JOC Article

Total Syntheses of (±)-Crinine, (±)-Crinamine, and (±)-6a-*epi*-Crinamine via the Regioselective Synthesis and Diels−Alder Reaction of 3-Aryl-5-bromo-2-pyrone

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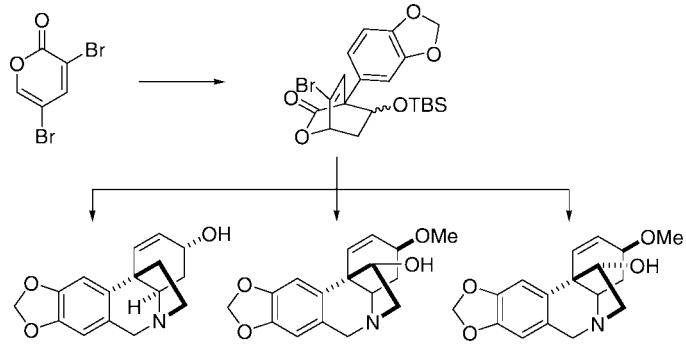

We have devised a new unified synthetic protocol to (±)-crinine, (±)-crinamine, and (±)-6a-*epi*-crinamine from the Diels−Alder cycloadduct of 3-(3,4-methylenedioxyphenyl)-5-bromo-2-pyrone with TBS vinyl ether. The requisite 3-(3,4-methylenedioxyphenyl)-5-bromo-2-pyrone was prepared from the C3-selective Stille coupling reaction of 3,5-dibromo-2-pyrone. Also noted is that the vinyl bromide can be used as a handle for further derivatization.

Introduction

Belonging to the *Amaryllidaceae* natural product family, the crinine-type alkaloids **1**−**3**[1] (Figure 1) elicit continued interest in the synthetic community[2] due in part to their intriguing physiological activities, 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.[3]

Crinine alkaloids are closely related to other major *Amaryllidaceae* family natural products, lycorane- and galanthamine-type alkaloids, in the sense of biogenesis, being derived from the same precursor norbelladine.[4] As a part of our ongoing research program on 3,5-dibromo-2-pyrone **4** and its derivatives as novel enophile synthons,[5] we have explored their potential applicability to the target-oriented synthesis with the maximum use of the resultant densely functionalized cycloadducts. Scheme 1 shows our previous efforts in this context, total syntheses of (±)-*trans*-dihydronarciclasine[5b] and (±)-joubertinamine.[5c] The

(1) For a review on crinine type alkaloids, see: (a) Mori, M. *Chem. Pharm. Bull.* **2005**, *53*, 457. (b) Jin, Z.; Li, Z.; Huang, R. *Nat. Prod. Rep.* **2002**, *19*, 454. (c) Hoshino, O. In *The Alkaloids*; Brossi, A., Ed.; Academic Press: New York, 1998; Vol. 51, p 323. (d) Martin, S. F. In *The Alkaloids*; Brossi. A., Ed.; Academic Press: New York, 1987; Vol. 30, p 251.

(2) For a synthesis of crinine and related alkaloids, see: (a) Bohno, M.; Sugie, K.; Imase, H.; Yusof, Y. B.; Oishi, T.; Chida, N. *Tetrahedron* **2007**, *63*, 6977. (b) Lebeuf, R.; Robert, F.; Schenk, K.; Landais, Y. *Org. Lett.* **2006**, *8*, 4755. (c) 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. (d) Bru, C.; Guillou, C. *Tetrahedron* **2006**, *62*, 9043. (e) Nishimata, T.; Sato, Y.; Mori, M. *J. Org. Chem.* **2004**, *69*, 1837. (f) Bohno, M.; Imase, H.; Chida, N. *Chem. Commun.* **2004**, 1086. (g) Banwell, M. G.; Harvey, J. E.; Jolliffe, K. A. *J. Chem. Soc., Perkin Trans 1* **2001**, *17*, 2002. (h) Baldwin, S. W.; Debenham, J. S. *Org. Lett.* **2000**, *2*, 99. (i) Watson, D. J.; Meyers, A. I. *Tetrahedron Lett.* **2000**, *41*, 1519. (j) Rigby, J. H.; Cavezza, A.; Heeg, M. J. *J. Am. Chem. Soc.* **1998**, *120*, 3664. (k) Pearson, W. H.; Lovering, F. E. *J. Org. Chem.* **1998**, *63*, 3607. (l) Pearson, W. H.; Lovering, F. E. *J. Am. Chem. Soc.* **1995**, *117*, 12336. (m) Martin, S. F.; Campbell, C. L. *J. Org. Chem.* **1988**, *53*, 3184. (n) Martin, S. F.; Campbell, C. L. *Tetrahedron Lett.* **1987**, *28*, 503. (o) Overman, L. E.; Sugai, S. *Helv. Chim. Acta* **1985**, *68*, 745. (p) Overman, L. E.; Mendelson, L. T.; Jacobsen, E. J. *J. Am. Chem. Soc.* **1983**, *105*, 6629. (q) Sanchez, I. H.; Lopez, F. J.; Soria, J. J.; Larraza, M. I.; Flores, H. J. *J. Am. Chem. Soc.* **1983**, *105*, 7640. (r) Danishefsky, S.; Morris, J.; Mullen, G.; Gammill, R. *J. Am. Chem. Soc.* **1982**, *104*, 7591. (s) Overman, L. E.; Mendelson, L. T. *J. Am. Chem. Soc.* **1981**, *103*, 5579. (t) Sanchez, I. H.; Mendoza, M. T. *Tetrahedron Lett.* **1980**, *21*, 3651. (u) Isobe, K.; Taga, J.; Tsuda, Y. *Tetrahedron Lett.* **1976**, 2331. (v) Brossi, A.; Teitel, S. *J. Org. Chem.* **1970**, *35*, 3559. (w) Whitlock, H. W., Jr.; Smith, G. L. *J. Am. Chem. Soc.* **1967**, *89*, 3600. (x) Muxfeldt, H.; Schneider, R. S.; Mooberry, J. B. *J. Am. Chem. Soc.* **1966**, *88*, 3670.

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

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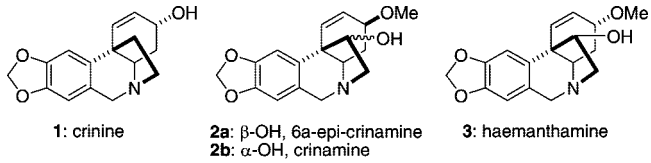

FIGURE 1. Selected examples of crinine-type alkaloids.

Diels−Alder reaction of **4** with the highly functionalized styrene **5** provided bicyclolactone **6** in 98% yield 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. A subsequent eight-step process including a Curtius rearrangement and Bischler−Napielaski reaction completed the first total synthesis of (±)-*trans*-dihydronarciclasine. The synthesis of (±)-joubertinamine required the installation of 3,4-dimethoxyphenyl moiety at C3 position prior to the cycloaddition. The Stille coupling reaction with aryltin **8** furnished the requisite 2-pyrone diene **9** in good yield and regioselectivity. The cycloaddition with phenyl vinyl thioether as an ethylene equivalent provided a mixture of *endo*/*exo*-bicyclolactones **10** (2:1, 82% combined yield). Only moderate *endo*/*exo* diastereomeric selectivity was observed, unlike the parent 3,5-dibromo-2-pyrone, more similar to the cycloaddition reactions of the analogous C3-substituted-2-pyrones.[6] 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 needs to be removed later. Thus, both isomers were carried through the sequence to furnish (±)-joubertinamine.

On the basis of these investigations, we have further envisaged the 2-pyrone-regioselective coupling-Diels−Alder strategy could be effective in the synthesis of the crinine-type alkaloids. Herein, we report the full account of our synthetic approach to (±)-crinine **1**,[7] (±)-6a-*epi*-crinamine **2a**, and (±)-crinamine **2b**.

