Ester-Enolate Claisen Rearrangement of α-Amino Acid Derivatives

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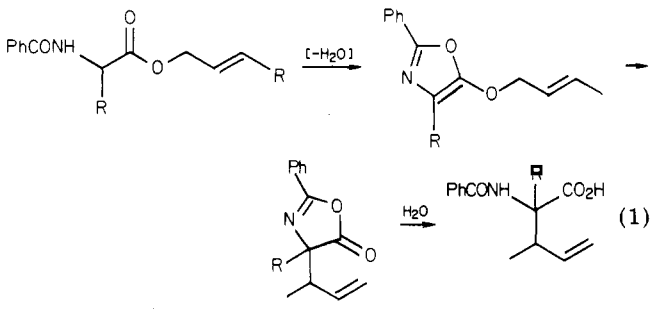
With the standard procedure for the Ireland–Claisen rearrangement, using 2 equiv of base, allylic esters of *N*-acyl α-amino acids are converted to the rearranged γ,δ-unsaturated α-amino acids in moderate to good yield and diastereoselectivity. Moderate variation, but not reversal, of stereoselectivity is seen on using different solvents or conditions. Variation in the substituents on the amino group, α-position, and allylic alcohol moiety was also studied. For each case in which the stereochemistry of the rearranged product was proven, it was consistent with predominant formation of the *E* enolate (enolate oxygen and anionic acylamido substituent cis). The rearrangement was also applied successfully to the synthesis of highly hindered amino acids and to cycloalkenyl-substituted analogues. In a number of instances, comparison was made with an alternative rearrangement procedure involving an oxazole intermediate.

The ester–enolate version of the Claisen rearrangement has become an important method for acyclic stereocontrol since Ireland and his co-workers developed a practical procedure several years ago.[1] Because of our interest in this topic, we studied the influence of heteroatom substituents in the α-position of the carboxylic acid moiety, seeking to extend the scope of the Ireland–Claisen rearrangement to the synthesis of α-hydroxy and α-amino acid derivatives. Among other considerations, we wanted to explore the possibility that such α substituents, particularly ionizable ones, could influence or control the stereochemistry of enolate formation and hence of the stereochemical course of the rearrangement. Apart from interest in the ester–enolate Claisen rearrangement per se, we were stimulated to apply this reaction to α-amino acid derivatives because of the increasing importance of γ,δ-unsaturated analogues as naturally occurring, biologically active compounds[2-4] and as synthetic precursors to related materials.[5] In this paper we report our findings in the α-amino acid series; the following paper concerns the Claisen rearrangement of α-hydroxy acid derivatives.

Prior to our investigation, a version of the Claisen rearrangement had been developed for *N*-benzoyl α-amino acid esters by Steglich and his co-workers.[6] This process involves formation and rearrangement of an intermediate oxazole (eq 1). The sequence proceeds in good to excellent



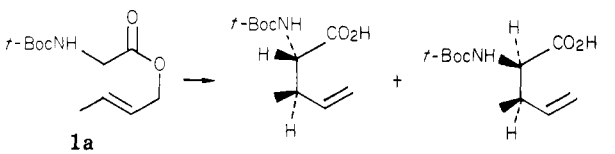
(1)

yield in a number of cases and has the advantage of clearly controlling the stereochemistry of the enol double bond. Because only a limited stereochemical investigation had been undertaken, in the course of our work we compared this process with the ester–enolate procedure for several substrates.

Synthesis of Ester Substrates. The allylic ester derivatives that we employed as substrates were synthesized in a straightforward manner by coupling the appropriate carboxylic acid and allylic alcohol using dicyclohexylcarbodiimide and 4-(dimethylamino)pyridine.[7] The only difficulty worthy of note was obtaining pure *trans*-crotyl alcohol: the commercially available material we received[8] was contaminated with 8–10% of the cis isomer and required purification by spinning-band distillation. In some of our experiments, we used stereochemically pure *trans*-crotyl alcohol which was prepared by the diisobutylaluminum hydride reduction of crotonaldehyde.

Rearrangement of *trans*-2-Butenyl *N*-(*tert*-Butoxycarbonyl)glycinate (1): Influence of Deprotona-

Table I. Influence of Conditions on Rearrangement of 1



entry	conditions[a]	yield,[b] %	ratio of 2a-*t*/2a-*e*[c]
1	standard	60-65	9
2	ether solvent	45	10
3	20% HMPT/THF solvent	51	4
4	2.2 equiv of TMEDA included with base	36	*d*
5	KDA as base	0[e]	
6	1.1 equiv of $MgCl_2$ included with ester	42	10
7	bromomagnesium isopropylcyclohexylamide as base	29	2

[a] Standard conditions: deprotonation at −75 °C with 2.1 equiv of lithium isopropylcyclohexylamide or lithium diisopropylamide; silylation with Me_3SiCl after 10 min; warming to reflux for 1 h; hydrolysis of silyl ester. Modifications of solvent or base or the inclusion of additional reagents are indicated. [b] Isolated yield of material >95% pure. [c] Determined by ^{13}C NMR. [d] Ratio not determined. [e] Product isolated was *N*-(*tert*-butoxycarbonyl)glycine.

(1) (a) R. E. Ireland, R. H. Mueller, and A. K. Willard, *J. Am. Chem. Soc.*, *98*, 2868 (1976); (b) R. E. Ireland and C. S. Wilcox, Jr., *Tetrahedron Lett.*, 2839 (1977).

(2) (a) S. Santoso, T. Kemmer, and W. Trowitzsch, *Liebigs Ann. Chem.*, 642 (1981); (b) *ibid.*, 658 (1981).

(3) V. Cramer, A. G. Rehfeldt, and F. Spener, *Biochemistry*, **19**, 3074 (1980).

(4) O. Scannell, D. Preuss, T. Demny, F. Weiss, J. Williams, and A. Stemple, *J. Antibiot.*, **4**, 329 (1971); M. Orlowski, D. Rheingold, and M. Stanley, *J. Neurochem.*, **28**, 349 (1977); M. Johnston, R. Raines, M. Chang, N. Esaki, K. Soda, and C. Walsh, *Biochemistry*, **20**, 4325 (1981); J. E. Semple, P. C. Wang, Z. Lysenko, and M. M. Joullié, *J. Am. Chem. Soc.*, *102*, 7505 (1980).

(5) P. A. Bartlett, D. J. Tanzella, and J. F. Barstow, *Tetrahedron Lett.*, 619 (1982).

(6) (a) N. Engel, B. Kübel, and W. Steglich, *Angew. Chem., Int. Edit. Engl.*, **16**, 394 (1977); (b) B. Kübel, G. Höfle, and W. Steglich, *ibid.*, **14**, 58 (1975).

(7) A. Hassner and V. Alexanian, *Tetrahedron Lett.*, 4475 (1978).

(8) Aldrich Chemical Co., Pfalz & Bauer, or Fluka.

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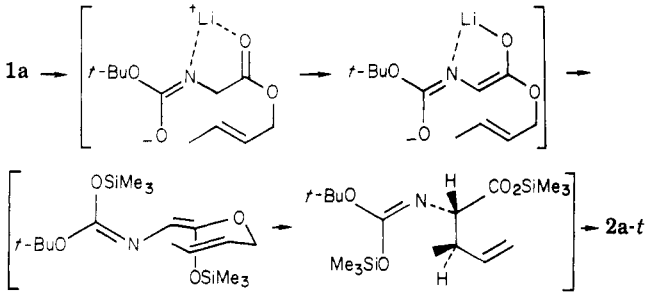
Scheme I



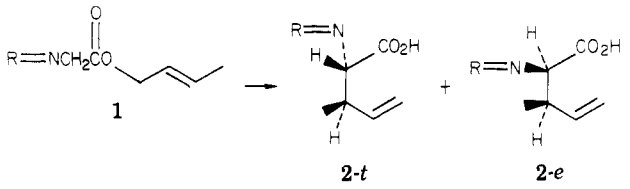
tion Conditions. Our initial work involved optimization of the ester–enolate rearrangement for *trans*-crotyl *N*-(*tert*-butoxycarbonyl)glycinate (**1a**), focussing on both yield and diastereoselectivity. The results are presented in Table I. The "standard conditions"[1a] (entry 1) proved to be the best by both criteria. Deprotonation of the ester with lithium diisopropylamide (LDA, 2.1 equiv) in THF at −75 °C, silylation after 10 min with trimethylsilyl chloride, and warming to reflux for 1 h provide the rearranged product **2a** as a 9:1 mixture of diastereomers in 60–65% yield. Shorter (2.5 min) or longer (40 min) enolate generation times have no significant influence on yield or stereoselectivity. Nor does the use of *tert*-butyldimethylsilyl chloride as the silylating agent[1a] offer any advantage. Reaction in a less polar solvent, ether (entry 2), results in a lower yield, but the stereoselectivity is unaffected. In contrast, the more highly dissociating systems with hexamethylphosphoric triamide (HMPT) as a cosolvent (entry 3) or tetramethylethylenediamine (TMEDA) as an additive (entry 4) show both lower yields and lower stereoselectivity. Attempts with counterions other than lithium met with mixed success: an experiment with potassium diisopropylamide gave *N*-(*tert*-butoxycarbonyl)-glycine as the only acidic product (entry 5), whereas the use of bromomagnesium isopropylcyclohexylamide (prepared from ethylmagnesium bromide and isopropylcyclohexylamine; entry 7) showed both poor yield and poor stereoselectivity. Inclusion of magnesium chloride with the ester solution as it is added to the LDA, on the other hand, gives high selectivity (entry 6), although offering no advantage over the standard conditions.

