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# BORON ANNULATION IN ORGANIC SYNTHESIS. 3. STEREOSELECTIVITY AND THE FORMAL SYNTHESIS OF (±)-HELENALIN

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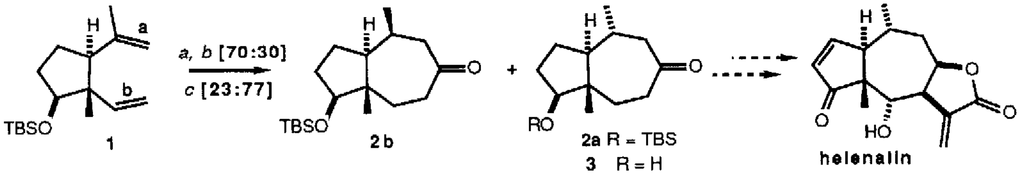
Summary: Stereochemical aspects of boron cycloheptanone annulation and an improved formal total synthesis of (±)-helenalin are described.

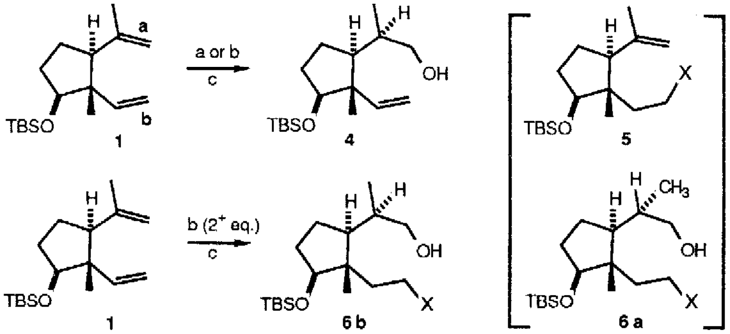
In previous communications the successful application of boron annulation methodology to provide access to the ambrosanolide[1] and helenanolide[2] series of sesquiterpene lactones were reported, the former of which provides for a direct and stereochemically controlled approach to confertin. It was further suggested that variance in the size and nature of the stitching reagent used could provide ready access to the isomeric helenanolide and ambrosanolide series of compounds from the same diene substrate. Reported herein is (i) the realization of that suggestion providing a selective approach to these isomeric pseudogauianolide systems, (ii) a formal total synthesis of (±)-helenalin and (iii) arguments as to the source of the regio- and stereoselective addition of boron hydrides to olefins **a** and **b** in **1**.



$^a$ThxBH$_2$; NaCN; $(CF_3CO)_2O$; NaOH, $H_2O_2$. $^b$ThxBrBH; KIPBH; NaCN; $(CF_3CO)_2O$; NaOH, $H_2O_2$
$^c$$H_2BBr$-DMS, $C_5H_{12}$; $CH_3ONa$, $CH_3OH$; $Et_3COLi$, $CH_3OCHCl_2$,THF; NaOH, $H_2O_2$.

Thexylborane or bromothexylborane then hydride[3] with **1** followed by cyanidation furnishes[1] a separable mixture of hydroazulone isomers **2** in the ratio of 30:70 [**2a**:**2b**]. Stitching with monobromoborane-dimethyl sulfide complex[4] and base catalyzed riveting with dichloromethyl methyl ether[5] furnishes the expected mixture of hydroazulone isomers (**2**, 40%), but with a reversal of C-10 isomers found with thexylborane (77:23, **2a**:**2b**, $^1$H NMR integration).[6] Separation of the isomers ($SiO_2$), followed by cleavage[7] of the *tert*-butyldimethylsilyl (TBS) ether gives hydroxy-ketone **3** (95%) whose spectral (ir, 400 MHz $^1$H NMR) characteristics are in agreement with those reported by Heathcock[8] thereby completing a formal synthesis of (±)-helenalin.[8,9]

Investigating this divergence, 9-BBN, thexylborane, thexylbromoborane[3], monobromoborane-dimethyl sulfide complex[4] and $BH_3$ were added to diene **1** and closely related structures with the selectivities of these reagents being determined by oxidation or riveting of the resultant boralanes. Substrate **1** with monohydrides, thexylbromoborane and 9-BBN, afforded diastereomer **4** (72%[15] and 68% yield, respectively) following oxidative work-up, which resulted from selective addition to olefin **a**. Variation of conditions with either of these boranes failed to give any detectable amounts of the isomeric enol **5** (X = OH, addition to olefin **b**) previously characterized in the course of preparing diene 1. Intermolecular borane addition to olefin **b** in **1** was eventually evidenced through formation of diol **6b** ($H_2O_2$/NaOH oxidation, 42%) as a single diastereomer *via* employing an excess of 2 equivalents of thexylbromoborane and extended reaction times. Diene **1** with $BH_3$ or $BrBH_2$ and oxidation gave **6a** (X = OH, 70$^+$:30$^-$, **6a**:**6b**) as the major hydroboration product.



