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Synthetic Methods

A Novel Pd-Catalysed Annulation Reaction for the Syntheses of Pyrroloindoles and Pyrroloquinolines

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Abstract: Pd-catalysed annulation reactions between indole derivatives and internal alkyne esters leading to various pyrrolo[1,2-*a*]indoles and pyrroloquinolines have been developed. The strategy involves an intermolecular addition of the indole nitrogen on to the internal alkyne ester followed by an intramolecular insertion of a vinyl–palladium complex into the carbonyl group. This method offers a facile and practical approach to pyrrolo[1,2-*a*]indoles and pyrroloquinolines.

Pd-catalysed annulation reactions are very important in organic synthesis, providing an access to the rapid construction of organic molecules. These annulation reactions have received much attention due to their broad scope and a high functional-group tolerance.[1] Alkyne annulation, one such potent method, has received considerable attention from synthetic chemists for the synthesis of a wide variety of complex carba- and heterocycles, such as indoles,[2] benzofurans,[3a,b] benzopyrans,[3a] isocoumarins,[3a] indenones,[3c] isoquinolines,[3d,e] α-pyrones[3f] and polycyclic aromatic hydrocarbons.[3g–i]

Pyrroloindole- and pyrroloquinoline-substituted moieties have been found in a wide range of potent biologically active natural products (Figure 1).[4] For example, mitomycins exhibit a diverse array of biological properties, including antibacterial, antitumour and anticancer activities.[5] Flinderoles A and B exhibit selective antimalarial activity.[6] Pyrroloquinolines are active against histamine, platelet activating factor (PAF) and leukotrienes, which are recognised to be of great importance in asthma.[4g] Oxidised and reduced derivatives of pyrroloquinolines have gained considerable attention in the area of drug discovery, agrochemistry and material science.[7] Excellent biological activity and medicinal importance of these molecules encourage synthetic chemists to develop facile synthetic approaches to access pyrrolo[1,2-*a*]indoles and pyrroloquinolines.

Our prior report describing the synthesis of highly substituted pyrrolo[1,2-*a*]indoles involved $Cu(OTf)_2$ catalysed formal [3+2] cycloaddition reaction, which generated three contiguous stereocentres in a highly regio- and diastereoselective manner.[8] However, this method was limited in substrate scope as only more activated ethylindole cinnamates (push–pull ester) acted as dienophiles and underwent a formal [3+2] cycloaddition reaction. All the other dienophiles, such as various cinnamate derivatives and the corresponding alkyne ester derivatives, failed to undergo a cycloaddition reaction. Inspired by many reports in the literature regarding annulation reactions of alkynes using metal catalysts, it was envisioned that alkyne activation by metals followed by an intermolecular nucleophilic attack of the indole nitrogen and insertion of the resulting vinyl–metal complex would afford the desired pyrroloindole derivatives (Scheme 1). To check our hypothesis, secondary alcohol **5** was treated with internal alkyne ester **10** using metal catalysts, such as $Pd(OAc)_2$, $[Pd(PPh_3)_2Cl_2]$ and $[Pd(CH_3CN)_2Cl_2]$, but to our disappointment all these catalysts failed to work for the synthesis of pyrroloindoles. The main

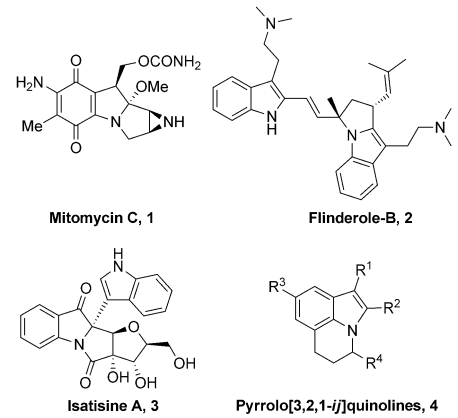
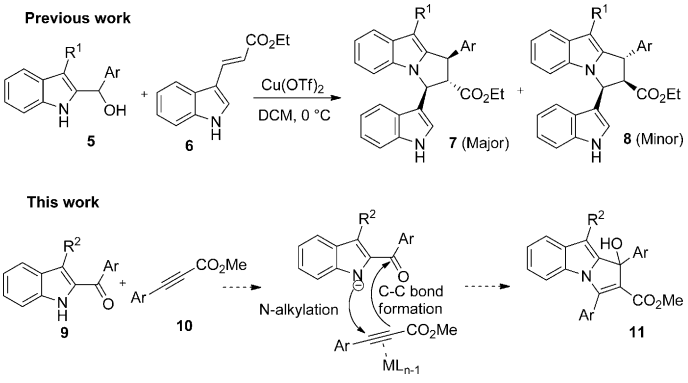


Figure 1. Biologically active pyrroloindole and pyrroloquinoline derivatives.



