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ORIGINAL ARTICLE

Diastereoselective functionalisation of Baylis–Hillman adducts: a convenient approach to α-methyl-α-amino acids

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Abstract The *N*-tosyl carbamates **4a–e**, easily prepared starting from the Baylis–Hillman adducts **3a–e**, underwent cyclization carried out with I_2/NIS in the presence of NaH, to give the corresponding 2-oxo-1,3-oxazolidines **5a–e** in good yield and total stereoselection when the substituent at C-5 is Ar. After the removal of tosyl group, followed by the cleavage of the heterocyclic ring, the α-methyl-α-amino acids **8a,b** and **10** were obtained in good yield as hydrochlorides.

Keywords α-Methyl-α-amino acid · Functionalisation · Diastereoselection · Baylis–Hillman adducts

Introduction

Quaternary stereocenters are common structural motifs in bioactive natural products such as α-methyl-α-amino acids (Mosey et al. 2008; Balducci et al. 2009), which are part of molecules such as neurotropic lactacystin (Pattenden and Rescourio 2008; Li et al. 2009), the immunosuppressive agent myriocin (Imai et al. 2008; Jones and Marsden 2008) and the antifungal agents sphingofungins (Trost and Lee 2001). These constrained building blocks have become important in bio-organic chemistry, since their incorporation introduces conformational restrictions into peptide chains and increases constraints within the peptidomimetic structures, consequently stabilizing the helical conformations. In some cases they force peptides into their biologically active conformations, often leading to peptidomimetics with remarkable resistance to enzymatic degradation (Toniolo et al. 2006). Moreover, α-methyl-α-amino acids are frequently employed in bio organic synthesis, so that a versatile route to these compounds in the enantiomerically pure form is desirable (Wirth 1997; Cativiela and Diaz-De-Villegas 1998; Xu et al. 2005; Vogt and Brase 2007; Davies et al. 2007; Balducci et al. 2009).

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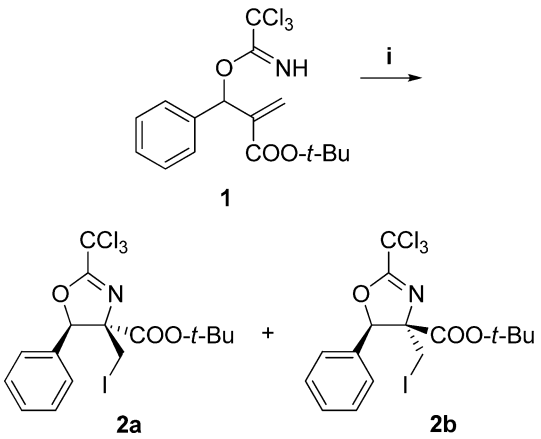
Results and discussion

Within this topic, we devised that the stereocontrolled intramolecular addition of a nucleophile to a *gem*-disubstituted double bond activated by an electrophile can give rise to a one-step construction of such highly congested motif (Orena 1995b). In addition, when an enantiomerically pure starting material is available, functionalization allows to introduce stereocenters with the appropriate configuration (Cardillo and Orena 1995), and the approach we report here is particularly attractive since Baylis–Hillman adducts can be obtained with high enantiomeric purity according to a lot of synthetic procedures (Basavaiah et al. 2003; Basavaiah et al. 2007). Directed towards this goal, the imidate **1**, arising from a Baylis–Hillman adduct, was treated with NIS in $CHCl_3$, and diastereomeric 4,5-dihydro-1,3-oxazoles **2a** and **2b** were obtained in good yield but 80:20 d.r, the *cis*-isomer being the major component of the reaction mixture. The diastereomers were separated by silica gel chromatography and configurations were assigned

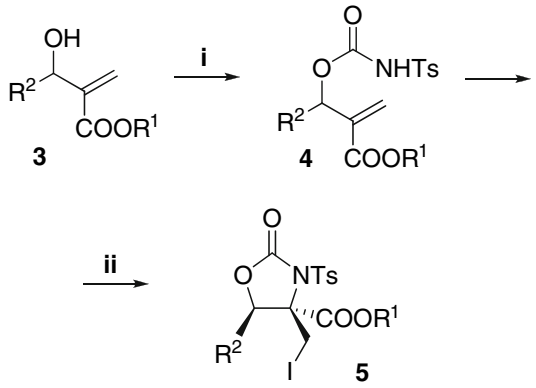


Scheme 1 *i*. NIS, $CHCl_3$, rt, 88%, 80:20 d.r

by means of ^{1}H-NMR spectral data and subsequently confirmed by NOE experiments (Scheme 1) (Galeazzi et al. 2004a).

Thus, with the aim to improve stereoselection of the chirality transfer from C-3 to C-2 of the Baylis–Hillman adducts **3**, we at first devised to use *N*-acyl carbamates of Baylis–Hillman adducts (Ciclosi et al. 2002) in order to increase the stereoselection of the cyclization reaction. In fact *N*-trichloroacetyl, *N*-phenyloxycarbonyl and *N*-(4-methoxybenzyloxy)carbonyl carbamates prepared starting from the Baylis–Hillman adduct **3a** were treated under the reported conditions (Fujita et al. 1997), but we were unable to find any cyclized product in the reaction mixture, the starting material being invariably recovered. Eventually, we devised to use *N*-tosyl carbamates **4a–e**, obtained in almost quantitative yield by reaction of Baylis–Hillman adducts with tosyl isocyanate (Scheme 2). The *N*-tosyl carbamate moiety was already employed in order to introduce a nitrogen atom onto a double bond, but the stereoselection of the cyclofunctionalization was not satisfactory, invariably leading to a diastereomeric mixture (Hirama et al. 1984), the sole useful cyclization involving allenic derivatives (Friesen 1990; Friesen and Kolaczewska 1991; Kimura et al. 1991). However, when the compounds **4a–e** underwent cyclization in THF on treatment with an equimolar amount of sodium hydride, followed by NIS/I_2, the cyclization products **5a–e** were exclusively obtained in high yield and with total stereoselection when R^2 is Ar. The *cis*-relationship between R^2 and the iodomethyl group in these compounds was evidenced by the strong shielding effect observed in the ^{1}H-NMR spectra for the protons of the iodomethyl group, in analogy with the products arising from the cyclization of amides of aza-Baylis–Hillman adducts (Galeazzi et al. 2004b).

