Organic & Biomolecular Chemistry

ROYAL SOCIETY OF CHEMISTRY

COMMUNICATION

View Article Online
View Journal | View Issue

Cite this: *Org. Biomol. Chem.*, 2021, **19**, 9641

Received 7th October 2021,
Accepted 27th October 2021

DOI: 10.1039/d1ob01966j

rsc.li/obc

Synthesis of tetracyclic spiroindolines by an interrupted Bischler–Napieralski reaction: total synthesis of akuammicine†

Matteo Faltracco and Eelco Ruijter *

Judicious substrate design allows interruption of the classical Bischler–Napieralski reaction, providing access to a range of diversely substituted tetracyclic spiroindolines. These complex polycyclic scaffolds are valuable building blocks for the construction of indole alkaloids, as showcased in a concise total synthesis of (±)-akuammicine.

Cascade reactions allow the rapid generation of molecular complexity through multiple sequential bond-forming (and bond-breaking) events in a one-pot process. These exceptional advantages over traditional stepwise procedures make them particularly suited to efficiently access complex molecules such as natural products.[1] Consequently, the use of cascade reactions in total synthesis is a well-established and prolific field that is constantly expanding in both methodology and scope, covering polyketides,[2] alkaloids,[3] terpenes,[4] and steroids.[5] Owing to their abundance, structural variety, and diverse biological activities, indole alkaloids occupy a prominent position among natural products (Fig. 1).[6] As a result, they have attracted considerable interest from the synthetic community, leading to numerous novel approaches to this compound class in recent years.[7]

Synthetic approaches toward β-carboline alkaloids (such as harmicine (**1**), Fig. 1) continue to rely on the classical Pictet-Spengler and Bischler–Napieralski reactions and their variations. Discovered as early as 1893, the Bischler–Napieralski reaction[8] (together with its contemporary variations) is still an object of intensive study in natural product synthesis.[9]

Following our interest in indole alkaloids and related compounds,[10] we recently discovered that reaction of styrylacetamides **4** under typical Bischler–Napieralski conditions ($POCl_3$, MeCN, Δ) leads to near-quantitative formation of carbazoles **5** instead of the expected dihydro-β-carbolines (Scheme 1A).[11] Our ensuing mechanistic investigation revealed a highly complex cascade pathway (Scheme 2) which proceeds *via* several intriguing intermediates.[11] In particular, the tetracyclic spiroindoline **10** caught our interest, owing to its wide-spread presence in indole alkaloids.[7i] Unfortunately, our efforts to isolate **10** (R^1 = H) were futile, frustrated by an elimination step (Scheme 2A) that always follows. Indeed, we only succeeded in diverting the cascade towards a different carbazole product if R_3 = Br (**6**, Scheme 1A). This strongly suggests that

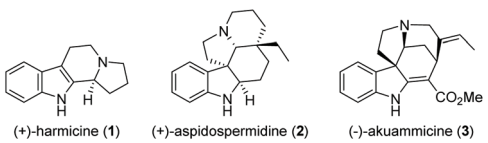
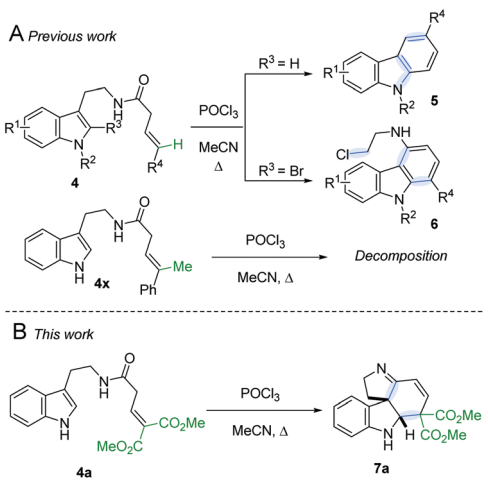


