ChemComm

Accepted Manuscript

This article can be cited before page numbers have been issued, to do this please use: P. D. Fedoseev, G. A. Coppola, G. M. Ojeda and E. V. Van der Eycken, *Chem. Commun.*, 2018, DOI: 10.1039/C8CC01474D.

ROYAL SOCIETY OF CHEMISTRY

rsc.li/chemcomm

View Article Online
DOI: 10.1039/C8CC01474D

Chemical Communications

COMMUNICATION

Synthesis of spiroindolenines by intramolecular *ipso*-iodocyclization of indol ynones

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

www.rsc.org/

Pavel Fedoseev[a], Guglielmo Coppola[a], Gerardo M. Ojeda[a,b] and Erik V. Van der Eycken[a,c,*]

A high-yielding fast spirocyclization of easily available indol ynones has been developed applying *N*-iodosuccinimide. The formation of the desired product occurs in an atom-economical way, under mild conditions, instantly after the addition of the reagent. The expected 1,2-rearrangent was not observed. The procedure represents a metal free spirocyclization of indoles with the opportunity of further functionalizations.

During the last few years spirocycles have attracted great attention due to their privileged structure.[1] Their non-planar skeleton can be found in many biologically active compounds.[2] However, the synthesis of such spiro-structures is complicated due to the need for dearomatization or the fact that their construction requires a multistep synthesis and condensations.[3] The synthesis of spiroindolenines, which are widely spread in nature (Figure 1), is known to be even more complicated as they are prone to 1,2-rearrangement towards C2-substituted indoles.[4] Their hydrogenated analogues spiroindolines are also widespread in nature and are of great interest regarding bioactivity.[5] Until now, only few reports on the synthesis of spiroindolenines and spiroindolines appeared, and the vast majority includes transition metal catalysis.[3f, 4a, 4f, 6]

In 2010 the group of You reported a work based on Ir catalysis.[7] Later on, our group has reported the procedure of gold-catalysed spirocyclization of indoles, resulting in a mixture of both spiro- and 1,2-rearranged products.[8] This was soon followed by the work of Unsworth and Taylor with multiple reports on indoles spirocyclization involving Ag, Cu and Au catalysis.[9] It is worthwile to mention that all reports on indole spirocyclization involved transition metal catalysts, until 2017 when our group reported the first metal-free spirocyclization of indoles.[10] In continuation of this research, we began to search a suitable procedure for indol ynone annulation. This directed our interest to iodine-catalysed

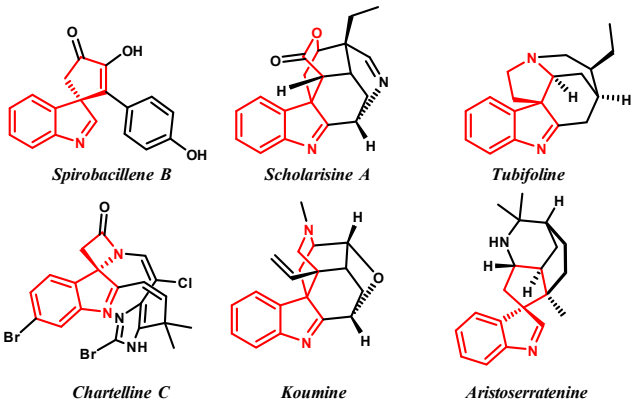


Figure 1. Biologically active spiroindolenines

cyclizations, largely reported in the past decade.[11] Recently, our group has also reported various annulation procedures involving iodine chemistry.[12]

Iodine reagents appear to be efficient tools to activate a triple bond for nucleophilic attack.[11] The reaction products may further be functionalized employing the high reactivity of the introduced C-I bond. Herein we report a new high-yielding atom-economical spirocyclization procedure of indol ynones for the formation of iodine-substituted spiroindolenines employing *N*-iodosuccinimide (NIS) for activation of the triple bond.

