ORGANIC LETTERS

2006
Vol. 8, No. 15
3403−3406

Total Syntheses of (±)-*cis*-Trikentrin A and (±)-*cis*-Trikentrin B via Electrocyclic Ring Closures of 2,3-Divinylpyrrolines

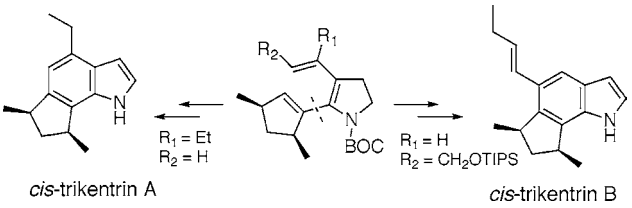
Raymond J. Huntley and Raymond L. Funk*

Department of Chemistry, Pennsylvania State University, University Park, Pennsylvania 16802

rlf@chem.psu.edu

Received May 23, 2006 *(Revised Manuscript Received June 17, 2006)*

ABSTRACT



A convergent and versatile strategy for the diastereoselective syntheses of (±)-*cis*-trikentrin A and B in 10 and 12 steps, respectively, from commercially available *N*-BOC-2-pyrrolidinone is described. The key step in each of the total syntheses is the construction of the central benzene ring via a facile 6π-electrocyclic ring closure of an appropriately substituted 2,3-divinylpyrroline, in turn, readily available by a Stille coupling reaction.

The trikentrin series of polyalkylated indoles (Figure 1) were isolated by Capon and co-workers from the marine sponge

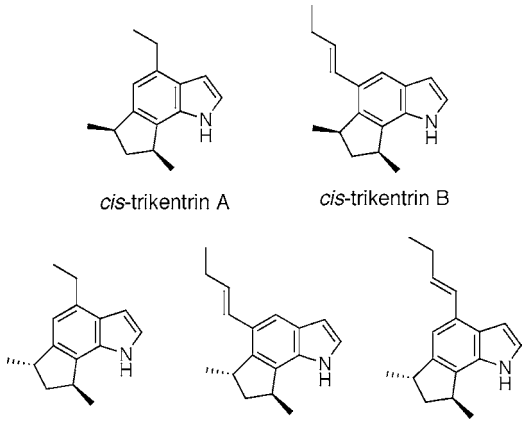


Figure 1. The trikentrin indole natural products.

Trikentrion flabelliforme, collected from coastal waters off Darwin, Australia.[1] They were shown to exhibit antimicrobial activity against the gram positive bacteria *Bacillus subtillus.* Unlike most other indole alkaloids, the trikentrins lack substituents at either C(2) or C(3), suggesting a nontryptophan based biosynthesis.

The unusual cyclopentannelated ring system of the trikentrins, combined with their biological activity, has attracted the interest of a number of synthetic groups, culminating in several racemic[2] and enantioselective[3] syntheses. The synthetic challenge posed by the complexly substituted indole rings of the trikentrins is reflected in the variety of strategies that have been undertaken for their construction and without exception do not make use of more classical methods for the preparation of indoles.

(1) Capon, R. J.; MacLeod, J. K.; Scammells, P. J. *Tetrahedron* **1986**, *42*, 6545.