Results and Discussion

Synthesis of (±)-Crinine 1. Our synthetic program was conceived by the retrosynthesis (Scheme 2) involving the disconnections of both tetrahydroisoquinoline and pyrrolidine rings to reveal the cyclohexene **13**, which bears all functional groups required for the synthesis of crinine. The final and key elaboration called for bicyclolactone **14**, the Diels−Alder adduct of 2-pyrone **15** and TBS vinyl ether **16**. The *endo*- and *exo*-cycloadducts are tactically equivalent as the silyl ether group would be oxidized to ketone (**13** to **12**).

The synthesis began with the C3-selective Stille coupling reaction[8] of 3,5-dibromo-2-pyrone **4** with aryltin **17**,[9] to give 3-(3,4-methylenedioxyphenyl)-5-bromo-2-pyrone **15** in 72% yield (Scheme 3). Subsequent Diels−Alder cycloaddition reaction with TBS vinyl ether **16** provided bicyclolactone **14** as a mixture of endo/exo isomers (2:1, 71% combined yield). Again, only moderate endo/exo diastereomeric selectivity was observed, due to the steric bulk of the C3-aryl group (vide supra).

The *endo*-adduct **14a** was then separated and carried through the reaction sequence to facilitate the structural characterizations (Scheme 4). Methanolysis of **14a** gave alcohol **18** in 90% yield. Protection of the resultant hydroxyl group as a MOM ether followed by DIBAL reduction and mesylation afforded **19** in good overall yield. As the Wittig olefination approach previously employed in the joubertinamine synthesis[5c] turned out to be unsatisfactory, a direct cyanation route was investigated. Gratifyingly, when heated with NaCN in DMSO at 80 °C, the neopentyl mesylate **19** afforded **20** in an unusually high yield (72%).[10] Reduction of the nitrile group with $LiAlH_4$ followed by Boc protection gave **21** in 71% overall yield. Removal of the silyl group and oxidation of the resultant secondary alcohol with the Dess−Martin periodinane (DMP) provided ketone **22** in 78% yield over two steps from **21**.[11] Subsequent treatment with $ZnBr_2$ in CH_2Cl_2 effected both Boc removal[12] and formation of the cyclic imine, which was then reduced with $LiAlH_4$ in ether to give **23** in 62% overall yield. The ring C in **24** was assembled upon heating with paraformaldehyde in the presence of 6 N HCl at 50 °C, according to the procedure reported by Pearson and co-workers.[2k] Reductive removal of the vinyl bromide group followed by the inversion of the allylic hydroxyl group through the known one-pot three-step process[2k] furnished (±)-crinine **1**.

Synthesis of (±)-6a-*epi*-Crinamine 2a and (±)-Crinamine 2b. Further application of our strategy toward the synthesis of (±)-crinamine required stereoselective installation of hydroxyl group on the α-C2 bridge of crinine. To this end, we have prepared olefin **28** by following the four-step sequence composed of methylation, reduction, oxidation, and the Wittig reaction (Scheme 5). However, this sterically hindered terminal olefin underwent little or no epoxidation reaction under the conditions we employed. The dihydroxylation reaction with OsO_4 proceeded well in high yield, but with no diastereoselectivity, providing 1:1 mixture of two diol products. We then investigated the epoxidation reaction of aldehyde **27** (Table 1). While the epoxidation with sulfonium ylide[13] gave only moderate selectivity and yield, the reaction with CH_2I_2/MeLi[14] afforded two inseparable diastereomeric epoxides **29a** and **29b** in good selectivity (~6:1, ^{1}H NMR ratio) and total yield (85%).

Upon epoxide opening with NaN_3 and protection with MOM group, the epoxide mixture **29** was converted into two diastereomeric MOM ethers, **31a** and **31b**, which were readily separated with column chromatography. We did not know the relative stereochemistry of the major isomer **31a** (to be as shown) until the completion of the synthesis of **2a** (vide infra).

(5) 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.

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

(7) Portion of this work has been published in communication form: Tam, N. T.; Cho, C.-G. *Org. Lett.* **2008**, *10*, 601.

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

(9) 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.

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

(11) The isolated *exo*-adduct was subjected to the similar reaction sequence to provide **23** in somewhat lower overall yield.

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

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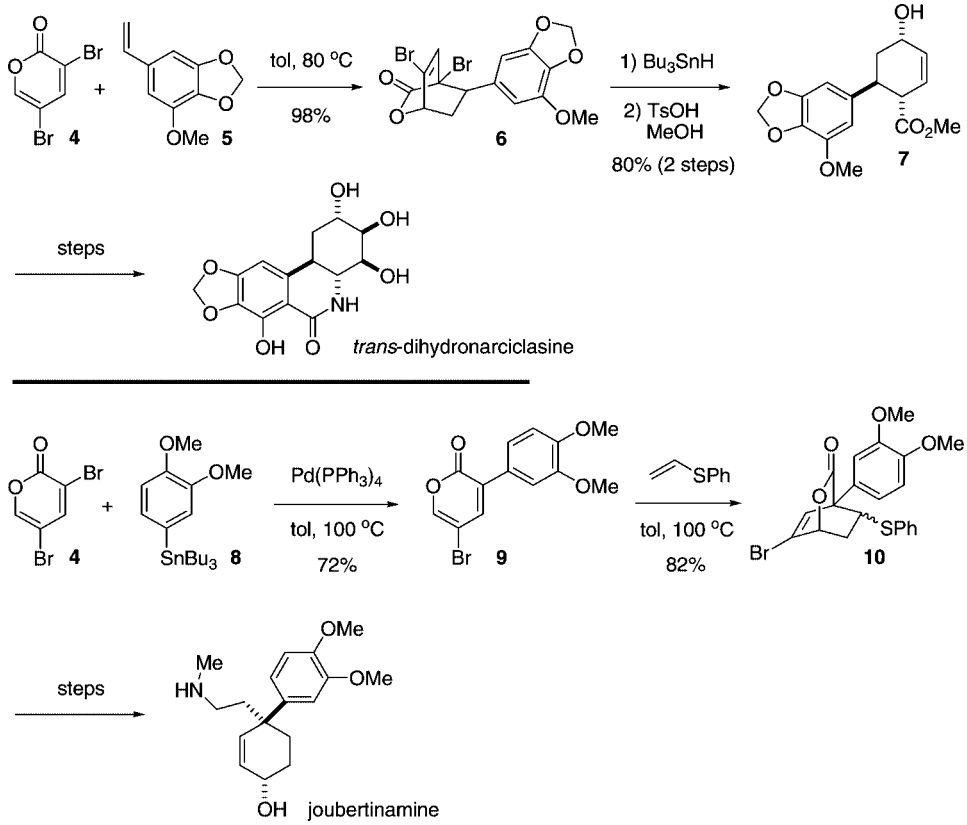
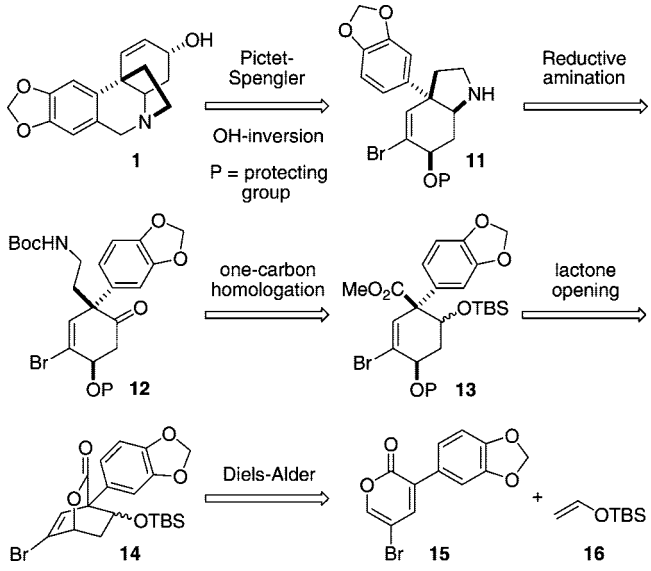
(15) Likhitwitayawuid, K.; Angerhofer, C. K.; Chai, H.; Pezzuto, J. M.; Cordell, G. A. *J. Nat. Prod.* **1993**, *56*, 1331.

