7, and 8 all form the same sulfurane oxide, 10. The demethylation transition state of 7 provides stabilization by having electrons donated to the antibonding O-S-O orbital, as the equatorial oxygen becomes more negatively charged as the CH_3 moves to pyridine from 7, via 16a. There is only a small (4.3) methylation rate increase for sulfurane oxide 6 relative to sulfurane 5 because the oxygen of 6 does not become much more negative as the CH_3 leaves, although the sulfur becomes less positive as the S-C bond is broken.

Acknowledgment. The research was partially funded by a joint U.S./Japan Award 8613516. More research funds for the Martin group were from NSF 8910896, and for the Akiba group from JSPS.

Asymmetric Synthesis of Monosubstituted and α,α-Disubstituted α-Amino Acids via Diastereoselective Glycine Enolate Alkylations

Robert M. Williams* and Myeong-Nyeo Im

Contribution from the Department of Chemistry, Colorado State University, Fort Collins, Colorado 80523. *Received May 13, 1991*

Abstract: The enolates derived from the optically active (5*S*,6*R*)- and (5*R*,6*S*)-4(*tert*-butyloxycarbonyl)-5,6-diphenyl-2,3,5,6-tetrahydro-4*H*-1,4-oxazin-2-one (**1a,b**) and (5*S*,6*R*)- and (5*R*,6*S*)-4-(benzyloxycarbonyl)-5,6-diphenyl-2,3,5,6-tetrahydro-4*H*-1,4-oxazin-2-ones (**2a,b**) efficiently couple with alkyl halides to afford the corresponding anti-α-monosubstituted oxazinones (**3** and **4**). The enolate alkylation of the α-monosubstituted oxazinones (**3** and **4**) provides the corresponding α,α-disubstituted oxazinones (**7** and **8**). Dissolving-metal reduction of the homologated oxazinones allows the direct preparation of *t*-BOC-protected α-amino acids. In the case of a dissolving-metal-reducible functionality, hydrogenation over a Pd^0 catalyst furnishes the zwitterionic amino acids. By employing this protocol several amino acids or their corresponding *N*-*t*-BOC derivatives, such as allylglycine, alanine, phenylalanine, β-ethylaspartic acid, α-methylphenylalanine, *N*-(*tert*-butyloxycarbonyl)dimethallylglycine, *N*-(*tert*-butyloxycarbonyl)-2-(2′-propenyl)norvaline, *N*-(*tert*-butyloxycarbonyl)-2-(3′-methyl-2′-butenyl)alanine, *N*-(*tert*-butyloxycarbonyl)-2-(2′-propenyl)alanine, 2-(3′-phenylpropyl)alanine, 2-amino-6-(acetyloxy)hexanoic acid, and 2-(*tert*-butyloxycarbonyl)amino-6-[(*p*-methoxybenzyl)thio]hexanoic acid, are prepared in high enantiomeric excess.

Introduction

Nonproteinogenic, unnatural α-amino acids have increasingly attracted the attention of numerous disciplines in connection with the design and synthesis of enzyme inhibitors as potential constituents of pharmaceuticals, as optically active starting materials for a variety of synthetic applications, and for the study of enzymatic reaction mechanisms. As a consequence, numerous and versatile approaches to the synthesis of nonproteinogenic, natural and unnatural amino acids in optically active form have been reported in the past decade; several reviews have recently appeared on this subject.[1-3]

The established methods for the asymmetric synthesis of amino acids can be divided into roughly six categories:[1] (1) highly stereoselective hydrogenation of chiral, nonracemic dehydroamino acid derivatives or asymmetric hydrogenation of prochiral dehydroamino acid derivatives. Chiral glycine equivalents serve as useful α-amino acid templates undergoing homologation via carbon-carbon bond formation at the α-position through nucleophilic carbanion alkylation (2) or electrophilic carbocation substitution (3). In addition, both nucleophilic amination (4) and electrophilic amination (5) of optically active carbonyl derivatives have very recently been developed. (6) Enzymatic and whole cell-based syntheses have recently become more attractive in terms of substrate versatility, cost, and scale. All of these methods have their relative strengths and weaknesses; the optimum method for each individual application must still be considered on a case-by-case basis with respect to functionality, quantity desired, cost, and time.

We have previously reported on the utility of the diphenyloxazinones (**1** and **2**) as versatile templates from which both electrophilic[4] and nucleophilic[5a,6] C-C bond-forming strategies can be employed to access a variety of nonproteinogenic α-amino acids.[7] In this report, we detail our studies on the glycine enolate alkylations[5] of these systems for accessing a variety of α-monosubstituted and α,α-disubstituted α-amino acids. The α,α-disubstituted α-amino acids are particularly significant in that they

(1) For reviews, see: (a) Barrett, G. C. Ed. *Chemistry and Biochemistry of the Amino Acids*; Chapman and Hall: London, 1985. (b) Wagner, I.; Musso, H. *Angew. Chem., Int. Ed. Engl.* **1983**, *22*, 816. (c) Greenstein, J. P.; Winitz, M. *Chemistry of the Amino Acids*; Robert E. Krieger: Malabar, FL, 1984; Vols. 1-3. (d) Williams, R. M. *Synthesis of Optically Active α-Amino Acids*; Pergamon Press: Oxford, 1989; Vol. 7. And also, see: (e) O'Donnell, Martin J., Ed. *α-Amino Acid Synthesis. Tetrahedron* **1988**, *44*, 5253.

(2) (a) Herbert, R. A. *The Biosynthesis of Secondary Metabolites*; Chapman and Hall: London, 1981. (b) Izumi, Y.; Chibata, I.; Itoh, T. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 176.

(3) (a) Coppola, G. M.; Schuster, H. F. *Asymmetric Synthesis: Construction of Chiral Molecules Using Amino Acids*; Wiley-Interscience: New York, 1987. (b) Martens, J. *Top. Curr. Chem.* **1984**, *125*, 165. (c) Valentine, D.; Scott, J. W. *Synthesis* **1978**, 329. (d) Drauz, K.; Kleeman, A.; Martens, J. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 584.

(4) (a) Sinclair, P. J.; Zhai, D.; Reibenspies, J.; Williams, R. M. *J. Am. Chem. Soc.* **1986**, *108*, 1103. (b) Williams, R. M.; Sinclair, P. J.; Zhai, D.; Chen, D. *J. Am. Chem. Soc.* **1988**, *110*, 1547. (c) Sinclair, P. J. Ph.D. Thesis, Colorado State University, Fort Collins, CO, 1987. (d) Williams, R. M.; Zhai, D.; Sinclair, P. J. *J. Org. Chem.* **1986**, *51*, 5021. (e) Williams, R. M.; Sinclair, P. J.; Zhai, W. *J. Am. Chem. Soc.* **1988**, *110*, 482. (f) Williams, R. M.; Zhai, W. *Tetrahedron* **1988**, *44*, 5425. (g) Zhai, D.; Zhai, W.; Williams, R. M. *J. Am. Chem. Soc.* **1988**, *110*, 2501. (h) Williams, R. M.; Hendrix, J. A. *J. Org. Chem.* **1990**, *55*, 3723.

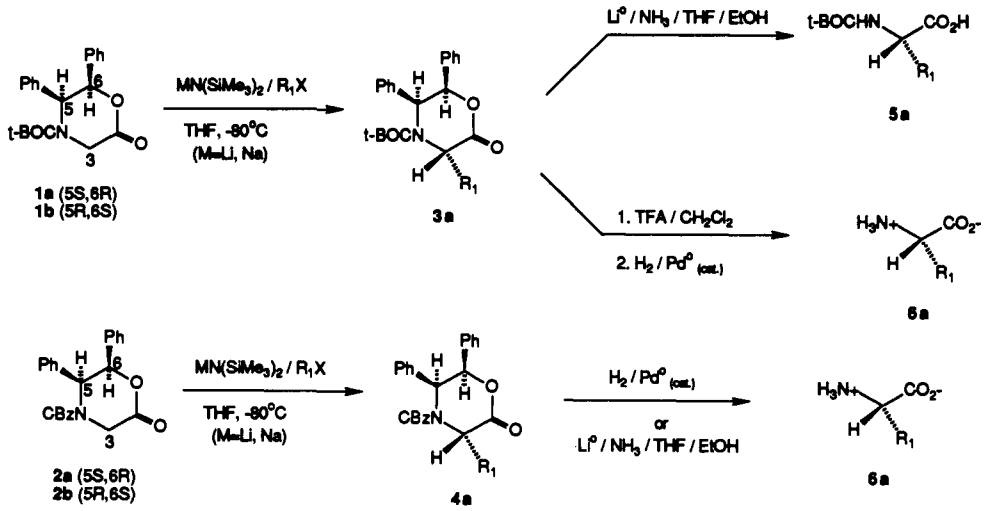
(5) (a) Williams, R. M.; Im, M.-N. *Tetrahedron Lett.* **1988**, *29*, 6075. For related oxazinone enolate alkylations on a phenylglycinol-derived substrate, see: (b) Dellaria, J. F.; Santarsiero, B. D. *Tetrahedron Lett.* **1988**, *29*, 6079. (c) Dellaria, J. F.; Santarsiero, B. D. *J. Org. Chem.* **1989**, *54*, 3916. (d) Ornstein, P. L. *J. Org. Chem.* **1989**, *54*, 2251.

(6) Reno, D. S.; Lotz, B. T.; Miller, M. J. *Tetrahedron Lett.* **1990**, *31*, 827.

(7) Lactones **1** and **2** are commercially available from Aldrich Chemical Co.: **1a**, catalog no. 33-181-3; **1b**, catalog no. 33,184-8; **2a**, catalog no. 33-185-6; **2b**, catalog no. 33,187-2.

0002-7863/91/1513-9276$02.50/0

Scheme I



are generally more difficult to prepare by any of the known methods[1] with structurally diverse side chain functionality. These amino acids have attracted increasing interest as conformationally restrictive amino acid surrogates, which also impart desirable protease resistance in synthetic peptides of biological interest. α,α-Disubstituted amino acids[8] have become of significant medicinal and biochemical interest as they are powerful enzyme inhibitors (e.g., for dopa,[9] ornithine, glutamate, (*S*)-adenosylmethionine (SAM) decarboxylases,[10] and aspartate aminotransferase).[11] These substances have also found utility as conformational modifiers for physiologically active peptides.[12] Many excellent methods exist for the synthesis of simple α,α-disubstituted amino acids in optically active form.[1] The most commonly encountered methods employ glycine enolate dialkylation, and the most common substitution is the α-methylated derivative of the proteinogenic amino acids. In general, it is very difficult to prepare α-disubstituted α-amino acids where both α-substituents are derived from nonactivated electrophiles or are branched at the β-position. A notable exception is the diastereoselective alkylation of monosubstituted optically active imidazolidinones with ethyl iodide and isopropyl iodide, reported by Seebach,[8m,n,o] and the earlier related imidazolinones reported by Schollkopf.[8u] Moreover, preparation of N-acylated-α,α-disubstituted α-amino acids by standard acylating conditions from the free zwitterions for peptide coupling is also often difficult due to the attenuation of the nucleophilicity of the amine group resulting from steric encumbrance. The strength of the methodology to be described below lies in the capacity to directly access the *N*-*t*-BOC derivatives of these hindered substances.

Results and Discussion

A. α-Monosubstituted α-Amino Acids. We have recently described in a preliminary account[5a] the stereoselective enolate alkylations of **1** and **2**, resulting in the monoalkylated oxazinones **3** and **4** (Scheme I). Generation of the enolate with lithium or sodium hexamethyldisilylamide for 30–40 min in THF at low temperature followed by addition of an alkyl halide results in the formation of highly diastereoselective (typically >99% de) crystalline trans-alkylation products **3** and **4**. This protocol is effective for alkylations with activated alkyl halides, such as benzylic bromides, allyl halides, and methyl iodide. With unactivated alkyl halides, such as *n*-propyl iodide, unreacted starting material or substantial decomposition was observed under the same conditions. Raising the reaction temperature or admixing good solvating agents, such as HMPA, promoted decomposition of the enolate as evidenced by the lower recovery of starting material. In the case of the activated alkylating agents, we observed significant amounts of the disubstituted products (**7** or **8** where $R_1 = R_2$) if more than 1 equiv of base was employed. If the reaction conditions are not carefully controlled as described below, the dialkylated products could be detected along with unreacted starting material, even when 1 molar equiv of base was employed as in the case of dimethallyl, allyl, and benzyl alkylations. A simple and reliable protocol that obviates these problems involves the addition of lithium or sodium hexamethyldisilylamide to a −80 °C THF solution of the oxazinone *containing* the alkylating agent. In this way, high chemical yields of the monoalkylation products can be obtained with very high diastereoselectivities and little or no contaminating dialkylated material. For the unactivated alkyl halides, addition of HMPA (THF/HMPA, 10:1) significantly improves the chemical yields. We have examined a variety of bases and found that either lithium or sodium hexamethyldisilylamide gives the best results; in no case have we been able to obtain satisfactory alkylation results with LDA or other strong bases (*n*-BuLi, *t*-BuLi, NaH). In addition, potassium hexamethyldisilylamide seems to be too reactive for the monoalkylations, giving decomposition and disubstituted alkylation products. The results of these alkylation reactions are collected in Table I.

To explain the significantly different outcomes between these protocols, it is reasonable to assume that, when the enolate is preformed and the electrophile is added at a subsequent time, the

(8) For some noteworthy syntheses of α,α-disubstituted α-amino acids, see: (a) Schollkopf, U.; Scheuer, R. *Liebigs Ann. Chem.* **1984**, 939. (b) Groth, U.; Schollkopf, U.; Chiang, Y-C. *Synthesis* **1982**, 864. (c) Schollkopf, Y.; Bardenhagen, J. *Liebigs Ann. Chem.* **1987**, 393. (d) Schollkopf, U.; Schroder, J. *Liebigs Ann. Chem.* **1988**, 87. (e) Schollkopf, U.; Westphalen, K.-O.; Schroder, J.; Horn, K. *Liebigs Ann. Chem.* **1988**, 781. (f) Schollkopf, U.; Hinrichs, R.; Lonsky, R. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 143. (g) Schollkopf, U.; Tolle, R.; Egert, E.; Nieger, M. *Liebigs Ann. Chem.* **1987**, 399. (h) Gander-Coquoz, M.; Seebach, D. *Helv. Chim. Acta* **1988**, *71*, 224. (i) Fadel, A.; Salaun, J. *Tetrahedron Lett.* **1987**, *28*, 2243. (j) Karady, S.; Amato, J. S.; Weinstock, L. M. *Tetrahedron Lett.* **1984**, *25*, 4337. (k) Weber, T.; Aeschimann, R.; Maetzke, T.; Seebach, D. *Helv. Chim. Acta* **1986**, *69*, 1365. (l) Seebach, D.; Juaristi, E.; Miller, D. D.; Schickli, C.; Weber, T. *Helv. Chim. Acta* **1987**, *70*, 237. (m) Aebi, J. D.; Seebach, D. *Helv. Chim. Acta* **1985**, *68*, 1507. (n) Calderari, G.; Seebach, D. *Helv. Chim. Acta* **1985**, *68*, 1592. (o) Seebach, D.; Aebi, J. D.; Naef, R.; Weber, T. *Helv. Chim. Acta* **1985**, *68*, 144. (p) Kruizinga, W. H.; Bolster, J.; Kellogg, R. M.; Kamphius, J.; Boesten, W. H. J.; Meijer, E. M.; Schoemaker, H. *J. Org. Chem.* **1988**, *53*, 1826. (q) Lalonde, J. J.; Bergbreiter, D. E.; Wong, C.-H. *J. Org. Chem.* **1988**, *53*, 2323. (r) Seebach, D.; Burger, H. M.; Schickli, C. P. *Liebigs Ann. Chem.* **1991**, 669. (s) Seebach, D.; Vettiger, T.; Muller, H.-M.; Plattner, D. A.; Petter, W. *Liebigs Ann. Chem.* **1990**, 687. (t) Ojima, I.; Komata, T.; Qiu, X. *J. Am. Chem. Soc.* **1990**, *112*, 770. See also ref 1d. (u) Schollkopf, U.; Hausberg, H. H.; Hoppe, I.; Segal, M.; Reiter, U. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 117.

