of enantiomeric recognition. It should be pointed out that the enantiomeric preference observed between host **2c** and guests (*R*)- and (*S*)-HNEA$^+$ (which amounts to 0.7 kcal/mol) is better than what Izatt et al. observed for their triazole-containing macrocycle **1a** (0.1 kcal/mol).

The competition experiments were carried out by mixing each host with (*R*)- and (*S*)-HNEA$^+$ chlorides in $CDCl_3$ in 1:1:1 ratios and recording the spectra without filtering the excess solid substrates. Only the completely resolved guest signal from the diastereomeric complexes were integrated. For N-unsubstituted host **2a**, no guest signal separation at any region of the spectrum was observed, and for **2b**, the study was hampered by extensive signal overlap. However, in the case of the dodecyl derivative **2c**, a 2.5 *R*/*S* ratio was observed (from the integration of the methyne signals of the guests).

Ammonium salt transport through liquid membrane is currently under investigation. The enanioselective transport toward (*R*)-HNEA$^+$ by both chiral hosts **2b** and **2c** has been observed in preliminary experiments.

Experimental Section

All NMR spectra were measured in $CDCl_3$ and recorded at either 200 MHz (structural assignment of host molecules) or at 400 MHz (complexation studies). Sample concentrations for complexation studies were ca. 4 mM, and all chemical shift data for the complexes in Tables I and II were recorded at 1:1 host to guest ratio. COSY and NOESY spectra were acquired in 1K by 512 data matrix and zero-filled to 1K by 1K. Binding constants were measured at 21 °C.

The hydrochloride salts of (*R*)- and (*S*)-phenylethylamine as well as (*R*)- and (*S*)-naphthylethylamine were prepared by bubbling HCl gas into solutions of the amine in a small amount of methanol. The salts were precipitated by ether and recrystallized from acetonitrile.

Cholesteryl [(2*S*,16*S*)-2,16-Dimethyl-3,6,9,12,15-pentaoxa-18,19,20-triazabicyclo[15.2.1]eicosa-1,17-dien-18-yl]acetate (2b). A mixture of the macrocyclic triazole **2a**[12] (0.8 mmol), potassium carbonate (1 mmol), potassium iodide (0.5 mmol), and cholesteryl chloroacetate (0.8 mmol) in dry acetone (30 mL) was stirred at 50 °C for 24 h. The reaction was monitored by TLC. The solvent was eliminated at reduced pressure, the residue was extracted with methylene chloride, and the solvent was evaporated to dryness. The product was purified by trituration with hot *n*-heptane: yield 85%; viscous oil; $[\alpha]_{25} = -37.4°$ (c = 1.5 g/100 mL); ^{1}H NMR δ 0.69 (s, 3 H, H-18′), 0.8–2.4 (m, 28 H, cholesteryl), 0.85 (d, 9 H, H-21′, H-26′, H-27′), 1.04 (s, 3 H, H-19′), 1.57 (d, 3 H, J = 6.6 Hz, CH_3 on C-16), 1.60 (d, 3 H, J = 6.6 Hz, CH_3 on C-2), 3.4–3.8 (m, 16 H, OCH_2), 4.59 (q, 1 H, J = 6.6 Hz, H-2), 4.7 (m, 1 H, H-3′), 5.01 (q, 1 H, J = 6.6 Hz, H-16), 5.12 (AB system, 2 H, J = 17.6 Hz, NCH_2CO), 5.4 (m, 1 H, H-6′); ^{13}C NMR δ 11.8 (C-18′), 18.6 (C-21′), 19.2 (C-19′), 19.8, 19.9 (CH_3 on C-2, C-16), 20.9 (C-11′), 22.6, 22.7 (C-26′, C-27′), 23.7 24.2, 27.5, 27.9, 28.1, 28.9, 31.8, 35.7, 36.1, 36.4, 36.7, 37.8, 39.4, 39.6, 42.2, 49.9, 50.3 (cholesteryl, NH_2CO), 56.0, 56.6 (C-14′, C-17′), 68.1, 68.4, 70.0, 70.2, 70.4, 71.2 (C-2, C-4, C-5, C-7, C-8, C-10, C-11, C-13, C-14, C-16), 75.8 (C-3′), 123.0 (C-6′), 139.0 (C-5′), 157.0 (C-17), 163.4 (C-1), 166.7 (C=O). Anal. Calcd for $C_{43}H_{71}N_3O_7$: C, 69.60; H, 9.64; N, 5.66. Found: C, 69.65; H, 9.80; N, 5.37.

(2*S*,16*S*)-18-Dodecyl-2,16-dimethyl-3,6,9,12,15-pentaoxa-18,19,20-triazabicyclo[15.2.1]eicosa-1,17-diene (2c). Finely powdered potassium carbonate (15 mmol), tetrabutylammonium hydrogen sulfate (0.05 mmol), and dodecyl bromide (0.4 mmol) were added to a solution of **2a** (0.2 mmol) in acetonitrile (10 mL). The mixture was stirred for 3 h at 60 °C. The inorganic salts were filtered off and washed with acetonitrile. The filtrates were evaporated at reduced pressure, the residue was dissolved in hexane, and the solution was thoroughly washed with water, dried with anhydrous magnesium sulfate, and evaporated to give a colorless oil. Purification was achieved by silica gel chromatography (short column, dichloromethane–methanol (10:1): yield 90%; oil; $[\alpha]_{25} = -16.3°$ (c = 1.5 g/100 mL); ^{1}H NMR δ 0.89 (t, 3 H, H-12′), 1.2–1.4 (m, 18 H, H-3′ to H-11′), 1.56, 1.57 (2xd, 6 H, J = 6.7 Hz, CH_3 on C-2, C-16), 1.9 (m, 2 H, H-2′), 3.4–3.7 (m, 16 H, OCH_2), 4.2 (m, 2 H, H-1′), 4.59 (q, 1 H, J = 6.7 Hz, H-2), 4.94 (q, 1 H, J = 6.7 Hz, H-16). ^{13}C NMR δ 14.0 (C-12′), 19.9, 20.0 (CH_3 on C-2, C-16), 22.6 (C-11′), 26.7, 29.1, 29.2, 29.4, 29.5, 30.0 (C-3′ to C-10′), 31.8 (C-2′), 48.9 (C-1′), 67.9, 68.1, 70.0, 70.1, 70.3, 70.4, 70.5, 70.6, 71.4 (C-2 to C-16), 155.6 (C-17), 163.0 (C-1). Anal. Calcd for $C_{28}H_{49}N_3O_5$: C, 64.56; H, 10.21; N, 8.69. Found: C, 64.79; H, 10.41; N, 8.59.

Acknowledgment. We are indebted to the National Institutes of Health (Grant GM 33940) and to "Comisión Interministerial de Ciencla y Tecnología, Spain" (CICYT Grant PTR 89-0028) for financial support. Technical assistance by F. Fernández-Lázaro is also gratefully acknowledged.

Synthesis of Chiral Vinylglycines

Pierre L. Beaulieu,* Jean-Simon Duceppe, and Carolyne Johnson

Bio-Méga Inc., 2100 Cunard Street, Laval, Québec, Canada H7S 2G5

Received October 11, 1990

(*R*)- or (*S*)-benzyl 4-formyl-2,2-dimethyl-3-oxazolidinecarboxylate (**7a**) and (*R*)- or (*S*)-1,1-dimethylethyl 4-formyl-2,2-dimethyl-3-oxazolidinecarboxylate (**7b**), readily available from serine, react with Wittig reagents to give alkenes **8**. Selective deprotection followed by oxidation of the resulting unsaturated amino alcohols **9** provides vinylglycines **5** of defined configuration (>95% ee) and double-bond geometry. D-Vinylglycines are obtained from L-serine, and conversely, D-serine gives β,γ-unsaturated amino acids with the L configuration. The double-bond geometry is controlled by the nature of the phosphorous ylide employed. The scope and limitations of this new methodology for the preparation of chiral vinylglycines is examined.

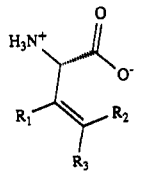
In recent years, β,γ-unsaturated α-amino acids **1** (vinylglycines) have surfaced as an important class of α-amino acids. The parent compound, L-vinylglycine (**1**; $R_1 = R_2 = R_3 = H$), is a naturally occurring substance first isolated from mushrooms[1] and has been implicated in a variety of biochemical processes[2] (Figure 1).

One of the interests in β,γ-unsaturated amino acids stems from their antimicrobial properties and the fact that they can function as suicide inhibitors of a variety of enzymes.[3] In addition, they are versatile synthetic inter-

(1) Dardenne, G.; Casimar, J.; Marlier, M. *Phytochemistry* **1974**, *13*, 1897.

(2) (a) Posner, B. I.; Flavin, M. *J. Biol. Chem.* **1972**, *247*, 6402. (b) Flavin, M.; Slaughter, C. *J. Biol. Chem.* **1960**, *235*, 1112.

0022-3263/91/1956-4196$02.50/0



1

Figure 1.

Scheme I

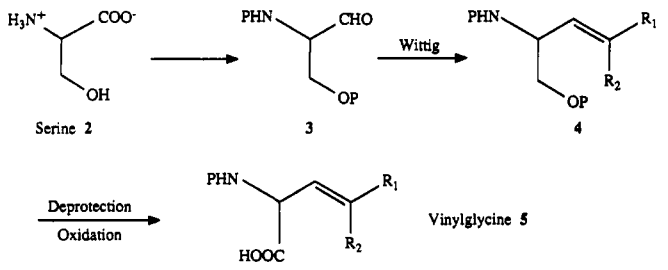


Figure 2.

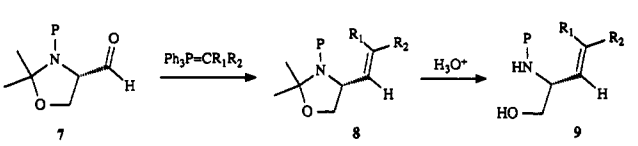


Table I. Wittig Condensation of Aldehyde 7. Preparation of Amino Alcohols 9

					% yield		
entries	compd	R_1	R_2	P	8	9	% $\mathcal{D}$
1	a	H	H	Boc	27[a]	89	
2	b	Me	H	Boc	62[a]	86	93
3	c	Ph	H	Boc	84[b]	75	40
4	d	n-C_5H_{11}	H	Boc	78[a]	87	>98
5	e	CH_2CH_2Ph	H	Boc	96[a]	75	>98
6	f	$(CH_2)_2COOH$	H	Boc	73[c]	79[g]	>98
7	g	$(CH_2)_2CN$	H	Cbz	78[d]	*h*	>98
8	h	$(CH_2)_3CN$	H	Cbz	78[d]	*h*	>98
9	i	COOMe	H	Cbz	85	89	0
10	j	Et	Me	Boc	50[a,e]	76	70

[a] Ylide generated from phosphonium salt using n-BuLi. [b] Ylide generated using KHMDS. [c] Ylide generated using LiHMDS. [d] Ylide generated using LDA. [e] Yield based on recovered starting material. [f] Determined by ^1H and ^{13}C NMR. [g] The acetonide was hydrolyzed in wet acetonitrile. [h] Compounds **8g** and **8h** were elaborated to lysine analogues **11a** and **11b** (Scheme II).[10]

mediates[4] and provide convenient access to radiolabeled amino acids (via catalytic tritiation) useful as biochemical tools. They also serve as conformationally restricted analogues of naturally occurring amino acids, which, when incorporated into peptides, can provide insight into the biologically active conformation of such molecules.

Efficient syntheses of the parent chiral amino acid, vinylglycine (1; $R_1 = R_2 = R_3 = H$), have appeared in the literature. Examples involve the oxidative degradation of glutamic acid,[5a] methionine,[5b] and homoserine[5c] derivatives. Several routes also exist that can provide access to a variety of substituted vinylglycine derivatives in racemic form.[6] However, methodologies that deliver 1 in enantiomerically pure form with defined double-bond geometry are scarce owing mainly to the instability of these highly functionalized molecules toward both racemization and isomerization to α,β-dehydro amino acids. At present, we are only aware of four such procedures. Two of them make use of chiral glycine equivalents[7a,b] and one utilizes the aldol condensation of a β-anion generated from aspartic acid.[7c] Julia coupling of a serine-derived sulfone has also been used in a multistep synthesis of a propenylglycine.[7d] Most of these methods, however, seem to be limited by the nature of the alkyl substituent and suffer from either poor control of double-bond geometry or variable enantiomeric purity.

