

ChemComm

Chemical Communications

rsc.li/chemcomm



ISSN 1359-7345

COMMUNICATION

Wei Sun, David C. Harrowven *et al.*

New approaches to ondansetron and alosetron inspire a versatile, flow photochemical method for indole synthesis



Cite this: *Chem. Commun.*, 2022, **58**, 383

Received 8th October 2021,
Accepted 26th November 2021

DOI: 10.1039/d1cc05700f

rsc.li/chemcomm

An oxidative photocyclisation of *N*-arylenaminones to indoles is described, that mirrors the Fischer indole synthesis but uses anilines in place of arylhydrazines. Its value is exemplified with new approaches to the WHO-listed APIs ondansetron and alosetron.

Tetrahydrocarbazolones and related heterocyclic ring systems are privileged structures in medicinal chemistry with a number of active pharmaceutical ingredients bearing such motifs.¹ For example, alosetron **1** is a 5-HT₃ antagonist used in the management of chronic irritable bowel syndrome (IBS),² while ondansetron **2** is a WHO listed essential medicine used to treat nausea in cancer and COVID-19 patients.^{3,4} The pandemic has given impetus to calls for the on-shoring of the manufacture of such essential medicines and in that context, we sought to develop a synthesis of the tetrahydrocarbazolone core **4** of ondansetron **2** that was cheaper and more benign than the published strategies (Fig. 1).^{5–20} The approach we envisioned (Scheme 1) used the known condensation of bulk chemicals *N*-methylaniline and 1,3-cyclohexadione **12**, followed by photocyclization of the resulting adduct **5a** under oxidative conditions.²¹ Herein we describe our realisation of that goal leading to the development of a general method for the synthesis of indoles that mirrors the Fischer indole synthesis but uses anilines in place of arylhydrazines.⁶

An attractive feature of the strategy was its potential to effect the synthesis without recourse to stoichiometric reagents, metal catalysts or harsh reaction conditions. It also offered high atom-economy with a reduced and more benign waste-stream compared to the current industrial synthesis involving a palladium catalysed cyclisation of aryl bromide **5d** (R = Me).¹³

^a Chemistry, University of Southampton, Highfield, Southampton, SO17 1BJ, UK.
E-mail: dch2@soton.ac.uk

^b School of Chemistry, University of Bristol, Cantock's Close, Bristol, BS8 1TS, UK

† In memory of Dr Lucette Duhamel.

‡ Electronic supplementary information (ESI) available: Experimental accounts, spectral and analytical data, and NMR spectra. See DOI: [10.1039/d1cc05700f](https://doi.org/10.1039/d1cc05700f)

New approaches to ondansetron and alosetron inspire a versatile, flow photochemical method for indole synthesis†‡

Wei Sun,*^a William A. T. Raimbach,^a Luke D. Elliott,^b Kevin I. Booker-Milburn^b and David C. Harrowven^a

The conversion of adduct **5a** to ondansetron precursor **4** has been described previously using catalytic palladium acetate in acetic acid at 100 °C under an oxygen atmosphere.^{9,20} Its cyclization to dihydroindole **13** has also been reported to proceed in benzene using a 400 W medium pressure mercury lamp, with subsequent oxidation to **4** accomplished using DDQ or Mn(OAc)₃.¹⁰

Thus, our initial focus was to establish conditions to achieve the direct conversion of **5a** to **4**, photochemically under flow. A viable method was established when a 0.02 M solution of **5a** in acetonitrile containing 5 mol% iodine underwent conversion to **4** in 85% yield following irradiation with a 36 W Philips UVC lamp for 1 h.^{22–24} Analogous reactions with UVA and UVB lamps had proven ineffective, largely returning the starting material with trace by-products. Similarly, the reaction was slowed when

