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Studies on the Alkylation of Dipeptide Substrates

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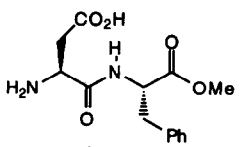
Abstract: Alkylations of anions derived from dipeptides with a glycine at the *C*-terminus have been investigated. A hydrocarbon sedition in the *N*-terminal residue does impart some asymmetric induction. The use of a chiral ester derivative provides the potential for double asymmetric induction and good selectivity. With an aspartyl residue at the *N*-terminus, problems were encountered due to competing side reactions. The use of an azetidinone could circumvent some of these, but the observed induction was not high.

α-Amino acids have been prepared by a wide variety of methods.[1] Alkylation of a glycine derivative is one such general approach. Treatment of glycine itself in THF with an excess of butyl lithium followed by reaction with benzyl bromide gave, albeit in low yield and with a number of other products, a detectable amount of phenylalanine.[2] To observe asymmetric induction for the alkylation of an amino acid derivative, a variety of chiral auxiliaries have been employed both within the substrate and as part of the base system.[3,4] In addition to glycine alkylations, functionalisation of a carbon framework by the addition of an amino or carboxylate group can be used to access amino acid derivatives.[1,5] As glycine is a cheap, readily available starting material, our efforts have concentrated around the introduction of the side chain as an electrophilic unit.[6] How to effect alkylation of dipeptides at the *C*-terminal residue through the use of a chiral imine derivative,[3] such as those used to prepare phenylalanine, is difficult to envisage. We chose, therefore, to investigate the use of chiral esters.[7,8] This work was performed with the knowledge that the outcome of these types of alkylation reactions can be affected greatly by the choice of reaction conditions, and that the literature is somewhat confused.[9] Our primary target for these studies was the commercially lucrative, sweet dipeptide, aspartylphenylalanine, methyl ester (**1**).



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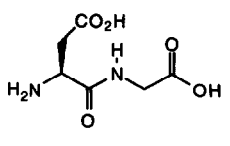

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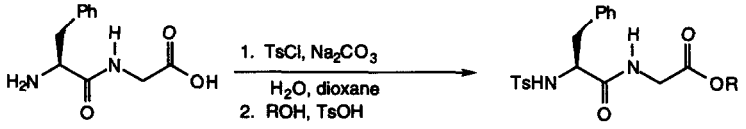
The studies described in this paper are based on alkylations of simple amino acid derivatives and the observation by Seebach that complex peptides can undergo alkylation reactions with

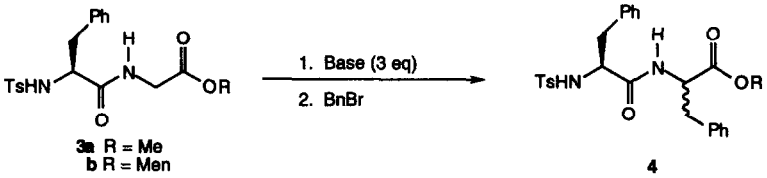
remarkable regio- and enantioselectivity at glycine residues.[10] Our hypothesis was that if aspartylglycine (**2**) was used as the substrate, asymmetric induction caused by the aspartic acid sidechain might be observed, particularly if complexation of the carboxylate group by a metal ion occurred. Further, if the induction was not high, use of a chiral ester might allow for double asymmetric induction. We followed two approaches: The first was to investigate the stereochemistry of the alkylation with a dipeptide whose *N*-terminal residue's sidechain could not participate in complex formation with a metal ion, and to see if double asymmetric induction could be observed if a chiral ester was also present. The second approach was to use a dipeptide where the sidechain on the chiral *N*-terminal amino acid could form a complex with the ester enolate. Information obtained from the first approach would be instrumental in the experimental design that might allow the use of the unprotected dipeptide (**2**).

The dipeptide phenylalanylglycine (**3**) was chosen as the model compound for the first approach. To alleviate any problems surrounding deprotonation at the *N*-terminus or amide enolate geometry issues, and to ensure retention of configuration at the chiral centre, tosyl was chosen as the form of protection for this end of the molecule (Scheme. 1).[11]



Scheme 1.

It was determined that three equivalents of base were necessary to obtain good yields of alkylated products. For the purposes of this study, benzyl bromide was taken as the model electrophile. Representative results of the reaction (Scheme 2) are summarised in Table 1.



Scheme 2.

