Stereoselective synthesis of a set of two functionalized (*E*)-alkene dipeptide isosteres of L-amino acid-L-Glu and L-amino acid-D-Glu

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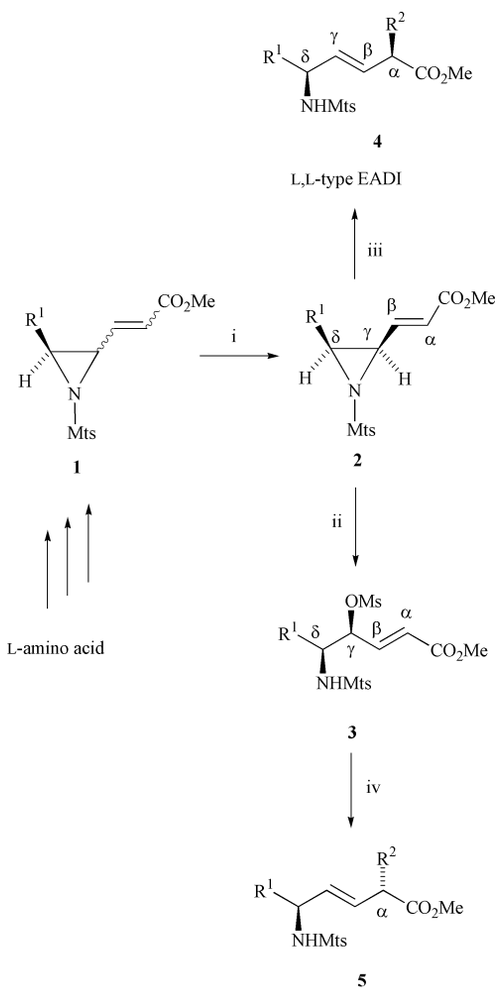
Received (in Cambridge, UK) 27th April 2001, Accepted 30th July 2001
First published as an Advance Article on the web 11th September 2001

Treatment of *N*-arylsulfonyl-γ,δ-*cis*- or -*trans*-γ,δ-epimino (*E*)-α,β-enoates with HCl–1,4-dioxane affords regio- and stereo-selective ring-opened products, δ-aminated γ-chloro-α,β-enoates. This ring-opening reaction provides a useful method for the stereoselective synthesis of a set of diastereomeric (L-Xaa, L-Glu)-type and (L-Xaa, D-Glu)-type (*E*)-alkene dipeptide isosteres (EADIs) from a single substrate of γ,δ-epimino (*E*)-α,β-enoate using organozinc–copper reagents.

Introduction

The utility of (*E*)-alkene dipeptide isosteres (EADIs)[1] as potential mimics of amide bonds in bioactive peptides has been intensively investigated by us[2] and others.[3] Among these EADIs, L,D-type and D,L-type EADIs are of comparable value to L,L-type and D,D-type EADIs in the field of medicinal chemistry, since L,D-type (or D,L-type) EADIs have potentiality as backbone replacements of the (*i* + 1)–(*i* + 2) site in type-II (or -II′) β-turn structures.[4] We recently established a completely stereocontrolled synthetic process for L,L-type, L,D-type, D,D-type and D,L-type EADIs starting from L-amino acids or D-amino acids as chiral pools (Scheme 1).[5] In this process, regio- and stereo-selective ring-opening reactions of *N*-(2,4,6-trimethylphenylsulfonyl)-γ,δ-*cis*-γ,δ-epimino (*E*)-α,β-enoates with methanesulfonic acid (MSA) were utilized for the stereo-selective synthesis of a set of two diastereomeric EADIs from a single substrate of γ,δ-epimino (*E*)-α,β-enoate. As shown in Scheme 1, four stereoisomeric γ,δ-epimino-α,β-enoates **1**, which are obtained from an L-amino acid, can be convergently transformed into the single *cis*-(*E*)-isomer **2** by exposure to a Pd(0)-catalyst.[6] The aziridine **2** provides an L,L-type EADI **4** by treatment with organocopper reagents. On the other hand, MSA treatment of **2** gives the γ-mesylester **3**, which can be converted into an L,D-type EADI **5** by treatment with organo-copper reagents. A D-amino acid leads to D,D-type and D,L-type EADIs in the same manner. One potential limitation to the use of these procedures for synthesis of peptide mimetics is the introduction of functional groups into the side chain (R^2) at the α-position. In our initial effort to prepare an (L-Ser, D-Glu)-type EADI, we attempted S_N2'-substitution of a $CH_2CH_2CO_2Me$ group onto δ-aminated γ-mesyloxy-α,β-enamide **7**, which was previously synthesized by the ring-opening reaction of *N*-Mts-γ,δ-*cis*-γ,δ-epimino (*E*)-α,β-enamide **6** with MSA, using organozinc–copper reagent $IZn(CN)CuCH_2CH_2CO_2Me\cdot 2LiCl$ (prepared by the reaction of the soluble copper salt $CuCN\cdot 2LiCl$ with zinc organometallic reagent $IZnCH_2CH_2CO_2Me$) (Scheme 2).[7] However, the reaction quantitatively regenerated aziridine **6** without forming the desired compound **8**. Since the aziridinyl ring was considered to be formed due to the basicity of the organocopper reagent, $BF_3\cdot Et_2O$ was added to

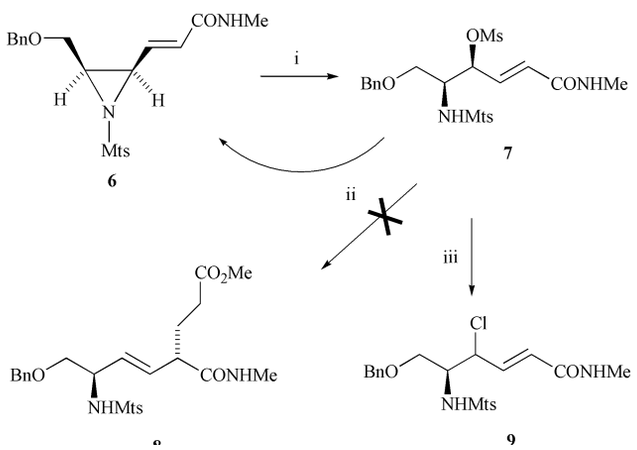


Scheme 1 R^1, R^2 = alkyl; Ms = methanesulfonyl; Mts = 2,4,6-trimethylphenylsulfonyl; *reagents*: i, $Pd(PPh_3)_4$; ii, CH_3SO_3H in $CHCl_3$; iii, $R^2Cu(CN)MgCl\cdot 2LiCl$; iv, $R^2Cu(CN)MgCl\cdot BF_3$; D-amino acids lead to D,D-type and D,L-type EADIs in the same way.

DOI: 10.1039/b103833h

Table 1 Ring-opening of *N*-Ts- or *N*-Mts-γ,δ-epimino (*E*)-α,β-enoates with HCl–1,4-dioxane and the following addition of $CH_2CH_2CO_2R$ groups using organozinc–copper reagents

Entry	Substrate	Ring-opening product (yield %)	Organozinc–copper reagent	Addition product (yield %)
1	**10**	**14** (92)	$IZnCu(CN)CH_2CH_2CO_2Me{\cdot}2LiCl$	**18** (93)
2	**10**		$IZnCu(CN)CH_2CH_2CO_2Bn{\cdot}2LiCl$	**19** (91)
3	**11**	**15** (92)	$IZnCu(CN)CH_2CH_2CO_2Me{\cdot}2LiCl$	**20** (99)
4	**11**		$IZnCu(CN)CH_2CH_2CO_2Bn{\cdot}2LiCl$	**21** (99)
5	**12**	**16** (96)	$IZnCu(CN)CH_2CH_2CO_2Me{\cdot}2LiCl$	**22** (81)
6	**12**		$IZnCu(CN)CH_2CH_2CO_2Bn{\cdot}2LiCl$	**23** (89)
7	**13**	**17** (91)	$IZnCu(CN)CH_2CH_2CO_2Me{\cdot}2LiCl$	**24** (91)
8	**13**		$IZnCu(CN)CH_2CH_2CO_2Bn{\cdot}2LiCl$	**25** (92)



