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Interrupted Fischer Indolization Approach toward the Communesin Alkaloids and Perophoramidine

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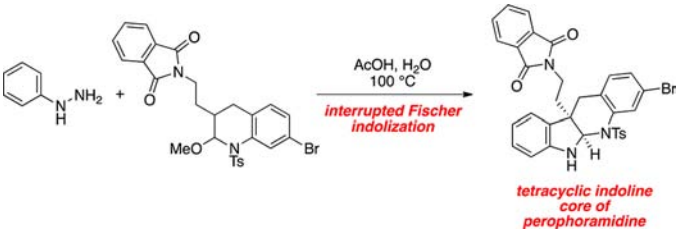
ABSTRACT



A concise approach toward the total synthesis of the communesin alkaloids and perophoramidine is reported. The strategy relies on the use of the interrupted Fischer indolization to build the tetracyclic indoline core of the natural products. Studies to probe the scope and limitations of this plan are presented. Although the methodology does not tolerate a C8-allyl substituent en route to the challenging vicinal quaternary stereocenters, variation at C7 and on the C ring is permitted.

The communesin family of natural products and perophoramidine have been popular targets for chemical synthesis (Figure 1).[1] Communesins A (**1**) and B (**2**) were isolated in 1993 by Numata and co-workers from a *Penicillium* mold found growing on the marine algae *Enteromorpha intestinalis*.[2] Over the past decade, several additional communesin alkaloids (e.g., **3**–**8**) have been discovered,[3] in addition to perophoramidine (**9**).[4] Some of the communesins exhibit moderate insecticidal activity, whereas communesin B (**2**) also shows activity against the P-388 leukemia cell line (ED_{50} = 0.88 μM).[5] Furthermore, **9** is cytotoxic toward the HCT116 colon cancer cell line (IC_{50} = 60 μM).[4]

The alkaloids **1**–**9** possess a number of structural features that render them attractive and challenging targets for total synthesis. Communesins **1**–**8** bear a heptacyclic skeleton, which contains a heterocycle-fused indoline core. Other characteristics of these natural products include the vicinal quaternary centers at C7 and C8 and two aminal linkages at C6 and C9.[6] Perophoramidine (**9**) is similar to the communesins, although it lacks the seven-membered G ring and has an opposite sense of relative stereochemistry with respect to C7 and C8. Additionally, perophoramidine (**9**) is more highly oxidized in comparison to the communesins as noted by the aromatic halogenation pattern and presence of amidine functional groups instead of aminals. Synthetic endeavors toward these natural products have

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(6) Compounds **1**–**9** are numbered in a manner that is consistent with that of Numata et al. (see ref 2).

(7) (a) May, J. A.; Zeidan, R. K.; Stoltz, B. M. *Tetrahedron Lett.* **2003**, *44*, 1203–1205. (b) Crawley, S. L.; Funk, R. L. *Org. Lett.* **2003**, *5*, 3169–3171. (c) May, J. A.; Stoltz, B. M. *Tetrahedron* **2006**, *62*, 5262–5271. (d) Yang, J.; Song, H.; Xiao, X.; Wang, J.; Qin, Y. *Org. Lett.* **2006**, *8*, 2187–2190. (e) Crawley, S. L.; Funk, R. L. *Org. Lett.* **2006**, *8*, 3995–3998. (f) Sabahi, A.; Novikov, A.; Rainier, J. D. *Angew. Chem., Int. Ed.* **2006**, *45*, 4317–4320. (g) George, J. H.; Adlington, R. M. *Synlett* **2008**, 2093–2096.

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led to several promising routes,[7] in addition to a few recently completed total syntheses by the groups of Weinreb,[8] Funk,[9] Ma,[10] and Qin.[11]

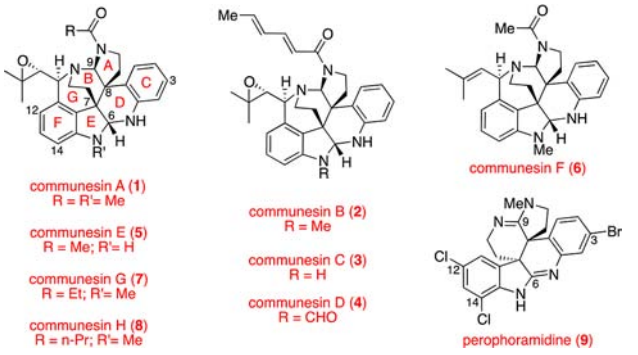

Figure 1. Communesins (**1**–**8**) and perophoramidine (**9**).