Scheme 1. Planning for the annulation reaction.

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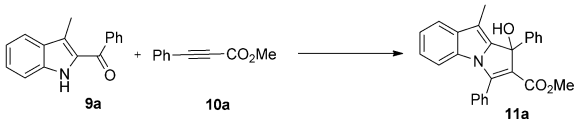
problem in this reaction was the compatibility of the highly reactive secondary alcohol with a comparatively less reactive alkyne moiety; thus it was decided to synthesise 2-carbonyl indoles. Because of the high nucleophilicity of the indole C-3 position, it has always been challenging to achieve the alkylation at N-1 in preference to C-3 position. Numerous reports are available in the literature describing a metal-catalysed C-3 alkylation but very few of them are for the alkylation at C-2 or N-1 position.[9] To avoid the complications initially we blocked C-3 position of the indole.

To verify our hypothesis depicted in Scheme 1, ketone **9a** and alkyne ester **10a** were treated with various metal catalysts in combination with different types of bases and oxidants. Preliminary studies were performed with the aim to find a suitable catalyst to promote the reaction between **9a** and **10a**. Since the annulation reactions of alkyne compounds are known mostly with $Pd(OAc)_2$ as a metal catalyst, we also chose it as our initial screening catalyst.

Initially the reaction was performed using $Pd(OAc)_2$ (5 mol%) and $CuCl_2$ as oxidant in DMF at 75 °C (Table 1); however, it failed to afford the desired product and the starting material was recovered. Uses of other oxidants, such as CuCl, CuBr and phenyliodine diacetate (PIDA), were also unsuccessful. To our delight, treatment of the mixture of ketone **9a** and alkyne ester **10a** with $Pd(OAc)_2$ (5 mol%) and AgOAc (2 equiv) in CH_3CN/dioxane (1:1) at 75 °C afforded compound **11a** in 22% yield. Encouraged by this result, various solvents and bases/oxidants were screened. The best results were obtained when $Pd(OAc)_2$ was used in presence of Cs_2CO_3 (2 equiv) in DMF at 75 °C with the highest yield of 95% (entry 15). This annulation reaction with other bases/oxidants, such as AgOAc, K_2CO_3, $Cu(OAc)_2$, KOH and KO*t*Bu, gave lower yields compared to Cs_2CO_3 (entries 9–14). Among several Pd catalysts screened, $[Pd(CH_3CN)_2Cl_2]$ (entry 16) and $[Pd(PPh_3)_2Cl_2]$ (entry 17) gave 77% and 93% yield, respectively. It is worth mentioning that a decrease in catalyst and base loadings lowered the rate of reaction, although the rate and yields of the reaction were unaffected when a higher catalyst and base loading were used. The reaction was sluggish at room temperature, and 75 °C was found to be the optimum temperature.

Table 1. Optimisation of the annulation reaction.[a]



Entry	Catalyst	Base/Oxidant	Solvent	Yield [%]
1	$Pd(OAc)_2$	$CuCl_2$	DMF	NR
2	$Pd(OAc)_2$	CuCl	DMF	NR
3	$Pd(OAc)_2$	CuBr	DMF	NR
4	$Pd(OAc)_2$	PIDA	DMF	NR
5	$Pd(OAc)_2$	AgOAc	1,4-dioxane	NR
6	$Pd(OAc)_2$	AgOAc	toluene	NR
7	$Pd(OAc)_2$	AgOAc	acetonitrile	NR
8	$Pd(OAc)_2$	AgOAc	CH_3CN/1,4-dioxane (1:1)	22
9	$Pd(OAc)_2$	AgOAc	DMSO	28
10	$Pd(OAc)_2$	AgOAc	DMF	44
11	$Pd(OAc)_2$	K_2CO_3	DMF	47
12	$Pd(OAc)_2$	$Cu(OAc)_2$	DMF	61
13	$Pd(OAc)_2$	KOH	DMF	trace
14	$Pd(OAc)_2$	KO*t*Bu	DMF	trace
15	$Pd(OAc)_2$	Cs_2CO_3	DMF	95
16	$[Pd(CH_3CN)_2Cl_2]$	Cs_2CO_3	DMF	77
17	$[Pd(PPh_3)_2Cl_2]$	Cs_2CO_3	DMF	93
18	$[Pd(PPh_3)_2Cl_2]$	Cs_2CO_3	CH_3CN	48
19	$[Pd(PPh_3)_2Cl_2]$	Cs_2CO_3	toluene	46