Scheme 2 *Reagents*: i, CH_3SO_3H in $CHCl_3$; ii, $IZn(CN)CuCH_2CH_2CO_2Me{\cdot}2LiCl$; iii, $IZn(CN)CuCH_2CH_2CO_2Me{\cdot}BF_3{\cdot}2LiCl$.

the above organocopper reagent. Unexpectedly, this reaction afforded δ-aminated γ-chloro-α,β-enamide **9** (the absolute configuration of the γ-carbon center of **9** was not identified). Nakamura *et al.* reported a stereoselective S_N2' reaction mediated by organometallics of zinc and copper when using allylic chlorides as substrates.[7] Thus, we attempted to utilize γ-chloro-α,β-enamide **9** as a substrate of the S_N2'-type organometallic reaction to yield an (L-Ser, D-Glu)-type EADI, and initially to find effective methods for affording diastereomerically pure δ-aminated γ-chloro-α,β-enoates (enamides). In this paper, we report the regio- and stereo-selective ring-opening reactions of *N*-arylsulfonyl-γ,δ-*cis*- or -*trans*-γ,δ-epimino (*E*)-α,β-enoates (enamides) with HCl–1,4-dioxane to yield δ-aminated γ-chloro-α,β-enoates (enamides). Furthermore, we also report the stereoselective synthesis of a set of two functionalized (L-Xaa, L-Glu)-type and (L-Xaa, D-Glu)-type diastereomeric EADIs from a single substrate of γ,δ-epimino (*E*)-α,β-enoate (enamide) using an organozinc–copper reagent $IZn(CN)CuCH_2CH_2CO_2R$.

Results and discussion

Ring-opening reactions of *N*-(4-methylphenylsulfonyl) (Ts)- or *N*-(2,4,6-trimethylphenylsulfonyl) (Mts)-γ,δ-epimino (*E*)-α,β-enoates with HCl–1,4-dioxane

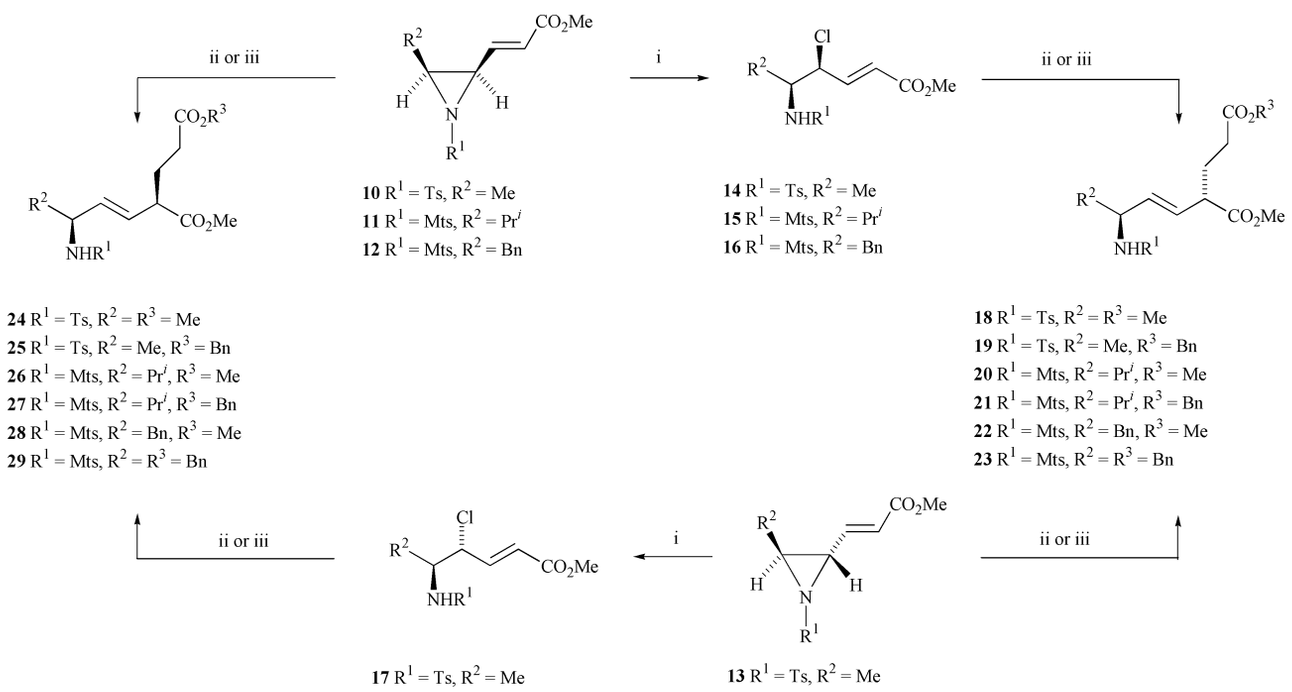
To date, many precedents for aziridine ring-opening, namely, that several nucleophilic reagents,[8] including acids such as AcOH,[9] TFA[10] and toluene-*p*-sulfonic acid in aqueous acetone,[11] attack simple aziridines[12] at either of the two carbon atoms, to yield the corresponding ring-opened products, have been described. We have also reported TFA- or MSA-mediated ring-opening reactions of *N*-Mts-protected (and activated) aziridines bearing α,β-unsaturated esters as described in the Introduction.[5] Thus, we initially examined ring-opening reactions of *N*-Ts- or *N*-Mts-γ,δ-epimino (*E*)-α,β-enoates with HCl–1,4-dioxane to afford δ-aminated γ-chloro-α,β-enoates. Exposure of *N*-Ts-γ,δ-*cis*-γ,δ-epimino (*E*)-α,β-enoate **10**, derived from L-threonine,[6] to 4 M HCl–1,4-dioxane (10 equiv.) at rt for 30 min afforded exclusively δ-aminated γ-chloro-α,β-enoate **14** in an essentially quantitative yield (Scheme 3 and Table 1). Since X-ray analysis of **14** showed that it has (4*S*)-configuration, this ring-opening reaction was confirmed to operate *via* the regio- and stereo-selective S_N2 reaction at the γ-carbon position. We investigated ring-opening of other aziridines, *N*-Mts-γ,δ-*cis*-γ,δ-epimino (*E*)-α,β-enoates, **11** and **12**, derived from L-valine and L-phenylalanine, respectively, according to the reported methods.[6] The regiospecific ring-opening reactions were successfully carried out to yield γ-chloro-α,β-enoates **15** and **16**. The *trans*-(*E*)-isomer **13** afforded the γ,δ-*anti*-isomer **17** by a similar S_N2 ring-opening reaction. In all cases, ring-opened products generated by nucleophilic attack at the α-, β- or δ-carbon position could not be detected. Regiochemical assignments for the γ-chloro-α,β-enoates **14**–**17** were readily made by ^{1}H-NMR spectroscopy (^{1}H–^{1}H COSY). The γ,δ-*syn* stereochemistry of **14**–**16** and the γ,δ-*anti* stereochemistry of **17** are based on X-ray analysis of **14**.

