S_N2' Ring opening of aziridines bearing an α,β-unsaturated ester group with organocopper reagents. A new stereoselective synthetic route to (*E*)-alkene dipeptide isosteres

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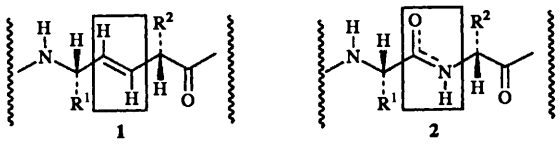
Regio- and stereo-selective synthesis of (*E*)-alkene dipeptide isosteres has been successfully achieved by exposing both (*E*)- and (*Z*)-*N*-(4-methylphenyl)sulfonyl-γ,δ-epimino-α,β-enoates to organocopper reagents at −78 °C for 30 min.

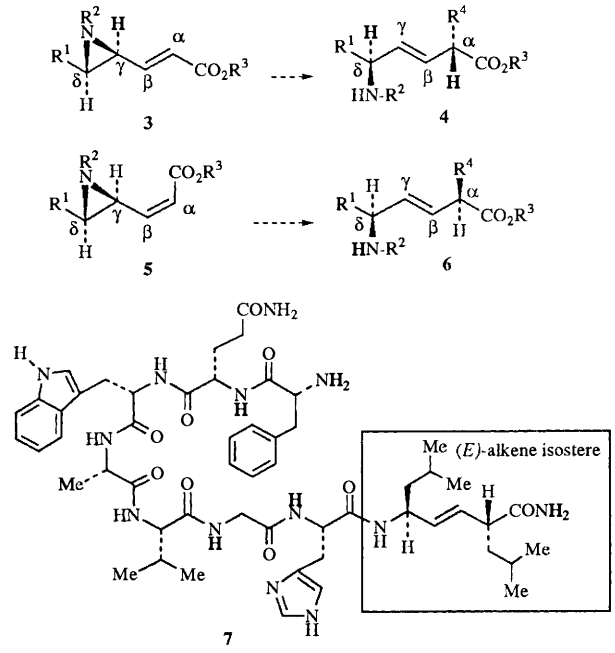
Recently, there has been considerable interest in the backbone modification of amide bonds in biologically active peptides.†[1] Among the known isosteric units, the (*E*)-double bond has been a topic of long-standing interest in the synthetic,[2] theoretical[3] and biological arena.[4] The (*E*)-CH=CH double bond in the mimic **1** closely resembles the three-dimensional structure of the parent amide bond in peptides **2** (Scheme 1).



Scheme 1

We have been interested in the synthetically useful ring-opening of γ,δ-epimino-α,β-enoates **3** and **5** with organocopper reagents in connection with synthetic studies on dipeptide isosteres **4** and **6** with stereochemically well defined structures (Scheme 2).[5] Various types of γ,δ-epimino-α,β-enoates have been successfully used in the synthesis of natural products such as pyrrolizidine alkaloids by Hudlicky,[6] Pearson[7] and others.[8] Recently, a report dealing with the palladium-catalysed reaction of γ,δ-epimino-α,β-enoates has been published;[9] however, prior to the initiation of our studies no information was available regarding the regio- and stereo-chemistry of organocopper-mediated reactions of γ,δ-epimino-α,β-enoates **3** and **5**. Previously we demonstrated that the highly *anti*-S_N2' nature of the reactions of α,β-enoates having an electron-withdrawing group at the γ-position with organocopper reagents could be used to relay the stereochemistry of the γ-position to the α-position in a highly stereoselective manner.[10] A similar relation can be expected to hold for the reaction of γ,δ-epimino-α,β-enoates **3** and **5** with organocopper reagents. From an experimental point of view, the γ,δ-epimino-α,β-enoates have the advantage in that they are usually stable and are readily purified by recrystallization.

It has been reported that the stereochemistry at the α-carbon centre in dipeptide isosteres is one of the essential factors for enzyme inhibition.[4a] The importance of optically active (*E*)-alkene isosteres as key intermediates for the synthesis of various



Scheme 2

types of polypeptides has been demonstrated by many groups.[4] We have also recently reported that the synthesized isosteric peptide **7** is a potent bombesin receptor antagonist.[11] We anticipated the need to synthesize large quantities of peptides containing (*E*)-alkene dipeptide isosteres and therefore a more reliable synthesis of (*E*)-alkene dipeptide isosteres than those reported to date was required. While this manuscript was being prepared, a report was published that described a similar synthetic route to the synthesis of (*E*)-alkene isosteres from *N*-*tert*-butoxycarbonyl-γ,δ-epimino-(*E*)-α,β-enoates.[12]

The present study was undertaken with two goals in mind: (1) to find reaction conditions whereby ψ[(*E*)-CH=CH] dipeptide isosteres **4** and **6** can be synthesized from readily available γ,δ-epimino-α,β-enoates **3** and **5** in high chemical yields and (2) to examine the stereochemical relationship between substrate and product stereochemistry.

Results and discussion

It is well documented that the reactivity of the *N*-unactivated of aziridines towards nucleophiles is relatively low; hence,

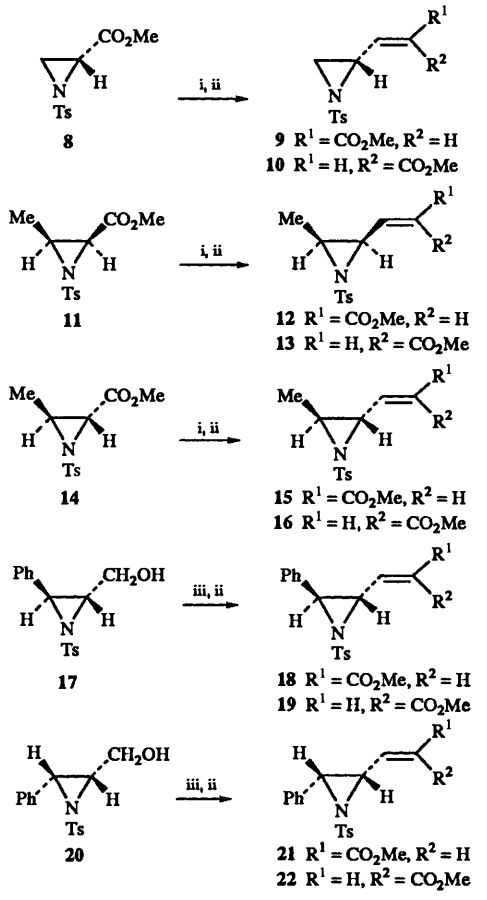
† According to IUPAC rules, the structure inside the bracket following ψ is the unit substituting for the amide bond, see: IUPAC–IUB Joint Commission on Biochemical Nomenclature, *Eur. J. Biochem.*, 1984, **138**, 9.

activation by the introduction of an electron-withdrawing protecting group on the nitrogen atom of the aziridine is required. The term 'activated aziridines' has been introduced by Ham for aziridines that easily undergo nucleophilic S_N2-type ring-opening.[13] The 4-methylphenylsulfonyl (tosyl) group serves as a most effective activating group. In addition, the *N*-tosyl group can withstand a wide range of chemical manipulations and yet be removed by the use of Baldwin's protocol.[14]

The four possible positions for attack by nucleophiles are α (S_N2' reaction), β (1,4-addition), γ (S_N2 reaction) or δ (S_N2 reaction) of the activated γ,δ-epimino-α,β-unsaturated esters. Thus, it is not easy to predict whether α, β, γ or δ is the most reactive position in the reaction with nucleophilic reagents. Although the regio- and stereo-selectivity of the reaction is expected to be controlled by a balance of steric as well as electronic factors, it was our expectation to be able to synthesize stereochemically pure (*E*)-alkene isosteres from *N*-tosyl-γ,δ-epimino-α,β-unsaturated esters by employing organocopper-mediated *anti*-S_N2' reactions.[10a-d] In this context, several (*E*)/(*Z*)-pairs of *N*-tosyl-γ,δ-epimino-α,β-unsaturated esters were synthesized.

Synthesis of (*E*)/(*Z*)-pairs of *N*-tosyl-γ,δ-epimino-α,β-unsaturated esters

As shown in Scheme 3, the requisite *N*-tosyl-γ,δ-epimino-α,β-



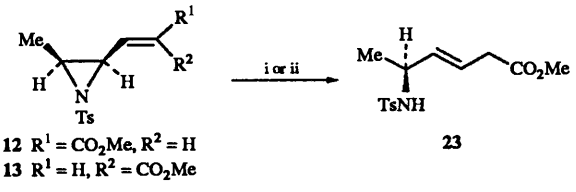
Scheme 3 *Reagents and conditions:* i, DIBAL, −78 °C; ii, $Ph_3P{=}CHCO_2Me$ or $(MeO)_2P(O)CH(Na)CO_2Me$; iii, $(COCl)_2$–DMSO, −78 °C and then $EtN(Pr^i)_2$

enoates **9**, **10**, **12**, **13**, **15** and **16** were readily prepared from known methyl (2*R*)-1-tosylaziridine-2-carboxylate **8**,[14,15] methyl (2*S*,3*S*)-3-methyl-1-tosylaziridine-2-carboxylate **11**[16a] and methyl (2*R*,3*S*)-3-methyl-1-tosylaziridine-2-carboxylate **14**,[16b] respectively. Typically, the aziridine **8** was treated successively with diisobutylaluminium hydride (DIBAL; 1.2 equiv., −78–0 °C) in dichloromethane–water at −78 °C, and (methoxycarbonylmethylene)triphenylphosphorane (1 equiv., −78–0 °C) in a one-pot reaction to give a separable 36:64 mixture of (*E*)- and (*Z*)-α,β-enoates **9** and **10** in an 81% combined yield. In an analogous manner, the aziridines **11** and **14** were converted into the enoates **12**, **13**, **15** and **16**, respectively, in comparable yields. Although the synthetic procedure described above gives (*Z*)-α,β-enoates **10**, **13** and **16** as the major products, the (*E*)-enoates can be obtained as the major product by using the sodium salt of trimethylphosphonoacetate instead of (methoxycarbonylmethylene)triphenylphosphorane. For example, successive treatment of **11** with DIBAL at −78 °C, saturated aqueous ammonium chloride at −78 °C, and the sodium salt of trimethylphosphonoacetate at 0 °C in a one-pot reaction gave the (*E*)-enoate **12** as the major product (**12**:**13** = 83:17, 92% combined yield).

The other α,β-enoates **18**, **21** and **22** that have a phenyl group on the aziridine moiety were synthesized from 3-phenyl-1-tosylaziridin-2-ylmethanols **17**[16b] and **20**,[16b] respectively, by Swern oxidation followed by exposure to (methoxycarbonylmethylene)triphenylphosphorane. The (*Z*)-enoate **19** could not be isolated in a pure state due to its instability. The (*E*)- and (*Z*)-stereochemistry for all α,β-enoates synthesized were assigned on the basis of ^1H NMR spectral analyses.

Reaction of *N*-tosyl-γ,δ-epimino-α,β-enoates with organocopper reagents. Synthesis of (*E*)-alkene dipeptide isosteres

The scope of the organocopper-mediated reaction was determined by using the four stereoisomeric substrates **12**, **13**, **15** and **16**. It was not surprising, as shown in Scheme 4, that the



Scheme 4 *Reagents and conditions:* i, $Me_2Cu(CN)Li_2{\cdot}2LiBr$, −78 °C, 30 min; ii, $Me_2CuLi{\cdot}LiI{\cdot}2LiBr$, −78 °C, 30 min

reaction of (*E*)-enoate **12** and its (*Z*)-isomer **13** with either 'higher order' cyanocuprate‡[17] or Gilman reagent[18] gave exclusively (entries 1 and 2, Table 1) or predominantly (entry 3, Table 1) the unwanted reduced (*E*)-β,γ-unsaturated ester **23**. A similar trend was reported for $R_2CuLi{\cdot}LiI$- or $R_2Cu(CN)Li_2$-mediated reactions of γ-mesyloxy-α,β-enoates.[10a,b,f-h]

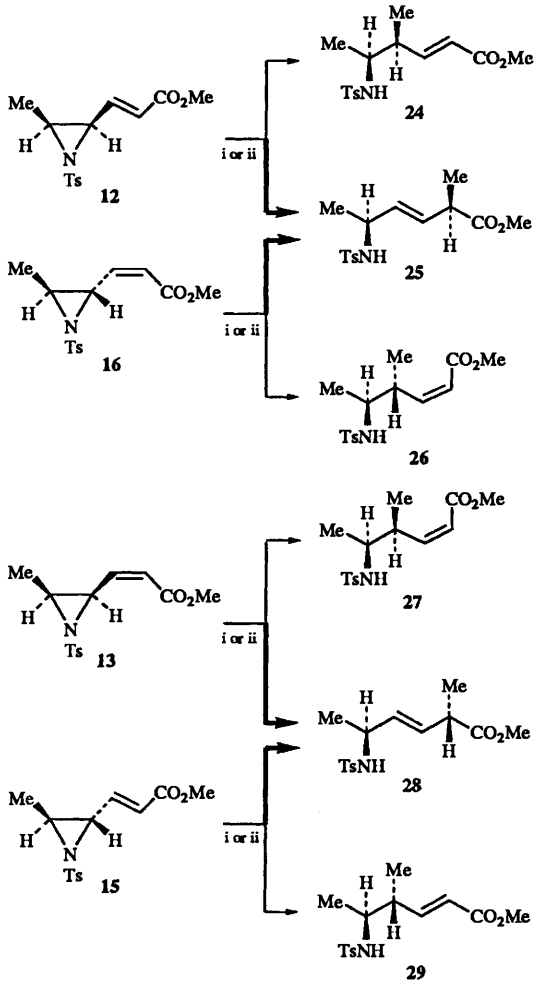
It was found that MeZnCl in the presence of 10 mol% CuCN did not produce a clean reaction (entry 6, Table 1). The difficulty was overcome by using either 'lower order' methylcyanocuprate or dimethylzinc (or trimethylzincate) in the presence of 20–30 mol% CuCN. It should be noted that the selection of the organometallic reagent is important and holds the key to successful transformation. As can be seen from Scheme 5 and Table 1, both the (*E*)-α,β-enoates (entries 4, 5, 10, 11, Table 1) and the (*Z*)-α,β-enoates (entries 7–9, 12, 13, Table 1) produced predominantly the desired (*E*)-alkene dipeptide isosteres with a methyl group at the α-position, presumably *via*

‡ Although reagents prepared from CuCN and 2 equiv. of RLi may be represented as $R_2CuLi{\cdot}LiCN$ by analogy to Gilman reagents, $R_2CuLi{\cdot}LiI$ for the cuprates prepared from CuI and 2 equiv. of RLi as suggested by Dr Bertz and others, the constitutional formula $R_2Cu(CN)Li_2$ has been used throughout this paper as a matter of convenience. We are not concerned about the exact constitution, but watch the reactive species as a reagent system. For higher order reagents, see ref. 17.

