Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron 63 (2007) 12388–12395
Tetrahedron

Stereoselective dimerization of 3-arylisoxazoles to cage-shaped bis-β-lactams *syn* 2,6-diaryl-3,7-diazatricyclo[4.2.0.0^{2,5}]-octan-4,8-diones induced by hindered lithium amides

Leonardo Di Nunno,[a,*] Paola Vitale,[a] Antonio Scilimati,[a] Laura Simone[a] and Francesco Capitelli[b]

[a]*Dipartimento Farmaco-Chimico, Università degli Studi di Bari, Via E. Orabona 4, 70125 Bari, Italy*
[b]*Istituto di Cristallografia (IC-CNR), Via Amendola 122/o, 70125 Bari, Italy*

Received 11 July 2007; revised 5 September 2007; accepted 20 September 2007
Available online 23 September 2007

Abstract—3-Arylisoxazoles react with hindered lithium amides giving *syn* 2,6-diaryl-3,7-diazatricyclo[4.2.0.0^{2,5}]octan-4,8-diones in good to fair yields. Stereochemistry of the so-obtained cage-shaped bis-β-lactams was assigned by X-ray diffraction analysis. Concerning the mechanism of formation of such hitherto unknown molecules, dimerization of an azetinone anion intermediate stereoselectively induced by Li^+ chelation is suggested.

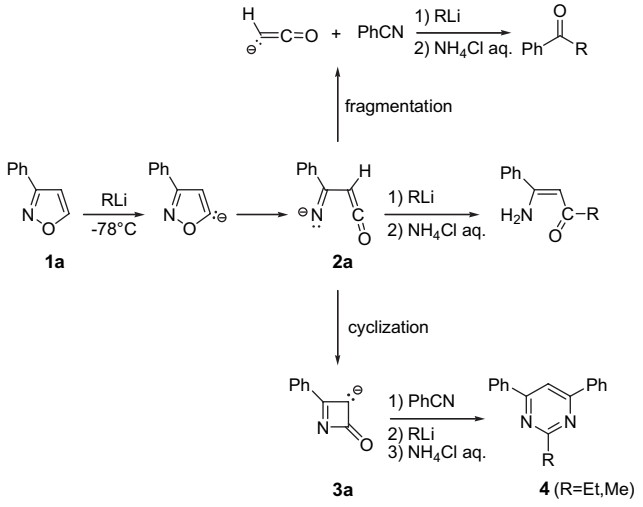
1. Introduction

β-Lactams and their derivatives are used in a very large number of clinically important therapeutic areas in defence against bacterial infection.[1] In organic and medicinal chemistry they are used as building blocks,[2] synthons for short peptides,[3] natural products,[4] and β-amino acids synthesis.[5]

Cage-shaped bis-β-lactams constitute a new class of compounds not explored as yet. Herein, a novel one-pot stereoselective synthetic approach from 3-arylisoxazoles to cage-shaped bis-azetidinones different from the classical β-lactam structures and that could find applications at least in the above mentioned fields is reported.

Previous investigations[6] concerning the reactivity of 3-phenylisoxazole (**1a**) with alkyllithiums ascertained a rather complex behaviour (Scheme 1).

In all cases the starting reaction is represented by C_5–H abstraction by RLi, followed by ring-opening to form lithium iminoketene **2a**. This, in turn, is assumed as the common intermediate precursor of all the isolated products deriving from fragmentation or further nucleophilic addition of RLi.



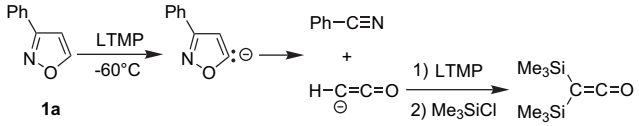
Scheme 1. Reaction of 3-phenylisoxazole (**1a**) with RLi.

Among other formed products and concerning some alkyllithiums (MeLi, EtLi) we isolated alkyldiphenylpyrimidines **4**, arising from a preliminary cyclization of lithium iminoketene **2a** to azetinone anion **3a** and subsequent reaction with PhCN and RLi.[6]

It must be pointed out that C_5–H abstraction from 3-phenylisoxazole (**1a**) was previously described also using LTMP as a base. In such a case, only products of fragmentation were reported (Scheme 2).[7]

Keywords: 3-Arylisoxazoles; Cage-shaped bis-β-lactams; Hindered lithium amides; Lithium iminoketene; Azetinone anion.
* Corresponding author. Tel.: +39 80 5442734; fax: +39 80 5442231; e-mail: dinunno@farmchim.uniba.it

0040–4020/$ - see front matter © 2007 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2007.09.040

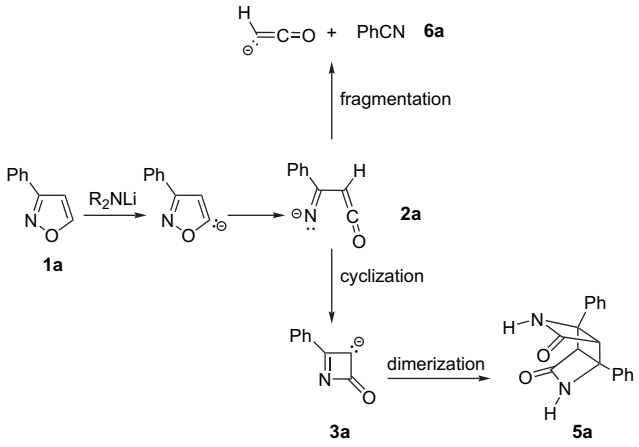


Scheme 2. Reaction of 3-phenylisoxazole (**1a**) with LTMP.[7]

2. Results and discussion

We have now repeated the reaction with LTMP at various temperatures, extending it also to other lithium amides (LDA, LHMDS).

In all cases no products of nucleophilic addition subsequent both to isoxazole ring-opening (i.e., onto lithium iminoketene **2a** and azetinone anion **3a**) and ring-fragmentation (i.e., onto PhCN) were found, as instead observed (Scheme 1) for reactions carried out with alkyllithiums. At variance, *syn* 2,6-diphenyl-3,7-diazatricyclo[4.2.0.0^{2,5}]octan-4,8-dione (**5a**), plausibly formed by dimerization of azetinone anion intermediate **3a**, was isolated in high yields (Scheme 3 and Table 1).



Scheme 3. Reaction of 3-phenylisoxazole (**1a**) with R_2NLi.

Only small amounts of such a dimer could seldom be observed, on the contrary, in reactions with alkyllithiums.

Concerning the absence of products of subsequent nucleophilic addition of R_2NLi, it was clearly expected by considering the well-known non-nucleophilic character of the used lithium amides.

And this, presumably, is also an important factor favouring the formation of bis-azetidinone **5a**. Lack of any nucleophilic addition by lithium amides should in fact directly or indirectly enhance the availability of azetinone anion **3a**, so determining the best conditions for dimerization.

