of a blue color. Oxygen was bubbled through the reaction mixture to remove excess ozone, followed by the addition of dimethyl sulfide (0.5 mL) and pyridine (0.5 mL). The mixture was stirred for 5 min, poured into H_2O, and extracted with CH_2Cl_2 (2 × 50 mL). The combined extracts were dried over $MgSO_4$ and filtered, and the solvent was removed in vacuo. The crude product was purified by flash chromatography on silica gel. Elution with 55% ethyl acetate/hexane gave 160 mg (53%) of **5b** as an amorphous solid: ^{1}H NMR ($CDCl_3$) δ 7.37-7.07 (m, 10 H, aromatic), 6.42 (dd, 1 H, J = 24.0 Hz, J = 6.5 Hz, NH), 5.42 (m, 1 H, CH phenylalanine), 5.23 (m, 1 H, NH), 5.09 and 5.08 (2 s, 2 H, CH_2 benzyl), 4.30 and 4.29 (2 q, 2 H, J = 7.1 Hz, CH_2CH_3), 3.97 (m, 1 H, CH valine), 3.23 (dd, 1 H, J = 13.9 Hz, J = 6.4 Hz, CH_2 phenylalanine), 3.02 (m, 1 H, CH_2 phenylalanine), 2.06 (m, 1 H, $CH(CH_3)_2$), 1.35 (t, 3 H, J = 7.3 Hz, CH_2CH_3), 0.91 (d, 3 H, J = 7.2 Hz, CH_3 valine), 0.85 (d, 6 H, J = 7.2 Hz, CH_3 valine), 0.79 (d, 3 H, J = 7.2 Hz, CH_3 valine); ^{13}C NMR ($CDCl_3$) δ 191.66, 191.54, 171.04, 171.00, 160.12, 156.26, 136.06, 134.95, 134.84, 129.27, 129.22, 128.78, 128.54, 128.22, 128.05, 127.36, 67.16, 67.13, 62.89, 60.06, 65.44, 36.90, 30.85, 30.66, 19.13, 19.08, 17.59, 17.28, 13.91; IR (KBr) ν 3294, 2960, 1724, 1692, 1654, 1538, 1296, 1246 cm^{-1}; MS (DCI/CH_4) m/z (rel intensity) 455 (MH^+, 100), 411 (10), 91 (10); MS m/z (MH^+) calcd 455.2182, obsd 455.2162.

Anal. Calcd for $C_{25}H_{30}N_2O_6$: C, 66.06; H, 6.65; N, 6.16. Found: C, 65.90; H, 6.74; N, 6.03.

Registry No. **1a**, 1161-13-3; **1b**, 19542-51-9; **2a**, 114744-85-3; **2b**, 121253-52-9; **3a**, 121253-53-0; **3b**, 121253-54-1; **4a**, 121253-55-2; **4b**, 121253-56-3; **5a**, 121253-57-4; **5b**, 121253-58-5; EtOCH=CH_2, 109-92-2.

Enantioselective Synthesis of α-Amino Acid Derivatives via the Stereoselective Alkylation of a Homochiral Glycine Enolate Synthon[1]

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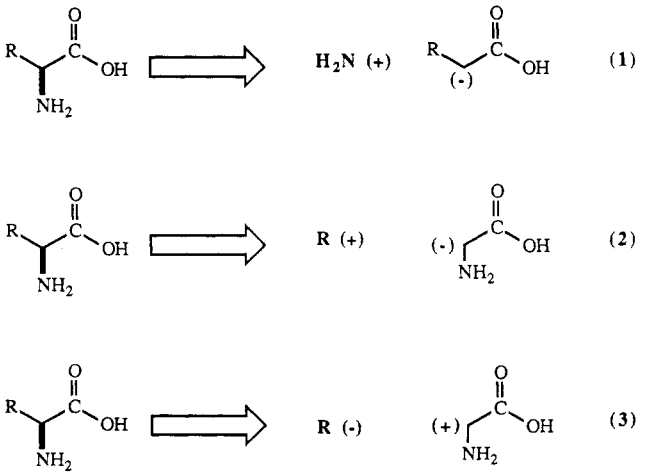
A new synthetic method for the enantioselective preparation of α-amino acid derivatives is presented. The key step involves the diastereoselective alkylation of the new chiral glycine enolate synthons **7** and **8** providing alkylation adducts with de of ≥97.6% in good yields (73-90%). The reactivities of the enolates of **7** and **8** were extraordinarily sensitive to the metal counterion and solvent. Experimental conditions are described to maintain high diastereoselectivities in the alkylation step for electrophiles varying from highly reactive (α-haloacetate esters) to less reactive (*n*-butyl iodide). The alkylation diastereoselectivities were established to be under kinetic control by equilibration experiments on selected alkylation products. A model is presented which hinges on an A(1,3) interaction between the termini of the N_4-acyl protecting group and the C_5-phenyl group of **7** and **8** which in turn dictates the π-facial selectivity of the enolate. The model successfully accounts for the observed results and is corroborated by the conformation of an alkylation adduct as revealed by a single-crystal X-ray determination. A simple one-pot, three-step deprotection procedure provides the desired α-amino acid as the ethyl ester hydrochloride salts (60-80% overall yield) with no attending racemization as determined by conversion of the amino acid esters to the corresponding (+)- or (-)-Mosher amides.

Current interest in developing peptide-derived chemotherapeutics has heightened the importance of rare and nonproteinogenic enantiomerically pure amino acids.[3] Consequently it has become desirabe to develop new and general synthetic methodology for the expeditious preparation of compounds in this genre. Recent advances in this endeavor have been made in the asymmetric electrophilic amination of chiral enolates (eq 1),[4] diastereoselective alkylation of chiral glycine enolate synthons (eq 2),[5] and diastereoselective nucleophilic additions to a chiral electrophilic glycinate synthon (eq 3).[6] Recently, the stereoselective alkylation of homochiral glycine enolates derived from *N*-acyl-2,3,5,6-tetrahydro-4*H*-oxazin-2-ones (henceforth referred to as oxazinones) bearing either 5-phenyl or 5,6-diphenyl substituents were reported by us[7a] and Williams[7b] and co-workers, respectively. We now provide a full account of our studies on the alkylation of homochiral *N*-acyl oxazinones and the conversion of the resulting alkylation adducts to homochiral α-amino acid derivatives.



Design and Synthesis of the Chiral Enolate Synthon. At the outset of this investigation, it was clear that

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(1) Presented in part at the International Symposium on the Chemistry of Natural Products, June 23-26, 1985, Edmonton, Alberta, Canada.

(2) (a) NIH Postdoctoral Fellow, 1982-1984, Grant GM 08803. (b) Present address: Abbott Laboratories, Department 47K, Abbott Park, IL 60064.

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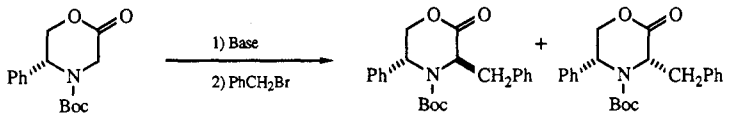
Table I. Solvent and Counterion Study

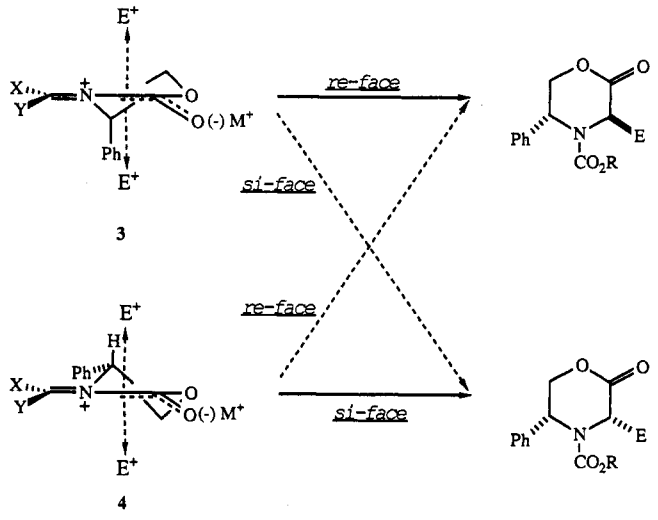


7 9R 9S

entry	base	solvent	T, °C	time, h	ratio 9R:9S[a]	% conversion
1	LDA	THF	−78 → 0	4.0		0
2	LDA	DME	−63 → −23	3.0	>200:1	67
3	NaHMDS	DME	−63	0.25	130:1	96
4	NaHMDS	THF	−78	3.0	>200:1	75
5	NaHMDS	THF/DME (1:1)	−78	0.50	>200:1	98

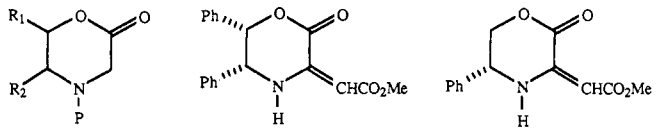
[a] Ratios determined by analytical capillary gas chromatography.

Scheme I[a]



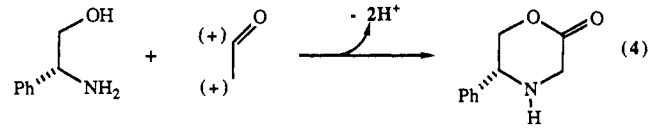
[a] X, Y = O⁻, OR.

a high and predictable diastereofacial bias in the alkylation step should result from the generation of a geometrically homogeneous enolate ensconced in a rigid infrastructure.[8] Bearing these requirements in mind, we chose a substituted form of the oxazinone ring system (1) for the study. The ability of a C_5-substituent in **1** to provide a diastereofacial bias at C_3 had already been implicated by hydrogenation studies on **2a** and **2b**. The most remarkable results were those of Kagan[9a] where hydrogenation of **2a** and subsequent hydrogenolysis provided γ-methylaspartic acid in >98% enantiomeric excess. Interestingly, when **2b** was similarly converted to γ-methylaspartic acid, only a modest level (17%) of enantiomeric excess was observed.[9b]



1 2a 2b

We elected to pursue the monosubstituted 5-phenyl oxazinone (**1a**, P = R_1 = H, R_2 = Ph) in that it could be prepared in either enantiomeric series by the condensation of commercially available phenylglycinol[10] and an appropriate biselectrophilic form of acetate (eq 4). Furthermore,



(4)

1a

there was substantial literature precedent which suggested that utilizing an N_4-acyl protecting group would augment the meager diastereofacial bias observed in **2b** by taking advantage of A(1,3) strain (Scheme I).[11-13] Transition states 4-*re* and 4-*si*[14] would be energetically disfavored relative to transition states 3-*re* and 3-*si* due to the destabilizing A(1,3) interaction between the C_5-phenyl substituent and the termini of the acyl moiety. Transition state 3-*re* would be the energetically preferred reaction manifold as it would not suffer from the 1,3-diaxial interaction encountered in the approach of the electrophile from the 3-*si* face. A similar line of reasoning for boat-like transition states leads to the same conclusion. We were therefore confident that the electrophile would be intro-

(3) For a recent review, see: Wagner, I.; Musso, H. *Angew. Chem., Int. Ed. Engl.* **1983**, *22*, 816.

(4) (a) Gennari, C.; Colombo, L.; Bertolini, G. *J. Am. Chem. Soc.* **1986**, *108*, 6394. (b) Evans, D. A.; Britton, T. C.; Dorow, R. L.; Dellaria, J. F. *Ibid.* **1986**, *108*, 6395. (c) Trimble, L. A.; Vederas, J. C. *Ibid.* **1986**, *108*, 6397.

(5) (a) Chenard, J. Y.; Commereuc, D.; Chauvin, Y. *J. Chem. Soc., Chem. Comm.* **1972**, 750. (b) Okawara, T.; Harada, K. *J. Org. Chem.* **1972**, *37*, 3286. (c) Yamada, S.-I.; Orari, T.; Shioiri, T. *J. Chem. Soc., Chem. Commun.* **1976**, 136. (d) Oruri, T.; Shiori, T.; Yamada, S.-I. *Chem. Pharm. Bull.* **1977**, 2287. (e) Harada, K.; Tamura, M.; Suzuki, S. *Bull. Chem. Soc. Jpn.* **1978**, *51*, 2171. (f) Kolb, M.; Barth, J. *Tetrahedron Lett.* **1979**, 2999–3002. (g) Bajgrowicz, J. A.; Cossec, B.; Pigierre, Ch.; Jacquier, R.; Viellefont, Ph. *Tetrahedron Lett.* **1983**, *24*, 3721. (h) Schollkpf, U. *Top. Curr. Chem.* **1983**, *109*, 66–84. (i) Marco, J. L.; Royer, J.; Husson, H.-P. *Tetrahedron Lett.* **1986**, *27*, 3403. (j) Ikegami, S.; Hayama, T.; Katsuki, T.; Yamaguchi, M. *Tetrahedron Lett.* **1986**, *27*, 3403.