Synthesis of (L-Xaa, D-Glu)-type and (L-Xaa, L-Glu)-type EADIs from δ-aminated γ-chloro-α,β-enoates

We examined the feasibility of the stereoselective synthesis of (L-Xaa, D-Glu)-type and (L-Xaa, L-Glu)-type EADIs by treatment of the ring-opened products with organozinc–copper reagents. Treatment of the above γ-chloro-α,β-enoate **14** with $IZnCu(CN)CH_2CH_2CO_2Me{\cdot}2LiCl$ (4 equiv.) in THF at 0 °C for 30 min yielded the protected (L-Ala, D-Glu)-type (4*S*,7*S*)-EADI, Ts-L-Ala-ψ[(*E*)-CH=CH]-D-Glu(OMe)-OMe, **18** in 93% yield (diastereoselection > 99 : 1 from NMR analysis) as shown in Scheme 3 and Table 1. This reaction occurred by a sole *anti*-S_N2' mechanism. In contrast, an *anti*-S_N2' reaction of the *cis*-(*E*)-enoate **10** under the same reaction conditions afforded the protected (L-Ala, L-Glu)-type (4*R*,7*S*)-EADI, Ts-L-Ala-ψ[(*E*)-CH=CH]-L-Glu(OMe)-OMe, **24** in 99% yield as shown in Scheme 3 and Table 2. In a similar way, treatment of **14** with $IZnCu(CN)CH_2CH_2CO_2Bn{\cdot}2LiCl$ yielded the (4*S*,7*S*)-EADI, Ts-L-Ala-ψ[(*E*)-CH=CH]-D-Glu(OBn)-OMe, **19** whereas treatment of **10** with $IZnCu(CN)CH_2CH_2CO_2Bn{\cdot}2LiCl$ afforded the (4*R*,7*S*)-EADI, Ts-L-Ala-ψ[(*E*)-CH=CH]-L-Glu(OBn)-OMe, **25**. The most important point of the HCl-mediated ring-opening reactions is the inversion of configuration at the C-γ carbon *via* an S_N2 mechanism. Thus, *cis*-(*E*)-enoates lead to *syn*-(*E*)-chlorides, which are converted into (L-Xaa, D-Glu)-type EADIs upon treatment of organozinc–copper reagents. On the other hand, *cis*-(*E*)-enoates themselves provide (L-Xaa, L-Glu)-type EADIs with organozinc–copper reagents. We investigated the applicability of these synthetic procedures to other aziridine *cis*-(*E*)-enoates, **11** and **12**. Treatment of the γ-chloride **15** with $IZnCu(CN)CH_2CH_2CO_2Me{\cdot}2LiCl$ and $IZnCu(CN)CH_2CH_2CO_2Bn{\cdot}2LiCl$ yielded the (4*S*,7*S*)-EADIs, Mts-L-Val-ψ[(*E*)-CH=CH]-D-Glu(OMe)-OMe, **20** and Mts-L-Val-ψ[(*E*)-CH=CH]-D-Glu(OBn)-OMe, **21**, respectively, whereas treatment of the *cis*-(*E*)-enoate **11** with $IZnCu(CN)CH_2CH_2CO_2Me{\cdot}2LiCl$ and

Table 2 Direct addition of $CH_2CH_2CO_2R$ groups into *N*-Ts- or *N*-Mts-γ,δ-epimino (*E*)-α,β-enoates using organozinc–copper reagents

Entry	Substrate	Organozinc–copper reagent	Addition product (yield %)
1	**10**	$IZnCu(CN)CH_2CH_2CO_2Me{\cdot}2LiCl$	**24** (99)
2	**10**	$IZnCu(CN)CH_2CH_2CO_2Bn{\cdot}2LiCl$	**25** (95)
3	**11**	$IZnCu(CN)CH_2CH_2CO_2Me{\cdot}2LiCl$	**26** (52)
4	**11**	$IZnCu(CN)CH_2CH_2CO_2Bn{\cdot}2LiCl$	**27** (45)
5	**12**	$IZnCu(CN)CH_2CH_2CO_2Me{\cdot}2LiCl$	**28** (97)
6	**12**	$IZnCu(CN)CH_2CH_2CO_2Bn{\cdot}2LiCl$	**29** (99)
7	**13**	$IZnCu(CN)CH_2CH_2CO_2Me{\cdot}2LiCl$	**18** (99)
8	**13**	$IZnCu(CN)CH_2CH_2CO_2Bn{\cdot}2LiCl$	**19** (92)

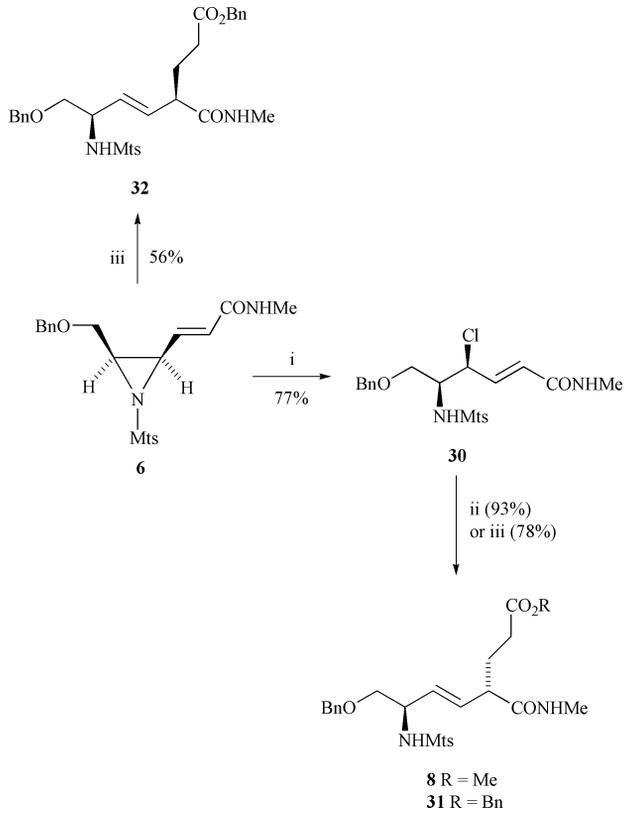


Scheme 3 *Reagents*: i, 4 M HCl–1,4-dioxane; ii, $IZn(CN)CuCH_2CH_2CO_2Me{\cdot}2LiCl$; iii, $IZn(CN)CuCH_2CH_2CO_2Bn{\cdot}2LiCl$.

$IZnCu(CN)CH_2CH_2CO_2Bn{\cdot}2LiCl$ yielded the (4*R*,7*S*)-EADIs, Mts-L-Val-ψ[(*E*)-CH=CH]-L-Glu(OMe)-OMe, **26** and Mts-L-Val-ψ[(*E*)-CH=CH]-L-Glu(OBn)-OMe, **27**, respectively. In the same manner, the γ-chloride **16** provided the corresponding (4*S*,7*S*)-EADIs, **22** and **23**, whereas the *cis*-(*E*)-enoate **12** afforded the corresponding (4*R*,7*S*)-EADIs, **28** and **29**, respectively. In a comparative study, the *anti*-(*E*)-chloride **17**, derived from the *trans*-(*E*)-enoate **13**, was converted into the protected (L-Ala, L-Glu)-type (4*R*,7*S*)-EADIs, Ts-L-Ala-ψ[(*E*)-CH=CH]-L-Glu(OMe)-OMe, **24** and Ts-L-Ala-ψ[(*E*)-CH=CH]-L-Glu(OBn)-OMe, **25** with $IZnCu(CN)CH_2CH_2CO_2Me{\cdot}2LiCl$ and $IZnCu(CN)CH_2CH_2CO_2Bn{\cdot}2LiCl$, respectively. On the other hand, treatment of the *trans*-(*E*)-enoate **13** with $IZnCu(CN)CH_2CH_2CO_2Me{\cdot}2LiCl$ and $IZnCu(CN)CH_2CH_2CO_2Bn{\cdot}2LiCl$ afforded the protected (L-Ala, D-Glu)-type (4*S*,7*S*)-EADIs, Ts-L-Ala-ψ[(*E*)-CH=CH]-D-Glu(OMe)-OMe, **18** and Ts-L-Ala-ψ[(*E*)-CH=CH]-D-Glu(OBn)-OMe, **19**, respectively. Thus, two types of EADIs were stereoselectively synthesized from either the *cis*- or *trans*-(*E*)-enoate. These synthetic procedures are applicable to aziridinyl *cis*- or *trans*-(*E*)-enoates. The (*E*)-geometry of the double bond in the synthesized EADIs was assigned based on the coupling constant of the two olefinic protons on ^1H-NMR analysis. The absolute configuration of the α-alkylated carbon center in the EADI **22** was confirmed by X-ray analysis as 4*S*.