The stereochemistry of the products was proved by hydrogenation and deprotection to give the isoleucine diastereomers. ^{13}C NMR comparison with authentic material showed that the minor diastereomer corresponded to the natural isomer of isoleucine. This result, coupled with the known proclivity for the Claisen rearrangement of acyclic substrates to proceed via a chairlike transition state,[9] defines the geometric preference for dianion formation to be *E*, as shown in Scheme I. The fact that more highly dissociating conditions tend to reduce the stereoselectivity of the process implies that coordination of the counterion between the carbonyl oxygen and anionic nitrogen substituent is at least partly responsible for this *E* selectivity.

Influence of N-Protecting Groups on Rearrangement of *trans*-2-Butenyl Glycinates. We explored a variety of other N-protected derivatives of the basic crotyl glycinate substrate using the "standard" deprotonation and rearrangement conditions (Table II). Although both the carbobenzoxy (Cbz) and benzoyl derivatives (entries 2 and 3, respectively) rearrange in comparable yield, the stereoselectivity is lower than for the Boc analogue. As noted

(9) P. Vittorelli, H.-J. Hansen, and H. Schmid, *Helv. Chim. Acta*, *58*, 1293 (1975); W. S. Johnson, et al., *J. Am. Chem. Soc.*, **92**, 741 (1970).

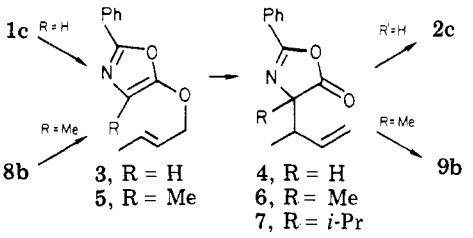
Table II. Influence of N-Protecting Group



entry	substrate	R	yield,[a] %	ratio of 2-*t*/2-*e*[b]
1	1a	*t*-BuO_2C, H	60–65	9
2	1b	$PhCH_2O_2C$, H	65	4
3	1c	PhCO, H	65	5.4
4	1d	CF_3CO, H	58	1.5
5	1e	phthaloyl	0	
6	1f	Et_2	0	

[a] Isolated yield of material >95% pure. Rearrangement by the "standard" method. [b] Determined by ^{13}C NMR.

Scheme II



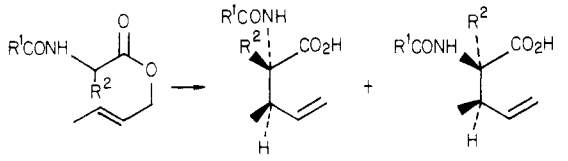
below, this is not always the case, so we usually investigated both the *N*-benzoyl and *N*-Boc derivatives within each substrate class. The overall yield with *trans*-crotyl hippurate (**1c**) is also unaffected by the enolate generation time (10–40 min) but is reduced to only 27% in 20% HMPT/THF. The stereochemistry of the *N*-benzoyl, *N*-Cbz, and *N*-trifluoroacetyl products was correlated with that of the *N*-Boc compounds by their interconversion.

With the *N*-benzoyl derivative **1c** we were able to employ Steglich's procedure for generation and rearrangement of oxazoles.[5] It became apparent that this sequence is limited to α-alkyl α-amino acid derivatives: the oxazole **3** derived from *trans*-crotyl hippurate is formed in only 32% yield on using a triphenylphosphine/carbon tetrachloride dehydrating agent,[6a] and the product resulting from subsequent rearrangement is obtained as a 1:1 mixture of diastereomers, presumably as a result of facile epimerization of the intermediate oxazolone **4** (Scheme II).

The reduced stereoselectivity with trifluoroacetyl derivative **1d** (Table II, entry 4) may reflect reduced importance of the chelation depicted above because of greater acidity of the nitrogen. Our inability to isolate a rearranged product from reactions of the *N*-phthaloyl and *N*,*N*-diethyl analogues (entries 5 and 6) surprised us but points to the importance of an extended conjugated system for nitrogen-substituted enolate stabilization, even if this system must bear two negative charges.

Influence of α Substituents on Rearrangement of *trans*-2-Butenyl Esters. Retaining the *trans*-crotyl ester moiety, we explored *N*-benzoyl- and *N*-Boc-protected alanine and valine esters as rearrangement substrates (Table III). In the alanine series, the *N*-benzoyl derivative rearranges with higher selectivity and yield than the Boc analogue (entries 1 and 2). The Steglich procedure (entry 3) affords nearly a quantitative yield of rearranged product, although with very low stereoselectivity in spite of the specific enol geometry embodied in the oxazole intermediate **5**. Because there is no possibility for epimerization of the oxazolone intermediate **6** in this case and since there

Table III. Influence of α Substitution



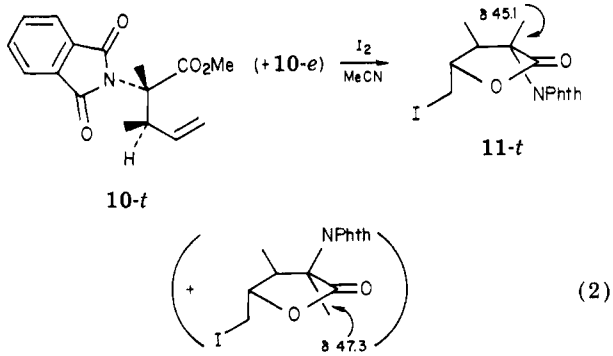
9-t 9-e

entry	substrate	R^1	R^2	method[a]	yield,[b] %	ratio of 9-t/9-e[c]
1	8a	t-BuO	Me	enolate	59	3
2	8b	Ph	Me	enolate	71	4
3	8b	Ph	Me	oxazole	81	1.5
4	8c	t-BuO	i-Pr	enolate	0	
5	8d	Ph	i-Pr	enolate	90[d]	0.77[e]
6	8d	Ph	i-Pr	oxazole	43[d]	2[e]

[a] Enolate, "standard" method; oxazole, Ph_3P, CCl_4, and Et_3N in MeCN at 21 °C, 1 N HCl, and THF.[6a] [b] Isolated yield of material >95% pure. [c] Determined by ^{13}C NMR. [d] Yield of oxazolone 7. [e] Stereochemistry not proven; see text.

is no obvious difficulty in attaining the chair conformation for rearrangement, it is surprising that the boatlike pathway is so competitive.

