ORGANIC LETTERS

2011
Vol. 13, No. 19
5164–5167

Concise, Stereocontrolled Synthesis of the Citrinadin B Core Architecture

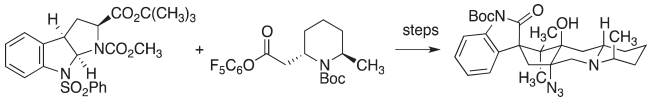
Carlos A. Guerrero[†] and Erik J. Sorensen*

Frick Laboratory, Department of Chemistry, Princeton University, Princeton, New Jersey 08544, United States

ejs@princeton.edu

Received July 27, 2011

ABSTRACT



A concise, stereocontrolled synthesis of the citrinadin B core architecture from scalemic, readily available starting materials is disclosed. Highlights include ready access to both cyclic tryptophan tautomer and *trans*-2,6-disubstituted piperidine fragments, an efficient, stereoretentive mixed Claisen acylation for the coupling of these halves, and further diastereoselective carbonyl addition and oxidative rearrangement for assembly of the core.

In complex, small molecule synthesis, the adoption of reagent- or substrate-directed strategies to achieve stereocontrol – or a combination thereof – depends on the particular challenges posed by the synthesis target of interest. In the case of citrinadin B[1] (**1**, Figure 1) – a scarce, cytotoxic, marine meroterpene alkaloid – the density of stereocenters in the center of the molecule would seem to favor a strategy wherein a merger of prefabricated, scalemic fragments would permit the management of remote stereochemical relationships. The central cyclopentane has four fully substituted carbon atoms, three of which are centers of asymmetry. However, the establishment of such stereocenters by enantioselective methods lags behind those methods that set tertiary carbon stereocenters,[2] and pre-existing elements of complexity may render predictions of the stereochemical course difficult. In contrast, the advantages of relative stereocontrol mentioned above might be realized in the context of a synthesis of the citrinadin B core architecture; the successful implementation of this strategy is reported herein.[3]

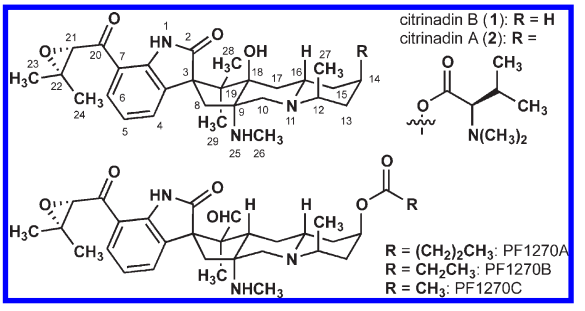


Figure 1. Structures of the citrinadins and PF1270A–C.

The citrinadins[1,4] (**1** and **2**) and PF1270A–PF1270C[5,6] (see Figure 1) comprise a tryptophan portion, a piperidine fragment, and two isoprene units, one bonded peripherally to C7 (heterocycle numbering) of the oxindole, whereas the other is deeply embedded such that a carbon–carbon bond is expressed to all three central carbons of this isoprene

[†] Present address: Department of Chemistry and Biochemistry, University of California, San Diego, 9500 Gilman Drive #0358, Pacific Hall Room 5100C, La Jolla, CA 92093-0358.

(1) Mugishima, T.; Tsuda, M.; Kasai, Y.; Ishiyama, H.; Fukushi, E.; Kawabata, J.; Watanabe, M.; Akao, K.; Kobayashi, J. *J. Org. Chem.* **2005**, *70*, 9430–9435.

(2) (a) Liao, X.; Stanley, L. M.; Hartwig, J. F. *J. Am. Chem. Soc.* **2011**, *133*, 2088. (b) Douglas, C. J.; Overman, L. E. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5363. (c) The 2001 Nobel Prize in Chemistry recognized enantioselective hydrogenation and oxidation reactions, yet the former obviously cannot be used for the establishment of quaternary stereocenters starting from π-systems.

(3) For a previous report from our laboratory directed toward the citrinadin B structure, see: Chandler, B. D.; Roland, J. T.; Li, Y.; Sorensen, E. J. *Org. Lett.* **2010**, *12*, 2746.