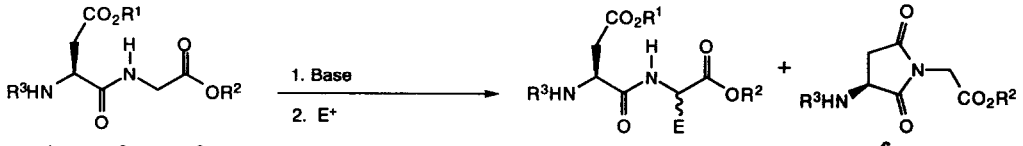
Table 1.
Results of the alkylation reactions of **3** (3 equivs base)

Ester	Base	Additive	de	Major
Me	*t*-BuLi	TMEDA (3)	41	R
Me	LDA	HMPA (3)	57	R
Me	LDA	TMEDA (1)	58	R
(–)-Men	LDA	TMEDA (1)	38.6	S
(+)-Men	LDA	LiCl (5) + HMPA (1)	50.3	R
(+)-Men	LDA	LiCl (10) + HMPA (1)	45.6	R
(+)-Men	LDA	LiCl (5)	45.4	R

In all reactions, the chemical yields were good (>70%). The additive has little effect on the degree of diastereoselection. When an achiral ester was present, the amino acid sidechain provided sufficient asymmetric environment for de's >50% to be observed. When the menthyl esters were employed, the (–)-menthyl ester gave a decrease in the diastereoselectivity and the induction was reversed at the alkylation centre. This suggested that this was a mis-matched pair. However, when the (+)-menthyl ester was used, de's were not significantly increased over the methyl esters. It, therefore, does not seem likely that double asymmetric induction is observed in this case; the effect of the ester is overriding that of the amino acid centre. The degree of asymmetric induction is in line with our results from the hippuric acid series.[7,9]

The initial reactions for the functionalised amino acid side-chain were conducted with aspartylglycine (**2**) itself. However, treatment of this dipeptide with excess base at a variety of temperatures in ethereal solvents gave no alkylation products with methyl iodide or benzyl bromide as the electrophile. The use of additives, such as TMEDA, did not improve the situation. The starting material was recovered in high yield. Seebach has reported that peptides are soluble in organic solvents through the addition of lithium salts.[10,12] When **2** was treated with lithium halides, with or without base being present, it did not dissolve in THF, even after prolonged times.[13] Thus, it seems that the dipeptide **2** is too polar for lithium to allow dissolution in THF, and no reaction is observed. Also, the use of a titanium counterion did not improve the situation.[10] The use of dimsyl sodium in DMSO led to the formation of only trace amounts of alkylation products. These observations led us to continue our investigation with derivatives of **2**.

The aspartylglycine derivatives were either obtained commercially or prepared from standard coupling reactions of the protected aspartic derivative with a glycine ester. The desired alkylation reaction (Scheme 3) required the presence of TMEDA and then proceeded only in low yield (10-20%). However, some diastereoselection was seen (70:30) in the alkylation products (**5**) for the reaction of the β-aspartyl esters (e.g., **4a**, **4b**) with benzyl bromide as electrophile and lithium counterions. The major isomer was determined to have the *R*-configuration at the new stereocentre.[14] This is consistent with the results for the dipeptides with hydrocarbon sidechains (*vide supra*).[13]



4a R^1 = Bn, R^2 = Me, R^3 = t-Boc
b R^1 = t-Bu, R^2 = Me, R^3 = t=Boc
c R^1 = Bn, R^2 = H, R^3 = t-Boc
d R^1 = Bn, R^2 = Me, R^3 = Z
e R^1 = H, R^2 = Me, R^3 = t-Boc

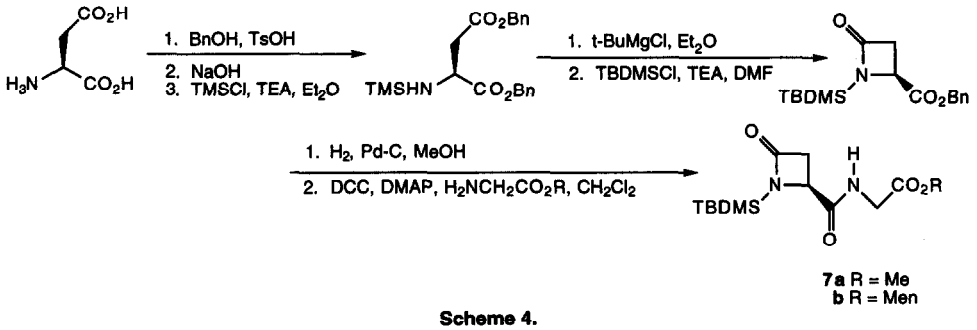
5

6

Scheme 3.

