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A NEW APPROACH TO THE SYNTHESIS OF ENANTIOMERICALLY PURE 2,3-DIAMINOACIDS THROUGH CHIRAL IMIDAZOLIDIN-2-ONES

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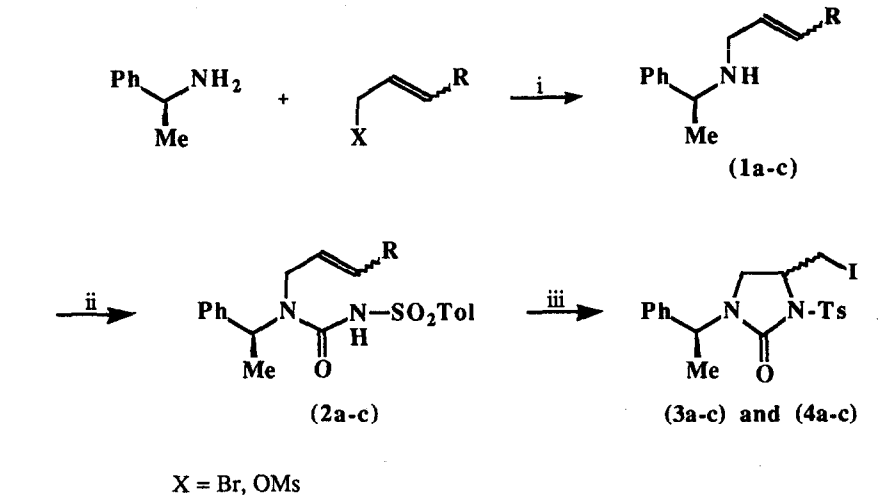
ABSTRACT: The synthesis of enantiomerically pure 5-iodomethylimidazolidin-2-ones (**3a-c**) and (**4a-c**) is reported, by means of iodocyclisation of allylic tosylureas (**2a-c**). Starting from pure (**3a**) and (**4a**), a synthesis of both (R)- and (S)-2,3-diaminopropanoic acid is described. Furthermore the cyclisation of the homoallylic tosylurea (**2d**), occurring with total diastereoselection, is depicted.

The synthesis of 1,2- and 1,3-diamines has recently attracted considerable attention, due to the important role that this kind of compounds play as intermediates of biological active molecules [1] and as starting materials for the synthesis of substituted bis-aminoethanetiols (BAT) derivatives. [2,3]

In this last period we have been interested in the synthesis of chiral vicinal diamines [4] obtained from the hydrolysis of chiral imidazolidin-2-ones. In this work we wish to report the synthesis of enantiomerically pure N-tosyl imidazolidin-2-ones and N-tosyl tetrahydropyrimidin-2-ones from chiral N-tosyl ureas [5] and the subsequent conversion of these heterocycles into non proteinogenic α-amino acids.

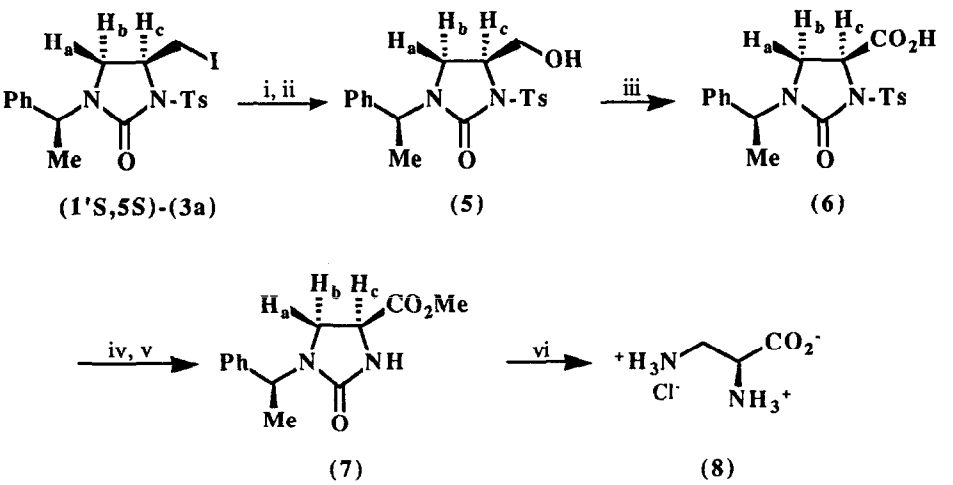
Thus treatment of the N-allylamines (**1a-c**) with p-toluenesulfonyl isocyanate at room temperature in the absence of solvent affords the corresponding N-tosyl ureas (**2a-c**) in quantitative yield (**Scheme 1**). The cyclisation of these compounds is easily performed in quantitative yield simply by treating the N-tosyl ureas (**2a-c**) with iodine in a biphasic system (THF/$NaHCO_3$, aqueous saturated solution). [6] The corresponding N-tosyl imidazolidin-2-ones are obtained as a mixture of diastereoisomers (**3a-c**) and (**4a-c**), that are easily separated by silica gel chromatography. The absolute configuration of the stereogenic centres introduced with the iodocyclisation is assigned on the comparison of the ^1H NMR spectra of the isolated diastereoisomers. [7]

