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A Diastereoselective Total Synthesis of *trans*-Trikentrin A: A Ring Contraction Approach

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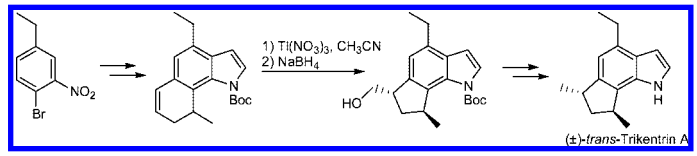
ABSTRACT



A new route to obtain the polyalkylated indole (±)-*trans*-trikentrin A was developed. The synthesis of this natural alkaloid features a thallium(III)-mediated ring contraction reaction to obtain the *trans*-1,3-disubstituted five-membered ring in a diastereoselective manner. Thallium(III) is chemoselective in this rearrangement, reacting with the olefin without oxidation of the indole moiety. Other key transformations are the Bartoli's reaction to construct the heterocyclic ring and a Heck coupling to add the carbons atom that will originate the nonaromatic cycle.

Alkaloids bearing the indole moiety constitute one of the most important groups of natural products, mainly due to their remarkable biological activity.[1] Usually, these heterocyclic compounds are substituted in the very reactive two and three position.[1] However, trikentrins and herbindoles form a small group of alkaloids isolated from sponges that lack substituents at these positions. In addition, a substituted five-membered ring is fused to the indole moiety (Figure 1).[2] These cyclopenta[*g*]indoles possess antimicrobial activity,[2a] are cytotoxic against KB cells[2b] and are fish antifeedants.[2b] Furthermore, molecules with a related tricyclic ring system can inhibit the human nonpancreatic secretory phospholipase A_2, which is associated with diseases, such as arthritis and atherosclerosis.[3] Considering this scenario, the synthesis of these alkaloids has been continuously investigated.[4,5] Several approaches were developed for *cis*-trikentrins and herbindoles, which bear a *cis*-1,3-dimethylcyclopentyl unit.[4] In contrast, there are only a few routes available for the *trans*-trikentrins, all requiring the delicate separation of *cis*/*trans* diastereomers, because of the low selectivity of the formation of the *trans*-1,3-disubstituted five-membered ring.[5] Indeed, in the syntheses of *trans*-trikentrin A, the *trans*-compound was not the major diastereomer in the formation of the cyclopentyl unit (*cis*:*trans* selectivity = 1:1,[4j] 4:3,[4k,m] and 55:40,[4i] respectively).

An efficient method to obtain exclusively *trans*-1,3-disubstituted five-membered ring is the ring contraction[6] of

(1) For selected reviews, see: (a) Higuchi, K.; Kawasaki, T. *Nat. Prod. Rep.* **2007**, *24*, 843. (b) Gul, W.; Hamann, M. T. *Life Sci.* **2005**, *78*, 442, and references therein.

(2) (a) Capon, R. J.; MacLeod, J. K.; Scammels, P. J. *Tetrahedron* **1986**, *42*, 6545. (b) Herb, R.; Carroll, A. R.; Yoshida, W. Y.; Scheuer, P. J.; Paul, V. J. *Tetrahedron* **1990**, *46*, 3089.

(3) Sawyer, J. S.; Beight, D. W.; Smith, E. C. R.; Snyder, D. W.; Chastain, M. K.; Tielkin, R. L.; Hartley, L. W.; Carlson, D. G. *J. Med. Chem.* **2005**, *48*, 893.

