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Synthetic Studies toward the Citrinadin A and B Core Architecture

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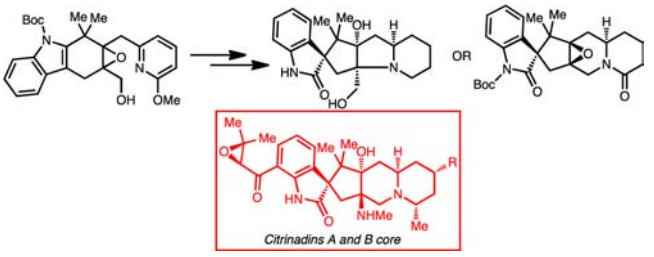
ABSTRACT



The core architecture of the citrinadin alkaloids has been prepared in racemic form by utilizing a strategy that exploits the alkylation of 2-methoxypyridines. An initially planned indolizidine to quinolizidine transformation to build the D/E rings was unsuccessful. Success was ultimately gained by a direct alkylation to establish the citrinadin core architecture.

Citrinadins A (**1**, Figure 1) and B (**2**) are oxindole alkaloid natural products that were isolated from *Penicillium citrinum* by Jun'ichi Kobayashi and co-workers in 2004 and 2005, respectively.[1,2] Recently, highly elegant total syntheses of alkaloids **1** and **2** have been completed by the groups of Martin and Wood, respectively.[3,4] These contributions have resulted in the revision of the relative stereochemistry of the citrinadins to the representations shown for **1** and **2** in Figure 1. These stereochemical revisions now bring the structures of the citrinadins in line with the related PF1270 spiro-oxindole natural products (A–C, **3**–**5**), which were isolated from *Penicillium waksmanii* (strain PF1270) by Kushida et al.[5]

Synthetic interest in the citrinadins has been driven by their unusual structures, which feature a substituted quinolizidine and a cyclopentane ring replete with four tetrasubstituted carbon atoms, two of which are quaternary.

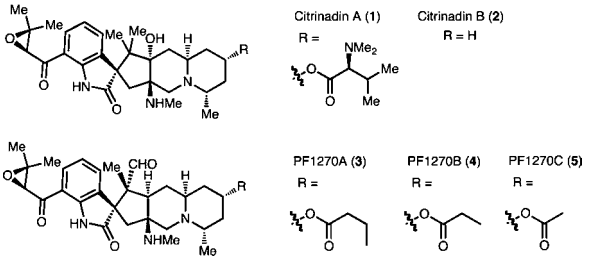


Figure 1. Citrinadins and PF1270 alkaloids.

In addition to their challenging structural attributes, which may inspire new synthetic strategies and tactics, **1** and **2**, as well as related spiro-oxindoles such as **3**–**5**, possess notable biological activity (e.g., cytotoxicity against murine leukemia L1210 cells for **1** (IC_{50} = 6.2 μg/mL) and **2** (IC_{50} = 10 μg/mL), whereas **3**–**5** are potent agonists of rat and human histamine receptor H3). As such, the syntheses of **1** and **2** or **3**–**5** could offer opportunities for a more comprehensive examination of their anticancer activity and their effects on the central nervous system. This is especially significant given the limited availability of these materials from their natural sources. It is therefore not surprising that, in addition to the recently completed total

(1) Tsuda, M.; Kasai, Y.; Komatsu, K.; Sone, T.; Tanaka, M.; Mikami, Y.; Kobayashi, J. *Org. Lett.* **2004**, *6*, 3087.
(2) Mugishima, T.; Tsuda, M.; Kasai, Y.; Ishiyama, H.; Fukushi, E.; Kawabata, J.; Watanabe, M.; Akao, K.; Kobayashi, J. *J. Org. Chem.* **2005**, *70*, 9430.
(3) Bian, Z.; Marvin, C. C.; Martin, S. F. *J. Am. Chem. Soc.* **2013**, *135*, 10886.
(4) Kong, K.; Enquist, J. A., Jr.; McCallum, M. E.; Smith, G. M.; Matsumaru, T.; Menhaji-Klotz, E.; Wood, J. L. *J. Am. Chem. Soc.* **2013**, *135*, 10890.
(5) Kushida, N.; Watanabe, N.; Okuda, T.; Yokoyama, F.; Gyobu, Y.; Yaguchi, T. *J. Antibiot.* **2007**, *60*, 667.

