Natural Products Synthesis

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Efficient Entry to the Hasubanan Alkaloids: First Enantioselective Total Syntheses of (−)-Hasubanonine, (−)-Runanine, (−)-Delavayine, and (+)-Periglaucine B**

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In memory of David Y. Gin

We describe herein a simple and general logic strategy to synthesize the hasubanan alkaloids,[1] a family of over 40 botanical natural products that share a common tetracyclic propellane skeleton (see structure **1**, Figure 1). The versatility

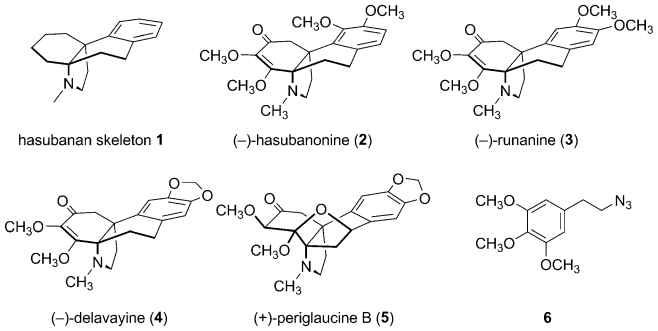
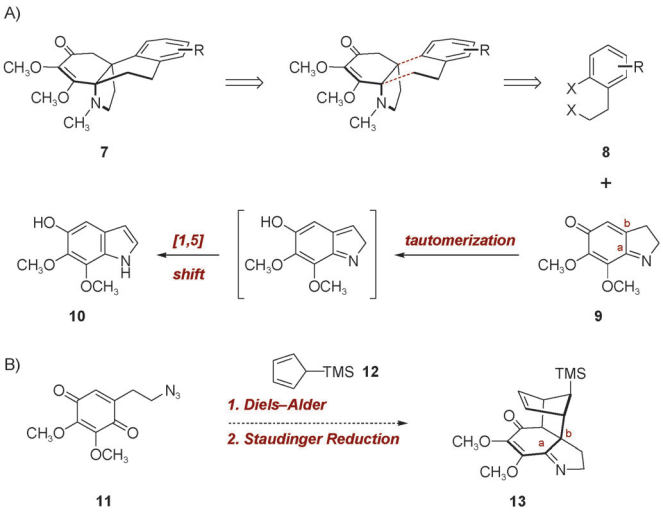


Figure 1. Structures of the hasuban skeleton **1**, the alkaloids **2**–**5**, and the starting material (**6**) used in this work.

of our approach is evinced by the first enantioselective synthesis of (−)-hasubanonine (**2**),[2] the foremost member of this family to be isolated, as well as by those of (−)-runanine (**3**),[3] (−)-delavayine (**4**),[4] and (+)-periglaucine B (**5**),[5] in eight or nine steps from 5-(2-azidoethyl)-1,2,3-trimethoxybenzene (**6**).[6] Hasubanonine (**2**)[7] and the related metabolites metaphanine[8] and cepharamine[9] have been previously prepared in racemic form, and numerous partial and formal syntheses of other hasubanan alkaloids have also been reported.[10] However, the only enantioselective total syntheses of alkaloids bearing similarity to **2**–**5** are Schultz's synthesis of (+)-cepharamine[11] and Castle's synthesis of (−)-acutumine.[12]

Our approach was designed to permit access to a maximal number of targets. Retrosynthetically, deconstruction of the hasubanan scaffold **7** by the pathway shown in Scheme 1 A



Scheme 1. Synthetic strategy to access the hasubanan alkaloids. A) Retrosynthetic analysis. B) Proposed synthesis of the intermediate **13**.

affords the pronucleophile **8** and the azaquinone **9** as hypothetical intermediates. We anticipated that **8** would serve as a useful branching point for incorporation of the varying arene substitution patterns found in the hasubanans. The azaquinone **9**, which contains the trioxygenated cyclohexanone fragment common to **2**–**5** and electrophilic sites (labeled a and b) for attachment of **8**, served as a nearly ideal synthetic intermediate.

