Tetrahedron 67 (2011) 1463–1467

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Chemoselective opening of Vince lactam epoxide with nitrogen nucleophiles

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ARTICLE INFO

Article history:
Received 30 August 2010
Received in revised form 19 November 2010
Accepted 13 December 2010
Available online 17 December 2010

Keywords:
Chemoselectivity
Vince lactam
Nucleophilic addition
Epoxide
Oxazolidinones

ABSTRACT

Here is reported the chemoselective opening of the amide bond on a Vince lactam derivative with amines, without the cleavage of the epoxide-moiety, getting five new epoxides. Also reported is the rearrangement of the epoxides into the respective five new oxazolidinones with the use of $BF_3 \cdot Et_2O$. Crystal structures of some molecules and hydrogen bonding interactions are discussed.

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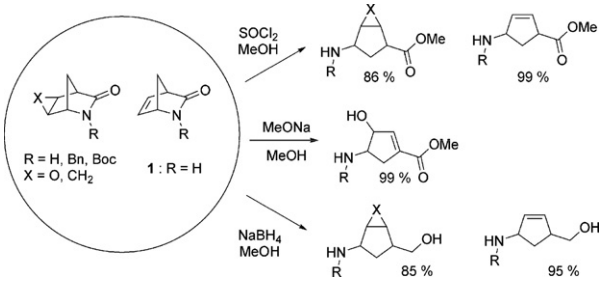
1. Introduction

Commercially available 2-azabicyclo[2.2.1]hept-5-en-3-one (**1**) (Vince lactam), is a useful synthon for the preparation of a growing number of pharmacologically active molecules, such as anticancer and antiviral agents.[1] The most important chemical compounds developed are the carbocyclic nucleoside analogues, in which the starting Vince lactam is modified to mimic the sugar moiety of the nucleoside. The majority of the works upon this starting material, concern the stereoselective modification of the double bond to obtain epoxides,[2] cyclopropanes,[3] aziridines[4] and vicinal diols,[5] which, in turn, can be modified to get a wide variety of new compounds. In all of these works the amide bond of the Vince lactam and of its derivatives has been opened using mainly three procedures: (a) $SOCl_2$ in methanol; (b) MeONa in methanol; or (c) $NaBH_4$ in methanol, as reported in Scheme 1.



Scheme 1.

Recently, we reported the preparation of a series of γ-aminocyclopentene sulfonic acids and amides of general structure **A**, (R=alkyl or aminoacid radical), by diastereoselective cycloaddition/ring-opening sequence affording peptidomimetic molecules[6] (Fig. 1).

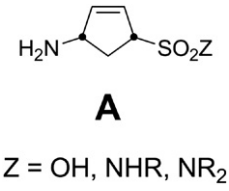


Fig. 1. Amino Cyclopentenesulfonic acid and amides.

As a further development, in this paper we consider the Vince lactam as a substrate for access to analogous rotationally restricted carboamides. To the best of our knowledge there is only one report describing the opening of the amide bond using an amine, in particular ethylamine, in which the double bond has not been transformed.[7] So, it was decided to study the reactivity of the amide bond in the presence of the epoxy group on Vince lactam **3**. Here, we describe the chemoselective and stereoselective synthesis of functionalized cyclopentane derivatives.

2. Results and discussion

Compound **3** was obtained, as reported in literature, starting from commercially available 2-azabicyclo[2.2.1]hept-5-en-3-one **1** treated with Boc-anhydride in the presence of DMAP and TEA and

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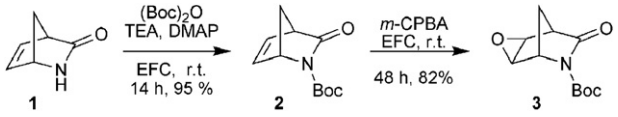
0040-4020/$ – see front matter © 2010 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2010.12.031

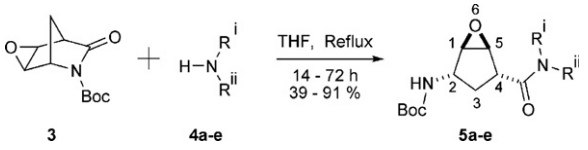
then *m*-CPBA for epoxidation (Scheme 2).[8,9] Epoxidation is completely regioselective using a bulky *N*-protecting group, getting only the *exo*-compound. For these two steps ethanol-free-chloroform (EFC) was used as solvent. It has allowed us to obtain compound **2** in high yield and to increase that of the further epoxidation product **3** by about 15%.



Scheme 2.

Compound **3** has been further attacked by some selected nitrogen-based nucleophiles as shown in Table 1. For this study four aliphatic amines (three primary and one secondary) and one aromatic primary amine were chosen. All the reactions have good yields, except that involving the use of aniline. Moreover, all the reactions show a strong chemoselectivity of the substrate, because only the amide group reacts, leaving intact the epoxide-moiety, on which further reactions are possible.[10] The first nucleophile we used was an ethylamine solution (70% in water) that, after purification, produced compound **4a** in a good yield (85%, Table 1, entry 1).

Table 1
Nucleophilic addition of amines



Amine **4**		Product **5**		Equiv	Time (h)	Temp (°C)	Yield (%)
H_2N	**4a**	Boc, N, H, N, O	**5a**	4	14	70	85
H_2N OH	**4b**	Boc, N, H, N, OH, O	**5b**	2	14	70	75
H_2N, COOMe, O Bn	**4c**	Boc, N, H, N, COOMe, O Bn, O	**5c**	3.6	20	70	91
H_2N	**4d**	Boc, N, H, N, O	**5d**	1.1	72	100	39
N H	**4e**	Boc, N, H, N, O	**5e**	5	48	100	68

The second nucleophile we used is a bidentate reagent: 3-amino-1-propanol **4b**, commercially available, and chosen to study competition between oxygen and nitrogen. By ^{1}H NMR it has been established the presence of a single product, and X-ray crystallography confirmed the structure of compound **5b**. As it can be seen from the ORTEP drawing (Fig. 2) only the nitrogen atom attacks the amide bond getting the desired product with 75% yield. This experiment confirms the strong chemoselectivity of the lactam against the epoxide, and also shows a further chemoselectivity towards the nucleophilic reagent.