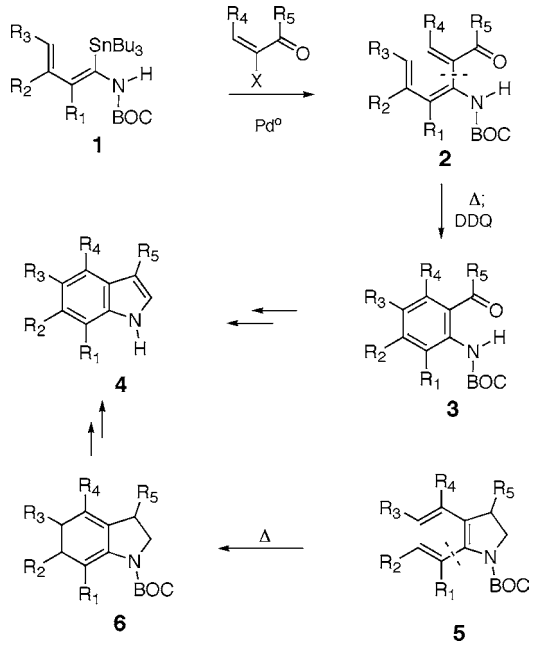
(2) (a) MacLeod, J. K.; Monahan, L. C. *Tetrahedron Lett.* **1988**, *29*, 391. (b) Yasukouchi, T.; Kanematsu, K. *Tetrahedron Lett.* **1989**, *30*, 6559. (c) MacLeod, J. K.; Monahan, L. C. *Aust. J. Chem.* **1990**, *43*, 329. (d) Muratake, H.; Watanabe, M.; Goto, K.; Natsume, M. *Tetrahedron* **1990**, *46*, 4179. (e) Boger, D. L.; Zhang, M. *J. Am. Chem. Soc.* **1991**, *113*, 4230. (f) Widenau, P.; Monse, B.; Blechert, S. *Tetrahedron* **1995**, *51*, 1167. (g) Jackson, S. K.; Banfield, S. K.; Kerr, M. A. *Org. Lett.* **2005**, *7*, 1215.

(3) (a) Muratake, H.; Mikawa, A.; Seino, T.; Natsume, M. *Chem. Pharm. Bull.* **1994**, *42*, 854. (b) Lee, M.; Ikeda, I.; Kawabe, T.; Mori, S.; Kanematsu, K. *J. Org. Chem.* **1996**, *61*, 3406.

10.1021/ol061259a CCC: $33.50
Published on Web 06/27/2006

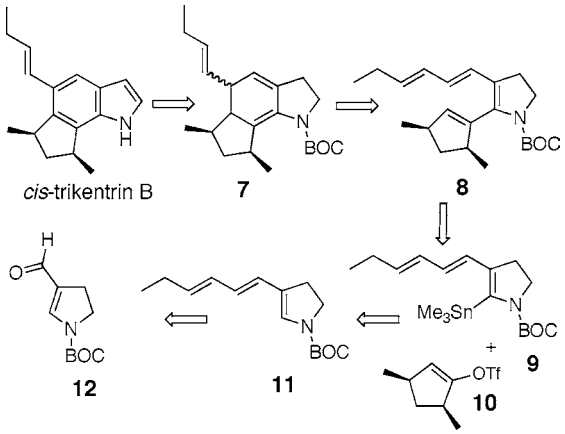
We were intrigued by the possibility that we could develop a concise, diastereoselective route to the trikentrin natural products through an extension of methodology we recently developed for the synthesis of polysubstituted indoles.[4] This methodology made use of the Stille coupling reactions of stannanes **1** for the synthesis of trienecarbamates **2**, which were shown to undergo facile thermal electrocyclic ring closure (typically in refluxing toluene for 1−3 h) and concomitant oxidation to anilines **3**. The anilines were then readily converted into indoles **4**. The facility of these 6π-electrocyclic ring closures was ascribed to a push/pull type mechanism of the hydrogen bonded enecarbamate functionality with the proximal carbonyl group en route to the resonance stabilized vinylogous imide product. However, the ketone carbonyl group of triene carbamate **2** is not absolutely essential for smooth rearrangement since it was found for a single example (coupling with 1-cyclohexenyltriflate) that the cyclization still took place under relatively mild conditions (120 °C, 12 h). This result suggested that the electrocyclic ring closures of divinylpyrrolines **5** to tetrahydroindoles **6** might proceed more smoothly than the previously reported divinyl*pyrrole* counterparts,[5] thereby affording an alternative strategy for the construction of indoles **4**. Moreover, the divinylpyrrolines **5** could be easily prepared via Stille coupling reactions analogous to those used to assemble trienecarbamates **2**. We report herein the validation of this approach in the total syntheses of *cis*-trikentrin A and B.

