A Diastereoselective Route to Substituted β-Amino Acids using Enolate Claisen Rearrangements

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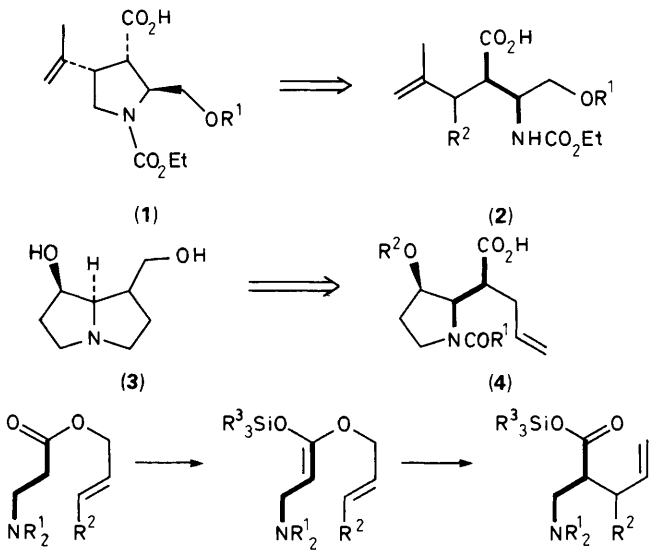
Ireland-type enolate Claisen rearrangements of esters derived from allylic alcohols and *N*-alkoxycarbonyl-β-alanines lead to good yields of α-allyl-β-amino acids with generally high stereoselectivities.

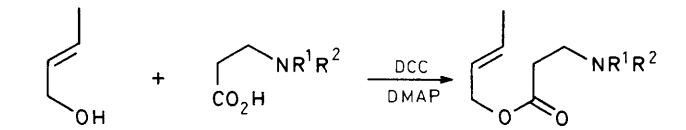
Our recent enantiospecific synthesis of (−)-kainic acid[1] proceeded *via* a key intermediate (**1**) obtained using an alicyclic enolate Claisen rearrangement[2] of an appropriate aza-lactone. It occurred to us that a possible alternative strategy for the elaboration of this intermediate could involve the formation of a suitable α-allyl-β-amino acid derivative (**2**). We also noted that a range of bicyclic pyrrolidine [*e.g.* (**3**)] and indolizidine systems could potentially be derived from related precursors [*e.g.* (**4**)] which already contain a pyrrolidine ring. It appeared that both these types of intermediate could be obtained from enolate Claisen rearrangements of allyl esters of suitably protected β-amino acids (Scheme 1) which should in turn be readily available using a straightforward esterification protocol. Herein, we report that such rearrangements are indeed viable and provide a brief and stereoselective route to substituted β-amino acids of a type which are amenable to a wide range of subsequent modifications.

Our first series of experiments were carried out using a group of allyl esters (**7**) easily obtained from (*E*)-crotyl alcohol (**5**) and the protected β-amino acids (**6**) using the *N,N*-dicyclohexyl carbodiimide–4-dimethylaminopyridine (DCC–DMAP) coupling method.[3] Enolisation and *O*-silylation of these esters (**7**) were effected by brief treatment with lithium di-isopropylamide (LDA) in tetrahydrofuran (THF) at −78 °C, followed by the addition of trimethylsilyl chloride (TMSCl); the reaction mixtures were then allowed to warm to ambient temperature and finally refluxed in order to effect the desired Claisen rearrangement (Scheme 1).[4] The first two esters examined gave disappointing results; in the case of the benzyloxycarbonyl derivative (**7a**), small yields of the desired products were isolated along with other materials which appeared to arise from metallation at the benzylic position whereas the *N*-phthalimido derivative (**7b**) gave virtually no α-allyl-β-amino acid product, the intermediate enolate apparently decomposing *via* a β-elimination pathway. However, we were pleased to find that sequential treatment of the *N*-methoxycarbonyl analogue (**7c**) with LDA (3 equiv.) and trimethylsilyl chloride (3 equiv.) in THF at −78 °C followed by reflux for 4 h and finally hydrolysis of the silyl esters produced using wet methanol gave, in 71% yield, a 79 : 21 stereochemical mixture of the desired product which was fully characterised as the methyl esters (**8**), after esterification using ethereal diazomethane. The diastereoisomeric ratios were determined in this case and in all subsequent examples by careful integration of the methyl ester resonances in the 400 MHz NMR spectra of the products. The corresponding *N*-BOC allyl ester (**7d**) (BOC = t-butoxycarbonyl) also underwent the rearrangement successfully under the same conditions to provide the expected α-allyl-β-amino acid ester in 88% isolated yield after esterification, as an 86 : 14 mixture of diastereoisomers (entry 1, Table 1). Subsequent experiments were conducted with such *N*-BOC derivatives as this group is much easier to remove. Finally, these preliminary trials were completed by the observation that the *N,N*-dimethylamino ester (**7e**) could also be rearranged in this way to give a 70 : 30 mixture of diastereoisomers (**9**) in 70% yield. However, as the dimethylamino function is much less useful in terms of subsequent manipulations (elimination to the corresponding α-methylene-ester being the most viable),[5] the use of this group was not further investigated. Such a Claisen rearrangement of an allyl ester of an *N,N*-dialkylamino-β-amino acid has literature precedent as a key step in an elegant synthesis of the sesquiterpene lactone frullanolide.[6]