[a] Unless specified, reactions were carried out by treating **9a** (0.3 mmol) and **10a** (0.3 mmol) with catalyst (5 mol%) and base (2 equiv) in solvent (2 mL) at 75 °C. NR = no result; PIDA = phenyliodine diacetate.

The substrate scope of the reaction was examined by preparing various pyrroloindole derivatives (Scheme 2). Both electron-withdrawing and -donating substituents on the benzene ring were well tolerated and gave high yields of pyrroloindole derivatives. Heteroaryls, like furan-, thiophene- and naphthalene-substituted internal alkynes also reacted quite well and gave high yields. The structure of pyrroloindole derivative was unambiguously established by single-crystal X-ray analysis of compound **11n** (Figure 2).[10]

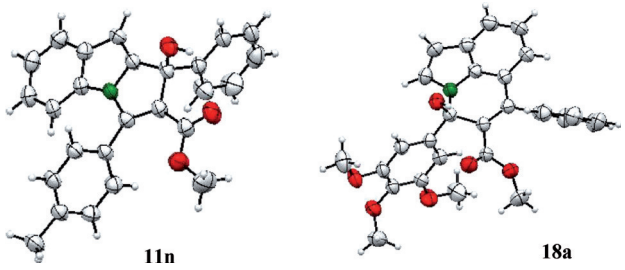
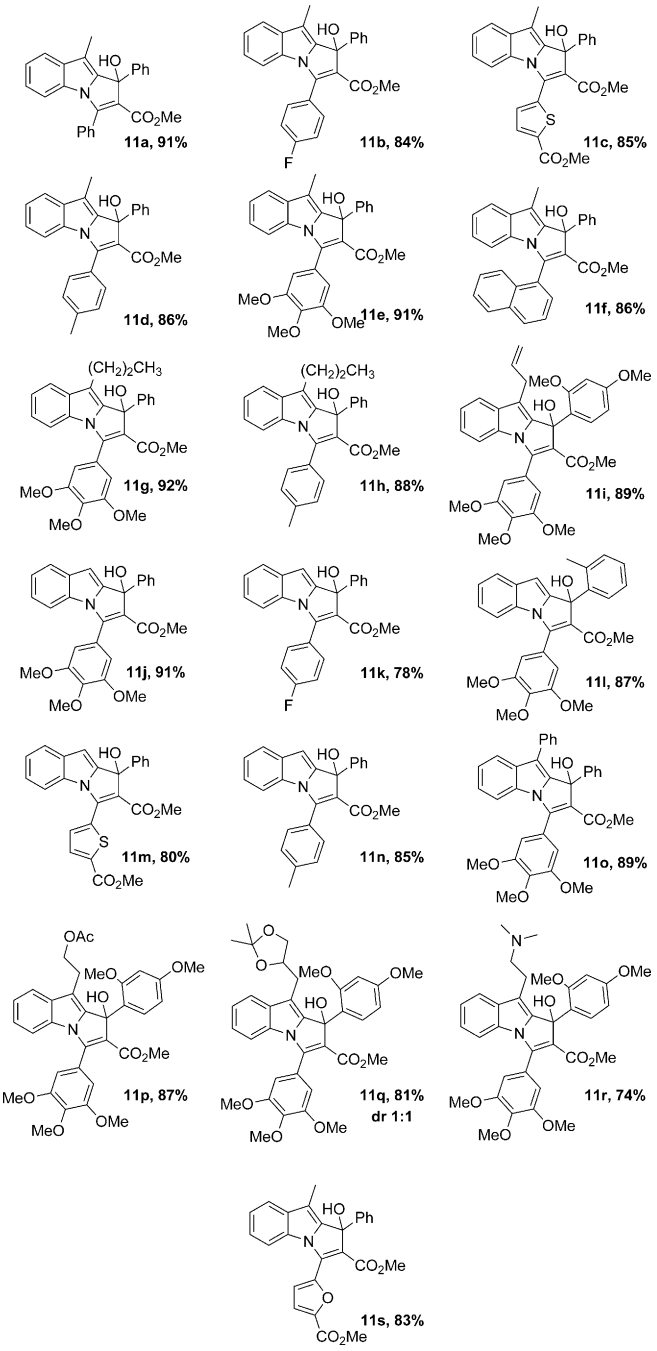


Figure 2. X-ray crystal structures of **11n** and **18a**. Nitrogen (green) and oxygen (red).

