H), 2.15 (m, 1H), 2.45 (tt, *J* = 12.1, 7.5, 1H), 3.74 (s, 1H), 3.79 (s, 3H), 3.84 (t, *J* = 9.7, 1H), 4.03 (t, *J* = 8.9, 1H), 4.21 (dd, *J* = 9.7, 8.4, 1H), 6.30 (d, *J* = 9.8, 1H), 6.50 (d, *J* = 10.2, 1H), 6.63 (d, *J* = 2.6, 1H), 6.73 (dd, *J* = 8.2, 2.7, 1H), 6.98 (d, *J* = 8.2, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) 14.1 (q), 22.7 (t), 24.4 (q), 26.2 (q, 3C), 27.8 (t), 29.7 (t), 33.5 (s), 36.1 (q), 43.5 (s), 55.2 (q), 56.5 (t), 66.4 (d), 68.5 (t), 75.8 (d), 111.2 (d), 111.9 (d), 121.2 (s), 124.4 (d), 130.8 (d), 134.7 (s), 134.8 (d), 158.9 (s), 170.2 (s); IR (thin film) 1666, 1602, 1571 cm^{-1}; *m/z* 398 (M^+), 341, 299, 284; HRMS calcd for $C_{25}H_{38}N_2O_2$ 398.2933, found 398.2912.

(*S*)-(α-Methylbenzyl)benzylamine (5). To a stirred, cooled (0 °C) solution of (*S*)-α-methylbenzylamine (5.0 g, 41.3 mmol) in methanol (35 mL) was added 5 N hydrochloric acid (2.9 mL), followed by benzaldehyde (2.2 g, 20.6 mmol) and sodium cyanoborohydride (777 mg, 12.4 mmol). After stirring at rt for 7 d, the mixture was treated with concentrated hydrochloric acid to pH 1.0 and concentrated. The residue was dissolved in water (50 mL), extracted with ether (2×), neutralized with 20% NaOH solution, and extracted with ether. This ether extract was washed with brine, dried over $MgSO_4$, and concentrated. Flash chromatography (25% EtOAc/hexane) gave (*S*)-(α-methylbenzyl)benzylamine (**5**) (3.6 g, 82%) as a clear oil: $[\alpha]_D$ −53.4° (*c* 3.35, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) 1.40 (d, *J* = 6.6, 1H), 1.70 (bs, 1H, N−*H*), 3.62 (d, *J* = 13.1, 1H), 3.70 (d, *J* = 13.2, 1H), 3.84 (q, *J* = 6.6, 1H), 7.15–7.75 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$) 24.4 (s), 51.6 (t), 57.4 (d), 126.7 (d, 2C), 126.8 (d), 126.9 (d), 128.1 (d, 2C), 128.3 (d, 2C), 128.4 (d, 2C), 140.6 (s), 145.5 (s); IR (thin film) 3322, 1603 cm^{-1}; *m/z* 211 (M^+), 196, 134.

1-Naphthoic Acid *tert*-Butyl Ester (6). To a solution of 1-naphthoic acid (3.0 g, 17.4 mmol) in dichloromethane (50 mL) at rt were added oxalyl chloride (4.7 g, 37.2 mmol) and DMF (3 drops). After stirring at rt for 1.5 h, the mixture was concentrated, redissolved in dichloromethane (50 mL), cooled to 0 °C, and treated with Et_3N (2.1 g, 20.4 mmol) and *tert*-butyl alcohol (6.5 g, 87.0 mmol). The mixture was allowed to warm to room temperature and stirred for 7 d. The resulting solution was poured into 0.5 N NaOH solution and extracted with ether. The organic layer was washed with 0.5 N NaOH solution (2×), water, and brine and dried over $MgSO_4$. Concentration and flash chromatography (3% EtOAc/hexane) gave 1-naphthoic acid *tert*-butyl ester (**6**) (2.2 g, 55.4%) as a clear oil: ^1H NMR (300 MHz, $CDCl_3$) 1.70 (s, 9H), 7.41–7.86 (m, 3H), 7.86 (dd, *J* = 8.3, 0.8, 1H), 7.97 (d, *J* = 8.2, 1H), 8.10 (dd, *J* = 7.2, 1.2, 1H), 8.90 (d, *J* = 8.6, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) 28.3 (q, 3C), 81.4 (s), 124.4 (d), 125.8 (d), 126.0 (d), 127.3 (d), 128.4 (d), 129.2 (s), 129.6 (d), 131.2 (s), 132.6 (d), 133.8 (s), 167.1 (s); IR (thin film) 1712 cm^{-1}; *m/z* 228 (M^+), 172, 155.

