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Iodine(III)-Promoted Ring Contraction of 1,2-Dihydronaphthalenes: A Diastereoselective Total Synthesis of (±)-Indatraline†

Luiz F. Silva, Jr.,*,‡ Fernanda A. Siqueira,‡† Eliane C. Pedrozo,‡ Fabiana Y. M. Vieira,‡ and Antônio C. Doriguetto§

Instituto de Química, Universidade de São Paulo, Av. Prof. Lineu Prestes, 748, CP 26077, CEP 05513-970 São Paulo SP, Brazil, and Departamento de Ciências Exatas, Universidade Federal de Alfenas, Rua Gabriel Monteiro da Silva, 714, CEP 37130-000 Alfenas MG, Brazil

luizfsjr@iq.usp.br

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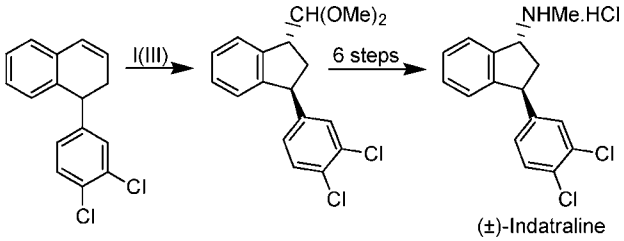
ABSTRACT



A new approach for the synthesis of (±)-indatraline, which is a 3-phenyl-1-indanamine that displays several biological activities, is described. The strategy features as the key step a diastereoselective ring contraction of a 1,2-dihydronaphthalene promoted by PhI(OTs)OH, to construct the indan ring system. The oxidative rearrangement of other 1,2-dihydronaphthalenes was also investigated, generalizing this method to obtain indans.

The abuse of drugs such as cocaine and amphetamines is an important health problem in several countries. A possible treatment for drug dependence is the use of a medication that would display a drug-like behavior, but with slower onset and longer duration of action than the drug.[1b] A molecule with these properties is (+)-indatraline (**1**),[1] which decreased the cocaine self-administration in *Rhesus monkeys*.[1f] Previous studies toward the synthesis of the *trans*-3-aryl-1-aminoindan ring system of indatraline relied on the preparation of a 1-indanone, which was transformed into the target 3-phenyl-1-indanamine through classic reactions.[1a,d,e,2] An asymmetric synthesis of indatraline was reported from **2**, using this approach (Scheme 1).[2a]

We envisioned that (±)-indatraline (**1**) could be efficiently obtained from the *trans*-1,3-disubstituted indan **3**, using a Hofmann rearrangement promoted by I(III) and functional group transformations. The indan **3** would be formed through an I(III)-mediated ring contraction of the 1,2-dihydronaphthalene **4**, which would be prepared by classical reactions from the known tetralone **5** (Scheme 2). The ketone **5** is produced in an optically pure form on an industrial scale, because it constitutes the starting material of the antidepres-

† This paper is dedicated in memoriam to Monica Grazini.
‡ Universidade de São Paulo.
§ Universidade Federal de Alfenas.

(1) For leading references concerning (+)-indatraline and its derivatives, see: (a) Bogeso, K. P.; Christensen, A. V.; Hyttel, J.; Liljefors, T. *J. Med. Chem.* **1985**, *28*, 1817. (b) Negus, S. S.; Brandt, M. R.; Mello, N. K. *J. Pharmacol. Exp. Ther.* **1999**, *291*, 60. (c) Partilla, J. S.; Dersch, C. M.; Yu, H.; Rice, K. C.; Rothman, R. B. *Brain Res. Bull.* **2000**, *53*, 821. (d) Gu, X.-H.; Yu, H.; Jacobson, A. E.; Rothman, R. B.; Dersch, C. M.; George, C.; Flippen-Anderson, J. L.; Rice, K. C. *J. Med. Chem.* **2000**, *43*, 4868. (e) Froimowitz, M.; Wu, K.-M.; Moussa, A.; Haidar, R. M.; Jurayj, J.; George, C.; Gardner, E. L. *J. Med. Chem.* **2000**, *43*, 4981. (f) Mello, N. K.; Negus, S. S. *Neuropsychopharmacology* **2001**, *25*, 104. (g) Schenk, S. *Psychopharmacology* **2002**, *160*, 263. (h) Yu, H.; Kim, I. J.; Folk, J. E.; Tian, X.; Rothman, R. B.; Baumann, M. H.; Dersch, C. M.; Flippen-Anderson, J. L.; Parrish, D.; Jacobson, A. E.; Rice, K. C. *J. Med. Chem.* **2004**, *47*, 2624. (i) Li, S.-M.; Campbell, B. L.; Katz, J. L. *J. Pharmacol. Exp. Ther.* **2006**, *317*, 1088.