(4) Syntheses of *cis*-trikentrins and of herbindoles: (a) Jackson, S. K.; Kerr, M. A. *J. Org. Chem.* **2007**, *72*, 1405. (b) Huntley, R. J.; Funk, R. L. *Org. Lett.* **2006**, *8*, 3403. (c) Jackson, S. K.; Banfield, S. C.; Kerr, M. A. *Org. Lett.* **2005**, *7*, 1215. (d) Lee, M.; Ikeda, I.; Kawabe, T.; Mori, S.; Kanematsu, K. *J. Org. Chem.* **1996**, *61*, 3406. (e) Wiedenau, P.; Monse, B.; Blechert, S. *Tetrahedron* **1995**, *51*, 1167. (f) Muratake, H.; Mikawa, A.; Seino, T.; Natsume, M. *Chem. Pharm. Bull.* **1994**, *42*, 854. (g) Muratake, H.; Seino, T.; Natsume, M. *Tetrahedron Lett.* **1993**, *34*, 4815. (h) Muratake, H.; Mikawa, A.; Natsume, M. *Tetrahedron Lett.* **1992**, *33*, 4595. (i) Boger, D. L.; Zhang, M. *J. Am. Chem. Soc.* **1991**, *113*, 4230. (j) MacLeod, J. K.; Monahan, L. C. *Aust. J. Chem.* **1990**, *43*, 329. (k) Muratake, H.; Watanabe, M.; Goto, K.; Natsume, M. *Tetrahedron* **1990**, *46*, 4179. (l) Yasukouchi, T.; Kanematsu, K. *Tetrahedron Lett.* **1989**, *30*, 6559. (m) Muratake, H.; Natsume, M. *Tetrahedron Lett.* **1989**, *30*, 5771. (n) MacLeod, J. K.; Monahan, L. C. *Tetrahedron Lett.* **1988**, *29*, 391.

(5) Syntheses of *trans*-trikentrins: MacLeod, J. K.; Ward, A.; Willis, A. C. *Aust. J. Chem.* **1998**, *51*, 177 and refs 4f,g,i,j,k, and m.

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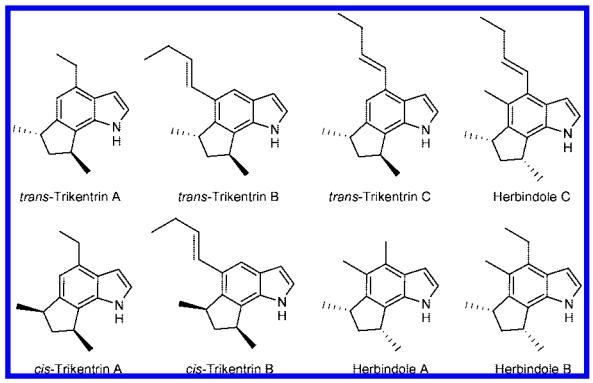
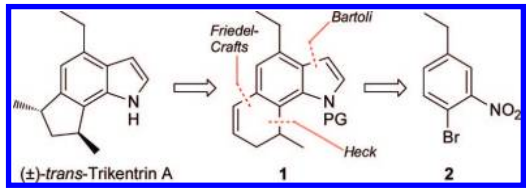


Figure 1. Structure of trikentrins and herbindoles.

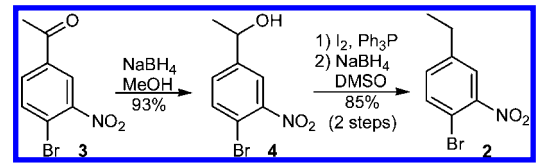
a 1-substituted-1,2-dihydronaphthalene using either thallium trinitrate (TTN)[7] or [hydroxy(tosyloxy)iodo]benzene (HTIB).[8] We envisioned that such a reaction could be used in the synthesis of *trans*-trikentrins, provided the electrophilic reagent could mediate the ring contraction of a compound such as **1** without disturbing the indole ring.[9f] This could be challenging because Tl(III) and I(III) readily reacts with indoles.[9] Herein, we describe a ring contraction approach for the first diastereoselective synthesis of *trans*-trikentrin A, starting from the functionalized benzene **2** (Scheme 1).

Scheme 1. Ring Contraction Approach for *trans*-Trikentrin A



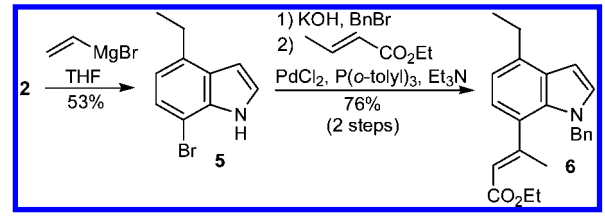
The 1-bromo-4-ethyl-2-nitrobenzene (**2**) was prepared in three steps from the commercially available acetophenone **3**, in 79% overall yield (Scheme 2).[10] This sequence is better than the nitration of 4-ethylbromobenzene, which gives a mixture of regioisomers, necessitating a difficult chromatographic separation.