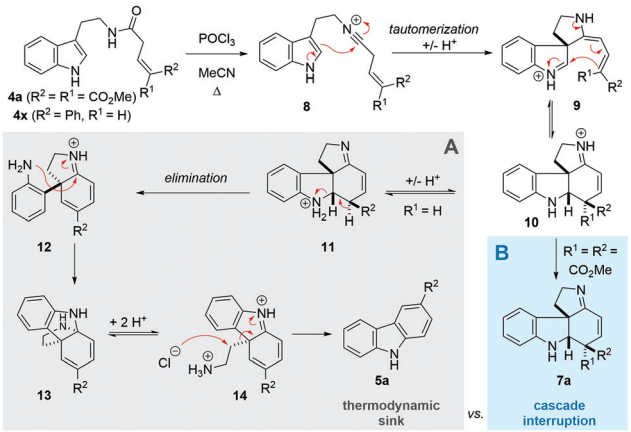
Fig. 1 Representative indole alkaloids.



Scheme 1 A. Previously reported carbazole formation B. Cascade interrupted at the tetracyclic intermediate.

Department of Chemistry & Pharmaceutical Sciences, Amsterdam Institute of Molecular & Life Sciences (AIMMS), Vrije Universiteit Amsterdam, De Boelelaan 1108, 1081 HZ Amsterdam, The Netherlands. E-mail: e.ruijter@vu.nl

†Electronic supplementary information (ESI) available: Experimental procedures, characterization data and ^{1}H and ^{13}C NMR spectra. See DOI: 10.1039/d1ob01966j



Scheme 2 Previous cascade mechanism towards carbazoles (A) and interruption at the tetracyclic intermediate (B).

interrupting the cascade at the stage of tetracyclic scaffold **10** is challenging due to the high thermodynamic driving force for the system to evolve towards aromatic products. Moreover, the intermediate **10** could revert back to **9** by retro-Mannich reaction and subsequently undergo Plancher rearrangement, irreversibly leading to β-carbolines.[12]

A potentially viable strategy to achieve the desired interruption would be to employ a γ,γ-disubstituted vinylacetamide as the substrate, as the elimination cannot occur in this case. Since the introduction of a methyl group at this position only led to decomposition (Scheme 1A), and given our success in employing ester R^4 substituents,[11] we identified malonate-derived tryptamide **4a** as a promising substrate. To our delight, upon subjecting **4a** to the cyclization conditions (Scheme 1B), we were able to isolate imine **7a** in 27% yield after basic workup. Optimization of the conditions (Table 1) showed that only $POCl_3$ is able to promote the reaction (entries 1–5). Conveniently, we could avoid the strictly anhydrous conditions required for (both reactions and storage of) the highly reactive Tf_2O that is often employed for related transformations.[9a–d]

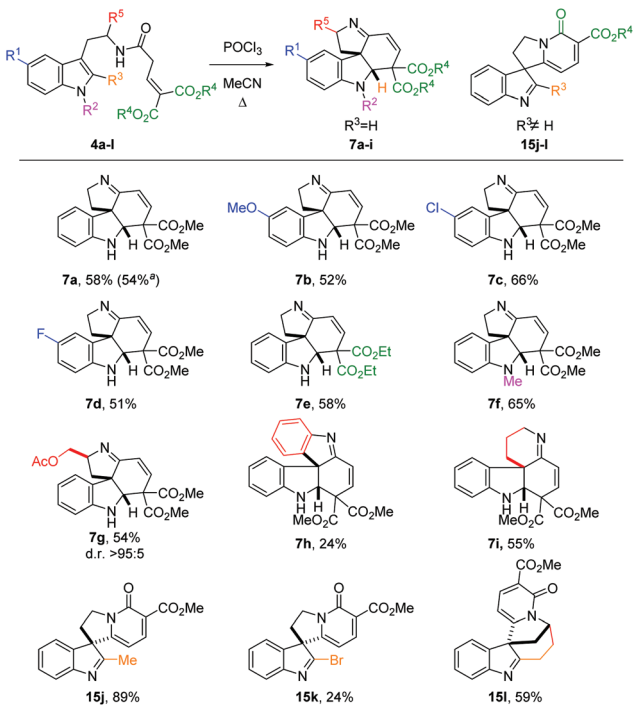
Small adjustments of $POCl_3$ stoichiometry and reaction time (entries 6–10) allowed us to increase the isolated yield of **7a** to 58%. The reaction proceeded with nearly identical efficiency on a 1.5 g scale.