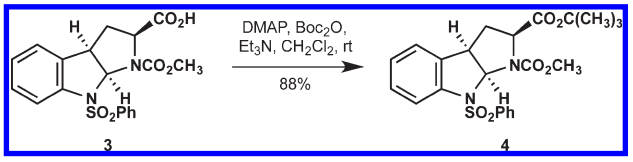
(4) Tsuda, M.; Kasai, Y.; Komatsu, K.; Sone, T.; Tanaka, M.; Mikami, Y; Kobayashi, J. *Org. Lett.* **2004**, *6*, 3087.

10.1021/ol2020362
Published on Web 09/06/2011

unit. As the isoprene units are small, their installation allows for considerable flexibility. In contrast, we opted to commence with tryptophan and piperidine fragments and find suitable means for their stereocontrolled synthesis and union.

The utility of cyclic tautomers of tryptophan[7,8] in the stereoselective synthesis of amino acid derivatives has been studied.[9,10] Chain-to-ring tautomerism gives structures with a pronounced folded topology; in the wake of enolization events, trappings with electrophiles would occur on the convex face of the molecule.[11,12] We relied on this propensity to stereoselectively join two halves of roughly equal complexity. Subsequent chemo- and/or diastereoselective transformations were then used to complete a synthesis of the citrinadin B core.

Scheme 1. Preparation of *tert*-Butyl Ester **4**[a]

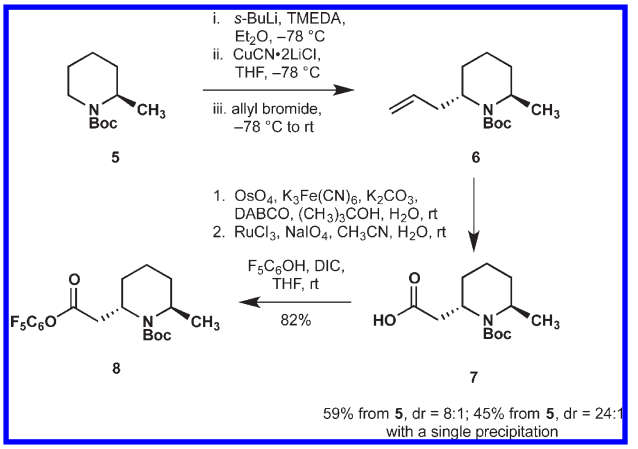


[a] DMAP = 4-(dimethylamino)pyridine.

Readily available acid **3**[13] is esterified in good yield though the intermediacy of an *in situ* generated mixed carbonate, giving *tert*-butyl ester **4** (see Scheme 1).

The piperidine portion (see Scheme 2) is generated in scalemic form starting with a classical resolution of (±)-2-methylpiperidine.[14] Neutralization/carbamoylation then gives *N*-*tert*-butoxycarbonyl-(*R*)-2-methylpiperidine (**5**). This material is alkylated stereoselectively by modifying conditions originally reported by Beak and co-workers.[15] In particular, transmetalation to a Cu(I) salt promotes efficient carbon−carbon bond formation and suppresses byproduct formation with allyl bromide as an electrophile; strict temperature control is required for desirable diastereoselectivity favoring piperidine **6**.[16] Two-step oxidative cleavage by initial dihydroxylation with substoichiometric OsO_4 and 1,4-diazabicyclo-[2.2.2]octane using $K_3Fe(CN)_6$ as a terminal oxidant followed by cleavage with substoichiometric $RuCl_3$ and excess $NaIO_4$ furnishes acid **7**. At this point, electrophile **8** is formed by simple dehydrative esterification of acid **7** with di-isopropylcarbodiimide and pentafluorophenol.

Scheme 2. Preparation of Ester **8**[a]



[a] *s*-BuLi = *sec*-butyllithium; DABCO = 1,4-diazabicyclo[2.2.2]-octane; DIC = di-isopropylcarbodiimide; TMEDA = *N*,*N*,*N*′,*N*′-tetramethylethylenediamine; THF = tetrahydrofuran.