To prove the stereochemistry of the alanine-derived products, we sought to convert one of them to a conformationally fixed derivative such as an iodo lactone.[5] All attempts to iodolactonize either the *N*-benzoyl- or *N*-Boc-protected products under conditions which would lead selectively to the β,γ-*trans* stereochemistry[10] resulted in poor yields of mixtures of products, presumably as the result of competing attack by the *N*-acyl moiety. This problem was avoided by cleavage of the Boc group and conversion of the resulting amino acid to the phthaloyl-protected methyl ester **10**. This material undergoes iodolactonization with iodine in acetonitrile to give the lactones **11** cleanly (eq 2), albeit in only 30% yield. A

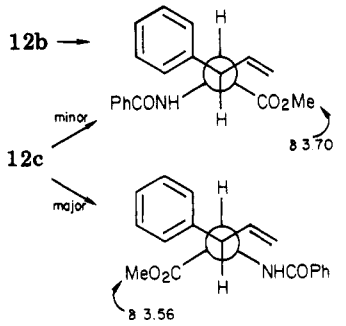


10-t 11-t

11-e (2)

cyclization carried out on a sample of isomer **10**-*t* that had been purified by HPLC ensured that kinetic resolution of an isomer mixture would not invalidate the results. The major isomer from rearrangement gives rise to lactone **11**-*t*, in which the α-methyl group shows an upfield shift in the ^{13}C NMR in comparison to that for isomer **11**-*e* (in which steric compression from the β-methyl is absent).[11] The preference for the *E* enolate is retained with the alanine derivative, therefore. The stereochemistries of the *N*-benzoyl isomers were correlated by benzoylation of the amino acid mixture obtained by deprotection of **9a**. All attempts to remove the benzoyl group from **9b** itself failed;

Scheme III



we either recovered starting material (NaOH, aqueous Me_2SO, Δ, 6 days; Na_2O_2;[12] $Et_3O^+BF_4^-$, MeOH, H^+;[13] PCl_5, MeOH[14]) or saw decomposition (aqueous H_2SO_4, Δ; aqueous $HClO_4$, HOAc[15]).

In the valine series, the disparity between the benzoyl and Boc derivatives becomes most dramatic: no rearranged product is obtained from the *N*-Boc compound (Table III, entry 4), while the *N*-benzoyl derivative affords a 90% yield of product by the enolate procedure, albeit almost nonstereoselectively (entry 5). Under the normal workup conditions, the carboxylic acids **9d** are not isolated directly from rearrangement of *N*-benzoyl derivative **8d**; rather, the oxazolone **7** is obtained. Considering the highly substituted nature of this compound, it is not surprising that cyclization is facile.[16] Interestingly, the low stereoselectivity observed in the enolate rearrangement of **8d** is opposite that obtained via the oxazole method (Table III, entry 6).

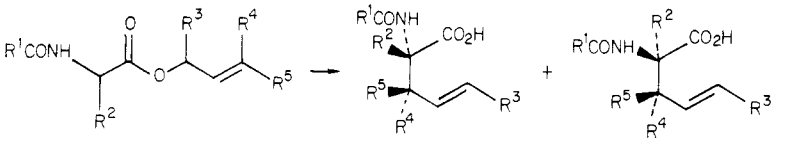
Unfortunately, we were unable to prove the stereochemistry of the valine-derived products conclusively. As in the alanine series, all attempts to cleave the benzamide met with failure, and we were unable to prepare a suitable substrate for iodolactonization. Other strategies for functionalization of the double bond and eventual lactonization were also unsuccessful (inter alia: $O_3 \rightarrow NaBH_4$; $NaIO_4 \rightarrow NaBH_4$; I_2, $NaHCO_3 \rightarrow$ MeOH, $K_2CO_3 \rightarrow$ NaOH $\rightarrow NaIO_4 \rightarrow NaBH_4$). Nonetheless, a downward trend in stereoselectivity is seen on going from the glycine to alanine to valine esters, suggesting a competition between the electron effects of the acylamido group and the steric influence of an α substituent.

Influence of Substituents on the Allylic Alcohol Group. In addition to variations in N-protecting groups and substituents in the α-position, we studied variation in the allylic alcohol moiety as well (Table IV). For the crotyl (*tert*-butoxycarbonyl)glycinate and cinnamyl hippurate esters (entries 1–4), the expected dependence on double bond configuration is observed, although the precedented[1b] reduction in selectivity is seen for the *cis*-cinnamyl substrate **12c**. In the cinnamyl series, the methyl esters of the rearrangement products gave ^1H NMR spectra which are consistent with the expected stereostructures: the major product from the cis isomer **12c** shows an upfield methyl resonance because of shielding by the β-phenyl ring in the most stable conformer,[17] as illustrated in Scheme III.

Of major interest is the ability to construct highly substituted α-amino acids by the Claisen rearrangement, as

(10) P. A. Bartlett and J. Myerson, *J. Am. Chem. Soc.*, **100**, 3950 (1978).
(11) N. K. Wilson and J. B. Stothers, *Top. Stereochem.*, 8, 1 (1974).
(12) H. L. Vaughn and M. D. Robbins, *J. Org. Chem.*, **40**, 1187 (1975).
(13) H. Muxfeldt and W. Rogalski, *J. Am. Chem. Soc.*, **87**, 932 (1965).
(14) R. R. Chauvette, et al., *J. Org. Chem.*, **36**, 1259 (1971).
(15) R. J. L. Martin, *Aust. J. Chem.*, **18**, 807 (1965).
(16) N. L. Allinger and L. Zalkow, *J. Org. Chem.*, **25**, 701 (1960).
(17) E.g., D. Y. Curtin and S. Dayagi, *Can. J. Chem.*, **42**, 867 (1964).

Table IV. Influence of Allylic Alcohol Substituents

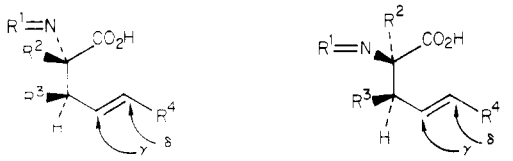


12 13-*t* 13-*e*

entry	substrate	R^1	R^2	R^3	R^4	R^5	method[a]	yield,[b] %	ratio of 13-*t*/13-*e*[c]
1	1a	*t*-BuO	H	H	H	Me	enolate	60–65	9
2	12a	*t*-BuO	H	H	Me	H	enolate	60	6
3	12b	Ph	H	H	H	Ph	enolate	68	>20[e]
4	12c	Ph	H	H	Ph	H	enolate	50	2.5
5	12d	Ph	Me	H	Me	C_6H_{11}[d]	enolate	80	>20[e,f]
6	12d	Ph	Me	H	Me	C_6H_{11}[d]	oxazole	78	>20[e,f]
7	12e	*t*-BuO	H	H	Me	C_6H_{11}[d]	enolate	56	>20[e,f]
8	12f	*t*-BuO	H	H	Me	Me	enolate	77	
9	12g	*t*-BuO	H	Me	H	Me	enolate	90	10–15

[a–c] See corresponding footnotes to Table III. [d] $C_6H_{11} = CH_2CH_2CH{=}C(CH_3)_2$. [e] Other isomer not discernible in the ^{13}C NMR. [f] Stereochemistry not proven; see text.

Table V. ^{13}C NMR Olefinic Chemical Shifts of γ,δ-Dehydro Amino Acid Diastereomers

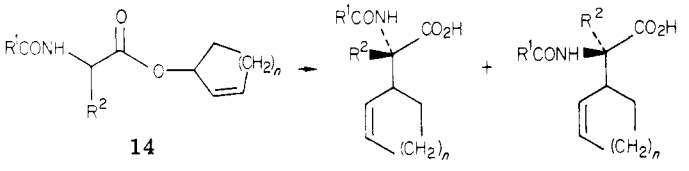


RS,SR *RR,SS*

					chemical shift,[a] δ			
					RS,SR isomer		*RR,SS* isomer	
compd	R^1	R^2	R^3	R^4	C-γ	C-δ	C-γ	C-δ
2a	*t*-BuO_2C, H	H	Me	H	138.6	115.9	137.6	116.7
2b	$PhCH_2O_2C$, H	H	Me	H	138.3	116.1	137.3	117.1
2c	PhCO, H	H	Me	H	138.5	116.5	137.8	116.9
2d	CF_3CO, H	H	Me	H	137.3	117.3	136.5	118.0
9b	PhCO, H	Me	Me	H	134.3	117.2	134.0	118.1
	phthaloyl	Me	Me	H	138.8	116.2	138.4	116.5
13b	PhCO, H	H	Ph	H	136.9	115.5	136.6	116.1
13g	*t*-BuO_2C, H	H	Me	Me	131.3	126.8	130.1	128.0

[a] In $CDCl_3$, referenced to solvent as δ 77.0

Table VI. Rearrangement of 2-Cycloalkenyl Esters



14 15-*e* 15-*t*

entry	substrate	R^1	R^2	*n*	method[a]	yield,[b] %	ratio of 15-*e*/15-*t*[c]
1	14a	Ph	H	1	enolate	45	1
2	14b	*t*-BuO	H	1	enolate	73	3
3	14c	Ph	H	2	enolate	22	1.5
4	14d	*t*-BuO	H	2	enolate	40	20
5	14e	Ph	Me	2	enolate	64	2[d]
6	14e	Ph	Me	2	oxazole	87[e]	>20[d]
7	14f	*t*-BuO	Me	2	enolate	0	