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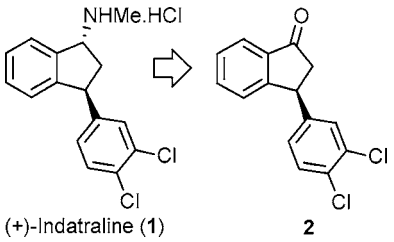
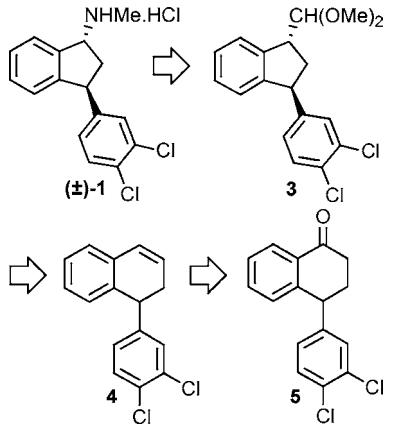
Scheme 1. Retrosynthesis for Indatraline: Previous Approaches



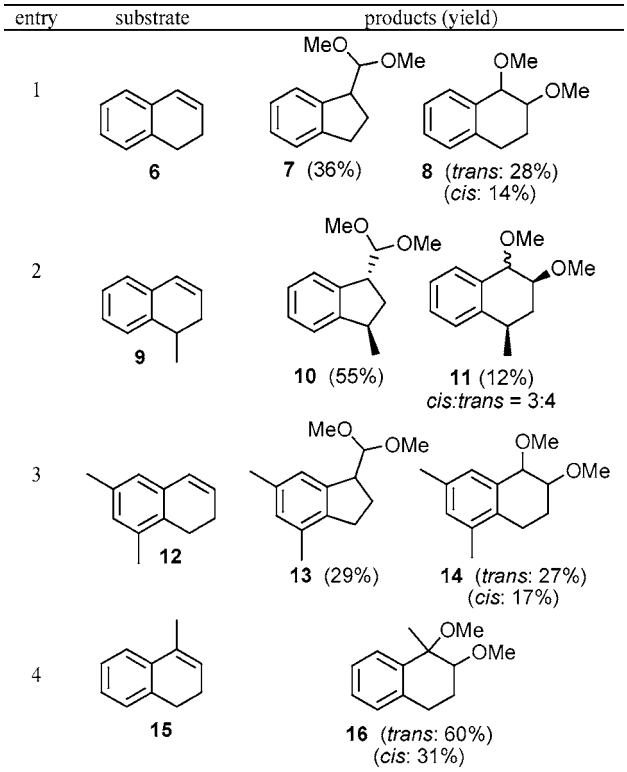
Scheme 2. Retrosynthesis for (±)-Indatraline Using a Ring Contraction Approach



sive (+)-sertraline, one of the top selling drugs.[3] Thus, the adaptation of our approach to the synthesis of (+)-indatraline would be straightforward. On the basis of this strategy, we herein report a short, diastereoselective synthesis of (±)-**1** using a hypervalent I(III) reagent for the construction of the indan skeleton. The oxidative rearrangement of other 1,2-dihydronaphthalenes was also investigated, generalizing this method to obtain indans.