The last primary aliphatic amine used is a (2*S*,3*R*)-threonine derivative, protected as methyl ester and *O*-benzylated (Table 1, entry 3). This reagent was synthesized from (2*S*,3*R*)-Fmoc-*O*-benzyl-threonine, which is commercially available. Using standard

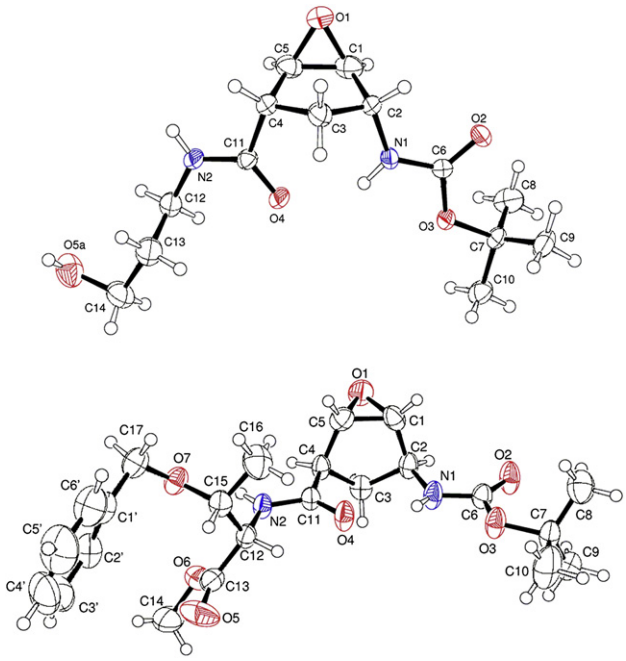
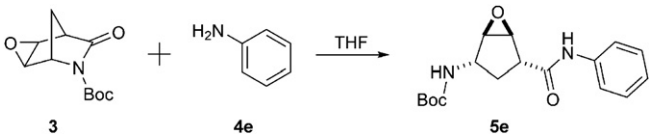


Fig. 2. ORTEP drawings of **5b** (top) and **5c** (bottom). Ellipsoids enclose 50% probability.

procedures, we first esterified the free acid, and then deprotected the amino group to get amine **4c**. The choice of this particular α-aminoacid is due to its hindered side chain. Moreover, it was decided to synthesize a chiral epoxide **3**, starting from (*S*)-2-aza-bicyclo[2.2.1]hept-5-en-3-one with the same reactions seen above, to avoid problems in the characterization of the product. Compound **5c** was isolated with a yield of 91% using only 1.1 equiv of the reagent. From X-ray analysis it was established the structure and the lack of racemization of the dipeptide **5c** (Fig. 2).

In the case of aniline (**4d**), as nucleophile, it was necessary to carry out the reaction in a sealed tube for a longer time. Also, increasing the amount of reagent to 3.6 equiv, the yield was only 39% (Table 2, entry 4), probably due to the low nucleophilicity of aniline. Even in the case of diethylamine **4e**, chosen as a model for secondary amines, it was necessary to carry out the reaction in a sealed tube, due to the low boiling point of the reagent. But, despite the large excess and the increasing of the temperature to 100 °C, the yield was only 68%. This approach wasn't necessary with ethylamine. The NMR characterization of the product **5e** required the use of C_6D_6 as solvent at 400 MHz instrument to see clearly distinguished signals. From ^{1}H NMR spectrum (see Experimental section and Supplementary data) it is possible to notice that the two *N*-ethyl chains are chemically different. In fact, because of the sterically hindered rotation there are two distinct triplets. Not surprisingly, the two NCH_2 appear as multiplets and not as quartets, because they are diastereotopic. The same effect is observed in the ^{13}C NMR spectrum.

Table 2
Reaction with aniline

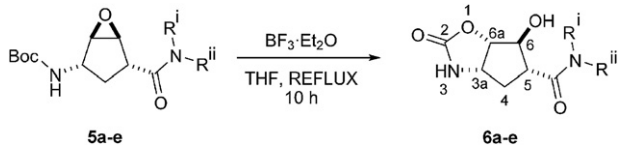


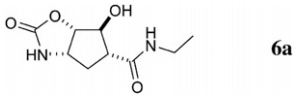
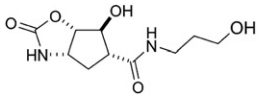
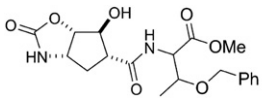
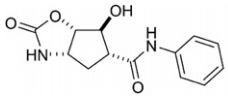
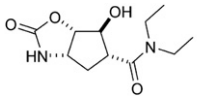
Entry	Temp	Equiv	Time	Apparatus	Yield
1	70 °C	1.2	14 h	Reflux	–
2	70 °C	2.4	2 days	Reflux	14%
3	70 °C	2.4	14 h	Reflux+$BF_3 \cdot Et_2O$	Traces
4	100 °C	3.6	3 days	Sealed tube	39%

In our attempts to obtain new products and enlarge the reactivity of this scaffold, we tried to modify the epoxide ring, choosing compound **5a** as a model. The first method we used is that reported by Salvador et al.,[11] and it consists the use of hydrazine sulfate as catalyst (10 mol %) to afford a regioselective ring-opening of styrene oxides and epoxysteroids with primary, secondary and tertiary alcohols. Unfortunately, this procedure doesn't work with our substrates by using the conditions reported in the literature.

