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Total Synthesis of (±)-Joubertinamine from 3-(3,4-Dimethoxyphenyl)-5-bromo-2-pyrone

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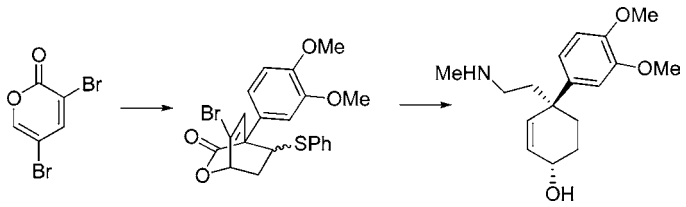
ABSTRACT



The regioselective synthesis and Diels−Alder cycloaddition of 3-(3,4-dimethoxyphenyl)-5-bromo-2-pyrone provided a new efficient synthetic route to joubertinamine (9.6% total yield over 10 steps).

The sceletium family of mesembrine alkaloids as well as their seco-congeners have been the synthetic target of considerable efforts over the past decades (Figure 1).[1] Long known to the Khoi-khoi and San peoples as a mood enhancer, sedative, analgesic, and appetite/thirst suppressant, these compounds have recently proven potentially useful in the treatment of depressive states, psychological or psychiatric disorders with an anxiety component, alcohol and drug dependence, bulimia nervosa, and obsessive−compulsive disorders.[2]

Unlike mesembrine **2**, there are only a few synthetic studies reported in the literature for joubertinamine **1**, with incomplete characterizations.[1n−r,3] In connection with our recent effort exploring the synthetic utility of 3,5-dibromo-2-pyrone,[4] we envisioned that the basic carbon skeletons, including the characteristic quarternary carbon center of sceletium family alkaloids, could be efficiently constructed by the Diels−Alder cycloaddition reaction of

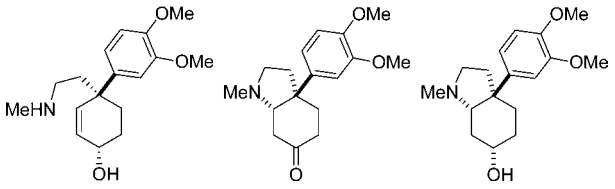


Figure 1. Selected examples of sceletium alkaloids.

(1) For the synthesis of mesembrine, see: (a) Paul, T.; Malachowski, W. P.; Lee, J. *Org. Lett.* **2006**, *8*, 4007. (b) Taber, D. F.; He, Y. *J. Org. Chem.* **2005**, *70*, 7711. (c) Chavan, S. P.; Khobragade, D. A.; Pathak, A. B.; Kalkote, U. R. *Tetrahedron Lett.* **2004**, *45*, 5263. (d) Rigby, J. H.; Dong, W. *Org. Lett*. **2000**, *2*, 1673. (e) Ogasawara, K.; Yamada, O. *Tetrahedron Lett.* **1998**, *39*, 7747. (f) Langlois, Y.; Dalko, P. I.; Brun, V. *Tetrahedron Lett.* **1998**, *39*, 8979. (g) Denmark, S. E.; Marcin, L. R. *J. Org. Chem.* **1997**, *62*, 1675. (h) Mori, M.; Kuroda, S.; Zhang, C.; Sato, Y. *J. Org. Chem.* **1997**, *62*, 3263. (i) Yoshimitsu, T.; Ogasawara, K. *Heterocycles* **1996**, *42*, 135. (j) Nemoto, H.; Tanabe, T.; Fukumoto, K. *J. Org. Chem.* **1995**, *60*, 6785. (k) Takano, S.; Samizu, K.; Ogasawara, K. *Chem. Lett.* **1990**, 1239. (l) Kosugi, H.; Miura, Y.; Kanna, H.; Uda, H. *Tetrahedron*: *Asymmetry* **1993**, *4*, 1409. (m) Meyers, A. I.; Hanreich, R.; Wanner, K. T. *J. Am. Chem. Soc*. **1985**, *107*, 7776. For the synthesis of joubertinamine, see: (n) Hoshino, O.; Ishizaki, M.; Sawaki, S.; Yuasa, M.; Umezawa, *Chem. Pharm. Bull*. **1988**, *36*, 3373. (o) Jeffs, P. W.; Redfearn, R.; Wolfram, J. *J. Org. Chem*. **1983**, *48*, 3861. (p) Sánchez, I. H.; Soria, J. J.; Larraza, M. I.; Flores, H. J. *Tetrahedron Lett*. **1983**, *24*, 551. (q) Psotta, K.; Wiechers, A. *Tetrahedron Lett*. **1979**, *35*, 255. (r) Psotta, K.; Strelow, F.; Wiechers, A. *J. Chem. Soc., Perkin Trans. 1* **1979**, 1063.

