Tetrahedron Letters 53 (2012) 5426–5429

Contents lists available at SciVerse ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

A furoindoline synthesis by remote radical functionalization

Matthew B. Calvert, Jonathan Sperry *

School of Chemical Sciences, University of Auckland, 23 Symonds Street, Auckland, New Zealand

ARTICLE INFO

Article history:
Received 24 May 2012
Revised 13 July 2012
Accepted 27 July 2012
Available online 3 August 2012

Keywords:
Furoindoline
Radical
Remote functionalization
Heterocycle
Indoline

ABSTRACT

The preliminary results of an investigation toward a synthesis of furoindolines from 3-(2-hydroxyethyl)indolines by remote radical functionalization are described. Using an oxidative radical cyclization, it was discovered that the intramolecular hydrogen abstraction was only successful when the resulting radical (and hence carbocation) was resonance stabilized by adjacent tertiary amine and phenyl groups. The successful cyclization affords diastereomeric furoindolines, one of which contains a highly strained trans-fused 5,5-ring system. This furoindoline synthesis contains a rare example of an alkoxy radical promoted hydrogen atom transfer of a proton attached to a nitrogen-substituted carbon.

The furoindoline motif (**1**) is found in several natural products with interesting biological properties and some members of this class are shown in Figure 1. Physovenine was first isolated over a century ago[1] and possesses both anticholinergic and miotic activities[2] along with potential for the treatment of Alzheimer's disease.[3] Madindoline A inhibits the growth of IL-6-dependent cell lines by targeting gp130[4] and aspidophylline A reverses drug resistance in resistant KB cells.[5]

The majority of furoindoline syntheses rely on the cyclization of a precursor of type **2**, which is usually generated from an oxindole **3** or tryptophol **4**[6–9] (Scheme 1).

Although the synthetic methods outlined above have been successful in accessing furoindolines, they can require harsh (often acidic) conditions which may restrict their use with delicate substrates. In what would constitute a novel approach based on remote radical functionalization, we chose to investigate the synthesis of furoindolines using an alkoxy radical promoted 1,5-hydrogen atom transfer (1,5-HAT) reaction that has found widespread application in the synthesis of tetrahydrofurans,[10] spiroketals,[11] and carbohydrates.[12] It was envisioned that the reduced tryptophols [3-(2-hydroxyethyl)indolines, **5**] could undergo initial hypoiodite (**6**) formation from reaction with acetyl hypoiodite, which is generated in situ from iodobenzene diacetate and iodine. Photolytic cleavage of **6** would give the alkoxy radical **7** that, in what constitutes the key remote functionalization step, would be expected to undergo an intramolecular hydrogen abstraction (1,5-HAT) to generate radical **8**. Oxidation generates the resonance stabilized carbocation **9** which undergoes cyclization to the desired furoindoline **1** (Scheme 2). To the best of our knowledge, the alkoxy radical promoted abstraction of a H-atom attached to a nitrogen-substituted carbon under oxidative conditions is not known.[13]

Attempting the standard oxidative radical cyclization reaction conditions[10] on 3-(2-hydroxyethyl)indoline [(±)-**10**][14] failed to give the furoindoline (±)-**11** and simply caused rapid degradation of the starting material. This negative result was unsurprising and attributed to competing N-iodination, and hence the reactive amine was masked in order to eradicate any unwanted iodination at this site. Accordingly, triethylsilane-mediated reduction of *N*-methyltryptophol (**12**)[15] gave *N*-methyl-3-(2-hydroxyethyl)

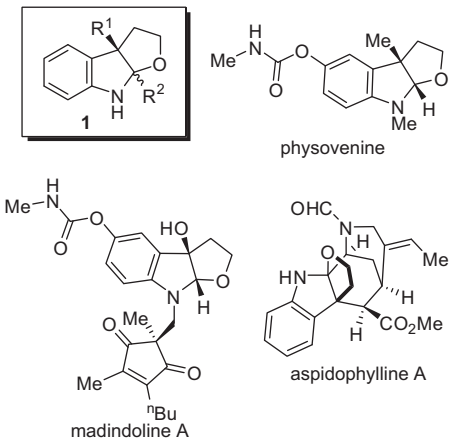
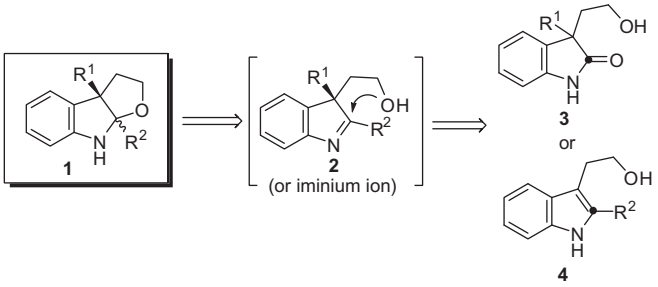