However, another important factor promoting the dimerization seems also to be involved. X-ray diffraction analysis (see Section 2) established in fact that the isolated bis-azetidinone **5a** has exclusively the *syn* geometry, as represented in Figure 1.

And this strongly suggests an important role of Li^+ chelation during the dimerization (Scheme 4). The above hypothesis seems to be very reasonable, as stereoselective reactions promoted by intramolecular Li^+ chelation are not new.[8]

Besides, we could obtain a direct evidence of the above hypothesis by performing the reaction of 3-phenylisoxazole (**1a**) with bis(trimethylsilyl)amides with different metal counterions (Na^+, K^+) (Table 2). In this case, formation of bis-azetidinone **5a** largely decreases with NaHMDS and is completely suppressed with KHMDS.

Correspondingly, fragmentation is progressively favoured, as indicated by the increasing amounts of PhCN **6a** (in this case not further reacted with R_2NLi, as expected).

The observed behaviour parallels the decreasing binding affinity on going from Li^+ to K^+, as determined in other cases (e.g., in the case of various azines).[9] So, this strongly supports the leading role of chelation in the dimerization of **3a**.

When in fact such an interaction is less important, dimerization becomes correspondingly more difficult, so that other possible reactions (fragmentation, in our case) can compete or even prevail.

On the other hand, the observed dimerization is not a special behaviour of 3-phenylisoxazole (**1a**).

Reactions of a number of other arylisoxazoles[10] bearing either electron-withdrawing or electron-donating groups[11] indicate in fact similar results, the yields of bis-azetidinones depending on the nature of the substituent (Table 3).

Table 1. Percentages of products formed in the reaction of 3-phenylisoxazole (**1a**) and lithium amides

Entry	Base	**1a**/Base	*T* (°C)	*t* (h)	**1a** (%)	**5a**[a] (%)	**6a**[b] (%)
1	LTMP	1:2	−60→rt	0.7	—	75	<1
2	LTMP	1:1.5	−78	1	—	78	7
3	LTMP	1:1.5	0	1	—	85	<1
4	LHMDS	1:1	−78	1	84[c]	16[c]	<1
5	LHMDS	1:1.1	0	0.5	50[c]	50[c]	<1
6	LHMDS	1:1.1	0	1	34[c]	66[c]	<1
7	LHMDS	1:1.5	0	1	—	83	<1
8	LDA	1:1.5	0	1	—	80	<1
9	LDA	1:1.5	0→rt	1	—	68	10
10	LDA	1:1.5	−78	1	—	80	2

[a] Isolated yields (unless otherwise indicated).
[b] Detected by GC on reaction crudes and then distilled off in vacuo.
[c] Percentages determined by ^{1}H NMR spectra recorded on reaction crudes.

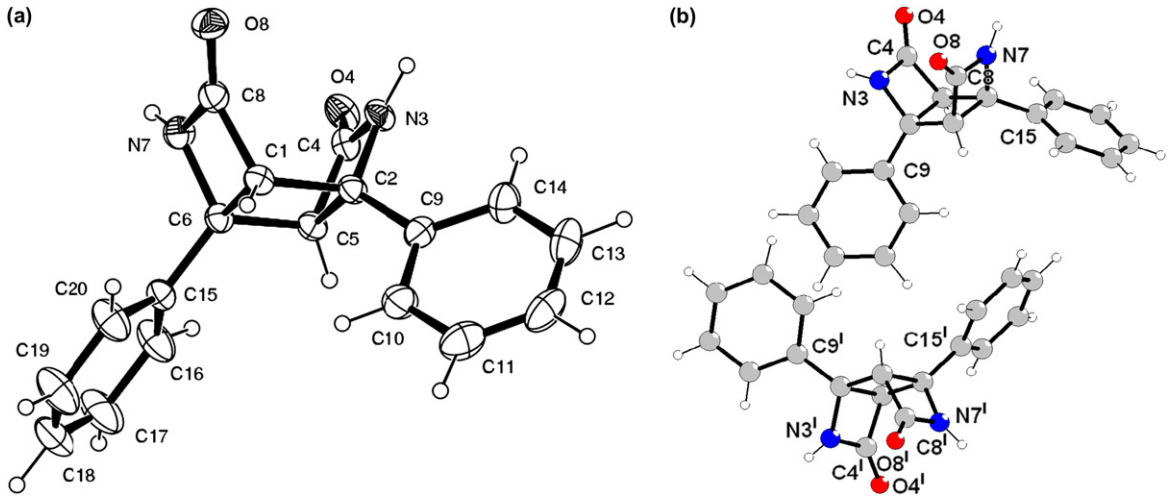
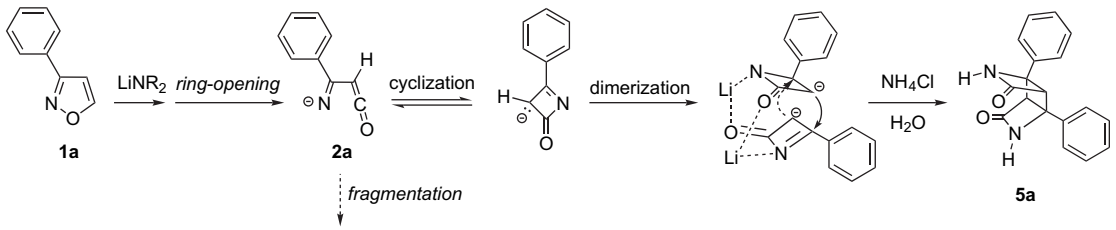


Figure 1. (a) ORTEP view of crystal structure of bis-azetidinone **5a**. (b) View of enantiomers of bis-azetidinone **5a**; symmetry: I) $x, -y+1/2, +z+1/2$ (related by inversion centre).



Scheme 4. Proposed mechanism of dimerization of 3-phenylisoxazole (**1a**) induced by R_2NLi.

Table 2. Yields of products from the reaction of 3-phenylisoxazole (**1a**) with bis(trimethylsilyl)amides[a]

Entry	Base	Bis-azetidinone **5a**[b] (%)	PhCN **6a**[b] (%)
1	LHMDS	83	<1[c]
2	NaHMDS	43[d]	57[d]
3	KHMDS	—	90

[a] Reactions were conducted in THF at 0 °C for 1 h, with isoxazole **1a**/base ratio=1:1.5.
[b] Isolated yields (unless otherwise indicated).
[c] Detected by GC on reaction crudes and then distilled off in vacuo.
[d] Percentages determined by ^{1}H NMR spectra recorded on reaction crudes.