As reported by Katagiri et al.,[8] by using $BF_3 \cdot Et_2O$, the carbonyl moiety of the Boc protecting group opens the epoxide ring to form a new oxazolidinone fused ring, and loses the *tert*-butyl chain. We tried to use a nucleophile, such as **4b** and **4c**, in combination with $BF_3 \cdot Et_2O$, thinking that in this case the protecting group doesn't participate to the reaction, but every time we obtained the Boc rearrangement. At this point it was decided to transform the five epoxides **5a**–**e** to the correspondents oxazolidinones (**6a**–**e**) using $BF_3 \cdot Et_2O$ and without adding any nucleophile. In Table 3, the five products and the respective yields are reported. Moreover, it has been observed that the Boc-rearrangement can be obtained in methanol without Lewis acid, but in this case, the reaction time is extended to 15 days. The five epoxides and the five oxazolidinones were fully characterized with mono- and bidimensional NMR spectra, together with MS analyses. Given the lack of reactivity of the epoxides **5a**–**e** towards amines in the presence of $BF_3 \cdot Et_2O$, it was decided to obtain the oxazolidinones **6a**–**e** directly from compound **3**, but unfortunately the reaction stops at the first step, forming only the epoxide derivative.

Table 3
Rearrangement of epoxides **5** to oxazolidinones **6**



Product		Yield (%)
	**6a**	78
	**6b**	87
	**6c**	88
	**6d**	93
	**6e**	90

3. Conclusion

The strategy described herein offers an efficient access to five new epoxides through the chemoselective cleavage of the amide bond of a Vince lactam derivative with a selected variety of amines; and the rearrangement to the correspondent oxazolidinones. Moreover, in our continuing study to develop new and more general methods for the preparation of peptidomimetics, it has been synthesized compound **5c**, an interesting molecule because with a few theoretical steps it could be possible to obtain pharmacologically active compounds.

4. Experimental section

4.1. General

Melting points were determined with a Kofler hot stage and are uncorrected. ^1H and ^{13}C NMR spectra were recorded at 27 °C ($CDCl_3$), unless otherwise stated, with a Bruker AC200 MHz instrument operating at 200.13 and 50.33 MHz, respectively, or with a Bruker Avance 400 MHz instrument operating at 400.13 and 100.62 MHz, respectively. Chemical shifts are reported in parts per million from internal TMS. The ^1H NMR data are reported as follows: s=singlet, d=doublet, t=triplet, m=multiplet, br s=broad singlet, br d=broad doublet, br t=broad triplet; coupling constant (s) in hertz. Mass spectra were recorded in the positive or negative ion mode with an LCQ-DECA Thermo instrument by using electrospray ionization. All solvents were previously dried according to standard procedures. Analytical TLC was performed on silica gel 60 F_{254} plates. Flash column chromatography was carried out on silica gel (0.040–0.063 mm). IR spectra were recorded with a Perkin–Elmer Spectrum BX. Specific rotation was recorded with a Perkin–Elmer 343 polarimeter. Crystallographic data (excluding structure factors) for the structures in this paper have been deposited at the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-789245 (**5b**), CCDC-789244 (**5c**), CCDC-789246 (**6b**). Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK, (fax: +44 (0)1223 336033 or e-mail: deposit@ccdc.cam.ac.Uk).

*4.1.1. tert-Butyl (1S,4R)-3-oxo-2-azabicyclo[2.2.1]hept-5-en-2-carboxylate (**2**)[1b].* (1*S*)-(+)-2-Azabicyclo[2.2.1]hept-5-en-3-one **1** (0.65 g, 5.96 mmol), Boc_2O (2.08 g, 9.54 mmol, 1.6 equiv) and DMAP (0.73 g, 5.96 mmol, 1 equiv) were dissolved in dry EFC (12 mL) and TEA (0.83 mL, 5.96 mmol) was added. The mixture was stirred at rt for 18 h. After this time, the solvent was evaporated in vacuo. The residue was purified by chromatography on silica gel (petroleum ether/Et_2O 1:3) to yield **2** (1.18 g, 5.64 mmol, 95%) as a white solid. Mp: 85–87 °C; ^1H NMR (400 MHz, $CDCl_3$): δ=1.44 (s, 9H, Boc), 2.09 (d, ^2J=8.4 Hz, 1H, H7a), 2.29 (d, ^2J=8.4 Hz, 1H, H7b), 3.32 (m, 1H, H4), 4.90 (m, 1H, H1), 6.60 (m, 1H, H5), 6.84 (m, 1H, H6). MS (ESI): *m*/*z*=232 $[M+Na]^+$.

*4.1.2. tert-Butyl (1R,2S,4R,5S)-7-oxo-3-oxa-6-azatricyclo[3.2.1.0^{2,4}]octan-6-carboxylate (**3**)[1b].* Boc-azabicyclo **2** (1.18 g, 5.64 mmol) and *m*-CPBA (3.88 g, 22.5 mmol, 4 equiv) were dissolved in dry EFC (40 mL). The mixture was stirred at rt for three days. After this time, the reaction was diluted with $CHCl_3$ (150 mL) and washed with saturated Na_2CO_3 solution (3×40 mL). The organic phase was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The white solid was purified by chromatography on silica gel (1° eluent petroleum ether/Et_2O 3:1, 2° eluent Et_2O) getting **3** (1.04 g, 4.62 mmol, 82%) as a white solid. Mp: 120–122 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 1.51 (s, 9H, Boc), 1.62 (d, ^2J=10 Hz, 1H, H8b), 1.80 (d, ^2J=10 Hz, 1H, H8a), 3.05 (s, 1H, H1), 3.60 (m, 1H, H2), 3.76 (m, 1H, H4), 4.60 (s, 1H, H5). MS (ESI): *m*/*z*=248 $[M+Na]^+$.

