Pergamon

SCIENCE DIRECT®

Tetrahedron: *Asymmetry* 14 (2003) 993–998

TETRAHEDRON: *ASYMMETRY*

Lewis acid-catalyzed electrocyclization of 2-aza-1,3-butadienes to *NH*-β-lactams

Alessandro Bongini,[a,*] Mauro Panunzio,[a,*] Emiliano Tamanini,[a] Giorgio Martelli,[b] Paola Vicennati[b] and Magda Monari[a]

[a]*ISOF-CNR and Universita', Dipartimento di Chimica 'G. Ciamician' Via Selmi 2, 40126 Bologna, Italy*
[b]*ISOF-CNR, Via Gobetti 101, 40129 Bologna, Italy*

Received 29 October 2002; accepted 6 February 2003

Abstract—Lewis acid-catalyzed cyclization of 2-aza-3-trimethylsilyloxy-buta-1,3-diene is reported. Stereochemical differences with the uncatalyzed cyclization are discussed.

1. Introduction

The presence of the azetidin-2-one (β-lactam) ring in several widely used families of antibiotics, such as penicillins, cephalosporins, carbapenems and monocyclic β-lactams (for example aztreonam), coupled with the recent discoveries that β-lactams can serve as mechanism-based inhibitors of serine protease[1–3] and as inhibitors of acyl-CoA cholesterol acyltransferase (ACAT)[4] which is responsible for atherosclerotic coronary heart disease, has stimulated considerable research efforts toward stereoselective routes for the synthesis of this important building block. Moreover, additional impetus has been provided by the introduction of the β-lactam synthon methodology,[5–8] according to which enantiomerically pure β-lactams can be employed as useful intermediates for organic synthesis. One of the most popular methods for the preparation of the β-lactam ring involves the venerable [2+2] cycloaddition of ketenes and imines.[9–12] Recently, in a series of papers[13–18] we have reported on a variant of this methodology which allows the isolation of a neutral stable intermediate: a 2-aza-3-trimethylsilyloxy-1,3-butadiene[19–21] which may be considered a neutral equivalent to the classical zwitterionic intermediate invoked in the Staudinger reaction.[17,22–25] As a matter of fact both neutral and zwitterionic intermediates undergo uncatalyzed conrotatory electrocyclization. For its nature and on the basis of the accepted reaction mechanism, a classical Staudinger reaction may be catalyzed in the first step (formation of the zwitterionic intermediate), but not in the second one (conrotatory ring closure) due to the impossibility to isolate this highly reactive species. In our case, the possibility of having a stable azadiene opens new scenarios for the Staudinger reaction. The conrotatory cyclization step, which is spontaneous in the classical procedure due to the high energy of the zwitterionic intermediate, may be controlled, in the case of a neutral stable intermediate, by means of a Lewis acid (LA).[26] Moreover, the formation of β-lactam for the uncatalyzed reaction requires forcing conditions ($T = 100$°C) to achieve ring closure,[17] whereas the catalyzed reaction takes place at lower temperatures (see below).

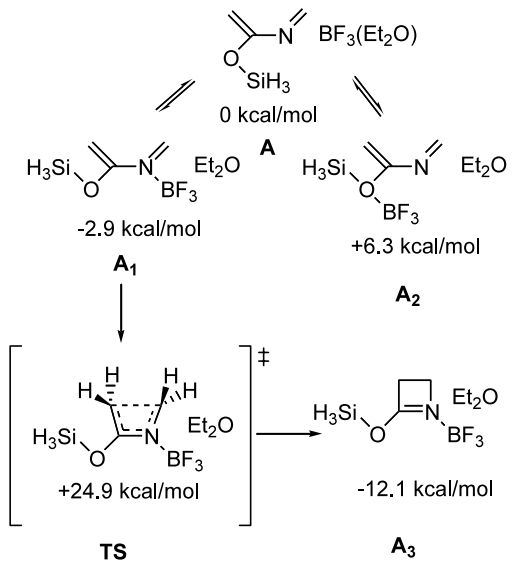
2. Results and discussions

2.1. Theoretical calculations

In order to explore this possibility an ab initio theoretical calculations at MP2/6-31G* level[27] using unsubstituted 3-silyloxy-2-azadiene **A** as model compounds and BF_3 etherate as LA have been performed with the goal of stressing the differences, if any, between the uncatalyzed mechanism and this new LA-catalyzed ring closure (Scheme 1). The calculations show that of the two possible adducts $\mathbf{A_1}$ and $\mathbf{A_2}$, the most thermodynamically stable is the adduct $\mathbf{A_1}$ (–2.9 kcal/mol versus +6.3 kcal/mol) in which the coordination of the LA with the