(9) (a) Saari, W. S.; Freedman, M. B.; Hartman, R. D.; King, S. W.; Raab, A. W.; Randall, W. C.; Engelhardt, E. L.; Hirschmann, R.; Rosegay, A.; Ludden, C. T.; Scriabine, A. *J. Med. Chem.* **1978**, *21*, 746. (b) Saari, W. S.; Halczenko, W.; Cochran, D. W.; Dobrinska, M. R.; Vincek, W. C.; Titus, D. G.; Gaul, S. L.; Sweet, C. S. *Ibid.* **1984**, *27*, 713.

(10) Ramalingam, K.; Woodard, R. W. *Tetrahedron Lett.* **1985**, *26*, 1135.

(11) Walsh, J. J.; Metzler, D. E.; Powell, D.; Jacobson, R. A. *J. Am. Chem. Soc.* **1980**, *102*, 7136.

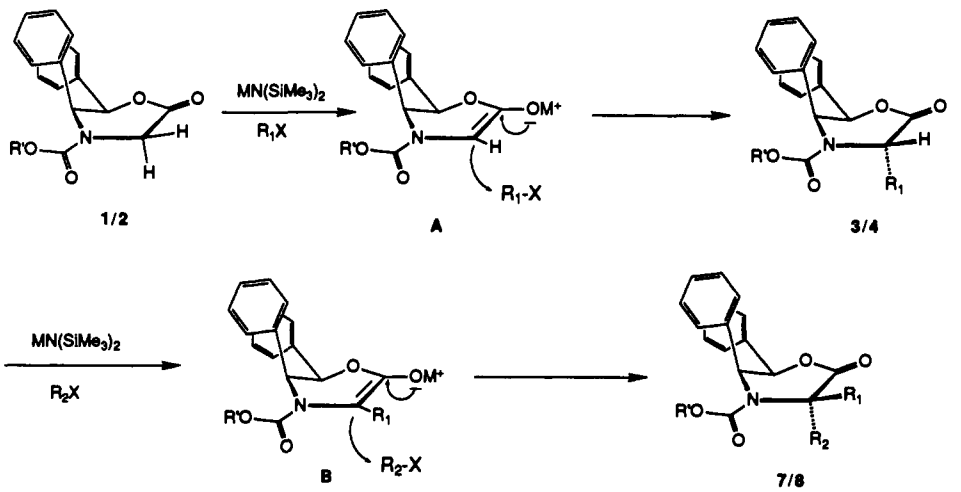
(12) Paul, P. K. C.; Sukumar, M.; Bardi, R.; Piazzesi, A. M.; Valle, G.; Toniolo, C.; Balaram, P. *J. Am. Chem. Soc.* **1986**, *108*, 6363 and references cited therein.

Table I. Enolate Alkylations of Oxazinones **1** and **2**

entry	oxazinone substrate	**3** or **4** yield, %	RX	method[c]	base (equiv)	amino acid yield, %	% ee
1	**1a**	20	CH_2=$CHCH_2Br$	A	$LiN(SiMe_3)_2$ (1)		
2	**1a**	71 (12)[b]	CH_2=$CHCH_2Br$	A	$LiN(SiMe_3)_2$ (2)		
3	**1a**	48 (21)[a]	CH_2=$CHCH_2Br$	A	$NaN(SiMe_3)_2$ (1)		
4	**1a**	86 (5)[a]	CH_2=$CHCH_2I$	B	$LiN(SiMe_3)_2$ (1.2)	50–70	98
5	**2a**	82	CH_2=$CHCH_2I$	B	$LiN(SiMe_3)_2$ (1.2)		
6	**1a**	91	CH_3I	A	$NaN(SiMe_3)_2$ (1.1)	54	97
7	**2a**	88	CH_3I	B	$NaN(SiMe_3)_2$ (1.5)		
8	**1a**	70 (9)[a]	$PhCH_2Br$	A	$NaN(SiMe_3)_2$ (1)	76	98
9	**2b**	77 (6)[b]	$PhCH_2Br$	B	$NaN(SiMe_3)_2$ (1.2)	93	>99
10	**1a**	68 (20)[a]	Me_2C=$CHCH_2Br$	A	$NaN(SiMe_3)_2$ (1)		
11	**1a**	84 (2)[b]	Me_2C=$CHCH_2Br$	B	$NaN(SiMe_3)_2$ (1.1)	52	>99
12	**1a**	64	$BrCH_2CO_3Et$	A	$NaN(SiMe_3)_2$ (1.1)		
13	**1b**	61 (20)[a]	$BrCH_2CO_2Et$	A	$NaN(SiMe_3)_2$ (1)	71	96
14	**1a**	0	n-C_3H_7I	A	$NaN(SiMe_3)_2$ (1.2)		
15	**1a**	77 (12)[b]	n-C_3H_7I	B	$NaN(SiMe_3)_2$ (1.5)		
16	**2a**	76 (3)[a]	n-C_3H_7I	B	$NaN(SiMe_3)_2$ (1.5)		
17	**2a**	79	$I(CH_2)_4I$	B	$LiN(SiMe_3)_2$ (1.5)		
18	**2b**	61	$I(CH_2)_4I$	B	$LiN(SiMe_3)_2$ (1.5)		
19	**2b**	47	ICH_2CH_2CH=CH_2	B	$LiN(SiMe_3)_2$ (1.8)		
20	**1b**	72	$I(CH_2)_3Cl$	B	$LiN(SiMe_3)_2$ (1.5)		
21	**1b**	86	$I(CH_2)_3I$	B	$LiN(SiMe_3)_2$ (1.5)		

[a] Number in parentheses denotes recovered starting material. [b] Number in parentheses denotes dialkylated product. [c] Method A involves addition of the base to the oxazinone at −80 °C followed by addition of the electrophile; method B involves addition of the base to a −80 °C mixture of the oxazinone containing the electrophile.

Scheme II



enolate species has the opportunity to form aggregated complexes.[13] Alkylation would then occur from the aggregation sphere. The fact that more dialkylated products are produced under these conditions also supports the notion of aggregation phenomena, since the initially formed monoalkylation product in an aggregation complex would be held proximal to neighboring enolates; subsequent intermolecular proton transfer (but intraaggregate) between an enolate and a monoalkylation product would generate the substituted enolate, which can then undergo the second alkylation reaction. In the case of the alternate protocol employing the addition of base to a mixture of the oxazinone and the electrophile, the enolate species can competitively alkylate with resulting enolate aggregate formation and thus attenuate the opportunities for intermolecular proton transfer, resulting in dialkylated products. Furthermore, it is significant to note in this context that unactivated alkyl halides such as *n*-propyl iodide do not give any detectable alkylation products when the sequential enolization/electrophilic quenching protocol is employed. Alkylation products employing unactivated alkyl halides are formed only when the base is added to a mixture of the oxazinone and the electrophile (compare entries 14 and 15, Table I).

(13) (a) Galiano-Roth, A. S.; Collum, D. B. *J. Am. Chem. Soc.* **1989**, *111*, 6772. (b) Beak, P.; Meyers, A. I. *Acc. Chem. Res.* **1986**, *19*, 356. (c) Rawson, D. J.; Meyers, A. I. *Tetrahedron Lett.* **1991**, *32*, 2095. (d) Laube, T.; Dunitz, J. D.; Seebach, D. *Helv. Chim. Acta* **1985**, *68*, 1373.

As previously recorded,[4] the *N*-*t*-BOC lactones (**3**) can be directly converted into the corresponding *N*-*t*-BOC-α-amino acids (**5**) by dissolving-metal reduction. Alternatively, trifluoroacetic acid removal of the *t*-BOC group followed by hydrogenation over a Pd(0) catalyst furnishes the zwitterionic α-amino acids (**6**). In all cases, the % ee exceeded 95%. The *N*-carbobenzyloxy (*N*-CBz) lactone homologation products **4** can be directly hydrogenated over a palladium catalyst, providing the zwitterionic amino acids (**6**).

The diastereoselectivity of these enolate alkylations can be readily rationalized by considering the expected twist-boat conformation (A, Scheme II) that disposes the phenyl ring at C-5 of the oxazinone in a pseudoaxial orientation, creating steric shielding of the C-3 position of the same face from electrophilic attack. The anti relative stereochemistry of these alkylation products was secured for R = methyl, allyl, benzyl, and (ethoxycarbonyl)methyl by comparing the absolute configurations of the final synthetic amino acids to known amino acids. In all other cases, the relative stereochemistry was established by comparison of the $\Delta\delta$ values for the methine protons at C-5 and C-6 of the oxazinones (**3** and **4**). We have previously reported[4b] a reliable analytical paradigm for relative stereochemical assignments of the *syn*- and *anti*-oxazinones by ^{1}H NMR. The *anti*-oxazinones display a larger $\Delta\delta$ value (typically 0.9–1.1 ppm) for the methine protons than the corresponding syn isomers (typically <0.7 ppm). Thus, the *n*-propyl substrate has a $\Delta\delta$ = 1.03, and for the di-

Scheme III

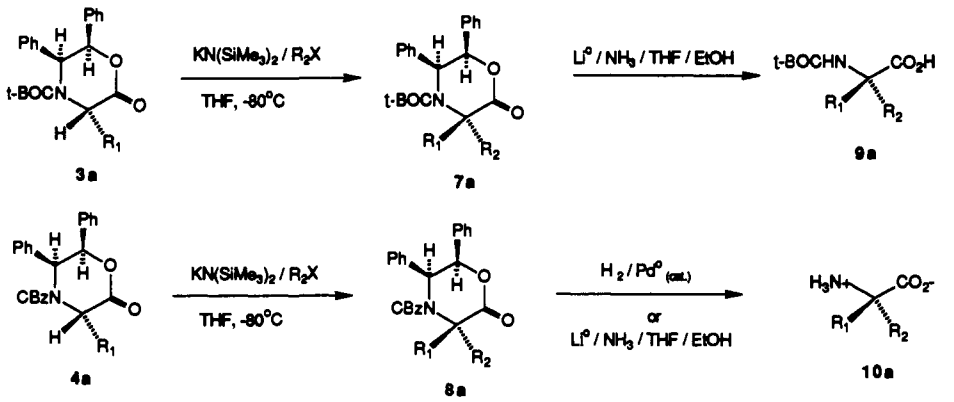


Table II. Enolate Dialkylations of Oxazinones **3** and **4**

entry[a]	oxazinone substrate	R_1	yield, %	R_2X	base (equiv)	amino acid yield, %	% ee
1	**3a**	Me	trace	CH_2=$CHCH_2I$	$NaN(SiMe_3)_2$ (2)		
2	**3a**	Me	87	CH_2=$CHCH_2I$	$KN(SiMe_3)_2$ (2)	70	100
3	**3a**	Me	80	Me_2C=$CHCH_2Br$	$KN(SiMe_3)_2$ (2)	65	100
4	**3a**	*n*-C_3H_7	90	CH_2=$CHCH_2I$	$KN(SiMe_3)_2$ (2)	60	100
5	**4a**	Me	84	$PhCH_2Br$	$KN(SiMe_3)_2$ (2)	93	100
6	**4a**	Me	80	PhCH=$CHCH_2Br$	$KN(SiMe_3)_2$ (2)	95	100
7	**4a**	*n*-C_3H_7	0	$PhCH_2Br$	$KN(SiMe_3)_2$ (2)		
8	**4a**	*n*-C_3H_7	38	$PhCH_2Br$	$KN(SiMe_3)_2$ (4)		
9	**4a**	*n*-C_3H_7	85	$PhCH_2Br$	$KN(SiMe_3)_2$ (5)		
10	**4a**	allyl	84	$PhCH_2Br$	$KN(SiMe_3)_2$ (3)		

[a] For entries 1 and 2, HMPA/THF (10:1) was used as solvent; for entries 3–10, THF was used as solvent.

methallyl system $\Delta\delta$ = 1.04. In addition, the *syn*-oxazinones tend to be oily, whereas the anti isomers tend to be crystalline. Taking both characteristics into consideration, the alkylations reported herein all proceed with very high levels of diastereoselectivity, giving the *anti*-oxazinones.

The enantiomeric excess of each amino acid was determined by acylation of the corresponding ethyl or methyl ester with either (+)- or (−)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride and then examination of the crude mixture by ^{19}F NMR and comparison with the authentic diastereomeric mixture obtained from the racemic amino acids. In each case, excellent enantiomeric excess was observed (Table I).

B. Synthesis of α,α-Disubstituted Amino Acids. We first examined the enolate alkylation of α-methyl-substituted oxazinone **3a** (R = Me) by employing method A (i.e., enolate generation followed by electrophilic quenching). Unfortunately, the homologated products **7** were not detected. Even when potassium bis(trimethylsilyl)amide and allyl iodide were used, none of the desired product **7** could be detected; only decomposition of the starting material was observed. By employing the protocol described above (method B) involving addition of the base to a mixture of oxazinone containing the electrophile, the enolate alkylations of the α-methyl-substituted oxazinones **3a** were realized, as shown in Scheme III. First, sodium bis(trimethylsilyl)amide was examined to determine whether it was reactive enough for the second alkylation. To a solution of **3a** (R = Me) and allyl iodide in THF/HMPA was added sodium bis(trimethylsilyl)amide at −78 °C. The homologated oxazinone **7a** (R_1 = Me, R_2 = allyl) was detected only in trace amounts by TLC. The same procedure was performed with use of potassium bis(trimethylsilyl)amide instead of sodium bis(trimethylsilyl)amide. After standard aqueous workup, the α-methyl-α-allyloxazinone **7a** was produced in 57% yield. This substance proved to be one diastereomer by ^1H NMR analysis. If the solvating reagent HMPA is *not* used as the cosolvent, the yield is significantly enhanced (57% to 87%). It is presumed that the employment of HMPA is not effective for the more reactive potassium enolates and only promotes decomposition.

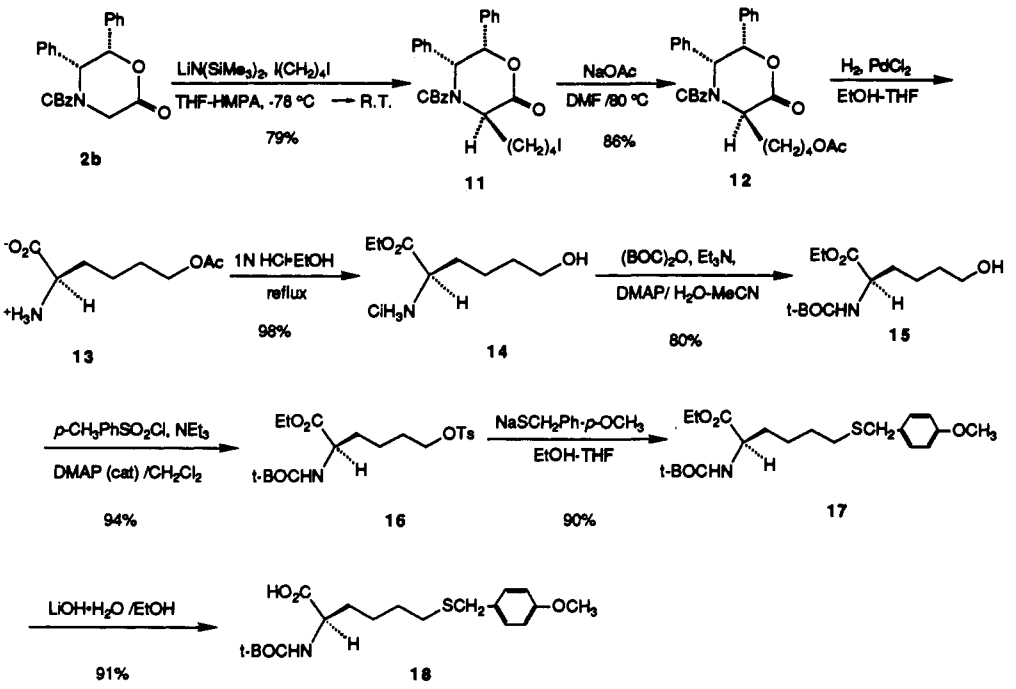
With this encouraging result, we studied a series of dialkylations. Oxazinone **3a** smoothly underwent coupling with dimethallyl bromide in the presence of potassium bis(trimethylsilyl)amide to afford the α-methyl-α-dimethallyloxazinone in 80% yield as a single diastereomer. The results of couplings with allyl iodide, dimethallyl bromide, benzyl bromide, and cinnamyl bromide are presented in Table II. In all cases, we observed the production of a single diastereomer in good-to-excellent chemical yields. The unsymmetrically disubstituted lactones **7** were smoothly converted into the *N*-*t*-BOC-protected amino acids in good yields in the same manner as that employed (Na^0/liquid ammonia) for the monosubstituted lactones **3**.

