55.6, 55.7, 56.5, 58.3, 60.2, 77.1, 78.7, 95.9, 98.6, 101.1, 104.5, 116.1, 117.0, 131.3, 134.9, 142.6, 148.6, 158.7, 161.0, 173.3, 173.6, 192.0, 202.4.

Conversion of Tetramic Acid 21 to Tirandamycin B. Tetramic acid **21** (6.7 mg, 9.1 μmol) was dissolved in trifluoroacetic acid (2.0 mL), and the resulting red solution was stirred at room temperature for 5 min. The reaction mixture was concentrated in vacuo, redissolved in toluene (10 mL), and reconcentrated in vacuo. The residue was purified by filtration through a short column of Bio-Sil A (3 cm, 5% EtOH/CH_2Cl_2) to give 5.0 mg (98%) TIPS-tirandamycin B **22**: IR ($CHCl_3$) 3447 (m), 2928 (s), 2872 (s), 1792 (m), 1726 (s), 1660 (s), 1616 (vs), 1569 (vs), 1454 (vs), 1390 (m), 1294 (s), 1143 (vs), 1085 (s), 1006 (s), 883 (m); ^1H NMR ($CDCl_3$) 0.71 (d, 3, J = 7.0), 0.92–1.14 (m, 24), 1.52 (s, 3), 1.89 (s, 3), 1.93–2.01 (m), 2.76–2.87 (m, 1), 3.57–4.15 (m, 7), 5.84 (bd s, 1), 6.18 (d, 1, J = 9.8), 7.13 (d, 1, J = 15.8), 7.55 (d, 1, J = 15.8); ^{13}C NMR ($CDCl_3$) 11.4, 11.9, 12.3, 16.9, 17.6, 17.8, 17.9, 23.4, 34.6, 51.5, 56.6, 58.3, 60.1, 77.1, 78.7, 96.0, 100.0, 116.8, 134.9, 143.5, 149.7, 175.1, 176.4, 192.3, 202.4.

Tetrabutylammonium fluoride (5.8 μL of a 1.0 M solution in THF, 5.8 μmol) was added to a solution of TIPS-tirandamycin B **22** (0.3 mg, 5.3 μmol) in 2.0 mL of THF. The reaction mixture was stirred at room temperature for 21 h. Deionized water (10 mL) and CH_2Cl_2 (10 mL) were added and the phases partitioned. The aqueous layer was washed with CH_2Cl_2 (3 × 10 mL). The organic layers were combined and concentrated in vacuo. The residue was dissolved in toluene (10 mL) and reconcentrated in vacuo. The resulting yellow oil was purified by filtration through a short column of Bio-Sil A (3 cm, 50% EtOAc/$CHCl_3$) to give 0.2 mg of tirandamycin B (**1**). This material was identical by TLC, IR, and ^1H NMR with an authentic sample of (+)-tirandamycin B provided by Upjohn Co.: IR ($CHCl_3$) 3450 (m), 2943 (m), 2930 (m), 2856 (m), 1728 (m), 1662 (s), 1616 (vs), 1568 (s), 1455 (s), 1118 (m), 1099 (s), 1005 (s); ^1H NMR ($CDCl_3$) 0.70 (d, 3, J = 7.0), 1.10 (d, 3, J = 7.0), 1.56 (s, 3), 1.90 (s, 3), 1.94–2.07 (m, 1), 2.80–2.87 (m, 1), 3.62–4.05 (m, 7), 5.67 (bd s, 1), 6.17 (d, 1, J = 9.9), 7.14 (d, 1, J = 15.8), 7.59 (d, 1, J = 15.8).

Oxidation/Silylation of Tirandamycin B. Osmium tetroxide (15.0 μL of a 2.5 wt % solution in t-BuOH, 1.2 μmol) was added to a solution of (+)-tirandamycin B (23.2 mg, 0.054 mmol) in 75% 1,4-dioxane (3.75 mL)/water (1.25 mL). Ground sodium periodate (24.2 mg, 0.113 mmol) was subsequently added and the reaction mixture stirred for 3 days at room temperature. Brine (10 mL) was added and the solution was extracted with Et_2O (3 × 10 mL). The ethereal layers were combined, dried ($MgSO_4$), and concentrated in vacuo. Purification by filtration through a short column of silica gel (3 cm, 25% EtOAc/hexane) gave 12.2 mg (73%) of the corresponding enal: IR (CCl_4) 3610 (w), 2981 (s), 2960 (s), 2929 (s), 2870 (m), 2850 (m), 2710 (w), 1742 (vs), 1695 (s), 1572 (vs), 1373 (s), 1240 (vs), 1048 (s), 1007 (m); ^1H NMR ($CDCl_3$) 0.72 (d, 3, J = 7.0), 1.15 (d, 3, J = 7.0), 1.58 (s, 3), 1.74 (d, 3, J = 1.3), 1.81–2.01 (m, 1), 2.86–2.99 (m, 1), 3.68 (dd, 1, J = 11.5, 2.0), 3.69 (s, 1), 3.99 (bd s, 2), 6.60 (dd, 1, J = 10.1, 1.3).

Triisopropylsilyl triflate (10.0 μL, 0.037 mmol) was added to a 0 °C solution of enal (4.2 mg, 0.014 mmol) and imidazole (4.5 mg, 0.071 mmol) in DMF (3.0 mL). The reaction mixture was stirred at 0 °C for 3 h. The solution was diluted with Et_2O (10 mL) and washed with 1% HCl (10 mL). The ethereal layer was dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by filtration through a short column of silica gel (3 cm, Et_2O) to give 6.3 mg (99%) of TIPS enal **19**: IR (CCl_4) 2960 (vs), 2925 (vs), 2860 (s), 1725 (s), 1690 (vs), 1460 (m), 1365 (m), 1260 (vs), 1090 (vs), 1000 (vs); ^1H NMR ($CDCl_3$) 0.72 (d, 3, J = 7.1), 0.92–1.10 (m, 21), 1.14 (d, 3, J = 7.0), 1.53 (s, 3), 1.74 (d, 3, J = 1.2), 1.86–1.99 (m, 1), 2.89–2.99 (m, 1), 3.61–3.69 (m, 2), 3.99–4.10 (m, 3), 6.60 (dd, 1, J = 10.1, 1.3), 9.43 (s, 1); ^{13}C NMR ($CDCl_3$) 11.4, 12.0, 12.6, 16.4, 17.6, 17.9, 23.4, 34.5, 34.8, 56.7, 58.7, 60.2, 77.5, 78.7, 96.2, 140.2, 151.6, 194.7, 201.9.

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Asymmetric Syntheses of 1-Aminocyclopropane-1-carboxylic Acid Derivatives

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Abstract: Optically active D-*erythro*-4-(*tert*-butoxycarbonyl)-3-(dimethoxyphosphoryl)-5,6-diphenyl-2,3,5,6-tetrahydro-4*H*-1,4-oxazin-2-one (**13**) can be efficiently condensed with various aldehydes via the Emmons–Horner–Wadsworth procedure to provide α,β-dehydrolactone adducts (**14**). It was found that the adducts (**14**) were smoothly cyclopropanated with the ylide of racemic [[(diethylamino)methyl]phenyl]oxosulfonium tetrafluoroborate to furnish in high chemical and optical yields the desired cyclopropanes (**15**). Final deblocking to the requisite amino acids was accomplished with dissolving-metal reduction. The syntheses of [$^2H_2$]ACC, MeACC (norcoronamic acid), EtACC (coronamic acid), and BuACC are described.

Introduction

During the past decade, much effort has been directed toward the syntheses of 1-aminocyclopropane-1-carboxylic acid (**1**, ACC) derivatives; this work has recently been reviewed.[1,2] Several members of this unique class of amino acids are naturally occurring; the first example being the isolation of the parent compound (ACC) from cider apples and perry pears by Burroughs[3a] and from cowberries by Virtanen.[3b] Subsequently, coronamic acid (**2**) was isolated from the hydrolysis of coronatine (**4**), a plant toxin produced by *Pseudomonas coronafacience* var. *atropupurea*,[4] and norcoronamic acid (**3**) was similarly isolated from norcoronatine (**5**), a minor component of the phytotoxic fraction of *Pseudomonas syringae* pv. *glycinea*.[5] In addition, N-methylated norcoronamic acid has been found to be a constituent of the cyclic peptide portion of the newly discovered DNA-intercalating antibiotics of the quinomycin family (**8–10**), isolated from *Streptomyces braegensis*

(1) Stammer, C. H. *Tetrahedron* **1990**, *46*, 2231 and references cited therein.

(2) Williams, R. M. *Synthesis of Optically Active α-Amino Acids*; Baldwin, J. E., Series Ed.; Organic Chemistry Series; Pergamon Press: Oxford, 1989. (It must be noted that the cyclopropanation of **14a** with dimethyloxosulfonium methylide was erroneously reported to be essentially completely disatereoselective on p 113 in this monograph.)

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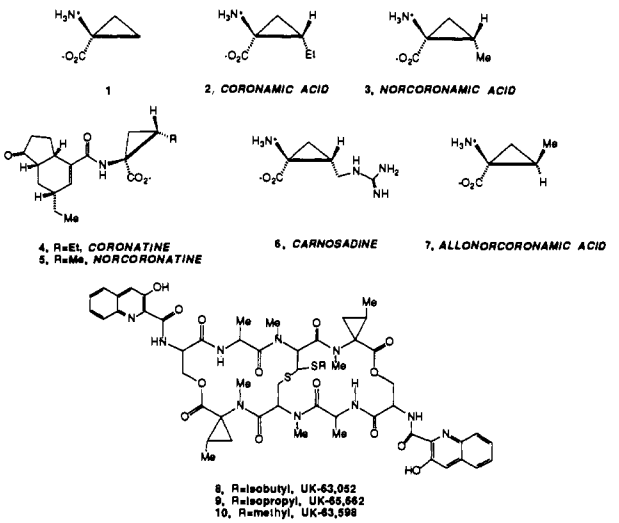
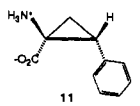


subsp. *japonicus*,[6] and the guanidine-containing ACC, carnosadine (**6**), has been isolated from the marine red algae *Grateloupia carnosa*.[7]

This family of amino acids is of tremendous interest because of their biological activity and potential use in conformationally restricted peptides and as biosynthetic and mechanistic probes.[1] For example, ACC has been found to be the biosynthetic precursor to the plant hormone ethylene[8] and is a substrate to the PLP-linked enzyme ACPC deaminase, which converts ACC to ammonia and 2-ketobutyrate.[9] It has also been shown that allonorcoronamic acid (**7**) is a substrate and the strongest known competitive inhibitor of the ethylene-forming enzyme (EFE) in mung bean hypocotyls.[10]

Cyclopropane amino acids have been incorporated into several peptides and their properties studied.[11] Two interesting examples involving the use of methanophenylalanine (**11**)[12] were enkephalin



analogues, [D-Ala^2,Leu^5,(−)- and (+)-∇^E-Phe^4]enkephalins, and aspartame analogues, Asp-∇-Phe-OR. All four enkephalin analogues were reported to show reduced activity in the mouse vas deferens and guinea pig ileum (GPI) muscle assays, the peptides showing a strong preference for the δ-receptor of the GPI.[13] These studies illustrate the potential medicinal utility of peptides incorporating ACC derivatives. In the case of aspartame analogues, it was expected that at least one of the four diastereomers of Asp-∇-Phe-OMe would be sweet and allow a close mapping of the "sweetness receptor". Unfortunately, all of these compounds were found to be tasteless.[14] In two earlier studies, however, a series of aspartyl dipeptide esters containing 1-aminocyclopropane-1-carboxylic acid at the carboxyl terminus was shown to have a distinct sweet taste.[15] The sweetest of the series, Asp-ACC-O(n-C_3H_7), was found to have 250–300 times the sweetness potency of sucrose.[16] Continued studies of ACC-containing peptides may reveal many interesting properties, such as the following: (1) steric constraints that may alter the chemical reactivity and molecular recognition properties of pendant functional groups along the peptide chain; (2) conformational restriction of the peptide, imparting stabilization from enzymatic hydrolysis and altered receptor-binding properties; and (3) the exposure of potential electrophilic character for covalent modification and/or metal-assisted electrophilic ring opening, ultimately resulting in enzyme inhibition.