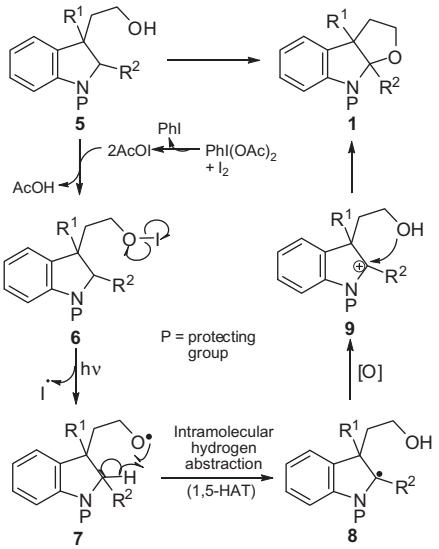
Figure 1. Examples of furoindoline natural products.

* Corresponding author. Tel.: +64 9 373 7599x88269; fax: +64 9 373 7422.
E-mail address: j.sperry@auckland.ac.nz (J. Sperry).

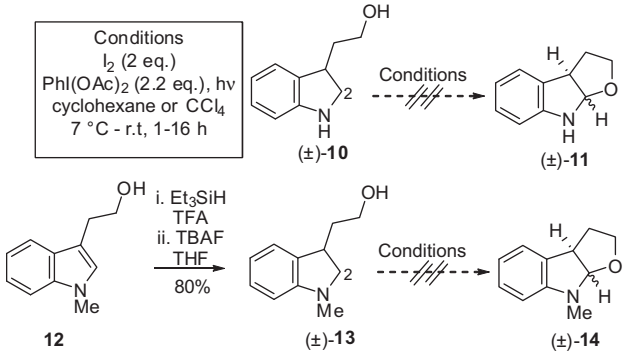
0040-4039/$ - see front matter © 2012 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.tetlet.2012.07.115



Scheme 1. Traditional approaches to furoindolines (**1**).



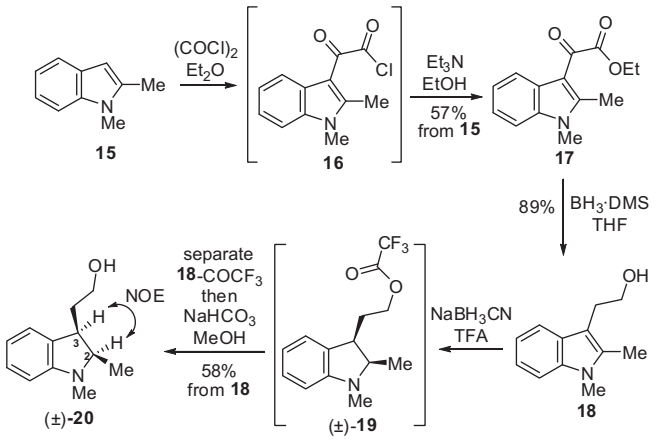
Scheme 2. Proposed synthesis of furoindolines from 3-(2-hydroxyethyl)indolines by remote radical functionalization.



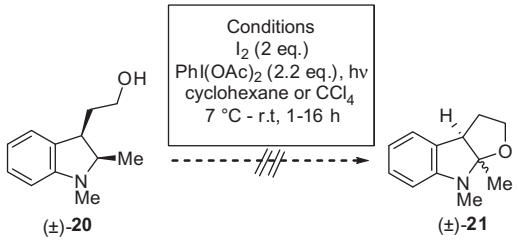
Scheme 3. Failed cyclization of 3-(2-hydroxyethyl)indolines [(±)-**10**] and [(±)-**13**].

indoline [(±)-**13**].[16] Disappointingly, subjecting (±)-**13** to the same reaction conditions led to a complex mixture of products, none of which could be identified as furoindoline (±)-**14** (Scheme 3).

At this stage it was considered that the secondary hydrogens present at C2 in (±)-**13** may not possess the requisite reactivity to undergo successful abstraction by the alkoxy radical. In order to test this hypothesis, we set out to employ a substrate that would necessitate abstraction of a tertiary hydrogen, hence forming a more stable tertiary radical (and tertiary carbocation upon oxidation). 1,2-Dimethylindole (**15**) was converted into the ethyl glyoxylate **17** via glyoxylyl chloride **16** by initial treatment with



Scheme 4. Synthesis of 3-(2-hydroxyethyl)indoline [(±)-**20**].