Next, we attempted to synthesize highly functionalized (L-Ser, D-Glu)-type and (L-Ser, L-Glu)-type EADIs, our initial synthetic targets. The ring-opening reaction of the *cis*-(*E*)-enamide **6** with HCl–1,4-dioxane yielded the corresponding γ-chloro-α,β-enamide **30**, which was converted into the protected (L-Ser, D-Glu)-type (4*S*,7*S*)-EADIs, Mts-L-Ser(*O*-Bn)-ψ[(*E*)-CH=CH]-D-Glu(OMe)-NHMe, **8** and Mts-L-Ser(*O*-Bn)-ψ[(*E*)-CH=CH]-D-Glu(OBn)-NHMe, **31** with $IZnCu(CN)CH_2CH_2CO_2Me{\cdot}2LiCl$ and $IZnCu(CN)CH_2CH_2CO_2Bn{\cdot}2LiCl$, respectively, as shown in Scheme 4. In contrast, treatment of the *cis*-(*E*)-enamide **6** with $IZnCu(CN)CH_2CH_2CO_2Bn{\cdot}2LiCl$ afforded the protected (L-Ser, L-Glu)-type (4*R*,7*S*)-EADI, Mts-L-Ser(*O*-Bn)-ψ[(*E*)-CH=CH]-L-Glu(OBn)-NHMe, **32**.

In conclusion, we have found regio- and stereo-specific ring-opening reactions of *N*-Ts- or *N*-Mts-protected aziridines bearing α,β-unsaturated esters (amides) [*cis*-(*E*)- and *trans*-(*E*)-α,β-enoates (enamides)] by HCl–1,4-dioxane. The HCl-mediated ring-opened products (γ,δ-*syn*-δ-aminated γ-chloro-α,β-enoates or enamides) yield (L-Xaa, D-Glu)-type EADIs by the addition with organozinc–copper reagents. On the other hand, aziridines [*cis*-(*E*)-α,β-enoates (enamides)] afford (L-Xaa, L-Glu)-type EADIs with organozinc–copper reagents. The present ring-opening reactions provide useful methodology for stereoselective synthesis of both (L-Xaa, L-Glu)-type and (L-Xaa, D-Glu)-type EADIs from a single substrate of either a γ,δ-*cis*- or -*trans*-γ,δ-epimino (*E*)-α,β-unsaturated ester (amide). Four stereoisomers of γ,δ-epimino-α,β-unsaturated esters (amides), which can be prepared from the corresponding chiral amino aldehydes, are converted into *cis*-(*E*)-isomers by Pd(0)-catalyzed equilibration.[6] Taken together, a completely stereocontrolled synthetic process for a set of (L-Xaa, L-Glu)-type and (L-Xaa, D-Glu)-type EADIs starting from L-amino acids has been established.



Scheme 4 *Reagents*: i, 4 M HCl–1,4-dioxane; ii, IZn(CN)CuCH$_2$-CH$_2$CO$_2$Me·2LiCl; iii, IZn(CN)CuCH$_2$CH$_2$CO$_2$Bn·2LiCl.

Experimental

General

^{1}H-NMR spectra were recorded using a JEOL EX-270 or a Bruker AC 300 spectrometer at 270 or 300 MHz ^{1}H frequency for samples in $CDCl_3$. Chemical shifts (δ) are reported in parts per million downfield from internal tetramethylsilane. *J*-Values are in Hz. Nominal (LRMS) and exact mass (HRMS) spectra were recorded on a JEOL JMS-01SG-2 or JMS-HX/HX 110A mass spectrometer. Optical rotations were measured in $CHCl_3$ with a JASCO DIP-360 digital polarimeter (Tokyo, Japan) or a Horiba high-sensitive polarimeter SEPA-200 (Kyoto, Japan). $[\alpha]_D$-Values are given in units of 10^{-1} deg cm^2 g^{-1}. X-Ray analyses were made on a Rigaku AFC5R diffractometer with graphite-monochromated Cu-Kα radiation and a rotating anode generator. Mps were measured by a hot-stage melting-point apparatus and are uncorrected. For flash chromatography, silica gel 60 H (silica gel for TLC, Merck) and Wakogel C-200 (silica gel for column chromatography) were employed.

Methyl (2*E*,4*R*,5*S*)-6-phenyl-4,5-[*N*-(2,4,6-trimethylphenylsulfonyl)epimino]hex-2-enoate 12

According to our previous procedure,[6] the *cis*-(*E*)-enoate **12** (2.23 g, 5.58 mmol, 93%) was prepared from the known vinylaziridine[6] (2.04 g, 6.00 mmol) as colorless crystals, mp 51–53 °C [from *n*-hexane–Et$_2$O (3 : 1)] (Found: C, 66.26; H, 6.46; N, 3.51. Calc. for $C_{22}H_{25}NO_4S$: C, 66.14; H, 6.31; N, 3.51%); $[\alpha]_D^{26}$ −63.75 (*c* 1.19); δ_H(300 MHz) 2.30 (3 H, s, CMe), 2.56 (6 H, s, 2 × CMe), 2.64 (1 H, dd, *J* 14.5 and 8.0, C*H*H), 2.76 (1 H, dd, *J* 14.5 and 5.3, CH*H*), 3.18 (1 H, ddd, *J* 7.9, 7.2 and 5.3, 5-H), 3.55 (1 H, m, 4-H), 3.76 (3 H, s, OMe), 6.19 (1 H, dd, *J* 15.5 and 1.0, CH=), 6.84 (1 H, dd, *J* 15.5 and 6.6, CH=), 6.85 (2 H, s, ArH), 6.94 (2 H, m, ArH), 7.04–7.15 (3 H, m, ArH).

General procedure for the ring-opening reaction of *N*-Ts- or *N*-Mts-γ,δ-epimino (*E*)-α,β-enoates (enamides) by treatment with HCl–1,4-dioxane. Representative: methyl (2*E*,4*S*,5*S*)-4-chloro-5-(4-methylphenylsulfonylamino)hex-2-enoate 14

The *cis*-(*E*)-enoate **10** (295 mg, 1.00 mmol) was dissolved in 4 M HCl solution in 1,4-dioxane (10.0 mmol, 2.5 cm^3) at rt and the mixture was stirred for 30 min at this temperature. Concentration under reduced pressure gave an oily residue, which was purified by flash chromatography over silica gel with *n*-hexane–EtOAc (4 : 1) to yield 306 mg (0.922 mmol, 92%) of the title compound **14** as colorless crystals, mp 168–169 °C [from *n*-hexane–EtOAc (1 : 1)] (Found: C, 50.74; H, 5.54; N, 4.17. $C_{14}H_{18}ClNO_4S$ requires C, 50.68; H, 5.47; N, 4.22%); $[\alpha]_D^{21}$ −78.75 (*c* 0.965); δ_H(300 MHz) 1.16 (3 H, d, *J* 6.7, CMe), 2.43 (3 H, s, CMe), 3.69 (1 H, m, 5-H), 3.74 (3 H, s OMe), 4.51 (1 H, ddd, *J* 7.4, 3.5 and 1.2, 4-H), 4.85 (1 H, d, *J* 8.5, NH), 6.02 (1 H, dd, *J* 15.4 and 1.2, CH=), 6.80 (1 H, dd, *J* 15.4 and 7.4, CH=), 7.30 (2 H, m, ArH), 7.74 (2 H, m, ArH).

Crystal structure determination of compound 14†

Crystal data. $C_{14}H_{18}ClNO_4S$, $M = 331.81$, orthorhombic, $a = 9.685(4)$, $b = 21.585(5)$, $c = 7.745(4)$ Å, $V = 1619(1)$ Å^3, $T = 296$ K, space group $P2_12_12_1$ (no. 19), $Z = 4$, μ(Cu-Kα) = 34.27 mm^{-1}, 1580 reflections measured, 1484 [$I > 3\sigma(I)$] were used in all calculations. The final *wR* was 0.066.

