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Synthesis of novel isoxazoline-fused cyclic β-amino esters by regio- and stereoselective 1,3-dipolar cycloaddition

Melinda Nonn [a], Loránd Kiss [a], Enikő Forró [a], Zoltán Mucsi [c], Ferenc Fülöp [a,b,*]

[a] Institute of Pharmaceutical Chemistry, University of Szeged, H-6720 Szeged, Eötvös u. 6, Hungary
[b] Research Group of Stereochemistry of the Hungarian Academy of Sciences, University of Szeged, H-6720 Szeged, Eötvös u. 6, Hungary
[c] Department of Chemical Informatic, University of Szeged, H-6725 Szeged, Hungary

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ABSTRACT

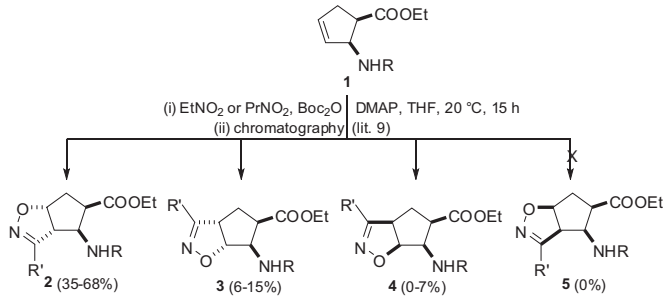
Isoxazoline-fused 2-aminocyclopentanecarboxylate derivatives were regio- and stereo-selectively synthesized by nitrile oxide 1,3-dipolar cycloaddition to *cis*- or *trans*-ethyl-2-aminocyclopent-3-ene-carboxylates. The compounds were prepared in enantiomerically pure form by enzymatic resolution of the racemic bicyclic β-lactam.

1. Introduction

The 1,3-dipolar cycloaddition of nitrile oxides to alkenes has become widely used as a highly efficient method for the synthesis of isoxazolines.[1] Nitrile oxides can be generated in situ by either the base-induced dehydrohalogenation of hydroximoyl chlorides (methodology of Huisgen[2]), or the dehydration of primary nitroalkane derivatives (methodology of Mukaiyama[3]). The 1,3-dipolar cycloaddition of nitrile oxides is a powerful technique to functionalize olefins since the isoxazoline ring formed may be regarded as a masked iminoalcohol, hydroxyketone or aminoalcohol.[1] A number of nitrile oxide cycloadditions to cyclic α- or γ-amino acid derivatives have been performed in recent years with the aim of the synthesis of different biologically active compounds. For example, isoxazole carboxylic acids, such as conformationally constrained aspartate and glutamate analogues have been synthesized via addition to α-amino cyclopentene esters.[4] The derivatives prepared proved to be inhibitors of excitatory amino acid transporters with neuroprotective activity.[4] Cycloaddition to γ-amino cyclopentene acids was applied for the stereoselective synthesis of novel multisubstituted cyclopentene derivatives, which were described as antiviral agents.[5] A novel route to isoxazoline/carbocyclic nucleosides involved the regio- and stereo-selective 1,3-dipolar cycloaddition of nitrile oxides to 2-azanorbornenes, followed by ring opening and a purine or pyrimidine base construction strategy.[6] Alicyclic β-amino acids have acquired great interest in recent years because of their pharmacological potential.[7] The naturally occurring β-amino acid cispentacin (1*R*,2*S*-2-aminocyclopentanecarboxylic acid), an antibiotic and (1*R*,2*S*)-2-amino-4-methylenecyclopentane-carboxylic acid (Icofungipen), a strong antifungal agent, for instance, are important examples of this class of compounds.[7] A number of cyclic, conformationally restricted β-amino acids have been used as building blocks for the synthesis of new peptides.[8]

2. Results and discussion

We recently reported novel isoxazoline-fused cispentacin regio- and stereo-isomers via a strategy of 1,3-dipolar cycloaddition of nitrile oxides to protected *cis*-2-aminocyclopent-3-ene carboxylates.[9] The nitrile oxides were generated from primary nitroalkanes (RNO_2) in the presence of *tert*-butoxycarbonyl anhydride (Boc_2O) and 4-dimethylaminopyridine (DMAP) according to the methodology of Mukaiyama. The cycloadditions to *cis*-amino esters **1** resulted in three of the four possible regio- and stereo-isomers **2**, **3** and **4**. Although the cycloaddition was not selective, three isoxazoline-fused cispentacin derivatives **2**, **3** and **4** could be isolated (Scheme 1).



Scheme 1. Synthesis of isoxazoline-fused β-amino esters from *cis*-2-aminocyclopentenecarboxylates **1** (R=Boc, COPh; R′=Me, Et)[9].

* Corresponding author. E-mail address: fulop@pharm.u-szeged.hu (F. Fülöp).

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Since the above procedure was not selective, we continued our experiments to search for other synthetic routes for the preparation of isoxazoline-fused cispentacins with higher selectivity. Dehydration of primary nitroalkanes to generate nitrile oxides may be accomplished not only with Boc_2O and DMAP (Scheme 1), but also with phenyl isocyanate (PhNCO) and triethylamine (Et_3N). Compounds **1a**,**b** were subjected to 1,3-dipolar cycloaddition under these conditions, using RNO_2, PhNCO, Et_3N in THF at 65 °C (Scheme 2).

Scheme 2. Regio- and stereo-selective synthesis of isoxazoline-fused β-amino esters **2a**–**d** from *cis*-2-aminocyclopentenecarboxylates **1a**,**b**.

The reactions with the nitrile oxides derived from $EtNO_2$ or $PrNO_2$ in the presence of PhNCO resulted selectively in **2a**–**d**, in which the isoxazoline ring is trans to the carbamate and ester groups, and the *O*-atom of the isoxazoline skeleton is farthest from the carbamate (Scheme 2). The explanation of the unexpected selectivity in this reaction is not yet clear. We are not aware of any similar example in the literature.

