Pergamon

SCIENCE DIRECT®

Tetrahedron 59 (2003) 10195–10201

TETRAHEDRON

α-Oxohydrazones as imine component in the synthesis of 4-functionalized azetidinones by the Staudinger reaction

Lara Bianchi, Carlo Dell'Erba, Massimo Maccagno, Angelo Mugnoli, Marino Novi, Giovanni Petrillo, Fernando Sancassan and Cinzia Tavani*

Dipartimento di Chimica e Chimica Industriale, Università di Genova, Via Dodecaneso 31, I-16146 Genoa, Italy

Received 3 July 2003; revised 2 October 2003; accepted 23 October 2003

Abstract—1-(Methyl-*p*-tolyl-amino)-3-phenoxy-2-azetidinones 4-COX and 4-R substituted (COX: X=Me, Et, Ph, NMe_2, NEt_2, OBu^t; R=Me, Et, Ph) were smoothly prepared from the corresponding α-(methyl-*p*-tolyl)hydrazonylated ketones, amides and esters via [2+2] cycloaddition with phenoxyketene. The reaction was generally high-yielding and diastereoselective, leading to β-lactams with a *cis* relationship between the PhO and the COX moieties, except for R=Ph, where an opposite stereoselectivity was instead observed. The azetidinones represent interesting intermediates which couple protection at N(1) and functionalization at position 4 of the ring. Deprotection of N(1) can be easily attained by oxidative N–N cleavage with magnesium monoperoxyphthalate.
© 2003 Elsevier Ltd. All rights reserved.

1. Introduction

The presence of the 2-azetidinone ring in several families of bicyclic antibiotics has stimulated continuous interest in the synthesis of β-lactams.[1] Moreover, in recent years, a number of naturally occurring monocyclic β-lactams was shown to exhibit high antibacterial activity, suggesting that the biological activity is strictly correlated to the presence of a suitably functionalized 2-azetidinone ring.[2] In particular, some 3,4-disubstituted and 1,3,4-trisubstituted 2-azetidinones have shown antielastase activity[3] or have proven to be effective inhibitors of cholesterol absorption,[4a–c] of human cytomegalovirus protease[4d,e] and of thrombin.[4f] It should be also considered that functionalized β-lactams constitute excellent building-blocks for the synthesis of α and β-amino acid derivatives, which are in turn useful intermediates in the fields of heterocyclic chemistry and peptide synthesis.[5]

Stereoselection at positions 3 and 4 of the 2-azetidinone ring is obviously of utmost importance in the perspective of its participation in biologically or pharmacologically-active molecules.[5]

Among the stereocontrolled syntheses of β-lactams, one of the most direct and versatile methods is the [2+2] cycloaddition reaction of ketenes to imines (the Staudinger reaction).[6,7] The reaction has been extensively studied and frequently reviewed, and simple empirical rules have been recently suggested to predict its stereochemical outcome.[7]

Among the variants of the Staudinger reaction, the employment of hydrazones as the imine component, leading to 1-amino-2-azetidinones, has been only scantily reported[8] in spite of their stability and ready availability. Very recently, furthermore, the use of chiral hydrazono moieties has also opened up the possibility to perform highly enantioselective cycloadditions,[8a,b] with the possibility to easily remove the 1-amino substituent by oxidative cleavage of the N–N bond.

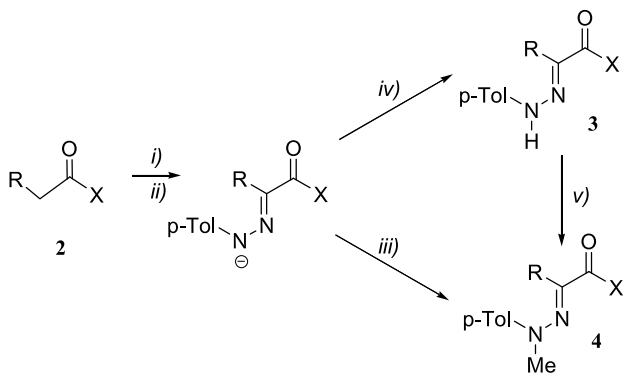
In previous papers[9] we have shown that α-hydrazonylated carbonyl derivatives **4a-l** of (*E*)-configuration are easily obtainable in excellent yields by reaction of *tert*-butyl *p*-tolylazo sulfide **1** with the enolates of ketones,[9a] esters and amides[9b] (Scheme 1); we have also reported some of the useful transformations that compounds **4** may undergo,[9,10] owing to the simultaneous presence of the adjacent hydrazono and oxo functionalities.

In this context, as a further example of synthetic exploitation of compounds **4** we report herein on their utilization as the imine components in the [2+2] cycloaddition with phenoxyketene, allowing a stereoselective access to the polyfunctionalized 2-azetidinones **5** which are characterized in particular by a COX functionality at position 4 of the heteroring.

It is relevant to note that, for instance, an electron-withdrawing carboxylic ester group at C(4) is present in

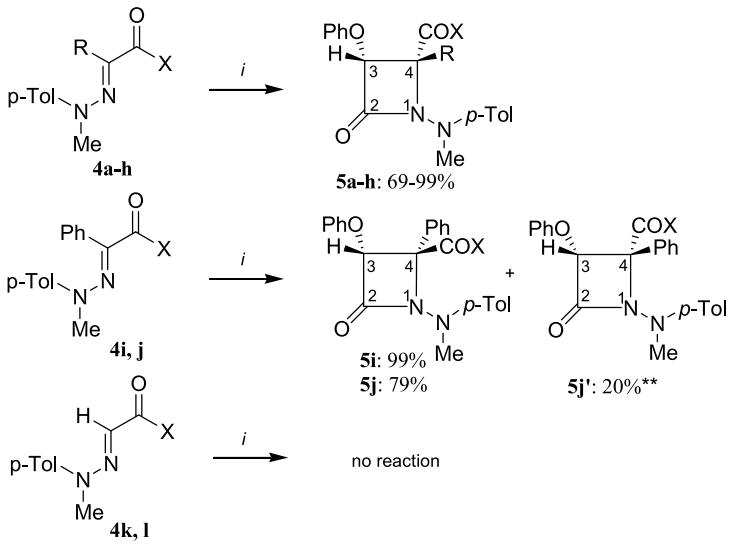
Keywords: azetidinones; Staudinger reaction; α-hydrazono-ketones, -amides, -esters.
* Corresponding author. Tel.: +39-010-3536122; fax: +39-010-3536118; e-mail: tavani@chimica.unige.it