Scheme 5. Failed cyclization of (±)-**20.**

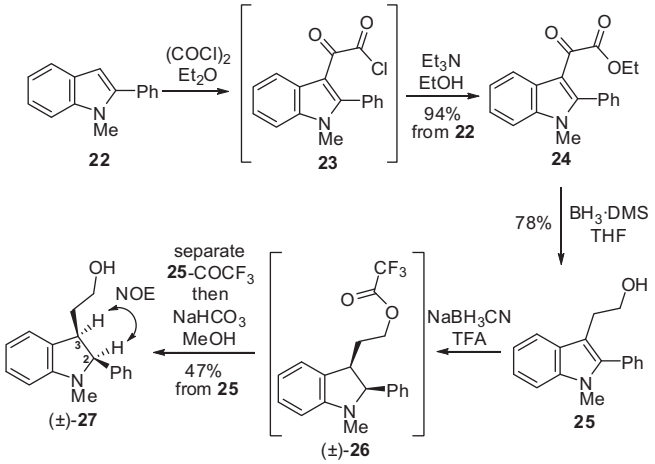
oxalyl chloride followed by ethanol. Borane-mediated reduction of **17** gave tryptophol **18** that underwent reduction using Gribble's conditions[17] to give trifluoroacetate (±)-**19** along with trifluoroacetylated starting material (±)-**18**-$COCF_3$. Chromatographic purification of (±)-**19** followed by basic hydrolysis gave the desired reduced tryptophol (±)-**20**. 2D NMR experiments confirmed the *syn*-relationship between the protons at C2 and C3 in compound (±)-**20**, with no anti-isomer observed (Scheme 4). Even though the hydroxyethyl side chain (C3) and the proton at C2 were anti, models suggested this would not have a detrimental effect on the proposed intramolecular hydrogen abstraction (1,5-HAT) event.

Disappointingly, the substrate (±)-**20** failed to undergo cyclization, again leading to a complex mixture of products from which the furoindoline (±)-**21** could not be identified (Scheme 5). This disappointing result suggested that the proton at C2 still did not possess the requisite reactivity and accordingly, we set out to build a substrate that would be more susceptible to intramolecular hydrogen abstraction by the alkoxy radical.

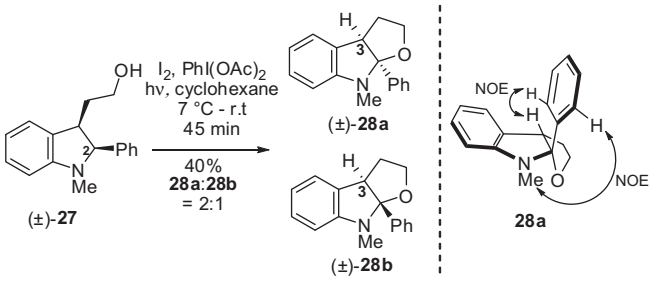
In an analogous synthesis to that outlined in Scheme 4, 1-methyl-2-phenylindole (**22**)[18] underwent reaction with oxalyl chloride and the resulting intermediate **23** was treated with ethanol under basic conditions to give **24**. Borane-mediated reduction gave tryptophol **25** which underwent further reduction to give the desired reduced tryptophol (±)-**27** after basic hydrolysis of the trifluoroacetate (±)-**26** (Scheme 6).

2D NMR experiments again confirmed the *syn*-relationship between the protons at C2 and C3 in compound (±)-**27**, with no anti-isomer observed (Scheme 6). Gratifyingly, upon subjecting (±)-**27** to the standard oxidative radical cyclization conditions, the furoindolines (±)-**28a** and (±)-**28b** were isolated in a 2:1 ratio (Scheme 7).[19]

Due to the high level of ring strain present in trans-fused 5,5-ring systems compared to their cis-fused counterparts,[20] it was naturally assumed (±)-**28a** was the major diastereomer and this



Scheme 6. Synthesis of 3-(2-hydroxyethyl)indoline [(±)-**27**].



Scheme 7. Successful furoindoline synthesis and key NOE interactions in (±)-**28a** (ent-**28a** drawn for clarity purposes).[19]

was confirmed based on the conclusive NOE interactions depicted in Scheme 7. Despite (±)-**28b** being the minor diastereomer, the formation of a strained trans-fused 5,5-ring system[20] is noteworthy and speaks to the kinetic nature of this cyclization reaction.