Addition of Lithium Piperidide to 1-Naphthoic acid *tert*-Butyl Ester (6). To a stirred, cooled (−5 °C) solution of piperidine (74.6 mg, 0.88 mmol) in THF (7 mL) was added *n*-butyllithium (2.64 M of hexane solution, 0.33 mL, 0.86 mmol). After stirring for 50 min at −5 °C, the mixture was cooled to −78 °C, treated with HMPA (157 mg, 0.86 mmol), stirred for 5 min, to dissolve HMPA, and treated with 1-naphthoic acid *tert*-butyl ester (100 mg, 438 μmol) in THF (0.4 mL). The resulting yellow solution was maintained at −78 °C for 1 h, allowed to warm to −50 °C gradually, then recooled to −78 °C, and treated with iodomethane (124 mg, 0.86 mmol). After stirring for 20 min at −78 °C, the mixture was allowed to warm to −20 °C over 3 h. The resulting solution was poured into water and extracted with ethyl acetate. The organic layer was washed with water (2×) and brine, dried over $MgSO_4$, and concentrated. Flash chromatography (hexane:ethyl acetate: dichloromethane 15:1:15, then hexane:ethyl acetate 1:2) gave carboxamide **8** (33 mg, 32%) as a white solid (mp 94.5–95.0 °C) [^1H NMR (300 MHz, $CDCl_3$) 1.38 (m, 2H), 1.58–1.77 (m, 4H), 3.11 (t, *J* = 5.7, 1H), 3.78–3.94 (m, 2H), 7.38 (dd, *J* = 6.9, 1.2, 1H), 7.44 (d, *J* = 8.1, 1H), 7.46–7.54 (m, 2H), 7.77–7.87 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) 24.5 (t), 25.8 (t), 26.7 (t), 42.6 (t), 48.3 (t), 123.4 (d), 124.9 (d), 125.2 (d), 126.3 (d), 126.8 (d), 128.3 (d), 128.8 (d), 129.6 (s), 133.4 (s), 134.8 (s), 169.2 (s); IR (thin film) 3056, 2936, 2855, 1633, 1508, 1470, 1442, 1285 cm^{-1}; *m/z* 239 (M^+), 238, 155] and the (±)-adduct **7** (92 mg, 64%) as a white solid (mp 93.9–95.0 °C) [^1H NMR (300 MHz, $CDCl_3$) 1.25 (m, 2H), 1.28 (m, 4H), 1.35 (s, 3H), 1.55 (s, 9H), 2.36 (m, 2H), 2.47 (m, 2H), 3.33 (d, *J* = 5.5, 1H), 5.83 (dd, *J* = 9.9, 5.5, 1H), 6.64 (d, *J* = 9.9, 1H), 7.03 (dd, *J* = 7.2, 1.8, 1H), 7.06–7.21 (m, 2H), 7.41 (dd, *J* = 7.4, 1.3, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) 24.4 (t), 26.1 (t, 2C), 28.3 (q, 3C), 28.8 (q), 49.4 (t, 2C), 51.3 (s), 67.3 (d), 80.0 (s), 121.0 (d), 126.0 (d), 127.1 (d), 127.4 (d), 127.7 (d), 129.4 (d), 131.3 (s), 139.2 (s), 173.0 (s); IR (thin film) 1732 cm^{-1}; *m/z* 328 (M^+), 270, 226.

Addition of *n*-Butyllithium to Intermediate A Followed by Subsequent Reaction with Iodomethane. To a stirred, cooled (−5 °C) solution of piperidine (50 mg, 0.59 mmol) in THF (6 mL) was added *n*-butyllithium (2.51 M of hexane solution, 0.24 mL, 0.59 mmol). After stirring for 45 min at −5 °C, the mixture was cooled to −78 °C, treated with HMPA (106 mg, 0.59 mmol), stirred for 5 min to dissolve HMPA, and treated with naphthyloxazoline **1** (100 mg, 0.40 mmol) in THF (0.4 mL). The resulting yellow solution was maintained at −78 °C for 1 h, allowed to warm to −50 °C gradually, then recooled to −78 °C, and treated with *n*-butyllithium (2.51 M of hexane solution, 0.32 mL, 0.79 mmol). After stirring for 1 h at −78 °C, the mixture was allowed to warm to −65 °C over 2 h. The resulting solution was recooled to −78 °C, treated with iodomethane (224 mg, 1.58 mmol), and stirred at −78 °C for 1 h. The mixture was allowed to warm to −30 °C gradually, poured into water, and extracted with ethyl acetate. The organic layer was washed with water (2×)

(34) (a) Savignac, P.; Lerou, Y. *J. Organomet. Chem.* **1973**, *57*, C47. (b) Abatjoglou, A. G.; Eliel, E. L. *J. Org. Chem.* **1974**, *39*, 3042.

and brine, dried over $MgSO_4$, and concentrated. The ^1H NMR of the crude mixture showed no trace of the amino adduct **3d** but gave only *n*-butyl adduct **9**[13] which was detected as the major product (ca. 85% purity).