Mono- and disubstituted ACCs provide a significant challenge to synthetic chemists due to the difficulty in controlling the relative and absolute stereochemistry around the cyclopropane ring. Existing approaches to the synthesis of this class of amino acids generally involve the following: (1) tandem dialkylation of a glycine equivalent with a 1,2-dibromoalkane or a similar 1,2-disubstituted electrophile (eqs 1 and 2);[17] (2) diazoalkane or dimethylsulfoxonium methylide addition to dehydroamino acid derivatives, followed by extrusion of N_2 gas or elimination of DMSO, respectively (eq 3);[18] (3) use of a resolved dihalocyclopropanecarboxylic acid derivative (eq 4);[9c,19] (4) elaboration of a chiral, nonracemic epoxide (eq 5);[9c] (5) Lewis acid activated ring opening of a substituted epoxide with a lithiated glycine equivalent followed by subsequent cyclization (eq 1);[20] and (6) cyanide addition to α-chloro ketimines or base-induced cyclization of β-chloroimines (eq 6).[21] All of these approaches have their individual strengths and weaknesses and there is no single, general

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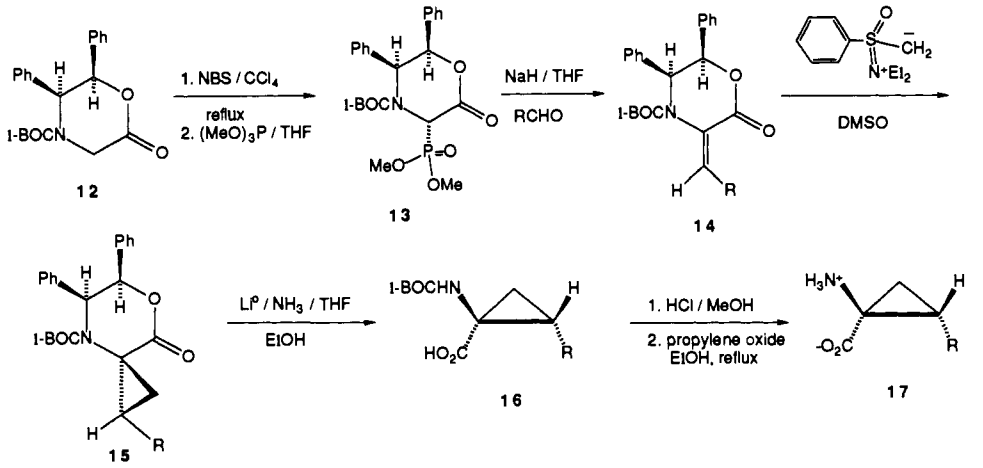
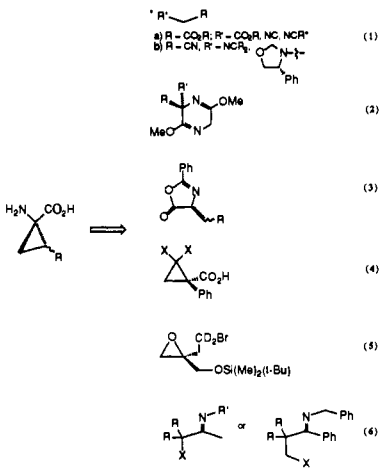
Scheme I



stereocontrolled approach to differentially substituted ACC derivatives in optically pure form. Most of the available syntheses of 2-substituted ACC derivatives are racemic in design, can involve lengthy procedures, and incorporate enzymatic or chemical resolutions as the final step. To date, there exists only three genuine asymmetric syntheses of the title amino acids,[9c,17h,1,18o] and there are no known protocols in which a chiral cyclopropanating reagent has been used to synthesize these compounds. In this account we describe the asymmetric syntheses of [$^2H_2$]-ACC and three representative 2-substituted ACCs that can be obtained by employing the phosphonate ester (**13**).[22] This approach promises to be a general solution to the (*E*)-2-alkyl ACC nucleus and permits the construction of the title amino acids in either *d* or *l* enantiomorphic forms in high optical purity.



Results and Discussion

Lactone **12** was readily brominated as previously detailed[23] with 1.1 mol equiv of *N*-bromosuccinimide (NBS) in refluxing CCl_4 to afford, after cooling and filtration of insoluble succinimide, the α-bromolactone as an amorphous white solid. The crude bromide

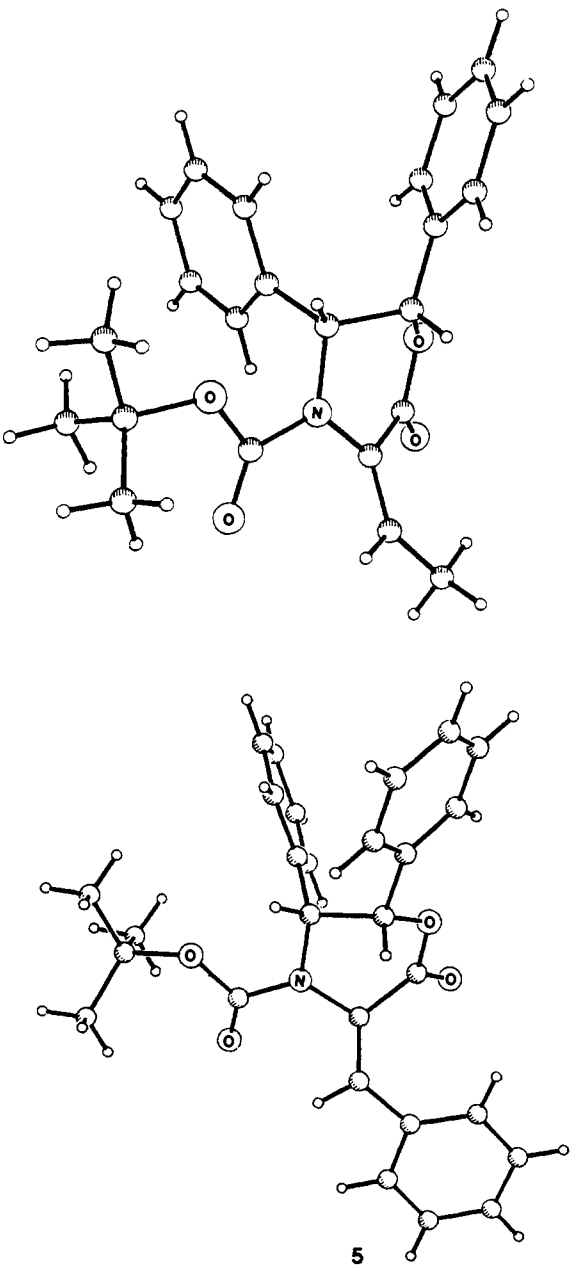


Figure 1. X-ray stereostructures of **14b** and **14f**. Spheres are of fixed, arbitrary radii.

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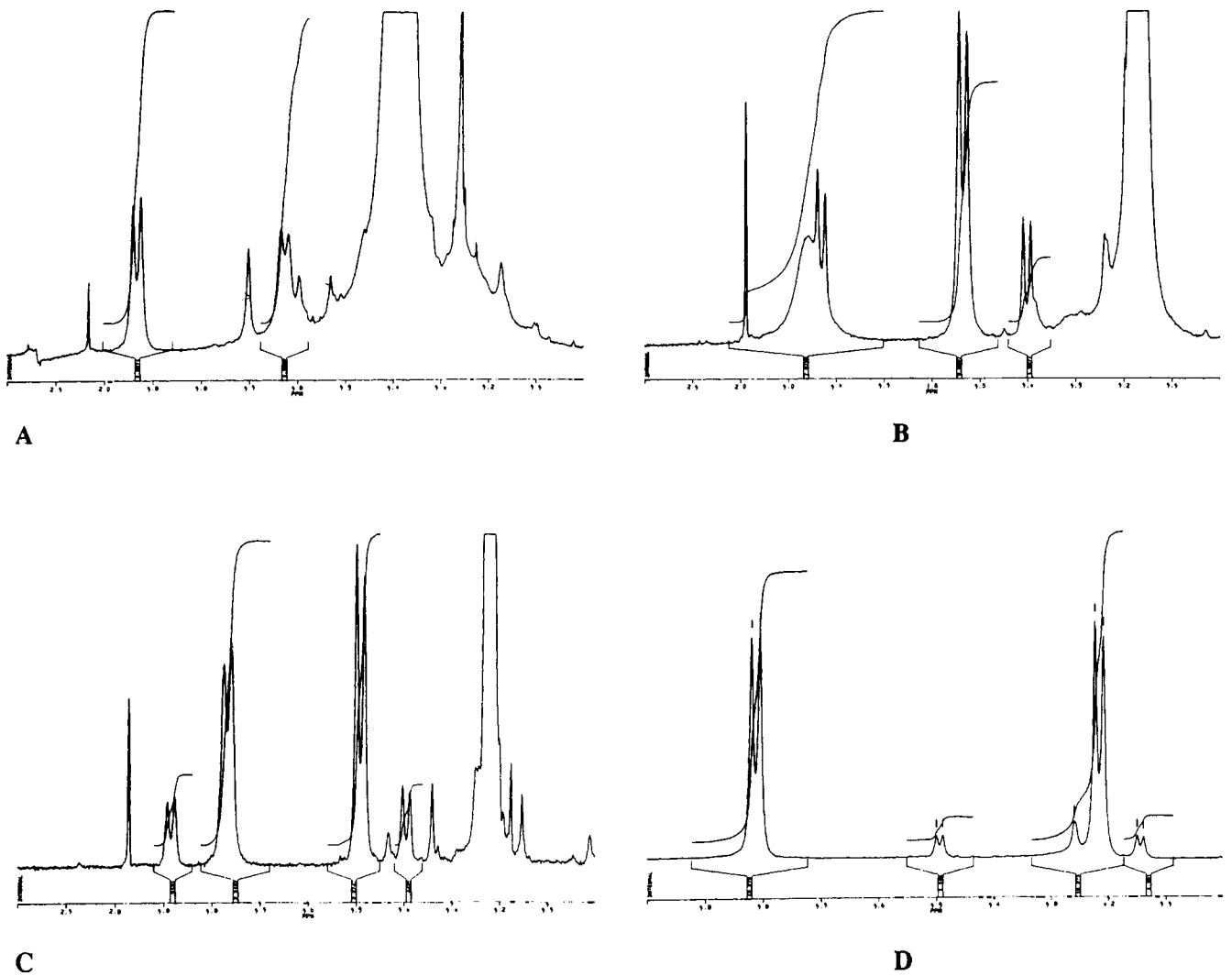


Figure 2. Cyclopropyl resonances from ^1H NMR spectra of **18/19** in $CDCl_3$ (A); DMSO-d_6 at 297 K (B); at 325 K (C); and **22/23** in $CDCl_3$ (D). Spectra A–C were derived from **14a** + dimethyloxosulfonium methylide; D was derived from **14a** + [(diethylamino)phenyl]oxosulfonium methylide.

was immediately dissolved in THF and gently refluxed with a slight excess of trimethyl phosphite to provide the white crystalline phosphonate ester **13** in 86% overall yield (Scheme I). Subsequent treatment of **13** with base and an aldehyde[24] provided the (*E*)-α,β-dehydrolactone adducts **14** in generally high yields (Table I). The assignment of the *E* stereochemistry was firmly established for **14b** and **14f** by X-ray crystallographic analysis (Figure 1). Since all of the final amino acids have a cis orientation of the carboxyl and R groups (vida infra), it follows that **14c–e** and **14g** also possess the *E* stereochemistry.

Attention was then directed to finding a reagent that could cyclopropanate **14** in a highly stereoselective fashion (Scheme I). The first such reagent attempted in this endeavor was the Corey ylide, dimethyloxosulfonium methylide.[25] Upon treatment of **14a** with 1 molar equiv of the NaH-derived ylide, cyclopropanation products were obtained in 92% yield. Initially, the reaction appeared to be 100% stereoselective as determined by ^1H NMR[26] in $CDCl_3$. However, when the product was analyzed in DMSO-d_6, the pair of doublets representing the diastereotopic cyclopropyl methylene protons split into a partially resolved four-doublet system, representing not one but rather two diastereomers in an approximately 3:1 ratio (**18/19**). High-temperature (ca. 75–100 °C) ^1H NMR provided an unambiguous spectrum clearly showing a major and minor diastereomer. Also, the ^1H NMR spectra of **18/19** were only useful for a crude estimation of the diastereomeric ratio since base-line resolution of the *tert*-butoxycarbonyl and cyclopropyl resonances could not be accomplished (Figure 2). In order to obtain a more accurate ratio, **18/19** was deblocked with 20 equiv of TFA in CH_2Cl_2 between 0 °C and room temperature to provide **22/23** in 93% yield (Scheme II).