(6) Sinclair, P. J.; Zhai, D.; Reibenspies, J.; Williams, R. M. *J. Am. Chem. Soc.* **1986**, *108*, 1103.

(7) (a) Dellaria, J. F.; Santarsiero, B. D. *Tetrahedron Lett.* **1988**, *29*(47), 6079–82. (b) Williams, R. M.; Im, M.-N. *Tetrahedron Lett.* **1988**, *29*(47), 6075–78.

(8) For a recent review on the topic, refer to: Evans, D. A. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press, Inc.: New York, 1984; Vol. 3, Chapter 1.

(9) (a) Vigneron, J. P.; Kagan, H.; Horeau, A. *Tetrahedron Lett.* **1968**, 5681. (b) Tamura, M.; Harada, K. *Bull. Chem. Soc. Jpn.* **1980**, *53*, 561.

(10) Both D- and L-phenylglycinol are commercially available as are the immediate precursors (*R*)-(−)- and (*S*)-(+)-2-phenylglycine, which may be efficiently reduced to provide the corresponding amino alcohols; see: Poindexter, G. S.; Meyers, A. I. *Tetrahedron Lett.* **1977**, 3527.

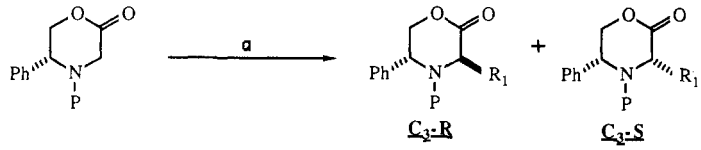
(11) Johnson, F. *Chem. Rev.* **1968**, *68*, 375 and reference cited therein.

(12) (a) Quick, J.; Mondello, C.; Humora, M.; Brenna, T. *J. Org. Chem.* **1978**, *43*, 2705. (b) Sugg, E. E.; Griffin, J. F.; Portoghese, P. S. *J. Org. Chem.* **1985**, *50*, 5032.

(13) During the preparation of this paper, Professor R. M. Williams and co-workers (ref 6, this paper) published a complimentary approach to the enantioselective synthesis of α-amino acids where an N_4-acyl protected oxazinone was employed as the electrophile in condensation reactions with nucleophiles. This serves to further highlight the generality of this strategy.

(14) For the sake of clarity, these transition-state arguments are presented in reference to the glycine enolate synthon derived from D-2-phenylglycinol. The opposite conclusions would be arrived at with the L-2-phenylglycinol-derived series.

Table II. Survey of Electrophiles



entry	P	R_1	X	product	kinetic[b] ratio 3R:3S	purified yield, %
1	Boc	benzyl	Br	9	>200:1	78
2	Boc	methyl	I	10	>200:1	85
3	Cbz	benzyl	Br	11	>200:1	71
4	Cbz	methyl	I	12	160:1	83
5	Boc	methallyl	I	13	>200:1	90
6	Boc	allyl	Br	14	>200:1	86
7[c]	Boc	*n*-butyl	I	15	83:1	78
8	Boc	*n*-butyl	I	15		0
9	Cbz	Cbz-methyl	Br	16	3.5:1	75

[a] NaHMDS (0.98 equiv), 1:1 THF/DME (~0.2 M), R_1X, -78 °C. [b] Ratios determined by analytical capillary gas chromatography. [c] NaHMDS (0.98 equiv), DME (~0.2 M), R_1X, -63 °C.

duced from the *re* face of the enolate when an N_4-acyl protecting group was employed.

The parent oxazinone was readily prepared in a one-pot, two-step condensation of D-2-phenylglycinol (**5**) with phenyl bromoacetate (**6**)[15] in the presence of diisopropylethylamine[16] in acetonitrile. After chromatographic removal of phenol,[17] treatment of **1a**[18] with di-*tert*-butyl dicarbonate or benzyl chloroformate under standard conditions afforded **7** and **8**, respectively, in 50–60% recrystallized overall yields from **5**.

Discussion and Results

Enolate Formation and Alkylation Studies. Extensive investigation revealed that the mode of deprotonation and the amount of base employed were crucial to obtain high facial selectivity and excellent yields in the alkylation step. When **7** or **8** was added in dry THF to sodium bis(trimethylsilyl)amide (NaHMDS)[19] in THF at -78 °C and subsequently alkylated with benzyl bromide, the corresponding alkylation adducts **9** or **11** were consistently obtained in 30–33% yields in 96% de in addition to 14–20% of recovered **7** or **8**. However, when the base (NaHMDS, 0.98 equiv) was added in THF (~0.5 M) to **7** or **8** in THF (~0.5 M) at -78 °C, the derived enolates were alkylated by benzyl bromide to provide excellent yields (78% and 71%, respectively) of the alkylation adducts **9** and **11** with de >99.5% (appropriate experiments were carried out to unequivocally establish the depicted sense of asymmetric induction (vide infra)). Further experimentation revealed that the reactivity of the enolate was extraordinarily sensitive to solvent and counterion effects. These results are tabulated in Table I and are best understood in terms of the intimacy of the metal counterion and the enolate association.

The influence of solvent on the reactivity of the resulting enolate is demonstrated by entry pairs 1/2 and 3/4 (Table I). In each instance the enolate was more reactive in DME as solvent. This is presumably due to the superior metal chelating properties of DME, which reduces the covalent character between the metal and the enolate, providing a more reactive enolate. The sodium enolate is more reactive (entry 2 vs 3) than the corresponding lithium enolate, once again, due to a reduction in the covalent character between the metal and the enolate. The optimum solvent system in this study was determined to be a mixed-solvent system of THF and DME (1:1), providing both a short reaction time and excellent diastereoselection. An alternative solvent system, THF and 2 equiv of HMPA, provides comparable results with the sodium enolates of **7** and **8**.

The 1:1 mixture of THF and DME was adopted as the "standard solvent" to study the alkylation of the sodium enolates of **7** and **8** with various electrophiles. The results from this study are summarized in Table II. As can be seen, the yields varied from good to excellent in all cases. It is noteworthy that in all cases the alkylation products were crystalline and one or two recrystallizations provided >99.5% diastereomerically pure products. In most cases the epimers were separable by standard chromatographic methods on a preparative scale. Entry pairs 1/3 and 2/4 (Table II) demonstrate the equivalence of the Cbz and *t*-Boc groups in that alkylation of each affords essentially identical diastereomer ratios and yields. The Boc-protected series is the operationally preferred glycine enolate synthon on the basis of solubility properties of **7** and ease of deprotection to the derived amino acid derivative (vide infra).

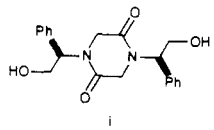
Alkylating agents at either end of the reactivity spectrum provided poor diastereoselectivities under the "standard" reaction conditions (entries 8 and 9, Table II). Each was independently investigated to identify experimental conditions that would provide acceptable diastereoselectivities. In the case of *n*-butyl iodide, a more nucleophilic enolate was needed. This was achieved by employing DME as the solvent (entry 7). Another solvent and counterion study (Table III) revealed that the nucleophilicity of the enolate had to be attenuated to obtain high diastereoselectivities for the α-haloacetate esters. The lithium enolate in THF provided the alkylation adduct in

(15) Dellaria, J. F.; Nordeen, C.; Swett, L. R. *Synth. Commun.* **1986**, *16*, 1043.

(16) Diisopropylethylamine was found to be superior to the less expensive triethylamine. ^1H NMR experiments indicated that triethylamine reacted with **6** whereas diisopropylethylamine did not.

(17) Control experiments established that a 20–25% loss of **1a** was incurred when exposing **1a** to an extractive recovery from an aqueous phase.

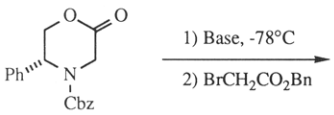
(18) To avoid dimerization of **1a** to **i**, it is recommended that the protection step be carried out immediately after isolation of **1a**.



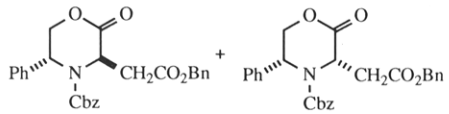
i

(19) Initially this reagent was prepared according to the procedure of Brown (Brown, C. A. *J. Org. Chem.* **1974**, *39*, 3913). Subsequently, it was found that commercially available solutions of NaHMDS in THF (1.0 M, Aldrich) provided comparable results.

Table III. Solvent and Counterion Study for Benzyl Bromoacetate



8



16R **16S**

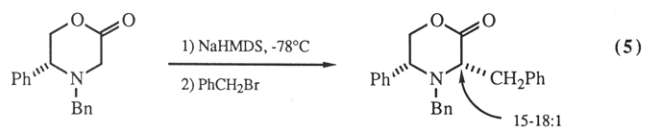
entry	base	solvent	kinetic ratio **16R**:**16S**	% yield/recovered **8**
1	NaHMDS	THF/DME (1:1)	3.5:1[a]	59/17
2	NaHMDS	THF	11:1[a]	62/16
3	LiHMDS	THF	185:1[b]	65/18

[a] Ratios determined by ^1H NMR integration. [b] Ratio determined by analytical HPLC.

a good yield with high diastereoselectivity (entry 3, Table III).

A single-crystal X-ray structural determination was undertaken on **9** to investigate the stereochemical outcome and, more interestingly, to determine the influence of A(1,3) strain on the conformation of the alkylation adduct. It was gratifying to find that our prediction for the importance of the A(1,3) interaction between the urethane termini and the C_5-phenyl group was borne out by the crystal structure. As depicted in Figure 1, both the C_5-phenyl and C_3-benzyl groups were in the axial position to avoid the A(1,3) interaction encountered in the corresponding equatorial position.[20] The overhead perspective (**9b**) reveals that the *o*-hydrogen of the C_5-phenyl group is held underneath the ring. Inspection of Dreiding models of the enolate indicates that this structural feature is maintained in the enolate as well, thus providing the source of the observed high facial selectivity in the alkylation of the enolate.

Alkylation of the *N*-benzyl protected glycine enolate synthon **17** was investigated to determine what the facial selectivity would be in the absence of A(1,3) strain. The parent enolate synthon **1a** was smoothly benzylated by treatment with benzyl bromide and diisopropylethylamine in acetonitrile. Alkylation of **17** was carried out by conversion to the sodium enolate (0.98 equiv of NaHMDS, 1:1 THF/DME) and quenching with benzyl bromide to provide **18** as a mixture of two isomers (15–18:1) in an 83% purified yield (eq 5). Standard spectroscopic techniques



(5)

17 **18**

on the oily mixture failed to permit an unequivocal assignment of the stereochemical outcome. Recourse was made to chemical correlation (Scheme II), which revealed the opposite sense of diastereoselection for the *N*-benzyl protected glycine enolate synthon. The underlying principle(s) responsible for the dramatic change in diastereoselectivity for **17** remain to be elucidated by further experimentation.

The alkylation of the Boc- and Cbz-protected glycine enolate synthons (**7** and **8**) were demonstrated to be the

(20) The single-crystal X-ray structure determination reported by Williams and co-workers on a related compound (ref 6, this paper) parallels our findings.