Bicyclic azaquinones such as **9** are unstable toward isomerization to 5-hydroxyindoles (**10**)[13] by a pathway that may comprise tautomerization and a 1,5-hydrogen atom shift, as shown. Transient introduction of a quaternary center on the azaquinone (at position b) was expected to mitigate this pathway and convert **9** to a viable synthetic intermediate. Thus, we considered implementing a Diels–Alder reaction between the azidoquinone **11** and 5-trimethylsilylcyclopentadiene (**12**, Scheme 1 B). Staudinger reduction would then afford the tetracyclic imine **13**. Following bond formation to

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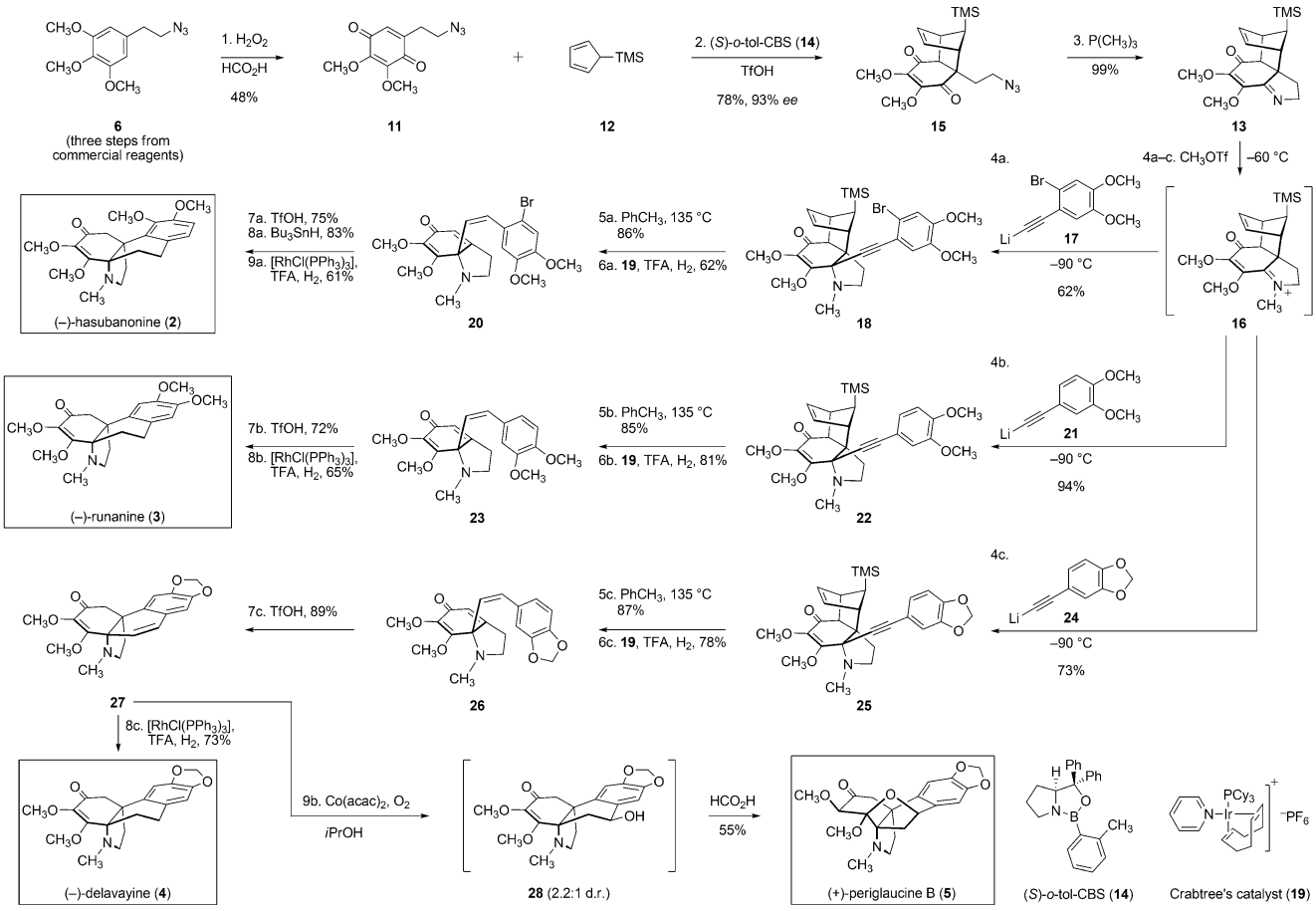
the imine (position a), the unsaturation required for addition to position b may be regenerated by a retro-cycloaddition reaction, rendering **13** functionally equivalent to **9**. Conceptually related strategies have been previously applied using cyclopentadiene or anthracene as blocking groups.[14] However, in the absence of two activating substituents, retro-cycloaddition reactions of these adducts require conditions (220–250 °C, diphenyl ether, or 400–500 °C, flash-vacuum pyrolysis) that were expected to be incompatible with functionalized advanced intermediates. By comparison, Diels–Alder adducts incorporating the 7-(trimethylsilyl)bicyclo[2.2.1]hept-2-ene substructure have been shown to undergo significantly faster retro-cycloaddition reactions.[15] This rate enhancement has been attributed to donation of electron density from the carbon–silicon bonding orbital to the antibonding orbitals of the carbon–carbon σ bonds that are breaking in the reaction transition state. We also envisioned that the cyclopentene fragment of **13** might provide a handle for stereocontrol, although enantioselective Diels–Alder reactions employing **12** were unknown at the outset of our studies.

