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The Total Synthesis of the Crinine Alkaloid Hamayne via a Pd[0]-Catalyzed Intramolecular Alder-Ene Reaction

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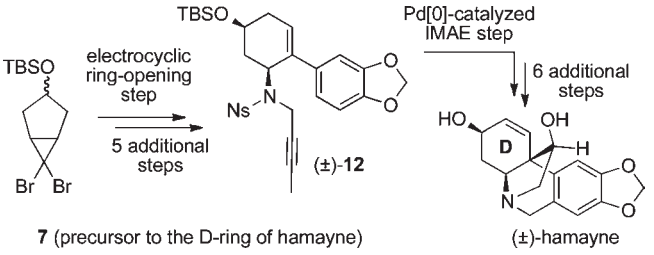
ABSTRACT



7 (precursor to the D-ring of hamayne) (±)-hamayne

The racemic form of the title alkaloid, 1, has been prepared in 13 steps from the ring-fused *gem*-dibromocyclopropane 7. Key transformations include the thermally induced electrocyclic ring-opening of compound 7, the Pd[0]-catalyzed intramolecular Alder-ene (IMAE) reaction of the derived sulfonamide (±)-12, and the conversion of the ensuing C-3a-arylhexahydroindole (±)-16 into (±)-hamayne via a Pictet–Spengler reaction.

In 1976 Ochi et al. described the isolation of the crinine alkaloid hamayne (**1**, aka *O*-demethylcrinamine, Figure 1) from the fruit and seeds of *Crinum asiaticum* L. *var. japonicum* Baker.[1] Its structure was assigned using a combination of spectroscopic and chemical correlation techniques.[1] The compound has also been isolated from the bulbs of certain *Crinum* and *Brunsvigia* species[2−4] used in traditional African medicine for the treatment of various ailments including coughs and colds,[2] memory loss,[4] renal and hepatic conditions,[2] infertility, and back pains.[2] Hamayne itself shows some antiplasmodial and cytotoxic activities.[3] It also inhibits acetylcholinesterase (AChE), an effect that is attributed to the presence of the two free hydroxyl groups.[4]

Structurally speaking, hamayne is a member of that subset of crinine alkaloids incorporating oxygenation in both the C- and D-rings, namely at C-11 and C-3 respectively.

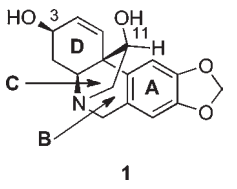


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Figure 1. Structure of the crinine alkaloid hamayne (**1**).

Thus far, there have been no reports on the synthesis of hamayne, and a survey[5] of the existing methods available for the construction of crinine alkaloids clearly indicates that the stereocontrolled introduction of functionality at

(1) Ochi, M.; Otsuki, H.; Nagao, K. *Bull. Chem. Soc. Jpn.* **1976**, *49*, 3363.

(2) Viladomat, F.; Bastida, J.; Codina, C.; Campbell, W. E.; Mathee, S. *Phytochemistry* **1994**, *35*, 809.

(3) Campbell, W. E.; Nair, J. J.; Gammon, D. W.; Codina, C.; Bastida, J.; Viladomat, F.; Smith, P. J.; Albrecht, C. F. *Phytochemistry* **2000**, *53*, 587.

(4) Houghton, P. J.; Agbedahunsi, J. M.; Adegbulugbe, A. *Phytochemistry* **2004**, *65*, 2893.

(5) For reviews, see: (a) Lewis, J. R. *Nat. Prod. Rep.* **1998**, *15*, 107. (b) Jin, Z. *Nat. Prod. Rep.* **2011**, *28*, 1126. For selected examples, see: (c) Overman, L. E.; Sugai, S. *Helv. Chim. Acta* **1985**, *68*, 745. (d) Bohno, M.; Imase, H.; Chida, N. *Chem. Commun.* **2004**, 1086. (e) Nishimata, T.; Sato, Y.; Mori, M. *J. Org. Chem.* **2004**, *69*, 1837. (f) Bru, C.; Guillou, C. *Tetrahedron* **2006**, *62*, 9043. (g) Bohno, M.; Sugie, K.; Imase, H.; Yusof, Y. B.; Oishi, T.; Chida, N. *Tetrahedron* **2007**, *63*, 6977. (h) Tam, N. T.; Chang, J.; Jung, E.-J.; Cho, C.-G. *J. Org. Chem.* **2008**, *73*, 6258. (i) Liu, J.-D.; Wang, S.-H.; Zhang, F.-M.; Tu, Y.-Q.; Zhang, Y.-Q. *Synlett* **2009**, 3040. (j) Findlay, A. D.; Banwell, M. G. *Org. Lett.* **2009**, *11*, 3160.