The **Table** reports three examples containing a terminal double bond (**entry a**), an E-double bond (**entry b**) and a Z-double bond (**entry c**). While compound (**2a**), containing a terminal double bond, affords, as expected, a 1:1 diastereoisomeric mixture of N-tosyl imidazolidin-2-ones (**3a**) and (**4a**) on cyclisation, entries **b** and **c**, in which a disubstituted double bond is present, show a different behaviour. In fact, when N-tosylurea (**2b**) undergoes cyclisation, no diastereoselectivity results, probably owing to the E-configuration of the double bond, that minimises the steric interactions in the transition state. On the other hand, when the urea (**2c**) is cyclised, the reaction proceeds with low diastereoselectivity [1:2 diastereoisomeric ratio (**3c**):(**4c**)]: this result can be ascribed to interactions between the substituents of the Z-double bond in the transition state.



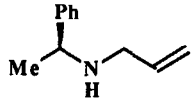
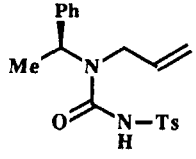
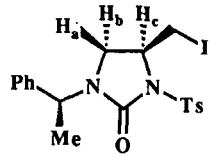
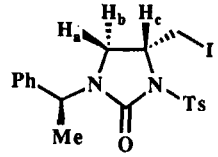
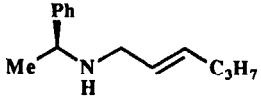
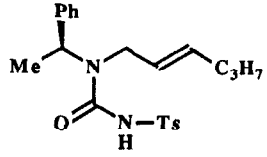
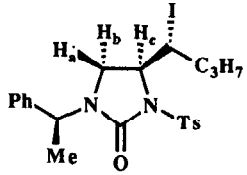
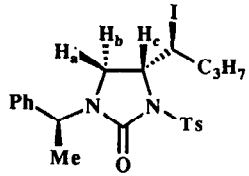
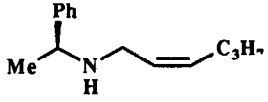
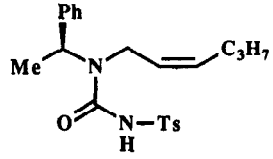
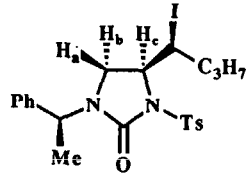
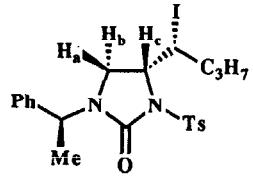
Scheme 1. i) r. t., then $NaHCO_3$ acqueous solution; ii) $TolSO_2$-NCO, r. t.; iii) I_2 in THF/$NaHCO_3$ acqueous solution, silica gel chromatography

The imidazolidin-2-ones **(1'S, 5S)-(3a)** and **(1'S,5R)-(4a)**, intermediates suitable for further transformations, are obtained pure after a simple chromatographic separation.



Scheme 2. i) AcOAg in AcOH, reflux; ii) K_2CO_3 in ethanol; iii) Jones oxidation; iv) Li (20 equiv)/NH_3, -70 °C; v) MeOH, $SOCl_2$; vi) HCl conc., reflux.

Table.

entry	amine (1)	tosylurea (2)	cyclisation products (3)	(4)	cyclisation yield	diastereoisomeric ratio (3)/(4)
a			 (1'S,5S)	 (1'S,5R)	92%	1 : 1
b			 (1'S,1"S,5S)	 (1'S,1"R,5R)	94%	1 : 1
c			 (1'S,1"R,5S)	 (1'S,1"S,5R)	90%	1 : 2

Thus starting from pure (**3a**) and (**4a**), a synthesis of both (R)- and (S)-2,3-diaminopropanoic acid, uncommon naturally occurring α-amino acids, has been devised (**Scheme 2**).

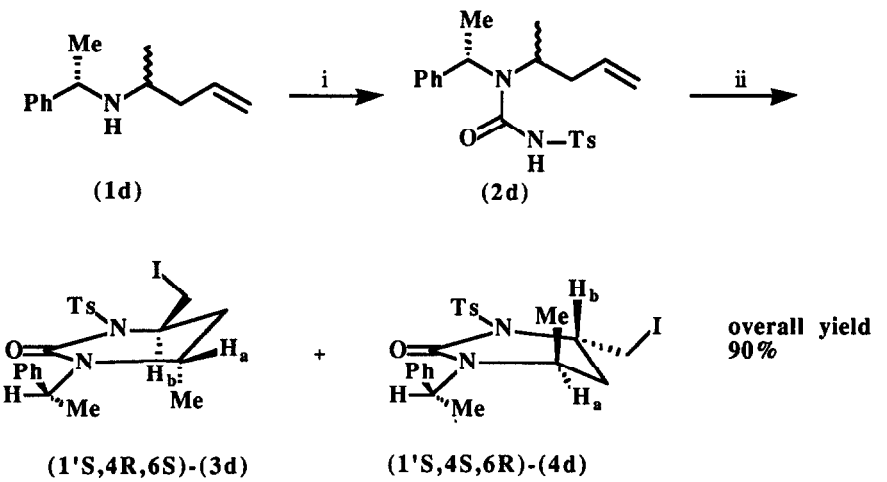
The synthetic pathway reported for (**3a**) involves the nucleophilic displacement of the iodine with silver acetate, [7] followed by hydrolysis of the acetate, to give the alcohol (**5**). After oxidation performed with the Jones reagent, the corresponding acid is obtained as its methyl ester (**6**).