The dialkylation was also carried out on the *N*-CBz-protected methyloxazinone **4a** (R = Me). The enolate alkylation of this substrate with benzyl bromide in the presence of potassium bis(trimethylsilyl)amide proceeded smoothly to afford the homologated lactone **8a** (R_1 = Me, R_2 = benzyl) in 84% yield (~100% de). Similarly, treatment of **4a** with cinnamyl bromide provided the disubstituted lactone in 80% yield (~100% de). The homologated oxazinones **8** were directly converted into the corresponding zwitterionic amino acids **10** by catalytic hydrogenolysis. Again, high chemical yields and high optical purities were obtained (~100% ee).

Next, we decided to study the enolate alkylation of more congested oxazinones, which were expected to be more difficult to obtain. The *n*-propyloxazinone **3a** (R = *n*-propyl) underwent coupling with allyl iodide in the presence of potassium bis(trimethylsilyl)amide to afford the α-allyl-α-*n*-propyloxazinone **7a** in 90% yield. This substance was directly converted into the *N*-*t*-BOC amino acid **9a** by dissolving-metal reduction. Again, an essentially optically pure product was obtained (100% ee).

The dialkylation of these oxazinones with less reactive alkyl halides (relative to allyl iodide) was studied by employing the same protocol described above. Thus, adding 2 equiv of potassium bis(trimethylsilyl)amide to a THF solution of oxazinone **3** or **4** containing benzyl bromide or methyl iodide at −78 °C and then quenching with H_2O after 30–40 min did not furnish the desired products. In all of the cases presented above, the enolate alkylations were performed with use of 2 equiv of potassium bis(trimethylsilyl)amide. We were surprised to find that the employment of additional excess base for the dialkylation of hindered oxazinones solved this problem. Thus, the allyl lactone **4a** was

Scheme IV



alkylated efficiently with benzyl bromide in the presence of 3 equiv of potassium bis(trimethylsilyl)amide to furnish the α-allyl-α-benzyloxazinone **8a** in 84% yield (Table II, entry 10). The enolate alkylation of **4a** (R = *n*-propyl) required 5 equiv of potassium bis(trimethylsilyl)amide (compare entries 8–10, Table II).

In most of the monoalkylations studied, the dialkylated product was often obtained. Even in the case of the attempted monoalkylation of **1a** with *n*-propyl iodide, the congested α,α-di-*n*-propyloxazinone was observed in the presence of a mere 1.5 equiv of sodium bis(trimethylsilyl)amide. However, treating the isolated monoalkylated oxazinones under the same reaction conditions to induce the second alkylation failed. These paradoxical results are still quite puzzling.

The enantiomeric excess of each amino acid was determined by using the same protocol as that employed for the monosubstituted amino acids. However, formation of the methyl esters of the dialkylated amino acids did not take place in refluxing 1 N methanolic hydrochloride solution. The employment of more drastic conditions (~5 N HCl/MeOH, refluxing) led to complex reaction mixtures. A method to prepare the methyl esters of the hindered dialkylated amino acids is described in detail in the Experimental Section and involves refluxing the free amino acids (**10**) in methanolic thionyl chloride solution.

As expected, the second alkylation proceeded anti to the two phenyl rings of the oxazinone. A parallel conformational analysis to that discussed above of the incipient enolate derived from **3** and **4** can be invoked (Scheme II, enolate B). A single-crystal X-ray analysis of **8a** (where R_1 = Me and R_2 = benzyl) further corroborates this, as shown in Figure 1. The structure clearly shows that the attack of the second electrophile (in this case, benzyl bromide) on the enolate occurs from the less hindered face of the oxazinone enolate.

The methodology described herein is quite useful for the preparation of a wide variety of α,α-disubstituted amino acids with predetermined stereochemistry by employing each enantiomorphic form of the oxazinone. In the present case, final deblocking of the amino acids is readily performed under mild reductive conditions in the same way as described for the α-monosubstituted amino acids, while in most other syntheses, hydrolysis for the final deprotection requires drastic conditions or even fails. The direct method of preparation of *N*-*t*-BOC-protected disubstituted amino acids, which are in a suitable form for direct peptide coupling, is very advantageous because acylating α,α-dialkylated amino acids is difficult to achieve due to steric hindrance.

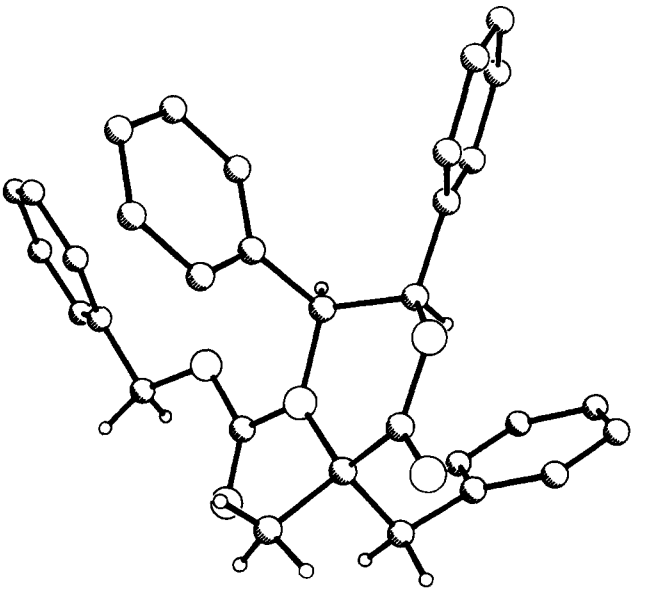


Figure 1. Molecular structure of **8a** (R_1 = Me, R_2 = benzyl). Atoms are shown as spheres of fixed, arbitrary radius.

C. Synthesis of 2-Amino-6-[(*p*-methoxybenzyl)thio]hexanoic Acid. An additional example of this methodology is illustrated with the synthesis 2-[(*tert*-butyloxycarbonyl)amino]-6-[(*p*-methoxybenzyl)thio]hexanoic acid **18** in both enantiomeric forms. This protected "extended cysteine" residue may be of potential utility for preparing stabilized helix-turn-helix peptides, a common motif in DNA-binding proteins.[14]

As shown in Scheme IV, generation of the enolate from **2b** and subsequent treatment with 1,4-diiodobutane in the presence of lithium bis(trimethylsilyl)amide furnished the homologated iodide **11** in 79% yield. The displacement of iodide by acetate in hot

(14) The use of the protected "long cysteine" in peptide synthesis was examined in Professor Peter G. Schultz's laboratory at Berkeley. Compound **18** was incorporated into several small peptides by standard carbodiimide coupling chemistry. Unfortunately, all attempts to cleave the *p*-methoxybenzyl group to release the free sulfhydryl (HF, DDQ, TFA, etc) resulted in cleavage of the nonbenzylic C–S bond. Prof. Schultz is acknowledged for suggesting the synthesis of this amino acid and for helpful discussions.

DMF afforded the acetate **12** in 86% yield. Catalytic hydrogenation over $PdCl_2$ in the standard manner gave the amino acid **13**, which was converted into the amino ester salt **14** (98%, two steps) in refluxing ethanolic HCl solution. Treatment of **14** with *tert*-butylpyrocarbonate gave the *t*-BOC ethyl ester **15**, which was subsequently treated with tosyl chloride in the presence of triethylamine and a catalytic amount of DMAP to furnish the tosylate **16** in 94% yield. In the absence of DMAP, the tosylate is produced in only 46–58% yield accompanied by a substantial amount of unreacted starting material. Nucleophilic substitution of the tosylate with *p*-methoxybenzyl thioalcohol produced the sulfide **17** (90%). This compound proved to be very unstable in silica gel and air and required immediate purification and careful handling. Finally, the ester was hydrolyzed in ethanolic lithium hydroxide solution to afford the D-amino acid **18**. The enantiomer of **18** was prepared in the same manner as the D isomer, only starting with **2a**. The enantiomeric excess of each isomer was determined by using the intermediate acetate **13** because the ester of **17** was unstable and not isolable. In the case of the L isomer, 97% ee was determined; the D isomer was obtained in >99% ee.

It is worthwhile to compare the complementary cationic and anionic reactivities of the oxazinones for constructing variously substituted α-amino acids. The amino acids alanine and allylglycine have been prepared from the electrophilic route by use of CH_3ZnCl and allyltrimethylsilane couplings, respectively.[4] In both cases, the *anti*-oxazinones are obtained. The alkylation of the enolate derived from **2a** by CH_3I and allyl iodide led to the same relative stereochemistry. However, the yield of the CH_3I alkylation (88%) is far superior to the CH_3ZnCl coupling to the α-bromo lactone (46%) due to a competing one-electron reduction pathway observed for the relatively basic organozinc reagents. In the allyl case, alkylation of the enolate derived from the lactone **1a** with allyl iodide also gave a higher yield (86%) than the allyltrimethylsilane coupling to the electrophilic system (63%). The ethyl bromoacetate alkylation also furnishes the *anti*-oxazinone as the exclusive product. The *syn*-oxazinone, however, is obtained in similar yield and % ee by coupling the ketene silyl acetal of ethyl acetate to the electrophilic system. A 45:1 ratio of syn/anti products results from S_N2 displacement of the *anti*-α-bromide derived from **2a** in this coupling. The phenylalanine manifold, which is not readily accessible from the electrophilic system, can be accessed by alkylation of the enolate with the appropriate benzylic halide. The couplings via the enolate derived from the α-monosubstituted lactones also provide access to a wide variety of α,α-disubstituted amino acids that cannot be prepared by the electrophilic route. On the other hand, it is anticipated that it would be very difficult to directly prepare the biologically important amino acids such as alkynyl-, vinyl-, cyclopropyl-, and arylglycines in optically active forms by glycine enolate coupling. The enolate alkylation with *sec*- and *tert*-alkyl halides, which are prone to hydrohalide elimination in the presence of base, is also anticipated to be very difficult via the present approach. The boron enolates of the oxazinones[6] (**1** and **2**) have been shown to undergo coupling with aldehydes (even very hindered aldehydes)[15] to provide the aldol products. The aldol condensation of these boron enolates with ketones has not been reported yet.

The potassium enolates generated from the α-monosubstituted oxazinones couple efficiently with activated alkyl bromides and iodides to furnish the corresponding α-disubstituted oxazinones. However, we have not yet been able to establish reaction conditions for the second alkylation of the enolate with unactivated alkyl halides.

The enolate approach discussed herein provides access to structurally diverse α-monosubstituted amino acids through nucleophilic carbanion alkylation in high optical purity (95–100% ee's). This approach also provides access to α,α-disubstituted amino acids in essentially optically pure forms (100% ee's). In either circumstance, the *N*-*t*-BOC derivatives or the corresponding zwitterions can be prepared. The present technology nicely complements the existing glycine enolate or glycine electrophilic couplings; efforts to continue to expand the scope of oxazinones **1** and **2** to additional structurally important classes of amino acids are being pursued in these laboratories.

(15) Williams, R. M.; Im, M.-N.; Cao, J. *J. Am. Chem. Soc.* **1991**, *113*, 6976.

Experimental Section

General Information. ^1H NMR spectra were obtained on the following instruments: a Bruker WP-200SY 200-MHz spectrometer, a Brucker WP-270SY 270-MHz spectrometer, or a Brucker AC 300-MHz spectrometer. ^{19}F NMR spectra were recorded on the Brucker WP-200 SY 200-MHz spectrometer. Chemical shifts are reported in parts per million downfield from the internal standard. Infrared spectra were recorded on a Perkin-Elmer 1600 series FTIR and are reported as λ_{max} in cm^{-1}. Melting points were determined in open-ended capillary tubes on a Mel-Temp apparatus and are uncorrected. Optical rotations were obtained on a Rudolph Research Autopol III automatic polarimeter at wavelength 589 nm (sodium D line) in a 1.0-dm cell with a total volume of 1 mL. Specific rotations, $[\alpha]_D$, are reported in degrees per decimeter at the specified temperature and the concentration (*c*) given in grams per 100 mL in the specified solvent. Elemental analyses were performed by M-H-W Laboratories, Phoenix, AZ, and are accurate to within the calculated values by ±0.4%. High-resolution mass spectra were carried out by the Midwest Center for Mass Spectrometry, Department of Chemistry, University of Nebraska—Lincoln, NE. Thin-layer chromatography (TLC) was performed on 0.25-mm E. Merck precoated silica gel glass plates. Visualization on TLC was achieved with ultraviolet light, an I_2 developing chamber, and/or heating of TLC plates submerged in a 5% solution of phosphomolybdic acid in 95% ethanol. Preparative chromatography was performed by the following methods. Column chromatography was performed with Merck silica gel, grade 60, 230–400 mesh, 60 Å. Radial chromatography was done with 1-, 2-, and 4-mm silica gel plates using E. Merck silica gel 60 PF-254 containing gypsum on a Harrison Research Chromatotron Model 7924. Reagents and solvents were commercial grades and were used as supplied with the following exceptions. Tetrahydrofuran was freshly distilled from sodium benzophenone ketyl. Dry methylene chloride and carbon tetrachloride were obtained by distillation over CaH_2. DMF and HMPA were dried over activated 4-Å molecular sieves. All moisture-sensitive reactions were carried out in glassware that was flame-dried under high vacuum (0.5–2.0 mmHg) and then purged with N_2. The term "concentrated" refers to solvent removal using a Buchi Rotavapor. The amino acids furnished crude from the hydrogenation were always obtained in greater than the theoretical yield due to a certain fraction of HCl salt resulting from the $PdCl_2$ catalyst. To ascertain the exact amount of amino acid by weight in the residue, the mixture was dissolved in D_2O with a known amount of terleucine (purity titrated against ultrapure acetamide), and ^1H NMR integration of a well-resolved resonance of the amino acid against the nine-proton singlet of terleucine was carried out, averaged, and calculated to give the adjusted chemical yields. Low-temperature reactions reported at −78 to −82 °C are the bath temperatures of the dry ice–acetone cooling bath and reflect reaction temperatures to within ±5 °C.