With the need for a general and practical route to enantiomerically pure β,γ-unsaturated amino acids of defined double-bond geometry, we have developed an approach to this class of molecules that is based on the use of serine as a chiral starting material.

The strategy to convert serine **2** into chiral vinylglycines **5** is outlined in Scheme I. It was envisaged that serine could be converted into a suitably protected form of aldehyde **3**, which on subjection to Wittig olefination would provide the desired substituted alkene. Deprotection and oxidation would then produce vinylglycines **5** of opposite configuration. The L-vinylglycines would be available from D-serine, and conversely, D-vinylglycines would be accessible starting from L-serine.[8] The reverse approach, which would make use of the Wittig condensation of a serine-derived phosphorous ylide with aldehydes, has been reported to give very low yields of olefination products (5–13%).[9a] More recently, we became aware of an alaninol synthon derived from serine that produces β,γ-unsaturated amino alcohols in good yields, but the degree of control of the double bond geometry is variable.[9b] The conversion of these amino alcohols into the corresponding vinylglycines was not examined.

In spite of the configurational lability of amino aldehydes in general, certain protected serinal derivatives are being recognized more and more as useful synthons for the preparation of unusual amino acids[10,11] and other poly-

(3) (a) Scannell, J. P.; Preuss, D. L.; Demney, T. C.; Sello, L. H.; Williams, T.; Stempel, A. *J. Antibiot.* **1972**, *25*, 122. (b) Rando, R. R. *Science* **1974**, *183*, 320. (c) Rando, R. R. *Nature (London)* **1974**, *250*, 586. (d) Rando, R. R. *Acc. Chem. Res.* **1975**, *8*, 281. (e) Metcalf, B. W.; Jund, K. *Tetrahedron Lett.* **1977**, *18*, 3689. (f) Greenlee, W. J.; Taub, D.; Patchett, A. A. *Tetrahedron Lett.* **1978**, 3999. (g) Abeles, R. H. *Pure Appl. Chem.* **1981**, *53*, 149. (h) Walsh, C. *Tetrahedron* **1982**, *38*, 871. (i) Castelhano, A. L.; Plivra, D. H.; Taylor, G. J.; Hsieh, K. C.; Krantz, A. *J. Am. Chem. Soc.* **1984**, *106*, 2734.

(4) (a) Hagedorn, A. A., III; Miller, B. J.; Nagy, J. U. *Tetrahedron Lett.* **1980**, *21*, 229. (b) Chang, M. N. T.; Walsh, C. *J. Am. Chem. Soc.* **1980**, *102*, 7368.

(5) (a) Hanessian, S.; Sahoo, S. P. *Tetrahedron Lett.* **1984**, *25*, 1425. (b) Azfali-Ardakani, A.; Rapoport, H. *J. Org. Chem.* **1980**, *45*, 4817. (c) Pelliciari, R.; Natalini, B.; Marinozzi, M. *Synth. Commun.* **1988**, *18*, 1715.

(6) (a) Greenlee, W. J. *J. Org. Chem.* **1984**, *49*, 2632. (b) Castelhano, A. L.; Horne, S.; Billedeau, R.; Krantz, A. *Tetrahedron Lett.* **1986**, *27*, 2435. (c) Fitzner, J. N.; Pratt, D. V.; Hopkins, P. B. *Tetrahedron Lett.* **1985**, *26*, 1959. (d) Agouridas, K.; Girodeau, J. M.; Pineau, R. *Tetrahedron Lett.* **1985**, *26*, 3115.

(7) (a) Schöllkopf, U.; Nozulak, R. M.; Groth, U. *Tetrahedron* **1984**, *40*, 1409. (b) Williams, R. M.; Zhai, W. *Tetrahedron* **1988**, *44*, 5425. (c) Baldwin, J. E.; Moloney, M. G.; North, M. *Tetrahedron* **1989**, *45*, 6319. (d) Sasaki, N. A.; Mashimoto, C.; Pauly, R. *Tetrahedron Lett.* **1989**, *30*, 1943.

(8) The use of L-serine for the preparation of D-amino acids has been recognized: Maurer, P. J.; Takahata, H.; Rapoport, H. *J. Am. Chem. Soc.* **1984**, *106*, 1095.

(9) (a) Itaya, T.; Mizutani, A. *Tetrahedron Lett.* **1985**, *26*, 347. (b) Sibi, M. P.; Renhowe, P. A. *Tetrahedron Lett.* **1990**, *31*, 7407.

(10) Beaulieu, P. L.; Schiller, P. W. *Tetrahedron Lett.* **1988**, *29*, 2019.

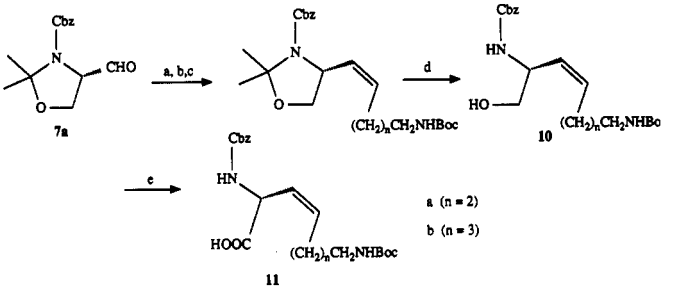
functional molecules of interest.[11c,d] Two good examples of stable serinal derivatives that offer some resistance to racemization are the oxazolidine compounds **7a** and **7b**[10,12] (Figure 2).

Both aldehydes, readily available from serine in optically pure form, are configurationally stable and can be prepared easily in multigram quantities. The behavior of aldehyde **7b** under conditions of the Wittig reaction has previously been explored. Methylenetriphenylphosphorane has been reported to react with **7b** to give a racemized olefination product,[13] while Wittig–Horner conditions (triethyl phosphonoacetate/K_2CO_3) provided a good yield of enantiomerically pure α,β-unsaturated ester.[14] However, the elaboration of the olefinic products into vinylglycines was not examined. We investigated the scope and limitations of the Wittig condensation of phosphorous ylides with aldehydes **7a** and **7b** as a means of preparing chiral β,γ-unsaturated amino acids with defined double-bond geometry.[15]

Results and Discussion

Treatment of aldehydes **7a** or **7b** derived from L-serine[10,12] with a variety of phosphorous ylides provided *Z* alkenes **8** (27–96%; Table I). The bases used for the formation of the ylides, as indicated in the footnotes to Table I, were found to be the preferred ones to give the best yields of olefinic products. For example, better yields of styrene derivative **8c** were obtained using potassium hexamethyldisilazane then other strong bases (e.g., *n*-BuLi). Proof of the double-bond geometry was complicated by the occurrence of slowly interconverting conformers that caused considerable line broadening and duplication of signals in the ^1H NMR spectra.[12] More easily interpretable spectra were obtained after hydrolytic removal of the acetonide protecting group to give the amino aclohols **9**. The double-bond geometry could be easily determined from ^1H NMR coupling constants (10–12 Hz for $ZJ_{CH=CH}$, >15 Hz for $EJ_{CH=CH}$). In most instances where unstabilized ylides were used, *Z* olefins were formed almost exclusively (98%; Table I). One exception is the case where R_1 is phenyl (entry 3) when the alkene product was obtained as a 60:40 *E*/*Z* mixture. Trisubstituted alkene **8j** (entry 10) was also obtained as a 70:30 mixture of double bond isomers in favor of the *Z* olefin. Usually, the geometrical isomers could be separated by either flash chromatography or recrystallization at the amino alcohol stage. Exceptions were acetonides **8b** and **8j**, which remained contaminated with 7 and 30%, respectively, of the *E* isomer throughout the sequence. Methyltriphenylphosphorane, when generated from triphenylphosphonium bromide and *n*-butyllithium in THF, behaved differently from other ylides in Table I in that it reacted very poorly with aldehyde **7b**. The olefination product was isolated in 27% yield only. The isolated material was found to have a 69% enantiomeric excess as shown by the optical rotation of the derived amino alcohol **9a** [$[\alpha]^{27}_D$ −20.1° (*c* = 1.34, $CHCl_3$) (lit.[13] $[\alpha]^{26}_D$ −29° (*c* = 2.5, $CHCl_3$))]. This is to be compared with the results obtained with the phosphorane generated using potassium hydride in benzene, which produced racemic material.[13] The explanation for this observation is unclear but could be related to the increased basicity of the ylide. Because good procedures already exist for the preparation of enantiomerically pure ethenylglycine (**1**; $R_1 = R_2 = R_3 = H$)[5a–c,13], we did not pursue this example further.

Scheme II[a]



[a] Reagents and conditions:[10] (a) $Ph_3P{=}CH(CH_2)_nCN$, THF, −78 °C to RT (78%); (b) $NaBH_4/CoCl_2$ in MeOH, 0 °C; (c) Boc dicarbonate, rt (50–60%, 2 steps); (d) wet methanol, TsOH (cat), reflux (92–100%); (e) Jones' in acetone (87–92%).

One limitation of this methodology involved the construction of molecules carrying amine functionality in the side chain. We have encountered difficulties in preparing Wittig reagents containing amine functions in variously protected forms (e.g., ω-bromoalkylamines protected as the *N*-phthalimido, *N*-Boc, or *N*-Cbz derivatives). However, the use of ylides having nitrile substituents followed by hydride reduction of the olefination products to unmask the desired amine functionality has allowed us to develop an efficient synthesis of vinylglycines that are conformationally restricted analogues of the amino acid lysine **11**.[10] As shown in Scheme II, condensation of aldehyde **7a** with unstabilized phosphonium ylides generated from ω-bromonitriles gave the expected unsaturated nitriles that were selectively reduced with $NaBH_4/CoCl_2$ in methanol.[16] Manipulation of the protecting group gave **10**, which after partial deprotection followed by oxidation gave vinylglycine derivatives **11**.

Selective deprotection of olefination products **8** proved straightforward. The amino alcohols **9** were obtained in good to excellent yields (75–98%) by stirring the acetonides **8** in wet methanol or acetonitrile in the presence of Dowex 50W strong H^+ resin (Aldrich) for 18–24 h (Table I). Acetonitrile was used for entry 6 to avoid esterification (up to 40%) of the free carboxyl group.

The oxidation of amino alcohols **9** to (*Z*)-vinylglycines **5** proved to be most challenging. The presence of a reactive double bond and its propensity to isomerize from the β,γ-position to the α,β-unsaturated position precluded the use of many oxidation procedures such as $RuCl_3/NaIO_4$,[17] $KMnO_4/AcOH$,[18] silver oxide,[19] TEMPO radical-based methodologies[20] and sodium bromite.[21] In most cases, degradation of the substrate was observed or α,β-dehydro

(11) (a) Garner, P.; Park, J. M. *J. Org. Chem.* **1988**, *53*, 2979. (b) Garner, P. *Tetrahedron Lett.* **1984**, *25*, 5855. (c) Jurczak, J.; Gołębiowski, A. *Chem. Rev.* **1989**, *89*, 149. (d) Giannis, A.; Henk, T. *Tetrahedron Lett.* **1990**, *31*, 1253.

(12) Garner, P.; Park, J. M. *J. Org. Chem.* **1987**, *52*, 2361.

(13) Moriwake, T.; Hamano, S.-I.; Sato, S.; Torii, S. *Chem. Lett.* **1987**, 2085.

(14) Jako, I.; Uiber, P.; Mann, A.; Taddei, M.; Wermuth, C.-G. *Tetrahedron Lett.* **1990**, *31*, 1011.

(15) Luly, J. R.; Dellaria, J. F.; Plattner, J. J.; Soderquist, J. L.; Yi, N. *J. Org. Chem.* **1987**, *52*, 1487.

(16) Satoh, T.; Suzuki, S.; Suzuki, Y.; Miyaji, Y.; Imai, Z. *Tetrahedron Lett.* **1969**, *10*, 4555.

(17) Carlsen, Per H.-J.; Katsuki, T.; Martin, V. S.; Sharpless, K. B. *J. Org. Chem.* **1981**, *46*, 3936.

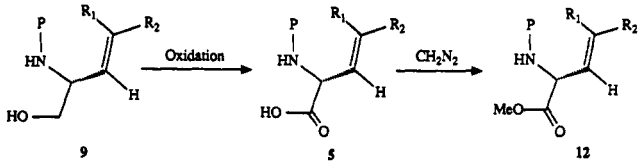
(18) Sabnis, S. D.; Mathur, H. H.; Bhattacharyya, S. C. *J. Chem. Soc.* **1963**, 2477.