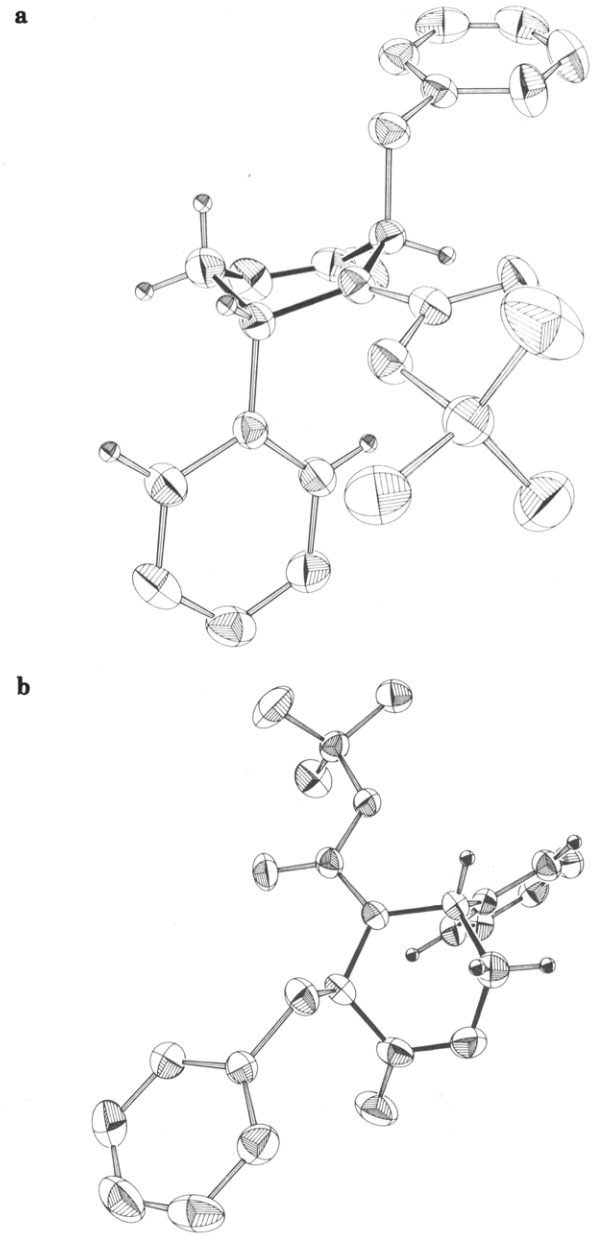
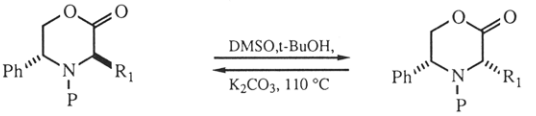


Figure 1. Molecular structure of **9R** from two perspectives as determined by a single-crystal X-ray structure determination. Atoms are shown as spheres of a fixed arbitrary radius, and most hydrogens have been omitted for clarity. Perspective a is a side perspective viewed down the Boc-group axis. Perspective b is an overhead perspective viewed from the C_3-benzyl side.

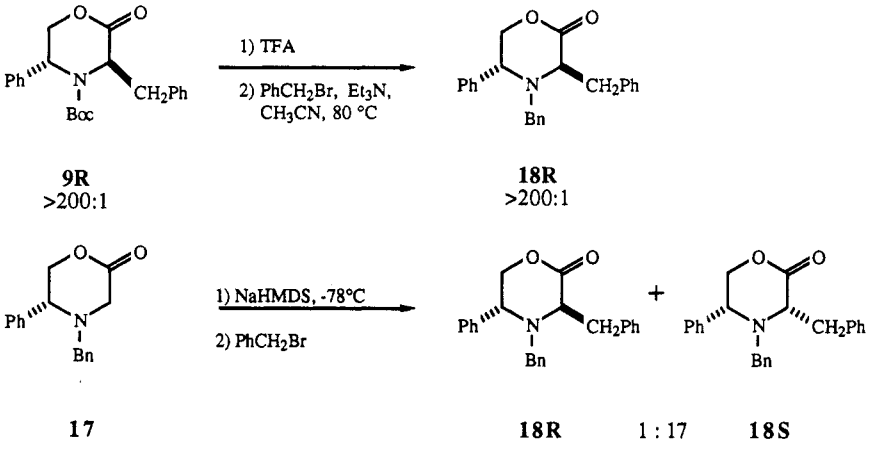
Table IV. Thermodynamic Equilibration Studies



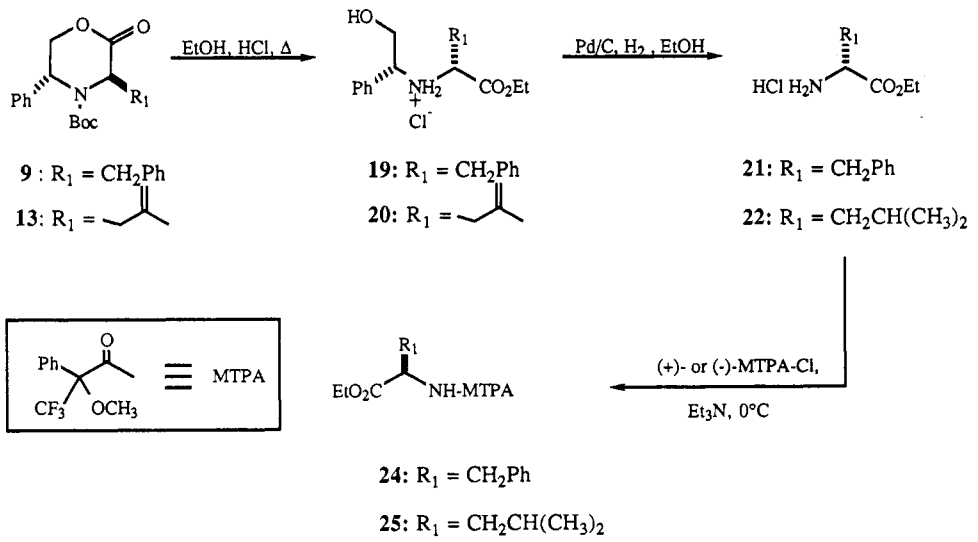
C_3-R C_3-S

entry	compd	P	R_1	ratio *R*:*S*
1	**11**	Cbz	CH_2Ph	1.88:1
2	**12**	Cbz	CH_3	1.30:1
3	**15**	Boc	$(CH_2)_3CH_3$	3.40:1

Scheme II

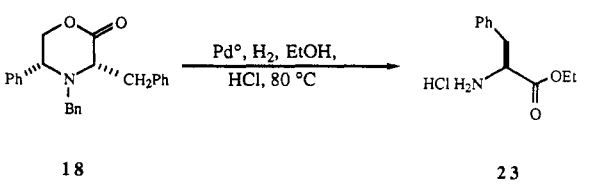


Scheme III



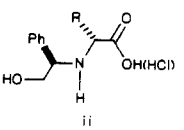
result of kinetic control by equilibration experiments for selected alkylation adducts (Table IV). In each case the equilibrium favored the kinetically preferred 3*R* isomer but in a drastically reduced ratio. Entries 1 and 2 (Table IV) represent convergent values obtained by approaching the equilibrium from both directions.

Deprotection of the Alkylation Adducts. A simple one-pot, three-step deprotection scheme was developed for the *t*-Boc-protected alkylation adducts. The procedure is exemplified by the conversion of **9** and **13** to the ethyl ester hydrochloride salts of D-phenylalanine (**21**) and D-leucine (**22**), respectively (Scheme III). Exposure of **9** or **13** to excess refluxing ethanolic hydrogen chloride for 1 h and removal of the volatiles provided **19** and **20** quantitatively.[21] The hydrochloride salts were taken up in absolute ethanol and hydrogenolyzed to the final amino acid derivatives under the influence of a palladium catalyst (5–10% Pd/C, 10% $Pd(OH)_2/C$, or Pd^0 prepared in situ from $PdCl_2$) and hydrogen (15 psi) at room temperature. Pure ethyl ester hydrochloride salts of the amino acids can be conveniently isolated in about 60% overall yield by precipitation from a minimum volume of ethanol with anhydrous ether or by an aqueous extraction method.[22] Alkylation adduct **18** was also converted to the corresponding L-phenylalanine derivative. Interestingly, in this case the entire deprotection could be achieved without isolating the intermediate with the chiral auxiliary still attached (e.g., **19**). Thus, exposure of **18** to Pd^0, hydrogen (15 psi), and refluxing excess ethanolic hydrogen chloride for 1–4 h provided L-(+)-phenylalanine ethyl ester hydrochloride salt (**23**) in an 81% yield (eq 6).



(6)

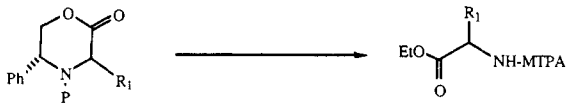
(21) Conversion of the alkylation adducts to the ethyl ester was a matter of convenience for isolation and further analysis for optical purity. Fully deprotected amino acids may be obtained by utilizing an aqueous solvent system for the acidic hydrolysis in lieu of absolute ethanol. The resulting amino acid derivative ii can be deprotected by treatment with periodic acid (private communication from Professor Robert M. Williams). This deprotection extends the scope of functionality in the newly introduced side chain which can be tolerated during the deprotection procedure.



ii

(22) The entire deprotection can be carried out by treatment of the alkylation adducts with refluxing ethanolic hydrogen chloride under the influence of a palladium catalyst and hydrogen; however, the yields were capricious, and it was more difficult to isolate the final product in good purity.

Table V. Final Amino Acid Diastereomeric Purity



starting material	P	R_1	diastereomer ratio C_3-R/S	product	R_1	diastereomer ratio C_2-R/S
9	Boc	β-CH_2Ph	99.81:0.19	24	β-CH_2Ph	99.87:0.13
13	Boc	β-methallyl	99.82:0.18	25	β-$CH_2CH(CH_3)_2$	99.66:0.34
18	CH_2Ph	α-CH_2Ph	1:17	26	α-CH_2Ph	1:18

Enantiomeric Excess of the Isolated Amino Acid Derivatives. The enantiomeric purity of the synthetic amino acids was probed by converting the ethyl ester hydrochloride salts to the corresponding Mosher amides[23,24] (Scheme III). Analytical capillary gas–liquid chromatographic analysis on both (+)- and (−)-Mosher amides, without purification, provided a measure of the enantiomeric purity of the final amino acids. The results from this study are tabulated in Table V. As can be seen, the diastereomeric excesses observed in the purified alkylation adducts translated to essentially identical enantiomeric excesses in the final amino acid derivatives.

Conclusions

We have described new methodology which provides the basis for the preparation of nonproteinogenic and uncommon amino acid derivatives in high enantiomeric purity via the alkylation of a new chiral glycine enolate synthon. Either enantiomeric series is accessible by preparing the glycine enolate synthons **7** or **8** in a simple two-pot, three-step sequence from commercially available D- or L-2-phenylglycinol. Conditions for alkylating metal enolates of **7** were delineated based on the activity of the electrophile: very reactive (α-halo esters), reactive (allylic halides, benzylic halides, and methyl iodide), and unreactive (*n*-alkyl iodides). The alkylations proceeded with a *minimum* de of 97.6% for the unreactive electrophiles and de ≥ 98% for the reactive and very reactive electrophiles. Purification by chromatography or recrystallization provided good to excellent yields of the alkylation adducts with de ≥ 99%. A simple one-pot, three-step procedure provided the ethyl ester hydrochloride salts of the final amino acids without racemization.

The key design element is the use of an N_4-urethane protecting group which forces the C_5-phenyl substituent into an axial disposition in the enolate to avoid an A(1,3) interaction with the termini of the urethane. The lowest energy transition state involves approach of the electrophile from the face opposite the axially disposed C_5-substituent. The veracity of this model is supported by the conformation of an alkylation adduct (**9**), as resolved by a single-crystal X-ray structural determination, and the alkylation of the *N*-benzyl protected glycine enolate synthon **16** which provided the opposite sense of asymmetric induction.

Experimental Section

General. Melting points were determined with a Büchi SMP-20 melting point apparatus and are uncorrected. Infrared spectra were recorded on a Beckman 4210 spectrophotometer. Optical rotations are the average of 10 independent measurements determined on a JASCO DIP-181 digital polarimeter at the sodium D line (589 nm) and are reported as follows: $[\alpha]^{25}_D$ (solvent, concentration (*l* in g/100 mL)). Analytical gas–liquid chromatography was carried out on a Hewlett-Packard 5880A gas chromatograph employing a fused silica capillary column (30 m × 0.32 mm) coated with DB-1. Unless indicated otherwise, injector and detector temperatures were 250 °C. Data are reported as follows: oven temperature; retention time (t_R).

^1H NMR spectra were recorded at 80, 90, or 300 MHz on a Varian Associates HFT-80, a Varian Associates EM-390, or a Bruker AM-300 spectrometer, respectively. ^{13}C NMR spectra were recorded at 22.5 or 75 MHz on a JEOL FX-90Q or a Bruker AM-300 spectrometer. Due to hindered rotation about the urethane protecting groups, many spectra (^1H and ^{13}C) were determined at elevated temperatures to obtain completely time averaged resonances. Spectra were recorded in a number of solvents and are reported in parts per million on the δ scale from tetramethylsilane (TMS) or 3-(trimethylsilyl)propionic acid sodium salt (TPS). Spectra are reported as follows: (MHz, solvent, internal standard, temperature (°C) [when other than ambient]) chemical shift (multiplicity [s = singlet, d = doublet, t = triplet, q = quartet, qn = quintet, m = multiplet, br = broad], coupling constant (in Hz), and interpretation).

Combustion analyses were performed by Gailbraith Laboratories (Knoxville, TN) or Lawrence Henling (California Institute of Technology).

