Organic & Biomolecular Chemistry

Cite this: *Org. Biomol. Chem.*, 2012, **10**, 2780

www.rsc.org/obc

PAPER

One-pot sequential Ti-/Cu-catalysis for tandem amidation/Ullmann-type cyclization: synthesis of model benzodiazepine(di)ones promoted by microwave irradiation†

Leonardo Ciofi,[a] Andrea Trabocchi,*[a] Claudia Lalli,[b] Gloria Menchi[a] and Antonio Guarna[a]

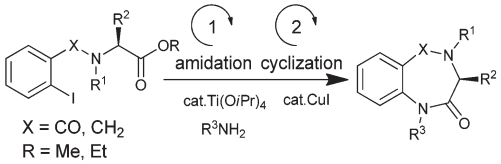
Received 9th December 2011, Accepted 30th January 2012
DOI: 10.1039/c2ob07063d

The application of sequential Ti-/Cu-catalysis in the model one-pot synthesis of benzodiazepine(di)ones promoted by microwave irradiation demonstrates the expediency of dual catalysis in coupling-cyclization methods useful for diversity-oriented synthesis.

Introduction

The search for efficient and mild methodologies for the preparation of heterocycles is a challenge of increasing impact for chemists involved in the construction of organic molecules with enhanced complexity and chemical diversity. From this point of view, it is well recognized that the development of multi-bond forming protocols, such as multicomponent reactions,[1] domino reactions,[2] or one-pot multi-step processes are important issues for the construction of small molecules in diversity-oriented synthesis from operational simplicity and assembly efficiency.[3] Efforts in improving library generation are focusing on the concepts of step economy and tandem catalysis, in order to proceed rapidly with the generation of wide arrays of small molecule collections. Tandem transformations are usually operated in one-pot without the need for intermediate workups or purifications, and recently, multicatalytic approaches have attracted growing interest in this field.[4] In multicatalytic processes, multiple distinct catalytic steps are executed during a single operation, in either a tandem or sequential fashion. Although there has been increasing recognition of the power of multicatalytic synthesis, the number and range of examples disclosed in this area to date is still limited.[3h,5]

We envisioned the possibility of exploring catalyzed processes for key coupling-cyclization steps in the generation of heterocyclic chemotypes. Accordingly, it would be highly valuable to develop sequential one-pot processes to achieve arrays of heterocycles in a diversity-oriented manner. As a case study, we envisaged the possibility of exploring a new Ti-/Cu-catalyzed sequential one-pot process for the generation of 1,4-benzodiazepine-2,5-diones and 1,4-benzodiazepine-2-ones (Scheme 1).



Scheme 1 Sequential catalytic approach to cyclic chemotypes.

The relevance of such heterocyclic compounds in medicinal chemistry is remarkable, for instance the synthesis and analysis of 12 melanocortin receptor agonists using the 1,4-benzodiazepine-2,5-dione template has been recently reported.[6] These heterocyclic compounds proved to possess anticonvulsant, anxiolytic, and antitumor properties, as well as being antagonists of cholecystokinin receptor (CCK), opiate receptor, and platelet glycoprotein IIb–IIIa.[7] In addition, the 1,4-benzodiazepine-2,5-dione moiety appears in a number of natural products,[8] and it has been extensively studied in combinatorial chemistry as a molecular platform for appendage diversity.[9] We planned to combine the concept of sequential catalytic processes to microwave-assisted synthetic technique, as the interest to microwave-assisted reactions has been increasing among organic and medicinal chemists in recent years, not only because these reactions exhibit particular or unexpected reactivity in some cases, but also because they are significantly useful for green chemistry.[10]

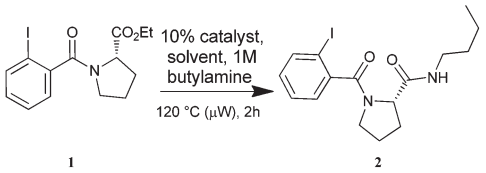
Results and discussion

We initially explored the reactivity of *N*-(2-iodobenzoyl) proline esters in the amidation reaction with butylamine using the Zr-catalyzed process, as reported by Porco and collaborators.[11] This process is a straightforward route for the preparation of amides

[a]*Department of Chemistry "Ugo Schiff", University of Florence, Via della Lastruccia 13, I-50019 Sesto Fiorentino, Florence, Italy. E-mail: andrea.trabocchi@unifi.it; Fax: +39 055 457 3531; Tel: +39 055 457 3507*
[b]*Centre de Recherche de Gif, Institut de Chimie des Substances Naturelles CNRS, Avenue de la Terrasse, 91198 Gif-sur-Yvette Cedex, France*

†Electronic supplementary information (ESI) available: copies of ^{1}H and ^{13}C NMR spectra. See DOI: 10.1039/c2ob07063d

Table 1 Exploration of the reaction conditions for the first step of the process



1 2

Entry	Catalyst	Additive	Solvent	Conversion,[a] %
1	—	—	DMSO	0
2	—	—	Toluene	0
3	$Zr(OtBu)_4$	HOAt	Toluene	20
4	$ZrCl_4$	HYP	Toluene	0
5	$Ti(OiPr)_4$	HYP	Toluene	89
6	$Ti(OiPr)_4$	—	Toluene	91
7	$Ti(OiPr)_4$	—	DMSO	0

[a] Measured by ^{1}H NMR.

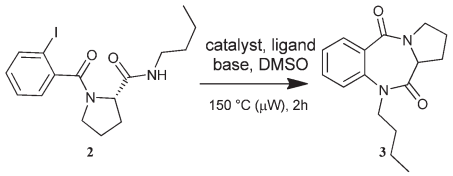
from unactivated esters and amines using a catalytic system comprising group (IV) metal alkoxides in conjunction with additives, including 1-hydroxy-7-azabenzotriazole (HOAt), which was found to be general and of wide applicability using a variety of structurally diverse esters and amines.

Control experiments using proline derivative **1** as the substrate showed the reaction did not occur in the absence of the catalyst both in toluene and DMSO (Table 1, entries 1–2). We found this reaction to proceed sluggishly with $Zr(OtBu)_4$ using this substrate, with only 20% conversion after 2 h at 120 °C (entry 3). We moved then on the cheaper and easier to handle $ZrCl_4$ and $Ti(OiPr)_4$, and whereas $ZrCl_4$ did not lead to any product, even with the use of 2-hydroxypyridine (HYP) as an additive, the application of $Ti(OiPr)_4$ resulted in the successful conversion to the desired amide. No improvements in presence of the additive were observed (entries 4–6), and a test reaction in DMSO failed to succeed, thus impairing the application of the two-steps process in the same solvent (entry 7).