(19) Clarke, T. G.; Hampson, N. A.; Lee, J. B.; Morley, J. R.; Scanlon, B. *Tetrahedron Lett.* **1968**, *9*, 5685.

(20) (a) Inokuchi, T.; Matsumoto, S.; Nishiyama, T.; Torii, S. *J. Org. Chem.* **1990**, *55*, 462. (b) Anelli, P. L.; Banfi, S.; Montanari, F.; Quici, S. *J. Org. Chem.* **1989**, *54*, 2970. (c) Cella, J. A.; Kelley, J. A.; Kenehan, E. F. *J. Org. Chem.* **1975**, *40*, 1860.

(21) (a) Veeraiah, T.; Periasamy, M. *Synth. Commun.* **1989**, *19*, 2151. (b) Kageyama, T.; Kawahara, S.; Kitamura, K.; Ueno, Y.; Okawara, M. *Chem. Lett.* **1983**, 1097.

Table II. Oxidation of Amino Alcohols 9. Preparation of Vinylglycines 5 and Methyl Esters 12



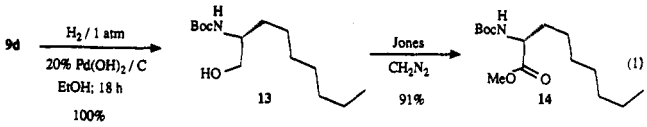
entries	amino alcohol	method	12 % yield[a]	% ee[b]
1	**9b**	B	44	>95
2	**9c**	A	0	
3	**9d**	B	50	93
4	**9e**	B	40	82
5	**9f**	B	37	90
6	**10a**	A	87	>95
7	**10b**	A	92	>95
8	**9i**	B	0	
9	**9j**	B	42	>95

[a] Vinylglycines **5** were isolated and purified as their methyl esters **12**. [b] The enantiomeric purity of the products was determined by capillary GC analysis on a chiral column[23] (see text).

amino acids or the starting alcohol was isolated. To prevent scrambling of the easily racemizable chiral center, oxidations under basic conditions had to be avoided (e.g., $KMnO_4/NaOH$[11b]). Ultimately, the best conditions found were either the Jones' oxidation (*method A*) or pyridinium dichromate (PDC)[7d] in the presence of activated powdered 4-Å molecular sieves in *N,N*-dimethylformamide as solvent (*method B*). Protected β,γ-unsaturated amino acids **5** were obtained in 37–90% yields as shown in Table II. For characterization purposes, crude vinylglycines **5** were treated with excess diazomethane and the corresponding methyl esters **12** were isolated in pure form after flash chromatography. The crude vinylglycines **5**, however, were obtained in sufficient purity for most purposes.

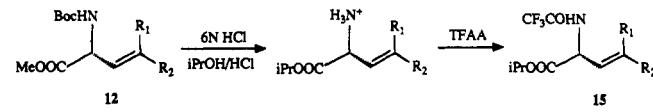
A limitation of this methodology is that aromatic amino alcohol **9c** and α,β-unsaturated ester **9i** could not be oxidized to the corresponding vinylglycines (entries 2 and 8, Table II). In these cases, decomposition of the substrate was the predominant outcome of the reaction.

This methodology can also be used to prepare saturated amino acids via catalytic hydrogenation of the double bond in the vinylglycine derivatives **5**. The preferred procedure involves saturation of the double bond prior to oxidation of the amino alcohol into the corresponding amino acid (eq 1). Oxidation of saturated amino alcohols (e.g., **13**)



proceeded in better yields than for the unsaturated derivatives (91 versus 50%). It is also conceivable that the use of tritium gas in the hydrogenation step should allow the preparation of radiolabeled amino acid analogues, useful for biochemical studies.

Because of the well-known sensitivity of vinylglycines toward racemization, the enantiomeric purity of our final products was an important concern for us. To determine the extent of racemization that could have taken place in the olefination step of the sequence, amino alcohol **9e** was prepared in both *R* and *S* forms starting from L-serine and D-serine, respectively. The amino alcohols were converted to their Mosher esters using (*S*)-Mosher acid chloride,[22] and the two epimeric products were compared by NMR spectroscopy. The two diastereomers were found to be clearly distinguishable and showed less than 5% contamination from racemized material. The chiral integrity of amino alcohols **9** having been established, that of the vinylglycines **5** and **12** was verified by capillary GC analysis using a chiral column.[23] For this purpose, *N*-Boc-vinylglycine methyl esters **12** were deprotected and derivatized based on the procedure of Frank et al. as shown in eq 2



(see Experimental Section). Chiral GC analysis of **15** revealed one major peak for the D isomer contaminated with less than 5% of the opposite L isomer. For selected cases, comparison of the derivatized amino acid with a sample obtained starting from D-serine instead of L-serine and using the same reaction sequence confirmed the extent of racemization to be less than ca. 5%. Vinylglycine derivatives **12** were found to be stable under the derivatization conditions described in eq 2. Derivatives **15** showed ^1H and ^{13}C NMR and mass spectral parameters consistent with their structure (no decomposition or isomerization of the vinylglycine derivatives was detected). Furthermore, the thermal stability of **15** under capillary GC conditions was verified in the case of **15d** by GC–MS analysis.[24] To further substantiate the optical purity of our products, both enantiomers of **12e** were shown to exhibit equal and opposite rotations. As a final proof, the optical rotation of (*S*)-**5b** was found to be comparable to that reported in the literature [$[\alpha]^{30}_D$ +98.6° (*c* = 1.52, MeOH) (lit.[7d] $[\alpha]^{20}_D$ +103° (*c* = 2, MeOH)].

Summary

We have developed a procedure for the elaboration of serine into vinylglycines with defined configuration and double-bond geometry. The methodology allows for a variety of functional groups and delivers the products in essentially enantiomerically pure form. We hope that these interesting molecules will become useful synthons for the construction of more complex targets of biological interest.

Experimental Section

General Experimental Procedure. Melting points were determined on an Electrothermal melting point apparatus and are uncorrected. NMR spectra were recorded in $CDCl_3$ on a Bruker AC200 (200.13 MHz for ^1H NMR, 50.8 MHz for ^{13}C NMR), AMX 400 (400.13 MHz for ^1H NMR, 100.6 MHz for ^{13}C NMR), or AM 500 (500.14 MHz for ^1H NMR) spectrometer and were referenced to TMS as an internal standard (δ scale). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, b = broad), coupling constants (hertz), and integration. IR spectra were recorded on a Perkin–Elmer 781 spectrophotometer. High- and low-resolution FAB mass spectra were obtained on a MF 50 TATC instrument operating at 6 kV and 1 mA using thioglycerol as a matrix support. CI and EI mass spectra were recorded on the

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

(23) (a) Frank, H.; Rettenmeier, A.; Welcker, H.; Nicholson, G. J.; Baeyer, E. *Anal. Chem.* **1982**, *54*, 715. (b) Liu, R. H.; Ku, W. W. *J. Chromatogr.* **1983**, *271*, 309. A CHIRASIL-VAL column (Alltech Ass. Inc.) was used for evaluation of enantiomeric purities.

(24) To eliminate the possibility that the diastereomeric environment created by the chiral capillary GC column could lead to enrichment or selected epimerization of vinylglycine derivatives **15**, we also prepared diastereomeric (*R*)-2-octanol esters of the vinylglycines by replacing isopropanol with (*R*)-2-octanol in the derivatization procedure of eq 2. These diastereomeric derivatives were then analyzed on an achiral capillary GC column (Supelco Wax 10, 30 m × 0.25 mm), and in all cases studied, the calculated enantiomeric excess (% ee) was comparable to the one determined on the chiral column.

same instrument operating at 70 eV. Optical rotations were measured on a Perkin-Elmer 241 MC polarimeter at the sodium D line with a 1-dm path length, 1-mL cell kept at constant temperature. Elemental analyses were carried out on a Carlo Erba elemental analyzer (Model 1106). Capillary GC analyses were performed on a Shimadzu GC-9AM instrument with a 0.25 mm × 25 m CHIRASIL-VAL column.[23]

Flash chromatography[25] was performed on Merck silica gel 60 (0.040–0.063 mm) using nitrogen pressure. Analytical thin-layer chromatography (TLC) was carried out on precoated (0.25-mm) Merck silica gel F-254 plates. Visualization was achieved by UV irradiation (254 nm) and staining with phosphomolybdic acid/sulfuric acid at 110 °C or basic (2% sodium carbonate) potassium permanganate (1%) solution. All reactions requiring anhydrous conditions were conducted under a positive argon atmosphere in oven-dried glassware using standard syringe techniques.

Tetrahydrofuran (THF) was distilled from potassium/benzophenone immediately prior to use. *N,N*-Dimethylformamide (DMF) was distilled from calcium hydride under reduced pressure and stored over activated 4-Å molecular sieves. Methanol, acetonitrile, acetone, ethyl acetate, and hexanes were reagent grade and used without further purification. *n*-BuLi (Aldrich) was standardized by titration using diphenylacetic acid.[26] Boc-L-serine and Boc-D-serine were obtained from Bachem (USA) and used as received. Dowex 50W strong H^+ resin was washed with methanol before use.

General Procedure for the Preparation of Triphenylphosphonium Salts. Triphenylphosphine (1 equiv) and an alkyl bromide or iodide (1 equiv) were dissolved in toluene, and the solution was refluxed under argon for 16–20 h. A white insoluble solid was generally formed. After the reaction mixture was cooled, the product was collected by filtration, washed with ether, and dried under vacuum. When the salts were formed as immiscible oils, the supernatant was decanted and, after trituration of the residue with ether, white solids were obtained that were isolated as described previously.

Generation of Triphenylphosphonium Ylides. Method A. The triphenylphosphonium salt (1.1 equiv) was suspended in dry THF in a three-necked flask under an argon atmosphere. The suspension was cooled to −75 °C, and *n*-BuLi (1.0 equiv, 1.3 M in hexane) was added dropwise. The mixture was stirred for 0.5 h, allowing the temperature to reach 0 °C at which point it was stirred for 1 additional h. The resulting dark red solution was used immediately for condensation with the serine aldehyde.

Method B. The same procedure was used as in method A except that KHMDS (1.0 equiv, 0.5 M in toluene, Aldrich) was used instead of *n*-BuLi.

Method C. Same procedure as in the previous text but LiHMDS (generated from 1.1 equiv of 1,1,1,3,3,3-hexamethyldisilazane and 1.0 equiv of *n*-BuLi at −20 °C in THF) was used as the base.

Method D. Same procedure as in the previous text but LDA (generated from 1.1 equiv of *N,N*-diisopropylamine and 1.0 equiv of *n*-BuLi at −20 °C in THF) was used as the base.

(*S*)-*N*-Boc-2,2-dimethyl-4-ethenyloxazolidine (8a).[13] The ylide was generated in THF (50 mL) from methyltriphenylphosphonium brimide (Aldrich; 1.950 g, 5.45 mmol) using method A. To the cooled solution (−75 °C) was added 1,1-dimethylethyl (*R*)-4-formyl-2,2-dimethyl-3-oxazolidinecarboxylate (*R*)-**7b**[12] (1.00 g, 4.36 mmol) in THF (10 mL + 2 mL rinse) dropwise over a 10-min period. The reaction mixture was stirred under argon, allowing the temperature to reach 25 °C at which point it was stirred for another 4 h. After the mixture was quenched with saturated aqueous ammonium chloride (50 mL), the THF was evaporated under reduced pressure and the residue extracted with ethyl acetate (3 × 25 mL). The combined organic phases were washed with water (25 mL) and brine (25 mL) and dried over magnesium sulfate. After evaporation of the solvent under reduced pressure, the residue was purified by flash chromatography using 9:2 hexane/ethyl acetate as eluant. The product was obtained as a colorless oil (0.270 g, 27% yield): R_f 0.48 (9:1 hexane/ethyl acetate); $[\alpha]^{30}_D$ 0° (*c* = 1.00, MeOH);[13] ^{1}H NMR ($CDCl_3$, 200 MHz) δ 5.83 (dt, *J* = 17.2, 8.8 Hz, 1 H), 5.14 (b d, *J* = 10.0 Hz, 2 H), 4.31 (b m, 1 H), 4.06 (dd, *J* = 8.4, 6.0 Hz, 1 H), 3.76 (dd, *J* = 9.2, 3.2 Hz, 1 H), 1.60 (s, 3 H), 1.51 (s, 3 H), 1.44 (s, 9 H); IR (neat) 3000–2800, 1700, 1380, 1255, 1175, 1095, 1060 cm^{-1}; MS (CI) *m/z* (rel intensity) 228 (0.8, MH^+), 172 (100, MH^+ − *tert*-butyl), 128 (60, MH^+ − Boc).