Liquid chromatography was performed by using a forced air flow system (5–10 psi) of the indicated solvent system on EM Reagents silica gel 60 (230–400 mesh). Data are reported as follows: column height and diameter, weight of silica, and eluant composition. Medium-pressure liquid chromatography (MPLC) was carried out by using EM Reagents LoBar silica gel 60 prepacked columns (A–C indicates size) on a Chromatronix MPLC apparatus equipped with a Fluid Metering Inc. Model RP-SY lab pump. MPLC data are reported as follows: column size and eluant composition (number of fractions collected of the denoted system when multiple solvent systems were employed). Analytical high-performance liquid chromatography (HPLC) was carried out by employing a Waters 5μ Radial Pak silica gel column equipped with an ISCO Model 2300 pump. Integrations were obtained with a Hewlett Packard 3390A integrator in conjunction with an ISCO V^4 absorbance detector (UV, 250 nm). Compounds are reported in order of increasing elution time. Analytical thin-layer chromatography (TLC) was performed by using EM Reagents 0.25-mm silica gel 60 F-254 plates in the denoted solvent system.

Unless specified otherwise, commercially available solvents and reagents were used as received. Tetrahydrofuran (THF), diethyl ether (Et_2O), benzene (PhH), and toluene ($PhCH_3$) were distilled from sodium metal/benzophenone ketyl. Dichloromethane, diisopropylethylamine, diisopropylamine, triethylamine, and acetonitrile were distilled from calcium hydride. Dimethyl sulfoxide and dimethylformamide were distilled under reduced pressure from calcium hydride and stored over activated 4-Å molecular sieves.

Stock solutions of ethanolic hydrogen chloride were prepared by bubbling a known amount of dry HCl into a known volume of ice-cooled absolute ethanol and were stored under Ar. D-(−)-α-Phenylglycinol was obtained from the Sigma Chemical Co. or from Aldrich Chemical Co. Lithium bis(trimethylsilyl)amide (1.0 M solution in hexanes) and (+)- and (−)-α-methoxy-α-(trifluoromethyl)phenylacetic acid were available from the Aldrich Chemical Co. (occasionally the optical purities of the received acids

(23) Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543.

(24) The optical purity of the (+)- and (−)-α-methoxy-α-(trifluoromethyl)phenylacetic acids should be monitored as some lots were found to have as low as 93% ee by conversion to the amides of *R*-(+)- or *S*-(−)-α-methylbenzylamine.

were <99%).[24] Unless specified otherwise, all nonaqueous reactions were conducted under an inert atmosphere (argon or nitrogen), using flame-dried glassware.

Phenyl α-Bromoacetate (6). The title compound was prepared by melting bromoacetyl bromide (20.0 g, 100 mmol) and phenol (6.0 g, 64 mmol) at 80 °C with stirring for 1 h.[15] The reaction mixture was cooled to room temperature while under vacuum (~10 mm). Kugelrohr distillation (b.p. 112 °C, 2 mmHg) of the resulting oil provided 10.6 g (77%) of pure **6**, which solidifies upon storage in the refrigerator. Essentially no decomposition was detected over several weeks when **6** was stored in the refrigerator under anhydrous conditions. **6**: IR (film on NaCl) 1780, 1600, 1495, 1285, 1190, 1160 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$, TMS) δ 6.9–7.5 (m, 5 H, *Ph*), 3.93 (s, 2 H, $BrCH_2$).

(5*R*)-3,4,5,6-Tetrahydro-5-phenyl-2*H*-1,4-oxazin-2-one (1a). A solution of D-(−)-α-phenylglycinol (**5**) (8.0 g, 58.3 mmol, 1.0 equiv) and diisopropylethylamine (25 mL, 146 mmol, 2.5 equiv) in acetonitrile (200 mL, from a freshly opened bottle) were added in a dropwise fashion (1.5–2.0 h) from a side-arm pressure-equalizing addition funnel to phenyl α-bromoacetate (**6**) (13.79 g, 64.1 mmol, 1.1 equiv) in acetonitrile (50 mL) at room temperature. The resulting gold solution was stirred overnight (15–18 h) and the volume reduced in vacuo (to avoid dimerization,[18] heating bath temperatures ≤40 °C are recommended) to about 20 mL. The gold liquid, in chloroform (20–30 mL), was immediately loaded onto a flash column[17] (~1 inch Na_2CO_3 precolumn pad, 21 × 6.5 cm, 300 g of silica, 50% ethyl acetate/hexanes until **1a** begins to elute (~3 column volumes), then 1 L of ethyl acetate) to afford 8.01 g (78%, yields varied from 40% to 83%) of **1a**, sometimes as white clumpy crystals (mp 53.5–54.0 °C) or else as a light yellow oil (R_f = 0.58; 20% acetone/ethyl acetate): IR (film on NaCl) 3460 (br), 3300 (br), 3060, 3030, 2960, 2890, 1735, 1450, 1400, 1310, 1295, 1230, 1210, 1095, 1020, 750, 690 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$, TMS) δ 7.35 (br s, 5 H, *Ph*), 4.2 (five-lined m, 3 H, PhC*H* and OCH_2), 3.86 (AB, J_{AB} = 18 Hz, HNC*H*H), 3.70 (AB, J_{AB} = 18 Hz, HNCH*H*), 2.1 (br s, N*H*); ^{13}C NMR (22.5 MHz, $CDCl_3$, TMS) δ 167.5, 137.4, 128.8, 128.5, 126.8, 74.3, 56.3, 48.4. *NOTE*: To avoid substantial loss of **1a** to dimerization, the N-protection should be performed immediately.

(5*R*)-2,3,5,6-Tetrahydro-5-phenyl-*N*-(*tert*-butyloxycarbonyl)-4*H*-1,4-oxazin-2-one (7). The oxazinone **1a** (7.81 g, 44.1 mmol, 1.0 equiv), di-*tert*-butyl dicarbonate (10.3 g, 48.5 mmol), and triethylamine (6.2 mL, 44.1 mmol, 1.0 equiv) were dissolved in ethyl acetate (180 mL) and stirred at room temperature for 4–6 h. The reaction mixture was then diluted with ethyl ether, washed successively with 10% aqueous hydrochloric acid and saturated aqueous sodium bicarbonate, dried ($MgSO_4$), filtered, and concentrated in vacuo to give 14.2 g (116% mass balance) of a yellow oil. Recrystallization from ethyl ether/hexanes gave 6.72 g of white crystalline **7**. Flash chromatography of the recrystallization mother liquors (14.0 × 6.0 cm, 150 g, 35% ethyl acetate/hexanes) gave 2.76 g of additional product. The combined purified yield was 9.48 g (78%). The overall yield from amino alcohol (**5**) was 60%. An analytical sample was obtained by recrystallization (2×) from ethyl ether/hexanes: mp 87–88 °C; R_f = 0.55 (50% ethyl acetate/hexanes); IR ($CDCl_3$) 2985, 1765, 1695, 1400, 1370, 1160, 1125, 690 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$, TMS) δ 7.33 (br m, 5 H, *Ph*), 5.06 (br d, d, *J* = 5, 5 Hz, PhC*H*), 4.63 (AB, *J* = 18 Hz, O_2CCHHN), 4.56 (m, 2 H, OC*H*H and OCH*H*), 4.10 (AB, J_{AB} = 18 Hz, O_2CCHHN), 1.30 (s, $C(CH_3)_3$; ^{13}C NMR (22.5 MHz, $CDCl_3$, TMS) δ 167.6, 153.6, 137.9, 128.9, 128.0, 126.0, 81.4, 69.9, 54.1, 44.4, 28.1; $[\alpha]^{25}_D$ = 67.5° (CH_2Cl_2, *c* = 1.0). Anal. Calcd for $C_{15}H_{19}NO_4$: C, 64.96; H, 6.91; N, 5.05. Found: C, 65.04; H, 6.87; N, 5.03.

(5*R*)-2,3,5,6-Tetrahydro-5-phenyl-*N*-(benzyloxycarbonyl)-4*H*-1,4-oxazin-2-one (8). A solution of benzyl chloroformate (1.87 g, 11.0 mmol (90% pure), 1.1 equiv) in dichloromethane (10 mL) was added in a dropwise fashion from a side-arm pressure-equalizing addition funnel to an ice-cooled dichloromethane (30 mL) solution of the oxazinone (**1a**) (1.77 g, 10.0 mmol, 1.0 equiv) and diisopropylethylamine (1.86 mL, 11.0 mmol, 1.1 equiv) over a period of 10 min. The reaction mixture was stirred for an additional 0.5 h, poured into 10% aqueous hydrochloric acid, and extracted with two portions of ethyl ether. The combined organic layers were washed with saturated aqueous sodium bicarbonate, dried ($MgSO_4$), filtered, and concentrated in vacuo to give 3.01 g (96% mass balance) of white crystals. Recrystallization (3×) of the unpurified products from acetone/hexanes provided 1.84 g (59%) of pure **8**. Flash chromatography on the combined recrystallization mother liquors (11 × 4.0 cm, 65 g silica, 50% ethyl acetate/hexanes) provided an additional 0.694 g (22%) of pure crystalline **8**. Thus the combined purified yield of **8** was 2.53 g (81%): mp 97–98 °C; IR ($CHCl_3$) 3050, 3020, 2940, 2910, 2880, 1755, 1695, 1400, 1380, 1340, 1320, 1110, 1030, 750, 680 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$, TMS) δ 6.95–7.4 (br m, 5 H, *Ph*), 5.16 (d, d, *J* = 4, 4 Hz, PhC*H*), 5.06 (s, $PhCH_2O$), 4.6 (AB, J_{AB} = 18 Hz, NC*H*H), 4.67–4.30 (m, 2 H, PhCHC*HH*), 4.15 (AB, J_{AB} = 18 Hz, NCH*H*); ^{13}C NMR (22.5 MHz, $CDCl_3$, TMS) δ 166.9, 154.4, 137.1, 135.6, 128.9, 128.4, 128.2, 127.8, 126.0, 69.7, 67.8, 53.9, 44.6; $[\alpha]^{25}_D$ = −56.6° (CH_2Cl_2, *c* = 1.00). Anal. Calcd for $C_{18}H_{17}NO_4$: C, 69.44; H, 5.48; N, 4.50. Found: C, 69.14; H, 5.48; N, 4.46.

(5*R*)-2,3,5,6-Tetrahydro-5-phenyl-*N*-benzyl-4*H*-1,4-oxazin-2-one (17). To oxazinone **1a** (0.931 g, 5.25 mmol, 1.0 equiv) and diisopropylethylamine (1.80 mL, 10.5 mmol, 2.0 equiv) in acetonitrile (15 mL) was added benzyl bromide (0.940 mL, 7.88 mmol, 1.5 equiv) in acetonitrile (6 mL). The resulting solution was stirred at room temperature for 3–5 h, diluted with dichloromethane, washed successively with saturated aqueous sodium bicarbonate and saturated aqueous sodium chloride, dried ($MgSO_4$), and concentrated in vacuo to give 2.38 g of unpurified product. MPLC of this material (Merck C, 25% ethyl acetate/hexanes) gave 1.21 g (86%) of pure crystalline **17**. Recrystallization (2×) from ethyl ether/hexanes gave an analytical sample of **17**: mp 92.5–93.5 °C; IR ($CDCl_3$) 3080, 3060, 3030, 2950, 2800, 1735, 1320, 1240, 1220, 1130, 1080, 1060, 1040, 1020, 685 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$, TMS) δ 7.3–7.6 (m, 5 H, *Ph*), 7.27 (br s, 5 H, *Ph*), 4.2–4.5 (five-lined m, 2 H), 3.56–3.9 (six-lined m, 2 H), 2.86–3.2 (four-lined m, 2 H); ^{13}C NMR (22.5 MHz, $CDCl_3$, TMS) δ 167.7, 136.3, 129.1, 128.7, 128.4, 128.2, 127.5, 73.1, 62.9, 58.7, 53.6; $[\alpha]^{25}_D$ = −59.1° (CH_2Cl_2, *c* = 1.00). Anal. Calcd for $C_{17}H_{17}NO_2$: C, 76.38; H, 6.41; N, 5.24. Found: C, 76.34; H, 6.47; N, 5.20.

General Alkylation Procedure for N-Protected Oxazinones 7, 8, and 17. The following alkylation reactions were carried out under a nitrogen atmosphere on scales ranging from 0.3 to 5.65 mmol at concentrations of ca. 0.25 M. All reagent additions were made via hypodermic syringe. Alkylating agents were passed through a pad of neutral alumina immediately prior to use.