A possible reason for $Ti(OiPr)_4$ showing better catalytic activity compared to $Zr(OtBu)_4$ could be less hindrance of the former towards the bulky *o*-iodobenzoyl-proline ethyl ester used as the starting material. The choice of ethyl esters as substrates was due to the high reactivity of the corresponding methyl derivatives, which provided the trans-esterified isopropyl ester derivatives in significant amounts. Thus, a putative ligand exchange process with the organometallic species resulted in a capping reaction towards the desired amidation process. In fact, the isopropyl ester does not proceed in the amidation reaction due to high hindrance displayed by this ester, as reported.[11] Ethyl ester substrates proved to work without any trans-esterification side reactions even at high temperatures (120 °C), thus giving the desired products in good yields.

For the cyclization step consisting of the *N*-arylation process, both Cu- and Pd-based catalysts were taken into account, as reported (Table 2).[12] Poor yields were observed for the Pd-based catalytic process, whereas an Ullmann-type reaction catalyzed by CuI was optimal when used in an amount of 20% and in the presence of 40% mol equivalents of thiophene-2-carboxylic acid as a ligand for copper.

Table 2 Exploration of the reaction conditions for the second step of the process

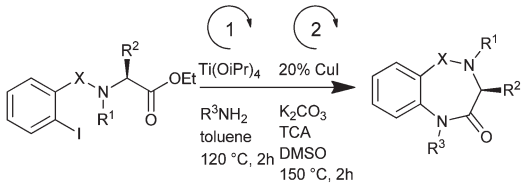


2 3

Entry	Catalyst	Ligand	Base	Conversion,[a] %
1	$Pd(OAc)_2$	BINAP	KOAc	0
2	$(PPh_3)_2PdCl_2$	—	KOAc	10
3	$PdCl_2$	Dppf	KOAc	0
4	CuI (10% mol)	TCA[b]	K_2CO_3	43
5	CuI (20% mol)	TCA[b]	K_2CO_3	68

[a] Measured by ^{1}H NMR. [b] Thiophene-2-carboxylic acid.

Table 3 Exploration of the reaction conditions for the second step of the process



Cmpd	X	R^1	R^2	R^3	Yield, %
3	CO	$-(CH_2)_3-$		$CH_2CH_2CH_2CH_3$	63
4	CO	$-(CH_2)_3-$		$CH_2CH(CH_3)_3$	67
5	CO	$-(CH_2)_3-$		CH_2Ph	56
6	CO	$-(CH_2)_3-$		$CH_2CH{=}CH_2$	62
7	CO	$-(CH_2)_3-$		$CH_2CH_2OCH_3$	42
8	CO	$-(CH_2)_3-$		$CH_2CH(OCH_3)_2$	45
9	CO	$-(CH_2)_3-$		CH_2CH_2OH	19
10	CO	H	$CH_2CH(CH_3)_3$	$CH_2CH_2CH_2CH_3$	18
11	CO	H	$CH(CH_3)_3$	$CH_2CH_2CH_2CH_3$	28
12	CO	H	CH_2Ph	$CH_2CH_2CH_2CH_3$	24
13	CO	CH_2Ph	H	$CH_2CH{=}CH_2$	26
14	CH_2	$-(CH_2)_3-$		$CH_2CH_2CH_2CH_3$	43
15	CH_2	$-(CH_2)_3-$		$CH_2CH{=}CH_2$	18
16	CH_2	Ac	H	$CH_2CH_2CH_2CH_3$	60
17	CH_2	Ac	H	$CH_2CH{=}CH_2$	53

The sequential one-pot process proved to work successfully, as the Cu-catalyzed reaction was found not to be altered by the presence of $Ti(OiPr)_4$. Specifically, the two-steps process consisted of carrying out the first process in a concentrated toluene solution, followed by addition to the more diluted DMSO solution containing the second catalytic system. The presence of toluene in the solvent mixture, although in lower amounts with respect to DMSO, did not affect the outcome of the second step.

The one-pot process was analyzed for its scope on an array of substrates as reported in Table 3. *N*-(2-Iodobenzoyl)proline ethyl ester proved to succeed in giving the title benzodiazepinediones **3–8** for aliphatic amines, allylamine and benzylamine, with overall yields ranging from 42 to 67%. When aminoethanol was used as the amino component, the yield for the corresponding compound **9** dropped to 19%, possibly due to the coordinating

role of the hydroxyl group towards copper, thus impairing the cyclization step. Also, *N*-(2-iodobenzoyl)amino esters derivatives from primary amino acids such as phenylalanine, leucine and valine gave benzodiazepinediones **10–12** in poor yields ranging from 18 to 28%, respectively, suggesting the amide proton as an interfering element in the cyclization process promoted by copper. Accordingly, when the capped *N*-acetyl-*N*′-(2-iodobenzyl)glycine ethyl ester not bearing any amide protons was taken into account, the corresponding benzodiazepinones **16–17** were achieved in 53 and 60% yield by reacting with allylamine and butylamine, respectively. The dual catalytic one-pot process was assayed on *N*-(2′-iodobenzyl)proline ethyl ester as an example of tertiary amine, to probe the compatibility of the method with a different substrate. The reaction with butylamine resulted in the corresponding benzodiazepinone **14** in 60%, thus indicating full compatibility also with tertiary amines. Nevertheless, the amine reactant proved to play a role in the successful outcome of the process, as bulky amines and substrates possessing a β-branched hindrance, such as *t*-butylamine, cyclohexylamine and cyclopropylamine, failed to work. Accordingly, it has to be mentioned that amidation reaction needs fine tuning to give best yields, as reported,[11] specifically in varying solvent, concentration and additives depending on selected starting esters and amines. In our process, with aim to extend the concept on library development, we found important to select a unique protocol for different substrates and reagents which however gave good overall yields and proved to work in a sequential fashion with the subsequent arylation reaction.

