1,2-Asymmetric induction in dianionic functionalization reactions of L-aspartic acid diesters[1]

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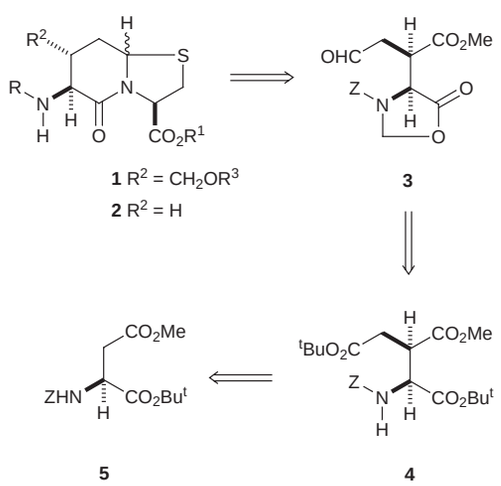
Functionalization of the dianions derived from N-protected aspartic acid esters is a simple route to the preparation of novel α-amino acids and peptidomimetic precursors. We have demonstrated previously that high levels of 1,2-asymmetric induction may be obtained in this reaction under the appropriate conditions (I.B. Parr, *et al.*, *J. Med. Chem.*, 1996, **39**, 2367). The observed diastereoselectivity results from the complicated interaction of a number of experimental factors. We now report that the nature of the electrophile and the work-up protocol both influence the level of stereocontrol in the alkylation of *N*-benzyloxycarbonyl aspartic acid esters. In addition, the stereochemical preference for high *anti* selectivity in the reaction can be reversed by increasing the steric bulk of the α-ester. Application of these observations has allowed the stereocontrolled preparation of two novel, N-protected, chimeric α-amino acids and a peptidomimetic precursor. The molecular basis for 1,2-asymmetric induction in the alkylation reaction can be rationalized on the basis of the configurational preferences of the lithium ester enolate formed from the N-protected aspartate diester used in these studies.

Introduction

The preparation of non-natural amino acids by diastereoselective and enantioselective synthesis has been the focus of considerable research.[2] Such compounds have proven to be important (i) in drug discovery, and (ii) as structural and mechanistic probes of biological systems.[3] Non-natural α-amino acids also represent key intermediates in the synthesis of conformationally constrained molecular scaffolds as elements in the design of small molecule combinatorial libraries.[4] In this regard, we were interested in developing a synthetic route for the preparation of the substituted rigid bicyclic β-turn mimetic **1** (Scheme 1). Although the synthesis of the unsubstituted compound **2** is described in a number of reports,[5] extension of these approaches to obtain ring-functionalized mimetics such as **1** do not appear to have been pursued.

We based our retrosynthetic analysis on known methods for the construction of bicyclic frameworks by reaction of protected aldehydes with cysteine derivatives.[6] We therefore envisaged that the aldehyde **3** represented a useful intermediate in the synthesis of **1** (Scheme 1), and that this compound could be obtained by regiospecific transformation of the triester **4**. In turn, functionalization of the dianion derived from deprotonation of the β-carbon of the aspartic acid diesters **5** with an appropriate haloacetate was expected to give **4** in good yield. Alkylation of suitably protected aspartic acid esters has been shown to be a practical approach to obtaining a variety of compounds in optically pure form, including non-natural amino acids and alkaloids.[7] Indeed, our group has employed this reaction to prepare a series of analogs capable of defining the bound conformation of substrate in the C-terminal domain of the enzyme asparagine synthetase.[8] On the other hand, while 1,2-asymmetric induction in the alkylation of aspartic acid ester enolates is well documented, the effect of experimental conditions on the stereochemical outcome of the reaction appears to be complex.[7,8] For example, recent work has shown that very high *anti* diastereoselectivities can be achieved using lithium as the counter-ion in the presence of additives such as HMPA.[7a] The nature of the metal counter-ion also appears to define the ester enolate geometry in the anionic intermediate.[7b] There have been no systematic studies, however, of the role of other experimental variables in defining the level of 1,2-asymmetric induction. We now report that the diastereoselectivity in the β-functionalization of diester **5** is dependent on the reactivity of the electrophile, the steric bulk of the C-2 ester substituent and the procedure employed to quench the reaction. The molecular basis for 1,2-asymmetric induction in the alkylation reaction can be rationalized on the basis of the likely configurational preferences of the lithium ester enolate formed from diester **5**. Application of these observations has allowed



Scheme 1 Retrosynthetic analysis of functionalized peptidomimetic **1**.

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Table 1 Effect of reaction conditions on 1,2-asymmetric induction in the reaction of *tert*-butyl chloroacetate and the dianion derived from deprotonation of **5** by LiHMDS

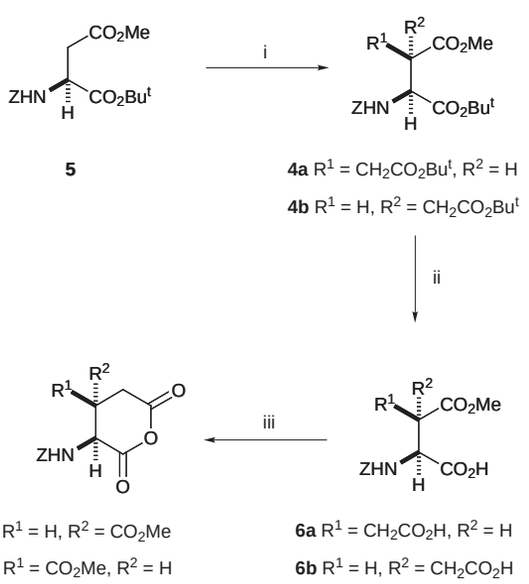
Entry	*T*/°C	*t*/h	Salt[a]	Ionic strength	Workup	**4a**:**4b**
1	0	3	None	0.087	A[b]	mixture
2	−20	3	None	0.087	A	mixture
3	−30	3	None	0.087	A	>99:1
4	−30	3	None	0.087	B	2:1
5	−82	18	None	0.087	A	>99:1
6	−82	18	None	0.087	B	2:1
7	−82	18	None	0.087	C	2:1
8	−75	6	1 equiv. LiCl	0.116	A	>99:1
9	−75	6	2.5 equiv. LiCl	0.160	A	>99:1
10	−75	6	5 equiv. LiCl	0.232	A	>99:1
11	−75	6	10 equiv. LiCl	0.377	A	>99:1

[a] Salt was added to the solution of the enolate at low temperature before addition of the electrophile. [b] A: Cold reaction solution is poured into 1 M HCl at rt; B: reaction solution warmed to rt before addition to 1 M HCl; C: 1 M HCl added to cold reaction solution, and then warmed to rt.

the stereocontrolled preparation of two novel, N-protected, chimeric α-amino acids[9] and a differentially protected aspartate precursor for peptidomimetic **1**.

Results and discussion

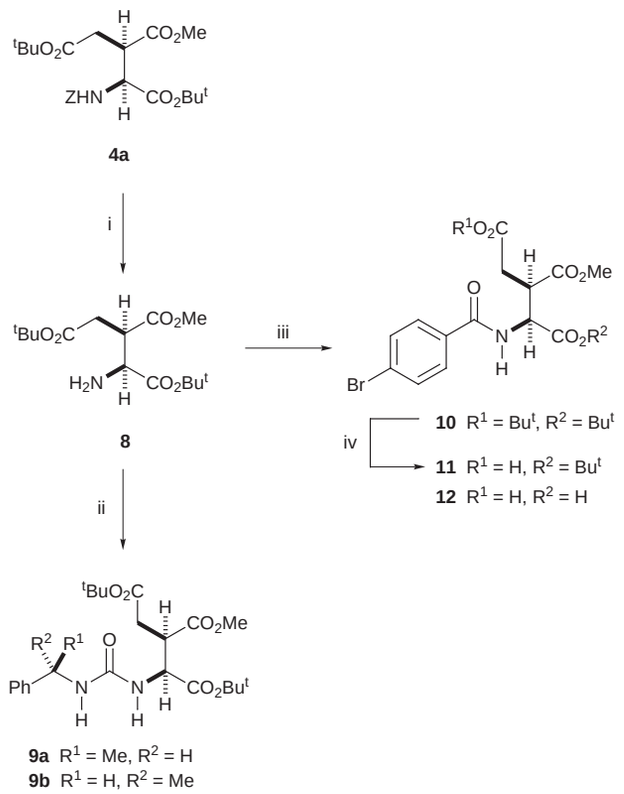
The L-aspartate diester **5** was synthesized from L-aspartic acid in three steps following literature procedures.[10] Our initial experiments involved generation of the dianion derived from **5** using two equivalents of lithium hexamethyldisilazide (LiHMDS)[11] in THF at −35 °C. The desired triester **4** was then obtained as a mixture of diastereoisomers (**4a**:**4b**) by overnight reaction of the dianion with *tert*-butyl chloroacetate at room temperature (Scheme 2). No N-alkylation was observed



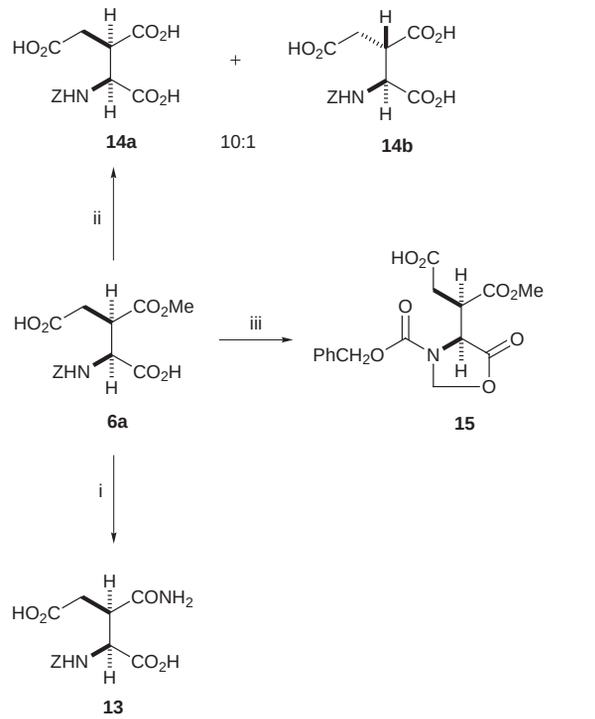
Scheme 2 Z = $PhCH_2OC(=O)$: i) LiHMDS, THF, −75 °C, then $ClCH_2CO_2Bu^t$, −75 °C, 62%; ii) CF_3CO_2H, CH_2Cl_2, 70%; iii) Ac_2O, 60 °C, 80%.

in any experiment described in this paper. Although a lack of diastereoselectivity during the alkylation of the dianion obtained from **5** had been reported previously for a number of other electrophiles,[7] we decided to investigate the reaction conditions in a systematic fashion to determine whether selectivity could be improved. Subsequently we discovered that two factors appeared to cause the poor stereoselectivity observed in our initial experiments. First, reaction temperature was an important variable. Maintaining the temperature below −50 °C during alkylation of the dianion was an essential element in obtaining high levels of 1,2-asymmetric induction. The procedure for quenching the monoanion formed after functionalization of the dianion, however, represented a second important, and unanticipated, variable. For example, addition of acid to the reaction solution at low temperature followed by warming, as reported in the literature,[7] gave a mixture of diastereomeric products **4a** and **4b** (Table 1). In contrast, the triester **4** was obtained as a single diastereoisomer if the reaction was quenched by pouring the cold solution of the monoanion into aqueous acid.