Our study began by examining the reaction of 1.5 equiv of iodine in acetonitrile with indol ynone **1a** which was used as a model compound (Table 1, entry 1). To our surprize, the reaction was already completed right after the addition of the reagent, yielding the desired **2a** in 40%. Variation of the amount of iodine did not result in a significant change of the yield (Table 1, entries 2 and 3). In order to neutralize the formed HI, 1.5 equiv of $NaHCO_3$ were added, resulting in an increased yield of 62% (Table 1, entry 4). Switching to ICl lead

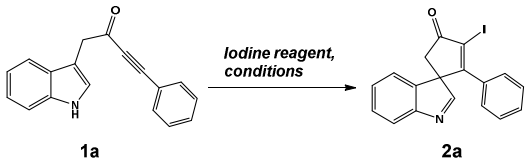
[a] *Laboratory for Organic & Microwave-Assisted Chemistry (LOMAC), Department of Chemistry, University of Leuven (KU Leuven), Celestijnenlaan 200F, Leuven, Belgium.*
[b] *Center for Natural Products Research, Faculty of Chemistry, University of Havana, Zapata y G, 10400 Havana, Cuba.*
[c] *Peoples' Friendship University of Russia (RUDN University), Miklukho-Maklaya Street 6, Moscow, Russia.*

Electronic Supplementary Information (ESI) available: See

View Article Online
DOI: 10.1039/C8CC01474D

to decreased yields (Table 1, entries 8-10). To our delight, when *N*-iodocuccinimide was employed, the yield increased dramatically up to 89% at 0 ºC within 5 minutes (Table 1, entry 11). Performing the reaction in DCM or toluene did not result in any product formation (Table 1, entries 13 and 14). However, treating **1a** with NIS at rt lead to an impressive 99% yield (Table 1, entry 16).

Table 1. Optimization of the iodocyclization on ynone **1a**[a]



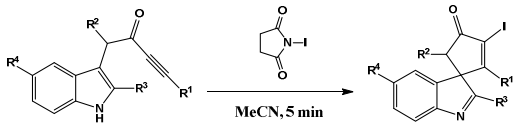
1a **2a**

№	Iodine reagent	Equiv	Additive	Temp.	Solvent	Time (min)	Yield (NMR)
1	I_2	1.5	-	rt	MeCN	5	40
2	I_2	2.0	-	rt	MeCN	5	44
3	I_2	1.05	-	rt	MeCN	5	39
4	I_2	1.5	$NaHCO_3$	rt	MeCN	5	62
5	I_2	2.0	$NaHCO_3$	rt	MeCN	5	42
6	I_2	1.05	$NaHCO_3$	rt	MeCN	5	63
7	I_2	1.05	$NaHCO_3$	0°C	MeCN	5	48
8	ICl	1.05	$NaHCO_3$	rt	MeCN	5	40
9	ICl	1.5	$NaHCO_3$	rt	MeCN	5	37
10	ICl	1.05	$NaHCO_3$	0°C	MeCN	5	29
11	NIS	1.05	-	0°C	MeCN	5	89
12	NIS	1.05	-	rt	Ethanol	5	90
13	NIS	1.05	-	rt	CH_2Cl_2	5	-
14	NIS	1.05	-	rt	THF	5	87
15	NIS	1.05	-	rt	Toluene	5	-
16	NIS	1.05	-	rt	MeCN	5	99 (98)[b]

[a] The reactions were run on a 0.1 mmol scale of **1a** in 1.0 mL of the indicated solvent with 2 equiv of the additive when mentioned. The data were obtained *via* ^{1}H NMR using CH_2Br_2 as an internal standard. d; [b] Isolated yield.