En route to the total synthesis of compounds **1**–**9** and a variety of other alkaloids, we have developed a cascade reaction that provides access to fused indoline scaffolds.[12] The transformation, termed the "interrupted Fischer[13–15] indolization", allows for aryl hydrazines **10** and latent aldehydes **11** to be converted to indoline products **12** (Figure 2). The reaction is operationally simple and broad in scope, requires mild reaction conditions, and has shown utility in synthesis.[12] In our initial attempts, we found that the interrupted Fischer indolization of *N*-methylphenylhydrazine (**13**) with *N,O*-acetal **14** efficiently delivered tetracycle **15**.[12a,b] Of note, this reaction provides rapid access to the 6,5,6,6 F–E–D–C ring system of the communesins and perophoramidine and provides a unique approach to these highly sought after alkaloids.

By further varying the reaction partners in the key interrupted Fischer indolization reaction, we envisioned that more highly functionalized derivatives of **15** could be readily accessible. This would provide not only advanced

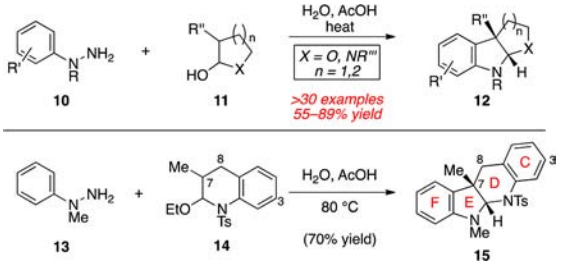

Figure 2. Interrupted Fischer indolization methodology and approach toward alkaloids **1**–**9**.

intermediates for our total synthesis objectives but also an opportunity to study the scope and limitations of the interrupted Fischer indolization methodology. Herein, we report the outcome of the interrupted Fischer indolization reaction as variations in the *N,O*-acetal coupling fragment (at C7, C8, or C3) are considered.

The first point of variation we explored was the substituent at C7 of the *N,O*-acetal component, as a C7-aminoethyl substituent would be necessary for the synthesis of the communesin family of natural products and also for perophoramidine (Scheme 1). Acetal **16**, a readily available known compound,[16] was treated with TMSOTf in the presence of Hünig's base to afford enol ether **17** as an inconsequential mixture of *E*/*Z* isomers. Subsequently, enol ether **17** underwent a hetero-Diels–Alder reaction with sulfonamide **18**[17] to deliver the desired *N,O*-acetal substrate **19** in 70% yield. In the interrupted Fischer indolization reaction, treatment of **19** with *N*-methylphenylhydrazine (**13**) furnished tetracycles **20** and **21** in a combined 67% yield (approximately 3:1 ratio of **20** to **21**).[18] Thus, we were able to construct the key indoline scaffold, which bears a nitrogen functional handle useful for the synthesis of the communesin alkaloids.

Encouraged by these results, we also explored the interrupted Fischer indolization of two reaction partners that could plausibly allow for assembly of the seven-membered G ring of the communesins. Thus, hydrazine **22**[19] underwent reaction with *N,O*-acetal **23**[20] to provide tetracyclic indoline **24** in 54% yield (Scheme 2). Subsequent removal of the phthalyl group was achieved upon treatment of **24** with hydrazine monohydrate to give primary amine **25**. With the aim of forging the G ring via a Pictet–Spengler cyclization,[21] amine **25** was condensed with 3-methylbut-2-enal to furnish imine **26**. Unfortunately our efforts to

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(9) Fuchs, J. R.; Funk, R. L. *J. Am. Chem. Soc.* **2004**, *126*, 5068–5069.

(10) (a) Zuo, Z.; Ma, D. *Angew. Chem., Int. Ed.* **2011**, *50*, 12008–12011. (b) Zuo, Z.; Xie, W.; Ma, D. *J. Am. Chem. Soc.* **2010**, *132*, 13226–13228.

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(15) For the use of the interrupted Fischer indolization to access flustramine derivatives, see: Bunders, C.; Cavanagh, J.; Melander, C. *Org. Biomol. Chem.* **2011**, *9*, 5476–5481.

(16) (a) Paz Muñoz, M.; de la Torre, M. C.; Sierra, M. A. *Adv. Synth. Catal.* **2010**, *352*, 2189–2194. (b) Kowalski, P.; Jaśkowska, J. *Arch. Pharm. (Weinheim, Ger.)* **2012**, *345*, 81–85.

