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Total Synthesis of (±)-Crinine via the Regioselective Stille Coupling and Diels–Alder Reaction of 3,5-Dibromo-2-pyrone

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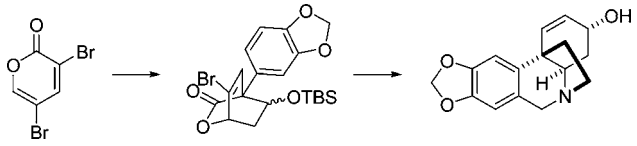
ABSTRACT



The regioselective synthesis and Diels–Alder cycloaddition of 3-(3,4-methylenedioxyphenyl)-5-bromo-2-pyrone provided a new synthetic route to crinine. The vinyl bromide group can be used as a handle for further derivatization.

Belonging to the Amarylidaceae natural product family, the crinane-type alkaloids **1**−**3** (Figure 1) elicit continuing interest in the synthetic community[1] due in part to their intriguing physiological acitivities as exemplified by the recent study unveiling the highly selective apoptosis induction properties of crinamine **2** and haemanthamine **3** against tumor cells at as low as micromolar concentration.[2]

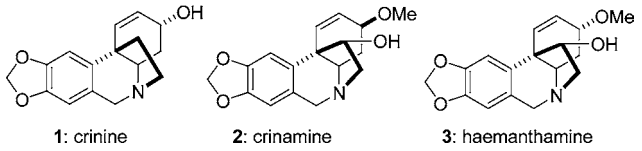


Figure 1. Selected examples of crinane-type alkaloids.

Crinane alkaloids are closely related with other major *Amarylidaceae* family natural products, lycorane- and galanthamine-type alkaloids, in the sense of biogenesis, being derived from the same precursor norbelladine.[3] Structurally, they have the characteristic alpha-*C*2 bridge embedded in azabicyclo[4,3,0]nonane skeleton commonly found in aspidospermidine and strychnine type alkaloids.

As a part of our ongoing research program on 3,5-dibromo-2-pyrone **4** and its derivatives as novel enophile synthons,[4] we have explored their potential applicability to the target-oriented synthesis with the maximum use of the resultant densely functionalized cycloadducts. Schemes 1 and 2 show our previous efforts in this context; total syntheses of (±)-*trans*-dihydronarciclasine[4b] and (±)-joubertinamine.[4c]

The Diels−Alder reaction of **4** with the highly functionalized styrene **5** provided bicyclolactone **6** in 98% yield and

(1) (a) Lebeuf, R.; Robert, F.; Schenk, K.; Landais, Y. *Org. Lett*. **2006**, *8*, 4755. (b) Zhang, F.-M.; Tu, Y.-Q.; Liu, J.-D.; Fan, X.-H.; Shi, L.; Hu, X.-D.; Wang, S.-H.; Zhang, Y.-Q. *Tetrahedron* **2006**, *62*, 9446. (c) Pearson, W. H.; Lovering, F. E. *J. Org. Chem*. **1998**, *63*, 3607. (d) Martin, S. F.; Campbell, C. L. *J. Org. Chem*. **1988**, *53*, 3184. (e) Overman, L. E.; Mendelson, L. T. *J. Am. Chem. Soc*. **1981**, *103*, 5579.

(2) McNulty, J.; Nair, J. J.; Codina, C.; Bastida, J.; Pandey, S.; Gerasimoff, J.; Griffin, C. *Phytochemistry* **2007**, *68*, 1068.

(3) Jeffs, P. W.; Campbell, H. F.; Farrier, D. S.; Ganguli, G.; Martin, N. H.; Molina, G. *Phytochemistry* **1974**, *13*, 933.

(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) Tam, T.; Cho, C.-G. *Org. Lett*. **2007**, *9*, 3391. (d) Shin, J.-T.; Hong, S.-C.; Shin, S.; Cho, C.-G. *Org. Lett*. **2006**, *8*, 3339. (e) Ryu, K.; Cho, Y.-S.; Cho, C.-G. *Org. Lett*. **2006**, *8*, 3343. (f) Chung, S.-I.; Seo, J.; Cho, C.-G. *J. Org. Chem*. **2006**, *71*, 6701. (g) Shin, J.-T.; Shin, S.; Cho, C.-G. *Tetrahedron Lett*. **2004**, *45*, 5857. (h) Pang, S.-J. Min, S.-H.; Lee, H.; Cho, C.-G. *J. Org. Chem*. **2003**, *68*, 10191. For the preparation of **4**, see: (i) Cho, C.-G.; Kim, Y.-W.; Lim, Y.-K.; Park, J.-S.; Lee, H.; Koo, S. *J. Org. Chem*. **2002**, *67*, 290.