With the optimized condition in hand, we explored the scope of the protocol with various substrates **1a**-**m** (Table 2). First, we performed the reaction with the model compound **1a** in a gram-scale, what resulted in an excellent 96% yield (Table 2, entry 2). Then, the spirocyclization was investigated with an *ortho*- **1b**, *meta*- **1c** and *para*-tolyl **1d** R^1-substitutents, resulting in excellent yields in all cases (Table 2, entries 3, 4 and 5). Electron-donating and electron-withdrawing groups were also tested resulting in 96% of **2e** and 92% of **2f**, respectively (Table 2, entries 6 and 7). Alkyl substituents at the triple bond similarly showed clean conversion to the desired molecules **2g** and **2h** (Table 2, entries 8 and 9). An electron-donating 5-methoxy group on the indole core resulted in a slightly lower yield of 84% (**2i**), while a *para*-chlorine phenyl R^3-substituent resulted in an even more decreased yield (**2j**). Electron-withdrawing 5-bromo substituent showed excellent reactivity under the current conditions (**2k**) (Table 2, entries 10 and 11). Substrates with R^2 and R^3-substituens were also cleanly converted into the desired products **2l** and **2m** (Table 2, entries 12 and 13).[13]

Table 2. Substrate scope[a]

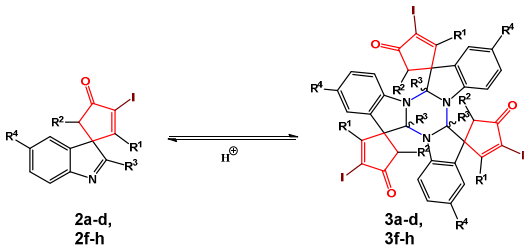


Entry	Starting material	Product	Yield (%)
1	**1a** Ar = Ph	**2a** Ar = Ph	98
2	**1a** Ar = Ph **(1.3 g)**	**2a** Ar = Ph	96
3	**1b** Ar = *o*-Me-Ph	**2b**[b] Ar = *o*-Me-Ph	94
4	**1c** Ar = *m*-Me-Ph	**2c** Ar = *m*-Me-Ph	93
5	**1d** Ar = *p*-Me-Ph	**2d** Ar = *p*-Me-Ph	94
6	**1e** Ar = *p*-OMe-Ph	**2e** Ar = *p*-OMe-Ph	96
7	**1f** Ar = *p*-F-Ph	**2f** Ar = *p*-F-Ph	92
8	**1g** Alkyl = Pr	**2g** Alkyl = n-Pr	98
9	**1h** Alkyl = cyclohexyl	**2h** Alkyl = cyclohexyl	99
10	**1i** Ar = Ph	**2i** Ar = Ph	84
11	**1j** Ar = *p*-Cl-Ph	**2j** Ar = *p*-Cl-Ph	76
12	**1k** Ar = Ph	**2k** Ar = Ph	99
13	**1l** Ar = Ph	**2l** Ar = Ph	99
14	**1m** Ar = Ph	**2m**[c] Ar = Ph	99

[a] The reactions were run on a 0.3 mmol scale (except entry 2) under the optimized conditions from table 1, entry 16. The yields are isolated; [b] appears as a mixture of rotamers with dr = 1.2:1; [c] dr = 3:2.

View Article Online
DOI: 10.1039/C8CC01474D

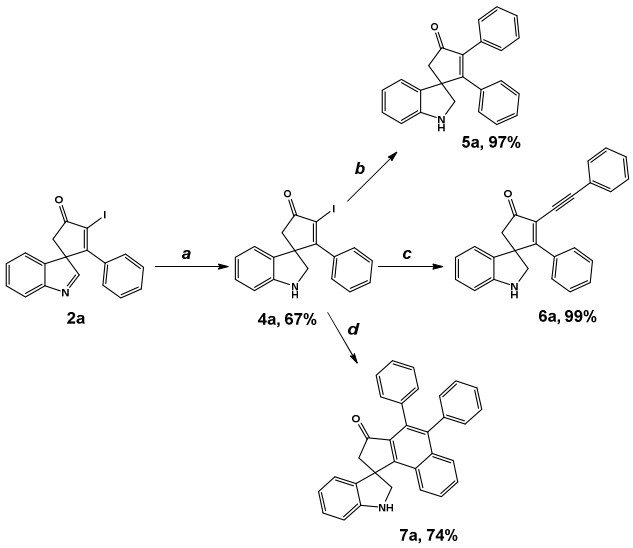
Interestingly, the majority of the formed products showed slow trimerization towards the products **3a-d** and **3f-h** (Scheme 1) in solution. However, this could be reversed under slightly acidic conditions.[9c, 9d, 14] In our case, quantitative conversion to the monomer was achieved by the addition of a few drops of TFA,



Scheme 1. Trimerization of **2a-d** and **2f-h**

what was proven by ^{1}H and ^{13}C NMRs (see the supporting information).

