1 PERKIN

Synthesis of chiral oxazolidin-2-ones from *N*-alkoxycarbonyl amino epoxides: a computational study †

F. Javier Casado-Bellver,[a] M. Eugenia González-Rosende,*[b] Amparo Asensio,[a] J. Miquel Jordá-Gregori,[a] Angeles Alvarez-Sorolla,[a] José Sepúlveda-Arques,*[b] Mario Orena[c] and Roberta Galeazzi*[c]

[a] *University of Valencia, Avda. Vicent Andrés Estelles s/n, 46100 Burjassot, Valencia, Spain. E-mail: jose.sepulveda@uv.es; Fax: +34 96 386493; Tel: +34 96 3864938*
[b] *Department of Chemistry, University Cardenal Herrera-CEU, Edificio Seminario s/n, 46133 Moncada, Valencia, Spain. E-mail: eugenia@uch.ceu.es; Fax: +34 96 1395272; Tel: +34 96 1369000*
[c] *Dipartimento di Scienze dei Materiali e della Terra, University of Ancona, Via Brecce Bianche, I-60131 Ancona, Italy. E-mail: roberta@popcsi.unian.it; Fax: +39 71 2204714; Tel: +39 71 2204707*

Received (in Cambridge, UK) 17th April 2002, Accepted 30th May 2002
First published as an Advance Article on the web 24th June 2002

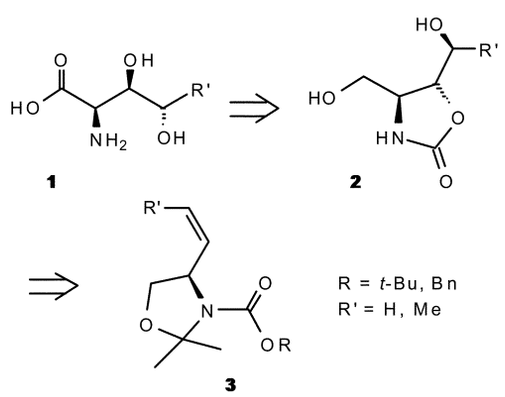
threo-N-Alkoxycarbonylamino epoxides **5a**–**d**, containing the oxazolidine moiety, were converted into *trans*-4,5-disubstituted-2-oxazolidin-2-ones **2** with total regio- and stereoselection by means of nucleophilic intramolecular attack of the carbamate moiety to the protonated oxirane ring. Theoretical calculations confirmed both the regioselection and the preference of the cyclocarbamation reaction *vs.* the intermolecular attack by the solvent, arising from different behaviour in comparison with the analogous iodonium ions.

Introduction

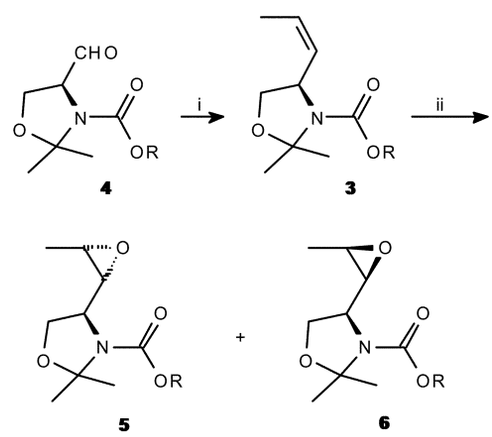
Oxazolidines having definite configuration are widely recognized as useful chiral auxiliaries[1,2] and enantiomerically pure epoxides have been frequently used in stereocontrolled synthesis.[3,4] However, both epoxide and oxazolidine moieties involved together in intramolecular processes are little reported in the literature.[5] As a part of an ongoing research program aimed at the synthesis of biologically relevant hydroxy amino acids,[6] starting from chiral epoxy oxazolidines **5**, we report here a new, stereoselective approach to *trans*-4,5-disubstituted 2-oxazolidinones **2**, which can be precursors of β,γ-dihydroxy-α-amino acids **1** (Scheme 1).

Results and discussion

First, alkenyl oxazolidines **3a**–**d** were obtained starting from Garner's protected aldehydes **4a**,**b**[7] by using standard procedures.[8] Then, treatment of **3** with *m*-chloroperbenzoic acid in CH_2Cl_2 gave the corresponding *threo* **5a**–**d** and *erythro* **6a**–**c**, *N*-carbamoyl epoxides (Scheme 2).[9] The reaction



Scheme 1



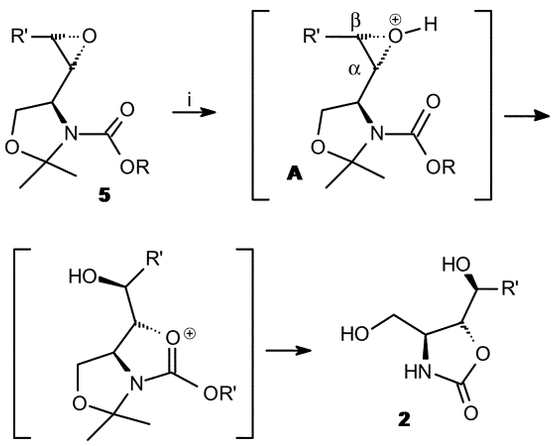
Scheme 2 *Reagents and conditions (and yields)*: i, for **3a**,**b**: methyltriphenylphosphonium iodide, LiHMDS, −78 °C (**a**, R = *t*-Bu, R′ = H, 38%; **b**, R = Bn, R′ = H, 53%); for **3c**,**d**, ethyltriphenylphosphonium iodide, LiHMDS, −78 °C (**c**, R = *t*-Bu, R′ = Me, 58%; **d**, R = Bn, R′ = Me, 73%); ii, *m*-chloroperbenzoic acid, CH_2Cl_2, at reflux starting from **3a** or **3b**, rt starting from **3c** or **3d**, 48 h (**a**, 42%, d.r. 67 : 33; **b**, 63%, d.r. 63 : 37; **c**, 57%, d.r. 70 : 30; **d**, 77%, d.r. 100 : 0).

proceeded with moderate to high stereoselection,[10] the *threo* diastereomer being always the major product, and pure isolated diastereomers were easily obtained by column chromatography. Moreover, when toluene-*p*-sulfonic acid was added to a solution of the epoxides **5a**–**d** in dry methanol, oxazolidin-2-ones **2a**,**b** were exclusively obtained whereas oxazin-2-ones arising from 6-*endo* cyclisation were not observed.[11] The *trans*-4,5-relationship in these compounds was assigned on the basis of the values of coupling constants between the protons H_4 and H_5 in the ^1H NMR spectrum of **2b** ($J_{4,5}$ = 4.9 Hz).[12]

† Electronic supplementary information (ESI) available: structures of localized transition states. See http://www.rsc.org/suppdata/p1/b2/b203702e/

 DOI: 10.1039/b203702e

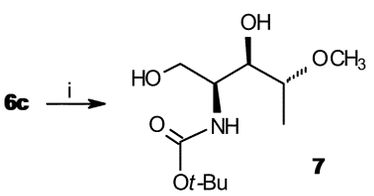
This regio- and stereoselective cyclocarbamation proceeds through an intramolecular nucleophilic attack of the carbonyl group on the C-α of the protonated epoxide (Scheme 3).