Scheme 2. Preparation of 1-Bromo-4-ethyl-2-nitrobenzene (**2**)



The nitro group was used to construct the indole moiety using Bartoli's method.[11] Thus, **2** was treated with vinyl magnesium bromide to give the bromo-indole **5**, which was protected with a benzyl group. The construction of the nonaromatic six-membered ring of **1** was then required. First, a Heck coupling between the protected indole and ethyl crotonate[4e,12] gave the unsaturated ester **6**. The *E* configuration of the double bond was assigned by comparison to an analogous compound.[12] (Scheme 3).

Scheme 3. Synthesis of the Unsaturated Ester **6**



The following sequence of steps was used to conduct the homologation of **6**. First, the conjugated double bond was reduced using Mg/MeOH.[4e,13] The ester moiety was reduced with DIBAL, giving **7**. This alcohol was transformed into the corresponding mesylate, which was treated with KCN to give, after hydrolysis with KOH, the carboxylic acid **8** in 78% yield from **7** (Scheme 4).

The intramolecular acylation reaction of **8** to give the tricyclic compound **9** was performed using TFA/TFAA. On the other hand, when **8** was treated with H_3PO_4 the migration of the benzyl group to the position 2 also took place,[4e] delivering **10** (Scheme 5).

The reduction of the ketone moiety of **9** gave an alcohol that was treated with PTSA, yielding the olefin **11**, on which

(6) For reviews concerning ring contraction reactions, see: (a) Redmore, D.; Gutsche, C. D. In *Advances in Alicyclic Chemistry*; Hart, H., Karabastos, G. J., Eds.; Academic Press: New York and London, 1971; Vol. 3, p 1. (b) Silva, L. F., Jr *Tetrahedron* **2002**, *58*, 9137.

(7) (a) Ferraz, H. M. C.; Silva, L. F., Jr.; Vieira, T. O. *Tetrahedron* **2001**, *57*, 1709. (b) Ferraz, H. M. C.; Aguilar, A. M.; Silva, L. F. *Tetrahedron* **2003**, *59*, 5817. For a review concerning Tl(III)-mediated ring contractions, see: (c) Ferraz, H. M. C.; Silva, L. F., Jr. *Quim. Nova* 2000, *23*, 216. For Tl(III)-mediated ring contraction in the synthesis of alkaloids, see: (d) Rigby, J. H.; Pigge, F. C. *J. Org. Chem.* **1995**, *60*, 7392. (e) See also references cited in reviews 6b and 7c.

(8) Silva, L. F., Jr.; Siqueira, F. A.; Pedrozo, E. C.; Vieira, F. Y. M.; Doriguetto, A. C. *Org. Lett.* **2007**, *9*, 1433.

(9) For examples, see: (a) Somei, M.; Hasegawa, T.; Kaneko, C. *Heterocycles* **1983**, *20*, 1983. (b) Banerji, A.; Nandi, G. *Heterocycles* **1987**, *26*, 1221. (c) Tholander, J.; Bergman, J. *Tetrahedron* **1999**, *55*, 12595. (d) Ishikawa, H.; Takayama, H.; Aimi, N. *Tetrahedron Lett.* **2002**, *43*, 5637. (e) Takayama, H.; Misawa, K.; Okada, N.; Ishikawa, H.; Kitajima, M.; Hatori, Y.; Murayama, T.; Wongseripipatana, S.; Tashima, K.; Matsumoto, K.; Horie, S. *Org. Lett.* **2006**, *8*, 5705. (f) Silva, L. F., Jr.; Craveiro, M. V.; Gambardella, M. T. P. *Synthesis* **2007**, 3851. (g) Dohi, T.; Morimoto, K.; Takenaga, N.; Goto, A.; Maruyama, A.; Kiyono, Y.; Tohma, H.; Kita, Y. *J. Org. Chem.* **2007**, *72*, 109.