*4.1.3. (1S,2R,4S,5R) and (1R,2S,4R,5S) tert-Butyl 4-(ethylcarbamoyl)-6-oxabicyclo[3.1.0]hexan-2-ylcarbamate (**5a**).* Compound **3** (0.33 g, 1.47 mmol) was dissolved in 10 mL of THF, ethylamine solution (70% in H_2O) (240 μL, 2.94 mmol) was added, and the reaction was refluxed for 14 h. After this time, the solvent was removed under reduced pressure and the residue diluted in $CHCl_3$ and washed with water (×3). The organic phase was dried over Na_2SO_4, filtered and

concentrated under vacuum obtaining **5a** (0.34 g, 1.26 mmol, 85%) as a white solid, mp: 143–142 °C; ν_{max}(KBr) 3343, 2981, 1694, 1653, 1557, 1524, 1321, 1240, 1170, 1059 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.10 (t, ^3J=7.3 Hz, 3H, CH_3), 1.38 (s, 9H, Boc), 1.63 (d, ^2J=14.3 Hz, 1H, H3), 1.88 (dt, J=14.3, 7.8 Hz, 1H, H3′), 2.89 (d, ^3J=7.9 Hz, 1H, H4), 3.23 (m, 2H, CH_2CH_3), 3.39 (d, ^3J=2 Hz, 1H, H5), 3.48 (d, ^3J=2 Hz, 1H, H1), 4.25 (br t, ^3J=8.3 Hz, 1H, H2), 6.46 (br d, ^3J=9 Hz, 1H, *NH* amide), 6.56 (br t, ^3J=8 Hz, 1H, *NH* carbamate). ^{13}C NMR (200 MHz, $CDCl_3$) δ 14.6 (CH_2CH_3), 28.4 (Boc), 31.6 (C3), 34.7 (CH_2CH_3), 46.2 (C4), 50.1 (C2), 58.6 (C5), 59.2 (C1), 79.2 (Boc), 155.5 (CO carbamate), 172.7 (CO amide). MS (ESI): m/z=271 $[M+H]^+$, 293 $[M+Na]^+$. $C_{13}H_{22}N_2O_4$ (270.32): calcd C 57.76; H 8.20; N 10.36; found C 57.70; H 8.37; N 10.20.

*4.1.4. (1S,2R,4S,5R) and (1R,2S,4R,5S) tert-Butyl 4-(3-hydroxypropylcarbamoyl)-6-oxabicyclo[3.1.0]hexan-2-ylcarbamate (**5b**).* Compound **3** (0.31 g, 1.38 mmol) was dissolved in 10 mL of dry THF, 3-aminopropan-1-ol (210 μL, 2.76 mmol) was added and the reaction was refluxed for 14 h. After this time, the solvent was removed under reduced pressure and the residue was diluted in $CHCl_3$ and washed with water (×3). The organic phase was dried over Na_2SO_4, filtered and concentrated under vacuum obtaining **5b** (0.31 g, 1.03 mmol, 75%) as a white solid, mp: 168–170 °C; ν_{max}(KBr) 3313, 2966, 2937, 1686, 1657, 1517, 1240, 1174, 1067 cm^{-1}; ^{1}H NMR (400 MHz, CD_3OD) δ 1.46 (s, 9H, Boc), 1.65 (d, ^2J=14.4 Hz, 1H, H3), 1.75 (m, 2H, $CH_2CH_2CH_2$), 1.93 (dt, J=14.4, 7.4 Hz, 1H, H3′), 3.05 (d, ^3J=8 Hz, 1H, H4), 3.30 (t, ^3J=7 Hz, 2H, CH_2NH), 3.41 (d, ^3J=1.8 Hz, 1H, H5), 3.58 (d, ^3J=1.8 Hz, 1H, H1), 3.62 (t, ^3J=6.2 Hz, 2H, CH_2OH), 4.17 (d, ^3J=7.2 Hz, 1H, H2). ^{13}C NMR (200 MHz, $CDCl_3$) δ 28.4 (Boc), 31.6 ($CH_2CH_2CH_2$), 31.7 (C3), 37.2 (CH_2NH), 46.0 (C4), 50.0 (C2), 58.6 (CH_2OH), 59.2 (C5), 60.0 (C1), 79.4 (Boc), 155.5 (CO carbamate), 173.6 (CO amide). MS (ESI): m/z=323 $[M+Na]^+$. $C_{14}H_{24}N_2O_5$ (300.35): calcd C 55.98; H 8.05; N 9.33; found C 55.72; H 8.08; N 9.29.

*4.1.5. (2S,3R)-N-Fmoc-O-benzyl-threonine methyl ester (**7**).* To a solution of (2*S*,3*R*)-Fmoc-*O*-benzyl-threonine (2.80 g, 6.49 mmol) in methanol (20 mL) was added three drops of H_2SO_4 and the reaction was stirred at rt for 16 h. After this time, the solvent was removed under vacuum and the residue was dissolved in $CHCl_3$ (40 mL) and washed with water (3×15 mL). The organic phase was dried over Na_2SO_4, filtered and concentrated under reduced pressure and treated with ether obtaining **7** (2.60 g, 5.84 mmol, 90%) as a foamy white solid without any other purification. $[\alpha]_D^{20}$ +6.8 (*c* 0.02, MeOH); ν_{max}(KBr) 3396, 2918, 2852, 1751, 1724, 1602, 1516, 1448, 1318, 1207, 1083 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.29 (d, ^3J=6.2 Hz, 3H, CH_3CH), 3,70 (s, 3H, COOCH_3), 4.15 (m, 1H, CH_3CH), 4.29 (t, ^3J=8.4 Hz, 1H, CHCH$_2$), 4.42 (d, ^3J=3.4 Hz, 1H, NHCHCOOMe), 4.52 (AB system ^2J=11.8 Hz, 2H, PhCH_2O), 5.66 (d, ^3J=8.4 Hz, 2H, CHCH_2), 7.28–7.45 (m, 9H, Ph), 7.62–7.68 (m, 2H, Ph), 7.75–7.80 (d, ^3J=7.3 Hz, 2H, Ph). MS (ESI): m/z=446 $[M+H]^+$, 468 $[M+Na]^+$. $C_{27}H_{27}NO_5$ (445.51): calcd C 72.79; H 6.11; N 3.14; found C 72.81; H 6.15; N 3.13.