Eventually, the relative configuration of compounds **5** was confirmed by single-crystal X-ray diffraction analysis of compound **5e** (Fig. 1).



Scheme 2 **a** $R^1 = CH_3$, $R^2 = C_6H_5$; **b** $R^1 = CH_3$, $R^2 = (CH_3)_2CHCH_2$; **c** $R^1 = t\text{-}C_4H_9$ $R^2 = C_6H_5$; **d** $R^1 = C_2H_5$, R^2 = 2-naphthyl; **e**, $R^1 = C_2H_5$, R^2 = 4-Cl-C_6H_4. *i*. TsNCO, DCM, rt, 30 min: **4a** 94% yield; **4b** 93% yield; **4c** 96% yield; **4d** 98% yield; **4e** 95% yield. *ii*. NaH, THF, then I_2/NIS, rt: **5a** 75% yield; **5b** 63% yield (*cis*/*trans* ≈ 9/1); **5c** 66% yield; **5d** 49% yield; **5e** 59% yield

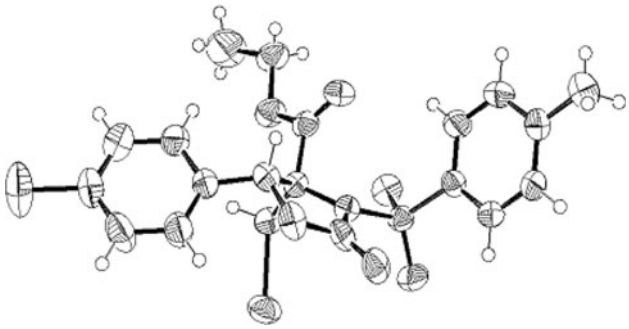
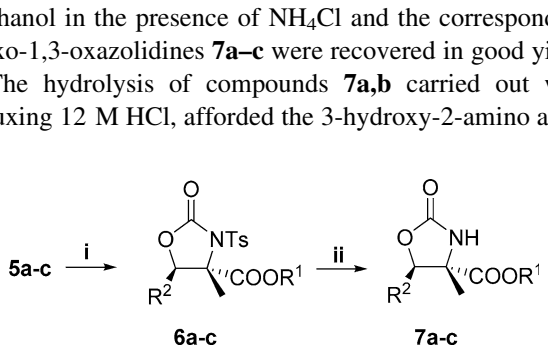


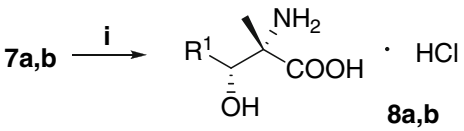
Fig. 1 Computer-generated ORTEP drawing of **5e** at 50% probability as determined by single-crystal X-ray diffraction analysis

With compounds **5** in hand, the cleavage of the C–I bond was performed with *N*-ethylpiperidinium hypophosphite (Galeazzi et al. 2004a), starting from **5a–c**, to give the corresponding 4-methyl derivatives **6a–c** in high yield (Scheme 3). The subsequent removal of the tosyl group of **6a–c** was carried out using Mg in refluxing methanol in the presence of NH_4Cl and the corresponding 2-oxo-1,3-oxazolidines **7a–c** were recovered in good yield.

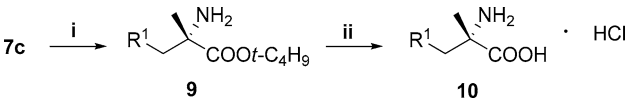
The hydrolysis of compounds **7a,b** carried out with refluxing 12 M HCl, afforded the 3-hydroxy-2-amino acids



Scheme 3 **a** $R^1 = CH_3$, $R^2 = C_6H_5$; **b** $R^1 = CH_3$, $R^2 = (CH_3)_2CHCH_2$; **c** $R^1 = t\text{-}C_4H_9$, $R^2 = C_6H_5$. *i*. H_3PO_2, N-ethylpiperidine, AIBN, refluxing toluene, 2 h: **6a** 67% yield; **6b** 87% yield; **6c** 64% yield. *ii*. Mg, NH_4Cl, refluxing methanol, 45 min: **7a** quantitative yield; **7b** 75% yield; **7c** 98% yield



Scheme 4 **a** $R^1 = C_6H_5$; **b** $R^1 = (CH_3)_2CHCH_2$. *i*. Refluxing 12 M HCl, **a** 67% yield; **b** 95% yield



Scheme 5 $R^1 = C_6H_5$. *i*. 10% Pd on charcoal, H_2, methanol, 3 h, 86% yield. *ii*. 6 M HCl at reflux for 24 h, 78% yield

8a,b in moderate yield (Scheme 4) (Schöllkopf et al. 1981a,b; Schöllkopf 1983; Avenoza et al. 2000).

On the other hand, when compound **7c** was treated with hydrogen in the presence of 10% Pd on charcoal, the amino ester **9** was obtained and subsequent hydrolysis carried out with 6 M HCl afforded the amino acid **10**, having the α-quaternary center, as the corresponding hydrochloride (Scheme 5) (Wang et al. 2007; Lu and Lin 2008; Tomooka et al. 2008).