Scheme 3 *Reagents and conditions (and yields)*: i, toluene-*p*-sulfonic acid, methanol, −20 °C [**2a** from **5a** (R = *t*-Bu, R′ = H), 70%; **2a** from **5b** (R = Bn, R′ = H), 62%; **2b** from **5c** (R = *t*-Bu, R′ = Me), 96%; **2b** from **5d** (R = Bn, R′ = Me), 86%].

Although such participation of a carbamate in the intramolecular epoxide ring opening under acid conditions has been previously observed,[3,11,13,14] to the best of our knowledge this is the first example of an intramolecular nucleophilic epoxide opening reaction starting from 4-oxiranyloxazolidines.

The good results obtained in the case of compounds **5a**–**d** suggested that the epoxide *erythro*-**6c** might react in a similar manner. However, when **6c** was treated under the same conditions, an intermolecular reaction with the methanol occurred leading to compound **7**, exclusively (Scheme 4). Therefore, for



Scheme 4 *Reagents, conditions and yields*: i, toluene-*p*-sulfonic acid, methanol, −20 °C, 68%.

obtaining deeper mechanistic information on the regioselection of the ring closure, theoretical calculations were performed. First, the geometry of both epoxides **5c** and **6c** was optimised and epoxide **5c** turned out to be more stable than **6c** by 0.6 kcal mol^{-1}, in good agreement with the observed d.r.[15–17] Then, in order to explain the exclusive five-membered ring formation, E_{HOMO}, E_{LUMO} and frontier electron density for significant carbon and oxygen atoms for both protonated epoxides **A** and **B** (Fig. 1) were calculated at the RHF/6-31G* level. Thus, for **A**,

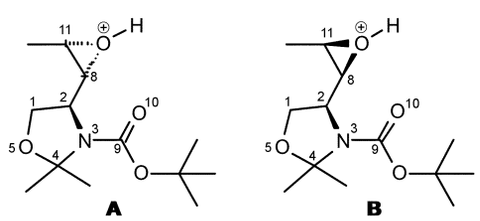


Fig. 1 Numbering system for cations **A** and **B**.

the 3D shapes for HOMO and LUMO were obtained (E_{HOMO} = −0.51966 eV and E_{LUMO} = −0.03773 eV) and the results show that HOMO lies mainly on carbonylic O-10 [f_r^E(HOMO) 0.110], whereas the difference between the LUMOs at C-8 and C-11 is small [f_r^N(LUMO), C-8, 0.423, and C-11, 0.458, respectively].[18] In analogy, the 3D shapes for HOMO and LUMO were also obtained for **B**, (E_{HOMO} = −0.51204 eV and E_{LUMO} = −0.01854 eV) and the result was that the HOMO lies mainly on carbonylic O-11 [f_r^E(HOMO) 0.109], whereas the difference between the LUMOs at C-8 and C-11 is still small [f_r^N(LUMO), C-8, 0.240, and C-11, 0.282, respectively].

The small difference between C-8 and C-11 does not explain the observed regioselection, and other factors must be involved, unlike the intermediate iodonium cations we have already considered.[6] Accordingly, two possible reaction pathways proceeding *via* either five-*exo* or six-*endo* mode were investigated at the AM1 level.[15–17] For the formation of a five-membered ring the energies of both **A** and **2b** were calculated, and the corresponding transition state TS-1 was localised (Figs. 2 and 3). Following the same procedure, but for a

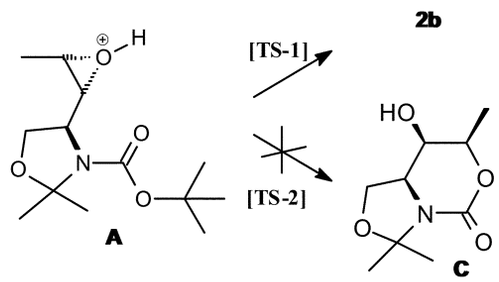


Fig. 2 Regioselective formation of **2b**.

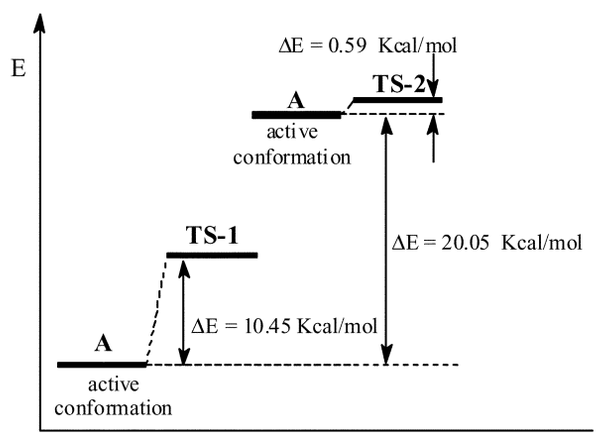


Fig. 3 Energies for pathways leading to either **2b** or compound **C** (five- *vs.* six-membered ring formation).

pathway leading to a six-membered ring, the energies of both **A** and **C** were calculated and TS-2 was localised. The results show that the formation of a five-membered ring is strongly favoured owing to a lower activation energy for the pathway **A** ⟶ TS-1 (10.45 kcal mol^{-1} *vs.* 20.74 kcal mol^{-1}). In fact, in order to give **C**, the cation **A** must reach an active conformation which is about 20 kcal mol^{-1} higher than the active conformation leading to **2b**, so this is the rate determining step of the process.