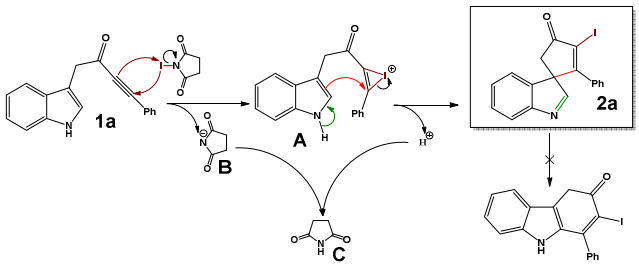
The iodocyclized products can also be decorated giving rise to various structures applying palladium chemistry. However, it was found that the indolenine core should first be reduced to the indoline, in order to prevent any side reaction on the electrophilic C2-site. To our great delight, the indoline **4a** easily underwent Suzuki and Sonogashira reaction as well as alkyne carboannulation, yielding **5a**, **6a** and **7a** in excellent yields (Scheme 2).



a: $NaCNBH_3$ (2 equiv), DCM, overnight; b: $PhB(OH)_2$ (2 equiv), $Pd(OAc)_2$ (5 mol%), PPh_3 (10 mol %), K_2CO_3 (2 equiv), dioxane/water 4:1, 60 °C, 2 h; c: phenylacetylene (2 equiv), $Pd(OAc)_2$ (5 mol%), PPh_3 (10 mol%), AgOTf (10 mol %), Cs_2CO_3 (2 equiv), THF, 60 °C, 1 h; d: diphenylacetylene (2 equiv), $Pd(OAc)_2$ (5 mol %), NaOAc (2 equiv), n-Bu_4NCl (3 equiv), DMF, 80 °C, 2 h.

Scheme 2. Palladium-catalysed transformations of **2a**

A plausible mechanism is depicted in Scheme 3. First, the triple bond of the ynone **1a** is activated upon reaction with NIS, resulting in the formation of a reactive iodonium intermediate **A**. In the next step *ipso*-attack of the indole results in the formation of spiroindolenine **2a**. The side product succinimide **C** is formed by protonation of the succinimidium anion **B**. The rearrangement towards C2-substituted indole does not occur.



Scheme 3. The plausible mechanism

In summary, a simple, high-yielding approach for the fast formation of spiroindolenines was developed from easily available indole ynones. The reaction requires mild conditions and shows broad reactivity. The high selectivity under metal-free conditions without the formation of the rearranged product is an additional asset of the protocol. All obtained products can be further easily functionalized towards various spiroindolines.

PF is grateful to the University of Leuven (KU Leuven) for funding the scholarship. GC appreciates Unipharma-Graduates for providing an Erasmus+ scholarship. GO acknowledges VLIR-UOS for financial support of a TEAM project (project code CU2018TEA458A101) involving Flemish and Cuban institutions and providing a doctoral scholarship. We thank the FWO [Fund for Scientific Research – Flanders (Belgium)] for financial support. We acknowledge the support of RUDN University Program 5-100. We thank Jef Rozensky for HRMS measurements. This research has been supported by the Belgian Development Cooperation through VLIR-UOS. VLIR-UOS supports partnerships between universities and university colleges in Flanders (Belgium) and the South looking for innovative responses to global and local challenges. Visit www.vliruos.be for more information.

Conflicts of interest

There are no conflicts to declare.

Notes and references

1. (a) M. Amireddy and K. Chen, *RSC Adv.*, 2016, **6**, 77474-77480; (b) B. S. Donslund, N. I. Jessen, J. B. Jakobsen, A. Monleon, R. P. Nielsen and K. A. Jorgensen, *Chem. Commun.*, 2016, **52**, 12474-12477; (c) A. K. Franz, N. V.