We established the relative stereochemistry of the single diastereoisomeric triester **4** by converting this product to the cyclic anhydride **7** (Scheme 2). This was accomplished by treatment of **4** with trifluoroacetic acid in dichloromethane to remove the *tert*-butyl esters, and subsequent cyclization of the resulting diacid **6** using acetic anhydride.[12] Careful control of the temperature in the latter reaction was necessary, however, to avoid extensive decomposition of the product. ^{1}H NMR spectroscopy showed that the vicinal coupling constant for the C-2 and C-3 protons (J_{23}) of the isolated anhydride **7** was 12.1 Hz, consistent with diastereoisomer **7a**. Given that epimerization did not occur under the deprotection and cyclization conditions, triester **4a** must have been obtained as the sole product under our modified conditions for the alkylation reaction. Thus, the alkylation reaction proceeded with *anti* selectivity, as seen for other electrophiles in previous studies.[7a] We confirmed our stereochemical assignment by transforming a 4:1 mixture of the diastereoisomeric triesters **4a** and **4b** (prepared using the literature procedures for alkylation of aspartate derivative **5**) to the corresponding mixture of anhydrides **7a** and **7b**. The ^{1}H NMR resonances for the C-2 protons of **7a** and **7b** in the mixture were easily differentiated, and J_{23} for the minor isomer **7b** was determined to be 5.2 Hz. This value is consistent with the stereochemistry assigned to **7b**, based on previous studies of β-chloroglutamates.[13] A number of approaches were employed to ensure that the integrity of the chiral center at C-2 in starting diester **5** was maintained under the alkylation conditions. First, the optical rotation of unreacted, recovered diester **5** was identical to that of the pure starting material. Second, the triester product **4a** was converted to the amine **8** using catalytic hydrogen transfer to remove the benzyloxycarbonyl protecting group. Reaction of **8** with chiral isocyanates, in two separate experiments,[14] then gave the urea derivatives **9a** and **9b** (Scheme 3). The methyl ester resonances in **9a** and **9b** were clearly differentiable and provided a method of assessing the optical purity of the triester **4a** formed in the reaction. Thus, if there were any racemization of **5** before alkylation, derivatization of the resulting triester **4a** would yield **9a** and the enantiomer of **9b**, giving rise to two methyl ester singlets in the ^{1}H NMR of the product. Only a single methyl ester resonance was observed for the crude material formed by reaction of **8** with either enantiomerically pure isocyanate. This was confirmed by doping the NMR sample of **9a** with increasing amounts of **9b** formed in the other derivatization reaction to give two methyl ester



Scheme 3 Z = $PhCH_2OC(=O)$: i) H_2, 10% Pd/C, 95%; ii) (*S*)-$PhCH(CH_3)N{=}C{=}O$ or (*R*)-$PhCH(CH_3)N{=}C{=}O$, THF, 100%; iii) BrC_6H_4COCl, Et_3N, 58%; iv) CF_3CO_2H, CH_2Cl_2.



Scheme 4 Z = $PhCH_2OC(=O)$: i) NH_4OH, rt, 77%; ii) LiOH, 4:1 MeOH–H_2O, 73%; iii) $(CH_2O)_n$, cat. *p*-TsOH, 88%.

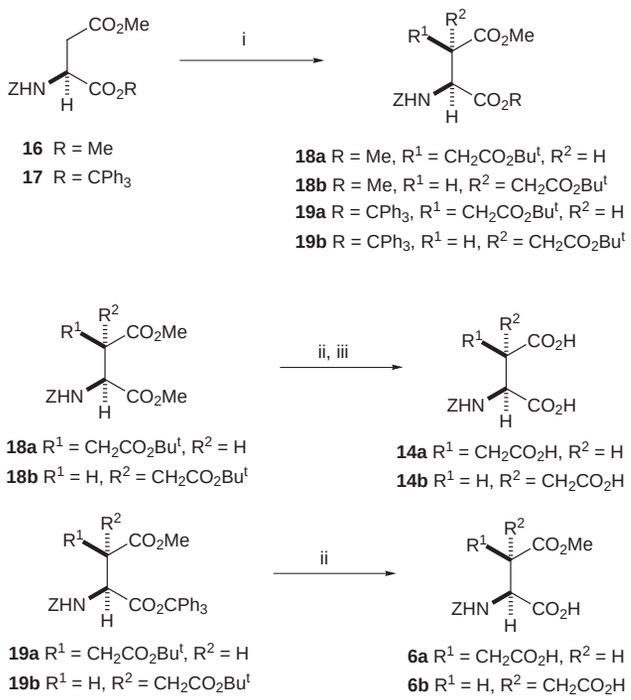
signals. In separate efforts to confirm the relative and absolute stereochemistry of the triester **4a**, the amine **8** was also reacted with 4-bromobenzoyl chloride to give the triester **10**. Removal of the *tert*-butyl protecting groups using trifluoroacetic acid yielded a mixture of acids **11** and **12**, which could be separated using reversed-phase HPLC. Although both of these products were solids, recrystallization only gave needles that were unsuitable for X-ray structure determination. In the last set of experiments, the dianion of **5** was generated at −75 °C using 2.1 equivalents of LiHMDS following our standard procedure. Quenching using D_2O and recovery of the diester **5** only yielded material in which deuterium had been incorporated at C-3, suggesting that any deprotonation at C-2 occurs at levels below the detection limit of NMR. It is not yet clear how simple modification of the work-up conditions should play such an important role in modulating the stereochemical outcome of the reaction. Explanations that invoke equilibration under reported work-up conditions in studies of the β-alkylation of diester **5** seem to be ruled out by semi-empirical calculations that suggest triester **4a** is more thermodynamically stable than **4b**.[15,16] Additional experiments are under way to address this question.

Having established the stereochemical outcome of the alkylation reaction using *tert*-butyl chloroacetate, we examined the conversion of diacid **6a** into derivatives with potential utility in investigating the structure and chemical mechanism of asparagine synthetase (Scheme 4).[8] Alkylation of **5** using *tert*-butyl chloroacetate represents a novel route for synthesizing β-functionalized glutamic acid analogs.[17] We note that structurally related compounds exhibit potent biological activity, particularly at specific classes of receptor in the central nervous system.[18] In our initial experiments, treatment of the diacid **6a** with aqueous ammonia yielded amide **13** in reasonable yield. No epimerization at C-3 was observed under these reaction conditions. The highly functionalized, novel α-amino acid **13** has potential utility in the development of asparagine synthetase inhibitors because it represents a protected chimera of asparagine and glutamate, both products of the enzyme-catalyzed reaction.[8] The preparation of chimeric amino acids has received considerable attention.[9] In related studies, hydrolysis of the methyl ester **6a** using LiOH proceeded smoothly to give the triacid **14a**, after HPLC purification, in good yield.[19] A small amount of the diastereoisomeric triacid **14b** was also produced under the reaction conditions, consistent with previous reports of epimerization at C-3 in aspartate analogs of similar structure.[20] Triacid **14** is another interesting structure, being a chimera of aspartic acid and glutamic acid. Finally, reaction of **6a** with paraformaldehyde, in the presence of a catalytic amount of toluene-*p*-sulfonic acid,[21] gave the desired oxazolidinone **15** in good yield. This compound is a useful precursor of aldehyde **3** given the pattern of differential protection.

In light of the high level of 1,2-asymmetric induction observed in the preparation of triester **6a**, we undertook a systematic investigation of the role of experimental variables in determining the stereochemical outcome of the alkylation reaction. Thus, the reactivity of the electrophilic species was modified using *in situ* halide exchange. In these experiments *tert*-butyl chloroacetate was stirred with a halide salt for 2 hours directly prior to its reaction with the dianion formed by treatment of **5** with LiHMDS. Whereas the addition of LiBr or NaI did indeed increase the overall yield of the alkylation reaction, the triester product obtained under these conditions was a mixture of diastereoisomers **4a** and **4b**. For example, the presence of NaI gave **4a**:**4b** in a 3:1 ratio, even using our modified workup protocol. Two possible effects were hypothesized to give rise to the observed decrease in stereochemical control. In order to rule out modulation of diastereoselectivity from salt effects, the dianion of **5** was reacted with *tert*-butyl chloroacetate in the presence of increasing amounts of LiCl (Table 1). In these experiments, the salt was mixed with the dianion prior to addition of the electrophile. No effect on the diastereoselectivity of the reaction was observed, even if LiBr or LiI were present. In all cases, only triester **6a** was obtained using our modified workup conditions. This suggested that halide exchange was occurring in our original experiments, and that therefore the decreased 1,2-asymmetric induction resulted from reaction of the dianion with the *tert*-butyl bromoacetate formed *in situ*. Evidence to support this conclusion was

obtained in two ways. First, we confirmed that stirring *tert*-butyl chloroacetate with LiBr in THF for 2 hours at ambient temperature gave a 3:2 mixture of the chloro- and bromoacetates as determined by ^{1}H NMR measurements. Second, reaction of the dianion derived from **5** with *tert*-butyl bromoacetate gave the triester **6** as a 3:2 mixture of **6a** and **6b** under our standard reaction conditions.