Methyl (2*E*,4*S*,5*S*)-4-chloro-6-methyl-5-(2,4,6-trimethylphenylsulfonylamino)hept-2-enoate 15

By use of a procedure identical with that described for the preparation of **14** from **10**, the *cis*-(*E*)-enoate **11** (351 mg, 1.00 mmol) was converted into the title compound **15** (360 mg, 0.928 mmol, 92%) as colorless crystals, mp 111–113 °C [from *n*-hexane–EtOAc (2 : 1)] (Found: C, 55.71; H, 6.95; N, 3.56. $C_{18}H_{26}ClNO_4S$ requires C, 55.73; H, 6.76; N, 3.61%); $[\alpha]_D^{27}$ −13.3 (*c* 0.822); δ_H(300 MHz) 0.97 (6 H, m, 2 × CMe), 1.88–2.05 (1 H, m, 6-H), 2.28 (3 H, s, CMe), 2.61 (6 H, s, 2 × CMe), 3.45 (1 H, ddd, *J* 9.5, 7.8 and 2.4, 5-H), 3.64 (3 H, s, OMe), 4.66 (1 H, ddd, *J* 6.4, 2.4 and 1.5, 4-H), 4.73 (1 H, d, *J* 9.5, NH), 5.87 (1 H, dd, *J* 15.2 and 1.5, CH=), 6.56 (1 H, dd, *J* 15.2 and 6.4, CH=), 6.90 (2 H, s, ArH).

Methyl (2*E*,4*S*,5*S*)-4-chloro-6-phenyl-5-(2,4,6-trimethylphenylsulfonylamino)hex-2-enoate 16

By use of a procedure identical with that described for the preparation of **14** from **10**, the *cis*-(*E*)-enoate **12** (399 mg, 1.00 mmol) was converted into the title compound **16** (422 mg, 0.967 mmol, 96%) as colorless crystals, mp 108–109 °C [from *n*-hexane–EtOAc (2 : 1)] (Found: C, 60.59; H, 6.07; N, 3.20. $C_{22}H_{26}ClNO_4S$ requires C, 60.61; H, 6.01; N, 3.21%); $[\alpha]_D^{28}$ −57.8 (*c* 0.570); δ_H(300 MHz) 2.27 (3 H, s, CMe), 2.53 (6 H, s, 2 × CMe), 2.79 (1 H, dd, *J* 13.7 and 6.8, C*H*H), 3.04 (1 H, dd, *J* 13.7 and 8.2, CH*H*), 3.65 (1 H, m, 5-H), 3.70 (3 H, s, OMe), 4.59 (1 H, *J* 6.4, 2.5 and 1.5, 4-H), 4.86 (1 H, d, *J* 8.6, NH), 5.95 (1 H, dd, *J* 15.3 and 1.5, CH=), 6.67 (1 H, dd, *J* 15.3 and 6.4, CH=), 6.85 (2 H, m, ArH), 7.01–7.07 (2 H, m, ArH), 7.17–7.23 (3 H, m, ArH).

Methyl (2*E*,4*R*,5*S*)-4-chloro-5-(4-methylphenylsulfonylamino)-hex-2-enoate 17

By use of a procedure identical with that described for the preparation of **14** from **10**, the *cis*-(*E*)-enoate **13** (295 mg, 1.00 mmol) was converted into the title compound **17** (303 mg, 0.913 mmol, 91%) as a colorless crystalline mass, mp 69–71 °C (from *n*-hexane) (Found: C, 50.63; H, 5.60; N, 3.95. $C_{14}H_{18}$-$ClNO_4S$ requires C, 50.68; H, 5.47; N, 4.22%); $[\alpha]_D^{25}$ −7.92

† CCDC reference number(s) 166365 and 166366. See http://www.rsc.org/suppdata/p1/b1/b103833h/ for crystallographic files in .cif or other electronic format.

(*c* 1.00); δ_H(300 MHz) 1.07 (3 H, d, *J* 6.6, CMe), 2.43 (3 H, s, CMe), 3.69 (1 H, m, 5-H), 3.74 (3 H, s, OMe), 4.59 (1 H, ddd, *J* 6.6, 3.3 and 1.4, 4-H), 4.94 (1 H, d, *J* 9.1, NH), 6.06 (1 H, dd, *J* 15.3 and 1.4, CH=), 6.77 (1 H, dd, *J* 15.3 and 6.7, CH=), 7.32 (2 H, m, ArH), 7.76 (2 H, m, ArH).

General procedure for the preparation of (L-Xaa, D-Glu)-type EADIs from γ-chloro-α,β-enoates. Representative: Ts-L-Ala-ψ[(*E*)-CH=CH]-D-Glu(OMe)-OMe 18

To a supension of zinc dust (157 mg, 2.41 mmol) in dry THF (0.20 cm^3), which was subjected to treatment for activation, was added methyl 3-iodopropionate (257 mg, 1.20 mmol) [obtained by treatment of methyl 3-bromopropionate in acetone with sodium iodide followed by distillation] in dry THF (1.00 cm^3) at rt, and the mixture was stirred for 1 h at this temperature. The organozinc reagent was added to a stirred suspension of CuCN (107 mg, 1.20 mmol) and LiCl (102 mg, 2.41 mmol) in dry THF (1.20 cm^3) under argon at −78 °C, and the mixture was allowed to warm to 0 °C and was stirred at this temperature for 10 min. To the solution of organozinc–copper reagent was added dropwise a solution of the ester **14** (100 mg, 0.301 mmol) in dry THF (1.00 cm^3) at −78 °C with stirring, and the mixture was stirred at 0 °C for 30 min followed by quenching with 1 : 1 saturated aq. NH_4Cl–28% NH_4OH (2 cm^3). The mixture was extracted with Et_2O, and the extract was washed with water, and dried over $MgSO_4$. Concentration under reduced pressure gave a colorless oil, which was purified by flash chromatography over silica gel with *n*-hexane–EtOAc (3 : 1) to yield the title compound **18** (108 mg, 0.282 mmol, 93%) as a colorless oil [Found (FAB): $(M + H)^+$, 384.1470. $C_{18}H_{26}NO_6S$ requires *M* + H, 384.1481]; $[\alpha]_D^{27}$ −4.06 (*c* 1.47); δ_H(300 MHz) 1.16 (3 H, d, *J* 6.7, CMe), 1.70 (1 H, dq, *J* 13.8 and 7.6, C*H*H), 1.89–2.03 (1 H, m, CH*H*), 2.21 (2 H, t, *J* 7.6, CH_2), 2.41 (3 H, s, CMe), 2.91 (1 H, m, 4-H), 3.65 (3 H, s, OMe), 3.66 (3 H, s, OMe), 3.84–3.96 (1 H, m, 7-H), 4.84 (1 H, d, *J* 7.6, NH), 5.34–5.50 (2 H, m, 2 × CH=), 7.28 (2 H, m, ArH), 7.73 (2 H, m, ArH); *m*/*z* (FAB-LRMS) 384 (MH^+, base peak), 213, 198, 181, 155, 149, 121, 91.

Ts-L-Ala-ψ[(*E*)-CH=CH]-D-Glu(OBn)-OMe 19

By use of a procedure identical with that described for the preparation of **18** from **14**, treatment of the ester **14** (100 mg, 0.301 mmol) with IZn(CN)$CuCH_2CH_2CO_2$Bn·2LiCl [benzyl 3-iodopropionate was obtained by successive treatment of 3-bromopropionic acid with benzyl alcohol–benzene–cat. TsOH and sodium iodide–acetone] in THF gave the title compound **19** (127 mg, 0.276 mmol, 91%) as a colorless oil [Found (FAB): $(M + H)^+$, 460.1785. $C_{24}H_{30}NO_6S$ requires *M* + H, 460.1794]; $[\alpha]_D^{26}$ −3.62 (*c* 1.38); δ_H(300 MHz) 1.14 (3 H, d, *J* 6.7, CMe), 1.65–1.79 (1 H, m, C*H*H), 1.91–2.04 (1 H, m, CH*H*), 2.25 (2 H, m, CH_2), 2.39 (3 H, s, CMe), 2.91 (1 H, m, 4-H), 3.65 (3 H, s, OMe), 3.88 (1 H, m, 7-H), 4.59 (1 H, d, *J* 7.6, NH), 5.10 (2 H, s, OCH_2), 5.33 (1 H, dd, *J* 15.5 and 5.2, CH=), 5.43 (1 H, m, CH=), 7.23–7.29 (2 H, m, ArH), 7.31–7.38 (5 H, m, ArH), 7.69–7.75 (2 H, m, ArH); *m*/*z* (FAB-LRMS) 460 (MH^+, base peak), 391, 352, 304, 289, 257, 239, 198, 181, 167, 155, 149.