View Article Online
DOI: 10.1039/C8CC01474D

Hanhan and N. R. Ball-Jones, *ACS Catal.*, 2013, **3**, 540-553; (d) C. R. Reddy, S. K. Prajapti, K. Warudikar, R. Ranjan and B. B. Rao, *Org. Biomol. Chem.*, 2017, **15**, 3130-3151; (e) R. Rios, *Chem. Soc. Rev.*, 2012, **41**, 1060-1074; (f) L. K. Smith and I. R. Baxendale, *Org. Biomol. Chem.*, 2015, **13**, 9907-9933; (g) W. Wei, H. Cui, D. Yang, H. Yue, C. He, Y. Zhanga and H. Wang, *Green Chem.*, 2017, **19**, 5608-5613; (h) X. P. Yin, X. P. Zeng, Y. L. Liu, F. M. Liao, J. S. Yu, F. Zhou and J. Zhou, *Angew. Chem., Int. Ed.*, 2014, **53**, 13740-13745.

2. (a) A. J. Friedman, *Cutis*, 2015, **96**, 216-217; (b) C. Kiesecker, E. Zitron, S. Luck, R. Bloehs, E. P. Scholz, S. Kathofer, D. Thomas, V. A. W. Kreye, H. A. Katus, W. Schoels, C. A. Karle and J. Kiehn, *N-S Arch. Pharmacol.*, 2004, **370**, 423-435; (c) M. Livendahl, J. Jamroskovic, M. Hedenstrom, T. Gorlich, N. Sabouri and E. Chorell, *Org. Biomol. Chem.*, 2017, **15**, 3265-3275; (d) H. B. Park, Y. J. Kim, J. K. Lee, K. R. Lee and H. C. Kwon, *Org. Lett.*, 2012, **14**, 5002-5005; (e) Y. J. Zheng, C. M. Tice and S. B. Singh, *Bioorg. Med. Chem. Lett.*, 2014, **24**, 3673-3682.

3. (a) M. J. James, P. O'Brien, R. J. K. Taylor and W. P. Unsworth, *Chem.-Eur. J.*, 2016, **22**, 2856-2881; (b) S. P. Roche and J. A. Porco, *Angew. Chem., Int. Ed.*, 2011, **50**, 4068-4093; (c) S. P. Roche, J. J. Y. Tendoung and B. Treguier, *Tetrahedron*, 2015, **71**, 3549-3591; (d) W. T. Wu, L. M. Zhang and S. L. You, *Chem. Soc. Rev.*, 2016, **45**, 1570-1580; eC. Zheng and S. L. You, *Chem*, 2016, **1**, 830-857; (f) D. Y. Zhu, L. Fang, H. Han, Y. Wang and J. B. Xia, *Org. Lett.*, 2017, **19**, 4259-4262; (g) C. X. Zhuo, W. Zhang and S. L. You, *Angew. Chem., Int. Ed.*, 2012, **51**, 12662-12686.

4. (a) P. Linnepe, A. M. Schmidt and P. Eilbracht, *Org. Biomol. Chem.*, 2006, **4**, 302-313; (b) K. G. Liu, A. J. Robichaud, J. R. Lo, J. F. Mattes and Y. X. Cai, *Org. Lett.*, 2006, **8**, 5769-5771; (c) Q. F. Wu, C. Zheng and S. L. You, *Angew. Chem., Int. Ed.*, 2012, **51**, 1680-1683; (d) Q. F. Wu, C. Zheng, C. X. Zhuo and S. L. You, *Chem. Sci.*, 2016, **7**, 4453-4459; (e) C. Zheng, Q. F. Wu and S. L. You, *J. Org. Chem.*, 2013, **78**, 4357-4365; fY. Wang, C. Zheng and S. L. You, *Angew. Chem., Int. Ed.,* 2017, **56**, 15093-15097.