0040–4020/$ - see front matter © 2003 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2003.10.072



2-4	R	X
a	Me	Me
b	Me	Et
c	Me	Ph
d	Et	Me
e	Me	NMe_2
f	Et	NMe_2
g	Me	OBu^t
h	Et	OBu^t
i	Ph	NEt_2
j	Ph	OBu^t
k	H	Ph
l	H	NMe_2

Scheme 1. *Reagents and conditions*: When X=alkyl, phenyl: (i) Bu^tOK/DMSO, rt, 15 min; (ii) *p*-tolyl-N=N–SBu^t (**1**), rt, 40–120 min; (iii) MeI quenching. When X=*tert*-butoxy, dialkylamino: (i) $KN(SiMe_3)_2$/toluene or $NaN(SiMe_3)_2$/THF, −78°C, 30 min; (ii) *p*-tolyl-N=N–SBu^t (**1**), −78°C to rt; (iv) acidic quenching; (v) $KN(SiMe_3)_2$/toluene or $NaN(SiMe_3)_2$/THF, −78°C, 30 min, and then MeI.



Scheme 2. * (i) $PhOCH_2COCl$, NEt_3, CH_2Cl_2, 10°C→ rt, 24 h. (∗) Only one enantiomer is drawn. (**) Not isolated (see Section 4).

HLE inhibitors,[11a] in thrombin inhibitors[4f] and in prostate-specific antigen inhibitors.[11b]

2. Results and discussion

The results of the cycloaddition reaction of compounds **4a-l** with in situ-generated phenoxyketene according to Scheme 2 are collected in Table 1. In the reactions on **4a-j** good to excellent yields of the expected cycloaddition products (**5a-j**) were obtained, while no reaction was observed with hydrazones **4k** and **4l** (R=H) (Table 1, entries 11 and 12): in both these cases, the starting material was quantitatively recovered, in good agreement with previous reports[8c] for analogous reactions on aldehyde hydrazones (monosubstituted hydrazonylated carbon). From the stereochemical point of view (to be discussed below in the text) it should be noticed that the reaction was completely diastereoselective in every case but one: in the case of entry 10, in fact, two diastereomeric products **5j** and **5j′** were obtained in a 4:1 ratio (^{1}H NMR spectroscopy), although only the major component (**5j**) could be isolated and fully characterized (Scheme 2).

Table 1. Yields of 2-azetidinones **5** from the reaction of hydrazones **4a-l** with phenoxyacetylchloride and triethylamine in dry methylene chloride[a]

Entry	R	X	**5** (yield, %)[b]
1	Me	Me	**5a**: 53 (98)
2	Me	Et	**5b**: 75 (94)
3	Me	Ph	**5c**: 80
4	Et	Me	**5d**: 63 (75)
5	Me	NMe_2	**5e**: 99
6	Et	NMe_2	**5f**: 99
7	Me	OBu^t	**5g**: 88 (99)
8	Et	OBu^t	**5h**: 69
9	Ph	NEt_2	**5i**: 74 (99)
10	Ph	OBu^t	**5j**: 79; **5j′**: 20[c]
11	H	Ph	[d]
12	H	NMe_2	[d]

[a] [**4**]: 0.08 M; [triethylamine]: 0.24 M; [$PhOCH_2COCl$]: 0.2 M in dry methylene choride, 10°C to rt, 24 h.

[b] Yields are of products purified by (column) chromatography, confirmed by quantitative ^{1}H NMR analysis on crude from independent experiments. Yields calculated on the amount of **4** consumed are reported in parentheses.

[c] The two diastereoisomers are not separable by chromatography. By fractional crystallization (from light petroleum) of the crude, 223 mg (49%) of pure **5j** could be obtained. The absolute yields of **5j** and **5j′** were calculated by ^{1}H NMR analysis of the crude reaction mixture.

[d] Quantitative recovery of unreacted substrate.

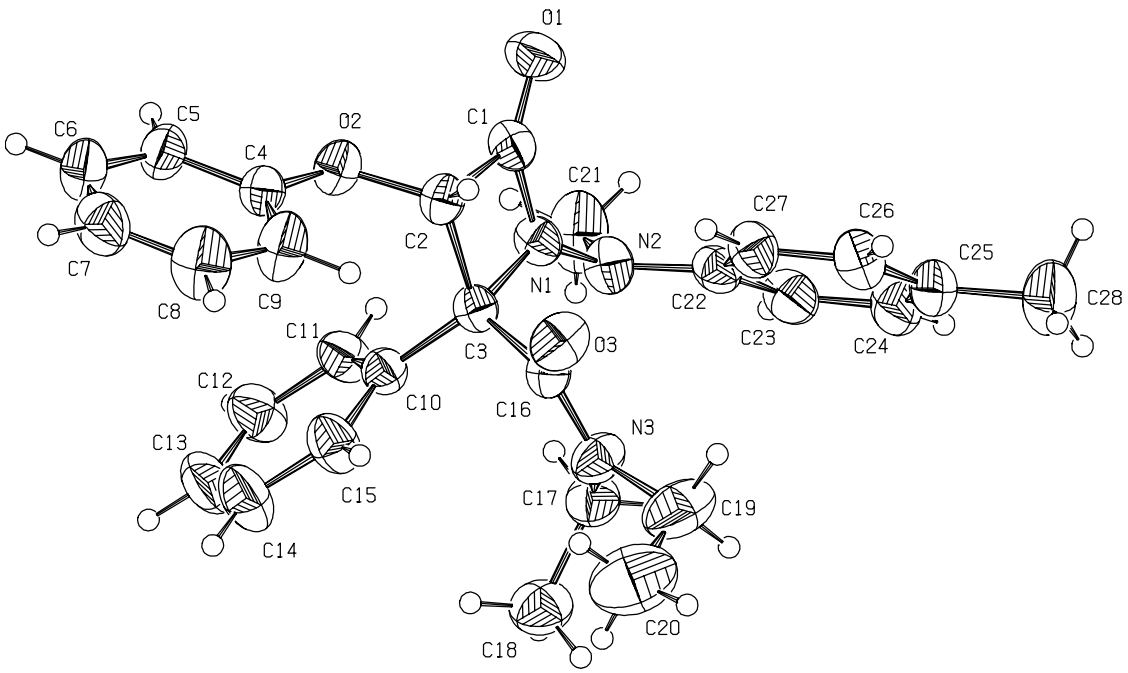


Figure 1. A molecule of **5i** with the atomic numbering scheme. Displacement ellipsoids are drawn at the 40% probability level. Hydrogen atoms are on an arbitrary scale.