Enolate Generation. A. Sodium Enolate. The desired N-protected oxazinone **7**, **8**, or **17** was placed in a flame-dried, nitrogen-filled, two-necked, 25-mL flask equipped with two septa and a magnetic stirrer, dissolved in the requisite anhydrous solvent (tetrahydrofuran (THF) or dimethoxyethane (DME)), to give a ca. 0.5 M solution, and cooled to −78 °C. The sodium bis(trimethylsilyl)amide[19] (0.98 equiv weighed out in a dry box) was dissolved in the indicated anhydrous solvent (THF or DME, to give a ca. 0.5 M solution) in a separate flask fitted with a septum and magnetic stir bar under a nitrogen atmosphere and was introduced into the −78 °C reaction vessel via cannulation. After being stirred for 30 min at −78 °C, the desired enolate was ready for alkylation.

B. Lithium Enolate. The lithium enolates of **7**, **8**, and **17** were prepared in an analogous manner to the corresponding sodium enolates with the following changes: (1) the oxazinone was dissolved in the indicated anhydrous solvent (THF or DME, to give a ca. 0.25 M solution) and (2) the lithium bis(trimethylsilyl)amide (0.98 equiv) was introduced as a 1.0 M solution in hexanes.

Enolate Alkylation. To the cold enolate solutions (−78 °C), prepared as described above, were added the indicated neat electrophiles (1–5 equiv). The temperature and duration of the alkylation reactions were variables specific to each experiment. The reactions were quenched by introducing a saturated aqueous solution of ammonium chloride (1 mL per mmol of enolate). The resulting two-phased solutions were diluted with ethyl ether and washed successively with 10% aqueous hydrochloric acid, saturated aqueous sodium bicarbonate, and saturated aqueous sodium chloride, dried ($MgSO_4$), filtered, and concentrated in vacuo to afford the unpurified alkylation adducts. Analytical gas chromatography analysis was performed on the unpurified mixtures to determine the diastereoselectivity of each alkylation reaction. Products were obtained in purified form by MPLC or flash chromatography as indicated.

Preparation and Isolation of Authentic 3*S*-Alkylation Isomers. The 3*R*-alkylation products were deprotonated (1.0 equiv of sodium bis(trimethylsilyl)amide, −78 °C, 2 h, 0.25 M in THF) and quenched with saturated aqueous ammonium chloride and the unpurified products isolated as previously described. In a few cases, the 3*R* and 3*S* isomers were separated by MPLC to provide an authentic sample of the 3*S*-alkylation products. For the remaining examples, coinjection experiments by capillary GC or HPLC established the identity of the 3*S* isomers.

(3*R*,5*R*)-2,3,5,6-Tetrahydro-5-phenyl-3-(phenylmethyl)-*N*-(*tert*-butyloxycarbonyl)-4*H*-1,4-oxazin-2-one (9). To a cooled solution (−78 °C) of the sodium enolate of **7** (5.10 mmol, 0.25 M in 1:1 THF/DME) was added benzyl bromide (0.68 mL, 5.7 mmol, 1.1 equiv). The reaction was quenched after stirring for 2 h at −78 °C, and the product was isolated as previously described, to provide 2.00 g (107% mass balance) of unpurified product. Diastereomer analysis (DB-1, 200 °C, injection temperature 225 °C, 15 psi, t_R (3*R*)-**9** = 8.17 min, t_R (3*S*)-**9** = 8.93 min) afforded a ratio of (3*R*)-**9**:(3*S*)-**9** > 200:1. The product was purified by MPLC (Merck C, 25% ethyl acetate/hexanes) to provide 1.68 g (90%) of **9** as a white crystalline material (yields ranged from 78% to 90%). Recrystallization (3×) from acetone/hexans provided an analytical sample of **9**: mp 176–177 °C; IR ($CDCl_3$) 3040, 2980, 1750, 1690, 1400, 1370, 1360, 1250, 1165, 1125, 1075, 965, 855, 690 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$, TMS) δ 6.95–7.5 (m, 15 H, *Ph* and 2 *Ph*CH_2), 5.05–5.25 (br d, d, J = 6, 3 Hz, 1 H), 5.7–6.0 (br s, 1 H), 3.97 (br d, J = 12 Hz, 1 H), 3.57 (ABX, J_{AB} = 15, J_{AX} = 6 Hz, 1 H), 3.37 and 3.15–3.45 (ABX and an overlapping m, J_{AB} = 15, J_{AX} = 3 Hz, 2 H), 1.35 (br s, $C(CH_3)_3$]; ^{13}C NMR (22.5 MHz, $CDCl_3$, TMS) δ 169.2, 153.6 (br), 140.1 (br), 136.2 (br), 129.8, 128.8, 127.6, 127.5, 125.3, 81.3 (br), 69.2 (br), 58.7 (br), 54.1 (br), 38.9 (br), 28.1; ^{13}C NMR (22.5 MHz, $CDCl_3$ TMS, 60 °C) δ 169.0, 153.7, 140.0, 136.3, 130.0, 128.8, 127.7, 127.5, 125.5, 81.4, 69.3, 58.9, 54.3, 39.4, 28.1; $[\alpha]^{25}_D$ = −205.9° (CH_2Cl_2, c = 1.00). Anal. Calcd for $C_{22}H_{25}NO_4$: C, 71.91; H, 6.86; N, 3.81. Found: C, 72.11; H, 6.87; N, 3.82.

(3*R*,5*R*)-2,3,5,6-Tetrahydro-3-(phenylmethyl)-5-phenyl-*N*-(benzyloxycarbonyl)-4*H*-1,4-oxazin-2-one (11). To a cooled solution of the sodium enolate (−78 °C) of **8** (0.965 mmol, 0.25 M in 1:1 THF/DME) was added benzyl bromide (126 μL, 1.06 mmol, 1.1 equiv). The reaction was quenched after 1 h of stirring at −78 °C, and the unpurified products were isolated as previously described to give 0.312 g (81% mass balance) of a white semicrystalline substance. Diastereomer analysis (DB-1, 250 °C, 15 psi, t_R (3*R*)-**11** = 5.8 min, t_R (3*S*)-**11** = 6.2 min) afforded a ratio of (3*R*)-**11**:(3*S*)-**11** > 200:1. Purification was achieved by MPLC (Merck B, 35% ethyl acetate/hexanes) to afford 0.261 g (67%) of white crystalline **11** (yields varied from 67% to 78%). Recrystallization (2×) from acetone/hexanes provided an analytical sample of **11**: mp 158.5–159 °C; IR ($CDCl_3$) 3080, 3040, 1750, 1700, 1450, 1410, 1380, 1350, 1330, 1120, 1075, 980, 700 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$, TMS) δ 6.75–7.4 (m, 15 H, *Ph* and 2 CH_2*Ph*), 5.10 (br s, 3 H), 4.80 (br s, 1 H), 3.9 (br AB, J_{AB} = 12 Hz, 1 H), 3.0–3.7 (br m, 2 H), 3.25 (ABX, J_{AB} = 14, J_{AX} = 3 Hz, 1 H); ^1H NMR (90 MHz, benzene-d_6, TMS, 67 °C) δ 7.35–7.85 (m, 15 H, *Ph* and 2 *Ph*CH_2), 6.88 ((AB*X*)$_1$, J_{AX} = 4.4, J_{BX} = 7.2 Hz, 1 H), 5.58 (s, 2 H, OCH_2Ph), 5.27 (br s, width at $h_{1/2}$ = 5.2 Hz, 1 H), 4.17 ((*A*BX)$_1$, J_{AB} = 15.9, J_{AX} = 7.2 Hz, 1 H), 4.15 ((*A*BX)$_2$, J_{AB} = 13.5, J_{AX} = 1.6, 1 H), 3.38 ((*AB*X)$_1$, J_{BA} = 15.9, J_{BX} = 4.4 Hz, 1 H), 3.27 ((*AB*X)$_2$, J_{BA} = 13.5, J_{BX} = 3.6); ^{13}C NMR (22.5 MHz, $CDCl_3$, 67 °C) δ 168.7, 154.4, 139.3, 135.9, 135.6, 129.8, 129.0, 128.8, 128.3, 127.8, 127.6, 125.4, 69.1, 67.6, 58.9, 53.9, 38.5; $[\alpha]^{25}_D$ = −194.0° (CH_2Cl_2, c = 1.00). Anal. Calcd for $C_{25}H_{23}NO_4$: C, 74.79; H, 5.77; N, 3.49. Found: C, 74.66; H, 5.86; N, 3.43.

Authentic (3*S*)-11. Following the previously described procedure, (3*R*)-**11** (100 mg, 0.249 mmol) was deprotonated and quenched to give 93.7 mg (94% mass balance) of an unpurified mixture of (3*R*)- and (3*S*)-**11**. Diastereomer analysis gave a ratio of (3*R*)-**11**:(3*S*)-**11** = 3.4:1. Separation by MPLC (Merck B, 10% ethyl acetate/carbon tetrachloride (tubes 1–30), then 20% ethyl acetate/carbon tetrachloride) afforded, in the order of elution, 48.4 mg (48%) of (3*R*)-**11** and 18.1 mg (18%) of (3*S*)-**11**. (3*S*)-**11**: ^1H NMR (90 MHz, $CDCl_3$, TMS) δ 6.9–6.4 (m, 15 H, *Ph*, CH_2*Ph*, and OCH_2*Ph*), 5.2 (d, d, J = 7.5, 7.5 Hz, *H*CCH_2Ph), ca. 5.1 (1 H, PhC*H*CH_2O), 5.06 (*AB*, J_{AB} = 12 Hz, OC*H*HPh), 4.85 (*AB*, J_{BA} = 12 Hz, OCH*H*Ph), 4.45 (br s, −HCC*H*HO−), 4.37 (br d, J = 1.5 Hz, −HCCH*H*O−), 3.23 (d, J = 7.5 Hz, HCCH_2Ph).

(3*S*,5*R*)-2,3,5,6-Tetrahydro-5-phenyl-3,4-bis(phenylmethyl)-4*H*-1,4-oxazin-2-one (18). To a cooled solution (−78 °C) of the sodium enolate of **17** (3.68 mmol, 0.25 M in THF) was added neat benzyl bromide (533 μL, 4.49 mmol, 1.2 equiv). The reaction was quenched after 4 h, and 1.47 g of unpurified products (110% mass balance) was isolated as previously described. Diastereomer analysis (DB-1, 235 °C, 15 psi; t_R (3*S*)-**18** = 5.4 min, t_R (3*R*)-**18** = 5.7 min) afforded a ratio of (3*S*)-**18**:(3*R*)-**18** = 17.2:1. Purification was achieved by MPLC (Merck C, 10% ethyl acetate/hexanes) to provide 1.01 g (77%) of **18** as a colorless oil. A center-cut fraction from the MPLC purification gave an analytical sample of **18**: IR ($CDCl_3$) 3080, 3035, 2950, 2810, 1730, 1450, 1320, 1250, 1130, 1055, 1040, 685 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$, TMS) δ 7.0–7.45 (m, 15 H, *Ph* and 2 *Ph*CH_2) 3.96 (AB*X*, J_{AX} = 5, J_{BX} = 6 Hz, 1 H), 3.55–3.8 (m, 3 H), 3.1–3.5 (seven-lined m, 2 H), 2.95 (*ABX*, J_{AB} = 13, J_{AX} = 5 Hz, 1 H), 2.65 (A*BX*, J_{BA} = 13, J_{BX} = 6 Hz, 1 H); ^{13}C NMR (22.5 MHz, $CDCl_3$, TMS) δ 171.1, 137.8, 136.9, 136.5, 130.1, 129.8, 128.9, 128.5, 128.1, 128.0, 127.8, 127.2, 127.0, 70.6, 63.8, 61.7, 57.6, 41.1; $[\alpha]^{25}_D$ = +76.2° (CH_2Cl_2, c = 1.07). Anal. Calcd for $C_{24}H_{23}NO_2$: C, 80.64; H, 6.49; N, 3.92. Found: C, 80.83; H, 6.59; N, 3.98.

Proof of the absolute configuration in this instance was obtained by chemical correlation (vide supra).

Chemical Correlation of (3*R*)-9 and (3*R*)-18. To a dichloromethane (600 μL) solution of **9** (62 mg, 1.70 μmol) was added trifluoroacetic acid (ca. 1.0 mL). After 2 h, the reaction mixture was diluted with chloroform and covered with water and saturated aqueous sodium carbonate added in small portions until the aqueous layer tested basic to pH paper. The organic layer was drawn off and the aqueous layer extracted with two portions of chloroform. The combined organic extracts were dried ($MgSO_4$), filtered, and concentrated in vacuo to afford 22.4 mg (50%) of the unpurified N-deprotected material, which was carried on without purification. Thus, 20 mg (75 μmol) of N-deprotected material was treated with benzyl bromide (13 μL, 112 μmol, 1.5 equiv) and diisopropylethylamine (38 μL, 225 μmol, 3.0 equiv) in acetonitrile (500 μL) and heated at reflux for 8 h. Following the procedure described for the isolation of (3*S*)-**18**, 11.3 mg of unpurified (3*R*)-**18** was obtained. Diastereomer analysis (please see the experimental details for **18**) gave a ratio of (3*R*)-**18**:(3*S*)-**18** > 200:1, which was in agreement with the diastereomer ratio in **9** (3*R*:3*S* > 200:1).