The surprising result of these reactions was the tendency for the aspartyl moiety to cyclise to form the succinimide **6**. As our target molecule, **1**, has to have the α-linkage, this observation was extremely disappointing. In all cases, the alkoxide is extruded to afford the succinimide, even when the

β-*tert*-butyl ester is used. This strongly suggests that this reaction is thermodynamically favourable. Unfortunately when the free β-carboxylate group was present in the substrate, **4e**, complex mixtures resulted with unreacted starting material being the major component. In addition, attempts to alkylate the succinimide resulted in the recovery of unreacted starting material, showing that alkylation via **5** was not going to be a trivial task, even if regioselective ring opening to afford the α-dipeptide could be effected. Chiral ester analogues of **4** were not prepared because of this cyclisation tendency. To circumvent the problem, the β-carboxyl acid moiety of aspartic acid was masked by incorporation into a β-lactam. The method of preparation is outlined in Scheme 4. All of the reactions in this sequence were relatively straightforward and had precedence in the literature (see Experimental).[15]



Scheme 4.

This approach also allowed for the inclusion of a chiral ester on the glycine moiety. The results of alkylation studies with this class of compounds are summarised in Table 2.

Table 2.
Alkylations of β-Lactams **6**.

Substrate	Base	Yield (%)	ds
7a	LDA	0	-
	NaHMDS	0	-
	LDA, TMEDA	74	60:40
7b	LDA, TMEDA	~20	70:30

Once again, TMEDA was used to effect alkylations. Without this additive, no alkylation was observed. The TMEDA to LDA ratio was kept at 1:1. With 2.2 equivalents, or more, of base the methyl ester **7a** gave the alkylation product with reaction occurring at the former glycine carbon atom. Alkylation in the β-lactam was not a major competing reaction. Although diastereoselection was observed for the methyl ester (**7a**), the ratio was not improved over the open chain series (7:3). However, the β-lactam had now removed the troublesome succinimide formation and the chemical yield was respectable (75%). When the menthyl ester (**7b**) was subjected to base treatment, the ester enolate was formed only very slowly, even with excess base (5 equivs.). Reaction with an electrophile gave only a very low yield of alkylated product and then the diastereoisomers were formed in about the same ratio as the methyl ester analogue. Again, as the starting material was recovered, deprotonation in the β-lactam moiety was not competing. Thus, it would seem that the menthyl ester is imparting too

much steric hindrance around the reaction site. This is borne out by the structure suggested from modelling studies. The bulky menthyl group causes the β-lactam moiety to assume a position that effectively buries the active hydrogens of the glycine ester. Although the methylene group of the glycine residue is relatively well set up for enolate formation as one of the hydrogens is close to the plane of the carbonyl π-bond, it is masked from reaction with base by the relatively large menthyl and β-lactam groups. This can rationalise the low alkylation yield and the slow deprotonation.

Figure 1 shows the enol of the amide as both top and side views. The size of the β-lactam moiety should be significantly larger than shown as the TBDMSi group has been omitted for the purposes of these calculations. The overall geometry of this enol is not significantly different to that of the parent molecule **7b**. Once again, the glycine methylene group is masked by the groups attached to the ends of this amino acid residue; in particular, the hydrogen closest to the plane of the carbonyl π-bond (this goes back in the top view) suffers significant steric hindrance to approach by a base. It is not clear why deprotonation of the β-lactam does not compete, as alkylation of these systems is well known.[15,16] In our case, the amide enolate is, presumably, formed very rapidly. Thus, deprotonation of the β-lactam would require formation of a dianion; this coupled with the inherent ring strain of the resultant enolate could be sufficient to slow down the deprotonation so that it does not compete.