Subsequently, in order to explain the different behaviour of the intermediate cations **A** and **B**, the structures of both **A** and the transition state TS-1 were optimised at the RHF/6-31G* level and their energies calculated at the B3LYP/6-31G*//RHF/6-31G* level.[19–23] The activation energy was obtained and the result was that TS-1 has exactly one imaginary vibrational frequency (Figs. 4, 5 and 6).

Moreover, the structures of both **B** and the transition state TS-3, leading to the five-membered compound **D**, were optimised at the RHF/6-31G* level and the energy was obtained at the B3LYP/6-31G*//RHF/6-31G* level. At both levels a high activation energy was observed for the pathway **A** ⟶ TS-1, with respect to the very low activation energy for the pathway **B** ⟶ TS-3. However, a strong difference in energy was

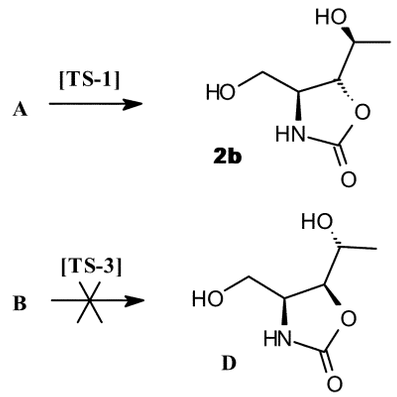


Fig. 4 Comparison between the behaviour of cations **A** and **B**.

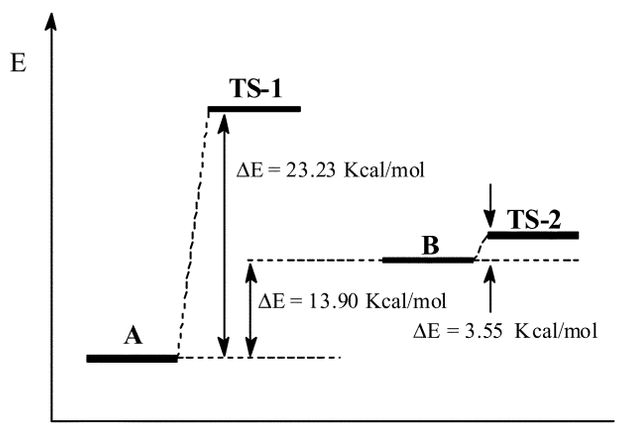


Fig. 5 Energies for pathways **A** ⟶ TS-1 and **B** ⟶ TS-3 calculated at the RHF/6-31G* level [**A** (−859.9310337 au); TS-1 (−859.89401 au); **B** (−859.908872 au); TS-3 (−859.89401 au)].

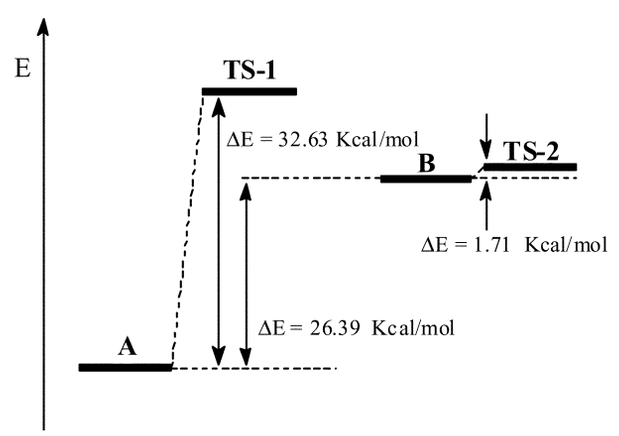


Fig. 6 Energies for pathways **A** ⟶ TS-1 and **B** ⟶ TS-3 calculated at the B3LYP/6-31G*//RHF/6-31G* level [**A** (−865.241716 au); TS-1 (−865.189717 au); **B** (−865.1996634 au); TS-3 (−865.196932 au)].

found for **A** with respect to **B**, so it seems reasonable that **A** can give the five-membered ring through TS-1, whereas **B** does not form, the reaction proceeding through a different pathway involving an external nucleophile (MeOH) to give the acyclic compound **7** (Fig. 6).

Conclusions

In summary, treatment of *threo* amino epoxides **5a**–**d** with catalytic toluene-*p*-sulfonic acid in anhydrous methanol led to a highly regio- and stereoselective intramolecular epoxide-opening reaction involving the *N*-Boc and *N*-Cbz neighbouring groups, and we succeeded in preparing the corresponding 4,5-*trans*-disubstituted oxazolidin-2-ones **2a**,**b** *via* a cyclisation proceeding in a 5-*exo*-*tet* mode. In addition, theoretical calculations confirmed the preference for the intramolecular *vs.* intermolecular nucleophilic attack in *threo* isomers **5a**–**d**.[24] Applications of this cyclisation strategy to the asymmetric synthesis of non-proteinogenic α-amino-β-hydroxy acids are currently under investigation in our group and will be reported in due course.

Experimental

General

All reactions were carried out under argon by using standard techniques. Mps. were determined with a Kofler hot-stage apparatus and are uncorrected. Optical rotations were measured at 25 °C on a Perkin–Elmer 241 polarimeter. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$, unless specified otherwise, on a Bruker AC-250 and an AC-300 spectrometer using TMS as internal reference and coupling constants are given in Hz. All assignments were determined *via* DEPT and ^{13}C–^{1}H COSY techniques. Infrared spectra were recorded on a Perkin–Elmer FT–IR instrument. High-resolution mass spectra were obtained on a VG Autospec, TRIO 1000 (Fisons) instrument. The ionization mode used in obtaining the mass spectra was electron impact (EI), chemical ionization (CI) at 70 eV or fast atom bombardment (FAB). Flash chromatography was performed using silica gel (Merck 60, 70–230 mesh). Compounds **3a**–**d** were prepared according to the literature method.[8]

Epoxidation of allylic carbamates 3: general procedure

To a solution of the appropriate allylic carbamate **3** (2.2 mmol) in dry CH_2Cl_2 (30 ml), *m*-chloroperbenzoic acid (70 % in weight; 1.48 g, 6.6 mmol) was added at −20 °C. After being stirred at rt for 48 h (**3c** and **3d**) or at reflux temperature (**3a** and **3b**), the reaction mixture was washed with 10% Na_2SO_3 (3 × 70 ml), 5% $NaHCO_3$ (3 × 70 ml) and brine. After extraction with CH_2Cl_2 (2 × 150 ml), the organic layers were dried (Na_2SO_4) and the solvent removed under reduced pressure. The residue was purified by flash chromatography (hexane–ethyl acetate, gradient elution 95 : 5 to 20 : 80) to give pure isolated products **5** and **6**.[25]