The relative configuration between the C(3) and C(4) ring atoms of the isolated 2-azetidinones could be assessed on the basis of both the results of NOE experiments and the comparison of consistent chemical shifts.

In the case of 4-methyl derivatives (**5a**-**c**,**e**,**g**) irradiation of the C(4)CH_3 protons produced a 12–17% enhancement in the intensity of the C(3)*H* signal, thus supporting a *cis* relationship between these structural moieties. The very close similarity in the C(3)*H* chemical shifts within the pairs **5a** (4.99 ppm) and **5d** (4.98 ppm), **5e** (5.04 ppm) and **5f** (5.05 ppm), **5g** (4.95 ppm) and **5h** (4.98 ppm) strongly supports an analogous *cis* relationship between C(3)H and C(4)CH_2CH_3 in **5d**, **5f** and **5h**.

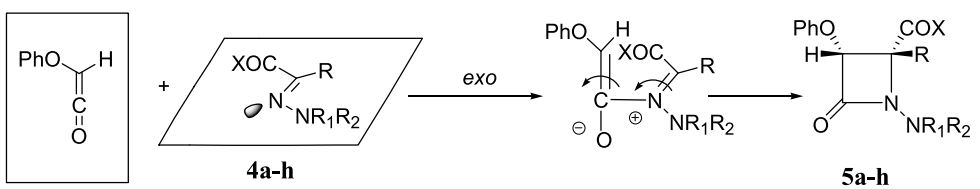
As to the 4-phenyl derivatives (**5i**,**j**,**j′**), NOE experiments were run by checking the possible enhancement of the signal of the *ortho* protons of the C(4)*Ph* moiety when irradiating C(3)*H*: a 7.5% enhancement was observed only for the minor compound **5j′** in an experiment run on a 2:1 **5j**/**5j′** mixture, while no appreciable NOE effect could be detected for **5i** and **5j**. Thus, a *trans* relationship between C(3)*H* and C(4)*Ph* was assigned to compounds **5i** and **5j**, while **5j′** appears to have the *cis* relationship. The structure of **5i** was further confirmed by single-crystal X-ray diffraction: the molecular structure and labelling scheme are shown in Figure 1, where numbering of atoms follows a different pattern with respect to the chemical nomenclature.

The azetidinone ring is planar within 0.01 Å. The C2-phenoxy and the C3-phenyl groups are *syn*-periplanar, the torsion angle O2–C2–C3–C10 being −8.6(3)°.

The observed diastereoselectivity for the reactions of hydrazones **4a**-**h** can be explained assuming that they proceed with a mechanism similar to that proposed for the reactions of (*E*)-aldimines.[12] Thus, an *exo* approach (i.e. with the PhO group on the opposite side with respect to the incoming nitrogen lone pair) of the (*E*)-hydrazone to the ketene generates a zwitterionic intermediate (Scheme 3), which then evolves to the final 2-azetidinone derivative via an electrocyclic conrotatory ring closure with no preliminary stereomutation at the C=N double bond of the starting hydrazone.

It should be reminded that, independently on the bulk of the substituents on the reagents (and hence on steric effects on the first step), the *exo* approach has been reported[12] to be favoured in the presence of an electron-donor substituent on the ketene, such as the phenoxy group in our case, on the grounds of torquoelectronic effects:[13] thus, to the zwitterionic intermediate of Scheme 3 an 'outward' rotation of the phenoxy group is allowed, which leads to an energetically favourable transition state for the ring-closure step.[13]

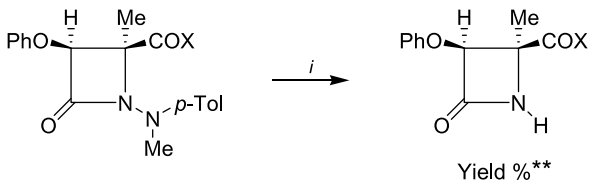
Stereomutation at the C=N double bond level may be invoked, though, in the case of the phenyl derivatives **4i** and



Scheme 3. Only one enantiomer is drawn.

4j and this can explain the exclusive or preferential formation (respectively) of the 2-azetidinones **5i** and **5j** which present the PhO and COX groups in a relative *trans* position. In this regard, it has been actually reported[12] that for (*E*)-imines deriving from benzaldehyde (bearing a phenyl group capable of stabilizing a positive charge, and consequently able to confer a strong carbocationic character to the iminic carbon of the zwitterion), the intermediate may undergo isomerization before cyclization, eventually producing the thermodynamically more stable β-lactam having the substituents PhO and Ph *trans* to each other.

In the perspective of the employment of compounds **5** as precursors of target molecules, the evidence provided by the literature that *N*-unsubstituted β-lactams are key intermediates in the synthesis of a number of antibiotics[1a,14] has prompted us to verify the feasibility of deprotection of the N(1) atom. The goal was easily achieved on the representative azetidinones **5b**, **5e** and **5g** by oxidative N–N cleavage with magnesium monoperoxyphthalate (MMPP) (Scheme 4): satisfactory yields of the N(1)-deprotected β-lactam derivatives **6b**, **6e** and **6g** were obtained, together with small amounts (10–16%) of unreacted **5** and *p*-nitrotoluene as by-product.