Table 3. Percentages of products formed in the reaction of 3-arylisoxazoles **1a–e** with LDA[a]

Entry	Ar	Bis-azetidinones **5a–e**[b] (%)	ArCN **6a–e** (%)
1	Phenyl- (**1a**)	80	<1[c]
2	4-Methylphenyl- (**1b**)	58[d]	38[d]
3	4-Methoxyphenyl- (**1c**)	33[d]	56[d]
4	4-Fluorophenyl- (**1d**)	79	—
5	4-Trifluoromethylphenyl- (**1e**)	80	—

[a] Reactions were conducted in THF at 0 °C for 1 h, with isoxazole **1a–e**/base ratio=1:1.5.
[b] Isolated yields (unless otherwise indicated).
[c] Detected by GC on reaction crudes and then distilled off in vacuo.
[d] Percentages determined by ^{1}H NMR spectra recorded on reaction crudes; some unreacted 3-arylisoxazole (≤4 and ≤11% for **1b** and **1c**, respectively) was also detected.

In particular, electron-withdrawing groups again give high yields of the above azetidinones, while electron-donating groups lower the yields in favour of the fragmentation products, seemingly to an extent depending on the magnitude of the electron-donating effect of the substituent. The above results seem to be related to the lower stability of the lithium imminoketene intermediate in the presence of electron-donating groups, which should actually favour the fragmentation, just as observed. Further investigations are in progress on this point.

In conclusion, the present investigation has disclosed a new interesting reaction involving 3-arylisoxazoles, with formation of a type of β-lactams hitherto unknown.

Next investigations will concern a further expansion of the scope of the reaction, as well as a study of the chemical and biological properties of such cage-shaped bis-β-lactams.

3. Experimental section

3.1. General methods

Melting points taken on Electrothermal apparatus were uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Varian-Inova-400 MHz spectrometer and on a Bruker-Aspect 3000 console-500 MHz spectrometer, and chemical shifts are reported in parts per million (δ). ^{19}F NMR spectra were recorded by using $CFCl_3$ as internal standard. Absolute

values of the coupling constant are reported. Infrared spectra were recorded on a FT Perkin–Elmer 681 spectrometer. GC analyses were performed by using a HP1 column (methyl siloxane; 30 m×0.32 mm×0.25 μm film thickness) on a HP 6890 model, Series II. Thin-layer chromatography (TLC) was performed on silica gel sheets with fluorescent indicator, the spots on the TLC were observed under ultraviolet light or were visualized by I_2 vapour. Chromatography was conducted by using silica gel 60 with a particle size distribution 40–63 μm and 230–400 mesh ASTM. GC–MS analyses were performed on an HP 5995C model and elemental analyses on an Elemental Analyzer 1106-Carlo Erba-instrument. ESI-MS analyses were performed on Agilent 1100 LC/MSD trap VL system. Crystallographic data (excluding structure factors) for the structure in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC 615266. 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).

3.2. Materials

Tetrahydrofuran (THF) from commercial source was purified by distillation (twice) from sodium wire under nitrogen. DMF from commercial source was purified by distillation from CaH_2 under reduced pressure. Standardized (2.5 M) *n*-butyllithium in hexanes was purchased from Aldrich Chemical Co. and its titration was performed with *N*-pivaloyl-*o*-toluidine.[12] NaHMDS in THF (1.0 M) and KHMDS in toluene (0.5 M) were purchased from Aldrich Chemical Co. Bis(trimethylsilyl)amine, diisopropylamine and 2,2,6,6-tetramethylpiperidine were purified by distillation from CaH_2. All other chemicals and solvents were of commercial grade and further purified by distillation or crystallization prior to use.

All the used 3-arylisoxazoles **1a–e** were prepared via the corresponding 3-aryl-5-hydroxy-2-isoxazolines **7a–e** (see below), by using the previously described procedure.[10] Arylnitrile oxides were prepared from aldehydes through their conversion into the corresponding oximes and then into *N*-hydroxybenzimidoyl chloride.[10,13] These were finally converted into nitrile oxides by treatment with NEt_3, followed by vacuum filtration of $NEt_3 \cdot HCl$ from the solution.[10,13] Oximes, prepared from reaction of aldehydes/EtOH and $NH_2OH \cdot HCl$/aq NaOH, had analytical and spectroscopic data identical to those previously reported or commercially available.

3.2.1. 4-Methylbenzaldehyde oxime.[14] Yield: 60% (2.182 g). Yellow solid. R_f=0.5 (petroleum ether/ethyl acetate=80:20). ^{1}H NMR (400 MHz, $CDCl_3$, δ): 8.10 (s, 1H), 7.46–7.43 (m, 2H, aromatic protons), 7.18–7.16 (m, 2H, aromatic protons), 2.35 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): 150.3, 140.3, 129.5, 129.1, 127.0, 21.4.

3.2.2. 4-Methoxybenzaldehyde oxime.[14,15] Yield: 67% (2.428 g). White solid. R_f=0.5 (petroleum ether/ethyl acetate=80:20). ^{1}H NMR (400 MHz, $CDCl_3$, δ): 8.20–7.80 (br s, 1H, OH: exchanges with D_2O), 8.09 (s, 1H), 7.50–7.47 (m, 2H, aromatic protons), 6.89–6.86 (m, 2H, aromatic protons), 3.78 (s, 3H). GC–MS (70 eV) *m/z* (rel int.): 151 (M^+, 100), 134 (22), 108 (58), 92 (21), 77 (29), 63 (17), 51 (9).

3.2.3. 4-Fluorobenzaldehyde oxime.[14–16] Yield: 88% (3.483 g). Yellow solid. R_f=0.4 (petroleum ether/ethyl acetate=80:20). ^{1}H NMR (400 MHz, $CDCl_3$, δ): 9.40–8.60 (br s, 1H, OH: exchanges with D_2O), 8.15 (s, 1H), 7.58–7.54 (m, 2H, aromatic protons), 7.10–7.06 (m, 2H, aromatic protons). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 163.8 (d, $^1J_{19F-13C}$=249 Hz), 149.3, 128.9 (d, $^3J_{19F-13C}$=8.5 Hz), 128.0 (d, $^4J_{19F-13C}$=3.2 Hz), 116.0 (d, $^2J_{19F-13C}$=21.8 Hz). ^{19}F NMR (376 MHz, $CDCl_3$, δ): −110.3.

3.2.4. 4-(Trifluoromethyl)benzaldehyde oxime.[15,17] Yield: 92% (3.814 g). White crystals. R_f=0.5 (petroleum ether/ethyl acetate=70:30). Mp 100–101 °C. IR (neat): 3293, 2922, 1618, 1413, 1325, 1067, 971, 940, 872, 834 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$, δ): 9.40–9.10 (br s, 1H, OH: exchanges with D_2O), 8.21 (s, 1H), 7.70–7.63 (m, 4H, aromatic protons). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 149.2, 135.1, 131.7 (q, $^2J_{19F-13C}$=32.5 Hz), 127.2, 125.7 (q, $^3J_{19F-13C}$=3.7 Hz), 123.8 (q, $^1J_{19F-13C}$=270.8 Hz). ^{19}F NMR (376 MHz, $CDCl_3$, δ): −63.2.