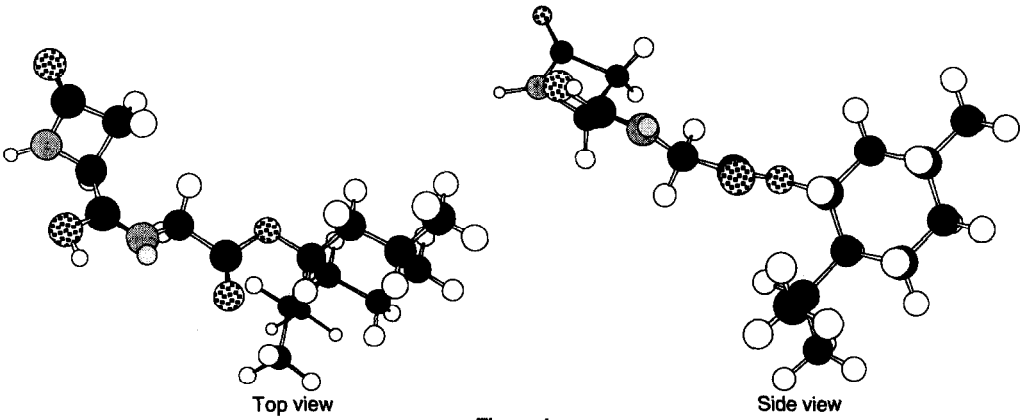


Figure 1

Seebach also notes diastereomeric excesses in the same ranges as we have seen in this study. In addition, the majority of literature examples are for the alkylation of sarcosine residues;[10] we have shown that glycine residues, even in a small dipeptide can be alkylated effectively. The induction from a chiral ester seems to override that derived from an *N*-amino acid residue. When a functionalised side chain, as derived from aspartic acid, was used to allow complex formation with the metal counterion, succinimide formation became the major pathway. When this reaction mode was removed by use of a β-lactam, the use of a menthyl ester showed that the ester enolate can become very sterically demanding, and that even deprotonation is very slow. The degree of diastereoselectivity was consistent in magnitude to that observed for hydrocarbon amino acid sidechains.

Experimental

Dipeptides were purchased unless otherwise noted. Alkylation products were analysed by comparison with authentic samples or by degradation to the constituent amino acids and then analysed for D versus L by standard methods. All hplc analyses were run in isocratic mode on a 10 cm C18-reverse phase column utilising 62% acetonitrile, with 38% water containing 0.001% trifluoroacetic acid. Column chromatography was used to separate the components. ^1H and ^{13}C NMR were run in $CDCl_3$ solution at 300 and 75 MHz respectively on a Bruker AC300 or GE QE300 spectrometers.

Molecular modelling was performed with MM2 parameters and MacroModel.

Preparation of Ts-Phe-Gly-OMe: To a solution of Phe-Gly (0.7 g, 3.15 mmol) in 10 mL of 10% $NaHCO_3$ was added a solution of 0.7 g of TsCl in 8 mL of dioxane. The mixture was stirred for 2 h at room temperature, poured into 200 mL of water and extracted twice with ether. The aqueous phase was acidified to pH 2, extracted three times with EtOAc, the extracts washed with H_2O, dried and concentrated to a foam (1.2 g). This was dissolved in 50 mL of methanol containing 0.15 g TsOH and the solution heated under reflux for 1h. Solid $NaHCO_3$ was added, the solution was evaporated to a solid that was extracted with EtOAc. The extracts were washed, dried and evaporated to give a solid (0.93 g, 73%); mp 118-120°C; ^1H NMR 7.50 (d 2H, J = 8.2 Hz), 7.16 (m, 5H), 6.93 (dd, 2H, J = 1.4, 7.1 Hz), 6.85 (bt, 1H), 4.98 (d, 1H, J = 6.5 Hz), 4.08 and 4.02 (1/2ABq, 1H, J = 5.9 Hz), 3.97-3.80 (m, 2H), 3.70 (s, 3H), 2.96 (d, 2H, J = 6.0 Hz), 2.42 (s, 3H); ^{13}C NMR: 170.8, 169.9, 143.9, 135.8, 135.3, 129.9, 129.3, 128.9, 127.2, 57.9, 52.5, 41.4, 38.3, 21.6.

Anal. Calcd. for $C_{19}H_{22}N_2O_5S$. C; 58.45, H; 5.68, N; 7.17. Found: C; 58.12, H; 5.58; N; 7.00%.

Preparation of Ts-Phe-Gly-O-(–)-Men: To a solution of Phe-Gly dipeptide (1.56 g, 7 mmol) dissolved in 20 mL 10% Na_2CO_3 was added a solution of 1.7 g (9 mmol) of TsCl in 18 mL of dioxane. The mixture was stirred for 2 h at ambient temperature, poured into 250 mL of water, cooled in ice, acidified with conc. HCl and extracted with EtOAc (3 x 100 mL). Unreacted dipeptide was filtered from the extract and the filtrate was concentrated to give a solid (2.46 g) which was dissolved in 60 mL benzene. 1.2 g (7.7 mmol) of (–)-menthol, 0.3 g TsOH were added and the solution was heated under reflux for 2 h. Standard work up afforded a solid (2.88 g) which was recrystallised from Et_2O/EtOAc to give 1.72 g (48%) of the dipeptide ester; mp 141-143°C; ^1H NMR: 7.50 (d, 2H, J = 8.2 Hz), 7.16 (m, 5H), 6.93 (m, 2H), 6.75 (bt, 1H), 4.92 (d, 1H, J = 6.5 Hz), 4.72 (dt, 1H, J = 4.4, 9.0 Hz), 3.97-3.80 (m, 3H), 2.96-2.92 (m, 2H), 2.40 (s, 3H), 2.00-0.70 (m, 18H); ^{13}C NMR: 170.3, 168.7, 143.8, 135.6, 135.1, 129.8, 129.1, 128.9, 127.2, 75.8, 57.7, 46.9, 41.5, 40.7, 38.3, 34.1, 31.4, 26.3, 23.4, 21.9, 21.6, 20.7, 16.3.

