



Toward A Potential Total Synthesis of Gelsemine: A Regioselective Hydroboration Directed by a Remote Olefin

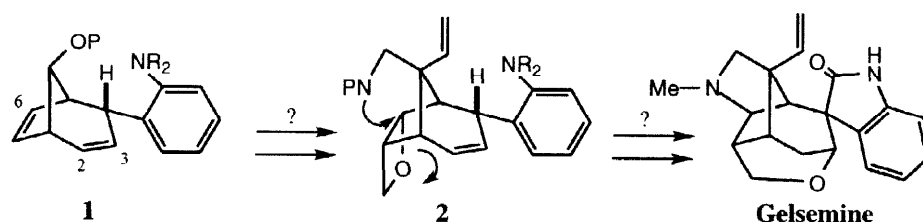
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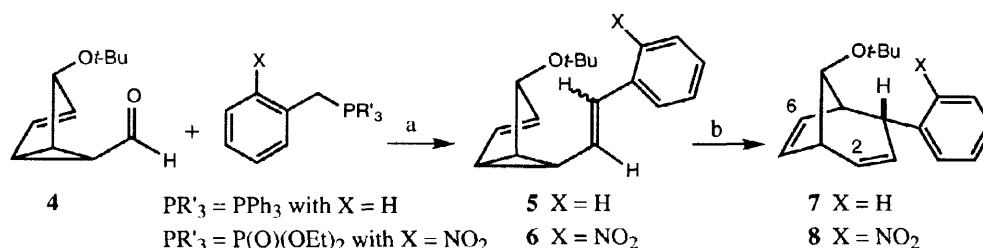
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Abstract: Hydroboration of bicyclo[3.2.1]octa-2,6-diene derivatives occurred exclusively on one olefin, and within this olefin, remarkable regioselective addition of boron to one carbon terminus was observed. This regioselectivity was significantly improved with more electrophilic hydroborating agents. The regioselectivity is attributed to the directive effect of a remote olefin.
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In the course of an ongoing approach to our synthesis of gelsemine^{1,2} we have noted an instance where a non-reacting transannular olefin is able to impart remarkable directing bias to another double bond undergoing hydration through either hydroboration or solvomercuration. Our approach to the synthesis of gelsemine anticipated access to an oxetane intermediate **2**. We presumed that latent functionality derivable from **2** could be elaborated into gelsemine and sought to synthesize this compound by regiospecific functionalization of diene **1**. We found that hydroboration of various permutations of compound **1** occurs exclusively on the C6-C7 olefin and the boron atom becomes appended to C6.³



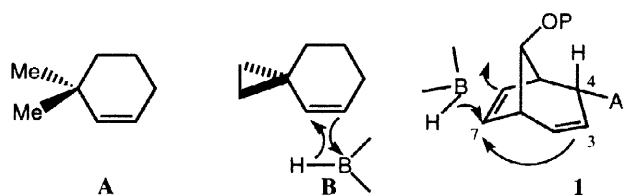
The synthesis of substrates required to test our predictions concerning regioselective hydroboration commenced with aldehyde **4**.^{4,5} Wittig reactions on this aldehyde gave rise to **5** and **6** which upon divinylcyclopropane - cycloheptadiene rearrangement, afforded **7** and **8** respectively.⁶



a) For $\text{X} = \text{H}$: *n*-BuLi, THF, reflux; for $\text{X} = \text{NO}_2$: DMF, NaOMe, rt. b) For **5**: Sealed tube, 150°C; for **6**: rt.

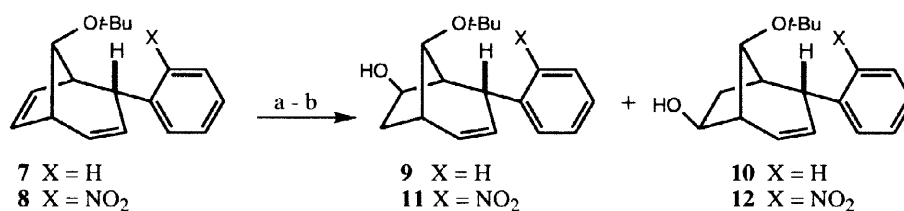
While substrate **7** serves as a simple model compound, **8** incorporates a potentially useful nitro group for reaching the gelsemine goal. The more strained C6-C7 double-bond in the two-carbon bridge of these dienes reacts faster than the olefin in the three-carbon bridge.⁷ We hoped that high regioselectivity could be realized in the hydroboration of the C6 - C7 double bond. We felt that the non-reacting C2-C3 olefin would favor C7 as the

preferred site for any kryptocationoid character that might be imparted during the course of the reaction. In projecting this possibility, we were not unmindful of the high fidelity to cis-addition manifested in the classical Brown hydroboration method.⁸ The stereochemical index thus speaks to a high degree of concert in the addition of R_2BH across the olefin. However, a tantalizing hint that strict suprafaciality in the addition event does not preclude the manifestation of dominant polar like effects, is seen in comparison of the hydroboration of **A** and **B**. With **A** as the substrate, there is virtually no regioselection in the hydroboration.⁹ Yet with **B** (which would be expected to be comparable to **A** in terms of steric biases) the sense of the hydroboration is as shown.¹⁰ By analogy to the directivity provided by the “cyclopropylcarbiny” effect in **B**, one might anticipate a “homoallyl” effect in **1** (see arrows).