(3*R*,5*R*)-2,3,5,6-Tetrahydro-3-methyl-5-phenyl-*N*-(benzyloxycarbonyl)-4*H*-1,4-oxazin-2-one (12). To a cooled solution (−78 °C) of the sodium enolate of **8** (0.322 mmol, 0.25 M in 1:1 THF/DME) was added neat methyl iodide (100 μL, 1.61 mmol, 5 equiv). The reaction was quenched after 1 h, and 0.105 g (101% mass balance) of unpurified products was isolated as previously described. Diastereomer analysis (DB-1, 150 °C, 10 psi; t_R (3*R*)-**12** = 18.3 min, t_R (3*S*)-**12** = 19.0 min) afforded a ratio of (3*R*)-**12**:(3*S*)-**12** = 160:1. Purification was achieved by MPLC (Merck B, 20% ethyl acetate/carbon tetrachloride) to provide 86.4 mg (83%) of pure crystalline **12**. Recrystallization (2×) from hexane/carbon tetrachloride provided an analytical sample of **12**: mp 85–86 °C; IR (CH_2Cl_2) 3060, 2990, 1760, 1710, 1405, 1340, 1285–1250 (br), 1120, 1045, 890 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$, TMS) δ 6.9–7.45 (m, 10 H, *Ph* and *Ph*CH_2), 4.85–5.25 (m, 4 H), 4.75 (*ABX*, J_{AB} = 12, J_{AX} = 3 Hz, 1 H), 4.4 (A*BX*, J_{BA} = 12, J_{BX} = 2 Hz, 1 H), 1.62 (d, J = 8 Hz, CHCH_3); $[\alpha]^{25}_D$ = −166.5° (CH_2Cl_2, c = 1.00). Anal. Calcd for $C_{19}H_{19}NO_4$: C, 70.14; H, 5.89; N, 4.31. Found: C, 70.07; H, 5.98; N, 4.28.

Authentic (3*S*)-12. Following the previously described procedure, (3*R*)-**12** (58.8 mg, 0.181 mmol) was deprotonated and quenched to give 45.4 mg (77% mass balance) of an unpurified mixture of (3*R*)- and (3*S*)-**12**. Diastereomer analysis gave a ratio of (3*R*)-**12**:(3*S*)-**12** = 1.5:1. Separation by MPLC (Merck B, 20% ethyl acetate/carbon tetrachloride) gave, in the order of elution, 18.5 mg of (3*S*)-**12** (31%) and 17.9 mg (30%) of (3*R*)-**12**. (3*S*)-**12**: ^1H NMR (90 MHz, $CDCl_3$, TMS) δ 6.9–7.3 (m, 10 H, *Ph* and OCH_2*Ph*), 4.94–5.2 (m, 1 H), 5.03 (s, 2 H, OCH_2Ph), 4.96 (q, J = 7.5 Hz, *H*CCH_3), 4.5 (s, 1 H, PhCHC*H*HO), 4.06 (br s, 1 H, PhCHCH*H*O), 1.52 (d, J = 7.5 Hz, CHCH_3).

(3*R*,5*R*)-2,3,5,6-Tetrahydro-3-methyl-5-phenyl-*N*-(*tert*-butyloxycarbonyl)-4*H*-1,4-oxazin-2-one (10). To a cooled solution (−78 °C) of the sodium enolate of **7** (2.88 mmol, 0.25 M

in 1:1 DME/THF) was added neat methyl iodide (0.55 mL, 8.8 mmol, 3.0 equiv). The reaction was quenched after 1.5 h, and 0.78 g (91% mass balance) of unpurified products was isolated as previously described. Diastereomer analysis (DB-1, 160 °C, 5 psi; t_R (3*R*)-**10** = 18.5 min, t_R (3*S*)-**10** = 19.5 min) afforded a ratio of (3*R*)-**10**:(3*S*)-**10** > 200:1. Purification was achieved by MPLC (Merck C, chloroform loading solvent, 20% ethyl acetate/carbon tetrachloride) to provide 0.731 g (87%) of pure crystalline **10**. Recrystallization (2×) from ethyl ether/hexanes provided an analytical sample: mp 142–143 °C; IR ($CDCl_3$) 3000, 2980, 2930, 1760, 1690, 1400, 1370, 1295, 1255, 1245, 1175, 1135, 1070, 1040, 975, 860, 690 cm^{-1}; ^1H NMR (80 MHz, $CDCl_3$, TMS) δ 6.95–7.4 (m, 5 H, *Ph*), 5.07 (br s, 1 H), 4.7–5.0 (m, 1 H), 4.75 (*A*BX, J_{AB} = 12, J_{AX} = 2.0 Hz, 1 H), 4.4 (A*B*X, J_{BA} = 12, J_{BX} = 1.5 Hz, 1 H), 1.63 (d, J = 8 Hz, $CHCH_3$), 1.27 (br s, $OC(CH_3)_3$); ^{13}C NMR (75 MHz, $CDCl_3$, TMS, 67 °C) δ 170.1, 153.4, 139.9, 128.9, 127.8, 125.7, 81.2, 70.0, 54.8, 52.7, 28.2, 20.1; $[\alpha]^{25}_D$ = 181.7° (CH_2Cl_2, c = 1.00). Anal. Calcd for $C_{16}H_{21}NO_4$: C, 65.96; H, 7.27; N, 4.81. Found: C, 65.99; H, 7.30; N, 4.80.

Authentic (3*S*)-10. Following the previously described procedure, (3*R*)-**10** (25.8 mg, 0.089 mmol) was deprotonated and quenched to give 19.6 mg (76% mass balance) of an unpurified mixture of (3*R*)- and (3*S*)-**10**. Diastereomer analysis gave a ratio of (3*R*)-**10**:(3*S*)-**10** = 2.37:1. Separation by MPLC (Merck B, 20% ethyl acetate/carbon tetrachloride) afforded in order of elution 11.0 mg (43%) of (3*R*)-**10** and 4.7 mg (18%) of (3*S*)-**10**. (3*S*)-**10**: ^1H NMR (80 MHz, $CDCl_3$, TMS) δ 6.9–7.4 (m, 5 H, *Ph*), 5.07 (br s, 1 H), ca. 4.7–5.0 (m, 1 H), 4.79 (*A*BX, J_{AB} = 12, J_{AX} = 3.5 Hz, OC*H*HCH), 4.43 (A*B*X, J_{BA} = 12, J_{BX} = 2 Hz, OCHCH*H*CH), 1.63 (d, J = 7.5 Hz, $HCCH_3$), 1.31 (br s, $C(CH_3)_3$).

(3*R*,5*R*)-2,3,5,6-Tetrahydro-3-(2-methylprop-1-en-3-yl)-5-phenyl-*N*-(*tert*-butyloxycarbonyl)-4*H*-1,4-oxazin-2-one (13). To a cooled solution (−78 °C) of the sodium enolate of **7** (3.99 mmol, 0.25 M in 1:1 THF/DME) was added neat methallyl iodide (1.76 g, 9.65 mmol, 2.2 equiv). The reaction was quenched after 2 h, and 1.41 g (107% mass balance) of unpurified products was isolated as previously described. Diastereomer analysis (DB-1, 175 °C, 15 psi; t_R (3*R*)-**13** = 7.2 min, t_R (3*S*)-**13** = 7.4 min) afforded a ratio of (3*R*)-**13**:(3*S*)-**13** > 200:1. Purification was achieved by MPLC (Merck C, 20% ethyl acetate/carbon tetrachloride, chloroform load solvent) to provide 1.19 g (90%) of pure crystalline **13**. Recrystallization (2×) from ethyl acetate/hexane provided an analytical sample: mp 133–134 °C; IR ($CDCl_3$) 2980, 1760, 1690, 1450, 1395, 1370, 1240, 1160, 1120, 1070, 690 cm^{-1}; ^1H NMR (80 MHz, $CDCl_3$, TMS) δ 7.0–7.5 (m, 5 H, *Ph*), 4.75–5.2 (m, 5 H), 4.38 (d, d, J = 12, 2 Hz, 1 H), 2.4–3.0 (m, 2 H, $CH_2C(CH_3)(CH_2)$), 1.93 (d, d, J = 1.0, 1.0 Hz, $CH_2C(CH_2)(CH_3)$), 1.30 (br s, $OC(CH_3)_3$); ^{13}C NMR (75 MHz, $CDCl_3$, TMS, 67 °C) δ 168.2, 153.5, 140.6, 140.3, 128.9, 127.8, 125.7, 115.3, 81.3, 69.8, 56.6, 55.0, 42.7, 28.2, 22.3; $[\alpha]^{25}_D$ = −159.5° (CH_2Cl_2, c = 1.00). Anal. Calcd for $C_{19}H_{25}NO_4$: C, 68.86; H, 7.60; N, 4.23. Found: C, 68.94; H, 7.53; N, 4.21.

Authentic **(3*S*)-13.** Following the previously described procedure, (3*R*)-**13** (30.0 mg, 0.091 mmol) was deprotonated and quenched to give 29.6 mg (98% mass balance) of an unpurified mixture of (3*R*)- and (3*S*)-**13**. Diastereomer analysis gave a ratio of (3*R*)-**13**:(3*S*)-**13** = 1.5:1. No attempt was made to separate the isomers. The identity of the mixture was established in coinjection experiments by capillary GC with an authentic sample of (3*R*)-**13** and by the appearance of the following new absorptions in the ^1H NMR spectrum: (80 MHz, $CDCl_3$, TMS) δ 3.35 (*AB*, J_{AB} = 16 Hz, HCC*H*HC), 3.45 (br AB, J_{BA} = 16 Hz, HCH*H*C), and 1.22 (d, d, J = 2, 2 Hz, CH_3).

(3*R*,5*R*)-2,3,5,6-Tetrahydro-5-phenyl-3-prop-1-en-3-yl-*N*-(*tert*-butyloxycarbonyl)-4*H*-1,4-oxazin-2-one (14). To a cooled solution (−78 °C) of the sodium enolate of **7** (4.38 mmol, 0.25 M in 1:1 THF/DME) was added neat allyl bromide (0.77 mL, 8.9 mmol, 2.0 equiv). The reaction was quenched after 1.5 h, and 1.43 g (101% mass balance) of unpurified products was isolated as previously described. Diastereomer analysis (DB-1, 175 °C, 15 psi; t_R (3*R*)-**14** = 5.8 min, t_R (3*S*)-**14** = 6.0 min) afforded a ratio of (3*R*)-**14**:(3*S*)-**14** > 200:1. Purification was achieved by MPLC (Merck C, the unpurified mixture was loaded in 2 mL of CH_2Cl_2, 20% ethyl acetate/carbon tetrachloride) to provide 1.20 g (86%) of pure crystalline **14**. Recrystallization (2×) from ethyl ether/hexanes provided an analytical sample: mp 94–95 °C; IR ($CDCl_3$) 2980, 1755, 1690, 1460, 1370, 1350, 1240, 1160, 1120, 1070, 690 cm^{-1}; ^1H NMR (80 MHz, $CDCl_3$, TMS) δ 6.95–7.45 (m, 5 H, *Ph*), 5.87 (d, d, d, d, J = 7.5, 7.5, 9.0, 16.0 Hz, CH_2CHCH_2), 5.25 (br m, 1 H, $H_2CCH(CHH)$), 5.07 (br m, 1 H, $H_2CCH(CHH)$), 4.75–5.2 (br m, 1 H), 4.8 (*A*BX, J_{AB} = 12, J_{AX} = 3.5 Hz, 1 H), 4.33 (A*B*X, J_{BA} = 12, J_{BX} = 2.0 Hz, 1 H), 2.72 (br d, d, J = 7.5, 7.5, 1 H), 1.27 (br s, $OC(CH_3)_3$); ^{13}C NMR (75 MHz, $CDCl_3$, TMS, 67 °C) δ 168.4, 153.6, 140.1, 132.7, 128.8, 127.7, 125.7, 119.1, 81.3, 69.8, 57.3, 54.8, 38.7, 28.1; $[\alpha]^{25}_D$ = −177.8° (CH_2Cl_2, c = 1.00). Anal. Calcd for $C_{18}H_{23}NO_4$: C, 68.12; H, 7.30; N, 4.41. Found: C, 68.23; H, 7.40; N, 4.38.