Removal of the *t*-BOC moiety was used subsequent to all cyclopropanations of **14a**, and the ^1H NMR data of the **22/23** was used exclusively to determine the diastereomeric excess and

Table I. Preparation of α,β-Dehydrolactones **14**

entry	aldehyde	reaction conditions	**14**, % yield[a]	H =, R =
1	H_2CO (^2H_2CO)	NaH/THF, 25 °C	**14a**, quant	^2H, ^2H (H,H)
2	acetaldehyde	LDA/THF, 0 °C → rt	**14b**, 92.8	H, Me
3	propion-aldehyde	LDA/THF, 0 °C → rt	**14c**, 91.5	H, Et
4	butyraldehyde	LDA/THF, 0 °C → rt	**14d**, 81.8	H, *n*-Pr
5	isobutyr-aldehyde	LDA/THF, 0 °C → rt	**14e**, 18.8	H, *i*-Pr
6	benzaldehyde	NaH/ϕH,[b] rt → 80 °C	**14f**, 96.4	H, Ph
7	4-nitrobenz-aldehyde	NaH/ϕH, rt → 80 °C	**14g**, 84.0	H, *p*-NO_2Ph

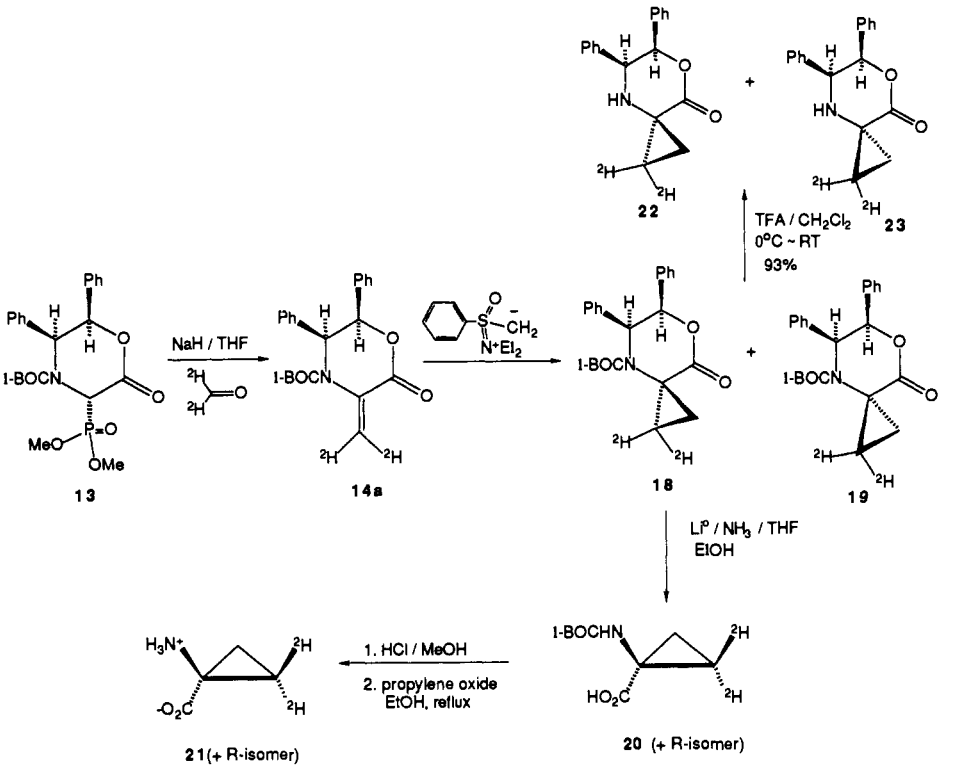
[a] The *E* stereochemistry of the olefin was obtained exclusively for all compounds. [b] ϕH = benzene.

(24) It is assumed that the aldehyde approaches only from the less hindered face of the oxazinone ring, eliminating the other two diastereomeric transition states (see: Reno, D. S.; Lotz, B. T.; Miller, M. J. *Tetrahedron Lett.* **1990**, *31*, 827).

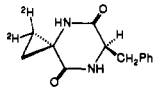
(25) Corey, E. J.; Chaykovsky, M. *J. Am. Chem. Soc.* **1965**, *87*, 1353.

(26) Only one set of cyclopropyl methylene doublets appeared in $CDCl_3$.

Scheme II



thus, the enantiomeric excess of the final amino acid.[27] The facial selectivity of this reaction (vida infra) was *not* in accord with our expectations that attack of the cyclopropanating reagent should occur from the less hindered face of the lactone, anti to the two phenyl rings. The fundamental basis for this stereoselectivity is, at present, undetermined. Confirmation that the stereoselectivity of this cyclopropanation gave **18** as the major isomer was obtained by conversion of the derived amino acid **20** (as a mixture with the inseparable *R* isomer) into the corresponding L-phenylalanine diketopiperazine (i) and comparison of the chemical shifts for the cyclopropyl methylene protons with those reported by Arigoni and associates on the same substance.[9c-e]



i

It is not clear whether the disappointing diastereoselectivity of the Corey ylide is a consequence of poor facial discrimination of the ylide on the α- and β-faces of the olefin, a result of β,γ-rotation of the enolate adduct prior to displacement of DMSO, or a combination of both effects. Nonetheless, these results prompted us to examine alternative cyclopropanating reagents. It seemed reasonable that a 1,3-dipolar cycloaddition of diazomethane to **14a** would produce the desired diastereofacial selectivity[18o] and should also preclude the possibility of bond rotation prior to formation of a spirocyclic adduct (in the present case, pyrazoline). In spite of the unexpected facial preference for the Corey ylide discussed above, it was expected that attack of the 1,3-dipole should occur from the less hindered α-face due to steric interference from the C-5 and/or C-6 phenyl rings. In any event, when **14a** was treated with 10 mol equiv of CH_2N_2 in Et_2O/THF, a mixture of pyrazolines (which were separable by silica gel chromatography) was produced. Subsequent photolysis of the mixture in a quartz tube gave **18** and **19** in a diastereomeric ratio of 1:2–3. This sense of facial selectivity is opposite to that obtained from the dimethyloxosulfonium methylide reaction and was in accord with our expectation that the α-face of the oxazinone should be more accessible. The relatively poor diastereoselection was disappointing and prompted a more detailed examination of additions to the double bond.

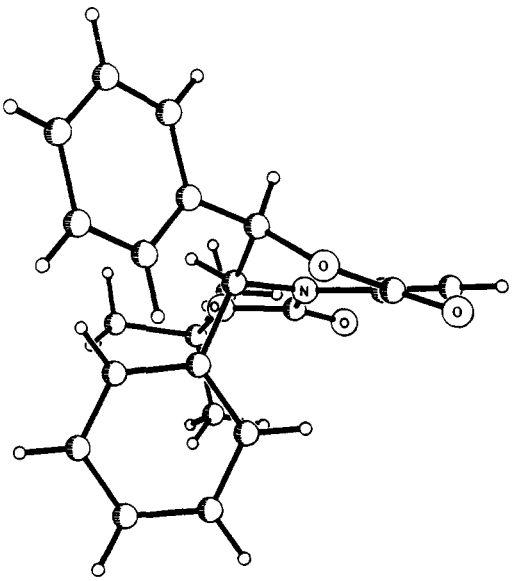


Figure 3. X-ray stereostructure of **14a**. Spheres are of fixed, arbitrary radii.

A closer analysis of the steric environment on the α- and β-faces of the dehydrolactone systems (see also Figure 6, below) was made possible through X-ray crystallography. Contrary to expectation, examination of the X-ray crystal structure of **14a**, **14b**, and **14f** (Figures 1 and 3) does not reveal convincing evidence that the C-5 phenyl ring significantly blocks the β-face of the olefin. As can be observed in Figure 3 for **14a**, the C-5 phenyl group is situated in a quasiaxial disposition relative to the boat-shaped

(27) (a) Reference 17h. (b) Reference 9c. In two previous syntheses of [$^2H_2$]-ACC, ^1H NMR was used as a direct and indirect means of assessing the % ee of the product amino acid. In the Woodard synthesis, a direct assessment of the enantiomeric excess was obtained from the corresponding deuterated cyclopropyl-containing Schollkopf bis(lactim ether). The Arigoni synthesis utilized the diketopiperazine, cyclo[(*S*)-Phe-[$^2H_2$]ACC], as the method to assign % ee.

Table II. Preparation of **15** and **18/19** via Cyclopropanations of **14**

entry	substrate	"CH_2:" reagent	conditions	**15**, % yield	diast ratio
1	**14a**	$(CH_3)_2S^+O(CH_3)I^-$	NaH/DMSO, rt	**18/19**, 98%	2–3:1
2	**14b**	$(CH_3)_2S^+O(CH_3)I^-$	NaH/DMSO, rt	**15b**, 77%	2–3:1
3	**14a**	CH_2N_2[b]	Et_2O, −78 °C → rt	**18/19**, 100%	1:2–3
4	**14b**	CH_2N_2[b]	Et_2O, −78 °C → rt	**15b**, 91%	1:1.6
5	**14a**	$(\pm)Ph(Et_2N)S^+O(CH_3)BF_4^-$	NaH/DMSO, 18 °C → rt	**18/19**, 97.1%	11:1
6	**14b**	$(\pm)Ph(Et_2N)S^+O(CH_3)BF_4^-$	NaH/DMSO, 18 °C → rt	**15b**, 82%	1:0[a]
7	**14c**	$(\pm)Ph(Et_2N)S^+O(CH_3)BF_4^-$	NaH/DMSO, 18 °C → rt	**15c**, 79.3%	1:0[a]
8	**14d**	$(\pm)Ph(Et_2N)S^+O(CH_3)BF_4^-$	NaH/DMSO, 18 °C → rt	**15d**, 88.2%	1:0[a]
9	**14f**	$(\pm)Ph(Et_2N)S^+O(CH_3)BF_4^-$	NaH/DMSO, 18 °C → rt	**15f**, 96.4%	1:0[a]

[a] Ratios determined by ^1H NMR analysis. [b] Diazomethane prepared from 1-methyl-3-nitro-1-nitrosoguanidine (MNNG) and 5 N NaOH (aq) at −15 °C.

oxazinone ring. However, unlike the reactive intermediates of these oxazinone systems with an endo π-system (i.e., enolate or iminium of **12**[23]; see also the X-ray of the *trans*-allyl lactone template previously recorded from this laboratory[23b]), the olefinic geometry of **14** (exo π-system) appears to orient the oxazinone α-carbon further away from the sphere of the C-5 phenyl ring (see Figures 1 and 3) and may account for the poorer facial discrimination relative to the iminium or enolate ions derived from **12**. A manifestation of this situation is the lack of coplanarity of the lactone carbonyl and the α,β-double bond. The dihedral angle between the α,β-alkenyl system and lactone carbonyl for **14a**, **14b**. and **14f** ranges from 22° to 43°, illustrating a significant lack of conjugation between the respective π-systems.

In similar fashion, when compound **14b** was treated with diazomethane followed by photolysis of the pyrazoline intermediate, a separable mixture (91%) of diastereomeric cyclopropanes (**15b** + 1*R*,3*R* diastereomer) in a ratio of 1:1.6 was obtained. As shown in Figure 4, the ^1H NMR spectra for both diastereomers is displayed along with that of the crude mixture. The benzylic methine protons at C-5 and C-6 serve as a useful handle for assessing the diastereomeric ratio. It was later observed that the pyrazoline diastereomers obtained from **14b** were also separable by flash chromatography in the dark and could be cleanly and stereospecifically photolyzed to **15b** plus the corresponding 1*R*,3*R* diastereomer as a toluene solution in quartz glass.

To test the limits of diazoalkane additions to adducts **14**, a solution of diphenyldiazomethane in EtOAc[28] was added to unlabeled **14a** and stirred for 11 days. The corresponding diphenylcyclopropane was obtained in 93% yield as a 6.2:1 mixture of diastereomers (relative stereochemistry not assigned). With this disappointing level of diastereofacial induction, it was clear that the cycloaddition approach would not provide the desired selectivity, regardless of whether bulky substituents were placed on the olefin or on the 1,3-dipole.