As the removal of the tosyl group fails by using hydrobromic acid in acetic acid, [8] the N-tosyl bond cleavage is carried out under controlled Birch reaction conditions (20 equiv of Li/NH_3, 5 minutes at -70 °C) in order to avoid racemisation at the stereogenic centre C-5.

Under these conditions no racemisation is observed, but the N-C bond of the chiral auxiliary remains unaffected. Thus ring opening and cleavage of the N-C bond of the chiral auxiliary are performed by treating the ester (**7**) with concentrated hydrochloric acid at reflux for 12 hours, to afford the (S)-2,3-diaminopropanoic acid hydrochloride (**8**). [9]

Following the same approach (R)-2,3-diaminopropanoic acid has been synthesised from imidazolidin-2-one (**4a**).

Furthermore it is noteworthy that iodocyclisation of the tosylurea (**2d**), obtained from the secondary homoallylic amine (**1d**), proceeds with high 1,3-asymmetric induction, due to the directing effect of the methyl group (**Scheme 3**). In fact the cyclisation of racemic (**2d**) occurs with total stereospecifity and leads to the two diastereoisomers where a 4,6-trans relationship takes place. [10] The analysis of the coupling constants of the ring hydrogens shows that the methyl substituent at C-4 is in the axial position, while the iodomethyl substituent of the newly formed stereogenic centre C-6 lies in the equatorial position. This conformation is the most stable for this kind of heterocycles, in agreement with the data previously reported. [11]



Scheme 3. i) $TolSO_2$-NCO, r.t.; ii) I_2 in THF/$NaHCO_3$ acqueous solution, silica gel chromatography.

Thus we have shown a new inexpensive method for the synthesis of chiral imidazolidin-2-ones and tetrahydropyrimidin-2-ones under mild conditions and in good yield. Furthermore the cyclisation of secondary ureas is diastereoselective, owing to the presence of a directing group in the tether.

The easy transformation of chiral imidazolidin-2-ones into both enantiomerically pure (R)- and (S)-2,3-diaminopropanoic acid has been also devised.

EXPERIMENTAL SECTION

Infrared spectra were recorded with a Perkin-Elmer 682 infrared spectrometer. Proton magnetic resonance (^{1}H NMR) spectra were recorded at 90 MHz on a Varian EM 390, at 200 MHz on a Varian Gemini 200 and at 300 MHz on a Varian Gemini 300. Carbon magnetic resonance (^{13}C NMR) spectra were determined at 75 MHz on a Varian Gemini 300. Melting points (Pirex capillary) were measured on a Buchi 510 hot stage apparatus and are uncorrected. Optical rotations were determined using a Perkin-Elmer 241 polarimeter. All reagents and solvents were purified and dried when required using standard methods.

(S)-N-(1-Phenyleth-1-yl)-N-(prop-2-en-1-yl)-amine (1a)

A mixture of (S)-1-phenylethylamine (30 mmol, 3.63 g) and allyl bromide (30 mmol, 3.63 g) was mechanically stirred at room temperature for 20 minutes. Then NaOH 1M was added and the solution was extracted twice with ethyl acetate. The organic layer was dried over Na_2SO_4 and concentrated under vacuum. The amine (**1a**) was obtained in 60% yield as a pale yellow oil; ν_{max} (film) 3300 (NH) cm^{-1}; δ_H (90 MHz) ($CDCl_3$) 1.33 (d, 3H, J = 6 Hz), 1.70 (bs, 1H, NH), 3.11 (m, 2H), 3.78 (q, 1H, J = 6 Hz), 5.10 (m, 2H), 5.82 (m, 1H), 7.25 (m, 5H). (Found: C, 81.68; H, 9.29; N, 8.57. Calcd. for $C_{11}H_{15}N$ C, 81.94; H, 9.38; N, 8.69).

(S)-N-(1-Phenyleth-1-yl)-N-[(E)-hex-2-en-1-yl]-amine (1b)

To a stirred solution of (E)-hex-2-en-1-ol (25 mmol, 2.50 g) and triethylamine (37.5 mmol, 5.22 ml) in dry CH_2Cl_2 (50 ml) was added dropwise mesyl chloride (30 mmol, 3.44 g) at 0 °C. After 1 hour at room temperature, the mixture was washed with water and the organic layer was dried and concentrated under vacuum. The crude mesyl derivative was transformed into the amine (**1b**) simply by stirring it with (S)-phenylethylamine (25 mmol, 3.03 g) at room temperature for 1 hour. Then NaOH 1M was added and the mixture was extracted with CH_2Cl_2. After the usual work-up the amine (**1b**) was obtained in 80% yield; ν_{max} (film) 3300 (NH) cm^{-1}; δ_H (90 MHz) ($CDCl_3$) 0.90 (t, 3H), 1.40 (m, 2H), 1.45 (d, 3H), 2.11 (m, 2H), 2.50 (bs, 1H, NH), 3.32 (m, 2H), 3.80 (q, 1H), 5.60 (m, 1H), 6.05 (m, 1H), 7.30 (m, 5H). (Found: C, 82.59; H, 10.38; N, 6.79. Calcd. for $C_{14}H_{21}N$ C, 82.70; H, 10.41; N, 6.89).