Initially, with an anticipation that the indole C-3 position would interfere in the reaction due to its higher nucleophilicity, we carried out all the reactions using C-3 substituted indoles. Just out of curiosity, later the annulation reaction was performed on C-3 unsubstituted indoles. Surprisingly, the reaction went smoothly to afford desired pyrroloindoles in excellent yields. No C-3 alkylation products were observed in these cases.

At this stage, we also became interested in the outcome of the reaction between the indoline derivative **9d'** and alkyne esters **10d** and **10e** following the same reaction conditions. Interestingly, indoline **9d'** on independent reactions with alkyne esters **10d** and **10e** generated pyrroloindoles **11j** and **11n**, respectively (Scheme 3), first by palladium-catalysed aromatisation of indoline to indole[11] and subsequent reaction with alkyne ester.

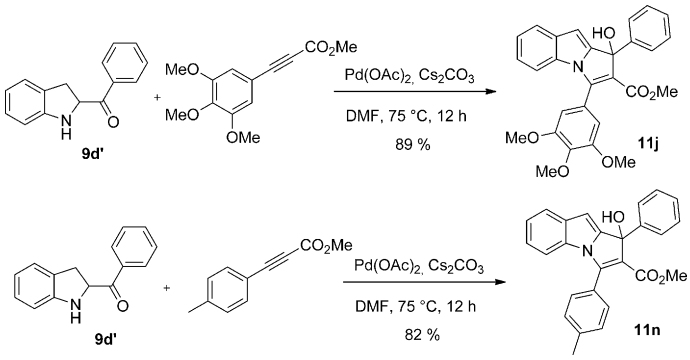
Furthermore, it was observed that pyrrolo[1,2-*a*]indole derivatives **11** converted to more stable compounds **12** when kept in $CDCl_3$ at room temperature for 5 min in the NMR tube (Scheme 4). These structures of **12** were established by spectroscopic data. A similar rearrangement was also observed



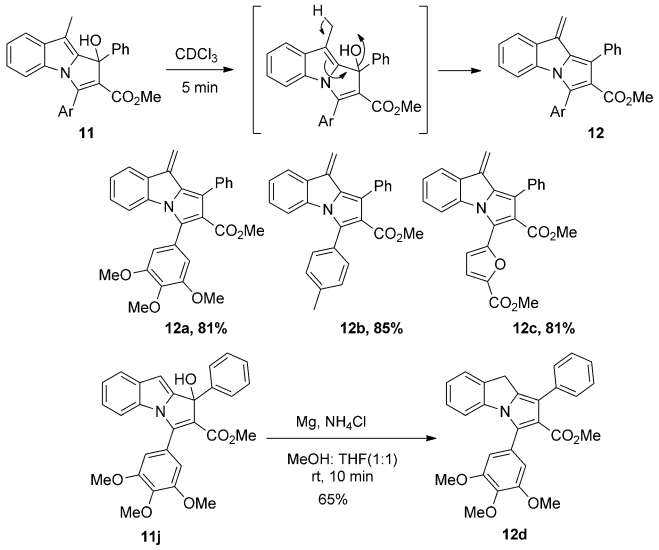
Scheme 2. Substrate scope of the reaction. In the case of compound **11 a** and **11 d**, the reaction was carried out on a 1.3 mmol scale.

under hydrogenation conditions, such as with $Pd/C/H_2$ or $Pd(OH)_2/H_2$ or Pt/H_2 and Mg/NH_4Cl, in the case of compound **11 j**.