When the process was carried out with pre-mixing of the two catalysts and all the reactants in a challenging fully one-pot operation, the two-steps reaction failed to produce the title bicyclic compound. This was probably due to inactivation of the first reaction step by the presence of the copper moiety. Moreover, the fully one-pot process was impaired by the solvent system, as the two steps required different solvents (see method development). Interestingly, a side-reaction consisting of the oxidation of the amine to the corresponding aldehyde was observed in low yield, possibly resulting from the Cu-catalyzed deamination process of the intermediate imine species in DMSO, similarly to a reported mechanism for the Cu-catalyzed aerobic oxidation of amines.[13]

Conclusions

In conclusion, we reported on a one-pot method for the generation of benzodiazepine(di)ones, which are relevant heterocycles for medicinal chemistry, starting from the corresponding amino ester derivatives as a benchmark for validating the sequential combination of Ti-catalyzed amidation and the Cu-catalyzed *N*-arylation reactions. When the two catalysts were added simultaneously, the process proved not to be working, as the amine reactant of the first step resulted in partial Cu-mediated oxidation to the corresponding aldehyde, in agreement with similar processes reported in the literature. Nevertheless, the multicatalytic one-pot process proved to work nicely on a sequential fashion for diverse substrates, giving the title product in 42–67% overall yield when a proline derivative was used as the substrate. It was ascertained that the process could not be used with substrates possessing polar hydrogen atoms as of secondary amides and hydroxyl groups. Successful sequential application of $Ti(OiPr)_4$ and CuI catalysts in a two-step process is a first evidence which may suggest further exploration towards other synthetic applications promoted by such catalysts. Efforts towards the exploration of new combinations of catalysts for dual or more complex syntheses are of great interest with aim to access more sustainable processes, taking advantage of the concepts of green chemistry and step-economy in multistep syntheses.

Experimental

General methods

NMR spectra were acquired on a Varian Inova 400 spectrometer running at 400 and 100 MHz for ^1H and ^{13}C, respectively and on a Varian Gemini 200 spectrometer, running at 200 and 50 MHz for ^1H and ^{13}C, respectively. Chemical shifts (δ) are reported in ppm relative to residual solvent signals ($CHCl_3$, 7.26 ppm for ^1H NMR; $CDCl_3$, 77.0 ppm for ^{13}C NMR). The following abbreviations are used to indicate the multiplicity in ^1H NMR spectra: s, singlet; d, doublet; t, triplet; m, multiplet; br, broad signal. ^{13}C NMR spectra were acquired on a broad band decoupled mode. ESI mass spectra were carried out on a ion-trap double quadrupole mass spectrometer using electrospray (ES^+) ionization technique. Chromatographic separations were performed on silica gel using flash-column techniques. Analytical grade solvents and commercially available reagents were used without further purification.

(A) Representative procedure for *N*-(2-iodobenzoyl)amino acid ethyl esters. 2-Iodobenzoic acid (1.2 eq.) was dissolved in CH_2Cl_2 and $SOCl_2$ (10 eq.) was added at rt. The mixture was refluxed for 1 h, then the solvent was evaporated. The crude was dissolved in CH_2Cl_2, and evaporated again for complete removal of thionyl chloride. Meanwhile, amino acid ethyl ester hydrochloride (1 eq.) was suspended in CH_2Cl_2 and put in an ice bath. Triethylamine (2 eq.) was added dropwise to achieve complete dissolution of the product. Then, the resulting acyl chloride was dissolved in dry CH_2Cl_2 and added dropwise at 0 °C to the solution containing the proline derivative. The reaction mixture was allowed to return to rt and stirred for 16 h, then washed with 5% HCl, 5% $NaHCO_3$ and brine. Organic phases were combined, dried over anhydrous Na_2SO_4, filtered and evaporated. Flash-column chromatography purification (1 : 1 EtOAc–petroleum ether) afforded pure *N*-(2-iodobenzoyl)amino acid ethyl ester (5.4 g, 14.3 mmol, 55% for proline as the amino acid substrate).

(B) General procedure for the synthesis of *N*-(2-iodobenzyl) amino acid ethyl ester. Amino acid ethyl ester hydrochloride (1 eq.) was suspended in CH_3CN (40 ml $mmol^{-1}$) and anhydrous K_2CO_3 (6 eq.) was added. 2-Iodobenzyl bromide (1 eq.) was added and reaction mixture was refluxed o.n., then allowed to return to rt. The resulting suspension was filtered through Celite and evaporated to give a crude that was subjected to flash-column chromatography (EtOAc–petroleum ether 1 : 1) to afford pure product.

(C) Representative procedure for microwave-assisted synthesis of benzodiazepine(di)ones. Reactions were performed on

0.2–0.5 mmol scale. Starting material (1 eq.) was dissolved in dry toluene (1 M) in a flame-dried, sealed microwave vial under N_2 atmosphere. Amine (1.1 eq.) and $Ti(OiPr)_4$ (0.1 eq.) were added in this order and the vessel was heated for 2 h at 120 °C in a microwave reactor. Meanwhile, in another vial a suspension of anhydrous K_2CO_3 (2 eq.), CuI (0.2 eq.) and thiophene-2-carboxylic acid (0.4 eq.) in DMSO (0.1 M) was degassed in a Schlenk line and put under N_2 atmosphere. Then, the reaction mixture was added *via* syringe and the suspension was heated for 2 h at 150 °C in a microwave reactor. The resulting suspension was then diluted with EtOAc (10×), and washed with 5% HCl and brine. Flash chromatography purification (1 : 3 EtOAc–petroleum ether) afforded pure products as yellow, orange or brown oils.

(*S*)-Ethyl 1-(2-iodobenzoyl)pyrrolidine-2-carboxylate (1)

Prepared in 55% yield according to general procedure A. $[\alpha]_D^{24}$ −136.9 (*c* 1.1, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) mixture of rotamers δ 7.90 (m, 1 H), 7.22 (m, 3 H), 4.77 (dd, J_1 = 8.4 Hz, J_2 = 3.8 Hz, 0.19 H, minor), 4.67 (dd, J_1 = 8.6 Hz, J_2 = 4.5 Hz, 0.81 H, major), 4.25 (qd, J_1 = 7.2 Hz, J_2 = 2.0 Hz, 0.65 H, major) and 4.00 (qd, J_1 = 7.1 Hz, J_2 = 3.2 Hz, 0.35 H, minor), 4.08 (dd, J_1 = 2.4 Hz, J_2 = 8.5 Hz, 2 × 0.35 H, minor) and 3.79 (m, 2 × 0.65 H, major), 3.31–3.24 (m, 1 H), 2.37–2.23 (m, 1 H), 2.13–1.89 (m, 2 H), 1.31 (t, J = 7.1 Hz, 3 × 0.65 H, major) and 1.12 (t, J = 7.1, 3 × 0.35 H, minor). ^{13}C NMR (50 MHz, $CDCl_3$) mixture of rotamers δ 171.8 and 171.7 (s), 168.9 (s), 142.9 and 141.4 (s), 139.1 and 138.9 (d), 130.7 and 130.3 (d), 128.3 and 128.0 (d), 127.8 and 127.2 (d), 92.2 and 91.6 (s), 61.3 and 61.2 (t), 61.0 and 58.6 (d), 48.7 and 46.2 (t), 31.2 and 29.5 (t), 24.7 and 22.8 (t), 14.1 and 14.0 (q). ESI-MSMS *m*/*z* (%) 374 [M^+ + 1, 20], 327 [M^+ − ethoxy, 100], 300 [M^+ − ethoxycarbonyl, 96]. Elemental analysis calcd (%) for $C_{14}H_{16}INO_3$: C 45.06, H 4.32, N 3.75; found C 45.14, H 4.34, N 3.67.