Finally, we could ascertain that the iodocyclization reaction occurs without any epimerization at the benzylic stereogenic center (e.g. compounds **3a,c,d**). In fact, we prepared the Baylis–Hillman adduct (*R*)-**3a** in 95% e.e. according to the literature method (Nakano et al. 2006), which was converted into the corresponding tosyl carbamate (*R*)-**4a**. This product underwent the iodocyclization reaction and the reaction mixture was analyzed by HPLC. The cyclized product (4*S*,5*R*)-**5a** was obtained in 95% e.e., thus confirming the total configuration retention at C-5. This result was further confirmed by conversion of (4*S*,5*R*)-**5a** into the hydrochloride (2*R*,3*R*)-**8a** which eventually, according to the reported method (Avenoza et al. 2000), gave the free amino acid (2*R*,3*R*)-**11** in 95% e.e. determined on the basis of the specific rotation value. It is noteworthy that, as experimentally verified for **5a**, the crystalline products (**5a**, **5d** and **5e**) can be easily obtained in the enantiopure form by fractional crystallization from ethyl acetate or dichloromethane.

Crystal structure of 5e

The crystal packing of **5e** (Fig. 2) consists of a 3D network of molecules joined by intermolecular interactions with participation of C–H…O atoms. Two interactions involve the O(2) atom belonging to the symmetry related x, ½-y, ½ + x molecule [C(6)–H(6)…O(2) and C(16)–H(16)…O(2) with D..A distances of 3·404(6) and 3·297(3) Å and D–H..A angles of 136·4° and 133·4°, respectively] and a third one involving O(3), x, ½-y, −1/2 + x [C(9)–H(9)…O(3) with D..A distance of 3·191(3) Å and D–H..A angle of 162·5°].

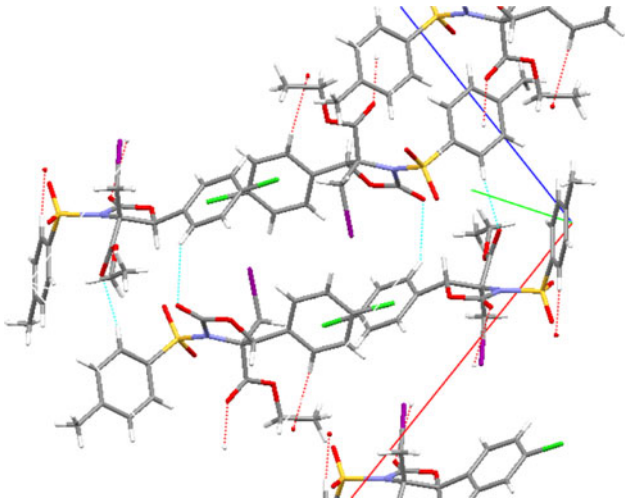


Fig. 2 Packing of **5e** showing the intermolecular H-bond network

Conclusions

In summary, starting from Baylis–Hillman adducts **3**, by means of a totally stereocontrolled cyclofunctionalisation, we obtained rapid access to compounds containing a quaternary carbon bearing nitrogen. In addition, we developed a short and highly selective method for the synthesis of α,α-dialkylated amino acids **8** and **10**, possessing a chiral quaternary carbon atom, which are interesting building blocks for the synthesis of more complex peptides.

Experimental

Melting points were measured on an Electrothermal IA 9000 apparatus and are uncorrected. ^{1}H- and ^{13}C-NMR spectra were recorded at 200 and 50 MHz respectively, on a Varian Gemini 200 spectrometer or at 400 and 100 MHz respectively, on a Varian MR-400 spectrometer. $CDCl_3$ was employed as a solvent unless otherwise stated. Chemical shifts (δ) are reported in ppm relative to TMS and coupling constants (J) in Hz. Optical rotations were measured on a Perkin Elmer 341 polarimeter. The samples were analyzed with a liquid chromatography Agilent Technologies HP1100, equipped with a Daicel Chiralcel OD-H column and a diode-array UV detector (210, 230 and 250 nm). n-Hexane and 2-propanol for HPLC were purchased from Aldrich. The MSD1100 mass detector was utilized under the following conditions: mass range 100–2,500 uma, positive scanning, energy of fragmentor

50 eV, drying gas flow (nitrogen) 10·0 mL/min, nebulizer pressure 45 psig, drying gas temperature 350°C and capillary voltage 4,500 V. Elemental analyses were performed using a Perkin Elmer 2400 CHN Elemental Analyzer. Column chromatography was performed with silica gel 60 (230–400 mesh).

Synthesis of compounds **4a-e**. General procedure

To a solution of the appropriate Baylis–Hillman adduct **3** (5 mmol) in dry dichloromethane (10 mL), tosyl isocyanate (0·85 mL; 5·25 mmol) was added at rt and the mixture was subsequently stirred for 30 min. After removal of the solvent under reduced pressure, the residue was purified by silica gel chromatography (cyclohexane:ethyl acetate 9:1) to give the corresponding *N*-tosylcarbamates **4** as colorless oils.

Methyl 2-[phenyl(tosylcarbamoyloxy)methyl]acrylate **(4a)**

The title compound was obtained in 94% yield. ^{1}H-NMR (200 MHz, $CDCl_3$) δ 2·42 (s, 3H), 3·64 (s, 3H), 5·82 (s, 1H), 6·40 (s, 1H), 6·55 (s, 1H), 7·18–7·35 (m, 7 ArH), 7·62 (br s, 1H, NH), 7·82 (d, $J = 8·5$ Hz, 2 ArH); ^{13}C-NMR (50 MHz, $CDCl_3$) δ 21·1, 51·6, 75·3, 126·4, 127·2, 127·7, 128·1, 128·3, 129·2, 135·3, 136·1, 138·2, 144·5, 149·4, 164·8; ESI–MS *m/z* 389·1 $[M]^+$, 412·1 $[M + Na]^+$. Anal Calcd for $C_{19}H_{19}NO_6S$ (389·09): C, 58·60; H, 4·92; N, 3·60. Found: C, 58·55; H, 4·85; N, 3·69.