The fragment union is accomplished by the following sequence: (1) initial enolization of a slight excess of *tert*-butyl ester **4** using lithium bis(trimethylsilyl)amide in cold THF; (2) *subsequent* addition of hexamethylphosphoramide; (3) addition by cannula of a cold solution of pentafluorophenyl ester **8**; and (4) cold-temperature quench with acetic acid (see Scheme 3).[17] The delayed addition of hexamethylphosphoramide minimizes deprotonation at the benzylic site of the ester **4** (i.e., "lateral" deprotonation) found to occur in optimization studies of this reaction. This mixed Claisen acylation generates β-keto ester **9** in 77% isolated yield and with high diastereoselectivity. The greatest erosion of diastereoselectivity arises if the reaction mixture is not quenched cold with glacial acetic acid, which leads to epimerization at C16 (citrinadin B numbering), ostensibly by a β-elimination−1,4-addition mechanism.

Compound **9** is converted to β-keto lactam **10** by a three-stage process wherein the following occurs: (1) the Boc group is selectively removed using *in situ*-generated HCl; (2) after evaporation to dryness of the methanolic mixture, the resultant residue is taken up in anhydrous toluene and treated with excess $POCl_3$, and the mixture is heated at

(5) Kushida, N.; Watanabe, N.; Okuda, T.; Yokoyama, F.; Gyobu, Y.; Yaguchi, T. *J. Antiobiot*. **2007**, *60*, 667.

(6) (a) Kushida, N.; Watanabe, N.; Yaguchi, T.; Yokoyama, F.; Tsujiuchi, G.; Okuda, T. Novel Physiologically Active Substances PF1270A, B and C. Eur. Pat. Appl. 1612273, 2004. (b) Kushida, N.; Watanabe, N.; Yaguchi, T.; Yokoyama, F.; Tsujiuchi, G.; Okuda, T. U.S. Patent 7,501,431, March 10, 2009.

(7) (a) Ohno, M.; Spande, T. F.; Witkop, B. *J. Am. Chem. Soc*. **1968**, *90*, 6521. (b) Ohno, M.; Spande, T. F.; Witkop, B. *J. Am. Chem. Soc*. **1970**, *92*, 343.

(8) Hino, T.; Taniguchi, M. *J. Am. Chem. Soc*. **1978**, *100*, 5564.

(9) Hino, T.; Nakagawa, M. Chemistry and Reactions of Cyclic Tautomers of Tryptamines and Tryptophans. In *The Alkaloids: Chemistry and Pharmacology*; Brossi, A., Ed.; Academic Press, Inc.: San Diego, 1988; Vol. 34, pp 1−75.

(10) Crich, D.; Banerjee, A. *Acc. Chem. Res*. **1997**, *40*, 151.

(11) Crich, D.; Davies, J. W. *Chem. Commun*. **1989**, 1418.

(12) Crich, D.; Bruncko, M. *Tetrahedron Lett*. **1992**, *33*, 6251.

(13) Prepared by saponification of the corresponding methyl ester. See Supporting Information for experimental procedure. The starting methyl ester has been reported (formerly available from Aldrich); see: Chan, C.-O.; Crich, D.; Natarajan, N. *Tetrahedron Lett*. **1992**, *33*, 3405.