A number of alternative conditions were also examined using ester (**7d**), but in all cases these resulted in either lower yields and/or reduced stereoselectivities. Trapping the enolate



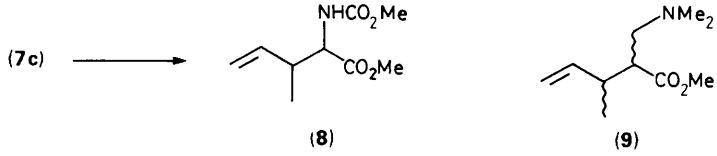
Scheme 1



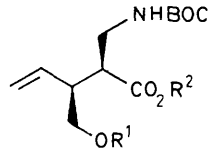
(**5**) (**6**)

(**7**)**a**; $R^1 = CO_2Bz$, $R^2 = H$
b; $R^1 = R^2 =$ phthalimido
c; $R^1 = CO_2Me$, $R^2 = H$
d; $R^1 = CO_2Bu^t$, $R^2 = H$
e; $R^1 = R^2 = Me$

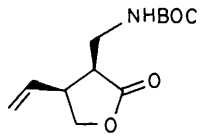
Bz = benzyl



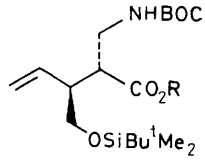
(**8**) (**9**)



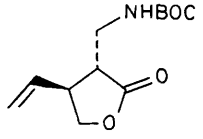
(10) **a**; $R^1 = OSiBu^tMe_2$, $R^2 = H$
b; $R^1 = R^2 = H$
c; $R^1 = OSiBu^tMe_2$, $R^2 = Me$



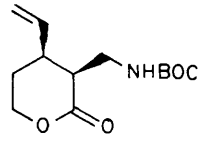
(11) $J_{2,3}$ = 8.4 Hz
$J_{3,4\alpha}$ = 3.2 Hz
$J_{3,4\beta}$ = 5.8 Hz



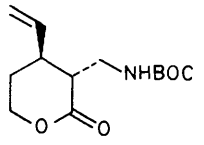
(12) **a**; R = H
b; R = Me



(13) $J_{2,3}$ = 11.4 Hz
$J_{3,4\alpha}$ = 8.2 Hz
$J_{3,4\beta}$ = 10.5 Hz

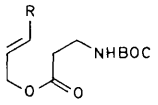
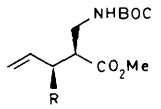
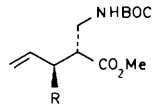
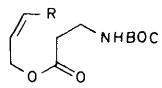


(14)



(15)

Table 1. Results of Claisen rearrangement using various substrates.