(*S*)-Ethyl 1-(2-iodobenzyl)pyrrolidine-2-carboxylate (18)

Prepared in 96% yield according to general procedure B. $[\alpha]_D^{24}$ −38.3 (*c* 4.8, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (d, J = 7.9 Hz, 1 H), 7.50 (d, J = 7.6 Hz, 1 H), 7.30 (t, J = 7.5 Hz, 1 H), 6.92 (t, J = 7.6 Hz, 1 H), 4.17 (q, J = 7.1 Hz, 2 H), 3.94 (part A of AB system, J = 4.1 Hz, 1 H), 3.74 (part B of AB system, J = 14.0 Hz, 1 H), 3.43 (m, 1 H), 3.07 (m, 1 H), 2.53 (m, 1 H), 2.15 (m, 1 H), 2.01–1.88 (m, 2 H), 1.85–1.78 (m, 1 H), 1.24 (t, J = 7.1 Hz, 3 H). ^{13}C NMR δ 173.9 (s), 141.0 (d), 139.1 (d), 130.3 (d), 128.5 (d), 128.0 (d), 99.8 (d), 65.3 (t), 62.1 (d), 60.4 (t), 53.0 (t), 29.3 (t), 23.3 (t), 21.4 (q). ESI-MSMS *m*/*z* (%): 360 [M^+ + 1, 4], 332 [free acid + 1, 16] 286 [M^+ − ethoxycarbonyl, 100], 217 [iodobenzyl, 19]. Elemental analysis calcd (%) for $C_{14}H_{18}INO_2$: C 46.81, H 5.05, N 3.90; found C 46.90, H 5.14, N 3.77.

Ethyl 2-(*N*-(2-iodobenzyl)acetamido)acetate (19)

N-2-Iodobenzoyl glycine ethyl ester was prepared according to general procedure B from glycine ethyl ester hydrochloride in 83% yield. The precursor (1.89 g, 5.91 mmol) was dissolved in anhydrous CH_2Cl_2 (25 ml) and triethylamine (1.65 ml, 11.8 mmol) was added. Acetyl chloride (462 µl, 6.50 mmol) was added dropwise at 0 °C, then the reaction mixture was allowed to stir at rt under N_2 atmosphere for 16 h. The resulting solution was washed with 5% HCl, 5% $NaHCO_3$ and brine. Flash chromatography purification (1 : 1 EtOAc–petroleum ether) afforded a yellowish oil (1.17 g, 3.23 mmol, 55%). ^{1}H NMR (400 MHz, $CDCl_3$, mixture of rotamers) δ 7.87 (d, J = 7.9 Hz, 1 × 0.72 H, major), 7.81 (d, J = 7.9 Hz, 1 × 0.28 H), 7.37 (t, J = 7.6 Hz, 1 × 0.72 H, major), 7.30 (t, J = 7.5 Hz, 1 × 0.28 H, minor), 7.23 (dd, J_1 = 1.4 Hz, J_2 = 7.7 Hz, 1 × 0.28 H, minor), 7.15 (d, J = 7.6 Hz, 1 × 0.72 H, major), 7.02 (t, J = 7.6 Hz, 1 × 0.72 H, major), 6.96 (t, J = 7.5 Hz, 1 × 0.72 H, major), 4.72 (s, 2 × 0.28 H, minor), 4.56 (s, 2 × 0.72 H, major), 4.18 (q, J = 7.1 Hz, 2 H, major and minor superimposed), 4.05 (s, 2 × 0.72 H, major), 3.94 (s, 2 × 0.28 H, minor), 2.15 (s, 3 × 0.72 H, major), 2.14 (m, 3 × 0.28 H, minor), 1.26 (t, J = 7.1 Hz, 3 H, major and minor superimposed). ^{13}C NMR δ (75 MHz, $CDCl_3$, mixture of rotamers): 171.7 and 171.2 (s), 169.0 and 168.8 (s), 139.9 and 139.5 (d), 138.7 and 137.7 (s), 129.5 and 129.2 (d), 128.7 and 128.5 (d), 127.1 (d), 99.2 and 97.7 (s), 61.6 and 61.2 (t), 58.3 and 54.1 (t), 49.6 and 47.4 (t), 21.5 and 21.3 (q), 14.2 (q). ESI-MSMS *m*/*z* (%): 361 [M^+, 2], 315 [M^+ − ethoxy, 100] 286 [M^+ − ethoxycarbonyl, 5], 217 [iodobenzyl, 9]. Elemental analysis calcd (%) for $C_{13}H_{16}INO_3$: C 43.23, H 4.47, N 3.88; found C 43.31, H 4.54, N 3.72.

(*S*)-10-Butyl-1,2,3,11a-tetrahydro-10*H*-benzo[*e*]pyrrolo[1,2-*a*][1,4]diazepine-5,11-dione (3)

Prepared according to general procedure C in 63% yield. $C_{16}H_{20}N_2O_2$: C 70.56, H 7.40, N 10.29; found C 70.71, H 7.49, N 10.11. NMR data as reported.[14]

(*S*)-10-Isobutyl-1,2,3,11a-tetrahydro-10*H*-benzo[*e*]pyrrolo[1,2-*a*][1,4]diazepine-5,11-dione (4)

Prepared according to general procedure C in 67% yield. $[\alpha]_D^{25}$ +97.8 (*c* 0.7, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (dd, J_1 = 7.8, J_2 = 1.6 Hz, 1 H), 7.50 (td, J_1 = 7.4 Hz, J_2 = 1.7 Hz, 1 H), 7.31 (dd, J_1 = 7.6 Hz, J_2 = 1.0, 1 H), 7.27 (d, J = 7.5 Hz, 1 H), 4.30 (dd, J = 13.7, 9.2 Hz, 1 H), 4.03 (dd, J_1 = 7.6 Hz, J_2 = 2.1, 1 H), 3.79 (m, 1 H), 3.56 (m, 1 H), 3.33 (dd, J_1 = 13.7, J_2 = 5.7 Hz, 1 H), 2.72 (m, 1 H), 2.13 (m, 1 H), 1.99 (m, 2 H), 1.70 (m, 2 H), 0.78 (d, J = 6.7 Hz, 3 H), 0.72 (d, J = 6.7 Hz, 3 H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 169.1 (s), 164.6 (s), 131.8 (d), 130.1 (d), 125.8 (d), 122.9 (d), 110.2 (d), 57.5 (d), 54.2 (t), 46.4 (t), 37.0 (t), 26.9 (t), 23.8 (d), 20.1 (q), 19.4 (q). ESI-MSMS *m*/*z* (%): 273 [M^+ + 1, 100], 217 [M^+ + 1-iBu, 78], 174 [M^+ + 1-Pro, 12]. Elemental analysis calcd (%) for $C_{16}H_{20}N_2O_2$: C 70.56, H 7.40, N 10.29; found C 70.67, H 7.44, N 10.11.