Anal. Calcd. for $C_{28}H_{38}N_2O_5S$. C; 65.34, H; 7.44, N; 5.44. Found: C; 64.99, H; 7.34; N; 5.22%.

Preparation of Ts-Phe-Gly-O-(+)-Men: In the same way as described for the (–)-menthyl ester, the (+) diastereoisomer was prepared; mp 218-220°C; ^1H NMR; 7.50 (d, 2H, J = 8.2 Hz), 7.16 (m, 5H), 6.93 (m, 2H), 6.75 (bt, 1H), 4.86 (d, 1H, J = 6.5 Hz), 4.72 (dt, 1H, J = 4.4, 9.0 Hz), 4.04-3.70 (m, 3H), 2.93 (d, 2H, J = 6.7 Hz), 2.40 (s, 3H), 2.00-0.70 (m, 18H); ^{13}C NMR; 170.2, 143.8, 135.0, 129.7, 129.1, 128.9, 127.3, 127.2, 75.8, 57.7, 46.9, 41.6, 40.7, 38.2, 34.1, 31.4, 26.3, 23.4, 21.9, 21.6, 20.7, 16.3.

Anal. Calcd. for $C_{28}H_{38}N_2O_5S$. C; 65.34, H; 7.44, N; 5.44. Found: C; 65.11, H; 7.39, N; 5.40%.

Preparation of authentic Ts-Phe-Phe-OMe: A cooled solution of *p*-TsCl (850 mg, 4.4 mmol) in 10 mL dioxane was added slowly to a cooled slurry of Na_2CO_3 and phenylalanylphenylalanine (1 g, 3.2 mmol) in dioxane. The mixture was stirred at ambient temperature for 2 h, poured into 125 mL of water, cooled in ice, acidified with conc. HCl and extracted with EtOAc (3 x 100 mL). Unreacted dipeptide was filtered from the extract and the filtrate was concentrated to a syrup. To this was added 30 mL of MeOH and 0.25 g *p*-TsOH and the mixture was heated under reflux for 1.5 h. Evaporation of the solvent gave a syrup which was chromatographed (hexane:$CHCl_3$:EtOAc, 5:4:1); ^1H NMR 7.52 (d, 2H, J = 8.3 Hz), 7.25-7.10 (m, 8H), 6.95-6.90 (m, 4H), 6.65 (d, 1H, J = 7.6 Hz), 5.13 (d, 1H, J = 7.4 Hz), 4.71 (q, 1H, J = 7.6 Hz), 3.88 (q, 1H, J = 7.1 Hz), 3.65 (s, 3H), 2.98 (d, 1H, J = 1.7 Hz), 2.96 (d, 1H, J = 2.0 Hz), 2.86 (d, 2H, J = 6.5 Hz), 2.37 (s, 3H); ^{13}C NMR: 171.0, 169.7, 143.7, 136.0, 135.5, 135.1, 129.7, 129.2, 128.8, 128.5, 127.1, 127.0, 57.6, 53.4, 52.3, 38.3, 37.8, 21.5.

Anal. Calcd. for $C_{26}H_{28}N_2O_5S$). C; 64.98, H; 5.87, N; 5.83. Found: C, 64.77, H; 5.81, N; 5.45%.

Preparation of authentic Ts-Phe-Phe-O-(–)-Men: The tosylation of the Phe-Phe dipeptide was done in the same manner as described above. To a solution of 200 mg (0.4 mmol) of this in toluene was added 100 mg of (–)-menthol and 150 mg of *p*-TsOH. The solution was heated under reflux for 2 h and worked up as described above to afford a syrup that showed only one peak on HPLC analysis.

Benzylation procedure:

Reaction using 3 eq LDA and 1 eq of TMEDA and the (–)-menthyl ester: An LDA solution prepared by mixing 210 µL (1.5 mmol) of diisopropylamine and 564 µL (1.5 mmol) of BuLi (2.66 M in hexane) in 2 mL of THF at 0°C under N_2 was cooled to -78°C. After stirring for 10 min, TMEDA (76 µL, 0.5 mmol) was added. After a further 20 min, a solution of the (–)-menthyl ester of TsPheGly (257 mg, 0.5 mmol) in 1.5 mL of THF was added. The

mixture turned brown and after 30 min, BnBr (120 μL, 1 mmol) was added. The solution was stirred at -78° for 1 h and then allowed to warm to ambient temperature over 30 min. The solution was poured into water, extracted with EtOAc and the organic phase dried and evaporated to afford a syrup (319 mg) which was chromatographed to give 131 mg (44%) of benzylated product and 112 mg of unreacted starting material. HPLC analysis gave a de of 38.6%.