***threo*-(4*S*,2′*R*)-*N*-*tert*-Butoxycarbonyl-2,2-dimethyl-4-(oxiran-2′-yl)oxazolidine 5a.** Yield 28%. Oil. ν_{max}(neat)/cm^{-1} 1700, 1260, 1211; δ_H($CDCl_3$) 1.44 ($3H_\alpha$ + $3H_\beta$ + $9H_\alpha$ + $9H_\beta$, s), 1.56 (3H, s)$_\beta$, 1.61 (3H, s)$_\alpha$, 2.70–2.86 ($2H_\alpha$ + $2H_\beta$, m), 2.98 ($1H_\alpha$ + $1H_\beta$, s), 3.38 ($1H_{\alpha\ or\ \beta}$, m), 3.53 ($1H_{\alpha\ or\ \beta}$, m), 4.0 ($2H_\alpha$ + $2H_\beta$, m); δ_C($CDCl_3$) 23.1 $(CH_3)_\alpha$, 24.3 $(CH_3)_\beta$, 26.7 $(CH_3)_\alpha$, 27.5 $(CH_3)_\beta$, 28.4 $(3CH_3)_{\alpha+\beta}$, 48.3 $(CH_2)_\alpha$, 48.4 $(CH_2)_\beta$, 52.0 $(CHN)_\beta$, 52.3 $(CHN)_\alpha$, 59.0 $(CH)_\alpha$, 59.3 $(CH)_\beta$, 65.5 $(CH_2)_\beta$, 66.1 $(CH_2)_\alpha$, 80.2 $(CH_2)_\alpha$, 80.5 $(CH_2)_\beta$, 93.9 $(C)_\beta$, 94.4 $(C)_\alpha$, 151.8 $(C)_{\alpha+\beta}$; $[\alpha]_D$ +10.0 (c = 1.0, $CHCl_3$); EI-HRMS (M^+) = 243.1465. Calculated for $C_{12}H_{21}NO_4$ 243.1470.

***erythro*-(4*S*,2′*S*)-*N*-*tert*-Butoxycarbonyl-2,2-dimethyl-4-(oxiran-2′-yl)oxazolidine 6a.** Yield 14%. Oil. ν_{max}(neat)/cm^{-1} 1696, 1260; δ_H($CDCl_3$) 1.41 ($9H_\alpha$ + $9H_\beta$ + $6H_\alpha$ + $6H_\beta$, m), 2.56, ($1H_\alpha$ + $1H_\beta$, s), 2.67 ($1H_\alpha$ + $1H_\beta$, dd, J 4.4, 4.3), 3.12 ($1H_\alpha$ + $1H_\beta$, m), 3.6–3.8 ($2H_\alpha$ + $2H_\beta$, m), 4.08 (1H s)$_{\alpha\ or\ \beta}$, 4.22 (1H, s)$_{\alpha\ or\ \beta}$; δ_C($CDCl_3$) 23.1 $(CH_3)_\alpha$, 24.3 $(CH_3)_\beta$, 26.4 $(CH_3)_\alpha$, 27.0 $(CH_3)_\beta$, 28.3 $(3CH_3)_{\alpha+\beta}$, 44.1 $(CH_2)_{\alpha+\beta}$, 51.0 $(CHN)_{\alpha+\beta}$, 56.3 $(CH)_{\alpha+\beta}$, 62.9 $(CH_2)_\alpha$, 63.1 $(CH)_\beta$, 80.2 $(C)_\alpha$, 80.6 (C_β), 93.8 $(C)_\beta$, 94.2 $(C)_\alpha$, 151.7 $(C)_\alpha$, 152.5 $(C)_\beta$; $[\alpha]_D$ −45.2 (c = 1.1, $CHCl_3$); FAB-HRMS (M + 1) = 244.1545. Calculated for $C_{12}H_{22}NO_4$ 244.1548.

***threo*-(4*S*,2′*R*)-*N*-Benzyloxycarbonyl-2,2-dimethyl-4-(oxiran-2′-yl)oxazolidine 5b.** Yield: 40%. Oil. ν_{max}(neat)/cm^{-1} 1692, 1257; δ_H($CDCl_3$) 1.45 (3H, s)$_\beta$, 1.53 (3H, s)$_\alpha$, 1.58 (3H, s)$_\beta$, 1.66 (3H, s)$_\alpha$, 2.44 (1H, dd, J 4.4, 2.5)$_\alpha$, 2.65 (1H, t, J 4.4)$_\alpha$, 2.8–

3.1 ($3H_\beta$ + $1H_\alpha$, m), 3.38 (1H, m)$_\alpha$, 3.48 (1H, m)$_\beta$, 4.0–4.1 ($2H_\alpha$ + $2H_\beta$, m), 5.0–5.2 ($2H_\alpha$ + $2H_\beta$, m), 7.3 ($5H_\alpha$ + $5H_\beta$, s); δ_C($CDCl_3$) 23.0 $(CH_3)_\alpha$, 24.3 $(CH_3)_\beta$, 26.5 $(CH_3)_\alpha$, 27.4 $(CH_3)_\beta$, 48.2 $(CH_2)_{\alpha+\beta}$, 51.7 $(CHN)_\beta$, 52.0 $(CHN)_\alpha$, 58.9 $(CH)_\alpha$, 59.7 $(CH)_\beta$, 65.6 $(CH_2)_\beta$, 66.2 $(CH_2)_\alpha$, 67.0 $(CH_2)_\alpha$, 67.3 $(CH_2)_\beta$, 94.6 $(C)_{\alpha+\beta}$, 128.0 $(2CH_{ar})_{\alpha+\beta}$, 128.3 $(2CH_{ar})_{\alpha+\beta}$, 128.5 $(CH_{ar})_{\alpha+\beta}$, 135.5 $(C_{ar})_{\alpha+\beta}$, 152.2 $(C)_{\alpha+\beta}$. $[a]_D$ +0.63 (c = 1.0, $CHCl_3$); EI-HRMS (M^+) = 277.1323. Calculated for $C_{15}H_{19}NO_4$ 277.1314.