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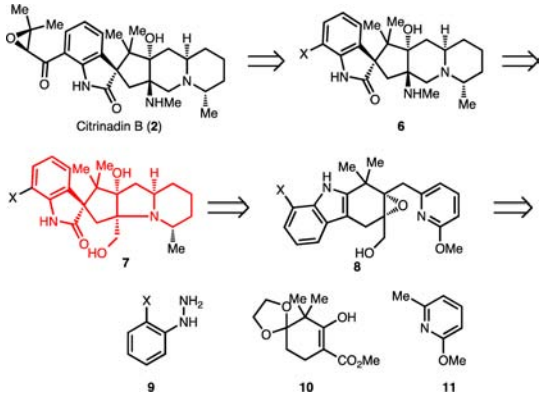
syntheses of **1** and **2**, there have been several approaches to these compounds that are each characterized by a creative, unique strategy to address the core architecture of these molecules.[6]

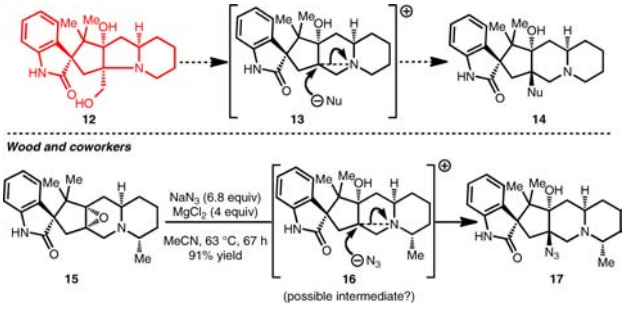
In this communication, we report our own synthetic studies toward the citrinadins, which is prompted by the recent disclosures of the Martin and Wood syntheses[3,4] of **1** and **2**, respectively, with which our approach shares several strategic features. As outlined in Scheme 1, we envisioned the citrinadins, particularly citrinadin B (**2**), arising (as was achieved in the Wood synthesis of **2**) from functionalization at C-7 of oxindole **6** (where X = Br or I). In one of the key transformations of the synthesis, quinolizidine **6** would arise from indolizidine **7** (discussed in more detail in Scheme 2 below). It was imagined that alkylation of the 2-methoxypyridine portion of **8** by the epoxide functional group would provide eventual access to indolizidine **7**. 2-Methoxypyridines offer several strategic advantages in complex molecule synthesis, which we have exploited in the past in the syntheses of several complex alkaloid natural products.[7] For example, they are excellent surrogates for piperidine groups where the basic nitrogen atom is in essence protected given the mitigated basicity of the methoxypyridine nitrogen. As a corollary of this reduced basicity/nucleophilicity of the 2-methoxypyridine nitrogen, alkylation of the 2-methoxypyridine group is not general, especially using electrophiles other than alkyl triflates or halides. Thus, the annulation strategy proposed herein (i.e., **8** to **7**) would serve to extend the scope of annulation reactions of 2-methoxypyridines. Fused indole tricycle **8** would in turn arise from hydrazine **9** (where X = Br or I), ketoester **10** (enol form shown), and 2-methoxypicoline **11**.

Scheme 1. Retrosynthetic Analysis of Citrinadin B



Particularly intriguing in our proposed approach to **2** is the conversion of **7** to **6**. At the time that we initiated our studies, no direct precedent existed for this particular transformation. As such, a plan to study this conversion on a model system (**12**, Scheme 2) was hatched. It was expected that appropriate activation of the primary hydroxyl group of **12** would lead to aziridinium intermediate **13**, which would form upon engaging the tertiary amine group. At that stage, the introduction of an appropriate nucleophile would lead to quinolizidine **14** by a S_N1-like or an asynchronous S_N2-like process capable of delivering the requisite stereochemistry (either via substrate or reagent control). While we cannot exclude the possibility of a the direct S_N2 opening of aziridinium intermediate **13**[8b] (which would lead to the stereochemistry opposite to that depicted in compound **14**), our hypothesis is supported by the recent reports from the Wood group, where the conversion of **15** to **17** may pass through an intermediate (**16**) where the tertiary amine offers a level of anchimeric assistance.[4,8]