The successful implementation of this strategy and total syntheses of **2**–**5** are shown in Scheme 2. Imine **13** was synthesized by a three-step sequence. First, 5-(2-azidoethyl)-1,2,3-trimethoxybenzene (**6**)[6] was oxidized with hydrogen peroxide in formic acid[16] to afford quinone **11** (48 %). Regio- and stereoselective Diels–Alder reaction with 5-trimethylsilylcyclopentadiene (**12**),[17] mediated by the protonated form of the Corey–Bakshi–Shibata oxazaborolidine **14**,[18] produced the *endo* adduct **15** in 78 % yield and 93 % *ee*. The selectivity of the addition reaction was anticipated based on existing mechanistic models[18c] and was confirmed by X-ray analysis of the related intermediate **29** (vide infra). Staudinger reduction of **15** provided imine **13** in quantitative yield.

Imine **13** was transformed to (−)-hasubanonine (**2**) by a short six-step sequence. First, **13** was activated toward



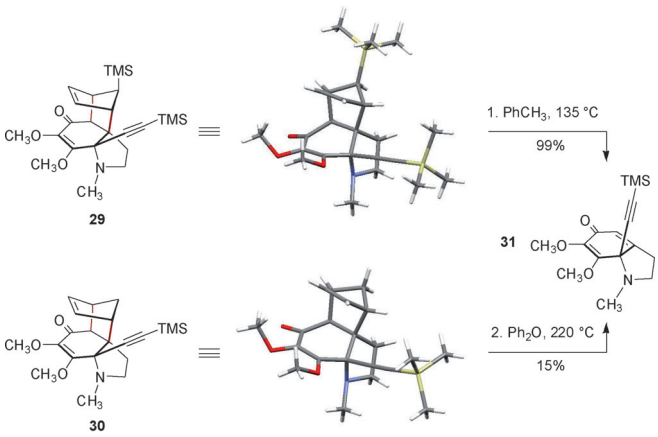
Scheme 2. Enantioselective total syntheses of (−)-hasubanonine (**2**), (−)-runanine (**3**), (−)-delavayine (**4**), and (+)-periglaucine B (**5**). Reagents and conditions: 1. H_2O_2, HCO_2H, 0 °C, 48 %; 2. (*S*)-*o*-tol-CBS (**14**, 25 mol %), TfOH (20 mol %), 5-trimethylsilylcyclopentadiene (**12**), CH_2Cl_2, −78 °C, 78 %, 93 % *ee*; 3. $P(CH_3)_3$, Et_2O, 0→24 °C, 99 %; 4a. CH_3OTf, THF, −78→−60→−90 °C, then **17**, 62 %; 5a. $PhCH_3$, 135 °C, 86 %; 6a. Crabtree's catalyst, TFA, H_2, CH_2Cl_2, 24 °C, 62 %; 7a. TfOH, CH_3CN, 0→24 °C, 75 %; 8a. Bu_3SnH, AIBN, $PhCH_3$, 90 °C, 83 %; 9a. $[RhCl(PPh_3)_3]$, H_2 (1000 psi), TFA, $PhCH_3$, 24 °C, 61 %. 4b. CH_3OTf, THF, −78→−60→−90 °C, then **21**, 94 %; 5b. $PhCH_3$, 135 °C, 85 %; 6b. Crabtree's catalyst, TFA, H_2, CH_2Cl_2, 24 °C, 81 %; 7b. TfOH, CH_2Cl_2, −30 °C, 72 %; 8b. $[RhCl(PPh_3)_3]$, H_2 (1000 psi), TFA, $PhCH_3$, 24 °C, 65 %. 