To clarify matters, DFT calculations[10] were carried out on the reaction of **1** and MeNCO by using the G03[11] program; the reaction enthalpies and Gibbs free energies of the transition states ($\Delta H^{\ddagger}$; $\Delta G^{\ddagger}$) and products (ΔH; ΔG) are listed in Table 1. Surprisingly, from a kinetic aspect, **4** was predicted to be the main product of the reaction, due to its lowest activation Gibbs free energy ($\Delta G^{\ddagger}$). Compounds **2** and **5** exhibited practically equal $\Delta G^{\ddagger}$ values, but the significantly higher energies (ca. 4 kJ mol^{-1}) suggest predicted concentrations of only a few per cent. The formation of **3** is least favourable, its formation being practically hindered. A possible explanation of the lowest-energy transition state of **4** is an intermolecular H-bond (HB) between MeNCO and the amide in **1**, as shown in Fig. 1. The same results were obtained at each level of computation [HF/3-21G, B3LYP/6-31G(d,p) and B3LYP/6-311++G(2d,2p)], irrespective of the solvent models applied [IEFPCM(THF)], and the theoretical model was therefore extended to a more complex description. It was earlier demonstrated that an explicit consideration of some selected solvent molecules or other components in the solvent provided a much more accurate picture of the mechanism.[12] In this particular case, the solvent is THF, which does not require the exact consideration of any THF molecule. However, excess $EtNO_2$ can be regarded as a cosolvent, strongly H-bonded to the amide in **1**. When the study of the ring closure mechanism included one explicit $EtNO_2$, the result altered. The lowest $\Delta G^{\ddagger}$ was computed for **2** (Fig. 1), but the value for **3** was very close, in agreement with experiment, where **3** was also detected in a significant amount beside the main component (**2**). For **4** and **5**, the $\Delta G^{\ddagger}$ values were in all cases higher than those calculated in vacuo, because the nitro compound occupied the reactive zone to some extent and hinders the attack of MeNCO (Fig. 1).

The result of cycloaddition of the nitrile oxide to *trans*-2-aminocyclopentenecarboxylate **6a**,**b** proved interesting (Scheme 3). Whereas the addition to the corresponding cis isomer (**1**) gave the three isomers **2**, **3** and **4** (Scheme 1), under the same experimental conditions (RNO_2, Boc_2O and DMAP) the trans counterparts **6a**,**b** furnished selectively only one cycloadduct isomer (**7a**–**d**) (Scheme 3). Compounds **7a**–**d** could also be prepared by the epimerization of **4a**–**c** at C-5 in the presence of NaOEt in EtOH, **4a**–**c** were prepared as very minor isomers by cycloaddition to **1** (Scheme 1).

The selectivity of formation of **7a**–**d** from **6a**,**b** is probably explained by: steric and H-bonding interactions, as presented in Fig. 2, i.e, steric repulsion in the transition state (**T7**) between the nitrile oxide and the ester group and an H-bonding interaction between the carbamate and the nitrile oxide (Scheme 3, Fig. 2).[4d]

The stereoselectivity in the reaction of **1** with the nitrile oxides (generated from RNO_2 and Boc_2O; Scheme 1) can probably be explained analogously. Steric repulsion between the ester moiety and the nitrile oxide determines the stereochemistry of **2** and **3** (Fig. 2). H-bonding interaction between the nitrile oxide and carbamate (*cis* to −COOEt) may be neglected in these cases (**T2** and **T3**). The regioselectivity is probably determined by the electron-withdrawing effect of the *N*-atom of the −NHBoc group, favouring attack of the nitrile oxide *O*-atom on C-4, distant from the carbamate. These two phenomena lead to the major products **2** and **3** (Scheme 1). Formation of the very minor product **4** is an indication that the H-bonding interaction between the carbamate and nitrile oxide in transition state can just overcome the ester/nitrile oxide steric repulsion (Fig. 2). The regioselectivity of the formation of **4** may also be explained on the basis of H-bonding interactions. The postulated transition state **T5**, which would lead to the fourth possible isomer in this reaction, involves highly unfavourable steric hindrance not only between the ester and the nitrile oxide, but also between the carbamate and the alkyl moiety (R) of the nitrile oxide. This explains why isomer **5** was never formed (Fig. 3, Scheme 1).

The results of calculations at different levels [B3LYP/6-31++G(d,p), B3LYP/6-311++G(d,p) and B3LYP/6-311++G(2d,2p)] relating to interpretation of the selectivity agreed well with the experimental finding that preferred product in the transformation of **6b** was **7b** (Table 2, Fig. 4).

These computations furnished eloquent proof that the selectivity of nitrile oxide addition to *trans*-2-aminocyclopentenecarboxylate is largely determined by the H-bonding effect in the transition state (Fig. 5).

The earlier synthesized isoxazoline-fused cispentacin derivatives (Scheme 1)[9] afforded an opportunity for the preparation of new transpentacin derivatives, regio- and stere-oisomers of **7**. Accordingly, **2a**–**d** and **3a**–**d** were epimerized at C-5 with NaOEt in EtOH to give izoxazoline-fused amino esters **8a**–**d** and **9a**–**d**, in which the amino and carboxylate functions were *trans*. Unfortunately, the yields were low and a relatively large amount of starting material was recovered during column chromatography purification of the products (Scheme 4).

The 100% regio- and stereo-selective synthesis of **2a** and **2c** (Scheme 2) and **7a** and **7c** (Scheme 3) was extended to their preparation in enantiomerically pure form. The starting material

Table 1
Enthalpy (in kJ mol^{-1}) and Gibbs free energy (in kJ mol^{-1}) of the transformation of **1b** to **2b**–**5b** in vacuo, with implicit solvent and with explicit solvent model

	In vacuo				In implicit solvent (THF)				With explicit cosolvent			
	$\Delta H^{\ddagger}$	$\Delta G^{\ddagger}$	ΔH	ΔG	$\Delta H^{\ddagger}$	$\Delta G^{\ddagger}$	ΔH	ΔG	$\Delta H^{\ddagger}$	$\Delta G^{\ddagger}$	ΔH	ΔG
2b	55.8	114.1	−169.5	−104.3	59.1	118.2	−165.7	−100.0	67.3	126.1	−164.1	−100.1
3b	75.1	128.3	−159.1	−97.2	79.3	132.5	−154.1	−92.0	70.1	129.3	−153.4	−92.0
4b	49.8	109.5	−164.1	−101.5	54.2	113.8	−160.3	−98.1	75.8	135.5	−160.2	−97.7
5b	54.9	113.7	−166.7	−100.9	58.2	117.9	−161.9	−96.3	95.4	153.9	−161.3	−96.5