Scheme 2. Proposed Indolizidine to Quinolizidine Conversion via an Aziridinium Intermediate



Our synthesis of the model indolizidine compound **12** commenced with the preparation of **24** as outlined in Scheme 3. Commercially available 2,2-dimethylcyclohexane-1,3-dione (**18**)[9] was converted to monoketal **19**, which was subjected to a Claisen reaction to afford **10**. A standard triflation of **10** followed by Negishi cross-coupling[10] with freshly prepared **21** smoothly affords the expected adduct, which upon hydrolysis of the ketal group yields ketone **22**. Fischer indolization[11] of **22** via the intermediacy of hydrazone **23** affords dihydrocarbazole derivative **24** (following Boc protection of the indole nitrogen).

Access to **24** set the stage for the synthesis of the indolizidone derivative **27** as outlined in Scheme 4. Reduction of ester **24** with DIBAL produces an allylic alcohol,

(6) (a) Pettersson, M.; Knueppel, D.; Martin, S. F. *Org. Lett.* **2007**, *9*, 4623. (b) McIver, A. L.; Deiters, A. *Org. Lett.* **2010**, *12*, 1288. (c) Chandler, B. D.; Roland, J. T.; Li, Y.; Sorensen, E. J. *Org. Lett.* **2010**, *12*, 2746. (d) Guerrero, C. A.; Sorensen, E. J. *Org. Lett.* **2011**, *13*, 5164. (e) Albertshofer, K.; Tan, B.; Barbas, C. F. *Org. Lett.* **2012**, *14*, 1834.

(7) (a) Bisai, A.; West, S. P.; Sarpong, R. *J. Am. Chem. Soc.* **2008**, *130*, 7222. (b) Larson, K. K.; Sarpong, R. *J. Am. Chem. Soc.* **2009**, *131*, 13244. (c) Bisai, V.; Sarpong, R. *Org. Lett.* **2010**, *12*, 2551. (d) Murphy, R. A.; Sarpong, R. *Org. Lett.* **2012**, *14*, 632. (e) Newton, J. N.; Fischer, D. F.; Sarpong, R. *Angew. Chem., Int. Ed.* **2013**, *52*, 1726.

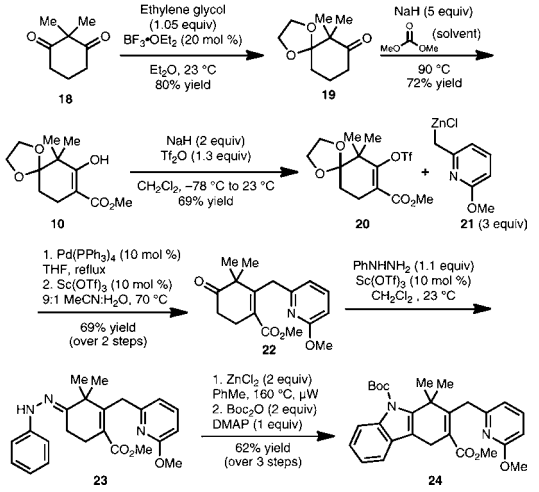
(8) (a) The Wood group has also demonstrated this epoxide opening on C-7 substituted derivatives of **15**. See: Smith, G. M. Progress toward the Total Synthesis of the Citrinadins, Ph.D. Thesis, Colorado State University, Fort Collins, CO, 2012. (b) The work of Wonjacynska et al. has shown that aziridinium openings may proceed with retention of stereochemistry, which supports the possible intermediacy of **16**: Wojaczynska, E.; Turowska-Tryk, I.; Skarzewski, J. *Tetrahedron* **2012**, *68*, 7848–7854.

(9) For a recent application of **18** in synthesis, see ref 3.

(10) For an early account, see: Negishi, E. *Acc. Chem. Res.* **1982**, *15*, 340.

