

## CP-225,917 synthetic studies: unusual hydroboration regioselectivity influenced by remote functional groups

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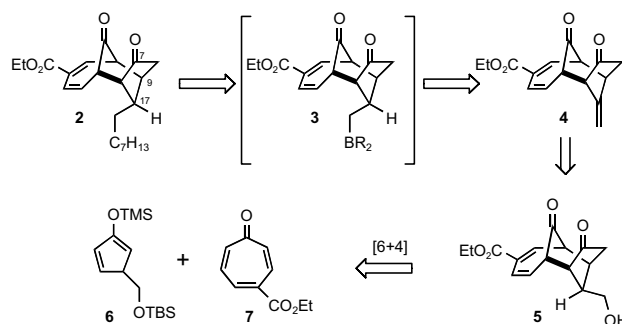
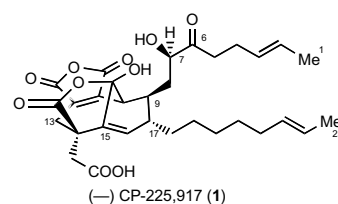
### Abstract

Hydroboration–oxidation of 1,1-disubstituted alkenes with borane–methyl sulfide complex in bridged tricyclic intermediates of the CP-225,917 ring system were observed to produce significant quantities of tertiary alcohol products. This net Markovnikov addition of water across an alkene is influenced by a combination of remote functional groups. Computations at the B3LYP/6-31G\* level of theory correctly predicted this reversal in selectivity and directed the selective removal of functional groups to restore selectivity for the primary alcohol.

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CP-225,917 and related compounds, isolated in the mid-1990s and shown to be modest inhibitors of squalene synthetase and Ras farnesyl transferase, are challenging targets for total synthesis and have spurred the development of numerous synthetic methods.<sup>1</sup> In the context of our own synthetic work on CP-225,917, we observed unexpected regioselectivity in the hydroboration of a 1,1-disubstituted alkene controlled by a unique array of remote functional groups. In this Letter, we describe an experimental and theoretical study of this unusual process. Furthermore, we show how these studies led to a revision of strategy, allowing for the installation of the C-17 stereocenter of CP-225,917.

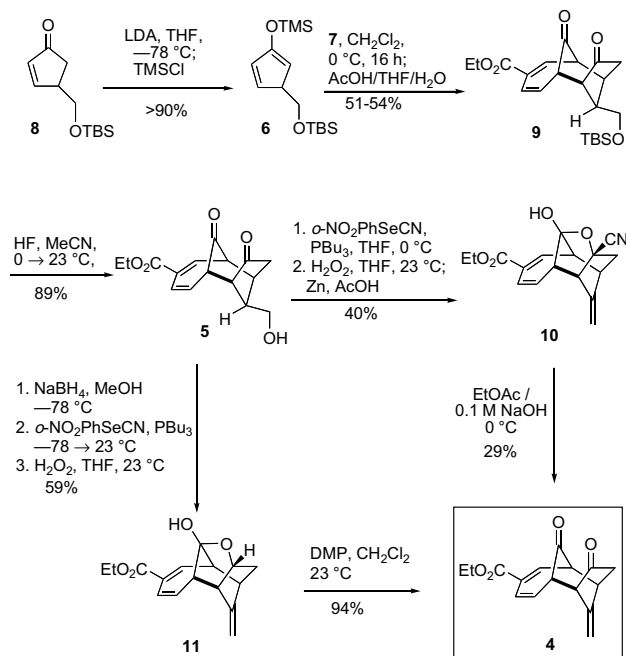
We previously reported the synthesis of the carbocyclic core of CP-225,917 using a [6+4] cycloaddition between substituted tropones and silyloxy dienes.<sup>2</sup> To extend this work toward a full synthesis of the natural product, we investigated the incorporation of the C-17 side chain via the [6+4] cycloaddition (Scheme 1). This process introduces the side chain with the incorrect stereochemistry, and we thus envisaged an elimination/hydroboration



Scheme 1. Retrosynthetic plan for the synthesis of diketone 2.

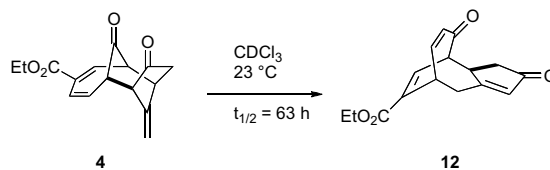
sequence on a nascent side chain to install the correct stereochemistry and set the stage for the incorporation of the full side chain, potentially through a metal-mediated cross coupling.

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Scheme 2. Synthesis of diketone **4**.