Piperidone 11g. The adduct **3g** (600 mg, 1.46 mmol) was treated with concentrated hydrochloric acid (28 mL) at 0 °C and then allowed to warm to rt. After 20 min, the mixture was poured into an aqueous NaOH solution (0 °C, NaOH, 15 g, water, 200 mL) and stirred for 5 min. The resulting mixture was filtered, and the white precipitate on the filter was washed several times with water and allowed to air-dry. The white solid was purified by flash chromatography (ethyl acetate) and gave piperidone **11g** (510 mg, 95%) as a white solid (mp 126.6–127.5 °C); $[\alpha]_D$ +565.5° (*c* 2.08, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) 0.99 (s, 9H), 1.52 (s, 3H), 2.22 (t, J = 6.0, 4H), 2.65–2.89 (m, 4H), 3.50 (d, J = 5.4, 1H), 3.93 (dd, J = 10.0, 6.9, 1H), 4.14 (t, J = 8.6, 1H), 4.25 (dd, J = 8.6, 7.0, 1H), 5.88 (dd, J = 9.9, 5.4, 1H), 6.67 (d, J = 9.9, 1H), 7.04–7.22 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) 25.9 (q, 3C), 29.7 (q), 33.7 (s), 42.3 (t, 2C), 46.1 (s), 48.9 (t, 2C), 67.7 (d), 68.8 (t), 75.4 (d), 121.4 (d), 126.7 (d), 127.4 (d), 127.5 (d), 127.8 (d), 129.6 (d), 130.7 (s), 138.5 (s), 170.1 (s), 209.6 (s); IR (thin film) 1715, 1656 cm^{-1}; *m/z* 366 (M^+), 309, 254, 181; HRMS calcd for $C_{23}H_{30}N_2O_2$ 366.2307, found 366.2298. Anal. Calcd for $C_{23}H_{30}N_2O_2$: C, 75.44; H, 8.25. Found: C, 75.38; H, 8.38.

Hydrolysis of 3g with 1 N HCl. The acetal derivative **3g** (78 mg, 0.19 mmol) was treated with 1 N hydrochloric acid (1.4 mL) at rt. After 5 h, the mixture was poured into a saturated $NaHCO_3$ solution and extracted with dichloromethane (3×). The combined organic layers were dried over $MgSO_4$ and concentrated. Flash chromatography (30% EtOAc/hexane, then EtOAc) gave amino ester **12g** (74 mg, 91%) as a clear oil: $[\alpha]_D$ +622.3° (*c* 2.78, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) 0.96 (s, 9H), 1.27 (bs, 2H, NH_2), 1.43 (s, 3H), 1.49 (t, J = 5.8, 4H), 2.46 (m, 2H), 2.59 (m, 2H), 2.84 (dd, J = 9.1, 2.9, 1H), 3.44 (d, J = 5.5, 1H), 3.75–3.87 (m, 5H), 4.54 (dd, J = 10.8, 3.0, 1H), 5.83 (dd, J = 9.8, 5.5, 1H), 6.64 (d, J = 9.9, 1H), 7.03 (dd, J = 7.1, 1.8, 1H), 7.08–7.22 (m, 2H), 7.36 (dd, J = 7.4, 1.7, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) 26.4 (q, 3C), 28.3 (q), 33.2 (s), 35.2-(t, 2C), 46.3 (t, 2C), 51.5 (s), 58.8 (d), 64.0 (t, 2C), 66.5 (d), 67.4 (t), 106.9 (s), 120.2 (d), 126.5 (d), 127.4 (d), 127.7 (d), 127.8 (d), 129.9 (d), 130.8 (s), 138.0 (s), 173.8 (s); IR (thin film) 1733 cm^{-1}.

Primary Amino Oxazoline 13g. Piperidone **11g** (500 mg, 1.36 mmol) was dissolved in a solution made up of NaOH pellets (435 mg, 10.9 mmol), *n*-butylamine (12 mL), and water (28 mL) and heated (120–125 °C) in a sealed tube for 12 h. The resulting mixture was concentrated to remove excess *n*-butylamine, extracted with ether (5×), and concentrated. Flash chromatography (ether, then ether:ethanol 7:1) gave primary amino oxazoline **13g** (318 mg, 82%) as a clear oil: $[\alpha]_D$ +95.38° (*c* 2.86, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) 0.85 (s, 9H), 1.61 (s, 3H), 1.97 (bs, 2H, NH_2), 3.53 (dd, J = 3.6, 1.7, 1H), 3.82 (dd, J = 10.2, 7.2, 1H), 3.96 (dd, J = 8.7, 7.2, 1H), 4.03 (dd, J = 10.2, 8.7, 1H), 6.01 (dd, J = 9.6, 3.8, 1H), 6.39 (dd, J = 9.6, 1.7, 1H), 7.04 (m, 1H), 7.14–7.23 (m, 2H), 7.35 (m, 1H) H); ^{13}C NMR (75 MHz, $CDCl_3$) 23.7 (q), 25.7 (q, 3C), 33.8 (s), 46.2 (s), 55.7 (d), 67.8 (t), 75.3 (d), 126.4 (d), 126.8 (d), 127.0 (d), 127.2 (d), 127.5 (d), 132.6 (s), 133.1 (d), 137.4 (s), 168.3 (s); IR (thin film) 3383, 3301, 3032, 1652 cm^{-1}; *m/z* 284 (M^+), 269, 242, 227. Instability of the amine prevented elemental analysis. This reaction was repeated under various condition as described in Table 4.