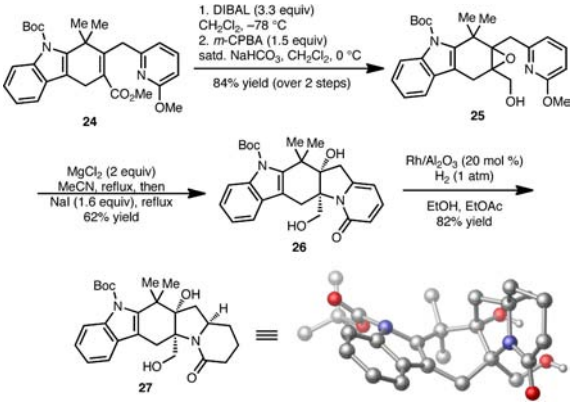
(11) For a review on the Fischer indole synthesis, see: Martin, M. J.; Dorn, L. J.; Cook, J. M. *Heterocycles* **1993**, *36*, 157.

Scheme 3. Synthesis of Dihydrocarbazole Derivative **24**



which upon epoxidation gives epoxide **25**. After a protracted optimization, conversion of **25** to **26** could be effected with $MgCl_2$ as the Lewis acid and NaI to accomplish the requisite demethylation. At this stage, hydrogenation of the pyridine occurs with good levels of diastereoselectivity to afford pentacycle **27**, the structure of which was unambiguously confirmed by single-crystal X-ray analysis.[12]

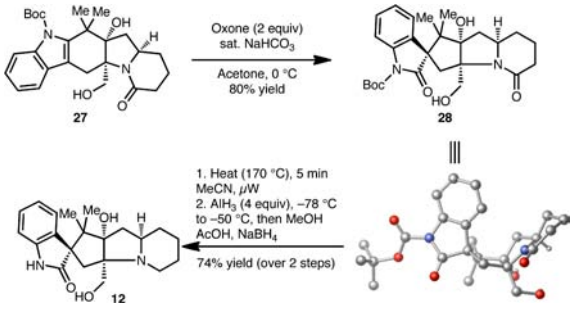
Scheme 4. Synthesis of Pentacycle **27**



The next task was to convert fused pentacycle **27** to spirocyclic oxindole **28** (Scheme 5), which is readily accomplished with high levels of diastereocontrol using in situ generated dimethyldioxirane (DMDO; from oxone and acetone). The excellent diastereoselectivity can in part be attributed to a convex face approach of the DMDO, which may also be directed to the α face of **27** by hydrogen bond interactions with the primary hydroxyl group at the C/D ring fusion. Sequential removal of the Boc and amide carbonyl groups in **28** gives **12**, which is the requisite

(12) CYLView depictions of the X-ray crystal structures are shown. Thermal ellipsoids shown at 50% probability. Most hydrogens removed for clarity. See the Supporting Information for more details.

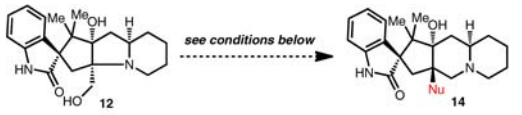
Scheme 5. Synthesis of Spiro-oxindole Indolizidine **12**



model compound to study the proposed key indolizidine to quinolizidine conversion that would deliver the citrinadin skeleton (see **12** to **14**, Scheme 2).[13]

Despite numerous attempts using a wide selection of conditions (Table 1) and the encouraging related precedent of Wood,[4,14] we have so far not had success in accomplishing the conversion of **12** to **14**. For example, treatment of **12** under Cossy's conditions[15] (entry 1) with trifluoroacetic anhydride and triethylamine results in the formation of an intermediate trifluoroacetate. However, quinolizidine formation did not occur, but instead, the starting material was recovered (presumably after base-promoted hydrolysis of the trifluoroacetate). Other conditions that combine hydroxyl activation followed by the introduction of a nucleophile simply result in the decomposition of **12**. Thus, while it would appear (from the precedent of Wood) that a quinolizidine structural motif may result if an aziridinium intermediate is accessed, our studies thus far suggest that indolizidine **12** may not represent the ideal substrate to access the requisite aziridinium species.