***erythro*-(4*S*,2′*S*)-*N*-Benzyloxycarbonyl-2,2-dimethyl-4-(oxiran-2′-yl)oxazolidine 6b.** Yield: 23%. Oil. ν_{max}(neat)/cm^{-1} 1705, 1261, 1211; δ_H($CDCl_3$) 1.38 (3H, s)$_\beta$, 1.45 (3H, s)$_\alpha$, 1.53 (3H, s)$_\alpha$, 1.61 (3H, s)$_\beta$, 2.5 (2H, dd, J 4.7, 2.5)$_{\alpha+\beta}$, 2.63 (2H, m)$_{\alpha+\beta}$, 3.1 (1H, m)$_\alpha$, 3.2 (1H, m)$_\beta$, 3.65–3.83 ($2H_\alpha$ + $2H_\beta$, m), 4.18 (1H, m)$_\alpha$, 4.28 (1H, m)$_\beta$, 5.07 (4H, m)$_{\alpha+\beta}$, 7.03 (10H, m)$_{\alpha+\beta}$; δ_C($CDCl_3$) 23.0 $(CH_3)_\alpha$, 24.3 $(CH_3)_\beta$, 26.8 $(CH_3)_\alpha$, 27.0 $(CH_3)_\beta$, 44.1 $(CH_2)_{\alpha+\beta}$, 50.8 $(CHN)_{\alpha+\beta}$, 56.1 $(CH)_\alpha$, 56.9 $(CH)_\beta$, 63.1 $(OCH_2)_{\alpha+\beta}$, 66.8 $(CH_2)_\beta$, 67.4 $(CH_2)_\alpha$, 94.5 $(C)_{\alpha+\beta}$, 128.0 $(2CH_{ar})_{\alpha+\beta}$, 128.3 $(2CH_{ar})_{\alpha+\beta}$, 128.5 $(CH_{ar})_{\alpha+\beta}$, 136.0 $(C_{ar})_{\alpha+\beta}$, 152.4 $(C)_{\alpha+\beta}$; $[a]_D$ −30.7 (c = 1.0, $CHCl_3$); EI-HRMS (M^+) = 277.1313. Calculated for $C_{15}H_{19}NO_4$ 277.1314.

***threo*-(4*S*,1′*R*,2′*S*)-*N*-*tert*-Butoxycarbonyl-2,2-dimethyl-4-(1′,2′-epoxypropan-1′-yl)oxazolidine 5c.** Yield: 40%. Oil. ν_{max}(neat)/cm^{-1} 1695, 1256, 1173; δ_H($CDCl_3$) 1.24 (3H, d, J 4.0)$_\beta$, 1.37 (3H, d, J 4.0)$_\alpha$, 1.42 ($9H_\beta$ + $9H_\alpha$ + $3H_\beta$ + $3H_\alpha$, m), 1.54 ($3H_\beta$ + $3H_\alpha$, m), 2.9–2.93 ($1H_\alpha$ + $1H_\beta$, m), 3.12–3.16 ($1H_\alpha$ + $1H_\beta$, m), 3.55–3.65 ($1H_\alpha$ + $1H_\beta$, m), 3.89–3.95 ($1H_\alpha$ + $1H_\beta$, dd, J 9.0, 6.0), 4.02–4.06 ($1H_\alpha$ + $1H_\beta$, dd, J 9.0, 2.0); δ_C($CDCl_3$) 13.8 $(CH_3)_\alpha$, 16.0 $(CH_3)_\beta$, 23.6 $(CH_3)_\beta$, 24.5 $(CH_3)_\alpha$, 26.3 $(CH_3)_\beta$, 27.5 $(CH_3)_\alpha$, 28.3 $(3CH_3)_{\alpha+\beta}$, 53.0 $(CHN)_\beta$, 54.0 $(CHN)_\alpha$, 54.9 $(CH)_\beta$, 57.6 $(CH)_\alpha$, 58.3 $(CH)_\beta$, 66.0 $(CH_2)_\alpha$, 66.3 $(CH_2)_\beta$, 80.2 $(C)_{\alpha+\beta}$, 93.9 $(C)_\alpha$, 94.9 $(C)_\beta$, 152.2 $(C)_{\alpha+\beta}$; $[a]_D$ +20.5 (c = 4.9, CH_2Cl_2). FAB-HRMS (M^+) = 257.1610. Calculated for $C_{13}H_{23}NO_4$ 257.1627.

***erythro*-(4*S*,1′*S*,2′*R*)-*N*-*tert*-Butoxycarbonyl-2,2-dimethyl-4-(1′,2′-epoxypropan-1′-yl)oxazolidine 6c.** Yield 17%. Oil. ν_{max} (neat)/cm^{-1} 1698, 1253, 1170; δ_H($CDCl_3$) 1.24 (3H, d, J 4.8), 1.43 (9H, s), 1.46 (3H, s), 1.54 (3H, s), 2.93–2.96 (2H, m), 3.75–3.8 (2H, m), 3.98 (1H, dd, J 9.2, 1.9); δ_C($CDCl_3$) 13.8 $(CH_3)_{\alpha+\beta}$, 23.6 $(CH_3)_\alpha$, 24.5 $(CH_3)_\beta$, 26.4 $(CH_3)_\alpha$, 27.5 $(CH_3)_\beta$, 28.3 $(3CH_3)_{\alpha+\beta}$, 51.0 $(CH)_{\alpha+\beta}$, 56.8 $(CH)_{\alpha+\beta}$, 59.0 $(CHN)_{\alpha+\beta}$, 65.7 $(CH_2)_{\alpha+\beta}$, 80.1 $(C)_{\alpha+\beta}$, 94.1 $(C)_{\alpha+\beta}$, 152.2 $(C)_{\alpha+\beta}$; $[a]_D$ +13.2 (c = 1, CH_2Cl_2). EI-HRMS (M^+) = 257.1637. Calculated for $C_{13}H_{23}NO_4$ 257.1627.