Methyl 5-methyl-2-methylene-3-(tosylcarbamoyloxy) hexanoate **(4b)**

The title compound was obtained in 95% yield. ^{1}H-NMR (200 MHz, $CDCl_3$) δ 0·76 (d, $J = 6·0$, 3H), 0·83 (d, $J = 6·0$. 3H), 1·08–1·50 (m, 3H), 2·44 (s, 3H), 3·72 (s, 3H), 5·56 (dd, $J = 6·0$, $J = 6·6$, 1H), 5·69 (s, 1H), 6·23 (s, 1H), 7·34 (d, $J = 7·3$, 2 ArH), 7·90 (d, $J = 7·3$, 2 ArH), 7·94 (br s, 1H, NH); ^{13}C-NMR (50 MHz, $CDCl_3$) δ 21·3, 21·5, 22·9, 24·4, 43·4, 52·0, 73·1, 126·0, 128·0, 129·4, 136·5, 139·5, 144·2, 151·5, 165·7; ESI–MS *m/z* 369·1 $[M]^+$, 392·1 $[M + Na]^+$. Anal Calcd for $C_{17}H_{23}NO_6S$ (369·12): C, 55·27; H, 6·28; N, 3·79. Found: C, 55·21; H, 6·34; N, 3·74.

t-Butyl 2-[phenyl(tosylcarbamoyloxy)methyl]acrylate **(4c)**

The title compound was obtained in 96% yield. ^{1}H-NMR (200 MHz, $CDCl_3$) δ 1·30 (s, 9H), 2·42 (s, 3H), 5·68 (s, 1H), 6·32 (s, 1H), 6·51 (s, 1H), 7·18–7·35 (m, 7 ArH), 7·68 (br s, 1H, NH), 7·83 (d, $J = 8·5$, 2 ArH); ^{13}C-NMR (50 MHz, $CDCl_3$) δ 21·6, 27·8, 81·7, 127·8, 128·3, 128·4, 128·7, 129·6, 135·4, 136·6, 140·0, 145·0, 149·2, 163·7; ESI–MS *m/z* 431·1 $[M]^+$, 454·1 $[M + Na]^+$. Anal Calcd for $C_{22}H_{25}NO_6S$ (431·14): C, 61·24; H, 5·84; N, 3·25. Found: C, 61·16; H, 5·90; N, 3·19.

Ethyl 2-[naphthalen-1-yl(tosylcarbamoyloxy)methyl] acrylate **(4d)**

The title compound was obtained in 98% yield. ^{1}H-NMR (200 MHz, $CDCl_3$) δ 1·14 (t, $J = 7·4$, 3H), 2·31 (s, 3H), 4·07 (q, $J = 7·4$, 2H), 5·90 (s, 1H), 6·45 (s, 1H), 6·73 (s, 1H), 7·09–7·15 (m, 2 ArH), 7·26–7·33 (m, 2 ArH), 7·45–7·51 (m, 2 ArH), 7·70–7·82 (m, 6 ArH + NH); ^{13}C-NMR (50 MHz, $CDCl_3$) δ 13·8, 21·5, 26·9, 61·2, 76·0, 124·9, 126·3, 126·5, 126·8, 127·2, 127·6, 128·1, 128·2, 128·3, 129·5, 132·9, 133·2, 133·8, 135·4, 138·6, 144·8, 149·7, 164·7; ESI–MS *m/z* 453·1 $[M]^+$, 476·1 $[M + Na]^+$. Anal Calcd for $C_{24}H_{23}NO_6S$ (453·12): C, 63·56; H, 5·11; N, 3·09. Found: C, 63·51; H, 5·06; N, 3·15.

Ethyl 2-[(4-chlorophenyl)(tosylcarbamoyloxy) methyl]acrylate **(4e)**

The title compound was obtained in 93% yield. ^{1}H-NMR (200 MHz, $CDCl_3$) δ 1·16 (t, $J = 7·4$, 3H), 2·43 (s, 3H), 4·08 (q, $J = 7·4$, 2H), 5·82 (s, 1H), 6·40 (s, 1H), 6·50 (s, 1H), 6,95–7·41 (m, 7H, 6 ArH + NH), 7·78 (d, $J = 8·3$, 2 ArH); ^{13}C-NMR (50 MHz, $CDCl_3$) δ 13·9, 21·7, 61·3, 75·2, 126·7, 128·2, 128·7, 129·1, 129·6, 134·6, 135·1, 138·3, 145·2, 149·5, 164·5; ESI–MS *m/z* 437·1 $[M]^+$, 460·1 $[M + Na]^+$. Anal Calcd for $C_{20}H_{20}ClNO_6S$ (437·07): C, 54·86; H, 4·60; N, 3·20. Found: C, 54·80; H, 4·56; N, 3·15.

Synthesis of compounds **5a-e**. General procedure

To a solution of compound **4a–e** (2·0 mmol) in dry THF (5 mL) under inert atmosphere, NaH (84 mg of 60% dispersion in mineral oil, 2·1 mmol) was slowly added. After the evolution of hydrogen had ceased, iodine (1·53 g, 6·0 mmol) and NIS (450 mg, 2·0 mmol) were added. When the conversion was almost complete (3–7 days), the reaction mixture was directly poured into a saturated solution of $Na_2S_2O_3$ (10 mL) and ethyl acetate (20 mL). After separation, the aqueous phase was further extracted with ethyl acetate (10 mL). The organic phases were dried (Na_2SO_4) and the solvent was removed under reduced pressure. The crude material was purified by chromatography over silica gel (cyclohexane/ethyl acetate 90:10 as eluent) obtaining pure compounds **5a–e**. Crystallization from ethyl acetate furnished crystalline samples of **5a**, **5d** and **5e**, although only **5e** was suitable for diffractometric analysis.