We then focused on the generality of the process, subjecting differently substituted amide precursors to the optimized conditions (Scheme 3). Substituents on the benzenoid ring do not significantly affect the reactivity: reaction of the 5-F- and 5-MeO-substituted tryptamides afforded the corresponding tetracyclic scaffolds **7b** and **7d** in nearly identical yield (51–52%). The best result was obtained using the Cl-substituted amide **4c**, producing the tetracyclic product **7c** in 66% yield. Ethyl esters are also well tolerated, affording the desired product **7e** in the same yield as the benchmark product **7a**. The introduction of an N1-substituent on the indole ring proved to be beneficial, possibly because of the more reactive iminium ion intermediate (*cf.* **9**, Scheme 2) favoring the cyclization step. Substituents on the R^5 position are also tolerated: amide **4g**, derived from tryptophanol, was converted to **7g** in good yield (54%) as a single diastereomer. Replacing the ethyl-

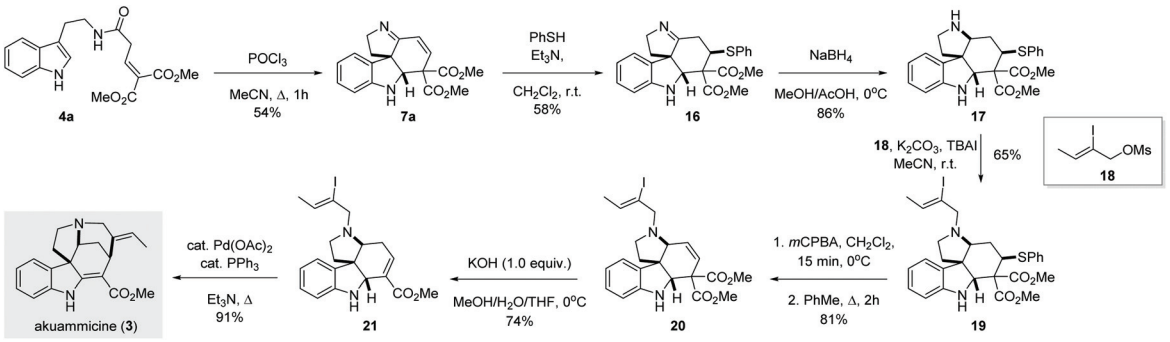
Table 1 Reaction optimization

Entry[a]	Reagent	Solvent	T (°C)	Yield[b] (%)
1	$POCl_3$	MeCN	Reflux	27[c]
2	Tf_2O/2-Cl-Py	MeCN	Reflux	—
3	Tf_2O/3-CN-Py	MeCN	Reflux	—
4	Ac_2O	MeCN	Reflux	—
5	TFAA	MeCN	Reflux	—
6	$POCl_3$	Toluene	90	16
7[d]	$POCl_3$	MeCN	Reflux	20
8[e]	$POCl_3$	MeCN	Reflux	18
9[f]	$POCl_3$	MeCN	Reflux	37
10[g]	$POCl_3$	MeCN	Reflux	58[c]
11[h]	$POCl_3$	MeCN	Reflux	48
12[g]	$POCl_3$	MeCN[i]	Reflux	58[c]

[a] Reaction conditions **4a** (0.2 mmol), reagent (0.3 mmol) solvent (1 mL). [b] Determined by ^1H NMR using 2,5-dimethylfuran as an internal standard. [c] Isolated yield. [d] Performed with 0.4 mmol of $POCl_3$. [e] Performed with 0.5 mmol of $POCl_3$. [f] Additional $POCl_3$ (0.1 mmol) added after 30 min (1 h total reaction time). [g] Additional $POCl_3$ (0.1 mmol) added after 30 min and 1 h (1.5 h total reaction time). [h] Additional $POCl_3$ (0.1 mmol) added after 30 min, 1 h and 1.5 h (2 h total reaction time). [i] Non-anhydrous MeCN was used.