Although the oxidative rearrangement of olefins mediated by I(III) was described in several papers,[4,5] the ring contraction of 1,2-dihydronaphthalenes was reported using only *p*-Tol-IF_2,[4c] which led to fluorinated indans. Thus, we decided first to investigate the reaction of a series of 1,2-dihydronaphthalenes with iodine(III) before the synthesis of indatraline. Considering the recent works regarding the rearrangement of olefins, we first focused on PhI(OTs)OH (HTIB or Koser reagent) in MeOH.[4a,d] The reaction of the olefin **6** with HTIB was performed under several conditions. The ring contraction product **7** was best obtained with HTIB in MeOH, albeit the addition product **8** was also isolated (Table 1, entry 1). When the reaction was performed at −10 °C, the overall isolated yield was lower (**7**, 24%; *trans*-**8**, 20%; *cis*-**8**, 15%) than at room temperature. The use of trimethylorthoformate (TMOF) as solvent, instead of MeOH, also decreased the global yield (**7**, 14%; *trans*-**8**, 12%; *cis*-**8**, 2%). These two trends are opposite that observed in analogous Tl(III) promoted oxidations.[6a,b] Although the indan **7** was obtained in only 36% yield from the olefin **6**, we decided to study the behavior of the methyl-substituted 1,2-

Table 1. Oxidation of 1,2-Dihydronaphthalenes with 1 equiv of HTIB in MeOH at Room Temperature



(2) (a) Davies, H. M. L.; Gregg, T. M. *Tetrahedron Lett.* **2002**, *43*, 4951. (b) Cossy, J.; Belotti, D.; Maguer, A. *Synlett* **2003**, 1515. (c) McConathy, J.; Owens, M. J.; Kilts, C. D.; Malveaux, E. J.; Votaw, J. R.; Nemeroff, C. B.; Goodman, M. M. *Nuclear Med. Biol.* **2005**, *32*, 593.

(3) For a leading reference, see: Hawkins, J. M.; Watson, T. J. N. *Angew. Chem., Int. Ed.* **2004**, *43*, 3224.

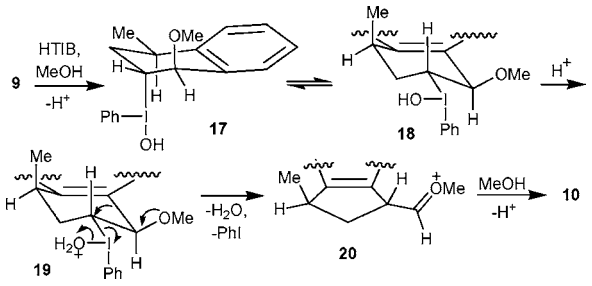
(4) For examples, see: (a) Justik, M. W.; Koser, G. F. *Tetrahedron Lett.* **2004**, *45*, 6159. (b) Harders, J.; Garming, A.; Jung, A.; Kaiser, V.; Monenschein, H.; Ries, M.; Rose, L.; Schöning, K-U.; Weber, T.; Kirschning, A. *Liebigs Ann.* **1997**, 2125. (c) Hara, S.; Nakahigashi, J.; Ishi-i, K.; Fukuhara, T.; Yoneda, N. *Tetrahedron Lett.* **1998**, *39*, 2589. (d) Justik, M. W.; Koser, G. F. *Molecules* **2005**, *10*, 217. (e) Kirschning, A. *Eur. J. Org. Chem.* **1998**, 2267. (f) Moriarty, R. M.; Prakash, O.; Duncan, M. P.; Vaid, R. K.; Rani, N. *J. Chem. Res. S* **1996**, 432. (g) Zefirov, N. S.; Caple, R.; Palyulin, V. A.; Berglund, B.; Tykvinskii, R.; Zhdankin, V. V.; Kozmin, A. S. *Bull. Acad. Sci. USSR, Div. Chem. Sci.* **1988**, *37*, 1289. For a review concerning ring contraction reactions promoted by I(III), see: (e) Silva, L. F., Jr. *Molecules* **2006**, *11*, 421.