Table 1. Attempted Indolizidine to Quinolizidine Conversion



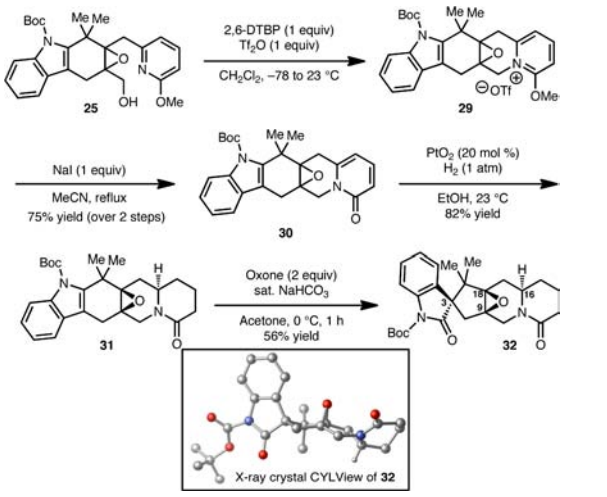
entry	conditions	result
1	$(CF_3CO)_2O$ (3 equiv) −78 °C, THF, 2 h then Et_3N, reflux 6 h; then NaOH	starting material
2	Tf_2O (1.5 equiv), CH_2Cl_2 −78 °C, then $MeNH_2$, reflux 1 h	complex mixture
3	DPPA (1.5 equiv), DBU (1.5 equiv) Toluene 0 to 60 °C, 6 h	complex mixture
4	XtalFluor-E (1.5 equiv), $TMSN_3$ DCE 80 °C, 4 h	complex mixture

(13) For examples of prolinol to piperidine ring expansions via aziridinium intermediates, see: (a) Cossy, J.; Dumas, C.; Pardo, D. G. *Eur. J. Org. Chem.* **1999**, 1693. (b) Cochi, A.; Pardo, D. G.; Cossy, J. *Eur. J. Org. Chem.* **2012**, 2023. (c) Wojaczynska, E.; Turowska-Tyrk, I.; Skarzewski, J. *Tetrahedron* **2012**, *68*, 7848. (d) Abe, H.; Aoyagi, S.; Kibayashi, C. *J. Am. Chem. Soc.* **2005**, *127*, 1473. (e) Jarvis, S. B. D.; Charette, A. B. *Org. Lett.* **2011**, *13*, 3830.

(14) Also see ref 8.

(15) See refs 13a and 13b.

Scheme 6. Synthesis of Spiro-oxindole **32**



Despite the disappointing observations in the attempted conversion of **12** to **14**, our synthetic studies have identified an alternative sequence to access the carbon skeleton of the citrinadins bearing a quinolizidone framework (Scheme 6). Thus, treatment of a solution of epoxy alcohol **25** with triflic anhydride in the presence of 2,6-di-*tert*-butylpyridine (2,6-DTBP) yields pyridinium salt **29**. Aqueous workup of this salt followed by treatment with sodium iodide in refluxing acetonitrile gives pentacyclic pyridone **30** in 75% yield over the two steps. Catalytic hydrogenation of pyridone **30** proceeds with excellent diastereoselectivity (> 20:1) to give epoxy quinolizidone **31** in 82% yield. At this stage, oxidation of indole **31** with dimethyldioxirane (generated in situ from oxone and acetone) gives spiro-oxindole **32**, the structure of which was unambiguously supported by single-crystal X-ray analysis (see CYLView in Scheme 6).[12] Although the relative stereochemistry at C-3 and C-16 (citrinadin numbering) in **32** is as desired, the C-18 stereocenter will require inversion. Studies to effect the inversion of the C-18 stereochemistry as well as nucleophilic opening of the epoxide group in **32** and derivatives thereof at C-8 are the subject of our ongoing studies.

In conclusion, we have applied a methoxypyridine alkylation strategy to the synthesis of the pentacyclic carbon skeleton of the citrinadin natural products. A planned indolizidine ring expansion/nucleophile trapping via an aziridinium intermediate has thus far not been successful despite encouraging literature precedent from the work of Wood et al. An alternative methoxypyridine alkylation has enabled access to the citrinadin pentacyclic core and sets the stage for future studies to construct the fully substituted pentacyclic core of the citrinadin natural products.

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Supporting Information Available. Experimental details and copies of ^{1}H and ^{13}C spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.