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C-11 within the 2,3,4,4a-tetrahydro-1*H*,6*H*-5,10b-ethanophenanthridine framework of such natural products can be a challenging matter. Indeed, quite involved protocols are often required to achieve such ends.[5g] Herein, therefore, we report a total synthesis of (±)-hamayne [(±)-**1**] that allows for the introduction of the associated C-11 hydroxyl group in a straightforward and completely stereocontrolled manner.

The strategy employed in the present work is shown in retrosynthetic form in Figure 2. Thus, the closing stages of the synthesis were to follow a pathway[5e,g–j] commonly used for the construction of crinine alkaloids, namely through formation of the B-ring of target (±)-**1** by subjecting a suitably protected C-3a-arylhexahydroindole, e.g. (±)-**2** (X = OH, Y = H), to a Pictet–Spengler reaction.[6] This was to be preceded by oxidative cleavage of the exocyclic double bond within (±)-**2** [X,Y = C(H)R] and exo-face selective reduction of the ensuing ketone (±)-**2** (X,Y = O) so as to install the required endo-orientated C-11 hydroxyl group. The ACD-ring system of the key subtarget (±)-**2** [X,Y = C(H)R], which incorporates the pivotal quaternary carbon associated with the crinine alkaloids, would itself be constructed by engaging the N-propargylated allylic amine derivative (±)-**3** in an intramolecular Alder-ene (IMAE) reaction.[7] Compound (±)-**3** would, in turn, be generated by coupling, in a Suzuki–Miyaura reaction,[8] a bromocyclohexene of the general form (±)-**4** with the relevant aryl boronic acid, and then N-propargylation of the associated secondary amine residue. Compound (±)-**4** was envisaged as being accessible through electrocyclic ring-opening of a 6,6-dibromobicyclo[3.1.0]-hexane of the general form **5**[9] and trapping of the resulting π-allyl cation with a suitable nitrogen-centered nucleophile. The details associated with the successful implementation of this strategy are presented in Scheme 1.

In the opening stages of the synthesis, the known[10] and readily obtained *tert*-butyldimethylsilyl (TBS) ether, **6**, of commercially available hepta-1,6-dien-4-ol was subjected

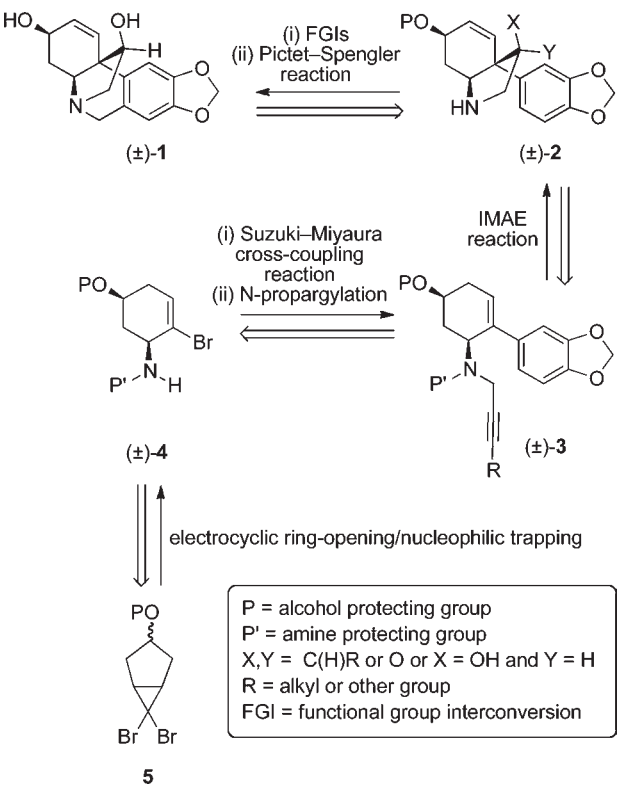

Figure 2. Retrosynthetic analysis of (±)-hamayne [(±)-**1**].

to a ring-closing metathesis (RCM) reaction[11] using Grubbs' first-generation catalyst[12] and the ensuing cyclopentene reacted with dibromocarbene generated under the Makosza conditions[9a] from bromoform and base in the presence of the phase-transfer catalyst triethylbenzylammonium chloride (TEBAC). As a result a ca. 5:1 mixture of the two possible adducts of the general form **7** was produced. The major diastereoisomer, which was readily obtained in pure form and 75% yield after flash chromatography, was subjected to thermally induced electrocyclic ring-opening in refluxing chlorobenzene and the ensuing 2,3-dibromocyclohexene treated with sodium azide in DMF, and by such means the allylic azide (±)-**8** was obtained in 86% yield although this was contaminated with ca. 6% of the corresponding and chromatographically inseparable *trans*-isomer. The spectral data obtained on this material were in full accord with the assigned structure, but final confirmation of this followed from a single-crystal X-ray analysis of a derivative (vide infra).