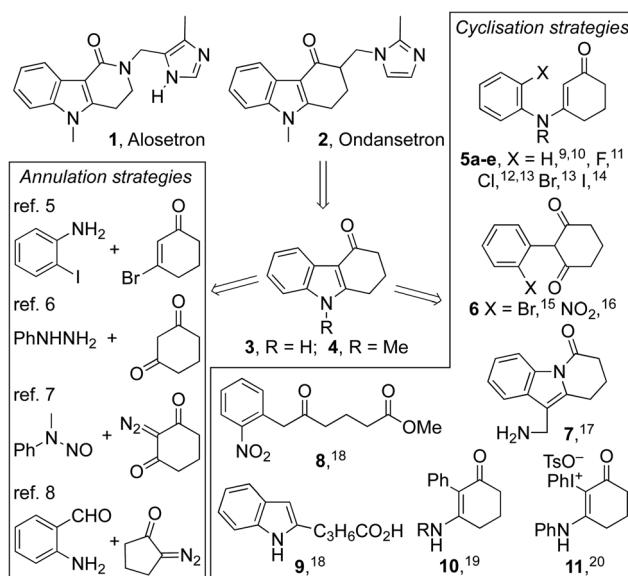
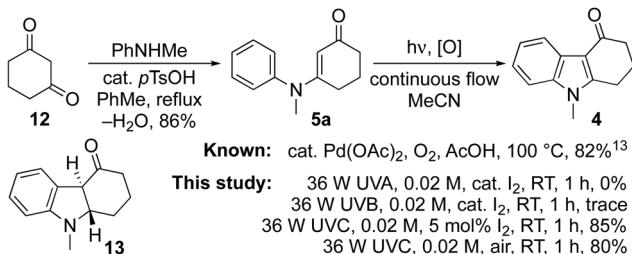


Fig. 1 Approaches to the tetrahydrocarbazolone core of ondansetron.





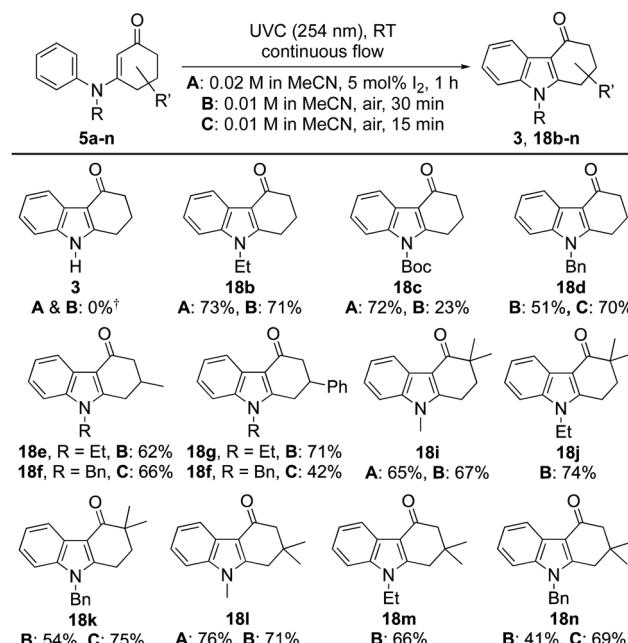
Scheme 1 Approaches to the tetrahydrocarbazolone core of ondansetron.

the concentration of iodine was increased, suggesting that it competed for photons with other components in the reaction mixture.²⁵ Pleasingly, air was also effective as an oxidant when introduced as bubbles into the flow stream. Though crude product mixtures were not as clean as those attained with catalytic iodine, the isolated yield of **4** was comparable.

Buoyed by this success, we next sought to apply the method in the preparation of alosetron precursor **14** (Scheme 2).^{2,26} We were disappointed to find that precursor **16** failed to give the anticipated product **14** on irradiation with UVC light under the aforementioned oxidative cyclization sequences, delivering instead an intractable product mixture. The failure was traced to a photochemical scission of cyclic amide **14**,²³ as evidenced by the formation of indole **15** as the primary product when methanolic solutions of **14** or **16** were irradiated with UVC. Pleasingly, the analogous Boc protected precursor **17** gave the reaction smoothly to deliver alosetron precursor **14** in 63% yield after deprotection with TFA.