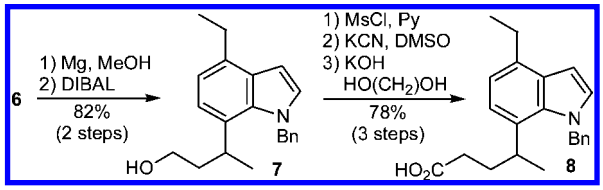
(10) For the reduction of alkyl halides using $NaBH_4$, see: Hutchins, R. O.; Kandasamy, D.; Dux, F., III; Maryanoff, C. A.; Rotstein, D.; Goldsmith, B.; Burgoyne, W.; Cistone, F.; Dalessandro, J.; Puglis, J. *J. Org. Chem.* **1978**, *43*, 2259.

(11) (a) Bartoli, G.; Palmieri, G.; Bosco, M.; Dalpozzo, R. *Tetrahedron Lett.* **1989**, *30*, 2129. (b) Dobbs, A. *J. Org. Chem.* **2001**, *66*, 638.

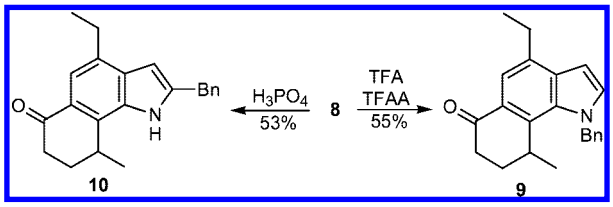
(12) Tonder, J. E.; Tanner, D. *Tetrahedron* **2003**, *59*, 6937.

(13) The product of this reaction was also obtained by an alternative route. See Supporting Information for details.

Scheme 4. Homologation of the Ester **6**

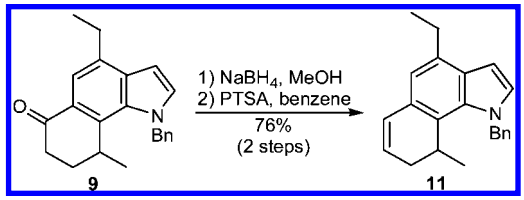


Scheme 5. Friedel−Crafts Acylation reactions



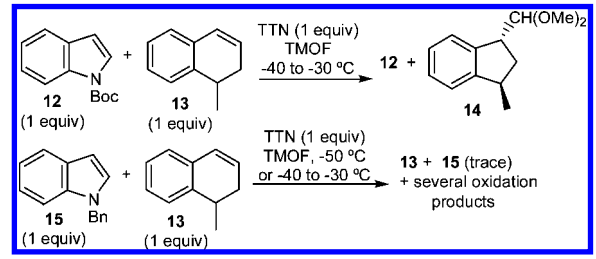
the ring contraction would be performed (Scheme 6). Treatment of **11** with TTN either in TMOF (trimethylortoformate)[6b] or in CH_3CN[14] at −40 °C gave a complex mixture of compounds in which the desired rearrangement product was not detected. HTIB was also ineffective in this reaction.

Scheme 6. Synthesis of the 1,2-Dihydronaphthalene **11**



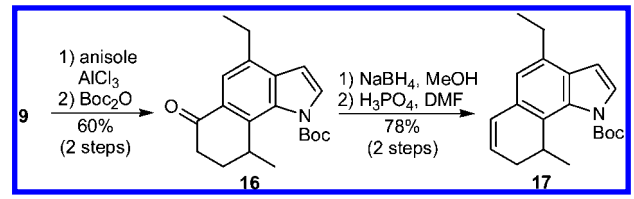
At this stage, we sought out further information about the chemoselectivity of the rearrangement step. Competitive reactions with simple substrates were then planned to compare the influence of N-protecting groups. When a 1:1 mixture of the indole **12** and the 1,2-dihydronaphthalene **13** was treated with a limited amount of TTN, we observed by TLC and NMR analysis that only the olefin **13** reacted, giving the *trans*-indane **14**.[15] However, in an equivalent experiment using the *N*-benzyl-indole **15**, the alkene **13** was the main component of the resulting mixture in all conditions tested (Scheme 7). Thus, the Boc group withdraws electrons, decreasing the reactivity of the indole **12** toward the electrophilic thallium(III), which reacts with the more available π electrons of the double bond of **13**. In contrast, the benzyl group would donate electrons, making the indole **15** more prone to an electrophile than the double bond of **13**. This would explain the disappointing results in the attempts to mediate the ring contraction of **11** with TTN.