Determination of Optical Purity: General Procedure. The amino acids (5–10 mg) were converted into the corresponding ester hydrochloride salts as follows: All of the α-monosubstituted amino acids were refluxed for 2 h in EtOH·HCl (2 mL, 1 N) or MeOH·HCl (2 mL, 1 N). The only exception was amino acid **6** (R = dimethallyl), which is labile to harsh acidic conditions and was stirred for 3 h at ambient temperature in EtOH·HCl (2 mL, 1 N). The α,α-disubstituted zwitterionic amino acids (**10**) were refluxed for 4 h in MeOH containing excess thionyl chloride. The *N*-*t*-BOC-protected α,α-disubstituted amino acids (**9**) were refluxed for 2 h in H_2O·HCl (2 mL, 1 N), concentrated, and dried in vacuo, and then the residue was refluxed for 4 h in MeOH containing excess thionyl chloride. All of the resulting reaction mixtures were cooled, concentrated, and dried in vacuo. The amino ester hydrochloride salts were treated with (+)- or (−)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride (1.2 equiv) in THF in the presence of excess propylene oxide at 50 °C. After 1 h, the solvent was evaporated and the residue was dried in vacuo. The crude Mosher amides were analyzed by ^1H and ^{19}F NMR spectroscopy and compared to spectra of authentic diastereomeric Mosher amides prepared from the corresponding synthetic, racemic amino acids.

(3*S*,5*S*,6*R*)-4-(*tert*-Butyloxycarbonyl)-5,6-diphenyl-3-methyl-2,3,5,6-tetrahydro-4*H*-1,4-oxazin-2-one (3a, R = CH_3). To a stirred solution of **1a** (500 mg, 1.416 mmol, 1 equiv) in THF (10 mL) was added sodium bis(trimethylsilyl)amide (1500 μL, 1.5 mmol, 1.06 equiv, 1 M solution in THF) dropwise via syringe at −82 °C. After 35 min, methyl iodide (900 μL, 14.46 mmol, 10.2 equiv) was added to the reaction mixture. The resulting solution was stirred for an additional 1.5 h at −82 °C and poured into water. The aqueous layer was extracted three times with ethyl acetate. The combined organic extracts were dried over an-

hydrous magnesium sulfate, filtered, concentrated, and separated by radial chromatography on silica gel (eluted with EtOAc/hexanes, 1:2) to afford 475 mg (91%) of **3a** as a white solid: ^{1}H NMR (200 MHz, DMSO-d_6, 393 K, vs TMS) δ 1.19 (9 H, s), 1.71 (3 H, d, J = 6.99 Hz), 4.88 (1 H, q, J = 7.12 Hz), 5.15 (1 H, d, J = 2.81 Hz), 6.18 (1 H, d, J = 2.87 Hz), 6.54 (2 H, m), 7.03–7.29 (8 H, m); IR (NaCl, CH_2Cl_2) 1752, 1702 cm^{-1}; mp 204–206 °C; $[\alpha]^{25}_D$ −61° (c 0.2, CH_2Cl_2). Anal. (recrystallized from Et_2O/hexanes) Calcd for $C_{22}H_{25}NO_4$: C, 71.93; H, 6.81; N, 3.81. Found: C, 71.89; H, 6.92; N, 3.76.

(*S*)-*N*-(*tert*-Butyloxycarbonyl)alanine (5a, R = CH_3). To a solution of Li^0 (14.5 mg, 2.084 mmol, 15 equiv) in liquid ammonia (20 mL, distilled from Na^0) was added a solution of **3a** (R = CH_3) (51 mg, 0.139 mmol, 1 equiv) and ethanol (150 μL) in THF (3 mL) at −33 °C. After 1 h, the reaction mixture was quenched with excess ammonium chloride. The reaction mixture was allowed to warm. After the ammonia was evaporated off, the residue was diluted with water. The aqueous layer was extracted two times with ether and acidified to pH 3 with 1 N HCl. After that the aqueous layer was extracted three times with ethyl acetate. The combined organic extracts were dried over anhydrous magnesium sulfate, filtered, concentrated, and separated by PTLC on silica gel (eluted with 5% MeOH in CH_2Cl_2) to afford 14 mg (54%) of **5a** as a white solid (>97% ee): ^{1}H NMR (200 MHz, DMSO-d_6, vs TMS) δ 1.21 (3 H, d, J = 7.34 Hz), 1.37 (9 H, s), 3.91 (1 H, m), 7.10 (1 H, d, D_2O exch, J = 7.60 Hz); IR (NaCl, $CDCl_3$) 3710, 1725, 1708 cm^{-1}; mp 81–82 °C; $[\alpha]^{25}_D$ −15.5° (c 2.75, CH_2Cl_2).

(3*S*,5*S*,6*R*)-4-(*tert*-Butyloxycarbonyl)-5,6-diphenyl-3-(2′-propenyl)-2,3,5,6-tetrahydro-4*H*-1,4-oxazin-2-one (3a, R = CH_2CH=CH_2). To a stirred solution of **1a** (300 mg, 0.849 mmol, 1 equiv) and allyl iodide (388 μL, 4.243 mmol, 5 equiv) in THF (5 mL) was added lithium bis(trimethylsilyl)amide (1019 μL, 1.019 mmol, 1.2 equiv, 1 M solution in THF) dropwise via syringe at −78 °C. After 40 min, the reaction mixture was poured into ethyl acetate. The organic layer was washed with water and brine, dried over anhydrous magnesium sulfate, filtered, concentrated, and separated by column chromatography on silica gel (eluted with EtOAc/hexanes, 2:5) to afford 286 mg (85%) of **3a** as a white solid and 15.7 mg (5%) of unreacted **1a**: ^{1}H NMR (200 MHz, DMSO-d_6, 393 K, vs TMS) δ 1.29 (9 H, s), 2.82–2.92 (2 H, m), 4.88 (1 H, t, J = 7.00 Hz), 5.16–5.30 (3 H, m), 5.84–6.05 (1 H, m), 6.18 (1 H, d, J = 3.07 Hz), 6.55–6.59 (2 H, m), 7.03–7.27 (8 H, m); IR (NaCl, CH_2Cl_2) 1755, 1690 cm^{-1}; mp 169–171 °C; $[\alpha]^{25}_D$ −48° (c 0.1, CH_2Cl_2).

(*S*)-*N*-(*tert*-Butyloxycarbonyl)allylglycine (5a, R = CH_2CH=CH_2). To a solution of Li^0 (14 mg, 2.017 mmol, 12 equiv) in liquid ammonia (20 mL, distilled from Na^0) was added a solution of **3a** (R = CH_2CH=CH_2) (66 mg, 0.168 mmol, 1 equiv) and ethanol (120 μL) in THF (3 mL) at −33 °C. After 10 min the blue color dissipated, and the reaction mixture was quenched with excess ammonium chloride. The reaction mixture was allowed to warm. After the ammonia was evaporated off, the residue was diluted with water. The aqueous layer was extracted two times with ether and acidified to pH 2 with 1 N HCl. After that the aqueous layer was extracted three times with ethyl acetate. The combined organic extracts were dried over anhydrous magnesium sulfate, filtered, concentrated, and separated by PTLC on silica gel (eluted with 5% MeOH in CH_2Cl_2) to afford 18 mg (50%) of **5a** as a colorless oil (98% ee): ^{1}H NMR (200 MHz, DMSO-d_6, vs TMS) δ 1.37 (9 H, s), 2.27–2.46 (2 H, m), 3.85–3.97 (1 H, m), 5.01–5.14 (2 H, m), 5.67–5.87 (1 H, m), 7.01 (1 H, d, D_2O exch, J = 8.04 Hz); IR (NaCl, $CDCl_3$) 3430, 3050, 1715 cm^{-1}; $[\alpha]^{25}_D$ −3.9° (c 1, CH_2Cl_2).

(3*S*,5*S*,6*R*)-4-(*tert*-Butyloxycarbonyl)-5,6-diphenyl-3-(3′-methyl-2′-butenyl)-2,3,5,6-tetrahydro-4*H*-1,4-oxazin-2-one (3a, R = CH_2CH=CMe_2). To a stirred solution of **1a** (300 mg, 0.849 mmol, 1 equiv) and 1-bromo-3-methyl-2-butene (493 μL, 4.241 mmol, 5 equiv) in THF (5 mL) was added sodium bis(trimethylsilyl)amide (934 μL, 0.934 mmol, 1.1 equiv, 1 M solution in THF) dropwise via syringe at −78 °C. After 30 min the dry ice bath was removed, and the reaction mixture was stirred for an additional 30 min. The reaction mixture was poured into ethyl acetate. The organic layer was washed with water and brine, dried over anhydrous magnesium sulfate, filtered, concentrated, and separated by column chromatography on silica gel (eluted with EtOAc/hexanes, 1:2) to afford 302 mg (84%) of **3a** as a white solid and 9.3 mg (2%) of dialkylated lactone as a colorless oil: ^{1}H NMR (200 MHz, DMSO-d_6, 393 K, vs TMS) δ 1.18 (9 H, s), 1.68 (3 H, s), 1.74 (3 H, s), 2.73–3.01 (2 H, m), 4.82 (1 H, dd, J = 7.79 Hz, J = 5.64 Hz), 5.12 (1 H, d, J = 2.75 Hz), 5.30 (1 H, t, J = 7.62 Hz), 6.16 (1 H, d, J = 3.11 Hz), 6.56 (2 H, m), 7.01–7.28 (8 H, m); IR (KBr, disc) 1734, 1692 cm^{-1}; mp 150–151 °C; $[\alpha]^{25}_D$ −19.5° (c 0.57, CH_2Cl_2). Anal. (recrystallized from Et_2O/hexanes) Calcd for $C_{26}H_{31}NO_4$: C, 74.11; H, 7.36; N, 3.33. Found: C, 74.24; H, 7.32; N, 3.28.

(*S*)-*N*-(*tert*-Butyloxycarbonyl)dimethallylglycine (5a, R = CH_2CH=CMe_2). To a solution of Li^0 (47 mg, 6.77 mmol, 13 equiv) in liquid ammonia (30 mL, distilled from Na^0) was added a solution of **3a** (R = CH_2CH=CMe_2) (220 mg, 0.52 mmol, 1 equiv) and ethanol (300 μL) in THF (5 mL) at −33 °C. After 1 h the reaction mixture was quenched with excess ammonium chloride. The reaction mixture was allowed to warm. After the ammonia was evaporated off, the residue was diluted with water. The aqueous layer was extracted two times with ether and acidified to pH 3 with 1 N HCl. After that the aqueous layer was extracted three times with ethyl acetate. The combined organic extracts were dried over anhydrous magnesium sulfate, filtered, concentrated, and separated by PTLC on silica gel (eluted with 5% MeOH in CH_2CL_2) to afford 66 mg (52%) of **5a** as a colorless oil (100% ee): ^{1}H NMR (200 MHz, DMSO-d_6, vs TMS) δ 1.37 (9 H, s), 1.57 (3 H, s), 1.65 (3 H, s), 2.19–2.39 (2 H, m), 3.77–3.91 (1 H, m), 5.08 (1 H, t, J = 6.79 Hz), 6.95 (1 H, d, D_2O exch, J = 8.07 Hz); IR (NaCl, $CDCl_3$) 3340, 1728, 1700 (sh) cm^{-1}; $[\alpha]^{25}_D$ +8.6° (c 0.67, CH_2Cl_2). Anal. Calcd for $C_{12}H_{21}NO_4$: C, 59.26; H, 8.64; N, 5.76. Found: C, 59.07; H, 8.64; N, 5.62.

(3*S*,5*S*,6*R*)-4-(*tert*-Butyloxycarbonyl)-5,6-diphenyl-3-(phenylmethyl)-2,3,5,6-tetrahydro-4*H*-1,4-oxazin-2-one (3a, R = CH_2Ph). To a stirred solution of **1a** (500 mg, 1.416 mmol, 1 equiv) in THF (10 mL) was added sodium bis(trimethylsilyl)amide (1420 μL, 1.42 mmol, 1 equiv, 1 M solution in THF) dropwise via syringe at −82 °C. After 40 min, benzyl bromide (170 μL, 1.43 mmol, 1 equiv) was added to the reaction mixture. The resulting solution was stirred additional 1.5 h at −82 °C and poured into water. The aqueous layer was extracted three times with ethyl acetate. The combined organic extracts were dried over anhydrous magnesium sulfate, filtered, concentrated, and separated by radial chromatography on silica gel (eluted with EtOAc/hexanes, 1:3) to afford 441 mg (70%) of **3a** as a white solid and 46 mg (9%) of unreacted **1a**: ^{1}H NMR (200 MHz, DMSO-d_6, 393 K, vs TMS) δ 1.19 (9 H, s), 3.35 (1 H, dd, J = 13.84 Hz, J = 4.67 Hz), 3.48 (1 H, dd, J = 13.80 Hz, J = 7.82 Hz), 5.03 (1 H, d, J = 2.97 Hz), 5.10 (1 H, dd, J = 4.91 Hz, J = 4.55 Hz), 5.44 (1 H, d, J = 2.51 Hz), 6.53 (2 H, m), 6.81–6.89 (2 H, m), 7.07–7.39 (11 H, m); IR (NaCl, CH_2Cl_2) 1754, 1697 cm^{-1}; mp 147–149 °C; $[\alpha]^{25}_D$ +49° (c 0.2, CH_2Cl_2). Anal. (recrystallized from Et_2O/hexanes) Calcd for $C_{28}H_{29}NO_4$: C, 75.85; H, 6.55; N, 3.16. Found: C, 75.76; H, 6.67; N, 3.05.

(*S*)-Phenylalanine (6a, R = CH_2Ph). To a stirred solution of **3a** (R = CH_2Ph) (104 mg, 0.235 mmol, 1 equiv) in CH_2Cl_2 (2 mL) was added trifluoroacetic acid (200 μL, 2.596 mmol, 11 equiv). After 4 h, the reaction mixture was neutralized with excess triethylamine, concentrated, and separated by PTLC on silica gel (eluted with 5% MeOH in CH_2Cl_2) to afford 65 mg (80%) of (3*S*,5*S*,6*R*)-5,6-diphenyl-3-(phenylmethyl)-2,3,5,6-tetrahydro-4*H*-1,4-oxazin-2-one as a white solid: ^{1}H NMR (270 MHz, $CDCl_3$, vs TMS) δ 2.01 (1 H, s, D_2O exch), 3.26–3.38 (2 H, m), 4.26 (1 H, dd, J = 8.56 Hz, J = 4.79 Hz), 4.61 (1 H, d, J = 3.64 Hz), 5.58 (1 H, d, J = 3.63 Hz), 6.80–6.89 (4 H, m), 7.11–7.30 (11 H, m); IR (NaCl, CH_2Cl_2) 3328, 1732 cm^{-1}. This material was used without further purification for the subsequent hydrogenation. To a solution of the *t*-BOC-deprotected lactone obtained above (67 mg, 0.195 mmol, 1 equiv) in THF and EtOH (2 mL, 1:1) was added palladium chloride (24 mg, 0.135 mmol, 0.7 equiv). The reaction mixture was hydrogenated at 42 psi for 29 h. The mixture was then purged with nitrogen, filtered through Celite to remove the catalyst, concentrated, and triturated with Et_2O to yield 33 mg (102%) of **6a** as a white solid (98% ee; adjusted chemical yield 76%): ^{1}H NMR (200 MHz, D_2O, vs HOD) δ 3.02 (1 H, dd, J = 14.92 Hz, J = 7.73 Hz), 3.20 (1 H, dd, J = 15.49 Hz, J = 5.54 Hz), 4.05 (1 H, dd, J = 7.31 Hz, J = 5.45 Hz), 7.28–7.34 (5 H, m).