Scheme 3 Scope of the cyclization. Reaction conditions: **4** (0.2 mmol), $POCl_3$ (0.3 mmol), MeCN (1.0 mL), 1.5 h, reflux. Additional portions of $POCl_3$ (0.1 mmol) were added after 30 min and 1 h. [a]Reaction performed on 4.49 mmol scale.



Scheme 4 Total synthesis of (±)-akuammicine.

ene linker with an *ortho*-phenylene linker also furnished the desired spiro product **7h**, albeit in lower yield (24%). Gratifyingly, the homotryptamine derivative **4i** was smoothly converted to the corresponding tetracycle **7i** in 55% yield. Interestingly, when substituents are present on the C2 position, a different type of product was observed (**15j–l**). Indeed, when $R^3 \neq H$, the C2-position of the indole becomes too hindered to undergo ring closure. In this case, enamine **9** can only undergo cycloaromatization (after *E*/*Z* isomerization) by attack on one of the two ester moieties to give the corresponding 2-pyridones **15**. Curiously, when R^3 = Me, we observed the highest yield (**15j**, 89%), possibly owing to the higher stability of the product. On the other hand, the bromide-substituted product **15k** was obtained in lower yield. This is hardly surprising, considering the typical lability of imidoyl bromides. Similarly, the intriguing, but rather strained polycycle **15l** was isolated in 59% yield. Indeed, for both **15k** and **15l** decomposition was already observed during purification, accounting for the lower yields.

Once we established the scope and limitation of this transformation, we set out to investigate the utility of these valuable intermediates in the total synthesis of indole alkaloids. Notably, we envisioned the transformation of **7a** to akuammicine (Scheme 4). Unfortunately, **7a** proved recalcitrant towards selective 1,2-reduction under various conditions ($NaBH_4$, $LiBH_4$, $NaBH_3CN$, $NaHB(OAc)_3$, or Et_3SiH, both in the presence and absence of acidic promotors). Presumably, the conjugated imine is too rigid and/or sterically congested to undergo efficient 1,2-reduction. To circumvent this issue, we first performed a conjugate addition with thiophenol to give imine **16**, which could then be smoothly reduced by treatment with $NaBH_4$ to give the desired amine **17** in 86% yield. Subsequent alkylation with **18** afforded the tertiary amine **19**. In order to reinstall the double bond, the thioether was first oxidized and then eliminated in a two-step procedure, producing the olefin **20** in 81% yield. Subsequently, the use of KOH (1.0 equiv.) in a MeOH/THF/H_2O mixture at 0 °C afforded **21** *via* one-pot saponification, decarboxylation and double bond migration.[13] Finally, known intermediate **21** was converted to (±)-akuammicine (**3**) by intramolecular Heck reaction as reported previously.[14]

In conclusion, we report an alternative, interrupted variation of our previously serendipitously discovered diverted Bischler–Napieralski cascade reaction. The reaction generates complex polycyclic scaffolds in a single step and is compatible with a wide range of substituents, allowing straightforward access to highly functionalized and versatile intermediates. Moreover, tetracyclic indoline **7a** could be converted in only six steps to akuammicine, constituting a very short and efficient total synthesis of this Strychnos-type alkaloid. The scope and variability of the interrupted Bischler–Napieralski cyclization likely allow access to various other natural products as well.

Conflicts of interest

The authors declare no competing financial interest.

Notes and references

1 (*a*) K. C. Nicolaou, D. J. Edmonds and P. G. Bulger, *Angew. Chem., Int. Ed.*, 2006, **45**, 7134–7186; (*b*) Y. Jiang, R. E. McNamee, P. J. Smith, A. Sozanschi, Z. Tong and E. A. Anderson, *Chem. Soc. Rev.*, 2021, **50**, 58–71.