(2) (a) Jin, Z. *Nat. Prod. Rep.* **2005**, *22*, 111. (b) Smith, M. T.; Crouch, N.; Gericke, N.; Hirst, M. *J. Ethnopharmacol*. **1996**, *50*, 119. (c) Gericke, N. P.; VanWyk, B.-E.; PCT Int. Appl., WO 9746234 CAN 128: 80030, 1997.

(3) No ^{13}C NMR data were reported. One report (ref 1o) contains incorrect ^{1}H NMR spectral data.

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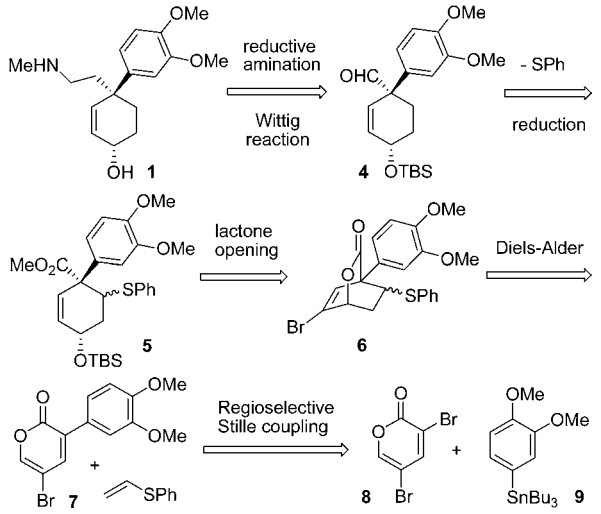
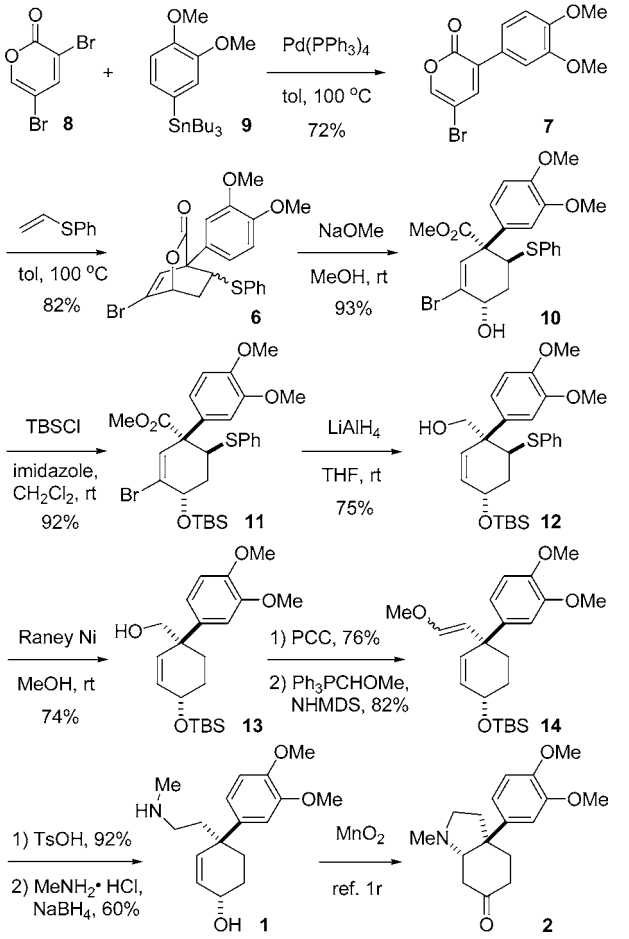
Scheme 1. Retrosynthesis