Methyl (4*S**,5*R**)-4-(iodomethyl)-2-oxo-5-phenyl-3-tosyloxazolidine-4-carboxylate **(5a)**

The title compound was obtained in 75% yield. White crystals; mp 170°C; ^{1}H-NMR (200 MHz, $CDCl_3$) δ 2·46 (s, 3H), 3·14 (d, J = 12·2 Hz, 1H), 3·95 (d, J = 12·2 Hz, 1H), 4·03 (s, 3H), 5·78 (s, 1H), 7·30–7·45 (m, 7 ArH), 8·07 (d, J = 8·5 Hz, 2 ArH); ^{13}C-NMR (50 MHz, $CDCl_3$) δ 3·3, 21·6, 54·3, 70·8, 82·4, 126·4, 128·3, 129·3, 129·6, 134·0, 146·0, 150·4, 167·5; ESI–MS *m/z* 515·0 $[M]^+$, 538·0 $[M + Na]^+$. Anal Calcd for $C_{19}H_{18}INO_6S$ (514·99): C, 44·28; H, 3·52; N, 2·72. Found: C, 44·23; H, 3·47; N, 2·77.

Methyl (4*S**,5*R**)-4-(iodomethyl)-5-isobutyl-2-oxo-3-tosyloxazolidine-4-carboxylate **(5b)**

The title compound was obtained in 63% yield as a separable diastereomeric mixture (9:1 d.r.). Major diastereomer (4*S**,5*R**): colorless oil; ^{1}H-NMR (200 MHz, $CDCl_3$) δ 0·89 (d, J = 6·6, 3H), 0·94 (d, J = 6·6, 3H), 1·30–1,55 (m, 1H), 1·65–1·83 (m, 1H), 2·08–2·27 (m, 1H), 2·45 (s, 3H), 3·65 (d, J = 12·6, 1H), 3·92 (s, 3H), 4·08 (d, J = 12·6, 1H), 4·68 (dd, J = 3·0, J = 10·4, 1H), 7·30 (d, J = 8·0, 2 ArH), 8·03 (d, J = 8·0, 2 ArH); ^{13}C-NMR (50 MHz, $CDCl_3$) δ 2·1, 21·7, 21·8, 22·8, 24·9, 35·0, 54·2, 70·7, 80·5, 129·4, 129·6, 134·3, 146·0, 150·9, 167·2. Minor diastereomer (4*S**,5*S**): colorless oil; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 0·92 (d, J = 6·8, 3H), 0·93 (s, J = 6·8, 3H), 1·21 (ddd, J = 2·4, J = 8·8, J = 14·0, 1H), 1·55 (ddd, J = 4·4, J = 10·8, J = 14·0, 1H), 1·77–1·87 (m, 1H), 2·45 (s, 3H), 3·75 (d, J = 12·0, 1H), 3·86 (s, 3H), 4·26 (d, J = 12·0, 1H), 4·54 (dd, J = 2·4, J = 11·2, 1H), 7·35 (d, J = 8·4, 2 ArH), 8·03 (d, J = 8·4, 2 ArH); ^{13}C-NMR (100 MHz, $CDCl_3$) 10·2, 21·5, 21·9, 23·3, 25·0, 39·0, 53·7, 71·5, 80·8, 129·4, 130·0, 134·5, 146·1, 151·4, 165·9; ESI–MS *m/z* 495·0 $[M]^+$, 518·0 $[M + Na]^+$. Anal Calcd for $C_{17}H_{22}INO_6S$ (495·02): C, 41·22; H, 4·48; N, 2·83. Found: C, 41·17; H, 4·41; N, 2·78.

t-Butyl (4*S**,5*R**)-4-(iodomethyl)-2-oxo-5-phenyl-3-tosyloxazolidine-4-carboxylate **(5c)**

The title compound was obtained in 66% yield. Colorless oil; ^{1}H-NMR (200 MHz, $CDCl_3$) δ 1·65 (s, 9H), 2·44 (s, 3H), 3·06 (d, J = 12·2 Hz, 1H), 3·94 (d, J = 12·2 Hz, 1H), 5·78 (s, 1H), 7·30–7·40 (m, 7 ArH), 8·07 (d, J = 8·5 Hz, 2 ArH); ^{13}C-NMR (50 MHz, $CDCl_3$) δ 3·9, 21·7, 27·7, 71·5, 82·8, 85·8, 126·4, 128·3, 129·2, 129·8, 129·9, 134·1, 145·8, 150·7, 165·8; ESI–MS *m/z* 557·0 $[M]^+$, 580·0 $[M + Na]^+$. Anal Calcd for $C_{22}H_{24}INO_6S$ (557·04): C, 47·41; H, 4·34; N, 2·51. Found: C, 47·38; H, 4·38; N, 2·46.

Ethyl (4*S**,5*R**)-4-(iodomethyl)-5-(naphthalen-1-yl)-2-oxo-3-tosyloxazolidine-4-carboxylate **(5d)**

The title compound was obtained in 49% yield. White crystals; mp 108°C; ^{1}H-NMR (200 MHz, $CDCl_3$) δ 1·49 (t, J = 7·1, 3H), 2·47 (s, 3H), 3·12 (d, J = 11·6, 1H), 3·97 (d, J = 11·6, 1H), 4·55 (q, J = 7·1, 2H), 5·95 (s, 1H), 7·25–7·60 (m, 5 ArH), 7·80–8·15 (m, 6 ArH); ^{13}C-NMR (50 MHz, $CDCl_3$) δ 3·7, 14·1, 21·9, 64·2, 71·1, 82·9, 123·0, 126·9, 127·0, 127·1, 127·2, 127·9, 128·3, 128·5, 129·5, 129·9, 132·5, 133·4, 134·2, 146·2, 150·8, 167·4; ESI–MS *m/z* 579·0 $[M]^+$, 602·0 $[M + Na]^+$. Anal Calcd for $C_{24}H_{22}INO_6S$ (579·02): C, 49·75; H, 3·83; N, 2·42. Found: C, 49·70; H, 3·87; N, 2·38.