(S)-N-(1-Phenyleth-1-yl)-N-[(Z)-hex-2-en-1-yl]-amine (1c)

Same procedure as for (**1b**); 75% yield; ν_{max} (film) 3300 (NH) cm^{-1}; δ_H (90 MHz) ($CDCl_3$) 0.85 (t, 3H), 1.40 (m, 2H), 1.45 (d, 3H, J = 6 Hz), 1.92 (m, 2H), 3.05 (bs, 1H, NH), 3.20 (m, 2H), 3.85 (q, 1H), 5.50

(m, 2H), 7.30 (m, 5H). (Found: C, 82.66; H, 10.31; N, 6.66. Calcd. for $C_{14}H_{21}N$ C, 82.70; H, 10.41; N, 6.89).

(1S,2S,R)-N-(1-Phenyleth-1-yl)-N-(pent-4-en-2-yl)-amine (1d)

Same procedure as for **(1b)**; a 1:1 mixture of diastereoisomer was obtained in 74% yield; ν_{max} (film) 3300 (NH) cm^{-1}; δ_H (90 MHz) ($CDCl_3$) (mixture of diastereoisomers) 0.95 and 1.05 (d, 3H), 1.32 (d, 3H), 1.75 (bs, 1H, NH), 2.15 (m, 2H), 2.60 (m, 1H), 3.90 (q, 1H), 5.05 (m, 2H), 5.70 (m, 1H), 7.30 (m, 5H). (Found: C, 82.29; H, 10.03; N, 7.12. Calcd. for $C_{13}H_{19}N$ C, 82.48; H, 10.12; N, 7.40).

General procedure for tosylureas (2)

To the amine **(1)** (20 mmol) p-toluenesulfonyl isocyanate (20 mmol, 3.94 g) was added dropwise at 0 °C and the mixture was mechanically stirred for 1 hour at room temperature. The tosylurea **(2)** was obtained in good yield and used without further purifications.

(S)-N-(1-Phenyleth-1-yl)-N-(prop-2-en-1-yl)-N'-tosylurea (2a)

Quantitative yield; ν_{max} (film) 3300 (NH), 1680 (CO) cm^{-1}; δ_H (200 MHz) ($CDCl_3$) 1.48 (d, 3H, J = 6 Hz), 2.35 (s, 3H), 3.65 (ABX, 2H), 5.25 (m, 2H), 5.65 (m, 2H), 7.32 (m, 8H), 7.95 (d, 2H). (Found: C, 63.60; H, 6.05; N, 7.65. Calcd. for $C_{19}H_{22}N_2SO_3$ C, 63.66; H, 6.19; N, 7.81).

(S)-N-(1-Phenyleth-1-yl)-N-[(E)-hex-2-en-1-yl]-N'-tosylurea (2b)

Quantitative yield; ν_{max} (film) 3300 (NH), 1680 (CO) cm^{-1}; δ_H (90 MHz) ($CDCl_3$) 0.98 (t, 3H), 1.40 (m, 2H), 1.43 (d, 3H), 1.98 (q, 2H), 2.40 (s, 3H), 3.54 (m, 2H), 4.90 (q, 1H), 5.18 (m, 1H), 5.80 (m, 1H), 6.85 (d, 1H), 7.25 (m, 7H), 7.70 (d, 2H). (Found: C, 65.90; H, 6.93; N, 6.81. Calcd. for $C_{22}H_{28}N_2SO_3$ C, 65.97; H, 7.05; N, 6.99).

(S)-N-(1-Phenyleth-1-yl)-N-[(Z)-hex-2-en-1-yl]-N'-tosylurea (2c)

95% yield; ν_{max} (film) 3300 (NH), 1680 (CO) cm^{-1}; δ_H (90 MHz) ($CDCl_3$) 0.95 (t, 3H), 1.40 (m, 2H), 1.43 (d, 3H), 1.95 (m, 2H), 2.43 (s, 3H), 3.45 (m, 2H), 4.85 (q, 1H), 5.40 (m, 2H), 6.90 (d, 1H), 7.25 (m, 7H), 7.70 (d, 2H). (Found: C, 65.80; H, 6.87; N, 6.87. Calcd. for $C_{22}H_{28}N_2SO_3$ C, 65.97; H, 7.05; N, 6.99).

(1S,2S,R)-N-(1-Phenyleth-1-yl)-N-(pent-4-en-2-yl)-N'-tosylurea (2d)

97% yield; ν_{max} (film) 3300 (NH), 1685 (CO) cm^{-1}; δ_H (200 MHz) ($CDCl_3$) (mixture of diastereoisomers) 1.10 and 1.30 (d, 3H), 1.70 (d, 3H), 2.32 (m, 2H), 2.45 (s, 3H), 4.10 (m, 1H), 4.95 (m, 3H), 5.60 (m, 2H), 7.31 (m, 7H), 7.80 (d, 2H). (Found: C, 65.13; H, 6.65; N, 7.35. Calcd. for $C_{21}H_{26}N_2SO_3$ C, 65.26; H, 6.78; N, 7.25).