Subjection of azide (±)-**8** to Staudinger reduction using triphenylphosphine in methanol/water and treatment of the ensuing primary amine with nosyl chloride[13] in the presence of triethylamine gave the sulfonamide (±)-**9** in 83% yield. Suzuki–Miyaura cross-coupling of this last compound with the commercially available boronic acid **10** then afforded the arylated cyclohexene (±)-**11** (78%)

(6) For a review of the Pictet–Spengler reaction, published on the 100th anniversary of its discovery, see: Stöckigt, J.; Antonchick, A. P.; Wu, F.; Waldmann, H. *Angew. Chem., Int. Ed.* **2011**, *50*, 8538.

(7) Mori et al. have employed a high temperature intramolecular carbonyl-ene reaction of a 2-arylated cyclohex-2-enylamine derivative to generate C-3a-arylhexahydroindoles relevant to the synthesis of crinines; see: ref 5e.

(8) Kürti, L.; Czakó, B. *Strategic Applications of Named Reactions in Organic Synthesis*; Elsevier: Amsterdam, 2005; pp 448–449.

(9) For reviews on methods for generating *gem*-dihalocyclopropanes and/or their exploitation in chemical synthesis, see: (a) Makosza, M. *Pure Appl. Chem.* **1975**, *43*, 439. (b) Banwell, M. G.; Reum, M. E. In *Advances in Strain in Organic Chemistry*; Halton, B., Ed.; JAI Press: London, 1991; Vol. 1, pp 19–64. (c) Xu, L.; Brinker, U. H. In *Synthetic Organic Sonochemistry*; Luche, J.-L., Ed.; Plenum Press: New York, 1998; pp 344–345. (d) Fedoryński, M. *Chem. Rev.* **2003**, *103*, 1099. (e) Banwell, M. G.; Beck, D. A. S.; Stanislawski, P. C.; Sydnes, M. O.; Taylor, R. M. *Curr. Org. Chem.* **2005**, *9*, 1589. (f) Halton, B.; Harvey, J. *Synlett* **2006**, 1975.

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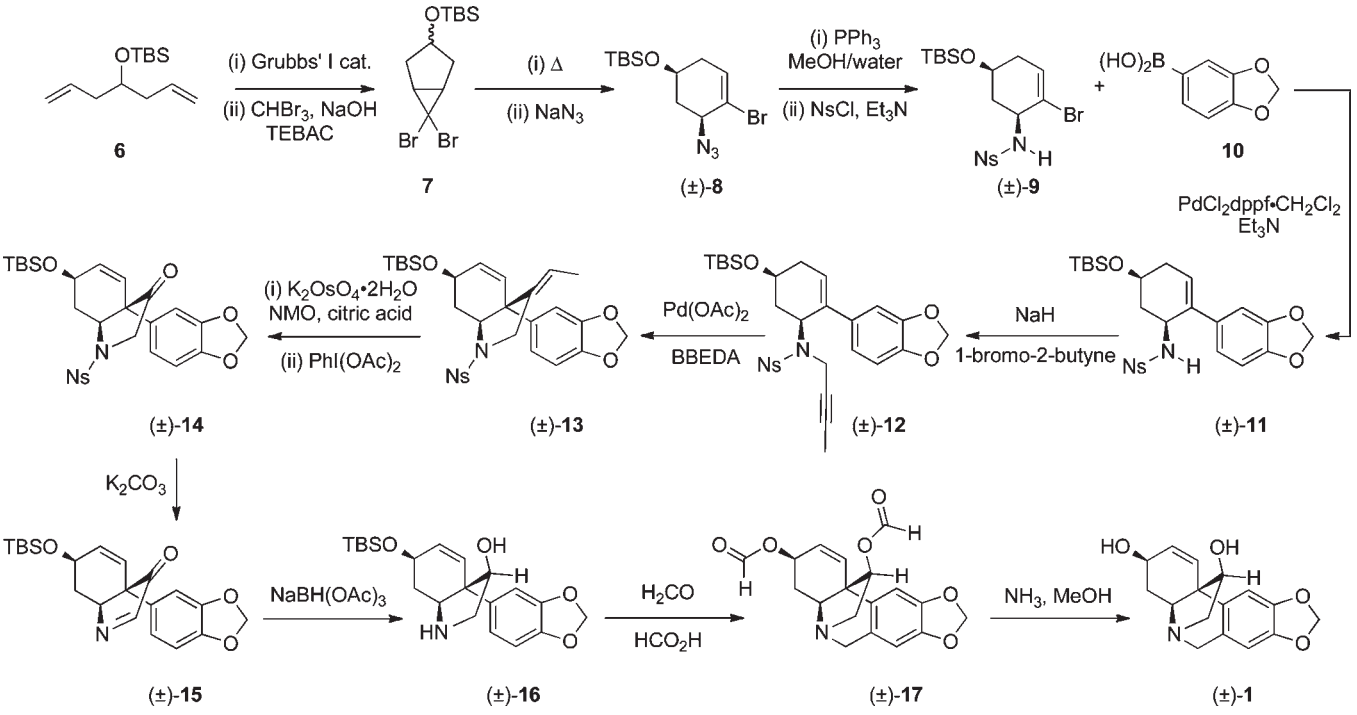
(12) Schwab, P.; Grubbs, R. H.; Ziller, J. W. *J. Am. Chem. Soc.* **1996**, *118*, 100.