Ethyl (4*S**,5*R**)-5-(4-chlorophenyl)-4-(iodomethyl)-2-oxo-3-tosyloxazolidine-4-carboxylate **(5e)**

The title compound was obtained in 59% yield. White crystals; mp 170°C; ^{1}H-NMR (200 MHz, $CDCl_3$) δ 1·44 (t, J = 7·4, 3H), 2·46 (s, 3H), 3·10 (d, J = 12·4, 1H), 3·96 (d, J = 12·4, 1H), 4·49 (q, J = 7·4, 2H, 50%), 4·50 (q, J = 7·4, 2H, 50%), 5·73 (s, 1H), 7·18–7·43 (m, 6 ArH), 7·98 (d, J = 8·3, 2 ArH); ^{13}C-NMR (50 MHz, $CDCl_3$) δ 3·5, 14·0, 21·8, 64·2, 70·8, 81·9, 128·0, 128·3, 128·6, 129·4, 129·7, 133·9, 135·3, 146·2, 150·4, 167·0; ESI–MS *m/z* 563·0 $[M]^+$, 586·0 $[M + Na]^+$. Anal Calcd for $C_{20}H_{19}ClINO_6S$ (562·97): C, 42·61; H, 3·40; N, 2·48. Found: C, 42·56; H, 3·44; N, 2·52.

Preparation of compounds **6a–c**. General Procedure

To a solution containing products **5a–c** (4·21 mmol) in toluene (12·6 mL), H_3PO_2 (4·4 mL, 42·1 mmol) and ethylpiperidine (5·9 mL, 42·1 mmol) were added and the mixture was heated at reflux. Then, AIBN (235 mg, 1·4 mmol) was added, followed by a further portion after 1 h (235 mg). After 1 h the reaction mixture was poured in H_2O (15 mL) and extracted with ethyl acetate (2 × 30 mL). After drying (Na_2SO_4), the solvent was removed under reduced pressure and the residue was purified by silica gel chromatography (cyclohexane:ethyl acetate 7:3), to give compounds **6a–c**.

Methyl (4*S**,5*R**)-4-methyl-2-oxo-5-phenyl-3-tosyloxazolidine-4-carboxylate **(6a)**

The title compound was obtained in 67% yield. White crystals; mp 122°C; ^{1}H-NMR (200 MHz, $CDCl_3$) δ 1·36 (s, 3H), 2·46 (s, 3H), 3·98 (s, 3H), 5·61 (s, 1H), 7·12–7·20 (m, 2 ArH), 7·30–7·43 (m, 5 ArH), 8·01 (d, J = 8·5, 2 ArH); ^{13}C-NMR (50 MHz, $CDCl_3$) δ 18·7, 21·5, 53·6, 70·2, 82·4, 128·6, 129·1, 129·3, 129·4, 131·6, 134·4, 145·7,

150·8, 170·2; ESI–MS *m/z* 389·1 $[M]^+$, 412·1 $[M + Na]^+$. Anal Calcd for $C_{19}H_{19}NO_6S$ (389·09): C, 58·60; H, 4·92; N, 3·60. Found: C, 58·55; H, 4·87; N, 3·64.

Methyl (4*S**,5*R**)-4-methyl-2-oxo-5-isobutyl-3-tosyloxazolidine-4-carboxylate **(6b)**

The title compound was obtained in 87% yield. Colorless oil; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 0·89 (d, $J = 6·8$, 3H), 0·92 (s, $J = 6·8$, 3H), 1·31 (ddd, $J = 3·2$, $J = 4·0$, $J = 14·0$, 1H), 1·64 (ddd, $J = 5·6$, $J = 10·0$, $J = 14·0$, 1H), 1·70–1·81 (m, 1H), 1·74 (s, 3H), 2·45 (s, 3H), 3·90 (s, 3H), 4·53 (dd, $J = 3·2$, $J = 10·0$, 1H), 7·35 (d, $J = 8·4$, 2 ArH), 7·99 (d, $J = 8·4$, 2 ArH); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 17·3, 21·8, 21·9, 23·0, 23·5, 24·8, 37·4, 53·8, 69·9, 80·4, 129·4, 129·6, 134·8, 145·8, 151·2, 170·3; ESI–MS *m/z* 369·1 $[M]^+$, 392·1 $[M + Na]^+$. Anal Calcd for $C_{17}H_{23}NO_6S$ (369·12): C, 55·27; H, 6·28; N, 3·79. Found: C, 55·16; H, 6·19; N, 3·85.

t-Butyl (4*S**,5*R**)-4-methyl-2-oxo-5-phenyl-3-tosyloxazolidine-4-carboxylate **(6c)**

The title compound was obtained in 64% yield. Colorless oil; ^{1}H-NMR (200 MHz, $CDCl_3$) δ 1·29 (s, 3H), 1·62 (s, 9H), 2·45 (s, 3H), 5·60 (s, 1H), 7·12–7·44 (m, 7 ArH), 8·02 (d, $J = 8·5$ Hz, 2 ArH); ^{13}C-NMR (50 MHz, $CDCl_3$) δ 18·6, 23·3, 27·7, 70·8, 82·8, 84·2, 125·8, 128·6, 129·2, 129·4, 132·1, 134·9, 145·5, 151·1, 168·6; ESI–MS *m/z* 431·1 $[M]^+$, 454·1 $[M + Na]^+$. Anal Calcd for $C_{22}H_{25}NO_6S$ (431·14): C, 61·24; H, 5·84; N, 3·25. Found: C, 61·29; H, 5·81; N, 3·29.

Preparation of compounds **7a-c**. General procedure

To a solution containing products **6a–c** (0·194 mmol) in dry methanol (6·0 mL), Mg turnings (47 mg, 1·94 mmol) and NH_4Cl (52 mg, 0·97 mmol) were added and suspension was refluxed for 2 h. After removal of the solvent under reduced pressure, the residue was purified by silica gel chromatography (cyclohexane:ethyl acetate 70:30), to give compounds **7a–c**.