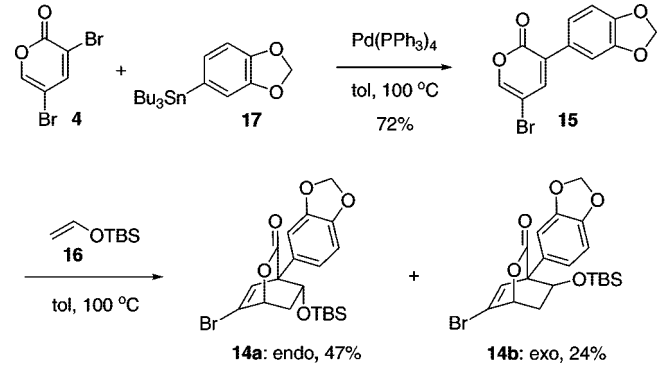
SCHEME 1. Syntheses of *trans*-Dihydronarciclasine and Joubertinamine



SCHEME 2. Retrosynthesis of (±)-Crinine 1



SCHEME 3. Synthesis of Bicyclolactone 14



The azide **31a** was hydrolyzed to amine with PPh_3/THF/H_2O, Boc protected, desilylated and oxidized to give ketone **33a.** The Boc removal and cyclic imine formation with $ZnBr_2$, followed by $LiAlH_4$ reduction furnished **34a**. Subsequent Pictet−Spengler reaction constructed the tetrahydroisoquinoline ring of **35a**. The debromination reaction afforded **2a** in good overall yield. Direct comparison of its ^{1}H and ^{13}C NMR data with the reported values of crinamine[15] proved our end product **2a** the 6a-epimer of crinamine (Scheme 6).

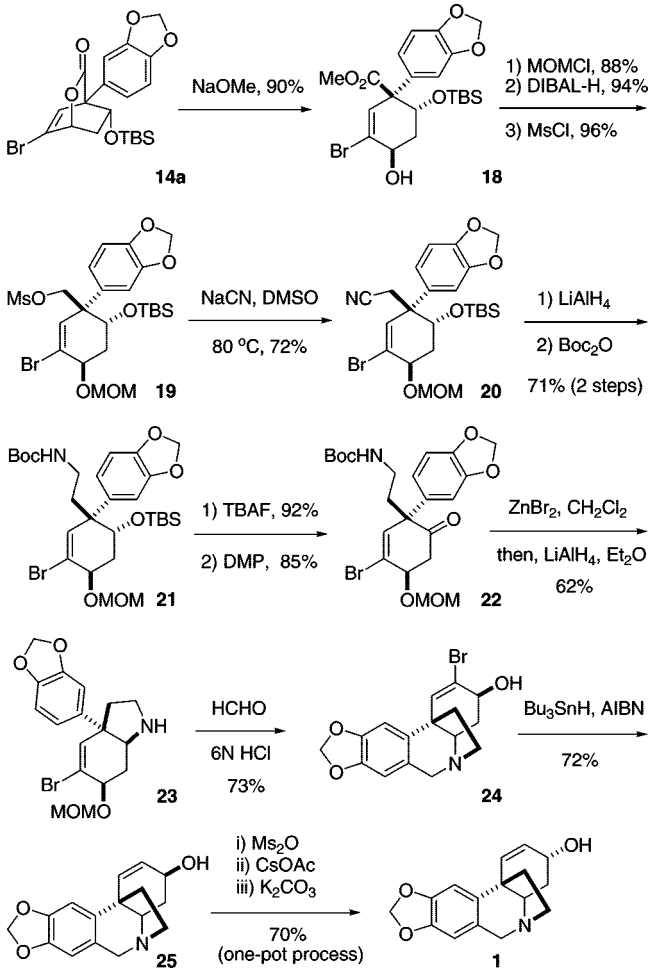
All attempts to epimerize the 6a-OH group of **2a** were fruitless (Scheme 6). Oxidation of the alcohol to ketone and $NaBH_4$ reduction provided 2:1 mixture of crinamine **2b** and 6a-*epi*-crinamine **2a** in total yield of 10%. These failures led us to investigate the epimerization of the OH group before the construction of tetrahydroisoquinoline ring (Table 2). While the conversions based on displacement reaction (entries 1 and 2)[16] were unsatisfactory, the oxidation followed by reduction approach was reasonably selective to afford 1:3 mixture of **36a** and **36b** with good overall total yield (88%).

Upon protection as a MOM ether, the azide **31b** was isolated and subjected into the same reaction sequence employed for (±)-6a-*epi*-crinamine **2a** (Scheme 4) to afford (±)-crinamine **2b** with similar overall yield (Scheme 7). Its ^{1}H and ^{13}C NMR data matched the literature values of crinamine.[15]

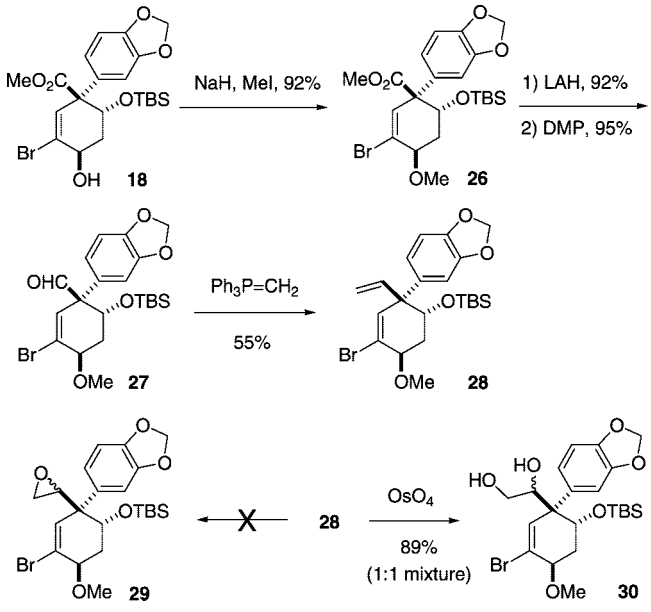
In summary, we have devised a new unified synthetic protocol to (±)-crinine, (±)-crinamine, and (±)-6a-*epi*-crinamine via the common intermediate **18** readily accessed from the Diels−Alder

(16) Moriarty, R. M.; Zhuang, H.; Penmasta, R.; Liu, K.; Awasthi, A. K.; Tuladhar, S. M.; Rao, M. S. C.; Singh, V. K. *Tetrahedron Lett.* **1993**, *34*, 8029.

SCHEME 4. Synthesis of (±)-Crinine 1

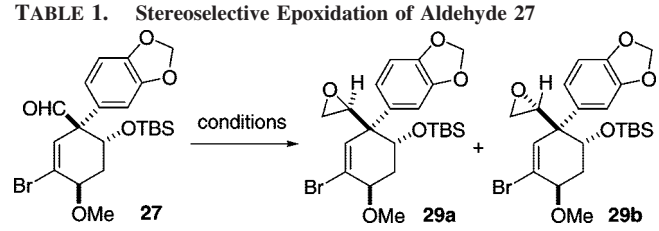


SCHEME 5. Attempted Installation of Hydroxyl Group



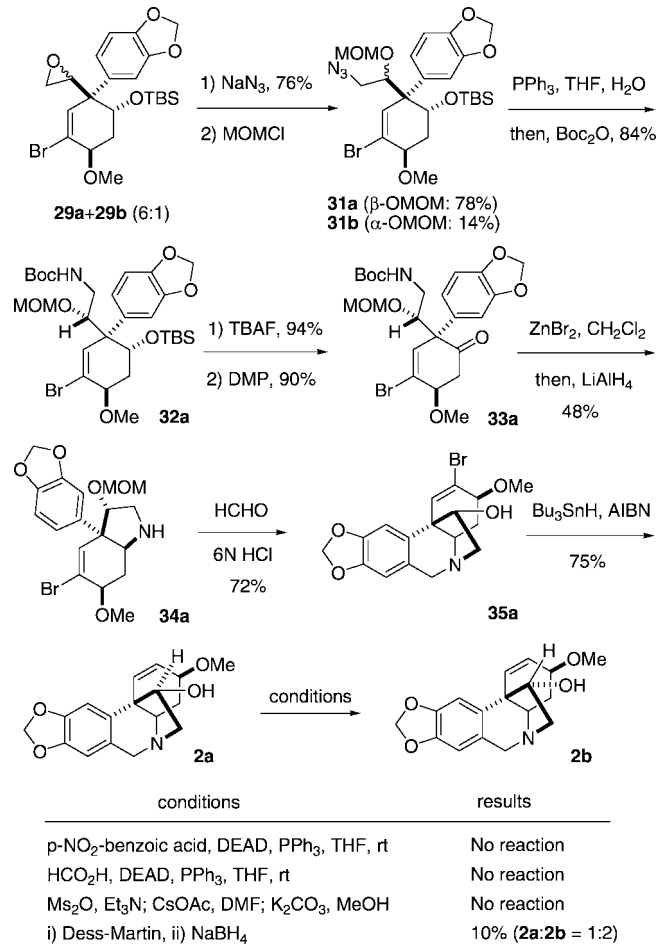
cycloaddition of 3-(3,4-methylenedioxyphenyl)-5-bromo-2-pyrone with TBS vinyl ether. We are currently applying our 2-pyrone strategy toward total synthesis of other related congeners, haemanthamine, precriwelline, and tazettine.