3.3. Synthesis of *N*-Hydroxybenzimidoyl chlorides: general procedure

In a round-bottom flask equipped with magnetic stirring the suitable benzaldoxime (3.483 g, 0.0251 mol) was dissolved in anhydrous DMF (60 mL), then the solution was cooled to 0 °C. NCS (3.686 g, 0.0276 mol) was slowly added and the suspension was stirred at 0 °C. When the reaction was complete (TLC), water was added to the reaction mixture that became a limpid yellow solution. The aqueous layer was extracted three times with ethyl acetate. The combined organic extracts were washed with water to remove succinimide, then the solution was dried over anhydrous Na_2SO_4. *N*-Hydroxybenzimidoyl chlorides (obtained in 77–90% yield after evaporation of the solvent under vacuum) had analytical and spectroscopic data identical to those ones previously reported and commercially available compounds.

3.3.1. *N*-Hydroxy-4-methylbenzimidoyl chloride.[18] Yield: 90% (2.305 g). Yellow solid. R_f=0.8 (petroleum ether/ethyl acetate=70:30). ^{1}H NMR ($CDCl_3$, 400 MHz, δ): 9.60–9.00 (s, 1H, br s, 1H, OH: exchanges with D_2O), 7.74–7.72 (m, 2H, aromatic protons), 7.21–7.19 (m, 2H, aromatic protons), 2.38 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): 141.1, 140.5, 129.6, 129.2, 127.1, 21.3.

3.3.2. *N*-Hydroxy-4-methoxybenzimidoyl chloride.[18–20] Yield: 77% (2.282 g). Oil. R_f=0.7 (petroleum ether/ethyl acetate=70:30). ^{1}H NMR ($CDCl_3$, 400 MHz, δ): 8.35–8.30 (br s, 1H, OH: exchanges with D_2O), 7.78–7.76 (m, 2H, aromatic protons, J=8.8 Hz), 6.92–6.90 (m, 2H, aromatic protons, J=8.8 Hz), 3.84 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): 161.5, 139.6, 132.0, 128.7, 113.8, 55.4.

3.3.3. *N*-Hydroxy-4-fluorobenzimidoyl chloride.[21] Yield: 88%. Yellow crystals. Mp 74–75 °C. R_f=0.8 (petroleum ether/ethyl acetate=90:10). ^{1}H NMR (400 MHz, $CDCl_3$, δ): 9.80–9.20 (br s, 1H, OH: exchanges with D_2O), 7.85–7.79 (m, 2H, aromatic protons), 7.10–7.04 (m, 2H, aromatic

protons). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 164.1 (d, $^1J_{19F-13C}$=250 Hz), 138.3, 129.1 (d, $^3J_{19F-13C}$=8.5 Hz), 128.8 (d, $^4J_{19F-13C}$=3.2 Hz), 115.5 (d, $^2J_{19F-13C}$=22.0 Hz). ^{19}F NMR (376 MHz, $CDCl_3$, δ): −110.1.

3.3.4. *N*-Hydroxy-4-trifluoromethylbenzimidoyl chloride.[17,19] Yield: 83%. Yellow solid. R_f=0.8 (petroleum ether/ethyl acetate=90:10). Mp 90–92 °C.[19] IR (neat): 3308, 2919, 2853, 1618, 1410, 1326, 1129, 1068, 1015, 940, 846 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, δ): 10.50–10.10 (br s, 1H, OH: exchanges with D_2O), 7.88–7.85 (m, 2H, aromatic protons), 7.55–7.54 (m, 2H, aromatic protons). ^{19}F NMR (376 MHz, $CDCl_3$, δ): −63.5.

3.4. Synthesis of 3-arylisoxazoles (1a–e): general procedure[10]

A solution of the enolate ion of acetaldehyde in anhydrous THF (10 mL) was dropwise added at room temperature to a solution of arylnitrile oxide in THF (10 mL) contained in a nitrogen-flushed three-necked flask equipped with a magnetic stirrer. After the reaction was completed, the reaction mixture was quenched by adding aq NH_4Cl. The two phases were separated and the aqueous phase was extracted three times with ethyl acetate. The organic extracts were combined, dried over anhydrous Na_2SO_4 and then the solvent evaporated under reduced pressure. Column chromatography (silica gel, petroleum ether/ethyl acetate=70:30) of the residue afforded the 3-aryl-5-hydroxy-2-isoxazolines **7a–e** in 60–85% yields.

In a round-bottom flask with magnetic stirrer, MeONa (0.654 g, 12.7 mmol) was added to a solution of 3-aryl-5-hydroxy-2-isoxazolines **7a–e** (1.885 g, 11.5 mmol) in MeOH (30 mL). The reaction mixture was then heated under reflux. After the reaction was completed, the reaction mixture was quenched by adding aq NH_4Cl. The MeOH was evaporated under reduced pressure and aqueous layer was extracted three times with ethyl acetate. The combined organic extracts were dried over anhydrous Na_2SO_4 and the solvent evaporated under reduced pressure. Column chromatography (silica gel, petroleum ether/ethyl acetate=10:1) of the residue afforded 3-arylisoxazoles **1a–e** in 65–94% yields. 5-Hydroxy-3-phenyl-2-isoxazoline (**7a**),[10] 3-phenylisoxazole (**1a**),[10] 3-(*p*-tolyl)isoxazole (**1b**),[22] 3-(*p*-anisyl)isoxazole (**1c**),[23] 3-(*p*-fluorophenyl)isoxazole (**1d**)[24] and 3-(*p*-trifluoromethylphenyl)isoxazole (**1e**)[25] had analytical and spectroscopic data identical to those previously reported.

3.4.1. 5-Hydroxy-3-(4-methylphenyl)-2-isoxazoline (7b). Yield: 60% (1.444 g). Mp 120.8–121.4 °C. Yellow crystals. R_f=0.3. IR (KBr): 3223, 3033, 2954, 2939, 1609, 1595, 1517, 1444, 1411, 1357, 1336, 1270, 1240, 1177, 1080, 928, 900, 844, 810, 786, 737 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, δ): 7.57–7.54 (m, 2H, aromatic protons), 7.20–7.18 (m, 2H, aromatic protons), 6.03 (d, 1H, J=6.6 Hz), 4.3–3.9 (br s, 1H, OH: exchanges with D_2O), 3.36 (dd, 1H, J=6.6, 7.6 Hz), 3.23 (d, 1H, J=17.6 Hz), 2.37 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$, δ): 156.9, 140.7, 129.5, 126.9, 126.1, 97.9, 42.6, 21.5. GC–MS (70 eV) *m*/*z* (rel int.): 177 (M^+, 97), 160 (23), 159 (19), 158 (18), 148 (100), 133 (27), 132 (31), 131 (23), 130 (18), 117 (57), 116 (25), 115 (32), 104 (16), 103 (12), 91 (74), 89 (22), 77 (24), 65 (31), 51 (13). Anal. Calcd for $C_{10}H_{11}NO_2$: C, 67.78; H, 6.26; N, 7.90. Found: C, 67.40; H, 6.28; N, 7.74.