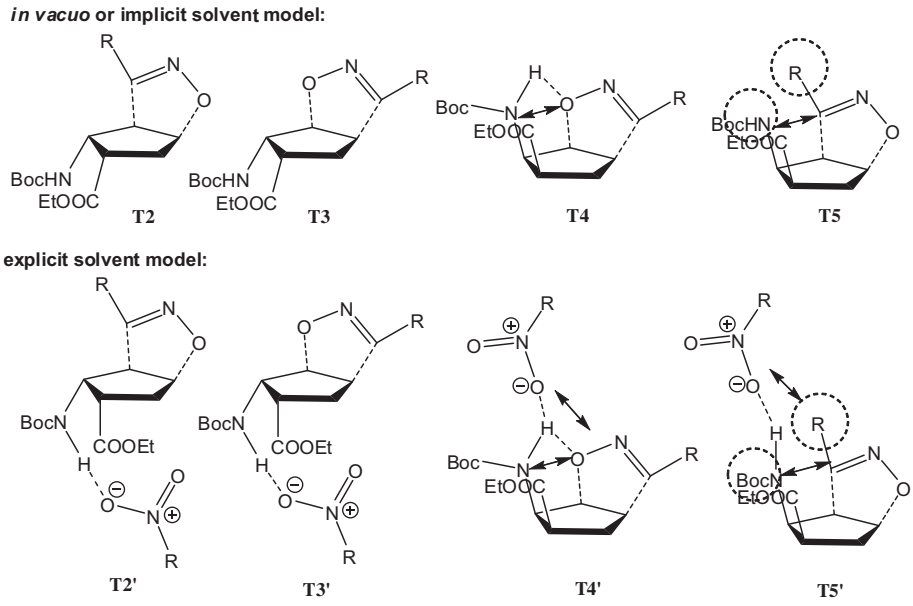
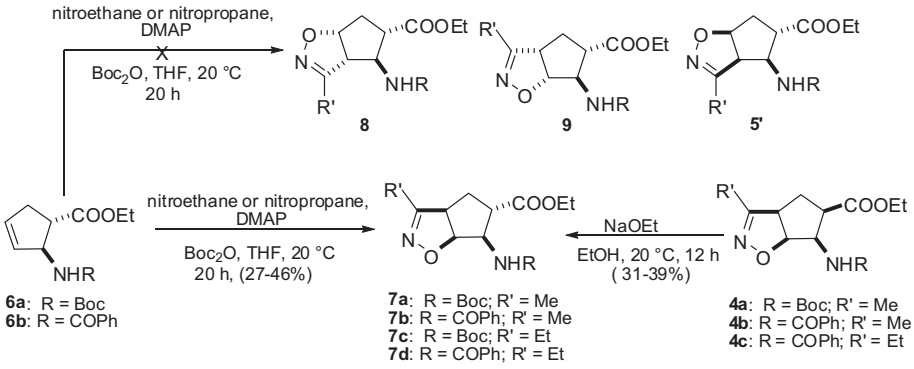


Fig. 1. Transition states **T2**, **T3** and **T4** in the formation of cycloadducts **2**–**5**; steric repulsions between –COOEt and nitrile oxides in **T2** and **T3**, and between –NHBoc and nitrile oxide and –COOEt and nitrile oxide in **T5** and hydrogen bonding interaction between –NHBoc and nitrile oxide in **T4**.



Scheme 3. Regio- and stereo-selective synthesis of isoxazoline-fused β-amino esters **7a**–**d** from *trans*-2-aminocyclopentenecarboxylates **6a**,**b**.

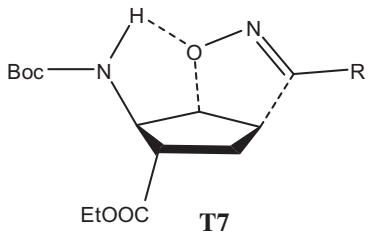


Fig. 2. Transition state **T7** stabilized by hydrogen bonding interactions during formation of cycloadducts **7a**–**d**.

the racemic bicyclic lactam **10** was subjected to enzymatic ring opening reaction with Lipolase in *i*-Pr_2O,[13] which afforded the desired amino acid enantiomer (+)-**11** in excellent enantiomeric excess (ee >99%).[14] Compound (+)-**11** was then transformed by known procedures to the corresponding protected amino ester (+)-**1a**.[15] Compound (+)-**1a** was next submitted to nitrile oxide (generated from $EtNO_2$ or $PrNO_2$ and PhNCO and Et_3N) cycloaddition, which resulted in the enantiomerically pure isoxazoline-fused cispentacin derivatives (−)-**2a** and (−)-**2c** in yield of 53% and 40% (Scheme 5).

Compounds (−)-**2a** and (−)-**2c** were epimerized in the presence of NaOEt in EtOH to the enantiomerically pure isoxazoline-fused transpentacin derivatives (+)-**8a** and (+)-**8c** (Scheme 5).

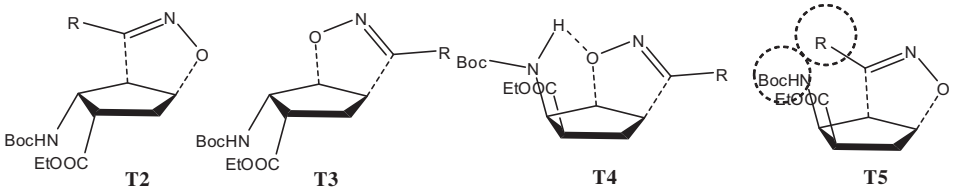


Fig. 3. Transition states **T2**, **T3** and **T4** in the formation of cycloadducts **2**–**5**; steric repulsions between –COOEt and nitrile oxides in **T2** **T3** and between –NHBoc and the nitrile oxide and between –COOEt and the nitrile oxide in **T5** and H-bonding interaction between –NHBoc and the nitrile oxide in **T4**.