***threo*-(4*S*,1′*R*,2′*S*)-*N*-Benzyloxycarbonyl-2,2-dimethyl-4-(1′,2′-epoxypropan-1′-yl)oxazolidine 5d.** Yield: 77%. Oil. ν_{max}(neat)/cm^{-1} 1705, 1254, 1216; δ_H($CDCl_3$) 0.93 (3H, d, J 4.8)$_\alpha$, 1.45 (6H, m)$_\beta$, 1.53 (3H, s)$_\alpha$, 1.58 (3H, s)$_\alpha$, 1.66 (3H, s)$_\beta$, 2.90 ($2H_\alpha$ + $1H_\beta$, s), 3.20 (1H, m)$_\beta$, 3.62 (1H, m)$_\alpha$, 3.75 (1H, m)$_\beta$, 4.0–4.1 ($2H_\alpha$ + $2H_\beta$, m,), 5.01 ($2H_\alpha$ + $2H_\beta$, s), 7.32 ($5H_\alpha$ + $5H_\beta$, s); δ_C($CDCl_3$) 13.2 $(CH_3)_\alpha$, 13.7 $(CH_3)_\beta$, 23.4 $(CH_3)_\alpha$, 24.6 $(CH_3)_\beta$, 26.3 $(CH_3)_\alpha$, 27.4 $(CH_3)_\beta$, 53.4 $(CHN)_\alpha$, 54.8 $(CHN)_\beta$, 54.9 $(CH)_\alpha$, 55.0 $(CH)_\beta$, 57.3 $(CH)_\beta$, 57.6 $(CH)_\alpha$, 66.2 $(CH_2)_\beta$, 66.6 $(CH_2)_\alpha$, 67.0 $(CH)_\alpha$, 67.3 0 $(CH)_\beta$, 94.5 (C_β), 95.0 (C_α), 128.0 $(CH_{ar})_{\alpha+\beta}$, 128.3 $(2CH_{ar})_{\alpha+\beta}$, 128.5 $(2CH_{ar})_{\alpha+\beta}$, 136.1 $(C_{ar})_{\alpha+\beta}$, 152.5 $(C)_{\alpha+\beta}$; $[a]_D$ +22.3 (c = 1.85, $CHCl_3$); EI-HRMS (M^+) = 291.1463. Calculated for $C_{16}H_{21}NO_4$ 291.1470.

Opening of epoxides 5a–d: general procedure

To a solution of the epoxide **5a**–**d** (1.92 mmol) in dry methanol (20 ml) toluene-*p*-sulfonic acid (0.073 g, 0.2 equiv.) was added at −20 °C. The mixture was stirred at rt for 2 h and then triethylamine was added in order to remove the acid. After evaporation of the solvent under reduced pressure, the residue was purified by flash chromatography using gradient elution (hexane–ethyl acetate, 95 : 5 to 0 : 100, followed by ethyl acetate–methanol, 90 : 10) to give pure compounds **2a** and **2b**.

***trans*-(4*S*,5*R*)-4,5-Bis(hydroxymethyl)-1,3-oxazolidin-2-one 2a.** Yield: 70% from **5a** and 62% from **5b**. White solid. Mp 134–137 °C. ν_{max}(CH_2Cl_2)/cm^{-1} 3379, 1738; δ_H(DMSO-d_6) 3.4–3.6 (6H, m), 4.32 (1H, m), 5.1 (1H, OH, t, J 5.0), 5.2 (1H, OH, t, J 5.0); δ_C(DMSO-d_6) 55.6 (CHN), 62.7 (CH_2OH), 63.2 (CH_2OH), 79.4 (CHO), 159.7 (C). $[a]_D$ −40.1 (c = 1, $CHCl_3$). EI-HRMS (MH^+) = 148.0615. Calculated for $C_5H_{10}NO_4$ 148.0609. Found: C. 40.78; H, 6.14; N, 9.55. $C_5H_9NO_4$ requires C, 40.82; H, 6.17; N, 9.52%.

***trans*-(4*S*,5*R*,1′*S*)-5-(1′-Hydroxyethyl)-4-hydroxymethyl-1,3-oxazolidin-2-one 2b.** Yield: 96% from **5c** and 86% from **5d**. White solid. Mp 125–127 °C; ν_{max}(CH_2Cl_2)/cm^{-1} 3415, 1742; δ_H(DMSO-d_6-D_2O) 1.17 (3H, d, J 6.5), 3.36 (2H, m), 3.56 (1H, H_4, m), 3.63 (1H, qd, J 6.5, 3.9), 4.07 (1H, H_5, dd, J 4.9, 3.9); δ_C(DMSO-d_6) 18.4 (CH_3), 54.7 (CHN), 63.1 (CH_2), 66.4 (CHOH), 81.0 (CHO), 158.6 (C). $[a]_D$ −43.3 (c = 1.1, MeOH). EI-HRMS (MH^+) = 162.0769. Calculated for $C_6H_{12}NO_4$ 162.0766. Found: C, 44.67; H. 6.92; N, 8.67. $C_6H_{11}NO_4$ requires C, 44.72; H, 6.88; N, 8.69%.

(2*S*,3*R*,4*R*)-2-*tert*-Butoxycarbonylamino-4-methoxypentane-1,3-diol 7

To a solution of the epoxide **6c** (1.92 mmol) in dry methanol (20 ml) was added toluene-*p*-sulfonic acid (0.073 g, 0.2 equiv.), at −20 °C. The mixture was stirred at rt for 2 h and then the solution was neutralised with triethylamine. After evaporation of the solvent under reduced pressure, the residue was purified by flash chromatography using gradient elution (hexane–ethyl acetate, 95 : 5 to 0 : 100, followed by ethyl acetate–methanol, 90 : 10) to give pure **7**. Yield: 68 %. Oil. ν_{max}(neat)/cm^{-1} 3421, 1692, 1510, 1392, 1367, 1250, 1170; δ_H($CDCl_3$) 1.07 (3H, d, J 5.8), 1.34 (9H, s), 3.17 (1H, m), 3.28 (3H, s), 3.57 (6H, m), 5.28 (1H, d, J 8.4); δ_C($CDCl_3$) 14.4 (CH_3), 28.2 (CH_3), 51.5 (CHN), 56.3 (OCH_3), 63.7 (CH_2OH), 74.8 (CH), 77.8 (CH), 79.4 (C), 156.1 (C). $[a]_D$ −19.3 (c = 0.75, MeOH). EI-HRMS (M^+ + 1) = 250.1648. Calculated for $C_{11}H_{24}NO_5$ 250.1654.

Computational methods

A detailed conformational analysis was performed on each compound at the semiempirical level (AM1)[15] and using the stochastic method Monte Carlo[16] for the conformational space scan. All the geometries were then optimized *ab initio* at the RHF/6-31G* level and then a single point calculation on these optimised structures was performed at the B3LYP/6-31G* level of theory to include the electronic correlation.