[a–c] See corresponding footnotes to Table III. [d] Stereochemistry not proven; see text. [e] Yield of oxazolone.

shown by entries 5–8. Steglich and his co-workers applied their oxazole procedure to the geranyl ester of *N*-benzoylalanine, **12d**, and obtained rearranged product in high yield, apparently as a single diastereomer.[6b] We have confirmed this result and shown that the ester enolate affords the same product, also in good yield and as a single isomer. By ^{13}C NMR or 250-MHz ^1H NMR, no evidence for diastereomeric material could be seen (≥5% could have been distinguished). Ester–enolate Claisen rearrangement of the geranyl ester of *N*-(*tert*-butoxycarbonyl)glycine

Table VII. Physical and Spectral Data for Starting Materials[a]

compd	yield, %	mp (recrystallization solvent) or bp (pressure, torr), °C	IR, cm^{-1}	^1H NMR, δ (J, Hz)
1a	77	100 (0.3)	3490, 3000, 1720, 1500	5.7 (m, 2), 5.3 (br t, 1, J = 6), 4.6 (br d, 2, J = 5), 3.9 (d, 2, J = 6), 1.8 (br d, 3, J = 5), 1.5 (s, 9)
1b	76	150 (0.15)	3350, 2950, 1710	7.3 (br s, 5), 5.6 (m, 2), 5.1 (s, 2), 4.5 (br d, 2, J = 5), 3.9 (d, 2, J = 6), 1.7 (br d, 3, J = 5)
1c	88	62.5-63.5 (hexane/ether)	3550, 2950, 1740, 1650	7.7 (m, 2), 7.3 (m, 3), 7.0 (br s, 1), 5.6 (m, 2), 4.5 (br d, 2, J = 5), 4.1 (d, 2, J = 5), 1.7 (br d, 3, J = 5)
1d	61	51-53 (hexane), 100 (0.2)	3430, 3050, 3000, 2960, 1730, 1545	7.2 (br s, 1), 6.00-5.25 (m, 2), 4.52 (d, 2, J = 6), 4.03 (d, 2, J = 6), 1.70 (d, 3, J = 6)
1e	45	89-90 (ethanol/water)	2950, 1750, 1720, 1420	7.90 (s, 5), 6.10-5.38 (m, 2), 4.56 (d, 2, J = 6), 4.42 (s, 2), 1.69 (d, 3, J = 6)
1f	89	100 (0.15)	2975, 1730	6.00-5.28 (m, 2), 4.55 (d, 2, J = 5), 3.28 (s, 2), 2.65 (q, 4, J = 7), 1.70 (br d, 3, J = 5), 1.08 (t, 6, J = 7)
8a	73	150 (0.1)	3440, 2980, 1710, 1600	6.00-5.20 (m, 2), 4.44 (d, 2, J = 6), 4.15 (quint, 1, J = 6), 1.67 (d, 3, J = 6), 1.43 (s, 9), 1.32 (d, 2)
8b	70	62.5-64.0 (hexane)	3450, 3000, 1740, 1660	7.80-7.53 (m, 2), 7.45-7.05 (m, 3), 6.80 (br d, 1, J = 7), 5.87-5.20 (m, 2), 4.61 (quint, 1, J = 7), 4.42 (d, 2, J = 6), 1.61 (d, 3, J = 7), 1.43 (d, 3, J = 7)
8c	59	190 (0.6)	2935, 1710, 1500	5.90-5.20 (m, 2), 4.94 (d, 1, J = 9), 4.33 (d, 2, J = 6), 4.03 (dd, 1, J = 9, 6), 2.17-1.75 (m, 1), 1.62 (d, 3, J = 6), 1.37 (s, 9), 0.87 (dd, 6, J = 6, 6)
8d	76	44.5-45.0 (hexane)	3440, 2960, 1720, 1660	7.77-7.60 (m, 2), 7.40-7.13 (m, 3), 6.70 (d, 1, J = 9), 5.90-5.20 (m, 2), 4.67 (dd, 1, J = 9, 6), 4.47 (d, 2, J = 6), 2.40-2.00 (m, 1), 1.67 (d, 3, J = 6), 0.98 (d, 6, J = 6)
12b	67	90.5-91.0 (hexane/benzene)	3450, 3000, 1740, 1660, 1610, 1580	8.87-7.18 (m, 6), 6.80-6.05 (m, 2), 4.83 (d, 2, J = 6), 4.27 (d, 2, J = 6)
12c	65	61-62 (hexane/ether)	3450, 3000, 1740, 1660, 1600, 1580	8.85-7.10 (m, 5), 7.00-6.50 (m, 2), 5.95-5.57 (m, 1), 4.90 (d, 2, J = 6), 4.20 (d, 2, J = 6)
12d	54	chromatographed[b]	3450, 3000, 1740, 1660, 1520	7.80-7.57 (m, 2), 7.40-6.90 (m, 4), 5.23 (t, J = 6), 4.94 (br m, 1), 4.59 (quint, 1, J = 7), 4.55 (d, 2, J = 7), 1.98 (br s, 2), 1.65 (br s, 6), 1.55 (s, 3), 1.43 (d, 3, J = 7)
12e	93	225 (0.3)	3440, 3000, 1720, 1515	5.35-5.00 (m, 2), 4.59 (d, 2, J = 7), 3.82 (d, 2, J = 5), 1.99 (br s, 4), 1.63, 1.61, 1.53 (s, 3), 1.38 (s, 9)
12f	74	100 (0.5)	3320, 2975, 1680, 1490	5.53-5.20 (m, 2), 4.67 (d, 2, J = 7), 3.90 (d, 2, J = 6), 1.75 (d, 6, J = 5), 1.45 (s, 9)
12g	56	150 (0.1)	3450, 3000, 1700, 1510	5.80-5.10 (m, 2), 3.72 (d, 2, J = 6), 1.62 (d, 3, J = 6), 1.42 (s, 9), 1.25 (d, 3, J = 6)
14a	30	84.5-86.0 (methylcyclohexane)	3400, 2930, 1750, 1650	7.90-7.78 (m, 2), 7.58-7.37 (m, 3), 7.00 (br s, 1), 6.18-6.11 (m, 1), 5.86-5.74 (m, 3), 2.60-2.45 (m, 1), 2.42-2.20 (m, 2), 1.95-1.80 (m, 1)
14b	92	200 (0.2)	3450, 2980, 1710, 1505	6.20-6.08 (m, 1), 5.87-5.70 (m, 2), 5.05 (br s, 1), 3.83 (d, 2), 2.60-1.78 (m, 4), 1.95 (s, 9)
14c	36	chromatographed[b]	3460, 2950, 1730, 1660	7.87-7.77 (m, 2), 7.50-7.25 (m, 3), 6.00-5.90 (m, 1), 5.83-5.65 (m, 2), 5.32 (br d, 2), 4.17 (d, 2, J = 6), 2.75-1.45 (m, 6)
14d	77	51-52 (hexane)	3470, 2950, 1730, 1510	5.86 (dt, 1, J = 14, 3), 5.60 (m, 1), 5.20 (m, 2), 3.78 (d, 2, J = 6), 2.15-1.26 (m, 12), 1.42 (s, 9)
14e	34	91-93 (hexane)	3450, 2950, 1730, 1660	7.86-7.00 (m, 6), 5.87 (m, 1), 5.57 (m, 1), 5.20 (br s, 1), 4.62 (dq, 1, J = 7, 7), 2.20-1.30 (m, 6), 1.43 (d, 3, J = 7)
14f	90	175 (0.2)	3460, 3000, 2960, 1720, 1510	5.95-5.70 (m, 1), 5.24-4.80 (m, 2), 4.13 (dq, 1, J = 7, 7), 2.10-1.50 (m, 6), 1.40 (s, 9), 1.32 (d, 3, J = 7)

[a] Noncrystalline compounds purified by preparative VPC (10% SE-30 on 100-120-mesh GasChrom Q) for analysis; satisfactory analytical data for all compounds were submitted for review. [b] Decomposed on attempted distillation.

similarly affords a single isomer as far as can be discerned from the ^1H and ^{13}C NMR spectra. The presence of only a single isomer and difficulties similar to those encountered in the valyl series prevented us from determining the stereostructure of the geranyl-derived products.