Mts-L-Val-ψ[(*E*)-CH=CH]-D-Glu(OMe)-OMe 20

By use of a procedure identical with that described for the preparation of **18** from **14**, treatment of the ester **15** (100 mg, 0.257 mmol) with IZn(CN)$CuCH_2CH_2CO_2$Me·2LiCl in THF gave the title compound **20** (113 mg, 0.257 mmol, 99%) as a colorless oil [Found (FAB): $(M + H)^+$, 440.2100. $C_{22}H_{34}NO_6S$ requires *M* + H, 440.2107]; $[\alpha]_D^{29}$ +20.4 (*c* 1.07); δ_H(300 MHz) 0.82 (3 H, d, *J* 6.7, CMe), 0.85 (3 H, d, *J* 6.8, CMe), 1.53–1.66 (1 H, m, C*H*H), 1.69–1.81 (1 H, m, CH), 1.82–1.96 (1 H, m, CH*H*), 2.16 (2 H, m, CH_2), 2.28 (3 H, s, CMe), 2.60 (6 H, s, 2 × CMe), 2.83 (1 H, m, 4-H), 3.55 (1 H, m, 7-H), 3.65 (6 H, s, 2 × OMe), 4.63 (1 H, d, *J* 7.7, NH), 5.20–5.35 (2 H, m, 2 × CH=), 6.90 (2 H, s, ArH); *m*/*z* (FAB-LRMS) 440 (MH^+), 396 (base peak), 364, 254, 241, 209, 183, 181, 177, 167, 149, 119.

Mts-L-Val-ψ[(*E*)-CH=CH]-D-Glu(OBn)-OMe 21

By use of a procedure identical with that described for the preparation of **18** from **14**, treatment of the ester **15** (100 mg, 0.257 mmol) with IZn(CN)$CuCH_2CH_2CO_2$Bn·2LiCl in THF gave the title compound **21** (132 mg, 0.255 mmol, 99%) as a colorless oil [Found (FAB): $(M + H)^+$, 516.2408. $C_{28}H_{38}NO_6S$ requires *M* + H, 516.2420]; $[\alpha]_D^{29}$ −13.3 (*c* 1.04); δ_H(300 MHz) 0.80 (3 H, d, *J* 6.7, CMe), 0.83 (3 H, d, *J* 6.8, CMe), 1.53–1.79 (2 H, m, C*H*H and CH), 1.84–1.97 (1 H, m, CH*H*), 2.20 (2 H, m, CH_2), 2.25 (3 H, s, CMe), 2.58 (6 H, s, 2 × CMe), 2.82 (1 H, m, 4-H), 3.53 (1 H, m, 7-H), 3.64 (3 H, s, OMe), 4.56 (1 H, d, *J* 7.7, NH), 5.09 (2 H, s, OCH_2), 5.14–5.33 (2 H, m, 2 × CH=), 6.87 (2 H, s, ArH), 7.29–7.40 (5 H, m, ArH); *m*/*z* (FAB-LRMS) 516 (MH^+, base peak), 472, 440, 332, 317, 285, 263, 254, 209.

Mts-L-Phe-ψ[(*E*)-CH=CH]-D-Glu(OMe)-OMe 22

By use of a procedure identical with that described for the preparation of **18** from **14**, treatment of the ester **16** (100 mg, 0.229 mmol) with IZn(CN)$CuCH_2CH_2CO_2$Me·2LiCl in THF gave the title compound **22** (97 mg, 0.200 mmol, 81%) as colorless crystals, mp 98–100 °C [from *n*-hexane–EtOAc (5 : 1)] (Found: C, 63.88; H, 6.87; N, 2.65. $C_{26}H_{33}NO_6S$ requires C, 64.04; H, 6.82; N, 2.87%); $[\alpha]_D^{23}$ +12.1 (*c* 1.64); δ_H(300 MHz) 1.54–1.67 (1 H, m, C*H*H), 1.81–1.94 (1 H, m, CH*H*), 2.09 (2 H, m, CH_2), 2.27 (3 H, s, CMe), 2.48 (6 H, s, 2 × CMe), 2.70–2.91 (3 H, m, PhCH_2 and 4-H), 3.65 (6 H, m, 2 × OMe), 3.92 (1 H, m, 7-H), 4.51 (1 H, d, *J* 6.4, NH), 5.34 (2 H, m, 2 × CH=), 6.87 (2 H, s, ArH), 7.00–7.05 (2 H, m, ArH), 7.15–7.25 (3 H, m, ArH).

Crystal structure determination of compound 22 †

Crystal data. $C_{26}H_{33}NO_6S$, *M* = 487.61, orthorhombic, *a* = 11.780(8), *b* = 35.92(1), *c* = 6.24(1) Å, *V* = 2639(4) $Å^3$, *T* = 296 K, space group $P2_12_12_1$ (no. 19), *Z* = 4, μ(Cu-Kα) = 14.14 mm^{-1}, 2628 reflections measured, 869 [$I > 3\sigma(I)$] were used in all calculations. The final *wR* was 0.101.

Mts-L-Phe-ψ[(*E*)-CH=CH]-D-Glu(OBn)-OMe 23

By use of a procedure identical with that described for the preparation of **18** from **14**, treatment of the ester **16** (100 mg, 0.229 mmol) with IZn(CN)$CuCH_2CH_2CO_2$Bn·2LiCl in THF gave the title compound **23** (115 mg, 0.204 mmol, 89%) as a colorless oil [Found (FAB): $(M + H)^+$, 564.2415. $C_{32}H_{38}NO_6S$ requires *M* + H, 564.2420]; $[\alpha]_D^{29}$ +12.2 (*c* 1.22); δ_H(300 MHz) 1.54–1.69 (1 H, m, C*H*H), 1.81–1.95 (1 H, m, CH*H*), 2.12 (2 H, m, CH_2), 2.25 (3 H, s, CMe), 2.47 (6 H, s, 2 × CMe), 2.68–2.89 (3 H, m, PhCH_2 and 4-H), 3.63 (3 H, s, OMe), 3.90 (1 H, m, 7-H), 4.54 (1 H, d, *J* 6.4, NH), 5.09 (2 H, s, OCH_2), 5.30 (2 H, m, 2 × CH=), 6.84 (2 H, s, ArH), 6.99 (2 H, m, ArH), 7.13–7.23 (3 H, m, ArH), 7.31–7.39 (5 H, m, ArH); *m*/*z* (FAB-LRMS) 586 (MNa^+), 564 (MH^+, base peak), 472, 440, 392, 365, 333, 315, 302, 289, 257, 225, 183.