(*S*)-10-Benzyl-1,2,3,11a-tetrahydro-10*H*-benzo[*e*]pyrrolo[1,2-*a*][1,4]diazepine-5,11-dione (5)

Prepared according to general procedure C in 56% yield. $C_{19}H_{18}N_2O_2$: C 74.49, H 5.92, N 9.14; found C 74.56, H 6.00, N 9.01. NMR data as reported.[14,15]

(*S*)-10-Allyl-1,2,3,11a-tetrahydro-10*H*-benzo[*e*]pyrrolo[1,2-*a*][1,4]diazepine-5,11-dione (6)

Prepared according to general procedure C in 62% yield. $C_{15}H_{16}N_2O_2$: C 70.29, H 6.29, N 10.93; found C 70.41, H 6.35, N 10.77. NMR data as reported.[15,16]

(*S*)-10-(2-Methoxy-ethyl)-1,2,3,11a-tetrahydro-10*H*-benzo[*e*]pyrrolo[1,2-*a*][1,4]diazepine-5,11-dione (7)

Prepared according to general procedure C in 42% yield. $C_{15}H_{18}N_2O_3$: C 65.68, H 6.61, N 10.21; found C 65.79, H 6.70, N 10.09. NMR data as reported.[17]

(*S*)-10-(2,2-Dimethoxy-ethyl)-1,2,3,11a-tetrahydro-10*H*-benzo[*e*]pyrrolo[1,2-*a*][1,4]diazepine-5,11-dione (8)

Prepared according to general procedure C in 45% yield. $[\alpha]_D^{24}$ +54.3 (*c* 1.7, $CHCl_3$). ^1H NMR δ 7.88 (d, J = 8.1 Hz, 1 H), 7.49 (d, J = 3.6 Hz, 2 H), 7.29 (m, 1 H), 4.61 (dd, J_1 = 4.7 Hz, J_2 = 6.4 Hz, 1 H), 4.11 (dd, J_1 = 14.0 Hz, J_2 = 6.5 Hz, 1 H), 4.06 (dd, J_1 = 7.7 Hz, J_2 = 2.0 Hz, 1 H), 3.78 (m, 2 H), 3.55 (m, 1 H), 3.36 (s, 3 H), 3.27 (s, 3 H), 2.69 (m, 1 H), 2.13 (m, 1 H), 2.00 (m, 3 H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 169.4 (s), 165.0 (s), 139.9 (s), 132.0 (d), 130.9 (s), 129.9 (d), 126.0 (d), 123.6 (d), 101.7 (d), 57.2 (d), 55.2 (q), 54.7 (q), 51.6 (t), 46.5 (t), 26.6 (t), 23.9 (t). ESI-MSMS *m*/*z* (%): 327 [M^+ + Na, 100], 295 [M^+ + Na − MeOH, 57]. Elemental analysis calcd (%) for $C_{16}H_{20}N_2O_4$: C 63.14, H 6.62, N 9.20; found C 63.21, H 6.64, N 9.01.

(*S*)-10-(2-Hydroxy-ethyl)-1,2,3,11a-tetrahydro-10*H*-benzo[*e*]pyrrolo[1,2-*a*][1,4]diazepine-5,11-dione (9)

Prepared according to general procedure C in 19% yield. ^1H NMR (400 MHz, $CDCl_3$) δ 7.87 (dd, J_1 = 7.8 Hz, J_2 = 1.6 Hz, 1 H), 7.51–7.46 (m, 1 H), 7.37–7.35 (m, 1 H), 7.31–7.29 (m, 1 H), 4.08–3.94 (m, 2 H), 3.90–3.84 (m, 2 H), 3.82–3.74 (m, 2 H), 3.56–3.49 (m, 1 H), 2.70–2.65 (m, 1 H), 2.04–1.92 (m, 4 H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 170.3 (s), 165.1 (s), 139.9 (s), 132.1 (d), 130.5 (d), 130.1 (d), 126.1 (d), 123.1 (s), 61.2 (t), 57.4 (d), 52.6 (t), 46.6 (t), 40.9 (t), 23.0 (t), 21.5 (t). $[\alpha]_D^{26}$ +2.6 (*c* 0.4, $CHCl_3$). ESI-MSMS *m*/*z* (%): 261 [M^+ + 1, 15], 243 [M^+ − H_2O, 82]. Elemental analysis calcd (%) for $C_{14}H_{16}N_2O_3$: C 64.60, H 6.20, N 10.76; found C 64.71, H 6.24, N 10.67.

(*S*)-3-Benzyl-1-isobutyl-3,4-dihydro-1*H*-benzo[*e*][1,4]diazepine-2,5-dione (10)

Prepared according to general procedure C in 18% yield. $[\alpha]_D^{25}$ −10.2 (*c* 0.5, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ 7.74 (d, J = 7.1 Hz, 1 H), 7.42 (t, J = 7.5 Hz, 1 H), 7.30 (m, 2 H), 6.97 (br, 1 H), 4.80 (m, 1 H), 3.27 (m, 1 H), 3.08 (m, 1 H), 2.99 (m, 2 H),1.65–1.57 (m, 4 H), 1.25–1.21 (m, 1 H), 0.78 (d, J = 6.7 Hz, 3 H), 0.76 (d, J = 6.7 Hz, 3 H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 170.6 (s), 167.1 (s), 136.7 (s), 134.4 (s), 131.8 (d), 129.3 (s), 128.8 (d), 128.7 (d), 128.6 (d), 127.0 (d), 125.8 (s), 118.8 (d), 118.5 (d), 55.3 (d), 54.9 (t), 46.9 (t), 38.7 (t), 28.2 (t), 19.9 (q, 2 C). ESI-MSMS *m*/*z* (%): 285 [M^+ + Na − CH_3, 100]. Elemental analysis calcd (%) $C_{20}H_{22}N_2O_2$: C 74.51, H 6.88, N 8.69; found C 74.59, H 6.95, N 8.61.