The third class of cyclopropanating reagents we examined were [(dimethylamino)- and [(diethylamino)phenyl]oxosulfonium methylides, first prepared by Johnson and co-workers.[29] The chemistry of these ylides parallels that of dimethyloxosulfonium methylide, with the added advantage of increased steric bulk and chirality on sulfur. The reaction between these ylides in their optically pure form and α,β-unsaturated carbonyl compounds has been shown to produce cyclopropanes with enantiomeric excesses of up to 43.2%.[29b,d,f] Although these reagents have been known for close to two decades,[30] no reports have appeared in which ACC derivatives were synthesized with these methylides. The preparation of the requisite ylides involves a straightforward, high-yield, three-step synthesis starting from thioanisole.[29c,d] Most significantly, we found that these reagents gave greatly improved

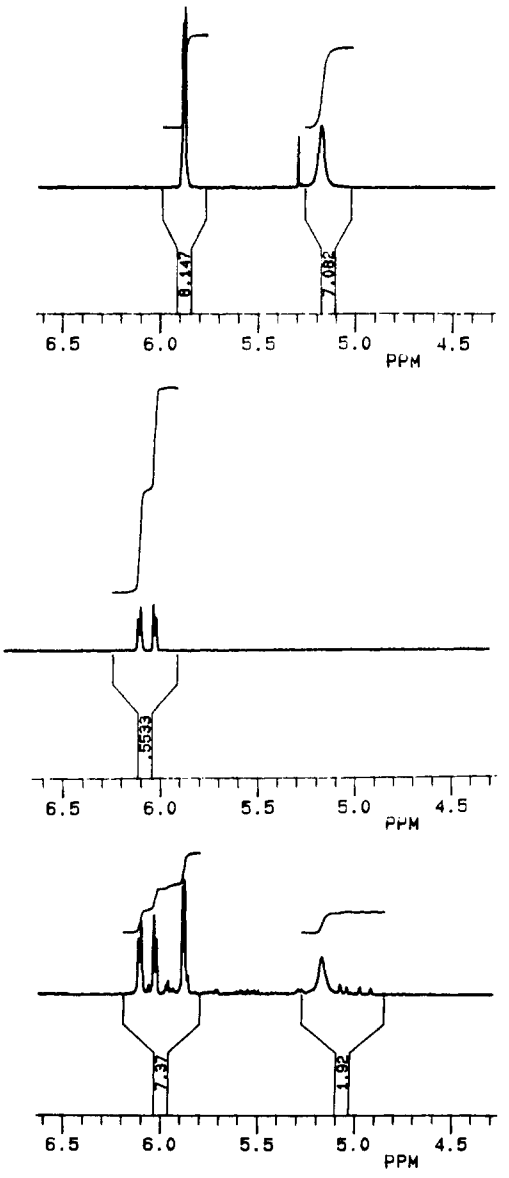


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Figure 4. Benzylic methine resonances from ^1H NMR spectra for **15b** and the corresponding 1*R*,3*R* diastereomer obtained from diazomethane addition to **14b**.

diastereoselectivities over those discussed above and gave the *same* sense of diastereofacial selection as that obtained with dimethyloxosulfonium methylide.

Cyclopropanation of **14a** with 2 molar equiv of [(dimethylamino)phenyl]oxosulfonium methylide in DMSO at room temperature provided a 76% yield of **18/19** (Scheme II) in an approximate ratio of 6.3:1. Similar treatment of **14a** with [(diethylamino)phenyl]oxosulfonium methylide provided cyclo-

(28) Trozzolo, A. M.; Murray, R. W. *J. Am. Chem. Soc.* **1961**, *26*, 3109.
(29) (a) Johnson, C. R.; Janiga, E. R.; Haake, M. *J. Am. Chem. Soc.* **1968**, *90*, 3890. (b) Johnson, C. R.; Schroeck, C. W. *J. Am. Chem. Soc.* **1968**, *90*, 6852. (c) Johnson, C. R.; Haake, M.; Schroeck, C. W. *J. Am. Chem. Soc.* **1970**, *92*, 6594. (d) Johnson, C. R.; Schroeck, C. W. *J. Am. Chem. Soc.* **1973**, *95*, 7418. (e) Johnson, C. R.; Schroeck, C. W.; Shanklin, J. R. *J. Am. Chem. Soc.* **1973**, *95*, 7424. (f) Johnson, C. R.; Janiga, E. R. *J. Am. Chem. Soc.* **1973**, *95*, 7692. (g) Johnson, C. R.; Rogers, P. E. *J. Org. Chem.* **1973**, *38*, 1793. (h) Johnson, C. R.; Rogers, P. E. *J. Org. Chem.* **1973**, *38*, 1798.
(30) For a comprehensive review on the synthetic applications of sulfoximines, see: Johnson, C. R. *Aldrichimica Acta* **1985**, *18*, 3.

Scheme III

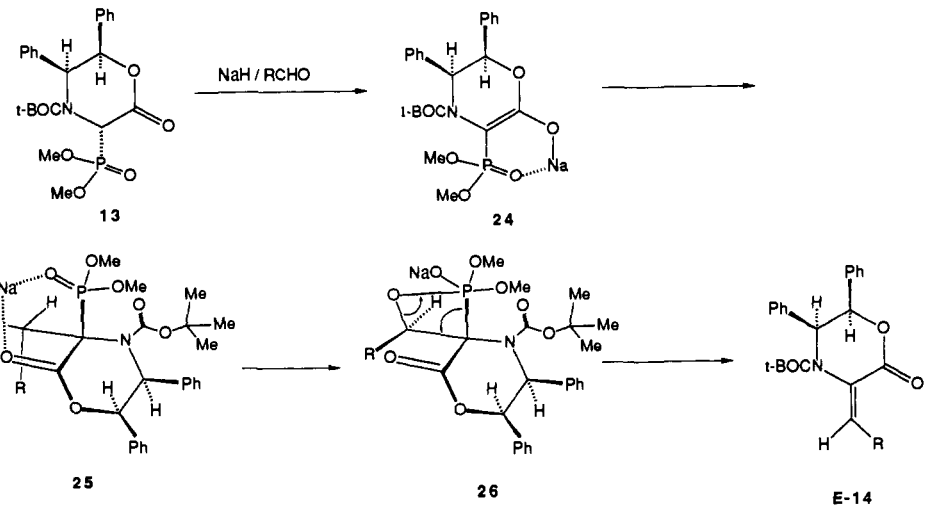


Table III. Cyclopropane Amino Acids

entry	substrate	*t*-BOC-amino acids (% yield)	free amino acids (% yields)	% ee
1	**18/19**	**20** (65.4)	**21** (100)	83.3
2	**15b**	**16b** (63.2)	**17b** (100)	>99
3	**15c**	**16c** (64.4)	**17c** (100)	>99
4	**15d**	**16d** (60.9)	**17d** (98.6)	>99

propanes **18** and **19** in 94.4% yield (as a 9.6:1 ratio). As expected, changing the amino alkyl substituent from methyl to ethyl on the ylide had a significant, albeit small, effect on the stereoselectivity of the cyclopropanation reaction. In addition, it was observed that by simply running the latter reaction at approximately 18 °C (freezing point of DMSO) followed by slow thawing, the ratio could be increased to 11:1. Utilizing the same freeze–thaw technique, adducts **14b–f** gave excellent yields of the corresponding cyclopropanes, and furthermore, only a single diastereomer was isolated in each case (Table II). As mentioned previously, assignment of the diastereochemical ratios could be determined by observing the C-5 and C-6 benzylic methine protons by ^{1}H NMR.

With high levels of diastereoselectivity now accessible, it was necessary to deblock the cyclopropyl lactones to the free amino acids and thus rigorously determine the absolute stereochemistry of each. Thus, treatment of cyclopropanes **15b–d** (and **18/19**) with Li^0 in liquid NH_3 (Schemes I and II) provided the *N*-*t*-BOC-protected amino acids (**16b–d, 20**) in good yield (Table III).

The phenylcyclopropyl lactone system **15f** could obviously not be deprotected by dissolving metal reduction to methanophenylalanine (**11**) due to both the lability of the aromatic ring to reduction and the highly reactive benzylic cyclopropane bond; this was verified experimentally. We have attempted to remove the chiral auxiliary by the stepwise hydrolysis/periodate cleavage protocol first described by Weinges[31] on a related heterocycle and employed successfully by us[32] on the α-aryl oxazinones to provide arylglycines. Unfortunately, **15f** has thus far proved recalcitrant to this procedure and will require additional study.

To remove the *t*-BOC protecting group, compounds **16b–d** and **20** were treated with 40 molar equiv of anhydrous 1 N HCl in MeOH, produced in situ from acetyl chloride and methanol. The hydrochloride salts of (**17b–d, 21**) were obtained quantitatively and immediately treated for 20 min with a refluxing mixture of excess propylene oxide in EtOH to produce, in essentially quantitative yield, the free amino acids coronamic acid (**2**), norcoronamic acid (**3**), **17d**, and **21** (Table III). This procedure works extremely well and obviates the need for ion-exchange chromatography.

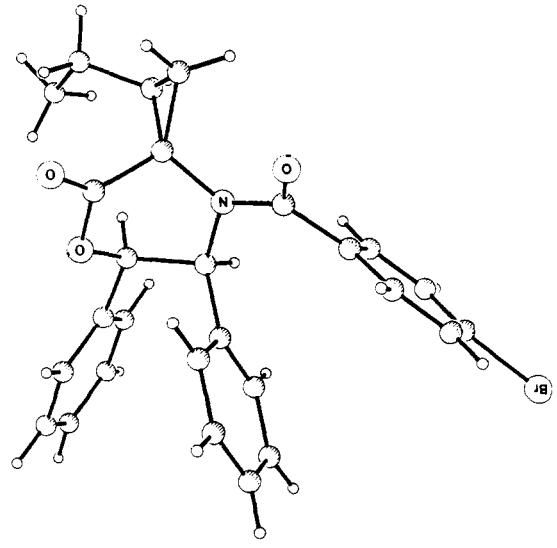


Figure 5. X-ray stereostructure of the *N*-*p*-bromobenzoyl derivative prepared from **15c**. Spheres are of fixed, arbitrary radii.

To confirm the absolute stereochemistry of the final cyclopropane amino acids, assignments were made, in part, by comparing the optical rotations of coronamic acid (**2**) and norcoronamic acid (**3**) with those reported in the literature.[17b,33] In addition, the relative stereochemistry of the cyclopropyl lactone **15c** was rigorously determined by X-ray analysis of the *N*-*p*-bromobenzoyl derivative (see the Experimental Section and Figure 5). This structure clearly shows both that the alkene geometry is preserved and that sulfoximine attack on the lactone proceeds from the top (β) face of the double bond. Since the absolute configuration of the lactone systems has been well-established, and presuming that all of the cyclopropanations with the sulfoximine proceed from the top face (β-face, Figure 6) (this is further corroborated by similarities in ^{1}H NMR behavior), the stereochemistry of all cyclopropane products (**15–23**) is, therefore, that depicted in the schemes.

Several interesting stereochemical points need to be mentioned. The stereoselectivity of the olefination reactions (**13** → **14**, Scheme I) is unusual both in the sense of stereochemistry (*E*-selective) and the complete absence of the *Z* isomer. This stereochemical outcome is probably a direct result of the steric interaction between the aldehyde R group and the bulky *t*-BOC protecting group experienced by the two diastereomeric betaine transition states (see **25**, Scheme III).[24] Generally, it has been observed that

(31) Weinges, K.; Brachmann, H.; Stahnecker, P.; Rodewald, H.; Nixdorf, M.; Irngartinger, H. *Liebigs Ann. Chem.* **1985**, 566.
(32) Williams, R. M.; Hendrix, J. A. *J. Org. Chem.* **1990**, *55*, 3723.
(33) Baldwin, J. E.; Adlington, R. M.; Rawlings, B. J.; Jones, R. H. *Tetrahedron Lett.* **1985**, *26*, 485.

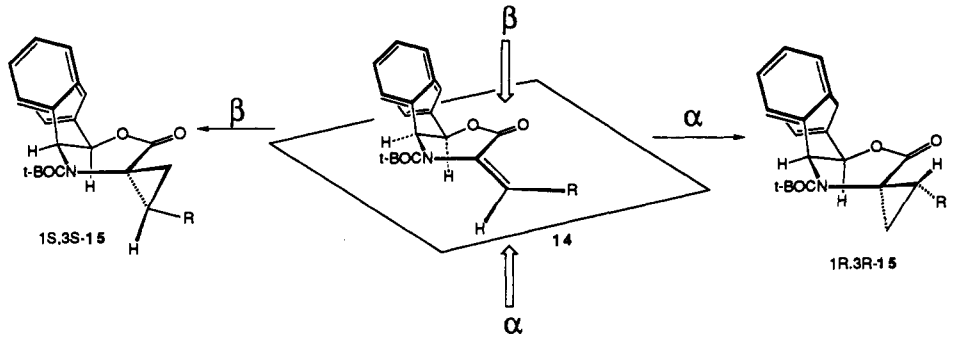
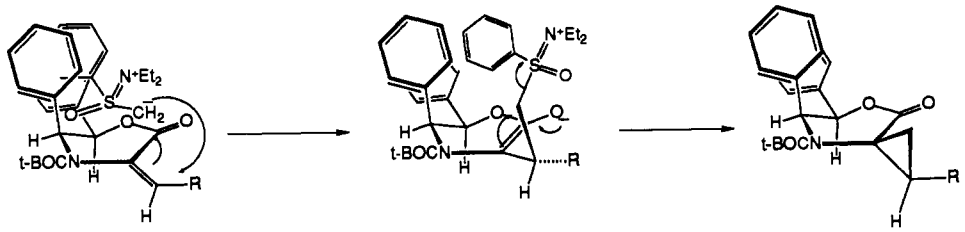


Figure 6.