The reactions of the other esters with base were carried out in an analogous manner.

Preparation of Dibenzyl *N*-Trimethylsilylaspartate:[15a] Sodium hydroxide (470 mL of a 1M solution) was added to a suspension of the *p*-toluenesulphonate salt of dibenzyl aspartate (230 g, 0.47 mol) in CH_2Cl_2 (2 L). The mixture was stirred and then the layers allowed to separate. The organic layer was washed with water, then brine, dried ($MgSO_4$), and evaporated to give the free amine as an oil (103.6 g, 70%). The diester was dissolved in ether (1 L) and cooled to 0° C, when triethylamine (46 mL, 33.4 g, 0.33 mol) was added followed by chlorotrimethylsilane (42 mL, 35.9 g, 0.33 mol). The reaction mixture was stirred and allowed to warm slowly to ambient temperature overnight. The salt was removed by filtration and the ethereal solution of the *N*-silylated ester used without further purification for the β-lactam formation; ^{1}H NMR: 7.31 (10H, br s), 5.09 (4H, s), 3.86 (1H, qu, J = 6.1 Hz), 2.9-2.6 (2H, m), and 0.01 (9H, s); ^{13}C NMR: 174.3, 170.5, 135.6, 128.4, 128.3, 128.2, 67.0, 66.7, 52.1, 41.5, -0.1.

Preparation of Benzyl 2-Azetidinone-4-carboxylate:[15,17] Dibenzyl *N*-trimethylsilylaspartate (38.5 g, 0.1 mol) in dry ether (500 mL) at 0° C was treated with *t*-butylmagnesium chloride (50 mL of a 2M solution in ether, 0.1 mol). The mixture was allowed to warm to ambient temperature overnight and then quenched with NH_4Cl (200 mL) to give the crude β-lactam (30.3 g) after evaporation of the organic layer. Attempts to purify the compound by column chromatography resulted in significant losses, but purification could be achieved by recrystallisation from EtOAc; mp 137-138°C; IR (KBr) ν_{max} 3200 (br), 1771, and 1735 cm^{-1}; ^{1}H NMR: 7.39 (5H, br s), 6.62 (1H, br s), 5.19 (2H, s), 4.19 (1H, m), 3.32 (1H, ddd, J = 0.5, 1.4, 14.4 Hz), and 3.03 (1H, ddd, J = 0.5, 14.4 Hz); ^{13}C NMR: 170.9, 166.5, 123.6, 123.4, 67.3, 47.2, 43.4.

Preparation of Benzyl 1-*tert*-Butyldimethylsilyl-2-Azetidinone-4-carboxylate:[15a] *t*-Butyldimethyl-silyl chloride (15.1 g, 0.1 mol) was added to a solution of the azetidinone (20.5 g, 0.1 mol) in DMF (100 mL) at 0° C, followed by the addition of NEt_3 (13.9 mL, 10.1 g, 0.1 mol). The reaction mixture was allowed to warm slowly to ambient temperature over 12 h, when it was poured into water (500 mL), and extracted with CH_2Cl_2. The combined extracts were washed with water and then brine, dried ($MgSO_4$), evaporated, and the product isolated as an oil after column chromatography (SiO_2, eluting with 1:1 ethyl acetate-hexane); 26.5 g (83%); ^{1}H NMR: 7.36 5H, br s), 5.19 (2H, s), 4.07 (1H, dd, J = 2.7, 6.0 Hz), 3.32 (1H, dd, J = 6.0, 15.2 Hz), 3.06 (1H, dd, J = 2.8, 15.2 Hz), 0.93 (9H, s), 0.25 (3H, s), and 0.06 (3H, s).

Preparation of 1-*tert*-Butyldimethylsilyl-2-azetidinone-4-carboxylic Acid:[15b] To slurry of 5% Pd-C (5.3 g) in MeOH (50 mL) (CAUTION: Fire hazard) was added a solution of the azetidinone (26.5 g, 0.83 mol) in MeOH (200 mL). The reaction mixture was placed in a Parr apparatus under hydrogen (60 psig) at ambient temperature for 1 h. The catalyst was removed by filtration, and the product obtained as a solid by evaporation of the methanol *in vacuo*, 18.1 g (95%); ^{1}H NMR: 4.03 (1H, dd, J = 2.2, 6.2 Hz), 3.32 (1H, dd, J = 6.0, 15.3 Hz), 2.92 (1H, dd, J = 2.3, 15.1 Hz), 0.913 (9H, s), 0.20 (3H, s), 0.01 (3H, s).