The only ester of an acyclic, secondary allylic alcohol we examined was the *N*-(*tert*-butoxycarbonyl)glycyl derivative of (*E*)-3-penten-2-ol, **12g**. This material rearranges in excellent yield to give a >12:1 ratio of diastereomers (Table IV, entry 9). The stereochemistry of the product was assigned by ^{13}C NMR comparison with analogues whose structures had been determined by other methods (see Table V). In each case, the pattern of vinyl resonances is similar: those of the *RS,SR* diastereomers lie outside those of the *RR,SS* isomers. On the basis of this empirical correlation, and in analogy with the related rearrangements

Table VIII. Physical and Spectral Data for Products of Ester-Enolate Rearrangement[a]

compd	yield, %	mp (recrystallization solvent) or bp (pressure, torr), °C	IR, cm^{-1}	^1H NMR, δ (J, Hz)	^{13}C NMR,[e] δ
2a	65	119-121 (acetonitrile)	3300, 2975, 1780, 1600	5.6 (m, 1), 5.1 (m, 2), 4.2 (m, 1), 2.7 (m, 1), 1.4 (s, 9), 1.1 (d, 3, J = 6)	175.1, 157.0, 138.6, 115.9, 79.7, 57.3, 40.2, 28.1, 14.9 [137.6, 116.7, 39.8, 16.0]
2b	65	118-119 (petroleum ether/ CH_2Cl_2)	3300, 3000, 1780, 1620	7.3 (br s, 5), 5.6 (m, 1), 5.1 (m, 4), 4.4 (m, 1), 2.7 (m, 1), 1.1 (d, 3, J = 7)	175.5, 156.6, 138.3, 136.1, 128.4, 128.1, 128.0, 116.1, 67.2, 40.7, 14.9 [137.3, 117.1, 39.7, 16.0]
2c	65	118-119.5 (petroleum ether/ CH_2Cl_2)	3400, 3000, 1700, 1640	7.8 (m, 2), 7.4 (m, 3), 6.7 (d, 1, J = 8), 5.8 (m, 1), 5.1 (m, 2), 4.9 (dd, 1, J = 8, 6), 2.9 (m, 1), 1.1 (d, 3, J = 8)	175.0, 168.1, 138.5, 133.7, 131.9, 128.6, 127.1, 116.5, 58.0, 40.6, 16.1 [137.8, 116.9, 39.9]
2d	58	chromatographed	3400, 3000, 1720, 1600	6.90 (d, J = 8), 5.75-5.50 (m, 1), 5.25-5.00 (m, 2), 4.75-4.50 (m, 1), 3.0-2.70 (m, 1), 1.25 (d, J = 7)	173.6, 137.3, 117.3, 56.7, 56.4, 55.1, 47.6, 40.2, 29.5, 24.7, 24.5, 19.2, 15.9, 15.1 [173.9, 136.5, 118.0, 39.7]
9a	59	128-130 (hexane)	2980, 1710, 1490	5.9-5.6 (m, 1), 5.3-5.1 (m, 2), 2.48 (s, 9), 1.10 (d, 3, J = 7); signal due to minor isomer 1.03 (d)	135.9, 117.3, 61.9, 45.7, 28.4, 20.4, 15.0 [118.2, 62.0, 15.2]
9b	71	119-120 (hexane)	3440, 3000, 1725, 1665, 1590	7.84-7.10 (m, 5), 7.00 (br s, 1), 6.18-5.44 (m, 1), 5.44-4.87 (m, 2), 2.98 (dd, 1, J = 7, 7), 1.98 (s, 3), 1.04 (d, 3, J = 6); signals due to minor isomer 1.98 (s), 1.18 (d, J = 6)	176.5, 167.6, 138.6, 134.3, 131.6, 128.5, 126.9, 117.2, 62.1, 44.2, 20.3, 17.8 [167.1, 134.0, 118.1, 62.6, 44.7]
13b	68	181-182 (hexane)	3450, 1725, 1660, 1610	8.00-7.20 (m, 6), 6.45-5.95 (m, 1), 5.35-5.00 (m, 2), 4.00 (dd, 1, J = 8, 8)	136.9, 130.6, 127.5, 127.4, 126.9, 126.2, 125.9, 115.5, 55.7, 51.1
13d	80	174.5-175.5 (methylcyclohexane)	2950, 1710, 1660, 1480	7.75-7.68 (m, 2), 7.54-7.36 (m, 3), 6.70 (s, 1), 6.17-6.05 (m, 1), 5.50-5.05 (m, 3)	176.3, 167.5, 142.8, 134.7, 131.5, 128.5, 126.9, 124.2, 116.7, 64.3, 46.3, 35.0, 25.5, 23.0, 18.4, 17.6, 16.7
13e[b]	56	chromatographed	2970, 1720, 1500	9.2 (br s, 1), 5.78-5.67 (m, 1), 5.17-4.92 (m, 3), 4.13 (d, 1, J = 9), 1.80 (m, 1), 1.59 (s, 2), 1.50 (s, 2), 1.37 (s, 9), 1.03 (s, 3), 1.59-1.03 (m, 2)	176.1, 155.6, 141.1, 131.6, 124.1, 115.8, 60.2, 43.2, 37.9, 28.3, 25.6, 22.6, 18.7, 17.6
13f	77	123-124 (cyclohexane)	3440, 2980, 1710, 1590	10.77 (s, 1), 6.10-4.80 (m, 3), 4.05 (d, 1, J = 9), 1.28 (s, 9), 1.10 (s, 6)	
13g	90	300 (0.025)	3450, 3000, 1710, 1500	6.20-4.80 (m, 3), 4.13 (m, 1), 2.53 (m, 1), 1.61 (d, 3, J = 6), 1.43 (s, 9), 1.04 (d, 3, J = 7)	175.8, 131.3, 126.8, 39.4, 28.2, 17.7 [130.1, 128.0]
15a	45	144.5-146 (methylcyclohexane)	3400-2500, 1725, 1680	7.85-7.75 (m, 2), 7.60-7.40 (m, 3), 6.50 (d, J = 8), 6.02 (m), 5.85 (m), 4.90 (m, 1), 2.45-1.00 (m, 5); signals due to minor isomer 6.67 (d, J = 8), 5.70 (m), 5.60 (m)	173.0,[c] 168.6, 133.1, 132.0, 131.0, 130.0, 129.1, 127.7, 126.6, 55.7, 31.3, 25.7 [130.9, 127.6, 55.9, 30.9, 25.2]
15b[d]	73	chromatographed	3450, 3000, 1710, 1500	6.40-5.50 (m, 2), 5.1 (d, 1, J = 7), 4.40 (m, 1), 3.22 (m, 1), 2.50-1.25 (m, 4), 1.47 (s, 9)	173.3, 155.8, 131.8, 129.9, 78.4, 66.8, 56.1, 47.6, 30.8, 26.8, 24.5 [133.2, 128.5, 31.2, 25.3]
15c	22	180-182 ($CHCl_3$)	1710, 1680	8.20-7.30 (m, 5), 6.83 (d, 1, J = 8), 6.00-5.50 (m, 2), 4.90 (dd, J = 8, 5), 2.95-2.70 (m, 1), 2.00-1.25 (m, 6); signals due to minor isomer 6.60 (d, J = 8), 6.89 (dd, J = 8, 4)	172.2,[c] 167.2, 133.9, 132.0, 131.5, 128.5, 126.9, 126.4, 55.7, 52.2, 38.3, 24.7, 24.4 [172.1, 167.3, 134.0, 131.6, 130.2, 38.8, 26.2, 24.8, 21.3, 21.2]
15d[d]	40	chromatographed	3050, 3000, 1710, 1500	6.20-5.50 (m, 3), 4.51 (d, J = 6), 2.95 (br s, 1), 2.35-1.45 (m, 6), 1.8 (s, 9)	176.0, 130.2, 126.7, 38.4, 28.2, 24.7, 24.0, 21.3

Table VIII (*Continued*)

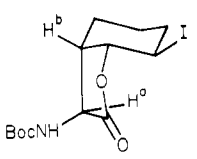
compd	yield, %	mp (recrystallization solvent) or bp (pressure, torr), °C	IR, cm^{-1}	^1H NMR, δ (*J*, Hz)	^{13}C NMR,[e] δ
15e	64	189-191 (acetone)	3400, 2925, 1730, 1650	7.87-7.18 (m, 6), 6.82-6.64 (br m, 2), 2.86 (m, 1), 2.0-1.3 (m, 6), 1.6 (s, 3)	169.9, 168.4, 130.7, 129.3, 127.6, 126.4, 125.3, 41.7, 24.1, 23.4, 21.2, 16.9, [128.7, 40.8]

[a] Noncrystalline compounds purified by preparative TLC; satisfactory analytical data were reported for all compounds. [b] Exact mass reported for $[M - CH_2{=}C(CH_3)_2]$ peak. [c] CD_3OD as the solvent. [d] Analysis performed on the methyl ester. [e] Signals due to the minor diastereomer are given in brackets.