3.4.2. 5-Hydroxy-3-(4-methoxyphenyl)-2-isoxazoline (7c). Yield: 85% (2.018 g). Yellow oil. R_f=0.3. IR (neat): 3200, 2924, 2850, 1606, 1518, 1465, 1363, 1257, 1180, 1077, 1020, 923, 898, 847, 832, 745 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, δ): 7.63–7.61 (m, 2H, aromatic protons), 6.93–6.90 (m, 2H, aromatic protons), 6.02 (dd, 1H, J=1.0, 6.4 Hz), 3.84 (s, 3H), 3.7–3.3 (br s, 1H, OH: exchanges with D_2O), 3.43 (dd, 1H, J=6.4, 17.3 Hz), 3.32 (dd, 1H, J=17.3, 1.0 Hz). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 161.2, 156.3, 128.5, 121.5, 114.1, 97.7, 55.3, 42.8. GC–MS (70 eV) *m*/*z* (rel int.): 193 (M^+, 100), 176 (35), 175 (32), 164 (84), 149 (31), 133 (64), 132 (71), 121 (15), 108 (25), 90 (24), 77 (31), 64 (19). Anal. Calcd for $C_{10}H_{11}NO_3$: C, 62.17; H, 5.74; N, 7.25. Found: C, 62.40; H, 5.68; N, 7.30.

3.4.3. 3-(4-Fluorophenyl)-5-hydroxy-2-isoxazoline (7d). Yield: 70% (2.109 g). Mp 109–111 °C. Yellow crystals. R_f=0.3. IR (KBr): 3370, 3073, 2960, 2930, 2854, 1603, 1514, 1415, 1356, 1235, 1159, 1081, 921, 890, 872, 836 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, δ): 7.62–7.57 (m, 2H, aromatic protons), 7.10–7.00 (m, 2H, aromatic protons), 6.02 (dd, 1H, J=6.7, 1.7 Hz), 5.3–4.8 (br s, 1H, OH: exchanges with D_2O), 3.34 (dd, 1H, J=6.7, 17.4 Hz), 3.17 (dd, 1H, J=17.4, 1.7 Hz). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 163.9 (d, $^1J_{19F-13C}$=250 Hz), 156.1, 128.9 (d, $^3J_{19F-13C}$=8.5 Hz), 125.1 (d, $^4J_{19F-13C}$=3.5 Hz), 115.9 (d, $^2J_{19F-13C}$=21.9 Hz), 98.1, 42.4. ^{19}F NMR (376 MHz, $CDCl_3$, δ): −105.5. GC–MS (70 eV) *m*/*z* (rel int): 181 (M^+, 58), 164 (21), 163 (87), 153 (52), 152 (96), 135 (38), 134 (37), 121 (80), 109 (38), 107 (39), 101 (19), 96 (21), 95 (100), 75 (56), 63 (11), 57 (17), 50 (14). Anal. Calcd for $C_9H_8FNO_2$: C, 59.67; H, 4.45; N, 7.73. Found: C, 59.40; H, 4.50; N, 7.55.

3.4.4. 5-Hydroxy-3-(4-trifluoromethylphenyl)-2-isoxazoline (7e). Yield: 84% (3.313 g). Mp 116.0–118.0 °C. Yellow crystals. R_f=0.3. IR (KBr): 3341, 2927, 2853, 1618, 1413, 1326, 1169, 1127, 1068, 1017, 844, 770 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$, δ): 7.79–7.77 (m, 2H, aromatic protons), 7.67–7.64 (m, 2H, aromatic protons), 6.10 (dd, 1H, J=6.3, 1.6 Hz), 4.5–3.5 (br s, 1H, OH: exchanges with D_2O), 3.44 (dd, 1H, J=6.3, 17.4 Hz), 3.26 (dd, 1H, J=17.4, 1.6 Hz). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 155.9, 132.3, 132.1 (q, $^2J_{19F-13C}$=32.7 Hz), 127.1, 125.7 (q, $^3J_{19F-13C}$=3.8 Hz), 123.8 (q, $^1J_{19F-13C}$=272.3 Hz), 98.4, 42.1. ^{19}F NMR (376 MHz, $CDCl_3$, δ): −63.3. GC–MS (70 eV) *m*/*z* (rel int.): 231 (M^+, 51), 214 (16), 213 (54), 212 (87), 203 (59), 202 (77), 194 (10), 185 (28), 171 (31), 158 (21), 145 (100), 125 (14), 95 (15), 75 (16). Anal. Calcd for $C_{10}H_8F_3NO_2$: C, 51.96; H, 3.49; N, 6.06. Found: C, 52.30; H, 3.68; N, 6.30.

3.4.5. 3-(4-Methylphenyl)isoxazole (1b).[22] Yield: 84% (1.013 g). Yellow oil. R_f=0.5 (petroleum ether/ethyl acetate=94:6). IR (neat): 3020, 2923, 1619, 1552, 1524, 1426, 1381, 1126, 1097, 881, 824, 777, 721, 689 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, δ): 8.42 (d, 1H, J=1.5 Hz), 7.72 (d, 2H, aromatic protons, J=8.0 Hz), 7.27 (d, 2H, aromatic protons, J=8.0 Hz), 6.63 (d, 1H, J=1.5 Hz), 2.40 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 161.7, 158.9, 140.4, 129.8, 127.0, 126.1, 102.6, 21.6. GC–MS (70 eV) *m*/*z* (rel

int.): 159 (M^+, 100), 158 (88), 131 (91), 130 (56), 116 (9), 103 (14), 91 (35), 89 (12), 77 (13), 65 (20), 51 (10).

3.4.6. 3-(4-Methoxyphenyl)isoxazole (1c).[23] Yield: 94% (1.541 g). Mp 48.0–49.0 °C. Yellow crystals. R_f=0.5 (petroleum ether/ethyl acetate=91:9). ^{1}H NMR (400 MHz, $CDCl_3$, δ): 8.40 (d, 1H, J=1.5 Hz), 7.75 (d, 2H, aromatic protons, J=8.8 Hz), 6.97 (d, 2H, aromatic protons, J=8.0 Hz), 6.59 (d, 1H, J=1.5 Hz), 3.84 (s, 3H). GC–MS (70 eV) m/z (rel int.): 175 (M^+, 100), 174 (38), 160 (21), 147 (26), 146 (35), 132 (51), 104 (9), 92 (8), 77 (16), 63 (9).