(3*S*,5*S*,6*R*)-4-(*tert*-Butyloxycarbonyl)-5,6-diphenyl-3-[(ethoxycarbonyl)methyl]-2,3,5,6-tetrahydro-4*H*-1,4-oxazin-2-one (3a, R = CH_2CO_2Et). To a stirred solution of **1a** (500 mg, 1.416 mmol, 1 equiv) in THF (10 mL) was added sodium bis(trimethylsilyl)amide (1420 μL, 1.42 mmol, 1 equiv, 1 M solution in THF) dropwise via syringe at −82 °C. After 40 min, ethyl bromoacetate (190 μL, 1.713 mmol, 1.2 equiv) was added to the reaction mixture. The resulting solution was stirred for an additional 2 h at −82 °C and poured into water. The aqueous layer was extracted three times with ethyl acetate. The combined organic extracts were dried over anhydrous magnesium sulfate, filtered, concentrated, and separated by radial chromatography on silica gel to afford 396 mg (64%) of **3a** as a white solid: ^{1}H NMR (200 MHz, DMSO-d_6, 393 K, vs TMS) δ 1.18 (9 H, s), 1.22 (3 H, t, J = 6.96 Hz), 3.12–3.19 (2 H, m), 4.16 (2 H, q, J = 7.14 Hz), 5.12 (1 H, d, J = 2.96 Hz), 5.20 (1 H, t, J = 6.73 Hz), 6.20 (1 H, d, J = 3.03 Hz), 6.59 (2 H, m), 7.00–7.28 (8 H, m); IR (NaCl, CH_2Cl_2) 1749, 1739, 1706 cm^{-1}; mp 126–128 °C; $[\alpha]^{25}_D$ −16.3° (c 0.26, CH_2Cl_2). Anal. (recrystallized from Et_2O/hexanes) Calcd for $C_{25}H_{29}NO_6$: C, 68.34; H, 6.61; N, 3.19. Found: C, 68.07; H, 6.49; N, 3.08.

(3*S*,5*S*,6*R*)-4-(*tert*-Butyloxycarbonyl)-5,6-diphenyl-3-propyl-2,3,5,6-tetrahydro-4*H*-1,4-oxazin-2-one (3a, R = *n*-C_3H_7). To a stirred solution of **1a** (500 mg, 1.416 mmol, 1 equiv) and *n*-propyl iodide (1380 μL, 14.15 mmol, 10 equiv) in THF (7 mL) and HMPA (0.7 mL) was added sodium bis(trimethylsilyl)amide (2123 μL, 2.123 mmol, 1.5 equiv, 1 M

solution in THF) dropwise via syringe at −78 °C. After 40 min, the reaction mixture was poured into ethyl acetate. The organic layer was washed with water and brine, dried over anhydrous magnesium sulfate, filtered, concentrated, and separated by column chromatography on silica gel (eluted with CH_2Cl_2/hexanes, 2:1) to afford 429 mg (77%) of **3a** as a white solid and 76 mg (12%) of dialkylated lactone as colorless oil: ^{1}H NMR (200 MHz, DMSO-d_6, 393 K, vs TMS) δ 1.00 (3 H, t, J = 7.28 Hz), 1.12 (9 H, s), 1.45–1.61 (2 H, m), 2.09–2.14 (2 H, m), 4.79 (1 H, t, J = 7.18 Hz), 5.14 (1 H, d, J = 2.64 Hz), 6.17 (1 H, d, J = 3.10 Hz), 6.53–6.59 (2 H, m), 7.02–7.27 (8 H, m); IR (NaCl, CH_2Cl_2) 1749, 1702 cm^{-1}; mp 182–183 °C; $[\alpha]^{25}_D$ −68.8° (c 0.56, CH_2Cl_2). Anal. (recrystallized from CH_2Cl_2/hexanes) Calcd for $C_{24}H_{29}NO_4$: C, 72.88; H, 7.39; N, 3.54. Found: C, 72.68; H, 7.38; N, 3.59.

(3*R*,5*R*,6*S*)-4-(Benzyloxycarbonyl)-5,6-diphenyl-3-(3′-butenyl)-2,3,5,6-tetrahydro-4*H*-1,4-oxazin-2-one (4b, R$_1$ = $CH_2CH_2CH{=}CH_2$). To a stirred solution of **2b** (3 g, 7.744 mmol, 1 equiv) and 4-iodobutene (4.2 mL, 39.35 mmol, 5.1 equiv) in warm THF (90 mL) and HMPA (9 mL) was added lithium bis(trimethylsilyl)amide (13.9 mL, 13.9 mmol, 1.8 equiv, 1 M solution in THF) dropwise via syringe at −78 °C. After 10 min the dry ice bath was removed. After 1 more h, the reaction mixture was poured into ethyl acetate. The organic layer was washed with water and brine, dried over anhydrous magnesium sulfate, filtered, concentrated, and separated by column chromatography on silica gel (eluted with EtOAc/hexanes, 1:2) to afford 1.59 g (46.5%) of **4b** as a white solid. The antipode was obtained from **2a** in 48.5% yield. Data: ^{1}H NMR (200 MHz, DMSO-d_6, 393 K, vs TMS) δ 2.18–2.31 (4 H, m), 4.81–5.16 (5 H, m), 5.27 (1 H, d, J = 2.93 Hz), 5.77–5.95 (1 H, m), 6.22 (1 H, d, J = 3.02 Hz), 6.54–6.59 (2 H, m), 7.02–7.24 (13 H, m); IR (NaCl, CH_2Cl_2) 1747, 1704 cm^{-1}; mp 146–147 °C; $[\alpha]^{25}_D$ +44.1° (c 0.49, CH_2Cl_2), antipode −45.2° (c 0.42, CH_2Cl_2). Anal. (recrystallized from CH_2Cl_2/hexanes) Calcd for $C_{28}H_{27}NO_4$: C, 76.17; H, 6.17; N, 3.17. Found: C, 76.07; H, 6.36; N, 3.20.

(3*R*,5*R*,6*S*)-4-(Benzyloxycarbonyl)-5,6-diphenyl-3-[(ethoxycarbonyl)methyl]-2,3,5,6-tetrahydro-4*H*-1,4-oxazin-2-one (4b, R = CH_2CO_2Et). To a stirred solution of **2b** (500 mg, 1.29 mmol, 1 equiv) in THF (20 mL) was added sodium bis(trimethylsilyl)amide (1420 μL, 1.42 mmol, 1.1 equiv, 1 M solution in THF) dropwise via syringe at −82 °C. After 40 min, ethyl bromoacetate (190 μL, 1.71 mmol, 1.3 equiv) was added to the reaction mixture. The resulting solution was stirred for 1 more h at −82 °C and then poured into water. The aqueous layer was extracted three times with ethyl acetate. The combined organic extracts were dried over anhydrous magnesium sulfate, filtered, concentrated, and separated by radial chromatography on silica gel (eluted with EtOAc/hexanes, 1:2) to afford 373 mg (61%) of **4b** as a white solid and 102 mg (20%) of unreacted **2b**: ^{1}H NMR (200 MHz, DMSO-d_6, 393 K, vs TMS) δ 1.24 (3 H, t, J = 7.05 Hz), 3.19 (2 H, dd, J = 3.71 Hz, J = 2.34 Hz), 4.15 (2 H, q, J = 7.07 Hz), 4.95 (1 H, $^1/_2$ AB q, J = 13.52 Hz), 5.04 (1 H, $^1/_2$ AB q, J = 13.56 Hz), 5.20–5.29 (2 H, m), 6.22 (1 H, d, J = 3.07 Hz), 6.56–6.63 (2 H, m), 6.98–7.27 (13 H, m); IR (NaCl, CH_2Cl_2) 1745, 1736, 1707 cm^{-1}; mp 150–151 °C; $[\alpha]^{25}_D$ −2.6° (c 0.5, CH_2Cl_2). Anal. (recrystallized from Et_2O/hexanes) Calcd for $C_{28}H_{27}NO_6$: C, 71.04; H, 5.71; N, 2.96. Found: C, 70.92; H, 5.71; N, 2.96.

(*R*)-β-Ethylaspartic Acid (6b, R = CH_2CO_2Et). To a solution of **4b** (R = CH_2CO_2Et) (135 mg, 0.28 mmol, 1 equiv) in THF and EtOH (1.5 mL, 1:2) was added palladium chloride (35 mg, 0.20 mmol, 0.7 equiv). The reaction mixture was hydrogenated at 50 psi for 24 h. The mixture was then purged with nitrogen, filtered through Celite to remove the catalyst, concentrated, and triturated with Et_2O to yield 48 mg (104%) of **6b** as a white solid (96% ee; adjusted chemical yield 71%): ^{1}H NMR (270 MHz, D_2O, vs HOD) δ 1.10 (3 H, t, J = 7.12 Hz), 2.93 (2 H, d, J = 5.43 Hz), 4.05 (2 H, q, J = 7.07 Hz), 4.24 (1 H, t, J = 5.67 Hz); IR (KBr, disc) 2989, 1740, 1715 cm^{-1}.

(*R*)-Diethyl Aspartate Hydrochloride. **6b** (R = CH_2CO_2Et) was dissolved in 1 N HCl·EtOH. The resulting solution was brought to reflux. After 2 h the solvent was evaporated off, and the residue was triturated with Et_2O to yield (*R*)-diethyl aspartate hydrochloride as a white solid: ^{1}H NMR (200 MHz, D_2O, vs HOD) δ 1.08–1.15 (6 H, m), 2.93 (1 H, dd, J = 16.89 Hz, J = 4.83 Hz), 3.07 (1 H, dd, J = 17.81 Hz, J = 5.82 Hz), 4.05 (2 H, q, J = 7.16 Hz), 4.14 (2 H, q, J = 7.17 Hz), 4.31 (1 H, t, J = 5.82 Hz); $[\alpha]^{25}_D$ −7.4° (c 0.7, H_2O) (lit. $[\alpha]^{25}_D$ L-diethyl aspartate hydrochloride +7.6° (c 1, H_2O)).

(3*R*,5*R*,6*S*)-4-(Benzyloxycarbonyl)-5,6-diphenyl-3-(phenylmethyl)-2,3,5,6-tetrahydro-4*H*-1,4-oxazin-2-one (4b, R = CH_2Ph). To a stirred solution of **2b** (300 mg, 0.774 mmol, 1 equiv) and benzyl bromide (276 μL, 2.32 mmol, 1.2 equiv) in THF (20 mL) was added sodium bis(trimethylsilyl)amide (929 μL, 0.929 mmol, 1.2 equiv, 1 M solution in THF) dropwise via syringe at −78 °C. After 40 min, the reaction mixture was poured into ethyl acetate. The organic layer was washed with water and brine, dried over anhydrous magnesium sulfate, filtered, concentrated, and separated by column chromatography on silica gel (eluted with EtOAc/hexanes, 1:2) to afford 286 mg (77%) of **4b** as a white solid and 29 mg (6%) of dialkylated product as a colorless oil: ^{1}H NMR (200 MHz, DMSO-d_6, 393 K, vs TMS) δ 3.37 (1 H, dd, J = 13.81 Hz, J = 4.31 Hz), 3.51 (1 H, dd, J = 13.74 Hz, J = 8.01 Hz), 5.03 (2 H, s), 5.12 (1 H, dd, J = 8.08 Hz, J = 4.40 Hz), 5.16 (1 H, d, J = 3.22 Hz), 5.46 (1 H, d, J = 1.24 Hz), 6.54–6.58 (2 H, m), 6.82–6.88 (2 H, m), 6.99–7.35 (16 H, m); IR (NaCl, CH_2Cl_2) 1753, 1706 cm^{-1}; mp 183–184 °C; $[\alpha]^{25}_D$ −62.8° (c 1, CH_2Cl_2). Anal. (recrystallized from CH_2Cl_2/hexanes) Calcd for $C_{31}H_{27}NO_4$: C, 77.96; H, 5.70; N, 2.93. Found: C, 78.12; H, 5.70; N, 2.95.

(*R*)-Phenylalanine (6b, R = CH_2Ph). To a solution of **4b** (R = CH_2Ph) (140 mg, 0.293 mmol, 1 equiv) in THF and EtOH (1.5 mL, 1:2) was added palladium chloride (15.6 mg, 0.088 mmol, 0.3 equiv). The reaction mixture was hydrogenated at 50 psi for 20 h. The mixture was then purged with nitrogen, filtered through Celite to remove the catalyst, concentrated, and triturated with Et_2O to yield 52 mg (107%) of **6b** as a white solid (>99% ee; adjusted chemical yield 93%): ^{1}H NMR (200 MHz, D_2O, vs HOD) δ 3.01 (1 H, dd, J = 14.53 Hz, J = 7.76 Hz), 3.18 (1 H, dd, J = 14.47 Hz, J = 5.38 Hz), 4.03 (1 H, dd, J = 7.27 Hz, J = 5.86 Hz), 7.12–7.28 (5 H, m).

(*R*)-Phenylalanine Ethyl Ester Hydrochloride. **6b** (R = CH_2Ph) was dissolved in 1 N HCl·EtOH. The resulting solution was brought to reflux. After 2 h the solvent was evaporated off, and the residue was triturated with Et_2O to yield (*R*)-phenylalanine ethyl ester hydrochloride as a white solid: ^{1}H NMR (270 MHz, D_2O, vs HOD) δ 1.09 (3 H, t, J = 6.85 Hz), 3.08 (1 H, dd, J = 17.02 Hz, J = 7.63 Hz), 3.19 (1 H, dd, J = 16.26 Hz, J = 6.94 Hz), 4.12 (2 H, q, J = 7.19 Hz), 4.23 (1 H, dd, J = 7.26 Hz, J = 6.18 Hz), 7.08–7.29 (5 H, m); IR (ZnS, MeOH), 2934, 1743 cm^{-1}; mp 153–154 °C (lit. mp L-phenylalanine ethyl ester hydrochloride 155–156 °C); $[\alpha]^{25}_D$ −32.3° (c 0.7 EtOH) (lit. $[\alpha]^{25}_D$ L-phenylalanine ethyl ester hydrochloride +33.2° (c 5, EtOH)).

(3*S*,5*S*,6*R*)-4-(Benzyloxycarbonyl)-5,6-diphenyl-3-methyl-2,3,5,6-tetrahydro-4*H*-1,4-oxazin-2-one (4a, R = CH_3). To a stirred solution of **2a** (2 g, 5.162 mmol, 1 equiv) and methyl iodide (3.21 mL, 51.56 mmol, 10 equiv) in THF (90 mL) was added sodium bis(trimethylsilyl)amide (7.74 mL, 7.74 mmol, 1.5 equiv, 1 M solution in THF) dropwise via syringe at −78 °C. After 30 min, the reaction mixture was poured into ethyl acetate. The organic layer was washed with water and brine, dried over anhydrous magnesium sulfate, filtered, concentrated, and separated by column chromatography on silica gel (eluted with EtOAc/hexanes, 1:5) to afford 1.83 g (88%) of **4a** as a white solid: ^{1}H NMR (200 MHz, DMSO-d_6, 393 K, vs TMS) δ 1.74 (3 H, d, J = 7.02 Hz), 4.92 (1 H, q, J = 7.21 Hz), 4.95 (1 H, $^1/_2$ AB q, J = 12.78 Hz), 5.08 (1 H, $^1/_2$ AB q, J = 12.69 Hz), 5.27 (1 H, d, J = 2.98 Hz), 6.23 (1 H, d, J = 3.03 Hz), 6.57 (2 H, d, J = 3.03 Hz), 7.03–7.28 (13 H, m); IR (NaCl, CH_2Cl_2) 1757, 1702 cm^{-1}; mp 186–187 °C; $[\alpha]^{25}_D$ −49.8° (c 1, CH_2Cl_2).