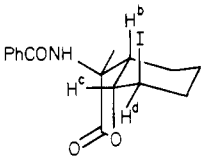
already discussed, we assign the *RS,SR* stereochemistry to the major product obtained from **12g** as well.

Rearrangement of Cyclic Allylic Esters. α-(2-Cycloalkenyl) α-amino acids have recently drawn attention because of their occurrence as unusual amino acids[3] and their ability to function as bacterial growth inhibitors.[2] The Claisen rearrangement has obvious potential for their stereocontrolled synthesis, and we have in fact reported our initial work in this regard in preliminary form.[18] As indicated in Table VI, for the glycine derivatives, the *N*-Boc protecting group offers obvious advantages over the *N*-benzoyl group in terms of yield and stereoselectivity. As we indicated previously, the *RS,SR* selectivity in this series arises from a preference for the boatlike transition state on rearrangement of the enol ethers derived from the expected *E* enolates. The surprisingly low selectivity seen for the hippuryl cases (Table VI, entries 1 and 3) could conceivably reflect the intermediacy of an easily epimerized oxazolone, as was actually isolated from ester–enolate rearrangement of *trans*-crotyl *N*-benzoylvalinate (Table III, entry 5), although we saw no other evidence for its presence in this instance.

The structure proofs for these isomers relied on correlation with the known *N*-acetyl derivatives[2,18] and on conversion of **15d**-*e* to the iodo lactone **16**.[18]



16 (J_{ab} = 12.7 Hz)



17 ($J_{bc} = J_{cd} \leq 4$ Hz)

In contrast to the glycine series, the *N*-benzoyl protecting group is of necessity for rearrangement of the 2-cyclohexenyl alaninates. Furthermore, in this case the oxazole rearrangement method of Steglich and co-workers[6] is clearly superior, affording an 87% yield of a single diastereomer (Table VI, entry 6), whereas the ester–enolate procedure gives a 2:1 mixture (entry 5). Although we were able to iodolactonize this material using the traditional, alkaline, two-phase system,[19] only the major diastereomer cyclizes. We assign structure 17 to this material in analogy with our other results, although no rigorous spectroscopic assignment could be made in the absence of the isomeric lactone.

Conclusion

The Ireland–Claisen rearrangement is clearly a versatile method for the diastereoselective synthesis of both α-substituted and α-unsubstituted γ,δ-unsaturated α-amino acids. Although in some instances the enolate method is surpassed by the complementary oxazole-mediated procedure, it has the advantage of being applicable when an easily cleaved N-protecting group is required or when a glycyl ester is the substrate.

Although the stereochemistry of some of the products was not rigorously proven, all of our observations are consistent with preferential formation of the *E* enolate, in which the anionic enolate substituents are cis to each other. This stereoelectronic preference, which extends to the enediolates from α-hydroxy esters as well (see following paper), appears to override other influences, although some variation in stereoselectivity is seen with different solvents and substituents.

Experimental Section

General Methods. Unless otherwise indicated, IR spectra were obtained in $CHCl_3$. NMR spectra were obtained with a Varian EM-390 (^1H only), with a Nicolet TT-23 (^{13}C only), or with a UCB-180, -200, or -250 spectrometer (multinuclear FT instruments equipped with Bruker (180) or Cryomagnets superconducting magnets and Nicolet computers). Unless otherwise indicated, the NMR solvent was $CDCl_3$, and chemical shifts are reported in parts per million on the δ scale, referenced to internal Me_4Si as 0 ppm (for ^1H spectra) or to the $CDCl_3$ solvent as 77.0 ppm (for ^{13}C spectra). ^1H NMR data are presented as chemical shift (multiplicity, number of protons, coupling constants in hertz); only the chemical shifts are presented for the ^{13}C data. The boiling point (pressure) data given are the oven temperature (system pressure) for bulb-to-bulb distillation. Analyses were performed by the Microanalytical Laboratory of the College of Chemistry, University of California, Berkeley.

General Procedure for Synthesis of Starting Materials: (*E*)-2-Butenyl 2-[[(1,1-Dimethylethoxy)carbonyl]amino]-acetate (1a). A mixture of 1.34 g (18 mmol) of *trans*-crotyl alcohol, 3.15 g (18 mmol) of *N*-(*tert*-butoxycarbonyl)glycine, 3.71 g (18 mmol) of dicyclohexylcarbodiimide, and a catalytic amount (ca. 10 mg) of 4-(dimethylamino)pyridine in 30 mL of dry ether was stirred for 18 h at 21 °C. After removal of the precipitated dicyclohexylurea by filtration, the solution was washed with two 5-mL portions of saturated $NaHCO_3$, dried (K_2CO_3), and concentrated at reduced pressure. The crude product was purified by bulb-to-bulb distillation [100 °C (0.3 torr)], affording 3.16 g (77% yield) of ester **1a**. See Table VII for physical data for **1a** and other starting materials.

General Procedure for Ester–Enolate Claisen Rearrangements. 3-Methyl-2-[[(1,1-dimethylethoxy)carbonyl]-amino]-4-pentenoic Acid (2a). To a solution of 0.38 mL (1.98 mmol) of isopropylcyclohexylamine in 6.5 mL of dry THF at 0 °C was added 0.80 mL of 2.4 M *n*-butyllithium in hexane (1.93 mmol). After 10 min, the solution was cooled to −75 °C, and 211 mg (0.92 mmol) of ester **1a** in 1 mL of THF was added over ca. 40 s. After stirring for 10 min, 0.25 mL (1.93 mmol) of trimethylsilyl chloride was added, and the solution was stirred for 5 min before being allowed to warm to 21 °C over a 15-min period. The mixture was then kept at 55–60 °C for 1 h, cooled, and diluted with 5 mL of methanol to hydrolyze the silyl esters (5 min). The solution was diluted with ether and extracted with four 3-mL

(18) P. A. Bartlett and J. F. Barstow, *Tetrahedron Lett.*, 623 (1982).
(19) E. E. van Tamelen and M. Shamma, *J. Am. Chem. Soc.*, 76, 2315 (1954).

Table IX. Physical and Spectral Data for Oxazolone Intermediates[e]

compd	yield, % oxazolone	yield, % acid[a]	IR, cm^{-1}	^1H NMR, δ (J, Hz)	^{13}C NMR,[f] δ
4[b]	32		2950, 1810–1700, 1640	8.20–7.20 (m, 6), 6.15–5.50 (m, 1), 5.40–4.90 (m, 2), 2.93 (m, 1), 1.30 (d, 3, J = 7); signals due to isomer 1.16 (d, J = 7)	137.1, 132.7, 128.7, 127.9, 127.6, 117.2, 70.5, 70.4, 40.4, 39.8 [138.0, 131.7, 116.6]
6	85	95	3000, 1810, 1650, 1610, 1580	8.00–7.30 (m, 6), 6.00–4.80 (m, 3), 2.54 (dq, 1, J = 8, 8), 1.42 (s, 3), 1.10 (d, 3, J = 8); signals due to minor isomer 0.95 (d, J = 8)	137.6, 132.4, 128.6, 127.8, 117.4, 45.2, 22.1, 14.9 [137.3, 21.8, 14.3]
7	43		3000, 1825, 1810, 1660	8.1–7.9 (m, 2), 7.7–7.4 (m, 3), 5.91–5.74 (m, 1), 5.25–5.05 (m, 2), 2.97–2.78 (m, 1), 2.38–1.96 (qq, 1, J = 6, 6), 1.07–0.93 (m, 9)	179.1, 160.1, 137.2, 132.4, 128.6, 127.8, 125.8, 117.1, 79.2, 41.9, 32.1, 32.0, 16.5, 16.3, 15.0 [159.9, 137.7, 41.5, 16.9, 15.8, 14.6]
c	87	43	2950, 1815, 1650, 1610	8.00–7.20 (m, 5), 5.72 (m, 1), 5.40 (m, 1), 2.55 (br m, 1), 2.15–1.2 (m, 6), 1.50 (s, 3)	132.3, 131.1, 128.6, 127.8, 124.8, 43.1, 24.8, 23.5, 21.5, 20.9
d	87	90	3000, 2950, 1820, 1660, 1460	8.00–7.80 (m, 2), 7.50–7.20 (m, 3), 6.07–5.67 (m, 1), 5.30–4.80 (m, 3), 2.10–1.10 (m, 2), 1.60 (s, 2), 1.52 (m, 2), 1.42 (s, 9), 1.23 (s, 3)	140.7, 132.4, 128.7, 127.9, 124.4, 116.3, 74.5, 46.4, 34.5, 25.5, 22.9, 19.8, 17.5, 15.4