4c. CH_3OTf, THF, −78→−60→−90 °C, then **24**, 73 %; 5c. $PhCH_3$, 135 °C, 87 %; 6c. Crabtree's catalyst, TFA, H_2, CH_2Cl_2, 24 °C, 78 %; 7c. TfOH, CH_2Cl_2, −40→−20 °C, 89 %; 8c. $[RhCl(PPh_3)_3]$, H_2 (1000 psi), TFA, $PhCH_3$, 24 °C, 73 %. 9b. $Co(acac)_2$, O_2 (1 atm), isopropanol, 75 °C, then HCO_2H, 75 °C, 55 % (ratio of **28**/diastereomer 2.2:1). THF = tetrahydrofuran, TFA = trifluoroacetic acid, Tf = trifluoromethanesulfonyl, AIBN = azobisisobutyronitrile, acac = acetylacetonate.

addition to the carbon–nitrogen π bond by treatment with methyl triflate at −60 °C. The temperature profile of this step was critical; lower temperatures resulted in incomplete methylation, whereas further warming promoted rapid retro-cycloaddition of the iminium salt **16**. The iminium salt **16** was then cooled to −90 °C and treated with the acetylide **17**, resulting in the formation of the 1,2-addition product **18** in 62% yield, as a single detectable diastereomer (^{1}H NMR analysis). The relative stereochemistry of the addition product **18** was assigned by elaboration to (−)-hasubanonine (**2**) and by analogy to that of the related crystalline product **29** (vide infra). The retro-cycloaddition reaction of **18** was achieved by heating in toluene at 135 °C (86% yield). Chemoselective hydrogenation using Crabtree's catalyst (**19**)[19] furnished the *cis* alkene **20** (62%). A three-step sequence comprising acid-mediated cyclization (75%), debromination (83%), and hydrogenation (61%) then provided synthetic (−)-hasubanonine (**2**).

We next prepared the alkaloids (−)-runanine (**3**) and (−)-delavayine (**4**). To access (−)-runanine (**3**), the acetylide **21** was added to the iminium ion **16**, to afford the 1,2-addition product **22** (94%). To access (−)-delavayine (**4**), the acetylide **24** was employed in the addition step, affording the 1,2-addition product **25** (73%). Two four-step sequences were used to convert **22** and **25** to (−)-runanine (**3**) and (−)-delavayine (**4**), respectively.

