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Homochiral oxazolidin-2-ones and imidazolidin-2-ones by tandem nucleophilic addition–conjugate addition

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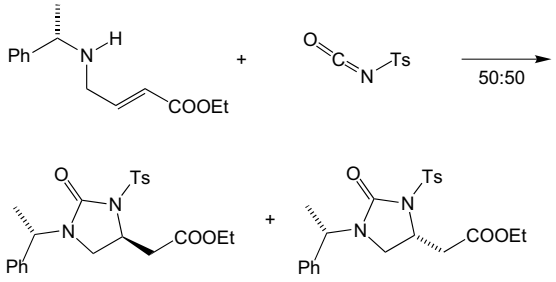
Abstract—Treatment of both primary alcohols **1a**,**b** and secondary amines **1c**,**d**, tethered to a Michael acceptor with (*R*)-phenylethyl isocyanate in the presence of DBU gave in good yield and high stereoselection diastereomeric mixtures of oxazolidin-2-ones **2a**,**b** and **3a**,**b** and imidazolidin-2-ones **2c**,**d** and **3c**,**d**, respectively. The cyclisation reaction was studied computationally by ab initio quantum mechanical methods. The observed stereoselectivity was explained on the basis of the different stability of both anions and transition states leading to **2a** and **3a**, respectively. The usefulness of the method was proven by conversion of **2a** into the enantiomerically pure bioactive amino acid **5**.

1. Introduction

In connection with our studies aimed at synthesising both nonproteinogenic amino acids and peptidomimetics in enantiomerically pure form, we focused on the preparation of polyfunctionalised compounds by means of conjugate addition reactions.[1–3] A nonstereoselective approach to chiral imidazolidin-2-ones starting from ethyl (*E*,*S*)-4-phenylethyl-2-butenoate and tosyl isocyanate has already been reported, the success of this procedure relying upon the easy separation of the equimolar mixture of the diastereomeric intermediates (Scheme 1).[4]



Scheme 1.

2. Results and discussion

As an extension of our interest in this field,[5,6] we planned to investigate if a chiral group lying on the isocyanate nitrogen atom involved in the cyclisation could induce a stereoselective ring closure. In first place, γ-hydroxyester **1a** and γ-hydroxy sulfone **1b** were treated with (*R*)-1-phenylethyl isocyanate in acetonitrile at rt in the presence of a catalytic amount of DBU (Scheme 2). Under these conditions, a tandem sequence takes place, involving the initial nucleophilic addition of the hydroxy group to (*R*)-phenylethyl isocyanate, followed by *N*-Michael conjugate addition to the activated double bond, to give in good yield diastereomeric mixtures of the corresponding oxazolidin-2-ones **2a**,**b** and **3a**,**b**. The intermediate carbamates could not be isolated, since an immediate cyclisation occurred leading to the formation of the heterocyclic compounds. The reaction proceeded with good stereoselectivity, and the highest asymmetric

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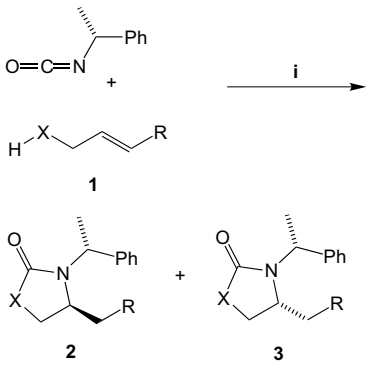


Scheme 2. Reagents and conditions: (i) DBU, CH_3CN, rt, then 40 °C for 2 h; (a) X = O, R = COOBn, 78%, dr 85:15; (b) X = O, R = SO_2Ph, 76%, dr 70:30; (c) X = Bn–N, R = COOEt, 74%, dr 80:20; (d) X = PMB–N, R = COOEt, 69%, dr 80:20.

induction was observed for the formation of oxazolidin-2-ones **2a**,**3a**. In addition, the diastereomeric mixtures of oxazolidin-2-ones were easily separated by silica gel chromatography, to give pure isolated compounds.

The configuration of the newly introduced stereogenic centre was assigned by comparison of ^1H NMR spectra of each diastereoisomer, after calculation of the minimum energy conformations, which are reported in Figures 1 and 2.

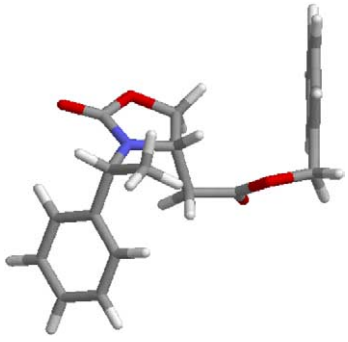


Figure 1. Lowest energy conformation of **2a**.