The effect of the steric bulk of the C-1 ester on the alkylation diastereoselectivity was also investigated (Scheme 5). Diester **16**



16 R = Me
17 R = CPh$_3$

18a R = Me, R^1 = CH$_2$CO$_2$Bu^t, R^2 = H
18b R = Me, R^1 = H, R^2 = CH$_2$CO$_2$Bu^t
19a R = CPh$_3$, R^1 = CH$_2$CO$_2$Bu^t, R^2 = H
19b R = CPh$_3$, R^1 = H, R^2 = CH$_2$CO$_2$Bu^t

18a R^1 = CH$_2$CO$_2$Bu^t, R^2 = H
18b R^1 = H, R^2 = CH$_2$CO$_2$Bu^t

14a R^1 = CH$_2$CO$_2$H, R^2 = H
14b R^1 = H, R^2 = CH$_2$CO$_2$H

19a R^1 = CH$_2$CO$_2$Bu^t, R^2 = H
19b R^1 = H, R^2 = CH$_2$CO$_2$Bu^t

6a R^1 = CH$_2$CO$_2$H, R^2 = H
6b R^1 = H, R^2 = CH$_2$CO$_2$H

Scheme 5 Z = PhCH$_2$OC(=O): i) LiHMDS, THF, −75 °C, then BrCH$_2$CO$_2$Bu^t, −75 °C; ii) CF$_3$CO$_2$H, CH$_2$Cl$_2$; iii) LiOH, 4:1 MeOH–H$_2$O.

was simply obtained by refluxing β-methyl *N*-benzyloxycarbonylaspartate,[10] an intermediate in the synthesis of **5**, with HCl in MeOH.[22] Similarly, the trityl derivative **17** could be synthesized in 98% yield by reaction of the caesium salt of β-methyl *N*-benzyloxycarbonylaspartate with trityl bromide in dry THF.[23] Diesters **16** and **17** were then alkylated by reaction of their respective lithium dianions with *tert*-butyl bromoacetate at −75 °C for 17 hours. As usual, each reaction was worked up by pouring the cold mixture into 1 M HCl at room temperature. The electrophile was specifically chosen as we knew that the triester products **18** and **19**, respectively, would be obtained as a mixture of diastereoisomers at C-3. Given that control of relative stereochemistry was the issue in these experiments, no effort was made to establish whether epimerization at C-2 had occurred under the reaction conditions. It is known, however, that deprotonation at C-2 can be an issue in the alkylation of aspartate diesters in which the α-proton is not sterically hindered, leading to partial racemization of the products.[24] As anticipated, ^{1}H NMR spectroscopy confirmed that the alkylation products **18** and **19** were obtained as a mixture of diastereoisomers. Stereochemical assignment of the major product **18a** was accomplished by conversion of triester **18** in two steps to a mixture of the triacids **14a** and **14b**. The triacid **14a** had been prepared previously and its reversed-phase HPLC retention time was known. Co-injection of an authentic sample of **14a** with the mixture obtained from **18** therefore allowed unambiguous assignment of the original product mixture. In the case of the triester **19**, purification of the desired product was complicated by partial deprotection of the trityl group under the acidic workup conditions. Hence the mixture

Table 2 Effect of the α-ester and electrophile on alkylation diastereoselectivity

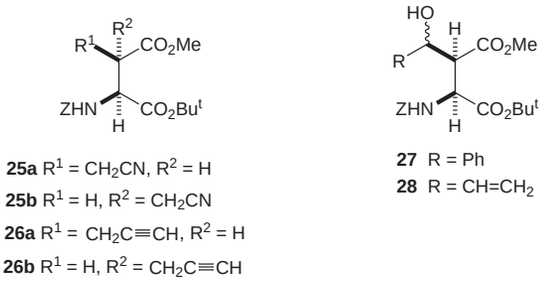
Ester	Electrophile	*3R*:*3S* Ratio
5	ClCH$_2$CO$_2$Bu^t	>99:1
5	BrCH$_2$CO$_2$Bu^t	3:2
16	BrCH$_2$CO$_2$Bu^t	2.5:1
17	BrCH$_2$CO$_2$Bu^t	1:1.2
5	BrCH$_2$CH=CH$_2$	>99:1
5	ICH$_2$CH=CH$_2$	8:1
5	BrCH$_2$CH≡CH	4:1
5	BrCH$_2$C≡N	2:1
5	PhCHO	>99:1[a]
5	H$_2$C=CHCHO	>99:1

[a] Aldehyde addition products are likely to be a 1:1 mixture of diastereoisomers at C-4.

of diastereoisomeric products, obtained by alkylation of the dianion of **17** with *tert*-butyl bromoacetate, was treated directly with trifluoroacetic acid to give the diacids **6a** and **6b**, which were easily separated by reversed-phase HPLC. Diacid **6b** was shown to be the major component of the reaction mixture by co-injection with an authentic sample, implying that **19b** was the major diastereoisomer formed in the alkylation of the dianion obtained from aspartic acid ester **17**. The observed *syn* diastereoselectivity was intriguing in that the increased steric bulk of the trityl group reverses the *anti* selectivity observed in β-alkylation of the diester **5** (Table 2).[7]

Having established reaction conditions for obtaining high levels of 1,2-asymmetric induction in the functionalization of **5** using *tert*-butyl chloroacetate, we next examined the stereochemical outcome when the dianion was reacted with other activated electrophiles (Table 2). In our initial experiments, β-allylation of **5** using allyl bromide gave **20** as a single diastereoisomer (Scheme 6), a result consistent with literature observations.[7,8a] The assignment of stereochemistry was accomplished using two approaches. First, diacid **21** was prepared in two steps by sequential reaction of the allylated diester **20** with trifluoroacetic acid and LiOH.[8a] In contrast to the behavior of **6a**, however, epimerization at C-3 was not observed during the deprotection of the methyl ester. Cyclization of **21** on treatment with acetic anhydride proceeded smoothly to give the anhydride **22**, for which the amide proton resonance was clearly evident in the ^{1}H NMR spectrum. Irradiation of the amide peak allowed us to assign that of the C-2 proton, which was visible as a doublet for which J_{23} was determined to be 10.2 Hz. This compares to the value of J_{23} = 5.6 Hz reported previously for the benzylated aspartate derivative **23**.[20] Thus, the allylation product was tentatively assigned to be **22a**. Subsequently, we prepared a mixture of **20a** and **20b** by reaction of the dianion of **5** with allyl iodide, and this was converted into the anhydrides **22a** and **22b**. As expected, the ^{1}H NMR resonances of the C-2 proton resonances in these diastereoisomeric anhydrides were well resolved. In this manner, we were able to determine the cognate coupling constant J_{23} for the minor diastereoisomer as 8.1 Hz, consistent with the predicted *anti*-relationship in **22b**. In the second approach, details of which have appeared elsewhere,[8a] the allylated diester **20a** was converted in several steps to **24** (Scheme 6). The stereochemistry of **24** has been defined by transformation to (2*S*,3*R*)-carboxyproline.[7b,8a,9b]

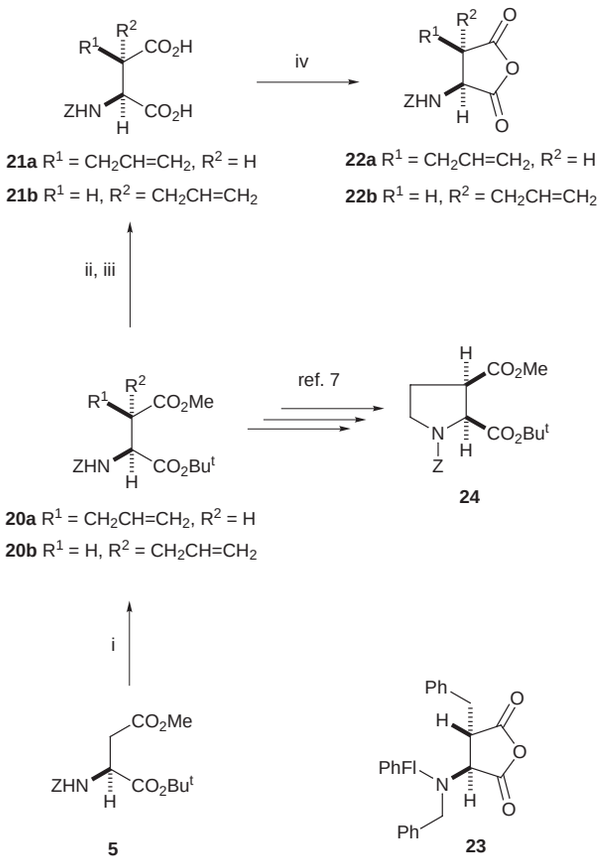
Reaction of the dianion generated from **5** by treatment with LiHMDS also proceeded smoothly with propargyl bromide (prop-2-ynyl bromide) or bromoacetonitrile, to give the novel diesters **25** and **26**, respectively (Fig. 1). Unfortunately, given the functionality can be generated by reaction of acetylenes and nitriles, both compounds were formed as a mixture of diastereoisomers. Although detailed stereochemical analysis of the products **25** and **26** was not performed, it is likely that the major isomer formed represents that formed by *anti* addition of the electrophile.[7a,8a] The dianion obtained from **5** was also



25a $R^1 = CH_2CN$, $R^2 = H$
25b $R^1 = H$, $R^2 = CH_2CN$
26a $R^1 = CH_2C{\equiv}CH$, $R^2 = H$
26b $R^1 = H$, $R^2 = CH_2C{\equiv}CH$

27 R = Ph
28 R = CH=CH_2

Fig. 1 Products obtained by reaction of various electrophiles with the aspartic ester enolate derived from **5**.