Scheme 1



Our retrosynthetic analysis for the synthesis of *cis*-trikentrin B is outlined in Scheme 2. Thus, it was hoped that

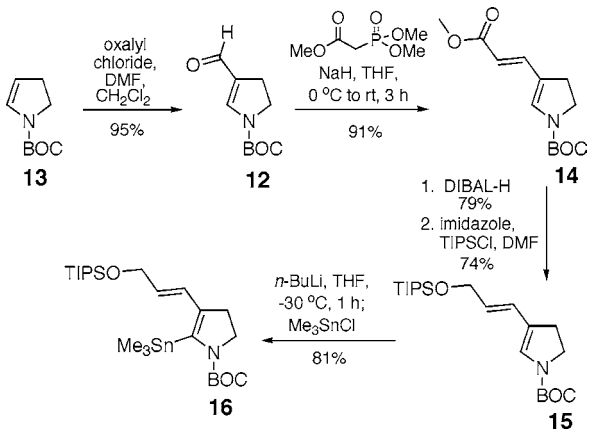
Scheme 2



the natural product could be obtained by oxidation of tetrahydroindole **7** followed by removal of the BOC protecting group. On the basis of the previous discussion, we believed that this triene would be readily accessible by an electrocyclic ring closure of tetraene **8**, in turn, available via Stille coupling of stannane **9** and enol triflate **10**. The stannane **9** could be derived from trienecarbamate **11** via a standard metalation/stannylation sequence, which could in turn be obtained by olefination of aldehyde **12**.

Aldehyde **12** was readily prepared from *N*-BOC-pyrroline **13**[6] via Vilsmeier−Haack formylation (Scheme 3). Unfor-

Scheme 3



tunately, all attempts to effect a Julia−Kocieñski olefination[7] of aldehyde **12** to arrive at the desired triene **11** were unsuccessful and gave only intractable mixtures of products. However, Horner−Wadsworth−Emmons olefination with trimethyl phosphonoacetate proceeded uneventfully to afford

(4) (a) Greshock, T. J.; Funk, R. L. *J. Am. Chem. Soc.* **2006**, *128*, 4946. (b) Greshock, T. J.; Funk, R. L. *Org. Lett.* **2006**, *8*, 2643.

(5) These electrocyclic closures are significantly slower (>200 °C), see the following: Moskal, J.; van Stralen, R.; Postma, D.; van Leusen, A. M. *Tetrahedron Lett.* **1986**, *27*, 2173.

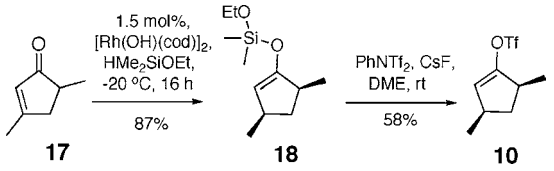
(6) Prepared in one step from commercially available *N*-BOC-2-pyrrolidinone; Yu, J.; Truc, V,; Riebel, P.; Hieryl, E.; Mudryk, B. *Tetrahedron Lett.* **2005**, *46*, 4011. See also Oliveira, D. F.; Miranda, P. C. M. L.; Correia, C. R. D. *J. Org. Chem.* **1999**, *64*, 6646.

(7) Blakemore, P. R.; Cole, W. J.; Kocieñski, P. J.; Morley, A. *Synlett.* **1998**, 26.

ester **14** that was adequately functionalized for introduction of the butenyl side chain at a later stage in the synthesis. To that end, reduction of the ester functionality and protection of the resulting hydroxyl group as the TIPS ether gave diene **15**. The synthesis of one of the reactants for the projected Stille coupling reaction, stannane **16**, was then completed by directed metalation of the diene **15** followed by stannylation with trimethyltin chloride.