3.4.7. 3-(4-Fluorophenyl)isoxazole (1d).[24] Yield: 65% (1.099 g). Colourless oil. R_f=0.8 (petroleum ether/ethyl acetate=80:20). IR (KBr): 3147, 3129, 3073, 2927, 2855, 1607, 1521, 1435, 1379, 1236, 1160, 1125, 1098, 1043, 1016, 947, 886, 842, 777, 685 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$, δ): 8.44 (d, 1H, J=1.8 Hz), 7.82–7.79 (m, 2H, aromatic protons), 7.16–7.12 (m, 2H, aromatic protons), 6.61 (d, 1H, J=1.8 Hz). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 163.7 (d, $^1J_{19F-13C}$=250 Hz), 160.5, 159.0, 128.7 (d, $^3J_{19F-13C}$=8.6 Hz), 124.9 (d, $^4J_{19F-13C}$=2.9 Hz), 116.0 (d, $^2J_{19F-13C}$=21.9 Hz), 102.3. GC–MS (70 eV) m/z (rel int.): 163 (M^+, 100), 162 (78), 135 (21), 134 (39), 121 (12), 108 (18), 107 (32), 95 (40), 75 (23). ^{19}F NMR (376 MHz, $CDCl_3$, δ): −114.8.

3.4.8. 3-(4-Trifluoromethylphenyl)isoxazole (1e).[25] Yield: 94% (2.900 g). Mp 99.0–101.0 °C. Yellow crystals. R_f=0.8 (petroleum ether/ethyl acetate=91:9). IR (KBr): 3159, 3138, 1620, 1554, 1435, 1330, 1166, 1113, 1067, 891, 856, 842, 787, 688, 597 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, δ): 8.46 (d, 1H, J=1.7 Hz), 7.90 (d, 2H, J=8.1 Hz, aromatic protons), 7.67 (d, 2H, J=8.1 Hz, aromatic protons), 6.66 (d, 1H, J=1.7 Hz). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 160.3, 159.4, 132.2, 131.7 (q, $^2J_{19F-13C}$=32.5 Hz), 127.1, 125.8 (q, $^3J_{19F-13C}$=3.7 Hz), 123.8 (q, $^1J_{19F-13C}$=270.8 Hz), 102.5. GC–MS (70 eV) m/z (rel int.): 213 (M^+, 78), 212 (100), 194 (14), 185 (10), 184 (20), 171 (8), 145 (41), 95 (9), 75 (9). ^{19}F NMR (376 MHz, $CDCl_3$, δ): −63.2.

3.5. Reaction of 3-arylisoxazoles (1a–e) with lithium amides: general procedure (the amount of 3-arylisoxazoles, $LiNR_2$ and solvent indicated below refer to a substrate/$LiNR_2$ ratio=1:1.5. See Table 1 for other substrate/$LiNR_2$ ratios)

A 2.5 M solution of *n*-BuLi in hexanes (0.310 mL, 0.776 mmol) was added to a solution of the dialkylamine or bis(trimethylsilyl)amine (0.776 mmol) in THF (2 mL) at 0 °C under nitrogen, using a nitrogen-flushed three-necked flask equipped with a magnetic stirrer and a nitrogen inlet. After 10 min, the solution of the 3-arylisoxazole **1a–e** (75 mg, 0.517 mmol) in THF (1 mL) was added dropwise and the obtained brown reaction mixture kept at 0 °C was stirred for the time indicated in Tables 1 and 3, and then quenched by adding aq NH_4Cl. The two phases were separated and the aqueous layer was extracted three times with ethyl acetate. The organic extracts combined were dried over anhydrous Na_2SO_4 and then the solvent evaporated under reduced pressure. Column chromatography (silica gel, petroleum ether/ethyl acetate=6:4) of the residue afforded the *syn* 2,6-diaryl-3,7-diazatricyclo[4.2.0.0^{2,5}]octan-4,8-diones **5a–e** as indicated in Scheme 3 and Tables 1 and 3. ^{1}H NMR signal (δ=4.10÷4.35 ppm) attributed to the proton at C_5 was a doublet with long-range coupling constant ^4J=2.2/2.6 Hz. ^4J ($\neq$0 Hz) was due to the 'W conformation' of the four σ bonds between H_5 and H_{amidic}. H_{amidic} peak was not split by H_5, its signal was broadened by the quadrupolar interaction. Aromatic nitriles **6a–c**, isolated as product of the reaction mentioned above, had the same analytical and spectroscopic data of the commercially available compounds.

3.6. Reaction of 3-phenylisoxazole (1a) with bis(trimethylsilyl)amides: general procedure

A solution of 3-phenylisoxazole (**1a**) (50 mg, 0.331 mmol) in THF (1 mL) was added to a solution of NaHMDS (or KHMDS) (0.496 mmol) in THF (1 mL) at 0 °C under nitrogen, using a nitrogen-flushed three-necked flask equipped with a magnetic stirrer and a nitrogen inlet. The brown reaction mixture was stirred at 0 °C for 1 h (Table 2), and then quenched by adding aq NH_4Cl. The two phases were separated and the aqueous layer was extracted three times with ethyl acetate. The organic extracts combined were dried over anhydrous Na_2SO_4 and then the solvent evaporated under reduced pressure.

3.6.1. *syn* 2,6-Bis(phenyl)-3,7-diazatricyclo [4.2.0.0^{2,5}]-octan-4,8-dione (5a). Yield: 85% (0.045 g). Mp 132.0–133.0 °C (dec). Yellow crystals. R_f=0.2. IR (KBr): 3279, 3091, 1760, 1738, 1498, 1447, 1365, 1308, 1161, 1038, 748, 693 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$, δ): 8.16–8.04 (br s, 2H, NH: exchange with D_2O), 7.44–7.38 (m, 8H, aromatic protons), 7.38–7.32 (m, 2H, aromatic protons), 4.25 (d, 2H, J=2.4 Hz). ^{13}C NMR (125 MHz, $CDCl_3$, δ): 167.2, 137.0, 129.3, 128.7, 126.1, 64.1, 52.3. LC–MS (ESI$^+$): 313 [M+Na]$^+$. Anal. Calcd for $C_{18}H_{14}N_2O_2$: C, 74.47; H, 4.86; N, 9.65. Found: C, 74.40; H, 5.01; N, 9.36.

3.6.2. *syn* 2,6-Bis(4-methylphenyl)-3,7-diazatricyclo[4.2.0.0^{2,5}]octan-4,8-dione (5b). Yield: 58% (0.029 g). Mp 150.1–151.3 °C. Yellow powder. R_f=0.2. IR (KBr): 3238, 2923, 2855, 1756, 1516, 1347, 1043, 812, 734 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, δ): 8.35–8.25 (br s, 2H, NH: exchange with D_2O), 7.32–7.30 (m, 4H, aromatic protons), 7.24–7.21 (m, 4H, aromatic protons), 4.17 (d, 2H, J=2.5 Hz), 2.37 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 167.3, 138.3, 133.9, 129.6, 125.8, 63.8, 51.9, 21.1. LC–MS (ESI$^+$): 341 [M+Na]$^+$. Anal. Calcd for $C_{20}H_{18}N_2O_2$: C, 75.45; H, 5.70; N, 8.80. Found: C, 75.52; H, 5.95; N, 8.70.