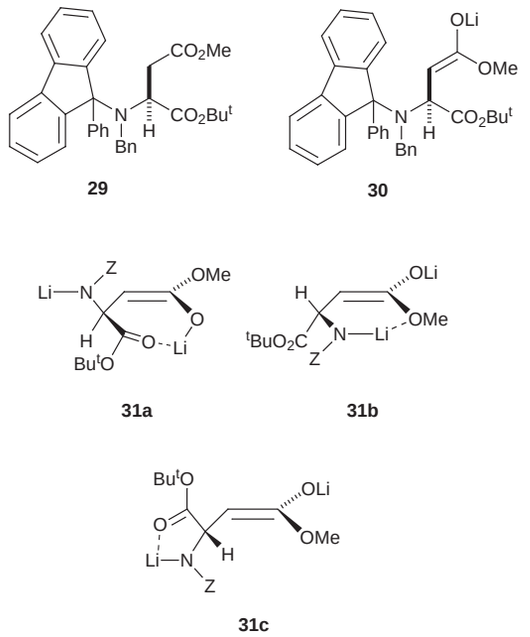


21a $R^1 = CH_2CH{=}CH_2$, $R^2 = H$
21b $R^1 = H$, $R^2 = CH_2CH{=}CH_2$
22a $R^1 = CH_2CH{=}CH_2$, $R^2 = H$
22b $R^1 = H$, $R^2 = CH_2CH{=}CH_2$
20a $R^1 = CH_2CH{=}CH_2$, $R^2 = H$
20b $R^1 = H$, $R^2 = CH_2CH{=}CH_2$
24
5
23

Scheme 6 Z = $PhCH_2OC(=O)$: i) LiHMDS, THF, −75 °C, then $BrCH_2CH{=}CH_2$, −75 °C, 60%; ii) CF_3CO_2H, CH_2Cl_2, 89%; iii) NaOH, 1:1 MeOH–H_2O, 58%; iv) Ac_2O, 75 °C, 100%.

reacted with acrolein and benzaldehyde to yield the the alcohols **27** and **28** as 1:1 mixtures of only two diastereoisomers, respectively. We currently assume that the diastereoisomers formed in these reactions represent of epimers at C-4, and that significant levels of 1,2-asymmetric induction has occurred at C-3. This is consistent with earlier observations using benzaldehyde as the electrophilic component in the β-alkylation of aspartate diesters.[25]

The observed preference for *anti* alkylation of the aspartic acid ester dianion can be rationalized by considering models of the intermediate in which there is chelation of the lithium counter-ion (Fig. 2). Although definitive proof is lacking, it is likely that deprotonation of the ester **5** using LiHMDS proceeds to yield the (*Z*)-lithium ester enolate. This assumption is contrary to previous reports that deprotonation of esters by LiHMDS in THF usually gives (*E*)-ester enolates,[26] but is precedented by trapping experiments which clearly show that monoanion **30**, formed by reaction of aspartic acid diester **29** with LiHMDS, is the (*Z*)-ester enolate (Fig. 2).[7b] Further, in the event that the (*E*)-lithium ester enolates were produced by deprotonation of **5** under our reaction conditions, the most



29
30
31a
31b
31c

Fig. 2 Putative models **31a**–**31c** to rationalize the observed 1,2-asymmetric induction in the reaction of the lithium ester of **5** with electrophiles. Z = $PhCH_2OC(=O)$.

favorable structure for the resulting dianion would be **31a** in which the metal is chelated by the α-ester group rather than the amide nitrogen (Fig. 2). Attack of the electrophile from the least hindered face of the double bond, would then yield the product of *syn* alkylation. This model is not therefore consistent with the diastereoselection seen in our experiments, unless the second lithium ion plays a role in directing electrophilic attack in the transition state. Two structures, **31b** and **31c**, can be envisaged in which lithium is chelated in the (*Z*)-lithium ester enolate formed by deprotonation of **5** (Fig. 2). Attack of the electrophile from the least hindered face of the double bond in **31b** would give the observed preference for *anti* alkylation, and such a model has been proposed previously to explain the stereochemical outcome of alkylations involving chiral β-hydroxyesters.[27] On the other hand, if chelation is playing a role in controlling the stereochemical outcome of the reaction, it seems likely that increasing the steric bulk of the α-ester should enhance *anti* selectivity in the alkylation reaction. Our experiments using the trityl derivative **17** are therefore difficult to reconcile with this model. In addition, increasing concentrations of LiCl might be expected to disrupt this structure and result in decreased diastereoselectivity. This was not observed under our reaction conditions (Table 1).

Intermediate **31c** represents an alternate structure for the dianion in which a (*Z*)-lithium ester enolate is present (Fig. 2). In this structure, the α-hydrogen is *syn*-periplanar to the enolate and the second lithium ion is chelated by the remaining ester. Electrophilic attack from the top face of the double bond would then yield the product arising from *anti* alkylation, and this model is consistent with that proposed to rationalize the high stereoselectivity observed in the allylation of monoanion **30**.[7b] This model also suggests that the top face of the double bond might be sterically hindered by a trityl ester favoring electrophilic attack from the lower face, giving the product of *syn* alkylation as the major isomer. While this simple model rationalizes our observations, it ignores the complexity of supramolecular enolate structures in non-polar solvents.[28] Further, the relevance of ground state conformational effects to the activation energy of competing reaction pathways is not always evident. Current efforts are therefore centered on validating this model using a combination of experiments, and *ab initio* calculations on the energetics of electrophilic attack on

models of ester enolates **31a**–**31c**. Our results will be reported in due course.

In summary, the work outlined here supports the utility of aspartic acid diester β-functionalization as a rapid route for the stereocontrolled preparation of novel α-amino acids, especially if careful attention is paid to optimizing the appropriate experimental variables. Work from other groups suggests that *syn* selectivity in 1,2-asymmetric induction can be obtained if potassium is employed as the counter-ion in the reaction. Appreciation of the role of other factors in defining the diastereoselectivity of functionalization at C-3 of aspartate, as outlined in this paper, may enhance our ability to control the level of 1,2-asymmetric induction when KHMDS is employed as a base. It is also likely that the availability of β-functionalized glutamates, such as **15**, will allow the construction of novel molecular scaffolds for use in creating functionally diverse combinatorial libraries.

Experimental

Commercially available amino acids and their derivatives were obtained from Sigma Chemical Company. All other reagents were purchased from Aldrich or Fisher Scientific, and were used without further purification. Moisture sensitive reactions were carried out under a nitrogen, or argon, atmosphere using standard techniques. Glassware used in these reactions was flame-dried with an inert gas sweep. THF was freshly distilled before use from sodium benzophenone ketyl. Methanol was dried using magnesium following standard procedures. Bis(trimethylsilyl)amine was distilled from CaH_2 before use. All other solvents were distilled before use. Throughout the experimental section, petroleum ether refers to the fraction with bp 60–80 °C, unless stated otherwise. Analytical TLC was performed on silica gel 60F-254 plates. Column chromatography was performed on Kieselgel 60 (230–400 mesh) using freshly distilled solvents. Analytical (250 mm × 4.6 mm) and preparative (50 mm × 21.4 mm) HPLC used Dynamax C_{18} and C_8 reversed-phase columns, with monitoring at 226 nm. Melting points are uncorrected. Elemental analyses were recorded at the Microanalytical Service Facility at the University of Florida. NMR spectra were recorded on General Electric GE-300, Bruker AM-360 or Varian Unity-500 spectrometers. ^{1}H chemical shifts are reported in ppm (δ) downfield of TMS as an internal reference (δ 0.0). ^{13}C chemical shifts are reported in ppm relative to TMS. Splitting patterns are abbreviated as follows: br, broad, s, singlet, d, doublet, t, triplet, q, quartet and m, multiplet. EI, CI and FAB mass spectra were recorded on a Finnegan MAT 25Q spectrometer. Chemical ionization employed either ammonia or isobutane.

Preparation of di-*tert*-butyl (2*S*,3*R*)-2-benzyloxycarbonylamino-3-methoxycarbonylglutarate (4a)

A solution of the diester **5** (1 g, 2.9 mmol) dissolved in dry THF (25 cm^3) was added dropwise to LiHMDS (6.5 cm^3 of a 1 M solution in THF, 6.5 mmol) at −80 °C, under nitrogen. After stirring for 30 min at −78 °C, the pale-yellow solution was warmed slowly to −30 °C and left for a further 2 h to ensure formation of the dianion. The resulting orange solution was re-cooled to −78 °C before the addition of neat *tert*-butyl chloroacetate (2.12 cm^3, 14.8 mmol) at such a rate that the reaction temperature did not exceed −75 °C. Stirring was continued for a further 17 h at −78 °C before the reaction mixture was poured into 1 M HCl (120 cm^3) at rt. This solution was then extracted using Et_2O (4 × 50 cm^3), and the organic phase was dried ($MgSO_4$) before removal of the solvent under reduced pressure. The crude product was purified by "flash" chromatography[29] (eluant: 4:1 petroleum ether–EtOAc) to give the reaction product (639 mg, 48%) as the first material from the column, followed by unreacted diester **5** (230 mg, 23%). The triester **4a** was a yellow oil that solidified on standing: mp 56–58 °C (from EtOAc) (Found: C, 60.9; H, 7.3; N, 3.0; $C_{23}H_{33}NO_8$ requires C, 60.9; H, 7.3; N, 3.0%); $[\alpha]_D^{20}$ +5.5 (*c* 0.2 in $CDCl_3$); ν_{max}(neat)/cm^{-1} 3358, 2979, 1732, 1506, 1456, 1223 and 1155; δ_H(360 MHz; $CDCl_3$; Me_4Si) 1.50 (18 H, s, (C*H*$_3$)$_3$C), 2.45 (1 H, dd, *J* 5.9 and 17.0, C*H*$_2$CH), 2.66 (1 H, dd, *J* 5.9 and 17.0, C*H*$_2$CH), 3.50–3.70 (1 H, m, NCHC*H*), 3.70 (3 H, s, OC*H*$_3$), 4.60 (1 H, dd, *J* 3.6 and 8.9, NC*H*CH), 5.12 (2 H, s, OC*H*$_2$), 5.55 (1 H, d, *J* 8.9, N*H*), 7.35 (5 H, s, Ph); δ_C(75.4 MHz; $CDCl_3$; $CDCl_3$) 27.80 (q), 27.97 (q), 33.91 (t), 43.57 (d), 51.98 (q), 54.88 (d), 67.10 (t), 81.12 (s), 82.80 (s), 128.08 (d), 128.12 (d), 128.47 (d), 136.15 (s), 156.29 (s), 169.09 (s), 170.35 (s), 172.19 (s); *m*/*z* (CI: NH_4Cl) 469 (MNH_4^+, 4), 452.2283 (MH^+, 22%. $C_{23}H_{34}NO_8$ requires 452.2284), 340 (100), 269 (78), 91 (73).