[a] Acid derived from oxazolone by alkaline hydrolysis. [b] An analytically pure sample of 4 could not be obtained due to instability; no molecular ion was observed in the mass spectrum. [c] 4-(2-Cyclohexenyl)-4-methyl-2-phenyl-5(4*H*)-oxazolone. [d] 4-(1-Ethenyl-1,5-dimethyl-4-hexenyl)-4-methyl-2-phenyl-5(4*H*)-oxazolone. [e] Satisfactory analytical data for the compounds (except as noted) were submitted for review. [f] Signals due to the minor isomer are given in brackets.

portions of 2 N NaOH; the combined aqueous layer was then acidified and extracted with three 3-mL portions of $CHCl_3$. The organic layer was dried ($MgSO_4$), filtered, and evaporated at reduced pressure to provide 137 mg (65% yield) of rearranged acid **2a** as a 9:1 mixture of diastereomers. See Table VIII for physical data for this and other ester–enolate rearrangement products. In subsequent experiments, lithium diisopropylamide was employed in place of lithium isopropylcyclohexylamide with no significant difference.

General Procedure for Rearrangement via Oxazoles. 4-Methyl-4-(1-methyl-2-propenyl)-2-phenyl-5(4*H*)-oxazolone (6). To a solution of 200 mg (0.81 mmol) of *trans*-crotyl benzoylalaninate 0.30 mL (2.2 mmol) of triethylamine, and 0.28 mL (1.82 mmol) of CCl_4 in 1.5 mL of acetonitrile was added 424 mg (1.62 mmol) of triphenylphosphine. The resulting mixture was stirred at 21 °C for 12 h, becoming dark brown and giving a heavy precipitate. After concentration at reduced pressure, the mixture was applied to a preparative TLC plate (750 mg/20 cm × 20 cm × 2 mm silica gel plate), which was developed with ether. From the band at the solvent front, ether eluted 157 mg (85% yield) of the oxazolone **6** (see Table IX for physical data for this and other oxazolones). This material was hydrolyzed in 1:1 2 N NaOH/methanol for 1.5 h at 55 °C. Acidification, extraction with $CHCl_3$,drying ($MgSO_4$), and evaporation afforded 161 mg (95% yield from **6**) of the acid **9b**. The yields of acids obtained by hydrolysis of the other oxazolones are given in Table IX.

Methyl (2*RS*,3*SR*)-2,3-Dimethyl-2-phthalimido-4-pentenoate (10-*t*). A 205-mg (0.843 mmol) sample of the Boc-protected acid **9a** was dissolved in 1.5 mL of trifluoroacetic acid and kept at 21 °C for 5 min. Evaporation gave the trifluoroacetate salt of the amino acid: ^1H NMR (D_2O) δ 5.75–5.5 (m, 1), 5.2–5.1 (m, 2), 2.6 (dq, 1, J = 7, 7), 1.45 (s, 3), 1.0 (d, 3, J = 6) (minor isomer 1.42 (s)); ^{13}C NMR (D_2O) δ 135.4, 120.5, 43.9, 20.3, 18.8, 14.3 (minor isomer 136.0, 120.0, 43.6, 13.5) (carbonyls not seen). A 630-mg (2.47 mmol) sample of similarly derived material was heated at reflux in 20 mL of toluene with 480 mg (3.21 mmol) of phthalic anhydride and 1.0 mL (7.4 mmol) of triethylamine for 12 h. After evaporation, the residue was dissolved in ether and extracted with three 5-mL portions of saturated $NaHCO_3$. The combined aqueous layers were acidified and extracted four times with 5 mL of $CHCl_3$, and the organic layer was dried ($MgSO_4$), filtered, and evaporated to give 670 mg (100% yield) of phthalimide **2e-*t***: IR 3000, 1715 cm^{-1}; ^1H NMR δ 7.9–7.7 (m, 4), 5.92–5.77 (m, 1), 5.11–4.9 (m, 2), 3.38 (m, 1, J = 6), 1.95 (s, 3), 1.15 (d, 3, J = 6.5) [additional resonances for minor isomer 6.15–6.0 (m), 1.25 (d, J = 6.5)]; ^{13}C NMR δ 168.2, 138.8, 133.9, 131.2, 123.0, 116.2, 76.3, 43.3, 21.1, 15.6 (additional resonances for minor isomer 168.3, 138.4, 133.8, 122.9, 116.5, 43.0, 19.4, 16.2). A solution of 120 mg (0.44 mmol) of this material in 2 mL of methanol was treated with excess diazomethane and evaporated to give methyl ester **10**. The major isomer [(*RS*,*SR*)-**10-*t***] was isolated in pure form by preparative HPLC (5% ethyl acetate/hexane on silica gel): IR 2950, 1720, 1600 cm^{-1}; ^1H NMR δ 7.9–7.7 (m, 4), 6.14–5.98 (m, 1), 5.1–4.92 (m, 2), 3.78 (s, 3), 3.34 (dq, 1, J = 7, 7), 1.87 (s, 3), 1.13 (d, 6) [the minor (*RR*,*SS*) isomer shows resonances at δ 5.88–5.73 (m) and 1.23 (d, J = 6)]. Anal. Calcd for $C_{16}H_{19}NO_3$: C, 70.31; H, 7.01; N, 5.12. Found: C, 70.05; H, 6.97; N, 5.11.

(2*RS*,3*RS*,4*RS*)-3,4-Dihydro-2-(iodomethyl)-3,4-dimethyl-4-phthalimidofuran-5(2*H*)-one (11-*t*). A mixture of 14 mg (0.049 mmol) of **10-*t*** and 23 mg (0.089 mmol) of iodine in 0.5 mL of acetonitrile was stirred at 21 °C in the dark for 1 day, diluted with ether, washed with saturated $Na_2S_2O_3$, water, and brine, dried ($MgSO_4$), filtered, and evaporated to give 10 mg (52% yield) of iodo lactone **11-*t*** as an oil: IR 2960, 2920, 1780, 1720 cm^{-1}; ^1H NMR δ 7.9–7.7 (m, 4), 4.13 (ddd, 1, J = 4.6, 6.2, 9.4), 3.54 (dd, 1, J = 4.6, 11.1), 3.45 (dd, 1, J = 6.3, 11.2), 2.74 (dq, 1, J = 9.5, 6.9), 1.96 (s, 3), 1.27 (d, 3, J = 7.0); ^{13}C NMR δ 174.5, 168.4, 134.4, 123.4, 81.5, 62.4, 45.1, 23.8, 11.5. When a mixture of **10-*t*** and **10-*e*** was treated in the same manner, additional resonances for **11-*t*** were discernible: ^1H NMR δ 3.64 (dd, 1, J = 4.2, 11.4), 3.38 (dd, 1, J = 4.0, 11.4), 1.05 (d, 3, J = 7.0); ^{13}C NMR δ 134.6, 123.5, 81.6, 47.3, 12.2. The analytical sample was purifed from this mixture by preparative TLC [10:10:3 hexane/$CHCl_3$/ethyl acetate (silica gel)]. Anal. Calcd for $C_{15}H_{14}NO_3I$: C, 45.13; H, 3.54; N, 3.51; I, 31.79. Found: C, 45.36; H, 3.69; N, 3.51; I, 31.5.

Methyl 2-(Benzoylamino)-3-phenyl-4-pentenoate. Diazomethane esterification of **12b**, the material obtained on rearrangement of *trans*-cinnamyl hippurate, afforded the *RS*,*RS* diastereomer of the title compound: ^1H NMR δ 7.75–7.30 (m, 10), 6.40 (br d, 1, J = 8), 6.30–6.05 (m, 3), 5.35–5.15 (m, 2), 3.95 (m, 1), 3.70 (s, 3). When the product from rearrangement of the *Z*

ester is esterified, additional resonances attributable to the *RR,SS* diastereomer are observed: δ 6.65 (br d, J = 8), 3.8 (m), 3.56 (s).