Scheme 2. Synthesis



3-(3,4-dimethoxyphenyl)-5-bromo-2-pyrone **7** with an ethylene equivalent (Scheme 1). The methanolysis of the resultant cycloadduct **6** and removal of phenylthio group would furnish the key cyclohexene intermediate **4**. Further elaboration including one-carbon homologation would permit rapid access to joubertinamine as well as mesembrine.

Scheme 2 summarizes our synthesis, beginning with the C3-selective Stille coupling reaction[5] of 3,5-dibromo-2-pyrone with aryltin **9**,[6] which produced 3-(3,4-dimethoxyphenyl)-5-bromo-2-pyrone **7** in 72% yield. The Diels−Alder cycloaddition reaction with phenyl vinyl sulfide provided bicyclolactone **6** as a mixture of *endo*/*exo* isomers (2:1, 82% combined yield). Although not necessary, the *endo*- and *exo*-adduct were separated and carried individually through the reaction sequence to facilitate the characterizations. Lactone opening and protection of the resultant hydroxyl group as a TBS ether afforded **11**. The reduction of the ester group of **11** using $LiAlH_4$ was accompanied by the concomitant removal of the vinyl bromide to give **12** in 75% yield. Subsequent removal of phenylthio group with Raney nickel furnished **13**[7] in 74% yield. The PCC oxidation to aldehyde **4** (Scheme 1) followed by the Wittig reaction provided enol ether **14** in 62% overall yield. Treatment of **14** with TsOH hydrolyzed both enol ether and TBS ether to afford aldehyde **15** (for structure, see the Supporting Information) in 92% yield. Reductive amination with methylamine hydrochloride furnished **1** in 60% yield after purification on neutral alumina.[8] Its structural integrity was further corroborated by the conversion to mesembrine **2** according to the known process.[1r,9]

In summary, we have devised a new efficient synthetic route to (±)-joubertinamine by utilizing the Diels−Alder cycloaddition reaction of 3-(3,4-dimethoxyphenyl)-5-bromo-2-pyrone (10 steps, 9.6% total yield).

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

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(4) For a recent review and selected articles, see: (a) Kim, H. Y.; Cho, C. G. *Prog. Heterocycl. Chem.* **2007**, *18*, 1. (b) Shin, I.-J.; Choi, E.-S.; Cho, C.-G. *Angew. Chem., Int. Ed.* **2007**, *46*, 2303. (c) Shin, J.-T.; Hong, S.-C.; Shin, S.; Cho, C.-G. *Org. Lett.* **2006**, *8*, 3339. (d) Ryu, K.; Cho, Y.-S.; Cho, C.-G. *Org. Lett.* **2006**, *8*, 3343. (e) Chung, S.-I.; Seo, J.; Cho, C.-G. *J. Org. Chem.* **2006**, *71*, 6701. (f) Shin, J.-T.; Shin, S.; Cho, C. G. *Tetrahedron Lett.* **2004**, *45*, 5857. (g) Pang, S.-J.; Min, S.-H.; Lee, H.; Cho, C.-G. *J. Org. Chem.* **2003**, *68*, 10191.

(5) Kim, W.-S.; Kim, H.-J.; Cho, C.-G. *J. Am. Chem. Soc.* **2003**, *125*, 14288.

(6) Suginomo, H.; Orito, K.; Yorita, K.; Ishikawa, M.; Shimoyama, N.; Sasaki, T. *J. Org. Chem.* **1995**, *60*, 3052.

(7) The isolated *exo*-adduct was subjected to the same reaction sequence to provide **13** in a similar overall yield.

(8) Protonated joubertinamine as an ammonium salt was obtained with silica gel column chromatography (different ^{1}H NMR pattern but identical HRMS data, when compared to **1**).

(9) The ^{1}H NMR spectrum of **2** matched the literature values.