A versatile new synthesis of Meyers' bicyclic lactams: singlet oxygen reacts with furan substrates to initiate a remarkable cascade reaction sequence**

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Dedicated to Professor K. C. Nicolaou

A new and powerful method for the synthesis Meyers' bicyclic lactams beginning from furans is reported herein that uses a remarkable one-pot singlet oxygen-initiated cascade reaction sequence to deliver the corresponding bicyclic lactams in high yield.

Ever since they were pioneered Meyers' homochiral bicyclic lactams^[1, 2] (**B**, Scheme 1) have been exceedingly popular and versatile scaffolds for the enantioselective construction of new stereogenic centres, including the most challenging type - quaternary carbon centres. They have been utilised in myriad different ways to target a wide variety of natural products,^[2, 3] non-natural molecules possessing interesting biological activity,^[2, 4] and, also in a diverse array of other synthetic endeavours.^[2, 5] The most general method for their synthesis, introduced in the seminal work of Meyers,^[1, 2] wherein a γ -ketoacid is condensed with an aminoalcohol under dehydrating conditions in refluxing toluene, is still, by far, the most commonly employed means of accessing the bicyclic scaffold **B**. Modifications have been made with the aim of introducing milder variants^[6] to the Meyers' lactamisation; these

range from harnessing microwave energy to accomplish the desired reaction^[6a] or employing Lewis acid catalysis,^[6b] to activating the acid.^[6c] A second commonly employed,^[7] but stepwise, route to these bicyclic lactams, also originally emanating from the Meyers' group,^[2a] relies heavily on *N*-acyliminium chemistry extensively elucidated by Speckamp.^[8] In this case, a succinimide intermediate is substituted at the C5 position (usually by addition of a Grignard reagent) and then encouraged to undergo intramolecular cyclisation under acidic conditions. Several domino reactions affording specific bicyclic lactams have also been reported recently,^[9] as well as, other stepwise approaches to the scaffold.^[10] This unceasing interest in finding new syntheses for the Meyer's bicyclic lactams in itself provides testament to the usefulness of the scaffold and the diversity of potential applications there are for it. Herein, we introduce a new and mild method for the synthesis of a wide variety of Meyers' bicyclic lactams. This entirely novel approach, which uses a singlet oxygen-mediated cascade reaction sequence, is made particularly powerful because the one-pot reaction begins from furan substrates which can be multiply-substituted (**A**, Scheme 1) at will and with ease, thus allowing access to highly substituted scaffolds, frequently with excellent stereoselectivity, as products from the initial reaction without extra manipulations. In this way, the new methodology also exhibits a very high degree of step-^[11] and atom-economy^[12] and utilises the selective green reagent, singlet oxygen, to achieve these very rapid increases in molecular complexity with precision and minimum waste, thereby attaining many of the recently established criteria for an ideal synthesis.^[13]

The idea for this new methodology was born from our experience in the field of furan photooxygenations^[14] which has taught us to regard the furan motif as a readily accessible and easy to manipulate, 1,4-dienone equivalent (or precursor).^[15] Once this fact was acknowledged, it seemed potentially very interesting to ask whether the aforementioned intermediate (**C**, Scheme 2) could be intercepted by an amino-alcohol, and, from thence, rearrange and cyclise (under acid catalysis) to afford the Meyer's bicyclic lactams, without resorting to the dehydrating conditions, or high temperatures, which have traditionally been employed. The highly ambitious concept is summarised, in mechanistic terms, in Scheme 2 (note: only selected steps are shown here). Thus, when a furan is oxidised, upon exposure to singlet oxygen in MeOH, intermediates of type **C** are known to form easily after the *in situ* reduction (with Me₂S) of a hydroperoxy functionality that remains after the solvent induced collapse of the initially formed endoperoxide adduct has occurred.^[14, 15] We hypothesised that introduction of an 1,2-aminoalcohol into the flask at this stage should regioselectively afford the amina **D** (via the more stable, more highly substituted,

Scheme 1. Generalised representation of the transformation achieved with this new methodology.

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[**] The research leading to these results has received funding from the European Research Council under the European Union's Seventh Framework Programme (FP7/2007-2013)/ERC grant agreement no. 277588. We also thank Prof. Robert Stockman and Mr. George Procopiou for their help in taking HRMS.