General procedure of cyclisation

To a stirred solution of tosylurea **(2)** (10 mmol) in THF (10 ml) and $NaHCO_3$ (aqueous saturated solution, 10 ml) was added I_2 (20 mmol, 5.0 g) in THF (15 ml). The mixture was stirred for 1 hour, then an aqueous saturated solution of $Na_2S_2O_3$ (50 ml) was added and the mixture was extracted twice with ethyl acetate. The

organic layer was dried over Na_2SO_4 and concentrated and the crude was chromatographed on silica gel (cyclohexane: ethyl acetate in different ratios). The heterocycles **(3)** and **(4)** were obtained as yellow oils in good yields.

1-Tosyl-3-(1'-phenyleth-1'-yl)-5-iodomethylimidazolidin-2-ones (3a) and (4a)
Overall yield 92%; diastereoisomeric ratio 1:1.
(1'S,5S)-(3a): ν_{max} (film) 1730 (CO) cm^{-1}; δ_H (300 MHz) ($CDCl_3$) 1.52 (d, 3H, J = 7.1 Hz), 2.48 (s, 3H), 3.11 (m, 2H, CH_2I), 3.49 (dd, 1H, H_b, J_{BC} = 7.6 Hz, J_{AB} = 10.3 Hz), 3.59 (dd, 1H, H_a, J_{AC} = 2.8 Hz, J_{AB} = 10.3 Hz), 4.22 (m, 1H, H_c), 5.23 (q, 1H, J = 7.1 Hz), 7.31 (m, 7H), 7.98 (d, 2H, J = 8.3 Hz); δ_C ($CDCl_3$) 153.65, 145.45, 139.18, 136.26, 130.12, 129.17, 128.82, 128.40, 127.46, 53.44, 50.58, 44.58, 21.82, 16.10, 10.61; $[\alpha]_D$ = -140.2° (c = 0.4 in $CHCl_3$). (Found: C, 47.02; H, 4.21; N, 5.66. Calcd. for $C_{19}H_{21}N_2SO_3I$ C, 47.12; H, 4.37; N, 5.78).
(1'S,5R)-(4a): ν_{max} (film) 1730 (CO) cm^{-1}; δ_H (300 MHz) ($CDCl_3$) 1.48 (d, 3H, J = 7.1 Hz), 2.45 (s, 3H), 2.79 (dd, 1H, H_b, J_{BC} = 4.4 Hz, J_{AB} = 9.8 Hz), 3.27 (dd, 1H, H_a, J_{AC} = 8.4 Hz, J_{AB} = 9.8 Hz), 3.54 (m, 2H, CH_2I), 4.30 (m, 1H, H_c), 5.19 (q, 1H, J = 7.1 Hz), 7.31 (m, 7H), 7.97 (d, 2H, J = 8.3 Hz); δ_C ($CDCl_3$) 153.63, 145.60, 139.41, 136.39, 130.26, 129.30, 128.91, 128.61, 127.78, 53.96, 51.07, 44.88, 21.93, 16.09, 9.87; $[\alpha]_D$ = +15.3° (c = 0.4 in $CHCl_3$). (Found: C, 47.01; H, 4.20; N, 5.60. Calcd. for $C_{19}H_{21}N_2SO_3I$ C, 47.12; H, 4.37; N, 5.78).

1-Tosyl-3-(1'-phenyleth-1'-yl)-5-(1"-iodoprop-1"-yl)-imidazolidin-2-ones (3b) and (4b)
Overall yield 94%; diastereoisomeric ratio 1:1.
(1'S,1"S,5S)-(3b): ν_{max} (film) 1725 (CO) cm^{-1}; δ_H (300 MHz) ($CDCl_3$) 0.92 (t, 3H), 1.52 (d, 3H, J = 7.1 Hz), 1.62 (m, 4H), 2.41 (s, 3H), 3.00 (dd, 1H, H_b, J_{AB} = J_{BC} = 9.4 Hz), 3.14 (dd, 1H, H_a, J_{AC} = 4.4 Hz, J_{AB} = 9.4 Hz), 3.70 (ddd, 1H, H_c, J = 2.8 Hz, J_{AC} = 4.4 Hz, J_{BC} = 9.4 Hz), 4.75 (ddd, 1H, CHI, J = 2.8 Hz, J = 4.6 Hz, J = 9.8 Hz), 5.23 (q, 1H, J = 7.1 Hz), 7.28 (m, 7H), 7.96 (d, 2H); δ_C ($CDCl_3$) 153.58, 145.28, 139.28, 136.52, 129.98, 129.17, 128.99, 128.36, 127.58, 56.80, 50.62, 43.63, 42.62, 37.58, 22.88, 21.80, 15.82, 13.42; $[\alpha]_D$ = -48.8° (c = 0.1 in $CHCl_3$). (Found: C, 50.02; H, 5.01; N, 5.45. Calcd. for $C_{22}H_{27}N_2SO_3I$ C, 50.20; H, 5.17; N, 5.32).
(1'S,1"R,5R)-(4b): ν_{max} (film) 1725 cm^{-1}; δ_H (300 MHz) ($CDCl_3$) 0.92 (t, 3H), 1.50 (d, 3H, J = 7.1 Hz), 1.58 (m, 4H), 2.47 (s, 3H), 2.85 (dd, 1H, H_b, J_{BC} = 4.8 Hz, J_{AB} = 9.6 Hz), 3.42 (t, 1H, H_a, J_{AB} = J_{AC} = 9.6 Hz), 3.81 (ddd, 1H, H_c, J = 2.9 Hz, J_{BC} = 4.8 Hz, J_{AC} = 9.6 Hz), 4.73 (m, 1H, CHI), 5.23 (q, 1H, J = 7.1 Hz), 7.32 (m, 7H), 8.00 (d, 2H); δ_C ($CDCl_3$) 153.81, 145.48, 139.09, 136.72, 130.18, 129.22, 129.18, 128.62, 128.38, 57.25, 51.16, 43.12, 41.99, 37.58, 23.05, 22.02, 16.12, 13.40; $[\alpha]_D$ = -53.3° (c = 0.1 in $CHCl_3$). (Found: C, 49.96; H, 5.10; N, 5.20. Calcd. for $C_{22}H_{27}N_2SO_3I$ C, 50.20; H, 5.17; N, 5.32).