* Corresponding authors. Tel.: +39 051 209 9508; fax: +39 051 209 9456; e-mail: panunzio@ciam.unibo.it

0957-4166/03/$ - see front matter
doi:10.1016/S0957-4166(03)00162-9



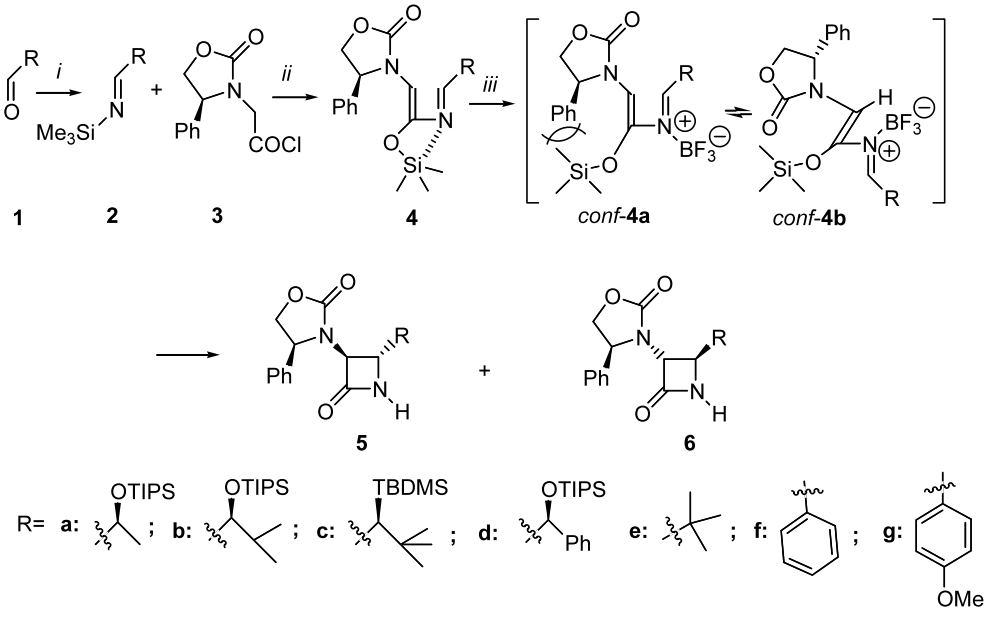
Scheme 1.

iminic nitrogen takes place. This adduct is characterized by the formation of an almost covalent bond between the boron and the nitrogen (N–B bond 1.69 Å, Wiberg bond index 0.41, C=N bond 1.28 Å, Wiberg bond index 1.68) and by a superior electrofilicity of the iminic methylene (+0.344 e^- versus +0.207 e^- in neutral azadiene). $\mathbf{A_1}$ then undergoes an electrocyclic conrotatory closure to the intermediate $\mathbf{A_3}$ through the transition state **TS** (Scheme 1). The reaction path described is strictly analogue to that obtained for uncomplexed azadiene both at MP2 and at B3LYP levels.[17,25] The electronic nature of the cyclization mechanism remains the same but some important differences must be emphasized. The first resides in the geometry of the involved molecules due to the presence of the BF_3, which, coordinating itself to the nitrogen, forbids the internal chelation of the silyl group. A further consequence of the complexation by the LA results in a decreasing of the activation energy from 32.2 kcal/mol for the uncatalyzed reaction to 27.8 kcal/mol for the catalyzed one.

2.2. Experimental results

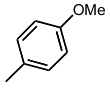
The theoretical results have been confirmed at the experimental level. Among the most popular LAs screening showed that the sole effective LA in achieving the cyclization reaction, in reasonable yields, was BF_3 etherate (Scheme 2). The other LAs tested ($TiCl_4$, $ZnCl_2$, $AlCl_3$), irrespective of their Lewis acidity and/or steric properties, were ineffective or scarcely effective. Table 1 reports the results obtained starting from a variety of azadienes prepared according to the literature procedure.[17]