In conclusion, we have investigated the synthesis of furoindolines from 3-(2-hydroxyethyl)indolines by a remote intramolecular free radical functionalization. It was discovered that the intramolecular hydrogen abstraction was only successful when the resulting radical (and hence carbocation) was resonance stabilized by nitrogen and an adjacent phenyl group. Although this appears to limit this methodology to the synthesis of furoindolines bearing a quaternary center at C2, the successful cyclization affords diastereomeric furoindolines, one of which contains a highly strained trans-fused 5,5-ring system. This reaction represents a rare example of an alkoxy radical promoted hydrogen atom transfer of a proton attached to a nitrogen substituted carbon.[13] The mild nature of these cyclization conditions infers potential application in the synthesis of other heterocyclic motifs (such as spiroaminals)[21] and other trans-fused 5,5-ring systems.

Acknowledgment

We thank the School of Chemical Sciences, University of Auckland for the award of a summer research scholarship (M.B.C.).

Supplementary data

Supplementary data (^{1}H, ^{13}C and associated 2D NMR spectra for compounds (±)-**27**, (±)-**28a** and (±)-**28b**) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.07.115.

References and notes

1. (a) Salway, A. H. *J. Chem. Soc.* **1911**, *99*, 2148; (b) Robinson, B. *J. Chem. Soc.* **1964**, 1503; (c) Takano, S.; Ogasawara, K. *Alkaloids* **1989**, *36*, 225.
2. (a) Triggle, D. J.; Mitchell, R.; Filler, R. *CNS Drug Rev.* **1998**, *4*, 87; (b) Giacobini, E. *Neurochem. Int.* **1998**, *32*, 413; (c) Sneader, W. *Drug News Perspect.* **1999**, *12*, 433.
3. Greig, N. H.; Pei, X.-F.; Soncrant, T. T.; Ingram, D. K.; Brossi, A. *Med. Res. Rev.* **1995**, *15*, 3.
4. (a) Hayashi, M.; Kim, Y.-P.; Takamatsu, S.; Enomoto, A.; Shinose, M.; Takahashi, Y.; Tanaka, H.; Komiyama, K.; Omura, S. *J. Antibiot.* **1996**, *49*, 1091; (b) Takamatsu, S.; Kim, Y.-P.; Enomoto, A.; Hayashi, M.; Tanaka, H.; Komiyama, K.; Omura, S. *J. Antibiot.* **1997**, *50*, 1069; (c) Omura, S.; Hayashi, M.; Tomoda, H. *Pure Appl. Chem.* **1999**, *71*, 1673.
5. (a) Subramaniam, G.; Hiraku, O.; Hayashi, M.; Koyano, T.; Komiyama, K.; Kam, T.-S. *J. Nat. Prod.* **2007**, *70*, 1783; (b) Subramaniam, G.; Kam, T.-S. *Helv. Chim. Acta* **2008**, *91*, 930.
6. From oxindoles: (a) Horne, S.; Taylor, N.; Collins, S.; Rodrigo, R. *J. Chem. Soc., Perkin Trans. 1* **1991**, *1*, 3047; (b) Matsuura, T.; Overman, L. E.; Poon, D. J. *J. Am. Chem. Soc.* **1998**, *120*, 6500; (c) Suarez-Castillo, O. R.; Sanchez-Zavala, M.; Melendez-Rodriguez, M.; Castelan-Duarte, L. E.; Morales-Rios, M. S.; Joseph-Nathan, P. *Tetrahedron* **2006**, *62*, 3040; (d) Itoh, T.; Ishikawa, H.; Hayashi, Y. *Org. Lett.* **2009**, *11*, 3854.
7. From tryptophols: (a) Sunazuka, T.; Hirose, T.; Shirahata, T.; Harigaya, Y.; Hayashi, M.; Komiyama, K.; Ohmura, S.; Smith, A. B., III *J. Am. Chem. Soc.* **2000**, *122*, 2122; (b) Trost, B. M.; Quancard, J. *J. Am. Chem. Soc.* **2006**, *128*, 6314; (c) Zhu, Y.; Rawal, V. H. *J. Am. Chem. Soc.* **2012**, *134*, 111; An interrupted Fischer reaction generates intermediates **2** directly from phenylhydrazines and lactols, see: (d) Boal, B. W.; Schammel, A. W.; Garg, N. K. *Org. Lett.* **2009**, *11*, 3458; (e) Schammel, A. W.; Boal, B. W.; Zu, L.; Mesganaw, T.; Garg, N. K. *Tetrahedron* **2010**, *66*, 4687.
8. (a) Kulkarni, M. G.; Dhondge, A. P.; Borhade, A. S.; Gaikwad, D. D.; Chavhan, S. W.; Shaikh, Y. B.; Nigdale, V. B.; Desai, M. P.; Birhade, D. R.; Shinde, M. P. *Eur. J. Org. Chem.* **2009**, 3875; For examples of complementary routes that do not rely on the classical cyclizations outlined in Scheme 1, see: (b) Liu, Y.; Xu, W.; Wang, X. *Org. Lett.* **2010**, *12*, 1448.
