Communication

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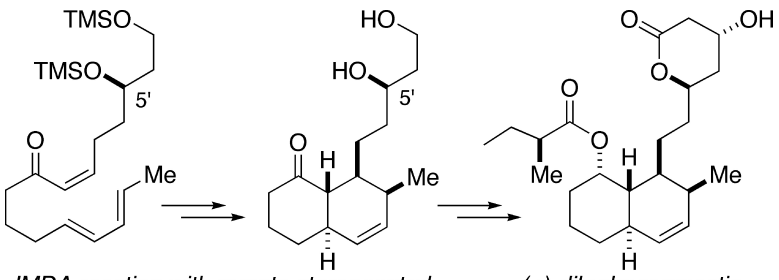

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Remote Asymmetric Induction in an Intramolecular Ionic Diels−Alder Reaction: Application to the Total Synthesis of (+)-Dihydrocompactin

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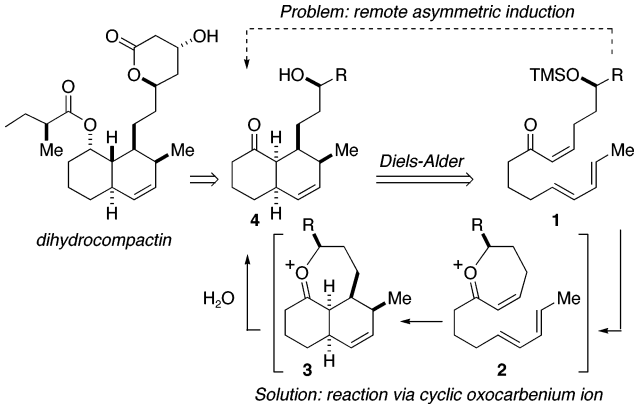
The mevinic acids are a medicinally important class of compounds that have been the subject of numerous synthetic studies.[1] One of these compounds, (+)-dihydrocompactin (Scheme 1), was originally isolated as a minor constituent of the fermentation broth of *Penicillium brevicompactum*[2,3] and contains an octahydronaphthalene (octalin) unit and a δ-lactone joined by an ethylene bridge. One of the challenges in synthesizing this molecule is controlling the stereochemistry between these two remote units, and most syntheses of mevinic acids have avoided this issue by coupling enantiomerically enriched fragments, or racemic fragments, and separating the resulting diastereomers.[4] In this communication, we report a synthesis of (+)-dihydrocompactin that proceeds with remote stereocontrol via an intramolecular ionic Diels−Alder cycloaddition as shown in the retrosynthesis depicted in Scheme 1. While this is arguably the most direct approach to this molecule, it has not been described in the literature because it requires that the cycloaddition proceed with remote stereocontrol. The Diels−Alder reaction is not intrinsically capable of this; however, we have previously described asymmetric ionic Diels−Alder reactions,[5,6] and we wished to apply this method to the synthesis of (+)-dihydrocompactin. We reasoned that intramolecular cycloaddition of oxocarbenium ion **2** could proceed to provide **3**, which upon hydrolysis would provide the (+)-dihydrocompactin core (**4**) with stereocontrol due to the conformational constraints of the cyclic dieneophile. This species, in turn, could be prepared in situ from the acyclic TMS ether **1**, thereby enabling the synthesis of **4** by this direct strategy. The broader significance of this study is that this method allows for the control of stereochemistry between remote sites in an intramolecular Diels−Alder reaction in a systematic way, thereby enhancing this already powerful reaction.