*4.1.6. (2S,3R)-O-benzyl-threonine methyl ester (**4c**).* (2*S*,3*R*)-*N*-Fmoc-*O*-benzyl-threonine methyl ester (2.60 g, 5.84 mmol) was dissolved in a solution of DMF with 20% of piperidine (DMF 32 mL+piperidine 8 mL) and was stirred at rt for 3 h. After this time, the reaction was diluted in $CHCl_3$ (120 mL) and washed with water (7×40 mL) to extract DMF. The organic phase was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by chromatography on silica gel (1° eluent petroleum ether/EtAc 3:1, 2° eluent EtAc/MeOH 1:1) to yield **4c** (0.95 g, 4.26 mmol, 73%) as a pale yellow oil. R_f (PE/EtAc 3:1) 0.03; R_f (EtAc/MeOH 1:1) 0.9; $[\alpha]_D^{20}$ −19 (*c* 0.01, $CHCl_3$); ν_{max}(liquid film) 3379, 3313, 2976, 2951, 2930, 1741, 1605, 1455, 1375, 1346, 1234, 1172, 1074 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.26 (d, ^3J=6 Hz, 3H, CH_3CH), 2.08 (br s, 2H, NH_2), 3.38 (d, ^3J=3.4 Hz, 1H, $H_2N$$CH$COOMe), 3.63 (s, 3H, COO$CH_3$), 3.92 (m, 1H, CH_3CH), 4.45 (AB system, ^2J=11.8 Hz, 2H, OCH_2Ph), 7.20–7.30 (m, 6H, Ph). MS (ESI): m/z=224 $[M+H]^+$, 246 $[M+Na]^+$. $C_{12}H_{17}NO_3$ (223.27): calcd C 64.55; H 7.67; N 6.27; found C 64.53; H 7.69; N 6.28.

*4.1.7. (2S,3R)-Methyl 3-(benzyloxy)-2-((1S,2R,4S,5R)-4-(tert-butoxycarbonylamino)-6-oxabicyclo [3.1.0] hexane-2-carboxamido)butanoate (**5c**).* To a solution of **3** (0.91 g, 4.04 mmol) in dry THF (10 mL) was added **4c** (0.99 g, 4.44 mmol) dissolved in dry THF (10 mL). The mixture was refluxed for 20 h. After this time, the solvent was removed under reduced pressure, and the residue was solubilized in $CHCl_3$ (100 mL) and washed with HCl 0.2 N (2×40 mL) and water (1×40 mL). The organic phase was dried over Na_2SO_4, filtered and concentrated under vacuum. The residue was washed with Et_2O obtaining compound **5c** (1.65 g, 3.68 mmol, 91%) as a white precipitate, mp: 164–165 °C; $[\alpha]_D^{20}$ −12 (*c* 0.02, MeOH); ν_{max}(KBr) 3321, 2980, 2929, 1747, 1661, 1525, 1458, 1438, 1394, 1384, 1344, 1320, 1245, 1211, 1166, 1092, 1053 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.22 (d, ^3J=6.6 Hz, 3H, CH_3CH), 1.41 (s, 9H, Boc), 1.69 (d, ^2J=14.6 Hz, 1H, H3), 1.97 (dt, J=14.6, 7.3 Hz, 1H, H3′), 3.03 (d, ^3J=8 Hz, 1H, H4), 3.46 (d, ^3J=1.7 Hz, H5), 3.53 (d, ^3J=1.7 Hz, H1), 3.64 (s, 3H, COOCH_3), 4.07–4.23 (m, 2H, H2+CH_3CH), 4.44 (AB system, ^2J=11.8 Hz, 2H, OCH_2Ph), 4.60 (d, ^3J=9.2 Hz, 1H, NHCHCO$_2$Me), 6.17 (d, ^3J=9.5 Hz, 1H, *NH*Boc), 6.53 (d, ^3J=9.2 Hz, 1H, *NH* amide), 7.17–7.25 (m, 2H, Ph), 7.25–7.35 (m, 3H, Ph). ^{13}C NMR (200 MHz, CD_3OD) δ 16.4 (CH_3CH), 28.7 (Boc), 32.3 (C3), 46.2 (C4), 49.4 (C2), 52.8 (COOCH_3), 58.5 (C5), 59.2 (NHCHCOOMe), 60.1 (C1), 72.0 (OCH_2Ph), 75.3 (CH_3CH), 81.2 (Boc), 128.8 (*p*-Ph), 129.0 (*o*-Ph), 129.3 (*m*-Ph), 139.4 (*q*-Ph), 157.3 (CO carbamate), 172.2 (CO ester), 176.0 (CO amide). MS (ESI): m/z=449 $[M+H]^+$, 471 $[M+Na]^+$. $C_{23}H_{32}N_2O_7$ (448.51): calcd C 61.59; H 7.19; N 6.25; found C 61.63; H 7.46; N 6.56.