3.6.3. *syn* 2,6-Bis(4-methoxyphenyl)-3,7-diazatricyclo[4.2.0.0^{2,5}]octan-4,8-dione (5c). Yield: 32% (0.016 g). Mp 132.0–133 °C. Orange powder. R_f=0.2. IR (KBr): 3262, 3173, 2924, 2852, 1750, 1729, 1610, 1515, 1255, 1178, 1031, 823 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, δ): 8.20–8.10 (br s, 2H, NH: exchange with D_2O), 7.35–7.31 (m, 4H, aromatic protons, J=8.6 Hz), 6.95–6.92 (m, 4H, aromatic protons, J=8.6 Hz), 4.16 (d, 2H, J=2.4 Hz), 3.82 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 167.2, 159.6, 128.7, 127.2, 114.3, 63.8, 55.4, 51.7. LC–MS (ESI$^+$): 373 [M+Na]$^+$. Anal. Calcd for $C_{20}H_{18}N_2O_4$: C, 68.56; H, 5.18; N, 8.00. Found: C, 68.59; H, 5.17; N, 7.98.

3.6.4. *syn* 2,6-Bis(4-fluorophenyl)-3,7-diazatricyclo-[4.2.0.0^{2,5}]octan-4,8-dione (5d). Yield: 79% (0.071 g). Mp 168–169 °C (dec). Yellow powder. R_f=0.2. IR (KBr): 3273, 3166, 2922, 2847, 1753, 1732, 1599, 1514, 1514, 1375, 1224, 1160, 1044, 836 cm^{-1}. ^{1}H NMR (400 MHz, $(CD_3)_2CO_3$, δ): 8.35–8.30 (br s, 2H, NH: exchange with D_2O), 7.61–7.57 (m, 4H, aromatic protons), 7.24–7.20 (m, 4H, aromatic protons), 4.35 (d, 2H, J=2.6 Hz). ^{13}C NMR (100 MHz, $(CD_3)_2CO_3$, δ): 169.5, 167.5 (d, $^1J_{19F-13C}$=250 Hz), 139.6 (d, $^4J_{19F-13C}$=3.2 Hz), 133.4 (d, $^3J_{19F-13C}$=8.4 Hz), 120.7 (d, $^2J_{19F-13C}$=21.9 Hz), 69.7, 55.6. LC–MS (ESI$^+$): 349 [M+Na]$^+$. Anal. Calcd for $C_{18}H_{12}F_2N_2O_2$: C, 66.26; H, 3.71; N, 8.59. Found: C, 66.20; H, 3.72; N, 8.80.

3.6.5. *syn* 2,6-Bis-(4-trifluoromethylphenyl)-3,7-diazatricyclo[4.2.0.0^{2,5}]octan-4,8-dione (5e). Yield: 80% (0.072 g). Mp 145–146 °C (dec). Yellow crystals. R_f=0.2. IR (KBr): 3273, 2923, 2853, 1760, 1746, 1620, 1412, 1326, 1165, 1116, 1068, 1017, 827 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$, δ): 8.60–8.50 (br s, 2H, NH: exchange with D_2O), 7.74–7.71 (m, 4H, aromatic protons), 7.58–7.55 (m, 4H, aromatic protons), 4.29 (d, 2H, J=2.2 Hz). ^{13}C NMR (100 MHz, $CDCl_3$, δ): 166.5, 140.4 (d, $^4J_{19F-13C}$=1.1 Hz), 131.1 (q, $^2J_{19F-13C}$=32.9 Hz), 126.4, 126.2 (q, $^3J_{19F-13C}$=3.8 Hz), 123.7 (q, $^1J_{19F-13C}$=272.5 Hz), 64.1, 51.9. ^{19}F NMR (376 MHz, $CDCl_3$, δ): −63.0. LC–MS (ESI$^-$): 425 [M−H]$^-$ (27), 382 (100). Anal. Calcd for $C_{20}H_{12}F_6N_2O_2$: C, 56.35; H, 2.84; N, 6.57. Found: C, 56.20; H, 3.22; N, 6.80.

3.7. X-ray crystallography data for compound (5a)

X-ray data were collected at 293(2) K on microscope-selected single crystals using a Nonius Kappa CCD area detector diffractometer, with Mo Kα radiation (λ= 0.71073 Å), in ϕ and ω scan modes; data collection: COLLECT;[26] cell refinement and data reduction: Evalccd.[27] The structure was solved through the direct method procedure of SIR97[28] and refined by a full-matrix least-squares technique based on F^2, SHELXL-97.[29] The non-hydrogen atoms were refined with anisotropic displacement parameters. The hydrogen atoms were localized through difference-Fourier map and refined isotropically. The final cycle of least-squares refinement included 255 parameters (weighting scheme applied: $w^{-1}=[\sigma^2(F_o^2)+(0.0497P)^2+0.2881P]$, with $P=[(F_o^2+2F_c^2)/3]$). The final residuals [$I>2\sigma(I)$] were R_1=0.0588 and wR_2=0.1081. Crystal data and structure refinement of **5a** are reported in Table 4; fractional atomic coordinates and equivalent isotropic parameters, bond lengths and angles are reported in Tables 5 and 6 in Supplementary data.

Table 4. Crystal data and structure refinement for *syn* 2,6-diphenyl-3,7-diazatricyclo[4.2.0.0^{2,5}]octan-4,8-dione (**5a**)

Empirical formula	$C_{18}H_{14}N_2O_2$
Formula weight	290.31
Temperature	293(2) K
Wavelength	0.71073 Å
Crystal system; space group	Monoclinic; $P2_1/c$
Unit cell refl; θ range	80; 4.15–19.39°
Unit cell dimensions	a=14.3880(10) Å
	b=11.8830(10) Å
	c=8.7360(10) Å
	β=97.276(7)°
Volume	1481.6(2) Å^3
Z; calculated density	4; 1.302 mg m^{-3}
Absorption coefficient	0.086 mm^{-1}
F(000)	608
Crystal size	0.04 mm×0.04 mm×0.07 mm
θ range for data collection	5.01–27.49°
Limiting indices	$-18\le h\le 12$
	$-14\le k\le 15$
	$-11\le l\le 11$
Reflections collected/unique	11,827/3378[R(int)=0.0534]
Completeness (θ=27.49°)	99.1% (θ=27.49°)
Refinement method	Full-matrix least-squares on F^2
Data/restraints/parameters	3378/0/255
Goodness-of-fit on F^2	1.016
Final R indices [$I>2\sigma(I)$]	R_1=0.0588, wR_2=0.1081
R indices (all data)	R_1=0.1364, wR_2=0.1329
Largest diff. peak and hole	0.230 and −0.180 eÅ^{-3}

Acknowledgements

This work was financially supported by National Project 'Stereoselezione in Sintesi Organica, Metodologie ed Applicazioni' MiUR (Rome), and the University of Bari. Thanks are due to Istituto di Chimica dei Composti OrganoMetallici (ICCOM-CNR, Bari) for NMR facilities.