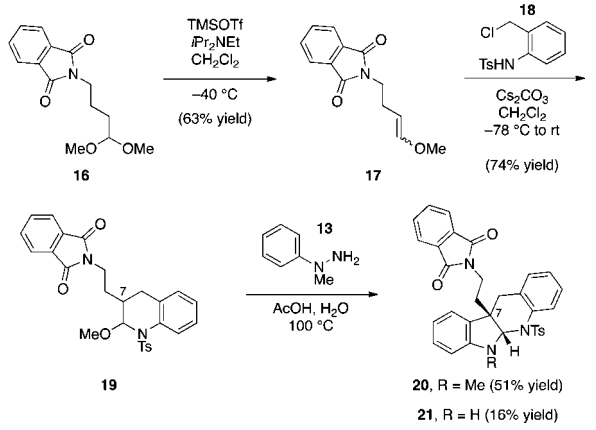
(17) Steinhagen, H.; Corey, E. J. *Angew. Chem., Int. Ed.* **1999**, *38*, 1928–1931.

(18) The formation of NMe and NH products is consistent with previous observations in the interrupted Fischer indolization; see ref 12a, 12b.

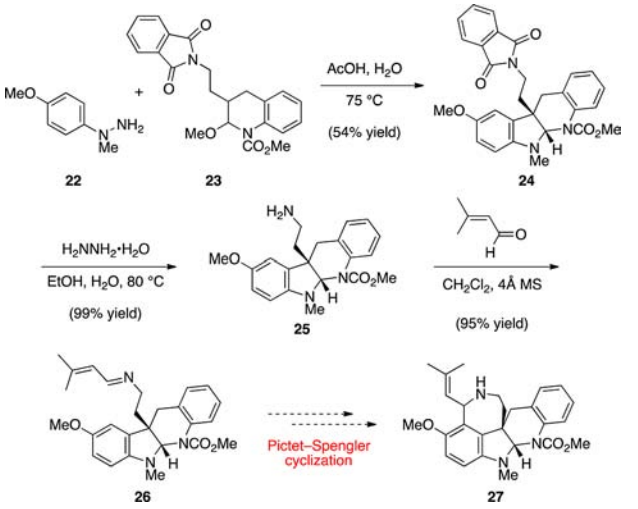
(19) Srivastava, S.; Ruane, P. H.; Toscano, J. P.; Sullivan, M. B.; Cramer, C. J.; Chiapperino, D.; Reed, E. C.; Falvey, D. E. *J. Am. Chem. Soc.* **2000**, *122*, 8271–8278.

(20) Carbamylated *N,O*-acetal **23** was employed in this study because it was found to be more readily removable compared to the *N*-Ts group.

Scheme 1. Interrupted Fischer Indolization of **19**



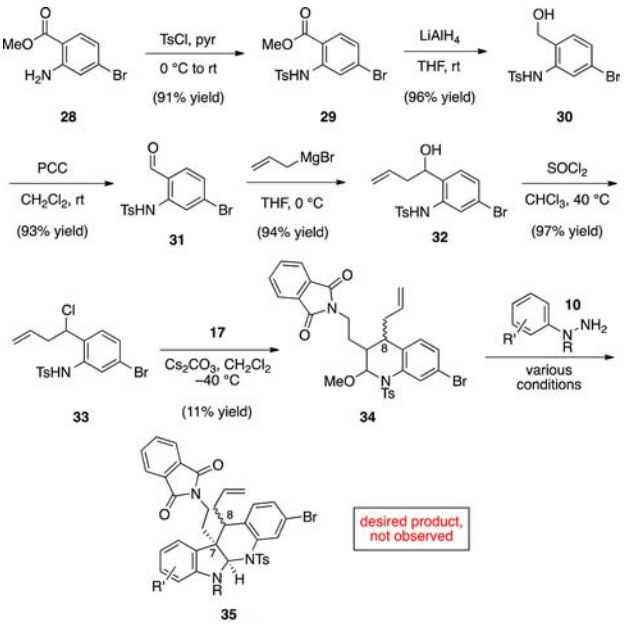
Scheme 2. Interrupted Fischer Indolization of **22** + **23** and Further Elaboration to **26**



arrive at pentacycle **27** through a Pictet–Spengler cyclization have been unsuccessful to date.[22]

Other aspects of the interrupted Fischer indolization we aimed to test involved substitution at C8 for the eventual installation of the C7/C8 vicinal quaternary stereocenters, in addition to the aryl bromide substituent present in perophoramidine. Our route to a suitable substrate is shown in Scheme 3. Commercially available aniline **28** was converted to sulfonamide **29**, which, in turn, underwent reduction upon treatment with lithium aluminum hydride to furnish alcohol **30**. Oxidation of alcohol **30** with PCC yielded aldehyde **31**, which was elaborated to alcohol **32** by the addition of allyl magnesium bromide. Treatment of alcohol **32** with thionyl chloride provided benzylic chloride **33**, which was the substrate for the hetero-Diels–Alder reaction. In the event, the desired C8 substituted acetal **34** was obtained, albeit in modest yield.[23] Attempts to effect the interrupted Fischer indolization on this substrate to arrive at **35** proved fruitless, despite exhaustive efforts using a variety of acid-mediated conditions, in addition to several arylhydrazine coupling partners.[24] Although this route proved ineffective for our planned total synthesis, these efforts reveal a steric limitation of the interrupted Fischer indolization methodology.