Table 1 Reaction of *N*-tosyl-γ,δ-epimino-α,β-enoates **12**, **13**, **15** and **16** with organometallic reagents[a]

Entry	Substrate	Reagent[b]	Conditions	Products (isolated yield)[c]		
				anti-S_N2'	S_N2	Reduction
1	**12**	$Me_2Cu(CN)Li_2$·2LiBr	THF–Et_2O (3:1), −78 °C, 30 min	—[d]	—[d]	**23** (72%)
2	**13**	$Me_2Cu(CN)Li_2$·2LiBr	THF–Et_2O (2:1), −78 °C, 30 min	—[d]	—[d]	**23** (85%)
3	**13**	Me_2CuLi·LiI·2LiBr	Et_2O, −78 °C, 1 h	**28** (11%)	**27** (15%)	**23** (62%)
4	**12**	Me_2Zn·2LiCl·2LiBr, 20 mol% CuCN	THF–Et_2O (2:1), −78 °C, 30 min	**25** (88%)	**24** (2%)	—[d]
5	**12**	MeCu(CN)Li·LiBr	THF–Et_2O (4:1), −78 °C, 30 min	**25** (92%)	**24** (3%)	—[d]
6	**13**	MeZnCl·LiCl·LiBr, 10 mol% CuCN	THF–Et_2O (5:1), −78 °C, 30 min	**28** (8%)	**27** —[d]	—[d]
7	**13**	Me_3ZnLi·2LiCl·3LiBr, 30 mol% CuCN	THF–Et_2O (5:1), −78 °C, 30 min	**28** (90%)	**27** (4%)	—[d]
8	**13**	Me_2Zn·2LiCl·2LiBr, 20 mol% CuCN	THF–Et_2O (2:1), −78 °C, 30 min	**28** (94%)	**27** (4%)	—[d]
9	**13**	MeCu(CN)Li·LiBr	THF–Et_2O (5:1), −78 °C, 30 min	**28** (93%)	**27** (6%)	—[d]
10	**15**	Me_2Zn·2LiCl·2LiBr, 20 mol% CuCN	THF–Et_2O (3:2), −78 °C, 30 min	**28** (92%)	**29** (3%)	—[d]
11	**15**	MeCu(CN)Li·LiBr	THF–Et_2O (5:1), −78 °C, 30 min	**28** (92%)	**29** (3%)	—[d]
12	**16**	Me_2Zn·2LiCl·2LiBr, 20 mol% CuCN	THF–Et_2O (3:2), −78 °C, 30 min	**25** (95%)	**26** (5%)	—[d]
13	**16**	MeCu(CN)Li·LiBr	THF–Et_2O (5:1), −78 °C, 30 min	**25** (82%)	**26** (4%)	—[d]

[a] All reactions were carried out with 3–4 mol equiv. of reagents. [b] Me_3ZnLi and Me_2Zn have been prepared from ethereal $ZnCl_2$ and ethereal MeLi as the LiBr complex. MeCu(CN)Li has been prepared by treatment of CuCN with ethereal MeLi as the LiBr complex. [c] All the new compounds have been fully characterized spectrally, and their elemental compositions have been determined by high-resolution mass spectrometry and/or combustion analysis. Diastereoisomeric purities (> 98%) of all isolated compounds were determined by HPLC. [d] Although we can not conclusively rule out its presence, we were unable to isolate the corresponding product.

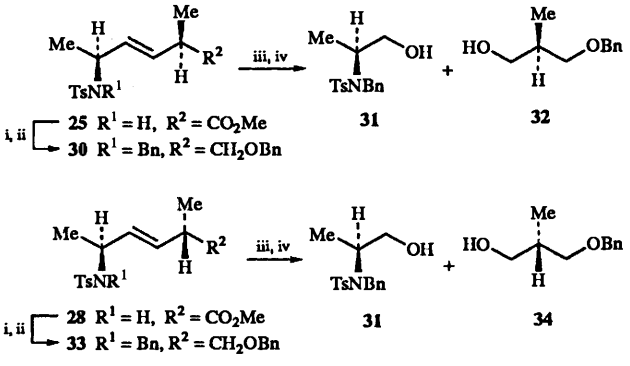


Scheme 5 *Reagents and conditions:* i, MeCu(CN)Li·LiBr, −78 °C; ii, Me_2Zn·2LiCl·2LiBr (or Me_3ZnLi·2LiCl·3LiBr), 20–30 mol% CuCN, −78 °C

the *anti*-S_N2' pathway. The minor product isolated in each reaction is that produced by the S_N2 reaction (compounds **24**, **26**, **27** and **29** in Scheme 5).

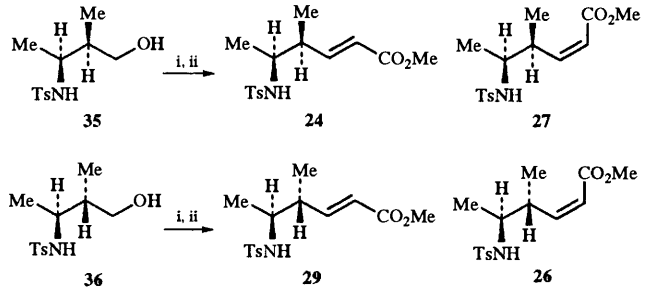
The absolute configuration of the methylated carbon centre in (*E*)-alkene isosteres can be determined by a circular dichroism measurement. We have previously reported that given the sign of the n→π* Cotton effect, the absolute configuration at the α-position in the (*E*)-alkene isosteres can be determined.[19] The isostere **25** shows a negative n→π* Cotton effect (Δε −0.62, 213.6 nm, in isooctane), whereas the isomeric isostere **28** exhibits a positive n→π* Cotton effect (Δε +2.15, 221.1 nm, in isooctane). Consequently, the absolute configuration at the methylated carbon centre in the isosteres **25** and **28** was assigned as *R* and *S*, respectively. However, a weak Cotton effect (1 > Δε > −1) leaves room for considerable uncertainty about the absolute stereochemistry at the α-position of the isostere **25**.

The absolute configuration at the methylated carbon centre in the S_N2'-products **25** and **28** was unambiguously established by chemical conversion of **25** and **28** into the known alcohols **32** and **34**,[10f,12,20] respectively, through a four-step sequence of reactions illustrated in Scheme 6. Thus, the isostere **25** was

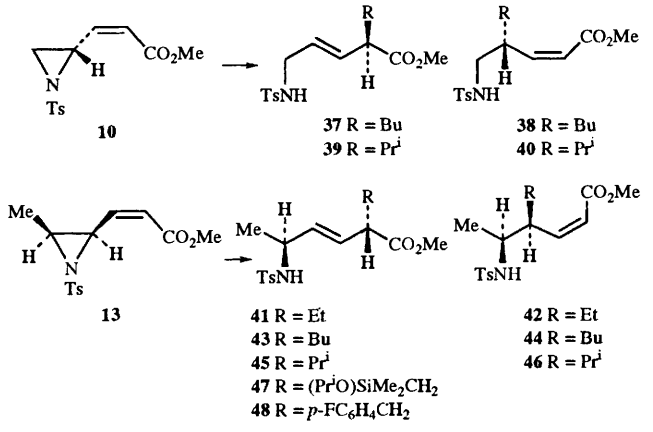


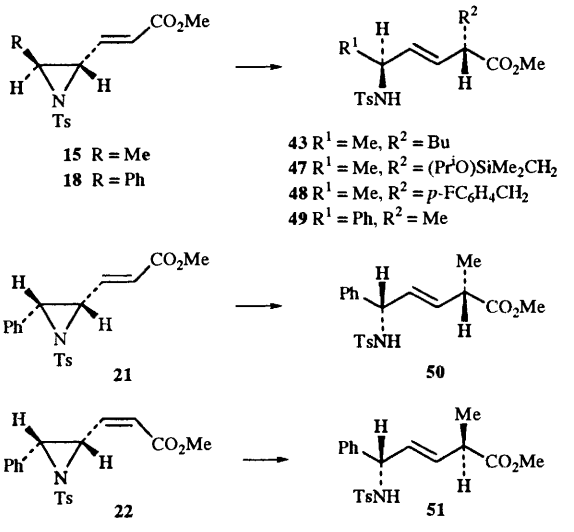
Scheme 6 *Reagents and conditions:* i, DIBAL, CH_2Cl_2, −78 °C–r.t.; ii, $PhCH_2Br$, NaH, DMF; iii, O_3, CH_2Cl_2, −78 °C; iv, DIBAL, CH_2Cl_2, −78–0 °C

treated with DIBAL followed by sodium hydride and benzyl bromide to give the benzyl ether **30**. Ozonolysis of **30**, followed by reduction with DIBAL at −78 °C produced the known benzyloxy alcohol **32**[10f,12,19] along with the amino alcohol **31**. The spectral data (^1H NMR, specific rotation, and HPLC analyses on chiral columns) for **32** were found to be identical with those of an authentic sample.[10f,12,20] The above reaction sequence was also performed by starting from the protected



Scheme 7 *Reagents:* i, $(COCl)_2$–DMSO, Et_3N; ii, $Ph_3P{=}CHCO_2Me$





Scheme 8

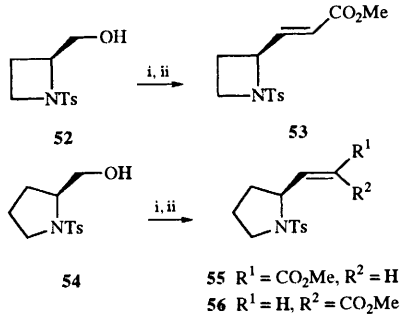
isostere **28** leading to the known benzyloxy alcohol **34**[10f,12,20] (see Experimental).

The structure and stereochemistry of the minor S_N2 by-products **24**, **26**, **27** and **29** were confirmed by comparison of their data (^1H NMR and specific rotation) with those of authentic samples prepared from the homochiral known alcohols **35** and **36**[21] by treatment with $(COCl)_2$–DMSO–Et_3N, followed by (methoxycarbonylmethylene)triphenylphosphorane and flash chromatographic separation, following an unambiguous, independent synthetic route (Scheme 7).

As can be seen from Scheme 8 and Table 2 (except for entry 3), comparably high chemical yields of *anti*-S_N2' products were obtained from the reaction of (*E*)-α,β-enoates **15**, **18** and **21** and (*Z*)-α,β-enoates **10**, **13** and **22** with organometallic reagents. It is of particular interest that these reactions exhibit high levels of regioselectivity, desired (*E*)-stereoselectivity of the β,γ-double bond, and an impressive degree of diastereoselectivity (> 98 : 2). All of the highly selective reactions were generally complete in a few minutes at −78 °C, but the reaction mixture was usually stirred for 30 min. In addition, this strategy also allows flexibility in introducing substituents such as Et, Bu, Pr^i, $(Pr^iO)Me_2SiCH_2$ and *p*-$FC_6H_4CH_2$ at the α-position of the ester group by merely changing the reagent (entries 1–13, Table 2).

It should be clearly noted that the treatment of substrates with lower order alkylcyanocuprates in the presence or absence of lithium salts such as lithium chloride afforded *anti*-S_N2' products either predominantly (entries 1, 2, 5, 6 and 8, Table 2) or exclusively (entries 9–15 and 17, Table 2). However, exposure of the enoate **13** to diethylzinc in the presence of 20 mol% CuCN only gave unchanged starting material (entry 3, Table 2). It was found that the addition of LiCl to a mixture of diethylzinc and 20 mol% CuCN was essential for optimizing the reaction rates and chemical yields (compare entry 3 with 4, 16 and 18, Table 2). Such lithium salt effects on organocopper-mediated reactions have been well documented.[10g,22]

Having established useful reaction conditions for the synthesis of (*E*)-alkene dipeptide isosteres from (*E*)- or (*Z*)-*N*-tosyl-γ,δ-epimino-α,β-enoates, the reaction of four- and five-membered heterocycles **53**, **55** and **56** with organocopper reagents was briefly investigated. The required chiral four- and five-membered heterocycles were readily prepared in high yields from the known alcohols **52**[21b] and **54**[21b] *via* a routine sequence of reactions (Scheme 9). As expected, we do not detect any ring-



Scheme 9 *Reagents:* i, $(COCl)_2$–DMSO, $EtN(Pr^i)_2$; ii, $Ph_3P{=}CH$-CO_2Me

opened products when the α,β-enoates **53**, **55** and **56** are treated with organocopper reagents. Only unchanged starting material was isolated. This clearly demonstrates that a small change in the ring size of aza-cycloalkanes alters their reactivity towards organocopper reagents.

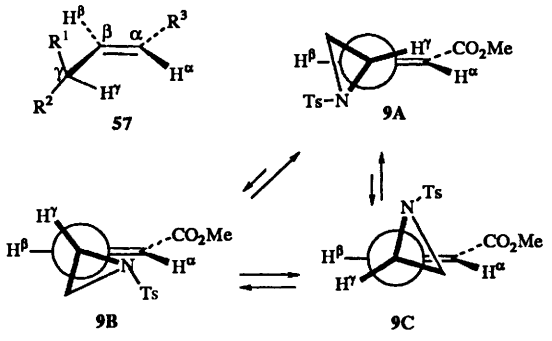
As stated before, the (*E*)- and (*Z*)-α,β-enoates produced the desired dipeptide isosteres with an (*E*)-double bond as the major or exclusive product(s) by treatment with either alkylzinc reagents or lower order alkylcyanocuprates. There remains the question of why both the (*E*)- and (*Z*)-α,β-enoates were transformed into the (*E*)-alkene isosteres.