General procedure for the preparation of (L-Xaa, L-Glu)-type EADIs from *N*-Ts- or *N*-Mts-γ,δ-epimino (*E*)-α,β-enoates. Representative: Ts-L-Ala-ψ[(*E*)-CH=CH]-L-Glu(OMe)-OMe 24 prepared from 10

To a suspension of zinc dust (177 mg, 2.70 mmol) in dry THF (0.60 cm^3), which was subjected to treatment for activation, was added methyl 3-iodopropionate (288 mg, 1.35 mmol) in dry THF (0.75 cm^3) at room temperature, and the mixture was stirred for 1 h at this temperature. The organozinc reagent was added to a stirred suspension of CuCN (121 mg, 1.35 mmol) and LiCl (114 mg, 2.70 mmol) in dry THF (1.35 cm^3) under

argon at −78 °C, and the mixture was allowed to warm to 0 °C and was stirred at this temperature for 15 min. To the solution of organozinc–copper reagent was added dropwise a solution of the *cis*-(*E*)-enoate **10** (100 mg, 0.338 mmol) in dry THF (1.00 cm^3) at −78 °C with stirring, and the mixture was stirred at 0 °C for 30 min followed by quenching with 1 : 1 saturated aq. NH_4Cl–28% NH_4OH (2 cm^3). The mixture was extracted with Et_2O, and the extract was washed with water, and dried over $MgSO_4$. Concentration under reduced pressure gave a colorless oil, which was purified by flash chromatography over silica gel with *n*-hexane–EtOAc (3 : 1) to yield the title compound **24** (129 mg, 0.336 mmol, 99%) as a colorless oil [Found (FAB): $(M + H)^+$, 384.1488. $C_{18}H_{26}NO_6S$ requires *M* + H, 384.1481]; $[\alpha]_D^{24}$ −74.3 (*c* 1.38); δ_H(300 MHz) 1.16 (3 H, d, *J* 6.7, CMe), 1.71 (1 H, dq, *J* 13.9 and 7.5, C*H*H), 1.88–2.02 (1 H, m, CH*H*), 2.19–2.27 (2 H, m, CH_2), 2.42 (3 H, s, CMe), 2.92 (1 H, m, 4-H), 3.64 (3 H, s, OMe), 3.66 (3 H, s, OMe), 3.81–3.93 (1 H, m, 7-H), 4.78 (1 H, d, *J* 7.4, NH), 5.35–5.49 (2 H, m, 2 × CH=), 7.29 (2 H, m, ArH), 7.74 (2 H, m, ArH); *m*/*z* (FAB-LRMS) 384 (MH^+, base), 228, 213, 198, 181.

Ts-L-Ala-ψ[(*E*)-CH=CH]-L-Glu(OBn)-OMe 25 prepared from 10

By use of a procedure identical with that described for the preparation of **24** from **10**, treatment of the *cis*-(*E*)-enoate **10** (100 mg, 0.338 mmol) with $IZn(CN)CuCH_2CH_2CO_2Bn{\cdot}2LiCl$ in THF gave the title compound **25** (148 mg, 0.322 mmol, 95%) as a colorless oil [Found (FAB): $(M + H)^+$, 460.1804. $C_{24}H_{30}NO_6S$ requires *M* + H, 460.1794]; $[\alpha]_D^{28}$ −52.0 (*c* 1.17); δ_H(300 MHz) 1.14 (3 H, d, *J* 6.7, CMe), 1.66–1.79 (1 H, m, C*H*H), 1.90–2.23 (1 H, m, CH*H*), 2.26 (2 H, m, CH_2), 2.38 (3 H, s, CMe), 2.91 (1 H, m, 4-H), 3.63 (3 H, s, OMe), 3.85 (1 H, m, 7-H), 4.69 (1 H, d, *J* 7.4, NH), 5.10 (2 H, m, OCH_2), 5.31–5.47 (2 H, m, 2 × CH=), 7.23–7.28 (2 H, m, ArH), 7.29–7.39 (5 H, m, ArH), 7.72 (2 H, m, ArH); *m*/*z* (FAB-LRMS) 460 (MH^+), 304, 289, 257, 239 (base peak), 198, 181, 167, 155, 149.

Mts-L-Val-ψ[(*E*)-CH=CH]-L-Glu(OMe)-OMe 26

By use of a procedure identical with that described for the preparation of **24** from **10**, treatment of the *cis*-(*E*)-enoate **11** (100 mg, 0.284 mmol) with $IZn(CN)CuCH_2CH_2CO_2Me{\cdot}2LiCl$ in THF gave the title compound **26** (65 mg, 0.149 mmol, 52%) as a colorless oil [Found (FAB): $(M + H)^+$, 440.2103. $C_{22}H_{34}NO_6S$ requires *M* + H, 440.2107]; $[\alpha]_D^{22}$ −43.2 (*c* 2.17); δ_H(300 MHz) 0.80 (3 H, d, *J* 6.7, CMe), 0.85 (3 H, d, *J* 6.8, CMe), 1.54–1.93 (3 H, m, CH_2 and CH), 2.17 (2 H, m, CH_2), 2.28 (3 H, s, CMe), 2.61 (6 H, s, 2 × CMe), 2.85 (1 H, m, 4-H), 3.49 (1 H, m, 7-H), 3.63 (3 H, s, OMe), 3.67 (3 H, s, OMe), 4.56 (1 H, d, *J* 7.9, NH), 5.19–5.34 (2 H, m, 2 × CH=), 6.92 (2 H, s, ArH); *m*/*z* (FAB-LRMS) 440 (MH^+, base peak), 396, 364, 254, 241, 209.

Mts-L-Val-ψ[(*E*)-CH=CH]-L-Glu(OBn)-OMe 27

By use of a procedure identical with that described for the preparation of **24** from **10**, treatment of the *cis*-(*E*)-enoate **11** (100 mg, 0.284 mmol) with $IZn(CN)CuCH_2CH_2CO_2Bn{\cdot}2LiCl$ in THF gave the title compound **27** (66 mg, 0.129 mmol, 45%) as a colorless oil [Found (FAB): $(M + H)^+$, 516.2439. $C_{28}H_{38}NO_6S$ requires *M* + H, 516.2420]; $[\alpha]_D^{27}$ −35.5 (*c* 1.68); δ_H(300 MHz) 0.79 (3 H, d, *J* 6.7, CMe), 0.84 (3 H, d, *J* 6.8, CMe), 1.54–1.77 (2 H, m, C*H*H and CH), 1.80–1.94 (1 H, m, CH*H*), 2.18–2.28 (5 H, m, CH_2 and CMe), 2.59 (6 H, s, 2 × CMe), 2.84 (1 H, m, 4-H), 3.47 (1 H, m, 7-H), 3.61 (3 H, s, OMe), 4.52 (1 H, d, *J* 7.9, NH), 5.11 (2 H, m, OCH_2), 5.21–5.26 (2 H, m, 2 × CH=), 6.88 (2 H, s, ArH), 7.31–7.39 (5 H, m, ArH); *m*/*z* (FAB-LRMS) 516 (MH^+, base peak), 514, 472, 440, 408, 380, 332, 317, 289, 285, 254, 209, 183, 167, 149.

Mts-L-Phe-ψ[(*E*)-CH=CH]-L-Glu(OMe)-OMe 28

By use of a procedure identical with that described for the preparation of **24** from **10**, treatment of the *cis*-(*E*)-enoate **12** (100 mg, 0.250 mmol) with $IZn(CN)CuCH_2CH_2CO_2Me{\cdot}2LiCl$ in THF gave the title compound **28** (119 mg, 0.244 mmol, 97%) as a colorless oil [Found (FAB): $(M + H)^+$, 488.2123. $C_{26}H_{34}NO_6S$ requires *M* + H, 488.2107]; $[\alpha]_D^{27}$ −56.4 (*c* 0.957); δ_H(300 MHz) 1.59–1.73 (1 H, m, C*H*H), 1.83–1.97 (1 H, m, CH*H*), 2.19 (2 H, m, CH_2), 2.27 (3 H, s, CMe), 2.48 (6 H, s, 2 × CMe), 2.78 (2 H, d, *J* 6.7, PhCH_2), 2.88 (1 H, m, 4-H), 3.61 (3 H, s, OMe), 3.66 (3 H, s, OMe), 3.89 (1 H, m, 7-H), 4.57 (1 H, d, *J* 6.6, NH), 5.30 (1 H, dd, *J* 15.5 and 7.8, CH=), 5.41 (1 H, dd, *J* 15.5 and 6.8, CH=), 6.87 (2 H, s, ArH), 6.98–7.04 (2 H, m, ArH), 7.15–7.27 (3 H, m, ArH); *m*/*z* (FAB-LRMS) 488 (MH^+, base peak), 396, 364, 302, 289, 257, 225.