TABLE 1. Stereoselective Epoxidation of Aldehyde 27



entry	conditions	yield (^{1}H NMR ratio)
1	$Me_3S^+I^-$, *n*BuLi, THF, 0 °C to rt, 1 h	40% (**29a**:**29b** = 2:1)
2	CH_2I_2 MeLi, THF, 0 °C, 30 min	85% (**29a**:**29b** = 6:1)

SCHEME 6. Synthesis of 6a-*epi*-Crinamine 2a



conditions	results
p-NO_2-benzoic acid, DEAD, PPh_3, THF, rt	No reaction
HCO_2H, DEAD, PPh_3, THF, rt	No reaction
Ms_2O, Et_3N; CsOAc, DMF; K_2CO_3, MeOH	No reaction
i) Dess-Martin, ii) $NaBH_4$	10% (**2a**:**2b** = 1:2)

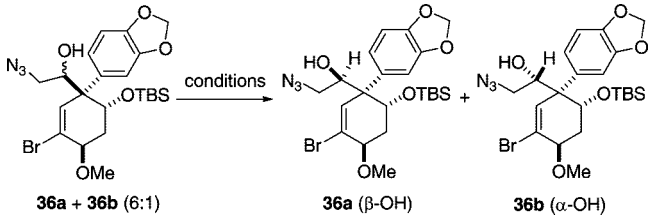
Experimental Section

General Materials and Methods. See Supporting Information.

Synthesis of (±)-Crinine 1. See Supporting Information.

Preparation of Methyl Ether 26. To a solution of **18** (700 mg, 1.44 mmol) in THF (14 mL) at 0 °C were added NaH (104 mg, 4.33 mmol) and MeI (0.45 mL, 7.21 mmol). After 2 h at room temperature, the reaction mixture was quenched by adding MeOH (1 mL), and the resulting solution was diluted with CH_2Cl_2 and water. The organic layer was separated, dried over $MgSO_4$, concentrated, and purified by column chromatography (hexane/EtOAc = 9.5:0.5) to give 660 mg of **26** as a tan oil in 92% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.75 (d, J = 8.4 Hz, 1H), 6.71 (d, J = 1.6 Hz, 1H), 6.64 (dd, J = 8.0, 1.6 Hz, 1H). 6.33 (s, 1H), 5.94 (d, J = 1.2 Hz, 2H), 4.61 (d, J = 6.0 Hz, 1H), 4.01 (t, J = 6.0 Hz, 1H), 3.68 (s, 3H), 3.44 (s, 3H), 2.13−2.07 (m, 1H), 1.98−1.92 (m, 1H), 0.75 (s, 9H), −0.03 (s, 3H), −0.32 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.5, 147.5, 146.9, 132.1, 131.5, 126.7,

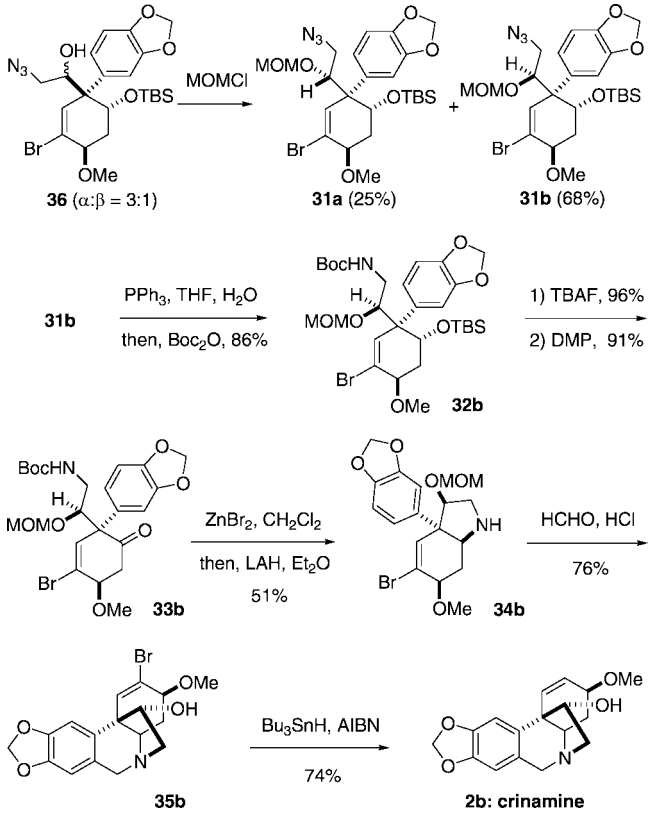
TABLE 2. Stereochemical Inversion of the Hydroxyl Group of 36a



entry	conditions	yield
1	DEAD, *p*-NO_2−PhCOOH, Ph_3P, PhH, 50 °C	no desired product[a]
2	(i) Tf_2O/pyr/DCM; (ii) KNO_2/18-C-6/DMF	65% (**36a**:**36b** = 1:1)
3	(i) Dess−Martin; (ii) $NaBH_4$	88% (**36a**:**36b** = 1:3)

[a] Desired product: *p*-NO_2-benzoate of **36b**.

SCHEME 7. Synthesis of Crinamine 2b



121.3, 109.2, 107.7, 101.1, 76.9, 69.8, 60.1, 57.1, 52.7, 34.7, 25.7, 17.9, −4.9, −5.5; FT-IR (CH_2Cl_2) 2947, 2930, 2843, 2857, 1732, 1491, 1246, 1043, 832, 782, 740 cm^{-1}; HRMS calcd for $C_{22}H_{31}BrNaO_6Si$ $[M + Na]^+$: 521.0965, found 521.0966.