2 (*a*) H. C. Hailes, S. Handa, P. F. Leadlay, I. C. Lennon, S. V. Ley and J. Staunton, *Tetrahedron Lett.*, 1994, **35**, 315–318; (*b*) S. V. Ley, D. S. Brown, J. A. Clase, A. J. Fairbanks, I. C. Lennon, H. M. I. Osborn, E. S. E. Stokes and D. J. Wadsworth, *J. Chem. Soc., Perkin Trans. 1*, 1998, 2259–2276; (*c*) R. Hofs, M. Walker and A. Zeeck, *Angew. Chem., Int. Ed.*, 2000, **39**, 3258–3261; (*d*) C. D. Vanderwal, D. A. Vosburg, S. Weiler and E. J. Sorensen, *J. Am. Chem. Soc.*, 2003, **125**, 5393–5407.

3 (*a*) G. I. Elliott, J. Velcicky, H. Ishikawa, Y. Li and D. L. Boger, *Angew. Chem., Int. Ed.*, 2006, **45**, 620–622; (*b*) L. F. Tietze and Y. Zhou, *Angew. Chem., Int. Ed.*, 1999, **38**, 2045–2047; (*c*) J. Cassayre, F. Gagosz and S. Z. Zard, *Angew. Chem., Int. Ed.*, 2002, **41**, 1783–1785; (*d*) C. H. Heathcock, M. M. Hansen, R. B. Ruggeri and J. C. Kath, *J. Org. Chem.*, 1992, **57**, 2544–2553; (*e*) F. von Nussbaum, *Angew. Chem., Int. Ed.*, 2003, **42**, 3068–3071.

4 (*a*) E. J. Corey and S. Lin, *J. Am. Chem. Soc.*, 1996, **118**, 8765–8766; (*b*) D. W. C. MacMillan, L. E. Overman and L. D. Pennington, *J. Am. Chem. Soc.*, 2001, **123**, 9033–9044; (*c*) E. Lee, C. H. Yoon, Y. Sung, Y. K. Kim, M. Yun and S. Kim, *J. Am. Chem. Soc.*, 1997, **119**, 8391–8392; (*d*) D. J. Kerr, A. C. Willis and B. L. Flynn, *Org. Lett.*, 2004, **6**, 457–460; (*e*) B. L. Ashfeld and S. F. Martin, *Org. Lett.*, 2005, **7**, 4535–4537.

5 M. B. Gravestock, W. S. Johnson, B. E. McCarry, R. J. Parry and B. E. Ratcliffe, *J. Am. Chem. Soc.*, 1978, 4274–4282.

6 (*a*) S. E. O'Connor and J. J. Maresh, *Nat. Prod. Rep.*, 2006, **23**, 532–547; (*b*) M. Ishikura, K. Yamada and T. Abe, *Nat. Prod. Rep.*, 2010, **27**, 1630–1680; (*c*) M. Ishikura, T. Abe, T. Choshi and S. Hibino, *Nat. Prod. Rep.*, 2013, **30**, 694–752; (*d*) M. Ishikura, T. Abe, T. Choshi and S. Hibino, *Nat. Prod. Rep.*, 2015, **32**, 1389–1471.

7 (*a*) B. M. Trost and M. Osipov, *Chem. – Eur. J.*, 2015, **21**, 16318–16343; (*b*) W. Zi, Z. Zuo and D. Ma, *Acc. Chem. Res.*, 2015, **48**, 702–711; (*c*) M. Ito, Y. K. Tahara and T. Shibata, *Chem. – Eur. J.*, 2016, **22**, 5468–5477; (*d*) M. M. Heravi, S. Rohani, V. Zadsirjan and N. Zahedi, *RSC Adv.*, 2017, **7**, 52852–52887; (*e*) H. Liu and Y. Jia, *Nat. Prod. Rep.*, 2017, **34**, 411–432; (*f*) J. Song, D.-F. Chen and L.-Z. Gong, *Natl. Sci. Rev.*, 2017, **4**, 381–396; (*g*) M. S. Kirillova, F. M. Miloserdov and A. M. Echavarren, *Org. Chem. Front.*, 2018, **5**, 273–287; (*h*) B. P. Pritchett and B. M. Stoltz, *Nat. Prod. Rep.*, 2018, **35**, 559–574; (*i*) J. M. Saya, E. Ruijter and R. V. A. Orru, *Chem. – Eur. J.*, 2019, **25**, 8916–8935.