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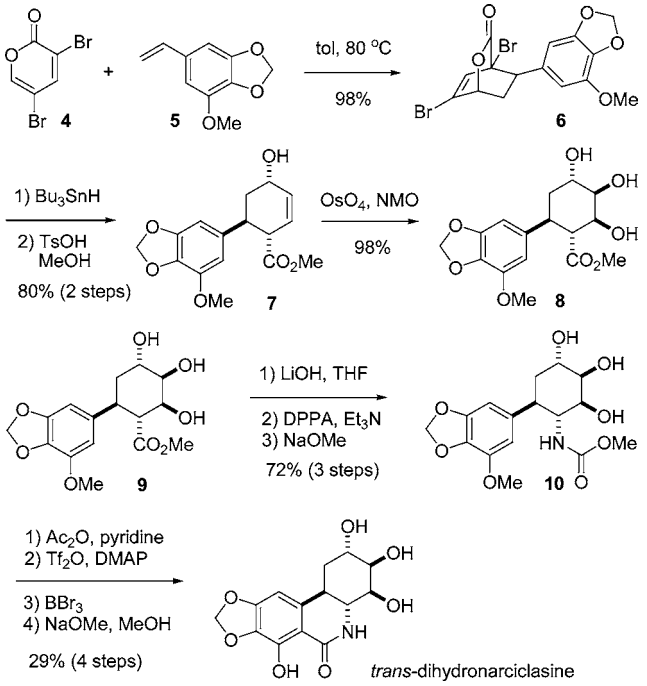
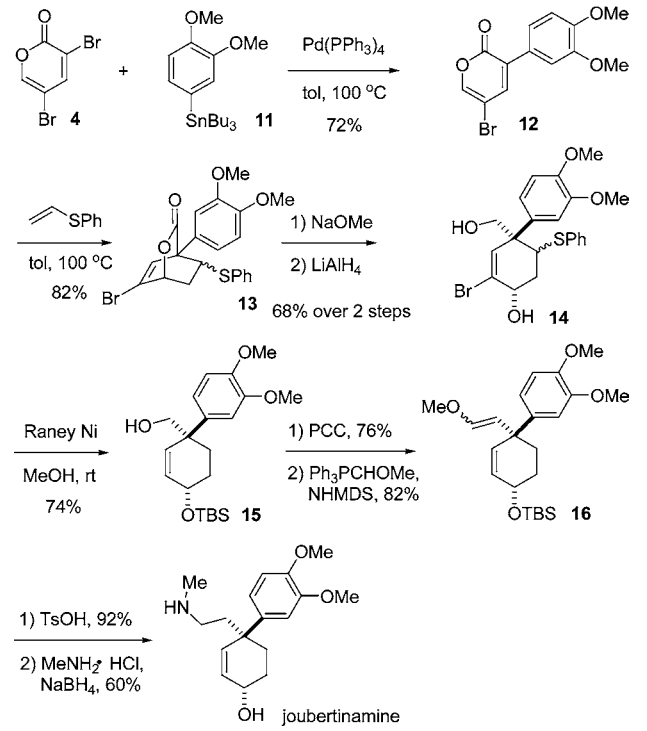
Scheme 1. Synthesis of (±)-*trans*-Dihydronarciclasine



with exclusive endo selectivity (Scheme 1). Debrominations followed by acid-catalyzed methanolysis afforded the key intermediate cyclohexene **7** containing all necessary functional groups and correct relative stereochemistry. The subsequent eight-step process including dihydroxylation, the Curtius rearrangement, and Bischler−Napielaski reaction