Scheme 7. Competitive Reactions with Thallium(III)



In this context, we concluded that the protecting group of **11** should be replaced with a Boc group. The benzyl group was removed from **11** with anisole/$AlCl_3$,[16,17] and the carbamate was inserted with Boc_2O leading to **16**, in 60% yield for the two steps. The ketone moiety was then reduced with $NaBH_4$, and the alcohol was dehydrated with phosphoric acid, giving **17** (Scheme 8).

Scheme 8. Synthesis of the 1,2-Dihydronaphthalene **17**



Before treating the olefin **17** with thallium(III), we evaluated some sequences to synthesize the *trans*-1,3-dimethyl cyclopentyl unit in a stereoselective manner. To this end, the 1,2-dihydronaphthalene **13** was used as a model substrate. The reaction of **13** with HTIB in CH_3CN[8,15] gave the aldehyde **18**, which was treated with ethanethiol, leading to the corresponding dithiane **19** as a mixture of diastereomers. As the epimerization took place, the reduction of **19** with Raney nickel was not performed. The Wolff−Kishner reduction of **18** gave the desired 1,3-dimethyl-Indane **20**, although as a *cis*/*trans* mixture. To avoid handling the aldehyde moiety of **18**, we performed its reduction in situ after the ring contraction.[18] The alkene was treated with TTN, and when TLC analysis indicated the formation of **18**, $NaBH_4$ was added, giving the alcohol **21** as a single diastereomer.[15]

(14) Ferraz, H. M. C.; Carneiro, V. M. T.; Silva, L. F., Jr. *Synthesis*; Accepted for publication.

(15) The mechanism for formation of the *trans*-isomer in ring contraction reactions has been previously discussed.[7a,b,8]

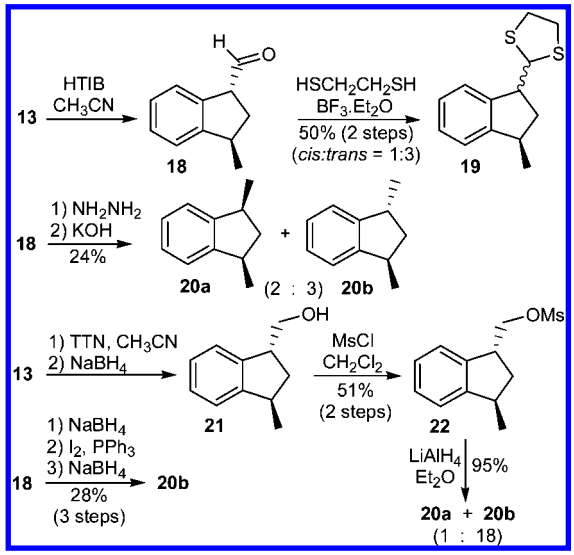
(16) A small amount of Bn-migration products, such as **11**, was also formed (details in Supporting Information). For deprotections using $AlCl_3$/anisole, see: Wada, Y.; Nagasaki, H.; Tokuda, M.; Orito, K. *J. Org. Chem.* **2007**, *72*, 2008.

(17) All attempts to obtain the ester **6** with a Boc group instead of the Bn failed in the Heck reaction.

(18) For reactions using TTN/$NaBH_4$, see: (a) Passacantilli, P. *Tetrahedron Lett.* **1989**, *30*, 5349. (b) Bettelli, E.; D'Andrea, P.; Mascanzoni, S.; Passacantilli, P.; Piancatelli, G. *Carbohydr. Res.* **1998**, *306*, 221.