5b:X = Et
5e: X = NMe_2
5g: X = OBu^t

Yield %**
6b: 86 (96)
6e: 82 (93)
6g: 75 (89)

Scheme 4. * (i) MMPP·$6H_2O$ in MeOH/CH_2Cl_2 3:1. (*) Only one enantiomer is drawn. (**) Yields calculated on the amount of **5** consumed are reported in parentheses.

3. Conclusions

The reactions described represent a further example[9,10] of synthetic exploitation of the easily accessible hydrazones **4**. Through a facile and stereoselective [2+2] cycloaddition reaction, compounds **4** lead to highly substituted *N*-protected 2-azetidinones with definite stereochemistry bearing, in particular, a COX (X=Me, Et, Ph, NR_2, OBu^t) functionality at the 4 position: the interest in such heterocycles is undoubtedly fostered also by very recent examples from the literature where 4-COX-2-azetidinones have proven to be efficient precursors of α-amino acids (X=OR)[15] via the breakage of the N(1)–C(2) bond, or of polycyclic β-lactams of potential pharmacological activity (X=Ph).[16] Furthermore, a mild and efficient cleavage of the originary N–N bond provides access to likewise appealing unprotected β-lactams. Thus, the employment of hydrazones (and in particular of α-carbonylhydrazones) as a valid alternative to the imine components in Staudinger-like processes (a use which, to our knowledge, has been very little explored until now[8]) seems to be very promising and surely deserving further investigations.

4. Experimental

4.1. General

Melting points were determined with a Büchi 535 apparatus and are uncorrected. ^1H NMR and ^{13}C NMR spectra were recorded using $CDCl_3$ solutions (unless otherwise stated) at 200 and 50 MHz, respectively, with a Varian Gemini 200 spectrometer; TMS was used as internal standard and chemical shifts are reported as δ values (ppm).

Petroleum ether and light petroleum refer to the fractions with bp 40–60 and 80–100°C, respectively. Dry methylene chloride was commercial, used as received; triethylamine was commercial, distilled before use and kept over KOH pellets; phenoxyacetyl chloride was commercial, distilled before use. Hydrazones **4a-l** were synthesized as previously reported.[9] Column (or preparative plate, PTLC) chromatography was performed on silica gel using petroleum ether and gradients (or appropriate mixtures) with CH_2Cl_2, Et_2O or AcOEt as eluents, the solvents being distilled before use.

4.2. Reactions of hydrazones 4a-l with phenoxyketene

To a solution of the hydrazone (1 mmol) and triethylamine (3 mmol) in dry methylene chloride (10 mL) cooled to 10°C, a solution of phenoxyacetyl chloride (2.5 mmol) in dry methylene chloride (2.5 mL) was added dropwise under magnetic stirring. The reaction mixture was left to reach room temperature. After stirring 24 h, the mixture was diluted to 50 mL, washed with saturated $NaHCO_3$ aqueous solution (2×15 mL), water (2×15 mL), and dried over Na_2SO_4. Concentration under vacuum of the solution gave a crude product which was purified by column chromatography over silica gel (petroleum ether/methylene chloride or ethyl acetate gradients as eluents).

4.2.1. (3*R*,4*R*) and (3*S*,4*S*) 4-Acetyl-4-methyl-1-(methyl-*p*-tolyl-amino)-3-phenoxy-2-azetidinone (5a). (179 mg, 53%). White solid, mp 129.8–131.7°C (light petroleum); ν_{max} (Nujol) 1771, 1722, 1599, 1508, 1235, 1112, 1084 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.71 (3H, s), 2.22 (3H, s), 2.30 (3H, s), 3.40 (3H, s), 4.99 (1H, s), 6.96–7.06 (5H, m), 7.11 (2H, d, *J*=8.4 Hz), 7.24–7.36 (2H, m); ^{13}C NMR ($CDCl_3$) δ 17.70 (q), 20.60 (q), 28.06 (q), 43.93 (q), 75.63 (s), 85.37 (d), 115.74 (d), 117.94 (d), 122.87 (d), 129.70 (d), 129.73 (d), 132.57 (s), 146.97 (s), 157.00 (s), 164.68 (s), 205.04 (s). Anal. calcd for $C_{20}H_{22}N_2O_3$: C, 71.0; H, 6.6; N, 8.3%. Found: C, 71.2; H, 6.7; N, 8.1%.

4.2.2. (3*R*,4*R*) and (3*S*,4*S*) 4-Methyl-1-(methyl-*p*-tolyl-amino)-3-phenoxy-4-propionyl-2-azetidinone (5b). (265 mg, 75%). White solid, mp 155.6–156.0°C (light petroleum); ν_{max} (Nujol) 1768, 1725, 1598, 1512, 1494, 1236, 1174, 1083 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.02 (3H, t, *J*=7.0 Hz), 1.72 (3H, s), 2.30 (3H, s), 2.44 (1H, dq, *J*=18.3, 7.0 Hz), 2.63 (1H, dq, *J*=18.3, 7.0 Hz), 3.43 (3H, s), 4.98 (1H, s), 6.95–7.15 (7H, m), 7.24–7.36 (2H, m); ^{13}C NMR ($CDCl_3$) δ 7.51 (q), 17.89 (q), 20.60 (q), 33.46 (t), 44.07 (q), 75.70 (s), 85.44 (d), 115.70 (d), 117.72 (d), 122.82 (d), 129.68 (d), 129.72 (d), 132.37 (s), 147.12 (s), 157.03 (s), 164.73 (s), 207.57 (s). Anal. calcd for $C_{21}H_{24}N_2O_3$: C, 71.6; H, 6.9; N, 7.9%. Found: C, 71.9; H, 7.2; N, 7.7%.