Piperidinol 14g. Piperidone **11g** (100 mg, 0.27 mmol) was dissolved in a solution of NaOH (50 mg, 2.16 mmol), *n*-butylamine (3 mL), and EtOH (8 mL) and heated (120–125 °C) in a sealed tube for 20 h. The resulting mixture was concentrated to remove excess *n*-butylamine, extracted with EtOAc, washed with water (2×) and brine, dried over $MgSO_4$, and concentrated. Flash chromatography (EtOAc) gave piperidinol oxazoline **14g** (86 mg, 86%) as a white solid (mp 144.2–146.1 °C): ^1H NMR (300 MHz, $CDCl_3$) 0.98 (s, 9H), 1.17–1.43 (m, 2H), 1.47 (s, 3H), 1.53 (d, J = 4.4, 1H, O*H*), 1.59 (m, 1H), 1.74 (m, 1H), 2.14 (m, 1H), 2.46–2.60 (m, 2H), 2.75 (m, 1H), 3.35 (d, J = 5.4, 1H), 3.47 (m, 1H), 3.88 (t, J = 8.3, 1H), 4.21 (d, J = 8.3, 1H), 5.87 (dd, J = 9.9, 5.4, 1H), 6.64 (d, J = 9.9, 1H), 6.99–7.17 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) 25.9 (q, 3C), 29.7 (q), 33.7 (s), 35.1 (t), 35.9 (t), 44.7 (t), 46.0 (s), 49.0 (t), 68.1 (d), 68.4 (d), 68.7 (t), 75.2 (d), 122.1 (d), 126.4 (d), 127.27 (d), 127.32 (d), 127.5 (d), 129.0 (d), 131.0 (s), 138.9 (s), 170.4 (s); IR (thin film) 3332, 1647 cm^{-1}; *m/z* 368 (M^+), 311, 254, 226. Anal. Calcd for $C_{23}H_{32}N_2O_2 \cdot {}^1/_{10}$AcOEt: C, 74.49; H, 8.76; N, 7.42. Found: C, 74.53; H, 8.81; N, 7.53.

Primary Amino Acid 10g. Amino oxazoline **13g** (98 mg, 0.35 mmol) was dissolved in 6 N hydrochloric acid (8 mL) and heated at reflux for 6 h. The resulting mixture was concentrated to remove excess hydrochloric acid, dissolved in ethanol (2 mL), and neutralized with excess solid sodium bicarbonate. Flash chromatography (30% ether/ethanol, then ethanol) gave amino acid **10g** (59.3 mg, 85%) as a white solid (mp <255 °C, dec): $[\alpha]_D$ +100.00° (*c* 0.177, DMSO); ^1H NMR (300 MHz, DMSO-d_6) 1.38 (s, 3H), 3.75 (d, J = 4.0, 1H), 6.02 (dd, J = 9.6, 4.1, 1H), 6.61 (d, J = 9.6, 1H), 7.07–7.27 (m, 3H), 7.38 (m, 1H), 9.31 (bs, 3H, NH_3^+); ^{13}C NMR (75 MHz, DMSO-d_6) 22.9 (q), 46.6 (s), 51.9 (d), 125.5 (d), 126.7 (d, 2C), 126.8 (d), 128.0 (d), 129.8 (d), 131.4 (s), 138.8 (s), 175.8 (s); IR (KBr) 2854, 1635 cm^{-1}; *m/z* 203 (M^+), 157, 142, 115. Anal. Calcd for $C_{12}H_{13}NO_2 \cdot {}^2/_3H_2O$: C, 66.96; H, 6.71. Found: C, 66.77; H, 6.62. (*S*)-*tert*-Leucinol (29 mg, 72%) was also recovered as a clear oil.

***β*-Lactam 15g.** To a stirred suspension of amino acid **10g** (90 mg, 0.44 mmol) in 2-propanol (10 mL) at 25 °C were added $NaHCO_3$ (446 mg, 5.3 mmol) and methansulfonyl chloride (127 mg, 1.11 mmol). After stirring at rt for 58 h, the mixture was diluted with EtOAc and filtered through a silica gel column. The filtrate was concentrated, and recrystallization (ether–hexane) gave *β*-lactam **15g** as a colorless crystalline solid (mp 166.3–167.5 °C): $[\alpha]_D$ +199.3° (*c* 1.05, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) 1.72 (s, 3H), 4.02 (d, J = 4.4, 1H), 5.93 (dd, J = 9.8, 4.4, 1H), 6.39 (bs, 1H, N*H*), 6.55 (d, J = 9.9, 1H), 7.11 (dd, J = 7.5, 1.1, 1H), 7.20 (td, J = 7.4, 1.2, 1H), 7.29 (td, J = 7.4, 1.4, 1H), 7.42 (d, J = 7.4, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) 22.9 (q), 54.9 (d), 55.9 (s), 122.9 (d), 126.6 (d), 127.4 (d), 127.9 (d), 129.1 (d), 130.0 (s), 130.8 (d), 133.1 (s), 172.0 (s); IR (KBr) 1750, 1725 cm^{-1}; *m/z* 185 (M^+), 160, 142, 141, 115. Anal. Calcd for $C_{12}H_{11}NO$: C, 77.81; H, 5.99. Found: C, 77.78; H, 6.01.