Preparation of di-*tert*-butyl (2*S*,3*R*)-2-benzyloxycarbonylamino-3-methoxycarbonylglutarate (4a) and di-*tert*-butyl (2*S*,3*S*)-2-benzyloxycarbonylamino-3-methoxycarbonylglutarate (4b)

A solution of the dianion of diester **5** (102 mg, 0.3 mmol) dissolved in dry THF (20 cm^3) under nitrogen was prepared using LiHMDS (0.75 mmol) at −80 °C, as described above. A solution of *tert*-butyl chloroacetate (1 cm^3, 7 mmol) and NaI (225 mg, 1.5 mmol) dissolved in dry THF (10 cm^3) was then added to the orange dianion at such a rate so that the reaction temperature did not exceed −75 °C. Stirring was continued for a further 17 h at this temperature before the reaction mixture was poured into 1 M HCl (120 cm^3) at rt. This solution was then extracted using Et_2O (4 × 50 cm^3), and the organic phase was dried ($MgSO_4$) before removal of the solvent under reduced pressure. The resulting pale yellow oil was purified by "flash" chromatography (eluant: 4:1 petroleum ether–EtOAc) to give the alkylated product, as the first material eluted from the column. The triester was obtained as a 2:1 mixture of diastereoisomers (**4a**:**4b**) (49 mg, 36%), based on ^{1}H NMR analysis: **4b** δ_H(360 MHz; $CDCl_3$; Me_4Si) 1.50 (18 H, s, (C*H*$_3$)$_3$C), 3.22 (1 H, dd, *J* 3.5 and 18.0, C*H*$_2$CH), 3.32–3.37 (1 H, m, NCHC*H*), 3.46 (1 H, dd, *J* 3.5 and 18.0, C*H*$_2$CH), 3.70 (3 H, s, OC*H*$_3$), 4.50–4.55 (1 H, m, NC*H*CH), 5.00 (2 H, s, OC*H*$_2$), 5.66 (1 H, d, *J* 8.0, N*H*), 7.35 (5 H, s, Ph).

Preparation of (2*S*,3*R*)-2-benzyloxycarbonylamino-3-methoxycarbonylglutaric acid (6a)

TFA (2 cm^3, 12 mmol) was added to a solution of the triester **4a** (200 mg, 0.44 mmol) dissolved in CH_2Cl_2 (40 cm^3) at 0 °C with vigorous stirring. After a further 2 h at this temperature, the reaction mixture was slowly warmed and stirred for 12 h at 15 °C. Removal of the volatiles under reduced pressure gave an oil that was purified using reversed-phase HPLC with gradient elution (C_{18} column; solvent flow rate 12 cm^3 min^{-1}; 80:20:1 H_2O–CH_3CN–TFA to 20:80:1 H_2O–CH_3CN–TFA over 30 min). The desired diacid **6a** (105 mg, 70%) was obtained as a white solid (retention time 13.8 min) after lyophilization: mp 82–84 °C (Found: C, 53.1; H, 5.3; N, 4.2; $C_{15}H_{17}NO_8$ requires C, 53.1; H, 5.05; N, 4.1%); $[\alpha]_D^{20}$ +32.0 (*c* 0.1 in CH_3CN); ν_{max}($CHCl_3$)/cm^{-1} 3550–2900, 2853, 1726, 1509 and 1460; δ_H(360 MHz; CD_3CN; Me_4Si) 2.65 (1 H, dd, *J* 6.7 and 17.5, C*H*$_2$CH), 2.80 (1 H, dd, *J* 7.5 and 17.5, C*H*$_2$CH), 3.55–3.65 (1 H, m, NCHC*H*), 3.70 (3 H, s, OC*H*$_3$), 4.70 (1 H, dd, *J* 3.8 and 9.1, NC*H*CH), 5.16 (2 H, s, OC*H*$_2$), 5.40–5.60 (2 H, br s, CO_2H), 6.05 (1 H, d, *J* 9.0, N*H*), 7.43 (5 H, s, Ph); δ_C(90.6 MHz; CD_3CN; CD_3CN) 31.63 (t), 43.19 (d), 51.92 (q), 54.06 (d), 66.56 (t), 127.76 (d), 128.01 (d), 128.49 (d), 137.10 (s), 156.16 (s), 170.87 (s), 171.91 (s), 172.14 (s); *m*/*z* (CI: NH_4Cl) 340.1059 (MH^+, 4%. $C_{15}H_{18}NO_8$ requires 340.1032), 278 (28), 205 (13), 188 (43), 142 (34), 108 (52), 91 (100).

Preparation of (2*S*,3*R*)-2-benzyloxycarbonylamino-3-methoxycarbonylglutaric anhydride (7a)

Diacid **6a** (60 mg, 0.17 mmol) was dissolved in Ac_2O (5 cm^3)

and the solution warmed to 60 °C. The reaction mixture was stirred at this temperature for 4 h before cooling and removal of the solvent under reduced pressure. The resulting white solid was filtered and washed carefully with a minimum of dry CH_2Cl_2 to give the desired anhydride **7a** (46 mg, 80%) as a white powder: mp 142–143 °C; $[a]_D^{20}$ +3.0 (*c* 0.1 in CH_3CN); ν_{max}(Nujol)/cm^{-1} 3370, 1826, 1790, 1730, 1701 and 1535; δ_H(360 MHz; CD_3CN; Me_4Si) 3.05–3.20 (2 H, m, CHCH_2), 3.45–3.55 (1 H, m, NCHC*H*), 3.72 (3 H, s, OCH_3), 4.70 (1 H, dd, *J* 8.6 and 12.1, NC*H*CH), 5.16 (2 H, s, OCH_2), 6.45 (1 H, d, *J* 8.6, N*H*), 7.35–7.50 (5 H, m, Ph); δ_C(90.6 MHz; CD_3CN; CD_3CN) 32.50 (t), 43.30 (d), 52.40 (q), 54.06 (d), 66.70 (t), 127.80 (d), 128.10 (d), 128.50 (d), 145.80 (s), 156.10 (s), 164.30 (s), 170.60 (s), 172.10 (s); *m*/*z* (EI) 321 (M$^+$, 6%), 188 (14), 142 (13), 108 (20), 107 (29), 91 (100).

Preparation of (2*S*,3*R*)-2-benzyloxycarbonylamino-3-methoxycarbonylglutaric anhydride (7a) and (2*S*,3*S*)-2-benzyloxycarbonylamino-3-methoxycarbonylglutaric anhydride (7b)

The mixture of diastereoisomeric triesters **4a** and **4b** was converted to the corresponding mixture of cyclic anhydrides **7a** and **7b** using identical procedures to those outlined above. The ^{1}H NMR resonances of the two anhydrides in the mixture could be easily distinguished: **7b** δ_H(360 MHz; CD_3CN; Me_4Si) 3.17–3.19 (2 H, m, CHCH_2), 3.42–3.45 (1 H, m, NCHC*H*), 3.75 (3 H, s, OCH_3), 4.95 (1 H, dd, *J* 5.2 and 8.3, NC*H*CH), 5.18 (2 H, s, OCH_2), 6.35 (1 H, br s, N*H*), 7.35–7.50 (5 H, m, Ph).

Preparation of di-*tert*-butyl (2*S*,3*R*)-2-amino-3-methoxycarbonylglutarate (8)

10% Pd/C (20 mg) was added to a solution of the triester **6a** (630 mg, 1.4 mmol) dissolved in cyclohexene (20 cm^3) and MeOH (40 cm^3), and the resulting heterogeneous mixture refluxed for 28 h. The catalyst was removed by filtration through Celite and subsequently washed well with MeOH (400 cm^3). Solvent from the combined filtrate and washings was then removed under reduced pressure to yield a thick oil that was re-dissolved in EtOAc (30 cm^3). After washing with brine, the organic layer was dried ($MgSO_4$) and the solvent removed to give the desired amine **8** (419 mg, 95%) as a white solid that was used without further purification: mp 76–78 °C; $[a]_D^{20}$ +4.7 (*c* 0.01 in $CHCl_3$); ν_{max}($CHCl_3$)/cm^{-1} 3464, 2984, 2909, 1743, 1447, 1372 and 1243; δ_H(360 MHz; $CDCl_3$; Me_4Si) 1.44 (9 H, s, (CH_3)$_3$C), 1.47 (9 H, s, (CH_3)$_3$C), 2.71 (1 H, dd, *J* 5.5 and 16.9, CH_2CH), 2.82 (1 H, dd, *J* 8.3 and 16.9, CH_2CH), 3.52 (1 H, m, C*H*CH$_2$), 3.72 (3 H, s, OCH_3), 4.00 (1 H, d, *J* 2.0, NC*H*CH), 4.32–4.50 (2 H, br s, N*H*); δ_C(75.4 MHz; $CDCl_3$; $CDCl_3$) 28.31 (q), 28.43 (q), 34.33 (t), 45.58 (d), 52.27 (q), 55.90 (d), 81.44 (s), 82.47 (s), 171.54 (s), 172.78 (s), 172.86 (s); *m*/*z* (CI: NH_4Cl) 318.1917 (MH$^+$, 100%. $C_{15}H_{28}NO_6$ requires 318.1917), 262 (19), 160 (10).

Enantiomeric purity of di-*tert*-butyl (2*S*,3*R*)-2-amino-3-methoxycarbonylglutarate (8)

Neat (*S*)-α-methylbenzyl isocyanate (0.12 cm^3, 0.84 mmol) was added to a solution of amine **8** (80 mg, 0.25 mmol) in dry THF (10 cm^3) under an inert atmosphere of dry N_2. In a separate reaction, neat (*R*)-α-methylbenzyl isocyanate (0.16 cm^3, 1.1 mmol) was added to a solution of triester **6a** (130 mg, 0.4 mmol) in dry THF (10 cm^3) under an inert atmosphere of dry N_2. After being heated to reflux for 3 h, the volatile components of the resulting reaction mixtures were removed under reduced pressure. The desired urea derivatives, **9a** and **9b**, respectively, were obtained as oily residues that were examined directly by ^{1}H NMR. The methyl ester singlets of each urea in the ^{1}H NMR spectrum were clearly differentiated, and the limits of detection were determined by incremental doping experiments using pure samples of the two ureas **9a** and **9b**. This method demonstrated that the (2*S*,3*R*)-amine **8** was of >95% diastereoisomeric purity.

9a δ_H(500 MHz; $CDCl_3$; Me_4Si) 1.41 (9 H, s, (CH_3)$_3$C), 1.43 (9 H, s, (CH_3)$_3$C), 1.58 (3 H, d, *J* 7.0, CH_3CH), 2.30 (1 H, m, CH_2CH), 2.51 (1 H, dd, *J* 9.8 and 17.1, CH_2CH), 3.47 (1 H, dt, *J* 4.9 and 8.8, NCHC*H*), 3.61 (3 H, s, OCH_3), 4.08 (1 H, m, NC*H*CH), 4.82 (1 H, q, *J* 7.0, CH_3C*H*), 5.02 (1 H, br s, C(=O)N*H*), 5.52 (1 H, br s, C(=O)N*H*), 7.20–7.40 (5 H, m, Ph); δ_C(75.4 MHz; $CDCl_3$; $CDCl_3$) 22.38 (q), 27.72 (q), 27.91 (q), 33.80 (t), 44.08 (d), 50.22 (d), 51.73 (q), 54.46 (d), 80.75 (s), 82.40 (s), 125.19 (d), 126.67 (d), 128.48 (d), 142.32 (s), 156.92 (s), 170.27 (s), 170.65 (s), 172.47 (s).