Development of the procedure into a general method for the conversion of *N*-arylenaminones to indoles became our next goal. While similar 6*π*-photocyclization reactions have been described for the synthesis of indolines, these are characterised by poor productivity, low energy efficiency and limited substrate scope.^{10,27} Recent advances in photocatalysis have allowed cyclisations to be performed using blue light but the need for long irradiation times and expensive iridium catalysts limits its appeal.²⁸ The scope of the reaction has been shown to be good for carbamate protected *N*-arylenaminones under UVA irradiation,²⁹ but for API precursors **4** and **14** this would require subsequent deprotection, indoline oxidation and *N*-methylation steps. Thus, the UVC-induced oxidative cyclisation procedure had

Table 1 Benzoazocines from furopyridinones following UVA irradiation



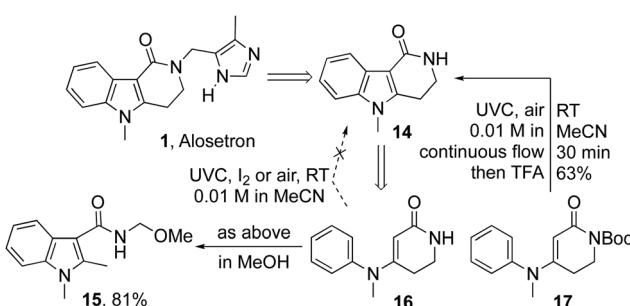
[†]3 can be formed in high yield by Boc deprotection of **18c**, as detailed in the ESI

the potential to provide a complimentary method for substrates bearing other nitrogen substituents.

To that end, we first targeted tetrahydrocarbazolones **18b–n** bearing substituents on nitrogen and the cyclohexene ring (Table 1). Pleasingly, each proceeded smoothly in yields of ~70%. Notably, substrates bearing an *N*-benzyl substituent required shorter residence times than those with *N*-methyl and *N*-ethyl residues. Though secondary enaminone **5a** (*R* = *R'* = H) failed to give tetrahydrocarbazolone **3**, that product could be accessed from the *N*-Boc-indole **18c**, which was delivered in high yield when using catalytic *I*₂ as the oxidant.

Attention next turned to the influence of aromatic substituents on the course of the reaction (Table 2). The *ortho*-, *meta*- and *para*-tolyl and anisole derivatives **19a–f** were each prepared and converted into indoles **20a–f** by the aforementioned protocols. In most cases, reactions proceeded well using air as the oxidant, with hydrolysis of the starting material accounting for much of the outstanding mass balance. Indeed, this proved especially significant for the *ortho*-tolyl derivative **19a** → **20a**, leading to a modest yield. In this case, switching the oxidant to catalytic *I*₂ had little impact on the efficiency of the reaction, in stark contrast to the *ortho*-anisole derivative **19d** where the switch elevated the yield of indole **20d** from 25% to 81%. Competitive hydrolysis also contributed to the modest 37% yield attained for indole **20g** while for the *para*-chloro analogue **20h** (49%), other side reactions reduced the yield significantly. The reaction failed to give indoles **20i** or **20j** from secondary enaminones **19i** and **19j** (*R* = H) but was extended successfully to the fused polycycles **20l** and **20m**.