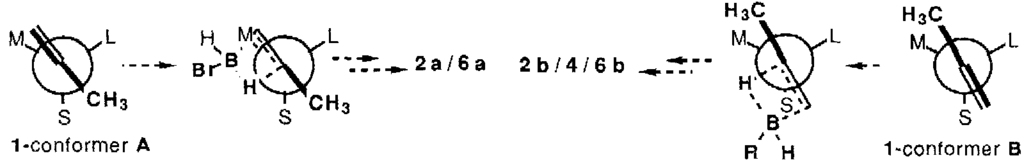
| Borane with **1** | **4** | **6b** |
|---|---|---|
| $ThxyBH_2$ (1eq) | - | 48% |
| ThxyBrBH (1eq) | 72% | 21% |
| ThxyBrBH (2eq) | - | 42% |
| 9-BBN(1eq to xs) | 68% | - |

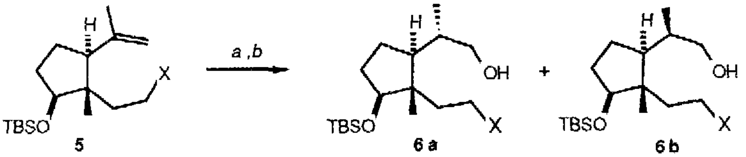
[X=OH]

$^a$9-BBN, THF; $^b$ThxBrBH, THF $^c$$H_2O_2$, NaOH

Efforts to expound upon this apparent reagent dependent stereoselectivity lead to molecular modeling[10] of diene **1**, generating two low energy conformations differing only in the orientation of the isopropenyl sidechain. Analysis of diene **1** in the context of the Houk perpendicular model[11] provides the possible transition states shown in Figure 1. Thexyl- and other hindered boranes would be expected to react through the transition state arising from conformer **B**, which minimizes interactions by positioning the sterically demanding alkyl group on boron in proximity to the "small" group (hydrogen) of the allylic carbon. The sterically less demanding monobromoborane and $BH_3$ are expected to react through the transition state arising from conformer **A**, which apparently reflects some subtle steric and electronic effects. Thus, *a transition state similar to conformer* **A** *translates to* the α-oriented C-10 methyl group and conformer **B** to the β-oriented C-10 methyl group. These observations are certainly consistent with the experimental findings of the "boron" addition of others,[12-14] and provide a satisfactory rationalization of the reagent dependent stereoselectivity. To further substantiate the facial selectivity of these different boron hydrides, enol **5** (X = OH) was hydroborated with 9-BBN and thexylborane then oxidized, selectively forming **6b**, analogous to results from stitching and riveting studies. With alcohol **5** (X = OH) the facial selectivity with sterically smaller boranes is altered such that **6b**, rather than the expected **6a**, is the major diol formed. The inferred hydroxyl group intramolecular delivery of borane in **5** (X = OH) is evidenced through comparison to the hydroboration of iodide **5** (X = I) with $BH_3$ where the reversal of epimers (**6a**:**6b**, 4:1, $^1$H NMR)[16] reappears. Other examples of this reversal in selectivity exist but do not appear to be of quite the magnitude of the reversal noted here.[12-14] Efforts are underway to exploit this annulation selectivity in natural products synthesis.

**Figure 1**

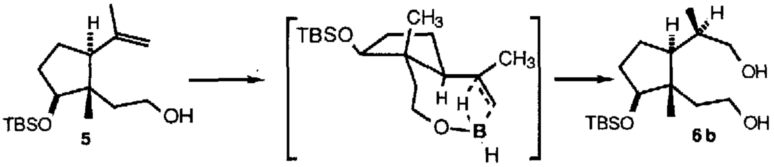




$^a$ThxBH$_2$, 9-BBN or $BH_3$ $^b$ $H_2O_2$/NaOH

| Borane with 5 | 6a:6b |
|---|---|
| $BH_3$ (1eq) | 1:7 |
| ThxyBH$_2$(1eq) | 1:11 |
| ThxyBH$_2$ (2eq) | 1:11 |
| 9-BBN(1eq to xs) | - :trace |

[X = OH]



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9. NIH (GM 34896) is gratefully acknowledged for support of this work.
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