Piperidone 16d. This was synthesized as a crude solid (460 mg) from the piperidone ethylene glycol acetal derivative **4d** (500 mg, 1.22 mmol) by the procedure described for **11g**. The authentic sample for physical data was prepared by recrystallization (hexane–EtOAc): a white solid (mp 139.8–140.0 °C); $[\alpha]_D$ +192.9° (*c* 1.54, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) 0.94 (s, 9H), 1.24 (s, 3H), 2.24 (m, 4H), 2.45 (m, 2H), 3.02 (m, 2H), 3.85 (s, 1H), 3.89 (dd, J = 9.8, 8.9, 1H), 4.08 (t, J = 8.6, 1H), 4.24 (dd, J = 9.9, 8.5, 1H), 6.38 (d, J = 9.8, 1H), 6.48 (d, J = 9.8, 1H), 7.02–7.13 (m, 2H), 7.16–7.27 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) 24.9 (q), 26.2 (q, 3C), 33.4 (s), 42.0 (t, 2C), 43.8 (s), 49.7 (t, 2C), 68.76 (d), 68.80 (t), 75.8 (d), 125.2 (d), 126.7 (d), 127.1 (d), 128.1 (d), 129.0 (d), 129.6 (d), 132.9 (s), 133.4 (d), 170.3 (s), 209.4 (s); IR (thin film) 1716, 1665 cm^{-1}; *m/z* 366 (M^+), 309, 269, 254. Anal. Calcd for $C_{23}H_{32}N_2O$: C, 75.44; H, 8.25. Found: C, 75.50; H, 8.32.

Amino Acid 17d. The crude piperidone derivative **16d** (460 mg, ca. 1.22 mmol) was dissolved in a solution of NaOH (340 mg, 8.5 mmol), *n*-butylamine (7 mL), and water (18 mL) and heated (140–150 °C) in a sealed tube for 20 h. The resulting mixture was concentrated to remove excess *n*-butylamine, diluted with water (35 mL), washed with ether (3×), acidified with concentrated HCl (pH 1), washed with ether (3×), and concentrated. The resulting residue was dissolved in ethanol (3 mL) and neutralized with excess $NaHCO_3$ powder. Flash chromatography (30% ether/ethanol, then ethanol) gave amino acid **17d** (179 mg, 72%) as a white solid (mp <250 °C, dec): $[\alpha]_D$ +22.58° (*c* 0.155, DMSO); ^1H NMR (300 MHz, DMSO-d_6) 1.04 (s, 3H), 4.14 (s, 1H), 6.04 (d, J = 9.6, 1H), 6.52 (d, J = 9.7, 1H), 7.20 (d, J = 7.3, 1H), 7.21–7.36 (m, 2H), 7.39 (d, J = 7.1, 1H), 8.85 (bs, 3H, NH_3^+); ^{13}C NMR (75 MHz, DMSO-d_6) 22.7 (q), 44.6 (s), 54.4 (d), 125.4 (d), 126.3 (d), 127.5 (d), 129.1 (d), 129.5 (d), 130.4 (s), 132.0 (s), 134.5 (d), 176.4 (s); IR (KBr) 3200–2300, 1574 cm^{-1}; *m/z* 203 (M^+), 188, 170, 158, 142; HRMS calcd for $C_{12}H_{13}NO_2$ 203.0946, found 203.0940.

Amide Esters 18b, 18d, and 18e. A typical procedure for **18d** is given, which is identical with the procedure that

produces **18b** and **18e**. Amino adduct **3d** (300 mg, 0.85 mmol) was treated with 1 N HCl (4.0 mL) at rt and stirred until **3d** disappeared (usually overnight). The mixture was diluted with THF (7 mL), cooled to −3 °C, and treated with a 2 N NaOH solution (3.5 mL) and acetic anhydride (265 mg, 2.6 mmol). The resulting heterogeneous solution was warmed to rt and stirred vigorously for 2 h. The mixture was poured into 3% $NaHCO_3$ solution, extracted with EtOAc, washed with a 3% $NaHCO_3$ solution and brine, dried over $MgSO_4$, and concentrated. Flash chromatography (40% ethyl acetate/hexane) gave amide ester **18d** (334 mg, 95%) as an amorphous solid: $[\alpha]_D$ +550.1° (*c* 1.00, $CHCl_3$); ^1H NMR (270 MHz, $CDCl_3$) 1.02 (s, 9H), 1.30 (m, 6H), 1.40 (s, 3H), 2.02 (s, 3H), 2.42 (bs, 4H), 3.38 (d, J = 5.6, 1H), 4.15−4.37 (m, 3H), 5.63 (bd, J = 9.2, 1H, N*H*Ac), 5.84 (dd, J = 9.9, 5.6, 1H), 6.65 (d, J = 9.9, 1H), 7.06 (dd, J = 6.6, 2.3, 1H), 7.10−7.24 (m, 2H), 7.38 (dd, J = 6.9, 2.0, 1H); ^{13}C NMR (68 MHz, $CDCl_3$) 23.5 (q), 24.2 (t,), 26.8 (q, 3C and t, 2C), 28.3 (q), 33.8 (s), 49.6 (t, 2C), 51.6 (s), 55.9 (d), 63.8 (t), 67.2 (d), 120.9 (d), 126.4 (d), 127.3 (d), 127.5 (d), 127.7 (d), 129.3 (d), 131.1 (s), 138.0 (s), 169.8 (s), 174.2 (s); IR (KBr) 3150, 1740 cm^{-1}; *m/z* 412 (M^+), 397, 355, 271, 226. Anal. Calcd for $C_{25}H_{36}N_2O_3 \cdot {}^1/_5H_2O$: C, 72.15; H, 8.77; N, 6.73. Found: C, 71.95; H, 8.89; N, 6.59.