(3*S*,5*S*,6*R*)-4-(Benzyloxycarbonyl)-5,6-diphenyl-3-propyl-2,3,5,6-tetrahydro-4*H*-1,4-oxazin-2-one (4a, R = *n*-C_3H_7). To a stirred solution of **2a** (300 mg, 0.774 mmol, 1 equiv) and *n*-propyl iodide (755 μL, 7.74 mmol, 10 equiv) in THF (16 mL) and HMPA (1.6 mL) was added sodium bis(trimethylsilyl)amide (1161 μL, 1.161 mmol, 1.5 equiv, 1 M solution in THF) dropwise via syringe at −78 °C. After 40 min, the reaction mixture was poured into ethyl acetate. The organic layer was washed with water and brine, dried over anhydrous magnesium sulfate, filtered, concentrated, and separated by column chromatography on silica gel (eluted with EtOAc/hexanes, 1:2) to afford 253 mg (76%) of **4a** as a white solid and 8 mg (3%) of unreacted **2a**: ^{1}H NMR (200 MHz, DMSO-d_6, 393 K, vs TMS) δ 0.96 (3 H, t, J = 7.24 Hz), 1.40–1.62 (2 H, m), 2.03–2.18 (2 H, m), 4.82 (1 H, t, J = 7.22 Hz), 4.93 (1 H, $^1/_2$ AB q, J = 12.40 Hz), 5.03 (1 H, $^1/_2$ AB q, J = 12.40 Hz), 5.26 (1 H, d, J = 3.06 Hz), 6.21 (1 H, d, J = 3.07 Hz), 6.56 (2 H, d, J = 6.96 Hz), 7.02–7.28 (13 H, m); IR (NaCl, CH_2Cl_2) 1754, 1702 cm^{-1}; mp 141–142 °C; $[\alpha]^{25}_D$ −50.1° (c 1, CH_2Cl_2). Anal. (recrystallized from CH_2Cl_2/hexanes) Calcd for $C_{27}H_{27}NO_4$: C, 75.50; H, 6.34; N, 3.26. Found: C, 75.56; H, 6.27; N, 3.38.

(3*S*,5*S*,6*R*)-4-(*tert*-Butyloxycarbonyl)-5,6-diphenyl-3-methyl-3-(2′-propenyl)-2,3,5,6-tetrahydro-4*H*-1,4-oxazin-2-one (7a, R$_1$ = CH_3, R$_2$ = $CH_2CH{=}CH_2$). To a stirred solution of **3a** (R$_1$ = CH_3) (500 mg, 1.361 mmol, 1 equiv) and allyl iodide (373 μL, 4.079 mmol, 3 equiv) in THF (6 mL) was added potassium bis(trimethylsilyl)amide (1944 μL, 2.722 mmol, 2 equiv, 1.4 M solution in THF) dropwise via syringe at −78 °C. After 30 min, the reaction mixture was poured into ether acetate. The organic layer was washed with water and brine, dried over anhydrous magnesium sulfate, filtered, concentrated, and separated by column chromatography on silica gel (eluted with EtOAc/hexanes, 1:2) to afford 481 mg (87%) of **7a** as a white solid: ^{1}H NMR (200 MHz, DMSO-d_6, 393 K, vs TMS) δ 1.41 (9 H, s), 1.72 (3 H, s), 2.86 (1 H, dd, J = 13.92 Hz, J = 7.83 Hz), 3.32 (1 H, dd, J = 13.94 Hz, J = 7.31 Hz), 5.14–5.22

(2 H, m), 5.50 (1 H, d, J = 3.23 Hz), 5.78–5.99 (1 H, m), 6.14 (1 H, d, J = 3.32 Hz), 6.89–6.95 (2 H, m), 7.13–7.25 (8 H, m); IR (NaCl, CH_2Cl_2) 1746, 1700 cm^{-1}; mp 83–84 °C; $[\alpha]^{25}_D$ +46.5° (c 1, CH_2Cl_2). Anal. Calcd for $C_{25}H_{29}NO_4$: C, 73.68; H, 7.17; N, 3.44. Found: C, 73.55; H, 7.07; N, 3.45.

(*S*)-*N*-(*tert*-Butyloxycarbonyl)-2-(2′-propenyl)alanine (9a, R_1 = CH_3, R_2 = $CH_2CH{=}CH_2$). To a solution of Na^0 (169 mg, 7.35 mmol, 15 equiv) in liquid ammonia (50 mL, distilled from Na^0) was added a solution of **7a** (R_1 = CH_3, R_2 = $CH_2CH{=}CH_2$) (200 mg, 0.49 mmol, 1 equiv) and ethanol (300 μL) in THF (5 mL) via syringe at −33 °C. After 30 min, the reaction mixture was quenched with excess ammonium chloride and then allowed to warm. After the ammonia was evaporated off, the residue was diluted with water. The aqueous layer was extracted two times with ether and acidified to pH 2 with 1 N HCl. After that the aqueous layer was extracted three times with ethyl acetate. The combined organic extracts were dried over anhydrous magnesium sulfate, filtered, concentrated, and separated by PTLC on silica gel (eluted with 5% MeOH in CH_2Cl_2) to afford 79 mg (70%) of **9a** as a colorless oil (100% ee): ^1H NMR (200 MHz, DMSO-d_6, vs TMS) δ 1.25 (3 H, s), 1.37 (9 H, s), 2.36 (1 H, dd, J = 13.73 Hz, J = 7.64 Hz), 2.59 (1 H, dd, J = 13.56 Hz, J = 7.11 Hz), 4.99–5.11 (2 H, m), 5.59–5.80 (1 H, m), 6.88 (1 H, br s, D_2O exch); IR (NaCl, $CDCl_3$) 1715, 1694, 1651, 1500 cm^{-1}; $[\alpha]^{25}_D$ −13.6° (c 1.1, CH_2Cl_2). Anal. Calcd for $C_{11}H_{19}NO_4$: C, 57.62; H, 8.36; N, 6.11. Found: C, 57.88; H, 8.29; N, 6.06.

(3*S*,5*S*,6*R*)-4-(*tert*-Butyloxycarbonyl)-5,6-diphenyl-3-methyl-3-(3′-methyl-2′-butenyl)-2,3,5,6-tetrahydro-4*H*-1,4-oxazin-2-one (7a, R_1 = CH_3, R_2 = $CH_2CH{=}CMe_2$). To a stirred solution of **3a** (R_1 = CH_3) (500 mg, 1.361 mmol, 1 equiv) and 1-bromo-3-methyl-2-butene (791 μL, 6.804 mmol, 5 equiv) in THF (6 mL) was added potassium bis(trimethylsilyl)amide (1944 μL, 2.722 mmol, 2 equiv, 1.4 M solution in THF) dropwise via syringe at −78 °C. After 30 min, the reaction mixture was poured into ethyl acetate. The organic layer was washed with water and brine, dried over anhydrous magnesium sulfate, filtered, concentrated, and separated by column chromatography on silica gel (eluted with CH_2Cl_2/hexanes, 2:1) to afford 475 mg (80%) of **7a** as a white solid: ^1H NMR (200 MHz, DMSO-d_6, 393 K, vs TMS) δ 1.39 (9 H, s), 1.65 (3 H, s), 1.74 (3 H, s), 1.75 (3 H, s), 2.81 (1 H, dd, J = 13.46 Hz, J = 8.32 Hz), 3.27 (1 H, dd, J = 14.29 Hz, J = 7.50 Hz), 5.24 (1 H, t, J = 7.99 Hz), 5.44 (1 H, d, J = 3.17 Hz), 6.08 (1 H, d, J = 3.24 Hz), 6.87–6.92 (2 H, m), 7.10–7.25 (8 H, m); IR (NaCl, CH_2Cl_2) 1746, 1702 cm^{-1}; mp 139–140 °C; $[\alpha]^{25}_D$ +55.1° (c 0.9, CH_2Cl_2). Anal. (recrystallized from CH_2Cl_2/hexanes) Calcd for $C_{27}H_{33}NO_4$: C, 74.45; H, 7.64; N, 3.22. Found: C, 74.52; H, 7.78; N, 3.40.

(*S*)-*N*-(*tert*-Butyloxycarbonyl)-2-(3′-methyl-2′-butenyl)alanine (9a, R_1 = CH_3, R_2 = $CH_2CH{=}CMe_2$). To a solution of Na^0 (69 mg, 3.001 mmol, 13 equiv) in liquid ammonia (25 mL, distilled from Na^0) was added a solution of **7a** (R_1 = CH_3, R_2 = $CH_2CH{=}CMe_2$) (100 mg, 0.230 mmol, 1 equiv) and ethanol (200 μL) in THF (3 mL) via syringe at −33 °C. After 10 min, the reaction mixture was quenched with excess ammonium chloride and then allowed to warm. After the ammonia was evaporated off, the residue was diluted with water. The aqueous layer was extracted two times with ether and acidified to pH 2 with 1 N HCl. After that the aqueous layer was extracted three times with ethyl acetate. The combined organic extracts were dried over anhydrous magnesium sulfate, filtered, concentrated, and separated by PTLC on silica gel (eluted with 5% MeOH in CH_2Cl_2) to afford 38 mg (65%) of **9a** as a colorless oil (100% ee): ^1H NMR (200 MHz, DMSO-d_6, vs TMS) δ 1.24 (3 H, s), 1.35 (9 H, s), 1.56 (3 H, s), 1.67 (3 H, s), 2.30–2.57 (2 H, m), 5.03 (1 H, t, J = 7.06 Hz), 6.76 (1 H, br s, D_2O exch); IR (NaCl, $CDCl_3$) 1715, 1653, 1498 cm^{-1}; $[\alpha]^{25}_D$ −13.4° (c 0.87, CH_2Cl_2). Anal. Calcd for $C_{13}H_{23}NO_4$: C, 60.68; H, 9.01; N, 5.44. Found: C, 60.60; H, 9.06; N, 5.48.

(3*S*,5*S*,6*R*)-4-(*tert*-Butyloxycarbonyl)-5,6-diphenyl-3-(2′-propenyl)-3-propyl-2,3,5,6-tetrahydro-4*H*-1,4-oxazin-2-one (7a, R_1 = n-C_3H_7, R_2 = $CH_2CH{=}CH_2$). To a stirred solution of **3a** (R_1 = n-C_3H_7) (500 mg, 1.264 mmol, 1 equiv) and allyl iodide (578 μL, 6.321 mmol, 5 equiv) in THF (6 mL) was added potassium bis(trimethylsilyl)amide (1806 μL, 2.528 mmol, 2 equiv, 1.4 M solution in THF) dropwise via syringe at −78 °C. After 30 min, the reaction mixture was poured into ethyl acetate. The organic layer was washed with water and brine, dried over anhydrous magnesium sulfate, filtered, concentrated, and separated by column chromatography on silica gel (eluted with EtOAc/hexanes, 1:3) to afford 496 mg (90%) of **7a** as a colorless oil: ^1H NMR (200 MHz, DMSO-d_6, 393 K, vs TMS) δ 0.68 (3 H, t), 0.71–1.28 (2 H, m), 1.43 (9 H, s), 2.06–2.34 (2 H, m), 2.92 (1 H, dd, J = 14.08 Hz, J = 7.33 Hz), 3.19 (1 H, dd, J = 13.92 Hz, J = 7.41 Hz), 5.12–5.22 (2 H, m), 5.60 (1 H, d, J = 3.24 Hz), 6.26 (1 H, d, J = 3.41 Hz), 7.13–7.22 (10 H, m); IR (NaCl, CH_2Cl_2) 1746, 1697 cm^{-1}; $[\alpha]^{25}_D$ +54.9° (c 3.3, CH_2Cl_2). Anal. Calcd for $C_{27}H_{33}NO_4$: C, 74.45; H, 7.64; N, 3.22. Found: C, 74.49; H, 7.60; N, 3.25.

(*S*)-*N*-(*tert*-Butyloxycarbonyl)-2-(2′-propenyl)norvaline (9a, R_1 = n-C_3H_7, R_2 = $CH_2CH{=}CH_2$). To a solution of Na^0 (69 mg, 3.001 mmol, 13 equiv) in liquid ammonia (25 mL, distilled from Na^0) was added a solution of **7a** (R_1 = n-C_3H_7, R_2 = $CH_2CH{=}CH_2$) (100 mg, 0.230 mmol, 1 equiv) and ethanol (200 μL) in THF (3 mL) via syringe at −33 °C. After 15 min, the reaction mixture was quenched with excess ammonium chloride and then allowed to warm. After the ammonia was evaporated off, the residue was diluted with water. The aqueous layer was extracted two times with ether and acidified to pH 2 with 1 N HCl. After that the aqueous layer was extracted three times with ethyl acetate. The combined organic extracts were dried over anhydrous magnesium sulfate, filtered, concentrated, and separated by PTLC on silica gel (eluted with 5% MeOH in CH_2Cl_2) to afford 35 mg (60%) of **9a** as a colorless oil (100% ee): ^1H NMR (200 MHz, DMSO-d_6, vs TMS) δ 0.82 (3 H, t, J = 7.14 Hz), 1.07–1.22 (2 H, m), 1.36 (9 H, s), 1.52–1.81 (2 H, m), 2.51–2.60 (2 H, m), 4.98–5.06 (2 H, m), 5.50–5.70 (1 H, m), 6.49 (1 H, s, D_2O exch); IR (NaCl, $CDCl_3$) 1714, 1694, 1651, 1494 cm^{-1}; $[\alpha]^{25}_D$ −6.4° (c 0.45, CH_2Cl_2). Anal. Calcd for $C_{13}H_{23}NO_4$: C, 60.08; H, 9.01; N, 5.44. Found: C, 60.72; H, 9.01; N, 5.40.

(3*S*,5*S*,6*R*)-4-(Benzyloxycarbonyl)-5,6-diphenyl-3-methyl-3-(phenylmethyl)-2,3,5,6-tetrahydro-4*H*-1,4-oxazin-2-one (8a, R_1 = CH_3, R_2 = CH_2Ph). To a stirred solution of **4a** (R_1 = CH_3) (500 mg, 1.245 mmol, 1 equiv) and benzyl bromide (740 μL, 6.221 mmol, 5 equiv) in THF (12 mL) was added potassium bis(trimethylsilyl)amide (1779 μL, 2.49 mmol, 2 equiv, 1.4 M solution in THF) dropwise via syringe at −78 °C. After 30 min, the reaction mixture was poured into ethyl acetate. The organic layer was washed with water and brine, dried over anhydrous magnesium sulfate, filtered, concentrated, and separated by column chromatography on silica gel (eluted with EtOAc/hexanes, 1:3) to afford 514 mg (84%) of **8a** as a white solid: ^1H NMR (200 MHz, DMSO-d_6, 393 K, vs TMS) δ 2.95 (3 H, s), 3.16 (1 H, $^1/_2$ AB q, J = 13.44 Hz), 4.05 (1 H, $^1/_2$ AB q, J = 13.23 Hz), 4.30 (1 H, d, J = 3.31 Hz), 5.22 (2 H, s), 5.22 (1 H, d, J = 3.29 Hz), 6.68–6.74 (2 H, m), 6.82–6.88 (2 H, m), 7.09–7.15 (8 H, m), 7.29–7.34 (8 H, m); IR (NaCl, CH_2Cl_2) 1745, 1703 cm^{-1}; mp 134–135 °C; $[\alpha]^{25}_D$ +165.4° (c 0.8, CH_2Cl_2). Anal. (recrystallized from CH_2Cl_2/hexanes) Calcd for $C_{32}H_{29}NO_4$: C, 78.18; H, 5.95; N, 2.85. Found: C, 78.34; H, 6.03; N, 2.88. A single crystal of this material was subjected to X-ray analysis.[16]

(*S*)-α-Methylphenylalanine (10a, R_1 = CH_3, R_2 = CH_2Ph). To a solution of **8a** (R_1 = CH_3, R_2 = CH_2Ph) (100 mg, 0.203 mmol, 1 equiv) in THF and EtOH (3 mL, 1:1) was added palladium chloride (18 mg, 0.102 mmol, 0.5 equiv). The reaction mixture was hydrogenated at 50 psi for 48 h. The mixture was then purged with nitrogen, filtered through Celite to remove the catalyst, concentrated, and triturated with Et_2O to yield 39.2 mg (108%) of **10a** as a white solid (100% ee; adjusted chemical yield 93%).