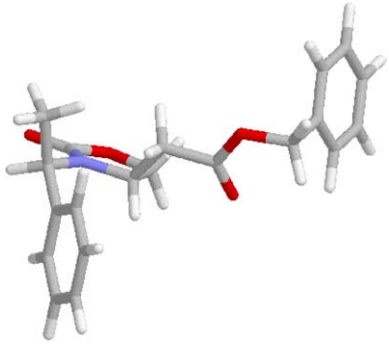


Figure 2. One of significant populated minimum energy conformers of **3a**.

For this purpose, a full analysis of the conformational space of both **2a** and **3a** was carried out by means of Monte Carlo search by using AMBER* force field.[7–10]

In order to model the solvent effect to validate the data collected, the simulations were conducted both in vacuo and in $CHCl_3$, using the implicit solvation model GB/SA. In fact in the diastereomer **3a** a shielding effect of the phenyl group of the chiral auxiliary on the H-4 was observed, owing to the existence of a clearly preferential conformation where the hydrogen at C-1′ partially eclipses the carbonyl group of the heterocyclic intermediate, which is missing in **2a**. In addition, the signal of the methylene group of the acetyl moiety in **2a** is strongly shielded with respect to **3a**, thus confirming the structural assignment as (4*S*,1′*R*) for **2a** and (4*R*,1′*R*) for **3a**, the ^1H NMR data being in agreement with the geometry of the calculated lowest energy conformations reported in Figures 1 and 2.[11]

Moreover, the analysis of the computational data resulted that diastereomer **2a** (4*S*,1′*S*) is the thermodynamic product since it is more stable than the diastereomer **3a** (4*R*,1′*R*) by 0.49 and 0.69 kcal/mol in $CHCl_3$ and in vacuo, respectively. These differences in energy correspond to a population ratio of 70:30 in chloroform and 77:23 in vacuo at 293 K, according with the experimental results.

The lowest energy conformations for **2b** and **3b** were also calculated, and are reported in Figures 3 and 4. Since the trend observed in the ^1H NMR was the same as observed for **2a** and **3a**, their configurations were assigned as (4*S*,1′*R*) for **2b** and (4*R*,1′*R*) for **3b**.[11]

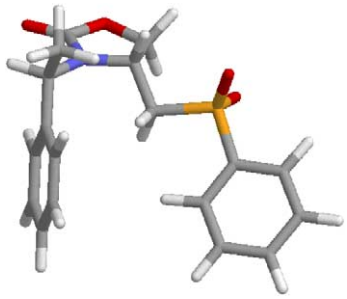


Figure 3. Lowest energy conformation of **2b**.

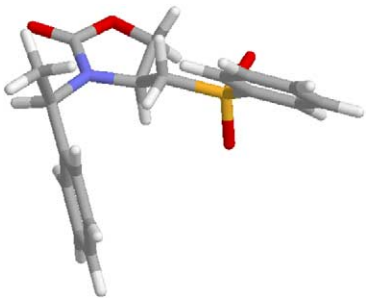


Figure 4. Minimum energy conformation of **3b**.

In analogy with compounds **2a**,**3a**, from the computational results the diastereomer (4*S*,1′*R*)-**2b** was identified as the thermodynamic product being more stable than the diastereomer (4*R*,1′*R*)-**3b** by 0.35 and 0.55 kcal/mol in $CHCl_3$ and in vacuo, respectively. These differences in

energy correspond to a population ratio of 65:35 in chloroform and 70.3:29.7 in vacuo at 293 K, again in agreement with the experimental results.

Moreover, with the aim to understand better the source of the stereoselectivity, a computational modeling study was carried out on the intermediate nitrogen anions, **A-1** and **A-2**, and the corresponding transition states **TS-1** and **TS-2**, leading to the oxazolidin-2-ones **2a** and **3a**, respectively. First a molecular dynamic (MD) conformational study was carried out on the nitrogen anions **A-1** and **A-2** in order to localise the lowest energy NACs (near attack conformers).[12] In fact the cyclisation pathway was studied ab initio optimising both anion conformers and transition structures.

The geometries of the NACs conformations for the nitrogen anion (reagents) were then fully optimised at RHF/6-31G* level of the theory and the energy calculated at DFT level by using the B3LYP/6-31G* basis set. The transition structures were localised on the PES and optimised at the same level of theory. The lowest energy conformers leading to both **TS-1** and **TS-2** (NACs) are very different in energy ($\Delta E = 2.07$ kcal/mol) (Table 1 and Fig. 5). Furthermore, the activation energy of the cyclisation leading to the thermodynamic product **2a** is lower than the energy of the cyclisation leading to compound **3a** ($\Delta E^{\#} = 1.32$ kcal/mol vs. $\Delta E^{\#} = 3.58$ kcal/mol, respectively), although both processes can be considered fast due to their low energy gap. Thus from the data collected the origin of the stereoselectivity must be ascribed mainly to the different stability of the NACs anion conformers as represented in Figure 5, which once formed lead quickly by ring closure to the most stable product (**2a** preferred over **3a**).