Amide Ester 18b. This was prepared (91%) from amino adduct **3b** by the procedure described for **18d**. **18b:** a white solid (mp 95.3−96.0 °C); $[\alpha]_D$ +498.69° (*c* 1.15, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) 0.82 (t, J = 7.2, 3H), 0.96 (s, 9H), 1.20 (m, 2H), 1.30 (m, 2H), 1.36 (s, 3H), 1.88 (s, 3H), 1.96 (s, 3H), 2.33 (m, 1H), 2.46 (m, 1H), 3.46 (d, J = 5.5, 1H), 4.10−4.32 (m, 3H), 5.70 (bd, J = 9.7, 1H, N*H*Ac), 5.75 (dd, J = 9.9, 5.5, 1H), 6.65 (d, J = 9.9, 1H), 7.04 (dd, J = 6.7, 2.2, 1H), 7.14 (m, 2H), 7.37 (dd, J = 6.9, 1.9, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) 14.0 (q), 20.3 (t), 23.5 (q), 26.7 (q, 3C), 28.2 (q), 30.5 (t), 33.8 (s), 35.5 (q), 51.5 (s), 55.0 (t), 55.9 (d), 63.4 (t), 65.5 (d), 120.2 (d), 126.4 (d), 127.3 (d), 127.5 (d), 127.6 (d), 129.7 (d), 131.1 (s), 138.0 (s), 169.9 (s), 174.2 (s); IR (neat) 3284, 1738 cm^{-1}; *m/z* 414 (M^+), 399, 357, 228, 142. Anal. Calcd for $C_{25}H_{38}N_2O_3$: C, 72.43; H, 9.24. Found: C, 72.55; H, 9.23.

Amide Ester 18e. This was prepared (96%) from amino adduct **3e** by the procedure described for **18d** (contaminated with amido acetate byproduct; ^1H NMR indicated a ratio of 94.6:5.4). **18e:** an amorphous solid; ^1H NMR (270 MHz, $CDCl_3$) 1.02 (s, 9H), 1.20−1.43 (m, 6H), 2.03 (s, 3H), 2.34 (dd, J = 13.5, 7.6, 1H), 2.43 (bs, 4H), 2.71 (dd, J = 13.5, 7.3, 1H), 3.43 (d, J = 5.3, 1H), 4.07−4.42 (m, 3H), 4.72 (dd, J = 17.2, 1.7, 1H), 4.89 (dd, J = 10.2, 2.0, 1H), 5.48 (m, 1H), 5.78 (bd, J = 9.2, 1H, N*H*Ac), 5.86 (dd, J = 9.9, 5.3, 1H), 6.64 (d, J = 9.9, 1H), 7.02−7.21 (m,3H), 7.36 (m, 1H); ^{13}C NMR (68 MHz, $CDCl_3$) 23.5 (q), 24.2 (t), 26.7 (t, 2C), 26.8 (q, 3C), 33.8 (s), 44.0 (t), 49.7 (t, 2C), 55.8 (s), 55.9 (d), 64.2 (t), 67.1 (d), 118.1 (t), 121.3 (d), 126.4 (d), 126.5 (d), 127.1 (d), 129.6 (d, 2C), 131.5 (s), 133.7 (d), 134.4 (s), 169.8 (s), 173.1 (s); IR (KBr) 3160, 1738, cm^{-1}; *m/z* 438 (M^+), 397, 297, 256, 252, 238.

***N,N*-Dialkylamino Acids 19b, 19d, and 19e.** A typical procedure for **19d** is given, which is identical with the procedure that produces **19b** and **19e**. Amido ester **18d** (300 mg, 0.73 mmol) was treated with an 8% NaOH solution (8 g of NaOH in 95 mL of EtOH and 5 mL of H_2O, 10 mL) and heated to reflux for 12 h. The resulting mixture was cooled to rt, neutralized with 6 N HCl (pH 7−8), and concentrated. The residue was extracted with EtOH−EtOAc (1:2) several times, and the combined extracts were concentrated. Flash chromatography (25% ethanol/EtOAc) gave *N,N*-dialkylamino acid **19d** (186 mg, 94%) as a white solid (mp 157.7−159.6 °C): $[\alpha]_D$ +250.4° (*c* 0.50, EtOH); ^1H NMR (270 MHz, $CDCl_3$) 1.25 (bs, 1H), 1.50 (bs, 5H), 1.65−1.93 (m, 3H), 2.27−2.55 (m, 2H), 2.79 (m, 1H), 3.11 (bd, J = 10.9, 1H), 3.51 (d, J = 6.3, 1H), 5.90 (dd, J = 9.9, 6.3, 1H), 6.91 (d, J = 9.9, 1H), 7.11 (dd, J = 6.9, 2.0, 1H), 7.17−7.32 (m, 2H), 7.72 (dd, J = 7.3, 1.7, 1H); ^{13}C NMR (68 MHz, $CDCl_3$) 22.6 (t), 24.2 (t,), 25.5 (t), 27.5 (q), 45.7 (t), 46.5 (s), 52.3 (t), 65.6 (d), 116.2 (d), 125.9 (d), 127.3 (d), 127.8 (d), 129.7 (d), 130.4 (s), 134.3 (d), 138.1 (s), 176.1 (s); IR (thin film) 3150, 2950, 1640, 1550, 1370 cm^{-1}; *m/z* 271 (M^+), 255, 226, 142. Anal. Calcd for $C_{17}H_{21}N_1O_2 \cdot {}^1/_{10}$EtOH: C, 74.86; H, 7.89; N, 5.08. Found: C, 74.75; H, 7.83; N, 5.17.