(*S*)-1-Butyl-3-isopropyl-3,4-dihydro-1*H*-benzo[*e*][1,4]diazepine-2,5-dione (11)

Prepared according to general procedure C in 28% yield. $[\alpha]_D^{26}$ −65.3 (*c* 0.5, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ 7.40 (dd, J_1 = 7.8 Hz, J_2 = 1.4 Hz, 1 H), 7.29 (t, J = 7.8 Hz, 1 H), 6.67 (d, J = 8.4 Hz, 1 H), 6.56 (t, J = 7.4 Hz, 1 H), 6.00 (br, 1 H), 4.32 (dd, J_1 = 8.3 Hz, J_2 = 7.3 Hz, 1 H), 3.26 (m, 2 H), 2.20 (sextuplet, J = 6.8 Hz, 1 H), 1.64 (m, 2 H), 1.33 (m, 2 H), 1.01 (d, J = 6.8 Hz, 6 H), 0.91 (t, J = 7.4 Hz, 3 H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 171.1 (s), 169.8 (s), 149.9 (s), 133.1 (d), 127.6 (d, 2 C), 114.5 (d), 111.6 (d), 58.7 (d), 42.7 (t), 39.3 (d), 31.6 (t), 31.3 (t), 20.4 (q), 20.0 (q), 19.3 (q). ESI-MSMS *m*/*z* (%): 275 [M^+ + 1, 36], 245 [M^+ + 1 − C_2H_6, 100], 231 [M^+ − iPr, 65]. Elemental analysis calcd (%) for $C_{16}H_{22}N_2O_2$: C 70.04, H 8.08, N 10.21; found C 70.10, H 8.11, N 10.18.

(*S*)-3-Benzyl-1-butyl-3,4-dihydro-1*H*-benzo[*e*][1,4]diazepine-2,5-dione (12)

Prepared according to general procedure C in 24% yield. $[\alpha]_D^{27}$ −7.8 (*c* 0.2, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ_H 7.75 (d, J = 7.2 Hz, 2 H), 7.51 (t, J = 7.4 Hz, 1 H),7.43 (t, J = 7.2 Hz, 2 H), 7.29 (m, 4 H), 6.95 (d, J = 7.8 Hz, 1 H), 5.65 (brs, 1 H), 4.76 (dd, J = 13.9 Hz, J = 8.2 Hz, 1 H), 3.17 (m, 4 H), 1.30 (m, 2 H), 1.19 (m, 2 H), 0.85 (t, J = 7.3 Hz, 3 H). ^{13}C NMR (50 MHz, $CDCl_3$) δ_C 170.4 (s), 166.9 (s), 137.4 (s), 136.7 (s), 133.7 (d), 131.8 (d), 129.3 (d), 129.0 (d), 128.7 (d), 128.6 (d), 126.7 (d), 55.2 (d), 39.3 (t), 31.6 (t), 31.3 (t), 19.9 (t), 13.7 (q). ESI-MSMS *m*/*z* (%): 324 [M^+ + 1, 31], 251 [M^+ − butylamine, 100]. Elemental analysis calcd (%) for $C_{20}H_{22}N_2O_2$: C 74.51, H 6.88, N 8.69; found C 74.64, H 7.00, N 8.63.

1-Allyl-4-benzyl-3,4-dihydro-1*H*-benzo[*e*][1,4]diazepine-2,5-dione (13)

Prepared according to general procedure C in 26% yield. ^1H NMR (400 MHz, $CDCl_3$) δ 7.86 (dd, J_1 = 8.0 Hz, J_2 = 1.6 Hz, 1 H), 7.41 (td, J_1 = 7.8 Hz, J_2 = 1.6 Hz, 1 H), 7.25 (m, 7 H), 5.79 (m, 1 H), 5.29 (d, part A of the AB system, J = 14.8 Hz, 1 H), 5.10 (m, 2 H), 4.44 (dd, part A of the ABX system, J_1 = 16.0 Hz, J_2 = 5.2 Hz, 1 H), 4.31 (dd, part B of the ABX system, J_1 = 16.0 Hz, J_2 = 5.2 Hz, 1 H), 4.28 (d, part B of the AB system, J = 14.8 Hz, 1 H), 3.83 (d, part A of the AB system, J = 14.6 Hz, 1 H), 3.62 (d, part B of the AB system, J = 14.6 Hz, 1 H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 167.7 (s), 162.3 (s), 140.3 (s), 136.2 (s), 132.9 (d), 132.1 (d), 131.0 (d), 129.2 (d), 128.7 (d), 128.5 (d), 128.3 (d), 127.9 (d), 125.9 (d), 123.5 (d), 121.4 (d), 117.5 (t), 51.3 (t), 50.5 (t, 2 C). ESI-MSMS *m*/*z* (%): 306 [M^+, 44]. Elemental analysis calcd (%) for $C_{19}H_{18}N_2O_2$: C 74.49, H 5.92, N 9.14; found C 74.54, H 5.99, N 9.03.

(*S*)-10-Butyl-1,2,3,5,10,11a-hexahydro-benzo[*e*]pyrrolo[1,2-*a*][1,4]diazepin-11-one (14)

Prepared according to general procedure C in 43% yield. $[\alpha]_D^{26}$ +289.7 (*c* 1.3, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ 7.35 (t, J = 7.2 Hz, 2 H), 7.20 (m, 2 H), 4.20 (m, 1 H), 3.82 (d, part A of the AB system, J = 10.9 Hz, 1 H), 3.54 (m, 2 H), 3.40 (d, part B of the AB system, J = 10.9 Hz, 1 H), 3.12 (m, 2 H), 2.41 (m, 1 H), 2.06 (m, 1 H), 1.87 (m, 1 H), 1.72 (m, 1 H), 1.60 (m, 1 H), 1.47 (m, 1 H), 1.30 (m, 2 H), 0.87 (t, J = 7.4 Hz, 3 H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 169.8 (s), 142.5 (s), 133.1 (s), 129.7 (d), 128.9 (d), 126.0 (d), 122.1 (d), 61.1 (d), 54.0 (t), 53.6 (t), 48.1 (t), 32.3 (t), 30.6 (t), 23.9 (t), 20.4 (t), 13.7 (q). ESI-MSMS *m*/*z* (%): 259 [M^+ + 1, 4], 231 [M^+ + 1 − CO, 23], 162 [M^+ + 1 − proline, 100]. Elemental analysis calcd (%) for $C_{16}H_{22}N_2O$: C 74.38, H 8.58, N 10.84; found C 74.51, H 8.62, N 10.77.