Authentic (3*S*)-14. Following the previously described procedure, (3*R*)-**14** (51.4 mg, 0.162 mmol) was deprotonated and quenched to give 34.9 mg (68% mass balance) of an unpurified mixture of (3*R*)- and (3*S*)-**14**. Diastereomer analysis gave a ratio of (3*R*)-**14**:(3*S*)-**14** = 8.35:1. No attempt was made to separate the mixture. Coinjection experiments on the capillary GC established the identity of (3*S*)-**14**.

(3*R*,5*R*)-2,3,5,6-Tetrahydro-3-(*n*-butyl)-5-phenyl-*N*-(*tert*-butyloxycarbonyl)-4*H*-1,4-oxazin-2-one (15). To a cooled solution (−68 °C, the higher temperature is necessary to prevent the solvent from freezing) of the sodium enolate of **7** (3.96 mmol, 0.25 M in DME) was added neat *n*-butyl iodide (1.38 mL, 12.1 mmol, 3.0 equiv). The reaction was quenched after 5.5 h, and 1.34 g (102% mass balance) of unpurified products was isolated as previously described. Diastereomer analysis (DB-1, 195 °C, 5 psi; t_R (3*S*)-**15** = 11.7 min, t_R (3*R*)-**15** = 12.2 min) afforded a ratio of (3*R*)-**15**:(3*S*)-**15** = 83.5:1.0. Purification was achieved by MPLC (Merck C, dichloromethane (3 mL) was used to load the unpurified mixture onto the column, 15% ethyl acetate/hexanes) to provide 1.03 g (78%) of pure crystalline **15**. Recrystallization (2×) from acetone/hexanes provided an analytical sample: mp 120–121 °C; IR ($CDCl_3$) 2960, 1755, 1690, 1396, 1370, 1245, 1210, 1165, 1125, 1075, 860, 690 cm^{-1}; ^1H NMR (80 MHz, $CDCl_3$, TMS) δ 6.90–7.40 (m, 5 H, *Ph*), 5.07 (br s, 1 H), ~4.6–4.9 (br m, 1 H), 4.75 (*A*BX, J_{AB} = 12, J_{AX} = 1.5 Hz, HCC*H*HO), 4.30 (A*B*X, J_{BA} = 12, J_{BX} = 1.0 Hz, −HCCH*H*O−), 0.75–2.2 (br m's, 9 H), 1.28 (br s, $OC(CH_3)_3$); ^{13}C NMR (75 MHz, $CDCl_3$, TMS, 67 °C) δ 168.9, 153.6, 140.3, 128.8, 127.7, 125.7, 81.1, 69.8, 57.2, 55.1, 34.5, 28.2, 28.1, 22.3, 13.8; $[\alpha]^{25}_D$ = −155.7° (CH_2Cl_2, c = 1.00). Anal. Calcd for $C_{19}H_{27}NO_4$: C, 68.44; H, 8.16; N, 4.20. Found: C, 68.34; H, 8.05; N, 4.17.

Authentic (3*S*)-15. Following the previously described procedure, (3*R*)-**15** (22.4 mg, 0.067 mmol) was deprotonated and quenched to give 23 mg (103% mass balance) of an unpurified mixture of (3*R*)- and (3*S*)-**15**. Diastereomer analysis gave a ratio of (3*R*)-**15**:(3*S*)-**15** = 32.9:1 (starting ratio = 100:1). No attempt was made to separate the mixture. The identity of (3*S*)-**15** was established by coinjection experiments on the capillary GC.

(3*R*,5*R*)-2,3,5,6-Tetrahydro-3-((benzyloxycarbonyl)-methyl)-5-phenyl-*N*-(benzyloxycarbonyl)-4*H*-1,4-oxazin-2-one (16) and the 3*S*,5*R* Isomer. To a cooled solution (−78 °C) of the sodium enolate of **8** (0.917 mmol, 0.25 M in 1:1 THF/DME) was added neat benzyl 2-bromoacetate (0.247 g, 1.16 mmol, 1.2 equiv). The reaction was quenched after 1 h, and the unpurified products were isolated as previously described. Diastereomer analysis was performed by mechanical separation during MPLC purification (vide infra) and afforded a ratio of (3*R*)-**16**:(3*S*)-**16** = 3.5:1. Purification was achieved by MPLC (Merck C, 15% ethyl acetate/carbon tetrachloride) to provide, in the order of elution, 0.247 g (59%) of the 3*R* product and 0.071 g (17%) of the 3*S* product. Recrystallization (2×) from ethyl ether/hexanes provided an analytical sample of (3*R*)-**16**: mp 93.5–94 °C; IR ($CDCl_3$) 3070, 3040, 2960, 1735 (br), 1700, 1405, 1380, 1340, 1280, 1165, 1115, 1075, 690 cm^{-1}; ^1H NMR (80 MHz, $CDCl_3$, TMS) δ 6.85–7.40 (m, 15 H, *Ph*, 2 OCH_2Ph), 4.75–5.2 (m, 7 H), 4.4 ($(ABX)_1$, J_{BA} = 12, J_{BX} = 2.0 Hz, 1 H), 3.45 ($(ABX)_2$, J_{AB} = 16, J_{AX} = 6 Hz, 1 H), 3.15 ($(ABX)_2$, J_{BA} = 16, J_{BX} = 5 Hz, 1 H), ^{13}C NMR (75 MHz, $CDCl_3$, TMS, 67 °C) δ 169.6, 167.8, 154.8, 139.3, 135.8, 129.1, 128.6, 128.5, 128.4, 128.2, 128.0, 127.9, 125.8, 69.9, 68.0, 67.1, 54.8, 54.1, 38.7; $[\alpha]^{25}_D$ = −160.5 (CH_2Cl_2, c = 5.00). Anal. Calcd for $C_{27}H_{25}NO_6$: C, 70.58; H, 5.48. Found: C, 70.89; H, 5.61. (3*S*)-**16**: ^1H NMR (80 MHz, $CDCl_3$, TMS) δ 7.0–7.35 (m, 15 H, *Ph*, 2 OCH_2Ph), 5.2–5.4 (m, 2 H), 4.95–5.15 (m, 4 H), 4.74 (*A*BX, J_{AB} = 12, J_{AX} = 6.0 Hz, 1 H), 4.47 (A*B*X, J_{BA} = 12, J_{BX} = 5 Hz, 1 H), 2.70 (d, J = 7 Hz, $-HCCH_2CO_2-$).

This alkylation was optimally performed by employing lithium bis(trimethylsilyl)amide to preform the lithium enolate of 8 (0.305 mmol, 0.25 M in THF) at −78 °C, alkylated with neat benzyl 2-bromoacetate (82.0 mg, 0.386 mmol, 1.3 equiv), quenched after 4 h, and the unpurified products isolated in the previously described fashion. Diastereomer analysis was performed by integration of the HPLC trace (85:15 isooctane/ethyl acetate; t_R (3*R*)-**16** = 7.4 min, t_R (3*S*)-**16** = 8.0 min; UV detection, 256 nm) to afford a ratio of (3*R*)-**16**:(3*S*)-**16** = 185:1. Purification was achieved by MPLC (Merck B, 35% ethyl acetate/hexanes) to provide, in the order of elution, 90.6 mg (65%) of crystalline **16** and 17.2 mg (18%) of recovered starting material **8**.

Thermodynamic Equilibration Studies. A solution of the desired alkylation adduct (**11R**, **11S**, **12R**, **12S**, or **15R**) and 1.0 equiv of K_2CO_3 in 1:1 DMSO/*t*-BuOH (0.25 M) was heated under N_2 in a resealable tube at 110 °C. The equilibration was monitored by analytical capillary gas chromatography using the conditions specified for the diastereomer analysis of the original alkylation adduct. The equilibration was considered complete when three consecutive time points, spaced by 30 min, gave the same ratio within 10% of the previously obtained result. The equilibrium values for **11** and **12** represent convergent values obtained by approaching the equilibrium from both directions. This provided values that were within 10% of one another. On the basis of these results, the equilibrium for **15** was approached only from the major diastereomer, **15R**. The time course for reaching equilibrium was on the order of 5–6 h.

Deprotection of 9 via Intermediate 19 To Provide D-(−)-Phenylalanine Ethyl Ester Hydrochloride Salt (21). The alkylation adduct **9** (0.3852 g, 1.05 mmol) was suspended in absolute ethanol (15 mL) containing a 6–10-fold excess of dry hydrochloric acid and refluxed under a nitrogen atmosphere for 2 h. The homogeneous solution was cooled and concentrated in vacuo to afford a white crystalline material, which was dissolved in chloroform and concentrated in vacuo to dryness (2× to remove excess HCl) to afford 0.3468 g (103% mass balance) of white crystalline **19** (R_1 = CH_2Ph), which was carried on without further purification. A small portion of **19** was neutralized by refluxing in absolute ethanol containing excess propylene oxide and concentrated in vacuo to provide a ^1H NMR sample. **19**: ^1H NMR (80 MHz, $CDCl_3$, TMS) δ 7.1–7.4 (m, 10 H, *Ph*, CH_2*Ph*), 3.85 (q, *J* = 7 Hz, CH_3CH_2O), 3.35–3.70 (m, 4 H), 2.95 (br s, CHC*H*HPh), 2.85 (br d, *J* = 3 Hz, CHCH*H*Ph), 2.25 (br s, 2 H, *HO*, *H*NR_2), 1.03 (t, *J* = 7 Hz, CH_3CH_2O). Unpurified **19** (R_1 = CH_2Ph) (0.3241 g, 0.981 mmol, ~97% pure) was dissolved in 3.0 mL of absolute ethanol and transferred via syringe to a glass sleeve, equipped with a magnetic stirring bar and a septum, charged with 1 mL of absolute ethanol and palladium black (0.196 mmol, 0.2 equiv; prepared in situ by exposing $PdCl_2$ (35.0 mg, 0.196 mmol) to a hydrogen atmosphere (~15 psi)). The resulting vigorously stirred suspension was evacuated and flushed with hydrogen (3×) before exposure of the reaction mixture to a hydrogen atmosphere (~15 psi, balloon filled with H_2). The reaction was found to be complete after 24 h (alternatively, if the hydrogenolysis is done at 50 psi, the reaction is complete in 14–18 h). After thorough flushing of the vigorously stirred reaction mixture with nitrogen, the catalyst was removed by filtration through a Celite filter cake, and the filtrates were concentrated in vacuo to give a semicrystalline material. The unpurified material was dissolved in a minimum volume of water, and the resulting aqueous solution was extracted with ethyl ether (1×). The aqueous layer was drawn off, the organic layer was back-extracted with water, and the combined aqueous layers were concentrated in vacuo with the assistance of absolute ethanol (azeotropes water and decreases the amount of hydrolysis during concentration). The resulting white crystals were dissolved in ethanolic hydrogen chloride, refluxed for 1 h under nitrogen, concentrated in vacuo, and dried overnight under vacuum to afford pure **21** (0.138 g, 61%) as white crystals. Alternatively, the neutral organic materials can be removed more conveniently from the unpurified hydrogenolysis products by precipitating **21** out of a minimum volume of absolute ethanol with anhydrous ethyl ether. **21**: ^1H NMR (80 MHz, 20% DCl/D_2O, TPS) δ 7.2–7.5 (m, 5 H, *Ph*) 4.41 (d, d, *J* = 7, 7 Hz, *H*CCH_2Ph), 4.28 (q, *J* = 8 Hz, OCH_2CH_3), 3.30 (d, *J* = 7 Hz, HCCH_2Ph) 1.22 (t, *J* = 8 Hz, OCH_2CH_3).

