Enantiomeric Recognition of Organic Ammonium Salts by Chiral Dialkyl-Substituted Triazole-18-crown-6 Ligands

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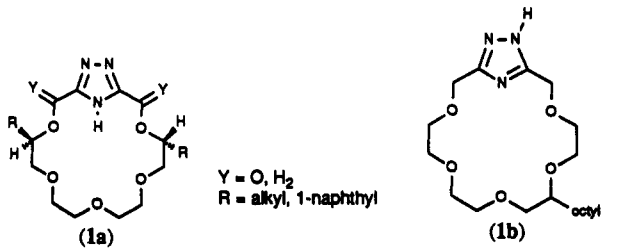
Four new chiral triazole-18-crown-6 ligands have been synthesized. The triazole-crowns contain two methyl substituents on the chiral macrocycles, and in the case of **2b** and **2c**, they also contain lipophilic side arms connected to the triazole ring. Binding constants (K_a) measured by the ^{1}H NMR titration technique showed that **2b** and **2c** exhibited chiral recognition for the enantiomers of [1-(1-naphthyl)ethyl]ammonium cation (HNEA$^+$) and to a lesser extent, for the enantiomers of [1-phenylethyl]ammonium cation (HPEA$^+$). Both *S,S* chiral hosts recognize preferentially *R* over *S* enantiomers.

Introduction

The potential applications of asymmetric macrocycles as chiral barriers for enantiomeric separations were recognized as soon as the first synthetic ionophores were reported by Pedersen in 1967.[1] Since the early 1970s, hundreds of chiral macrocyclic compounds have been synthesized and the enantiomeric selectivity of many of them has been studied by NMR spectroscopy, solvent extraction techniques, transport of amines through liquid membrane, as well as partial resolution using chromatography.[2-6]

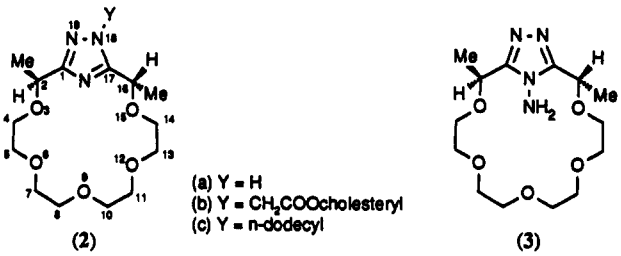
Relevant to the work reported here are the results published by Bradshaw et al. on the complexation properties between amines and alkylammonium cations and chiral macrocycles containing either the 1,2,4-triazole[7-9] or the pyridino[10] subcyclic unit. NMR studies showed that compound **1a** (*S,S* isomer, Y = O; R = CH_3) exhibits chiral recognition for the (*R*)-[1-(1-naphthyl)ethyl]ammonium cation ((*R*)-HNEA$^+$) over the *S* isomer, but not for the amines (NEA).[8]

These same authors have also incorporated lipophilic macrocycles having pyridone and triazole moieties into liquid membrane systems in order to effect the separation of silver from other metals or to study the competitive alkali cation transport.[11] In some of these compounds, such as **1b**, the fatty group (*n*-octyl) is attached to the polyether ring, so the triazole ring is able to transport cations by both neutral (in the case of Pb^{2+}) and proton-coupled (in the case of Ag^+) mechanisms. Asymmetric macrocycles of this kind have not been used as chiral barriers in alkylammonium salt transport.



(1a) (1b)

We report here the chiral recognition toward HNEA$^+$ and HPEA$^+$ observed for novel 1,2,4-triazole-containing macrocyclic derivatives **2b** and **2c**. These compounds can be prepared by alkylation of the corresponding NH precursor **2a**[12] with cholesteryl chloroacetate or *n*-dodecyl bromide, respectively. In the compounds studied, the host cavity provides a trigonal recognition site for the RNH_3 groups while the lipophilic side arm ($-CH_2COO$cholesteryl or $-C_{12}H_{25}$) was designed for increasing the transport efficiency by decreasing the water solubility of the carrier. In addition, the chiral centers in **2** are closer to the aromatic heterocycle than in **1a**, affording a more rigid chiral framework. This is expected to be important for the steric discrimination of enantiomers.