Preparation of Aldehyde 27. To a flask charged with **26** (500 mg, 1 mmol) in THF (10 mL) was added $LiAlH_4$ (57 mg, 1.5 mmol) in THF (2 mL) at 0 °C. The reaction mixture was stirred for 15 min and quenched with 20% NaOH (aq), and the resulting solution was extracted with CH_2Cl_2. The combined organic solution was dried, filtered, concentrated, and chromatographed (hexane/EtOAc = 9:1) to afford 432 mg of alcohol **26-a** as a colorless oil in 92% yield. ^1H NMR (400 MHz, $CDCl_3$) δ 6.91 (s, 1H), 6.77 (s, 2H), 6.35 (s, 1H), 5.95 (d, J = 3.2 Hz, 2H), 4.12 (dd, J = 12.0, 2.8 Hz, 1H), 4.04 (dd, J = 11.2, 3.2 Hz, 1H), 3.83−3.81 (m, 1H), 3.75−3.69 (m, 1H), 3.47 (s, 3H), 1.86−1.82 (m, 1H), 1.67−1.60 (m, 1H), 1.28 (dd, J = 9.6, 3.2 Hz, 1H), 0.88 (s, 9H), 0.12 (s, 3H), 0.07 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.5, 146.8, 136.1, 130.6, 124.1, 123.2, 110.2, 107.6, 101.1, 80.6, 66.8, 66.6, 57.9, 54.9, 33.4, 25.9, 18.0, −4.4, −4.7; FT-IR (CH_2Cl_2) 3448, 2926, 2883, 2846, 1507, 1483, 1341, 1236, 927, 841, 675 cm^{-1}; HRMS calcd for $C_{21}H_{31}BrNaO_5Si$ $[M + Na]^+$: 493.1016, found 493.1017. To a solution of alcohol **26-a** (380 mg, 0.81 mmol) and $NaHCO_3$ (338 mg, 4.03 mmol) in CH_2Cl_2 (8 mL) was added the Dess−Martin reagent (410 mg, 0.97 mmol). The reaction mixture was stirred at room temperature for 30 min, and the resulting mixture was filtered through a short pad of Celite, washed with ether. The filtrate was concentrated and chromatographed (hexane/EtOAc = 9.5:0.5) to afford 360 mg of **27** as a colorless oil in 95% yield. ^1H NMR (400 MHz, $CDCl_3$) δ 9.49 (s, 1H), 6.81 (d, J = 8.4 Hz, 1H), 6.71 (d, J = 1.6 Hz, 1H), 6.61 (dd, J = 8.4, 2.0 Hz, 1H), 6.21 (s, 1H), 5.97 (d, J = 1.6 Hz, 2H), 4.57 (dd, J = 7.6, 3.6 Hz, 1H), 3.99 (t, J = 5.2 Hz, 1H), 3.46 (s, 3H), 2.01−1.91 (m, 2H), 0.78 (s, 9H), 0.02 (s, 3H), −0.16 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.0, 147.9, 147.5, 128.5, 128.3, 128.1, 123.1, 110.4, 108.1, 101.3, 77.9, 67.2, 64.5, 57.4, 34.1, 25.7, 17.9, −4.7, −5.2; FT-IR (CH_2Cl_2) 2957, 2924, 2857, 2817, 1720, 1487, 1242, 1124, 1083, 935, 831, 787, 675 cm^{-1}; HRMS calcd for $C_{21}H_{29}BrNaO_5Si$ $[M + Na]^+$: 491.0860, found 491.0863.

Preparation of Epoxide 29 (29a:29b = 6:1). To a solution of **27** (390 mg, 0.83 mmol) and diiodomethane (0.12 mL, 1.45 mmol) in THF (8 mL) was added MeLi (1.3 mL, 1.6 M in ether) at 0 °C. After 30 min, the mixture was treated with ice and extracted with CH_2Cl_2. The organic extract was dried, filtered, concentrated, and purified by column chromatography (hexane/EtOAc = 9.5:0.5) to give an inseparable mixture of **29a** and **29b** (340 mg, ratio = 6:1, 85% total yield) as a tan oil. The following characterization of **29a** was made from the spectra of a 6:1 mixture of **29a** and **29b**. ^1H NMR (400 MHz, $CDCl_3$) δ 6.96 (d, J = 1.2 Hz, 1H), 6.81(dd, J = 8.4, 1.6 Hz, 1H), 6.74 (d, J = 8.4 Hz, 1H), 5.94 (s, 2H), 5.91 (s, 1H), 4.26 (dd, J = 10.8, 2.8 Hz, 1H), 3.88 (t, J = 4.0 Hz, 1H), 3.45 (s, 3H), 3.46−3.43 (m, 1H), 2.73 (t, J = 4.4 Hz, 1H), 2.55−2.53 (m, 1H), 2.04−1.99 (m, 1H), 1.85−1.78 (m, 1H), 0.87 (s, 9H), 0.08 (s, 3H), 0.03 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.2, 146.6, 132.4, 132.3, 125.4, 122.4, 110.0, 107.5, 101.1, 79.2, 69.8, 57.3, 55.8, 51.5, 43.9, 33.6, 25.9, 18.0, −4.4, −5.0.

Preparation of Azide 31a. A sealed tube was charged with epoxides **29** (272 mg, 0.563 mmol, **29a**:**29b** = 6:1), NaN_3 (366 mg, 5.63 mmol), NH_4Cl (300 mg), and MeOH (5 mL). After 36 h at 50 °C, the reaction mixture was diluted with CH_2Cl_2, washed with water, dried over $MgSO_4$, concentrated, and purified by column chromatography (hexane/EtOAc = 9.5:0.5) to afford 226 mg of the corresponding alcohols in 76% combined yield. To the solution of the resultant azido alcohols in CH_2Cl_2 were added MOMCl (0.16 mL, 5 equiv) and DIPEA (0.37 mL, 5 equiv). After 6 h at 40 °C, the reaction mixture was cooled to room temperature, diluted with CH_2Cl_2, washed with water, and dried over $MgSO_4$. After concentration, the residue was purified by column chromatography (hexane/EtOAc = 9.5:0.5) to give 192 mg of **31a** and 35 mg of **31b** (92% total yield, both in colorless oil). **31a** ^1H NMR (400 MHz, $CDCl_3$) δ 6.85 (s, 1H), 6.73 (s, 2H), 6.34 (s, 1H), 5.95 (s, 2H), 4.86 − 4.82 (m, 2H), 4.49 (dd, J = 12.4, 2.4 Hz, 1H), 4.17 (dd, J = 6.8, 2.4 Hz, 1H), 3.75 (d, J = 3.2 Hz, 1H), 3.45 (s, 3H), 3.44 (s, 3H), 3.28−3.17 (m, 2H), 1.87 (d, J = 13.6 Hz, 1H), 1.48 (td, J = 8.8, 4.4 Hz, 1H), 0.88 (s, 9H), 0.16 (s, 3H), 0.08 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.3, 146.8, 134.7, 131.0, 124.0, 123.3, 110.5, 107.4, 101.2, 98.7, 80.4, 80.2, 66.2, 57.7, 56.7, 56.4, 53.5, 33.5, 26.0, 18.2, −4.1, −4.3; FT-IR (CH_2Cl_2) 2928, 2892, 2856, 2112, 1505, 1487, 1361, 1241, 1145, 1097, 1037, 939, 743 cm^{-1}; HRMS calcd for $C_{24}H_{36}BrN_3NaO_6Si$ $[M + Na]^+$: 592.1449, found 592.1451.

Preparation of 32a. To a solution of **31a** (300 mg, 0.53 mmol) in THF (5 mL) and H_2O (0.25 mL) was added PPh_3 (207 mg, 0.79 mmol) at room temperature. After 2 h at 40 °C, the reaction solvent was evaporated and the water was removed azeotropically with benzene. After dilution in CH_2Cl_2 (5 mL), Et_3N (0.1 mL) and Boc anhydride (287 mg, 1.3 mmol) were added at 0 °C. The reaction was stirred for 3 h at 0 °C, quenched with water and extracted with CH_2Cl_2. The combined extract was dried over $MgSO_4$, concentrated, and purified by column chromatography (hexane/

EtOAc = 9:1) to give 282 mg of **32a** as a colorless oil in 84% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.86 (s, 1H), 6.72 (s, 2H), 6.22 (s, 1H), 5.94 (s, 2H), 5.34 (brs, 1H), 4.80−4.76 (m, 2H), 4.43 (d, J = 11.6 Hz, 1H), 4.14−4.12 (m, 1H), 3.75 (d, J = 3.6 Hz, 1H), 3.45 (s, 3H), 3.42 (s, 3H), 3.11−3.08 (m, 1H), 2.93−2.91 (m, 1H), 1.87 (d, J = 13.2 Hz, 1H), 1.52−1.45 (m, 1H), 1.40 (s, 9H), 0.90 (s, 9H), 0.13 (s, 3H), 0.06 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.0, 147.2, 146.8, 134.6, 130.8, 124.0, 123.3, 110.5, 107.3, 101.0, 98.8, 82.0, 80.2, 79.0, 66.1, 57.8, 56.8, 56.0, 41.8, 33.2, 28.4, 26.0, 18.2, −3.5, −4.3; FT-IR (CH_2Cl_2) 3368, 2954, 2888, 1712, 1505, 1368, 1244, 1104, 834, 776 cm^{-1}; HRMS calcd for $C_{29}H_{46}BrNNaO_8Si$ [M + Na]$^+$: 666.2068, found 666.2070.