Table 1. Calculated energies of both the anions **A-1** and **A-2** and transition structures **TS-1** and **TS-2** for the model reaction at ab initio DFT level (B3LYP/6-31G*, au)

Structure	B3LYP/6-31G*//RHF/6-31G*
Anion A-1	−1129.8485
A-1···**TS-1**	−1129.8464
Anion A-2	−1129.8452
A-2···**TS-2**	−1129.8395

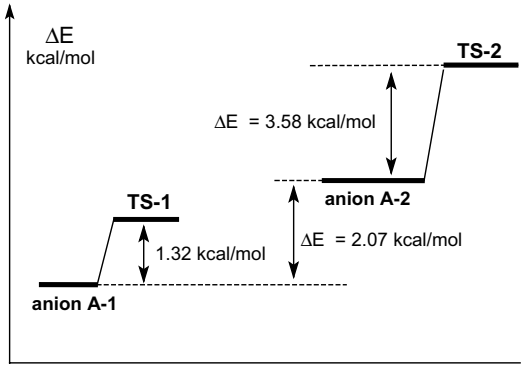


Figure 5. Anions and transitions states leading to **2a** and **3a**.

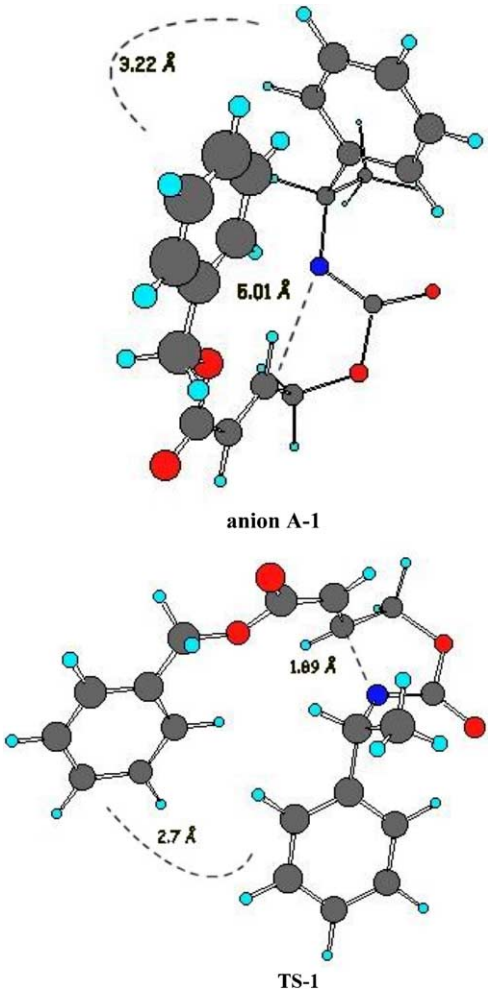


Figure 6. Structures of NAC conformer of **A-1** and related **TS-1**.

The major stability of anion **A-1** with respect to anion **A-2** can be ascribed to a particularly stabilising interaction between the phenyl groups, which lie orthogonally to each other, thus allowing a packed and ordered arrangement. This interaction is completely lacking in the conformer leading to **A-2** (Figs. 6 and 7).

The tandem process was carried out also starting from (*R*)-phenylethylisocyanate and γ-amino esters **1c** and **d**, with the aim of preparing enantiomerically pure imidazolidin-2-ones, which could be useful intermediates to chiral diamino acids. In fact imidazolidin-2-ones **2c** and **d** and **3c** and **d** were obtained in good yield and high stereoselectivity. However, the diastereomeric mixtures were hard to separate, but expedite configurational assignment of products **2c** and **d** and **3c** and **d** was carried out in analogy with **2a** and **b** and **3a** and **b**, since for each compound in both ^{1}H and ^{13}C spectra well definite line patterns could be observed.

Eventually, in order to test the usefulness of the above reported cyclisation, compound **2a** was treated with Li in liquid NH_3 at −78 °C. Under these conditions, both the phenylethyl and the benzyl groups were removed, to give the acid **4**, which underwent cleavage of the oxazolidin-2-one ring in refluxing 3 M NaOH, to give the

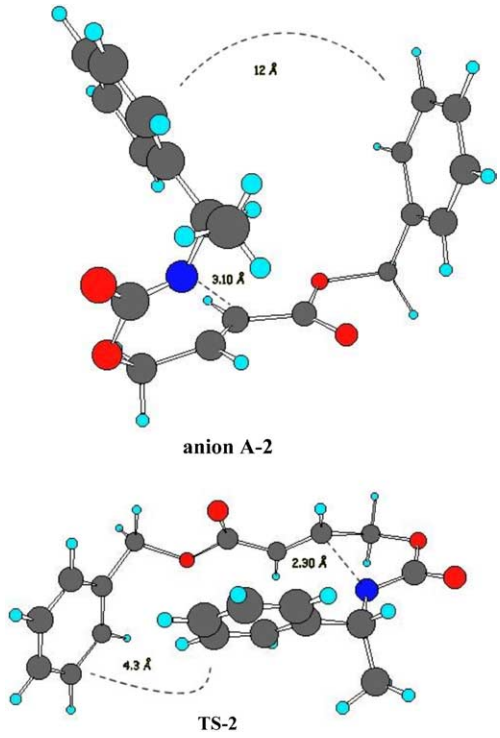
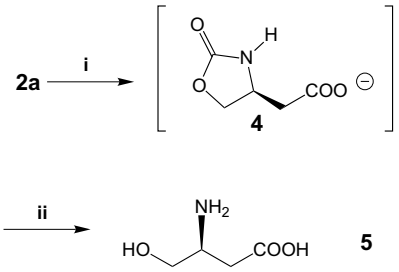