Scheme 3. Attempted Interrupted Fischer Indolization of C8-Allylated Compound **34**

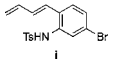


We also prepared a derivative of *N,O*-acetal **34** lacking the C8 allyl substituent and tested its viability in the

(21) For reviews of the Pictet–Spengler reaction, see: (a) Cox, E. D.; Cook, J. M. *Chem. Rev.* **1995**, *95*, 1797–1842. (b) Stökigt, J.; Antonchick, A. P.; Wu, F.; Waldmann, H. *Angew. Chem., Int. Ed.* **2011**, *50*, 8538–8564. For Pictet–Spengler reactions on similar systems, see: (c) Mahboobi, S.; Eluwa, S.; Koller, M.; Popp, A.; Schollmeyer, D. *J. Heterocycl. Chem.* **2000**, *37*, 1177–1185. (d) Somei, M.; Teranishi, S.; Yamada, K.; Yamada, F. *Chem. Pharm. Bull.* **2001**, *49*, 1159–1165. (e) Yamada, K.; Namerikawa, Y.; Haruyama, T.; Miwa, Y.; Yanada, R.; Ishikura, M. *Eur. J. Org. Chem.* **2009**, 5752–5759.

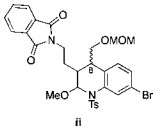
(22) Attempts to form the G ring through intermediate **26** led to hydrolysis of the imine, thus returning **25**. Base induced Pictet–Spengler reaction attempts led to the recovery of starting material (see ref 21e). Further efforts to introduce the G ring of the communesins are underway.

(23) This hetero-Diels–Alder reaction was hampered by the competitive formation of diene **i**, which presumably forms from elimination of the benzylic chloride. Efforts to suppress the formation of **i** were not undertaken because of the difficulty of the subsequent interrupted Fischer indolization.



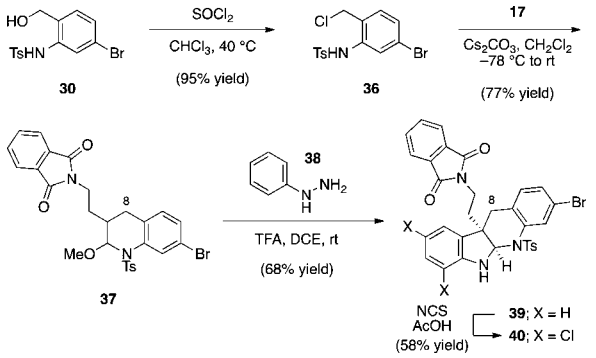
i

(24) MOM ether **ii** was also prepared but unfortunately proved ineffective in the interrupted Fischer indolization reaction under a variety of conditions.



ii

Scheme 4. Synthesis of Trihalotetracycle **40**



interrupted Fischer indolization reaction (Scheme 4). Alcohol **30** was treated with thionyl chloride to provide benzylic chloride **36** in 95% yield. Subsequent reaction of alkyl chloride **36** with enol ether **17** under basic conditions provided *N,O*-acetal **37** in significantly higher yield compared to the reaction of the C8-allylated material (see Scheme 3, **33** + **17** → **34**).[23] Fortunately, treatment of *N,O*-acetal **37** with phenylhydrazine (**38**) in the presence of TFA in dichloroethane generated tetracycle **39** in 68% yield.[25] The success of this transformation supports the notion that the interrupted Fischer indolization reaction of **34** fails (see Scheme 3) due to steric considerations. Finally, tetracycle **39** was exposed to NCS to furnish trihalotetracycle **40**.[9] Intermediate **40**, which is available in only six steps from commercially available materials, is expected to serve as a precursor to perophoramidine (**9**).[26]

In summary, we have established a promising synthetic strategy toward the communesin alkaloids and perophoramidine. The approach involves the use of the interrupted Fischer indolization methodology, which in turn enables the rapid assembly of tetracyclic scaffolds that are reminiscent of the cores of the desired natural products. Although the methodology does not tolerate a C8-allyl substituent en route to the challenging vicinal quaternary stereocenters, variation at C7 and on the C ring is permitted. Current efforts are dedicated to further elucidating the subtleties of the interrupted Fischer indolization methodology in the synthesis of indoline-containing natural products.

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Supporting Information Available. Experimental details and compound characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.

(25) The use of $AcOH/H_2O$ conditions for this transformation failed to deliver the desired product **39**.

(26) Intermediate **40** may plausibly be elaborated by initial benzylic oxidation to functionalize C8, followed by further manipulations.