1-Tosyl-3-(1'-phenyleth-1'-yl)-5-(1"-iodoprop-1"-yl)-imidazolidin-2-ones (3c) and (4c)
Overall yield 90%; diastereoisomeric ratio 2:1.
(1'S,1"R,5S)-(3c): ν_{max} (film) 1730 cm^{-1}; δ_H (300 MHz) ($CDCl_3$) 0.85 (t, 3H), 1.22 (m, 2H), 1.37 - 1.70 (m, 2H), 1.52 (d, 3H, J = 7.1 Hz), 2.47 (s, 3H), 3.06 (dd, 1H, H_b, J_{AB} = J_{BC} = 9.9 Hz), 3.31 (dd, 1H, H_a, J_{AC} = 3.4 Hz, J_{AB} = 9.9 Hz), 4.58 (dt, 1H, CHI, J = 3.4 Hz, J = 10.2 Hz), 4.65 (dt, 1H, H_c, J_{AC} = J_{CD} =

3.4 Hz, J_{BC} = 9.9 Hz), 5.25 (q, 1H, J = 7.1 Hz), 7.14 (m, 2H), 7.27 (m, 3H), 7.35 (d, 2H, J = 8.1 Hz), 7.95 (d, 2H, J = 8.1 Hz); δ_C ($CDCl_3$) 154.40, 145.57, 139.04, 136.57, 130.28, 129.29, 128.60, 128.55, 127.55, 58.88, 50.71, 41.49, 37.53, 32.39, 23.19, 21.88. 16.21, 13.25; $[\alpha]_D$ = -150.0° (c = 0.1 in $CHCl_3$). (Found: C, 50.12; H, 5.35; N, 5.29. Calcd. for $C_{22}H_{27}N_2SO_3I$ C, 50.20; H, 5.17; N, 5.32).

(1'S,1"S,5R)-(4c): ν_{max} (film) 1730 (CO) cm^{-1}; δ_H (300 MHz) ($CDCl_3$) 0.67 (t, 3H), 1.02 (m, 2H), 1.38 - 1.80 (m, 2H), 1.49 (d, 3H, J = 7.2 Hz), 2.45 (s, 3H), 3.01 (dd, 1H, H_b, J_{BC} = 3.4 Hz, J_{AB} = 9.9 Hz), 3.49 (dd, 1H, H_a, J_{AB} = J_{AC} = 9.9 Hz), 4.48 (dt, 1H, CHI, J = 3.4 Hz, J = 13.2 Hz), 4.73 (dt, 1H, H_c, J_{AC} = J_{CD} = 3.4 Hz, J_{BC} = 9.9 Hz), 5.24 (q, 1H, J = 7.2 Hz), 7.30 (m, 7H), 7.95 (d, 2H); δ_C ($CDCl_3$) 153.94, 145.57, 139.39, 136.67, 130.29, 129.26, 128.76, 128.59, 127.77, 58.89, 50.89, 41.30, 37.49, 32.03, 27.13, 23.02, 21.88, 15.38, 13.16; $[\alpha]_D$ = +16.1° (c = 0.1 in $CHCl_3$). (Found: C, 49.81; H, 5.25; N, 5.41. Calcd. for $C_{22}H_{27}N_2SO_3I$ C, 50.20; H, 5.17; N, 5.32).

1-Tosyl-3-(1'-phenyleth-1'-yl)-4-methyl-6-iodomethyltetrahydro-2(1H)-pyrimidin-2-ones (3d) and (4d)

Overall yield 90%.