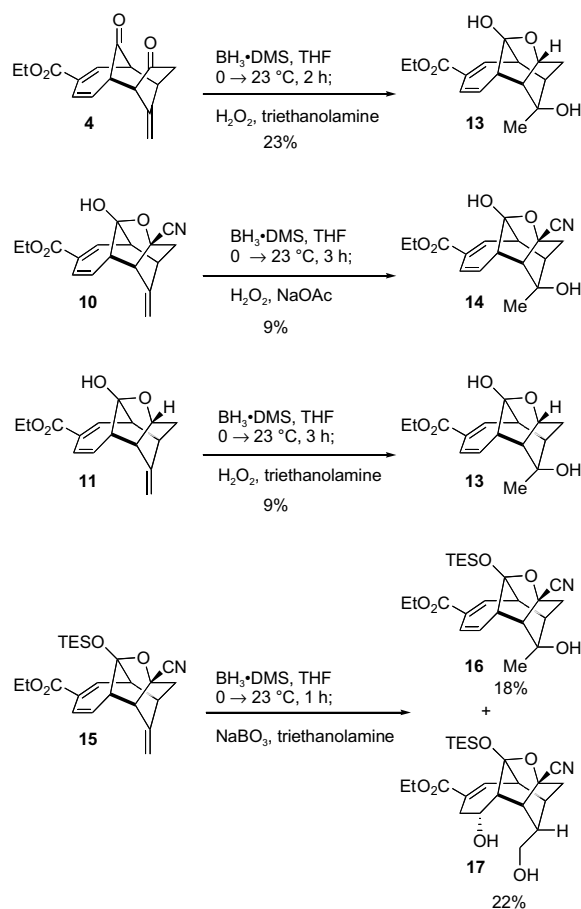
The hydroboration precursor was prepared starting with cyclopentadiene **6**, which was obtained by trapping the kinetic enolate of 4-(*tert*-butyldimethylsilyl)hydroxymethyl 2-cyclopentene-1-one (**8**) with TMSCl (Scheme 2).<sup>3</sup> [6+4]-Cycloaddition of **6** with tropone **7** proceeded smoothly at 0 °C over 16 h to provide cycloadduct **9** in 51–54% yield after acidic cleavage of the intermediate silyl enol ether. The product was isolated as a single diastereo- and regio-isomer. The primary alcohol was deprotected and subjected to selenide formation under the conditions of Grieco, followed by oxidation and elimination.<sup>4</sup> While the requisite 1,1-disubstituted alkene was readily formed, the product was isolated as a cyanohydrin hemiacetal **10**, which presumably formed from HCN generated during the selenation step. The free diketone could be liberated by treatment with cold, dilute NaOH but this was attended by considerable decomposition. Therefore, an alternative, higher-yielding route to **4** was developed where the diketone was reduced by NaBH<sub>4</sub> prior to the dehydration step. Reduction of diketone **5** followed by selenation/elimination gave alcohol **11** in 59% overall yield. Oxidation of alcohol **11** by Dess–Martin periodinane proceeded in 94% yield to afford diketone **4**.

The stability of exocyclic alkenes **4**, **10** and **11** was of concern, as it is known that cycloaddition of tropone with fulvenes results in analogous exocyclic alkenes which undergo Cope rearrangements at room temperature.<sup>5</sup> Diketone **4** slowly underwent rearrangement upon standing at room temperature for extended periods to afford Cope rearrangement product **12** (Scheme 3). The half-life for rearrangement of **4** was estimated at 63 h at 23 °C in CDCl<sub>3</sub> and was sufficiently long to allow **4** to be used in subsequent hydroboration reactions. The analogous Cope

Scheme 3. Cope rearrangement of diketone **4**.

rearrangement was not observed with either alcohol **11** or cyanohydrin **10**, even upon heating for 12 h at 60 °C.

With alkene **4** in hand, we were set to explore the key hydroboration step. Treatment of **4** with 9-BBN afforded only alcohol **11**, even in the presence of an excess of reagent. Similarly, attempted hydroboration of **4** with RhCl(PPh<sub>3</sub>)<sub>3</sub> and catecholborane resulted only in the reduction of the ketone. To our surprise, when alkene **4** was treated with BH<sub>3</sub>·DMS followed by oxidation with H<sub>2</sub>O<sub>2</sub>, the only identifiable product was tertiary alcohol **13**, isolated in 23% yield (Scheme 4).<sup>6</sup> Further examining this phenomenon, we found that hydroboration/oxidation of cyanohydrin **10** and alcohol **11** each afforded tertiary alcohols **14** and **13** in 9% yield as the sole identifiable products. Finally, hydroboration of silylated cyanohydrin **15** was significantly cleaner, affording both tertiary alcohol **16** and primary alcohol **17**, in 18% and 22% yields respectively. The stereochemistry of both **16** and **17** could be



Scheme 4.

assigned definitively by NOE.<sup>7</sup> In the case of diol **17**, the stereochemistry was consistent with intramolecular hydroboration of the diene by the intermediate 1° borane.