Mosher Amide 24, Derived from D-(−)-Phenylalanine Ethyl Ester Hydrochloride Salt (21). The purified, but unfractionated **21** (60.0 mg, 261 μmol, 1.0 equiv) and (+)-MTPA chloride (70.0 μL, 392 μmol, 1.5 equiv) were dissolved in chloroform (1 mL), and triethylamine (109 μL, 784 μmol, 3.0 equiv) was added. The resulting homogeneous solution was stirred at room temperature for 0.5 h and poured into ethyl ether. The organic layer was washed successively with 10% aqueous hydrochloric acid (1×) and saturated aqueous sodium bicarbonate (1×), dried ($MgSO_4$), filtered, and concentrated in vacuo to give 101.5 mg (95% mass balance) of a yellow oil. Diastereomer analysis[25] (DB-1, 175 °C, 15 psi; t_R (2*R*)-**24** = 11.0 min, t_R (2*S*)-**24** = 11.3 min) afforded a ratio of (2*R*)-**24**:(2*S*)-**24** > 200:1. Purification was achieved by flash chromatography (12 × 2 cm, 12 g of silica, 20% ethyl acetate/hexanes), to provide 82.6 mg (77%) of a clear colorless oil, which crystallized on standing. Recrystallization (2×) from ethyl ether/hexanes provided an analytical sample: mp 79–80 °C; IR ($CDCl_3$) 3400, 2940, 1720, 1685, 1490, 1180, 1150, 1100 cm^{-1}; ^1H NMR (80 MHz, $CDCl_3$, TMS) δ 7.35 (br s, 5 H, *Ph*), 6.8–6.95 and 7.0–7.25 (br m, 5 H, *Ph*), ca. 7.0 (m, 1 H, *H*NR_2), 4.93 (d, d, d, *J* = 6, 7, 8.5 Hz, HNC*H*CH_2), 4.17 (q, *J* = 7.5 Hz, OCH_2CH_3), 3.40 (q, *J* = 1.5, $CH_3OC(CF_3)$(Ph)), 3.15 (*A*B*X*, J_{AB} = 16, J_{AX} = 6 Hz, CHC*H*HPh), 2.96 (*A*B*X*, J_{BA} = 16, J_{BX} = 7 Hz, CHCH*H*Ph), 1.25 (t, *J* = 7.5 Hz, OCH_2CH_3). Anal. Calcd for $C_{21}H_{22}F_3NO_4$: C, 61.61; H, 5.42. Found: C, 61.80; H, 5.25.

Deprotection of 13 via Intermediate 20 To Provide D-(−)-Leucine Ethyl Ester Hydrochloride Salt (22). The alkylation product **13** was converted to the title compound in analogy to the conversion of **9** to phenylalanine ethyl ester hydrochloride salt **21**. Thus **13** (0.230 g, 0.694 mmol) was converted to the hydrochloride salt **20** (R_1 = methallyl); neutralization (refluxing absolute ethanol/propylene oxide) gave a ^1H NMR sample: (80 MHz, $CDCl_3$, TMS) δ 7.3 (br s, 5 H, *Ph*), 4.85 (br m, 1 H, CH_2CCH_3CHH), 4.80 (br m, 1 H, CH_2CCH_3CHH), 3.87 (q, *J* = 7.5 Hz, OCH_2CH_3), 3.55–3.75 (m, 3 H, NC*H*Ph, HOCH_2CHPh), 3.42 (t, *J* = 8 Hz, HNC*H*CH_2), 2.37 (br d, *J* = 8 Hz, NCHCH_2), 1.75 (t, *J* = 1.0 Hz, CH_3), 1.13 (t, *J* = 7.5 Hz, OCH_2CH_3). Unpurified **20** was treated with 10% palladium on carbon (150 mg, 0.139 mmol, 0.20 equiv) in absolute ethanol under hydrogen (50 psi) to give 0.125 g (92%) of pure crystalline **22** obtained according to the previously described aqueous extraction procedure: ^1H NMR (80 MHz, 20% DCl/D_2O, TPS) δ 4.28 (q, *J* = 7.5 Hz, OCH_2CH_3), 4.15 (t, *J* = 8 Hz, NC*H*CH_2), ca. 1.8 (m, 3 H, NCHCH_2, $CHCH_2CH(CH_3)_2$), 1.3 (t, *J* = 7.5 Hz, OCH_2CH_3), 0.95 (br d, *J* = 6 Hz, $CH(CH_3)_2$).

Mosher Amide 25 Derived from D-(−)-Leucine Ethyl Ester Hydrochloride Salt (22). The amino acid derivative **22** (35.0 mg, 0.179 mmol, 1.0 equiv) and (+)-MTPA chloride (64.0 μL, 0.358 mmol, 2.0 equiv) were dissolved in chloroform (~1 mL) and cooled to 0 °C, and triethylamine (75.0 μL, 0.537 mmol, 3.0 equiv) was added. The unpurified product was isolated as previously described. Diastereomer[25] analysis (DB-1, 150 °C, 15 psi; t_R (2*R*)-**25** = 7.4 min, t_R (2*S*)-**25** = 7.8 min) afforded a ratio of (2*R*)-**25**:(2*S*)-**25** > 200:1. Purification was achieved by flash chromatography (13 × 2 cm, 15 g of silica, 15% ethyl acetate/hexanes), which afforded 35.1 mg (52%) of pure **25** as a clear colorless oil. An analytical sample was obtained by concentration and vacuum drying of a center-cut fraction from the chromatography. **25**: IR ($CDCl_3$) 3420, 2950, 1730, 1690, 1500, 1265, 1180, 1160, 1105, 1095, 850 cm^{-1}; ^1H NMR (80 MHz, $CDCl_3$, TMS) δ 7.25–7.65 (m, 5 H, *Ph*), 6.90 (br d, *J* = 8.5 Hz, *H*N), 4.67 (d, d, d, *J* = 8.5, 8.5, 6 Hz, HNC*H*CH_2), 4.20 (q, *J* = 7.5 Hz, OCH_2CH_3), 3.55 (q, *J* = 1.5 Hz, $CH_3OC(CF_3)$Ph), 1.45–1.85 (m, 3 H, $CH_2CH(CH_3)_2$), 1.25 (t, *J* = 7.5 Hz, OCH_2CH_3), 0.91 (d, *J* = 7.0 Hz, $CH(CH_3)(CH_3)$), 0.86 (d, *J* = 6.0 Hz, $CH(CH_3)(CH_3)$). Anal. Calcd for $C_{18}H_{24}F_3NO_4$: C, 57.59; H, 6.44. Found: C, 57.87; H, 6.52.

Deprotection of 18 To Provide L-(+)-Phenylalanine Ethyl Ester Hydrochloride Salt (23). To a 5-mL, two-necked, round-bottomed flask, fitted with a magnetic stir bar and two septa, charged with Pd^0 (2–3 mg, ~0.05 equiv, formed in situ by

(25) Authentic mixtures of the (+)- and (−)-Mosher amide derivatives were prepared to unambiguously determine peak retention times.

(26) $R_F = \sum||F_o| - (F_c/k)|/\sum F_o$, $q^2 = 0.020$, $R_w = (\sum w\Delta^2/\sum wF_o^4)^{1/2}$ and $S = [\sum w\Delta^2/(n-v)]^{1/2}$, $\Delta = F_o^2 - (F_c/k)^2$, $w^{-1} = (s + r^2b + q^2I^2)k^4/(Lp)^2$, $I = s - rb$, $F_o = k(I/Lp)^{1/2}$, $k = 0.2247$ (17).

Table VI. Crystal and Intensity Collection Data for 9R[a]

space group	$P2_1$
a	10.6565 (11) Å
b	10.0957 (14) Å
c	9.4967 (11) Å
β	97.747 (13) Å
V	1012.4 (2) Å^3
Z	2
D_{calcd}	1.21 g/cm^{-3}
reflection settings	$\pm h,+k,\pm l$
scan width	1.2° above Kα_1, 1.2° below Kα_2
2θ range	4–30°, 29–55°
scan rate	2.02°/min, 0.99°/min
bkgd time/scan time	0.5, 0.3
no. of reflections	941, 4418
total no. of averaged data	2467

[a] All but six of the heavy atoms were indicated from a MULTAN run, using the set of phases with the highest combined figure-of-merit, and the Fourier map phases on this set of atoms revealed the remainder of the structure. The H atoms were located from difference maps. Least-squares refinement of the structure, nonhydrogen atoms with anisotropic U_{ij}'s, hydrogen atoms with isotropic B's, a scale factor, and isotropic secondary extinction, minimizing $\sum w[F_o^2 - (F_c/k)^2]^2$,[26] on all the data (2467 reflections), led to $S = 1.396$, $R_w = 0.0687$, and $R_F = 0.0569$ (invertomer: $S = 1.399$, $R_w = 0.0689$); final cycle, shift/errors <0.3, maximum deviations found in the $\Delta\rho$ map are about 0.3 e Å^{-3}. All calculations were carried out on a VAX 11/780 computer using the CRYRM system of programs.

exposure of the corresponding amount of $PdCl_2$ to a hydrogen atmosphere until the red salt was converted to a black clumpy suspension), were added 18 (86.9 mg, 243 μmol, 1.0 equiv) in absolute ethanol (1.5 mL) and 90 μL (1.5 equiv) of a 4.2 M solution of hydrogen chloride in absolute ethanol. This led to the immediate precipitation of the HCl salt of **18**. Freshly prepared palladium black (~7 mg, 490 μmol, 0.15 equiv) was transferred in absolute ethanol via pipet and the resulting suspension evacuated and flushed with hydrogen (3×) before exposure of the reaction mixture to a hydrogen atmosphere (~15 psi, balloon of H_2). The reaction mixture was heated at 80 °C until reaction was judged complete by TLC (1–4 h, depending on the run; sometimes it was necessary to add more catalyst to drive the reaction to completion). Following the previously described aqueous extraction isolation procedure for the D-(−)-phenylalanine series, 44.7 mg (80%) of crystalline **23** was isolated.

Mosher Amide 26 Derived from L-(+)-Phenylalanine Ethyl Ester Hydrochloride Salt (23). Following the procedure for the conversion of **21** to **24**, **23** (15 mg, 65.3 μmol) was reacted with (+)-MTPA-Cl (17.5 μL, 97.9 μmol, 1.5 equiv) and triethylamine (27.3 μL, 195.9 μmol, 3.0 equiv) in chloroform (0.5 mL). Processing of the reaction mixture as previously described provided 25.4 mg (95% mass balance) of the unpurified title compound. Diastereomer analysis was carried out as described for **24** to afford a ratio of (2*R*)-**26**:(2*S*)-**26** = 1:18.

X-ray Structure Determination. Single crystals of **9R** ($C_{22}H_{25}NO_4$; $M_r = 367.45$; 0.30 × 0.21 × 0.51 mm) were obtained from acetone/hexanes at 0 °C as colorless crystals. A series of oscillation and Weissenberg photographs indicated monoclinic symmetry and the space group $P2_1$ ($0k0$ absent for k odd); data were collected on a locally modified Syntex $P2_1$ diffractometer with graphite monochromator and Mo $K\alpha$ radiation (λ 0.71069 Å). The unit cell parameters (Table VI) were obtained by least-squares refinement of the average 2θ values of 26 reflections ($\pm 2\theta$, $21° < 2\theta < 38°$). The three check reflections indicated no decomposition, and the data were produced to F_o^2; the form factors were from the *International Tables for X-Ray Crystallography* (1974), including f' and f'' for C, N, and O. The details of data collection are included in Table VI.

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Registry No. **1a**, 121269-45-2; **5**, 56613-80-0; **6**, 620-72-4; **7**, 119878-90-9; **8**, 121269-46-3; (3*R*)-**9**, 121269-47-4; (3*R*)-**9**·TFA (N-deprotected), 121348-85-4; (3*S*)-**9**, 121348-75-2; (3*R*)-**10**, 121269-48-5; (3*S*)-**10**, 121348-76-3; (3*R*)-**11**, 121269-49-6; (3*S*)-**11**, 121348-77-4; (3*R*)-**12**, 121269-50-9; (3*S*)-**12**, 121348-78-5; (3*R*)-**13**, 121269-51-0; (3*S*)-**13**, 121348-79-6; (3*R*)-**14**, 121269-52-1; (3*S*)-**14**, 121348-80-9; (3*R*)-**15**, 121269-53-2; (3*S*)-**15**, 121348-81-0; (3*R*)-**16**, 121269-54-3; (3*S*)-**16**, 121348-82-1; **17**, 121269-55-4; (3*R*)-**18**, 121348-83-2; (3*S*)-**18**, 121269-56-5; **19**, 121269-57-6; **20**, 121269-58-7; **21**, 63060-94-6; **22**, 73913-65-2; **23**, 3182-93-2; **24**, 121269-59-8; **25**, 121269-60-1; **26**, 121269-61-2; (+)-MTPA-Cl, 20445-33-4; $BrCH_2COBr$, 598-21-0; $ClCO_2CH_2Ph$, 501-53-1; $PhCH_2Br$, 100-39-0; MeI, 74-88-4; $H_2C{=}C(CH_2)CH_2I$, 3756-30-7; $BrCH_2CH{=}CH_2$, 106-95-6; *n*-BuI, 542-69-8; $BrCH_2CO_2CH_2Ph$, 5437-45-6.

Supplementary Material Available: Atom coordinates and Gaussian amplitudes (Table i) and bond lengths and bond angles (Figure i) for the X-ray structure determination on **9R** (2 pages). Ordering information is given on any current masthead page.