4.2.3. (3*R*,4*R*) and (3*S*,4*S*) 4-Benzoyl-4-methyl-1-(methyl-*p*-tolyl-amino)-3-phenoxy-2-azetidinone (5c). (321 mg, 80%). White solid, mp 168.3–168.5°C (light petroleum); ν_{max} (Nujol) 1770, 1690, 1598, 1508, 1493, 1233, 1194, 1168, 1110, 1083 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.84 (3H, s), 2.29 (3H, s), 3.58 (3H, s), 5.29 (1H, s), 6.92–7.08 (5H, m), 7.11 (2H, d, J=8.2 Hz), 7.20–7.32 (2H, m), 7.40–7.64 (3H, m), 7.82–7.91 (2H, m); ^{13}C NMR (CD_3SOCD_3) δ 19.33 (q), 19.95 (q), 42.74 (q), 76.51 (s), 84.48 (d), 114.85 (d), 115.73 (d), 122.36 (d), 128.40 (d), 129.13 (d), 129.31 (s), 129.42 (d), 129.52 (d), 133.22 (d), 134.01 (s), 146.65 (s), 156.75 (s), 164.48 (s), 197.03 (s). Anal. calcd for $C_{25}H_{24}N_2O_3$: C, 75.0; H, 6.1; N, 7.0%. Found: C, 74.7; H, 6.5; N, 7.3%.

4.2.4. (3*R*,4*R*) and (3*S*,4*S*) 4-Acetyl-4-ethyl-1-(methyl-*p*-tolyl-amino)-3-phenoxy-2-azetidinone (5d). (222 mg, 63%). White solid, mp 142.8–143.7°C (light petroleum); ν_{max} (Nujol) 1770, 1722, 1598, 1511, 1494, 1228, 1117, 1090 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.93 (3H, t, J=7.5 Hz), 2.10 (1H, app. sext, J=7.5 Hz), 2.26 (3H, s), 2.29 (3H, s), 2.41 (1H, app. sext, J=7.5 Hz), 3.48 (3H, s), 5.01 (1H, s), 6.96 (2H, d, J=8.7 Hz), 7.00–7.15 (5H, m), 7.26–7.37 (2H, m); ^{13}C NMR ($CDCl_3$) δ 8.73 (q), 20.58 (q), 26.55 (t), 28.24 (q), 43.77 (q), 79.87 (s), 83.57 (d), 115.89 (d), 117.16 (d), 122.84 (d), 129.68 (d), 129.75 (d), 132.01 (s), 147.06 (s), 157.18 (s), 164.80 (s), 204.55 (s). Anal. calcd for $C_{21}H_{24}N_2O_3$: C, 71.6; H, 6.9; N, 7.9%. Found: C, 71.3; H, 6.9; N, 8.1%.

4.2.5. (3*R*,4*R*) and (3*S*,4*S*) 4-(*N*,*N*-Dimethylaminocarbonyl)-4-methyl-1-(methyl-*p*-tolyl-amino)-3-phenoxy-2-azetidinone (5e). (363 mg, 99%). White solid, mp 185.0–185.3°C (toluene); ν_{max} (Nujol) 1769, 1659, 1598, 1589, 1512, 1270, 1239, 1174, 1101, 1081 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.75 (3H, s), 2.27 (3H, s), 2.96 (3H, s), 3.04 (3H, s), 3.58 (3H, s), 5.05 (1H, s), 6.92 (2H, d, J=8.7 Hz), 6.99–7.21 (5H, m), 7.25–7.38 (2H, m); ^{13}C NMR ($CDCl_3$) δ 19.63 (q), 20.45 (q), 36.01 (q), 38.07 (q), 44.04 (q), 73.17 (s), 84.78 (d), 115.92 (d), 115.96 (d), 122.67 (d), 129.46 (d), 129.64 (d), 130.74 (s), 147.19 (s), 157.18 (s), 164.33 (s), 169.12 (s). Anal. calcd for $C_{21}H_{25}N_3O_3$: C, 68.6; H, 6.9; N, 11.4%. Found: C, 68.9; H, 7.1; N, 11.2%.

4.2.6. (3*R*,4*R*) and (3*S*,4*S*) 4-(*N*,*N*-Dimethylaminocarbonyl)-4-ethyl-1-(methyl-*p*-tolyl-amino)-3-phenoxy-2-azetidinone (5f). (378 mg, 99%). White solid, mp 181.6–182.0°C (toluene); ν_{max} (Nujol) 1769, 1658, 1610, 1597, 1588, 1507, 1493, 1405, 1267, 1237, 1173, 1105, 1088 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.98 (3H, t, J=7.5 Hz), 2.04 (1H, app. sext, J=7.5 Hz), 2.21–2.44 (4H in all, partially overlapped s and m), 2.96 (3H, s), 3.07 (3H, s), 3.58 (3H, s), 5.05 (1H, s), 6.99 (2H, d, J=8.7 Hz), 7.04–7.20 (5H, m), 7.26–7.38 (2H, m); ^{13}C NMR (CD_3SOCD_3) δ 8.52 (q), 19.96 (q), 26.62 (t), 35.47 (q), 37.54 (q), 42.72 (q), 77.33 (q), 82.10 (d), 114.55 (d), 115.80 (d), 122.17 (d), 128.86 (s), 129.10 (d), 129.48 (d), 146.79 (s), 157.05 (s), 164.59 (s), 167.39 (s). Anal. calcd for $C_{22}H_{27}N_3O_3$: C, 69.3; H, 7.1; N, 11.0%. Found: C, 69.5; H, 6.8; N, 10.7%.

4.2.7. (3*R*,4*R*) and (3*S*,4*S*) 4-*tert*-Butoxycarbonyl-4-methyl-1-(methyl-*p*-tolyl-amino)-3-phenoxy-2-azetidinone (5g). (348 mg, 88%). White solid, mp 154.3–154.9°C (light petroleum); ν_{max} (Nujol) 1789, 1732, 1613, 1599, 1510, 1491, 1364, 1347, 1277, 1239, 1174, 1157, 1133, 1109, 1086, 1032 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.33 (9H, s), 1.75 (3H, s), 2.28 (3H, s), 3.45 (3H, s), 4.95 (1H, s), 6.91 (2H, d, J=8.6 Hz), 6.95–7.13 (5H, m), 7.24–7.36 (2H, m); ^{13}C NMR ($CDCl_3$) δ 18.46 (q), 20.50 (q), 27.79 (q), 42.55 (q), 72.23 (s), 83.15 (s), 85.03 (d), 115.56 (d), 115.84 (d), 122.48 (d), 129.52 (d), 129.65 (d), 131.23 (s), 146.85 (s), 157.31 (s), 164.26 (s), 168.23 (s). Anal. calcd for $C_{23}H_{28}N_2O_4$: C, 69.7; H, 7.1; N, 7.1%. Found: C, 69.8; H, 6.8; N, 7.4%.