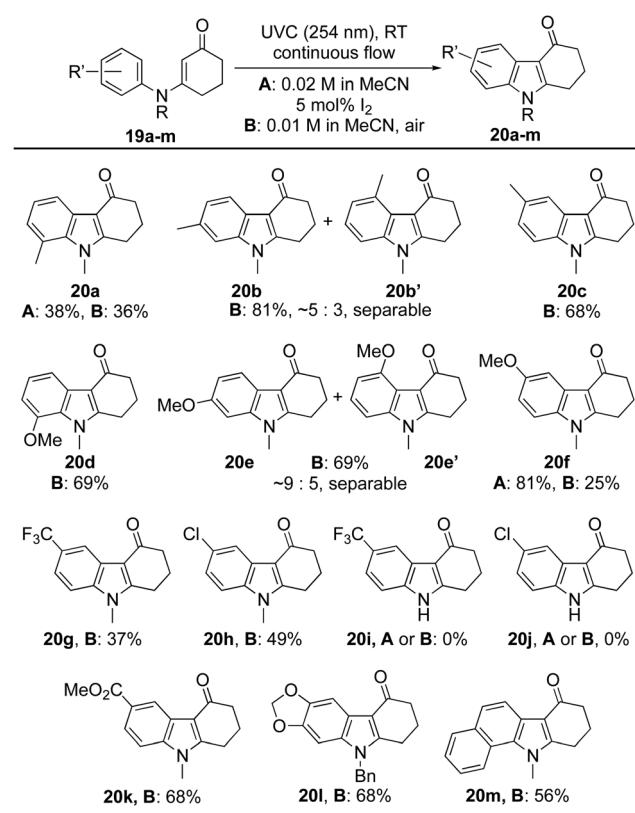
Changing the size of the cyclic enone had a dramatic effect on the reactions' efficiency (Table 3).²⁹ Indeed, for cyclopenten-



Scheme 2 A formal synthesis of alosetron **1**.

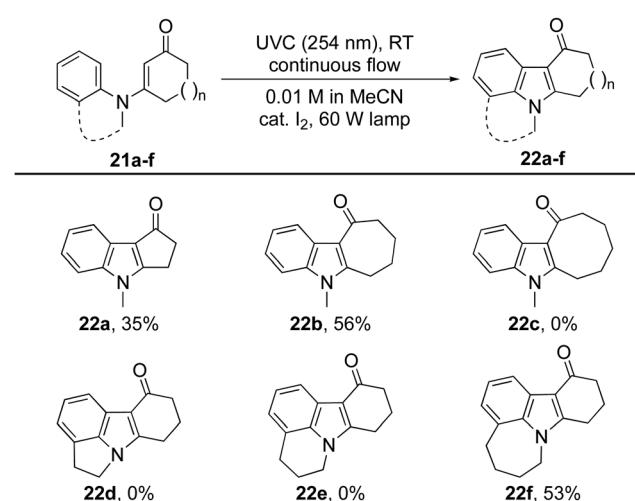


Table 2 Extension to substituted arenes



one **21a** ($n = 0$) only traces of the expected indole **22a** were observed using the aforementioned procedures. Optimization studies were rewarded with the production of indole **22a** in 35% isolated yield when cat. I_2 was used in conjunction with a 60 W lamp. Under these conditions, cyclisation was able to compete with hydrolysis of the starting material. The same conditions also allowed cycloheptenone **21b** to be transformed into indole

Table 3 Extension to other fused ring systems



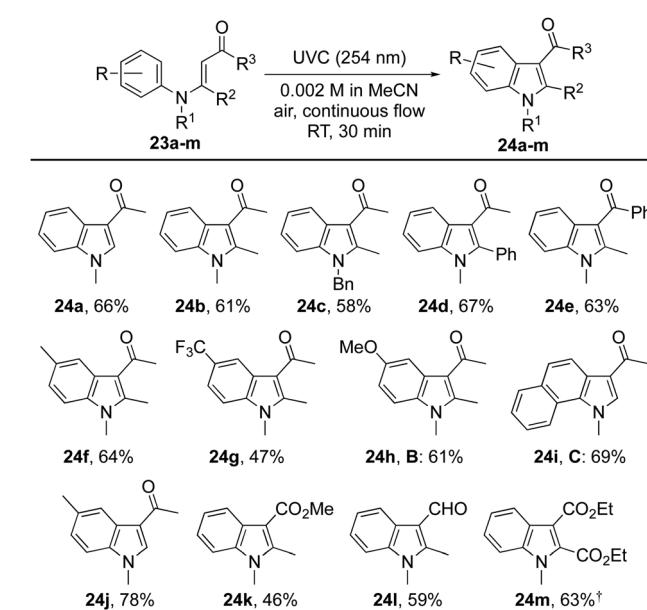
22b in 56% yield, but proved ineffective with cyclooctenone **21c**, which returned *N*-methylaniline as the major product.

