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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. 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, alkaloids, terpenes, and diverse biological activities, indole alkaloids occupy a prominent position among natural products (Fig. 1). As a result, they have attracted considerable interest from the synthetic community, leading to numerous novel approaches to this compound class in recent years.

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 reaction⁸ (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 (POCl₃, 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** (R¹ = 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

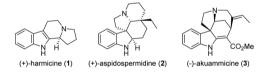
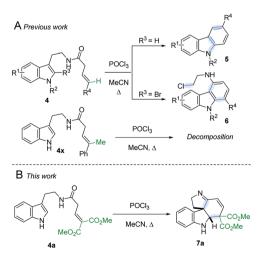


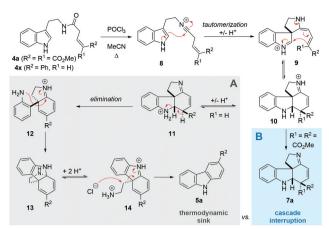
Fig. 1 Representative indole alkaloids.



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 ¹H and ¹³C NMR spectra. See DOI: 10.1039/d10b01966j



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 R4 substituents, 11 we identified malonatederived 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 POCl₃ 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 Tf₂O employed that is often for transformations. 9a-d

Small adjustments of POCl₃ 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 cycli-

Table 1 Reaction optimization

Entry ^a Reagent Solvent T (°C) Yie	$\operatorname{eld}^{b}\left(\%\right)$
1 POCl ₃ MeCN Reflux 27	с
2 Tf ₂ O/2-Cl-Py MeCN Reflux —	
3 Tf ₂ O/3-CN-Py MeCN Reflux —	
4 Ac ₂ O 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	с
11 ^h POCl ₃ MeCN Reflux 48	
12 ^g $POCl_3$ $MeCN^i$ Reflux 58	с

 a Reaction conditions 4a (0.2 mmol), reagent (0.3 mmol) solvent (1 mL). b Determined by 1 H NMR using 2,5-dimethylfuran as an internal standard. c Isolated yield. d Performed with 0.4 mmol of POCl₃. ^e Performed with 0.5 mmol of POCl₃. ^fAdditional POCl₃ (0.1 mmol) added after 30 min (1 h total reaction time). g Additional POCl₃ (0.1 mmol) added after 30 min and 1 h (1.5 h total reaction time). h Additional POCl₃ (0.1 mmol) added after 30 min, 1 h and 1.5 h (2 h total reaction time). Non-anhydrous MeCN was used.

Scheme 3 Scope of the cyclization. Reaction conditions: 4 (0.2 mmol), POCl₃ (0.3 mmol), MeCN (1.0 mL), 1.5 h, reflux. Additional portions of POCl₃ (0.1 mmol) were added after 30 min and 1 h. ^aReaction performed on 4.49 mmol scale.

zation step. Substituents on the R⁵ position are also tolerated: amide 4g, derived from tryptophanol, was converted to 7g in good yield (54%) as a single diastereomer. Replacing the ethyl-

Scheme 4 Total synthesis of (\pm) -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 (NaBH₄, LiBH₄, NaBH₃CN, NaHB(OAc)₃, or Et₃SiH, 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 NaBH₄ 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/H2O 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, 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.
- (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.
- (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.
- (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.