9b δ_H(500 MHz; $CDCl_3$; Me_4Si) 1.41 (18 H, s, (CH_3)$_3$C), 1.58 (3 H, d, *J* 6.8, CH_3CH), 2.44 (1 H, dd, *J* 4.9 and 16.6, CH_2CH), 2.63 (1 H, dd, *J* 9.3 and 17.1, CH_2CH), 3.49 (1 H, m, NCHC*H*), 3.63 (3 H, s, OCH_3), 4.08 (1 H, m, NC*H*CH), 4.85 (1 H, q, *J* 6.8, CH_3C*H*), 5.02 (1 H, br s, C(=O)N*H*), 5.48 (1 H, br s, C(=O)N*H*), 7.28–7.38 (5 H, m, Ph); δ_C(75.4 MHz; $CDCl_3$; $CDCl_3$) 23.02 (q), 27.73 (q), 27.89 (q), 34.06 (t), 43.98 (d), 49.93 (d), 51.72 (q), 54.48 (d), 80.78 (s), 82.32 (s), 125.20 (d), 126.94 (d), 128.48 (d), 142.33 (s), 157.08 (s), 170.37 (s), 170.68 (s), 172.58 (s).

Preparation of di-*tert*-butyl (2*S*,3*R*)-2-(4-bromophenyl)-carbonylamino-3-methoxycarbonylglutarate (10)

A suspension of 4-bromobenzoyl chloride (269 mg, 1.22 mmol) in benzene (6 cm^3) was added to a solution of the amine **8** (388 mg, 1.22 mmol) and triethylamine (0.17 cm^3, 1.22 mmol) in benzene (10 cm^3). The reaction mixture was stirred vigorously for 20 h before the solvent was removed under reduced pressure. The residue was suspended in EtOAc and the solid removed by filtration. The crude diester, obtained as an oil after removal of the solvent, was then purified by column chromatography on silica (eluant: 85:15 petroleum ether–EtOAc). The desired diester **10** (356 mg, 58%) was isolated as a colorless oil: $[a]_D^{20}$ +31.1 (*c* 3.2 in CH_2Cl_2); ν_{max}(neat)/cm^{-1} 3419, 2980, 1732, 1668, 1480, 1369 and 1153; δ_H(300 MHz; $CDCl_3$; Me_4Si) 1.43 (9 H, s, (CH_3)$_3$C), 1.48 (9 H, s, (CH_3)$_3$C), 2.55 (1 H, dd, *J* 6.0 and 17.1, CH_2CH), 2.67 (1 H, dd, *J* 8.4 and 17.1, CH_2CH), 3.65 (1 H, m, NCHC*H*), 3.74 (3 H, s, OCH_3), 5.02 (1 H, dd, *J* 3.4 and 8.5, NC*H*CH), 6.96 (1 H, d, *J* 8.5, N*H*), 7.57 (2 H, m, 3′,5′-PhH_2), 7.80 (2 H, m, 2′,6′-PhH_2); δ_C(75.4 MHz; $CDCl_3$; $CDCl_3$) 27.82 (q), 27.95 (q), 34.32 (t), 43.35 (d), 52.01 (q), 53.37 (d), 81.25 (s), 83.03 (s), 126.48 (s), 128.73 (d), 131.76 (d), 132.63 (s), 166.36 (s), 169.02 (s), 170.28 (s), 172.61 (s); *m*/*z* (CI: NBA) 500.1150 (MH$^+$, 24%. $C_{22}H_{31}BrNO_7$ requires 500.1280), 444 (10), 390 (100), 388 (99), 185 (21).

Preparation of *tert*-butyl (2*S*,3*R*)-2-(4-bromophenyl)carbonyl-amino-3-methoxycarbonylglutaric acid monoester (11) and (2*S*,3*R*)-2-(4-bromophenyl)carbonylamino-3-methoxy-carbonylglutaric acid (12)

TFA (0.46 cm^3, 6 mmol) was added dropwise to a solution of the triester **10** (300 mg, 0.6 mmol) in CH_2Cl_2 (20 cm^3) at rt. The reaction was stirred for 5 days before the volatile components were removed under reduced pressure. The resulting oily residue was then dissolved in EtOAc to give a solution that was extracted with 5% w/v aq. Na_2CO_3. The combined aqueous extracts were then acidified to pH 1 using 6 M HCl, and then extracted with EtOAc. After drying (Na_2SO_4) the solvent was removed under reduced pressure to give a brown oil which was purified using reversed-phase HPLC with gradient elution (C_{18} column; solvent flow rate 12 cm^3 min^{-1}; 80:20:1 H_2O–CH_3CN–TFA to 20:80:1 H_2O–CH_3CN–TFA over 30 min). The monoacid **11** (49 mg, 19%) was obtained as a white solid after lyophilization: mp 56–57 °C; ν_{max}($CHCl_3$)/cm^{-1} 3542–2835, 3423, 3019, 1737, 1667, 1592, 1516, 1480 and 1370; δ_H(300 MHz; $CDCl_3$; Me_4Si) 1.48 (9 H, s, (CH_3)$_3$C), 2.63 (1 H, dd, *J* 6.9 and 17.3, CH_2CH), 2.76 (1 H, dd, *J* 7.6 and 17.3, CH_2CH), 3.71 (1 H, m, NCHC*H*), 3.74 (3 H, s, OCH_3), 5.10 (1 H, dd,

J 3.4 and 8.3, NC*H*CH), 7.01 (1 H, d, *J* 8.3, N*H*), 7.57 (2 H, m, 3′,5′-PhH_2), 7.67 (2 H, m, 2′,6′-PhH_2), 8.10–8.70 (1 H, br s, CO_2H); δ_C(75.4 MHz; $CDCl_3$; $CDCl_3$) 27.82 (q), 32.61 (t), 43.39 (d), 52.25 (q), 53.26 (d), 83.48 (s), 126.78 (s), 128.77 (d), 131.88 (d), 132.29 (s), 166.95 (s), 168.69 (s), 172.22 (s), 175.12 (s); *m*/*z* (FAB: NBA) 444.0654 (MH^+, 17%. $C_{18}H_{23}BrNO_7$ requires 444.0658), 390 (100), 388 (91), 185 (48), 183 (48).

On continued elution, the diacid **12** (38 mg, 16%) was also obtained as a white solid after lyophilization: mp 155–157 °C; ν_{max}($CHCl_3$)/cm^{-1} 3500–3000, 3620, 3541, 1742, 1670, 1633, and 1482; δ_H(300 MHz; CD_3CN; Me_4Si) 2.63 (1 H, dd, *J* 6.6 and 17.4, CH_2CH), 2.81 (1 H, dd, *J* 7.4 and 17.4, CH_2CH), 3.20–4.00 (1 H, br s, CO_2H), 3.58 (1 H, m, NCHC*H*), 3.68 (3 H, s, OCH_3), 5.06 (1 H, dd, *J* 4.1 and 8.4, NC*H*CH), 7.30 (1 H, d, *J* 7.8, N*H*), 7.64 (2 H, m, 3′,5′-PhH_2), 7.71 (2 H, m, 2′,6′-PhH_2), 8.10–8.70 (1 H, br s, CO_2H); δ_C(75.4 MHz; CD_3CN; CD_3CN) 32.31 (t), 43.77 (d), 52.80 (q), 84.07 (d), 128.77 (s), 130.08 (d), 132.58 (d), 133.88 (s), 167.43 (s), 170.00 (s), 173.08 (s), 177.08 (s); *m*/*z* (FAB: NBA) 388.0018 (MH^+, 15%. $C_{14}H_{25}BrNO_7$ requires 388.0032), 289 (8), 154 (100), 136 (70).

Preparation of (2*S*,3*R*)-2-benzyloxycarbonylamino-3-carbamoylglutaric acid (13)

Diacid **6a** (200 mg, 0.59 mmol) was dissolved in conc. NH_4OH (4 cm^3) at 0 °C. The reaction mixture was then warmed to rt, and stirred for 4 days before being poured into 1 M aq. HCl (50 cm^3). This solution was then extracted with EtOAc (4 × 20 cm^3), and the combined organic fractions dried ($MgSO_4$). Removal of the solvent gave a white solid that was purified by reversed-phase HPLC with gradient elution (C_{18} column; solvent flow rate 10 cm^3 min^{-1}; 80:20:1 H_2O–CH_3CN–TFA to 20:80:1 H_2O–CH_3CN–TFA over 30 min). The desired diacid **13** (48 mg, 25%) was obtained as a white solid after lyophilization: mp 145–147 °C (Found: C, 51.8; H, 4.9; N, 8.4; $C_{14}H_{16}N_2O_7$ requires C, 51.8; H, 5.0; N, 8.6%); ν_{max}($CHCl_3$)/cm^{-1} 3550–2900, 3423, 3340, 3019, 1739, 1693, 1650, 1531 and 1275; δ_H(300 MHz; CD_3OD; Me_4Si) 2.57 (2 H, ddd, *J* 7.2, 7.4 and 17.2, CH_2CH), 3.34 (1 H, m, NCHC*H*), 4.42 (1 H, d, *J* 5.0, NC*H*CH), 5.12 (2 H, s, OCH_2), 7.15–7.29 (5 H, s, Ph); δ_C(90.6 MHz; CD_3OD; CD_3OD) 33.27 (t), 42.39 (d), 54.59 (d), 66.50 (t), 127.37 (d), 127.61 (d), 128.05 (d), 135.55 (s), 157.19 (s), 171.90 (s), 172.10 (s), 173.22 (s); *m*/*z* (FAB: Gly, TFA) 325.1004 (MH^+, 100%. $C_{14}H_{17}N_2O_7$ requires 325.1035), 281 (20), 207 (30), 186 (25).