(5) For reviews concerning I(III) chemistry, including rearrangement reactions, see: (a) Varvoglis, A. *Tetrahedron* **1997**, *53*, 1179. (b) Stang, P. J.; Zhdankin, V. V. *Chem. Rev.* **1996**, *96*, 1123. (c) Wirth, T. *Angew. Chem., Int. Ed.* **2005**, *44*, 3656. For a review concerning HTIB, see: (d) Koser, G. F. *Aldrichim. Acta* **2000**, *34*, 89.

(6) For examples of Tl(III)-mediated oxidation of 1,2-dihydronaphthalenes, see: (a) Ferraz, H. M. C.; Silva, L. F., Jr.; Vieira, T. O. *Tetrahedron* **2001**, *57*, 1709. (b) Silva, L. F., Jr.; Sousa, R. M. F.; Ferraz, H. M. C.; Aguilar, A. M. *J. Braz. Chem. Soc.* **2005**, *16*, 1160. (c) Silva, L. F., Jr.; Quintiliano, S. A. P.; Craveiro, M. V.; Vieira, F. Y.; Ferraz, H. M. C. *Synthesis* **2007**, 355. (d) Ferraz, H. M. C.; Silva, L. F., Jr. *Tetrahedron* **2001**, *57*, 9939. (e) Ferraz, H. M. C.; Aguilar, A. M.; Silva, L. F., Jr. *Synthesis* **2003**, 1031. For papers comparing Tl(III) to I(III), see: (f) Prakash, O. *Aldrichim. Acta* **1995**, *28*, 63. (g) Moriarty, R. M.; Khosrowshahi, J. S.; Prakash, O. *Tetrahedron Lett.* **1985**, *26*, 2961.

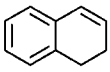
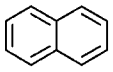
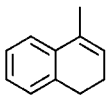
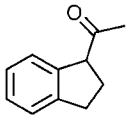
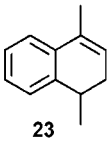
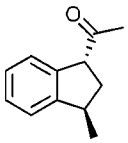
dihydronaphthalene **9**, hoping to obtain a higher yield of the ring contraction product, similar to that reported in the Tl-(III) reactions.[6a] Indeed, when **9** was treated with HTIB, the desired *trans*-indan **10** was obtained in 55% yield, together with the addition product **11** (entry 2). The relative configuration of **10** was assigned by comparison with the literature.[6a] The exclusive formation of the *trans*-indan **10** can be explained by the mechanism of the ring contraction.[4,6] The electrophilic *anti*-addition of HTIB to the double bond would lead to **17**. This adduct would equilibrate to its more stable conformational diastereomer **18**, on which the required *anti*-periplanarity for the rearrangement is achieved. Migration of the aryl group on **19** would displace PhI giving the oxonium **20**, which would furnish the indan **10**, after addition of MeOH (Scheme 3).