Figure 7. Structures of NAC conformer of **A-2** and related **TS-2**.



Scheme 3. Reagents and conditions: (i) Li, NH_3, −78 °C; (ii) 3 M NaOH at reflux, then Dowex 50WX2, 1 M NH_4OH as eluent.

amino acid **5** (GOBAB) after elution on a column of Dowex 50WX2 (Scheme 3).[13,14]

3. Experimental

3.1. General procedures

Melting points were measured on an Electrothermal IA 9000 apparatus and are uncorrected. IR spectra were recorded in $CHCl_3$ on a Nicolet Fourier Transform Infrared 20-SX spectrophotometer. Diastereomeric ratios (dr) were determined by GC analysis using a Chrompack 9001 instrument equipped with a Chrompack 7720 capillary column (50 m×0.25 mm i.d.; stationary phase CP-Sil-5 CB). ^1H and ^{13}C NMR spectra were recorded at 200 and 50 MHz, respectively, on a Varian Gemini 200 spectrometer, using $CDCl_3$ as a solvent unless otherwise reported. Chemical shifts (δ) are reported in ppm relative to TMS and coupling constants (J) in Hz. Assignments were aided by decoupling and homonuclear two-dimensional experiments. Optical rotations were measured on a Perkin Elmer 241 polarimeter. Mass spectra (MS) were obtained by electron impact on a Hewlett-Packard spectrometer 5890, series II. Column chromatography was performed with silica gel 60 (230–400 mesh).

3.2. Benzyl (*E*)-4-hydroxy-2-butenoate 1a

To a solution containing benzyl 3-butenoate (3.5 g; 20 mmol) in chloroform (100 mL) was added *m*-chloroperbenzoic acid (50%; 8.6 g; 25 mmol) and the mixture was refluxed for 5 h. The solvent was then evaporated under reduced pressure, the residue dissolved in ethyl acetate (100 mL) and the organic layer washed with saturated aq Na_2CO_3 (2×50 mL). After drying (Na_2SO_4) and removal of the solvent, the residue was dissolved in DCM (60 mL) and then DBU (0.2 mL) was added at rt. After 2 h, the organic phase was washed first with 1 M HCl (50 mL) and then with brine. After drying over Na_2SO_4 and removal of the solvent, the residue was purified by silica gel chromatography (cyclohexane–ethyl acetate 60:40) to give the ester **1a** in 78% yield. Colourless oil. IR ($CHCl_3$): 3350, 1698 cm^{-1}; ^1H NMR: 1.78 (br s, 1H, OH), 4.36 (dd, 2H, $J = 2.2$, $J = 3.9$), 5.20 (s, 2H), 6.16 (dt, 1H, $J = 2.2$, $J = 15.8$), 7.09 (dt, 1H, $J = 3.9$, $J = 15.8$), 7.29–7.42 (m, 5ArH); ^{13}C NMR: 62.3, 66.7, 120.3, 128.6, 128.7, 128.9, 129.0, 136.4, 148.0, 166.7; MS (EI): m/z 192 (M^+), 161, 101, 91, 77. Anal. Calcd for $C_{11}H_{12}O_3$: C, 68.74; H, 6.29. Found: C, 68.70; H, 6.25.

3.3. 3-Benzenesulfonyl-2-propen-1-ol 1b

Following the procedure above reported for compound **1a**, but starting from allylphenylsulfone, the title compound was obtained in 74% yield. White solid, mp 138–139 °C (lit.[15] 140–141 °C). IR ($CHCl_3$): 3350 cm^{-1}; ^1H NMR: 1.88 (br s, 1H, OH), 4.41 (m, 2H), 6.67 (dt, 1H, $J = 2.2$, $J = 14.9$), 7.07 (dt, 1H, $J = 3.3$, $J = 14.9$), 7.48–7.71 (m, 3ArH), 7.85–7.97 (m, 2ArH); ^{13}C NMR: 60.5, 127.8, 129.1, 129.7, 133.9, 140.4, 147.1; MS (EI): m/z 198 (M^+), 169, 125, 91. Anal. Calcd for $C_9H_{10}O_3S$: C, 54.53; H, 5.08. Found: C, 54.48; H, 5.04.