*4.1.8. (1S,2R,4S,5R) and (1R,2S,4R,5S) tert-Butyl 4-(phenylcarbamoyl)-6-oxabicyclo[3.1.0]hexan-2-ylcarbamate (**5d**).* In a sealed tube, to a solution of **3** (0.22 g, 0.98 mmol) in dry THF (10 mL) freshly distilled aniline (320 μL, 3.53 mmol) was added. The mixture was heated at 100 °C for 72 h. After this time, the solvent was removed under reduced pressure, and the residue was solubilized in $CHCl_3$ (60 mL) and washed with HCl 0.2 N (2×20 mL) and water (1×20 mL). The organic phase was dried over Na_2SO_4, filtered and concentrated under vacuum obtaining compound **5d** (0.12 g, 0.38 mmol, 39%) as a white solid, mp: 192–194 °C; ν_{max}(KBr) 3418, 2969, 2948, 1700, 1654, 1558, 1340, 1322, 1247, 1162, 1063 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.45 (s, 9H, Boc), 1.81 (d, ^3J=14 Hz, 1H, H3), 2.01 (dt, J=14, 7.4 Hz, 1H, H3′), 3.12 (d, ^3J=8 Hz, 1H, H4), 3.50 (s, 1H, H5), 3.67 (s, 1H, H1), 4.37 (br t, ^3J=8 Hz, 1H, H2), 6.30 (d, ^3J=9.2 Hz, 1H, NH carbamate), 7.14 (t, ^3J=7.4 Hz, 1H, Ph–H_{para}), 7.33 (t, ^3J=7.4 Hz, 2H, Ph–H_{meta}), 7.52 (d, ^3J=7.4 Hz, 2H, Ph–H_{ortho}), 8.20 (br s, 1H, NH amide). ^{13}C NMR (400 MHz, $CDCl_3$) δ 28.4 (Boc), 32.0 (C3), 47.2 (C4), 50.2 (C2), 58.8 (C5), 59.3 (C1), 79.5 (Boc), 120.4 (Ph–C_{ortho}), 125.1 (Ph–C_{para}), 129.1 (Ph–C_{meta}), 137.2 (Ph–C_{ipso}), 155.6 (CO carbamate), 171.5 (CO amide). MS(ESI): m/z=318.8 $[M+H]^+$, 341 $[M+Na]^+$. $C_{17}H_{22}N_2O_4$ (318.37): calcd C 64.13; H 6.97; N 8.80; found C 63.91; H 7.31; N 8.97.

*4.1.9. (1S,2R,4S,5R) and (1R,2S,4R,5S) tert-Butyl 4-(diethylcarbamoyl)-6-oxabicyclo[3.1.0]hexan-2-ylcarbamate (**5e**).* In a sealed tube, to a solution of **3** (0.22 g, 0.98 mmol) in dry THF (10 mL) freshly distilled diethylamine (510 μL, 4.9 mmol) was added. The mixture was heated at 100 °C for 72 h. After this time, the solvent was removed under reduced pressure, and the residue was solubilized in $CHCl_3$ (60 mL) and washed with HCl 0.2 N (2×20 mL) and H_2O (1×20 mL). The organic phase was dried over Na_2SO_4, filtered and concentrated under vacuum getting compound **5e** (0.2 g, 0.67 mmol, 68%) as a pale yellow oil. ν_{max}(KBr) 3334, 2977, 2937, 1749, 1718, 1610, 1457, 1396, 1170, 1151, 1055 cm^{-1}; ^{1}H NMR (400 MHz, C_6D_6) δ 0.53 (t, ^3J=7 Hz,

3H, CH_2CH_3), 0.79 (t, ^3J=7 Hz, 3H, CH_2CH_3), 1.46 (s, 9H, Boc), 1.59 (d, ^2J=14.4 Hz, 1H, H3), 1.77 (dt, J=14.4, 7.4 Hz, 1H, H3′), 2.49 (m, 1H, CH_2CH_3), 2.60 (m, 1H, CH_2CH_3), 2.85 (d, ^3J=8 Hz, 1H, H4), 2.97 (m, 2H, CH_2CH_3), 3.13 (s, 1H, H5), 3.48 (s, 1H, H1), 4.69 (t, ^3J=8.4 Hz, 1H, H2), 7.08 (d, ^3J=8 Hz, 1H, NH). ^{13}C NMR (400 MHz, C_6D_6) δ 12.9 (CH_2CH_3), 14.4 (CH_2CH_3), 28.5 (Boc), 32.3 (C3), 40.6 (C4), 41.9 (CH_2CH_3), 42.2 (CH_2CH_3), 51.0 (C2), 58.9 (C5), 58.9 (C1), 78.7 (Boc), 155.7 (CO carbamate), 172.1 (CO amide). MS(ESI): m/z=299 $[M+H]^+$, 321 $[M+Na]^+$. $C_{15}H_{26}N_2O_4$ (298.38): calcd C 60.38; H 8.78; N 9.39; found C 60.14; H 8.82; N 9.02.

4.2. General procedure for the rearrangement of epoxides to oxazolidinones

$BF_3\cdot Et_2O$ (120 μL, 1 mmol) was added with a micro-syringe to a solution of epoxide **5a**–**e** (1.0 mmol) in dry THF (10 mL) and the mixture was stirred in a sealed tube for 14 h. After this time the solvent was removed under reduced pressure and the residue was solubilized in $CHCl_3$ (60 mL) and washed with saturated $NaHCO_3$ (2×20 mL) and brine (1×20 mL). The organic phase was dried over Na_2SO_4, filtered and concentrated under vacuum getting compound **6** as a white solid after treatment with ether, except for compound **6e**, that is, a pale yellow oil.