Semiempirical calculations were performed using the AM1 Hamiltonian[15] within the framework of HyperChem 5.2.[17] All the torsional degrees of freedom were included in the conformational search. The torsional space of each molecule was randomly varied with the usage-directed Monte Carlo conformational search.[16] Duplicate conformations and those with an energy exceeding the global minimum by 5 kcal mol^{-1} were discarded.

Ab initio molecular orbitals and DFT calculations were carried out using the GAUSSIAN 94 program package.[18] For DFT calculations the hybrid functional B3LYP which contains gradient corrections for both exchange and correlation was chosen. The geometry of the reactants, products and transition structures was fully optimized at the RHF/6-31G* theory level. The calculated stationary points (local minima and saddle points) were characterized by harmonic vibrational frequency calculations at both HF/6-31G* and B3LYP/6-31G* levels.[19–22] Transitions structures were characterized by a single imaginary frequency whereas reactant and products had none.

Significant conformational parameters for transition structures TS-1 and TS-2 (optimised at the AM1 level)

TS-1. Torsional angles: (N-3)–(C-2)–(C-8)–(C-11) = −34.30°; (C-2)–(N-3)–(C-9)–(O-10) = 0.13°; (C-9)–(N-3)–(C-2)–(C-8) = −36.33°.

Distances between the reaction centres: $d_{O10–C8}$ = 2.58 Å; $d_{O^+–C8}$ = 2.42 Å.

Torsional angles related to conformations of the five membered ring: (C-4)–(O-5)–(C-1)–(C-2) = −22.10°; (N-3)–(C-4)–(O-5)–(C-1) = 20.0°; (O-5)–(C-1)–(C-2)–(N-3) = 16.28°; (C-1)–(C-2)–(N-3)–(C-4) = −4.49°.

TS-2. Torsional angles: (N-3)–(C-2)–(C-8)–(C-11) = 7.78°; (C-2)–(N-3)–(C-9)–(O-10) = 27.73°; (C-9)–(N-3)–(C-2)–(C-8) = −77.62°.

Distances between the reaction centres: $d_{O10–C11}$ = 2.96 Å; $d_{O^+–C11}$ = 2.94 Å.

Torsional angles related to conformations of the five membered ring: (C-4)–(O-5)–(C-1)–(C-2) = −22.69°; (N-3)–(C-4)–(O-5)–(C-1) = 26.64°; (O-5)–(C-1)–(C-2)–(N-3) = 9.28°; (C-1)–(C-2)–(N-3)–(C-4) = 6.99°.

Significant conformational parameters for transition structures TS-1 and TS-3 (optimised at RHF/6-31G* level)

TS-1. Torsional angles: (N-3)–(C-2)–(C-8)–(C-11) = −21.42°; (C-2)–(N-3)–(C-9)–(O-10) = 7.19°; (C-9)–(N-3)–(C-2)–(C-8) = −56.22°.

Distances between the reaction centres: $d_{O10–C8}$ = 2.67 Å; $d_{O^+–C8}$ = 2.43 Å.

Torsional angles related to conformations of the five membered ring: (C-4)–(O-5)–(C-1)–(C-2) = −36.04°; (N-3)–(C-4)–(O-5)–(C-1) = 31.48°; (O-5)–(C-1)–(C-2)–(N-3) = 24.36°; (C-1)–(C-2)–(N-3)–(C-4) = −6.15°.

TS-3. Torsional angles: (N-3)–(C-2)–(C-8)–(C-11) = 121.26°; (C-2)–(N-3)–(C-9)–(O-10) = 16.20°; (C-9)–(N-3)–(C-2)–(C-8) = −73.58°.

Distances between the reaction centres: $d_{O10–C8}$ = 2.83 Å; $d_{O^+–C8}$ = 1.60 Å.

Torsional angles related to conformations of the five membered ring: (C-4)–(O-5)–(C-1)–(C-2) = −26.90°; (N-3)–(C-4)–(O-5)–(C-1) = 28.95°; (O-5)–(C-1)–(C-2)–(N-3) = 12.17°; (C-1)–(C-2)–(N-3)–(C-4) = 5.11°.

Acknowledgements

We are grateful to both the Ministerio de Educación y Ciencia (Spain, Project PB98-1451) and MIUR (Italy, PRIN 2000) for financial support for this work.