(1'S,4R,6S)-(3d): ν_{max} (film) 1705 cm^{-1}; δ_H (200 MHz) ($CDCl_3$) 0.59 (d, 3H, J = 6.8 Hz), 1.55 (d, 3H, J = 7.1 Hz), 1.68 (ddd, 1H, J = 2.2 Hz, J = 5.1 Hz, J_{gem} = 13.3 Hz), 2.24 (ddd, 1H, J = 2.6 Hz, J = 5.1 Hz, J_{gem} = 13.3 Hz), 2.41 (s, 3H), 2.87 (dd, 1H, HCHI, J_{gem} = J = 9.7 Hz), 3.31 (dd, 1H, HCHI, J = 4.4 Hz, J_{gem} = 9.7 Hz), 3.52 (ddq, 1H, H_a, J = 2.6 Hz, J = 5.1 Hz, J = 6.8 Hz), 4.51 (dddd, J = 4.4 Hz, J = 5.1 Hz, J = 5.1 Hz, J = 9.7 Hz, 1H, H_b), 5.98 (q, 1H, J = 7.1 Hz), 7.25 (d, 2H), 7.38 (m, 5H), 7.83 (d, 2H); δ_C ($CDCl_3$) 154.53, 142.29, 141.77, 138.69, 129.47, 129.14, 128.89, 128.69, 127.24, 75.66, 55.89, 45.30, 35.17, 21.55, 19.57, 15.41, 4.59; [a]$_D$ = -104.26° (c = 0.5 in $CHCl_3$). (Found: C, 49.15; H, 4.81; N, 5.29. Calcd. for $C_{21}H_{25}N_2SO_3I$ C, 49.23; H, 4.92; N, 5.47).

(1'S,4S,6R)-(4d): ν_{max} (film) 1705 cm^{-1}; δ_H (300 MHz) ($CDCl_3$) 1.28 (d, 3H, J = 6.8 Hz), 1.30 (m, 1H), 1.62 (d, 3H, J = 7.1 Hz), 2.06 (ddd, 1H, J = 2.2 Hz, J = 4.1 Hz, J_{gem} = 13.6 Hz), 2.41 (s, 3H), 2.90 (dd, 1H, HCHI, J_{gem} = J = 10.1 Hz), 3.31 (m, 2H, HCHI and H_a), 4.52 (m, 1H, H_b), 6.01 (q, 1H, J = 7.1 Hz), 7.31 (m, 7H), 7.84 (d, 2H); δ_C ($CDCl_3$) 154.86, 142.32, 141.76, 138.95, 129.47, 129.32, 128.89, 127.71, 127.28, 75.60, 55.86, 44.87, 34.72, 21.56, 20.74, 16.70, 4.94; $[\alpha]_D$ = -23.7° (c = 0.4 in $CHCl_3$). (Found: C, 49.30; H, 4.75; N, 5.57. Calcd. for $C_{21}H_{25}N_2SO_3I$ C, 49.23; H, 4.92; N, 5.47).

(1'S,5S)-1-Tosyl-3-(1'-phenyleth-1'-yl)-5-hydroxymethylimidazolidin-2-one (5)

A stirred solution of imidazolidin-2-one (**3a**) (7 mmol, 3.39 g) and silver acetate (7.7 mmol, 1.28 g) in acetic acid (20 ml) was refluxed for 5 hours. After cooling down, the solution was separated from silver iodide by filtration and concentrated. Then ethyl acetate (50 ml) was added and the mixture was washed twice with a saturated solution of $NaHCO_3$, dried and concentrated. A waxy solid was obtained (2.75 g). The IR spectra of the crude showed a band at 1740 cm^{-1}, typical of the acetoxy derivative that was directly hydrolised by stirring a solution of the waxy solid in dry ethanol (20 ml) with K_2CO_3 (8 mmol, 1.11 g) at room temperature for 5 hours. After filtration the mixture was concentrated and the residue was chromatographed on silica gel (cyclohexane:ethyl acetate 1:1 as eluent). The alcohol (**5**) was obtained as a low melting solid in 80% overall yield (2.09 g); ν_{max} (film) 3400 (OH), 1730 (CO) cm^{-1}; δ_H (300 MHz) ($CDCl_3$) 1.49 (d, 3H, J = 7.2 Hz),

2.46 (s, 3H), 2.74 (bs, 1H, OH), 3.01 (dd, 1H, H_b, $J_{AB} = J_{BC} = 9.3$ Hz), 3.30 (dd, 1H, H_a, $J_{AC} = 4.4$ Hz, $J_{AB} = 9.3$ Hz), 3.81 (m, 1H), 3.92 (m, 1H), 4.19 (m, 1H, H_c), 5.19 (q, 1H, J = 7.2 Hz), 7.08 (m, 2H), 7.25 (m, 3H), 7.31 (d, 2H), 7.93 (d, 2H); δ_C ($CDCl_3$) 154.48, 145.58, 139.64, 136.41, 130.43, 129.29, 128.80, 128.46, 127.62, 64.53, 55.69, 50.77, 40.70, 22.02, 16.36; $[\alpha]_D = -165.1°$ (c = 0.7 in $CHCl_3$). (Found: C, 60.58; H, 5.63; N, 7.32. Calcd. for $C_{19}H_{22}N_2SO_4$ C, 60.94; H, 5.92; N, 7.48).