3.4. Ethyl (*E*)-4-benzylamino-2-butenoate 1c

According to the literature method,[16] the title compound was obtained in 59% yield. Colourless oil. IR ($CHCl_3$): 3347, 1704 cm^{-1}; ^1H NMR: 1.28 (t, 3H, $J = 7.0$), 1.51 (br s, 1H, NH), 3.42 (dd, 2H, $J = 1.8$, $J = 5.5$), 3.80 (s, 2H), 4.19 (q, 2H, $J = 7.0$), 6.02 (dt, 1H, $J = 1.8$, $J = 15.7$), 7.01 (dt, 1H, $J = 5.5$, $J = 15.7$), 7.22–7.36 (m, 5ArH); ^{13}C NMR: 14.7, 49.9, 53.7, 60.7, 122.0, 127.5, 128.5, 128.8, 128.9, 140.4, 147.2, 166.8; MS (EI): m/z 220 (M^++1), 205, 129, 105, 77. Anal. Calcd for

$C_{13}H_{17}NO_2$: C, 71.21; H, 7.81; N, 6.39. Found: C, 71.17; H, 7.76; N, 6.43.

3.5. Ethyl (*E*)-4-*p*-methoxybenzylamino-2-butenoate 1d

According to the literature method,[16] the title compound was obtained in 60% yield. Yellow oil. IR ($CHCl_3$): 3344, 1708 cm^{-1}; ^1H NMR: 1.28 (t, 3H, $J = 7.2$), 1.62 (br s, 1H, NH), 3.40 (dd, 2H, $J = 1.8$, $J = 5.5$), 3.73 (s, 2H), 3.79 (s, 3H), 4.19 (q, 2H, $J = 7.2$), 6.00 (dt, 1H, $J = 1.8$, $J = 15.8$), 6.86 (d, 2ArH, $J = 8.7$), 7.00 (dt, 1H, $J = 5.5$, $J = 15.8$), 7.23 (d, 2ArH, $J = 8.7$); ^{13}C NMR: 14.6, 49.8, 53.1, 55.6, 60.7, 114.2, 122.0, 129.7, 132.4, 147.2, 159.2, 166.8; MS (EI): m/z 250 (M^++1), 235, 234, 121, 113. Anal. Calcd for $C_{14}H_{19}NO_3$: C, 67.45; H, 7.68; N, 5.62. Found: C, 67.41; H, 7.65; N, 5.58.

3.6. Benzyl (4*S*,1′*R*)-[3-(1′-phenylethyl)-1,3-oxazolidin-2-on-4-yl]acetate 2a and benzyl (4*R*,1′*R*)-[3-(1′-phenylethyl)-1,3-oxazolidin-2-on-4-yl]acetate 3a

To a solution containing the hydroxy ester **1a** (1.0 g; 5 mmol) and DBU (0.2 mL) in acetonitrile (50 mL) (*R*)-phenylethylisocyanate (0.74 g; 5 mmol) was added at room temperature and subsequently the mixture was stirred at 40 °C for 2 h. After cooling, the solvent was removed under reduced pressure, the residue was dissolved in ethyl acetate (150 mL) and the organic layer was washed with 0.1 M HCl (50 mL) and then with H_2O (100 mL). After drying over Na_2SO_4, the solvent was removed under reduced pressure and the residue was purified by silica gel chromatography (cyclohexane–ethyl acetate 70:30) to give pure isolated **2a** and **3a** in 78% overall yield and 85:15 dr MS (EI): m/z 340 (M^+), 325, 235, 191, 105, 91, 77.

3.6.1. Benzyl (4*S*,1′*R*)-[3-(1′-phenylethyl)-1,3-oxazolidin-2-on-4-yl] acetate 2a. Colourless oil. IR ($CHCl_3$): 1750, 1744 cm^{-1}; ^1H NMR: 1.68 (d, 3H, $J = 7.3$), 2.12 (dd, 1H, $J = 9.0$, $J = 16.9$), 2.38 (dd, 1H, $J = 4.5$, $J = 16.9$), 3.97 (dd, 1H, $J = 5.2$, $J = 8.8$), 4.14–4.28 (m, 1H), 4.46 (dd, 1H, $J = 8.5$, $J = 8.8$), 5.02 (s, 2H), 5.15 (q, 1H, $J = 7.3$), 7.21–7.42 (m, 10ArH); ^{13}C NMR: 16.7, 38.8, 50.8, 52.0, 67.3, 68.5, 127.5, 128.5, 128.9, 129.0, 129.1, 129.2, 135.6, 141.2, 157.3, 170.3; $[\alpha]_D = +78.5$ (*c* 1, $CHCl_3$). Anal. Calcd for $C_{20}H_{22}NO_4$: C, 70.57; H, 6.51; N, 4.11. Found: C, 70.53; H, 6.55; N, 4.07.