(2) (3)

Results and Discussion

The host–guest interaction of **2a–c** with HNEA$^+$ and HPEA$^+$ chloride was studied in $CDCl_3$. The most significant ^{1}H NMR data for each guest are collected in Table I. Signal assignments were confirmed by homonuclear 2D COSY and in some cases NOESY experiments. For all macrocycles, different chemical shift changes were ob-

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Table I. ^{1}H NMR Chemical Shifts (δ) for 2a–2c and Their Complexes with HNEA$^+$Cl$^-$ and HPEA$^+$Cl$^-$ Enantiomers in $CDCl_3$[a]

	proton position								
	host					guest			
compd	H-2 (q)	H-16 (q)	Ha (d)	Hb (d)	H-1′ (m)	Me2[b] (d)	Me16[b] (d)	H[c] (q)	Me[c] (d)
HNEA$^+$								5.34	1.85
HPEA$^+$								4.37	1.67
2a	4.87					1.68			
2a·(*R*)-HNEA$^+$	4.93					1.70		5.36	1.87
	(26)					(10)		(8)	(8)
2a·(*S*)-HNEA$^+$	4.87					1.66		5.35	1.86
	(1)					(−9)		(3)	(2)
2a·(*R*)-HPEA$^+$	4.89					1.68		4.38	1.69[d]
	(10)					(−1)		(2)	(9)
2a·(*S*)-HPEA$^+$	4.86					1.67		4.39	1.68[d]
	(−5)					(−5)		(7)	(4)
2b	4.59	5.01	4.97	5.23		1.53	1.58		
2b·(*R*)-HNEA$^+$	4.58	5.25[d]	5.18	5.28		1.59	1.60	5.37[d]	1.87
	(−1)	(97)	(84)	(18)		(23)	(10)	(13)	(8)
2b·(*S*)-HNEA$^+$	4.55	5.09[d]	5.08	5.16		1.52	1.47	5.37[d]	1.86
	(−16)	(34)	(44)	(−28)		(−4)	(−42)	(11)	(2)
2b·(*R*)-HPEA$^+$	4.53	5.18[d]	5.18	5.18		1.57	1.55	4.40	1.70
	(−22)	(71)	(86)	(−20)		(15)	(−11)	(10)	(12)
2b·(*S*)-HPEA$^+$	4.53	5.15[d]	5.08	5.16		1.55	1.52	4.40	1.68
	(−23)	(56)	(80)	(−16)		(9)	(−23)	(9)	(5)
2c	4.59	4.93			4.18	1.56	1.58		
2c·(*R*)-HNEA$^+$	4.62	5.04			4.17	1.59	1.61	5.46	1.91
	(10)	(42)			(−3)	(13)	(11)	(48)	(22)
2c·(*S*)-HNAE$^+$	4.56	4.92			4.13	1.52	1.46	5.39	1.87
	(−12)	(−6)			(−21)	(−16)	(−48)	(21)	(5)
2c·(*R*)-HPEA$^+$	4.53	5.00			4.17	1.57	1.57	4.43	1.72
	(−26)	(28)			(−6)	(2)	(−3)	(23)	(19)
2c·(*S*)-HPEA$^+$	4.53	4.97			4.16	1.55	1.53	4.41	1.69
	(−25)	(15)			(−8)	(−4)	(−18)	(16)	(8)

[a] Data in parentheses represent chemical shift differences $\delta_{complex} - \delta_{host/guest}$ in Hz. [b] Methyl groups attached to the chiral centers at positions 2 and 16 of the host. [c] Proton and methyl groups at the chiral center of the guest. [d] Estimated value because of signal overlap.