N-Arylenaminones derived from bicyclic amines were also investigated (Table 3). While the dihydroindole and dihydroquinoline derivatives failed to give indoles **22d** and **22e**, the corresponding tetrahydrobenzoazepine was successfully converted into tetracyclic indole **22f**. These observations indicate that the size of the ring fused to the *N*-arylenaminone determines whether a reactive conformer with good orbital overlap can be achieved.²⁴

Initial attempts to induce cyclisations of acyclic *N*-arylenaminones (Table 4) were beset by low yields and the recovery of starting material.³⁰ A breakthrough came with the observation that reactions could be induced under conditions of high dilution. Thus, at 0.002 M in acetonitrile using air as the oxidant, we were able to realize each of the oxidative cyclisation reactions of enamines **23a-l** to indoles **24a-l**. A notable anomaly was enamine **23m** ($R = H$, $R^1 = Me$, $R^2 = R^3 = CO_2Me$), which was returned under these conditions but gave indole **24m** in 63% when acetic acid was added to the reaction mixture. We presume that acetic acid catalyses the proton transfer step, **25** \rightarrow **26**, that follows conrotatory 6 π -electrocyclisation of **23** via its singlet excited state (Scheme 3). Another point of note is that the substitution pattern for indole **24e** mirrors that of the nonsteroidal anti-inflammatory and analgesic, pravadolone.³¹

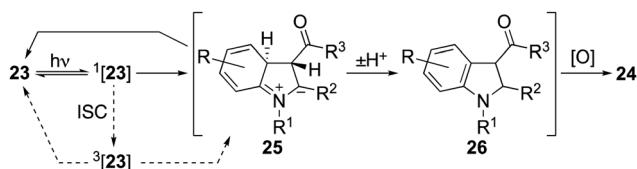
Finally, the method has been extended to *N*-arylenaminones where the amine is bound to the α -carbon of the enone, and bond formation occurs to its β -carbon (Table 5).³² As with the aforementioned examples, the cyclohexanone derivatives **27a-c** each gave the corresponding indoles **28a-c** in good yield after a residence time of 1 h, while the yield for cyclisation of the acyclic enone **27d** to indole **28d** was modest.

Table 4 Extension to acyclic enamines



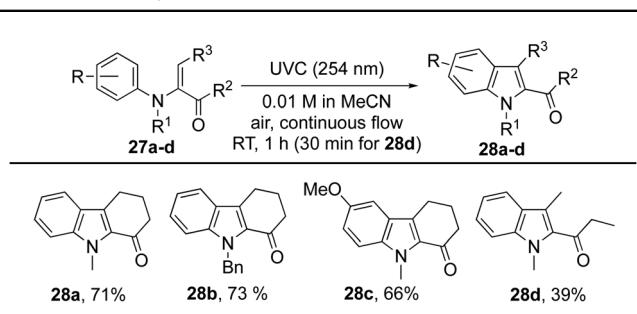
[†]Required the addition of AcOH, as detailed in the ESI





Scheme 3 Mechanistic course of the reaction.

Table 5 Reversing the polarization of the enamine



In conclusion, we have developed a cheap, efficient and atom economic route to indoles that has wide applicability. Strategically, the method mirrors the Fischer indole synthesis but replaces the arylhydrazine component with an aniline which are generally cheaper, less toxic and more widely available. The method allows products such as the ondansetron precursor **4** to be synthesized on a gram per hour basis using a standard laboratory set-up (see ESI†). Efforts to scale the reaction further are currently under investigation along with extensions to other APIs and fused heteroaromatic ring systems.

Wei Sun and William Rimbach performed all of the reported experiments and contributed equally in respect of the practical work. Kevin Booker-Milburn, Luke Elliott and David Harrowven conceived the project and acquired the funding to support it. David Harrowven was the primary supervisor.

We gratefully acknowledge financial support from EPSRC [EP/P013341/1, EP/L003325/1 and EP/K039466/1] and the European Regional Development Fund [ERDF Interreg Va programme (Project 121)].

Conflicts of interest

There are no conflicts to declare.