(3*RS*,3a*RS*,7*SR*,7a*SR*)-Hexahydro-7-iodo-3-[[(1,1-dimethylethoxy)carbonyl]amino]benzofuran-2(3*H*)-one (16). A mixture of 100 mg (0.39 mmol) of cyclohexenylglycine derivative **15d**-*e*, 109 mg (0.43 mmol) of iodine, and 143 mg (0.86 mmol) of KI in 3 mL of saturated $NaHCO_3$ and 3 mL of ether was stirred for 12 h at 21 °C in the dark. The layers were separated, and the organic phase was washed with saturated $Na_2S_2O_3$, water, and brine, dried ($MgSO_4$), filtered, and evaporated to give 115 mg (78% yield) of iodo lactone **16**. A sample was purified for analysis by preparative TLC: IR 3475, 2950, 1790, 1710, 1510 cm^{-1}; ^1H NMR δ 5.1 (br d, 1, J = 8.5), 4.69 (dd, 1, J = 7.5, 9.7), 4.52 (dd, 1, J = 12, 8.5), 3.96 (ddd, J = 4, 10, 13), 2.65–2.4 (m, 2), 2.18–1.4 (m, 6), 1.48 (s, 9); ^{13}C NMR δ 140.4, 83.4, 50.4, 43.4, 36.6, 28.2, 27.0, 23.3, 22.4. Anal. Calcd for $C_{13}H_{19}NO_4I$: C, 40.96; H, 5.29; N, 3.67; I, 33.29. Found: C, 40.68; H, 5.31; N, 3.50; I, 33.0.

(3*RS*,3a*RS*,7*SR*,7a*SR*)-3-(Benzoylamino)hexahydro-7-iodo-3-methylbenzofuran-2(3*H*)-one (17). A mixture of 250 mg (0.92 mmol) of cyclohexenylalanine derivative **15e**-*e*, 255 mg (1.0 mmol) of iodine, and 1 g (6.1 mmol) of KI in 5 mL of saturated $NaHCO_3$ and 10 mL of ether was stirred for 30 min at 21 °C in the dark. A workup similar to that described above afforded 80 mg (22% yield) of iodo lactone **17**. Recrystallization from benzene gave analytically pure material: mp 174.5–176 °C; IR 3440, 2950, 1780, 1660, 1600, 1500 cm^{-1}; ^1H NMR δ 7.8–7.6 (m, 2), 7.6–7.2 (m, 3), 6.58 (br s, 1), 4.97 (br s, 1, $\Delta\nu_{1/2}$ < 10 Hz), 4.87 (br s, 1, $\Delta\nu_{1/2}$ < 10 Hz), 3.41 (ddd, 1, J = 3.8, 6.0, 12.3), 2.0–1.25 (m, 7), 1.67 (s, 3); ^{13}C NMR δ 133.5, 131.9, 128.6, 80.8, 63.3, 41.3, 29.1, 26.6, 22.6, 19.5, 19.4. Anal. Calcd for $C_{16}H_{18}NO_3I$: C, 48.14; H, 4.54; N, 3.51; I, 31.79. Found: C, 48.05; H, 4.57; N, 3.42; I, 31.66.

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Registry No. 1a, 82634-92-2; **1b**, 82706-21-6; **1c**, 82706-22-7; **1d**, 82706-23-8; **1e**, 82706-24-9; **1f**, 82706-25-0; **2a**-t, 82634-94-4; **2a**-e, 82634-95-5; **2b**-t, 82706-26-1; **2b**-e, 82706-72-7; **2c**-t, 82706-27-2; **2c**-e, 82706-73-8; **2d**-t, 82706-28-3; **2d**-e, 82706-74-9; **2e**-t, 82706-29-4; **2e**-e, 82706-69-2; **4**, 82706-30-7; **6**, 82706-31-8; **7**, 82706-32-9; **8a**, 82706-33-0; **8b**, 82706-34-1; **8c**, 82706-35-2; **8d**, 82706-36-3; **9a**-t, 82706-37-4; unblocked **9a**-t·TFA, 82706-66-9; **9a**-e, 82706-75-0; unblocked **9a**-e·TFA, 82706-68-1; (*RS,SR*)-**9b** (R^1 = PhCO, H; R^2 = R^3 = Me; R^4 = H), 82706-38-5; (*RR,SS*)-**9b** (R^1 = PhCO, H; R^2 = R^3 = Me; R^4 = H), 82706-39-6; (*RS,SR*)-**9b** (R^1 = phthaloyl; R^2 = R^3 = Me; R^4 = H), 82706-40-9; (*RR,SS*)-9b (R^1 = phthaloyl; R^2 = R^3 = Me; R^4 = H), 82706-41-0; (*RS,SR*)-**10**-t, 82706-42-1; (*RR,SS*)-**10**-e, 82706-70-5; **11**-t, 82706-43-2; **12a**, 82634-92-2; **12b**, 82706-44-3; **12c**, 82740-44-1; **12d**, 53777-91-6; **12e**, 82731-47-3; **12f**, 82706-45-4; **12g**, 82706-46-5; **13b**, 82706-47-6; **13d**, 82706-48-7; **13e**, 82706-49-8; **13f**, 82706-50-1; **13g**, 82706-51-2; **14a**, 82300-72-9; **14b**, 82706-52-3; **14c**, 82300-74-1; **14d**, 82706-53-4; **14e**, 82706-54-5; **14f**, 58400-62-7; **15a**, 82706-55-6; **15b**, 82706-56-7; **15c**, 82706-57-8; **15d**-e, 62090-89-5; **15d**-t, 82706-71-6; **16**, 82706-58-9; **17**, 82706-59-0; *N*-(*tert*-butoxycarbonyl)glycine, 4530-20-5; *trans*-crotyl *N*-benzoylalaninate, 82706-64-7; (*RS,RS*)-methyl 2-benzoylamino-3-phenyl-4-pentenoate, 82706-60-3; methyl (*RR,SS*)-2-benzoylamino-3-phenyl-4-pentenoate, 82706-61-4; 4-(2-cyclohexenyl)-4-methyl-2-phenyl-5(4*H*)-oxazolone, 82706-63-6; 4-(1-ethenyl)-1,5-dimethyl-4-hexenyl)-4-methyl-2-phenyl-5(4*H*)-oxazolone, 82706-62-5.

Ester-Enolate Claisen Rearrangement of Lactic Acid Derivatives

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The ester–enolate Claisen rearrangement of a number of allylic esters of α-hydroxy acids and O-protected derivatives was studied. Crotyl lactate (**1b**), for example, is converted to the enediolate, silylated, and rearranged to afford the *RS,SR* and *RR,SS* diastereomers **2b** and **3b** in 30% yield and a ratio of 4:1; rearrangement of the benzyl ether of crotyl lactate shows a similar stereospecificity but higher yield. The enediolate derived from crotyl mandelate is rearranged without silylation to provide the phenyl analogues **2c** and **3c** in 59% yield and 12:1 stereoselectivity. Only modest variation in stereoselectivity is seen on varying the solvent or conditions. On the assumption that the Claisen rearrangements proceed via the chairlike transition state, the *E* stereochemistry is shown to be the preferred geometry of the alkoxy enediolate and dialkoxy enolate intermediates.

The preceding paper[1] presents the results of our study of the Ireland–Claisen rearrangement[2] as a method for the stereocontrolled construction of α-amino acid derivatives. In this report, we discuss its extension to the synthesis of α-hydroxy and α-alkoxy acids. Although there have been isolated examples in cyclic systems of the application of the ester–enolate rearrangement procedure to allylic esters of α-alkoxy carboxylic acids,[3] no systematic study of this variant has been undertaken. Nor has the possibility of applying the procedure to the unprotected α-hydroxy analogues been reported.[4] For these reasons, we studied the rearrangement of a variety of acyclic O-protected and -unprotected allylic lactate, glycolate, and mandelate esters. Although our results indicate that the utility of the ester–enolate Claisen rearrangement of such derivatives is often limited by either modest stereoselectivity or low yields, we were able to deduce the preferred stereochemistry of dialkoxy enolate or alkoxy enediolate formation for a variety of derivatives.

Rearrangement Yield and Stereoselectivity

The ester–enolate Claisen rearrangement was studied most thoroughly with use of the crotyl esters of lactic acid (**1b**) and its *O*-benzyl derivative (**1a**). With use of lithium isopropylcyclohexylamide (LICA) as the base,[5,6] these es-

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(4) While this work was in progress, Professor D. E. Bergbreiter and Professor M. Newcomb, Department of Chemistry, Texas A & M University, informed us of their independent observation of the Claisen rearrangement of the enediolate of crotyl mandelate.

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