Supplementary data

^{1}H and ^{13}C NMR spectra for the new compounds and X-ray crystal structure data for **5a**. Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2007.09.040.

References and notes

1. (a) Southgate, R. *Contemp. Org. Synth.* **1994**, *1*, 417–431; (b) Neu, H. C. *The Chemistry of β-Lactams*; Page, M. I., Ed.; Blackie: Glasgow, 1992; pp 101–128.
2. (a) Alcaide, B.; Almendros, P. *Chem. Soc. Rev.* **2001**, *30*, 226–240; (b) Palomo, C.; Aizpurua, J. M.; Ganboa, I.; Oiarbide, M. *Synlett* **2001**, 1813–1826.
3. (a) Stahl, S. S.; Gellman, S. H.; Lee, S. E.; Ilker, F. M.; Weisblum, B.; Kissounko, D. A. *(Wisconsin Alumni Research Foundation, USA).* PCT Int. Appl. **2007**; Patent WO2007025141, 2007; (b) Palomo, C.; Aizpurua, J. M.; Balentová, E.; Jimenez, A.; Oyarbide, J.; Fratila, M. R.; Miranda, J. J. *Org. Lett.* **2007**, *9*, 101–104.
4. (a) Mishra, R. K.; Coates, C. M.; Revell, K. D.; Turos, E. *Org. Lett.* **2007**, *9*, 575–578; (b) Wasserman, H. H.; Matsuyama, H.; Robinson, R. P. *Tetrahedron* **2002**, *58*, 7177–7190.
5. (a) Angelaud, R.; Zhong, Y.-L.; Maligres, P.; Lee, J.; Askin, D. *J. Org. Chem.* **2005**, *70*, 1949–1952; (b) Palomo, C.; Aizpurua, J. M.; Ganboa, I. *Enantioselective Synthesis of β-Amino Acids*; Juaristi, E., Ed.; Wiley-VCH: New York, NY, 1997; p 279; (c) Ojima, I.; Delaloge, F. *Chem. Soc. Rev.* **1997**, *26*, 377–386.
6. Di Nunno, L.; Scilimati, A.; Vitale, P. *Tetrahedron* **2005**, *61*, 2623–2630.
7. Hoppe, I.; Schollkopf, U. *Liebigs Ann. Chem.* **1979**, 219–226.
8. Hassner, A.; Ghera, E.; Yechezkel, T.; Kleiman, V.; Balasubramanian, T.; Ostercamp, D. *Pure Appl. Chem.* **2000**, *72*, 1671–1683.

9. Amunugama, R.; Rodgers, M. T. *Int. J. Mass Spectrom.* **2000**, *195–196*, 439–457.
10. For the synthetic methodology see: Di Nunno, L.; Scilimati, A. *Tetrahedron* **1987**, *43*, 2181–2189.
11. Reference to the Hammett σ_p values (CF_3=0.53; F=0.15; H=0; Me=−0.14; OMe=−0.28), see: Smith, M. B.; March, J. *March's Advanced Organic Chemistry: Reactions, Mechanisms and Structure*, 6th ed.; John Wiley and Sons, Inc.: Hoboken, NJ, 2007; Chapter 9, p 404.
12. Suffert, J. *J. Org. Chem.* **1989**, *54*, 509–510.
13. Di Nunno, L.; Vitale, P.; Scilimati, A.; Tacconelli, S.; Patrignani, P. *J. Med. Chem.* **2004**, *47*, 4881–4890.
14. Jain, N.; Kumar, A.; Chauhan, S. M. S. *Tetrahedron Lett.* **2005**, *46*, 2599–2602.
15. Blackwell, M.; Dunn, P. J.; Graham, A. B.; Grigg, R.; Higginson, P.; Saba, I. S.; Thornton-Pett, M. *Tetrahedron* **2002**, *58*, 7715–7725.
16. Barbachyn, M. R.; Cleek, G. J.; Dolak, L. A.; Garmon, S. A.; Morris, J.; Seest, E. P.; Thomas, R. C.; Toops, D. S.; Watt, W.; Wishka, D. G.; Ford, C. W.; Zurenko, G. E.; Hamel, J. C.; Schaadt, R. D.; Stapert, D.; Yagi, B. H.; Adams, W. J.; Friis, J. M.; Slatter, J. G.; Sams, J. P.; Oien, N. L.; Zaya, M. J.; Wienkers, L. C.; Wynalda, M. A. *J. Med. Chem.* **2003**, *46*, 284–302.
17. Liu, K. X.; Shelton, B. R.; Howe, R. *J. Org. Chem.* **1980**, *45*, 3916–3918.
18. Kanemasa, S.; Matsuda, H.; Kamimura, A.; Kakinami, T. *Tetrahedron* **2000**, *56*, 1057–1064.
19. Kim, J. N.; Ryu, E. K. *J. Org. Chem.* **1992**, *57*, 6649–6650.
20. Hamper, B. C.; Leschinsky, K. L.; Massey, S. S.; Bell, C. L.; Brannigan, L. H.; Prosch, S. D. *J. Agric. Food Chem.* **1995**, *43*, 219–228.
21. Genco, N. A.; Partis, R. A.; Alper, H. *J. Org. Chem.* **1973**, *58*, 4365–4367.
22. Sheng, S.-R.; Xin, Q.; Liu, X.-L.; Sun, W.-K.; Guo, R.; Huang, X. *Synthesis* **2006**, 2293–2296.
23. Shvekhgeimer, G. A.; Baranski, A.; Grzegozek, M. *Synthesis* **1976**, 612–614.
24. Sheng, S.-R.; Liu, X.-L.; Xu, Q.; Song, C.-S. *Synthesis* **2003**, 2763–2764.
25. Gołębiewski, W. M.; Gucma, M. *J. Heterocycl. Chem.* **2006**, *43*, 509–513.
26. Nonius. *COLLECT*; Nonius BV: Delft, The Netherlands, 1998.
27. Duisenberg, A. J. M.; Kroon-Batenburg, L. M. J.; Schreurs, A. *J. Appl. Crystallogr.* **2003**, *36*, 220–229.
28. Altomare, A.; Burla, M. C.; Camalli, M.; Cascarano, G. L.; Giacovazzo, C.; Guagliardi, A.; Moliterni, A. G.; Polidori, G.; Spagna, R. *J. Appl. Crystallogr.* **1999**, *32*, 115–119.
29. Sheldrick, G. M. *SHELXL-97: Program for the Refinement of Crystal Structures*; University of Gottingen: Gottingen, Germany, 1997.