The data reported show that in analogy to the uncatalyzed cyclization reaction, diastereomeric *trans*-azetidinones were obtained. This stereochemistry is in agreement with conrotatory cyclization of the azadienes presenting the *EZ* configuration.[17] The main difference between the uncatalyzed and catalyzed reactions lies in the distribution of diastereoisomers arising from the facial diastereoselectivity of the reactions. In a previous paper we have reported[17] that the facial diastereoselectivity arises from a constrained conformation due to chelation of the silicon to the nitrogen. In the present LA-catalyzed process, the coordination of BF_3 to the nitrogen, as demonstrated by the theoretical calculations reported above, prevents this internal chelation. The consequent loss of molecular rigidity increases the rotational freedom along the *s*-C–N bond (Scheme 2) and as a consequence, different mechanistic pathways, from the diastereomeric point of view, may take place. The presence of the Evans chiral auxiliary is in the



Scheme 2. *Reagents and conditions*: (i), (ii) Refs. 17 and 29; (iii) $BF_3{\cdot}Et_2O$, –78°C to rt; CH_2Cl_2.

Table 1. Azetidinones **5** and **6** from aldehydes **1**

Exp	R	Products (ratio)[a] [ratio][b]	Yield%[c]	Ref
1		**5a/6a** (33/67) *[80/20]*	42 *[59]*	17
2		**5b/6b** (93/7) *[73/27]*	35 *[48]*	17
3		**5c/6c** (43/57) *[88/12]*	47 *[84]*	17
4		**5d/6d** (50/50) *[80/20]*	42 *[57]*	17
5		**5e/6e** (68/32) *[65/35]*	38 *[56]*	
6		**5f/6f** (98/2) *[46/54]*	32 *[23]*	
7		**5g/6g** (88/12) *[5/95]*	22 *[16]*	

[a] The diastereomeric ratio values, determined by ^{1}H NMR on the crude reaction mixture, are identical with those obtained upon isolation of the products by flash chromatography. The *trans* stereochemistry of the azetidinones was assigned from H_3–H_4 coupling constants (J_{trans} 2–3 Hz) whereas the facial stereochemistry for the products of entry 5 was assigned on the basis of the observation that similar compounds of known configuration (see Ref. 17) show a δ value of the chemical shift of the (*S*)-C_3H series (compounds **5**) always higher than that of the (*R*)-C_3H series (compounds **6**). The absolute configuration for the compounds **5f** and **5g** (entries 6 and 7) was assigned by X-ray analysis (see Figs. 1 and 2).

[b] The diastereomeric ratios obtained in the uncatalyzed reactions are reported in square brackets.

[c] Overall yields are for pure isolated products and are based on the starting aldehydes from which azadienes were obtained.

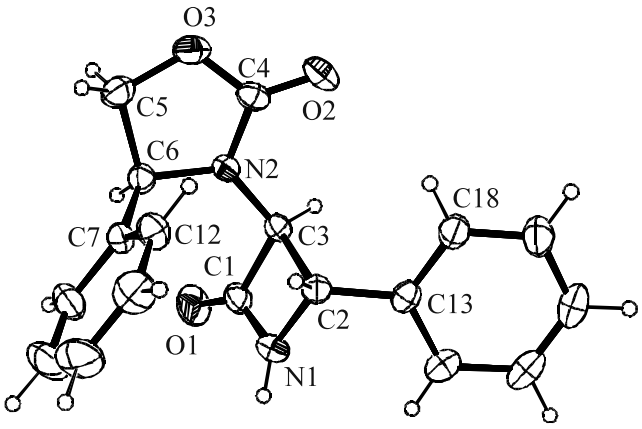


Figure 1. ORTEP drawing of compound **5f**. Thermal ellipsoids are set at the 30% probability level.

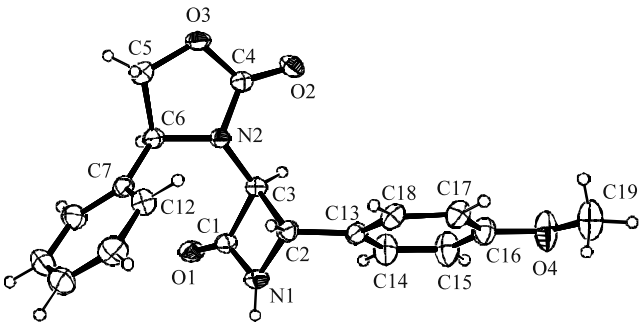


Figure 2. ORTEP drawing of compound **5g**. Thermal ellipsoids are set at the 30% probability level.