*4.2.1. (3aS,5R,6S,6aS) and (3aR,5S,6R,6aR)-N-ethyl-6-hydroxy-2-oxohexahydro-2H-cyclopenta[d]oxazole-5-carboxamide (**6a**).* White solid; yield=78%; mp: 178–181 °C; ν_{max}(KBr) 3291, 2966, 2944, 2878, 1756, 1638, 1557, 1454, 1391, 1244, 1214, 1093 cm^{-1}; ^{1}H NMR (200 MHz, CD_3OD) δ 1.10 (t, ^3J=7.3 Hz, 3H, CH_2CH_3), 1.82 (dt, ^3J=6.8 Hz, 1H, H4), 2.29 (dt, ^3J=6.8 Hz, 1H, H4′), 2.54 (m, 1H, H5), 3.20 (q, ^3J=7.3 Hz, 2H, CH_2CH_3), 4.18 (m, 1H, H3a), 4.29 (m, 1H, H6), 4.64 (m, 1H, H6a). ^{13}C NMR (400 MHz, CD_3OD) δ 14.8 (CH_2CH_3), 28.8 (C4), 35.4 (C5), 36.2 (CH_2CH_3), 54.9 (C3a), 82.2 (C6), 88.4 (C6a), 160.9 (CO carbamate), 173.8 (CO amide). MS (ESI): m/z=215 $[M+H]^+$, 237 $[M+Na]^+$. $C_9H_{14}N_2O_4$ (214.22): calcd C 50.46; H 6.59; N 13.08; found C 50.65; H 6.85; N 12.99.

*4.2.2. (3aS,5R,6S,6aS) and (3aR,5S,6R,6aR)-6-hydroxy-N-(3-hydroxypropyl)-2-oxohexahydro-2H-cyclopenta[d]oxazole-5-carboxamide (**6b**).* White solid; yield=87%; mp: 156–157 °C; ν_{max}(KBr) 3284, 2966, 2929, 2878, 1749, 1712, 1612, 1395, 1240, 1218, 1067, 1048 cm^{-1}; ^{1}H NMR (400 MHz, CD_3OD) δ 1.69 (m, 2H, $CH_2CH_2CH_2$), 1.83 (dt, ^3J=6.9 Hz, 1H, H4), 2.29 (dt, ^3J=6.9 Hz, 1H, H4′), 2.56 (m, 1H, H5), 3.27 (t, ^3J=7.6 Hz, 2H, CH_2NH), 3.57 (t, ^3J=7.6 Hz, 2H, CH_2OH), 4.18 (q, ^3J=7 Hz, 1H, H3a), 4.29 (m, 1H, H6), 4.64 (m, 1H, H6a). ^{13}C NMR (200 MHz, CD_3OD) δ 33.1 ($CH_2CH_2CH_2$), 36.2 (C4), 37.6 (CH_2NH), 50.1 (C5), 54.3 (C3a), 60.3 (CH_2OH), 81.2 (C6), 87.9 (C6a), 161.1 (CO carbamate), 174.2 (CO amide). MS(ESI): m/z=267 $[M+Na]^+$. $C_{10}H_{16}N_2O_5$ (244.24): calcd C 49.17; H 6.60; N 11.47; found C 49.19; H 6.67; N 11.64.

*4.2.3. (2S,3R)-Methyl 3-(benzyloxy)-2-((3aS,5R,6S,6aS)-6-hydroxy-2-oxohexahydro-2H-cyclopenta[d]oxazole-5-carboxamido)butanoate (**6c**).* White solid; yield=88%; mp: 134–135 °C; $[\alpha]_D^{20}$ +30.48 (*c* 0.01, MeOH); ν_{max}(KBr) 3343, 3062, 2937, 1767, 1725, 1707, 1655, 1542, 1238, 1063 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.25 (d, ^3J=6.4 Hz, 3H, CH_3CH), 2.06 (m, 1H, H4), 2.42 (m, 1H, H4′), 2.72 (m, 1H, H5), 3.68 (s, 3H, $COOCH_3$), 4.13–4.21 (m, 2H, H3a+CH_3CH), 4.38 (AB system, d, ^2J=12 Hz, 1H, OCH_2Ph), 4.46 (m, 1H, H6), 4.59 (AB system, d, ^2J=12 Hz, 1H, OCH_2Ph), 4.69 (d, ^3J=9.2 Hz, 1H, NHCHCOOMe), 4.74 (m, 1H, H6a), 5.53 (br s, 1H, OH), 6.73 (d, J=9.2 Hz, 1H, NH amide), 7.24–7.30 (m, 2H, Ph), 7.30–7.39 (m, 3H, Ph). ^{13}C NMR (200 MHz, $CDCl_3$) δ 16.2 (CH_3CH), 33.7 (C4), 48.2 (C5), 52.4 ($COOCH_3$), 52.7 (C3a), 56.7 (NHCHCOOMe), 70.8 (OCH_2Ph), 74.2 (CH_3CH), 79.9 (C6), 86.3 (C6a), 127.8 (*o*-Ph, *p*-Ph), 128.4 (*m*-Ph), 137.7 (*q*-Ph), 158.6 (CO carbamate), 171.1 (CO ester), 172.0 (CO amide). MS(ESI): m/z=393 $[M+H]^+$, 415 $[M+Na]^+$. $C_{19}H_{24}N_2O_7$ (392.40): calcd C 58.16; H 6.16; N 7.14; found C 57.91; H 5.85; N 7.10.

*4.2.4. (3aS,5R,6S,6aS) and (3aR,5S,6R,6aR) 6-hydroxy-2-oxo-N-phenylhexahydro-2H-cyclopenta[d]oxazole-5-carboxamide (**6d**).* Yellow oil; yield=93%; ν_{max}(KBr) 3366, 3249, 2942, 2866, 1752, 1708, 1628, 1560, 1388, 1316, 1239, 1218, 1113, 1083, 1064 cm^{-1}; ^{1}H NMR (400 MHz, CD_3OD) δ 1.93 (dt, ^3J=7 Hz, 1H, H4), 2.43 (dt, ^3J=7 Hz, 1H, H4′), 2.81 (m, 1H, H5), 4.26 (m, 1H, H3a), 4.43 (m, 1H, H6), 4.72 (m, 1H, H6a), 7.09 (t, ^3J=7.7 Hz, 1H, Ph–H_{para}), 7.29 (t, ^3J=7.7 Hz, 2H, Ph–H_{meta}), 7.56 (d, ^3J=7.7 Hz, 2H, Ph–H_{ortho}). ^{13}C NMR (400 MHz, CD_3OD) δ 13.3 (CH_2CH_3), 14.7 (CH_2CH_3), 33.1 (C4), 37.0 (C5), 43.3 (CH_2CH_3), 43.8 (CH_2CH_3), 54.6 (C3a), 82.4 (C6), 88.7 (C6a), 160.6 (CO carbamate), 172.9 (CO amide). MS(ESI): m/z=263 $[M+H]^+$. $C_{13}H_{14}N_2O_4$ (262.26): calcd C 59.54; H 5.38; N 10.68; found C 59.68; H 5.16; N 10.43.