4.2.8. (3*R*,4*R*) and (3*S*,4*S*) 4-*tert*-Butoxycarbonyl-4-ethyl-1-(methyl-*p*-tolyl-amino)-3-phenoxy-2-azetidinone (5h). (282 mg, 69%). White solid, mp 147.5–148.2°C (light petroleum); ν_{max} (Nujol) 1785, 1730, 1598, 1589, 1511, 1486, 1259, 1228, 1174, 1155, 1138, 1114, 1098, 1083 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.94 (3H, t, J=7.4 Hz), 1.35 (9H, s), 2.02 (1H, app. sext, J=7.4 Hz), 2.28 (3H, s), 2.51 (1H, app. sext, J=7.4 Hz), 3.51 (3H, s), 4.98 (1H, s), 6.89 (2H, d, J=8.7 Hz), 6.98–7.13 (5H, m), 7.24–7.36 (2H, m); ^{13}C NMR ($CDCl_3$) δ 8.77 (q), 20.47 (q), 27.39 (t), 27.79 (q), 42.75 (q), 76.61 (s), 82.97 (s), 83.28 (d), 115.49 (d), 115.60 (d), 122.38 (d), 129.43 (d), 129.68 (d), 130.96 (s), 146.86 (s), 157.40 (s), 164.71 (s), 167.61 (s). Anal. calcd for $C_{24}H_{30}N_2O_4$: C, 70.2; H, 7.4; N, 6.8%. Found: C, 70.0; H, 7.3; N, 6.6%.

4.2.9. (3*R*,4*S*) and (3*S*,4*R*) 4-(*N*,*N*-Diethylaminocarbonyl)-1-(methyl-*p*-tolyl-amino)-3-phenoxy-4-phenyl-2-azetidinone (5i). (340 mg, 74%). White solid, mp 180.0–180.6°C (light petroleum); ν_{max} (Nujol) 1781, 1623, 1591, 1488, 1274, 1230, 1095, 1074 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.48 (3H, t, J=7.0 Hz), 0.99 (3H, t, J=7.0 Hz), 2.28 (3H, s), 2.81 (1H, app. sext, J=7.0 Hz), 3.13 (1H, app. sext, J=7.0 Hz), 3.25–3.62 (5H in all, partially overlapped s and m), 6.39 (1H, s), 6.83–6.95 (5H, m), 7.05–7.16 (4H, m), 7.17–7.34 (5H, m); ^{13}C NMR ($CDCl_3$) δ 11.88 (q), 11.95 (q), 20.52 (q), 39.98 (t), 42.25 (t), 43.78 (q), 79.07 (s), 82.85 (d), 115.41 (d), 116.23 (d), 121.80 (d), 126.84 (d), 128.19 (d), 128.35 (d), 129.13 (d), 129.81 (d), 131.68 (s), 133.96 (s), 146.18 (s), 156.81 (s), 166.88 (s), 167.46 (s). Anal. calcd for $C_{28}H_{31}N_3O_3$: C, 73.5; H, 6.8; N, 9.2%. Found: C, 73.6; H, 6.8; N, 9.2%.

4.2.10. (3*R*,4*S*) and (3*S*,4*R*) 4-*tert*-Butoxycarbonyl-1-(methyl-*p*-tolyl-amino)-3-phenoxy-4-phenyl-2-azetidinone (5j) and (3*R*,4*R*) and (3*S*,4*S*) 4-*tert*-butoxycarbonyl-1-(methyl-*p*-tolyl-amino)-3-phenoxy-4-phenyl-2-azetidinone (5j′). Compound **5j** (223 mg, 49%: see footnote c of Table 1). White solid, mp 130.8–131.4°C (light petroleum); ν_{max} (Nujol) 1780, 1717, 1599, 1591, 1513, 1493, 1287, 1226, 1192, 1154, 1102 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.22 (9H, s), 2.28 (3H, s), 3.24 (3H, s), 5.83 (1H, s), 6.75 (2H, d, J=8.8 Hz), 6.84–6.96 (3H, m), 7.03–7.20 (4H, m), 7.22–7.30 (3H, m), 7.34–7.44 (2H, m); ^{13}C NMR ($CDCl_3$) δ 20.41 (q), 27.38 (q), 41.12 (q), 77.41 (s), 81.74 (d), 84.20 (s), 114.95 (d), 115.46 (d), 122.03 (d), 127.80 (d), 127.98 (d), 128.64 (d), 129.18 (d), 129.75 (d), 130.68 (s), 132.41 (s), 146.20 (s), 156.63 (s), 165.82 (s), 168.24 (s). Anal. calcd for $C_{28}H_{30}N_2O_4$: C, 73.3; H, 6.6; N, 6.1%. Found: C, 73.3; H, 6.6; N, 6.1%. **5j′** (in mixture with compound **5j**: see footnote c of Table 1). Only a few signals are clearly

detectable in the ^{1}H NMR of the two diastereoisomers mixture: ^{1}H NMR ($CDCl_3$) δ 1.30 (9H, s), 2.19 (3H, s), 3.45 (3H, s), 5.65 (1H, s), 6.60 (2H, d, J=8.8 Hz).

4.3. Crystal structure data of compound 5i

All the measurements were performed using graphite-monochromatized Mo Kα radiation at 294 K: $C_{28}H_{31}N_3O_3$, MW 457.56, monoclinic, space group $P2_1/c$, a=11.340(4) Å, b=18.072(2) Å, c=13.198(3) Å, β=110.95(2)°, V=2525.9(11) Å^3, Z=4, d_{calc}=1.203 g cm^{-3}, μ=0.079 mm^{-1}, crystal size 0.46×0.39×0.10 mm^3. A total of 4197 independent reflections were collected (θ_{max}=24.5°), 2488 having $I>2\sigma(I)$. The structure was solved by direct methods (NRCVAX)[17] and refined by full-matrix least-squares techniques against F^2 (SHELXL-97).[18] Figure 1 was prepared using PLATON.[19] Owing to the small number of high-angle significant reflections the number of parameters was decreased considering the three benzene rings as rigid groups and refining the H atoms (with idealized geometries) as riding on the bonded carbon atom. For 277 parameters the final R indices are R=0.0604 (over 2488 data) and wR^2=0.1725 (over all 4197 data; GOF=1.048). All crystallographic data (excluding structure factors) have been deposited with the Cambridge Crystallographic Data Centre (CCDC 213836).