3.6.2. Benzyl (4*R*,1′*R*)-[3-(1′-phenylethyl)-1,3-oxazolidin-2-on-4-yl] acetate 3a. Colourless oil. IR ($CHCl_3$): 1751, 1744 cm^{-1}; ^1H NMR: 1.65 (d, 3H, $J = 7.3$), 2.57 (dd, 1H, $J = 9.8$, $J = 16.6$), 2.78 (dd, 1H, $J = 3.7$, $J = 16.6$), 3.74–3.88 (m, 1H), 4.16 (dd, 1H, $J = 5.1$, $J = 9.0$), 4.36 (dd, 1H, $J = 8.8$, $J = 9.0$), 5.07 (s, 2H), 5.14 (q, 1H, $J = 7.3$), 7.24–7.43 (m, 10ArH); ^{13}C NMR: 19.1, 39.6, 51.5, 53.3, 67.4, 68.4, 127.5, 127.7, 128.5, 128.6, 128.7, 128.9, 129.1, 129.2, 129.4, 135.6, 139.4, 158.4, 170.1; $[\alpha]_D = +69.4$ (*c* 1, $CHCl_3$). Anal. Calcd for $C_{20}H_{22}NO_4$: C, 70.57; H, 6.51; N, 4.11. Found: C, 70.54; H, 6.47; N, 4.15.

3.7. (4*R*,1′*R*)-4-Benzenesulfonylmethyl-3-(1′-phenylethyl)-1,3-oxazolidin-2-one 2b and its (4*S*,1′*R*)-isomer 3b

Following the same procedure as for **2a** and **3a**, but starting from the hydroxysulfone **1b** (1.0 g; 5 mmol), pure isolated compounds **2b** and **3b** were obtained in 76% overall yield and 70:30 dr MS (EI): m/z 345 (M^+), 330, 204, 141, 105, 91, 77.

3.7.1. (4*R*,1′*R*)-Benzenesulfonylmethyl-3-(1′-phenylethyl)-1,3-oxazolidin-2-one 2b. White solid, mp: 55-57 °C. ^1H NMR: 1.53 (d, 3H, $J = 7.2$), 2.52 (dd, 1H, $J = 1.3$, $J = 14.1$), 2.81 (dd, 1H, $J = 10.2$, $J = 14.1$), 4.21–4.49 (m, 3H), 5.16 (q, 1H, $J = 7.2$), 7.21–7.41 (m, 5ArH), 7.52–7.65 (m, 2ArH), 7.66–7.75 (m, 3ArH); ^{13}C NMR: 16.5, 48.9, 52.1, 58.0, 68.4, 127.7, 128.2, 128.9, 129.5, 130.0, 134.9, 139.2, 140.3, 157.9; $[\alpha]_D = -67.1$ (*c* 0.5, CH_3OH). Anal. calcd for $C_{18}H_{19}NO_4S$: C, 62.59; H, 5.54; N, 4.06. Found: C, 62.55; H, 5.49; N, 4.02.

3.7.2. (4*S*,1′*R*)-4-Benzenesulfonylmethyl-3-(1′-phenylethyl)-1,3-oxazolidin-2-one 3b. White solid, mp: 66-68 °C. ^1H NMR: 1.57 (d, 3H, $J = 7.2$), 3.29 (dd, 1H, $J = 9.8$, $J = 14.0$), 3.37 (dd, 1H, $J = 3.3$, $J = 14.0$), 3.73–3.85 (m, 1H), 4.28–4.38 (m, 2H), 5.11 (q, 1H, $J = 7.2$), 7.12–7.21 (m, 3ArH), 7.24–7.32 (m, 3ArH), 7.51–7.62 (m, 2ArH), 7.66–7.78 (m, 2ArH); ^{13}C NMR: 19.1, 50.2, 53.5, 59.1, 68.0, 127.4, 127.6, 128.2, 128.8, 128.9, 129.3, 129.4, 130.2, 134.9, 138.6, 139.0, 157.9; $[\alpha]_D = +21.8$ (*c* 0.5, CH_3OH). Anal. Calcd for $C_{18}H_{19}NO_5S$: C, 62.59; H, 5.54; N, 4.06. Found: C, 62.55; H, 5.51; N, 4.09.

3.8. Ethyl (5*S*,1′*R*)-[3-benzyl-1-(1′-phenylethyl)imidazolidin-2-on-5-yl]acetate 2c and its (5*R*,1′*R*)-isomer 3c

Following the same procedure as for **2a** and **3a** but starting from the amino ester **1c** (1.0 g; 5.0 mmol), a mixture of compounds **2c** and **3c** very difficult to separate was obtained in 74% overall yield and 80:20 dr, which gave however definite patterns in ^1H and ^{13}C NMR spectra. MS (EI): m/z 366 (M^+), 351, 260, 155, 105, 91. Anal. Calcd for $C_{22}H_{26}N_2O_3$: C, 72.11; H, 7.15; N, 7.64. Found: C, 72.14; H, 7.11; N, 7.60.