Although the ground-state and the reactive conformer are not necessarily the same, the ground-state conformations of various types of substrates have been reported to play an important role in the stereochemical outcome of π-facial selectivity.[23,24] The preferred conformation of many olefinic molecules containing the propene moiety shows a hydrogen atom at the sp^3-carbon in the propene moiety eclipsing the double bond (structure **57** in Scheme 10).[25] In this conformation allylic 1,3-strain would be minimized.[23,26] In this context, the preferred conformations of the five *N*-tosyl-γ,δ-epimino-α,β-enoates **9**, **10**, **12**, **13** and **18** have been studied in $[^2H_8]$THF by a variable-temperature (VT) ^1H NMR technique. $[^2H_8]$THF was chosen because the reactions with these enoates had been carried out in THF or THF mixtures at −78 °C. The VT ^1H NMR data for compounds **9**, **10**, **12**, **13** and

Table 2 Reaction of *N*-tosyl-γ,δ-epimino-α,β-enoates **10**, **13**, **15**, **18**, **21** and **22** with organometallic reagents[a]

Entry	Substrate	Reagent[b]	Conditions	Products (isolated yield)[c] *anti*-S_N2'	S_N2
1	**10**	BuCu(CN)Li	THF–hexane (3:1)	**37** (93%)	**38** (6.5%)
2	**10**	$Pr^iCu(CN)MgCl\cdot 2LiCl$	THF	**39** (90%)	**40** (8%)
3	**13**	Et_2Zn, 20 mol% CuCN	THF–hexane (2:1)	—[d]	—[d]
4	**13**	$Et_2Zn\cdot 2LiCl$, 20 mol% CuCN	THF–hexane (2:1)	**41** (81%)	**42** (2%)
5	**13**	$EtCu(CN)MgCl\cdot 4LiCl$	THF–Et_2O (4:1)	**41** (92%)	**42** (8%)
6	**13**	BuCu(CN)Li	THF–hexane (4:1)	**43** (90%)	**44** (2.5%)
7	**13**	$Bu_3ZnLi\cdot 2LiCl$, 30 mol% CuCN	THF–hexane (4:1)	**43** (97%)	**44** (1%)
8	**13**	$Pr^iCu(CN)MgCl\cdot 2LiCl$	THF	**45** (97%)	**46** (2%)
9	**13**	$(Pr^iO)Me_2SiCH_2Cu(CN)MgCl\cdot 2LiCl$	THF	**47** (75%)	—[d]
10	**13**	$p\text{-}FC_6H_4CH_2Cu(CN)MgCl\cdot 2LiCl$	THF	**48** (98%)	—[d]
11	**15**	BuCu(CN)Li	THF–hexane (3:1)	**43** (96%)	—[d]
12	**15**	$(Pr^iO)Me_2SiCH_2Cu(CN)MgCl\cdot 2LiCl$	THF	**47** (83%)	—[d]
13	**15**	$p\text{-}FC_6H_4CH_2Cu(CN)MgCl\cdot 2LiCl$	THF	**48** (98%)	—[d]
14	**18**	$MeCu(CN)Li\cdot LiBr$	THF–Et_2O (6:1)	**49** (85%)	—[d]
15	**21**	$MeCu(CN)Li\cdot LiBr$	THF–Et_2O (4:1)	**50** (91%)	—[d]
16	**21**	$Me_2Zn\cdot 2LiCl\cdot 2LiBr$, 20 mol% CuCN	THF–Et_2O (2:1)	**50** (99%)	—[d]
17	**22**	$MeCu(CN)Li\cdot LiBr$	THF–Et_2O (4:1)	**51** (81%)	—[d]
18	**22**	$Me_2Zn\cdot 2LiCl\cdot 2LiBr$, 20 mol% CuCN	THF–Et_2O (2:1)	**51** (91%)	—[d]

[a] All reactions were carried out with 3–4 mol equiv. of reagents at −78 °C for 30 min. [b] MeCu(CN)Li has been prepared by treatment of CuCN with ethereal MeLi as the LiBr complex. [c] All the new compounds have been fully characterized spectrally, and their elemental compositions have been determined by high-resolution mass spectrometry and/or combustion analysis. Diastereoisomeric purities (> 98%) of all isolated compounds were determined by HPLC. [d] Although we can not conclusively rule out its presence, we were unable to isolate the corresponding product.



Scheme 10 Three isomeric eclipsed conformers (**9A**, CH-eclipsed form; **9B**, CN-eclipsed form; and **9C**, CC-eclipsed form) formed by rotation around the C^β–C^γ bond of **9**

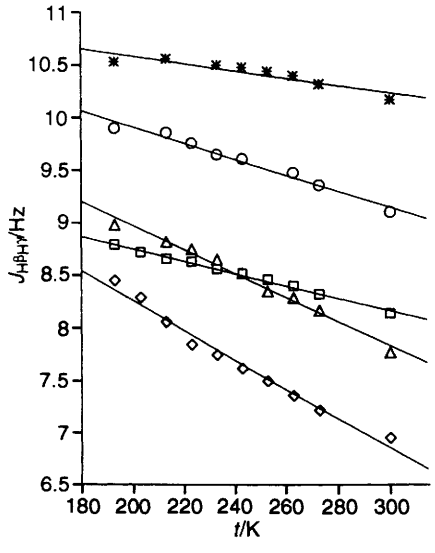


Fig. 1 Spin–spin coupling constants ($J_{H^\beta H^\gamma}$/Hz) as a function of temperature for **9** (○), **10** (△), **12** (◇) **13** (□) and **18** (*)

18 are shown in Fig. 1. It was not surprising that all of the enoates displayed a considerably larger three-bond coupling ($^3J_{H^\beta H^\gamma}$) at 300 K, indicating that the CH-eclipsed form is more populated. As can be seen from Fig. 1, the three-bond coupling constants ($^3J_{H^\beta H^\gamma}$) become larger as the temperature decreases. For example, $^3J_{H^\beta H^\gamma}$ of **9** increased as the temperature was lowered, which indicates that the CH-eclipsed form **9A** becomes a favoured conformer rather than the CN-eclipsed form **9B** or the CC-eclipsed conformer **9C**, as shown in Scheme 10. In other words, the predominant conformer could be represented as **9A**, in which the four atoms ($H^\gamma C^\gamma C^\beta C^\alpha$) are nearly coplanar.

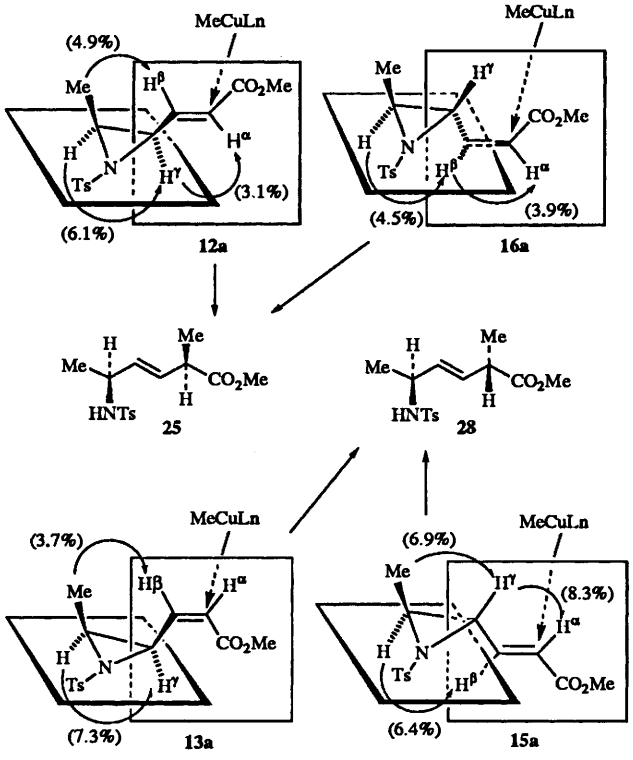
In addition, the NOE data in [$^2H_8$]THF for the four isomeric (*Z*)- and (*E*)-enoates **12**, **13**, **15** and **16** suggest that the preferred conformation could be drawn as depicted in **12a**, **13a**, **15a** and **16a** (Scheme 11). This finding agreed closely with that observed in related systems such as vinylcyclopropanes[27] and vinyloxiranes.[28] In addition, X-ray analytical data for (*Z*)- and (*E*)-substrates **13** and **15** show that the C^α=C^β–C^γ–H^γ dihedral angles are only 9.3° and 1.7°, respectively.[5] This indicates that the solid-state conformations of **13** and **15** are quite similar to those in solution depicted in Scheme 11. Organocopper reagents will attack the α-position on the most abundant conformations of **12a**, **13a**, **15a** and **16a** from the less hindered surface *anti* to the leaving C^γ–N bond to give the overall *anti*-S_N2' products having an (*E*)-double bond as the major or exclusive product.

In summary, we have shown that the reaction of both (*E*)- and (*Z*)-*N*-tosyl-γ,δ-epimino-α,β-enoates with trialkylzincates or dialkylzinc in the presence of CuCN, or 'lower order' alkylcyanocuprates proceeds well to give (*E*)-alkene dipeptide isosteres of very high isomeric purity as the major or exclusive products.

Experimental

General methods

Mps were determined on a hot stage melting point apparatus and are uncorrected. IR spectra were taken on a Shimadzu IR-400 spectrometer in chloroform. ^1H NMR spectra were recorded using a JEOL EX-270 (270 MHz), a Bruker AC-300 (300 MHz), or a Bruker AM-600 (600 MHz) spectrometer in deuteriochloroform. Chemical shifts are reported in parts per million downfield from internal tetramethylsilane. *J*-Values are given in Hz. Nominal and exact mass spectra were recorded on



Scheme 11 Preferred conformations **12a**, **13a**, **15a** and **16a** of **12**, **13**, **15** and **16**, respectively, in solution ([$^2H_8$]THF; 600 MHz; 300 K). Observed relevant NOE values are given in parentheses.

a JEOL-JMS-HX-HX-110A mass spectrometer (abbreviations: EI, electron impact; CI, chemical ionization; FAB, fast atom bombardment). Optical rotations were measured on a JASCO DIP-360 digital polarimeter and are given in units of 10^{-1} deg cm^2 g^{-1}. Circular dichroisms were measured with a JASCO J-500A spectrometer in isooctane at 30 °C. For flash chromatography, silica gel 60 H (silica gel for thin-layer chromatography, Merck) and/or Wakogel C-200 (silica gel for column chromatography) was employed.

Methyl (4*S*,2*E*)-4,5-epimino-*N*-[(4-methylphenyl)sulfonyl]-pent-2-enoate 9 and methyl (4*S*,2*Z*)-4,5-epimino-*N*-[(4-methylphenyl)sulfonyl]pent-2-enoate 10

To a stirred solution of methyl (2*R*)-*N*-(4-methylphenyl)-sulfonylaziridine-2-carboxylate **8** (20.7 g, 81 mmol) in CH_2Cl_2 (150 cm^3) at −78 °C under argon was added dropwise diisobutylaluminium hydride (1 mol dm^{-3} solution in toluene; 98 cm^3, 98 mmol, 1.21 equiv.). After 1 h saturated aqueous NH_4Cl (50 cm^3) was added to it with stirring at −78 °C, followed by (methoxycarbonylmethylene)triphenylphosphorane (27 g, 81 mmol, 1 equiv.). The mixture was stirred for 18 h during which time it was allowed to warm to room temperature. The inorganic salts were removed by filtration through Celite. The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure to give an oil, which was flash chromatographed on silica gel, eluting with hexane–EtOAc (3:1) to give the *cis*-enoate **10** (11.6 g, 51%). Continued elution gave the *trans*-enoate **9** (6.8 g, 28%).

Compound **9**, colourless crystals, mp 45 °C [from hexane–Et_2O (1:4)] (Found: C, 55.7; H, 5.3; N, 4.9. $C_{13}H_{15}O_4NS$ requires C, 55.5; H, 5.4; N, 5.0%); $[\alpha]_D^{20}$ +78 (*c* 1.57 in $CHCl_3$); δ_H(300 MHz; $CDCl_3$) 2.27 (1 H, d, *J* 4.2, CH*H*), 2.45 (3 H, s, CMe), 2.88 (1 H, d, *J* 7.3, C*H*H), 3.34 (1 H, dddd, *J* 7.5, 7.3, 4.2 and 0.8, 4-H), 3.72 (3 H, s, OMe), 6.11 (1 H, dd, *J* 15.6 and 0.8, 2-H), 6.56 (1 H, dd, *J* 15.6 and 7.5, 3-H), 7.34–7.37 (2 H, m, Ph) and 7.80–7.84 (2 H, m, Ph).

Compound **10**, colourless crystals, mp 81 °C (from Et_2O) (Found: C, 55.8; H, 5.4; N, 4.9. $C_{13}H_{15}O_4NS$ requires C, 55.5; H, 5.4; N, 5.0%); $[\alpha]_D^{18}$ −135 (*c* 1.05 in $CHCl_3$); δ_H(300 MHz; $CDCl_3$) 2.25 (1 H, d, *J* 4.3, CH*H*), 2.44 (3 H, s, CMe), 2.92 (1 H, d, *J* 7.3, C*H*H), 3.76 (3 H, s, OMe), 4.50 (1 H, dddd, *J* 11.5, 7.3, 4.3 and 0.9, 4-H), 5.69 (1 H, dd, *J* 11.5 and 8.9, 3-H), 5.95 (1 H, dd, *J* 11.5 and 0.9, 2-H), 7.32–7.36 (2 H, m, Ph) and 7.82–7.86 (2 H, m, Ph).

Methyl (4*R*,5*S*,2*E*)-4,5-epimino-*N*-[(4-methylphenyl)sulfonyl]-hex-2-enoate 12 and methyl (4*R*,5*S*,2*Z*)-4,5-epimino-*N*-[(4-methylphenyl)sulfonyl]hex-2-enoate 13

By a procedure identical with that described for the preparation of the enoates **9** and **10**, (2*S*, 3*S*)-2-methoxycarbonyl-3-methyl-1-(4-methylphenyl)sulfonylaziridine **11** (808 mg, 3 mmol) was converted into the enoates **12** (51.4 mg, 6%) and **13** (803.6 mg, 91%) by treatment with diisobutylaluminium hydride (1.02 mol dm^{-3} solution in toluene; 3.23 cm^3, 3.3 mmol, 1.1 equiv.), followed by (methoxycarbonylmethylene)triphenylphosphorane (1 g, 3 mmol, 1 equiv.).

By using the sodium salt of trimethylphosphonoacetate instead of (methoxycarbonylmethylene)triphenylphosphorane the *trans*-enoate **12** was obtained as the major product (**12**:**13** = 83:17; 92% combined yield). To a stirred solution of the ester **11** (808 mg, 3 mmol) in CH_2Cl_2 (10 cm^3) at −78 °C under argon was added dropwise diisobutylaluminium hydride (1.02 mol dm^{-3} solution in toluene; 3.23 cm^3, 3.3 mmol, 1.1 equiv.). After 0.5 h saturated aqueous NH_4Cl (1 cm^3) was added to it with stirring at −78 °C, followed by a solution of the sodium salt of trimethylphosphonoacetate (0.72 mol dm^{-3} solution in DMF; 12.5 cm^3, 9 mmol, 3 equiv.). The mixture was stirred for 2 h during which time it was allowed to warm to 0 °C. The mixture was poured into 1% hydrochloric acid (10 cm^3) at 0 °C with vigorous stirring, and the whole was extracted with EtOAc. The extract was washed successively with water, 10% aqueous citric acid, water, saturated aqueous $NaHCO_3$ and water, then dried ($MgSO_4$). Concentration under reduced pressure gave an oily residue, which was purified by flash chromatography over silica gel with hexane–EtOAc (3:1) to give the *cis*-enoate **13** (139 mg, 16%). Continued elution gave the *trans*-enoate **12** (678 mg, 76%).

Compound **12**, colourless crystals, mp 92–93 °C [from hexane–Et_2O (1:3)] (Found: C, 56.8; H, 5.8; N, 4.6. $C_{14}H_{17}NO_4S$ requires C, 56.9; H, 5.8; N, 4.7%); $[\alpha]_D^{32}$ −89 (*c* 0.725 in $CHCl_3$); ν_{max}/cm^{-1} 1710 (CO) and 1653 (C=C); δ_H(200 MHz; $CDCl_3$) 1.21 (3 H, d, *J* 5.9, CMe), 2.45 (3 H, s, CMe), 3.14 (1 H, m, 5-H), 3.40 (1 H, ddd, *J* 7.6, 6.6 and 1.0, 4-H), 3.72 (3 H, s, OMe), 6.07 (1 H, dd, *J* 15.6 and 1.0, 2-H), 6.66 (1 H, dd, *J* 15.6 and 6.6, 3-H), 7.31–7.37 (2 H, m, Ph) and 7.78–7.84 (2 H, m, Ph).