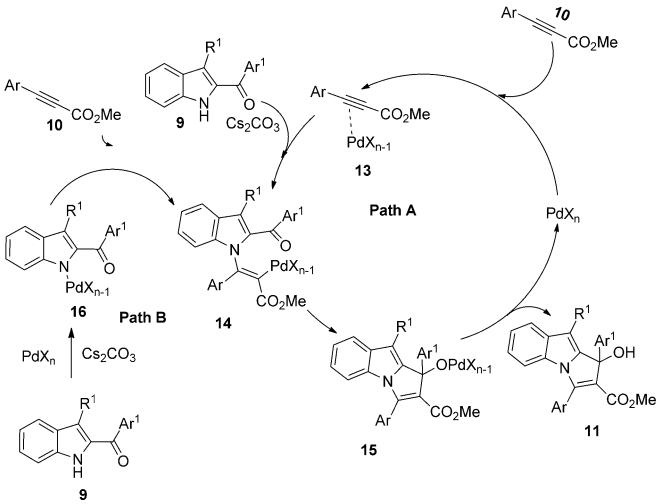
Mechanistically, two different plausible reaction pathways for this annulation reaction are proposed (Scheme 5). In path A, an intermolecular addition of the indole nitrogen of **9** onto the internal alkyne ester **13** activated by the Pd catalyst takes place first to form vinyl–palladium complex **14**, which followed by intramolecular insertion into the carbonyl group forms intermediate **15**.[12] Finally, protonolysis of the resulting metal complex generates tertiary alcohol **11**. In path B, pallada-



Scheme 3. Annulation reaction with 2-carbonyl indoline.



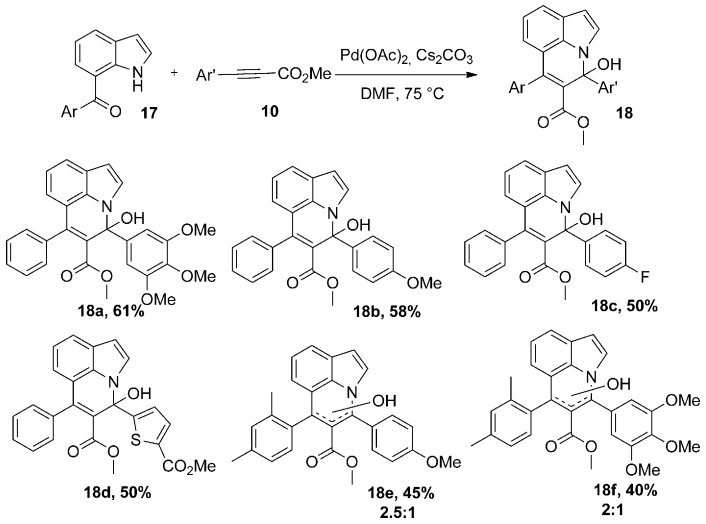
Scheme 4. Rearrangement of allylic tertiary alcohol. In the case of compound **12 a**, the reaction was carried out on a 1.0 mmol scale.



Scheme 5. Plausible mechanism.

tion of indole **9** yields the palladium intermediate **16.** This is followed by a *syn* addition of **16** to the alkyne ester to generate **14**, which then affords **11** as explained in path A.

Finally, we also became interested in the reaction of compound **17** with internal alkyne ester **10**. The annulation reaction between 7-carbonylindole **17** and **10** in the presence of $Pd(OAc)_2$ (5 mol%) and Cs_2CO_3 (2 equiv) in DMF at 75 °C generated pyrroloquinoline **18**, presumably by isomerisation of the initially formed allylic tertiary alcohol to the N,O-acetal (Scheme 6). The structure of the pyrroloquinoline derivative was unambiguously established by single-crystal X-ray analysis of compound **18a** (Figure 2).[10] This reaction was also found to be general with a larger substrate scope. Many examples of pyrroloquinoline derivatives were prepared in good yields.



Scheme 6. Synthesis of pyrroloquinolines. In the case of compound **18c**, the reaction was carried out on a 1.1 mmol scale.

In conclusion, a novel and facile synthetic method for the syntheses of pyrroloindoles and pyrroloquinolines has been developed using a Pd-catalysed annulation reaction of internal alkyne esters with 2- or 7-carbonyl indoles. The highlight of this method is the construction of C–N and C–C bond formation in one pot.

Experimental Section

Full details of experimental procedures, characterisation data and NMR spectra can be found in the Supporting Information.