As the alkene **27**, which is the penultimate precursor to (−)-delavayine (**4**), might be converted to (+)-periglaucine B (**5**) directly by a formal olefin hydration/conjugate addition sequence, we surveyed a number of conditions to effect this transformation. We found that the desired hydration product **28** could be formed by heating a mixture of **27** and cobalt bis(acetylacetonate) in isopropanol under an atmosphere of dioxygen.[20] The diastereoselectivity in the hydration step was 2.2:1 in favor of **28**. Addition of excess formic acid directly to the reaction mixture promoted cyclization of **28**, providing (+)-perglaucine B (**5**) in 55% yield.[21]

In the context of the work reported herein, 5-trimethylsilylcyclopentadiene (**12**) has served the dual purpose of stabilizing the azaquinone **9** and providing a handle for setting the absolute stereochemistry. The facility with which the retro-cycloaddition reaction occurs, even in the presence of only a single activating group, suggests this novel controlling group may find application in other settings. To illustrate clearly the rate enhancement provided by the trimethylsilyl substituent, we prepared the homologous 2-(trimethylsilyl)-acetylene addition products **29** and **30** (Scheme 3, see the Supporting Information for details). Thermolysis of **29** (toluene, 135 °C, 3 h) afforded the retro-cycloaddition product **31** in quantitative yield. By comparison, higher temperature (220 °C) was required to promote retro-cycloaddition of the unsubstituted adduct **30**, leading to extensive decomposition and low yield of **31** (15%).[22] Relevant to the experiments above, both **29** and **30** were highly crystalline, allowing unambiguous determination of relative (and in the case of **29**, absolute) stereochemistry by X-ray analysis.[23] The crystallographic data reveal that the carbon–carbon σ bonds that are broken in these transformations (shown in red) are of nearly the same length in **29** and **30** (1.56–1.57 Å). Thus, the inductive effect of the trimethylsilyl substituent is manifested primarily in the transition state for the retro-cycloaddition reaction, potentially in the form of an asynchronous, polarized transition structure.



Scheme 3. Retro-cycloaddition of the 2-(trimethylsilyl)acetylene addition products **29** and **30**. 1. $PhCH_3$, 135 °C, 99%; 2. Ph_2O, 220 °C, 15%.

In summary, we have completed the first enantioselective total syntheses of (−)-hasubanonine (**2**), (−)-runanine (**3**), (−)-delavayine (**4**), and (+)-periglaucine B (**5**). Our route to each target proceeds in eight or nine steps from the aryl azide **6** (the latter was obtained in three steps from commercial reagents, without purification of intermediates). Our approach has also demonstrated the utility of 5-trimethylsilylcyclopentadiene **12** as an easily removable, stabilizing, stereocontrol element in the synthesis of complex molecules. The logic developed in these studies is likely to find application in the synthesis of other members of this large family of alkaloids.

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[21] NMR spectroscopic data for synthetic **2**–**5** were in complete accord with those reported for the natural isolates. However, inspection of these data revealed that many of the resonances of natural **2**–**5** were incorrectly assigned. These were clarified by 2D NMR and NOESY experiments. Complete spectroscopic data and revised assignments are presented in the Supporting Information.

[22] Grieco has reported efficient Lewis acid catalyzed retro-cycloaddition reactions of cyclopentadiene Diels–Alder adducts. P. A. Grieco, N. Abood, *J. Org. Chem.* **1989**, *54*, 6008. However, **30** did not undergo retro-cycloaddition in the presence of several Lewis and protic acid additives.

[23] Intermediate **29** was prepared in enantiomerically enriched form using the catalyst **14**. The absolute stereochemistry depicted is supported by the observed Flack [0.15(0.14)] and Hooft [0.00(0.12)] parameters. Intermediate **30** was prepared as a racemate. CCDC 819339 (**29**) and 819340 (**30**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