Supporting information for this article is available on the WWW under <http://www.angewandte.org> or from the author.

Scheme 2. Mechanistic summary for the one-pot cascade reaction sequence that transforms furans A into bicyclic lactams B.

oxonium cation) that would open to imino enal **E**, as shown in Scheme 2, and then close again to afford 2-pyrrolidinone **G**, via 2H-pyrrol-2-ol **F**. It was hoped that addition of an acid at this point, would affect the desired hydroxy-acyl imminium cyclisation to give the corresponding bicyclic lactam (**H** → **B**) as the final product of a highly ambitious one-pot cascade reaction sequence.

Gratifyingly, and, despite the extraordinary complexity of the designed reaction cascade, we were able to successfully transfer the concept from a hypothetical “on paper” idea to a working laboratory protocol, as the results detailed in Table 1 clearly show. Thus, in the simplest case where 2-methylfuran was oxidised with singlet oxygen,^[16] followed by in situ reduction (Me₂S) of the resultant peroxide, and then by the addition of 2-aminoethanol, and later catalytic TFA (30 mol%), to the same flask, the desired corresponding Meyers’ bicyclic lactam was obtained (Entry 1, Table 1).

With this proof of principle in hand, we set out to systematically investigate the effect of varying both the furan and 1,2-aminoalcohol substitution patterns, and, concomitantly, delineate the precise stereochemical outcomes of the cascade reaction sequence (Table 1). Commercially available furan starting materials were used throughout except in the cases of 2-benzylfuran (Entries 2, 4, 6) and the furan shown in Entry 7, where the requisite substrates were synthesised using known procedures.^[17] In general, the yields are remarkably high when the large increase in molecular complexity that has been achieved in this one-pot procedure is taken into consideration, and given the intricate nature of the cascade reaction sequence that has been successfully implemented. Regarding the stereochemical outcomes (confirmed by NOE studies),^[18] it was found that having a defined stereogenic centre adjacent to the amino

Table 1. One-pot synthesis of various bicyclic lactams starting from furan substrates.

Entry	Substrate	Trapping agent	Product	Yield (%)
1		HOCH ₂ CH ₂ NH ₂		55
2		HOCH ₂ CH ₂ NH ₂		30
3		HOCH(Ph)CH ₂ CO ₂ Et		68
4		HOCH(Ph)CH ₂ CO ₂ Et		59
5		HOCH(Ph)CH ₂ NH ₂		65
6		HOCH(Ph)CH ₂ NH ₂		58
7 ^[a]		HOCH(Ph)CH ₂ NH ₂		75
8 ^[a]		HOCH(Ph)CH ₂ NH ₂		60
9		HOCH(Ph)CH ₂ NH ₂		80
10		HOCH(Me)CH ₂ NH ₂		65
11 ^[b]		HOCH(Me)CH ₂ NH ₂		68

[a] separable diastereoisomers. [b] inseparable diastereoisomers.

group (R⁴ attachment position) on the 1,2-aminoalcohol induces highly stereoselective formation of the product’s ring junction (position R¹ in the product, Scheme 1), as can be seen from Entries 3 – 10 (Table 1). In contrast, having a defined stereogenic centre adjacent to the alcohol (R⁵ attachment position) on the 1,2-aminoalcohol leads to no significant stereoselectivity being achieved for the overall reaction, with both ring junction isomers being formed (dr = 55:45, R¹/R⁵ *anti*: R¹/R⁵ *syn*, Entry 11). Similarly, substituents at the R² and R³ positions of the furan substrate are incorporated in

Scheme 3. Acid catalysed dimerisation of bicyclic lactams.

the final bicyclic lactam products with no significant stereoselectivity (dr = 55:45, R^1/R^3 *anti*: R^1/R^3 *syn*, Entry 7; dr = 55:45, R^1/R^2 *syn*: R^1/R^2 *anti*, Entry 8), except in the case of menthofuran (Entry 9) which is unique in its fused bicyclic nature.