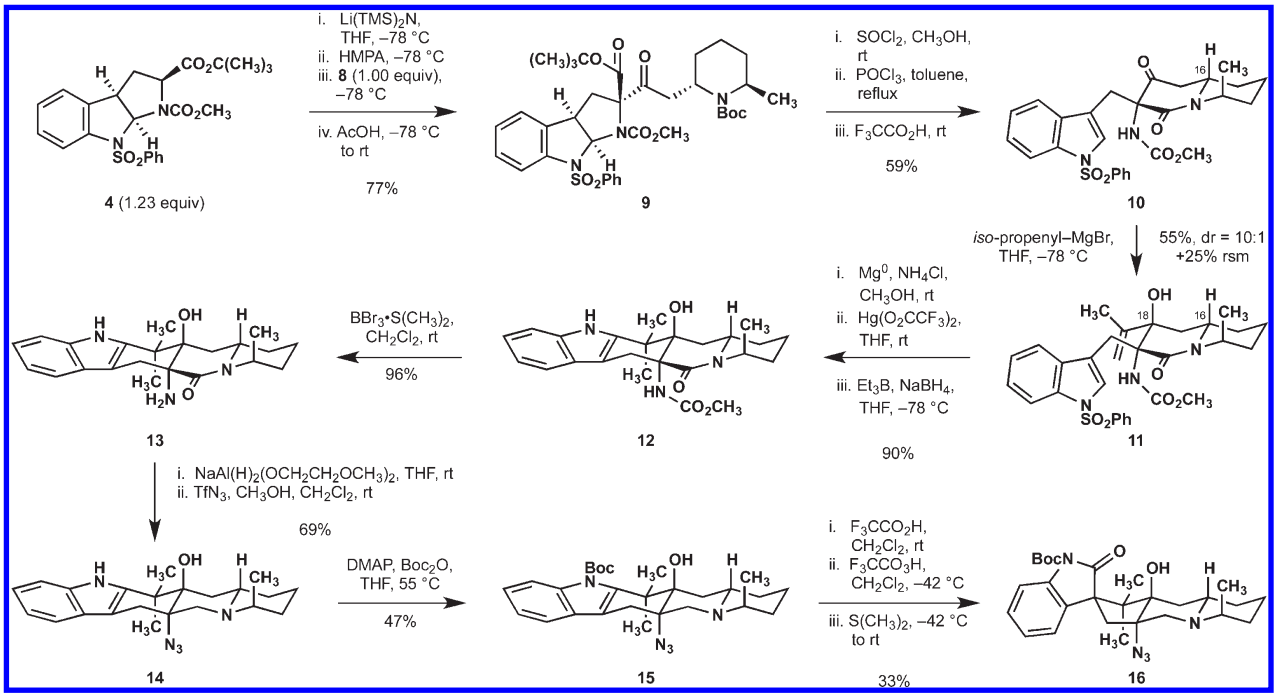
(14) Craig, J. C.; Pinder, A. R. *J. Org. Chem*. **1971**, *36*, 3648. A modified procedure was employed, the details of which are provided in the Supporting Information.

(15) (a) Beak, P.; Lee, W.-K. *Tetrahedron Lett*. **1989**, *30*, 1187. (b) Beak, P.; Lee, W.-K. *J. Org. Chem*. **1993**, *58*, 1109.

(16) Dieter, R. K.; Oba, G.; Chandupatla, K. R.; Topping, C. M.; Lu, K.; Watson, R. T. *J. Org. Chem*. **2004**, *69*, 3076.

(17) For a similar strategic union via mixed Claisen acylation, see: Vaswani, R. G.; Chamberlin, A. R. *J. Org. Chem*. **2008**, *73*, 1661.

Scheme 3. Toward Citrinadin B: Attainment of the Core Architecture[a]



[a] HMPA = hexamethylphosphoramide; Tf = trifluoromethansulfonyl; TMS = trimethylsilyl; rt = room temperature.

reflux; (3) the resultant mixture is evaporated to dryness, dissolved in neat TFA, and stirred for two days.[10] After neutralization, workup, and flash column chromatography, lactam **10** is obtained in 59% overall yield from β-keto ester **9**. This sequence of operations constitutes a refined process for lactamization and ring-to-chain tautomerism as the pyrroloindoline topology of **4** is superfluous after fragment coupling and the original indole structure must be restored. Numerous other methods for unimolecular amide bond formation were surveyed but provided inferior results on scale due to the propensity of the intermediate β-keto acid to undergo decarboxylation, a process driven by favorable entropic gains and release of strain. The use of $POCl_3$ directly on a *tert*-butyl ester of type **9** had a twofold motivation: (1) the interaction between the ester carbonyl and oxophilic $POCl_3$ might induce ionization of the *tert*-butyl group, rendering a separate hydrolysis step unnecessary, and (2) the resulting acyl phosphate intermediate might mimic the reactivity seen with the intermediates invoked in phosphonium-based amide bond-forming reactions;[18] neutralization of the secondary amine would then lead to spontaneous lactamization. In practice, cyclization occurs spontaneously without an exogenous base during treatment with $POCl_3$ in boiling toluene. The reaction mixture that results contains mostly the ring tautomer of **10**; this material is easily converted to **10** as described above.