(13) Fukuyama, T.; Jow, C.-K.; Cheung, M. *Tetrahedron Lett.* **1995**, *36*, 6373.

Scheme 1. The Total Synthesis of (±)-Hamayne [(±)-**1**]



that remained contaminated with some of the corresponding *trans*-isomer. Reaction of sulfonamide (±)-**11** with sodium hydride and then 1-bromo-2-butyne[14] afforded compound (±)-**12** (96%) that could now be obtained in a crystalline and, therefore, diastereoisomerically pure form. Accordingly, this material was subjected to single-crystal X-ray analysis and its structure confirmed. The derived ORTEP is shown in Figure 3, and further details of this analysis are presented in the Supporting Information.[15]

While the ORTEP shown in Figure 3 suggests that the olefinic and acetylenic moieties within compound (±)-**12** can adopt the required orientation, the compound failed to engage in the desired IMAE reaction on heating. In contrast, and following protocols introduced by Trost and Pedregal,[16] microwave irradiation of a benzene solution of it containing $Pd(OAc)_2$ and *N*,*N*′-bis(benzylidene)ethylenediamine (BBEDA) at 120 °C for 4 h afforded the anticipated product (±)-**13** in 75% yield. The reaction did not proceed in the absence of microwave irradiation. Treatment of compound (±)-**13** under the Upjohn

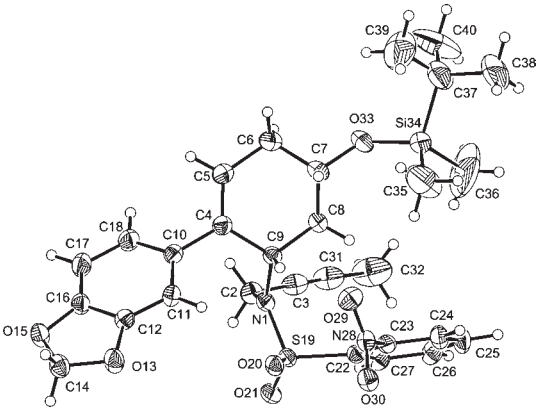


Figure 3. ORTEP derived from the single-crystal X-ray analysis of compound (±)-**12** with labeling of non-hydrogen atoms. A minor alternative site for the Si atom is not shown. Thermal ellipsoids are drawn at the 30% probability level. H atoms are shown as spheres of arbitrary radius.

dihydroxylation conditions in the presence of citric acid[17] resulted in regioselective dihydroxylation of the more substituted (and electron-rich) double bond within diene (±)-**13**. Reaction of the ensuing diol with phenyliodonium diacetate[18] in dichloromethane then gave the ketone (±)-**14** in 53% yield. Attempts to

(14) The use of this electrophile follows from our earlier studies which established that terminal alkynes failed to engage in the desired IMAE reactions due to competing dimerization processes. See: Lehmann, A. L.; Willis, A. C.; Banwell, M. G. *Aust. J. Chem.* **2010**, *63*, 1665.

(15) CCDC 840331 contains the supplementary crystallographic data for compound (±)-**12**. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

(16) (a) Trost, B. M. *Acc. Chem. Res.* **1990**, *23*, 34. (b) Trost, B. M.; Pedregal, C. *J. Am. Chem. Soc.* **1992**, *114*, 7292.