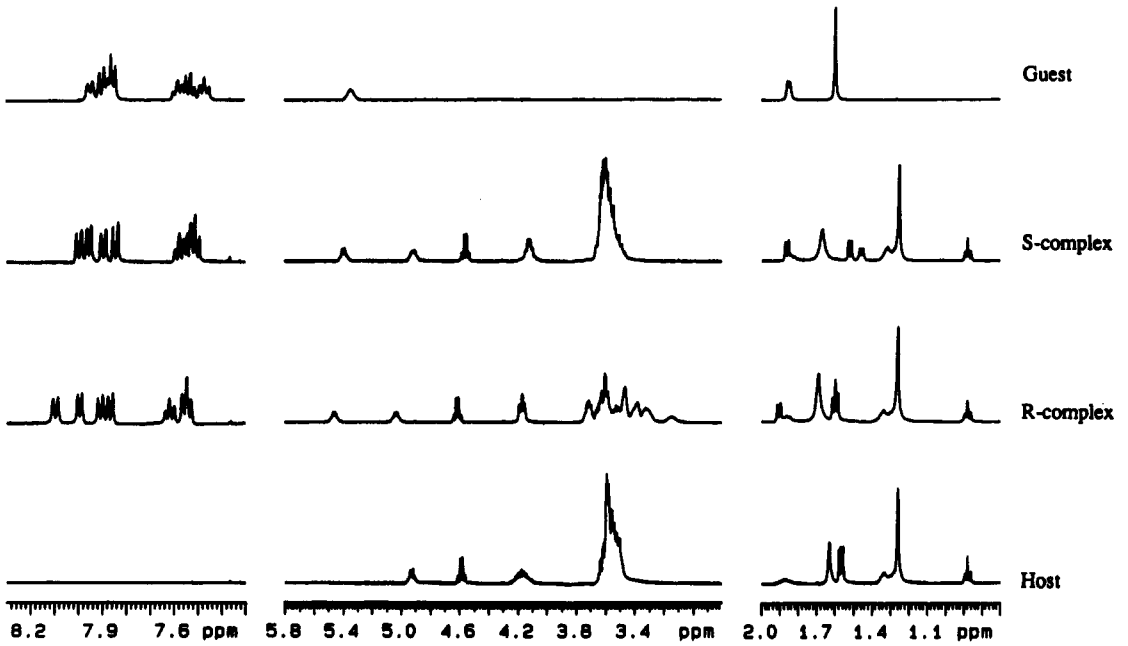

Figure 1. ^{1}H NMR spectra of host **2c**, HNEA$^+$Cl$^-$, and their diastereomeric complexes in $CDCl_3$.

served upon addition of each guest enantiomer (values in parentheses), revealing the formation of diastereomeric molecular complexes. No such chemical shift changes were observed for the *N*-amino-substituted host **3**, probably due to intramolecular hydrogen bonding, which prevents further interaction with the ammonium guests.[12]

The most significant spectral difference in the presence of the two enantiomeric guests was observed for the two methyl groups (Me-2 and Me-16) at the chiral centers of the hosts **2b** and **2c**: they were downfield shifted in the presence of the *R* enantiomer, but upfield shifted in the presence of the *S* enantiomer. The resonance for Me-16 shifted so much (−42 and −48 Hz for **2b** and **2c** with (*S*)-HNEA$^+$, respectively) that the relative order of the signals was exchanged (Figure 1). It was also noticed that in the case of **2b** the two protons of the methylene group that connects the triazole ring to the COOcholesteryl side arms had a substantially different shift upon complexation: 84 and 18 Hz for the complex with (*R*)-HNEA$^+$, while 44 and −28 Hz were observed with (*S*)-HNEA$^+$. This unusual difference within an AB system strongly suggests that the molecular structure at this region is fairly rigid. The same

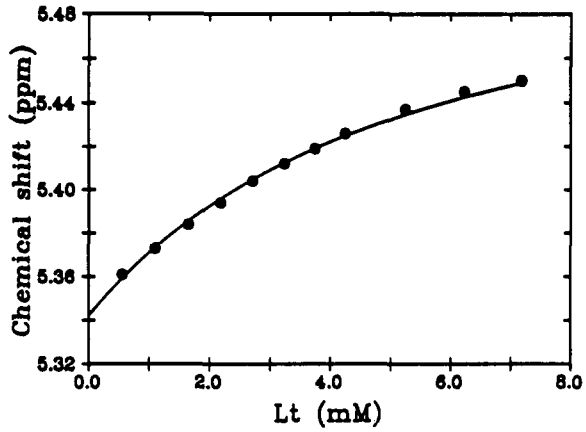

Figure 2. ^{1}H NMR titration data and curve fitting for the complex of **2c** with (*S*)-HNEA$^+$Cl$^-$ in $CDCl_3$. Lt represents the total concentration of the host.

Table II. Stability Constants K_a (M^{-1}) for 2a–c Complexes in $CDCl_3$ at 21 °C[a]

	2a	2b	2c
(*R*)-HNEA$^+$Cl$^-$	497 ● 110	209 ● 43[b]	811 ± 168
(*S*)-HNEA$^+$Cl$^-$	*c*	*c*	239 ± 26
(*R*)-HPEA$^+$Cl$^-$		165 ± 17	467 ± 82
(*S*)-HPEA$^+$Cl$^-$		56 ± 6	161 ± 18

[a] Measured using the proton at the guest chiral center. [b] Measured using the methyl group of the guest chiral center. [c] The guest signal shift upon complexation is too small to allow accurate curve fitting.

group (H-1′) of the dodecyl chain of **2c** also showed a different shift in the presence of enantiomeric pairs of HNEA$^+$ and HPEA$^+$, but to a lesser extent.

From Figure 1 it is clearly seen that the multiple host signals of **2c** (or **2b**) between 3.4–3.7 ppm (the crown moiety) spread out more significantly upon complexation with the *R* than with the *S* enantiomer, indicating a better H-bonding formation between the macrocycle and the ammonium cation of the guest. These differences are much smaller in the case of **2a**. Another spectral feature was observed for the naphthyl group of the guests at 7.4–8.4 ppm. For all three hosts, the naphthyl signals spread out and were downfield shifted in the presence of (*R*)-HNEA$^+$. The shift was less pronounced in the presence of (*S*)-HNEA$^+$. Very similar spectral patterns were observed for **2b** and **2c**, implying a similar conformation around the major binding site for both macrocycles.