Entry	Substrate	Diastereoisomers	
			
1	R = Me	86:14	(88%)[a]
2	R = Ph	55:45	(31%)
3	R = Pr^i	80:20	(85%)
4	R = CH_2OTBDMS	92: 8	(77%)
5	R = $(CH_2)_2$OTBDMS	93: 7	(75%)
			
6	R = Me	12:88	(73%)
7	R = Ph	77:23	(40%)
8	R = Pr^i	81:19	(81%)
9	R = CH_2OTBDMS	6:94	(68%)
10	R = $(CH_2)_2$OTBDMS	15:85	(70%)
11			
		(*E*) only	(83%)

[a] Yields in parentheses refer to pure products which showed satisfactory microanalytical and spectroscopic data.

with t-butyldimethylsilyl chloride [which required the addition of hexamethylphosphoramide (HMPA)] gave only a 2 : 1 ratio of diastereoisomers as did treating the ester with a pre-mixed solution of LDA–TMSCl. Slightly higher stereoselectivities were obtained under the usual conditions at higher temperatures but the yields were considerably reduced (*e.g.* 91 : 9 mix in 25% yield at −20 °C). The use of potassium bis(trimethylsilyl)amide as base resulted in high yields (80%) but with virtually no stereoselectivity.

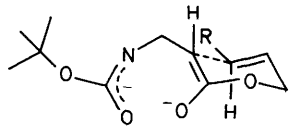


Figure 1

We next proceeded to examine the scope of the rearrangement and the results are presented in Table 1. The stereochemical assignments were made on the basis of comparative NMR data and by lactonisations of the hydroxymethyl derivatives (entries 4 and 9) as described below. The likely involvement of a single predominant transition state in most cases is indicated by the direct relationship between the allylic alcohol geometry in the starting ester and the nature of the major diastereoisomer in the products. An exception to this is when the allylic alcohol residue contains a branch α to the six-centred transition state (entries 2, 3, 7, and 8); in all such examples, the 2,3-*syn* isomer predominates (*vide infra*). The low yields obtained from the cinnamyl derivatives (entries 2 and 7) appeared to be due to rupture of the ester linkage during enolisation. A final stereospecific example (entry 11) indicates that the substituent methyl group adopts only a pseudo-equatorial position in the transition state(s).

The stereochemical assignments were made largely on the basis of conversions of the silyloxymethyl products (entries 4 and 9) into the corresponding butyrolactones. Thus, the initial product (**10a**) obtained from the (*E*)-allyl ester (entry 4) as a 92 : 8 mixture of diastereoisomers was desilylated [tetra-n-butylammonium fluoride (TBAF), THF, 0 °C] to give the hydroxy acid (**10b**) which was then cyclised using 2-chloro-1-methylpyridinium iodide (CH_2Cl_2, Et_3N, 20 °C)[7] to give lactone (**11**) (69%), after separation by column chromatography, which was assigned the *cis*-stereochemistry shown both on the basis of proton NMR coupling constants [see data associated with formula (**11**)] and by the contrasting behaviour of the corresponding 2,3-*anti*-isomer (**12a**) derived from the (*Z*)-allylic alcohol (entry 9). Treatment of this latter product with TBAF or with HCl (2 M) led to the direct formation of the *trans*-butyrolactone (**13**) (85% after chromatography); all attempts to isolate the intermediate hydroxy acid were unsuccessful. Similarly, desilylation of the ester (**12b**) also led directly to lactone (**13**). In contrast, brief exposure of the 2,3-*syn* ester (**10c**) to TBAF gave an isolable hydroxy ester while prolonged reaction with TBAF gave the more thermodynamically stable *trans*-lactone (**13**), presumably by epimerisation α to the carbonyl function. These assignments were confirmed by the magnitude of the respective proton coupling constants; it is well established[5,8] that such *trans*-lactones exhibit $J_{2,3}$ values in the range 10—12 Hz whereas the corresponding *cis*-lactones show $J_{2,3}$ values of *ca.* 8 Hz. The remaining NMR data are also fully consistent with these assignments. The homologous products (entries 5 and 10) were similarly converted into the valerolactones (**14**) and (**15**).

The foregoing results are consistent with the predominant involvement of a chair-like transition state (Figure 1) in which the enolate oxygen and the ionised *N*-BOC function are *cis* to each other, a configuration possibly assisted by chelation. The similar stereochemical results obtained when R = Ph or Pr^i (entries 2, 3, 7 and 8) could imply that in the (*Z*)-isomers of these substrates, the chair conformation is rather crowded and that the rearrangements proceed instead *via* a boat-like transition state.

The present study has established the viability of this approach to β-amino acid derivatives and work is in progress to apply the methodology to a variety of natural product targets.

We are grateful to the S.E.R.C. for financial support and to Paul Fish and Mark Tankard for carrying out some preliminary studies.

Received, 10th August 1989; Com. 9/03442K

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