Preparation of (2*S*,3*R*)-2-benzyloxycarbonylamino-3-carboxyglutaric acid (14a) and (2*S*,3*S*)-2-benzyloxycarbonylamino-3-carboxyglutaric acid (14b)

The N-protected diacid **6a** (249 mg, 0.73 mmol) was dissolved in a 4:1 mixture of MeOH–H_2O so as to yield an 0.1 M solution. Four equivalents of $LiOH·H_2O$ were then added and the reaction stirred at rt until complete consumption of starting material had occurred. After concentration under reduced pressure, the residue was added to an excess of 1 M aq. HCl and the resulting solution extraced well with EtOAc. The combined organic extracts were then dried ($MgSO_4$) before removal of the solvent yielded the crude triacid as an oil. Purification of the product was accomplished using reversed-phase HPLC with gradient elution (C_8 column; solvent flow rate 20 cm^3 min^{-1}; 80:20:1 H_2O–CH_3CN–TFA to 60:40:1 H_2O–CH_3CN–TFA over 40 min). The desired triacid **14a** (159 mg, 67%) was obtained as a white solid (retention time 13.3 min) after lyophilization (Found: C, 51.6; H, 4.6; N, 4.2; $C_{14}H_{15}NO_8$ requires C, 51.7; H, 4.6; N, 4.3%); ν_{max}($CHCl_3$)/cm^{-1} 3713–2319, 1714, 1518, 1416, 1345, 1216, 1063 and 758; δ_H(300 MHz; CD_3CN; Me_4Si) 2.55 (1 H, dd, *J* 7.3 and 19.3, CH_2CH), 2.72 (1 H, dd, *J* 7.0 and 17.5, CH_2CH), 3.46–3.53 (1 H, m, NCHC*H*), 4.63 (1 H, dd, *J* 3.6 and 9.2, NC*H*CH), 5.12 (2 H, s, OCH_2), 5.93 (1 H, d, *J* 9.0, N*H*), 7.30–7.40 (5 H, m, Ph), 7.80–8.80 (3 H, br s, CO_2H); δ_C(75.4 MHz; CD_3OD; CD_3OD) 32.01 (t), 43.18 (d), 54.15 (d), 66.49 (t), 127.36 (d), 127.58 (d), 128.03 (d), 137.10 (s), 157.19 (s), 172.06 (s), 172.70 (s), 173.56 (s); *m*/*z* (FAB) 326.0860 (MH^+, 41%. $C_{14}H_{16}NO_8$ requires 326.0880), 282 (29), 93 (100).

Continued elution gave a small amount of the diastereoisomeric triacid **14b** (16 mg, 7%) as a white solid (retention time 13.7 min) after lyophilization: δ_H(300 MHz; CD_3CN; Me_4Si) 2.55 (1 H, dd, *J* 4.4 and 17.2, CH_2CH), 2.72 (1 H, dd, *J* 9.4 and 17.2, CH_2CH), 3.30 (1 H, m, NCHC*H*), 4.66 (1 H, dd, *J* 5.0 and 9.2, NC*H*CH), 5.09 (2 H, s, OCH_2), 5.50–6.00 (3 H, br s, CO_2H), 6.12 (1 H, d, *J* 9.0, N*H*), 7.30-7.40 (5 H, m, Ph).

Preparation of (4*S*)-3-benzyloxycarbonyl-4-[(1*R*)-methoxycarbonyl-2-carboxyethyl)-5-oxooxazolidine (15)

A suspension of diacid **6a** (100 mg, 0.3 mmol), paraformaldehyde (65 mg) and pTsOH (6 mg) in toluene (50 cm^3) was refluxed, with azeotropic removal of water using activated 4 Å molecular sieves, for 4 h. After this time, a further portion of paraformaldehyde (80 mg) was added and refluxing continued for 1.5 h. After cooling, the reaction mixture was loaded onto a silica column and eluted initially with toluene (100 cm^3) and then EtOAc (400 cm^3). Removal of the solvent from the combined EtOAc fractions then yielded a yellow oil that crystallized on standing. The desired acid **15** (90 mg, 88%) was then obtained as a white solid after recrystallization from Et_2O–EtOAc: mp 156–158 °C; $[\alpha]_D^{20}$ +66.5 (*c* 0.2 in $CHCl_3$); ν_{max}($CHCl_3$)/cm^{-1} 3550–2900, 1813, 1748, 1705 and 1415; δ_H(300 MHz; CD_3CN; Me_4Si) 2.75 (1 H, m, CH_2CH), 2.85 (1 H, m, CH_2CH), 3.62 (1 H, dt, *J* 2.7 and 5.8, NCHC*H*), 3.72 (3 H, s, OCH_3), 4.68 (1 H, d, *J* 2.7, NC*H*CH), 5.18 (2 H, s, OCH_2Ph), 5.22 (2 H, s, OCH_2N), 5.58 (1 H, d, *J* 4.3, N*H*), 7.40 (5 H, s, Ph); δ_C(74.5 MHz; CD_3CN; CD_3CN) 32.66 (t), 43.42 (d), 52.89 (q), 55.85 (d), 66.77 (t), 79.03 (t), 128.67 (d), 128.87 (d), 128.92 (d), 135.05 (s), 155.16 (s), 171.18 (s), 172.57 (s), 176.36 (s); *m*/*z* (EI) 352.1019 (MH^+, 5%. $C_{16}H_{18}NO_8$ requires 352.1032), 198 (10),170 (18), 156 (8), 91 (100).

Preparation of triphenylmethyl (2*S*)-2-benzyloxycarbonylamino-3-methoxycarbonylpropionate (17)

(2*S*)-2-benzyloxycarbonylamino-3-methoxycarbonylpropionic acid (750 mg, 2.67 mmol) was dissolved in aq. Cs_2CO_3 (435 mg in 20 cm^3). The caesium salt was then isolated as a glassy solid after removal of the solvent by lyophilization. This solid was redissolved in dry THF (20 cm^3) together with triphenylmethyl bromide (970 mg, 3 mmol), and the solution heated to reflux for 3.5 h. After cooling to rt and filtration, the solvent was removed to give the diester **17** (1.35 g, 98%) as a colorless oil: $[\alpha]_D^{20}$ −14.1 (*c* 6.7 in $CHCl_3$); ν_{max}($CHCl_3$)/cm^{-1} 3427, 3060, 3052, 1732, 1494, and 1448; δ_H(300 MHz; $CDCl_3$; Me_4Si) 2.80–3.07 (2 H, dd, *J* 4.5 and 16.7, CHCH_2CO), 3.54 (3 H, s, OCH_3), 4.68–4.76 (1 H, m, NC*H*CH_2), 5.07 (2 H, m), 5.89 (1 H, d, *J* 9.0, N*H*), 7.20–7.37 (20 H, m, Ph); δ_C(75.4 MHz; $CDCl_3$; $CDCl_3$) 36.25 (t), 51.54 (d), 51.91 (q), 67.16 (t), 82.02 (s), 92.01 (s), 127.21 (d), 127.52 (d), 127.90 (d), 128.02 (d), 128.16 (d), 128.44 (d), 142.76 (s), 147.07 (s), 168.39 (s), 171.04 (s); *m*/*z* (FAB: TFA) 524 (MH^+, 2%), 324 (17), 282 (100), 243 (85), 238 (50), 185 (85).

Preparation of (2*S*,3*R*)-2-benzyloxycarbonylamino-3-(prop-2-enyl)succinic anhydride (22a)

The N-protected diacid **21a** (60 mg, 0.29 mmol) was dissolved in Ac_2O (5 cm^3), and the solution heated at 75 °C for 3 h. Removal of the solvent under reduced pressure then gave the desired anhydride **22a** (54 mg, 99%) as a colorless oil: $[\alpha]_D^{20}$ +73.5 (*c* 0.68 in CH_3CN); ν_{max}(neat)/cm^{-1} 3366, 3036, 2931, 1872, 1790, 1728, 1520, 1455, 1227 and 1220; δ_H(300 MHz; CD_3CN; Me_4Si) 2.20–2.30 (1 H, m, CHCH_2CH), 2.45–2.55 (1 H, m, CHCH_2CH), 3.30–3.40 (1 H, m, NCHC*H*), 4.60 (1 H, dd, *J* 7.8

and 10.2, NC*H*CH), 5.03–5.15 (4 H, m, OCH_2Ph and CH_2=CH), 5.78–5.92 (1 H, m, CH$_2$=C*H*), 6.52 (1 H, d, *J* 7.8, N*H*), 7.31–7.42 (5 H, m, Ph); δ_C(75.4 MHz; CD_3CN; CD_3CN) 28.82 (t), 42.62 (d), 52.35 (d), 67.21 (t), 116.68 (t), 127.95 (d), 128.22 (d), 128.51 (d), 134.43 (d), 136.40 (s), 156.70 (s), 170.63 (s), 172.32 (s); *m*/*z* (EI) 289.0935 (M^+, 2%. $C_{15}H_{15}NO_5$ requires 289.0950), 218 (9), 172 (12), 108 (64), 91 (100).

Preparation of (2*S*,3*R*)-2-benzyloxycarbonylamino-3-(prop-2-enyl)succinic anhydride (22a) and (2*S*,3*S*)-2-benzyloxycarbonylamino-3-(prop-2-enyl)succinic anhydride (22b)

A mixture of the diastereoisomeric acids **21a** and **21b** was treated with Ac_2O as described above for the pure diastereoisomer **21a**. The product mixture of anhydrides **22a** and **22b** was analyzed using ^{1}H NMR spectroscopy. **22b**: δ_H(300 MHz; CD_3CN; Me_4Si) 2.45–2.57 (1 H, m, CHCH_2CH), 2.61–2.72 (1 H, m, CHCH_2CH), 3.37–3.47 (1 H, dt, *J* 5.4 and 8.1, NCHC*H*), 4.42 (1 H, dd, *J* 8.0 and 8.1, NC*H*CH), 5.05–5.30 (4 H, m, OCH_2Ph and CH_2=CH), 5.75–5.90 (1 H, m, CH$_2$=C*H*), 6.49 (1 H, d, *J* 8.0, N*H*), 7.35–7.45 (5 H, m, Ph).