(*S*)-α-Methylphenylalanine Hydrochloride. 10a (R_1 = CH_3, R_2 = CH_2Ph) was dissolved in 1 N HCl·H_2O. The resulting solution was brought to reflux. After 2 h the solvent was evaporated off, and the residue was triturated with Et_2O to yield (*S*)-α-methylphenylalanine hydrochloride as a white solid: ^1H NMR (200 MHz, D_2O, vs HOD) δ 1.44 (3 H, s), 2.89 (1 H, $^1/_2$ AB q, J = 14.33 Hz), 3.18 (1 H, $^1/_2$ AB q, J = 14.30 Hz), 7.08–7.11 (2 H, m), 7.21–7.26 (3 H, m); IR (ZnS, MeOH) 3406, 2925, 1733 cm^{-1}; mp 203–205 °C dec; $[\alpha]^{25}_D$ −9.6° (c 0.2, H_2O). Anal. (recrystallized from EtOH/Et_2O) Calcd for $C_{10}H_{14}ClNO_2$: C, 55.69; H, 6.54; N, 6.49. Found: C, 55.48; H, 6.49; N, 6.29.

(3*S*,5*S*,6*R*)-4-(Benzyloxycarbonyl)-5,6-diphenyl-3-methyl-3-(3′-phenyl-2′-propenyl)-2,3,5,6-tetrahydro-4*H*-1,4-oxazin-2-one (8a, R_1 = CH_3, R_2 = $CH_2CH{=}CHPh$). To a stirred solution of **4a** (R_1 = CH_3) (354 mg, 0.882 mmol, 1 equiv) and cinnamyl bromide (869 mg, 4.409 mmol, 5 equiv) in THF (12 mL) was added potassium bis(trimethylsilyl)amide (1260 μL, 1.764 mmol, 2 equiv, 1.4 M solution in THF) dropwise via syringe at −78 °C. After 30 min, the reaction mixture was poured into ethyl acetate. The organic layer was washed with water and brine, dried over anhydrous magnesium sulfate, filtered, concentrated, and separated by column chromatography on silica gel (eluted with CH_2Cl_2/hexanes, 1:1, then 2:1) to afford 366 mg (80%) of **8a** as a white solid: ^1H NMR (200 MHz, DMSO-d_6, 393 K, vs TMS) δ 1.81 (3 H, s), 3.04 (1 H, dd, J = 13.76 Hz, J = 7.84 Hz), 3.48 (1 H, dd, J = 13.88 Hz, J = 6.75 Hz), 5.13 (1 H, $^1/_2$ AB q, J = 12.51 Hz), 5.21 (1 H, $^1/_2$ AB q, J = 12.60 Hz), 5.58 (1 H, d, J = 3.17 Hz), 6.16 (1 H, d, J = 3.20 Hz), 6.20–6.35 (1 H, m), 6.47–6.54 (1 H, m), 6.85–6.92 (2 H, m), 7.05–7.41 (18 H, m); IR (NaCl, CH_2Cl_2) 1746, 1705 cm^{-1}; mp 162–163 °C; $[\alpha]^{25}_D$ +127.8° (c 1, CH_2Cl_2). Anal. (recrystallized from CH_2Cl_2/hexanes) Calcd for $C_{34}H_{31}NO_4$: C, 78.89; H, 6.04; N, 2.71. Found: C, 78.93; H, 6.15; N, 2.76.

(*S*)-2-(3′-Phenylpropyl)alanine (10a, R_1 = CH_3, R_2 = $CH_2CH_2CH_2Ph$). To a solution of **8a** (R_1 = CH_3, R_2 = $CH_2CH{=}$

(16) Thompson, M. A.; Anderson, O. P. *Acta Crystallogr.*, in press.

CHPh) (100 mg, 0.193 mmol, 1 equiv) in THF and EtOH (4 mL, 1:1) was added palladium chloride (24 mg, 0.135 mmol, 0.7 equiv). The reaction mixture was hydrogenated at 50 psi for 37 h. The mixture was then purged with nitrogen, filtered through Celite to remove the catalyst, concentrated, and triturated with Et_2O to yield 43.3 mg (108%) of **10a** as a white solid (100% ee; adjusted chemical yield 95%).

(*S*)-2-(3′-Phenylpropyl)alanine Hydrochloride. 10a ($R_1 = CH_3$, $R_2 = CH_2CH_2CH_2Ph$) was dissolved in 1 N HCl·H_2O. The resulting solution was brought to reflux. After 2 h the solvent was evaporated off, and the residue was triturated with Et_2O to yield (*S*)-2-(3′-phenylpropyl)alanine hydrochloride as a white solid: ^1H NMR (200 MHz, D_2O, vs HOD) δ 1.37 (3 H, s), 1.40–1.82 (4 H, m), 2.53 (2 H, t, J = 7.19 Hz), 7.10–7.28 (5 H, m); IR (ZnS, MeOH) 2944, 1738, 1594, 1499 cm^{-1}; mp 246–248 °C dec; $[\alpha]^{25}_D$ +8.1° (*c* 0.2, H_2O). Anal. (recrystallized from *i*-PrOH/Et_2O) Calcd for $C_{12}H_{18}ClNO_2$: C, 59.13; H, 7.44; N, 5.75. Found: C, 59.00; H, 7.57; N, 5.67.

(3*S*,5*S*,6*R*)-4-(Benzyloxycarbonyl)-5,6-diphenyl-3-(phenylmethyl)-3-propyl-2,3,5,6-tetrahydro-4*H*-1,4-oxazin-2-one (8a, $R_1 = n$-C_3H_7, $R_2 = CH_2Ph$). To a stirred solution of **4a** ($R_1 = n$-C_3H_7) (44 mg, 0.102 mmol, 1 equiv) and benzyl bromide (121 μL, 1.02 mmol, 10 equiv) in THF (1 mL) was added potassium bis(trimethylsilyl)amide (366 μL, 0.512 mmol, 5 equiv, 1.4 M solution in THF) dropwise via syringe at −78 °C. After 30 min, the reaction mixture was poured into ethyl acetate. The organic layer was washed with water and brine, dried over anhydrous magnesium sulfate, filtered, concentrated, and separated by PTLC on silica gel (eluted with EtOAc/hexanes, 1:3) to afford 45 mg (85%) of **8a** as a colorless oil: ^1H NMR (200 MHz, DMSO-d_6, 393 K, vs TMS) δ 0.61 (3 H, t, J = 6.11 Hz), 0.62–0.79 (1 H, m), 0.85–1.04 (1 H, m), 2.10–2.24 (1 H, m), 2.37–2.52 (1 H, m), 3.20 (1 H, $^1/_2$ AB q, J = 13.51 Hz), 3.94 (1 H, $^1/_2$ AB q, J = 13.53 Hz), 4.59 (1 H, d, J = 3.33 Hz), 5.25 (1 H, $^1/_2$ AB q, J = 12.30 Hz), 5.31 (1 H, $^1/_2$ AB q, J = 12.48 Hz), 5.42 (1 H, d, J = 3.48 Hz), 6.86–6.92 (2 H, m), 7.05–7.42 (18 H, m); IR (NaCl, CH_2Cl_2) 1744, 1703 cm^{-1}; $[\alpha]^{25}_D$ +127.8° (*c* 1, CH_2Cl_2). Anal. (recrystallized from CH_2Cl_2/hexanes) Calcd for $C_{34}H_{31}NO_4$: C, 78.89; H, 6.04; N, 2.71. Found: C, 78.93; H, 6.15; N, 2.76.

(3*S*,5*S*,6*R*)-4-(Benzyloxycarbonyl)-5,6-diphenyl-3-(phenylmethyl)-3-(2′-propenyl)-2,3,5,6-tetrahydro-4*H*-1,4-oxazin-2-one (8a, $R_1 = CH_2$-$CH{=}CH_2$, $R_2 = CH_2Ph$). To a stirred solution of **4a** ($R_1 = CH_2CH{=}CH_2$) (50 mg, 0.117 mmol, 1 equiv) and benzyl bromide (70 μL, 0.589 mmol, 5 equiv) in THF (1 mL) was added potassium bis(trimethylsilyl)amide (251 μL, 0.351 mmol, 3 equiv, 1.4 M solution in THF) dropwise via syringe at −78 °C. After 30 min, the reaction mixture was poured into ethyl acetate. The organic layer was washed with water and brine, dried over anhydrous magnesium sulfate, filtered, concentrated, and separated by PTLC on silica gel (eluted with EtOAc/hexanes, 1:3) to afford 51 mg (84%) of **8a** as a colorless oil: ^1H NMR (200 MHz, DMSO-d_6, 393 K, vs TMS) δ 2.90–3.00 (1 H, m), 3.19–3.32 (1 H, m), 3.23 (1 H, $^1/_2$ AB q, J = 13.58 Hz), 3.97 (1 H, $^1/_2$ AB q, J = 13.56 H), 4.53 (1 H, d, J = 3.44 Hz), 4.61–4.86 (2 H, m), 5.19–5.41 (1 H, m), 5.26 (2 H, s), 5.33 (1 H, d, J = 3.29 Hz), 6.79–6.83 (2 H, m), 7.02–7.12 (10 H, m), 7.28–7.36 (8 H, m); IR (NaCl, CH_2Cl_2) 1744, 1702 cm^{-1}; $[\alpha]^{25}_D$ +127.8° (*c* 1, CH_2Cl_2). Anal. (recrystallized from CH_2Cl_2/hexanes) Calcd for $C_{34}H_{31}NO_4$: C, 78.89; H, 6.04; N, 2.71. Found: C, 78.93; H, 6.15; N, 2.76.

(3*R*,5*R*,6*S*)-4-(Benzyloxycarbonyl)-5,6-diphenyl-3-(4′-iodobutyl)-2,3,5,6-tetrahydro-4*H*-1,4-oxazin-2-one (11 (or 4b, $R_1 = (CH_2)_4I$)). To a stirred solution of **2b** (1.5 g, 3.87 mmol, 1 equiv) and 1,4-diiodobutane (2.55 mL, 19.34 mmol, 5 equiv) in THF (130 mL) and HMPA (13 mL) was added lithium bis(trimethylsilyl)amide (5.8 mL, 5.8 mmol, 1.5 equiv, 1 M solution in THF) dropwise via syringe at −78 °C. After 30 min the dry ice bath was removed. After an additional 30 min, the reaction mixture was poured into ethyl acetate. The organic layer was washed with water and brine, dried over anhydrous magnesium sulfate, filtered, concentrated, and crystallized in hexanes to afford 1.73 g (78.6%) of **11** as a yellowish solid. The antipode (**4a**, $R_1 = (CH_2)_4I$) was obtained from **1a** in 61% yield. Data: ^1H NMR (200 MHz, DMSO-d_6, 393 K, vs TMS) δ 1.55–1.66 (2 H, m), 1.81–1.93 (2 H, m), 2.10–2.22 (2 H, m), 3.01 (2 H, t, J = 6.83 Hz), 4.82 (1 H, t, J = 5.72 Hz), 4.94 (1 H, $^1/_2$ AB q, J = 12.50 Hz), 5.05 (1 H, $^1/_2$ AB q, J = 12.28 Hz), 5.29 (1 H, d, J = 3.01 Hz), 6.01 (1 H, d, J = 2.98 Hz), 6.53–6.59 (2 H, m), 7.01–7.26 (13 H, m); IR (NaCl, CH_2Cl_2) 1756, 1705 cm^{-1}; mp 163–164 °C; $[\alpha]^{25}_D$ +22.9° (*c* 1.63, CH_2Cl_2). Anal. (recrystallized from CH_2Cl_2/hexanes) Calcd for $C_{28}H_{28}INO_4$: C, 59.06; H, 4.96; N, 2.46. Found: C, 59.26; H, 5.16; N, 2.50.

(3*R*,5*R*,6*S*)-4-(Benzyloxycarbonyl)-5,6-diphenyl-3-[4′-(acetyloxy)-butyl]-2,3,5,6-tetrahydro-4*H*-1,4-oxazin-2-one (12 (or 4b, $R_1 = (CH_2)_4OAc$)). To a solution of **11** (or **4b**, $R_1 = (CH_2)_4I$) (1.58 g, 2.77 mmol, 1 equiv) in DMF (100 mL) was added sodium acetate (2.27 g, 27.7 mmol, 10 equiv). The reaction mixture was heated to 80 °C. After 4 h, the reaction mixture was cooled down and poured into ethyl acetate. The organic layer was washed with water and brine, dried over anhydrous magnesium sulfate, filtered, concentrated, and separated via radial chromatography on silica gel (eluted with EtOAc/hexanes, 1:2) to afford 1.12 g (80.6%) of **12** (or **4b**, $R_1 = (CH_2)_4OAc$) as a white solid. The antipode (**4b**, $R_1 = (CH_2)_4OAc$) was obtained from **4a** ($R_1 = (CH_2)_4I$) in 85.8% yield. Data: ^1H NMR (200 MHz, DMSO-d_6, 393 K, vs TMS) δ 1.48–1.73 (4 H, m), 1.99 (3 H, s), 2.15 (2 H, q, J = 7.81 Hz), 4.03 (2 H, t, J = 6.25 Hz), 4.80 (1 H, t, J = 7.36 Hz), 4.90–5.19 (2 H, m), 5.27 (1 H, d, J = 3.03 Hz), 6.22 (1 H, d, J = 3.03 Hz), 6.53–6.59 (2 H, m), 7.02–7.27 (13 H, m); IR (NaCl, CH_2Cl_2) 1756, 1735, 1704 cm^{-1}; mp 124–125 °C; $[\alpha]^{25}_D$ +35.3° (*c* 1.41, CH_2Cl_2). Anal. (recrystallized from CH_2Cl_2/hexanes) Calcd for $C_{30}H_{31}NO_6$: C, 71.84; H, 6.23; N, 2.79. Found: C, 71.91; H, 6.23; N, 2.79.

(2*R*)-2-Amino-6-(acetyloxy)hexanoic Acid (13 (or 6b, $R_1 = (CH_2)_4OAc$)). To a solution of **12** (or **4b**, $R_1 = (CH_2)_4OAc$) (559 mg, 1.11 mmol, 1 equiv) in THF and EtOH (3 mL, 1:2) was added palladium chloride (59.3 mg, 0.33 mmol, 0.3 equiv). The reaction mixture was hydrogenated at 50 psi for 20 h. The mixture was then purged with nitrogen, filtered through Celite to remove the catalyst, concentrated, and triturated with Et_2O to yield **13** (or **6b**, $R_1 = (CH_2)_4OAc$) as a white solid (97% ee; antipode (**6a**, $R_1 = (CH_2)_4OAc$) 100% ee): ^1H NMR (270 MHz, D_2O, vs HOD) δ 1.25–1.38 (2 H, m), 1.48–1.60 (2 H, m), 1.70–1.84 (2 H, m), 1.92 (3 H, s), 3.77 (1 H, t, J = 6.12 Hz), 3.96 (2 H, t, J = 6.48 Hz); IR (ZnS, MeOH) 3030, 1732, 1697 (sh) cm^{-1}; mp 190–192 °C dec; $[\alpha]^{25}_D$ −12.8° (*c* 0.5, 1 N HCl).

(2*R*)-Ethyl 2-Amino-6-hydroxyheptanoate Hydrochloride (14). Amino acid **13** (or **6b**, $R_1 = (CH_2)_4OAc$) was refluxed in 1 N HCl·EtOH. After 2 h the ethanol was evaporated, and the residue was dried completely in vacuo to afford 232 mg (98%, two steps) of **14** as a colorless oil. The antipode was obtained in 98% yield. ^1H NMR (270 MHz, D_2O, vs HOD) δ 1.13 (3 H, t, J = 7.11 Hz), 1.21–1.48 (4 H, m), 1.72–1.89 (2 H, m), 3.44 (2 H, t, J = 6.16 Hz), 3.96 (1 H, t, J = 6.31 Hz), 4.13 (2 H, q, J = 7.15 Hz); IR (ZnS, EtOH) 3346, 1744 cm^{-1}; $[\alpha]^{25}_D$ −8.2° (*c* 1.32, H_2O).