In the event, when diene **7** was subjected to hydroboration-oxidation in the usual fashion, using borane ($BH_3 \cdot THF$) at $0^\circ C$, the major product was the desired isomer **9**, obtained in a 4:1 ratio relative to **10**. Interestingly, hydroboration of **7**, with 9-BBN¹¹ at rt gave the same compounds in a ratio of 6:1. We reasoned that a more electrophilic hydroborating reagent might enhance the electron-deficient character transition state and hence, result in a higher regioselectivity in the desired sense. Therefore, we subjected diene **7** to hydroboration using monochloroborane ($BH_2Cl \cdot DMS$), and dichloroborane ($BHCl_2 \cdot DMS$) at $0^\circ C$.¹² Reaction with the latter reagent was impractically sluggish, but hydroboration followed by oxidation proceeded cleanly to give the desired isomer **9** in a much improved ratio of 16:1.

After obtaining encouraging results with **7**, we proceeded to examine the regioselective hydroboration-oxidation of substrate **8** bearing the nitro substituent. Reaction of this substrate was examined with both 9-BBN and $BH_2Cl \cdot DMS$. Following oxidation, regioisomers **11**¹³ and **12** were obtained in a 13:1 ratio in the latter experiment and a 6:1 ratio was observed with 9-BBN.

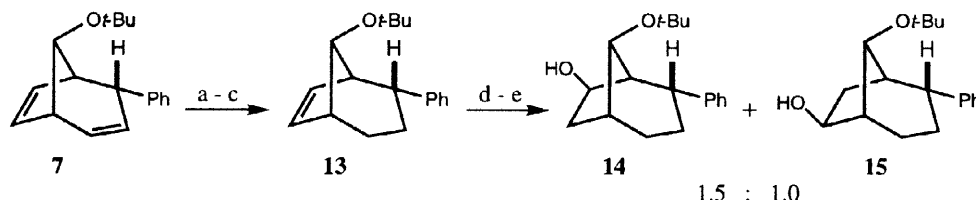


a) Boron reagent, THF. b) 30% H_2O_2 , NaOH, EtOH.

To further support the notion that the regioselectivity is indeed induced by the remote olefin and not by any other unrecognized steric factors, we synthesized a probe substrate without a non-reacting olefin. Compound **13** was synthesized from **7** by a three step procedure. The C6-C7 olefin is distinguished as epoxide

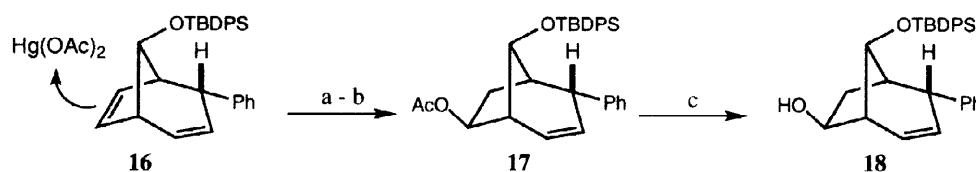
by reaction with dimethyl dioxirane.¹⁴ The 2,3-double bond was hydrogenated with H_2 -Pd/C. After the reduction step, the epoxide was deoxygenated with SmI_2 to secure compound **13**.¹⁵

Having deleted the directing olefin from diene **7**, we anticipated non-regioselective hydroboration of **13**. Indeed, when this compound was treated under the same reaction conditions with $\text{BH}_2\text{Cl}\cdot\text{DMS}$, the product mixture was a 1.5:1.0 mixture of the two regioisomers **14** and **15**. The structure of **14** was confirmed by its identity with the product that arises from hydrogenation of **9**.



a) Dimethyl dioxirane, acetone, rt. b) Pd/C, MeOH, H_2 balloon, rt. c) SmI_2 , THF, *t*-BuOH, reflux. d) $\text{BH}_2\text{Cl}\cdot\text{DMS}$, Et_2O , 0°C . e) 30% H_2O_2 , NaOH, EtOH.

Not unexpectedly, oxymercuration of **16**¹⁶ using $\text{Hg}(\text{OAc})_2$ produced only **17**. After reductive deacetylation of compound **17**, alcohol **18** was obtained. This result finds precedent from studies of Sakai⁷ in the parent system, and again suggests intercession of cationoid character at C7 arising from preferential mercuration at C6.



TBDPS = *t*-butyldiphenylsilyl

a) $\text{Hg}(\text{OAc})_2$, THF, H_2O , rt. b) 3N NaOH, NaBH_4 , rt. c) Dibal-H, CH_2Cl_2 , -78°C .

In summary, hydroboration of the 6,7-double bond of system **1** is strongly regioselective for “boration” at C6. In a complimentary reaction, which is presumably governed by the same electronic logic, oxymercuration occurs with mercuration at C6 and solvolytic attack at C7. We have pressed on and have successfully generated the oxetane intermediate of the type **2** from alcohol **11**. The results of our studies in pursuit of a total synthesis of gelsemine will be reported in due course.

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