Compound **13**, colourless crystals, mp 75–77 °C [from hexane–Et_2O–CH_2Cl_2 (4:4:1)] (Found: C, 56.9; H, 5.8; N, 4.5. $C_{14}H_{17}NO_4S$ requires C, 56.9; H, 5.8; N, 4.7%); $[\alpha]_D^{27}$ +10.1 (*c* 0.915 in $CHCl_3$); ν_{max}/cm^{-1} 1720 (CO) and 1644 (C=C); δ_H(200 MHz; $CDCl_3$) 1.22 (3 H, d, *J* 5.9, CMe), 2.44 (3 H, s, CMe), 3.15 (1 H, m, 5-H), 3.76 (3 H, s, OMe), 4.36 (1 H, d, *J* 7.6 and 0.7, 4-H), 5.88 (1 H, dd, *J* 11.7 and 7.6, 3-H), 6.01 (1 H, dd, *J* 11.7 and 0.7, 2-H), 7.31–7.35 (2 H, m, Ph) and 7.80–7.84 (2 H, m, Ph).

Methyl (4*S*,5*S*,2*E*)-4,5-epimino-*N*-[(4-methylphenyl)sulfonyl]-hex-2-enoate 15 and methyl (4*S*,5*S*,2*Z*)-4,5-epimino-*N*-[(4-methylphenyl)sulfonyl]hex-2-enoate 16

By a procedure identical with that described for the preparation of the enoates **9** and **10**, (2*R*,3*S*)-2-methoxycarbonyl-3-methyl-1-(4-methylphenyl)sulfonylaziridine **14** (200 mg, 0.743 mmol) was converted into the enoates **15** (104 mg, 47%) and **16** (44.4 mg, 20%) by treatment with diisobutylaluminium hydride (0.93

mol dm^{-3} solution in toluene; 2.4 cm^3, 2.23 mmol, 3 equiv.), followed by (methoxycarbonylmethylene)triphenylphosphorane (497 mg, 1.49 mmol, 2 equiv.).

Compound **15**, colourless crystals, mp 84 °C (from Et_2O) (Found: C, 56.8; H, 5.8; N, 4.7. $C_{14}H_{17}NO_4S$ requires C, 56.9; H, 5.8; N, 4.7%); $[\alpha]_D^{20}$ +28.4 (*c* 1.07 in $CHCl_3$); ν_{max}/cm^{-1} 1720 (CO), 1655 and 1603 (C=C); δ_H(200 MHz; $CDCl_3$) 1.54 (3 H, d, *J* 5.9, CMe), 2.44 (3 H, s, CMe), 3.01 (1 H, ddd, *J* 11.5, 5.6 and 4.1, 5-H), 3.21 (1 H, dd, *J* 8.8 and 4.1, 4-H), 3.73 (3 H, s, OMe), 6.08 (1 H, d, *J* 15.6, 2-H), 6.87 (1 H, dd, *J* 15.6 and 8.8, 3-H), 7.30–7.34 (2 H, m, Ph) and 7.79–7.84 (2 H, m, Ph).

Compound **16**, colourless crystals, mp 51 °C [from hexane–Et_2O (1:2)] [Found (EI): M^+, 295.0887. $C_{14}H_{17}O_4NS$ requires *M*, 295.0878]; $[\alpha]_D^{20}$ −181 (*c* 1.13 in $CHCl_3$); ν_{max}/cm^{-1} 1720 (CO), 1645 and 1601 (C=C); δ_H(200 MHz; $CDCl_3$) 1.50 (3 H, d, *J* 5.6, CMe), 2.44 (3 H, s, CMe), 3.01 (1 H, ddd, *J* 11.5, 5.9 and 4.2, 5-H), 3.75 (3 H, s, OMe), 4.42 (1 H, dd, *J* 9.3 and 4.2, 4-H), 6.01 (1 H, d, *J* 11.5, 2-H), 6.23 (1 H, dd, *J* 11.5 and 9.3, 3-H), 7.30–7.34 (2 H, m, Ph) and 7.80–7.84 (2 H, m, Ph); *m/z* (EI) 295 (M^+), 280, 264, 198, 155, 140 (base peak), 112, 108, 99 and 91.

Methyl (4*S*,5*S*,2*E*)-4,5-epimino-*N*-(4-methylphenyl)sulfonyl-5-phenylpent-2-enoate 18 and methyl (4*S*,5*S*,2*Z*)-4,5-epimino-*N*-(4-methylphenyl)sulfonyl-5-phenylpent-2-enoate 19

To a stirred solution of oxalyl chloride (0.26 cm^3, 3 mmol, 1.5 equiv.) in dry CH_2Cl_2 (20 cm^3) at −78 °C under argon was added dropwise a solution of DMSO (0.71 cm^3, 10 mmol, 5 equiv.) in CH_2Cl_2 (2 cm^3). After 20 min, a solution of the 3-phenylaziridin-2-ylmethanol **17** (600 mg, 2 mmol) in CH_2Cl_2 (2 cm^3) was added to the above reagent at −78 °C, and the mixture was stirred for 30 min when diisopropylethylamine (0.7 cm^3, 40 mmol, 20 equiv.) was added dropwise to the above solution at −78 °C, and the mixture was stirred for 0.5 h at that temperature. (Methoxycarbonylmethylene)triphenylphosphorane (1.34 g, 4 mmol, 2 equiv.) was added to the mixture at −78 °C, and the mixture was stirred for 2 h during which time it was allowed to warm to 0 °C. The mixture was extracted with Et_2O and the extract was washed successively with water, 10% aqueous citric acid, water, saturated aqueous $NaHCO_3$ and water, and dried ($MgSO_4$). Concentration under reduced pressure gave an oily residue, which was flash chromatographed on silica gel, eluting with hexane–EtOAc (3:1) to give the *trans*-enoate **18** (370 mg, 52%) as a colourless oil. The *cis*-isomer **19** could not be isolated in a pure state due to its instability.

Compound **18**, colourless oil [Found (FAB): $(M + H)^+$, 358.1116. $C_{19}H_{20}NO_4S$ requires *M* + H, 358.1113]; $[\alpha]_D^{20}$ −34 (*c* 0.97 in $CHCl_3$); δ_H(270 MHz; $CDCl_3$) 2.41 (3 H, s, CMe), 3.43 (1 H, dd, *J* 10.2 and 3.6, 4-H), 3.78 (3 H, s, OMe), 4.14 (1 H, d, *J* 3.6, 5-H), 6.20 (1 H, d, *J* 15.5, 2-H), 7.16–7.36 (8 H, m, Ph and 3-H) and 7.84 (2 H, m, Ph); *m/z* FAB-LRMS 358 (MH^+), 326, 298, 202 (base peak), 171, 155, 144, 115 and 91.

Methyl (4*S*,5*R*,2*E*)-4,5-epimino-*N*-(4-methylphenyl)sulfonyl-5-phenylpent-2-enoate 21 and methyl (4*S*,5*R*,2*Z*)-4,5-epimino-*N*-(4-methylphenyl)sulfonyl-5-phenylpent-2-enoate 22

By a procedure identical with that described for the preparation of the enoate **18**, (2*R*,3*R*)-*N*-(4-methylphenyl)sulfonyl-3-phenylaziridin-2-ylmethanol **20** (6.07 g, 20 mmol) was converted into the enoates **21** (2.08 g, 29%) and **22** (4.96 g, 69.5%).

Compound **21**, colourless crystals, mp 148 °C [from hexane–Et_2O (1:1)] (Found: C, 63.6; H, 5.3; N, 3.7. $C_{19}H_{19}NO_4S$ requires C, 63.9; H, 5.4; N, 3.9%); $[\alpha]_D^{20}$ −46.1 (*c* 0.75 in $CHCl_3$); δ_H(270 MHz; $CDCl_3$) 2.45 (3 H, s, CMe), 3.64 (3 H, s, OMe), 3.69 (1 H, dd, *J* 7.6 and 7.3, 4-H), 4.18 (1 H, d, *J* 7.3, 5-H), 6.09 (1 H, d, *J* 15.7, 2-H), 6.33 (1 H, dd, *J* 15.7 and 7.6, 3-H), 7.19–7.31 (5 H, m, Ph), 7.34–7.37 (2 H, m, Ph) and 7.87–7.90 (2 H, m, Ph).

Compound **22**, colourless oil (Found: C, 63.8; H, 5.3; N, 3.8. $C_{19}H_{19}NO_4S$ requires C, 63.9; H, 5.4; N, 3.9%); $[\alpha]_D^{20}$ +71.9 (*c* 0.69 in $CHCl_3$); δ_H(270 MHz; $CDCl_3$) 2.44 (3 H, s, CMe), 3.75 (3 H, s, OMe), 4.18 (1 H, d, *J* 7.3, 5-H), 4.76 (1 H, ddd, *J* 8.6, 7.3 and 0.8, 4-H), 5.59 (1 H, dd, *J* 11.6 and 8.6, 3-H), 5.85 (1 H, dd, *J* 11.6 and 0.8, 2-H), 7.22–7.29 (5 H, m, Ph), 7.33–7.36 (2 H, m, Ph) and 7.88–7.93 (2 H, m, Ph).

Methyl (5*S*,3*E*)-5-[(4-methylphenyl)sulfonylamino]hex-3-enoate 23

To a stirred slurry of CuCN (121.5 mg, 1.36 mmol, 4 equiv.) in dry THF (3 cm^3) under argon was added *via* syringe MeLi·LiBr (1.5 mol dm^{-3} solution in Et_2O; 1.8 cm^3, 2.7 mmol, 8 equiv.) at −78 °C, and the mixture was allowed to warm to 0 °C and was stirred at this temperature for 15 min. A solution of the α,β-enoate **12** (100 mg, 0.34 mmol) in dry THF (3 cm^3) was added dropwise to the above reagent at −78 °C with stirring, and the stirring was continued for 30 min followed by quenching with aqueous saturated NH_4Cl–28% NH_4OH (1:1; 2 cm^3). The mixture was extracted with Et_2O–CH_2Cl_2 (4:1) and the extract was washed with water and dried ($MgSO_4$). Concentration under reduced pressure gave an oily residue, which was flash chromatographed on silica gel, eluting with hexane–EtOAc (4:1) to give the reduction product **23** (72.5 mg, 72%) as a colourless oil. By a procedure identical with that described above for the reaction of **12** with $Me_2Cu(CN)Li_2$·2LiBr, the α,β-enoate **13** (100 mg, 0.34 mmol) was converted into the reduction product **23** (85.2 mg, 85%) by treatment with $Me_2Cu(CN)Li_2$·2LiBr (1.36 mmol) in THF–Et_2O (2:1) at −78 °C for 30 min, colourless oil [Found (EI): M^+, 297.1042. $C_{14}H_{19}NO_4S$ requires *M*, 297.1035]; $[\alpha]_D^{20}$ −27.8 (*c* 0.842 in $CHCl_3$); ν_{max}/cm^{-1} 3390 (NH), 1733 (CO) and 1600 (C=C); δ_H(300 MHz; $CDCl_3$) 1.18 (3 H, d, *J* 6.8, CMe), 2.42 (3 H, s, CMe), 2.91 (1 H, s, C*H*H), 2.94 (1 H, s, CH*H*), 3.67 (3 H, s, OMe), 3.89 (1 H, m, 5-H), 4.52 (1 H, m, NH), 5.36 (1 H, dddd, *J* 15.5, 6.2, 1.4 and 1.4, CH=), 5.52 (1 H, dddd, *J* 15.5, 6.9, 6.9 and 1.4, CH=), 7.27–7.30 (2 H, m, Ph) and 7.71–7.76 (2 H, m, Ph); *m/z* (EI) 297 (M^+), 282, 250, 238, 155, 142 (base peak), 110 and 91.

Methyl (4*S*,5*S*,2*E*)-4-methyl-5-[(4-methylphenyl)sulfonylamino]hex-2-enoate 24 and methyl (2*R*,5*S*,3*E*)-2-methyl-5-[(4-methylphenyl)sulfonylamino]hex-3-enoate 25

To a stirred slurry of CuCN (179.2 mg, 2 mmol) in dry THF (12 cm^3) under argon was added *via* syringe MeLi·LiBr (0.96 mol dm^{-3} solution in Et_2O; 2.08 cm^3, 2 mmol, 4 equiv.) at −78 °C, and the mixture was allowed to warm to 0 °C and stirred at this temperature for 15 min. A solution of the α,β-enoate **12** (148 mg, 0.5 mmol) in dry THF (2 cm^3) was then added dropwise to the above reagent at −78 °C with stirring, and stirring was continued for 30 min followed by quenching with aqueous saturated NH_4Cl–28% NH_4OH (1:1; 2 cm^3). The mixture was extracted with Et_2O–CH_2Cl_2 (4:1) and the extract was washed with water and dried ($MgSO_4$). Concentration under reduced pressure gave a mixture of products as a colourless oil, which was separated by flash chromatography over silica gel eluting with hexane–EtOAc (4:1), to give, in order of elution, the S_N2-product **24** (4.7 mg, 3%) and the *anti*-S_N2'-product **25** (143 mg, 92%).

Compound **24**, colourless crystals, mp 99 °C [from hexane–Et_2O (1:5)] (Found: C, 57.7; H, 6.7; N, 4.5. $C_{15}H_{21}NO_4S$ requires C, 57.9; H, 6.8; N, 4.5%); δ_H(300 MHz; $CDCl_3$) 0.96 (3 H, d, *J* 6.8, CMe), 1.01 (3 H, d, *J* 6.9, CMe), 2.42 (1 H, m, 4-H), 2.43 (3 H, s, CMe), 3.35 (1 H, m, 5-H), 3.72 (3 H, s, OMe), 4.35 (1 H, d, *J* 8.8, NH), 5.77 (1 H, dd, *J* 15.7 and 1.1, 2-H), 6.76 (1

H, dd, *J* 15.7 and 8.3, 3-H), 7.28–7.31 (2 H, m, Ph) and 7.73–7.77 (2 H, m, Ph). The ^{1}H NMR spectrum is identical with that of the authentic sample of **24** prepared from the protected amino alcohol **35**.

Compound **25**, colourless oil [Found (EI): M^+, 311.1182. $C_{15}H_{21}NO_4S$ requires *M*, 311.1191; $[\alpha]_D^{20}$ −52.5 (*c* 0.942 in $CHCl_3$); $\Delta\varepsilon$ −0.62 (213.6 nm in isooctane); ν_{max}/cm^{-1} 3400, 3275 (NH), 1728 (CO) and 1601 (C=C); δ_H(300 MHz; $CDCl_3$) 1.11 (3 H, d, *J* 7.1, CMe), 1.17 (3 H, d, *J* 6.7, CMe), 2.42 (3 H, s, CMe), 2.99 (1 H, m, 2-H), 3.66 (3 H, s, OMe), 3.89 (1 H, m, 5-H), 4.53 (1 H, d, *J* 7.5, NH), 5.32 (1 H, ddd, *J* 15.5, 6.3 and 1.1, CH=), 5.54 (1 H, ddd, *J* 15.5, 7.6 and 1.1, CH=), 7.27–7.30 (2 H, m, Ph) and 7.72–7.76 (2 H, m, Ph); *m/z* (EI) 311 (M^+), 296, 264, 252, 224, 198, 156 (base peak), 140, 124 and 91.