4.4. Cleavage of N–N bond in compounds 5

In a flask, the azetidinone (**5b**, **5e**, or **5g**) (0.3 mmol) was dissolved in methanol (7.5 mL) and methylene chloride (2.5 mL), and MMPP·6H$_2$O (0.9 mmol) was added in portions. The mixture was stirred at room temperature for 24 h, then poured into water (50 mL), extracted with methylene chloride (3×20 mL); the organic extracts were washed with 5% Na_2SO_3 aqueous solution (2×15 mL), water (2×15 mL), and dried over Na_2SO_4. Concentration under vacuum of the solution gave a crude which was purified by column chromatography over silica gel (petroleum ether/methylene chloride/AcOEt gradients as eluents) to give compound **6** together with *p*-nitrotoluene (not quantified) and small amounts (10–16%) of unreacted **5**.

4.4.1. (3*R*,4*R*) and (3*S*,4*S*) 4-Methyl-3-phenoxy-4-propionyl-2-azetidinone (6b). (60 mg, 86%). White solid, mp 169.0–169.9°C (ethanol); ν_{max} (Nujol) 3325, 1722, 1598, 1492, 1345, 1242, 1096 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.11 (3H, t, J=7.2 Hz), 1.72 (3H, s), 2.51–2.86 (2H, m), 5.06 (1H, d, J=1.8 Hz), 6.74 (1H, br s), 6.96–7.09 (3H, m), 7.24–7.35 (2H, m); ^{13}C NMR ($CDCl_3$) δ 7.46 (q), 20.88 (t), 33.13 (d), 67.27 (s), 88.95 (d), 115.78 (d), 122.89 (d), 129.67 (d), 157.09 (s), 165.09 (s), 208.51 (s). Anal. calcd for $C_{13}H_{15}NO_3$: C, 66.9; H, 6.5; N, 6.0%. Found: C, 67.0; H, 6.5; N, 6.0%.

4.4.2. (3*R*,4*R*) and (3*S*,4*S*) 4-(*N*,*N*-Dimethylaminocarbonyl)-4-methyl-3-phenoxy-2-azetidinone (6e). (61 mg, 82%). White solid, mp 195.8–196.5°C (ethanol); ν_{max} (Nujol) 3205, 1768, 1631, 1590, 1485, 1402, 1336, 1241, 1098 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.74 (3H, s), 3.02 (3H, s), 3.08 (3H, s), 5.08 (1H, d, J=2.2 Hz), 6.74 (1H, br s), 6.95–7.16 (3H, m), 7.25–7.36 (2H, m); ^{13}C NMR ($CDCl_3$) δ 23.32 (q), 36.12 (q), 38.16 (q), 62.93 (s), 87.45 (d), 115.84 (d), 122.65 (d), 129.67 (d), 157.20 (s), 163.77 (s), 169.25 (s). Anal. calcd for $C_{13}H_{16}N_2O_3$: C, 62.9; H, 6.5; N, 11.3%. Found: C, 63.1; H, 6.4; N, 11.2%.

4.4.3. (3*R*,4*R*) and (3*S*,4*S*) 4-*tert*-Butoxycarbonyl-4-methyl-3-phenoxy-2-azetidinone (6g). (62 mg, 75%). White solid, mp 156.6–156.9°C (ethanol); ν_{max} (Nujol) 3400 (br), 1787, 1733, 1600, 1276, 1241, 1174, 1158, 1133, 1086 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.32 (9H, s), 1.79 (3H, s), 5.03 (1H, s), 6.59 (1H, br s), 6.92–7.08 (3H, m), 7.24–7.36 (2H, m); ^{13}C NMR ($CDCl_3$) δ 21.65 (q), 27.72 (q), 63.62 (s), 83.01 (s), 87.97 (d), 115.52 (d), 122.38 (d), 129.45 (d), 157.36 (s), 164.62 (s), 169.27 (s). Anal. calcd for $C_{15}H_{19}NO_4$: C, 65.0; H, 6.9; N, 5.1%. Found: C, 64.8; H, 7.0; N, 4.9%.

Acknowledgements

Financial support was provided by grants from Università di Genova and Ministero dell'Istruzione, dell'Università e della Ricerca (MIUR-COFIN 2002).

References

1. For reviews see: (a) Georg, G. I.; Ravikumar, V. In *The Organic Chemistry of β-Lactams*; Georg, G. I., Ed.; VCH: New York, 1993. (b) *The Chemistry of β-Lactams*; Page, M. I., Ed.; Chapman & Hall: London, 1992. (c) Ghosez, L.; Marchand-Brynaert, J. In *Comprehensive Organic Synthesis*; Trost, B., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 5, p 85. (d) Southgate, R.; Branch, C.; Coulton, S.; Hunt, E. *Recent Progress in the Chemical Synthesis of Antibiotics and Related Microbial Products*; Lukacs, G., Ed.; Springer: Berlin, 1993; Vol. 2, p 621. (e) *Recent Aspects of the Chemistry of β-Lactams-II. Tetrahedron*; Miller, M. J., Ed.;, 2000; 56, pp 5553–5742. (f) Singh, G. S. Recent Progress in the Synthesis and Chemistry of Azetidinones. *Tetrahedron* **2003**, 7631–7649.
2. (a) Page, M. I. *Acc. Chem. Res.* **1984**, *17*, 144–151. (b) Beauve, C.; Bouchet, M.; Touillaux, R.; Fastrez, J.; Marchand-Brynaert, J. *Tetrahedron* **1999**, *55*, 13301–13320. (c) Gérard, S.; Dive, G.; Clamot, B.; Touillaux, R.; Marchand-Brynaert, J. *Tetrahedron* **2002**, *58*, 2423–2433.
3. For rewiews see: (a) Mascaretti, O. A.; Boschetti, C. E.; Danelon, G. O.; Mata, E. G.; Roveri, O. A. *Curr. Med. Chem.* **1995**, *1*, 441–470. (b) Edwards, P. D.; Bernstein, P. R. *Med. Res. Rev.* **1994**, *14*, 127–194.
4. (a) Vaccaro, W. D.; Davis, H. R., Jr. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 313–318. (b) Vaccaro, W. D.; Sher, R.; Davis, H. R., Jr. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 35–40. (c) Burnett, D. A. *Tetrahedron Lett.* **1994**, *35*, 7339–7342. (d) Borthwick, A. D.; Weingarten, G.; Haley, T. M.; Tomaszewski, M.; Wang, W.; Hu, Z.; Bedard, J.; Jin, H.; Yuen, L.; Mansour, T. S. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 365–370. (e) Ogilvie, W.; Bailey, M.; Poupart, M.-A.; Abraham, A.; Bhavsar, A.; Bonneau, P.; Bordeleau, J.; Bousquet, Y.; Chabot, C.; Duceppe, J.-S.; Fazal, G.; Goulet, S.; Grand-Maitre, C.; Guse, I.; Halmos, T.; Lavallee, P.; Leach, M.; Malefant, E.; O'Meara, J.; Plante, R.; Plouffe, C.; Poirier, M.; Soucy, F.; Yoakim, C.; Deziel, R.