Preparation of Methyl N-[1-*tert*-Butyldimethylsilyl-2-azetidinone-4-carboxy]glycinate (7a): DCC (6.19 g, 30 mmol) was added to a solution of 1-*tert*-butyldimethylsilyl-2-azetidinone-4-carboxylic acid (6.87 g, 30 mmol) in CH_2Cl_2 (50 mL) containing DMAP (~100 mg), cooled to 0° C. The mixture was stirred for 2 min, then methyl glycinate (2.69 g, 30 mmol) in CH_2Cl_2 was added. The reaction mixture was allowed to warm to ambient temperature overnight. The mixture was filtered. The filtrate was washed with water and then brine, dried ($MgSO_4$), and the product obtained by column chromatography, 7.53 g (84%); ^{1}H NMR: 6.79 (1H, m), 4.10 (2H, m), 3.77 (3H, s), 3.40 (1H, dd, J = 5.0, 16.0 Hz), 3.05 (1H, dd, J = 2.7, 15.5 Hz), 0.98 (9H, s), 0.35 (3H, s), and 0.16 (3H, s);

^{13}C NMR: 171.7, 171.6, 169.8, 52.4, 50.1, 44.6, 40.9, 26.1, 18.6, -5.7, and -6.5.

Anal. Calcd. for $C_{13}H_{25}N_2O_4Si$. C; 51.80, H; 8.36, N;9.29. Found: C; 51.72, H, 8.55, N; 9.44%.

Preparation of Menthyl Glycinate:

Preparation of Menthyl Cbz-glycinate: To a slurry of Cbz-glycine (20.9 g, 0.1 mol) in CH_2Cl_2 (200 mL), containing a catalytic amount of DMAP (~0.5 g) and cooled to 0° C, was added a solution of DCC (20.6 g, 0.1 mol) in CH_2Cl_2 (100 mL). Once this addition was complete, menthol (15.6 g, 0.1 mol) in CH_2Cl_2 was added rapidly. The mixture was allowed to come to ambient temperature, stirred overnight, and then filtered. The filtrate was washed sequentially with water and brine, dried ($MgSO_4$), and then evaporated to give the crude ester which was purified by column chromatography on SiO_2 (1:1 hexane-EtOAc) to give 31.9 g (92%) of the product as an oil; IR (KBr) 3318, 1726, 1640 cm^{-1}; ^{1}H NMR: 7.81 (2H, m), 7.6-7.4 (3H, m), 6.74 (1H, br s), 4.80 (1H, dt, J = 4.5, 10.9 Hz), 4.22 (2H, d, J = 4.5 Hz), 2.05-0.7 (18H, m overlaid with dt at 0.91, J = 5.1, 1.6 Hz, and

d at 0.77, J = 7.0 Hz); ^{13}C NMR: 170.1, 167.7, 134.2, 132.1, 129.9, 127.4, 76.3, 47.3, 42.4, 41.2, 34.5, 31.8, 36.7, 23.8, 22.4, 21.1, 16.7.
Anal. Calcd. for $C_{20}H_{29}NO_4$. C; 69.14, H; 8.41, N; 4.03. Found: C; 69.25, H; 8.51, N; 4.26%.

Preparation of Menthyl glycinate:[18] To a mixture of 5% Pd-C (6.38 g) was added MeOH (50 mL) under an N_2 blanket (CAUTION: Fire hazard), followed by the menthyl derivative (31.9 g, 92 mmol) in MeOH (200 mL). The reaction mixture was placed under H_2 (60 psig) in a Parr apparatus for 3 h at ambient temperature. The mixture was then filtered through fiber glass and the solvent removed under reduced pressure. The resultant oil was distilled to give the ester[8b] (17.2 g, 88%); bp 155°/ 0.2 mm Hg; ^{1}H NMR: 4.77 (1H, ddt, J = 1.2, 4.4, 11.3 Hz), 3.40 (2H, s with hyperfine splitting), 2.1-0.7 (20H, m); ^{13}C NMR: 173.8, 74.7, 46.9, 44.1, 40.8, 34.1, 31.3, 26.2, 23.4, 21.9, 20.7, 16.3.

Preparation of Menthyl *N*-[1-*tert*-Butyldimethylsilyl-2-azetidinone-4-carboxy]glycinate (7b): The compounds were prepared as described for the methyl ester except menthyl glycinate (6.39 g, 30 mmol) was used in place of the methyl ester. The product was obtained as a gum (11.19g, 88%); ^{1}H NMR: 6.63 (1H, br t), 4.78 (1H, dt, J = 4.5, 10.9 Hz), 4.15-3.95 (3H, m), 3.40 (1H, dd, J = 5.2, 15.4 Hz), 3.06 (1H, dd, J = 2.9, 15.4 Hz), 2.0-0.7 (28H, m overlaid with s at 0.98, dt at 0.91, and d at 0.76, J = 6.9 Hz), 0.37 (3H, s), and 0.16 (3H, s); ^{13}C NMR: 171.6, 171.5, 169.0, 75.93, 50.1, 46.86, 44.7, 41.2, 40.7, 34.0, 31.3, 26.2, 26.2, 23.3, 21.9, 20.6, 18.7, 16.3, -5.6, -6.4.
Anal. Calcd. for $C_{22}H_{41}N_2O_4Si$. C; 62.08, H; 9.71, N; 6.58. Found: C; 61.86, H, 9.79, N; 6.77%.