(*Z*)-(*S*)-*N*-Boc-2,2-dimethyl-4-(1-propenyl)oxazolidine ((*S*)-8b). The ylide was generated in THF (50 mL) from the phosphonium salt (3.19 g, 7.65 mmol; prepared from triphenylphosphine and ethyl iodide) and reacted with aldehyde (*R*)-**7b** (1.00 g, 4.36 mmol) following method A. After a reaction time of 3 h at room temperature, product (*S*)-**8b** (0.655 g, 62% yield) was isolated as an oil after flash chromatography (9:2 hexane/ethyl acetate). The product was contaminated with 7% of the *E* isomer as determined by ^{1}H NMR: R_f 0.40 (9:1 hexane/ethyl acetate); $[\alpha]^{30}_D$ −54.0° (*c* = 1.2, MeOH); ^{1}H NMR ($CDCl_3$, 200 MHz) δ (*Z* isomer) 5.5 (m, 2 H), 4.67 (b m, 1 H), 4.08 (dd, *J* = 8.7, 6.2 Hz, 1 H), 3.65 (dd, *J* = 8.7, 3.2 Hz, 1 H), 1.68 (d, *J* = 5.3 Hz, 3 H), 1.60 (s, 3 H), 1.52 (s, 3 H), 1.46 (s, 9 H), (*E* isomer) 4.02 (dd, *J* = 8.7, 6.1 Hz, 1 H), 3.70 (dd, *J* = 8.8, 2.1 Hz, 1 H); IR (neat) 3100–2850, 1700, 1380, 1255, 1180, 1090, 1065, 855 cm^{-1}; high-resolution MS (EI) *m/z* (rel intensity) calcd for $C_{13}H_{24}NO_3$ 242.1756, found 242.1745 (25, MH^+), 186 (100, MH^+ − *tert*-butyl), 170 (95, MH^+ − *tert*-butyl alcohol), 142 (45, MH^+ − Boc), 126 (65).

(*Z*)-(*R*)-*N*-Boc-2,2-dimethyl-4-(1-propenyl)oxazolidine ((*R*)-8b). This compound was prepared following the procedure described for the *S* enantiomer using aldehyde (*S*)-**7b** derived from L-serine. Both enantiomers were identical in all respects except for optical rotations. (*R*)-**8b**: $[\alpha]^{30}_D$ +63° (*c* = 1.02, MeOH).

(*E*)- and (*Z*)-(*R*)-*N*-Boc-2,2-dimethyl-4-(2-phenylethenyl)oxazolidine (8c). The ylide was generated in THF (50 mL) from the phosphonium salt (1.42 g, 3.27 mmol; prepared from triphenylphosphine and benzyl bromide) and reacted with aldehyde (*S*)-**7b** (0.500 g, 2.18 mmol) following method B. Reaction time was 4 h at room temperature. Product **8c** was obtained as a colorless oil (0.555 g, 84% yield) and consisted of an unseperable 4:6 mixture of *E* and *Z* isomers: R_f 0.59 (9:2 hexane/ethyl acetate); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.2–7.4 (m, 5 H), 6.59 (b d, *J* = 16 Hz, 0.4 H), 6.48 (b d, *J* = 16 Hz, 0.6 H), 6.16 (b m, 1 H), 4.58 (b s, 0.4 H), 4.42 (b s, 0.6 H), 4.12 (t, *J* = 8 Hz, 1 H), 3.84 (d, *J* = 9.3 Hz, 1 H), 1.70 (s, 1.8 H), 1.65 (s, 1.2 H), 1.58 (s, 3 H), 1.50 (s, 3.6 H), 1.40 (s, 5.4 H); IR (neat) 2880–3060, 1700, 1480, 1455, 1380, 1255, 1175, 1100 cm^{-1}; MS (CI) *m/z* (rel intensity) 304 (12, MH^+), 248 (94, MH^+ − *tert*-butyl), 204 (35, MH^+ − Boc), 144 (100). Anal. Calcd for $C_{18}H_{25}NO_3$: C, 71.26; H, 8.31; N, 4.62. Found: C, 71.09; H, 8.41; N, 4.55.

(*Z*)-(*R*)-*N*-Boc-2,2-dimethyl-4-(1-heptenyl)oxazolidine ((*R*)-8d). The ylide was generated in THF (50 mL) from the phosphonium salt (2.58 g, 5.43 mmol; prepared from triphenylphosphine and 1-iodohexane) using method A. Aldehyde (*S*)-**7b** (1.00 g, 4.36 mmol) was added at −75 °C, and the reaction was allowed to proceed for 1.5 h at room temperature. Usual workup as described for **8a** gave *Z* alkene **8d** (1.01 g, 78% yield) as a colorless oil after purification by flash chromatography using 14:1 hexane/ethyl acetate as eluant: R_f 0.38 (9:1 hexane/ethyl acetate); $[\alpha]^{30}_D$ +49.1° (*c* = 1.02, MeOH); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 5.3–5.5 (m, 2 H), 4.62 (b s, 1 H), 4.08 (dd, *J* = 8.6, 6.4 Hz, 1 H), 3.65 (dd, *J* = 8.6, 4.1 Hz, 1 H), 2.1 (b m, 2 H), 1.60 (s, 3 H), 1.45 (s, 9 H), 1.29 (m, 6 H), 0.90 (t, *J* = 6.8 Hz, 3 H); IR (neat) 2830–3010, 1695, 1375, 1250, 1175, 1090, 1050, 850, 765 cm^{-1}; MS (CI) *m/z* (rel intensity) 298 (10, MH^+), 282 (9, $MH^+ - CH_3$), 270 (8, $MH^+ - C_2H_4$), 242 (100, MH^+ − *tert*-butyl), 198 (79, MH^+ − Boc), 184 (25); high-resolution FAB MS *m/z* calcd for $C_{17}H_{32}NO_3$ (MH^+) 298.2382, found 298.2375. Anal. Calcd for $C_{17}H_{31}NO_3$: C, 63.17; H, 9.54; N, 4.91. Found: C, 62.83; H, 9.84; N, 4.74.

(*Z*)-(*S*)-*N*-Boc-2,2-dimethyl-4-(1-heptenyl)oxazolidine ((*S*)-8d). This compound was prepared following the procedure described for the *R* isomer using aldehyde (*R*)-**7b** derived from D-serine. Both enantiomers were identical in all respects except for the optical rotations, which were of opposite signs. *S* isomer: $[\alpha]^{30}_D$ −48.9° (*c* = 1.06, MeOH).

(*Z*)-(*R*)-*N*-Boc-2,2-dimethyl-4-(4-phenyl-1-butenyl)oxazolidine (8e). The ylide was generated in THF (50 mL) from the phosphonium salt (3.01 g, 6.54 mmol; prepared from triphenylphosphine and 1-bromo-3-phenylpropane) using method A. Aldehyde (*S*)-**7b** (1.00 g, 4.36 mmol) was added at −75 °C, and the reaction was allowed to proceed for 45 min at room tem-

(25) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.
(26) Kofron, W. G.; Baclawski, L. M. *J. Org. Chem.* **1976**, *41*, 1879.

perature. After workup and flash chromatography (14:1 hexane/ethyl acetate), **8e** (1.39 g, 96% yield) was obtained as a colorless oil: R_f 0.66 (9:1 hexane/ethyl acetate); $[\alpha]^{30}_D$ +84.4° (*c* = 1.01, MeOH); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.1–7.35 (m, 5 H), 5.48 (m, 1 H), 5.39 (t, *J* = 8.7 Hz, 1 H), 4.44 (b m, 1 H), 3.70 (b m, 1 H), 3.25 (b m, 1 H), 2.80 (m, 1 H), 2.59 (q, *J* = 7.8 Hz, 1 H), 2.5 (m, 2 H), 1.55 (s, 3 H), 1.50 (s, 3 H), 1.43 (s, 9 H); IR (neat) 2870–3100, 1705, 1510, 1375, 1250, 1180, 1090, 855, 750, 705 cm^{-1}; high-resolution FAB MS *m/z* (rel intensity) calcd for $C_{20}H_{30}NO_3$ (MH^+) 332.2227, found 332.2197, 276 (100, MH^+ – *tert*-butyl), 232 (41, MH^+ – Boc). Anal. Calcd for $C_{20}H_{29}NO_3$: C, 72.47; H, 8.82; N, 4.23. Found: C, 72.38; H, 8.99; N, 3.95.

(*Z*)-(*R*)-*N*-Boc-2,2-dimethyl-4-(4-carboxy-1-butenyl)oxazolidine (8f). The ylide was generated in THF (50 mL) from the phosphonium salt (3.89 g, 9.07 mmol; prepared from triphenylphosphine and 4-bromobutyric acid) and LiHMDS (17.7 mmol) following method C. Aldehyde (*S*)-**7b** (1.22 g, 5.34 mmol) was added at –75 °C, and the reaction was allowed to proceed for 30 min at 0 °C then 1 h at room temperature. Crude **8f** (1.12 g, 73% yield) was obtained as a clear oil after workup and used without further purification: R_f 0.87 (3:1 ethyl acetate/methanol); $[\alpha]^{30}_D$ +53.7° (*c* = 1.01, MeOH); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 5.49 (m, 2 H), 2.67 (b m, 1 H), 4.08 (dd, *J* = 9.2, 5.3 Hz, 1 H), 2.45 (m, 4 H), 1.59 (s, 3 H), 1.52 (s, 3 H), 1.47 (s, 9 H); IR (neat) 2400–3700, 1715, 1693, 1395, 1255, 1220, 1175, 1105, 1060, 853 cm^{-1}; high-resolution MS (EI) *m/z* (rel intensity) calcd for $C_{15}H_{25}NO_5$ 299.1733, found 299.1763 (45, M^+), 284 (6, $M^+ - CH_3$), 184 (97, $M^+ - CH_3$ – Boc), 142 (13), 57 (100, *tert*-butyl$^+$). Anal. Calcd for $C_{15}H_{25}NO_5$: C, 60.18; H, 8.42; N, 4.68. Found: C, 59.13; H, 8.31; N, 4.15.

(*Z*)-(*R*)-*N*-Cbz-2,2-dimethyl-4-(4-cyano-1-butenyl)oxazolidine (8g). The ylide was generated in THF (50 mL) from the phosphonium salt (100.26 g, 25 mmol; prepared from triphenylphosphine and 4-bromobutyronitrile) using method D. Aldehyde (*S*)-**7a**[10] (4.235 g, 16.1 mmol) was added at –75 °C and was allowed to react for 75 min at room temperature. After the usual workup and purification by flash chromatography (4:1 hexane/ethyl acetate), product **8g** (3.682 g, 73% yield) was obtained as a colorless oil: R_f 0.34 (2:1 hexane/ethyl acetate); $[\alpha]^{30}_D$ +36.0° (*c* = 0.75, MeOH); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.23–7.4 (m, 5 H), 5.4 (m, 1 H), 5.1 (m, 2 H), 4.7 (m, 1 H), 4.10 (dd, *J* = 8.8, 6.0 Hz, 0.6 H), 3.95 (m, 0.4 H), 3.75 (d, *J* = 7.5 Hz, 0.5 H), 3.68 (dd, *J* = 8.7, 2.6 Hz, 0.5 H), 3.1 (m, 2 H), 1.4–1.7 (m, 6 H); IR (CH_2Cl_2) 2850–3150, 2290, 1720, 1430, 1370, 1285, 1110, 1080 cm^{-1}; high-resolution MS (FAB) *m/z* calcd for $C_{18}H_{22}N_2O_3$ 314.1630, found 314.1718.