Methyl (2*R*,5*S*,3*E*)-2-methyl-5-[(4-methylphenyl)sulfonylamino]hex-3-enoate 25 and methyl (4*R*,5*S*,2*Z*)-4-methyl-5-[(4-methylphenyl)sulfonylamino]hex-2-enoate 26

To a stirred solution of $ZnCl_2$ (1 mol dm^{-3} solution in Et_2O; 2 cm^3, 2 mmol, 4 equiv.) in THF (4 cm^3) at −78 °C under argon was added *via* syringe MeLi·LiBr (1.5 mol dm^{-3} solution in Et_2O; 2.67 cm^3, 4 mmol, 8 equiv.), and the mixture was allowed to warm to 0 °C and stirred at this temperature for 10 min. Cuprous cyanide (35.8 mg, 0.4 mmol) was added to the above mixture at −78 °C and the mixture was stirred for 5 min. A solution of the α,β-enoate **16** (148 mg, 0.5 mmol) in dry THF (2 cm^3) was added dropwise to the above reagent at −78 °C with stirring, and the stirring was continued for 30 min followed by quenching with aqueous saturated NH_4Cl–28% NH_4OH (1:1; 4 cm^3). The mixture was extracted with Et_2O–CH_2Cl_2 (4:1) and the extract was washed with water and dried ($MgSO_4$). Concentration under reduced pressure gave a mixture of products as a colourless oil, which was separated by flash chromatography over silica gel eluting with hexane–EtOAc (4:1), to give, in order of elution, **26** (7.3 mg, 5%) and **25** (148 mg, 95%).

Compound **25**, colourless oil [Found (EI): M^+, 311.1182. $C_{15}H_{21}NO_4S$ requires *M*, 311.1191); $[\alpha]_D^{20}$ −58 (*c* 0.414 in $CHCl_3$); ν_{max}/cm^{-1} 3400, 3275 (NH), 1728 (CO) and 1600 (C=C); δ_H(270 MHz; $CDCl_3$) 1.11 (3 H, d, *J* 7.0, CMe), 1.17 (3 H, d, *J* 6.5, CMe), 2.42 (3 H, s, CMe), 2.99 (1 H, m, 2-H), 3.65 (3 H, s, OMe), 3.89 (1 H, m, 5-H), 4.57 (1 H, m, NH), 5.32 (1 H, ddd, *J* 15.5, 6.3 and 1.1, CH=), 5.54 (1 H, ddd, *J* 15.5, 7.6 and 1.1, CH=), 7.27–7.30 (2 H, m, Ph) and 7.71–7.75 (2 H, m, Ph); *m/z* (EI) 311 (M^+), 296, 264, 252, 224, 198, 156 (base peak), 140, 124 and 91.

Compound **26**, colourless oil; $[\alpha]_D^{20}$ −95.3 (*c* 0.445 in $CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-1}$ 3370 (NH), 1709 (CO), 1645 and 1603 (C=C); δ_H(200 MHz; $CDCl_3$) 0.96 (3 H, d, *J* 6.4, CMe), 1.08 (3 H, d, *J* 6.5, CMe), 2.42 (3 H, s, CMe), 3.18 (1 H, m, 5-H), 3.32 (1 H, m, 4-H), 3.72 (3 H, s, OMe), 5.07 (1 H, d, *J* 7.8, NH), 5.66 (1 H, d, *J* 11.5, 2-H), 5.74 (1 H, dd, *J* 11.5 and 9.3, 3-H), 7.26–7.30 (2 H, m, Ph) and 7.67–7.72 (2 H, m, Ph). The spectral data (IR, ^{1}H NMR) for **26** are identical with those of an authentic sample of **26** prepared from **36**.

Methyl (4*S*,5*S*,2*Z*)-4-methyl-5-[(4-methylphenyl)sulfonylamino]hex-2-enoate 27 and methyl (2*S*,5*S*,3*E*)-2-methyl-5-[(4-methylphenyl)sulfonylamino]hex-3-enoate 28

By a procedure identical with that described for the reaction of **12** with MeCu(CN)Li·LiBr, the enoate **13** (295 mg, 1 mmol) was converted into a mixture of the enoates **27** and **28** by treatment with MeCu(CN)Li·LiBr (4 mmol) in THF–Et_2O (5:1) at −78 °C for 30 min. The mixture of products was separated by flash chromatography over silica gel eluting with hexane–EtOAc (4:1), to give, in order of elution, the S_N2-product **27** (19 mg, 6%) and the *anti*-S_N2'-product **28** (289 mg, 93%).

Compound **27**, colourless crystals, mp 92 °C [from hexane–Et_2O (4:1)] [Found (EI): M^+, 311.1182. $C_{15}H_{21}NO_4S$ requires *M*, 311.1190]; $[\alpha]_D^{20}$ +6.0 (*c* 0.601 in $CHCl_3$); ν_{max}/cm^{-1} 3400, 3220 (NH), 1713 (CO), 1645 and 1602 (C=C); δ_H(200 MHz; $CDCl_3$) 0.95 (3 H, d, *J* 6.8, CMe), 1.01 (3 H, d, *J* 6.6, CMe), 2.43 (3 H, s, CMe), 3.27 (1 H, m, 5-H), 3.41 (1 H, m, 4-H), 3.72 (3 H, s, OMe), 5.04 (1 H, d, *J* 7.8, NH), 5.79 (1 H, d, *J* 11.7, 2-H), 6.01 (1 H, dd, *J* 11.7 and 10.0, 3-H), 7.28–7.32 (2 H, m, Ph) and 7.76–7.80 (2 H, m, Ph); *m/z* (EI) 311 (M^+), 280, 199, 198 (base peak), 158, 114 and 91.

Compound **28**, colourless crystals, mp 66 °C [from hexane–Et_2O (5:1)] (Found: C, 57.7; H, 6.9; N, 4.5. $C_{15}H_{21}NO_4S$ requires C, 57.9; H, 6.8; N, 4.5%); $[\alpha]_D^{20}$ −22.2 (*c* 1.24 in $CHCl_3$); $\Delta\varepsilon$ +2.15 (221.1 nm in isooctane); ν_{max}/cm^{-1} 3390 (NH), 1728 (CO) and 1600 (C=C); δ_H (300 MHz; $CDCl_3$) 1.11 (3 H, d, *J* 7.1, CMe), 1.17 (3 H, d, *J* 6.8, CMe), 2.42 (3 H, s, CMe), 2.98 (1 H, m, 2-H), 3.66 (3 H, s, OMe), 3.90 (1 H, m, 5-H), 4.58 (1 H, d, *J* 7.6, NH), 5.33 (1 H, ddd, *J* 15.6, 6.0 and 1.1, CH=), 5.55 (1 H, ddd, *J* 15.6, 7.4 and 1.3, CH=), 7.26–7.30 (2 H, m, Ph) and 7.72–7.76 (2 H, m, Ph).

Methyl (2*S*,5*S*,3*E*)-2-methyl-5-[(4-methylphenyl)sulfonylamino]hex-3-enoate 28 and methyl (4*R*,5*S*,2*E*)-4-methyl-5-[(4-methylphenyl)sulfonylamino]hex-2-enoate 29

By a procedure identical with that described for the reaction of **12** with MeCu(CN)Li·LiBr, the enoate **15** (148 mg, 0.5 mmol) was converted into a mixture of the enoates **28** and **29** by treatment with MeCu(CN)Li·LiBr (2 mmol) in THF–Et_2O (5:1) at −78 °C for 30 min. The mixture of products was separated by flash chromatography over silica gel eluting with hexane–EtOAc (4:1), to give, in order of elution, the S_N2-product **29** (5 mg, 3%) and the *anti*-S_N2'-product **28** (143 mg, 92%).

Compound **28**, colourless crystals, mp 64 °C [from hexane–Et_2O (5:1)] (Found: C, 57.6; H, 6.7; N, 4.4. $C_{15}H_{21}NO_4S$ requires C, 57.9; H, 6.8; N, 4.5%); $[\alpha]_D^{20}$ −18.9 (*c* 0.53 in $CHCl_3$); δ_H(200 MHz; $CDCl_3$) 1.11 (3 H, d, *J* 7.1, CMe), 1.17 (3 H, d, *J* 6.8, CMe), 2.42 (3 H, s, CMe), 2.98 (1 H, m, 2-H), 3.66 (3 H, s, OMe), 3.92 (1 H, m, 5-H), 4.62 (1 H, m, NH), 5.33 (1 H, ddd, *J* 15.6, 6.0 and 1.1, CH=), 5.55 (1 H, ddd, *J* 15.6, 7.4 and 1.3, CH=), 7.26–7.30 (2 H, m, Ph) and 7.72–7.76 (2 H, m, Ph).

Compound **29**, colourless crystals, mp 79 °C [from hexane–Et_2O (1:3)]; $[\alpha]_D^{20}$ −10.5 (*c* 0.90 in $CHCl_3$); δ_H(300 MHz; $CDCl_3$) 0.97 (3 H, d, *J* 6.8, CMe), 1.01 (3 H, d, *J* 6.8, CMe), 2.42 (1 H, m, 4-H), 2.43 (3 H, s, CMe), 3.36 (1 H, m, 5-H), 3.72 (3 H, s, OMe), 4.41 (1 H, m, NH), 5.80 (1 H, dd, *J* 15.7 and 1.1, CH=), 6.75 (1 H, dd, *J* 15.7 and 7.7, CH=), 7.29–7.31 (2 H, m, Ph) and 7.72–7.76 (2 H, m, Ph). The ^{1}H NMR spectrum in $CDCl_3$ is identical with that of an authentic sample of **29** prepared from the amino alcohol **36**.

(2*R*,5*S*,3*E*)-2-Methyl-5-[*N*-benzyl-*N*-(4-methylphenyl)-sulfonylamino]hex-3-en-1-yl benzyl ether 30

To a stirred solution of the ester **25** (218 mg, 0.7 mmol) in CH_2Cl_2 (4 cm^3) at −78 °C was added diisobutylaluminium hydride (0.98 mol dm^{-3} solution in hexane; 3 cm^3, 2.8 mmol, 4 equiv.), and the mixture was stirred for 18 h during which time it was allowed to warm to room temperature. The excess of reagent was decomposed with aqueous saturated Na_2SO_4 (5 cm^3) at 0 °C. The inorganic salts were removed by filtration through Celite. The usual workup of the filtrate led to a colourless oil, which was purified by flash chromatography over silica gel eluting with hexane–EtOAc (3:1) to yield an alcohol (93 mg, 47%) as a colourless oil. To a stirred suspension of NaH (31.8 mg, 1.31 mmol) in dry DMF (2 cm^3) was added a solution of the above alcohol (93 mg) in dry DMF (2 cm^3) at 0 °C, followed by benzyl bromide (0.1 cm^3) and the mixture was stirred for 18 h at room temperature when it was poured into ice–water and extracted

with Et_2O. The extract was washed with water and dried ($MgSO_4$). Concentration under reduced pressure followed by flash chromatography over silica gel eluting with hexane–EtOAc (8:1) gave the benzyl ether **30** (137 mg, 90%) as a colourless syrup [Found (CI): $(M + H)^+$, 464.2264. $C_{28}H_{34}NO_3S$ requires M + H, 464.2259]; $[\alpha]_D^{20}$ −29.1 (*c* 0.53 in $CHCl_3$); δ_H(270 MHz; $CDCl_3$) 0.83 (3 H, d, *J* 7.0, CMe), 1.04 (3 H, d, *J* 7.0, CMe), 2.30 (1 H, m, 2-H), 2.41 (3 H, s, CMe), 3.14 (1 H, dd, *J* 8.9 and 6.5, 1-H), 3.18 (1 H, dd, *J* 8.9 and 6.9, 1-H), 4.24 (1 H, d, *J* 16.2, NC*H*H), 4.40 (1 H, d, *J* 16.2, NCH*H*), 4.44 (2 H, s, OCH_2), 4.52 (1 H, m, 5-H), 5.17 (1 H, ddd, *J* 15.7, 5.1 and 0.5, CH=), 5.31 (1 H, ddd, *J* 15.7, 6.9 and 0.9, CH=), 7.18–7.37 (12 H, m, Ph) and 7.67–7.70 (2 H, m, Ph); *m/z* (CI) 464 (MH^+), 352, 288, 262, 203 (base peak), 95 and 91.

(2*S*)-2-{*N*-Benzyl-*N*-[(4-methylphenyl)sulfonyl]amino}propan-1-ol 31 and (2*R*)-3-hydroxy-2-methylpropyl benzyl ether 32

Ozone was bubbled through a solution of the benzyl ether **30** (127 mg, 0.274 mmol) in CH_2Cl_2 (15 cm^3) at −78 °C until a blue colour persisted. The solution was stirred for 30 min during which time it was allowed to warm to 0 °C. It was then recooled to −78 °C and diisobutylaluminium hydride (0.93 mol dm^{-3} solution in hexane; 7 cm^3, 6.5 mmol, 23.7 equiv.) was added dropwise to the mixture, which was then stirred for 2 h at −20 °C. Saturated aqueous NH_4Cl (2 cm^3) was added with vigorous stirring at −78 °C and the mixture was allowed to warm to 0 °C. The mixture was made acidic with 5% HCl at 0 °C and extracted with CH_2Cl_2. The extract was dried ($MgSO_4$) and concentrated under reduced pressure to leave a colourless oil, which was purified by flash chromatography over silica gel eluting with hexane–EtOAc (3:1) to give the benzyl ether **32** (28 mg, 57%). Continued elution gave the protected amino alcohol **31** (75.5 mg, 86%).

Compound **31**, colourless crystals, mp 117 °C [from hexane–Et_2O (1:1)] (Found: C, 63.9; H, 6.7; N, 4.2. $C_{17}H_{21}NO_3S$ requires C, 63.9; H, 6.6; N, 4.4%); $[\alpha]_D^{20}$ +32.0 (*c* 1.246 in $CHCl_3$); δ_H(270 MHz; $CDCl_3$) 0.91 (3 H, d, *J* 7.3, CMe), 1.67 (1 H, dd, *J* 6.2 and 6.2, OH), 2.44 (3 H, s, CMe), 3.26 (1 H, d, *J* 7.0, 1-H), 3.28 (1 H, d, *J* 6.2, 1-H), 4.02 (1 H, ddd, *J* 14.0, 14.0 and 7.0, 2-H), 4.16 (1 H, d, *J* 15.8, NC*H*H), 4.67 (1 H, d, *J* 15.8, NCH*H*), 7.24–7.44 (7 H, m, Ph) and 7.72–7.75 (2 H, m, Ph).