(*S*)-10-Allyl-1,2,3,5,10,11a-hexahydro-benzo[*e*]pyrrolo[1,2-*a*][1,4]diazepin-11-one (15)

Prepared according to general procedure C in 18% yield. $[\alpha]_D^{26}$ +271.6 (*c* 0.8, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ 7.35 (m, 2 H), 7.22 (m, 2 H), 5.90 (m, 1 H), 5.15 (m, 2 H), 4.49 (m, 2 H), 3.85 (d, part A of the AB system, J = 11.0 Hz, 1 H), 3.62 (dd, J_1 = 7.8 Hz, J_2 = 2.0 Hz, 1 H), 3.41 (d, part B of the AB system, J = 11.0 Hz, 1 H), 3.13 (dd, J_1 = 8.5 Hz, J_2 = 1.9 Hz, 1 H), 2.50 (dd, J_1 = 17.4 Hz, J_2 = 9.2 Hz, 1 H), 2.44 (m, 1 H), 2.07 (m, 1 H), 1.90 (m, 1 H), 1.76 (m, 1 H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 169.7 (s), 142.6 (s), 133.5 (d), 132.5 (s), 129.7 (d), 128.9 (d), 126.2 (d), 122.0 (d), 117.4 (t), 61.2 (d), 53.9 (t), 53.6 (t), 51.1 (t), 24.0 (t), 23.9 (t). ESI-MSMS *m*/*z* (%): 243 [M^+ + 1, 22], 215 [M^+ + 1 − CO, 56], 146 [M^+ + 1 − proline, 100]. Elemental analysis calcd (%) for $C_{15}H_{18}N_2O$: C 74.35, H 7.49, N 11.56; found C 74.44, H 7.64, N 11.49.

4-Acetyl-1-butyl-1,3,4,5-tetrahydro-benzo[*e*][1,4]diazepin-2-one (16)

Prepared according to general procedure C in 60% yield. ^1H NMR (400 MHz, $CDCl_3$, mixture of rotamers) δ 7.46–7.19 (m, 4 H), 4.58–4.42 (m, 2 H), 4.06–3.84 (m, 4 H), 2.17 (s, 3 × 0.47 H, minor), 2.11 (s, 3 × 0.53 H, major), 1.49 (m, 2 H), 1.26 (m, 2 H), 0.85 (m, 3 H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 169.4 (s), 165.9 (s), 141.9 (s), 130.9 (s), 130.0 (d), 129.6 (d), 126.9 (d), 122.1 (d), 50.9 (t), 47.1 (t), 46.3 (t), 29.9 (t), 21.7 (t), 20.1 (q), 13.6 (q). ESI-MSMS *m*/*z* (%): 261 [M^+ + 1, 12], 219 [M^+ + 1 − CH_3CO, 20], 162 [M^+ + 1 − acetylglycine, 100]. Elemental analysis calcd (%) for $C_{15}H_{20}N_2O_2$: C 69.20, H 7.74, N 10.76; found C 69.31, H 7.80, N 10.65.

4-Acetyl-1-allyl-1,3,4,5-tetrahydro-benzo[*e*][1,4]diazepin-2-one (17)

Prepared according to general procedure C in 53% yield. ^1H NMR (400 MHz, $CDCl_3$, mixture of rotamers) δ 7.39–7.18 (m, 4 H), 5.81 (m, 1 H), 5.14 (m, 2 H), 4.54 (s, 2 H), 4.43 (m, 2 H), 4.07 (s, 2 × 0.25 H, minor), 3.93 (s, 2 × 0.75 H, major), 2.19 (s, 3 × 0.25 H, minor), 2.12 (s, 3 × 0.75 H, major). ^{13}C NMR (50 MHz, $CDCl_3$) δ 169.4 (s), 165.9 (s), 142.2 (s), 132.4 (s), 130.9 (d), 129.9 (d), 129.6 (d), 127.0 (d), 122.0 (d), 118.1 (t), 50.8 (t), 50.4 (t), 46.3 (t), 21.7 (q). ESI-MSMS *m*/*z* (%): 245 [M^+ + 1, 100], 203 [M^+ + 1 − CH_3CO, 58], 146 [M^+ + 1 − acetylglycine, 100]. Elemental analysis calcd (%) for $C_{14}H_{16}N_2O_2$: C 68.83, H 6.60, N 11.47; found C 68.91, H 6.71, N 11.36.

Acknowledgements

Fondazione Roma, CINMPIS, and MIUR are acknowledged for financial support.

Notes and references

1 (*a*) I. Ugi, S. Lohberger and R. Karl, in *Comprehensive Organic Synthesis*, ed. B. M. Trost and I. Fleming, Pergamon Press, Oxford, 1991, vol. 2, pp. 1083–1109; (*b*) R. W. Armstrong, A. P. Combs, P. A. Tempest, S. D. Brown and T. A. Keating, *Acc. Chem. Res.*, 1996, **29**, 123–131; (*c*) A. Dömling and I. Ugi, *Angew. Chem.*, 2000, **112**, 3300–3344; A. Dömling and I. Ugi, *Angew. Chem., Int. Ed.*, 2000, **39**, 3168–3210 (*d*) J. Zhu and H. Bienaymé, *Multicomponent Reactions*, Wiley-VCH, New York, 2005; (*e*) D. J. Ramón and M. Yus, *Angew. Chem., Int. Ed.*, 2005, **44**, 1602–1634.

2 (*a*) L. S. Hegedus, *Transition Metals in the Synthesis of Complex Organic Molecules*, University Science Books, Sausalito, 1999; (*b*) J. Tsuji, *Transition Metal Reagents and Catalysts*, Wiley & Sons, Sussex, 2000; (*c*) L. F. Tietze, G. Brasche and K. Gericke, *Domino Reactions in Organic Synthesis*, Wiley-VCH, Weinheim, 2006.