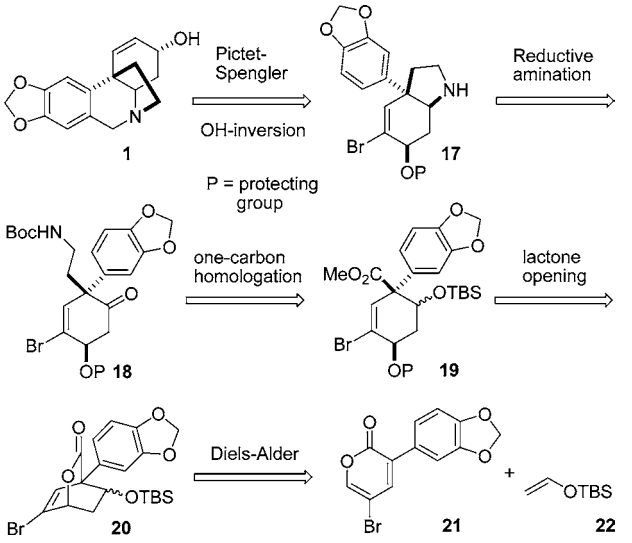
Scheme 2. Synthesis of (±)-Joubertinamine



completed the synthesis of (±)-*trans*-dihydronarciclasine. The synthesis of (±)-joubertinamine required the installation of 3,4-dimethoxyphenyl moiety at the C3 position prior to the cycloaddition. The Stille coupling reaction with aryltin **11** furnished the requisite 2-pyrone diene **12** in good yield and regioselectivity (Scheme 2). The cycloaddition with phenyl vinyl ether as an ethylene equivalent provided a mixture of *endo*/*exo*-bicyclolactones **13** (2:1, 82% combined yield). Only moderate endo/exo diastereomeric selectivity was observed, unlike the parent 3,5-dibromo-2-pyrone and more similar to the cycloaddition reactions of the similar C3-substituted 2-pyrones.[5] The steric bulk is presumed to destabilize the endo transition state at the cycloaddition stage. The stereochemistry of the phenythio group was not a concern in this case, as it needed to be removed later. Thus, both isomers were carried through the reaction sequence to furnish (±)-joubertinamine.

We have envisaged that the 2-pyrone−regioselective coupling−Diels−Alder strategy can also be effective for the synthesis of crinine as well as its congenors crinamine **2** and haemanthamine **3**. In this account, we report the total synthesis of (±)-crinine **1**, conceived by the retrosynthesis illustrated in Scheme 3.

Scheme 3. Retrosynthesis of (±)-Crinine **1**



The disconnections of both tetrahydroisoquinoline and pyrrolidine rings revealed the cyclohexene **18** bearing all functional groups required for the synthesis of crinine. The final and key elaboration called for bicyclolactone **20**, the Diels−Alder adduct of 2-pyrone **21**, and TBS vinyl ether **22**. The endo and exo cycloadduct are tactically equivalent as the silyl ether group would be oxidized to ketone (**19** to **18**).

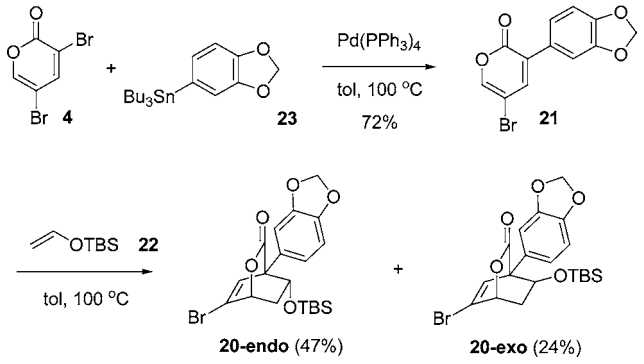
The synthesis began with the C3-selective Stille coupling reaction[6] of 3,5-dibromo-2-pyrone **4** with aryltin **23**[7] to give

(5) Kim, W.-S.; Lee, J.-H.; Kang, J.; Cho, C.-G. *Tetrahedron Lett.* **2004**, *45*, 1683.

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

3-(3,4-methylenedioxyphenyl)-5-bromo-2-pyrone **21** in 72% yield (Scheme 4). Subsequent Diels−Alder cycloaddition