Scheme IV



condensations involving dialkoxyphosphorylglycine derivatives and aldehydes result in the formation of *E*/*Z*-alkene isomer mixtures with the *Z* stereochemistry being predominant.[22d-m] Very recently, Seebach has reported the preparation of an (*E*)-α,β-dehydroamino acid derivative via the phosphoryl condensation approach.[22n]

The high degree of facial selectivity of the cyclopropanations with the sulfoximine versus the poorer selectivity of the other cyclopropanating reagents discussed above may be attributable to π-stacking interactions of the phenyl ring of the sulfur ylide and the phenyl rings of the oxazinone, thus delivering the methylide from the β-face of the double bond (**13** → **27**, Scheme IV; see also Figure 6). Although this hypothesis is purely speculative, it is hopeful that further studies of this reaction will provide a clearer explanation for the unusual selectivity. Examination of molecular models of the putative transition state leading to **27** reveals positioning of the methylide carbon directly over the β-carbon p orbital. As mentioned above, the X-ray structures[34] of the three α,β-dehydrolactones do not give a convincing impression that either the α-face or β-face is significantly shielded sterically nor is the alkene geometry distorted to any significant extent out of the trigonal plane. Finally, we did not detect the presence of the (*Z*)-cyclopropane adducts in any case that could have arisen by rotation of Michael-type adducts **27** (Scheme IV) prior to cyclization to the cyclopropane.

In summary, this paper serves to illustrate the utility of the optically active glycine phosphinate ester **13** as a practical and efficient vehicle to selectively prepare *E*-substituted 1-aminocyclopropane-1-carboxylic acid derivatives. Significantly, due to the propensity of phosphorylglycine olefinations to produce the *Z* isomers, cyclopropanations of these substrates also produce as major products, the *Z*-substituted cyclopropanes. The methodology described herein, therefore, nicely complements the existing approaches to this class of amino acids. Finally, the availability[35] of both enantiomers of **12** allows for the unambiguous preparation of either the *d* or *l* forms of the final amino acids. Additional studies aimed at elaborating the dehydrolactone derivatives at both the α- and β-positions as well as methods to prepare the methanophenylalanine and *Z* stereochemical series are under investigation in these laboratories and will be reported on in due course.

(34) The details of all X-ray crystal structure determinations will be published in detail elsewhere.

(35) Both antipodes of **12** are commercially available from the Aldrich Chemical Co.: 12: catalog no. 33-181-3; antipode of **12**: catalog no. 33, 184-8.

Experimental Section

General Information. ^{1}H NMR spectra were obtained on a Bruker AC 300 MHz spectrometer and 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 a wavelength of 589 nm (sodium "D" line) with 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 ±0.4% of the calculated values. Column chromatography was performed with Merck silica gel grade 60, 230–400 mesh, 60 Å. Reagents and solvents were dried or purified in the following ways. Tetrahydrofuran and benzene were distilled from sodium benzophenone ketyl. Carbon tetrachloride, dimethyl sulfoxide, and diisopropylamine were distilled from CaH_2. Methanol and trimethyl phosphite were distilled from Na^0. All aldehydes except [^{2}H]paraformaldehyde were dried over $CaCl_2$ and freshly distilled prior to use. *N*-Bromosuccinimide was recrystallized from H_2O and dried under vacuum prior to use. Purification of the free amino acids were accomplished by eluting an aqueous sample on a Sep-Pak C_{18} (reverse phase) cartridge manufactured by Waters, a division of Millipore Corp.

(3*S*,5*S*,6*R*)-4-(*tert*-Butoxycarbonyl)-3-(dimethoxyphosphoryl)-5,6-diphenyl-2,3,5,6-tetrahydro-4*H*-1,4-oxazin-2-one (13). To a flask containing **12**[35] (3.0 g, 8.49 mmol, 1.0 equiv) and NBS (1.7 g, 9.34 mmol, 1.1 equiv) was added CCl_4 (500 mL). The mixture was refluxed for 1 h and then cooled to 0 °C, filtered through Celite to remove succinimide, and concentrated in vacuo to yield the bromide as a white solid. To the crude bromide was added THF (36 mL) and trimethyl phosphite (1.1 mL, 9.34 mmol, 1.1 equiv) and the mixture was gently refluxed for 12 h. The mixture was then cooled to room temperature and concentrated providing a yellow viscous oil. Purification via flash silica chromatography (160 g silica, eluted with 1:10–1:1 EtOH/hexanes) provided 3.4 g (86.3%, two steps) of **13** as a white crystalline solid: ^{1}**H** NMR (300 MHz) (DMSO-d_6) δ TMS 1.03 (s) and 1.39 (s) (9 H), 3.81–3.93 (6 H, m), 5.25 (d, *J* = 3.1 Hz) and 5.33 (d, *J* = 2.9 Hz) (1 H), 5.54–5.68 (1 H, m), 6.18 (d, *J* = 2.9 Hz) and 6.33 (d, *J* = 3.1 Hz) (1 H), 6.55–6.59 (2 H, m), 7.04–7.31 (8 H, m); IR (KBr) ν 3030, 3019, 2976, 2964.7, 2921, 2856, 1959, 1889, 1747, 1703, 1295, 1273, 1049, 1028 cm^{-1}; $[\alpha]^{25}_D$ −38.55° (*c* 1.0, CH_2Cl_2); mp 143–144 °C. Anal. (recrystallized from EtOH) Calcd for $C_{23}H_{28}NO_7P$: C, 59.87; H, 6.12; N, 3.04. Found: C, 59.82; H, 6.21; N, 3.10.

(5*S*,6*R*)-4-(*tert*-Butoxycarbonyl)-5,6-diphenyl-3-([^{2}H$_2$]-methylidene)-2,3,5,6-tetrahydro-4*H*-1,4-oxazin-2-one (14a). To a flask containing **13** (619.7 mg, 1.34 mmol, 1.0 equiv) and a 50% NaH dispersion (64.5 mg, 1.34 mmol, 1.0 equiv) was added THF (15 mL) at

room temperature. The resulting solution was stirred for 1 h, and then paraformaldehyde-d_2 (43.0 mg, 1.34 mmol, 1.0 equiv) was added in one portion. After the reaction was stirred for 24 h, saturated NH_4Cl was added, followed by extraction with 3 × 5 mL EtOAc. The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated. Purifiation via flash silica chromatography (20 g of silica, eluted with 1:10–1:1 EtOAc/hexanes) provided 479 mg (97.1%) of **14a** as a white crystalline solid: ^{1}H NMR (300 MHz) ($CDCl_3$) δ TMS 1.27 (9 H, s), 5.29 (1 H, d, J = 2.8 Hz), 5.79 (1 H, d, J = 2.8 Hz), 6.65–6.68 (2 H, m), 7.00–7.32 (8 H, m); IR (KBr) ν 3090, 3065, 3034, 3004, 2985, 2932, 1954, 1889, 1736, 1705, 1570, 1560, 1455, 1387, 1353, 1297, 1282, 1269, 1154, 1066 cm^{-1}; $[\alpha]^{25}_D$ −111.3° (c 1.0, CH_2Cl_2); mp 163–165 °C. Anal. (recrystallized from EtOH) Calcd for $C_{22}H_{23}NO_4$: C, 72.31; H, 6.34; N, 3.83. Found: C, 72.54; H, 6.45; N, 3.86. A single-crystal X-ray analysis of this compound has been solved (Figure 3).[34]

(*E*)-(5*S*,6*R*)-4-(*tert*-Butoxycarbonyl)-5,6-diphenyl-3-ethylidene-2,3,5,6-tetrahydro-4*H*-1,4-oxazin-2-one (14b). To a 0 °C solution of **13** (1.0 g, 2.17 mmol, 1.0 equiv) in THF (5 mL) was added 0.5 M LDA in THF (4.35 mL, 2.17 mmol, 1.0 equiv) via cannula. After this mixture was stirred for 1 h, acetaldehyde (606 mL, 10.84 mmol, 5.0 equiv) was added rapidly via syringe, and the resulting mixture was stirred for 7 h at 0 °C and an additional 12 h at room temperature. The reaction was quenched with 3 mL of brine and extracted with 3 × 5 mL EtOAc. The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated. Purification via flash silica chromatography (50 g of silica, eluted with 1:10–1:1 EtOAc/hexanes) provided 763.3 mg (92.8%) of **14b** as a white crystalline solid: ^{1}H NMR (300 MHz) ($CDCl_3$) δ TMS 1.14 (9 H, s), 2.17 (3 H, d, J = 7.5 Hz), 5.16 (1 H, d, J = 1.9 Hz), 5.72 (1 H, d, J = 2.8 Hz), 6.66–6.83 (3 H, m), 6.96–6.99 (2 H, m), 7.07–7.28 (6 H, m); IR (KBr) ν 3065, 3027, 3016, 2989, 2974, 2929, 2918, 1749, 1713, 1637, 1630, 1458, 1378, 1371, 1353, 1333, 1280, 1259, 1233, 1152, 1061 cm^{-1}, $[\alpha]^{25}_D$ −123.3° (c 1.0, CH_2Cl_2); mp 168–170 °C. Anal. (recrystallized from EtOH) Calcd for $C_{23}H_{25}NO_4$: C, 72.80; H, 6.64; N, 3.69. Found: C, 72.77; H, 6.82; N, 3.73. A single-crystal X-ray analysis of this compound has been solved (Figure 1).[34]

(*E*)-(5*S*,6*R*)-4-(*tert*-Butoxycarbonyl)-5,6-diphenyl-3-propylidene-2,3,5,6-tetrahydro-4*H*-1,4-oxazin-2-one (14c). To a −15 °C solution (ice/MeOH) of **13** (1.0 g, 2.17 mmol, 1.0 equiv) in THF (2 mL) was added 3.7 mL of 0.6 M LDA in THF (2.17 mmol, 1.0 equiv) via syringe. The resulting reaction was stirred for 1.5 h, followed by addition of propionaldehyde (1.6 mL, 21.67 mmol, 10.0 equiv) at −15 °C. The reaction was slowly warmed to room temperature and stirred for 20 h, quenched with 5 mL of saturated NaCl, and extracted with 3 × 5 mL EtOAc. The organic fractions were combined, dried over $MgSO_4$, filtered, and the solvent removed in vacuo. Flash silica gel chromatography (68 g silica, eluted with 1:1 EtOAc/hexanes) provided 780 mg (91.5%) of **14c** as a white crystalline solid: ^{1}H NMR (300 MHz) ($CDCl_3$) δ TMS 1.14–1.19 (12 H, m), 2.51–2.74 (2 H, m), 5.16 (1 H, d, J = 1.95 Hz), 5.72 (1 H, d, J = 2.89 Hz), 6.63–6.70 (3 H, m), 6.96–6.99 (2 H, m), 7.07–7.28 (6 H, m); IR (NaCl, neat) ν 3089, 3067, 3033, 2978, 2933, 2878, 1739, 1711, 1628, 1283.3, 1233, 1161 cm^{-1}; $[\alpha]^{25}_D$ −135.3° (c 1.0, CH_2Cl_2); mp 158.5–160 °C. Anal. (recrystallized from EtOH) Calcd for $C_{24}H_{27}NO_4$: C, 73.26; H, 6.92; N, 3.56. Found: C, 73.06; H, 7.03; N, 3.65.

(*E*)-(5*S*,6*R*)-4-(*tert*-Butoxycarbonyl)-3-butylidene-5,6-diphenyl-2,3,5,6-tetrahydro-4*H*-1,4-oxazin-2-one (14d). To a 0 °C solution of **13** (1.0 g, 2.17 mmol, 1.0 equiv) in THF (4 mL) was added 0.5 M LDA in THF (4.3 mL, 2.17 mmol, 1.0 equiv). The mixture was stirred for 1 h at 0 °C, and then butyraldehyde (976.7 μL, 10.84 mmol, 5.0 equiv) was added via syringe, the temperature was maintained at 0 °C for 16 h, and the reaction was stirred at room temperature for 2 days. To the mixture was added brine (3 mL), followed by extraction with 3 × 5 mL EtOAc. The organic extracts were combined, dried over $MgSO_4$, filtered, and concentrated. Purification via flash silica chromatography (45 g silica, eluted with 1:10 EtOAc/hexanes) provided 722.5 mg (81.8%) of **14d** as a white crystalline solid and 64.1 mg (6.4%) of recovered starting material: ^{1}H NMR (300 MHz) ($CDCl_3$) δ TMS 1.01 (3 H, t, J = 7.4 Hz), 1.16 (9 H, s), 1.58 (2 H, m), 2.61 (2 H, m), 5.17 (1 H, apparent s), 5.71 (1 H, d, J = 2.9 Hz), 6.62–6.69 (3 H, m), 6.96–7.00 (2 H, m), 7.07–7.26 (6 H, m); IR (KBr) ν 3090, 3067, 3032, 3002, 2965, 2931, 2871, 1734, 1708, 1637, 1630, 1454, 1387, 1287, 1259, 1227, 1164, 1123, 1058 cm^{-1}; $[\alpha]^{26}_D$ −127.9° (c 1.0, CH_2Cl_2); mp 167–169 °C. Anal. (recrystallized from EtOH) Calcd for $C_{25}H_{29}NO_4$: C, 73.68; H, 7.17; N, 3.44. Found: C, 73.56; H, 7.18; N, 3.38.