Scheme 3. Mechanism of the Ring Contraction



The presence of donating groups at the aromatic group facilitates the rearrangement when 1,2-dihydronaphthalenes are treated with Tl(III) by increasing the migratory aptitude of the migrating carbon.[6b,e] However, the reaction of 1,2-dihydronaphthalenes with HTIB is probably not so sensitive to this electronic effect, because treatment of the olefin **12** with HTIB gave the indan **13**, in a yield comparable to that obtained for **6** (compare entry 1 to entry 3). Considering our previous experience in the oxidations of olefins mediated by Tl(III),[6a] we expected that the trisubstituted 1,2-dihydronaphthalene **15** would have a behavior toward HTIB different from that of the disubstituted alkene **6**. Indeed, when the olefin **15** was treated with HTIB in MeOH only the addition product **16** (*trans*, 60%; *cis*, 31%) was isolated (entry 4). The diastereoselectivity observed in this reaction can be explained by a mechanism similar to that proposed in analogous thallium(III) oxidations.[6b] The conditions used by Kirschning and co-workers[4b,e] in the oxidation of carbohydrates were also applied for the olefins **6**, **15**, and **23**. When **6** was treated with HTIB, using CH_3CN in the presence of molecular sieves, naphthalene (**21**) was obtained in only 30% yield (Table 2, entry 1).[7] Similarly, **21** was obtained in 48% yield when the reaction was performed in CH_2Cl_2, as solvent. However, to our delight, the indan **22** could be obtained in 51% yield, when **15** was treated with HTIB in CH_3CN (entry 2). Moreover, the trisubstituted olefin **23** could also be transformed into the indan **24** (entry 3). The relative

Table 2. Oxidation of 1,2-Dihydronaphthalenes with 1 equiv of HTIB in CH_3CN with Molecular Sieves 3 A at 0 °C

entry	substrate	product (yield)
1	 **6**	 **21** (30%)
2	 **15**	 **22** (51%)
3	 **23**	 **24** (60%) (*trans*:*cis* = 10:1)

configuration of **24** was assigned by comparison with the NMR data of analogous compounds.[6d] The diastereoselectivity of the rearrangement can be explained by the mechanism described for **9**. In summary, CH_3CN appears to be the optimum solvent for the ring contraction of 1,2-dihydronaphthalenes bearing an alkyl group at the double bond, such as **15** and **23** (Table 2), whereas MeOH is suitable for unsubstituted olefins, such as **9** (Table 1).

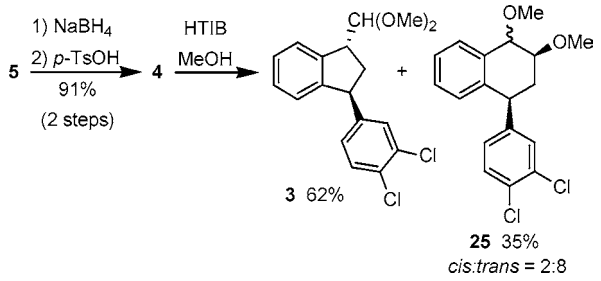
After studying the reaction of a series of 1,2-dihydronaphthalenes with iodine(III), the tetralone **5** was obtained by reaction of α-naphthol with 1,2-dichlorobenzene.[8] Next, the tetralone was reduced with $NaBH_4$, giving the corresponding 1-tetralol. The dehydration of the alcohol was performed with *p*-TsOH, which furnished the desired 1,2-dihydronaphthalene **4**, in 91% yield. The following step was the ring contraction of the 1,2-dihydronaphthalene **4**, which was performed with 3.6 equiv of HTIB in MeOH. Under this condition, the indan **3** was obtained in 62% yield, as a single diastereomer, together with the addition product **25**, in 35% yield (Scheme 4). With a lower amount of HTIB, the yield of the ring contraction product **3** is smaller. A similar pattern was also observed in Tl(III) reactions, where an excess of the oxidant increased the yield of the indan.[6c] In summary, the oxidative rearrangement of 1,2-dihydronaphthalenes mediated by I(III) can be used to construct indans with high diastereoselectivity and in good yield. In addition, the ring contraction product is obtained in higher yield with use of I(III) rather than Tl-(III),[6a] when 4-alkyl-1,2-dihydronaphthalenes, such as **15** and **23**, are used as substrates. However, Tl(III) gives higher yields of the indan derivative, for unsubstituted 1,2-dihydronaphthalenes, such as **4** and **9**.[6a] For example, treatment of the olefin **4** with thallium trinitrate (TMOF, 0 °C, 5 min) gave the indan **3**, in 88% yield.