***N,N*-Dialkylamino Acid 19b.** This was prepared (95%) from amido ester **18b** by the procedure described for **19d**. **19b:** an amorphous solid; $[\alpha]_D$ +141.72° (*c* 2.62, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) 0.88 (bs, 3H), 1.32 (bs, 2H), 1.43 (s, 3H), 1.55 (bs, 2H), 1.95 (bs, 3H), 2.20−3.20 (m, 2H), 3.60 (d, J = 5.0, 1H), 5.80 (m, 1H), 6.88 (d, J = 9.7, 1H), 7.04 (m, 1H), 7.17 (m, 2H), 7.63 (d, J = 6.8, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) 13.6 (q), 19.9 (t), 27.3 (q), 27.9 (t), 33.4 (q), 46.4 (s), 55.6 (t), 63.2 (d), 115.7 (d), 125.8 (d), 127.3 (d), 127.8 (d), 129.6 (d), 130.3 (s), 134.7 (d), 137.7 (s), 176.0 (s); IR (neat) 3467, 1634 cm^{-1}; *m/z* 274 (M^+), 258, 228, 206.

***N,N*-Dialkylamino Acid 19e.** This was prepared (90%) from amido ester **18e** by the procedure described for **19d**. **19e:** a clear oil; $[\alpha]_D$ +265.32° (*c* 0.82, $CHCl_3$); ^1H NMR (270 MHz, $CDCl_3$) 1.19 (m, 1H), 1.50 (bs, 2H), 1.52−1.91 (m, 3H), 2.14 (dd, J = 13.5, 10.2, 1H), 2.30−2.60 (m, 2H), 2.80 (m, 1H), 2.99 (m, 1H), 3.10 (bd, J = 10.6, 1H), 3.74 (d, J = 6.3, 1H), 5.04 (dt, J = 17.2, 2.0, 1H), 5.11 (dt, J = 10.2, 1.3, 1H), 5.85 (dd, J = 9.6, 6.3, 1H), 5.93 (m, 1H), 6.96 (d, J = 9.6, 1H), 7.13 (dd, J = 7.3, 1.7, 1H), 7.18−7.37 (m,2H), 7.85 (dd, J = 7.3, 1.3, 1H); ^{13}C NMR (68 MHz, $CDCl_3$) 22.4 (t), 23.9 (t), 25.2 (t), 44.3 (t), 46.0 (t), 49.6 (s), 51.9 (t), 62.1 (d), 115.2 (d), 118.7 (t), 126.2 (d), 127.3 (d), 127.8 (d), 129.7 (d), 130.5 (s), 135.1 (d), 135.5 (d), 137.4 (s), 1774.6 (s); IR (neat) 3200, 1650 cm^{-1}; *m/z* 297 (M^+), 256, 210, 168.

***N,N*-Dialkylamino Acids 20b and 20c.** A typical procedure for **20b** is given, which is identical with the procedure that produces **20c**. Amino oxazoline **4b** (350 mg, 1.03 mmol) was dissolved in 5 N HCl (20 mL) and heated to reflux for 16 h. The resulting mixture was concentrated to remove excess hydrochloric acid, dissolved in water (12 mL), washed with ether (3×), basified with 4 N aqueous NaOH (pH 14), washed with ether (5×), acidified with concentrated HCl (pH 4), and concentrated. The residue was dissolved in a small amount of ethanol and neutralized with excess solid $NaHCO_3$. Flash chromatography (ether:ethanol 2:1) gave amino acid **20b** (239 mg, 90%) as a white solid (mp <280 °C); $[\alpha]_D$ +254.4° (*c* 0.34, H_2O); ^1H NMR (300 MHz, D_2O) 1.11 (s, 3H), 1.58 (bs, 4H), 2.58 (m, 2H), 2.78 (m, 2H), 4.15 (s, 1H), 6.42 (d, J = 10.1, 1H), 6.51 (d, J = 10.0, 1H), 7.23 (d, J = 7.2, 1H), 7.27−7.44 (m, 3H); ^{13}C NMR (75 MHz, D_2O) 17.3 (t, 2C), 19.7 (q), 44.1 (s), 45.0 (t, 2C), 60.7 (d), 120.6 (d), 121.5 (d), 122.3 (d), 122.7 (s), 124.5 (d), 127.0 (d), 129.4 (s), 130.2 (d), 178.0 (s); IR (thin film) 3433, 1655 cm^{-1}; *m/z* 257 (M^+), 211, 196, 182, 155.

Amino Acid 20c. This was prepared (92%) from amino oxazoline **4c** by the procedure described for **20b**. **20c:** a white solid (mp 125.9.0−126.9 °C); $[\alpha]_D$ +71.2° (*c* 1.74, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) 1.00 (bs, 1H), 1.26 (s, 3H), 1.70 (bs, 6H), 2.50−3.60 (m, 3H), 3.87 (s, 1H), 6.33 (d, J = 9.7, 1H), 6.40 (d, J = 9.7, 1H), 7.10−7.18 (m, 2H), 7.26 (td, J = 7.4, 1.4, 1H), 7.35 (td, J = 7.4, 1.4, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) 22.3 (q), 24.4 (t,2C), 25.0 (q), 44.4 (s), 46.0 (t), 51.9 (t), 69.4 (d), 123.9 (s), 125.6 (d), 127.0 (d), 127.6 (d), 130.0 (d), 130.6 (d), 133.9 (s), 136.3 (d), 177.9 (s); IR (thin film) 3037, 1714 cm^{-1}; *m/z* 271 (M^+), 226, 198, 143. Anal. Calcd for $C_{17}H_{21}NO_2$: C, 75.25; H, 7.80. Found: C, 74.99; H, 7.82.