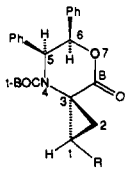
(*E*)-(5*S*,6*R*)-4-(*tert*-Butoxycarbonyl)-5,6-isobutylidene-2,3,5,6-tetrahydro-4*H*-1,4-oxazin-2-one (14e). To a −15 °C solution of **13** (354.2 mg, 0.77 mmol, 1.0 equiv) in THF (1 mL) was added 0.5 M LDA (1.6 mL, 0.77 mmol, 1.0 equiv) via cannula. After the solution was stirred for 15 min, isobutyraldehyde (697.1 μL, 7.68 mmol, 10.0 equiv) was added while a −15 °C temperature was maintained for 8.0 h. The reaction was then stirred for 30 h at room temperature, quenched with brine (3 mL), and extracted with 3 × 5 mL EtOAc. The organic fractions were combined, dried over $MgSO_4$, and filtered. Purification via flash silica chromatography (26 g of silica, eluted with 1:10–1:1 EtOAc/hexanes) provided 168.7 mg of **14e** contaminated with a coeluting byproduct (same R_f). The mixed fraction was recrystallized from EtOH to provide 72.1 mg (32.1%) of **14e** as a white crystalline solid: ^{1}H NMR (300 MHz) ($CDCl_3$) δ TMS 1.07 (3 H, d, J = 6.6 Hz), 1.18 (9 H, s), 1.27 (3 H, d, J = 6.6 Hz), 3.21–3.33 (1 H, m), 5.16 (1 H, apparent s), 5.71 (1 H, d, J = 2.9 Hz), 6.42 (1 H, m), 6.67–6.70 (2 H, m), 6.96–7.32 (8 H, m); IR (KBr) ν 3089, 3065, 3028, 3005, 2972, 2927, 2869, 1734, 1714, 1629, 1456, 1388, 1350, 1295, 1283, 1259, 1238, 1160, 1126, 1056 cm^{-1}; $[\alpha]^{25}_D$ −127.8° (c 1.0, CH_2Cl_2); mp 197–198.5 °C. Anal. (recrystallized from EtOH) Calcd for $C_{25}H_{29}NO_4$: C, 73.68; H, 7.17; N, 3.44. Found: C, 73.56; H, 7.18; N, 3.38.

(*E*)-(5*S*,6*R*)-3-Benzylidene-4-(*tert*-butoxycarbonyl)-5,6-diphenyl-2,3,5,6-tetrahydro-4*H*-1,4-oxazin-2-one (14f). To a flask containing **13** (1.0 g, 2.17 mmol, 1.0 equiv) and a 50% NaH dispersion in oil (104 mg, 2.17 mmol, 1.0 equiv) was added benzene (15 mL). The reaction was stirred for 6.5 h at room temperature, followed by the addition of benzaldehyde (242.3 μL, 2.38 mmol, 1.1 equiv) via syringe. The flask was fitted with a Dean–Stark trap and condenser, and the reaction was heated such that benzene could distill off at a slow rate. The reaction was concentrated to ~1 mL volume, heated gently overnight, cooled to room temperature, and purified via flash silica chromatography (30 g of silica, eluted with 1:10–1:1 EtOAc/hexanes) to provide 922.8 mg (96.4%) of **14f** as a white crystalline solid and ~4% recovered starting material: ^{1}H NMR (300 MHz) ($CDCl_3$) δ TMS 1.20 (9 H, s), 5.25 (1 H, d, J = 2.7 Hz), 5.89 (1 H, d, J = 2.7 Hz), 6.70–6.73 (2 H, m), 6.99–7.57 (14 H, m); IR (KBr) ν 3096, 3063, 3030, 2997, 2976, 2932, 1960, 1905, 1741, 1703, 1627, 1605, 1453, 1344, 1305, 1235, 1213, 1158 cm^{-1}; $[\alpha]^{25}_D$ −141.8° (c 1.0, CH_2Cl_2); mp 187–189 °C. Anal. (recrystallized from EtOH) Calcd for $C_{28}H_{27}NO_4$: C, 76.17; H, 6.16; N, 3.17. Found: C, 76.16; H, 6.12; N, 3.14. A single-crystal X-ray analysis of this compound has been solved (Figure 1).[34]

(*E*)-(5*S*,6*R*)-5,6-Diphenyl-3-(4′-nitrobenzylidene)-4-(*tert*-butoxycarbonyl)-2,3,5,6-tetrahydro-4*H*-1,4-oxazin-2-one (14g). To a mixture of **13** (200 mg, 0.43 mmol, 1.0 equiv) and degreased NaH (10.4 mg, 0.43 mmol, 1.0 equiv) was added benzene (10 mL). The resulting slurry was stirred for 1 h, followed by addition of 4-nitrobenzaldehyde (72.0 mg, 0.48 mmol, 1.1 equiv). After this mixture was stirred for 0.5 h, the flask was fitted with a Dean–Stark trap and condenser and the reaction was heated such that benzene could be distilled off at a slow rate. The reaction was concentrated to ~1 mL volume, heated gently for 5 h, and then cooled to room temperature. The crude residue was redissolved in CH_2Cl_2 (8 mL), washed with H_2O, dried over $MgSO_4$, filtered, and concentrated. Purification via flash silica gel chromatography (11.2 g of silica, eluted with 1:10 EtOAc/hexanes) provided 178.5 mg (84.7%) of **14g** as a light yellow crystalline solid: ^{1}H NMR (300 MHz) ($CDCl_3$) δ TMS 1.20 (9 H, s), 5.27 (1 H, d, J = 2.7 Hz), 5.90 (1 H, d, J = 2.7 Hz), 6.70 (2 H, apparent d, J = 7.3 Hz), 6.99–7.02 (2 H, m), 7.11–7.33 (6 H, m), 7.69 (3 H, apparent d, J = 9.1 Hz), 8.21 (2 H, d, J = 8.8 Hz); IR (KBr) ν 3067, 3034, 2977, 2934, 1750, 1709, 1599, 1519, 1346, 1284, 1258, 1209, 1155, 1059 cm^{-1}; $[\alpha]^{25}_D$ −150.1° (c 1.02, CH_2Cl_2); mp 156–158 °C. Anal. (recrystallized from EtOH) Calcd for $C_{28}H_{26}N_2O_6$: C, 69.13; H, 5.39; N, 5.76. Found: C, 68.95; H, 5.44; N, 5.73.

(3*S*,5*S*,6*R*)- and (3*R*,5*S*,6*R*)-4-(*tert*-Butoxycarbonyl)-1,1-dideuterio-5,6-diphenyl-7-oxa-4-azaspiro[2.5]octan-8-one (18/19).[36] To a mixture of (±)-[[(diethylamino)methyl]phenyl]oxosulfonium tetrafluoroborate (1.05 g, 3.52 mmol, 1.5 equiv) and a 50% NaH dispersion (168.9 g, 3.52 mmol, 1.5 equiv) was added DMSO (5 mL) at room temperature. The reaction was stirred for 1.0 h, and then the freshly prepared ylide was added via cannula to a partially frozen slurry of **14a** (862 mg, 2.35 mmol, 1.0 equiv) in DMSO (5 mL). The reaction was slowly warmed to room temperature and stirred for 4 days. To the mixture was added brine (3 mL), followed by extraction with 4 × 5 mL EtOAc. The organic fractions were combined, washed with several portions of H_2O, dried over $MgSO_4$, filtered, and concentrated. Puri-

(36) The numbering system for the spiro-fused cyclopropyl lactones is shown below:



fication via flash silica chromatography (6.7 g of silica, eluted with 1:10 EtOAc/hexanes) provided 856.4 mg (95.7%) of white crystalline **18/19** in an 11:1 ratio: ^{1}H NMR (300 MHz) (DMSO-d_6) δ TMS 1.17 (9 H, s), 1.40 (d, J = 4.7 Hz) and 1.53 (d, J = 4.9 Hz) (1 H), 1.82–1.86 (1 H, m), 5.47 (1 H, d, J = 3.0 Hz), 6.30 (1 H, d, J = 3.3 Hz), 6.80–6.83 (2 H, m), 7.12–7.31 (8 H, m); IR (KBr) ν 3109, 3090, 3065, 3034, 3004, 2985, 2932. 1954, 1889, 1736, 1705, 1570, 1560, 1455, 1387, 1353, 1297, 1282, 1269, 1154, 1066 cm^{-1}; $[\alpha]^{25}_D$ +52.6° (c 1.0, CH_2Cl_2); mp 110–112 °C. Anal. (recrystallized from EtOH) Calcd for $C_{23}H_{25}NO_4$: C, 72.80; H, 6.64; N, 3.69. Found: C, 72.74; H, 6.63; N, 3.70.

(3*S*,5*S*,6*R*)- and (3*R*,5*S*,6*R*)-1,1-Dideuterio-5,6-diphenyl-7-oxa-4-azaspiro[2.5]octan-8-one (22/23). To a 0 °C solution of **18/19** (93.5 mg, 0.25 mmol, 1.0 equiv) in CH_2Cl_2 (10 mL) was added trifluoroacetic acid (378 μL, 4.90 mmol, 20 equiv). The mixture was allowed to slowly warm to room temperature while stirring for 24 h. Solvent and excess TFA were removed in vacuo, and the crude trifluoroacetate salt was redissolved in CH_2Cl_2 (5 mL) followed by treatment with Et_3N (1 mL). The solution was washed with H_2O (to remove triethylammonium trifluoroacetate), dried over $MgSO_4$, filtered, and concentrated. Purification via flash chromatography (3 g of silica, eluted with 1:10 EtOAc/hexanes) provided 64.3 mg (93.2%) of white crystalline **22/23** in an 11:1 ratio: ^{1}H NMR (300 MHz) ($CDCl_3$) δ TMS 1.14 (d, J = 3.3 Hz) and 1.21 (d, J = 4.4 Hz) (1 H), 1.49 (d, J = 3.3 Hz) and 1.81 (d, J = 4.4 Hz) (1 H), 2.64 (1 H, broad s), 4.84 (1 H, d, J = 3.8 Hz), 5.90 (1 H, d, J = 3.8 Hz), 6.74–6.87 (4 H, m), 7.15–7.27 (6 H, m); IR (NaCl, neat) ν 3313, 3087, 3067, 3026, 2964, 2923, 2872, 1723, 1600, 1451, 1374, 1128, 1062, 1021 cm^{-1}; $[\alpha]^{25}_D$ +244.0° (c 1.0, CH_2Cl_2); mp 132–133 °C. Anal. (recrystallized from EtOH) Calcd for $C_{18}H_{17}NO_2$: C, 77.40; H, 6.13; N, 5.01. Found: C, 77.26; H, 6.09; N, 5.03.

(1*S*,3*S*,5*S*,6*R*)-4-(*tert*-Butoxycarbonyl)-5,6-diphenyl-1-methyl-7-oxa-4-azaspiro[2.5]octan-8-one (15b). To a mixture of (±)-[[(diethylamino)methyl]phenyl]oxosulfonium tetrafluoroborate (1.65 g, 5.51 mmol, 2.0 equiv) and a 50% NaH dispersion (264.3 mg, 5.55 mmol, 2.0 equiv) was added DMSO (8 mL) at room temperature. After stirring for 1 h, the ylide solution was added via cannula to a partially frozen slurry of **14b** (1.04 g, 2.75 mmol, 1.0 equiv) in DMSO (8 mL) at ~18 °C. The reaction was slowly thawed over several hours and stirred for 4 days at room temperature. To the mixture was added brine (4 mL), followed by extraction with 3 × 5 mL EtOAc. The organic fractions were combined, washed thoroughly with H_2O to remove DMSO, dried over $MgSO_4$, filtered, and concentrated. Purification via flash silica chromatography (30 g of silica, eluted with 1:10 EtOAc/hexanes) provided 928.8 mg (85.8%) of **15b** as a white crystalline solid: ^{1}H NMR (300 MHz) ($CDCl_3$) δ TMS 1.06 (9 H, s), 1.20 (3 H, d, J = 5.7 Hz), 1.72 (2 H, m), 2.67 (1 H, broad s), 5.18 (1 H, broad s), 5.88 (1 H, d, J = 3.3 Hz), 6.77 (2 H, d, J = 7.2 Hz), 7.00–7.26 (8 H, m); IR (KBr) ν 3109, 3089, 3065, 3032, 3006, 2980, 2930, 1754, 1713, 1705, 1458, 1386, 1365, 1162, 1152, 1103, 1079, 1064 cm^{-1}; $[\alpha]^{25}_D$ +11.49° (c 1.0, CH_2Cl_2); mp 155–157 °C. Anal. (recrystallized from EtOH/hexanes) Calcd for $C_{24}H_{27}NO_4$: C, 73.26; H, 6.92; N, 3.56. Found: C, 73.20; H, 6.90; N, 3.42.