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Keywords: alkynes · annulation · cyclization · heterocycles · palladium

[1] a) N. E. Schore, *Chem. Rev.* **1988**, *88*, 1081 – 1119; b) M. Pfeffer, *Recl. Trav. Chim. Pays-Bas.* **2010**, *109*, 567 – 576; c) E. Negishi, C. Cope'ret, S. Ma, S.-Y. Liou, F. Liu, *Chem. Rev.* **1996**, *96*, 365 – 394; d) I. Ojima, M. Tzamarioudaki, Z. Li, R. J. Donovan, *Chem. Rev.* **1996**, *96*, 635 – 662; e) W. Chen, J. Cao, X. Huang, *Org. Lett.* **2008**, *10*, 5537 – 5540; f) J. Zhao, K. Oniwa, N. Asao, Y. Yamamoto, T. Jin, *J. Am. Chem. Soc.* **2013**, *135*, 10222 – 10225; g) Z. Liu, R. C. Larock, *J. Org. Chem.* **2007**, *72*, 223 – 232; h) Z. Li, Y. Gao, Z. Jiao, N. Wu, D. Z. Wang, Z. Yang, *Org. Lett.* **2008**, *10*, 5163 – 5166; i) P. Gandeepan, C.-H. Cheng, *Org. Lett.* **2013**, *15*, 2084 – 2087.

[2] a) R. C. Larock, E. K. Yum, *J. Am. Chem. Soc.* **1991**, *113*, 6689 – 6690; b) R. C. Larock, E. K. Yum, M. D. Refvik, *J. Org. Chem.* **1998**, *63*, 7652 – 7662; c) S. G. Newman, M. Lautens, *J. Am. Chem. Soc.* **2010**, *132*, 11416 – 11417; d) T. Nanjo, C. Tsukano, Y. Takemoto, *Org. Lett.* **2012**, *14*, 4270 – 4273.

[3] a) R. C. Larock, E. K. Yum, M. J. Doty, K. K. C. Sham, *J. Org. Chem.* **1995**, *60*, 3270 – 3271; b) S. Wang, P. Li, L. Yu, L. Wang, *Org. Lett.* **2011**, *13*, 5968 – 5971; c) R. C. Larock, M. J. Doty, S. J. Cacchi, *J. Org. Chem.* **1993**, *58*, 4579 – 4583; d) K. R. Roesch, R. C. Larock, *J. Org. Chem.* **1998**, *63*, 5306 – 5307; e) D. Yang, S. Burugupalli, D. Daniel, Y. Chen, *J. Org. Chem.* **2012**, *77*, 4466 – 4472; f) R. C. Larock, X. Han, M. J. Doty, *Tetrahedron Lett.* **1998**, *39*, 5713 – 5716; g) R. C. Larock, M. J. Doty, Q. Tian, J. M. Zenner, *J. Org. Chem.* **1997**, *62*, 7536 – 7537; h) R. C. Larock, Q. Tian, *J. Org. Chem.* **1998**, *63*, 2002 – 2009; i) F. Ji, X. Li, W. Wu, H. Jiang, *J. Org. Chem.* **2014**, *79*, 11246 – 11253.

[4] For representative examples of pyrroloindoles see: a) L. Hao, Y. Pan, T. Wang, M. Lin, L. Chen, Z.-P. Zhan, *Adv. Synth. Catal.* **2010**, *352*, 3215 – 3222; b) R. Kakadiya, H. Dong, P.-C. Lee, N. Kapuriya, X. Zhang, T.-C. Chou, T.-C. Lee, K. Kapuriya, A. Shah, T.-L. Su, *Bioorg. Med. Chem.* **2009**, *17*, 5614 – 5626; c) M. Tanaka, S. Sagawa, J.-I. Hoshi, F. Shimoma, K. Yasue, M. Ubukata, T. Ikemoto, Y. Hase, M. Takahashi, T. Sasase, N. Ueda, M. Matsushita, T. Inaba, *Bioorg. Med. Chem.* **2006**, *14*, 5781 – 5794; d) G. Abbiati, A. Casoni, V. Canevari, D. Nava, E. Rossi, *Org. Lett.* **2006**, *8*, 4839 – 4842; for representative examples of pyrroloquinolines see: e) C. B. Hartline, E. A. Harden, S. L. Williams-Aziz, N. L. Kushner, R. L. Brideau, E. R. Kern, *Antiviral Res.* **2005**, *65*, 97 – 105; f) M. Layek, M. A. Reddy, R. A. V. Dhanunjaya, M. Alvala, M. K. Arunasree, A. Islam, K. Mukkanti, J. Iqbal, M. Pal, *Org. Biomol. Chem.* **2011**, *9*, 1004 – 1007; g) M. Isaac, A. Slassi, A. O'Brien, L. Edwards, N. MacLean, D. Bueschkens, D. K. H. Lee, K. McCallum, I. D. Lannoy, L. Demchyshyn, R. Kamboj, *Bioorg. Med. Chem. Lett.* **2000**, *10*, 919 – 921; h) D. Paris, M. Cottin, P. Demonchaux, G. Augert, P. Dupassieux, P. Lenoir, M. J. Peck, D. Jasserand, *J. Med. Chem.* **1995**, *38*, 669 – 685.