Methyl (4*S**,5*R**)-4-methyl-2-oxo-5-phenyloxazolidine-4-carboxylate **(7a)**

The title compound was obtained in quantitative yield. Colorless oil; ^{1}H-NMR (200 MHz, $CDCl_3$) δ 1·05 (s, 3H), 3·87 (s, 3H), 5·86 (s, 1H), 6·48 (br s, 1H, NH), 7·39 (m, 5 ArH); ^{13}C-NMR (50 MHz, $CDCl_3$) δ 21·8, 53·3, 64·3, 82·3, 126·4, 128·5, 128·9, 134·3, 157·7, 173·1; ESI–MS *m/z* 235·1 $[M]^+$, 258·1 $[M + Na]^+$. Anal Calcd for $C_{12}H_{13}NO_4$ (235·08): C, 61·27; H, 5·57; N, 5·95. Found: C, 61·21; H, 5·52; N, 6·01.

Methyl (4*S**,5*R**)-5-isobutyl-4-methyl-2-oxo-oxazolidine-4-carboxylate **(7b)**

The title compound was obtained in 75% yield. Colorless gum; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 0·96 (d, $J = 6·8$, 3H), 0·98 (s, $J = 6·8$, 3H), 1·40 (ddd, $J = 2·0$, $J = 9·2$, $J = 14·0$, 1H), 1·42 (s, 3H), 1·71 (ddd, $J = 4·4$, $J = 11·2$, $J = 14·0$, 1H), 1·83 – 1·93 (m, 1H), 3·79 (s, 3H), 4·71 (dd, $J = 2·0$, $J = 11·2$, 1H), 6·01 (br s, 1H, NH); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 19·9, 21·4, 23·6, 24·9, 38·4, 53·2, 63·4, 79·8, 157·7, 172·8; ESI–MS *m/z* 215·1 $[M]^+$, 238·1 $[M + Na]^+$. Anal Calcd for $C_{10}H_{17}NO_4$ (215·12): C, 55·80; H, 7·96; N, 6·51. Found: C, 55·69; H, 7·90; N, 6·42.

t-Butyl (4*S**,5*R**)-4-methyl-2-oxo-5-phenyloxazolidine-4-carboxylate **(7c)**

The title compound was obtained in 98% yield. Colorless oil; ^{1}H-NMR (200 MHz, $CDCl_3$) δ 1·01 (s, 3H), 1·55 (s, 9H), 5·63 (br s, 1H, NH), 5·84 (s, 1H), 7·39 (m, 5 ArH); ^{13}C-NMR (50 MHz, $CDCl_3$) δ 22·2, 27·9, 64·4, 82·2, 83·7, 126·5, 128·5, 128·9, 134·5, 157·1, 171·6; ESI–MS *m/z* 277·1 $[M]^+$, 300·1 $[M + Na]^+$. Anal Calcd for $C_{15}H_{19}NO_4$ (277·13): C, 64·97; H, 6·91; N, 5·05. Found: C, 64·92; H, 6·86; N, 5·01.

Cleavage of products **7a,b**. General procedure

To a solution containing compounds **7a**,**b** (1·0 mmol) in methanol (1 mL), 12 M HCl (5 mL) was added and the mixture was heated at reflux for 10 h. The solvents were removed under reduced pressure and another 12 M HCl (5 mL) was added. The mixture was heated at reflux for 10 h for **7a** and 20 h for **7b**. After partial removal of HCl under reduced pressure, the aqueous phase was diluted with water (10 mL), washed with ethyl acetate (3 × 5 mL) and finally evaporated under reduced pressure to give pure **8a,b**.

(2*S**,3*R**)-2-Amino-3-hydroxy-2-methyl-3-phenylpropanoic acid hydrochloride **(8a)**

The title compound was obtained in 67% yield as amorphous solid. ^{1}H-NMR (200 MHz, DMSO-d_6) δ 1·38 (s, 3H), 5·13 (s, 1H), 7·35–7·51 (m, 5 ArH); ^{13}C-NMR (50 MHz, DMSO-d_6) δ 18·9, 65·1, 75·8, 128·7, 129·6, 129·9, 138·9, 172·9; ESI–MS *m/z* 196·2 $[MH]^+$, 219·2 $[M + Na]^+$. Anal Calcd for $C_{10}H_{14}ClNO_3$ (231·17): C, 51·84; H, 6·09; N, 6·05. Found: C, 51·79; H, 6·03; N, 6·11.

(2*S**,3*R**)-2-Amino-3-hydroxy-2,5-dimethylhexanoic acid hydrochloride **(8b)**

The title compound was obtained in 95% yield as amorphous solid. ^{1}H-NMR (400 MHz, DMSO-d_6) δ 0·84 (d, J = 6·4, 3H), 0·90 (d, J = 6·4, 3H), 1·10–1·18 (m, 1H), 1·29 (s, 3H), 1·32–1·39 (m, 1H), 1·72–1·85 (m, 1H), 3·36 (br s, 4H, OH + NH), 3·77 (dd, J = 11·2, J = 1·6, 1H), 8·18 (br s, 1H, COOH); ^{13}C-NMR (100 MHz, DMSO-d_6) δ 17·3, 21·0, 23·8, 23·9, 39·2, 63·5, 70·4, 172·2; ESI–MS *m/z* 175·1 $[MH]^+$, 198·1 $[M + Na]^+$. Anal Calcd for $C_8H_{18}ClNO_3$ (211·10): C, 43·59; H, 8·57; N, 6·62. Found: C, 43·48; H, 8·46; N, 6·54.

t-Butyl (2*S**,3*R**)-2-amino-2-methyl-3-phenylpropanoate **(9)**

To a solution of compound **7c** (52·6 mg, 0·19 mmol) in dry methanol (0·19 mL) Pd–C 10% (19 mg) was added and the suspension was stirred under a hydrogen atmosphere. After 3 h the catalyst was filtered off and removal of the solvent gave the product **9** (39 mg, 86%) as a colorless oil. ^{1}H-NMR (200 MHz, $CDCl_3$) δ 1·34 (s, 3H), 1·45 (s, 9H), 1·63 (s, 2H, NH_2), 2·77 (d, J = 13·2 Hz, 1H), 3·11 (d, J = 13·2 Hz, 1H), 7·18–7·28 (m, 5 ArH); ^{13}C-NMR (50 MHz, $CDCl_3$) δ 27·0, 28·0, 46·4, 58·8, 81·1, 126·8, 128·2, 130·2, 136·8, 176·3; ESI–MS *m/z* 251·2 $[MH]^+$, 274·2 $[M + Na]^+$. Anal Calcd for $C_{14}H_{21}NO_3$ (251·15): C, 66·91; H, 8·42; N, 5·57. Found: C, 66·86; H, 8·46; N, 5·53.