9. Outside of the context of furoindoline synthesis, the cyclization of an oxygen nucleophile onto a carbon atom adjacent to nitrogen is typically achieved by amine→imine oxidation and subsequent nucleophilic attack. For representative examples, see: (a) Chen, C.-K.; Hortmann, A. G.; Marzabadi, M. R. *J. Am. Chem. Soc.* **1988**, *110*, 4829; (b) He, F.; Altom, J. D.; Corey, E. J. *J. Am. Chem. Soc.* **1998**, *121*, 6771; (c) Moldvai, I.; Czántay, C., Jr.; Czántay, C. *Heterocycles* **2001**, *55*, 2147.
10. (a) Paquette, L. A.; Sun, L. Q.; Friedrich, D.; Savage, P. B. *J. Am. Chem. Soc.* **1997**, *119*, 8438; (b) Chatgilialoglu, C.; Gimisis, T.; Spada, G. P. *Chem. Eur. J.* **1999**, *5*, 2866; (c) Bruke, S. D.; Kort, M. E.; Strickland, S. M. S.; Organ, H. M.; Silks, L. A. *Tetrahedron Lett.* **1994**, *35*, 1503; (d) Hatakeyama, S.; Kawamura, M.; Takano, S. *J. Am. Chem. Soc.* **1994**, *116*, 4081.
11. (a) Sperry, J.; Liu, Y.-C.; Brimble, M. A. *Org. Biomol. Chem.* **2010**, *8*, 29. The synthesis of spiroaminals by 1,5- or 1,6-HAT is restricted to the cyclization of an amine nucleophile onto a cation resonance stabilized by oxygen, see:; (b) Koag, M.; Lee, S. *Org. Lett.* **2011**, *13*, 4766. and references therein.
12. (a) Martín, A.; Pérez-Martín, I.; Quintanal, L. M.; Suárez, E. *Org. Lett.* **2007**, *9*, 1785; (b) Martín, A.; Quintanal, L. M.; Suárez, E. *Tetrahedron Lett.* **2007**, *48*, 5507; (c) Francisco, C. G.; Herrera, A. J.; Suárez, E. *J. Org. Chem.* **2002**, *67*, 7439; (d) Francisco, C. G.; Freire, R.; Herrera, A. J.; Pérez-Martín, I.; Suárez, E. *Org. Lett.* **2002**, *4*, 1959.
13. For an example of related 1,5-HAT under reductive conditions, see: Zhu, H.; Wickenden, J. G.; Campbell, N. E.; Leung, J. C. T.; Johnson, K. M.; Sammis, G. M. *Org. Lett.* **2009**, *11*, 2019 (see Table 2, compound **1i**).
14. Hirose, T.; Sunazuka, T.; Yamamoto, D.; Kojima, N.; Shirahata, T.; Harigaya, Y.; Kuwajima, I.; Ōmura, S. *Tetrahedron* **2005**, *61*, 6015.
15. Garden, S. J.; da Silva, R. B.; Pinto, A. C. *Tetrahedron* **2002**, *58*, 8399.
16. TBAF work-up was required to hydrolyze the TES–ether of **13**.
17. Gribble, G. W.; Hoffman, J. H. *Synthesis* **1977**, 859.
18. Ishikura, M.; Terashima, M. *J. Org. Chem.* **1994**, *59*, 2634.
19. (±)-*cis*-Furoindoline (**28a**) and (±)-*trans*-furoindoline (**28b**)
To a solution of (±)-**27** (40 mg, 160 μmol) in degassed cyclohexane (15 mL) was added I_2 (90 mg, 360 μmol) at room temperature. Upon dissolution of iodine, the solution was cooled to 7 °C and $PhI(OAc)_2$ (100 mg, 320 μmol) was added and the reaction mixture irradiated with a desk lamp (60 W) for 45 min. The reaction mixture was diluted with Et_2O (20 mL) and saturated $Na_2S_2O_3$ solution (50 mL) and the whole extracted with Et_2O (3 × 40 mL). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated in vacuo. Purification by preparative TLC eluting with CH_2Cl_2–MeOH (97.5:2.5) gave the *title compounds* **28a** (less polar) and **28b** as a 2:1 mixture of diastereomers.
Compound **28a**, brown solid (11 mg, 44 μmol, 27%); Mp 65–68 °C; ν_{max}/cm^{-1} 3260, 3061, 2927, 1703, 1602, 1464, 1361, 1040, 1014, 786, 701; HRMS Found: $[M]^+$, 251.1317. $[C_{17}H_{17}NO]^+$ requires 251.1305; ^{1}H NMR (400 MHz, acetone-d_6): δ_H = 8.00 (1 H, d, *J* = 1.6, ArH), 7.58–7.45 (7 H, m, ArH), 7.28 (1 H, d, *J* = 8.5, ArH), 3.74–3.69 (2 H, m, CH + CH of CH_2), 3.64–3.61 (1 H, m, CH of CH_2), 3.59 (3 H, s, NMe), 2.86 (2 H, t, *J* = 7.2, $CHCH_2$); ^{13}C NMR (100 MHz, acetone-d_6): δ_C = 140.5 (C), 137.0 (C), 131.6 (3 × CH), 130.4 (CH), 129.4 (CH), 129.2 (2 × CH) 128.6 (CH) 112.8 (CH), 110.3 (C), 82.7 (C), 63.2 (CH_2), 31.2 (NMe), 30.3 (CH), 29.2 (CH_2); *m/z* (APCI) 251 (M^+, 18%).