Compound **32**, colourless oil; bp 110 °C (Kugelrohr distillation; 2 mmHg) [Found (FAB): $(M + H)^+$, 181.1231. $C_{11}H_{17}O_2$ requires M + H, 181.1228]; $[\alpha]_D^{20}$ +17.6 (*c* 0.85 in $CHCl_3$); δ_H(270 MHz; $CDCl_3$) 0.89 (3 H, d, *J* 6.9, CMe), 2.08 (1 H, m, 2-H), 2.50 (1 H, dd, *J* 6.3 and 4.9, OH), 3.43 (1 H, dd, *J* 8.5 and 8.5, 1-H), 3.49–3.68 (3 H, m, 1-H and 3-H × 2), 4.52 (2 H, s, OCH_2) and 7.26–7.38 (5 H, m, Ph); *m/z* (FAB) 181 (MH^+), 149, 107, 91 (base peak), 69, 57, 55, 43 and 41.

(2*S*,5*S*,3*E*)-2-Methyl-5-{*N*-benzyl-*N*-[(4-methylphenyl)sulfonyl-amino]}hex-3-enyl benzyl ether 33

By a procedure identical with that described for the preparation of **30**, the enoate **28** (311 mg, 1 mmol) was converted into the benzyl ether **33** (162 mg, 63%) as a colourless oil [Found (CI): MH^+, 464.2254. $C_{28}H_{34}NO_3S$ requires MH, 464.2259]; $[\alpha]_D^{20}$ −36.9 (*c* 0.36 in $CHCl_3$); δ_H(270 MHz; $CDCl_3$) 0.83 (3 H, d, *J* 6.5, CMe), 1.04 (3 H, d, *J* 7.0, CMe), 2.30 (1 H, m, 2-H), 2.41 (3 H, s, CMe), 3.14 (2 H, d, *J* 6.5, 1-H), 4.25 (1 H, d, *J* 15.8, NC*H*H), 4.39 (1 H, d, *J* 15.8, NCH*H*), 4.44 (2 H, s, OCH_2), 4.52 (1 H, m, 5-H), 5.17 (1 H, dd, *J* 15.8 and 5.4, CH=), 5.30 (1 H, dd, *J* 15.8 and 6.5, CH=), 7.18–7.37 (12 H, m, Ph) and 7.67–7.70 (2 H, m, Ph); *m/z* (CI) 464 (MH^+), 352, 288, 262, 203 (base peak), 95 and 91.

(2*S*)-2-{*N*-Benzyl-*N*-[(4-methylphenyl)sulfonylamino]}propan-1-ol 31 and (2*S*)-3-hydroxy-2-methylpropyl benzyl ether 34

By a procedure identical with that described for the preparation of **31** and **32**, the benzyl ether **33** (152 mg, 0.328 mmol) was converted into the protected amino alcohol **31** (90.3 mg, 86%) and the benzyl ether **34** (36.0 mg, 61%). The ^1H NMR spectrum of the protected amino alcohol **31** was identical with that of an authentic sample prepared from **30**.

Compound **34**, colourless oil; bp 110 °C (Kugelrohr distillation; 2 mmHg) [Found (FAB): $(M + H)^+$ 181.1223. $C_{11}H_{17}O_2$ requires M + H, 181.1228]; $[\alpha]_D^{20}$ −17.1 (*c* 0.577 in $CHCl_3$); δ_H(270 MHz; $CDCl_3$) 0.89 (3 H, d, *J* 6.9, CMe), 2.08 (1 H, m, 2-H), 2.54 (1 H, m, OH), 3.43 (1 H, dd, *J* 8.5 and 8.5, 1-H), 3.49–3.68 (3 H, m, 1-H and 3-H × 2), 4.52 (2 H, s, OCH_2) and 7.26–7.38 (5 H, m, Ph); *m/z* (FAB) 181 (MH^+), 107, 91 (base peak), 69, 57, 55, 43 and 41.

Methyl (4*S*,5*S*,2*E*)-4-methyl-5-[(4-methylphenyl)sulfonyl-amino]hex-2-enoate 24 and methyl (4*S*,5*S*,2*Z*)-4-methyl-5-[(4-methylphenyl)sulfonylamino]hex-2-enoate 27

To a stirred solution of DMSO (0.3 cm^3, 4.31 mmol, 3.7 equiv.) in CH_2Cl_2 (3 cm^3) at −78 °C under argon was added dropwise a solution of oxalyl chloride (0.17 cm^3, 1.98 mmol, 1.7 equiv.) in dry CH_2Cl_2 (3 cm^3). After 20 min, a solution of the alcohol **35** (300 mg, 1.17 mmol) in CH_2Cl_2 (1.5 cm^3) was added to the above reagent at −78 °C, and the mixture was stirred for 20 min. Et_3N (1.26 cm^3, 9.01 mmol) was added dropwise to the above solution at −78 °C, and the mixture was allowed to warm to 0 °C and then recooled to −78 °C. Aqueous saturated NH_4Cl (4 cm^3) was added to the mixture and the mixture was extracted with Et_2O. The extract was washed successively with water, 10% aqueous citric acid and water, and dried ($MgSO_4$). Concentration under reduced pressure gave a crude aldehyde as a colourless oil. To a stirred solution of the above oily aldehyde in CH_2Cl_2 (5 cm^3) was added (methoxycarbonylmethylene)-triphenylphosphorane (780 mg, 2.33 mmol, 2 equiv.) at 0 °C, and the mixture was stirred for 1 h at room temperature. The mixture was concentrated under reduced pressure to an oil which was flash chromatographed on silica gel eluting with hexane–EtOAc (3:1) to give the *cis*-enoate **27** (16.5 mg, 4.5%). Continued elution gave the *trans*-enoate **24** (208 mg, 67%).

Compound **24**, colourless crystals, mp 99 °C [from hexane–Et_2O (1:5)] (Found: C, 57.7; H, 6.7; N, 4.5. $C_{15}H_{21}NO_4S$ requires C, 57.9; H, 6.8; N, 4.5%); δ_H(300 MHz; $CDCl_3$) 0.96 (3 H, d, *J* 6.8, CMe), 1.01 (3 H, d, *J* 6.9, CMe), 2.42 (1 H, m, 4-H), 2.43 (3 H, s, CMe), 3.35 (1 H, m, 5-H), 3.72 (3 H, s, OMe), 4.35 (1 H, d, *J* 8.8, NH), 5.77 (1 H, dd, *J* 15.7 and 1.1, 2-H), 6.76 (1 H, dd, *J* 15.7 and 8.3, 3-H), 7.28–7.31 (2 H, m, Ph) and 7.73–7.77 (2 H, m, Ph).

Compound **27**, colourless crystals, mp 91 °C [from hexane–Et_2O (4:1)] [Found (EI): M^+, 311.1180. $C_{15}H_{21}NO_4S$ requires M, 311.1190]; $[\alpha]_D^{20}$ +6.0 (*c* 0.60 in $CHCl_3$); ν_{max}/cm^{-1} 3400, 3220 (NH), 1713 (CO), 1645 and 1602 (C=C); δ_H(200 MHz; $CDCl_3$) 0.95 (3 H, d, *J* 6.8, CMe), 1.01 (3 H, d, *J* 6.6, CMe), 2.43 (3 H, s, CMe), 3.27 (1 H, m, 5-H), 3.41 (1 H, m, 4-H), 3.72 (3 H, s, OMe), 5.04 (1 H, d, *J* 7.8, NH), 5.79 (1 H, d, *J* 11.7, 2-H), 6.01 (1 H, dd, *J* 11.7 and 10.0, 3-H), 7.28–7.32 (2 H, m, Ph) and 7.76–7.80 (2 H, m, Ph); *m/z* (EI) 311 (M^+), 280, 199, 198 (base peak), 158, 114 and 91.

Methyl (4*R*,5*S*,2*Z*)-4-methyl-5-[(4-methylphenyl)sulfonyl-amino]hex-2-enoate 26 and methyl (4*R*,5*S*,2*E*)-4-methyl-5-[(4-methylphenyl)sulfonylamino]hex-2-enoate 29

By a procedure identical with that described for the preparation of **24** and **27**, the alcohol **36** (120 mg, 0.466 mmol) was converted into a 17:1 mixture of **29** and **26**. The mixture was separated by flash chromatography over silica gel, eluting with hexane–EtOAc (3:1) to give the *cis*-enoate **26** (6.1 mg, 4.2%), and further elution gave the *trans*-enoate **29** (105 mg, 72%).

Compound **26**, colourless oil [Found (EI): M^+, 311.1204. $C_{15}H_{21}NO_4S$ requires M, 311.1191]; $[\alpha]_D^{20}$ −101 (*c* 0.37 in

$CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-1}$ 3370 (NH), 1709 (CO), 1645 and 1603 (C=C); δ_H(300 MHz; $CDCl_3$) 0.96 (3 H, d, *J* 6.6, CMe), 1.08 (3 H, d, *J* 6.5, CMe), 2.42 (3 H, s, CMe), 3.18 (1 H, m, 5-H), 3.32 (1 H, m, 4-H), 3.72 (3 H, s, OMe), 5.07 (1 H, d, *J* 7.8, NH), 5.67 (1 H, d, *J* 11.5, CH=), 5.73 (1 H, dd, *J* 11.5 and 9.3, CH=), 7.27–7.32 (2 H, m, Ph) and 7.68–7.78 (2 H, m, Ph); *m/z* (EI), 311 (M^+), 296, 280, 198 (base peak), 155 and 91.

Compound **29**, colourless crystals, mp 78 °C [from hexane–Et_2O (1:3)] (Found: C, 57.7; H, 6.7; N, 4.5. $C_{15}H_{21}NO_4S$ requires C, 57.9; H, 6.8; N, 4.5%); $[\alpha]_D^{20}$ −9.9 (*c* 0.89 in $CHCl_3$); ν_{max}/cm^{-1} 3380 (NH), 1715 (CO), 1657 and 1601 (C=C); δ_H(300 MHz; $CDCl_3$) 0.97 (3 H, d, *J* 6.8, CMe), 1.01 (3 H, d, *J* 6.8, CMe), 2.42 (1 H, m, 4-H), 2.43 (3 H, s, CMe), 3.36 (1 H, m, 5-H), 3.72 (3 H, s, OMe), 4.41 (1 H, m, NH), 5.80 (1 H, dd, *J* 15.7 and 1.1, CH=), 6.75 (1 H, dd, *J* 15.7 and 7.7, CH=), 7.29–7.31 (2 H, m, Ph) and 7.72–7.76 (2 H, m, Ph).

Methyl (2*R*,3*E*)-2-butyl-5-[(4-methylphenyl)sulfonylamino]-pent-3-enoate 37 and methyl (4*R*,2*Z*)-4-butyl-5-[(4-methylphenyl)sulfonylamino]pent-2-enoate 38

To a stirred slurry of CuCN (179.1 mg, 2 mmol, 4 equiv.) in dry THF (2 cm^3) under argon at −78 °C was added *via* syringe butyllithium (1.63 mol dm^{-3} solution in hexane; 1.23 cm^3, 2 mmol, 4 equiv.), and the mixture was allowed to warm to 0 °C. After being stirred at this temperature for 10 min a solution of the α,β-enoate **10** (140.7 mg, 0.5 mmol, 1 equiv.) in dry THF (2 cm^3) was added dropwise to it at −78 °C with stirring, and stirring was continued for 30 min, followed by quenching with aqueous saturated NH_4Cl–28% NH_4OH (1:1; 4 cm^3). Usual workup led to a mixture of products as a colourless oil, which was separated by flash chromatography over silica gel eluting with hexane–EtOAc (2:1), yielding, in order of elution, **38** (11 mg, 6.5%) and **37** (158 mg, 93%).

Compound **37**, colourless oil; $[\alpha]_D^{20}$ −30.7 (*c* 1.40 in $CHCl_3$); $\Delta\varepsilon$ −0.313 (216.3 nm in isooctane); δ_H(270 MHz; $CDCl_3$) 0.87 (3 H, t, *J* 6.9, CMe), 1.10–1.32 (4 H, m, CH_2 × 2), 1.35–1.49 (1 H, m, CH), 1.60–1.74 (1 H, m, CH), 2.43 (3 H, s, CMe), 2.92 (1 H, dd, *J* 15.5 and 7.6, 2-H), 3.55 (2 H, m, CH_2), 3.65 (3 H, s, OMe), 4.46 (1 H, t, *J* 5.8, NH), 5.44 (1 H, ddd, *J* 15.5, 5.8 and 5.8, CH=), 5.58 (1 H, dd, *J* 15.5 and 8.4, CH=), 7.30–7.33 (2 H, m, Ph) and 7.72–7.77 (2 H, m, Ph); *m/z* (FAB) 340 (MH^+), 338, 280, 184, 169 (base peak), 155, 109 and 91 [Found (FAB): $(M + H)^+$, 340.1577. $C_{17}H_{26}NO_4S$ requires *M* + H, 340.1582].

Compound **38**, colourless oil [Found (FAB): $(M + H)^+$, 340.1587. $C_{17}H_{26}NO_4S$ requires *M* + H, 340.1582]; $[\alpha]_D^{20}$ −40.2 (*c* 1.25 in $CHCl_3$); δ_H(270 MHz; $CDCl_3$) 0.83 (3 H, apparent m, CMe), 1.12–1.43 (6 H, m, CH_2 × 3), 2.43 (3 H, s, CMe), 2.86 (1 H, ddd, *J* 11.5, 9.7 and 6.5, 5-H), 3.01 (1 H, ddd, *J* 11.5, 4.6 and 4.6, 5-H), 3.42 (1 H, m, 4-H), 3.72 (3 H, s, OMe), 5.05 (1 H, t, *J* 5.9, NH), 5.79–5.89 (2 H, m, CH= × 2), 7.28–7.31 (2 H, m, Ph) and 7.70–7.74 (2 H, m, Ph); FAB-LRMS, *m/z* 340 (MH^+), 308 (base peak), 184, 155 and 91.

Methyl (2*R*,3*E*)-2-isopropyl-5-[(4-methylphenyl)sulfonylamino]pent-3-enoate 39 and methyl (4*R*,2*Z*)-4-isopropyl-5-[(4-methylphenyl)sulfonylamino]pent-2-enoate 40

By a procedure identical with that described for the reaction of **10** with BuCu(CN)Li, the enoate **10** (112.5 mg, 0.4 mmol) was converted into a mixture of enoates **39** and **40** by treatment with $Pr^iCu(CN)MgCl{\cdot}2LiCl$ (1.6 mmol, 4 equiv.) in THF at −78 °C for 30 min. The mixture was separated by flash chromatography over silica gel eluting with hexane–EtOAc (2:1), yielding, in order of elution **40** (10.5 mg, 8%) and **39** (117 mg, 90%).

Compound **39**, colourless crystals, mp 74 °C [from hexane–Et_2O (1:3)] (Found: C, 58.9; H, 7.3; N, 4.2. $C_{16}H_{23}NO_4S$ requires C, 59.1; H, 7.1; N, 4.3%); $[\alpha]_D^{20}$ −42.2 (*c* 0.744 in $CHCl_3$); $\Delta\varepsilon$ −3.9 (216.3 nm in isooctane); δ_H(300 MHz; $CDCl_3$) 0.81 (3 H, d, *J* 6.8, CMe), 0.86 (3 H, d, *J* 6.8, CMe), 1.92 (1 H, m, CH), 2.43 (3 H, s, CMe), 2.66 (1 H, m, 2-H), 3.58 (2 H, m, 5-H), 3.65 (3 H, s, OMe), 4.40 (1 H, m, NH), 5.45 (1 H, ddd, *J* 15.4, 6.1 and 6.1, CH=), 5.60 (1 H, dddd, *J* 15.4, 9.2, 1.2 and 1.2, CH=), 7.30–7.32 (2 H, m, Ph) and 7.72–7.76 (2 H, m, Ph).