5. (a) J. P. Kutney, Abdurahm.N, P. Lequesne, E. Piers and I. Vlattas, *J. Am. Chem. Soc.*, 1966, **88**, 3656-3657; (b) M. E. Kuehne and F. Xu, *J. Org. Chem.*, 1993, **58**, 7490-7497; (c) J. Li and J. M. Cook, *J. Org. Chem.*, 1998, **63**, 4166-4167; (d) B. H. Lee, M. F. Clothier and S. S. Johnson, *Bioorg. Med. Chem. Lett.*, 2001, **11**, 553-554; (e) T. Sakamoto, M. Moriya, Y. Haga, T. Takahashi, T. Shibata, O. Okamoto, K. Nonoshita, H. Kitazawa, M. Hidaka, A. Gomori, H. Iwaasa, A. Ishihara, A. Kanatani, T. Fukami, Y. D. Gao, D. J. MacNeil and L. H. Yang, *Bioorg. Med. Chem. Lett.*, 2009, **19**, 1564-1568; (f) J. Yang, S. S. Zhou, L. Y. Ji, C. Zhang, S. W. Yu, Z. J. Li and X. B. Meng, *Bioorg. Med. Chem. Lett.*, 2014, **24**, 5055-5058; (g) W. F. Qin, T. Xiao, D. Zhang, L. F. Deng, Y. Wang and Y. Qin, *Chem. Commun.*, 2015, **51**, 16143-16146.

6. (a) S. J. Chambers, G. Coulthard, W. P. Unsworth, P. O'Brien and R. J. K. Taylor, *Chem.-Eur. J.*, 2016, **22**, 6496-6500; (b) G. F. Han, Q. Wang, L. W. Chen, Y. X. Liu and Q. M. Wang, *Adv. Synth. Catal*, 2016, **358**, 561-566; (c) Z. S. Liu, W. K. Li, T. R. Kang, L. He and Q. Z. Liu, *Org. Lett.*, 2015, **17**, 150-153; dG. Sirasani and R. B. Andrade, *Org. Lett.*, 2009, **11**, 2085-2088; (e) H. Zuleta-Prada and L. D. Miranda, *Tetrahedron Lett.*, 2009, **50**, 5336-5339; (f) K. G. Liu, J. R. Lo and A. J. Robichaud, *Tetrahedron*, 2010, **66**, 573-577; (g) K. J. Wu, L. X. Dai and S. L. You, *Org. Lett.*, 2012, **14**, 3772-3775; (h) Q. F. Wu, C. Zheng and S. L. You, *Angew. Chem., Int Ed.*, 2012, **51**, 1680-1683.

7. Q. F. Wu, H. He, W. B. Liu and S. L. You, *J. Am. Chem. Soc.*, 2010, **132**, 11418-11419.

8. V. A. Peshkov, O. P. Pereshivko and E. V. Van der Eycken, *Adv. Synth. Catal.*, 2012, **354**, 2841-2848.

9. (a) A. K. Clarke, M. J. James, P. O. Q. Brien, R. J. K. Taylor and W. P. Unsworth, *Angew. Chem., Int. Ed.*, 2016, **55**, 13798-13802; (b) M. J. James, P. O. I. Brien, R. J. K. Taylor and W. P. Unsworth, *Angew. Chem., Int. Ed.*, 2016, **55**, 9671-9675; (c) M. J. James, R. E. Clubley, K. Y. Palate, T. J. Procter, A. C. Wyton, P. O'Brien, R. J. K. Taylor and W. P. Unsworth, *Org. Lett.*, 2015, **17**, 4372-4375; (d) M. J. James, J. D. Cuthbertson, P. O'Brien, R. J. Taylor and W. P. Unsworth, *Angew. Chem., Int. Ed.*, 2015, **54**, 7640-7643; (e) J. T. Liddon, A. K. Clarke, R. J. Taylor and W. P. Unsworth, *Org. Lett.*, 2016, **18**, 6328-6331; (f) J. T. Liddon, M. J. James, A. K. Clarke, P. O'Brien, R. J. Taylor and W. P. Unsworth, *Chem.-Eur. J.*, 2016, **22**, 8777-8780.