Determination of Enantiomeric Excesses of Amino Acids. To a stirred, cooled (5 °C) suspension of amino acid **10g** (14 mg, 69 μmol) in water (0.4 mL) was added a 1 N NaOH solution (0.27 mL, 0.28 mmol), followed by THF (0.2 mL) and acetic anhydride (18.2 mg, 0.18 mmol). After stirring at rt for 25 min, the mixture was diluted with 0.5 N NaOH solution (1.5 mL), washed with ether (3×), neutralized with 2 N HCl, and extracted with ethyl acetate. The extract was washed with brine, dried over $MgSO_4$, and concentrated to give, gave the crude *N*-acetyl derivative (15 mg).

To a solution of the latter (15 mg) in THF (2.2 mL) at rt were added diisopropylethylamine (35 mg, 0.271mmol) and chloromethyl methyl ether (15 mg, 0.186 mmol). After stirring at rt for 1 h, the mixture was poured into 1% aqueous $NaHCO_3$, extracted with ethyl acetate, washed with water and brine, dried over $MgSO_4$, and concentrated. Flash chromatography (75% ethyl acetate/hexane) gave amide ester **21** (14 mg, 70%) as a clear oil: $[\alpha]_D$ +39.52° (*c* 1.05, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) 1.67 (s, 3H), 2.04 (s, 3H), 3.18 (s, 3H), 5.00−5.13 (m, 3H), 5 82 (dd, J = 9.6, 2.8, 1H), 6.42 (dd, J = 9.7, 2.6, 1H),

6.71 (bd, J = 10.8, 1H, N*H*), 7.03 (m, 1H), 7.17–7.26 (m, 2H), 7.42 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) 20.7 (q), 23.6 (q), 50.5 (s), 52.1 (d), 57.3 (q), 90.7 (t), 126.6 (d), 126.7 (d), 127.88 (d), 127.91 (d), 128.0 (d), 131.5 (d), 132.8 (s), 135.6 (s), 170.0 (s), 174.3 (s); IR (thin film) 3282, 1732, 1661 cm^{-1}; *m/z* 289 (M^+), 200, 158; HRMS calcd for $C_{16}H_{19}N_1O_4$ 289.1314, found 289.1305. Racemic amide ester **21** was prepared in an analogous fashion utilizing 1-(4′,4′-dimethyloxazolin-2′-yl)naphthalene.

Chiral HPLC analysis indicated that the amide ester **21** was enantiomerically pure (>99% ee). HPLC conditions were as follows: Chiralcel OD Column, hexane/ethanol (95:5), 1.0 mL/min, λ = 280 nm, **(1*R*,2*S*)-amide ester 21** t_R 26 min, **(1*S*,2*R*)-amide ester 21** t_R 32 min (see HPLC traces in supporting information).

Amide Ester 22. This was prepared (78%) from amino acid **17d** by the procedure described for **21**. **22:** a clear oil; $[\alpha]_D$ +1.52° (*c* 2.11, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) 1.42 (s, 3H), 1.99 (s, 3H), 3.34 (s, 3H), 5.12 (d, J = 6.0, 1H), 5.19 (d, J = 5.8, 1H), 5.40 (d, J = 10.0, 1H), 6.06 (d, J = 9.7, 1H), 6.45 (bd, J = 9.8, 1H, N*H*), 6.51 (d, J = 9.7, 1H), 7.05 (m, 1H), 7.16–7.32 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) 22.4 (q), 23.4 (q), 47.8 (s), 53.7 (d), 57.6 (q), 90.8 (t), 126.1 (d), 126.7 (d), 127.9 (d), 128.0 (d), 128.5 (d), 130.3 (d), 131.5 (s), 134.2 (s), 169.7 (s), 174.1 (s); IR (thin film) 3290, 1738, 1661 cm^{-1}; *m/z* 289 (M^+), 244, 228, 212, 200. Racemic amide ester **22** was prepared in an analogous fashion utilizing 2-(4′,4′-dimethyloxazolin-2′-yl)-naphthalene.

Chiral HPLC analysis showed that the amide ester **22** was enantiomerically pure (>99% ee). HPLC conditions were as follows: Chiralcel OD Column, hexane/2-propanol (95:5), 1.0 mL/min, λ = 280 nm, **(1*S*,2*R*)-amide ester 22** t_R 20 min, **(1*R*,2*S*)-amide ester 22** t_R 25 min (see HPLC).

Acknowledgment. The authors are grateful to the National Institutes of Health for financial support of this work. We are indebted to Miss M. Katori and Miss K. Shirafuji in Kyoto lab of Kaken Pharm. Co. Ltd. for a portion of the analytical and spectral data.

Supporting Information Available: HPLC chromatograms for chiral assays for **21** and **22** and NMR spectra for **1–4, 8, 10–15, 17, 19, 20,** and **21** (44 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

JO9512463