The remaining three carbon atoms of the central isoprene unit and another fully substituted stereocenter are incorporated by a diastereoselective carbonyl addition of *iso*-propenylmagnesium bromide to the ketocarbonyl of lactam **10**. Predictably higher diastereoselectivity is observed with lower reaction temperatures (10:1 at −78 °C). There are two noteworthy aspects of this outcome. First, in a control experiment, the cyclic tautomer of **10** furnished no products of ketocarbonyl addition, providing circumstantial evidence for a directed process[19,20] when chain tautomer **10** is subjected to the reaction conditions. Second, although no affirming correlations could be discerned in the NOESY spectrum of carbinol **11**, its C18 epimer (citrinadin B numbering; see structure **SI-3** in the Supporting Information) bore a correlation between both termini of the isopropenyl group and C16−H, thus establishing structure **11** by a process of elimination.

Although citrinadin B has a central cyclopentane core, we addressed this element indirectly by oxidative rearrangement of a 2,3-disubstituted indole to a 3,3-disubstituted oxindole for two reasons: first, given the high density of fully substituted carbons, it seemed logical to rearrange hindered, pre-existing bonds rather than attempting to generate such bonds to already-crowded centers directly; second, the factors giving rise to diastereoselection during oxidative rearrangement appeared predictable and

(18) Coste, J.; Frérot, E.; Jouin, P. *J. Org. Chem.* **1994**, *59*, 2437.

(19) For an authoritative review of directed reactions, see: Hoveyda, A. H.; Evans, D. A.; Fu, G. C. *Chem. Rev.* **1993**, *93*, 1307.

(20) Paquette has reported similar directivity: Hilmey, D. G.; Galluci, J. C.; Paquette, L. A. *Tetrahedron* **2005**, *61*, 11000.

possibly amenable to substrate control. Thus, carbinol **11** is reductively deprotected with Mg powder in methanol buffered with solid NH_4Cl furnishing a free indole that readily undergoes a formal cycloisomerization with a slight excess of $Hg(O_2CCF_3)_2$ followed by reductive demercuration of the resultant C−Hg σ-bond. Pentacycle **12** is isolated in 90% overall yield starting from pure carbinol **11**. Notably, the use of mixtures of **11** and its carbinol epimer at C18 is of no consequence since only the desired, predominant diastereomer undergoes mercurative cyclization.

Earlier investigations pointed to a protecting group liability during attempted oxidative rearrangement. Though the details are beyond the scope of this Letter, NMR and MS data suggest azetidine or cyclic imidate products from such reactions when the N25 atom or a carbamate group bonded to it has any appreciable nucleophilicity. The electrophilicity at C3 of indole during pinacol-like rearrangement may thus be diverted at the expense of oxindole formation. To address this difficulty, a protecting group exchange of carbamate for azide is performed. The methyl carbamate-protected nitrogen of **12** is deprotected with remarkable chemoselectivity with excess $BBr_3{\bullet}S(CH_3)_2$ at ambient temperature, furnishing amine **13** in 96% isolated yield, and this material is converted to azido amine **14** by a two-step sequence involving reduction of the lactam function by sodium bis(2-methoxyethoxy)-aluminum hydride and conversion of the primary amine to an azide upon treatment with trifluoromethanesulfonyl azide.[21] Finally, carbamoylation of the indole nitrogen occurs upon treatment with stoichiometric 4-(dimethylamino)pyridine and excess di-*tert*-butyl dicarbonate at 55 °C furnishing azido carbamate **15** in 47% isolated yield.