Table 2
Enthalpy (in kJ mol^{-1}) and Gibbs free energy (in kJ mol^{-1}) of the transformation of **6b** to **7b**, **8b**, **9b** and **5′b**

	6b→**TS**		**6b**→products	
	$\Delta H^{\neq}$	$\Delta G^{\neq}$	ΔH	ΔG
7b	47.76	102.21	−170.02	−106.24
8b	65.32	119.90	−154.35	−92.50
9b	76.83	130.31	−152.22	−90.46
5′b	55.36	113.99	−163.44	−100.12

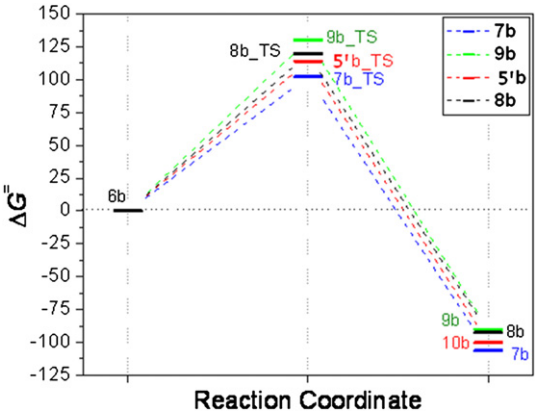


Fig. 4. Energy diagram for the transformation of **6b** to **7b**.

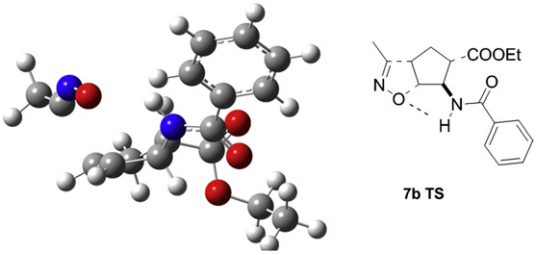
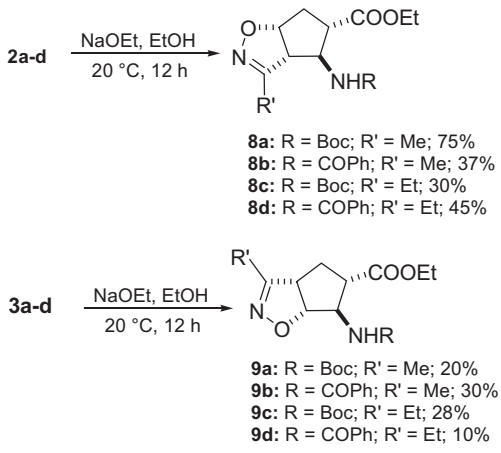
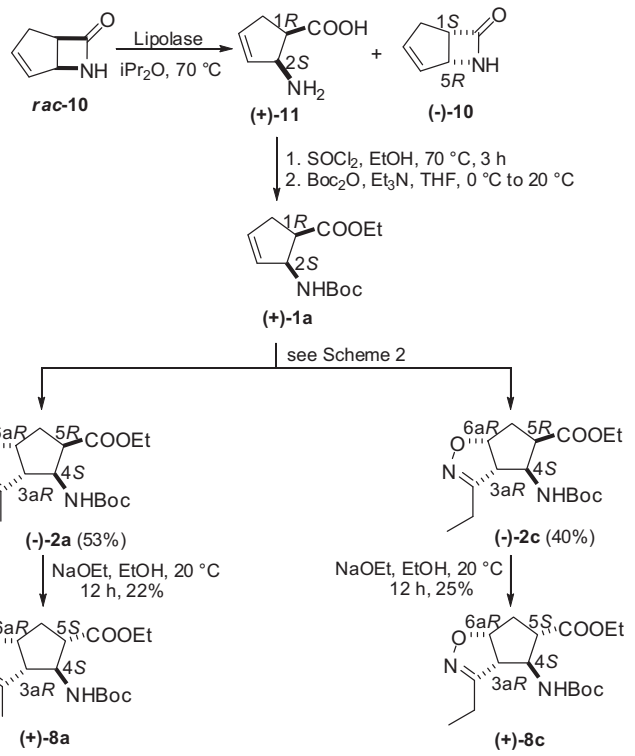


Fig. 5. H-bonding stabilization of **TS 7b** in the formation of **7b**.

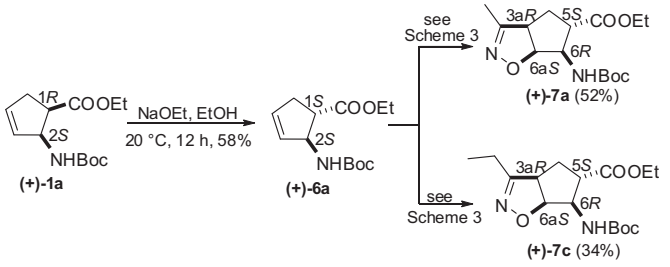


Scheme 4. Synthesis of isoxazoline-fused β-amino esters **8a**–**d** and **9a**–**d** by epimerization of **2a**–**d** and **3a**–**d**.

Boc-protected amino ester (+)-**1a** was isomerized to its *trans* derivative (+)-**6a**, which was then subjected to nitrile oxide (generated from $EtNO_2$ or $PrNO_2$ and Boc_2O and Et_3N) cycloaddition, giving the enantiomerically enriched isoxazoline-fused cispentacin derivatives (+)-**7a** and (+)-**7c** in yield of 52% and 34% (Scheme 6).



Scheme 5. Synthesis of the isoxazoline-fused β-amino ester enantiomers (−)-**2a**, (−)-**2c**, (+)-**8a** and (+)-**8c**.



Scheme 6. Synthesis of the isoxazoline-fused β-amino ester enantiomers (+)-**7a** and (+)-**7c**.

In conclusion, isoxazoline-fused cispentacin derivatives were synthesized regio- and stereo-selectively via the 1,3-dipolar cycloaddition of nitrile oxides to *cis*- and *trans*-ethyl 2-amino-3-cyclopentenecarboxylates. This synthetic pathway was also applied for the preparation of these compounds in enantiomerically pure form.