main responsible for the induction of the C-3 (*S*) stereoselectivity, as already reported.[17] In the LA-catalyzed ring closure we can postulate an equilibrium between different conformers (two of them are reported in Scheme 2): the conformer *conf*-**4b**, in particular, presents an inversion of the facial diastereotopicity compared with the chelate compound **4**. A different composition in the population of conformers is responsible for the decrease in classical stereoinduction. From the results reported in Table 1, we can deduce that the very nature of the R substituent (Scheme 2) is responsible for the decrease or inversion of the facial diastereoselectivity. The experimental results in Table 1 do not allow us to generalize this mechanistic pathway. This is further confirmation that the sum of weak interactions, difficult to predict, determines the final facial diastereoselectivity using a chiral oxazolidin-2-one auxiliary, as reported by Evans.[29]

3. Conclusion

The preliminary results presented in this paper demonstrate that the cyclization of azadienes to β-lactams can be promoted by LAs and that a conrotatory cyclization mechanism may be invoked in analogy to the uncatalyzed cyclization of the azadiene. The cyclization step takes place at lower temperature according to lower activation energy as demonstrated by theoretical calculations. The experimental findings may open up new options in the synthesis of optically active azetidinones by use of LA bearing optically active ligands. In conclusion, as far as we know, this is the first time that a formal Staudinger reaction has been catalyzed by LAs.[30]

4. Computational methods

All ab initio calculations were carried out at the MP2/6-31G* level using the GAUSSIAN 98 series of programs.[27] Geometries were fully optimized by standard gradient techniques and the fully optimized structures were checked by frequency analysis. The transition state showed only one imaginary frequency, the corresponding vibration being associated with the nuclear motion along the reaction coordinate. Wiberg bond orders were calculated with the natural bond orbital (NBO) method as implemented in GAUSSIAN 98.

5. Experimental

5.1. General

Melting points were taken on a Mel-Temp apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ on Varian Gemini-200. Chemical shifts are reported in δ scale and coupling constants (J) are reported in hertz. Infrared spectra were recorded as Nujol mulls on a Nicolet 205 FT-IR spectrophotometer. Optical rotation measurements were carried out on a Perkin–Elmer 343 Polarimeter and specific rotation $[\alpha]_D^{20}$ was reported in deg per dm at the specified temperature and with the concentration [c] given in g per 100 mL in $CHCl_3$. THF, toluene, and heptane were distilled from benzophenone ketyl.

5.2. Materials

N-Trialkylsilylimines **2** were prepared according to reported procedures starting from the parent aldehydes **1**.[28] Triethylamine was dried over KOH. Other solvents and reagents were obtained commercially and were used as received. All reactions were performed under inert atmosphere.

5.3. Synthesis of 5a/6a as typical example for catalyzed reaction

A solution of [(*S*)-2-triisopropylsilyloxy-propylidene]-(trimethylsilanyl)-imine **2a** was prepared by dropwise addition of a heptane solution (5 mL) of (*S*)-2-triisopropylsilyloxy-propanal (0.23 g, 1.00 mmol) to a cooled (−10°C) THF solution of lithium bis(trimethylsilyl)amide (LHMDS) (1.10 mL, 1.10 mmol). The reaction mixture was warmed to 0°C and stirred for 30 min at this temperature. The formation of the imine was confirmed from the infra-red spectrum of the reaction mixture (νCN = 1685 cm^{-1}). The imine solution was then warmed to rt, trimethylsilyl chloride (0.15 mL, 1.10 mmol) was added in one portion, and this mixture was allowed to stir for 1 h. The mixture was cooled to 0°C and triethylamine (0.30 mL, 2.20 mmol) was added in one portion. After stirring this mixture for 5 min at 0°C, a toluene solution of oxazolidinone-acetyl chloride **3** (1.1 equiv.), prepared according Boger's was added very slowly (during 5 min) by a syringe. Stirring was maintained for 30 min at 0°C and 90 min at rt. This yellow–orange mixture was then filtered through Celite, the solvent removed and substituted with methylene chloride (10 mL). This solution) was cooled at −78°C and a solution of $BF_3(Et_2O)$ (1 mmol) in CH_2Cl_2 (5 mL) was added dropwise. The reaction mixture was stirred overnight while the temperature was allowed to spontaneously reach rt. The crude mixture was poured into a saturated $NaHCO_3$ aqueous solution and extracted with CH_2Cl_2. Flash chromatography of the residue yielded the diastereomeric mixture of azetidinones **5a** and **6a** in 42% yield and 33/67 diastereomeric ratio.

Spectral data are identical to those reported in the literature.[17] The established synthetic protocol was applied to the set of azadienes, obtained from aliphatic and aromatic aldehydes **1**, reported in Table 1.