In all cases, the hydroboration process went to completion, with the remainder of the product mixtures consisting of more polar products, possibly diols and triols, which could not be isolated in pure form. Unfortunately, this precluded an accurate assessment of hydroboration selectivity. However, even if all unidentified products in the above reactions are primary alcohols, the hydroboration still produces between 9 and 23% of tertiary alcohol products in the cases studied. This stands in very stark contrast to hydroboration of other 1,1-disubstituted olefins which generally provide >99:1 selectivity for the primary alcohol.<sup>8,9</sup>

Hydroboration selectivity can be influenced by strong electron withdrawing groups (e.g., perfluoroalkyl) and in some instances anchimeric assistance has been proposed.<sup>10,11</sup> In the present case, tertiary alcohol formation does not appear to result from anchimeric assistance from either heteroatom functionality or the diene due to geometric constraints and the overall stereochemical course of the reaction.<sup>12</sup> This strongly suggests an electronic influence on the reaction. However, in all cases studied, any electron withdrawing groups are insulated by at least one carbon from the exocyclic olefin and thus the observation of up to 23% tertiary alcohol was quite striking.<sup>13</sup> To gain insight into this unusual effect, transition states were modeled using density functional theory at the B3LYP/6-31G\* level.<sup>14</sup> This level of theory has recently proven useful for modeling hydroboration reactions in both simple and complex systems.<sup>15</sup>

Using simplified trienediketone **A** (Fig. 1), a stable  $\pi$ -complex with  $\text{BH}_3$  was found and transition states leading from this  $\pi$ -complex to both the 1° and 3° alkylboranes could be located (Fig. 2). The computations indicated that the transition state leading to the 3° borane was 0.23 kcal/mol lower in enthalpy. For comparison, hydroboration of propene and methylenecyclopentane favors the formation of the 1° borane product by 2.35 and 5.10 kcal/mol, respectively, using the same level of theory. Incorporation of a cyano group as a model for the ethyl ester (structure **B**), increased the preference for the 3° borane by about 0.5 kcal/mol. The computations also showed that cyanohydrin **C** and acetal **D**, analogous to **10** and **11**, respectively, were both predicted to be selective for the 3° product.

Further information on the source of selectivity was revealed by systematic removal of functional groups. Removal of either ketone or the diene in **B** increased the selectivity for the 1° alkylborane (structures **E**, **F** and **H**). Of the three groups, the diene had the largest influence, followed by the ketone in the two-carbon bridge. The effects of each functional group were roughly additive as, for example, removal of both ketones (e.g., **G**) produced a change in activation enthalpy of 1.53 kcal/mol relative to **B**, similar to the sum of the changes in ketones **E** (0.79 kcal/mol) and **F** (0.60 kcal/mol). Removal of all functional groups resulted in a predicted  $\Delta\Delta H^\ddagger$  of 3.05 kcal/mol (**I**), strongly favoring the expected 1° borane.

While it was not possible to directly correlate with our experimental results due to low mass balance, the modeling results do clearly indicate that the source of significant 3° alcohol formation from **4**, **10**, **11**, and **15** originates from a combination of electron withdrawing groups flanking the exocyclic alkene. These presumably destabilize the transition state leading to the 1° borane, in which there is a buildup of positive charge on the internal carbon. Indeed, we observed a relationship between the charge on the internal carbon and the predicted  $\Delta\Delta H^\ddagger$ , with structures least able to accommodate charge in the 1° transition state affording the highest selectivity for 3° borane.<sup>16</sup> It is important to point out that the loss of selectivity results from additive effects from remote functional groups, not from a single strong electron withdrawing group directly attached to the alkene.

With results from the computational studies in hand, the diene in **4** was removed to alter the selectivity of the hydroboration (Scheme 5). Hydrogenation of the initial [6+4] cycloadduct **9** afforded **18** as an inseparable 2:1 mixture of diastereomers at the ester position. Selenation and elimination,