[5] a) U. Galm, M. H. Hager, S. G. V. Lanen, J. Ju, J. S. Thorson, B. Shen, *Chem. Rev.* **2005**, *105*, 739 – 758; b) W. A. Remers, R. T. Dorr, in *Alkaloids: Chemical and Biological Perspectives, Vol. 6* (Ed.: S. W. Pelletier), Wiley New York (USA), **1988**, 1 – 74; c) S. J. Danishefsky, J. M. Schkeryantz, *Synlett* **1995**, 475 – 490.

[6] a) L. S. Fernandez, M. F. Jobling, K. T. Andrews, V. M. Avery, *Phytother. Res.* **2008**, *22*, 1409 – 1412; b) L. S. Fernandez, M. S. Buchanan, A. R. Carroll, Y. J. Feng, R. J. Quinn, V. M. Avery, *Org. Lett.* **2009**, *11*, 329 – 332; c) L. S. Fernandez, M. L. Sykes, K. T. Andrews, V. M. Avery, *Int. J. Antimicrob. Agents* **2010**, *36*, 275 – 279; d) D. H. Dethe, R. D. Erande, A. Ranjan, *J. Am. Chem. Soc.* **2011**, *133*, 2864 – 2867; e) R. M. Zeldin, F. D. Toste, *Chem. Sci.* **2011**, *2*, 1706 – 1709; f) R. Vallakati, J. A. May, *J. Am. Chem. Soc.* **2012**, *134*, 6936 – 6939.

[7] Examples include: a) S. Lucas, M. Negri, R. Heim, C. Zimmer, R. W. Hartmann, *J. Med. Chem.* **2011**, *54*, 2307 – 2319; b) P. Angibaud, X. Bourdrez, A. Devine, D. W. End, E. Freyne, Y. Ligny, P. Muller, G. Mannens, I. Pilatte, V. Poncelet, S. Skrzat, G. Smets, J. Van Dun, P. Van Remoortere, M. Veneta, W. Wouters, *Bioorg. Med. Chem. Lett.* **2003**, *13*, 1543 – 1547; c) M. A. Ashwell, R. Palma, S. Eathiraj, U. S. Patent 7960134, **2011**.

[8] D. H. Dethe, R. Boda, S. Das, *Chem. Commun.* **2013**, *49*, 3260 – 3262.

[9] a) B. Gianluigi, M. B. Egle, F. Andrea, G. Silvia, *Beilstein J. Org. Chem.* **2012**, *8*, 1730 – 1746; b) L. Jiao, T. Bach, *J. Am. Chem. Soc.* **2011**, *133*, 12990 – 12993; c) L. Jiao, E. Herdtweck, T. Bach, *J. Am. Chem. Soc.* **2012**, *134*, 14563 – 14572; d) Y. Zhu, V. H. Rawal, *J. Am. Chem. Soc.* **2012**, *134*, 111 – 114; e) W. Lu, C. Jia, T. Kitamura, Y. Fujiwara, *Org. Lett.* **2000**, *2*, 2927 – 2930.

[10] CCDC 1411304 (**11 n**) and 1411305 (**18 a**) contain the supplementary crystallographic data for this paper. These data are provided free of charge by The Cambridge Crystallographic Data Centre.

[11] H. Takayoshi, M. Kohsuke, M. Tomoo, E. Kohki, K. Kiyotomi, *Tetrahedron Lett.* **2003**, *44*, 6207 – 6210.

[12] L. G. Quan, M. Lamrani, Y. Yamamoto, *J. Am. Chem. Soc.* **2000**, *122*, 4827 – 4828.

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