5.3.1. (4*S*)-3-[(3*S*,4*S*)-2-Oxo-4-(*tert*-butyl)-azetidine-3-yl]-4-phenyloxazolidin-2-one, 5e. Mp 181–185°C. $[\alpha]_D^{20}$ = +88.82 (c 2.04, $CHCl_3$): IR = 3295, 2924, 2853, 1747 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.40 (s, 5H), 5.90 (bs, 1H), 4.90 (dd, 1H, J = 6.6, 8.9 Hz), 4.68 (t, 1H, J = 8.9 Hz), 4.62 (d, 1H, J = 2.7 Hz), 4.21 (dd, 1H, J = 6.6, 8.9 Hz), 2.8 (d, 1H, J = 2.7 Hz), 0.78 (s, 9H). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 165.2, 157.2, 138.4, 129.5, 129.4, 127.5, 70.4, 63.6, 60.9, 58.9, 31.3, 24.9. MS; m/z: 288 [M+], 245 [M+ −43], 230. $C_{16}H_{20}N_2O_3$ (288.20); calcd C, 66.65; H, 6.99; N, 9.72; found: C, 66.93; H, 6.97; N, 9.79%.

5.3.2. (4*S*)-3-[(3*R*,4*R*)-2-Oxo-4-(*tert*-Butyl)-azetidine-3-yl]-4-phenyloxazolidin-2-one (6e). Mp 165–170°C (decomp.). $[\alpha]_D^{20}$ = +87.66 (c 1.54, $CHCl_3$): IR = 3296, 2923, 2853, 1753, 1716 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.40 (s, 5H), 5.95 (bs, 1H), 4.90 (dd, 1H, J = 8.0, 8.7 Hz), 4.68 (t, 1H, J = 8.7 Hz), 4.25 (dd, 1H, J = 8.0, 8.7 Hz), 4.03 (d, 1H, J = 2.8 Hz), 3.90 (d, 1H, J = 2.8 Hz), 0.65 (s, 9H). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 165.9, 157.2, 136.7, 129.7, 129.3, 127.9, 70.2, 62.1, 61.8, 60.6, 31.5, 25.0. MS; m/z: 245 [M+ −43], 230. $C_{16}H_{20}N_2O_3$ (288.20); calcd C, 66.65; H, 6.99; N, 9.72; found: C, 66.58; H, 7.03; N, 9.80%.

5.4. Uncatalyzed thermal cyclization: synthesis of 5e/6e as a typical example

A solution of (2,2-dimethyl-propyliden)-(trimethylsilanyl)-imine **2e** was prepared by dropwise addition of a solution of 2,2-dimethyl-propanal (0.086 g, 1.00 mmol) in heptane (5 mL) to a cooled (−10°C) solution of lithium bis(trimethylsilyl)amide (LHMDS) in THF (1.10 mL, 1.10 mmol). The reaction mixture was warmed to 0°C and stirred for 30 min at this temperature. The formation of the imine was confirmed by an infrared spectrum of the reaction mixture (νCN = 1685 cm^{-1}). The imine solution was then warmed to rt, trimethylsilyl chloride (0.15 mL, 1.10 mmol) was added in one portion, and this mixture was allowed to stir for 1 h. The mixture was cooled to 0°C and triethylamine (0.30 mL, 2.20 mmol) was added in one portion. After stirring this mixture for 5 min at 0°C, a toluene solution of oxazolidinone–acetyl chloride **3** (1.1 equiv.), prepared according Boger's was added very slowly (during 5 min) by a syringe. Stirring was maintained for 30 min at 0°C and 90 min at rt. This yellow–orange mixture was then filtered through Celite, the solvent removed and substituted with toluene (10 mL). The so obtained solution was allowed to reflux (110°C) for 8 h. The crude reaction mixture was cooled to rt, diluted with ethyl acetate, poured into an NH_4Cl solution and extracted with more ethyl acetate. The organic layer was washed with $NaHCO_3$ solution and dried over Na_2SO_4. After filtration the solvent was removed under reduced pressure and a ^{1}H NMR was run of the resulting crude residue. Flash chromatography of the residue yielded (56%) the title compounds. (Diastereomeric ratio = 65/35 **5e**/**6e**). The so established

synthetic protocol was applied for uncatalyzed preparation of compounds **5f**/**6f** and **5g**/**6g**. The yields and diastereomeric ratio are reported in Table 1 in italics.