The ketal moiety of **3** was oxidized by using Jones reagent giving the acid **26**, which, under classical conditions, was

(7) The formation of **21** probably occurs by a mechanism analogous to that proposed in the thallium(III) oxidations.[6]

(8) Repinskaya, I. B.; Koltunov, K. Y.; Shakirov, M. M.; Shchegoleva, L. N.; Koptyug, V. A. *Russ. J. Org. Chem.* **1993**, *29*, 803.

Scheme 4. Preparation of the Indan **3**



transformed into the amide **27**. X-ray analysis of the crystalline solid **26** clearly shows the *trans* relationship of the substituents in the cyclopentane ring (see the Supporting Information). The required Hofmann rearrangement of the amide **27** was performed by $PhI(OCOCF_3)_2$ (PIFA), cleanly giving the primary amine **28**, in the form of the hydrochloride.[9] This compound is also crystalline, which allowed the elucidation of the structure by X-ray analysis. The amino and the aryl group are in a *trans* relationship in the cyclopentane ring, which shows that the rearrangement occurred with retention of configuration as expected (see the Supporting Information). To conclude the synthesis, the primary amine **28** should be transformed into the corresponding secondary methylamine. After testing several protocols, we found that indatraline could be obtained from **28**, in three steps. The first step was the protection of the amine with the Boc group to yield the corresponding carbamate,[10] which was alkylated with MeI, furnishing the target molecule after treatment with HCl generated in situ (Scheme 5).[11,12] The mixture of solvents and the temperature were crucial for the success of the alkylation, because under other conditions epimerization and decomposition were observed.

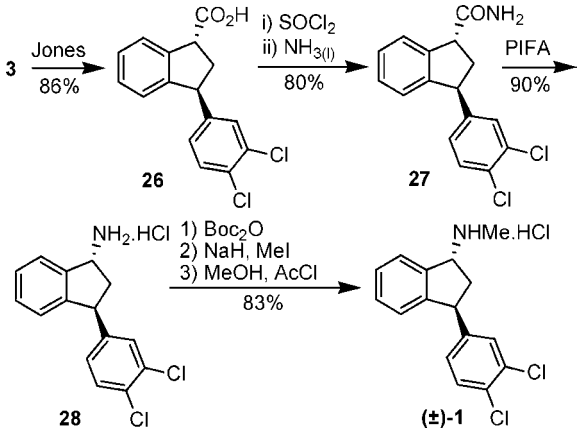
(9) Loudon, G. M.; Radhakrishna, A. S.; Almond, M. R.; Blodgett, J. K.; Boutin, R. H. *J. Org. Chem.* **1984**, *49*, 4272.

(10) Jacquemard, U.; Bénéteau, V.; Lefoix, M.; Routier, S.; Mérour, J.-Y.; Coudert, G. *Tetrahedron* **2004**, *60*, 10039.

(11) (a) Snider, B. B.; Lin, H. *J. Am. Chem. Soc.* **1999**, *121*, 7778. (b) Grieco, P. A.; Hon, Y. S.; Perez-Mendrano, A. *J. Am. Chem. Soc.* **1988**, *110*, 1630.

(12) Nudelman, A.; Bechor, Y.; Falb, E.; Fischer, B.; Wexler, B. A.; Nudelman, A. *Synth. Commun.* **1998**, *28*, 471.

Scheme 5. Completing the Synthesis of (±)-Indatraline



In conclusion, (±)-indatraline was synthesized in 9 steps from the readily available tetralone **5**, in 29% overall yield. This new approach features two diastereoselective rearrangements promoted by iodine(III), exemplifying the importance of this class of oxidant in synthetic organic chemistry. Furthermore, a new method for the synthesis of indans with use of HTIB was developed. Finally, the described route may be adapted to the asymmetric version starting from the (+)-tetralone. Further studies toward the ring contraction of 1,2-dihydronaphthalenes mediated by iodine(III) and its application toward the total synthesis of molecules with biological activity are in progress in our laboratories.

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

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