With stannane **16** in hand, our attention turned to the synthesis of triflate **10,** which we felt could be prepared from the less substituted enolate derivative of *cis*-2,4-dimethyl cyclopentanone. To that end, we examined the hydrosilylation of 3,5-dimethylcyclopentenone **17**[8] under a variety of conditions. We initially subjected cyclopentenone **17** to *tert*-butyldimethylsilane and platinum divinyltetramethyldisiloxane complex (Karstedt's catalyst) according to the Johnson protocol (70 °C, neat)[9] and obtained a disappointing mixture of cis/trans isomers (2:1). However, the diastereoselectivity could be improved by using triethylsilane (6:1) or dimethylethoxysilane at 0 °C (10:1). The best results were obtained using a modification of Mori's conditions[10] {$HSiMe_2(OEt)$, $[Rh(OH)(cod)]_2$, −20 °C} and gave rise to dimethylethoxysilylenol ether **18** with greater than 20:1 cis/trans selectivity by ^{1}H NMR spectroscopy (Scheme 4).[11,12] This

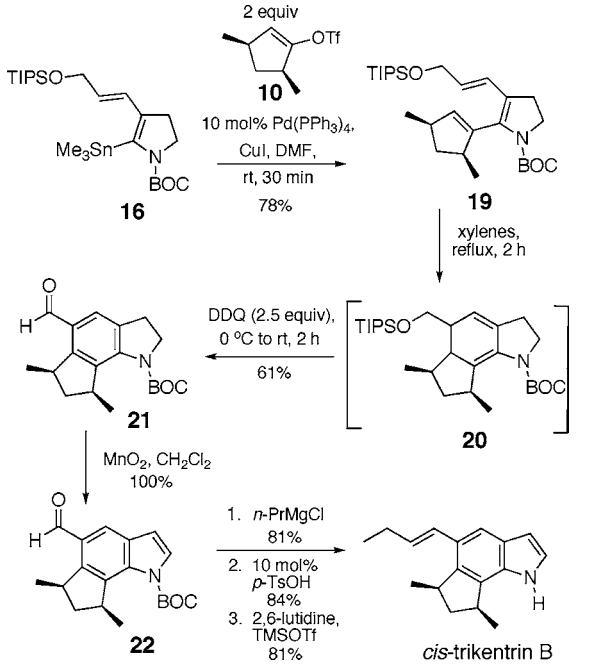
Scheme 4



enol ether was then directly converted into the desired enol triflate **10** via a protocol recently reported by Corey and coworkers.[13]

We now directed our attention to the construction of the central six-membered ring from the two five-membered ring building blocks. Thus, Stille coupling of stannane **16** with triflate **10** gave trienecarbamate **19** in good yield (Scheme 5). We were pleased to discover that triene **19** underwent an electrocyclic closure in refluxing xylenes to afford diene **20** that, in the same pot, could be aromatized with concomitant oxidative desilylation to indoline aldehyde **21** simply by lowering the reaction temperature to 0 °C and adding DDQ (2.5 equiv). Moreover, compound **21** was a crystalline

Scheme 5



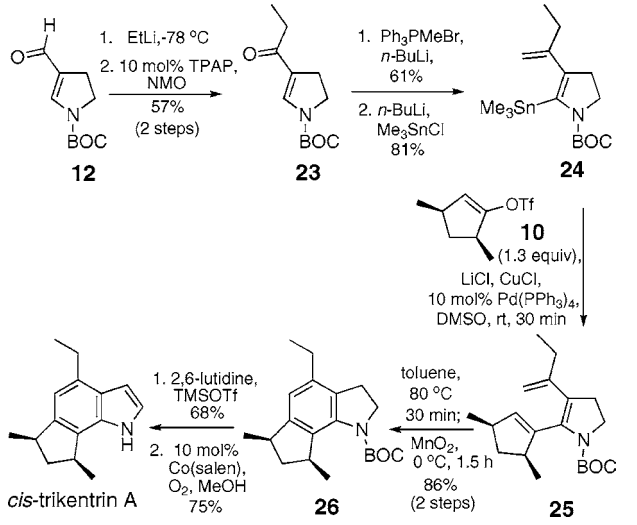
solid, and its structure and stereochemistry were confirmed by X-ray crystallography.