3. Experimental

3.1. General

The chemicals were purchased from Aldrich. Melting points were determined with a Kofler apparatus. NMR spectra were recorded on a Bruker DRX 400 spectrometer. Chemical shifts are given in parts per million relative to TMS as internal standard, with $CDCl_3$ or DMSO as solvent. The solvents were used as received from the supplier. Optical rotations were measured with a Perkin–Elmer 341 polarimeter. Mass spectra were recorded on a Finnigan MAT 95S spectrometer. Elemental analyses were performed with a Perkin–Elmer CHNS-2400 Ser II Elemental Analyzer.

The ee values for (−)-**2a**, (+)-**14a** and (+)-**7a** were determined by GC on a Chromopack Chiralsil-Dex CB column (25 m) [190 °C;

140 kPa; retention times (min): (−)-**2a**: 19.82 (antipode: 20.02); (+)-**7a**: 16.99 (antipode: 15.79); (+)-**8a**: 19.46 (antipode: 20.01)], while ee for (−)-**2c** was determined by GC on a CP-Chiralsil L-Val column (25 m) [190 °C; 100 kPa; retention time (min): 17.61 (antipode: 17.86)]. The ee value for (+)-**7c** was determined by HPLC on a Chiralcel^R OD 5 μ column (0.46 cm×25 cm) [mobile phase: *n*-hexane/2-propanol (95:5); flow rate 5 mL min^{-1}; detection at 205 nm; retention time (min): 25.06 (antipode: 32.39)], and ee for (+)-**8c** was determined by HPLC on a Chiral Pak IA 5 μ column (0.4 cm×1 cm) [mobile phase: *n*-heaxane/2-PrOH (90:10); flow rate 5 mL min^{-1}; detection at 205 nm; retention time (min): 21.86 (antipode: 18.46)].

3.2. Computational methods

All computations were carried out with the Gaussian03 program package (G03),[10,11] using standard convergence criteria, at B3LYP/6-31G(d,p), B3LYP/6-311++G(d,p) and B3LYP/6-311++G(2d,2 p) levels of theory. The vibrational frequencies were computed at the same levels of theory as used for geometry optimization in order to confirm all structures as residing at minima on their potential energy hypersurfaces. Thermodynamic functions U, H, G and S were computed at 298.15 K, using the quantum chemical, rather than the conventional, thermodynamic reference state.

3.3. General procedure for the synthesis of isoxazoline-fused-β-aminocyclopentanecarboxylates

Method A: To a solution of amino ester **1a** or **1b** (3.92 mmol) in THF (15 ml), RNO_2 (2 equiv), PhNCO (2 equiv) and Et_3N (2 equiv) were added and the mixture was stirred under reflux for 15 h. The reaction mixture was then diluted with EtOAc (50 ml), washed with H_2O (3×15 ml), dried (Na_2SO_4), and concentrated under reduced pressure. The crude residue was purified by column chromatography on silica gel (*n*-hexane/EtOAc), giving **2a**–**d**.[9]

Method B: To a solution of amino ester **6a** or **6b** (3 mmol) in THF (20 mL), RNO_2 (3.2 mmol), DMAP (0.6 mmol, 20 mol %) and Boc_2O (9 mmol, 3 equiv) were added and the mixture was stirred at 20 °C for 15 h. The reaction mixture was then diluted with H_2O (50 mL) and extracted with EtOAc (3×15 mL). The combined organic layer was washed with 5% HCl (15 mL) and brine (2×20 mL), dried (Na_2SO_4) and concentrated under reduced pressure. The crude residue was purified by column chromatography on silica gel (*n*-hexane/EtOAc), giving **7a**–**d**.

3.3.1. Ethyl (3aR,5S*,6R*,6aS*)-6-(tert-butoxycarbonylamino)-3-methyl-4,5,6,6a-tetrahydro-3aH-cyclopenta[d]isoxazole-5-carboxylate (**7a**).* A white solid; yield: 431 mg, 46%; mp 63–65 °C; R_f=0.25 (*n*-hexane/EtOAc 2:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.28 (t, 3H, CH_3, *J*=7.1 Hz), 1.46 (s, 9H, CH_3), 1.97–1.99 (s, 3H, CH_3), 2.00–2.05 (m, 1H, CH_2), 2.13–2.26 (m, 1H, CH_2), 2.38–2.48 (m, 1H, H-5), 3.63 (m, 1H, H-3a), 4.11–4.34 (m, 3H, H-6 and OCH_2), 4.89–4.94 (m, 1H, H-6a), 5.21 (br s, 1H, N–H); ^{13}C NMR (100 MHz, DMSO): δ=11.5, 14.8, 29.0, 30.7, 36.8, 45.7, 53.6, 60.4, 61.2, 83.9, 157.6, 172.7, 173.4; MS: (ESI) *m*/*z*=335 (M+Na). Anal. Calcd for $C_{15}H_{24}N_2O_5$: C, 57.68; H, 7.74; N, 8.97. Found: C, 57.41; H, 7.58; N, 8.82.

3.3.2. Ethyl (3aR,5S*,6R*,6aS*)-6-benzamido-3-methyl-4,5,6,6a-tetrahydro-3aH-cyclopenta[d]isoxazole-5-carboxylate (**7b**).* A white solid; yield: 398 mg, 42%; mp 172–174 °C; R_f=0.15 (*n*-hexane/EtOAc 2:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.16 (t, 3H, CH_3, *J*=7.1 Hz), 1.98–2.00 (s, 3H, CH_3), 2.03–2.10 (m, 1H, CH_2), 2.24–2.34 (m, 1H, CH_2), 2.51–2.59 (m, 1H, H-5), 3.69 (m, 1H, H-3a), 4.10–4.17 (m, 2H, OCH_2), 4.77–4.84 (m, 1H, H-6), 4.97–5.01 (m, 1H, H-6a), 6.70 (br s, 1H, N–H), 7.41–7.53 (m, 3H, Ar–H), 7.77–7.81 (m, 2H, Ar–H); ^{13}C NMR (100 MHz, DMSO): δ=11.6, 14.9, 30.8, 45.1, 53.9, 59.3, 61.0, 83.0, 128.4, 129.0, 132.1, 135.0, 157.7, 167.1, 173.3; MS: (ESI) *m*/*z*=317 (M+1). Anal. Calcd for $C_{17}H_{20}N_2O_4$: C, 64.54; H, 6.37; N, 8.86. Found: C, 64.38; H, 6.27; N, 8.75.