(1*S*,3*S*,5*S*,6*R*)-4-(*tert*-Butoxycarbonyl)-5,6-diphenyl-1-ethyl-7-oxa-4-azaspiro[2.5]octan-8-one (15c). To a mixture of (±)-[[(diethylamino)methyl]phenyl]oxosulfonium tetrafluoroborate (152 mg, 0.51 mmol, 2.0 equiv) and a 50% NaH dispersion (24.4 mg, 0.51 mmol, 2.0 equiv) was added DMSO (2 mL) at room temperature. After stirring for 1 h, the ylide solution was added via cannula to a partially frozen slurry of **14c** (100 mg, 0.25 mmol, 1.0 equiv) in DMSO (2 mL) at 18 °C. The reaction was slowly thawed over several hours and stirred for 4 days at room temperature. To the mixture was added brine (2 mL), followed by extraction with 3 × 5 mL EtOAc. The organic fractions were combined, washed repeatedly with H_2O, dried over $MgSO_4$, filtered, and concentrated. Purification via flash silica chromatography (9.9 g of silica, eluted with 1:10 EtOAc/hexanes) provided 104 mg (100%) of **15c** as a white crystalline solid: ^{1}H NMR (300 MHz) ($CDCl_3$) δ TMS 1.03–1.31 (13 H, m), 1.59–1.80 (3 H, m), 2.74 (1 H, broad s), 5.20 (1 H, apparent s), 5.96 (1 H, d, J = 3.2 Hz), 6.74–6.77 (2 H, m), 6.99–7.28 (8 H, m); IR (KBr) ν 3091, 3033, 3009, 2961, 2935, 1751, 1706, 1457, 1386, 1365, 1243, 1155, 1100, 1063 cm^{-1}; $[\alpha]^{20}_D$ +20.5° (c 1.0, CH_2Cl_2); mp 178–180 °C. Anal. (recrystallized from EtOH) Calcd for $C_{25}H_{29}NO_4$: C, 73.69; H, 7.17; N, 3.44. Found: C, 73.61; H, 7.10; N, 3.48.

(±)-5,6-Diphenyl-(*E*)-1-ethyl-7-oxa-4-azaspiro[2.5]octan-8-one. To a 0 °C solution of **(±)-15c** (486.7 mg, 1.19 mmol, 1.0 equiv) in CH_2Cl_2 (10 mL) was added TFA (1.8 mL, 23.89 mmol, 20 equiv). The mixture was allowed to warm to room temperature and stirred for 21 h. Solvent and excess TFA were removed in vacuo, and the crude trifluoroacetate salt was redissolved in CH_2Cl_2 (5 mL) followed by treatment with Et_3N (1 mL). The resulting solution was washed with H_2O (to remove triethylammonium trifluoroacetate), dried over $MgSO_4$, filtered, and concentrated. Purification via flash silica chromatography (22 g of silica, eluted with 1:10–1:1 EtOAc/hexanes) provided 345.4 mg (94.1%) of the racemic free amine of **15c** as a white crystalline solid: ^{1}H NMR (300 MHz) ($CDCl_3$) δ TMS 1.05 (3 H, t, J = 7.3 Hz), 1.29–1.34 (1 H, m), 1.40–1.48 (1 H, m), 1.51–1.68 (3 H, m), 2.42 (1 H, broad d, J = 7.8 Hz), 4.75 (1 H, broad d, J = 4.4 Hz), 5.86 (1 H, d, J = 4.2 Hz), 6.78–6.89 (4 H, m), 7.14–7.25 (6 H, m); IR (KBr) ν 3304, 3089, 3065, 3029, 2967, 2929, 2825, 1704, 1452, 1363, 1151, 1022 cm^{-1}; mp 113–115 °C. Anal. (recrystallized from EtOH) Calcd for $C_{20}H_{21}NO_2$: C, 78.15; H, 6.89; N, 4.56. Found: C, 78.31; H, 6.78; N, 4.59.

(±)-5,6-Diphenyl-(*E*)-1-ethyl-4-(4′-bromobenzoyl)-7-oxa-4-azaspiro[2.5]octan-8-one. To a solution containing (±)-5,6-diphenyl-(*E*)-1-ethyl-7-oxa-4-azaspiro[2.5]octa-8-one (50.0 mg, 0.16 mmol, 1.0 equiv) and 4-bromobenzoyl chloride (71.4 mg, 0.33 mmol, 2.0 equiv) in THF (5 mL) was added Et_3N (45.4 μL, 0.33 mmol, 2.0 equiv). The resulting mixture was refluxed for 14 h, cooled to room temperature, and the solvent removed in vacuo. The crude solid was purified via flash silica gel chromatography (8 g of silica, eluted with 1:10–1:1 EtOAc/hexanes) to provide 54.1 mg (67.8%) of racemic 4-bromobenzoyl-protected **15c** as a white crystalline solid: ^{1}H NMR (300 MHz) ($CDCl_3$) δ TMS 1.03 (3 H, t, J = 6.9 Hz), 1.10–1.22 (1 H, m), 1.35–1.82 (4 H, m), 5.34 (1 H, broad s), 6.09 (1 H, d, J = 4.0 Hz), 6.78 (2 H, broad d, J = 6.3 Hz), 6.90–7.23 (10 H, m), 7.45 (2 H, d, J = 8.2 Hz); IR (KBr) ν 3093, 3069, 3032, 2963, 2931, 2878, 2861, 1752, 1660, 1589, 1453, 1305, 1158, 1142, 1049 cm^{-1}; mp 204–205 °C. Anal. (recrystallized from EtOH) Calcd for $C_{27}H_{24}NO_3$: C, 66.13; H, 4.93; N, 2.86. Found: C, 66.08; H, 5.01; N, 2.82. A single-crystal X-ray analysis of this compound has been solved (Figure 5).[37]

(1*S*,3*S*,5*S*,6*R*)-4-(*tert*-Butoxycarbonyl)-5,6-diphenyl-1-propyl-7-oxa-4-azaspiro[2.5]octan-8-one (15d). To a mixture of (±)-[[(diethylamino)methyl]phenyl]oxosulfonium tetrafluoroborate (880.9 mg, 2.95 mmol, 2.0 equiv) and a 50% NaH dispersion (141.3 mg, 2.95 mmol, 2.0 equiv) was added DMSO (4 mL) at room temperature. After stirring for 1 h, the ylide solution was added via cannula to a partially frozen slurry of **14d** (600 mg, 1.47 mmol, 1.0 equiv) in DMSO (4 mL) at ~18 °C. The reaction was slowly thawed over several hours and stirred for 4 days at room temperature. To the mixture was added H_2O (5 mL) followed by extraction with 3 × 5 mL EtOAc. The organic fractions were washed thoroughly with H_2O, dried over $MgSO_4$, filtered, and concentrated. Purification via flash silica chromatography (35 g of silica, eluted with 1:10 EtOAc/hexanes) provided 547.2 mg (88.2%) of **15d** as a white crystalline solid: ^{1}H NMR (300 MHz) ($CDCl_3$) δ TMS 0.95 (3 H, t, J = 7.3 Hz), 1.07 (9 H, s), 1.15–1.23 (1 H, m), 1.42–1.55 (2 H, m), 1.58–1.66 (1 H, m), 1.72–1.80 (2 H, m), 2.75 (1 H, broad s), 5.19 (1 H, broad s), 5.93 (1 H, d, J = 3.2 Hz), 6.72 (2 H, m), 6.99–7.24 (8 H, m); IR (KBr) ν 3090, 3069, 3032, 3009, 2997, 2965, 2930, 2875, 1750, 1708, 1459, 1387, 1365, 1162, 1103, 1047 cm^{-1}; $[\alpha]^{25}_D$ +30.0° (c 1.0, CH_2Cl_2); mp 179–180 °C. Anal. (recrystallized from EtOH) Calcd for $C_{26}H_{31}NO_4$: C, 74.08; H, 7.41; N, 3.32. Found: C, 73.90; H, 7.41; N, 3.15.

(1*S*,3*S*,5*S*,6*R*)-4-(*tert*-Butoxycarbonyl)-1,5,6-triphenyl-7-oxa-4-azaspiro[2.5]octan-8-one (15f). To a solid mixture of racemic [[(diethylamino)methyl]phenyl]oxosulfonium tetrafluoroborate (1.08 g, 3.62 mmol, 2.0 equiv) and a 50% NaH dispersion (87 mg, 3.62 mmol, 2.0 equiv) was added DMSO (5 mL). The mixture was vigorously stirred for 1 h and was then added via cannula to an 18 °C slurry of **14f** (800 mg, 1.81 mmol, 1.0 equiv) in DMSO (5 mL). The reaction was allowed to slowly warm to room temperature over several hours and stirred for 4 days, followed by quenching with brine and extraction with 3 × 5 mL EtOAc. The organic fractions were combined, dried over $MgSO_4$, filtered, and concentrated. Purification was accomplished via recrystallization of the crude material from hot EtOH/THF, providing 650.4 mg (78.8%) of **15f** as fine white needles: ^{1}H NMR (300 MHz) ($CDCl_3$) δ TMS 1.06 (9 H, s), 2.66 (1 H, dd, J_{gem} = 9.3 Hz, J_{vic} = 2.0 Hz), 2.92 (1 H, t, J = 9.6 Hz), 3.27 (1 H, broad t, J = 8.3 Hz), 5.17 (1 H, d, J = 3.1 Hz), 5.86 (1 H, d, J = 3.1 Hz), 6.71–6.75 (2 H, m), 6.85–6.88 (2 H, m), 7.06–7.33 (11 H, m); IR (KBr) ν 3096, 3063, 3030, 2976, 2932, 1954, 1889, 1741, 1703, 1605, 1458, 1382, 1360, 1158, 1088, 1060 cm^{-1}; $[\alpha]^{25}_D$ +179.3° (c 1.0, CH_2Cl_2); mp 235–236 °C dec. Anal. (recrystallized from EtOH/THF) Calcd for $C_{29}H_{29}NO_4$: C, 76.46; H, 6.42; N, 3.07. Found: C, 76.44; H, 6.42; N, 3.07.

(1*S*)- and (1*R*)-1-(*N*-(*tert*-Butoxycarbonyl)amino)-2,2-dideuteriocyclopropane-1-carboxylic Acid (20). To a −78 °C solution containing **18/19** (557.2 mg, 1.46 mmol, 1.0 equiv) and anhydrous EtOH (857.2 μL, 14.6 mmol, 10.0 equiv) in THF (29.2 mL) and NH_3 (146 mL) was added lithium metal (~132 mg) in small pieces until a persistent blue color was obtained. The mixture was stirred an additional 5 min and then immediately quenched with solid NH_4Cl until the suspension turned snow white. The reaction was allowed to warm to room temperature, and the NH_3 evaporated completely. The white residue was dissolved in a min-

imum amount of H_2O, washed with 3 × 5 mL Et_2O, and carefully acidified to pH 2.5 with 2 N HCl while periodically extracting the product with EtOAc. The organic fractions were combined, dried over $MgSO_4$, filtered, and concentrated to provide 194.1 mg (65.4%) of **20** as a white crystalline solid: ^1H NMR (300 MHz) ($CDCl_3$) δ TMS 1.03 (1 H, d, J = 4.5 Hz), 1.46 (9 H, s), 1.55 (1 H, d, J = 4.6 Hz), 6.31 (2 H, broad s); IR (KBr) ν 3489, 3239, 3128, 3002, 2976, 2936, 1707, 1687.0, 1658, 1602, 1394, 1375, 1366, 1172, 1073, 1053, 1026 cm^{-1}; mp 161–162 °C (recrystallized from EtOH/hexanes).