(R,S)-2-Amino-2-methyl-3-phenylpropanoic acid hydrochloride **(10)**

The compound **9** (251 mg; 1·0 mmol) was dissolved in 6 M HCl (3 mL) and the solution was refluxed for 24 h. After washing of the aqueous layer with ethyl acetate (3 × 5 mL), water was removed under reduced pressure to give the product **10** (195 mg, 78%) as a colorless viscous oil. ^{1}H-NMR (200 MHz, CD_3OD) δ 1·48 (s, 3H), 3·12 (s, 2H), 7·21–7·36 (m, 5ArH), 8·49 (s, 3H); ^{13}C-NMR (50 MHz, CD_3OD) δ 21·9, 42·3, 59·9, 127·6, 128·7, 130·5, 134·1, 172·3. ESI–MS *m/z* 180·1 $[MH]^+$, 202·1 $[M + Na]^+$. Anal Calcd for $C_{10}H_{14}ClNO_2$ (215·07): C, 55·69; H, 6·54; N, 6·49. Found: C, 55·64; H, 6·50; N, 6·44.

Methyl *(R)*-3-hydroxy-2-methylene-3-phenylpropanoate *(R)*-**(3a)**

According to the reported literature (Nakano et al. 2006) the title compound was obtained as a colorless oil in 95% e.e. HPLC conditions: Daicel Chiralcel OD-H, hexane: 2-propanol 98:2 (0·25 mL/min), t_R 32·9 min (*R*) and 39·1 min (*S*). $[\alpha]_D$-124·0 (c 1·30, CH_3OH) [lit. (Nakano et al. 2006) $[\alpha]_D$-124·6 (c 1·30, CH_3OH)].

Methyl (4*S*,5*R*)-4-(iodomethyl)-2-oxo-5-phenyl-3-tosyloxazolidine-4-carboxylate (4*S*,5*R*)-**(5a)**

Starting from (*R*)-**3a**, methyl (*R*)-2-[phenyl(tosylcarbamoyloxy)methyl]acrylate (*R*)-**4a** was prepared as reported for compound **4a**, and the product was cyclized without purification to give the title compound as white crystals in 65% yield and 95% e.e. HPLC conditions: Daicel Chiralcel OD-H, hexane:2-propanol 80:20 (0·7 mL/min), t_R 17·2 min (4*S*,5*R*) and 19·3 min (4*R*,5*S*). $[\alpha]_D$ 14·1 (c 0·9, $CHCl_3$). Enantiopure (*R*)-**3a** was obtained by fractional crystallization from dichloromethane (86% yield of recovered product). $[\alpha]_D$ 14·9 (c 0·77, $CHCl_3$). It is worth mentioning that careful preparation of the samples was needed, owing to the very low solubility of the product in the elution mixture. In fact, the product was dissolved in dichloromethane (2 mL/mmol) and 4 μL of this solution was evaporated under reduced pressure. The residue (about 0·1 mg) was dissolved in 2-propanol (3 mL) and this solution was used for HPLC analysis.

(2*S*,3*R*)-2-Amino-3-hydroxy-2-methyl-3-phenylpropanoic acid **(11)**

In a way similar to that described for compound (2*S**,3*R**)-**8a**, starting from (4*S*,5*R*)-**5a** (2*S*,3*R*)-(***8a***) (154 mg) was obtained, directly dissolved in H_2O (1 mL) and subjected to ion exchange column (Dowex 50WX2, elution with 1 M NH_4OH) to give, after evaporation of water under reduced pressure, the corresponding amino acid **11** (68%) as a white solid. mp 228°C; ^{1}H-NMR (400 MHz, D_2O) δ 0·72 (s, 3H), 5·11 (s, 1H), 7·40–7·53 (m, 5 ArH); ^{13}C-NMR (100 MHz, D_2O) δ 18·5, 65·2, 74·9, 127·3, 128·6, 130·0, 137·3, 175·5; $[\alpha]_D$-34·7 [c 0·3, H_2O) [lit. (Avenoza et al., 2000) $[\alpha]_D$-35·6 (c 0·35, H_2O) for 96% e.e.)]. ESI–MS *m/z* 196·2 $[MH]^+$, 218·2 $[M + Na]^+$. Anal Calcd for $C_{10}H_{13}NO_3$ (195·22): C, 61·53; H, 6·71; N, 7·17. Found: C, 61·45; H, 6·61; N, 7·23.

X-ray data

Crystal data for **5e** were collected on a Oxford Xcalibur S with Mo–Kα radiation, λ = 0·71073 Å, monochromator graphite and equipped with a liquid nitrogen Oxford-Cryostream device, θ_{max} = 25°. A monoclinic *P21/c* space group is obtained for the compound studied. The structure was solved by direct methods (Altomare et al. 1993) and refined against F2 (Sheldrick 2008). A geometric check was performed with Platon (Spek 2008). The hydrogen atoms were constrained to calculated positions and refined using a riding model in all cases. An ORTEP plot in Fig. 1

illustrates the structure at 50% probability level and the crystallographic numbering (Farrugia 1997).

Mercury (MacRae et al. 2008) was used for the graphical representation of the crystal packing. CCDC 747429 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via http://www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: (+44)1223-336-033; or e-mail: deposit@ccdc.cam.ac.uk).

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