To complete the total synthesis, indoline **21** was oxidized with MnO_2 to give indole **22**. Next, the *trans*-butenyl side chain was installed using the same protocol reported by Natsume[3a] that was successful for the *N*-phenylsulfonylindole analogous to carbamate **22**, namely, via dehydration of the benzylic alcohol derived from Grignard addition to aldehyde **22**. Finally, removal of the BOC protecting group with TMSOTf [14] proceeded uneventfully to give (±)-*cis*-trikentrin B, whose spectra were very similar to the isolated natural product[1] and identical to previously synthesized material.[2d,g]

The versatility of this particular approach to the trikentrins was next examined in its straightforward application to the total synthesis of *cis*-trikentrin A. Thus, our immediate goal was the preparation of stannane **24** that now possesses the eventual C(4) ethyl substituent of trikentrin A (Scheme 6). To that end, addition of ethyllithium to aldehyde **12** followed by TPAP/NMO oxidation gave rise to ketone **23**. Wittig olefination followed by stannylation provided stannane **24**. A subsequent Stille coupling of stannane **24** with triflate **10** gave rise to the labile trienecarbamate **25** that decomposed during several attempts to purify it via column chromatography. Accordingly, the crude coupling product was heated in toluene in order to effect an especially facile electrocyclic ring closure (30 min, 80 °C) followed by in situ oxidation with MnO_2 to deliver the desired indoline **26**. This electrocyclic closure is accelerated relative to the triene **19** counterpart presumably because of the placement of the ethyl substituent, that is, it is not on the terminal carbon of the triene. Deprotection of the BOC protecting group with

(8) Toder, B. H.; Branca, S. J.; Dieter, R. K.; Smith, A. B., III. *Synth. Commun.* **1975**, *5*, 435.
(9) Johnson, C. R.; Raheja, R. K. *J. Org. Chem.* **1994**, *59*, 2287.
(10) Mori, A.; Kato, T. *Synlett*. **2002**, 1167.
(11) The stereochemistry was assigned by hydrolysis to the known[2d] *cis*-2,4-dimethylcyclopentanone
(12) Buchwald and co-workers reported have reported the enantio- and diastereoselective synthesis of 2,4-dialkylcyclopentanones via analogous silyl enol ethers that could render this synthesis enantioselective, albeit, with lower diastereoselectivity, see the following: Jurkauskas, V.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 2892.
(13) Mi, Y.; Schreiber, J. V.; Corey, E. J. *J. Am. Chem. Soc.* **2002**, *124*, 11290.
(14) Sakaitani, M.; Ohfune, Y. *J. Org. Chem.* **1990**, *55*, 870.

Scheme 6



TMSOTf and aromatization (Co(salen)/O_2/MeOH)[15] gave (±)-*cis*-trikentrin A whose spectral properties were very similar to those previously reported.[1]

(15) Inada, A.; Nakamura, Y.; Morita, Y. *Chem. Lett.* **1980**, 1287.

In conclusion, we have shown that 2,3-divinylpyrrolines undergo facile, electrocyclic ring closures in the context of concise, diastereoselective syntheses of (±)-*cis*-trikentrin A and B (10 and 12 steps, respectively, from commercially available *N*-BOC-2-pyrrolidinone). The convergency of this approach is noteworthy since the syntheses can be reduced to the preparation of the appropriate five-membered ring stannane and five-membered ring triflate coupling partners and could be readily adapted to the total syntheses of related indole natural products, for example, the herbindoles[16a] or dilemmaones.[16b]

Acknowledgment. We appreciate the financial support provided by the National Institutes of Health (Grant GM28663).

Supporting Information Available: Spectroscopic data and experimental details for the preparation of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL061259A

(16) (a) Herb, R.; Carroll, A. R.; Yoshida, W. Y.; Scheuer, P. J.; Paul, V. J. *Tetrahedron* **1990**, *46*, 3089. (b) Beukes, D. R.; Davies-Coleman, M. T.; Kelly-Borges, M.; Harper, M. K.; Faulkner, J. *J. Nat. Prod.* **1998**, *61*, 699.