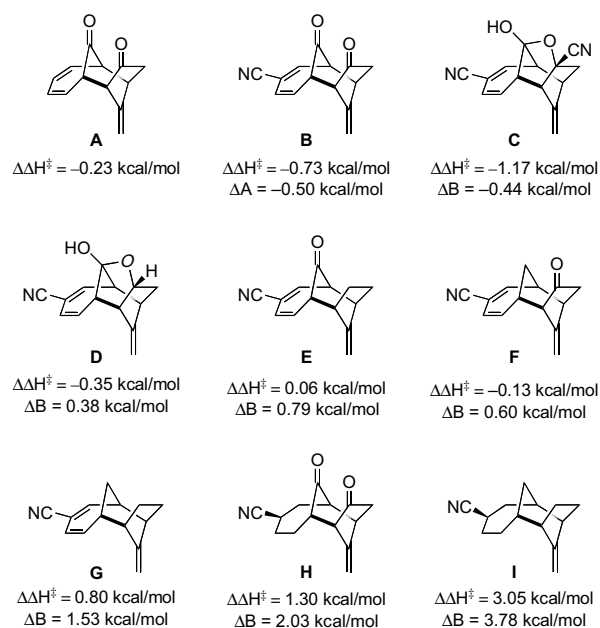


Fig. 1. Influence of structure on calculated hydroboration regioselectivity.  $\Delta\Delta H^\ddagger = \Delta H^\ddagger$  (1° borane formation) –  $\Delta H^\ddagger$  (3° borane formation).  $\Delta A$  = change in  $\Delta\Delta H^\ddagger$  relative to structure A.  $\Delta B$  = change in  $\Delta\Delta H^\ddagger$  relative to structure B.

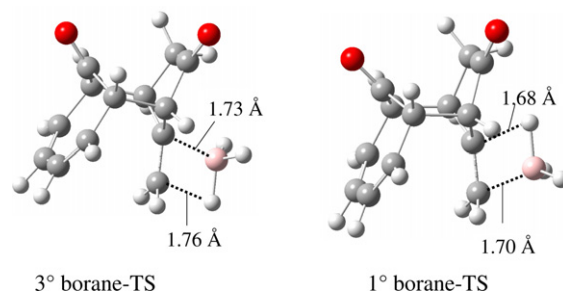
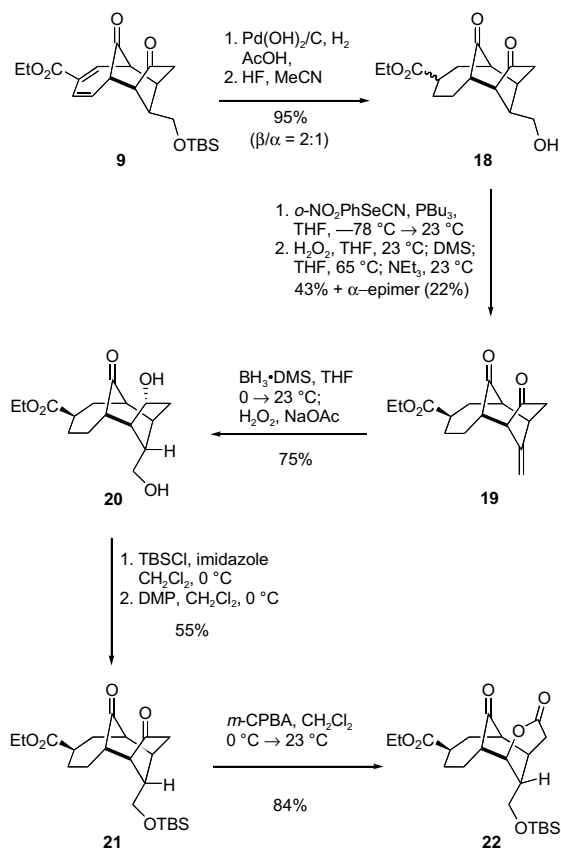


Fig. 2. Computed transition states for structure A.



Scheme 5.

as before, afforded diastereomeric exocyclic alkenes which could be separated by chromatography. In this sequence, cyanohydrin formation was again observed, but the diketone could easily be restored by treatment with triethylamine. Subjecting alkene **19** to hydroboration/oxidation now afforded the desired primary alcohol **20** in 75% yield with no trace of the tertiary alcohol product observed. In analogy with our previous studies, we found that diketone **21** underwent a site- and regioselective Baeyer–Villiger reaction to form lactone **22**, which contains the proper stereochemistry of the nascent C-9 and C-17 sidechains of CP-225,917.<sup>2,17</sup>

In conclusion, we have observed that a unique array of functional groups can conspire to significantly alter regioselectivity in hydroborations of 1,1-disubstituted olefins in caged ring systems. In the current context, high regioselectivity in the expected direction could be restored by removing a single functional group. The application of this strategy toward the synthesis of CP-225,917 is ongoing and will be reported in due course.

### Acknowledgments

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### Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.11.118.

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- See [Supplementary data for details](#). No significant charge differences were observed in the transition states leading to 3° boranes.
- Diketones of form **9** do not readily undergo Baeyer–Villiger oxidation due to steric hinderance about the ketone.