The following observations are also worthy of note. It has been reported in the literature^[19] that the product of the reaction shown in Entry 1, readily opens and reacts intermolecularly to form the centrosymmetric dimer under aqueous acidic conditions (Scheme 3). We found this to be true (indeed, it also applied to other more heavily substituted products, although to a lesser extent), but we also found that this undesired dimerisation could be avoided by moderating the amount of TFA employed in the cyclisation step, and, in the most vulnerable cases by neutralising this TFA with NEt_3 prior to concentration of the sample. In general, TFA 20 mol% was initially added and further additions (up to a maximum of 60 mol%) were only made when deemed necessary according to tlc analysis of the reaction mixture. The TFA cyclisation step took between 1 to 9 hours to reach completion. This tendency to dimerise may be the reason that, somewhat counter intuitively, it would appear that the bulkier the R^1 ring junction substitution is the higher the yields obtained are (Entries 7 and 9). Likewise, it has been reported in other methods^[10a] that mechanistically converge with ours by going through intermediates of type **G** (Scheme 2) that these intermediates were fleeting and could not be isolated and characterised; however, though they cannot be described as stable, we have been able to isolate and take ^1H and ^{13}C NMR spectra of some representative intermediates (see Supporting Info.).

In the case of Entry 8, the two stereoisomeric final products could be separated by column chromatography, but subsequently proved to be highly susceptible to racemisation (even on brief standing in CDCl_3 solution) via opening up of the bicyclic lactam to the 2-pyrrolidinone (analogous to intermediate **G**, Scheme 2) and subsequent reclosure. Finally, and again related to intermediate **G**; when 2-benzylfuran was photooxidised and reacted with 2-aminoethanol, the yield was a mere 30% (Entry 2, Table 1) and the product recovered was in equilibrium with an open form;^[20] however, when 2-aminoethanol is replaced with either *S*-serine ethyl ester (Entry 4, Table 1), or *R*-phenylglycinol (Entry 6, Table 1), the product yield improves dramatically to 59 and 58%, respectively, presumably due to the Thorpe-Ingold angle compression effect favouring ring closure.

In summary, we have introduced a new and versatile method for the synthesis of Meyers' bicyclic lactams using a green, step- and atom-economic singlet-oxygen-initiated cascade reaction sequence. The mild method's broad synthetic potential derives from the fact that it begins from simple furan substrates which can be readily synthesised and/or substituted to give many possible variations, as desired; a feature that contrasts with the limitations (both in terms of their synthesis and subsequent handling and purification) imposed by the γ -ketoacids precursors used in the traditional Meyers' synthesis.^[1,2] Furthermore, the cascade initiator, singlet oxygen is an extremely selective reagent conferring on its reactions very broad functional group tolerance and a complete lack of need for protecting groups.^[14] For all these reasons it is believed

that this method will prove to be a powerful addition to the synthetic chemist's armoury.

Received: ((will be filled in by the editorial staff))

Published online on ((will be filled in by the editorial staff))

Keywords: Meyers' bicyclic lactams · singlet oxygen · cascade reaction · furan oxidation · 2-pyrrolidinones