5.4.1. (4*S*)-3-[(3*S*,4*S*)-2-Oxo-4-phenyl-azetidine-3-yl]-4-phenyloxazolidin-2-one, 5f. Mp 169–172°C. $[\alpha]_D^{20}=+39.7$ (*c* 0.9, $CHCl_3$): IR = 3318, 1760 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): $\delta=7.40$–7.10 (m, 10H), 6.30 (bs, 1H), 5.01 (dd, 1H, $J=6.6$, 8.8 Hz), 4.71 (t, 1H, $J=8.8$ Hz), 4.64 (d, 1H, $J=2.4$ Hz), 4.23 (dd, 1H, $J=6.6$, 8.8 Hz), 4.21 (d, 1H, $J=2.4$ Hz). ^{13}C NMR (50 MHz, $CDCl_3$): $\delta=165.3$, 157.1, 138.0, 137.7, 129.6, 129.5, 128.9, 128.5, 127.4, 125.4, 70.5, 69.3, 59.3, 56.9. MS; *m*/*z*: 308 [M+], 265 [M+ −43], 145. $C_{18}H_{16}N_2O_3$ (308.16); calcd C, 70.12; H, 5.23; N, 9.09; found: C, 69.89; H, 5.26; N, 9.13%.

5.4.2. (4*S*)-3-[(3*R*,4*R*)-2-Oxo-4-phenyl-azetidine-3-yl]-4-phenyloxazolidin-2-one, 6f. Mp 155–159°C. $[\alpha]_D^{20}=+46.9$ (*c* 0.56, $CHCl_3$): IR = 3435, 1752, 1660 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): $\delta=7.40$–6.95 (m, 10H), 6.70 (bs, 1H), 4.98 (d, 1H, $J=2.4$ Hz), 4.84 (dd, 1H, $J=5.7$, 8.5 Hz), 4.69 (t, 1H, $J=8.5$ Hz), 4.23 (dd, 1H, $J=5.6$, 8.5 Hz), 3.94 (d, 1H, $J=2.4$ Hz). ^{13}C NMR (50 MHz, $CDCl_3$): $\delta=165.9$, 156.2, 137.7, 137.6, 129.3, 128.5, 128.1, 126.9, 126.8, 125.4, 70.4, 69.1, 61.5, 56.7. MS; *m*/*z*: 308 [M+], 265 [M+−43], 203, 145. $C_{18}H_{16}N_2O_3$(308.16); calcd C, 70.12; H, 5.23; N, 9.09; found: C, 70.35; H, 5.19; N, 9.06%.

5.4.3. (4*S*)-3-[(2*S*,3*S*)-2-(4-Methoxy-phenyl)-4-*oxo*-azetidine-3-yl]-4-phenyloxazolidin-2-one, 5g. Mp 190–195°C. $[\alpha]_D^{20}=+144.2$ (*c* 0.66, $CHCl_3$): IR = 3271, 1755, 1625, 1601 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): $\delta=7.45$ (s, 5H), 7.05 (d, 2H, $J=8.7$ Hz), 6.80 (d, 2H, $J=8.7$ Hz), 6.05 (bs, 1H), 5.00 (dd, 1H, $J=6.6$, 9.0 Hz), 4.71 (t, 1H, $J=9.0$ Hz), 4.62 (d, 1H, $J=2.4$ Hz), 4.23 (dd, 1H, $J=6.6$, 9.0 Hz), 4.14 (d, 1H, $J=2.4$ Hz), 3.85 (s, 3H). ^{13}C NMR (50 MHz, $CDCl_3$): $\delta=168.7$, 159.9, 157.2, 138.3, 135.4, 129.7, 129.6, 127.5, 126.9, 114.4, 70.8, 69.5, 59.3, 56.6, 55.3. MS; *m*/*z*: 339 [M+ +1], 295[M+ −43], 176. $C_{19}H_{18}N_2O_4$(338.18); calcd C, 65.74; H, 5.52; N, 9.58; found: C, 65.93; H, 5.54; N, 9.61%.

5.4.4. (4*S*)-3-[(2*R*,3*R*)-2-(4-Methoxy-phenyl)-4-oxo-azetidine-3-yl]-4-phenyloxazolidin-2-one, 6g. Oil. $[\alpha]_D^{20}=+61.3$ (*c* 1.5, $CHCl_3$): IR = 3430, 1757, 1601 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): $\delta=7.40$ (m, 5H, +NH), 7.10 (d, 2H, $J=8.7$ Hz), 6.85 (d, 2H, $J=8.7$ Hz), 5.00 (t, 1H, $J=8.3$ Hz), 4.85 (d, 1H, $J=3.6$ Hz), 4.70 (t, 1H, $J=8.3$ Hz), 4.34 (dd, 1H, $J=3.6$, 0.8 Hz), 4.21 (t, 1H, $J=8.3$ Hz), 3.80 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=$ 169.6, 159.8, 157.2, 138.1, 136.6, 129.5, 129.4, 127.2, 126.8, 114.3, 70.2, 69.3, 60.4, 56.6, 55.6. MS; *m*/*z*: 338 [M+], 295 [M+−43], 175. $C_{19}H_{18}N_2O_4$(338.18); calcd C, 65.74; H, 5.52; N, 9.58; found: C, 65.57; H, 5.49; N, 9.56%.