Compound **40**, colourless oil [Found (FAB): $(M + H)^+$, 326.1433. $C_{16}H_{24}NO_4S$ requires *M* + H, 326.1426]; $[\alpha]_D^{20}$ −51.1 (*c* 1.40 in $CHCl_3$); δ_H(300 MHz; $CDCl_3$) 0.83 (3 H, d, *J* 6.6, CMe), 0.85 (3 H, d, *J* 6.6, CMe), 1.62 (1 H, m, CH), 2.43 (3 H, s, CMe), 2.89 (1 H, ddd, *J* 11.6, 10.3 and 6.5, 5-H), 3.11 (1 H, ddd, *J* 11.6, 4.2 and 4.2, 5-H), 3.24 (1 H, m, 4-H), 3.73 (3 H, s, OMe), 5.03 (1 H, m, NH), 5.84–5.96 (2 H, m, CH=CH), 7.26–7.31 (2 H, m, Ph) and 7.69–7.74 (2 H, m, Ph); *m/z* (FAB) 326 (MH^+), 294 (base peak), 155, 149 and 91.

Methyl (2*S*,5*S*,3*E*)-2-ethyl-5-[(4-methylphenyl)sulfonylamino]-hex-3-enoate 41 and methyl (4*S*,5*S*,2*Z*)-4-ethyl-5-[(4-methylphenyl)sulfonylamino]hex-2-enoate 42

By a procedure identical with that described for the reaction of **10** with BuCu(CN)Li, the enoate **13** (148 mg, 0.5 mmol) was converted into a mixture of enoates **41** and **42** by treatment with $EtCu(CN)MgCl{\cdot}4LiCl$ (2 mmol, 4 equiv.) in THF at −78 °C for 30 min. The mixture was separated by flash chromatography over silica gel eluting with hexane–EtOAc (3:1), yielding, in order of elution **42** (12.5 mg, 8%) and **41** (149 mg, 92%).

Compound **41**, colourless oil [Found (FAB): $(M + H)^+$, 326.1424. $C_{16}H_{24}NO_4S$ requires *M* + H, 326.1426]; $[\alpha]_D^{20}$ +5.9 (*c* 0.597 in $CHCl_3$); δ_H(270 MHz; $CDCl_3$) 0.79 (3 H, t, *J* 7.3, CMe), 1.17 (3 H, d, *J* 6.5, CMe), 1.39 (1 H, m, C*H*H), 1.67 (1 H, m, CH*H*), 2.42 (3 H, s, CMe), 2.76 (1 H, dd, *J* 15.8 and 7.6, 2-H), 3.66 (3 H, s, OMe), 3.91 (1 H, m, 5-H), 4.56 (1 H, d, *J* 7.3, NH), 5.34 (1 H, dd, *J* 15.8 and 5.4, CH=), 5.46 (1 H, dd, *J* 15.8 and 8.6, CH=), 7.27–7.30 (2 H, m, Ph) and 7.72–7.75 (2 H, m, Ph); *m/z* (FAB) 326 (MH^+), 324, 310, 266, 155 (base peak) and 91.

Compound **42**, colourless oil; [Found (FAB): $(M + H)^+$, 326.1431. $C_{16}H_{24}NO_4S$ requires *M* + H, 326.1426]; $[\alpha]_D^{20}$ −6.6 (*c* 0.345 in $CHCl_3$); δ_H(270 MHz; $CDCl_3$) 0.72 (3 H, t, *J* 7.6, CMe), 1.04 (3 H, d, *J* 6.6, CMe), 1.21 (1 H, m, C*H*H), 1.49 (1 H, m, CH*H*), 2.43 (3 H, s, CMe), 3.17 (1 H, m, CH), 3.29 (1 H, m, CH), 3.73 (3 H, s, OMe), 5.29 (1 H, d, *J* 6.6, NH), 5.91 (1 H, dd, *J* 17.6 and 11.6, CH=), 5.93 (1 H, dd, *J* 11.6 and 11.6, CH=), 7.28–7.32 (2 H, m, Ph) and 7.77–7.81 (2 H, m, Ph); *m/z* (FAB) 326 (MH^+, base peak), 294, 198, 155, 95, 69, 57 and 55.

Methyl (2*S*,5*S*,3*E*)-2-butyl-5-[(4-methylphenyl)sulfonylamino]-hex-3-enoate 43 and methyl (4*S*,5*S*,2*Z*)-4-butyl-5-[(4-methylphenyl)sulfonylamino]hex-2-enoate 44

To a stirred mixture of $ZnCl_2$ (1.0 mol dm^{-3} solution in Et_2O; 2 cm^3, 2 mmol) in dry THF (10 cm^3) was added *via* syringe butyllithium (1.64 mol dm^{-3} solution in hexane; 3.66 cm^3, 6 mmol) at −78 °C, and the mixture was allowed to warm to 0 °C and stirred at this temperature for 10 min. The mixture was recooled to −78 °C, when CuCN (53.7 mg, 0.6 mmol) was added with stirring, and the mixture was allowed to warm to 0 °C and stirred at this temperature for 10 min. The α,β-enoate **13** (148 mg, 0.5 mmol) in dry THF (3 cm^3) was added dropwise to the above reagent at −78 °C with stirring, and stirring was continued for 1 h, followed by quenching with aqueous saturated NH_4Cl–28% NH_4OH (1:1; 4 cm^3). Usual workup led to a mixture of products as a colourless oil, which was separated by flash chromatography over silica gel eluting with hexane–EtOAc (4:1), to give, in order of elution, the title compounds **44** (1.8 mg, 1%) and **43** (170.5 mg, 97%).

Compound **43**, colourless oil [Found (EI): M^+, 353.1668. $C_{18}H_{27}NO_4S$ requires *M*, 353.1661]; $[\alpha]_D^{20}$ +1.48 (*c* 1.08 in $CHCl_3$); ν_{max}/cm^{-1} 3390 (NH), 1726 (CO) and 1598 (C=C); δ_H(270 MHz; $CDCl_3$) 0.86 (3 H, t, *J* 6.6, CMe), 1.05–1.65 (6 H, m, CH_2 × 3), 1.17 (3 H, d, *J* 6.8, CMe), 2.42 (3 H, s, CMe), 2.83

(1 H, m, 2-H), 3.66 (3 H, s, OMe), 3.91 (1 H, m, 5-H), 4.64 (1 H, d, *J* 7.6, NH), 5.32 (1 H, dd, *J* 15.6 and 5.4, CH=), 5.46 (1 H, ddd, *J* 15.6, 8.0 and 0.5, CH=), 7.27–7.30 (2 H, m, Ph) and 7.72–7.76 (2 H, m, Ph); *m/z* (EI) 353 (M^+), 338, 306, 294, 198 (base peak), 155 and 91.

Compound **44**, colourless oil [Found (EI): M^+, 353.1664. $C_{18}H_{27}NO_4S$ requires *M*, 353.1661]; $[\alpha]_D^{20}$ −27 (*c* 0.10 in $CHCl_3$); ν_{max}/cm^{-1} 3380, 3220 (NH), 1707 (CO) and 1598 (C=C); δ_H(300 MHz; $CDCl_3$) 0.79 (3 H, t, *J* 6.9, CMe), 1.00–1.40 (6 H, m, CH_2 × 3), 1.06 (3 H, d, *J* 6.6, CMe), 2.42 (3 H, s, CMe), 3.27 (2 H, m, 4- and 5-H), 3.74 (3 H, s, OMe), 5.26 (1 H, d, *J* 6.6, NH), 5.89 (1 H, dd, *J* 11.7 and 4.8, CH=), 5.93 (1 H, dd, *J* 11.7 and 4.9, CH=), 7.28–7.31 (2 H, m, Ph) and 7.77–7.81 (2 H, m, Ph); *m/z* (EI) 353 (M^+), 198 (base peak), 155 and 91.

Methyl (2*S*,5*S*,3*E*)-2-isopropyl-5-[(4-methylphenyl)sulfonylamino]hex-3-enoate 45 and methyl (4*S*,5*S*,2*Z*)-4-isopropyl-5-[(4-methylphenyl)sulfonylamino]hex-2-enoate 46

By a procedure identical with that described for the reaction of **10** with $Pr^iCu(CN)MgCl{\cdot}2LiCl$, the enoate **13** (148 mg, 0.5 mmol) was converted into a mixture of enoates **45** and **46** by treatment with $Pr^iCu(CN)MgCl{\cdot}2LiCl$ (2 mmol, 4 equiv.) in THF at −78 °C for 30 min. The mixture was separated by flash chromatography over silica gel eluting with hexane–EtOAc (2:1), to give, in order of elution **46** (3.3 mg, 2%) and **45** (166 mg, 97%).

Compound **45**, colourless oil (Found: C, 60.0; H, 7.3; N, 4.1. $C_{17}H_{25}NO_4S$ requires: C, 60.2; H, 7.4; N, 4.1%); $[\alpha]_D^{20}$ +15.4 (*c* 0.791 in $CHCl_3$); ν_{max}/cm^{-1} 3380 (NH), 1728 (CO) and 1600 (C=C); δ_H(200 MHz; $CDCl_3$) 0.75 (3 H, d, *J* 6.8, CMe), 0.83 (3 H, d, *J* 6.8, CMe), 1.18 (3 H, d, *J* 6.8, CMe), 1.88 (1 H, m, CH), 2.42 (3 H, s, CMe), 2.55 (1 H, t, *J* 8.5, 2-H), 3.67 (3 H, s, OMe), 3.90 (1 H, m, 5-H), 4.69 (1 H, m, NH), 5.33 (1 H, dd, *J* 15.6 and 5.4, CH=), 5.48 (1 H, ddd, *J* 15.6, 9.3 and 1.0, CH=), 7.26–7.30 (2 H, m, Ph) and 7.71–7.77 (2 H, m, Ph).

Compound **46**, colourless crystals, mp 69 °C [from hexane–Et_2O (3:1)] [Found (EI): M^+, 339.1494. $C_{17}H_{25}NO_4S$ requires *M*, 339.1504]; $[\alpha]_D^{27}$ −24.6 (*c* 0.26 in $CHCl_3$); δ_H(270 MHz; $CDCl_3$) 0.68 (3 H, d, *J* 6.6, CMe), 0.71 (3 H, d, *J* 6.6, CMe), 1.06 (3 H, d, *J* 6.6, CMe), 1.61 (1 H, m, CH), 2.43 (3 H, s, CMe), 2.89 (1 H, m, 4-H), 3.43 (1 H, m, 5-H), 3.76 (3 H, s, OMe), 5.64 (1 H, d, *J* 5.9, NH), 5.95 (1 H, dd, *J* 11.7 and 9.5, CH=), 6.03 (1 H, dd, *J* 11.7 and 0.5, CH=), 7.28–7.34 (2 H, m, Ph) and 7.80–7.85 (2 H, m, Ph); *m/z* (EI) 339 (M^+), 308, 198 (base peak), 155, 142 and 91.

Methyl (2*S*,5*S*,3*E*)-2-[(isopropoxy)dimethylsilylmethyl]-5-[(4-methylphenyl)sulfonylamino]hex-3-enoate 47

To a stirred solution of CuCN (358 mg, 4 mmol) and LiCl (339 mg, 8 mmol) in dry THF (5 cm^3) under argon was added *via* syringe $Pr^iOSi(Me)_2CH_2MgCl$ (0.8 mol dm^{-3} solution in THF; 5.0 cm^3, 4 mmol) at −78 °C, and the mixture was allowed to warm to 0 °C and stirred at this temperature for 10 min. A solution of the enoate **13** (295 mg, 1 mmol) in dry THF (2 cm^3) was added dropwise to the above reagent at −78 °C with stirring, and stirring was continued for 30 min, followed by quenching with aqueous saturated NH_4Cl–28% NH_4OH (1:1; 4 cm^3). The mixture was extracted with Et_2O–CH_2Cl_2 (4:1) and the extract was washed with water and dried ($MgSO_4$). Concentration under reduced pressure gave an oily residue, which was flash chromatographed on silica gel, eluting with hexane–EtOAc (4:1) to give the title compound (320 mg, 75%) (Found: C, 55.9; H, 8.1; N, 3.3. $C_{20}H_{33}NO_5SSi$ requires C, 56.2; H, 7.8; N, 3.3%); $[\alpha]_D^{20}$ 0 (*c* 0.65 in $CHCl_3$); δ_H(270 MHz; $CDCl_3$) 0.06 (6 H, s, $SiMe_2$), 0.73 (1 H, dd, *J* 14.9 and 7.3, C*H*HSi), 1.05 (1 H, dd, *J* 14.9 and 7.7, CH*H*Si), 1.12 (6 H, d, *J* 6.2, CMe × 2), 1.17 (3 H, d, *J* 6.5, CMe), 2.42 (3 H, s, CMe), 3.04 (1 H, dd, *J* 15.7 and 7.7, CH), 3.63 (3 H, s, OMe), 3.85–399 (2 H, m, 5-H and CH), 4.50 (1 H, d, *J* 7.3, NH), 5.35 (1 H, ddd, *J* 15.7, 6.2 and 0.5, CH=), 5.51 (1 H, ddd, *J* 15.7, 8.1 and 1.1, CH=), 7.27–7.30 (2 H, m, Ph) and 7.71–7.76 (2 H, m, Ph).

Methyl (2*S*,5*S*,3*E*)-2-(4-fluorophenylmethyl)-5-[(4-methylphenyl)sulfonylamino]hex-3-enoate 48

To a stirred solution of CuCN (358 mg, 4 mmol) and LiCl (339 mg, 8 mmol) in dry THF (5 cm^3) under argon was added *via* syringe p-$FC_6H_4CH_2MgCl$ (0.75 mol dm^{-3} solution in THF; 5.33 cm^3, 4 mmol) at −78 °C, and the mixture was allowed to warm to 0 °C, and stirred at this temperature for 10 min. The enoate **13** (295 mg, 1 mmol) in dry THF (2 cm^3) was added dropwise to the above reagent at −78 °C with stirring, and the stirring was continued for 30 min, followed by quenching with aqueous saturated NH_4Cl–28% NH_4OH (1:1; 4 cm^3). The mixture was extracted with Et_2O–CH_2Cl_2 (4:1) and the extract was washed with water and dried ($MgSO_4$). Concentration under reduced pressure gave an oily residue, which was flash chromatographed on silica gel, eluting with hexane–EtOAc (3:1) to give the title compound (397 mg, 98%) as a colourless oil (Found: C, 62.3; H, 6.1; N, 3.4. $C_{21}H_{24}FNO_4S$ requires C, 62.2; H, 6.0; N, 3.5%); $[\alpha]_D^{20}$ +3.17 (*c* 0.82 in $CHCl_3$); δ_H(270 MHz; $CDCl_3$) 1.09 (3 H, d, *J* 7.0, CMe), 2.42 (3 H, s, CMe), 2.62 (1 H, dd, *J* 13.5 and 7.0, PhC*H*H), 2.93 (1 H, dd, *J* 13.5 and 7.8, PhCH*H*), 3.09 (1 H, dd, *J* 15.7 and 7.8, 2-H), 3.62 (3 H, s, OMe), 3.84 (1 H, m, 5-H), 4.38 (1 H, d, *J* 7.8, NH), 5.20 (1 H, dd, *J* 15.5 and 5.9, CH=), 5.51 (1 H, ddd, *J* 15.5, 8.4 and 1.4, CH=), 6.89–7.04 (4 H, m, Ph), 7.26–7.30 (2 H, m, Ph) and 7.69–7.74 (2 H, m, Ph).