The alcohol **21** was transformed into the mesylate **22**, which was treated with $LiAlH_4$, giving the *trans*-1,3-dimethyl-indane as the major diastereomer (*trans*:*cis* = 18:1). Alternatively, **20b**[19] was prepared by reaction of an iodide, which was obtained from the alcohol **21**, with $NaBH_4$. The overall yield for the latter sequence was lower than through the mesylate **22**. In summary, a diastereoselective route to obtain *trans*-1,3-dimethyl-indane **20b** was developed (Scheme 9).[20] This indane was used as starting material in previous syntheses of *trans*-trikentrins.[5]

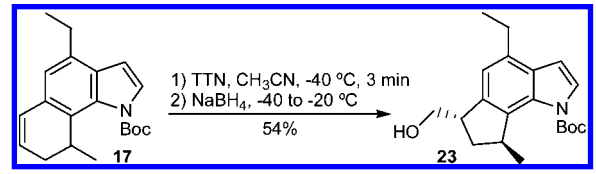
Scheme 9. Syntheses of *trans*-1,3-Dimethyl-indane (**20b**)



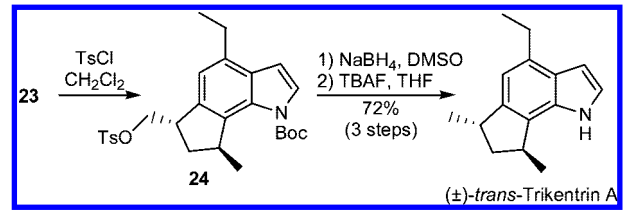
With these results in mind, we then focused on the final steps of the synthesis of *trans*-trikentrin A. The thallium(III)-mediated ring contraction of **17**, followed by an in situ reduction with $NaBH_4$, gave the desired product **23**, which bears the *trans*-1,3 five-membered ring (Scheme 10). The reaction conditions (specially the temperature) are crucial for the chemoselectivity of thallium(III).[9f]

The reduction of the alcohol moiety of **23** to the corresponding alkane was then investigated. The compound **23** was inert under the conditions used to obtain the iodide (I_2/PPh_3). The sequence through a mesylate was also unsuccessfull, because the reduction with $LiAlH_4$ gave an unidentified product. Finally, we found that the reduction of the tosylate **24** with $NaBH_4$[11] gave the desired product. To avoid acidic conditions, the Boc group was removed with TBAF,[21] furnishing (±)-*trans*-trikentrin A (Scheme 11). The spectroscopic data of our sample were equivalent to that reported in the literature for the natural compound.[2a,4i]

Scheme 10. Thallium(III)-Mediated Ring Contraction of **17**



Scheme 11. Completing the Synthesis of (±)-*trans*-Trikentrin A



In conclusion, a new route to obtain the natural alkaloid *trans*-trikentrin A was developed. This approach features as key reaction a chemo- and diastereoselective thallium(III)-promoted ring contraction reaction to construct the *trans*-1,3-disubstituted cyclopentyl unit. We are currently adaptating this route to (+)-*trans*-trikentrin A, whose synthesis has not been heretofore achieved.

Acknowledgment. The authors thank FAPESP and CNPq for support and Prof. Aguilar for discussion.

Supporting Information Available: Spectroscopic data and experimental procedures. This material is available free of charge via the Internet at http://pubs.acs.org.

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(19) Compound **20a** was not detected by ^1H NMR analysis.

(20) For stereoselective syntheses of indane **20**, see: (a) **20b** (30:1, *trans*:*cis*) Arp, F. O.; Fu, G. C. *J. Am. Chem. Soc.* **2005**, *127*, 10482. (b) **20a** (12:1, *cis*:*trans*) Bailey, W. F.; Mealy, M. J.; Wiberg, K. B. *Org. Lett.* **2002**, *4*, 791.

(21) Routier, S.; Saugé, L.; Ayerbe, N.; Coudert, G.; Mérour, J.-Y. *Tetrahedron Lett.* **2002**, *43*, 589.