5.5. Crystallography for 5f and 5g

The diffraction experiments were carried out for **5f** and **5g** at rt on a Bruker AXS SMART 2000 CCD based diffractometer using graphite monochromated Mo-Kα radiation ($\lambda=0.71073$ Å). Intensity data were measured over full diffraction spheres using 0.3° wide ω scans, crystal-to-detector distance 5.0 cm. The software SMART[31] was used for collecting frames of data, indexing reflections and determination of lattice parameters. The collected frames were then processed for integration by software SAINT[31] and an empirical absorption correction was applied with SADABS.[32] The structures were solved by direct methods (SIR97)[33] and subsequent Fourier syntheses, and refined by full-matrix least-squares calculations on F^2 (SHELXTL)[34] attributing anisotropic thermal parameters to the non-hydrogen atoms. The aromatic hydrogen atoms were placed in calculated positions and refined with idealized geometry (C(sp^2)–H = 0.93 Å), whereas the other H atoms were located in the Fourier map and refined isotropically.

5.5.1. Crystallographic data for 5f. $C_{18}H_{16}N_2O_3$, $M=$ 308.33, monoclinic, space group $P2_1$ (No. 4), $a=$ 9.8554(3), $b=7.2829(2)$, $c=11.5922(4)$ Å, $\beta=110.344(1)°$, $Z=2$, $V=780.14(4)$ Å^3, $d_{calcd}=1.313$ Mg m^{-3}, $\mu=0.091$ mm^{-1}. 10249 reflections were collected, 4535 unique, 4036 observed for $I>2\sigma(I)$, which were used in all calculations. Final *R* factors: $R_1=$ 0.0400 [$I>2\sigma(I)$], $wR_2=0.1158$ (all data).

5.5.2. Crystallographic data for 5g. $C_{19}H_{18}N_2O_4$, $M=$ 338.35, monoclinic, space group $P2_1$ (No. 4), $a=$ 11.4642(5), $b=6.4312(3)$, $c=11.8629(5)$ Å, $\beta=105.985(1)°$, $Z=2$, $V=840.82(6)$ Å^3, $d_{calcd}=1.336$ Mg m^{-3}, $\mu=0.095$ mm^{-1}. 10750 reflections were collected, 4875 unique, 2862 observed for $I>2\sigma(I)$, which were used in all calculations. Final *R* factors: $R_1=$ 0.0521 [$I>2\sigma(I)$], $wR_2=0.1169$ (all data).

Crystallographic data (excluding structure factors) for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 201907 for **5f** and CCDC 201908 for **5g**. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK [fax: +44(0)-1223336033 or e-mail: deposit@ccdc.cam.ac.uk].

Acknowledgements

One of us (P.V.) acknowledges a Biosearch Italia fellowship. The authors thank Dr. Elisa Bandini for helpful discussions.

References

1. Abell, A. D.; Oldham, M. D. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 497.
2. Annunziata, R.; Benaglia, M.; Cinquini, M.; Cozzi, F.; Puglisi, A. *Bioorg. Med. Chem.* **2002**, *10*, 1813–1818.
3. Haley, T. M.; Angier, S. J.; Borthwick, A. D.; Singh, R.; Micetich, R. G. *Drugs* **2000**, *3*, 512–517.