(1'S,5S)-1-Tosyl-3-(1'-phenyleth-1'-yl)-5-carboxyimidazolidin-2-one (6)

To a stirred solution of hydroxymethylimidazolidin-2-one (**5**) (5 mmol, 1.87 g) in dry acetone (40 ml) was added dropwise a solution of CrO_3 in concentrated H_2SO_4 (3.5 ml of 8N solution) at O °C. The mixture was stirred at room temperature for 5 hours and then filtrated and concentrated. Sodium hydroxide 1M (20 ml) was added and the mixture was extracted with CH_2Cl_2 to recover some starting material (350 mg). The water layer was acidified with 6M HCl and extracted twice with CH_2Cl_2. The acid (**6**) was obtained pure as a waxy solid in 60% yield (1.16 g) without further purifications; ν_{max} (film) 3150 (OH), 1730 (CO) cm^{-1}; δ_H (300 MHz) ($CDCl_3$) 1.46 (d, 3H, J = 7.1 Hz), 2.43 (s, 3H), 3.33 (dd, 1H, H_b, $J_{AB} = J_{BC} = 9.7$ Hz), 3.41 (dd, 1H, H_a, $J_{AC} = 5.1$ Hz, $J_{AB} = 9.7$ Hz), 4.79 (dd, 1H, H_c, $J_{AC} = 5.1$ Hz, $J_{BC} = 9.7$ Hz), 5.21 (q, 1H, J = 7.1 Hz), 7.23 (d, 2H), 7.31 (m, 5H), 8.01 (d, 2H), 9.22 (bs, 1H, OH); δ_C ($CDCl_3$) 173.23, 153.03, 145.15, 138.44, 135.39, 129.46, 128.93, 128.86, 128.13, 127.14, 53.83, 50.58, 41.13, 21.34, 15.74. (Found: C, 58.59; H, 5.06; N, 7.02. Calcd. for $C_{19}H_{20}N_2SO_5$ C, 58.75; H, 5.19; N, 7.21).

(1'S,4S)-1-(1'-Phenyleth-1'-yl)-4-methoxycarbonylimidazolidin-2-one (7)

A solution of lithium metal (80 mmol, 5.55 g) in anhydrous ammonia (100 ml) was stirred at -60 °C for 1 hour, then a solution of imidazolidin-2-one (**6**) (3 mmol, 1.16 g) in dry THF (20 ml) and t-BuOH (2 ml) was added all at once. After 5 minutes the reaction was quenched by addition of solid NH_4Cl (90 mmol, 4.81 g), the ammonia was allowed to evaporate and the volatile were removed under vacuum. Then ethyl acetate (50 ml) was added and the mixture was washed with 1M HCl (50 ml). The organic layer was separated, dried and concentrated and the acid was transformed into its methyl ester.

A solution of $SOCl_2$ (12 mmol, 0.85 ml) in dry MeOH (5 ml) was stirred at -10 °C for 30 minutes, then the acid was added and the mixture was stirred at room temperature for 2 additional hours. The solvent was evaporated and the ester (**7**) was obtained pure in 65% overall yield (0.48 g) after silica gel chromatography (cyclohexane:ethyl acetate 8:2 as eluent); ν_{max} (film) 1730 (CO ester), 1690 (cyclic CO) cm^{-1}; δ_H (200 MHz) ($CDCl_3$) 1.50 (d, 3H, J = 7.2 Hz), 3.25 (dd, 1H, H_b, $J_{AB} = J_{BC} = 9.2$ Hz), 3.52 (dd, 1H, H_a, $J_{AC} = 4.7$ Hz, $J_{AB} = 9.2$ Hz), 3.76 (s, 3H), 4.12 (dd, 1H, H_c, $J_{AC} = 4.7$ Hz, $J_{BC} = 9.2$ Hz), 5.26 (q, 1H, J = 7.2 Hz), 6.05 (bs, 1H, NH), 7.31 (m, 5H); δ_C ($CDCl_3$) 175.08, 162.41, 140.21, 129.13, 128.17, 127.57, 51.82, 50.15, 43.08, 31.05, 16.47; $[\alpha]_D = -28.9°$ (c = 0.5 in $CHCl_3$). (Found: C, 62.65; H, 6.31; N, 11.02. Calcd. for $C_{13}H_{16}N_2O_3$ C, 62.89; H, 6.50; N, 11.28).

(S)-2,3-Diaminopropanoic acid hydrochloride (8)

A stirred solution of imidazolidin-2-one (**7**) (1.5 mmol, 0.37 g), in MeOH (1 ml) and concentrated HCl (5 ml) was refluxed for 12 hours. After evaporation of the solvent, the product was crystalised from water/ethanol and obtained pure in 85% yield (133 mg); m.p. 234-235 °C; ν_{max} (film) 3140 (NH), 1610 (CO) cm^{-1}; δ_H (300

MHz) (D_2O) 3.29 (d, 2H, J = 7.2 Hz), 3.85 (t, 1H, J = 7.2 Hz); δ_C (D_2O) 171.11, 49.89, 38.38; $[\alpha]_D$ +25.0° (c = 0.5 in 1N HCl). [9]

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