(*Z*)-(*R*)-*N*-Cbz-2,2-dimethyl-4-(5-cyano-1-pentenyl)oxazolidine (8h). Same procedure as for **8g** but 5-bromovaleronitrile was used to prepare the phosphonium salt. Product **8h** was obtained as a colorless oil (78%) after flash chromatography (4:1 hexane/ethyl acetate as eluant): R_f 0.42 (2:1 hexane/ethyl acetate); $[\alpha]^{8}_D$ +61.5° (*c* = 1.03, MeOH); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.27–7.45 (m, 5 H), 5.55 (m, 1 H), 5.1 (m, 2 H), 4.7 (m, 1 H), 4.13 (dd, *J* = 8.7, 6.2 Hz, 1 H), 3.72 (dd, *J* = 8.8, 2.4 Hz, 1 H), 2.4 (m, 2 H), 2.1 (m, 2 H), 1.4–1.9 (m, 8 H); IR (neat) 2880–3100, 2250, 1700, 1410, 1350, 1255, 1090, 1060, 910, 840, 735 cm^{-1}; high-resolution MS (FAB) *m/z* calcd for $C_{19}H_{24}N_2O_3$ 329.1865, found 329.1817.

(*E*)-(*R*)-*N*-Cbz-2,2-dimethyl-4-(2-carboxyethenyl)oxazolidine Methyl Ester (8i). Aldehyde (*S*)-**7a** (0.231 g, 0.877 mmol) and methyl (triphenylphosphoranylidene)acetate (0.301 g, 0.900 mmol) were dissolved in benzene (10 mL), and the solution was stirred overnight at room temperature under an argon atmosphere. After evaporation of the solvent under reduced pressure, the product was purified by flash chromatography (4:1 hexane/ethyl acetate) to give **8i** as a clear oil (0.235 g, 85% yield): R_f 0.43 (2:1 hexane/ethyl acetate); $[\alpha]^{30}_D$ –49.9° (*c* = 0.75, MeOH); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.3–7.45 (m, 5 H), 7.86 (dd, *J* = 15.6, 8.5 Hz, 1 H), 6.6 (d, *J* = 15.6 Hz, 0.3 H), 5.87 (d, *J* = 15.6 Hz, 0.7 H), 5.5 (m, 2 H), 4.62 (b t, *J* = 6.2 Hz, 0.3 H), 4.72 (b t, *J* = 6.2 Hz, 0.7 H), 4.12 (dd, *J* = 9.2, 6.3 Hz, 1 H), 3.85 (dd, *J* = 9.2, 2.2 Hz, 1 H), 3.75 (s, 3 H), 1.69 (s, 2.1 H), 1.62 (s, 0.9 H), 1.58 (s, 2.1 H), 1.51 (s, 0.9 H); IR (neat) 1715, 1410, 1355, 1100, 1060, 702 cm^{-1}; high-resolution FAB MS *m/z* (rel intensity) calcd for $C_{15}H_{20}NO_5$ 294.1341, found 294.1344 (50, MH^+), 316 (30, M + Na^+), 236 (100), 214 (20), 146 (25), 128 (37).

(*E*)- and (*Z*)-(*R*)-*N*-Boc-2,2-dimethyl-4-(2-methyl-1-butenyl)oxazolidine (8j). The procedure used was that described for **8a** except that the phosphorous ylide was generated from the phosphonium salt (2.00 g, 5.17 mmol) prepared from triphenylphosphine and 2-iodobutane. The reaction was complete after stirring 2.5 h at room temperature. From aldehyde (*S*)-**7b** (0.790 g, 3.45 mmol), the product **8j** was isolated as a colorless oil (0.227 g, 50% yield based on recovered starting material) after flash chromatography (9:1 hexane/ethyl acetate). It consisted of an unseparable mixture of *E*/*Z* isomers: R_f 0.57 (9:1 hexane/ethyl acetate); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 5.14 (b d, *J* = 9.0 Hz, 1 H), 4.55 (b m, 1 H), 4.03 (m, 1 H), 3.61 (m, 1 H), 2.25 (m, 1 H), 2.02 (q, *J* = 7.7 Hz, 1 H), 1.7 (d, *J* = 13 Hz, 3 H), 1.58 (s, 3 H), 1.50 (s, 3 H), 1.42 (s, 9 H), 0.97 (m, 3 H); IR (neat) 3020–2880, 1705, 1400, 1255, 1180, 865 cm^{-1}; high-resolution MS (EI) *m/z* (rel intensity) calcd for $C_{15}H_{27}NO_3$ 269.1991, found 269.2012 (90, MH^+), 213 (100, MH^+ – *tert*-butyl), 197 (25, MH^+ – *tert*-butyl alcohol), 169 (13, MH^+ – Boc), 153 (55).

General Procedure for Hydrolysis of Acetonides 8 to Amino Alcohols 9. The acetonide (2–5 mmol) was dissolved in 90% aqueous methanol or acetonitrile (10 mL). Methanol-washed Dowex 50W strong H^+ resin (ca. 2 mL) was added, and the suspension was stirred overnight at room temperature. After filtration of the resin (methanol wash, 2 × 5 mL) and evaporation of the solvent under reduced pressure, amino alcohols **9** were obtained and purified by flash chromatography.

(*S*)-*N*-Boc-2-amino-3-butenol (9a).[13] Hydrolysis of **8a** (0.160 g, 0.70 mmol) in aqueous methanol followed by purification by flash chromatography (2:1 hexane/ethyl acetate) gave **9a** (0.117 g, 89% yield) as a yellowish oil. The material had spectral and physical properties comparable to those described in the literature.[13] R_f 0.23 (2:1 hexane/ethyl acetate); $[\alpha]^{27}_D$ –20.1° (*c* = 1.34, $CHCl_3$), the observed optical rotation corresponds to a 69% enantiomeric excess;[13] ^{1}H NMR ($CDCl_3$, 200 MHz) δ 5.82 (ddd, *J* = 17.7, 10.3, 5.3 Hz, 1 H), 5.27 (m, 2 H), 4.86 (b m, 1 H), 4.27 (b m, 1 H), 3.7 (b m, 2 H), 2.05 (b m, 1 H), 1.48 (s, 9 H); IR (neat) 3700–3100, 3050–2800, 1700, 1530, 1255, 1180, 930 cm^{-1}; MS (CI) *m/z* (rel intensity) 132 (30, MH^+ – *tert*-butyl), 114 (29, MH^+ – *tert*-butyl alcohol), 88 (38, MH^+ – Boc).

(*Z*)-(*R*)-*N*-Boc-2-amino-3-pentenol ((*R*)-9b).[7d] Hydrolysis of **8b** (0.070 g, 0.29 mmol) in aqueous methanol gave pure (*R*)-**9b** (0.050 g, 86% yield) as a white solid. The product was contaminated with 7% of the *E* isomer: R_f 0.30 (7:3 hexane/ethyl acetate); mp 55–56 °C; $[\alpha]^{30}_D$ +40.7° (*c* = 1.09, MeOH); ^{1}H NMR ($CDCl_3$, 200 MHz) δ (*Z* isomer) 5.68 (dq, *J* = 5.9, 1.0 Hz, 1 H), 5.31 (ddq, *J* = 10.7, 10.0, 1.7 Hz, 1 H), 4.87 (b d, *J* = 7.1 Hz, 1 H), 4.48 (quintet, *J* = 6.7 Hz, 1 H), 3.6 (m, 2 H), 3.0 (b s, 1 H), 1.72 (dd, *J* = 6.9, 1.7 Hz, 3 H), 1.47 (s, 9 H), (*E* isomer) 5.40 (ddq, *J* = 15.4, 6.0, 2.0 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 50.13 MHz) δ 156.3, 128.4, 127.5, 79.8, 65.9, 50.4, 28.3, 13.4; IR (neat) 3700–3100, 3050–2800, 1695, 1520, 1250, 1180, 1060 cm^{-1}; MS (CI) *m/z* (rel intensity) 202 (7, MH^+), 146 (100, MH^+ – *tert*-butyl), 128 (14, MH^+ – *tert*-butyl alcohol), 102 (44, MH^+ – Boc). Anal. Calcd for $C_{10}H_{19}NO_3$: C, 59.62; H, 9.52; N, 6.96. Found: C, 59.46; H, 9.55; N, 6.60.

(*Z*)-(*S*)-*N*-Boc-2-amino-3-pentenol ((*S*)-9b.[7d] Prepared as in the previous text for the *R* enantiomer. Physical and spectral properties were identical for both isomers except for optical rotations: $[\alpha]^{30}_D$ –38.5° (*c* = 1.1, MeOH).

(*E*)- and (*Z*)-(*R*)-*N*-Boc-2-amino-4-phenyl-3-butenol (9c). Hydrolysis in aqueous methanol of the isomeric mixture of **8c** (0.145 g, 0.48 mmol) gave, after purification by flash chromatography using 7:3 hexane/ethyl acetate as eluant, 0.095 g (75% yield) of **9c**: R_f 0.15 (7:3 hexane/ethyl acetate); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.15–7.4 (m, 5 H), 6.61 (d, *J* = 16.8 Hz, 1 H, *E* isomer), 6.15 (dd, *J* = 16.4, 6.3 Hz, 1 H, *E* isomer), 5.58 (dd, *J* = 12.0, 10.6 Hz, 1 H, *Z* isomer), 4.98 (b d, *J* = 7.7 Hz, 1 H), 4.76 (b m, 1 H), 4.42 (b m, 1 H), 3.73 (b m, 2 H), 1.50 (s, 9 H); IR (CH_2Cl_2) 3200–3600, 2860–3100, 1700, 1500, 1270, 1170 cm^{-1}; MS (CI) *m/z* (rel intensity) 264 (22, MH^+), 208 (100, MH^+ – *tert*-butyl), 190 (51, MH^+ – *tert*-butyl alcohol), 164 (21, MH^+ – Boc), 147 (67), 129 (69), 104 (91). Anal. Calcd for $C_{15}H_{21}NO_3$: C, 68.42; H, 8.04; N, 5.32. Found: C, 68.27; H, 8.17; N, 5.49.

(*Z*)-(*R*)-*N*-Boc-2-amino-3-nonenol ((*R*)-9d). Hydrolysis of **8d** (0.649 g, 2.18 mmol) in aqueous methanol and flash chromatography (7:3 hexane/ethyl acetate) gave **9d** (0.496 g, 87% yield)

as a white solid: R_f 0.26 (7:3 hexane/ethyl acetate); mp 85–86 °C; $[\alpha]^{30}_D$ +28.5° (c = 1.02, MeOH); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 5.59 (dt, J = 11.0, 7.8 Hz, 1 H), 5.76 (ddt, J = 10.5, 8.5, 3.6 Hz, 1 H), 4.67 (b s, 1 H), 4.48 (m, 1 H), 3.60 (b d, J = 6.9 Hz, 2 H), 2.14 (b q, J = 6.9 Hz, 2 H), 1.48 (s, 3 H), 1.3 (m, 6 H), 0.90 (t, J = 6.6 Hz, 3 H); IR ($CHCl_3$) 3380–3460, 2860–3040, 1700, 1500 cm^{-1}; MS (CI) m/z (rel intensity) 258 (2, MH^+), 219 (28, $MH^+ - C_3H_3$), 202 (100, MH^+ – *tert*-butyl), 184 (14, MH^+ – *tert*-butyl alcohol), 158 (74, MH^+ – Boc), 140 (13), 126 (16). Anal. Calcd for $C_{14}H_{27}NO_3$: C, 65.33; H, 10.57; N, 5.44. Found: C, 65.26; H, 10.88; N, 5.53.

(*Z*)-(*S*)-*N*-Boc-2-amino-3-nonenol ((*S*)-9d). Prepared as in the previous text for the *R* enantiomer. Physical and spectral properties were identical for both isomers except for optical rotations: $[\alpha]^{30}_D$ –26.7° (c = 1.03, MeOH); mp 86–87 °C.

(*S*)-Mosher Ester of (*R*)-9d. The ester was prepared as described in the literature[22] using the *S* enantiomer of Mosher's acid chloride: R_f 0.75 (1:1 hexane/ethyl acetate); $[\alpha]^{30}_D$ –21.2° (c = 1.99, MeOH); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.52 (m, 2 H), 7.4 (m, 3 H), 5.57 (dt, J = 11.2, 7.3 Hz, 1 H), 5.23 (ddt, J = 11.0, 10.0, 3.0 Hz, 1 H), 4.73 (b m, 1 H), 4.50 (b m, 1 H), 4.36 (m, 1 H), 4.27 (dd, J = 10.6, 6.6 Hz, 1 H), 3.57 (q, J = 1.0 Hz, 3 H), 2.09 (m, 2 H), 1.45 (s, 9 H), 1.3 (m, 6 H), 0.90 (t, J = 8.5 Hz, 3 H); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.5 (m, 5 H), 7.09 (d, J = 9.5 Hz, 1 H), 5.48 (dt, J = 10.5, 8.3 Hz, 1 H), 5.20 (t, J = 9.5 Hz, 1 H), 4.62 (m, 1 H), 4.2 (m, 2 H), 3.49 (s, 3 H), 2.08 (m, 1 H), 1.97 (m, 1 H), 1.37 (s, 9 H), 1.25 (m, 6 H), 0.87 (t, J = 8.0 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 50.8 MHz) δ 167.1, 154.8, 135.4, 132.3, 129.6, 128.4, 127.4, 125.2, 79.8, 67.8, 55.4, 47.1, 31.4, 29.4, 29.0, 28.4, 22.5, 13.9; MS (CI) m/z (rel intensity) 491 (91, $MH^+ + NH_3$), 474 (9, MH^+), 435 (100, MNH_4^+ – *tert*-butyl), 417 (20, MH^+ – *tert*-butyl), 374 (59, MH^+ – Boc).