4. Rosenblum, S. B.; Huynh, T.; Davis, H. R., Jr. *Tetrahedron* **2000**, *56*, 5735.
5. Ojima, I.; Habus, I.; Zhao, M.; Zucco, M.; Park, Y. H.; Sun, C. M.; Brigaud, T. *Tetrahedron* **1992**, *48*, 6985–7012.
6. Ojima, I. *Acc. Chem. Res.* **1995**, *28*, 383–389.
7. Palomo, C.; Aizpurua, J. M.; Ganboa, I. In *The Synthesis of β-Amino Acids and Their Derivatives from β-Lactams*; Juaristi, E., Ed.; Wiley-VCH: New York, 1997; pp. 279–350.
8. Boge, T. C.; Georg, G. I. In *The Medicinal Chemistry of β-Amino Acids*: *Paclitaxel as an Illustrative Example*; Juaristi, E., Ed.; Wiley-VCH: New York, 1997; pp. 1–82.
9. Taggi, A. E.; Hafez, A. M.; Wack, H.; Young, B.; Ferraris, D.; Lectka, T. *J. Am. Chem. Soc.* **2002**, *124*, 6626–6635.
10. Georg, G. I.; Ravikumar, V. T. In *Stereocontrolled Ketene-imine Cycloaddition Reaction*; Georg, G., Ed.; VCH: New York, 1993; pp. 318–323.
11. Palomo, C.; Aizpurua, J. M.; Ganboa, I.; Oiarbide, M. *Eur. J. Org. Chem.* **1999**, 3223–3235.
12. Hegedus, L. S.; Montgomery, J.; Narukawa, Y.; Snustad, D. C. *J. Am. Chem. Soc.* **1991**, *113*, 5784–5791.
13. Bacchi, S.; Bongini, A.; Panunzio, M.; Villa, M. *Synlett* **1998**, 843–844.
14. Bandini, E.; Martelli, G.; Spunta, G.; Bongini, A.; Panunzio, M. *Tetrahedron Lett.* **1996**, *37*, 4409–4412.
15. Bandini, E.; Martelli, G.; Spunta, G.; Panunzio, M. *Synlett* **1996**, 1017–1018.
16. Bandini, E.; Favi, G.; Martelli, G.; Panunzio, M.; Piersanti, G. *Org. Lett.* **2000**, 1077.
17. Bongini, A.; Panunzio, M.; Piersanti, G.; Bandini, E.; Martelli, G.; Spunta, G.; Venturini, A. *Eur. J. Org. Chem.* **2000**, 2379.
18. Panunzio, M.; Bacchi, S.; Campana, E.; Fiume, L.; Vicennati, P. *Tetrahedron Lett.* **1999**, *40*, 8495.
19. Jayakumar, S.; Ishar, M. P.; Mahajan, M. P. *Tetrahedron* **2002**, *58*, 379–471.
20. Ghosez, L.; Bayard, P.; Nshimyumukiza, P.; Gouverneur, V.; Sainte, F.; Beaudegnies, R.; Rivera, M.; Frisque-Hesbain, A. M.; Wynants, C. *Tetrahedron* **1995**, *51*, 11021–11042.
21. Ghosez, L. *Pure Appl. Chem.* **1996**, *68*, 15–22.
22. Sordo, A. J.; Gonzalez, J.; Sordo, T. L. *J. Am. Chem. Soc.* **1992**, *114*, 6249–6251.
23. Arrieta, A.; Lecea, B.; Cossío, F. P. *J. Org. Chem.* **1998**, *63*, 5869–5876.
24. Lecea, B.; Arrieta, A.; Cossío, F. P. *J. Org. Chem.* **1998**, *63*, 5216.
25. Cossio, F. P.; Arrieta, A.; Lecea, B. *J. Org. Chem.* **2000**, *65*, 8458.
26. Yamamoto, H. In *Lewis Acids in Organic Chemistry*; Yamamoto, H., Ed.; Wiley-VCH: Weinheim, 1999.
27. Frisch, M. J.; Al Gaussian 98 A 7; Revision A 7 ed.; Gaussian Inc,: Pittsburg PA, 1998.
28. Panunzio, M.; Zarantonello, P. *Org. Process Res. Dev.* **1998**, *2*, 49–59.
29. Evans, D. A.; Chapman, K. T.; Bisaha, J. *J. Am. Chem. Soc.* **1988**, *110*, 1238–1256.
30. For the first catalytic asymmetric synthesis of β-lactams, see: Ref. 9.
31. SMART & SAINT Software Reference Manuals, Version 5.051 (Windows NT Version), Bruker Analytical X-ray Instruments Inc.: Madison, Wi, 1998.
32. Sheldrick, G. M. SADABS, program for empirical absorption correction, University of Göttingen, Germany, 1996.
33. Altomare, A.; Burla, M. C.; Camalli, M.; Cascarano, G. L.; Giacovazzo, C.; Guagliardi, A.; Moliterni, A. G. G.; Polidori, G.; Spagna, R. *J. Appl. Cryst.* **1999**, *32*, 115–119.
34. Sheldrick, G. M. SHELXTL*plus* Version 5.1 (Windows NT version)-Structure Determination Package; Bruker Analytical X-ray Instruments Inc.: Madison, WI, 1998.