3 (*a*) J. A. Porco Jr., F. J. Schoenen, T. J. Stout, J. Clardy and S. L. Schreiber, *J. Am. Chem. Soc.*, 1990, **112**, 7410–7411; (*b*) E. Negishi, C. Coperet, S. Ma, S. Y. Liou and F. Liu, *Chem. Rev.*, 1996, **96**, 365–393; (*c*) G. A. Molander and C. R. Harris, *J. Am. Chem. Soc.*, 1996, **118**, 4059–4071; (*d*) L. F. Tietze, *Chem. Rev.*, 1996, **96**, 115; (*e*) S. E. Denmark and A. Thorarensen, *Chem. Rev.*, 1996, **96**, 137–165; (*f*) R. Grigg and V. Sridharan, *J. Organomet. Chem.*, 1999, **576**, 65–87; (*g*) C. Chen, M. E. Layton, S. M. Sheehan and M. D. Shair, *J. Am. Chem. Soc.*, 2000, **122**, 7424–7425; (*h*) K. Subburaj and J. Montgomery, *J. Am. Chem. Soc.*, 2003, **125**, 11210–11211; (*i*) J. Montgomery, *Angew. Chem., Int. Ed.*, 2004, **43**, 3890–3908; (*j*) K. Agapiou, D. F. Cauble and M. J. Krische, *J. Am. Chem. Soc.*, 2004, **126**, 4528–4529; (*k*) H.-C. Guo and J.-A. Ma, *Angew. Chem., Int. Ed.*, 2006, **45**, 354–366; (*l*) T. Miura and M. Murakami, *Chem. Commun.*, 2007, 217–224; (*m*) F. Shi, X. Li, Y. Xia, L. Zhang and Z.-X. Yu, *J. Am. Chem. Soc.*, 2007, **129**, 15503–15512; (*n*) S. W. Youn, J.-Y. Song and D. I. Jung, *J. Org. Chem.*, 2008, **73**, 5658–5661; (*o*) K.-G. Ji, X.-Z. Shu, J. Chen, S.-C. Zhao, Z.-J. Zheng, L. Lu, X.-Y. Liu and Y.-M. Liang, *Org. Lett.*, 2008, **10**, 3919–3922.

4 (*a*) A. Ajamian and J. L. Gleason, *Angew. Chem., Int. Ed.*, 2004, **43**, 3754–3760; (*b*) J. M. Lee, Y. Na, H. Han and S. Chang, *Chem. Soc. Rev.*, 2004, **33**, 302–312; (*c*) J. C. Wasilke, S. J. Obrey, R. T. Baker and G. C. Bazan, *Chem. Rev.*, 2005, **105**, 1001–1020; (*d*) D. Enders, C. Grondal and M. R. M. Huttl, *Angew. Chem., Int. Ed.*, 2007, **46**, 1570–1581; (*e*) C. J. Chapman and C. G. Frost, *Synthesis*, 2007, 1–21; (*f*) A. M. Walji and D. W. C. MacMillan, *Synlett*, 2007, 1477–1489; (*g*) L.-Q. Lu, Y.-J. Cao, X.-P. Liu, J. An, C.-J. Yao, Z.-H. Ming and W.-J. Xiao, *J. Am. Chem. Soc.*, 2008, **130**, 6946–6948; (*h*) T. A. Cernak and T. H. Lambert, *J. Am. Chem. Soc.*, 2009, **131**, 3124–3125 and references cited therein (*i*) B. D. Kelly, J. M. Allen, R. E. Tundel and T. H. Lambert, *Org. Lett.*, 2009, **11**, 1381–1383.

5 R. Grigg, V. Sridharan and J. Zhang, *Tetrahedron Lett.*, 1999, **40**, 8277–8280.

6 C. G. Joseph, K. R. Wilson, M. S. Wood, N. B. Sorenson, D. V. Phan, Z. Xiang, R. M. Witek and C. Haskell-Luevano, *J. Med. Chem.*, 2008, **51**, 1423–1431.

7 (*a*) T. A. Keating and R. W. A. Armstrong, *J. Org. Chem.*, 1996, **61**, 8935–8939; (*b*) C. Hulme, J. Peng, S. Y. Tang, C. J. Burns, I. Morize and R. Labaudiniere, *J. Org. Chem.*, 1998, **63**, 8021–8023;

(*16*) D. A. Horton, G. T. Bourne and M. L. Smythe, *Chem. Rev.*, 2003, **103**, 893–930.
8 (*a*) H. Smith, P. Wegfahrt and H. Rapoport, *J. Am. Chem. Soc.*, 1968, **90**, 1668–1669; (*b*) P. K. Martin, H. Rapoport, H. W. Smith and J. L. Wong, *J. Org. Chem.*, 1969, **34**, 1359–1363; (*c*) J. D. White, W. E. Haefliger and M. J. Dimsdale, *Tetrahedron*, 1970, **26**, 233–242.
9 L. Loudni, J. Roche, V. Potiron, J. Clarhaut, C. Bachmann, J.-P. Gesson and I. Tranoy-Opalinski, *Bioorg. Med. Chem. Lett.*, 2007, **17**, 4819–4823.
10 (*a*) N. J. Patmore, C. Hague, J. H. Cotgreave, M. F. Mahon, C. G. Frost and A. S. Weller, *Chem.–Eur. J.*, 2002, **8**, 2088; (*b*) J. M. Longmire, B. Wang and X. Zhang, *J. Am. Chem. Soc.*, 2002, **124**, 13400–13401; (*c*) C. Loncaric, K. Manabe and S. Kobayashi, *Adv. Synth. Catal.*, 2003, **345**, 475–477; (*d*) P. Lidstrom, J. Tierney, B. Wathey and J. Westman, *Tetrahedron*, 2001, **57**, 9225–9283; (*e*) B. M. Trost, *Angew. Chem., Int. Ed. Engl.*, 1995, **34**, 259–281 and references cited therein (*f*) C. O. Kappe, *Angew. Chem., Int. Ed.*, 2004, **43**, 6250–6284.
11 C. Han, J. P. Lee, E. Lobkovsky and J. A. Porco Jr., *J. Am. Chem. Soc.*, 2005, **127**, 10039–10044.
12 (*a*) G. Cuny, M. Bois-Choussy and J. Zhu, *J. Am. Chem. Soc.*, 2004, **126**, 14475–14484; (*b*) R. G. Browning, H. Mahmud, V. Badarinarayana and C. J. Lovely, *Tetrahedron Lett.*, 2001, **42**, 7155–7157.
13 J. Srogl and S. Voltrova, *Org. Lett.*, 2009, **11**, 843–845.
14 A. Kamal, K. L. Reddy, V. Devaiah, N. Shankaraiah, G. S. Reddy and S. Raghavan, *J. Comb. Chem.*, 2007, **9**, 29–42.
15 X. Lu, L. Shi, H. Zhang, Y. Jiang and D. Ma, *Tetrahedron*, 2010, **66**, 5714–5718.
16 H. Benzeid, E. M. Essassi, N. Saffon, B. Garrigues and S. W. Ng, *Acta Crystallogr., Sect. E: Struct. Rep. Online*, 2009, **65**, o2322.
17 Commercially available, CAS n. 1048957-24-9.