(1*S*,2*S*)-1-(*N*-(*tert*-Butoxycarbonyl)amino)-2-methylcyclopropane-1-carboxylic Acid (16b). In similar fashion as above, a −78 °C solution of **15b** (925 mg, 2.35 mmol, 1.0 equiv) in a mixture of anhydrous EtOH (1.4 mL, 23.51 mmol, 10.0 equiv), THF (26 mL), and NH_3 (168 mL) was treated with Li^0 pieces until a persistent blue color appeared. After the NH_4Cl quenching, the reaction was allowed to warm to room temperature, and the NH_3 completely evaporated. The white residue was dissolved in a minimum amount of H_2O, washed with 3 × 5 mL Et_2O, and carefully acidified to pH 2.5 with 2 N HCl while periodically extracting the product with EtOAc. The organic fractions were combined, dried over $MgSO_4$, filtered, and concentrated to provide 319.6 mg (63.2%) of **16b** as a white crystalline solid: ^1H NMR (CD_3OD) δ TMS 1.21 (1 H, dd, J_{vic} = 4.8 Hz, J_{gem} = 9.4 Hz), 1.23 (3 H, d, J = 6.3 Hz), 1.29–1.35 (1 H, m), 1.43–3.34 (10 H, m), 4.89 (2 H, s); IR (KBr) ν 3303, 3253, 3094, 3011, 2978, 2936, 2883, 2697, 2578, 2494, 1701, 1654, 1648, 1410, 1367, 1203, 1162 cm^{-1}; $[\alpha]^{25}_D$ +38.1° (*c* 1.0, CH_3OH); mp 182–183 °C. Anal. (recrystallized from EtOH/hexanes) Calcd for $C_{10}H_{17}HNO_4$: C, 55.80; H, 7.96; N, 6.51. Found: C, 56.00; H, 8.14; N, 6.57.

(1*S*,2*S*)-1-(*N*-(*tert*-Butoxycarbonyl)amino)-2-ethylcyclopropane-1-carboxylic Acid (16c). To a −78 °C solution of **15c** (559.4 mg, 1.37 mmol, 1.0 equiv) and anhydrous EtOH (805.6 μL, 13.73 mmol, 10.0 equiv) in THF (15 mL) and NH_3 (98 mL) was added Li^0 (~124 mg) until the persistent blue discharge was observed. After the NH_4Cl quenching, the reaction was allowed to warm to room temperature, and the NH_3 completely evaporated. The white residue was dissolved in a minimum amount of H_2O, washed with 3 × 5 mL Et_2O, and carefully acidified to pH 2.5 with 2 N HCl while periodically extracting the product with EtOAc. The organic fractions were combined, dried over $MgSO_4$, filtered, and concentrated to provide 202.7 mg (64.4%) of **16c** as a white crystalline solid: ^1H NMR (CD_3OD) δ TMS 0.98 (3 H, t, J = 7.4 Hz), 1.12–1.17 (1 H, m), 1.39–1.48 (11 H, m), 1.54–1.63 (2 H, m), 4.88 (2 H, broad s); IR (KBr) ν 3303, 3253, 3100, 2975, 2936, 2878, 2697, 2583, 2492, 1700, 1649, 1478, 1458, 1410, 1397, 1368, 1306, 1200, 1162 cm^{-1}; $[\alpha]^{25}_D$ +33.3° (*c* 1.0, CH_3OH); mp 126–127 °C. Anal. (recrystallized from EtOH/hexanes) Calcd for $C_{11}H_{19}NO_4$: C, 57.63; H, 8.35; N, 6.11. Found: C, 57.71; H, 8.41; N, 6.19.

(1*S*,2*S*)-1-(*N*-(*tert*-Butoxycarbonyl)amino)-2-propylcyclopropane-1-carboxylic Acid (16d). To a −78 °C solution of **15d** (545 mg, 1.29 mmol, 1.0 equiv) and anhydrous EtOH (1.2 mL, 20.47 mmol, 15.9 equiv) in THF (19 mL) and NH_3 (92 mL) was added Li^0 until the persistent blue discharge was observed. After the NH_4Cl quenching, the reaction was allowed to warm to room temperature, and the NH_3 completely evaporated. The white residue was dissolved in a minimum amount of H_2O, washed with 3 × 5 mL Et_2O, and carefully acidified to pH 2.5 with 2 N HCl while periodically extracting the product with EtOAc. The organic fractions were combined, dried over $MgSO_4$, filtered, and concentrated to provide 191.5 mg (60.9%) of **16d** as a white crystalline solid: ^1H NMR (CD_3OD) δ TMS 0.93 (3 H, t, J = 7.2 Hz), 1.14 (1 H, m), 1.33–1.59 (15 H, m), 4.87 (2 H, broad s); IR (KBr) ν 3295, 3247, 3096, 2981, 2962, 2933, 2875, 2702, 2583, 2494, 1698, 1655, 1649, 1401, 1368, 1202, 1167, 1062 cm^{-1}; $[\alpha]^{25}_D$ +41.8° (*c* 1.0, MeOH); mp 118–119 °C. Anal. (recrystallized from EtOH/hexanes) Calcd for $C_{12}H_{21}NO_4$: C, 59.24; H, 8.70; N, 5.76. Found: C, 59.49; H, 8.77; N, 5.84.

(1*S*)-1-Amino[2,2-$^2H_2$]cyclopropane-1-carboxylic Acid (21). A suspension of **20** in H_2O (3 mL) was refluxed for 12 h. After cooling, the reaction mixture was eluted through a C_{18} reverse-phase Sep-pak cartridge. Evaporation of the solvent provided 17.2 mg (100%) of **21** as a white crystalline solid. No further purification was necessary: ^1H NMR (300 MHz) (D_2O) δ HOD 1.04 (1 H, d, J = 5.9 Hz), 1.18 (1 H, d, J = 5.9 Hz); IR (KBr) δ 3430, 3017, 2732, 2634, 2545, 2113, 1791–1462, 1403, 1324, 1241 cm^{-1}; mp sublimes >200 °C, 237–239 °C dec.

(1*S*,2*S*)-2-Methyl-1-aminocyclopropane-1-carboxylic Acid (Norcoronamic Acid, 3). To a 0 °C solution of 1 N HCl in MeOH (18.6 mL, 18.6 mmol, 40.0 equiv) was added **16b** (100 mg, 0.47 mmol, 1.0 equiv). The mixture was stirred for 29 h at 0 °C, followed by removal of the solvent. To the white crystalline residue was added anhydrous EtOH (10 mL) and a large excess of propylene oxide. The mixture was refluxed for 20 min and the free amino acid partially precipitated. After removal of the EtOH, the white residue was dissolved in distilled H_2O (~2 mL) and eluted through a C_{18} reverse-phase Sep-pak cartridge, which after removal of H_2O, provided 54 mg (100%) of norcoronamic acid (**3**) as a white crystalline solid: ^1H NMR (300 MHz) (D_2O) δ HOD 1.03–1.19 (2 H, m), 1.05 (3 H, d, J = 6.2 Hz), 1.32–1.46 (1 H, m); IR (KBr) ν 3435, 3009, 2739, 2090, 1739, 1586, 1438, 1404, 1301, 1222, 1173, 1051 cm^{-1}; $[\alpha]^{25}_D$ +50.9° (*c* 1.0, H_2O); lit.[37] $[\alpha]^{20}_D$ +44° (*c* 1.0, H_2O); mp sublimes >205 °C.

(1*S*,2*S*)-2-Ethyl-1-aminocyclopropane-1-carboxylic Acid (Coronamic Acid, 2). To a 0 °C solution of 1 N HCl in MeOH (17.5 mL, 17.5 mmol, 40.0 equiv) was added **16c** (100 mg, 0.45 mmol, 1.0 equiv). The mixture was stirred for 24 h at 0 °C, followed by removal of the solvent. To the white crystalline residue was added anhydrous EtOH (10 mL) and a large excess of propylene oxide. The mixture was refluxed for 20 min and the free amino acid partially precipitated. After removal of the EtOH, the white residue was dissolved in distilled H_2O (2 mL) and eluted through a C_{18} reverse-phase Sep-pak cartridge, which after removal of H_2O, provided 56.0 mg (100%) of coronamic acid (**2**) as a white crystalline solid: ^1H NMR (300 MHz) (D_2O) δ HOD 0.79 (3 H, t, J = 7.2 Hz), 1.15 (2 H, apparent d, J = 8.3 Hz), 1.28–1.54 (3 H, m); IR (KBr) ν 3444, 2967, 2932, 2878, 2094, 1600 (br), 1398, 1295, 1218, 1175, 1044 cm^{-1}; $[\alpha]^{25}_D$ +14.5° (*c* 1.67, H_2O); lit.[17b] $[\alpha]^{25}_D$ +14.7° (*c* 1.67, H_2O); mp sublimes >185 °C.

(1*S*,2*S*)-2-Propyl-1-aminocyclopropane-1-carboxylic Acid (17d). To a 0 °C solution of 1 N HCl in MeOH (16.4 mL, 16.4 mmol, 40.0 equiv) was added **16d** (100 mg, 0.41 mmol, 1.0 equiv). The mixture was stirred for 24 h at 0 °C, followed by removal of the solvent. To the crystalline residue was added anhydrous EtOH (10 mL) and a large excess of propylene oxide. The mixture was refluxed for 20 min and the free amino acid partially precipitated. After removal of the EtOH, the white residue was dissolved in distilled H_2O (2 mL) and eluted through a C_{18} reverse-phase Sep-pak cartridge, which after removal of H_2O, provided 58.0 mg (98.6%) of **17d** as a white crystalline solid: ^1H NMR (300 MHz) (D_2O) δ HOD 0.74 (3 H, t, J = 7.3 Hz), 1.14–1.49 (7 H, m); IR (KBr) ν 3433, 2959, 2930, 2874, 2071, 1594 (br), 1442, 1404, 1300, 1273, 1213, 1175, 1049 cm^{-1}; $[\alpha]^{25}_D$ +26.1° (*c* 1.0, H_2O); mp sublimes >200 °C. Anal. (recrystallized from H_2O/acetone) Calcd for $C_7H_{13}NO_2$: C, 58.72; H, 9.15; N, 9.78. Found: C, 59.00; H, 8.92; N, 9.71.

General Procedure for the Mosher Amide Preparation of Amino Acids 2, 3, and 17d.[38] To a stirred suspension of **2** (5 mg, 0.04 mmol, 1.0 equiv) in THF (1 mL) was added Mosher's acid chloride[39] (11.0 mg, 0.04 mmol, 1.0 equiv) and propylene oxide (12.2 mL, 0.17 mmol, 4.0 equiv). The resulting mixture was heated to reflux for 0.5 h, cooled to room temperature, and thoroughly evaporated to provide a crude oil. The % ee was determined by ^{19}F NMR analysis of the MTPA amide. The same procedure was used for % ee analyses of **3** and **17d**.

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Registry No. **2**, 63393-56-6; **3**, 98244-42-9; **12**, 112741-49-8; **13**, 136328-42-2; **14a**, 136328-50-2; **14b**, 136328-51-3; **14c**, 136328-52-4; **14d**, 136328-53-5; **14e**, 136328-54-6; **14f**, 136328-55-7; **14g**, 136328-56-8; **15b**, 136328-43-3; (1*R*,3*R*)-**15b**, 136378-35-3; **15c**, 136328-44-4; (±)-**15c**, 136378-36-4; (±)-**15c** (*N*-deprotected), 136328-58-0; (±)-**15c** [*N*-(4-bromobenzoyl) derivative], 136328-59-1; **15d**, 136328-45-5; **15f**, 136328-46-6; **16b**, 136378-33-1; **16c**, 136378-34-2; **16d**, 136328-57-9; **17d**, 136328-39-7; **18**, 136328-47-7; **19**, 136378-31-9; **20**, 136328-48-8; **21**, 88454-70-0; **22**, 136328-49-9; **23**, 136378-32-0; i, 136328-60-4; CH_3CHO, 75-07-0; CH_3CH_2CHO, 123-38-6; $CH_3CH_2CH_2CHO$, 123-72-8; Me_2CHCHO, 78-84-2; PhCHO, 100-52-7; $4\text{-}NO_2C_6H_4CHO$, 555-16-8; $Me_3S^+(O)\cdot I^-$, 1774-47-6; (±)-$(Et_2N)MeS^+(O)Ph\cdot BF_4^-$, 136328-41-1; $4\text{-}BrC_6H_4COCl$, 586-75-4.

(37) Baldwin, J. E.; Adlington, R. M.; Rawlings, B. J.; Jones, R. J. *Tetrahedron Lett.* **1985**, *26*, 485. The optical rotation we obtained for norcoronamic acid is ~7° higher than that reported by Baldwin and co-workers where they used Porcine Kidney Acylase I to enzymatically resolve (±)-coronamic acid.

(38) The % ee of each amino acid was determined by examination of the ^{19}F NMR of the derived MTPA amides. Authentic racemic amino acids were synthesized and derivatized in like manner to provide the diastereomeric reference signals of the CF_3 groups.

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