3.3.3. Ethyl (3aR,5S*,6R*,6aS*)-6-(tert-butoxycarbonylamino)-3-ethyl-4,5,6,6a-tetrahydro-3aH-cyclopenta[d]isoxazole-5-carboxylate (**7c**).* A white solid; yield: 215 mg, 22%; mp 105–106 °C; R_f=0.36 (*n*-hexane/EtOAc 2:1); ^{1}H NMR (400 MHz, DMSO): δ=1.07 (t, 3H, CH_3, *J*=7.4 Hz), 1.17 (t, 3H, CH_3, *J*=7.2 Hz), 1.39 (s, 9H, CH_3), 1.85–2.03 (m, 2H, CH_2), 2.15–2.27 (m, 1H, CH_2), 2.29–2.37 (m, 1H, CH_2), 2.38–2.47 (m, 1H, H-5), 3.71 (m, 1H, H-3a), 3.97–4.13 (m, 3H, OCH_2 and H-6), 4.71–4.76 (m, 1H, H-6a), 6.74 (br s, 1H, N–H);[13] C NMR (100 MHz, $CDCl_3$): δ=11.4, 14.9, 19.5, 29.0, 30.9, 45.8, 52.3, 60.3, 61.0, 78.8, 83.1, 155.8, 161.9, 173.4; MS: (ESI) *m*/*z*=227 (M+1). Anal. Calcd for $C_{16}H_{26}N_2O_5$: C, 58.88; H, 8.03; N, 8.58. Found: C, 58.62; H, 7.92; N, 8.44.

3.3.4. Ethyl (3aR,5S*,6R*,6aS*)-6-benzamido-3-ethyl-4,5,6,6a-tetrahydro-3aH-cyclopenta[d]isoxazole-5-carboxylate (**7d**).* A white solid; yield: 436 mg, 44%; mp 127–129 °C; R_f=0.15 (*n*-hexane/EtOAc 2:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.19, (t, 3H, CH_3, *J*=7.1 Hz), 1.26 (t, 3H, CH_3, *J*=7.1 Hz), 2.06–2.12 (m, 1H, CH_2), 2.23–2.37 (m, 2H, CH_2), 2.44–2.63 (m, 2H, CH_2 and H-5), 3.77 (m, 1H, H-3a), 4.12–4.21 (m, 2H, OCH_2), 4.80–4.87 (m, 1H, H-6), 4.98–5.03 (m, 1H, H-6a), 6.75 (b rs, 1H, N–H), 7.44–7.49 (m, 2H, Ar–H), 7.51–7.56 (m, 1H, Ar–H), 7.77–7.85 (m, 2H, Ar–H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=11.1, 14.4, 19.9, 30.7, 47.1, 52.4, 59.0, 61.6, 83.5, 127.5, 129.0, 132.1, 134.5, 162.3, 167.5, 172.6; MS: (ESI) *m*/*z*=331 (M+1). Anal. Calcd for $C_{18}H_{22}N_2O_4$: C, 65.44; H, 6.71; N, 8.48. Found: C, 65.23; H, 6.63; N, 8.29.

3.4. General procedure for the synthesis of isoxazoline-fused-β-amino esters 8a–d and 9a–d by epimerization of 2a–d and 3a–d

To a solution of isoxazoline-fused β-aminocyclopentane-carboxylate **2a**–**d** and **3a**–**d** (1 mmol) in EtOH (10 ml), NaOEt (1.2 mmol) was added and the mixture was stirred at room temperature for 12 h. The mixture was then concentrated under reduced pressure, and the residue was then diluted with $CHCl_3$ (30 ml), washed with H_2O (3×10 ml), dried (Na_2SO_4) and concentrated under reduced pressure. The crude residue was purified by crystallization (*n*-hexane/EtOAc) or column chromatography on silica gel (*n*-hexane/EtOAc 5:1).

3.4.1. Ethyl (3aR,4S*,5S*,6aR*)-4-(tert-butoxycarbonylamino)-3-methyl-4,5,6,6a-tetrahydro-3aH-cyclopenta[d]isoxazole-5-carboxylate (**8a**).* A white solid; yield: 234 mg, 75%; mp 92–94 °C; R_f=0.63 (*n*-hexane/EtOAc 1:2); ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.28 (t, 3H, CH_3, *J*=7.1 Hz), 1.48 (s, 9H, CH_3), 2.11 (s, 3H, CH_3), 2.25–2.34 (m, 1H CH_2), 2.42–2.50 (m, 1H, CH_2), 2.82–2.91 (m, 1H, H-5), 3.49–3.57 (m, 1H, H-3a), 4.10–4.22 (m, OCH_2), 4.34–4.40 (m, 1H, H-4), 4.82 (br s, 1H, N–H), 5.06–5.13 (m, 1H, H-6a); ^{13}C NMR (100 MHz, $CDCl_3$): δ=12.2, 14.5, 28.7, 36.8, 49.7, 58.1, 61.6, 63.3, 83.9, 98.0, 106.9, 155.2, 172.1; MS: (ESI) *m*/*z*=313 (M+1). Anal. Calcd for $C_{15}H_{24}N_2O_5$: C, 57.68; H, 7.74; N, 8.97. Found: C, 57.43; H, 7.61; N, 8.90.

3.4.2. Ethyl (3aR,4S*,5S*,6aR*)-4-benzamido-3-methyl-4,5,6,6a-tetrahydro-3aH-cyclopenta[d]isoxazole-5-carboxylate (**8b**).* A white solid; yield: 117 mg, 37%; mp 142–144 °C; R_f=0.3 (*n*-hexane/EtOAc 1:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.22–1.3 (t, 3H, CH_3, *J*=7.1 Hz), 2.16 (s, 3H, CH_3), 2.26–2.36 (m, 1H, CH_2), 2.50–2.61 (m, 1H, CH_2), 3.05–3.13 (m, 1H, H-5), 3.69–3.76 (m, 1H, H-3a), 4.12–4.20 (m, 2H, OCH_2), 4.72–4.79 (m, 1H, H-4), 5.12–5.21 (m, 1H, H-6a), 6.47–6.69 (br s, 1H, N–H), 7.43–7.50 (m, 2H, Ar–H), 7.52–7.58 (m, 1H, Ar–H), 7.76–7.80 (m, 2H, Ar–H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=12.3, 14.5,

30.1, 36.9, 49.4, 57.5, 61.7, 63.0, 126.3, 127.3, 129.1, 132.4, 134.3, 156.3, 172.1; MS: (ESI) m/z=317 (M+1). Anal. Calcd for $C_{17}H_{20}N_2O_4$: C, 64.54; H, 6.37; N, 8.86. Found: C, 64.41; H, 6.21; N, 8.70.