3.8.1. Ethyl (5*S*,1′*R*)-[3-benzyl-1-(1′-phenylethyl)-imidazolidin-2-on-5-yl]acetate 2c. Colourless oil. IR ($CHCl_3$): 1744, 1657 cm^{-1}. ^1H NMR: 1.13 (t, 3H, $J = 7.1$), 1.66 (d, 3H, $J = 7.2$), 1.97 (dd, 1H, $J = 9.6$, $J = 16.2$), 2.14 (dd, 1H, $J = 4.0$, $J = 16.2$), 2.84 (dd, 1H, $J = 6.3$, $J = 9.0$), 3.42 (dd, 1H, $J = 8.8$, $J = 9.0$), 3.97 (q, 2H, $J = 7.1$), 3.94–3.06 (m, 1H), 4.41 (ABq, 2H, $J = 14.9$), 5.25 (q, 1H, $J = 7.2$), 7.18–7.42 (m, 10ArH); ^{13}C NMR: 14.4, 16.3, 19.4, 39.4, 48.5, 49.3, 51.0, 60.9, 127.6, 127.7, 127.8, 128.5, 128.8, 129.0, 137.6, 142.8, 160.9, 170.8.

3.8.2. Ethyl (5*R*,1′*R*)-[3-benzyl-1-(1′-phenylethyl)-imidazolidin-2-on-5-yl]acetate 3c. Colourless oil. IR ($CHCl_3$): 1744, 1659 cm^{-1}; ^1H NMR: 1.17 (t, 3H, $J = 7.1$), 1.65 (d, 3H, $J = 7.3$), 2.43 (dd, 1H, $J = 9.8$, $J = 16.0$), 2.70 (dd, 1H, $J = 3.7$, $J = 16.0$), 2.88 (dd, 1H, $J = 6.3$, $J = 9.0$), 3.31 (dd, 1H, $J = 8.8$, $J = 9.0$), 3.53–3.67 (m, 1H), 4.03 (q, 2H, $J = 7.1$), 4.39 (ABq, 2H, $J = 14.9$), 5.28 (q, 1H, $J = 7.3$), 7.19–7.45 (m, 10ArH); ^{13}C NMR: 14.6, 16.3, 21.4, 40.3, 48.6, 49.1, 52.3, 61.0, 127.6, 127.7, 127.8, 128.5, 128.8, 129.0, 140.8, 142.8, 160.8, 170.7.

3.9. Ethyl (5*S*,1′*R*)-[3-*p*-methoxybenzyl-1-(1′-phenylethyl)imidazolidin-2-on-5-yl]acetate 2d and its (5*R*,1′*R*)-isomer 3d

Following the same procedure as for **2a** and **3a**, but starting from the amino ester **1d** (1.0 g; 5 mmol), a mixture of compounds **2d** and **3d** was obtained in 69% overall yield and 85:15 dr, which gave however definite patterns in ^1H and ^{13}C NMR spectra. MS (EI): m/z 396 (M^+), 381, 305, 290, 259, 169, 121, 105, 91. Anal. Calcd for $C_{23}H_{28}N_2O_4$: C, 69.68; H, 7.12; N, 7.07. Found: C, 69.62; H, 7.07; N, 7.12.

3.9.1. Ethyl (5*S*,1′*R*)-[3-*p*-methoxybenzyl-1-(1′-phenylethyl)imidazolidin-2-on-5-yl]acetate 2d. ^1H NMR: 1.14 (t, 3H, $J = 7.1$), 1.64 (d, 3H, $J = 7.2$), 1.95 (dd, 1H, $J = 9.7$, $J = 16.3$), 2.13 (dd, 1H, $J = 4.0$, $J = 16.3$), 2.81 (dd, 1H, $J = 6.4$, $J = 9.1$), 3.40 (dd, 1H, $J = 8.8$, $J = 9.1$), 3.81 (s, 3H), 3.98 (q, 2H, $J = 7.1$), 3.93–4.06 (m, 1H), 4.35 (ABq, 2H, $J = 14.8$), 5.25 (q, 1H, $J = 7.2$), 6.86 (d, 2ArH, $J = 8.3$), 7.15–7.44 (m, 7ArH); ^{13}C NMR: 14.5, 16.3, 40.4, 47.9, 48.6, 49.2, 51.0, 55.6, 60.9, 114.5, 125.6, 127.7, 127.9, 128.8, 129.0, 129.6, 129.9, 142.9, 159.4, 170.9.