- [1] For first report, see: A. I. Meyers, M. Harre, R. Garland, *J. Am. Chem. Soc.* **1984**, *106*, 1146-1148.
- [2] For reviews of the field, see: a) D. Romo, A. I. Meyers, *Tetrahedron* **1991**, *47*, 9503-9569; b) M. D. Groaning, A. I. Meyers, *Tetrahedron* **2000**, *56*, 9843-9873.
- [3] For recent representative examples, see: a) M. E. Jung, J. J. Chang, *Org. Lett.* **2010**, *12*, 2962-2965; b) M. Saito, S. Kuwahara, *Biosci. Biotechnol. Biochem.* **2005**, *69*, 374-381; c) D. L. J. Clive, J. Wang, *J. Org. Chem.* **2004**, *69*, 2773-2784; d) R. C. Hughes, C. A. Dvorak, A. I. Meyers, *J. Org. Chem.* **2001**, *66*, 5545-5551; e) M. W. Carson, G. Kim, M. F. Hentemann, D. Trauner, S. J. Danishefsky, *Angew. Chem.* **2001**, *113*, 4582-4584; *Angew. Chem. Int. Ed.* **2001**, *40*, 4450-4452; f) D. Trauner, J. B. Schwarz, S. J. Danishefsky, *Angew. Chem.* **1999**, *111*, 3756-3758; *Angew. Chem. Int. Ed.* **1999**, *38*, 3542-3544.
- [4] For some representative examples, see: a) J. D. Hansen, B. J. Newhouse, S. Allen, A. Anderson, T. Eary, J. Schiro, J. Gaudino, E. Laird, A. C. Allen, D. Chantry, C. Eberhardt, L. E. Burgess, *Tetrahedron Lett.* **2006**, *47*, 69-72; b) D. P. Becker, D. L. Flynn, C. I. Villamil, *Bioorg. Med. Chem. Lett.* **2004**, *14*, 3073-3075; c) S. Demin, D. Van Haver, M. Vandewalle, P. J. De Clercq, R. Bouillon, A. Verstuyf, *Bioorg. Med. Chem. Lett.* **2004**, *14*, 3885-3888; d) T. D. Aicher, B. Balkan, P. A. Bell, L. J. Brand, S. H. Cheon, R. O. Deems, J. B. Fell, W. S. Fillers, J. D. Fraser, J. Gao, D. C. Knorr, G. G. Kahle, C. L. Leone, J. Nadelson, R. Simpson, H. C. Smith, *J. Med. Chem.* **1998**, *41*, 4556-4566; e) M. D. Ennis, R. L. Hoffman, N. B. Ghazal, D. W. Old, P. A. Mooney, *J. Org. Chem.* **1996**, *61*, 5813-5817; f) A. I. Meyers, L. Snyder, *J. Org. Chem.* **1993**, *58*, 36-42.
- [5] For selected representative examples, see: a) S. Sen, V. R. Potti, R. Surakanti, Y. L. N. Murthy, R. Pallepogu, *Org. Biomol. Chem.* **2011**, *9*, 358-360; b) J. E. Resek, *J. Org. Chem.* **2008**, *73*, 9792-9794; c) D. Enders, O. Niemeier, T. Balensiefer, *Angew. Chem.* **2006**, *118*, 1491-1495; *Angew. Chem. Int. Ed.* **2006**, *45*, 1463-1467; d) H. C. Shen, F.-X. Ding, S. L. Colletti, *Org. Lett.* **2006**, *8*, 1447-1450; e) T. E. Nielsen, S. Le Quement, M. Meldal, *Org. Lett.* **2005**, *7*, 3601-3604; f) M. D. Groaning, G. P. Brengel, A. I. Meyers, *Tetrahedron* **2001**, *57*, 2635-2642; g) J. A. Nieman, M. D. Ennis, *Org. Lett.* **2000**, *2*, 1395-1397.
- [6] a) M. Jida, R. Deprez-Poulain, S. Malaquin, P. Roussel, F. Agbossou-Niedercorn, B. Deprez, G. Laconde, *Green Chem.* **2010**, *12*, 961-964; b) A. N. Cayley, R. J. Cox, C. Ménard-Moyon, J. P. Schmidt, R. J. K. Taylor, *Tetrahedron Lett.* **2007**, *48*, 6556-6560; c) M. Penhoat, S. Leleu, G. Dupas, C. Papamicaël, F. Marsais, V. Levacher, *Tetrahedron Lett.* **2005**, *46*, 8385-8389; d) R. Deprez-Poulain, N. Willand, C. Boutillon, G. Nowogrocki, N. Azaroual, B. Deprez, *Tetrahedron Lett.* **2004**, *45*, 5287-5290.
- [7] For a recent example, see: A. A. Bahajaj, M. H. Moore, J. M. Vernon, *Tetrahedron* **2004**, *60*, 1235-1246.
- [8] W. N. Speckamp, H. Hiemstra, *Tetrahedron* **1985**, *41*, 4367-4416.
- [9] a) S. Comesse, A. Martel, A. Daich, *Org. Lett.* **2011**, *13*, 4004-4007; b) R. Medimagh, S. Marque, D. Prim, J. Marrot, S. Chatti, *Org. Lett.* **2009**, *11*, 1817-1820.
- [10] a) E. Ascić, J. F. Jensen, T. E. Nielsen, *Angew. Chem.* **2011**, *123*, 5294-5297; *Angew. Chem. Int. Ed.* **2011**, *50*, 5188-5191; b) I. Kanizsai, Z. Szakonyi, R. Sillanpää, M. D'hooghe, N. De Kimpe, F. Fülöp, *Tetrahedron Asymmetry* **2006**, *17*, 2857-2863.
- [11] P. A. Wender, B. L. Miller *Nature* **2009**, *460*, 197-201.
- [12] B. M. Trost, *Science* **1991**, *254*, 1471-1477.
- [13] a) I. S. Young, P. S. Baran, *Nature Chem.* **2009**, *1*, 193-205; b) T. Gaich, P. S. Baran, *J. Org. Chem.* **2010**, *75*, 4657-4673; c) T. Newhouse, P. S. Baran, R. W. Hoffmann, *Chem. Soc. Rev.* **2009**, *38*,