3.4.3. Ethyl (3aR,4S*,5S*,6aR*)-4-(tert-butoxycarbonylamino)-3-ethyl-4,5,6,6a-tetrahydro-3aH-cyclopenta[d]isoxazole-5-carboxylate (**8c**).* A white solid; yield: 98 mg, 30%; mp 119–121 °C; R_f=0.42 (*n*-hexane/EtOAc 2:1); ^{1}H NMR (400 MHz, DMSO): δ=1.07 (t, 3H, CH_3, J=7.47 Hz), 1.14 (t, 3H, CH_3, J=7.1 Hz), 1.38 (s, 9H, CH_3), 1.87–1.96 (m, 1H, CH_2), 2.23–2.46 (m, 3H, CH_2), 2.48–2.51 (m, 1H, H-5), 2.72–2.79 (m, 1H, H-3a), 3.45 (dd, 1H, H-4, J=5.0 and 5.1 Hz), 3.96–4.06 (m, 2H, OCH_2), 4.10–4.17 (m, 1H, H-6a), 4.89–4.96 (br s, 1H, N–H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=11.3, 14.8, 20.2, 29.0, 36.7, 49.7, 58.5, 61.2, 61.7, 79.1, 83.9, 155.7, 160.7, 172.7; MS: (ESI) m/z=327 (M+1). Anal. Calcd for $C_{16}H_{26}N_2O_5$: C, 58.88; H, 8.03; N, 8.58. Found: C, 58.71; H, 7.85; N, 8.30.

3.4.4. Ethyl (3aR,4S*,5S*,6aR*)-4-benzamido-3-ethyl-4,5,6,6a-tetrahydro-3aH-cyclopenta[d]isoxazole-5-carboxylate (**8d**).* A white solid; yield: 149 mg, 45%; mp 136–137 °C; R_f=0.46 (*n*-hexane/EtOAc 1:1); ^{1}H NMR (400 MHz, DMSO): δ=1.05 (t, 3H, CH_3, J=7.15 Hz), 1.07 (t, 3H, CH_3, J=7.2 Hz), 1.93–2.01 (m, 1H, CH_2), 2.23–2.34 (m, 1H, CH_2), 2.36–2.53 (m, 2H, CH_2), 2.91–2.99 (m, 1H, H-5), 3.63 (dd, 1H, H-3a, J=5.0 and 5.1 Hz), 3.93–4.01 (m, 2H, OCH_2), 4.57–4.64 (m, 1H, H-4), 4.95–5.02 (m, 1H, H-6a), 7.42–7.54 (m, 3H, Ar–H), 7.77–7.81 (m, 2H, Ar–H), 8.66 (br s, 1H, N–H); ^{13}C NMR (100 MHz, DMSO): δ=11.4, 14.7, 20.3, 36.9, 49.6, 57.4, 61.2, 61.5, 84.1, 128.1, 129.2, 132.3, 134.0, 136.5, 158.0, 171.8; MS: (ESI) m/z=331 (M+1). Anal. Calcd for $C_{18}H_{22}N_2O_4$: C, 65.44; H, 6.71; N, 8.48. Found: C, 65.21; H, 6.80; N, 8.30.

3.4.5. Ethyl (3aS,5S*,6R*,6aR*)-6-(tert-butoxycarbonylamino)-3-methyl-4,5,6,6a-tetrahydro-3aH-cyclopenta[d]isoxazole-5-carboxylate (**9a**).* A white solid; yield: 62 mg, 20%; mp 113–115 °C; R_f=0.47 (*n*-hexane/EtOAc 1:2); ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.26 (t, 3H, CH_3, J=7.2 Hz), 1.44 (s, 9H, CH_3), 1.97–1.98 (s, 3H, CH_3), 2.03–2.12 (m, 1H, CH_2), 2.24–2.34 (m, 1H, CH_2), 3.08–3.20 (m, 1H, H-5), 3.54–3.62 (m, 1H, H-3a), 3.93–4.04 (m, 1H, H-6), 4.11–4.18 (m, 2H, OCH_2), 4.83 (br s, 1H, N–H), 5.00–5.10 (m, 1H, H-6a); ^{13}C NMR (100 MHz, $CDCl_3$): δ=11.8, 14.5, 28.7, 28.8, 30.8, 53.7, 59.9, 61.5, 63.6, 101.3, 139.9, 155.4, 157.8; MS: (ESI) m/z=335 (M+Na). Anal. Calcd for $C_{15}H_{24}N_2O_5$: C, 57.68; H, 7.74; N, 8.97. Found: C, 57.41; H, 7.63; N, 8.92.

3.4.6. Ethyl (3aS,5S*,6R*,6aR*)-6-benzamido-3-methyl-4,5,6,6a-tetrahydro-3aH-cyclopenta[d]isoxazole-5-carboxylate (**9b**).* A white solid; yield: 95 mg, 30%; mp 181–183 °C; R_f=0.23 (*n*-hexane/EtOAc 1:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.23 (t, 3H, CH_3, J=7.2 Hz), 1.42 (s, 3H, CH_3), 2.05–2.12 (m, 1H, CH_2), 2.44–2.55 (m, 1H, CH_2), 3.49–3.58 (m, 1H, H-5), 3.71–3.79 (m, 1H, H-3a), 4.13–4.20 (m, 2H, OCH_2), 4.21–4.29 (m, 1H, H-6), 5.40 (dd, 1H, H-6a, J=5.0 and 5.2 Hz), 6.65 (br s, 1H, N–H), 7.44–7.49 (m, 2H, Ar–H), 7.52–7.57 (m, 1H, Ar–H), 7.76–7.80 (m, 2H, Ar–H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=11.86, 14.52, 27.56, 31.29, 47.26, 53.91, 61.59, 63.88, 88.26, 122.64, 126.92, 127.33, 129.05, 132.20, 148.00, 182.23; MS: (ESI) m/z=317 (M+1). Anal. Calcd for $C_{17}H_{20}N_2O_4$: C, 64.54; H, 6.37; N, 8.86. Found: C, 64.39; H, 6.25; N, 8.69.