References

1 C. Agami, F. Couty, L. Hamon and O. Venier, *J. Org. Chem.*, 1997, **62**, 2106.
2 M. Garcia-Valverde, R. Pedrosa, M. Vicente, S. Garcia-Granda and A. Gutierrez-Rodriguez, *Tetrahedron*, 1996, **52**, 10761.
3 N. Langlois and A. Moro, *Eur. J. Org. Chem.*, 1999, 3483.
4 A. Albeck and G. I. Estreicher, *Tetrahedron*, 1997, **53**, 5325; K. C. Nicolaou and E. J. Sorensen, *Classics in Total Synthesis*, VCH, New York, 1996; Y. Ohfune, *Acc. Chem. Res.*, 1992, **25**, 360; M. A. Pericàs, A. Riera and M. Manas, *Tetrahedron Lett.*, 1991, **47**, 6931; P. Meffre, L. Vo-Quang and Y. Vo-Quang, *Tetrahedron Lett.*, 1990, **31**, 2291; J. R. Luly, G. Bolis and J. F. Dellaria, *J. Med. Chem.*, 1988, **31**, 532; Y. Ohfune and N. Kurokawa, *J. Am. Chem. Soc.*, 1986, **108**, 6041; F. M. Hauser and S. R. Ellemberg, *J. Org. Chem.*, 1986, **51**, 50; H. Rapoport and J. R. Luly, *J. Org. Chem.*, 1985, **50**, 4515.
5 C. Agami, F. Couty, G. Evano and H. Mathieu, *Tetrahedron*, 2000, **56**, 367; H. Azuma, S. Tamagaki and K. Ogino, *J. Org. Chem.*, 2000, **65**, 3538; C. Hertweck and W. Boland, *J. Org. Chem.*, 1999, **64**, 4426; O. Thum, C. Hertweck, H. Simon and W. Bolan, *Synthesis*, 1999, 2145; C. Agami, F. Amiot, F. Couty, L. Dechoux, C. Kaminsky and O. Venier, *Tetrahedron: Asymmetry*, 1998, **9**, 3955; A. Bernardi, S. Cardani, C. Scolastico and R. Villa, *Tetrahedron*, 1990, **46**, 1987.
6 J. M. Jordà-Gregori, M. E. Gonzàlez-Rosende, P. Cava-Montesinos, J. Sepùlveda-Arques, R. Galeazzi and M. Orena, *Tetrahedron: Asymmetry*, 2000, **11**, 3769; J. M. Jordà-Gregori, M. E. Gonzàlez-Rosende, J. Sepùlveda-Arques, R. Galeazzi and M. Orena, *Tetrahedron: Asymmetry*, 1999, **10**, 1135.
7 P. Garner and J. M. Park, *Org. Synth.*, 1998, **Coll. Vol. IX**, 300; A. Dondoni and D. Perrone, *Synthesis*, 1997, 527; A. McKillop, R. J. K. Taylor, R. J. Watson and N. Lewis, *Synthesis*, 1994, 31; P. Garner and J. M. Park, *J. Org. Chem.*, 1987, **52**, 2361.
8 P. L. Beaulieu, J.-S. Duceppe and C. Johnson, *J. Org. Chem.*, 1991, **56**, 4196.
9 Oxiranyl derivatives **5a** and **5b** were previously obtained by means of dimethylsulfonium methylide epoxidation: see: J. W. Moore and F. A. Luzzio, *Tetrahedron Lett.*, 1995, **36**, 6599.
10 Diastereoselective peracid-mediated epoxidations of allylic carbamates have already been reported: see D. B. Berkowitz and M. L. Pedersen, *J. Org. Chem.*, 1995, **60**, 5368; A. Jenmalm, W. Berts, K. Luthman, I. Csoreg and U. Hacksell, *J. Org. Chem.*, 1995, **60**, 1026; A. Jenmalm and K. Luthman, *Tetrahedron Lett.*, 1998, **39**, 3213 . It is worth noting that the most commonly accepted model for hydroxy- or carbamate-directed epoxidations attributes the *threo* diastereoselection usually observed to $A^{(1,3)}$ interactions arising in the *erythro* transition state.
11 *tert*-Butyl carbamates **5a** and **5c** reacted faster and with higher yields than their benzyl analogues **5b** and **5d**: see C. Vanucci, X. Brusson, V. Verdel, F. Zana, H. Dhimane and G. Lhommet, *Tetrahedron Lett.*, 1995, **36**, 2971.
12 S. J. Kemp, J. Bao and S. F. Pedersen, *J. Org. Chem.*, 1996, **61**, 7162; D. D. Dhavale, L. Gentilucci, M. G. Piazza and C. Trombini, *Liebigs Ann. Chem.*, 1992, 1289; S. Futagawa, T. Inui and T. Shiba, *Bull. Chem. Soc. Jpn.*, 1973, **46**, 3308; T. A. Foglia and D. Swern, *J. Org. Chem.*, 1969, **34**, 1680.
13 C. Agami and F. Couty, *Tetrahedron*, 2002, **58**, 2701.
14 H. Urabe, Y. Aoyama and F. Sato, *Tetrahedron*, 1992, **48**, 5639; R. A. Farr, A. M. Holland, E. W. Huber, N. P. Peet and P. M. Weintraub, *Tetrahedron*, 1994, **50**, 1033; S. Romeo and D. H. Rich, *Tetrahedron Lett.*, 1993, **34**, 7187.
15 M. J. S. Dewar, E. G. Zoebisch, E. F. Healy and J. J. P. Stewart, *J. Am. Chem. Soc.*, 1985, **107**, 3902.
16 G. Chang, W. C. Guida and W. C. Still, *J. Am. Chem. Soc.*, 1989, **111**, 4379.
17 Hyperchem release 5.2; Chemplus release 2.0, HyperCube Inc., Gainesville, FL, USA.
18 $f_r^E = \Sigma(c_{HOMO,n})^2$, electrophilic atomic frontier electron densities and $f_r^N = \Sigma(c_{LUMO,n})^2$, nucleophilic atomic frontier electron densities, are pure numbers. $c_{HOMO,n}$ = coefficients of the atomic orbital X_n in the HOMO, whereas $c_{LUMO,n}$ = coefficients of the atomic orbital X_n in the LUMO.
19 GAUSSIAN 94, M. J. Frisch, J. W. Trucks, H. B. Schlegel, P. M. W. Gill, B. G. Johnson, M. A. Robb, J. R. Cheeseman, T. A. Keth, G. A. Petersson, J. A. Montgomery, K. Ragavachari, M. A. Al-Laham, V. G. Zakrzewski, J. V. Ortiz, J. B. Foresman, J. Cioslowski, B. B. Stefanov, A. Nanayakkara, M. Challacombe, C. Y. Peng, P. Y. Ayala, W. Chen, M. W. Wong, J. L. Andres, E. S. Replogle, R. Gomperts, R. L. Martin, D. J. Fox, J. S. Binkley, D. J. Defrees, J. Baker, J. P. Stewart, M. Head-Gordon, C. Gonzalez and J. A. Pople, Gaussian Inc., Pittsburg, PA, USA.
20 C. C. Roothan, *Rev. Mod. Phys.*, 1951, **23**, 69 . For a description of the basis set, see: W. Hehre, L. Radom, P. v. R. Schleyer and J. A. Pople, *Ab initio Molecular Orbital Theory*, Wiley, New York, 1986.
21 C. Lee, W. Yang and R. G. Parr, *Phys. Rev. B*, 1988, **37**, 785.
22 A. D. Becke, *Phys. Rev. A*, 1988, **38**, 3098; B. Mihelich, A. Savin, H. Stoll and H. Preuss, *Chem. Phys. Lett.*, 1989, **157**, 200.
23 A. D. Becke, *J. Chem. Phys.*, 1993, **98**, 5648.
24 Similar behaviour has already been reported for epoxy carbamates which react under basic conditions: T. Yamazaki, H. Hiwatsubo and T. Kitazume, *Tetrahedron: Asymmetry*, 1994, **5**, 1823.
25 The NMR spectra are for the α and β conformers. Although the NMR spectra at increased temperatures resulted in single absorptions, we utilised the conformer spectra since further substrate manipulation provided pertinent intermediates which displayed resolved spectra.