Preparation of 33a. To a solution of **32a** (390 mg, 0.61 mmol) in CH_2Cl_2 (6 mL) was added Et_3N (0.2 mL) and TBAF (1.2 mL, 1 M in THF) at 0 °C. After 4 h at 0 °C, the reaction mixture was warmed to room temperature and partitioned into water and CH_2Cl_2. The organic layer was separated, dried over $MgSO_4$, filtered, concentrated, and chromatographed (hexane/EtOAc/MeOH = 70:30:3) to give 302 mg of alcohol **32a-1** as a colorless oil in 94% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.90 (s, 1H), 6.80−6.76 (m, 2H), 6.22 (s, 1H), 5.97 (d, J = 5.2 Hz, 2H), 5.13 (brs, 1H), 4.82−4.75 (m, 2H), 4.35 (t, J = 9.6 Hz, 1H), 4.22 (d, J = 6.8 Hz, 1H), 3.79 (d, J = 3.6 Hz, 1H), 3.46 (s, 3H), 3.45 (s, 3H), 3.16 (ddd, J = 13.6, 6.8, 2.4 Hz, 1H), 3.01−2.90 (m, 1H), 1.97−1.94 (m, 2H), 1.54 (td, J = 12.8, 4.4 Hz, 1H), 1.41 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.9, 148.0, 147.1, 133.7, 130.3, 125.2, 122.6, 109.6, 108.2, 101.2, 98.9, 81.1, 80.2, 79.2, 64.7, 58.0, 56.2, 56.1, 41.7, 33.0, 28.4; FT-IR (CH_2Cl_2) 3388, 2969, 2931, 2903, 1695, 1505, 1490, 1238, 1025, 932, 816, 742 cm^{-1}; HRMS calcd for $C_{23}H_{32}BrNNaO_8$ [M + Na]$^+$: 552.1204, found 552.1205. To a mixture of alcohol **32a-1** (200 mg, 0.38 mmol), $NaHCO_3$ (158 mg, 1.89 mmol), and CH_2Cl_2 (4 mL) was added the Dess−Martin reagent (192 mg, 0.45 mmol). After 30 min at room temperature, the reaction mixture was filtered though a short pad of Celite and washed with ether, and the resultant filtrate was concentrated and chromatographed (hexane/EtOAc = 9.5:0.5) to afford 180 mg of **33a** as a colorless oil in 90% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.77−6.72 (m, 3H), 6.57 (s, 1H), 5.97 (d, J = 4.4 Hz, 2H), 5.43 (brs, 1H), 4.79 (d, J = 6.8 Hz, 1H), 4.59−4.54 (m, 2H), 4.29 (d, J = 3.2 Hz, 1H), 3.41 (s, 3H), 3.39 (s, 3H), 2.99−2.90 (m, 2H), 2.75 (d, J = 14.4, 5.2 Hz, 1H), 2.61−2.57 (m 1H), 1.40 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 203.9, 156.0, 148.6, 147.7, 132.8, 129.8, 123.8, 120.5, 108.8, 107.1, 101.5, 98.7, 81.0, 80.8, 79.0, 63.0, 56.5, 56.0, 42.4, 40.9, 28.4; FT-IR (CH_2Cl_2) 3366, 2970, 2889, 1714, 1695, 1513, 1487, 1368, 1236, 1161, 1035, 934 cm^{-1}; HRMS calcd for $C_{23}H_{30}BrNaNO_8$ [M + Na]$^+$: 550.1047, found 550.1049.

Preparation of 34a. A mixture of **33a** (45 mg, 0.085 mmol), excess $ZnBr_2$ (5 equiv), and CH_2Cl_2 (2 mL) was stirred at room temperature for 5 h. The reaction mixture was then diluted with ether (0.5 mL) and cannulated to a suspension of $LiAlH_4$ (32 mg, 0.85 mmol) in ether (1 mL) at −10 °C. After 15 min, the reaction mixture was quenched with aqueous 20% NaOH and extracted with CH_2Cl_2 several times. The combined organic solution was dried over $MgSO_4$, filtered, concentrated, and chromatographed (CH_2Cl_2/MeOH = 9.8:0.2 to 9.5:0.5) to afford 17 mg of **34a** as a tan oil in 48% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.87 (s, 1H), 6.76 (s, 2H), 6.32 (s, 1H), 5.95 (s, 2H), 4.35 (d, J = 6.8 Hz, 1H), 4.19 (d, J = 6.8 Hz, 1H), 4.06 (t, J = 4.8 Hz, 1H), 3.72 (brs, 1H), 3.69 (d, J = 3.6 Hz, 1H), 3.49 (s, 3H), 3.45 (dd, J = 12.8, 6.0 Hz, 1H), 3.06 (s, 3H), 2.95 (dd, J = 12.4, 3.6 Hz, 1H), 2.44 (d, J = 15.2 Hz, 1H), 1.79 (dt, J = 15.2, 3.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.4, 146.2, 135.3, 133.5, 122.9, 121.4, 109.1, 107.8, 101.1, 95.6, 84.6, 77.6, 60.5, 58.4, 57.3, 55.6, 52.7, 26.4; FT-IR (CH_2Cl_2) 3355, 2928, 2888, 2816, 1735, 1499, 1435, 1236, 1144, 941, 737 cm^{-1}; HRMS calcd for $C_{18}H_{22}BrNNaO_5$ [M + Na]$^+$: 434.0574, found 434.0575.

Preparation of 35a. To a solution of **34a** (45 mg, 0.11 mmol) in MeOH (0.8 mL) was added 1.0 mL of 37% aqueous solution of formaldehyde at room temperature. After 10 min, the reaction mixture was treated with 8 mL of 6 N HCl at room temperature. The mixture was warmed to 50 °C and stirred for 15 h. After cooling to room temperature, the reaction mixture was basified by the addition of solid K_2CO_3 and then extracted with CH_2Cl_2 several times. The combined organic solution was dried over $MgSO_4$, filtered, concentrated, and chromatoghraphed (CH_2Cl_2/MeOH = 9.5:0.5) to give 30 mg of **35a** as a white solid in 72% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.83 (s, 2H), 6.55 (s, 1H), 5.95 (s, 2H), 4.62−4.59 (m, 1H), 4.43 (d, J = 16.8 Hz, 1H), 4.01−3.97 (m, 1H), 3.82 (d, J = 16.8 Hz, 1H), 3.80 (d, J = 14.0 Hz, 1H), 3.48 (s, 3H), 3.35 (dd, J = 13.6, 3.6 Hz, 1H), 2.52 (dd, J = 14.0, 3.2 Hz, 1H), 2.36−2.30 (m, 1H), 1.90−1.81 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.2, 146.6, 131.4, 130.2, 127.3, 126.3, 107.2, 106.1, 101.3, 86.2, 77.7, 66.4, 62.6, 61.9, 57.1, 50.7, 31.6; FT-IR (CH_2Cl_2) 3317, 3052, 2928, 2823, 1506, 1486, 1361, 1329, 1108, 1036 cm^{-1}; HRMS calcd for $C_{17}H_{18}BrNNaO_4$ [M + Na]$^+$: 402.0311, found 402.0312.

Preparation of 2a. A sealed tube was charged with **35a** (30 mg, 0.08 mmol), benzene (1.5 mL), AIBN (13 mg, 0.08 mmol), and tributyltin hydride (0.1 mL). After 2 h at 80 °C, the reaction mixture was cooled to room temperature and partitioned into CH_2Cl_2 and aqueous KF solution. The organic solution was separated, dried over $MgSO_4$, filtered, concentrated, and purified by silica gel chromatography (CH_2Cl_2/MeOH = 9.5:0.5 to 9:1) to give 18 mg of (±)-6a-*epi*-crinamine **2a** as a while solid in 75% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.85 (s, 1H), 6.56 (s, 1H), 6.40 (dd, J = 10.4, 2.0 Hz, 1H), 5.95 (d, J = 2.0 Hz, 2H), 5.91 (d, J = 10.4 Hz, 1H), 4.55 (brs, 1H), 4.49 (d, J = 17.2 Hz, 1H), 4.00−3.96 (m, 1H), 3.87 (d, J = 17.2 Hz, 1H), 3.86−3.82 (m, 1H), 3.42 (s, 3H), 3.35 (d, J = 12.4 Hz, 1H), 2.56 (d, J = 14.0 Hz, 1H), 2.27−2.21 (m, 1H), 1.64 (q, J = 12.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.2, 146.8, 131.0, 130.2, 127.5, 125.7, 107.2, 106.3, 101.3, 86.3, 75.9, 67.0, 62.4, 61.9, 56.2, 48.5, 30.6; HRMS calcd for $C_{17}H_{19}NNaO_4$ [M + Na]$^+$: 324.1206, found 324.1207.