Notes and references

- (a) B. E. Evans, K. E. Rittle, M. G. Bock, R. M. DiPardo, R. M. Freidinger, W. L. Whitter, G. F. Lundell, D. F. Veber, P. S. Anderson, R. S. L. Chang, V. J. Lotti, D. J. Cerino, T. B. Chen, P. J. Kling, K. A. Kunkel, J. P. Springer and J. Hirshfieldt, *J. Med. Chem.*, 1988, **31**, 2235; (b) P. Schneider and G. Schneider, *Angew. Chem., Int. Ed.*, 2017, **56**, 7971.
- J. W. F. Whitehead, K. Mills, I. H. Coates, A. W. Oxford and P. C. North, *US Pat.*, 1993, 5196534.
- www.who.int/publications/item/WHOMVPEMPIAU2019.06 (accessed 6.10.2021).

- I. H. Coates, J. A. Bell, D. C. Humber and G. B. Ewan, *UK Pat.*, 1985, 2153821. See also www.who.int/publications/item/WHO-2019-nCoV-clinical-2021-1 (accessed 6.10.2021).
- F. Khan, M. Fatima, M. Shirzaei, Y. Vo, M. Amarasinghe, M. G. Banwell, C. Ma, J. S. Ward and M. G. Gardiner, *Org. Lett.*, 2019, **21**, 6342.
- D.-Q. Xu, J. Wu, S.-P. Luo, J.-X. Zhang, J.-Y. Wu, X.-H. Du and Z.-Y. Xu, *Green Chem.*, 2009, **11**, 1239.
- J. Wang, M. Wang, K. Chen, S. Zha, C. Song and J. Zhu, *Org. Lett.*, 2016, **18**, 1178.
- X. Yao, X. Shan and L. Zu, *Org. Lett.*, 2018, **20**, 6498.
- (a) S. Würz, S. Rakshit, J. J. Neumann, T. Dröge and F. Glorius, *Angew. Chem., Int. Ed.*, 2008, **47**, 7230; (b) J. J. Neumann, S. Rakshit, T. Dröge, S. Würz and F. Glorius, *Chem. – Eur. J.*, 2011, **17**, 7298; (c) W. Bi, X. Yun, Y. Fan, X. Qi, Y. Du and J. Huang, *Synlett*, 2010, 2899.
- C. Tietche, C. Garcia, D. Gardette, D. Dugat and J.-C. Gramain, *J. Heterocycl. Chem.*, 2002, **39**, 965.
- L. V. Kudzma, *Synthesis*, 2003, 1661.
- B. Knipp, R. Kucznierek, T. Sattelkau and T. Zeibig, *US Pat.*, 2007, 112054.
- A. Osuka, Y. Mori and H. Suzuki, *Chem. Lett.*, 1982, 2031.
- (a) U. S. Sørensen and E. Pombo-Villar, *Helv. Chim. Acta*, 2004, **87**, 82; (b) S. Yan, H. Wu, N. Wu and Y. Jiang, *Synlett*, 2007, 2699.
- (a) Y. Uozumi, M. Mori and M. Shibasaki, *Chem. Commun.*, 1991, 81; (b) M. Mori, Y. Uozumi and M. Shibasaki, *Heterocycles*, 1992, **33**, 819.
- (a) T. L. Scott and B. C. G. Söderberg, *Tetrahedron*, 2003, **59**, 6323; (b) D. Janreddy, V. Kavala, J. W. J. Bosco, C.-W. Kuo and C.-F. Yao, *Eur. J. Org. Chem.*, 2011, 2360.
- Y. Ban, K. Yoshida, J. Goto, T. Oishi and E. Takeda (née Ishigamori), *Tetrahedron*, 1983, **39**, 3657.
- R. A. Bunce and B. Nammalwar, *J. Heterocycl. Chem.*, 2009, **46**, 172.
- X. Ban, Y. Pan, Y. Lin, S. Wang, Y. Du and K. Zhao, *Org. Biomol. Chem.*, 2012, **10**, 3606.