(*S*)-Mosher Ester of (*S*)-9d. The procedure described for the preparation of the (*S*)-Mosher ester of (*R*)-9d was used: R_f 0.75 (1:1 hexane/ethyl acetate); $[\alpha]^{30}_D$ –30.2° (c = 1.35, MeOH); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.5 (m, 5 H), 5.56 (dt, J = 10, 7.8 Hz, 1 H), 5.21 (ddt, J = 10.6, 9.7, 1.7 Hz, 1 H), 4.73 (m, 1 H), 4.48 (b d, J = 8.2 Hz, 1 H), 4.37 (dd, J = 10.9, 4.6 Hz, 1 H), 4.27 (dd, J = 10.9, 5.5 Hz, 1 H), 3.58 (q, J = 1.1 Hz, 3 H), 2.1 (m, 2 H), 1.43 (s, 9 H), 1.28 (m, 6 H), 0.87 (t, J = 6.9 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 50.8 MHz) δ 166.6, 154.9, 135.4, 132.3, 129.7, 128.5, 127.4, 125.3, 79.8, 67.8, 55.5, 47.2, 31.4, 29.1, 28.4, 27.8, 22.5, 14.0.

(*Z*)-(*R*)-*N*-Boc-2-amino-6-phenyl-3-hexenol (9e). Hydrolysis of 8e (0.793 g, 2.39 mmol) and flash chromatography (7:3 hexane/ethyl acetate) gave 9e (0.550 g, 75% yield) as a white solid: R_f 0.31 (2:1 hexane/ethyl acetate); mp 38–40 °C; $[\alpha]^{30}_D$ +37.3° (c = 1.02, MeOH); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.35–7.1 (m, 5 H), 5.62 (dt, J = 10.5, 7.3 Hz, 1 H), 5.27 (ddt, J = 10.5, 10.0, 3.6 Hz, 1 H), 4.58 (b d, J = 6.8 Hz, 1 H), 4.38 (m, 1 H), 3.45 (t, J = 5.7 Hz, 2 H), 2.72 (m, 1 H), 2.48 (m, 1 H), 1.47 (s, 9 H); ^{13}C NMR ($CDCl_3$, 50.8 MHz) δ 157.1, 141.8, 132.7, 128.5, 128.3, 127.0, 126.0, 79.8, 66.3, 50.9, 35.6, 29.7, 28.4; IR (CH_2Cl_2) 3700–3200, 3100–2800, 1705, 1500, 1217, 1170 cm^{-1}; MS (FAB) m/z (rel intensity) 314 (9, M^+ + Na), 292 (28, MH^+), 236 (100, MH^+ – *tert*-butyl), 192 (28, MH^+ – Boc), 157 (51), 131 (30), 91 (82). Anal. Calcd for $C_{17}H_{25}NO_3$: C, 70.07; H, 8.65; N, 4.81. Found: C, 69.93; H, 8.75; N, 4.68.

(*Z*)-(*R*)-*N*-Boc-6-amino-7-hydroxy-4-heptenoic Acid (9f). Acetonide 8f (0.050 g, 0.17 mmol) was hydrolyzed according to the general procedure, but acetonitrile was used as solvent instead of methanol. The product 9f (0.033 g, 79% yield) was obtained as an oil: R_f 0.78 (3:1 ethyl acetate/methanol); $[\alpha]^{30}_D$ +29.2° (c = 1.5, MeOH); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 5.52 (m, 1 H), 5.33 (t, J = 9.6 Hz, 1 H), 5.08 (b m, 1 H), 4.50 (b m, 1 H), 3.60 (b m, 2 H), 2.44 (b m, 4 H), 1.44 (s, 9 H); IR (CH_2Cl_2) 3200–2400, 1715, 1505, 1220, 1170, 913 cm^{-1}. The product was further characterized as the methyl ester.

Methyl Ester of 9f. Hydroxy acid 9f was treated with excess diazomethane in ether. After evaporation of the solvent and flash chromatography (2:1 hexane/ethyl acetate), the corresponding methyl ester was obtained in quantitative yield as a colorless oil: R_f 0.26 (2:1 hexane/ethyl acetate); $[\alpha]^{30}_D$ +21.1° (c = 1.06, MeOH); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 5.52 (m, 1 H), 5.37 (t, J = 10.2 Hz, 1 H), 4.38 (b m, 1 H), 4.49 (b m, 1 H), 3.68 (s, 3 H), 3.62 (d, J = 5.8 Hz, 2 H), 2.43 (m, 4 H), 1.45 (s, 9 H); IR (neat) 3700–3100, 3100–2800, 1740, 1690, 1530, 1170, 1010, 860, 780, 760 cm^{-1}; MS (FAB) m/z (rel intensity) 296 (21, M^+ + Na), 274 (48, MH^+), 218 (65, MH^+ – *tert*-butyl), 174 (100, MH^+ – Boc), 157 (29), 142 (39), 125 (64), 107 (17), 82 (18). Anal. Calcd for $C_{13}H_{23}NO_5$: C, 57.13; H, 8.48; N, 5.12. Found: C, 57.26; H, 8.46; N, 4.62.

(*E*)-(*R*)-*N*-Cbz-4-amino-5-hydroxy-2-pentenoic Acid, Methyl Ester (9i). Acetonide 8i (1.476 g, 4.60 mmol) was hydrolyzed in aqueous methanol according to the general procedure. Pure 9i (1.150 g, 89% yield) was obtained after flash chromatography (1:1 hexane/ethyl acetate): R_f 0.19 (1:1 hexane/ethyl acetate); mp 59–60 °C; $[\alpha]^{30}_D$ –0.3° (c = 1.0, MeOH); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.37 (s, 5 H), 6.94 (dd, J = 15.7, 4.9 Hz, 1 H), 6.05 (dd, J = 15.7, 1.7 Hz, 1 H), 5.38 (b d, J = 8.5 Hz, 1 H), 5.13 (s, 2 H), 4.50 (b m, 1 H), 3.79 (b m, 2 H), 3.77 (s, 3 H), 2.20 (b s, 1 H); IR (CH_2Cl_2) 3550–3200, 1722, 1665, 1510, 895 cm^{-1}; high-resolution MS (FAB) m/z (rel intensity) calcd for $C_{14}H_{17}NO_5$ 279.1107, found 279.1114, 280 (15, MH^+), 262 (10, $MH^+ - H_2O$), 236 (40), 172 (50), 108 (30), 91 (100). Anal. Calcd for $C_{14}H_{17}NO_5$: C, 60.15; H, 6.14; N, 5.01. Found: C, 60.11; H, 6.45; N, 5.05.

(*E*)- and (*Z*)-(*R*)-*N*-Boc-2-amino-4-methyl-3-hexenol (9j). The *E*/*Z* mixture of acetonides 8j (0.200 g, 0.78 mmol) was hydrolyzed in aqueous methanol following the general procedure. After flash chromatography (9:1 hexane/ethyl acetate), 9j (0.127 g, 76% yield) was obtained as a white solid that consisted of an unseparable mixture of *E* and *Z* isomers: R_f 0.25 (9:1 hexane/ethyl acetate); mp 88–90 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 4.99 (b d, J = 9.1 Hz, 1 H), 4.60 (b m, 1 H), 4.42 (b m, 1 H), 3.57 (b m, 2 H), 2.01 (q, J = 7.7 Hz, 2 H), 1.72 (s, 3 H), 1.45 (s, 9 H), 1.03 (t, J = 7.7 Hz, 1.5 H), 1.01 (t, J = 7.7 Hz, 1.5 H); ^{13}C NMR ($CDCl_3$, 50.1 MHz) δ (major isomer) 156.3, 142.8, 121.1, 79.7, 66.7, 51.2, 28.3, 25.5, 22.7, 12.9, (minor isomer) 119.9, 51.6, 32.1, 31.5, 16.7, 14.0, 12.3; IR (CH_2Cl_2) 3700–2500, 1680, 1180, 760 cm^{-1}; high-resolution MS (EI) m/z (rel intensity) calcd for $C_{11}H_{20}NO_2$ ($MH^+ - CH_2OH$) 198.1494, found 198.1506; MS (CI) m/z (rel intensity) 230 (9, MH^+), 174 (100, MH^+ – *tert*-butyl), 156 (5, MH^+ – *tert*-butyl alcohol), 130 (5, MH^+ – Boc).

General Procedure for Oxidation of Amino Alcohols 9 into Vinylglycines 5. Method A. The amino alcohol 9 (0.5–1 mmol) was dissolved in acetone (ca. 5 mL), and excess Jones' reagent[27] was added dropwise with stirring until complete conversion of starting material to vinylglycine 5 as judged by TLC (1–2 h). The acetone was removed under reduced pressure, and the residue was partitioned between water (10–20 mL) and ethyl acetate (10–20 mL). The organic phase was separated, and the product was extracted into saturated aqueous sodium carbonate solution (20 mL). After acidification of the aqueous phase to pH 4 with acetic acid followed by extraction with ether, drying ($MgSO_4$), and evaporation of the solvent, the desired vinylglycine derivatives 5 were obtained as yellowish oils of good purity.

Method B. Powdered 4-Å molecular sieves (Aldrich; 0.5–1.0 g) were flame dried and cooled under an argon atmosphere. Alcohol 9 (0.1–0.2 mmol; 1 equiv) in DMF (2.5 mL) was added and the slurry stirred for 5 min at room temperature. Pyridinium dichromate (12 equiv) in DMF (7.5 mL) was added dropwise over 3 h using a syringe pump. After complete addition, the reaction mixture was stirred for another 9–12 h. DMF was evaporated by rotary evaporation at room temperature under high vacuum, and the residue was partitioned between ether and water. After filtration through Celite, the organic phase was separated and the workup completed as in method A.

For characterization purposes, vinylglycines 5 were converted into their respective methyl esters using excess diazomethane in ether. The crude product was purified by flash chromatography to give pure vinylglycine methyl esters 12.

Derivatization Procedure for Chiral Capillary GC Analysis.[23a] The amino acid derivative 12 (ca. 1 mg) was sealed under vacuum in a glass ampule with 0.2 mL of 6 N HCl. The mixture was heated 20 h at 110 °C. The hydrolyzate was evaporated to dryness at 110 °C, and 0.2 mL of 4 N HCl in 2-propanol was added. The reaction was allowed to proceed 30 min at 110–120 °C. The excess reagent was evaporated in a stream of nitrogen. The ester residue was then treated with 0.1 mL of trifluoroacetic anhydride for 10 min at 80–100 °C. After removal of the reagent

(27) Bowden, K.; Heilbron, I. M.; Jones, E. R. H.; Weedon, B. C. L. *J. Chem. Soc.* **1946**, 39.

with a stream of nitrogen at room temperature, the residue was dissolved in a small amount of acetonitrile and submitted for capillary GC analysis on a CHIRASIL-VAL column.

GC analyses were carried out under the following conditions: injector temperature, 200 °C; detector temperature, 225 °C; program, 140 °C for 15 min then 10 °C/min up to 190 °C; gas flow rate, 50 mL/min.