Preparation of *tert*-butyl (2*S*,3*R*)-2-benzyloxycarbonylamino-3-methoxycarbonyl-4-cyanobutyrate (25a) and *tert*-butyl (2*S*,3*S*)-2-benzyloxycarbonylamino-3-methoxycarbonyl-4-cyanobutyrate (25b)

A solution of the diester **5** (150 mg, 0.45 mmol) dissolved in dry THF (8 cm^3) was added dropwise to LiHMDS (1.2 cm^3 of a 1 M solution in THF, 1.2 mmol) at −80 °C, under nitrogen. After stirring for 30 min at −78 °C, the pale-yellow solution was warmed slowly to −30 °C and left for a further 2 h to ensure formation of the dianion. The resulting orange solution was re-cooled to −78 °C before the addition of neat bromoacetonitrile (0.25 cm^3, 2.5 mmol) at such a rate so that the reaction temperature did not exceed −75 °C. Stirring was continued for a further 16 h at −78 °C before the reaction mixture was poured into 1 M HCl (120 cm^3) at rt. Standard workup procedures, as outlined above, followed by "flash" chromatography (eluant: 17:3 petroleum ether–EtOAc) gave the diester **25** as an inseparable mixture of diastereoisomers (116 mg, 69%). ^{1}H NMR analysis of this oil showed a 2:1 ratio of **25a**:**25b**: ν_{max}(neat)/cm^{-1} 3357, 2980, 2251, 1742, 1732, 1513, 1372, 1227 and 1155; δ_H(300 MHz; $CDCl_3$; Me_4Si) 1.47 (9 H, s, (CH_3)$_3$C), 2.60–2.94 (2 H, m, CH_2CH), 3.44 (1 H, m, NCHC*H*), 3.75 (3 H, s, OCH_3), 4.60–4.70 (1 H, m, NC*H*CH), 5.13 (2 H, s, OCH_2), 5.63 (1 H, d, *J* 8.0, N*H*), 7.34–7.49 (5 H, s, Ph); δ_C(75.4 MHz; $CDCl_3$; $CDCl_3$) 16.79 (t), 27.80 (q), 44.51 (d), 52.75 (d), 54.91 (q), 67.46 (t), 83.99 (s), 117.45 (s), 128.20 (d), 128.33 (d), 128.56 (d), 135.79 (s), 156.47 (s), 167.91 (s), 167.96 (s); *m*/*z* (CI: CH_4) 377.1731 (MH^+, 10%. $C_{19}H_{25}N_2O_6$ requires 377.1713), 320 ($MH^+ - C_4H_9$, 8), 231 (6), 185 (4), 141 (5), 91 (100).

Preparation of *tert*-butyl (2*S*,3*R*)-2-benzyloxycarbonylamino-3-methoxycarbonylhex-5-ynoate (26a) and *tert*-butyl (2*S*,3*S*)-2-benzyloxycarbonylamino-3-methoxycarbonylhex-5-ynoate (26b)

A solution of the diester **5** (150 mg, 0.45 mmol) dissolved in dry THF (6 cm^3) was added dropwise to LiHMDS (0.94 cm^3 of a 1 M solution in THF, 0.93 mmol) at −80 °C, under nitrogen. After stirring for 30 min at −78 °C, the pale-yellow solution was warmed slowly to −30 °C and left for a further 2 h to ensure formation of the dianion. The resulting orange solution was re-cooled to −78 °C before the addition of propargyl bromide (prop-2-ynyl bromide), as an 80% w/v toluene solution (331 mg, 2.23 mmol) at such a rate that the reaction temperature did not exceed −75 °C. Stirring was continued for a further 18 h at −78 °C before the reaction mixture was poured into 1 M HCl (120 cm^3) at rt. This solution was then extracted using Et_2O (4 × 50 cm^3) and the organic phase was dried ($MgSO_4$) before removal of the solvent under reduced pressure. The crude product was then purified by "flash" chromatography (eluant: 17:3 petroleum ether–EtOAc) to give the diester **26** as a mixture of diastereoisomers (115 mg, 70%). ^{1}H NMR analysis of this oil showed a 4.5:1 ratio of **26a**:**26b**. Careful column chromatography gave the pure diester **26a** (67 mg, 41%) as a clear oil: $[a]_D^{20}$ +31.2 (*c* 0.64 in $CHCl_3$); ν_{max}($CHCl_3$)/cm^{-1} 3413, 3296, 2979, 1732, 1713, 1455, 1337, 1156 and 1056; δ_H(300 MHz; $CDCl_3$; Me_4Si) 1.45 (9 H, s, (CH_3)$_3$C), 2.16 (1 H, m, C≡C*H*), 2.49 (1 H, ddd, *J* 2.6, 8.6 and 17.0, CH_2CH), 2.66 (1 H, ddd, *J* 2.6, 6.5 and 17.0, CH_2CH), 3.32 (1 H, m, CC*H*), 3.71 (3 H, s, OCH_3), 4.88 (1 H, dd, *J* 3.2 and 9.4, NC*H*CH), 5.12 (2 H, s, OCH_2), 5.60 (1 H, d, *J* 9.4, N*H*), 7.30–7.45 (5 H, s, Ph); δ_C(75.4 MHz; $CDCl_3$; $CDCl_3$) 18.21 (t), 27.80 (q), 46.34 (d), 52.02 (q), 54.72 (d), 67.10 (t), 70.66 (s), 81.44 (s), 82.72 (s), 128.01 (d), 128.06 (d), 128.42 (d), 136.27 (s), 156.27 (s), 169.14 (s), 171.68 (s); *m*/*z* (CI: NBA) 376.1761 (MH^+, 37%. $C_{20}H_{26}NO_6$ requires 376.1760), 320 (100), 276 (57), 154 (42).

26b: δ_H(300 MHz; $CDCl_3$; Me_4Si) 1.45 (9 H, s, (CH_3)$_3$C), 2.16 (1 H, m, C≡C*H*), 2.49 (1 H, ddd, *J* 2.6, 8.6 and 17.0, CH_2CH), 2.66 (1 H, ddd, *J* 2.6, 6.5 and 17.0, CH_2CH), 3.32 (1 H, m, CC*H*), 3.71 (3 H, s, OCH_3), 4.88 (1 H, dd, *J* 3.2 and 9.4, NC*H*CH), 5.12 (2 H, s, OCH_2), 5.60 (1 H, d, *J* 9.4, N*H*), 7.30–7.45 (5 H, s, Ph).

Preparation of *tert*-butyl (2*S*,3*R*,4*R*)-2-benzyloxycarbonylamino-3-methoxycarbonyl-4-hydroxy-4-phenylbutanoate (27a) and (2*S*,3*R*,4*S*)-2-benzyloxycarbonylamino-3-methoxycarbonyl-4-hydroxy-4-phenylbutanoate (27b)

A solution of the diester **5** (135 mg, 0.40 mmol) dissolved in dry THF (6 cm^3) was added dropwise to LiHMDS (0.46 cm^3 of a 2 M solution in THF, 0.9 mmol) at −75 °C, under nitrogen. After stirring for 30 min at −78 °C, the pale-yellow solution was warmed slowly to −30 °C and left for a further 2 h to ensure formation of the dianion. The resulting orange solution was re-cooled to −78 °C before the addition of neat benzaldehyde (0.25 cm^3, 2.5 mmol) at such a rate that the reaction temperature did not exceed −75 °C. Stirring was continued for a further 27 h at −78 °C before the reaction mixture was worked up using standard procedures, as outlined above. "Flash" chromatography (eluant: 3:1 petroleum ether–EtOAc) gave the diester **27** as an inseparable mixture of diastereoisomers (118 mg, 67%): ν_{max}(CH_2Cl_2)/cm^{-1} 3414, 3053, 2979, 1727, 1505 and 1264; δ_H(300 MHz; $CDCl_3$; Me_4Si) 1.36 (9 H, s, (CH_3)$_3$C), 3.27 (1 H, m, NCHC*H*), 3.57 (3 H, s, OCH_3), 4.25 (1 H, m, C*H*-(OH)CH), 4.93 (1 H, d, *J* 8.0, NC*H*CH), 5.05 (2 H, s, OCH_2), 5.77 (1 H, d, *J* 8.0, N*H*), 7.20–7.35 (10 H, m, Ph); δ_C(75.4 MHz; $CDCl_3$; $CDCl_3$) 27.85 (q), 52.12 (q), 53.62 (d), 54.49 (d), 67.09 (t), 72.39 (d), 83.05 (s), 126.04 (d), 126.60 (d), 128.13 (d), 128.34 (d), 128.47 (d), 128.69 (d), 136.21 (s), 140.66 (s), 156.04 (s), 169.15 (s), 172.31 (s); *m*/*z* (CI: NH_4^+) 444.2040 (MH^+, 12%. $C_{24}H_{30}NO_7$ requires 444.2020), 413 (100), 370 (81), 326 (39), 91 (80).

Preparation of *tert*-butyl (2*S*,3*R*,4*R*)-2-benzyloxycarbonylamino-3-methoxycarbonyl-4-hydroxyhex-5-enoate (28a) and (2*S*,3*R*,4*S*)-2-benzyloxycarbonylamino-3-methoxycarbonyl-4-hydroxyhex-5-enoate (28a)

A solution of the diester **5** (200 mg, 0.60 mmol) dissolved in dry THF (6 cm^3) was added dropwise to LiHMDS (1.8 cm^3 of a 1 M solution in THF, 1.8 mmol) at −75 °C, under nitrogen. After stirring for 30 min at −78 °C, the pale-yellow solution was warmed slowly to −30 °C and left for a further 2 h to ensure formation of the dianion. The resulting orange solution was re-cooled to −78 °C before the addition of neat acrolein (0.2 cm^3, 3 mmol) at such a rate so that the reaction temperature did not exceed −75 °C. Stirring was continued for a further 27 h at −78 °C before the reaction mixture was worked up using the standard procedures outlined above. "Flash" chromatography (eluant: 4:1 petroleum ether–EtOAc) gave the diester **28** as an

inseparable mixture of diastereoisomers (126 mg, 54%): ν_{max}(neat)/cm^{-1} 3418, 2954, 1728, 1512, 1455, 1369, 1227 and 1157; δ_H(300 MHz; $CDCl_3$; Me_4Si) 1.45 (9 H, s, $(CH_3)_3C$), 3.05 (1 H, m, NCHC*H*), 3.40 (1 H, m, O*H*), 3.70 (3 H, s, OCH_3), 4.47 (1 H, m, C*H*(OH)CH), 4.64 (1 H, m, NC*H*CH), 5.12 (2 H, s, OCH_2), 5.13–5.40 (2 H, m, H_2C=CH), 5.69–5.99 (2 H, m, *NH* and H_2C=C*H*), 7.30–7.38 (5 H, s, Ph); δ_C(75.4 MHz; $CDCl_3$; $CDCl_3$) 27.84 (q), 52.07 (d), 52.47 (q), 53.29 (d), 67.20 (t), 70.05 (d), 83.01 (s), 117.03 (t), 128.10 (d), 128.20 (d), 128.49 (d), 136.55 (d), 137.63 (s), 169.23 (s), 171.70 (s), 172.08 (s); *m/z* (CI: NH_4^+) 394.1864 (MH^+, 87%. $C_{20}H_{28}NO_7$ requires 394.1863), 320 ($MH^+ - C_4H_9$, 8), 231 (6), 185 (4), 141 (5), 91 (100).

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