8 A. Bischler and B. Napieralski, *Chem. Ber.*, 1893, **26**, 1903–1908.

9 (*a*) S. Wang, R. Si, Q. Zhuang, X. Guo, T. Ke, X. Zhang, F. Zhang and Y. Tu, *Angew. Chem., Int. Ed.*, 2020, **59**, 21954–21958; (*b*) M. Mewald, J. W. Medley and M. Movassaghi, *Angew. Chem., Int. Ed.*, 2014, **53**, 11634–11639; (*c*) K. L. White and M. Movassaghi, *J. Am. Chem. Soc.*, 2016, **138**, 11383–11389; (*d*) T. Kang, K. L. White, T. J. Mann, A. H. Hoveyda and M. Movassaghi, *Angew. Chem., Int. Ed.*, 2017, **56**, 13857–13860; (*e*) P. Magnus, A. H. Payne and L. Hobson, *Tetrahedron Lett.*, 2000, **41**, 2077–2081; (*f*) P. Magnus, L. Gazzard, L. Hobson, A. H. Payne and V. Lynch, *Tetrahedron Lett.*, 1999, **40**, 5135–5138.

10 (*a*) C. de Graaff, L. Bensch, S. J. Boersma, R. C. Cioc, M. J. van Lint, E. Janssen, N. J. Turner, R. V. A. Orru and E. Ruijter, *Angew. Chem., Int. Ed.*, 2015, **54**, 14133–14136; (*b*) J. M. Saya, E. D. H. van Wordragen, R. V. A. Orru and E. Ruijter, *Eur. J. Org. Chem.*, 2019, 5156–5160; (*c*) J. M. Saya, T. R. Roose, J. J. Peek, B. Weijers, T. J. S. de Waal, C. M. L. Vande Velde, R. V. A. Orru and E. Ruijter, *Angew. Chem., Int. Ed.*, 2018, **57**, 15232–15236.

11 M. Faltracco, S. Ortega-Rosales, E. Janssen, R. C. Cioc, C. M. L. Vande Velde and E. Ruijter, *Org. Lett.*, 2021, **23**, 3100–3104.

12 (*a*) K. C. Nicolaou, S. M. Dalby, S. Li, T. Suzuki and D. Y.-K. Chen, *Angew. Chem., Int. Ed.*, 2009, **48**, 7616–7620; (*b*) W. Zhang, X. Chen, Y. An, J. Wang, C. Zhuang, P. Tang and F. Chen, *Chem. – Eur. J.*, 2020, **26**, 10439–10443; (*c*) Y. Liu, Q. Wang, Y. Zhang, J. Huang, L. Nie, J. Chen, W. Cao and X. Wu, *J. Org. Chem.*, 2013, **78**, 12009–12017; (*d*) G. He, B. List and M. Christmann, *Angew. Chem., Int. Ed.*, 2021, **60**, 13591–13596.

13 Several attempts to promote Krapcho decarboxylation of **18** (using LiCl, NaCl or KCl, with or without water, in both DMF and DMSO) only led to decomposition, most likely involving retro-Mannich reaction and Plancher rearrangement. The same result was observed when the hydrolysis was performed with LiOH.

14 (*a*) A. Y. Hong and C. D. Vanderwal, *J. Am. Chem. Soc.*, 2015, **137**, 7306–7309; (*b*) For an earlier application in the synthesis of dehydrotubifoline, see: V. H. Rawal, C. Michoud and R. Monestel, *J. Am. Chem. Soc.*, 1993, **115**, 3030–3031.