(*Z*)-(*S*)-*N*-Boc-2-amino-3-pentenoic Acid ((*S*)-5b).[7d] Amino alcohol (*S*)-**9b** (0.100 g, 0.49 mmol) was oxidized with PDC (2.24 g, 6.0 mmol) following the procedure of method B. (*S*)-**5b** (0.0462 g, 44% yield) was obtained as an oil. It was contaminated with 7% of the *E* isomer: $[\alpha]^{30}_D$ +98.6° (*c* = 1.52, MeOH);[7d] ^{1}H NMR ($CDCl_3$, 200 MHz) δ 5.80 (b m, 1 H), 5.33 (t, *J* = 9.5 Hz, 1 H), 5.03 (b m, 2 H), 1.82 (dd, *J* = 7.0, 1.6 Hz, 3 H), 1.46 (s, 9 H); IR (neat) 3600–2200, 1720, 1660, 1500, 1400, 1170, 1055, 760 cm^{-1}; MS (EI) *m/z* (rel intensity) 170 (48, $M^+ - CO_2$), 159 (56, MH^+ – *tertt*-butyl), 141 (33, M^+ – *tert*-butyl alcohol), 114 (100, M^+ – Boc); GC retention time on CHIRASIL-VAL column 10.29 (*Z* isomer, 93%), 10.45 (*E* isomer, 7%) min.

(*Z*)-(*R*)-*N*-Boc-2-amino-3-pentenoic Acid, Methyl Ester ((*R*)-12b). Amino alcohol **9b** (0.040 g, 0.19 mmol) was oxidized with PDC (0.896 g, 2.38 mmol) following method B. The crude acid **5b** was converted to its methyl ester (*R*)-**12b** using diazomethane and purified by flash chromatography (5:1 hexane/ethyl acetate). (*R*)-**12b** (0.016 g, 35% yield) was obtained as an oil. It was contaminated with 10% of the *E* isomer: R_f 0.54 (4:1 hexane/ethyl acetate); $[\alpha]^{30}_D$ –50.9° (*c* – 0.75, MeOH); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 5.77 (dq, *J* = 11.0, 6.8 Hz, 1 H), 5.26 (ddq, *J* = 11.0, 10.6, 1.9 Hz, 1 H), 5.07 (b m, 2 H), 3.74 (s, 3 H), 1.82 (dd, *J* = 6.9, 1.7 Hz, 3 H), 1.43 (s, 9 H); IR (neat) 3600–3200, 3100–2800, 1750, 1715, 1510, 1170, 920 cm^{-1}; high-resolution FAB MS *m/z* (rel intensity) calcd for $C_{11}H_{20}NO_4$ (MH^+) 230.1392, found 230.1412 (25, MH^+), 173 (100, MH^+ – *tert*-butyl), 129 (55, M^+ – Boc); GC retention time on CHIRASIL-VAL column 10.22 (*Z* isomer, 90%), 10.43 (*E* isomer, 10%) min.

(*Z*)-(*R*)-*N*-Boc-2-amino-3-nonenoic Acid, Methyl Ester ((*R*)-12d). Amino alcohol **9d** (0.050 g, 0.20 mmol) was oxidized with PDC (0.90 g, 2.4 mmol) following method B. The crude acid **5d** was converted to its methyl ester **12d** using diazomethane. After flash chromatography (4:1 hexane/ethyl acetate), the pure amino acid derivative **12d** (0.029 g, 50% yield) was obtained as a yellowish oil: R_f 0.61 (4:1 hexane/ethyl acetate); $[\alpha]^{30}_D$ –67.2° (*c* = 1.01, MeOH); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 5.68 (dt, *J* = 10.6, 7.3 Hz, 1 H), 5.22 (tt, *J* = 9.8, 2.1 Hz, 1 H), 5.08 (b m, 2 H), 3.74 (s, 3 H), 2.21 (q, *J* = 6.9 Hz, 2 H), 1.47 (s, 9 H), 1.3 (m, 6 H), 0.88 (t, *J* = 6.8 Hz, 3 H); IR (neat) 3600–3100, 3050–2800, 1750, 1710, 1500, 1370, 1240, 1160, 1055, 1025, 860 cm^{-1}; MS (CI) *m/z* (rel intensity) 286 (7, MH^+), 270 (17, $M^+ - CH_3$), 258 (33, $M^+ - C_2H_5$), 230 (100, MH^+ – *tert*-butyl), 214 (12, MH^+ – *tert*-butyl alcohol), 186 (99, MH^+ – Boc), 169 (31). Anal. Calcd for $C_{15}H_{27}NO_4$: C, 63.17; H, 9.54; N, 4.91. Found: C, 62.83; H, 9.84; N, 4.74.

(*Z*)-(*R*)-*N*-(Trifluoroacetyl)-2-amino-3-nonenoic acid, isopropyl ester ((*R*)-15d): GC retention time on CHIRASIL-VAL column 13.0 min (96%); ^{1}H NMR ($CDCl_3$, 400.1 MHz) δ 6.97 (b s, 1 H), 5.83 (dt, *J* = 10, 7.6 Hz, 1 H), 5.25 (m, 2 H), 5.08 (m, *J* = 6.3 Hz, 1 H), 2.27 (q, *J* = 7.4 Hz, 2 H), 1.45 (m, 2 H), 1.33 (m, 4 H), 1.30 (d, *J* = 6.3 Hz, 3 H), 1.25 (d, *J* = 6.2 Hz, 3 H), 0.91 (t, *J* = 7.0 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 170.0, 138.7, 121.4, 70.6, 50.9, 31.4, 28.8, 28.0, 22.5, 21.6, 21.4, 14.0; high-resolution MS (FAB) calcd for $C_{14}H_{23}F_3NO_3$ (MH^+) 310.163 00, found 310.163 00; MS (FAB) *m/z* (rel intensity) 310 (20, MH^+), 268 (30, $MH^+ - C_3H_7$), 222 (45, $M^+ - C_4H_7O_2$), 151 (50), 109 (100).

(*Z*)-(*S*)-*N*-Boc-2-amino-3-nonenoic Acid, Methyl Ester ((*S*)-12d). The *S* enantiomer was prepared as for the *R* isomer using amino alcohol (*S*)-**9d**. The final product (as the methyl ester) was identical in all respects with (*R*)-**12d** except for the optical rotation: $[\alpha]^{30}_D$ +66.7° (*c* = 1.01, MeOH). The GC retention time on the CHIRASIL-VAL column was 11.8 min (>95%).

(*Z*)-(*R*)-*N*-Boc-2-amino-6-phenyl-3-hexenoic Acid, Methyl Ester (12e). Amino alcohol **9e** (0.101 g, 0.34 mmol) was oxidized with PDC (1.55 g, 4.00 mmol) following the procedure of method B. Crude **5e** was converted to its methyl ester using diazomethane. After flash chromatography (4:1 hexane/ethyl acetate), **12e** (0.043 g, 40% yield) was obtained as a yellowish oil: R_f 0.54 (4:1 hexane/ethyl acetate); $[\alpha]^{30}_D$ –81.95° (*c* = 1.02, MeOH); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.23 (m, 5 H), 7.52 (dt, *J* = 10.1, 7.3 Hz, 1 H), 5.27 (tt, *J* = 9.6, 1.6 Hz, 1 H), 5.02 (b m, 2 H), 3.73 (s, 3 H), 2.75 (m, 2 H), 2.57 (m, 2 H), 1.45 (s, 9 H); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 172.0, 154.7, 141.3, 135.3, 128.5, 128.4, 126.0, 125.7, 80.0, 52.5, 34.8, 29.6, 28.3; IR (neat) 3700–3200, 3100–2800, 1745, 1710, 1498, 1170, 1055, 760 cm^{-1}; MS (FAB) $m/_z$ (rel intensity) 342 (3, MNa^+), 320 (5, MH^+), 264 (20, MH^+ – *tert*-butyl), 220 (46, MH^+ – Boc), 204 (15), 91 (100). GC retention time on CHIRASIL-VAL column 23.0 min (>95%). Anal. Calcd for $C_{18}H_{25}NO_4$: C, 67.69; H, 7.89; N, 4.39. Found: C, 67.20; H, 7.96; N, 4.03.

(*Z*)-(*R*)-*N*-Boc-2-amino-3-heptenedioic Acid, Dimethyl Ester (12f). Amino alcohol **9f** (0.095 g, 0.36 mmol) was converted to its methyl ester using diazomethane. After evaporation of the solvent under reduced pressure, the crude methyl ester was oxidized using PDC (1.65 g, 4.39 mmol) following the procedure of method B. The crude **5f** was converted to its dimethyl ester using diazomethane. **12f** (0.035 g, 32% yield) was obtained as a yellow oil after flash chromatography (4:1 hexane/ethyl acetate): R_f 0.32 (4:1 hexane/ethyl acetate); $[\alpha]^{30}_D$ –66.9° (*c* = 1.1, MeOH); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 5.70 (dt, *J* = 11.1, 5.0 Hz, 1 H), 5.32 (b t, *J* = 10.0 Hz, 1 H), 5.23 (b d, *J* = 7.3 Hz, 1 H), 5.03 (b m, 1 H), 3.77 (s, 3 H), 3.69 (s, 3 H), 2.57 (m, 2 H), 2.43 (m, 2 H), 1.44 (s, 9 H); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 173.2, 171.8, 154.9, 133.9, 125.4, 80.1, 52.6, 51.6, 33.5, 28.3, 23.3; IR (neat) 3700–3100, 3100–2800, 1740, 1720, 1520, 1445, 1375, 1170, 1060, 1030, 920, 870, 805, 740 cm^{-1}; MS (FAB) *m/z* (rel intensity) 324 (8, MNa^+), 246 (21, MH^+ – *tert*-butyl), 202 (100, MH^+ – Boc), 170 (35), 142 (46). GC retention time on CHIRASIL-VAL column 14.5 min (>95%). Anal. Calcd for $C_{14}H_{23}NO_6$: C, 55.80; H, 7.69; N, 4.65. Found: C, 55.99; H, 7.91; N, 4.45.

(*Z*)-(*R*)-2-[[(Benzyloxy)carbonyl]amino]-7-[[(*tert*-butyloxy)carbonyl]amino]-3-heptenoic Acid (11a). Amino alcohol **10a**[10] (0.428 g, 1.13 mmol) was oxidized with Jones' reagent[27] using method A. The crude amino acid derivative **11a** (0.388 g, 87% yield) was isolated as a yellow oil: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.37 (m, 5 H), 6.08 (b s, 1 H), 5.57 (b d, *J* = 7.2 Hz, 2 H), 5.36 (t, *J* = 10 Hz, 1 H), 5.13 (m, 2 H), 4.69 (b s, 1 H), 4.43 (b q, *J* = 7.4 Hz, 1 H), 3.10 (b m, 2 H), 1.44 (s, 9 H), 1.36 (b m, 2 H); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 175.8, 156.1, 136.3, 128.5, 128.2, 128.1, 79.4, 67.0, 53.6, 40.3, 32.3, 29.7, 28.4, 26.2, 24.6; IR (neat) 3700–2300, 1720, 1700, 1530, 1170, 1050, 910, 860 cm^{-1}. The product was further characterized as the methyl ester.

Methyl Ester of 11a. For characterization purposes, a small sample of the methyl ester was prepared with excess diazomethane. Purification by flash chromatography (7:3 hexane/ethyl acetate) gave the product as a yellowish oil: R_f 0.28 (2:1 hexane/ethyl acetate); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.38 (b s, 5 H), 5.68 (m, 1 H), 5.37 (b d, *J* = 8.2 Hz, 2 H), 5.30 (tt, *J* = 10, 2 Hz, 1 H), 5.13 (s, 2 H), 4.58 (b m, 1 H), 4.39 (m, 1 H), 3.76 (s, 3 H), 3.09 (b q, *J* = 6.3 Hz, 2 H), 1.47 (s, 9 H), 1.34 (m, 2 H); IR (neat) 3500–3200, 3100–2880, 1720, 1515, 1265, 1220, 1175, 1050 cm^{-1}; high-resolution MS (FAB) *m/z* calcd for $C_{21}H_{31}N_2O_6$ (MH^+) 407.2182, found 407.2187.

(*Z*)-(*R*)-2-[[(Benzyloxy)carbonyl]amino]-8-[[(*tert*-butyloxy)carbonyl]amino]-3-octenoic Acid (11b), Methyl Ester. Amino alcohol **10b**[10] (0.196 g, 0.497 mmol) was oxidized to amino acid **11b** (0.186 g, 92% yield) using method A. The crude acid was converted to its methyl ester with diazomethane and purified by flash chromatography with 4:1 hexane/ethyl acetate (0.173 g, 90% yield): R_f 0.24 (2:1 hexane/ethyl acetate); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.40 (m, 5 H), 5.74 (q, *J* = 11.2 Hz, 1 H), 5.49 (m, 1 H), 5.30 (m, 2 H), 5.15 (s, 2 H), 4.76 (m, 1 H), 4.54 (m, 1 H), 4.42 (m, 2 H), 3.78 (s, 3 H), 3.15 (m, 2 H), 1.48 (s, 9 H), 1.35 (m, 4 H); IR (neat) 3500–3200, 3100–2860, 1740, 1710, 1530, 1270, 1250, 1170, 1050 cm^{-1}; high-resolution MS (FAB) *m/z* calcd for $C_{17}H_{25}N_2O_4$ (MH^+ – Boc) 321.1814, found 321.1874.