The extent of chiral recognition was studied by binding constant measurement via NMR titrations[13] and competition experiments. Titration experiments were carried out with 1 mM total guest and a variable host concentration within a range of 0–10 mM. Data fitting was achieved by nonlinear regression analysis (program MINSQ) using a 1:1 complexation model. The most sensitive guest signals, those of the proton or methyl groups at the chiral center, were used for curve fitting. Figure 2 shows a representative example. From the titration curves it is clear that weak host–guest complexes are formed and that exchange is fast on the NMR time scale. The calculated binding constants are collected in Table II. The difference in the *K* values for the interaction of **2c** with the enantiomeric pair of HNEA$^+$ (3.4-fold) and HPEA$^+$ (2.9-fold), as well as for **2b** with HPEA$^+$ (2.9-fold), is taken to be conclusive evidence of chiral recognition by these macrocycles. These results clearly show the *R* selectivity of the hosts. In the cases of **2a** and **2b**, the titration data for (*S*)-HNEA$^+$ could not be fitted accurately since only a few Hz shift was observed after adding a large excess of host. Nevertheless, by comparing the total chemical shift during the titration ((*R*)-HNEA$^+$ shifts several times more than (*S*)-HNEA$^+$), the preferred binding with (*R*)-HNEA$^+$ seems also to hold for **2a** and **2b**.

Among these three chiral hosts, **2c** exhibits higher binding toward both ammonium cations than either **2a** or **2b**. The weaker binding exhibited by **2a** could be caused by two reasons. First, although the crystal structure of 3,6,9,12,15-pentaoxa-18,19,20-triazabicycloeicosa-1-(19),17-diene[7] (analogue of **2a** without the two methyl groups) showed that the triazolo proton was located on N-1 in the solid state. The annular tautomerism of this N-unsubstituted host in solution could result in a molecular structure with protonated N-4, therefore strongly reducing the cation binding ability of the macrocycle. Second, it has been reported[7] that the triazolo hydrogen takes part in a hydrogen bond to the perchlorate anion in the benzyl–ammonium complex. It is reasonable to assume that this interaction is also present between the triazolo hydrogen of **2a** and the chloride anion in the present case. Consequently, the electron density of the triazole ring would decrease, which would influence the H-bonding interaction of the host with the ammonium substrates. Therefore, from the point of view of design of these host molecules as ammonium transport carriers, the lipophilic chain attached at position N-1 of the triazole is not only essential for its lipophicility but also necessary to enhance the actual binding capability with the substrates.

It was somewhat surprising to observe lower binding for **2b**. This might be the result of the steric interaction between the large aromatic group of the guest and the carbonyl group of the host, which connects the bulk cholesteryl chain to the macrocycle. This close spatial relationship was indicated by the pronounced proton signal shift observed upon complexation at positions Ha and Hb of the host molecules (Table I), which was caused presumably by the ring current of the naphthyl or phenyl group of the guests.

A comparison of the binding constants between host **2b**,**2c** with HNEA$^+$ and HPEA$^+$ is interesting. All HPEA$^+$ complexes are less stable than the corresponding ones with HNEA$^+$. If one only considers steric effects in the complexation, a reasonable expectation would have been that HPEA$^+$ should form more stable complexes with the hosts than HNEA$^+$. However, experimental results show the contrary. These results suggest a possible π–π interaction between the aromatic groups of the hosts and the guests. Therefore, the weaker binding of the HPEA$^+$ complexes is consistent with a decreased π–π interaction caused by the smaller aromatic group of the guests.

Taken together, the binding constants as well as the NMR spectral information discussed above all suggest that the naphthyl or phenyl group of the guests are located on top of the triazole ring of the host. This structure agrees with the crystal structure of a similar system, dimethyl-substituted pyridino-18-crown-6–HNEA$^+$ complex, reported by Izatt et al.[10] In our case, however, the significantly different shifts observed for *R* and *S* complexes also suggest that the relative positions of the naphthyl or phenyl ring were different in the diastereomeric complexes. This information together with the modest chiral recognition exhibited by **2c** with the HNEA$^+$ enantiomers when compared with that exhibited with the HPEA$^+$ ones might imply that in the system studied there are not only steric effects but also π–π interactions involved in the process

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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.

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Synthesis of Chiral Vinylglycines

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(*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-

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