- D. Bhattacherjee, S. Ram, A. S. Chauhan, Yamini, Sheetal and P. Das, *Chem. – Eur. J.*, 2019, **25**, 5934.
- D. Szymor-Pietrzak, M. N. Khan, A. Pagès, A. Kumar, N. Depner and D. L. Clive, *J. Org. Chem.*, 2021, **86**, 619.
- (a) D. C. Harrowven, M. Mohamed, T. P. Gonçalves, R. J. Whitby, D. Bolien and H. F. Sneddon, *Angew. Chem., Int. Ed.*, 2012, **51**, 4405; (b) M. Mohamed, T. P. Gonçalves, R. J. Whitby, H. F. Sneddon and D. C. Harrowven, *Chem. – Eur. J.*, 2011, **17**, 13698; (c) T. P. Gonçalves, M. Mohamed, R. J. Whitby, H. F. Sneddon and D. C. Harrowven, *Angew. Chem., Int. Ed.*, 2015, **54**, 4531; (d) D. E. Collin, E. H. Jackman, N. Jouandon, W. Sun, M. E. Light, D. C. Harrowven and B. Linclau, *Synthesis*, 2021, 1307.
- M. A. Manning, W. Sun, M. E. Light and D. C. Harrowven, *Chem. Commun.*, 2021, **57**, 4556–4559.
- M. J. Ralph, D. C. Harrowven, S. Gaulier, S. Ng and K. I. Booker-Milburn, *Angew. Chem., Int. Ed.*, 2015, **54**, 1527.
- L. Liu, B. Yang, T. J. Katz and M. K. Poindexter, *J. Org. Chem.*, 1991, **56**, 3769.
- (a) B. Miao, S. Li, G. Li and S. Ma, *Org. Lett.*, 2016, **18**, 2556; (b) L. Li, X. Zhou, B. Yu and H. Huang, *Org. Lett.*, 2017, **19**, 4600.
- (a) J.-C. Gramain, H.-P. Husson and Y. Troin, *J. Org. Chem.*, 1985, **50**, 5517; (b) J.-C. Gramain, Y. Troin and H.-P. Husson, *J. Heterocycl. Chem.*, 1988, **25**, 201; (c) N. Benchekroun-Mounir, D. Dugat and J.-C. Gramain, *Tetrahedron Lett.*, 1992, **33**, 4001; (d) N. Benchekroun-Mounir, D. Dugat, J.-C. Gramain and H.-P. Husson, *J. Org. Chem.*, 1993, **58**, 6457; (e) F. Toda, H. Miyamoto, T. Tamashima, M. Kondo and Y. Ohashi, *J. Org. Chem.*, 1999, **64**, 2690; (f) J. L. Berry, D. R. Dillen and D. G. Watson, *Tetrahedron Lett.*, 1985, **26**, 143; (g) D. Dugat, J.-C. Gramain and G. Dauphin, *J. Chem. Soc., Perkin Trans. 2*, 1990, 605.
- C.-J. Wu, W.-X. Cao, T. Lei, Z.-H. Li, Q.-Y. Meng, X.-L. Yang, B. Chen, V. Ramamurthy, C.-H. Tung and L.-Z. Wu, *Chem. Commun.*, 2017, **53**, 8320.
- S. G. Modha, A. Pöthig, A. Dreuw and T. Bach, *J. Org. Chem.*, 2019, **84**, 1139.
- (a) J. L. Berry, D. R. Dillen and D. G. Watson, *Tetrahedron Lett.*, 1985, **26**, 143; (b) Y. Troin, M.-E. Sinibaldi, J.-C. Gramain, M. Rubiralta and A. Diez, *Tetrahedron Lett.*, 1991, **32**, 6129.
- G. Grieco, J. DeAndrade, E. Dorflinger, T. Kantor, J. Saelens, A. Sunshine, R. Wang, G. Wideman and V. Zellman, *Clin. Pharmacol. Ther.*, 1989, **42**, 123.
- J. C. Arnould, J. Cossy and J. P. Pete, *Tetrahedron*, 1980, **36**, 1585.