(17) (a) Dupau, P.; Epple, R.; Thomas, A. A.; Fokin, V. V.; Sharpless, K. B. *Adv. Synth. Catal.* **2002**, *344*, 421. (b) Él, A. H.; Closson, A.; Adolfsson, H.; Bäckvall, J.-E. *Adv. Synth. Catal.* **2003**, *345*, 1012.

(18) Nicolaou, K. C.; Adsool, V. A.; Hale, C. R. H. *Org. Lett.* **2010**, *12*, 1552 and references cited therein.

cleave the nosyl group within this last compound using the protocols reported by Fukuyama[13] failed to give a clean product. In contrast, when compound (±)-**14** was treated with potassium carbonate in THF/methanol, then an E1cb reaction took place and the acylimine (±)-**15** was obtained in 88% yield. This last compound was rather unstable so it was immediately subjected to reduction with freshly prepared sodium acetoxyborohydride in acetic acid/ethyl acetate at 0 °C, thus forming the aminoalcohol (±)-**16** in a completely stereoselective manner. Given the highly polar nature of compound (±)-**16** and the consequent difficulties in handling this material, it was immediately subjected to a Pictet−Spengler reaction using paraformaldehyde in formic acid at reflux. Under these conditions not only did the desired formation of the B-ring take place but also the TBDMS ether moiety was cleaved and the resulting diol was converted into the corresponding bis(formate) (±)-**17**. This was subjected to treatment with ammonia in methanol thereby affording (±)-hamayne [(±)-**1**] as an amorphous powder, in 65% yield over the three steps from acylimine (±)-**15**.

The ^{13}C and ^{1}H spectral data obtained on synthetically derived (±)-hamayne [(±)-**1**] were in complete accord with the assigned structure and in excellent agreement with those reported for the natural product (Table 1). Furthermore, the 70 eV EI mass spectrum of the synthetic material showed a weak molecular ion (ca. 4%) at *m*/*z* 287 and a base peak at *m*/*z* 269, essentially the same as is reported[2] for the natural product. The two sets of infrared spectral data also proved to be a good match. In contrast, while the melting range for the natural product is 82−84 °C,[2] the synthetically derived racemate did not melt even upon heating to 230 °C.

We are currently examining how the *meso* compound **7** used at the beginning of the above-mentioned reaction sequence might be desymmetrized so as to provide the corresponding ring-expanded product in enantiomerically enriched form, thus allowing for the adaptation of the strategy described above to the synthesis of (+)- or (−)-hamayne [(+)- or (−)-**1**] as required.

Table 1. Comparison of the ^{13}C and ^{1}H NMR Data Recorded for Synthetically Derived Compound (±)-**1** with Those Reported for Hamayne

^{13}C NMR data (δ_C)		^{1}H NMR data (δ_H)	
(±)-**1**[a]	hamayne[b]	(±)-**1**[c]	hamayne[d]
146.6	146.8	6.80, s, 1H	6.81, s, 1H
146.3	146.3	6.48, s, 1H	6.47, s, 1H
138.4	137.4	6.22, m, 2H	6.19, s, 2H
135.2	135.4	5.90, ABq, J = 1.6 Hz, 2H	5.90, s, 2H
126.5	125.2	4.42, m, 1H	4.35, m, 1H
123.1	122.9	4.32, d, J = 16.8 Hz, 1H	4.30, d, J = 16 Hz, 1H
106.9	106.8	4.00, m, 1H	4.00, m, 1H
103.2	103.3	3.70, d, J = 16.8 Hz, 1H	3.65, d, J = 16 Hz, 1H
100.9	101.0	3.45−3.31, complex m, 2H	3.35, m, 2H
79.9	79.5	3.25, dd, J = 12.8 and 4.8 Hz, 1H	3.25, dd, J = 13.5 and 4.5 Hz, 1H
67.7	67.0	2.18−2.01, complex m, 2H	2.10, m, 2H
66.3	65.6	–	–
63.4	63.0	–	–
61.2	60.5	–	–
50.0	49.8	–	–
34.2	33.2	–	–

[a] Data recorded in $CDCl_3$ at 100 MHz. [b] Data obtained from ref 2 and recorded in $CDCl_3$ at 50 MHz. [c] Data recorded in $CDCl_3$ at 400 MHz. [d] Data obtained from ref 2 and recorded in $CDCl_3$ at 200 MHz.

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Supporting Information Available. Full experimental procedures; the cif and data derived from the single-crystal X-ray analysis of compound (±)-**12**; ^{1}H and ^{13}C NMR spectra of compounds **7**, (±)-**8**, (±)-**9**, (±)-**11**, (±)-**12**, (±)-**13**, (±)-**14**, (±)-**15**, and (±)-**1**. This material is available free of charge via the Internet at http://pubs.acs.org.