References and notes:

1. Williams, R. M. *Synthesis of Optically Active Amino Acids*; Pergamon Press: New York, 1989.
2. Ager, D. J.; Hill, J. B. *Unpublished results*; .
3. McIntosh, J. M.; Cassidy, K. C. *Can. J. Chem.* **1988**, *66*, 3116; McIntosh, J. M.; Leavitt, R. K.; Mishra, P.; Cassidy, K. C.; Drake, J. E.; Chada, R. J. *J. Org. Chem.* **1988**, *53*, 1947; McIntosh, J. M.; Cassidy, K. C.; Matassa, L. C. *Tetrahedron* **1989**, *45*, 5449.
4. O'Donnell, M. J.; Bennett, W. D.; Bruder, W. D.; Jacobsen, W. N.; Knuth, K.; LeClef, B.; Polt, R. L.; Bordwell, F. G.; Mrozack, S. R.; Cripe, T. A. *J. Am. Chem. Soc.* **1988**, *110*, 8520; O'Donnell, M. J.; Bennett, W. D.; Wu, S. *J. Am. Chem. Soc.* **1989**, *111*, 2353; Martens, J. *Chemiker-Zeitung* **1986**, *110*, 169.
5. Katritzky, A. R.; Shobana, N.; Harris, P. A.; Hill, J. B.; Ager, D. J. *Org. Prep. Proced. Int.* **1992**, *24*, 121.
6. For the introduction of an alkyl sidechain by a radical method see, for example Baldwin, J. E.; Adlington, R. M.; Lowe, C.; A., O. I.; Sanders, G. L.; Schofield, C. J.; Sweeney, J. B. *J. Chem. Soc., Chem. Commun.* **1988**, 1030.
7. McIntosh, J. M.; Thangarasa, R.; Foley, N. K.; Ager, D. J.; Froen, D. E.; Klix, R. C. *Tetrahedron* Accompanying paper.
8. Chiral esters have also provided high asymmetric induction in anionic reactions in related reactions. For examples, see Ojima, I.; Habus, I. *Tetrahedron Lett.* **1990**, *31*, 4289;[b] Genet, J. P.; Kopola, N.; Juge, S.; Ruiz-Montes, J.; Antunes, O. A. C.; Tanier, S. *Tetrahedron Lett.* **1990**, *31*, 3133.
9. McIntosh, J. M.; Thangarasa, R.; Ager, D. J.; Zhi, B. *Tetrahedron* **1992**, *48*, 6219.
10. Seebach, D. *Aldrichimica Acta* **1992**, *25*, 59.
11. Knudsen, C. G.; Rapoport, H. *J. Org. Chem.* **1983**, *48*, 2260.
12. Seebach, D.; Thaler, A.; Beck, A. K. *Helv. Chim. Acta* **1989**, *72*, 857.
13. Seebach, D.; Bossler, H.; Gründler, H.; Shoda, S.-i.; Wenger, R. *Helv. Chim. Acta* **1991**, *74*, 197.
14. No racemisation of the stereogenic centre was observed under the reaction conditions (*c.f.* reference 13).
15. [a]Salzmann, T. N.; Ratcliffe, R. W.; Christensen, B. G.; Bouffard, F. A. *J. Am. Chem. Soc.* **1980**, *102*, 6161; [b] Baldwin, J. E.; Adlington, R. M.; Gollins, D. W.; Schofield, C. J. *Tetrahedron* **1990**, *46*, 4733;[c] Bouffard, F. A.; Salzmann, T. N. *Tetrahedron Lett.* **1985**, *26*, 6285.
16. Baldwin, J. E.; Adlington, R. M.; Gollins, D. W.; Schofield, C. J. *J. Chem. Soc., Chem. Commun.* **1990**, 720; Hanessian, S.; Sumi, K.; Vanesse, B. *Synlett* **1992**, 33.
17. Reider, P. J.; Grabowski, E. J. J. *Tetrahedron Lett.* **1982**, *23*, 2293.
18. Harada, K.; Hayakawa, T. *Bull. Chem. Soc., Jpn.* **1964**, 191.

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