Mts-L-Phe-ψ[(*E*)-CH=CH]-L-Glu(OBn)-OMe 29

By use of a procedure identical with that described for the preparation of **24** from **10**, treatment of the *cis*-(*E*)-enoate **12** (100 mg, 0.250 mmol) with $IZn(CN)CuCH_2CH_2CO_2Bn{\cdot}2LiCl$ in THF gave the title compound **29** (141 mg, 0.250 mmol, 99%) as a colorless oil [Found (FAB): $(M + H)^+$, 564.2432. $C_{32}H_{38}NO_6S$ requires *M* + H, 564.2420]; $[\alpha]_D^{28}$ −40.8 (*c* 1.29); δ_H(300 MHz) 1.60–1.74 (1 H, m, C*H*H), 1.85–1.98 (1 H, m, CH*H*), 2.20–2.27 (5 H, m, CH_2 and CMe), 2.46 (6 H, s, 2 × CMe), 2.77 (2 H, d, *J* 6.7, PhCH_2), 2.88 (1 H, m, 4-H), 3.60 (3 H, s, OMe), 3.88 (1 H, m, 7-H), 4.50 (1 H, d, *J* 6.7, NH), 5.11 (2 H, m, OCH_2), 5.25–5.41 (2 H, m, 2 × CH=), 6.84 (2 H, s, ArH), 6.98–7.03 (2 H, m, ArH), 7.15–7.24 (3 H, m, ArH), 7.31–7.38 (5 H, m, ArH); *m*/*z* (FAB-LRMS) 564 (MH^+, base peak), 474, 472, 440, 391, 365, 333, 315, 302, 289, 257, 225, 183.

(2*E*,4*S*,5*S*)-6-Benzyloxy-4-chloro-*N*-methyl-5-(2,4,6-trimethylphenylsulfonylamino)hex-2-enamide 30

By use of a procedure identical with that described for the preparation of **14** from **10**, the *cis*-(*E*)-enamide **6** (11.5 g, 26.7 mmol) was converted into the title compound **30** (9.53 g, 20.5 mmol, 77%) as colorless crystals, mp 131–133 °C (from Et_2O) (Found: C, 59.18; H, 6.17; N, 5.79. $C_{23}H_{29}ClN_2O_4S$ requires C, 59.41; H, 6.29; N, 6.02%); $[\alpha]_D^{28}$ −26.0 (*c* 0.50); δ_H(300 MHz) 2.29 (3 H, s, CMe), 2.58 (6 H, s, 2 × CMe), 2.85 (3 H, d, *J* 4.9, NMe), 3.45 (1 H, m, 5-H), 3.53–3.64 (2 H, m, OCH_2), 4.39 (2 H, s, OCH_2Ph), 4.81 (1 H, ddd, *J* 7.4, 3.4 and 1.2, 4-H), 5.08 (1 H, d, *J* 8.6, NH), 5.53 (1 H, br s, CONH), 5.94 (1 H, dd, *J* 15.1 and 1.2, CH=), 6.56 (1 H, dd, *J* 15.1 and 7.4, CH=), 6.91 (2 H, s, ArH), 7.19–7.38 (5 H, m, Ph).

Mts-L-Ser(*O*-Bn)-ψ[(*E*)-CH=CH]-D-Glu(OMe)-NHMe 8

By use of a procedure identical with that described for the preparation of **18** from **14**, treatment of the enamide **30** (2.32 g, 4.98 mmol) with $IZn(CN)CuCH_2CH_2CO_2Me{\cdot}2LiCl$ in THF gave the title compound **8** (2.40 g, 4.64 mmol, 93%) as a colorless oil [Found (FAB): $(M + H)^+$, 517.2368. $C_{27}H_{37}N_2O_6S$ requires *M* + H, 517.2372]; $[\alpha]_D^{28}$ −28.0 (*c* 0.50); δ_H(300 MHz) 1.70 (1 H, m, C*H*H), 2.19 (1 H, m, CH*H*), 2.23–2.26 (2 H, m, CH_2), 2.30 (3 H, s, CMe), 2.56 (6 H, s, 2 × CMe), 2.75 (3 H, d, *J* 4.7, NMe), 2.83 (1 H, m, 4-H), 3.33–3.43 (2 H, m, OCH_2), 3.62 (3 H, s, OMe), 3.69 (1 H, m, 7-H), 4.40 (2 H, s, OCH_2Ph), 5.22 (1 H, d, *J* 4.4, NH), 5.47 (1 H, dd, *J* 15.4 and 8.2, CH=), 5.55 (1 H, dd, *J* 15.5 and 7.2, CH=), 6.30 (1 H, br s, CONH), 6.92 (2 H, s, ArH), 7.19–7.38 (5 H, m, ArH); *m*/*z* (FAB-LRMS) 539 (MNa^+), 517 (MH^+), 485, 318, 228 (base peak), 196, 183, 119, 91.

Mts-L-Ser(*O*-Bn)-ψ[(*E*)-CH=CH]-D-Glu(OBn)-NHMe 31

By use of a procedure identical with that described for the preparation of **18** from **14**, treatment of the enamide **30** (600

mg, 1.29 mmol) with $IZn(CN)CuCH_2CH_2CO_2Bn{\cdot}2LiCl$ in THF gave the title compound **31** (595 mg, 1.01 mmol, 78%) as a colorless oil [Found (FAB): $(M - H)^-$, 591.2547. $C_{33}H_{39}N_2O_6S$ requires $M - H$, 591.2528]; $[\alpha]_D^{28}$ −11.9 (*c* 0.50); δ_H(270 MHz) 1.73 (1 H, m, C*H*H), 2.23 (1 H, m, CH*H*), 2.28 (2 H, m, CH_2), 2.29 (3 H, s, CMe), 2.54 (6 H, s, 2 × CMe), 2.73 (3 H, d, *J* 4.7, NMe), 2.80 (1 H, m, 4-H), 3.30–3.40 (2 H, m, OCH_2), 3.62 (1 H, m, 7-H), 4.37 (2 H, s, OCH_2Ph), 5.07 (2 H, s, OCH_2Ph), 5.21 (1 H, d, *J* 4.0, NH), 5.43 (1 H, dd, *J* 15.1 and 7.0, CH=), 5.51 (1 H, dd, *J* 15.1 and 7.0, CH=), 6.30 (1 H, br s, CONH), 6.92 (2 H, s, ArH), 7.18–7.39 (10 H, m, 2 × Ph); *m*/*z* (FAB-LRMS) 591 [$(M - H)^-$], 483 (base peak), 305, 199, 168, 153, 122.

Mts-L-Ser(*O*-Bn)-ψ[(*E*)-CH=CH]-L-Glu(OBn)-NHMe 32

By use of a procedure identical with that described for the preparation of **24** from **10**, treatment of the *cis*-(*E*)-enamide **6** (327 mg, 0.763 mmol) with $IZn(CN)CuCH_2CH_2CO_2Bn{\cdot}2LiCl$ in THF gave the title compound **32** (255 mg, 0.430 mmol, 56%) as a colorless oil [Found (FAB): $(M + H)^+$, 593.2700. $C_{33}H_{41}N_2O_6S$ requires $M + H$, 593.2685]; $[\alpha]_D^{28}$ −54.0 (*c* 0.50 in $CHCl_3$); δ_H(270 MHz) 1.74 (1 H, m, C*H*H), 2.13 (1 H, m, CH*H*), 2.28 (3 H, s, CMe), 2.34 (2 H, t, *J* 7.5, CH_2), 2.55 (6 H, s, 2 × CMe), 2.70 (3 H, d, *J* 4.7, NMe), 2.80 (1 H, m, 4-H), 3.28–3.40 (2 H, m, OCH_2), 3.69 (1 H, m, 7-H), 4.36 (2 H, s, OCH_2Ph), 5.10 (2 H, s, OCH_2Ph), 5.15 (1 H, d, *J* 4.7, NH), 5.43 (1 H, dd, *J* 15.5 and 8.7, CH=), 5.70 (1 H, dd, *J* 15.5 and 6.7, CH=), 6.07 (1 H, m, CONH), 6.91 (2 H, s, ArH), 7.17–7.38 (10 H, m, 2 × Ph); *m*/*z* (FAB-LRMS) 593 $(MH)^+$, 485 (base peak), 465, 394, 332, 196, 183, 119, 91.

Acknowledgements

This work was supported in part by a Grant-in-Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science and Technology, Japan and the Japan Health Science Foundation.

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