- 3010-3021; (d) For the first introduction to the "ideal synthesis" concept, see: Hendrickson, J. B. *J. Am. Chem. Soc.* **1975**, *97*, 5784.
- [14] For selected examples see: a) D. Noutsias, I. Alexopoulou, T. Montagnon, G. Vassilikogiannakis, *Green Chem.* **2012**, *14*, 601-604; b) A. Kouridaki, T. Montagnon, M. Tofi, G. Vassilikogiannakis, *Org. Lett.* **2012**, *14*, 2374-2377; c) G. Vassilikogiannakis, I. Alexopoulou, M. Tofi, T. Montagnon, *Chem. Commun.* **2011**, *47*, 259-261; d) T. Montagnon, D. Noutsias, I. Alexopoulou, M. Tofi, G. Vassilikogiannakis, *Org. Biomol. Chem.* **2011**, *9*, 2031-2039. e) M. Tofi, K. Koltsida, G. Vassilikogiannakis, *Org. Lett.* **2009**, *11*, 313-316; f) T. Montagnon, M. Tofi, G. Vassilikogiannakis, *Acc. Chem. Res.* **2008**, *41*, 1001-1011; g) T. Georgiou, M. Tofi, T. Montagnon, G. Vassilikogiannakis, *Org. Lett.* **2006**, *8*, 1945-1948; h) G. Vassilikogiannakis, M. Stratakis, *Angew. Chem.* **2003**, *115*, 5623-5626; *Angew. Chem. Int. Ed.* **2003**, *42*, 5465-5468;
- [15] For pioneering works on furan photooxygenations, see: a) C. S. Foote, M. T. Wuesthoff, S. Wexler, I. G. Burstain, R. Denny, G. O. Schenck, K. H. Schulte-Elte, *Tetrahedron* **1967**, *23*, 2583-2599; b) K. Gollnick, A. Griesbeck, *Tetrahedron* **1985**, *41*, 2057-2068; c) B. L. Feringa, *Recl. Trav. Chim. Pays-Bas* **1987**, *106*, 469-488.
- [16] The furan substrate in MeOH at 0 °C with rose bengal (10^{-4} M), added as photosensitiser, was exposed to irradiation from a xenon Variac Eimac Cermex 300W visible spectrum light for a period of 8 mins whilst oxygen was gently bubbled through the reaction mixture.
- [17] For synthesis of benzylfuran, see: Supporting Information for procedure; For synthesis of the furan substrate shown in Entry 7 (Table 1), see: A. Aponick, C.-Y. Li, J. Malinge, E. F. Marques, *Org. Lett.* **2009**, *11*, 4624-4627.
- [18] Full details of NOE studies are included in the Supporting Information.
- [19] C. Wedler, H. Schick, D. Scharfenberg-Pfeiffer, G. Reck, *Liebigs Ann. Chem.* **1992**, 29-32.
- [20] The open form corresponds to intermediate **G** except that the preferred 2-pyrrolidinone, in this instance, is that which places the double bond *exo* from the five-membered ring and in conjugation with the Ph group, namely, 5-benzylidene-1-(2-hydroxyethyl)pyrrolidin-2-one. The exact structure is given in the supporting information.

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Dimitris Kalaitzakis, Tamsyn Montagnon, Ioanna Alexopoulou and Georgios Vassilikogiannakis*

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