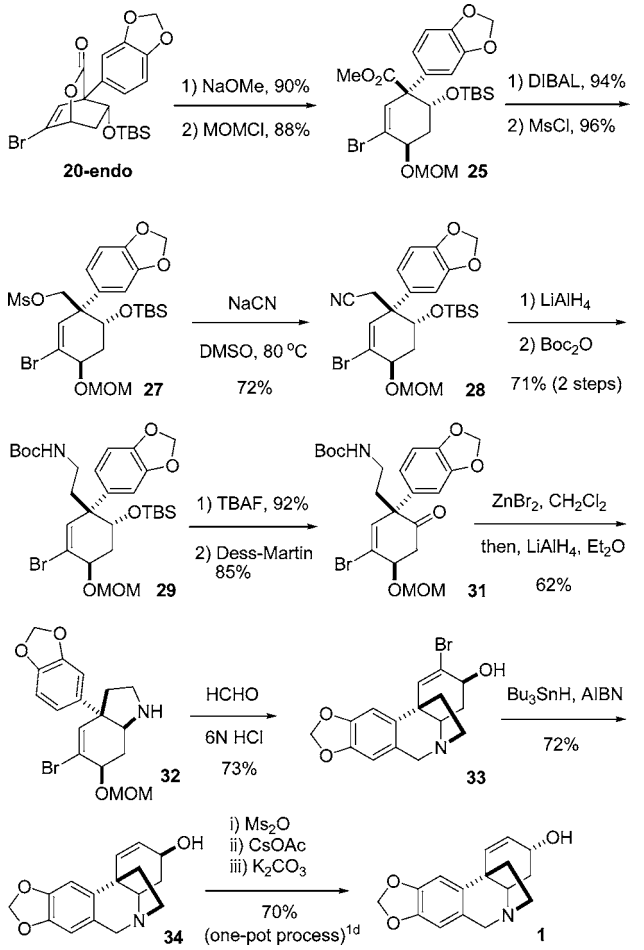
Scheme 4. Synthesis of Bicyclolactone **20**



reaction with TBS vinyl ether **22** provided bicyclolactone **20** as a mixture of endo/exo isomers (2:1, 71% combined yield). Again, the bulky substituent at the C3 position of 2-pyrone resulted in the moderate endo/exo selectivity.

The endo adduct was then separated and carried through the reaction sequence to facilitate the structural characterizations, albeit unnecessary (Scheme 5). Lactone opening and protection of the resultant hydroxyl group as a MOM ether afforded **25** in good overall yield. The reduction of the ester group followed by mesylation afforded **27** in 90% overall yield. As the Wittig olefination approach previously employed in the joubertinamine synthesis (**15** to **16**, Scheme 2) turned out unsatisfactory, direct cyanide displacement was investigated. Gratifyingly, when heated with NaCN in DMSO at 80 °C,[8] the neopentyl mesylate **27** afforded **28** in an unusually high yield (72%). Reduction of the nitrile group with $LiAlH_4$ followed by Boc protection gave **29** in 71% overall yield. Removal of silyl group and the Dess−Martin oxidation of the resultant secondary alcohol provided ketone **31** in 78% yield over two steps from **29**.[9] Subsequent treatment with $ZnBr_2$ in CH_2Cl_2 effected both removal of Boc group[10] and formation of the cyclic imine, which was directly reduced with $LiAlH_4$ in ether to give **32** in 62% overall yield. The ring C in **33** was assembled upon heating with paraformaldehyde in the presence of 6 N HCl at 50 °C, according to the procedure reported by Pearson and coworkers.[1d] Reductive removal of the vinyl bromide group

Scheme 5. Synthesis of (±)-Crinine **1**



followed by the inversion of the allylic hydroxyl group through the known one-pot, three-step process[1d] furnished (±)-crinine **1**.

In summary, we have devised a new synthetic route to (±)-crinine from 3,5-dibromo-2-pyrone via the regioselective synthesis and Diels−Alder cycloaddition of 3-(3,4-methylenedioxyphenyl)-5-bromo-2-pyrone with TBS vinyl ether. Note that the vinyl bromide can be used as a handle for further derivatization.

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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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(7) Prepared from the commerically available 1-bromo-3,4-(methylenedioxy)benzene via the Pd-catalyzed stannylation. Suginomo, H.; Orito, K.; Yorita, K.; Ishikawa, M.; Shimoyama, N.; Sasaki, T. *J. Org. Chem.* **1995**, *60*, 3052.

(8) Varseev, G. N.; Maier, M. E. *Org. Lett.* **2007**, *9*, 1461.

(9) The isolated exo adduct was subjected to the similar reaction sequence to provide **18** in somewhat lower overall yield.

(10) Williams, R. M.; Cao, J.; Tsujishima, H. *Angew. Chem., Int. Ed.* **2000**, *39*, 2540.