(*E*)- and (*Z*)-(*R*)-*N*-Boc-2-amino-4-methyl-3-hexenoic Acid, Methyl Ester (12j). Amino alcohol **9j** (0.050 g, 0.23 mmol) was oxidized with PDC (1.04 g, 2.77 mmol) following method B. The crude acid **5j** was converted to its methyl ester with diazomethane and purified by flash chromatography (5:1 hexane/ethyl acetate). **12j** (0.024 g, 42% yield) was obtained as an oil that consisted of an unseparable mixture of *E*/*Z* isomers: R_f 0.51 (4:1 hexane/ethyl acetate); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 5.0 (b m, 3 H), 3.72 (s, 3 H), 2.2 (m, 1.2 H), 2.03 (q, *J* = 7.4 Hz, 0.8 H), 1.30 (s, 1 H), 1.23 (s, 3 H), 1.46 (s, 9 H), 1.04 (t, *J* = 7.6 Hz, 2 H), 1.00

(t, J = 7.6 Hz, 1 H); IR (neat) 3600–3100, 3050–2800, 1750, 1720, 1305, 1170, 1050, 1030, 870, 790, 760 cm^{-1}; high-resolution FAB MS m/z (rel intensity) calcd for $C_{13}H_{24}NO_4$ (MH^+) 258.1705, found 258.1642 (25, MH^+), 202 (100, MH^+ – *tert*-butyl), 158 (18, MH^+ – Boc), 141 (65); GC retention times of CHIRASIL-VAL column 14.1 (minor isomer 40%), 14.75 (major isomer 60%) min.

(*R*)-*N*-Boc-2-Aminononanol (13). Unsaturated amino alcohol **9d** (0.200 g, 0.765 mmol) was hydrogenated overnight in 95% ethanol (10 mL) over 5% palladium on carbon (10 mg) under 1 atm of hydrogen gas. After filtration of the catalyst and removal of the solvent under reduced pressure, pure **13** (0.201 g, 100% yield) was obtained as a low-melting white solid: R_f 0.24 (4:1 hexane/ethyl acetate); mp 39–40 °C; $[\alpha]^{30}_D$ + 8.46° (c = 1.075, MeOH); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 4.6 (b m, 1 H), 3.6 (b m, 2 H), 2.38 (b s, 1 H), 1.46 (s, 9 H), 1.3 (m, 12 H), 0.89 (t, J = 6.6 Hz, 3 H); IR (neat) 3700–3200, 3010–2830, 1700, 1505, 1220, 1175 cm^{-1}; MS (CI) m/z (rel intensity) 260 (16, MH^+), 244 (7, M^+ – CH_3), 232 (13, MH^+ – C_2H_4), 204 (100, MH^+ – *tert*-butyl), 186 (26, MH^+ – *tert*-butyl alcohol), 160 (98, MH^+ – Boc). Anal. Calcd for $C_{14}H_{29}NO_3$: C, 64.83; H, 11.27; N, 5.40. Found: C, 64.63; H, 11.38; N, 5.17.

(*R*)-*N*-Boc-2-aminononanoic Acid, Methyl Ester (14). Amino alcohol **13** (0.077 g, 0.30 mmol) was oxidized following the procedure of method A using 4 × 1.5 mL of Jones' reagent[27] (1.4 M, 8.4 mmol). The oxidation was complete after 2 h as judged by TLC. After conversion of the free acid to its methyl ester using excess diazomethane in ether, pure **14** (0.078 g, 91% yield) was obtained as an oil after flash chromatography (5:1 hexane/ethyl acetate): R_f 0.43 (4:1 hexane/ethyl acetate); $[\alpha]^{30}_D$ +13.2° (c = 1.06, MeOH); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 4.99 (b d, J = 9.1 Hz, 1 H), 4.29 (b q, J = 5.9 Hz, 1 H), 3.74 (s, 3 H), 1.48 (s, 9 H), 1.32 (m, 12 H), 0.88 (t, J = 6.6 Hz, 3 H); IR (neat) 3600–3200, 3100–2800, 1745, 1720, 1510, 1450, 1370, 1250, 1175, 1055, 1030 cm^{-1}; high-resolution MS (FAB) m/z (rel intensity) calcd for $C_{15}H_{30}NO_4$ 288.2175, found 288.2171 (17, MH^+), 232 (97, MH^+ – *tert*-butyl), 216 (40, MH^+ – *tert*-butyl alcohol), 188 (100, MH^+ – Boc), 172 (57), 128 (97); GC retention time on CHIRASIL-VAL column 18.9 min (>95%).

Acknowledgment. We thank Dr. Neil Moss for helpful suggestions and Dr. François Bruderlein for performing the enantiomeric purity determinations. We would also like to acknowledge Dr. Michael Evans of the Université de Montréal mass spectral laboratory and Dr. Gordon Hanson of the analytical chemistry department of Boehringer Ingelheim Pharmaceuticals Inc. We are also grateful to the Natural Sciences and Engineering Research Council of Canada for a scholarship to one of us (C.J.).

Registry No. (*S*)-**5b** (*Z* isomer), 125700-58-5; (*S*)-**5b** (*E* isomer), 120133-46-2; (*S*)-**7a**, 117833-92-8; (*R*)-**7b**, 95715-87-0; (*S*)-**7b**, 102308-32-7; **8a**, 133625-87-3; (*R*)-**8b**, 133625-90-8; (*S*)-**8b** (*Z* isomer), 133625-88-4; (*S*)-**8b** (*E* isomer), 133625-89-5; **8c** (*Z* isomer), 132639-29-3; **8c** (*E* isomer), 132652-65-4; (*R*)-**8d**, 133625-91-9; (*S*)-**8d**, 133625-92-0; **8e**, 133625-93-1; **8f**, 133625-94-2; **8g**, 117833-93-9; **8h**, 117833-94-0; **8i**, 133625-95-3; **8j** (*Z* isomer), 133625-97-5; **8j** (*E* isomer), 133625-96-4; **9a**, 91103-37-6; (*R*)-**9b** (*Z* isomer), 125700-60-9; (*R*)-**9b** (*E* isomer), 133625-98-6; (*S*)-**9b**, 125700-57-4; **9c** (*Z* isomer), 132682-38-3; **9c** (*E* isomer), 133625-99-7; (*R*)-**9d**, 133626-00-3; (*R*)-**9d** (*S*-Mosher ester), 133626-07-0; (*S*)-**9d**, 133626-01-4; (*S*)-**9d** (*S*-Mosher ester), 133626-08-1; **9e**, 133626-02-5; **9f**, 133626-03-6; **9f** (methyl ester), 133626-09-2; **9i**, 133626-04-7; **9j** (*Z* isomer), 133626-05-8; **9j** (*E* isomer), 133626-06-9; **10a**, 133626-15-0; **10a** (acetonide), 117833-95-1; **10b**, 133626-16-1; **10b** (acetonide), 117833-96-2; **11a**, 117833-97-3; **11a** (methyl ester), 133626-17-2; **11b**, 117833-98-4; **11b** (methyl ester), 133626-18-3; (*R*)-**12b** (*Z* isomer), 133696-71-6; (*R*)-**12b** (*E* isomer), 133696-72-7; (*R*)-**12d**, 133696-73-8; (*S*)-**12d**, 133696-74-9; **12e**, 133626-10-5; **12f**, 133626-11-6; **12j** (*Z* isomer), 133626-13-8; **12j** (*E* isomer), 133626-12-7; **13**, 133626-19-4; **14**, 133626-20-7; (*R*)-**15d**, 133626-14-9; (*R*)-MTPA-Cl, 39637-99-5; EtI, 76-03-9; $PhCH_2Br$, 100-39-0; $Me(CH_2)_5I$, 638-45-9; $Br(CH_2)_3Ph$, 637-59-2; $Br(CH_2)_3COOH$, 2623-87-2; $Br(CH_2)_3CN$, 5332-06-9; $Br(CH_2)_4CN$, 5414-21-1; MeCHIEt, 513-48-4; $MePPh_3^+Br^-$, 1779-49-3; $Ph_3P{=}CHCOOMe$, 2605-67-6; $EtPPH_3^+I^-$, 4736-60-1; $PhCH_2PPh_3^+Br^-$, 1449-46-3; $Me(CH_2)_5PPh_3^+I^-$, 60106-53-8; $Ph(CH_2)_3PPh_3^+Br^-$, 7484-37-9; $HOOC(CH_2)_3PPh_3^+Br^-$, 17857-14-6; $NC(CH_2)_3PPh_3^+Br^-$, 7752-62-7; $NC(CH_2)_4PPh_3^+Br^-$, 7743-27-3; $MeEtCHPPh_3^+I^-$, 4762-30-5.

Supplementary Material Available: ^{1}H and/or ^{13}C NMR spectra for compounds **8**, **9**, and **11–14** (35 pages). Ordering information is given on any current masthead page.

Total Synthesis of Combretastatin D-2: Intramolecular Ullmann Macrocyclization Reaction

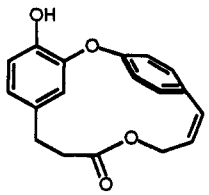
Dale L. Boger,* Subas M. Sakya, and Daniel Yohannes

Department of Chemistry, Purdue University, West Lafayette, Indiana 47907

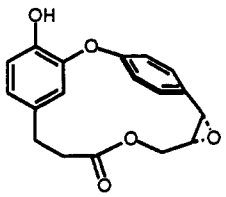
Received January 28, 1991

The total synthesis of combretastatin D-2, a cytotoxic constituent of *Combretum caffrum* (Combretaceae), is detailed and is based on the implementation of a key intramolecular Ullmann macrocyclization reaction for formation of the cyclic 15-membered caffrane biaryl ether.

Combretastatin D-2 (**1**),[1] a trace [(7.5×10^{-6})%] cytotoxic constituent of *Combretum caffrum* (Combretaceae) identified through extensive spectroscopic studies, has been shown to possess an unusual 15-membered meta- and paracyclophane subunit now characteristic of a range of antitumor antibiotics.[2-7]



1 Combretastatin D-2



2 Combretastatin D-1

In conjunction with our interest in the total synthesis and comparative evaluation of agents possessing this cyclic biaryl ether structural subunit[8-16] and as a consequence

(1) Singh, S. B.; Pettit, G. R. *J. Org. Chem.* **1990**, *55*, 2797.

(2) Pettit, G. R.; Singh, S. B.; Niven, M. L. *J. Am. Chem. Soc.* **1988**, *110*, 8539.

(3) Jolad, S. D.; Hoffmann, J. J.; Torrance, S. J.; Wiedhopf, R. M.; Cole, J. R.; Arora, S. K.; Bates, R. B.; Gargiulo, R. L.; Kriek, G. R. *J. Am. Chem. Soc.* **1977**, *99*, 8040.

(4) Itokawa, H.; Takeya, K.; Mori, N.; Sonobe, T.; Mihashi, S.; Hamanaka, T. *Chem. Pharm. Bull.* **1986**, *34*, 3762 and references cited therein.

(5) Sano, S.; Ikai, K.; Katayama, K.; Takesako, K.; Nakamura, T.; Obayashi, A.; Ezure, Y.; Enomoto, H. *J. Antibiot.* **1986**, *39*, 1685.

(6) Kase, H.; Kaneko, M.; Yamada, K. *J. Antibiot.* **1987**, *40*, 450.

(7) Tamai, S.; Kaneda, M.; Nakamura, S. *J. Antibiot.* **1982**, *35*, 1130, 1137.

(8) Boger, D. L.; Yohannes, D. *J. Am. Chem. Soc.* **1991**, *113*, 1427.

(9) Boger, D. L.; Yohannes, D. *J. Org. Chem.* **1991**, *56*, 1763.

(10) Boger, D. L.; Yohannes, D. *J. Org. Chem.* **1990**, *55*, 6000.

0022-3263/91/1956-4204$02.50/0