Preparation of 36 (36a:36b = 1:3). To a mixture of 260 mg (0.494 mmol) of 36 (**36a**:**36b** = 6:1, prepared from **29**, Scheme 6), $NaHCO_3$ (207 mg, 2.47 mmol), and CH_2Cl_2 (5 mL) was added the Dess−Martin reagent (250 mg, 0.593 mmol). After 30 min at room temperature, the reaction mixture was filtered though a short pad of Celite and washed with ether, and the filtrate was concentrated and chromatographed (hexane/EtOAc = 9.5:0.5) to afford 240 mg of ketone **36-a** as a colorless oil in 93% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.79 (d, J = 8.0 Hz, 1H), 6.66 (d, J = 1.2 Hz, 1H), 6.58 (dd, J = 8.0, 1.2 Hz, 1H), 6.31 (s, 1H), 5.96 (d, J = 3.2 Hz, 2H), 4.63 (d, J = 5.6 Hz, 1H), 4.06−4.02 (m, 1H), 3.94 (d, J = 17.6 Hz, 1H), 3.77 (d, J = 17.6 Hz, 1H), 3.43 (s, 3H), 2.27−2.21 (m, 1H), 1.96−1.90 (m, 1H), 0.72 (s, 9H), −0.04 (s, 3H), −0.44 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.7, 148.3, 147.5, 130.7, 130.5, 128.2, 121.1, 108.7, 108.5, 101.4, 76.2, 70.3, 64.3, 57.1, 54.8, 34.9, 25.7, 17.8, −4.9, −5.7; FT-IR (CH_2Cl_2) 2948, 2929, 2858, 2108, 1722, 1504, 1489, 1249, 1095, 964, 941, 836 cm^{-1}; HRMS calcd for $C_{22}H_{30}BrN_3NaO_5Si$ (M+1)$^+$: 546.1030, found 546.1032. To a solution of ketone **36-a** (225 mg, 0.43 mmol) in MeOH (4 mL) was added 65 mg (1.72 mmol) of $NaBH_4$ in MeOH (1 mL) at 0 °C. After 15 min, the reaction mixture was quenched with H_2O and extracted with CH_2Cl_2. The combined extract was dried over $MgSO_4$, concentrated and chromatographed (hexane/EtOAc = 9.5:0.5) to afford a mixture of **36a** and **36b** (215 mg, ratio = 1:3, 95% combined yield) as a colorless oil. Spectral data of **36b** were deduced from the mixture. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.98 (d, J = 1.6 Hz, 1H), 6.83−6.77 (m, 2H), 6.34 (s, 1H), 5.98−5.97 (m, 2H), 4.46−4.43 (m, 1H), 4.12 (dd, J = 11.6, 2.8 Hz, 1H), 3.77−3.76 (m, 1H), 3.45 (s, 3H), 3.40−3.31 (m, 2H), 1.83−1.79 (m, 1H), 1.58−1.49 (m, 1H), 0.90 (s, 9H), 0.13 (s, 3H), 0.07 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.8, 147.0, 133.2, 130.4, 124.6, 123.5, 110.2, 107.8, 101.3, 80.5, 73.2, 66.6, 58.1, 56.8 53.1, 33.7, 25.8, 18.0, −4.1, −4.6.

Preparation of 31b. A solution of 400 mg (0.76 mmol) of **36a** and **36b** (1:3), MOMCl (0.29 mL, 3.8 mmol), and DIPEA (0.65

mL, 3.8 mmol) was heated at 40 °C for 6 h. After cooling to room temperature, the reaction mixture was diluted with CH_2Cl_2, washed with water, dried over $MgSO_4$, concentrated, and purified by column chromatography (hexane/EtOAc = 9.5:0.5) to give 295 mg of **31b** and 108 mg of **31a** (93% total yield, both as a colorless oil). **31b** ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.07 (d, J = 0.8 Hz, 1H), 6.88 (d, J = 9.2 Hz, 1H), 6.74−6.72 (m, 1H), 6.50 (s, 1H), 5.94 (d, J = 3.2 Hz, 2H), 4.49 (d, J = 6.8 Hz, 1H), 4.35 (d, J = 6.8 Hz, 1H), 4.23−4.17 (m, 2H), 3.76−3.74 (m, 1H), 3.58 (dd, J = 13.2, 2.8 Hz, 1H), 3.44 (s, 3H), 3.38 (dd, J = 12.8, 7.2 Hz, 1H), 3.06 (s, 3H), 1.88−1.84 (m, 1H), 1.64−1.58 (m, 1H), 0.90 (s, 9H), 0.10 (s, 3H), 0.08 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.1, 146.5, 134.8, 132.8, 124.4, 123.4, 110.5, 107.2, 101.0, 97.6, 80.1, 79.8, 67.9, 57.9, 56.3, 56.0, 53.3, 33.7, 25.9, 18.1,-3.9, −4.5; FT-IR (CH_2Cl_2) 2949, 2925, 2885, 2853, 2104, 1506, 1482, 1101, 1034, 935, 836, 776 cm^{-1}; HRMS calcd for $C_{24}H_{36}BrN_3NaO_6Si$ [M + Na]$^+$: 592.1449, found 592.1450.

Preparation of 32b. A mixture of 290 mg (0.51 mmol) of **31b** in THF (5 mL), H_2O (0.3 mL) and 202 mg (0.76 mmol) of PPh_3 was heated at 40 °C for 2 h. The solvent was evaporated, and the water was removed azeotropically with benzene. The crude amine product was dissolved in 5 mL of CH_2Cl_2 and added to 0.17 mL of Et_3N and 278 mg (1.27 mmol) of Boc anhydride at 0 °C. The reaction was stirred for 3 h at 0 °C, quenched with water, and extracted with CH_2Cl_2. The combined extract was dried over $MgSO_4$, concentrated, and purified by column chromatography (hexane/EtOAc = 9:1) to give 283 mg of **32b** as a colorless oil in 86% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.04 (s, 1H), 6.84 (d, J = 8.0 Hz, 1H), 6.71 (d, J = 8.0 Hz, 1H), 6.44 (s, 1H), 5.94 (d, J = 2.4 Hz, 2H), 5.34 (brs, 1H), 4.13−4.27 (m, 2H), 4.22 (d, J = 6.8 Hz, 1H), 4.05 (d, J = 6.8 Hz, 1H), 3.74 (d, J = 2.8 Hz, 1H), 3.65 (dd, J = 12.8, 7.2 Hz, 1H), 3.42 (s, 3H), 3.02 (s, 3H), 3.08−3.04 (m, 1H), 1.82 (d, J = 13.6 Hz, 1H), 1.59−1.51 (m, 1H), 1.44 (s, 9H), 0.89 (s, 9H), 0.15 (s, 3H), 0.10 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.8, 147.0, 146.4, 134.6, 133.2, 124.3, 123.4, 110.5, 107.1, 101.0, 98.1, 83.0, 80.0, 79.0, 67.7, 57.6, 56.5, 55.9, 41.9, 33.9, 28.5, 25.9, 18.1, −4.1, −4.7; FT-IR (CH_2Cl_2) 3364, 2954, 2934, 2890, 1713, 1503, 1483, 1240, 1173, 1041, 938, 843 cm^{-1}; HRMS calcd for $C_{29}H_{46}BrNNaO_8Si$ [M + Na]$^+$: 666.2068, found 666.2068.