10. P. Fedoseev and E. Van der Eycken, *Chem. Commun.*, 2017, **53**, 7732-7735.

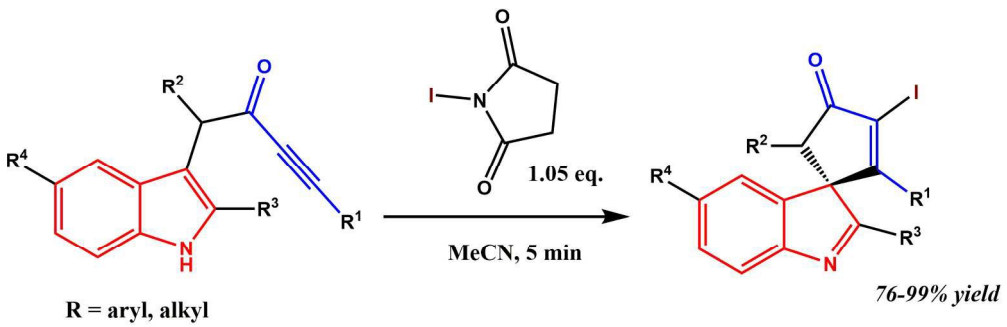
11. (a) Y. Chen, C. L. Huang, X. C. Liu, E. Perl, Z. W. Chen, J. Namgung, G. Subramaniam, G. Zhang and W. H. Hersh, *J. Org. Chem.*, 2014, **79**, 3452-3464; (b) Y. Chen, X. C. Liu, M. Lee, C. L. Huang, I. Inoyatov, Z. W. Chen, A. C. Perl and W. H. Hersh, *Chem.-Eur. J.*, 2013, **19**, 9795-9799; (c) T. Dohi, D. Kato, R. Hyodo, D. Yamashita, M. Shiro and Y. Kita, *Angew. Chem., Int. Ed.*, 2011, **50**, 3784-3787; (d) K. O. Hessian and B. L. Flynn, *Org. Lett.*, 2006, **8**, 243-246; (e) P. B. Koswatta, J. Das, M. Yousufuddin and C. J. Lovely, *Eur. J. Org. Chem.*, 2015, 2603-2613; (f) C. W. Li, C. I. Wang, H. Y. Liao, R. Chaudhuri and R. S. Liu, *J. Org. Chem.*, 2007, **72**, 9203-9207; (g) X. X. Zhang and R. C. Larock, *J. Am. Chem. Soc.*, 2005, **127**, 12230-12231; (h) C. X. Zhou, A. V. Dubrovsky and R. C. Larock, *J. Org. Chem.*, 2006, **71**, 1626-1632.

12. (a) P. Fedoseev, N. Sharma, R. Khunt, D. S. Ermolat'ev and E. V. Van der Eycken, *RSC Adv.*, 2016, **6**, 75202-75206; (b) N. M. Mishra, D. D. Vachhani, S. G. Modha and E. V. Van der Eycken, *Eur. J. Org. Chem.*, 2013, 693-700; (c) G. Tian, P. Fedoseev and E. V. Van der Eycken, *Chem.-Eur. J.*, 2017, **23**, 5224-5227.

13. An attempt to perform the intramolecular *ipso*-iodocyclization with the carbonyl reduced compound ($NaBH_4$) resulted in the formation of a complex mixture.

14. (a) J. S. L. Ibacetalizana, A. H. Jackson, N. Prasitpan and P. V. R. Shannon, *J. Chem. Soc. Perk. Trans. 2*, 1987, 1221-1226; (b) A. H. Jackson and B. Naidoo, *Tetrahedron*, 1969, **25**, 4843-4852; (c) A. H. Jackson and P. P. Lynch, *J. Chem. Soc. Perk. Trans. 2*, 1987, 1215-1219.

View Article Online
DOI: 10.1039/C8CC01474D



181x58mm (300 x 300 DPI)