The desired oxidative rearrangement[22,23] was achieved by sequential treatment of azido carbamate **15** with (1) a slight excess of trifluoroacetic acid to protonate and therefore protect the tertiary amine from oxidation; (2) at least 3 equiv of anhydrous, exogenously generated trifluoroperacetic acid;[24] and (3) 10 equiv of dimethyl sulfide to quench the unconsumed oxidant. After neutralization, workup, and purification, oxindole **16** is isolated in 33% yield. Analysis of the crude reaction mixture reveals that the desired product is the predominant species (see Supporting Information); the identity of the remaining products, however, remains to be determined. The refined protocol for oxidative rearrangement was identified based on previously observed complications and the finding that trifluoroperacetic acid is uniquely effective at converting carbamate **15** to oxindole **16**. This oxidant was chosen not only because other, less electrophilic peracids were found to be incapable of oxidation of the Boc-protected indole nucleus but also because the heightened acidity of this reagent might enable a substrate-directable chemical reaction wherein the tertiary hydroxyl group serves as a hydrogen bond acceptor, as opposed to a donor as seen with other hydroxyl-directed epoxidations.[25] Although this hypothesis served as a design element, more rigorous studies are required before such a conclusion can be firmly established. Nonetheless, the production of oxindole **16** demonstrates that the highly substituted, stereochemically rich core of citrinadin B is accessible via oxidative rearrangement of a 2,3-disubstituted indole.

The chemistry described herein serves as a milestone in our effort to synthesize citrinadin B.[26] Apart from the brevity and operational simplicity of our route, other points of note include (1) utilization of the stereochemistry of L-tryptophan in an overall "self-reproduction of chirality" event; (2) ready access to scalemic piperidine fragment **8**; (3) an efficient mixed Claisen acylation union; and (4) designed, diastereoselective carbonyl addition and oxidative rearrangement reactions to address remaining problems of stereocontrol in the citrinadin B context. These investigations place the projected completion of our synthesis on a firm foundation and may allow more general questions to be answered with regard to the physiological performance of this potential antileukemic agent.

Acknowledgment. We gratefully acknowledge financial support from the National Institutes of Health (R01-GM065483 to E.J.S.; F32-GM086035 to C.A.G.).[27] We thank Drs. István Pelczer and John Eng (both of Princeton University) for spectroscopic assistance. Graham Hone (Princeton University) is acknowledged for reproduction of experimental procedures.

Supporting Information Available. Detailed experimental procedures, characterization data, and spectra of isolated and purified intermediates. This material is available free of charge via the Internet at http://pubs.acs.org.

(21) Vasella, A.; Witzig, C.; Chiara, J.-L.; Martin-Lomas, M. *Helv. Chim. Acta* **1991**, *74*, 2073.

(22) Martin disclosed a similar oxidative ring contraction strategy toward citrinadin A: Pettersson, M.; Knueppel, D.; Martin, S. F. *Org. Lett.* **2007**, *9*, 4623.

(23) Both Martin's and our own work were based on Foote's observation that indoles bearing electron-withdrawing groups at N1 rearrange to oxindoles spontaneously upon epoxidation in contrast to ring opening to C3-hydroxyindolenines when the indole is unprotected: Zhang, X.; Foote, C. S. *J. Am. Chem. Soc.* **1993**, *115*, 8867.

(24) Generation of solutions of trifluoroperacetic acid: Ballini, R.; Marcantoni, E.; Petrini, M. *Tetrahedron Lett.* **1992**, *33*, 4835.

(25) McKittrick, B. A.; Ganem, B. *Tetrahedron Lett.* **1985**, *26*, 4895.

(26) For recent disclosures from other groups: (a) McIver, A. L.; Deiters, A. *Org. Lett.* **2010**, *6*, 1288. (b) At the 2011 Grasmere Heterocyclic and Synthesis Symposium (May 5−9, 2011) Prof. Stephen Martin presented a lecture describing his laboratory's synthesis of the penacyclic core structure of citrinadin B. (c) Kong, K.; Smith, G. M.; Wood, J. L. "Progress Towards the Total Synthesis of Citrinadins A & B." 42nd National Organic Symposium, June 6−9, 2011, Princeton, NJ.

(27) Research toward a synthesis of citrinadin B was conducted by CAG from February 2009 to April 2011.