Preparation of 33b. To a solution of **32b** (168 mg, 0.261 mmol) in CH_2Cl_2 (2.5 mL) was added Et_3N (0.1 mL) and TBAF (0.5 mL, 1 M in THF) at 0 °C. The reaction was stirred for 4 h at 0 °C. After warming to room temperature, the reaction mixture was treated with water and extracted with CH_2Cl_2. The organic layer was separated, dried over $MgSO_4$, filtered, concentrated, and chromatographed (hexane/EtOAc/MeOH = 70:30:3) to give 133 mg of alcohol **32b-1** as a colorless oil in 96% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.03 (s, 1H), 6.82 (d, J = 8.0 Hz, 1H), 6.76 (d, J = 8.0 Hz, 1H), 6.34 (s, 1H), 5.95 (d, J = 4.8 Hz, 2H), 5.30 (brs, 1H), 4.62−4.53 (m, 2H), 4.34 (d, J = 10.8 Hz, 1H), 4.01 (d, J = 4.8 Hz, 1H), 3.81 (s, 1H), 3.64−3.51 (m, 1H), 3.46 (s, 3H), 3.30 (s, 3H), 2.95−2.91 (m, 2H), 1.93 (d, J = 13.6 Hz, 1H), 1.63−1.56 (m, 1H), 1.44 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.2, 147.5, 146.7, 133.9, 131.3, 125.2, 123.1, 110.2, 107.6, 101.1, 98.2, 85.1, 80.0, 79.6, 67.1, 58.0, 56.1, 56.0, 43.0, 32.7, 28.4; FT-IR (CH_2Cl_2) 3389, 2978, 2932, 2891, 1714, 1502, 1249, 1162, 1038, 926, 744 cm^{-1}; HRMS calcd for $C_{23}H_{32}BrNNaO_8$ [M + Na]$^+$: 552.1204, found 552.1205. To a mixture of alcohol **32b-1** (133 mg, 0.251 mmol), $NaHCO_3$ (105 mg, 1.25 mmol), and CH_2Cl_2 (2.5 mL) was added the Dess−Martin reagent (128 mg, 0.3 mmol). After 30 min at room temperature, the reaction mixture was filtered through a short pad of Celite and washed with ether. The filtrate was concentrated and chromatographed (hexane/EtOAc = 8:2) to afford 120 mg of **33b** as a colorless oil in 91% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.90 (s, 1H), 6.83 (dd, J = 8.0, 1.2 Hz, 1H), 6.75 (d, J = 8.0 Hz, 1H), 6.69 (s, 1H), 5.95 (s, 2H), 5.39 (brs, 1H), 4.55 (t, J = 5.6 Hz, 1H), 4.36 (d, J = 6.8 Hz, 1H), 4.20−4.17 (m, 2H), 3.49 (s, 3H), 3.34−3.24 (m, 1H), 3.13−3.07 (m, 1H), 3.05 (s, 3H), 2.72−2.61 (m, 2H), 1.45 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 203.4, 155.8, 148.2, 147.4, 133.3, 131.4, 122.8, 120.9, 108.3, 107.8, 101.4, 97.3, 81.9, 80.4, 79.0, 62.2, 57.8, 55.8, 42.5, 42.2, 28.6; FT-IR (CH_2Cl_2) 3359, 2978, 2932, 2891, 1714, 1502, 1249, 1162, 1038, 926, 744 cm^{-1}; HRMS calcd for $C_{23}H_{30}BrNaNO_8$ [M + Na]$^+$: 550.1047, found 550.1050.

Preparation of 34b. A mixture of **33b** (40 mg, 0.076 mmol), excess $ZnBr_2$ (5 equiv), and CH_2Cl_2 (1.5 mL) was stirred at room temperature for 5 h. This mixture was diluted with ether (0.5 mL) and cannulated into a suspension of $LiAlH_4$ (0.29 mg, 0.76 mmol) in ether (1 mL) at −10 °C. After 15 min, the reaction mixture was quenched with aqueous 20% NaOH and extracted with CH_2Cl_2. The combined organic solution was dried over $MgSO_4$, filtered, concentrated, and chromatographed (CH_2Cl_2/MeOH = 9.5:0.5 to 9.0:1.0) to afford 16 mg of **34b** as a tan oil in 51% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.83 (d, J = 0.8 Hz, 1H), 6.78−6.73 (m, 2H), 6.52 (s, 1H), 5.95 (s, 2H), 4.64 (t, J = 7.6 Hz, 1H), 4.52 (d, J = 6.4 Hz, 1H), 4.47 (d, J = 6.4 Hz, 1H), 3.75 (d, J = 4.4 Hz, 1H), 3.50 (s, 3H), 3.40 (brs, 1H), 3.32−3.23 (m, 1H), 3.18 (s, 3H), 3.00−2.93 (m, 1H), 2.26 (dd, J = 15.2, 2.4 Hz, 1H), 1.71−1.65 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.1, 146.5, 135.2, 131.8, 123.6, 120.2, 108.3, 107.1, 101.2, 96.2, 85.0, 78.0, 61.5, 58.5, 56.3, 55.5, 50.3, 26.6; FT-IR (CH_2Cl_2) 3363, 2931, 2882, 1502, 1490, 1437, 1240, 1086, 1050, 941, 808, 739 cm^{-1}; HRMS calcd for $C_{18}H_{22}BrNNaO_5$ [M + Na]$^+$: 434.0574, found 434.0572.

Preparation of 35b. To a solution of **34b** (40 mg, 0.097 mmol) in MeOH (0.8 mL) was added 1.0 mL of 37% aqueous solution of formaldehyde. After 10 min, to this solution was added with 8.5 mL of 6N HCl at room temperature. After 15 h at 50 °C, the reaction mixture was cooled to room temperature, basified by adding solid K_2CO_3 and then extracted with CH_2Cl_2. The combined organic solution was dried over $MgSO_4$, filtered, concentrated, and chromatoghraphed to give 28 mg of **35b** as a while solid in 76% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.79 (s, 1H), 6.72 (s, 1H), 6.48 (s, 1H), 5.91 (s, 2H), 4.30 (d, J = 16.8 Hz, 1H), 4.08−3.98 (m, 2H), 3.68 (d, J = 16.8 Hz, 1H), 3.45 (s, 3H), 3.43−3.32 (m, 2H), 3.30−3.26 (m, 1H), 2.44−2.35 (m, 1H), 2.20−2.15 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.8, 146.6, 134.0, 131.7, 127.8, 126.5, 107.1, 103.2, 101.1, 80.2, 77.8, 66.0, 63.4, 61.2, 56.1, 52.9, 30.8; HRMS calcd for $C_{17}H_{18}BrNNaO_4$ [M + Na]$^+$: 402.0311, found 402.0308.

Preparation of 2b. A sealed tube was charged with **35b** (24 mg, 0.06 mmol), benzene (1.2 mL), AIBN (10 mg, 0.06 mmol), and tributyltin hydride (0.1 mL). After 2 h at 80 °C, the reaction mixture was cooled to room temperature, and partitioned into CH_2Cl_2 and aqueous KF solution. The organic layer was separated, dried over $MgSO_4$, filtered, concentrated, and purified by silica gel chromatography (CH_2Cl_2/MeOH = 9.5:0.5 to 9.0:1.0) to give 14 mg of (±)-crinamine **2b** as a while solid in 74% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.80 (s, 1H), 6.48 (s, 1H), 6.26 (s, 2H), 5.90 (d, J = 2.0 Hz, 2H), 4.33 (d, J = 17.0 Hz, 1H), 4.02 (dd, J = 10.4, 6.0 Hz, 1H), 3.98−3.96 (m, 1H), 3.71 (d, J = 17.0 Hz, 1H), 3.41 (s, 3H), 3.39−3.32 (m, 2H), 3.23 (dd, J = 13.2, 4.4 Hz, 1H), 2.17−2.07 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.6, 146.3, 136.2, 135.5, 126.7, 123.7, 106.9, 103.3, 100.9, 80.1, 76.1, 66.3, 63.6, 61.3, 55.9, 50.4, 30.3. The spectral data matched the literature values of crinamine.[16]

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Supporting Information Available: Experimental details for the synthesis of (±)-crinine **1** and copies of ^{1}H and ^{13}C NMR spectra of synthetic intermediates en route to the final products (±)-6a-*epi*-crinamine **2a** and (±)-crinamine **2b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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