*4.2.5. (3aS,5R,6S,6aS) and (3aR,5S,6R,6aR) N,N-diethyl-6-hydroxy-2-oxohexahydro-2H-cyclopenta[d]oxazole-5-carboxamide (**6e**).* Yellow oil; yield=88%; ν_{max}(KBr) 3306, 2940, 2858, 1741, 1616, 1465, 1456, 1383, 1367, 1249, 1218, 1112 cm^{-1}; ^{1}H NMR (400 MHz, CD_3OD) δ 1.07 (t, ^3J=7 Hz, 3H, CH_2CH_3), 1.17 (t, ^3J=7 Hz, 3H, CH_2CH_3), 1.74 (m, 1H, H4), 2.30 (m, 1H, H4′), 3.04 (m, 1H, H5), 3.24–3.37 (m, 2H, CH_2CH_3), 3.38–3.51 (m, 2H, CH_2CH_3), 4.20 (m, 1H, H3a), 4.34 (m, 1H, H6), 4.64 (m, 1H, H6a). ^{13}C NMR (400 MHz, CD_3OD) δ 13.3 (CH_2CH_3), 15.0 (CH_2CH_3), 36.9 (C4), 42.1 (C5), 43.4 (CH_2CH_3), 45.9 (CH_2CH_3), 54.3 (C3a), 82.2 (C6), 87.8 (C6a), 161.1 (CO carbamate), 173.4 (CO amide). MS (ESI): m/z=243 $[M+H]^+$. $C_{11}H_{18}N_2O_4$ (242.27): calcd C 54.53; H 7.49; N 11.56; found C 54.26; H 7.82; N 11.67.

Acknowledgements

This work was financially supported by the University of Siena as a PAR Project 2007. The authors wish to thank the 'Centro di Analisi e Determinazioni Strutturali' of the University of Siena for MS spectra and X-ray data collections and Dr. Sara Draghi for helpful collaborations.

Supplementery data

Spectroscopic data for compounds **5a**–**e** and **6a**–**e**. Supplementary data related to this article can be found online at doi:10.1016/j.tet.2010.12.031.

References and notes

1. (a) Faith, W. C.; Booth, C. A.; Foxman, B. M.; Snider, B. B. *J. Org. Chem.* **1985**, *50*, 1983–1985; (b) Ober, M.; Müller, H.; Pieck, C.; Gierlich, J.; Carell, T. *J. Am. Chem. Soc.* **2005**, *127*, 18143–18149; (c) Kiss, L.; Forró, E.; Sillanpää, R.; Fülöp, F. *Synthesis* **2010**, *1*, 153–160; (d) Zhang, H.; Schinazi, R. F.; Chu, C. K. *Bioorg. Med. Chem.* **2006**, *14*, 8314–8322; (e) Kothandaraman, S.; Vicario, P. P. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 1830–1834.
2. (a) Smith, M. E. B.; Derrien, N.; Lloyd, M. C.; Taylor, S. J. C.; Chaplin, D. A.; McCague, R. *Tetrahedron Lett.* **2001**, *42*, 1347–1350; (b) Kiss, L.; Forró, E.; Sillanpää, R.; Fülöp, F. *Nucleic Acids Symp. Ser.* **2008**, *52*, 551–552.
3. (a) Katagiri, N.; Yamatoya, Y.; Ishikura, M. *Tetrahedron Lett.* **1999**, *40*, 9069–9072; (b) Bhushan, R. G.; Vince, R. *Bioorg. Med. Chem.* **2002**, *10*, 2325–2333.
4. Ishikura, M.; Hasunuma, M.; Yamada, K.; Yanada, R. *Heterocycles* **2006**, *68*, 2253–2257.
5. (a) Palmer, C. F.; Bannister, R. M.; McCague, R. *Tetrahedron Lett.* **1999**, *40*, 6109–6112; (b) Rommel, M.; Ernst, A.; Koert, U. *Eur. J. Org. Chem.* **2007**, 4408–4430.
6. Papandrea, G.; Ponticelli, F. *Synth. Commun.* **2008**, *38*, 858–865.
7. Palmer, C. F.; McCague, R.; Ruecroft, G.; Savage, S.; Taylor, S. J. C.; Ries, C. *Tetrahedron Lett.* **1996**, *37*, 4601–4604.
8. Katagiri, N.; Matsuhashi, Y.; Kokufuda, H.; Takebayashi, M.; Kaneko, C. *Tetrahedron Lett.* **1997**, *38*, 1961–1964.
9. Dominguez, B. M.; Cullis, P. M. *Tetrahedron Lett.* **1999**, *40*, 5783–5786.
10. (a) Kiss, L.; Forró, E.; Sillanpää, R.; Fülöp, F. *J. Org. Chem.* **2007**, *72*, 8786–8790; (b) Kiss, L.; Forró, E.; Sillanpää, R.; Fülöp, F. *Tetrahedron* **2010**, *66*, 3599–3607.
11. Leitão, A. J. L.; Salvador, J. A. R.; Pinto, R. M. A.; Sá e Melo, M. L. *Tetrahedron Lett.* **2008**, *49*, 1694–1697.