3.9.2. Ethyl (5*R*,1′*R*)-[3-*p*-methoxybenzyl-1-(1′-phenylethyl)imidazolidin-2-on-5-yl]acetate 3d. ^1H NMR: 1.21 (t, 3H, $J = 7.1$), 1.64 (d, 3H, $J = 7.2$), 2.42 (dd, 1H, $J = 9.9$, $J = 16.1$), 2.69 (dd, 1H, $J = 3.7$, $J = 16.1$), 2.84 (dd, 1H, $J = 6.4$, $J = 9.1$), 3.29 (dd, 1H, $J = 8.9$, $J = 9.1$), 3.49–3.68 (m, 1H), 3.79 (s, 3H), 4.04 (q, 2H, $J = 7.1$), 4.33 (ABq, 2H, $J = 14.9$), 5.28 (q, 1H, $J = 7.2$), 6.84 (d, 2ArH, $J = 8.3$), 7.14–7.44 (m, 7ArH); ^{13}C NMR: 14.5, 19.4, 39.5, 47.9, 49.0, 49.2, 52.3, 55.6, 60.9, 114.5, 125.6, 127.7, 127.9, 128.8, 129.0, 129.6, 129.9, 140.8, 160.9, 170.7.

3.10. (*S*)-3-Amino-4-hydroxybutanoic acid 5

In a flask under inert atmosphere NH_3 (about 50 mL) was condensed at −78 °C and then Li (210 mg; 30 mmol) was added. When the metal was dissolved in NH_3, a solution containing **2a** (1.9 g; 5 mmol) in THF–*t*-BuOH 9:1 (20 mL) was quickly added. After 15 min NH_3 was removed, H_2O (15 mL) was slowly dropped and then the mixture was extracted with ethyl acetate (2×50 mL). To the aqueous solution NaOH (1.5 g) was added and the mixture was heated under reflux for 12 h. After removal of the H_2O under reduced pressure, the residue was redissolved in H_2O (5 mL) and the solution was adsorbed on ion-exchange resin Dowex 50WX2. The resin was washed with distilled water and then eluted with 1 M NH_4OH to give **5** in 51% yield as a white solid, mp 223-225 °C (lit.[13d] 228 °C); ^1H NMR (D_2O, DSS): 2.32–2.51 (m, 2H), 3.45–3.64 (m, 2H), 3.67–3.82 (m, 1H); ^1H NMR (CD_3OD+NaOH): 2.17 (dd, 1H, $J = 8.1$, $J = 16.6$), 2.34 (dd, 1H, $J = 5.1$, $J = 16.6$), 3.09–3.22 (m, 1H), 3.39 (dd, 1H, $J = 6.7$, $J = 10.7$), 3.54 (dd, 1H, $J = 4.8$, $J = 10.7$), 4.96 (br s, 3H, OH+NH_2); ^{13}C NMR (D_2O, DSS): 38.4, 53.6, 63.9, 180.4; ^{13}C NMR (CD_3OD+NaOH): 43.3, 52.2, 67.7, 180.6; $[\alpha]_D = -18.1$ (*c* 3, H_2O) [lit.[13d] −18.3 (*c* 1, H_2O)]; MS (CI): 120 (M^++1), 84. Anal. Calcd for $C_4H_9NO_3$: C, 40.33; H, 7.62; N, 11.76. Found: C, 40.29; H, 7.59; N, 11.79.

4. Computational methods

Molecular mechanics calculations were performed both using the implementation of Amber all-atom force field (AMBER*)[7] and MM2*[8] within the framework of Macromodel version 5.5[9] both in vacuo and using the implicit chloroform GB/SA solvation model of Still et al.[10] The torsional space of each molecule was randomly varied with the usage-directed Monte Carlo conformational search of Chang–Guida–Still.[10] For each search, at least 1000 starting structures for each variable torsion angle was generated and minimised until the gradient was less than 0.05 kJ/mol. Duplicate conformations and those with an energy in excess of 5 kcal/mol above the global minimum were discarded. The conformations of the anion were obtained by molecular dynamics simulation (MD) performed using CVFF force field[17] within the framework of INSIGHT II/DISCOVER® software package (Accelrys) onto an SGI workstation.[18] Molecular conformers were sampled during a 200 ps MD trajectory at 350 K. A time step of 1 fs was used and the system equilibrated for 6 ps. A conformation was stored each picosecond so that 200 conformers were recorded at the end of each simulation. Then after energy minimisation another MD simulation of 50 ps was run at 300 K with periodic jump to 600 K to supply the system with energy to pass conformational barriers. In this case the structures were stored each ps and minimised.

The structures of the anion NACs conformers and the transition structures were located and optimised at RHF/6-31G* level, and single point DFT calculation were carried out at B3LYP/6-31G* levels using the fully optimised geometries, in order to take into account the correlation energy. The results obtained are reported in Table 1. All DFT calculations were carried out using the standard tools available in the *Gaussian 98* package,[19] with the DFT/B3LYP functional (i.e., Becke's three parameter hybrid functional with the Lee–Yang–Parr correlation functional)[20] and the 6-31G(d) basis set. For all these structures a complete vibrational analysis was performed to check the nature of these stationary

points. The TS have only one imaginary frequency corresponding to the expected c.d.r.[21]

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