Methyl (2*S*,5*S*,3*E*)-2-butyl-5-[(4-methylphenyl)sulfonylamino]-hex-3-enoate 43

By a procedure identical with that described for the reaction of **10** with BuCu(CN)Li, the α,β-enoate **15** (148 mg, 0.5 mmol) was converted into the β,γ-enoate **43** (169 mg, 96%) by treatment with BuCu(CN)Li (2 mmol, 4 equiv.) in THF at −78 °C for 30 min. Compound **43**, colourless oil [Found (EI): M^+, 353.1667. $C_{18}H_{27}NO_4S$ requires *M*, 353.1661]; $[\alpha]_D^{20}$ +1.5 (*c* 1.0 in $CHCl_3$); ν_{max}/cm^{-1} 3390 (NH), 1726 (CO) and 1598 (C=C); δ_H(270 MHz; $CDCl_3$) 0.86 (3 H, t, *J* 6.6, CMe), 1.05–1.65 (6 H, m, CH_2 × 3), 1.17 (3 H, d, *J* 6.8, CMe), 2.42 (3 H, s, CMe), 2.83 (1 H, m, 2-H), 3.66 (3 H, s, OMe), 3.91 (1 H, m, 5-H), 4.64 (1 H, d, *J* 7.6, NH), 5.32 (1 H, dd, *J* 15.6 and 5.4, CH=), 5.46 (1 H, ddd, *J* 15.6, 8.0 and 0.5, CH=), 7.27–7.30 (2 H, m, Ph) and 7.72–7.76 (2 H, m, Ph); *m/z* (EI) 353 (M^+), 338, 306, 294, 198 (base peak), 155 and 91.

Methyl (2*S*,5*S*,3*E*)-2-[(isopropoxy)dimethylsilylmethyl]-5-[(4-methylphenyl)sulfonylamino]hex-3-enoate 47

By a procedure identical with that described for the reaction of **13** with $Pr^iOSi(Me)_2CH_2Cu(CN)MgCl{\cdot}2LiCl$, the α,β-enoate **15** (295 mg, 1 mmol) was converted into the β,γ-enoate **47** (356 mg, 83%) by treatment with $Pr^iOSi(Me)_2CH_2Cu(CN)MgCl{\cdot}2LiCl$ (2 mmol, 4 equiv.) in THF at −78 °C for 30 min. Compound **47**, colourless oil (Found: C, 55.9; H, 8.1; N, 3.3. $C_{20}H_{33}NO_5SSi$ requires C, 56.2; H, 7.8; N, 3.3%); δ_H(270 MHz; $CDCl_3$) 0.06 (6 H, s, $SiMe_2$), 0.73 (1 H, dd, *J* 14.9 and 7.3, C*H*HSi), 1.05 (1 H, dd, *J* 14.9 and 7.7, CH*H*Si), 1.12 (6 H, d, *J* 6.2, CMe × 2), 1.17 (3 H, d, *J* 6.5, CMe), 2.42 (3 H, s, CMe), 3.04 (1 H, dd, *J* 15.7 and 7.7, CH), 3.63 (3 H, s, OMe), 3.85–3.99 (2 H, m, 5-H and CH), 4.50 (1 H, d, *J* 7.3, NH), 5.35 (1 H, ddd, *J* 15.7, 6.2 and 0.5, CH=), 5.51 (1 H, ddd, *J* 15.7, 8.1 and 1.1, CH=), 7.27–7.30 (2 H, m, Ph) and 7.71–7.76 (2 H, m, Ph).

Methyl (2*S*,5*S*,3*E*)-2-(4-fluorophenylmethyl)-5-[(4-methylphenyl)sulfonylamino]hex-3-enoate 48

By a procedure identical with that described for the reaction of **13** with p-$FC_6H_4CH_2Cu(CN)MgCl{\cdot}2LiCl$, the α,β-enoate **15**

(295 mg, 1 mmol) was converted into the β,γ-enoate **48** (402 mg, 98%) by treatment with *p*-$FC_6H_4CH_2Cu(CN)MgCl{\cdot}2LiCl$ (4 mmol, 4 equiv.) in THF at −78 °C for 30 min. Compound **48**, colourless oil (Found: C, 62.3; H, 6.1; N, 3.4. $C_{21}H_{24}FNO_4S$ requires C, 62.2; H, 6.0; N, 3.5%); $[\alpha]_D^{20}$ +3.17 (*c* 0.82 in $CHCl_3$); δ_H(270 MHz; $CDCl_3$) 1.09 (3 H, d, *J* 7.0, CMe), 2.42 (3 H, s, CMe), 2.62 (1 H, dd, *J* 13.5 and 7.0, PhC*H*H), 2.93 (1 H, dd, *J* 13.5 and 7.8, PhCH*H*), 3.09 (1 H, dd, *J* 15.7 and 7.8, 2-H), 3.62 (3 H, s, OMe), 3.84 (1 H, m, 5-H), 4.38 (1 H, d, *J* 7.8, NH), 5.20 (1 H, dd, *J* 15.5 and 5.9, CH=), 5.51 (1 H, ddd, *J* 15.5, 8.4 and 1.4, CH=), 6.89–7.04 (4 H, m, Ph), 7.26–7.30 (2 H, m, Ph) and 7.69–7.74 (2 H, m, Ph).

Methyl (2*S*,5*R*,3*E*)-2-methyl-5-[(4-methylphenyl)sulfonylamino]-5-phenylpent-3-enoate 49

By a procedure identical with that described for the reaction of **12** with MeCu(CN)Li·LiBr, the α,β-enoate **18** (86 mg, 0.24 mmol) was converted into the β,γ-enoate **49** (77 mg, 85%) by treatment with MeCu(CN)Li·LiBr (0.96 mmol) in THF–Et_2O (6:1) at −78 °C for 30 min. Compound **49**, colourless oil [Found (FAB): $(M + H)^+$, 374.1418. $C_{20}H_{24}NO_4S$ requires *M* + H, 374.1426]; $[\alpha]_D^{15}$ +32 (*c* 0.97 in $CHCl_3$); δ_H(600 MHz; $CDCl_3$) 1.12 (3 H, d, *J* 7.0, CMe), 2.37 (3 H, s, CMe), 3.05 (1 H, ddd, *J* 14.0, 7.0 and 7.0, 2-H), 3.68 (3 H, s, OMe), 4.83 (1 H, d, *J* 7, NH), 4.93 (1 H, m, 5-H), 5.55 (1 H, dd, *J* 15.5 and 5.9, CH=), 5.61 (1 H, dd, *J* 15.5 and 7.14, CH=), 7.10–7.14 (2 H, m, Ph), 7.18–7.26 (5 H, m, Ph) and 7.61–7.62 (2 H, m, Ph); *m/z* (FAB) 374 (MH^+), 372, 260, 218, 203, 171, 143 (base peak) and 91.

Methyl (2*S*,5*S*,3*E*)-2-methyl-5-[(4-methylphenyl)sulfonylamino]-5-phenylpent-3-enoate 50

To a stirred solution of $ZnCl_2$ (1.0 mol dm^{-3} solution in Et_2O; 1.66 cm^3, 1.66 mmol, 5 equiv.) and THF (4 cm^3) at −78 °C under argon was added *via* syringe MeLi·LiBr (1.5 mol dm^{-3} solution in Et_2O; 2.22 cm^3, 3.3 mmol, 10 equiv.), and the mixture was allowed to warm to 0 °C. Cuprous cyanide (29.8 mg, 0.33 mmol) was added to the above mixture at −78 °C and the mixture was stirred for 5 min. A solution of α,β-enoate **21** (118 mg, 0.33 mmol) in dry THF (2 cm^3) was added dropwise to the above reagent at −78 °C with stirring, and stirring was continued for 30 min, followed by quenching with aqueous saturated NH_4Cl–28% NH_4OH (1:1; 4 cm^3). The mixture was extracted with Et_2O–CH_2Cl_2 (4:1) and the extract was washed with water and dried ($MgSO_4$). Concentration under reduced pressure gave an oily residue, which was flash chromatographed on silica gel eluting with hexane–EtOAc (4:1) to give the title compound (123 mg, 99%) as colourless crystals, mp 89 °C [from hexane–Et_2O (1:2)] (Found: C, 64.3; H, 6.3; N, 3.7. $C_{20}H_{23}NO_4S$ requires C, 64.3; H, 6.2; N, 3.8%); $[\alpha]_D^{20}$ +12.1 (*c* 0.86 in $CHCl_3$); δ_H(300 MHz; $CDCl_3$) 1.14 (3 H, d, *J* 7.1, CMe), 2.40 (3 H, s, CMe), 3.05 (1 H, m, 2-H), 3.65 (3 H, s, OMe), 4.78 (1 H, d, *J* 7.1, NH), 4.93 (1 H, m, 5-H), 5.55 (1 H, dd, *J* 15.4 and 5.5, CH=), 5.62 (1 H, dd, *J* 15.4 and 6.4, CH=), 7.10–7.15 (2 H, m, Ph), 7.19–7.25 (5 H, m, Ph) and 7.61–7.64 (2 H, m, Ph).

Methyl (2*R*,5*S*,3*E*)-2-methyl-5-[(4-methylphenyl)sulfonylamino]-5-phenylpent-3-enoate 51

By a procedure identical with that described for the reaction of **21** with $Me_2Zn{\cdot}2LiCl{\cdot}2LiBr$ in the presence of 20 mol% CuCN, the α,β-enoate **22** (118 mg, 0.33 mmol) was converted into the β,γ-enoate **51** (113 mg, 91%). Compound **51**, colourless crystals, mp 70 °C [from hexane–Et_2O (1:3)] (Found: C, 64.2; H, 6.2; N, 3.6. $C_{20}H_{23}NO_4S$ requires C, 64.3; H, 6.2; N, 3.8%); $[\alpha]_D^{20}$ −37.4 (*c* 0.73 in $CHCl_3$); δ_H(300 MHz; $CDCl_3$) 1.12 (3 H, d, *J* 7.0, CMe), 2.37 (3 H, s, CMe), 3.05 (1 H, m, 2-H), 3.68 (3 H, s, OMe), 4.77 (1 H, d, *J* 7.0, NH), 4.94 (1 H, m, 5-H), 5.55 (1 H, dd, *J* 15.5 and 5.4, CH=), 5.61 (1 H, dd, *J* 15.5 and 6.7, CH=), 7.09–7.13 (2 H, m, Ph), 7.18–7.24 (5 H, m, Ph) and 7.61–7.64 (2 H, m, Ph).

Methyl (2*E*)-3-{(2*S*)-1-[(4-methylphenyl)sulfonyl]azetidin-2-yl}prop-2-enoate 53

By a procedure identical with that described for the preparation of the enoates **18** and **19** from the alcohol **17**, the alcohol **52** (2.55 g, 10.6 mmol) was converted into the α,β-enoate **53** (822 mg, 26%), colourless crystals, mp 124 °C [from CH_2Cl_2–Et_2O (1:9)] (Found: C, 56.7; H, 5.9; N, 4.7. $C_{14}H_{17}NO_4S$ requires C, 56.9; H, 5.8; N, 4.7%); $[\alpha]_D^{20}$ −260 (*c* 0.714 in $CHCl_3$); δ_H(270 MHz; $CDCl_3$) 2.03–2.24 (2 H, m, CH_2), 2.46 (3 H, s, CMe), 3.68 (2 H, m, CH_2), 3.75 (3 H, s, OMe), 4.50 (1 H, m, CH), 6.12 (1 H, dd, *J* 15.6 and 1.5, CH=), 6.94 (1 H, dd, *J* 15.6 and 5.4, CH=), 7.36–7.41 (2 H, m, Ph) and 7.70–7.74 (2 H, m, Ph).

Methyl (2*E*)-3-{(2*S*)-1-[(4-methylphenyl)sulfonyl]pyrrolidin-2-yl}prop-2-enoate 55 and methyl (2*Z*)-3-{(2*S*)-1-[(4-methylphenyl)sulfonyl]pyrrolidin-2-yl}prop-2-enoate 56

By a procedure identical with that described for the preparation of the enoates **18** and **19** from the alcohol **17**, the alcohol **54** (255 mg, 1 mmol) was converted into the α,β-enoates **55** (193 mg, 63%) and **56** (34 mg, 11%).

Compound **55**, colourless crystals, mp 120 °C (from Et_2O) (Found: C, 58.1; H, 6.1; N, 4.4. $C_{15}H_{19}NO_4S$ requires C, 58.2; H, 6.2; N, 4.5%); $[\alpha]_D^{20}$ −144.8 (*c* 0.724 in $CHCl_3$); δ_H(270 MHz; $CDCl_3$) 1.62–1.87 (4 H, m, CH_2 × 2), 2.43 (3 H, s, CMe), 3.25 (1 H, m, CH), 3.47 (1 H, m, CH), 3.74 (3 H, s, OMe), 4.29 (1 H, m, CH), 6.07 (1 H, dd, *J* 15.4 and 1.6, CH=), 6.85 (1 H, dd, *J* 15.4 and 5.7, CH=), 7.31–7.37 (2 H, m, Ph) and 7.70–7.75 (2 H, m, Ph).

Compound **56**, colourless crystals, mp 98 °C (from hexane) (Found: C, 58.1; H, 6.1; N, 4.4. $C_{15}H_{19}NO_4S$ requires C, 58.2; H, 6.2; N, 4.5%); $[\alpha]_D^{20}$ −192 (*c* 0.778 in $CHCl_3$); δ_H(270 MHz; $CDCl_3$) 1.43–1.55 (1 H, m, CH), 1.57–1.68 (1 H, m, CH), 1.70–1.88 (1 H, m, CH), 2.04–2.20 (1 H, m, CH), 2.44 (3 H, s, CMe), 3.21 (1 H, ddd, *J* 10.5, 7.6 and 5.9, CH), 3.52 (1 H, ddd, *J* 10.5, 7.0 and 6.5, CH), 3.74 (3 H, s, OMe), 5.16 (1 H, dddd, *J* 15.3, 7.6, 7.6 and 1.4, CH), 5.81 (1 H, dd, *J* 11.6 and 1.4, CH=), 6.45 (1 H, dd, *J* 11.6 and 8.1, CH=), 7.31–7.34 (2 H, m, Ph) and 7.70–7.73 (2 H, m, Ph).

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