3.4.7. Ethyl (3aS,5S*,6R*,6aR*)-6-(tert-butoxycarbonylamino)-3-ethyl-4,5,6,6a-tetrahydro-3aH-cyclopenta[d]isoxazole-5-carboxylate (**9c**).* A white solid; yield: 75 mg, 23%; mp 113–115 °C; R_f=0.61 (*n*-hexane/EtOAc 1:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.21 (t, 3H, CH_3, J=7.5 Hz), 1.26–1.32 (t, 3H, CH_3, J=7.4 Hz), 1.47 (s, 9H, CH_3), 2.03–2.14 (m, 1H, CH_2), 2.24–2.38 (m, 2H, CH_2), 2.44–2.55 (m, 1H, CH_2), 3.11–3.25 (m, 1H, H-5), 3.62–3.70 (m, 1H, H-3a), 4.95–4.07 (m, 1H, H-6), 4.14–4.20 (m, 2H, OCH_2), 4.82–4.93 (m, 1H, H-6a), 5.08 (br s, 1H, N–H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=11.0, 14.5, 20.2, 28.7, 30.1, 31.1, 52.4, 61.5, 63.4, 117.5, 119.5, 124.4, 155.4, 162.3; MS: (ESI) m/z=349 (M+Na). Anal. Calcd for $C_{16}H_{26}N_2O_5$: C, 58.88; H, 8.03; N, 8.58. Found: C, 58.73; H, 7.85; N, 8.31.

3.4.8. Ethyl (3aS,5S*,6R*,6aR*)-6-benzamido-3-ethyl-4,5,6,6a-tetrahydro-3aH-cyclopenta[d]isoxazole-5-carboxylate (**9d**).* A white solid; yield: 33 mg, 10%; mp 192–194 °C; R_f=0.39 (*n*-hexane/EtOAc 1:1) and ^{1}H NMR (400 MHz, DMSO): δ=1.05 (t, 3H, CH_3, J=7.2 Hz), 1.10 (t, 3H, CH_3, J=7.2 Hz), 1.94–2.05 (m, 1H, CH_2), 2.21–2.43 (m, 3H, CH_2), 2.90–2.98 (m, 1H, H-5), 3.72–3.80 (m, 1H, H-3a), 3.92–4.05 (m, 2H, OCH_2), 4.40–4.47 (m, 1H, H-6), 4.92 (dd, 1H, H-6a, J=4.8 and 7.7 Hz), 7.44–7.57 (m, 3H, Ar–H), 7.83 (d, 2H, Ar–H, J=7.5 Hz), 8.65 (br s, 1H, N–H); ^{13}C NMR (100 MHz, DMSO): δ=11.3, 14.7, 19.9, 30.9, 48.7, 52.4, 61.2, 61.9, 89.1, 128.1, 129.2, 132.2, 135.1, 162.7, 167.1, 172.7; MS: (ESI) m/z=331 (M+1). Anal. Calcd for $C_{18}H_{22}N_2O_4$: C, 65.44; H, 6.71; N, 8.48. Found: C, 65.20; H, 6.56; N, 8.28.

3.5. Characterization of the enantiomers

The ^{1}H NMR spectra of the enantiomeric substances were the same as those of the corresponding racemic compounds.

*3.5.1. Ethyl (1S,2S)-2-(tert-butoxycarbonylamino)cyclopent-3-enecarboxylate [(+)-**6a**].* A white solid; yield: 58%; mp=58–60 °C; $[\alpha]_D^{25}$ +121.7 (*c* 0.38, EtOH).

*3.5.2. Ethyl (3aR,4S,5R,6aR)-4-(tert-butoxycarbonylamino)-3-methyl-4,5,6,6a-tetrahydro-3aH-cyclopenta[d]isoxazole-5-carboxylate [(−)-**2a**].* A white solid; yield: 53%; mp 80–82 °C; $[\alpha]_D^{25}$ −8.3 (*c* 0.4, EtOH).

*3.5.3. Ethyl (3aR,4S,5R,6aR)-4-(tert-butoxycarbonylamino)-3-ethyl-4,5,6,6a-tetrahydro-3aH-cyclopenta[d]isoxazole-5-carboxylate [(−)-**2c**].* A white solid; yield: 40%; mp 105–107 °C; $[\alpha]_D^{25}$ −2 (*c* 0.1, EtOH).

*3.5.4. Ethyl (3aR,4S,5S,6aR)-4-(tert-butoxycarbonylamino)-3-methyl-4,5,6,6a-tetrahydro-3aH-cyclopenta[d]isoxazole-5-carboxylate [(+)-**8a**].* A white solid; yield: 22%; mp 90–93 °C; $[\alpha]_D^{25}$ +20 (*c* 0.28, EtOH).

*3.5.5. Ethyl (3aR,4S,5S,6aR)-4-(tert-butoxycarbonylamino)-3-ethyl-4,5,6,6a-tetrahydro-3aH-cyclopenta[d]isoxazole-5-carboxylate [(+)-**8c**].* A white solid; yield: 25%; mp 119–121 °C; $[\alpha]_D^{25}$ +20 (*c* 0.37, EtOH).

*3.5.6. Ethyl (3aR,5S,6R,6aS)-6-(tert-butoxycarbonylamino)-3-methyl-4,5,6,6a-tetrahydro-3aH-cyclopenta[d]isoxazole-5-carboxylate [(+)-**7a**].* Yellow oil; yield: 52%; $[\alpha]_D^{25}$ +105 (*c* 0.39, EtOH).

*3.5.7. Ethyl (3aR,5S,6R,6aS)-6-(tert-butoxycarbonylamino)-3-ethyl-4,5,6,6a-tetrahydro-3aH-cyclopenta[d]isoxazole-5-carboxylate [(+)-**7c**].* A white solid; yield: 34%; mp 105–107 °C; $[\alpha]_D^{25}$ +136 (*c* 0.30, EtOH).

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