J. Med. Chem. **1997**, *40*, 4113–4135. (f) Han, W. T.; Trehan, A. K.; Wright, J. J. K.; Federici, M. E.; Seiler, S. M.; Meanwell, N. A. *Bioorg. Med. Chem.* **1995**, *3*, 1123–1143.
5. Palomo, C.; Aizpurua, J. M.; Ganboa, I.; Oiarbide, M. *Eur. J. Org. Chem.* **1999**, 3223–3235, and references therein.
6. Staudinger, H. *Liebigs Ann. Chem.* **1907**, *356*, 51–123.
7. Georg, G. I.; Ravikumar, V. In *The Organic Chemistry of β-Lactams*; Georg, G. I., Ed.; VCH: New York, 1993; pp 295–368, Chapter 6; and references therein.
8. (a) Fernández, R.; Ferrete, A.; Lassaletta, J. M.; Llera, J. M.; Martín-Zamora, E. *Angew. Chem. Int. Ed.* **2002**, *41*, 831–833. (b) Fernández, R.; Ferrete, A.; Lassaletta, J. M.; Llera, J. M.; Monge, A. *Angew. Chem. Int. Ed.* **2000**, *39*, 2893–2897. (c) Sharma, S. D.; Pandhi, S. B. *J. Org. Chem.* **1990**, *55*, 2196–2200. (d) Boruah, A.; Prajapati, D.; Sandhu, J. S. *Indian J. Chem. Sect. B* **1996**, *35*, 1148–1151.
9. (a) Dell'Erba, C.; Novi, M.; Petrillo, G.; Tavani, C. *Tetrahedron* **1994**, *50*, 11239–11248. (b) Dell'Erba, C.; Novi, M.; Petrillo, G.; Tavani, C. *Tetrahedron* **1996**, *52*, 5889–5898.
10. Caposcialli, N.; Dell'Erba, C.; Novi, M.; Petrillo, G.; Tavani, C. *Tetrahedron* **1998**, *54*, 5315–5324.
11. (a) Firestone, R. A.; Barker, P. L.; Pisano, J. M.; Ashe, B. M.; Dahlgren, M. E. *Tetrahedron* **1990**, *46*, 2255–2262. (b) Adlington, R. M.; Baldwin, J. E.; Chen, B. N.; Cooper, S. L.; McCoull, W.; Pritchard, G. J.; Howe, T. J.; Becker, G. W.; Hermann, R. B.; McNulty, A. M.; Neubauer, B. L. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 1689–1694.
12. (a) Georg, G. I.; Ravikumar, V. In *The Organic Chemistry of β-Lactams*; Georg, G. I., Ed.; VCH: New York, 1993; pp 331–335, Chapter 6. (b) Georg, G. I.; He, P.; Kant, J.; Wu, Z.-J. *J. Org. Chem.* **1993**, *58*, 5771–5778. (c) Hegedus, L. S.; Montgomery, J.; Narukawa, Y.; Snustad, D. C. *J. Am. Chem. Soc.* **1991**, *113*, 5784–5791. (d) Dumas, S.; Hegedus, L. S. *J. Org. Chem.* **1994**, *59*, 4967–4971.
13. Arrieta, A.; Cossio, F. P.; Lecea, B. *J. Org. Chem.* **2000**, *65*, 8458–8464. Walker, M. J.; Hietbrink, B. N.; Thomas, B. E., IV; Nakamura, K.; Kallel, E. A.; Houk, K. N. *J. Org. Chem.* **2001**, *66*, 6669–6672.
14. For reviews see: (a) Lukacs, G.; Ohno, M. *Recent Progress in the Chemical Synthesis of Antibiotics*; Springer: Berlin, 1990. (b) Bently, P. H.; Southgate, R. *Recent Advances in the Chemistry of β-Lactam Antibiotics*; The Royal Society of Chemistry: Burlington House: London, 1989; Vol. 4. p 380. (c) *Chemistry and Biology of β-Lactam Antibiotics*; Morin, R. B., Gorman, M., Eds.; Academic: New York, 1982; Vols. 1–3.
15. Gerona-Navarro, G.; García-López, M. T.; González-Muñiz, R. *Tetrahedron Lett.* **2003**, *44*, 6145–6148.
16. Del Buttero, P.; Molteni, G.; Papagni, A.; Pilati, T. *Tetrahedron* **2003**, *59*, 5259–5263.
17. Gabe, E. J.; Le Page, Y.; Charland, J.-P.; Lee, F. L.; White, P. S. *J. Appl. Crystallogr.* **1989**, *22*, 384–387.
18. Sheldrick, G. M. *SHELXL-97: A program for refinement of crystal structures*; University of Göttingen: Germany, 1997.
19. Spek, A. L. *PLATON: A multipurpose crystallographic tool*; Utrecht University: Utrecht, The Netherlands, 2002.