(2*R*)-Ethyl 2-(*tert*-Butyloxycarbonyl)amino-6-hydroxyheptanoate (15). To a stirred solution of **14** (382 mg, 1.81 mmol, 1 equiv) in H_2O (4.5 mL) was added a solution of di-*tert*-butyl dicarbonate (591 mg, 2.71 mmol, 1.5 equiv) in CH_3CN (4.5 mL), followed by addition of triethylamine (755 mL, 5.42 mmol, 3 equiv) and DMAP (44 mg, 0.36 mmol, 0.2 equiv). After 24 h, the reaction mixture was poured into ethyl acetate and the aqueous layer was separated. The organic layer was washed with 0.5 M citric acid, H_2O, and brine, dried over anhydrous magnesium sulfate, filtered, concentrated, and separated in column chromatography on silica gel (eluted with 5% MeOH in CH_2Cl_2) to afford 392 mg (83%) of **15** as a light amber oil. The antipode was obtained in 80% yield. Data: ^1H NMR (270 MHz, $CDCl_3$, vs TMS) δ 1.28 (3 H, t, J = 7.13 Hz), 1.45 (9 H, s), 1.53–1.91 (6 H, m), 3.65 (2 H, t, J = 6.26 Hz), 4.19 (2 H, q, J = 7.14 Hz), 4.22–4.35 (1 H, m), 5.06 (1 H, d, D_2O exch, J = 7.84 Hz); IR (NaCl, $CDCl_3$) 3436 (sh), 3360, 1732, 1710 cm^{-1}; $[\alpha]^{25}_D$ −3.9° (*c* 4.5, CH_2Cl_2). Anal. Calcd for $C_{13}H_{25}NO_5$: C, 56.70; H, 9.15; N, 5.09. Found: C, 56.64; H, 8.97; N, 5.13.

(2*R*)-Ethyl 2-(*tert*-Butyloxycarbonyl)amino-6-[(*p*-toluenesulfonyl)-oxy]heptanoate (16). To a stirred solution of **15** ($R_1 = (CH_2)_4OH$) (1.1 g, 3.99 mmol, 1 equiv) in CH_2Cl_2 (100 mL) was added *p*-toluenesulfonyl chloride (1.5 g, 7.87 mmol, 2 equiv) followed by addition of triethylamine (1.1 mL, 7.89 mmol, 2 equiv) and DMAP (98 mg, 0.80 mmol, 0.2 equiv). After 2 h the reaction mixture was poured into CH_2Cl_2. The methylene chloride solution was washed three times with 0.5 M citric acid, H_2O, and brine, dried over anhydrous magnesium sulfate, filtered, concentrated, and separated by radial chromatography on silica gel (eluted with EtOAc/hexanes, 1:2) to afford 1.61 g (93.8%) of **16** as a light amber oil. The antipode was similarly obtained in 94.4% yield. Data: ^1H NMR (270 MHz, $CDCl_3$, vs TMS) δ 1.27 (3 H, t, J = 7.17 Hz), 1.34–1.42 (2 H, m), 1.45 (9 H, s), 1.51–1.79 (4 H, m), 2.45 (3 H, s), 4.01 (2 H, t, J = 6.39 Hz), 4.18 (2 H, q, J = 7.14 Hz), 4.21–4.25 (1 H, m), 4.98 (1 H, d, D_2O exch, J = 7.76 Hz), 7.34 (2 H, d, J = 8.31 Hz), 7.79 (2 H, d, J = 8.29 Hz); IR (NaCl, $CDCl_3$) 3381, 1738, 1710, 1362, 1177 cm^{-1}; $[\alpha]^{25}_D$ −6.1° (*c* 1.29, CH_2Cl_2). Anal. Calcd for $C_{20}H_{31}NO_7S$: C, 55.92; H, 7.28; N, 3.26. Found: C, 55.77; H, 7.20; N, 3.29.

(2*R*)-Ethyl 2-(*tert*-Butyloxycarbonyl)amino-6-[(*p*-methoxybenzyl)-thio]heptanoate (17). To a vigorously stirred suspension of sodium ethoxide (69.4 mg, 1.02 mmol, 3 equiv) in EtOH (5 mL) was added *p*-methoxy-α-toluenethiol (142 mL, 1.02 mmol, 3 equiv). After 20 min, a solution of **16** ($R_1 = (CH_2)_4OTs$) (146 mg, 0.34 mmol, 1 equiv) in THF (5 mL) was added to the reaction mixture. After 45 min, the solvent was evaporated and the residue was diluted with THF. The white precipitate was filtered. The filtrate was concentrated and separated by radial chromatography on silica gel (eluted with EtOAc/hexanes, 1:4) to afford 126.5 mg (90%) of **17** as a colorless oil: ^1H NMR (270 MHz, $CDCl_3$,

vs TMS) δ 0.82–0.91 (2 H, m), 1.27 (3 H, t), 1.45 (9 H, s), 1.24–1.60 (4 H, m), 2.40 (2 H, t), 3.74 (2 H, s), 3.81 (3 H, s), 4.20 (2 H, q), 4.22–4.32 (1 H, m), 4.99 (1 H, d, D_2O exch), 6.85 (2 H, d), 7.22 (2 H, d); IR (NaCl, $CDCl_3$) 3370, 1738, 1710 cm^{-1}; mass spectrum (NH_3, CI), *m/e* 412 ($M^+ + 1$, 3.4).

(2*R*)-2-(*tert*-Butyloxycarbonyl)amino-6-[(*p*-methoxybenzyl)thio]hexanoic Acid (18). To a stirred solution of (2*R*)-ethyl 2-(*tert*-butyloxycarbonyl)amino-6-[(*p*-methoxybenzyl)thio]heptanoate (**17**) obtained above (1.54 g, 3.74 mmol, 1 equiv) in EtOH (120 mL) was added lithium hydroxide monohydrate (785 mg, 18.71 mmol, 5 equiv). After 15 h, ethanol was evaporated off and the residue was diluted with water. The aqueous solution was acidified to pH 2 with 1 N HCl and then extracted three times with EtOAc. The combined organic layer was dried over anhydrous magnesium sulfate, filtered, concentrated, and separated by radial chromatography on silica gel (eluted with 3% acetic acid in CH_2Cl_2) to afford 1.31 g (91.3%) of **18** as a light amber oil: ^1H NMR (270 MHz, DMSO-d_6, vs TMS) δ 1.37 (9 H, s), 1.20–1.69 (6 H, m), 2.34 (2 H, t, J = 7.03 Hz), 3.65 (2 H, s), 3.73 (3 H, s), 3.74–3.85 (1 H, m), 6.86 (2 H, d, J = 8.47 Hz), 6.99 (1 H, d, D_2O exch, J = 8.72 Hz), 7.21 (2 H, d, J = 8.50 Hz); IR (NaCl, $CDCl_3$) 3335, 1709, 1654 (sh) cm^{-1}; $[\alpha]^{25}_D$ −0.7° (*c* 1.2, CH_2Cl_2); exact mass calcd for $C_{19}H_{30}NO_5S$ 384.1845, found 384.1841.

(3*R*,5*R*,6*S*)-4-(*tert*-Butyloxycarbonyl)-5,6-diphenyl-3-(3′-chloropropyl)-2,3,5,6-tetrahydro-4*H*-1,4-oxazin-2-one (3b, $R_1 = (CH_2)_3Cl$). To a stirred solution of **1b** (707 mg, 2 mmol, 1 equiv) and 1-iodo-3-chloropropane (107 μL, 10 mmol, 5 eq) in THF (20 mL) and HMPA (2 mL) was added lithium bis(trimethylsilyl)amide (3 mL, 3 mmol, 1.5 equiv, 1.0 M solution in THF) dropwise via syringe at −78 °C. After 30 min, the reaction mixture was poured into ethyl acetate. The organic layer was washed with saturated aqueous NH_4Cl (20 mL), water, and brine, dried over anhydrous magnesium sulfate, filtered, concentrated, and triturated with *n*-hexanes to give the chloride (620 mg, 72%), which could be recrystallized from ethanol (mp 168 °C): ^1H NMR (270 MHz, $CDCl_3$) δ 1.10 (6 H, s), 1.26 (3 H, s), 1.47–2.54 (4 H, m), 3.66 (2 H, m), 4.81 ($^1/_2$ H, m), 5.02 (1 H, d, J = 3 Hz), 5.24 ($^1/_2$ H, d, J = 2 Hz), 5.95 (1 H, d, J = 3 Hz), 6.53–6.67 (2 H, m), 6.94–7.40 (8 H, m); IR (NaCl, Nujol) 1747, 1702, 1315, 1257, 1169, 1053, 886, 703 cm^{-1}. Anal. Calcd for $C_{24}H_{28}ClNO_4$: C, 67.05; H, 6.56; N, 3.26. Found: C, 66.91; H, 6.65; N, 3.11.

(3*R*,5*R*,6*S*)-4-(*tert*-Butyloxycarbonyl)-5,6-diphenyl-3-(3′-iodopropyl)-2,3,5,6-tetrahydro-4*H*-1,4-oxazin-2-one (3b, $R_1 = (CH_2)_3I$). To a stirred solution of **1b** (3.0 g, 8.5 mmol, 1 equiv) and 1,3-diiodopropane (5.6 mL, 42.4 mmol, 5 equiv) in THF (85 mL) and HMPA (8.5 mL) was added lithium bis(trimethylsilyl)amide (12.7 mL, 12.7 mmol, 1.5 equiv, 1.0 M solution in THF) dropwise via syringe at −78 °C. After 30 min, the reaction mixture was allowed to come to room temperature and then poured into ethyl acetate. The organic layer was washed with saturated aqueous NH_4Cl (20 mL), saturated aqueous $Na_2S_2O_3$, water, and brine, dried over anhydrous magnesium sulfate, filtered, concentrated, and triturated with *n*-hexanes to give the iodide (3.5 g, 86%), which could be recrystallized from ethanol (mp 172–173 °C): ^1H NMR (270 MHz, $CDCl_3$) δ 1.07 (6 H, s), 1.45 (3 H, s), 1.66–1.81 (2 H, m), 1.85–2.10 (2 H, m), 2.10–2.26 (1 H, m), 3.24 (2 H, t, J = 7 Hz), 4.82 ($^1/_2$ H, m), 5.01 (1 H, m), 5.21 ($^1/_2$ H, m), 5.92 (1 H, br s), 6.52–6.63 (2 H, m), 6.93–7.40 (8 H, m); IR (NaCl, Nujol) 1747, 1702, 1315, 1257, 1169, 1053, 886, 703 cm^{-1}. Anal. Calcd for $C_{24}H_{28}INO_4$: C, 55.29; H, 5.41; N, 2.69. Found: C, 55.33; H, 5.50; N, 2.53.

(3*R*,5*R*,6*S*)-4-Aza-5,6-diphenyl-2-oxo-1-oxabicyclo[4.3.0]nonane. To a solution of (3*R*,5*R*,6*S*)-4-(*tert*-butyloxycarbonyl)-5,6-diphenyl-3-(3′-chloropropyl)-2,3,5,6-tetrahydro-4*H*-1,4-oxazin-2-one (**3b**, $R_1 = (CH_2)_3Cl$) (36 mg, 0.08 mmol, 1 equiv) in CH_2Cl_2 (0.3 mL) was added trifluoroacetic acid (0.1 mL) at 0 °C. The mixture was stirred for 20 min at 0 °C and for 1 h at room temperature. The solvent was removed under reduced pressure, and the residue was partitioned between ethyl acetate and saturated aqueous $NaHCO_3$. The organic layer was separated, washed with H_2O, dried over anhydrous $MgSO_4$, and purified by silica gel TLC (eluted with EtOAc/hexanes, 2:5) to give the bicyclic product (22 mg, 80%) as an oil: ^1H NMR (270 MHz, $CDCl_3$) δ 1.70–1.94 (2 H, m), 2.10–2.26 (1 H, m), 2.32–2.46 (1 H, m), 2.50–2.62 (1 H, m), 3.08–3.18 (1 H, m), 4.15 (1 H, dd, J = 7.8 Hz and 9.4 Hz), 4.27 (1 H, d, J = 3.8 Hz), 5.59 (1 H, d, J = 3.8 Hz), 6.93–7.02 (2 H, m), 7.10–7.40 (8 H, m); IR (NaCl, neat) 1734, 1484, 1443, 1368, 1335, 1229, 1191, 1144, 1038 cm^{-1}; $[\alpha]^{25}_D$ −130.4° (*c* 2.6, CH_2Cl_2).

Acknowledgment. We are indebted to the National Science Foundation (CHE 8717017), the National Institutes of Health (GM 40988), and Hoffman-La Roche, Inc. for providing financial support. High-resolution mass spectra were obtained at the Midwest Center for Mass Spectrometry, Lincoln, NE (an NSF-funded Regional Instrumentation Facility). We are grateful to Professor Dave Evans and Dr. Joseph Dellaria for communicating their enolate alkylation results to us on a related system prior to publication.

Late Intermediates in the Biosynthesis of Cocaine: 4-(1-Methyl-2-pyrrolidinyl)-3-oxobutanoate and Methyl Ecgonine

Edward Leete,* Jeffrey A. Bjorklund, Maria M. Couladis, and Sung Hoon Kim

Contribution No. 223 from the Natural Products Laboratory, Department of Chemistry, University of Minnesota, Minneapolis, Minnesota 55455. *Received May 24, 1991*

Abstract: Methyl (*RS*)-[1,2-$^{13}C_2$,1-^{14}C]-4-(1-methyl-2-pyrrolidinyl)-3-oxobutanoate was synthesized from a mixture of sodium [1,2-$^{13}C_2$]- and [1-^{14}C]acetate. This β-keto ester was administered to intact *Erythroxylum coca* plants, resulting in the formation of labeled cocaine and methyl ecgonine. The presence of contiguous ^{13}C atoms in these alkaloids at C-2 and C-9 was established by ^{13}C NMR spectroscopy, and the presence of ^{14}C at C-9 was established by a chemical degradation. These results are consistent with our new hypothesis for the biosynthesis of cocaine, which involves the intermediacy of 4-(1-methyl-2-pyrrolidinyl)-3-oxobutanoate (rather than 2-(1-methyl-2-pyrrolidinyl)-3-oxobutanoate) in the formation of the tropane moiety of cocaine. Support for this biogenetic scheme was also obtained by a biomimetic synthesis of 2-carbomethoxy-3-tropinone by the oxidation of methyl 4-(1-methyl-2-pyrrolidinyl)-3-oxobutanoate with mercuric acetate. The formation of labeled cocaine and methyl ecgonine in leaf cuttings of *Erythroxylum coca* was observed after incubation with [9-^{14}C]-2-carbomethoxy-3-tropinone. The degree of incorporation of this precursor into cocaine was significantly increased by the concomitant administration of the *N*-acetylcysteamine thioester of benzoic acid, with a corresponding reduction in the degree of incorporation into methyl ecgonine.

Our current hypothesis for the biosynthesis of cocaine is illustrated in Scheme I. This pathway has been recently reviewed[1] and is based entirely on feeding experiments with putative labeled precursors, which were administered (by leaf painting) to intact plants of *Erythroxylum coca*. No work has been published on the enzymology of any of these hypothetical steps in the coca plant. In this scheme, the compounds which have so far been established as precursors of cocaine are enclosed in boxes. DL-[5-^{14}C]Ornithine (**1**) afforded labeled cocaine (**17**) in which the ^{14}C was equally distributed between its C-1 and C-5 positions.[2] This result led

(1) Leete, E. *Planta Med.* **1990**, *56*, 339–352.

0002-7863/91/1513-9286$02.50/0