Compound **28b**, brown oil (6 mg, 20 μmol, 13%); ν_{max}/cm^{-1} 3387, 3051, 2924, 1724, 1604, 1469, 1363, 1046, 1013, 704; HRMS Found: $[M+H]^+$, 252. $[C_{17}H_{17}NO+H]^+$ requires 252.1383; ^1H NMR (400 MHz, acetone-d_6): δ_H = 7.63 (1 H, d, *J* = 8.1, ArH), 7.57–7.53 (4 H, m, ArH), 7.52–7.45 (1 H, m, ArH), 7.39 (1 H, d, *J* = 8.3, ArH), 7.19 (1 H, t, *J* = 8.0, ArH), 7.08 (1 H, t, *J* = 7.4 ArH), 3.74 (2 H, dt, *J* = 7.5, 5.7, $CHCH_2$), 3.59 (3 H, s, NMe), 3.57 (1 H, t, *J* = 5.7, CH), 2.90 (2 H, t, *J* = 7.5, CH_2OC); ^{13}C NMR (75 MHz, acetone-d_6): δ_C = 139.0 (C), 137.5 (C), 130.7 (3 × CH), 129.6 (C), 128.3 (2 × CH), 128.0 (CH), 121.4 (CH), 118.9 (C), 118.8 (CH), 109.4 (CH), 62.3 (CH_2), 30.1 (CH), 29.1 (NMe), 28.6 (CH_2); *m/z* (ESI) 252.1363 ($[M+H]^+$, 82%), 234 (30), 126 (59).

20. trans-Fused 5,5-ring systems are quite rare. For examples, see: (a) Paquette, L. A.; Morwick, T. M. *J. Am. Chem. Soc.* **1997**, *119*, 1230; (b) Paquette, L. A.; Hamme, A. T., II; Kuo, L. H.; Doyon, J.; Kreuzholz, R. *J. Am. Chem. Soc.* **1997**, *119*, 1242; (c) Paquette, L. A.; Kuo, L. H.; Tae, J. *J. Org. Chem.* **1998**, *63*, 2010; (d) Molander, G. A.; Nichols, P. J.; Noll, B. C. *J. Org. Chem.* **1998**, *63*, 2292; (e) Jamison, T. F.; Shambayati, S.; Crowe, W. E.; Schreiber, S. L. *J. Am. Chem. Soc.* **1998**, *119*, 4253; (f) Kock, M.; Grube, A.; Seiple, I. B.; Baran, P. S. *Angew. Chem., Int. Ed.* **2007**, *46*, 6586.
21. Sinibaldi, M.-E.; Canet, I. *Eur. J. Org. Chem.* **2008**, 4391.