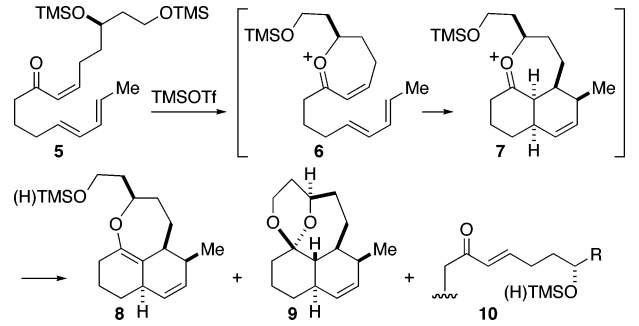
Our synthesis of the key intramolecular Diels−Alder substrate **5** is described in the Supporting Information, and with this compound in hand, we turned our attention to studying the cycloaddition. Our plan was to induce formation of the desired oxocarbenium ion by subjecting compound **5** to the Noyori ketalization reaction conditions.[7] This reaction involves treatment of a TMS ether and a ketone or aldehyde with TMSOTf and likely proceeds via the corresponding oxocarbenium ion. In the event, we were pleased to find that treatment of **5** with 5% TMSOTf in CH_2Cl_2 at −20 °C provided a mixture of two Diels−Alder adducts (**8** and **9**) as well as compound **10** in which the enone has undergone isomerization from cis to trans (Scheme 2). Cycloadducts **8** and **9** are formed with remote stereocontrol as a 9:1 mixture of diastereomers, presumably from intermediate **7** either by loss of a proton or by trapping of the oxocarbenium ion by the pendant TMS ether, respectively. The *trans*-enone (**10**) cannot form a cyclic oxocarbenium ion and as such does not provide any cycloadducts under these conditions, thereby simplifying the analysis of the products.

While this reaction worked well on small scale, we found that it provided erratic yields on gram scale. Triflic acid is produced as a byproduct in the formation of **8**, and we suspected that variable

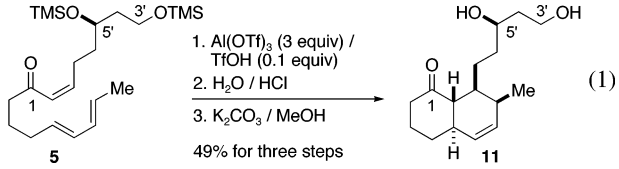
Scheme 1



Scheme 2



amounts of acid in the reaction mixture were responsible for this behavior. After careful experimentation, we found the combination of $Al(OTf)_3$ (3 equiv) and triflic acid (0.1 equiv) reproducibly provided a 70% yield of cycloadducts **8** and **9** in a 1:1 ratio along with 14% of **10** on gram scale. As such, treatment of **5** with this acid combination followed by acid-catalyzed hydrolysis of the resulting cycloadducts provided a mixture of *cis*- and *trans*-octalones, which upon treatment with K_2CO_3 in methanol underwent base-catalyzed epimerization to provide the *trans*-octalone (**11**) as a 9:1 mixture of diastereomers in 49% yield for the three-step sequence (eq 1). The structure of this material was confirmed by single-crystal X-ray analysis.



(1)

The stereochemical outcome of this reaction is such that the product is derived from attack of the diene from the same face as the pendant side chain in the cyclic oxocarbenium ion structure

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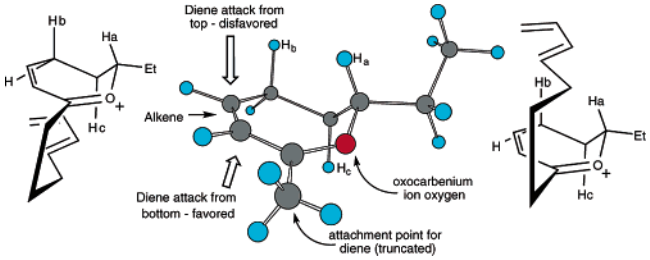
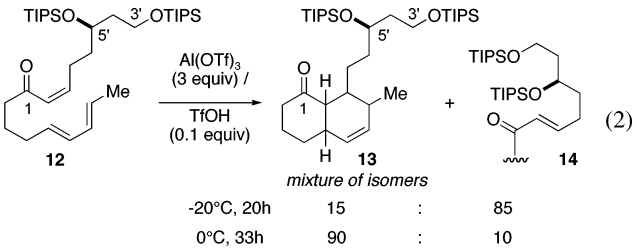


Figure 1. AM1 conformation of **6** and cycloaddition transition states.

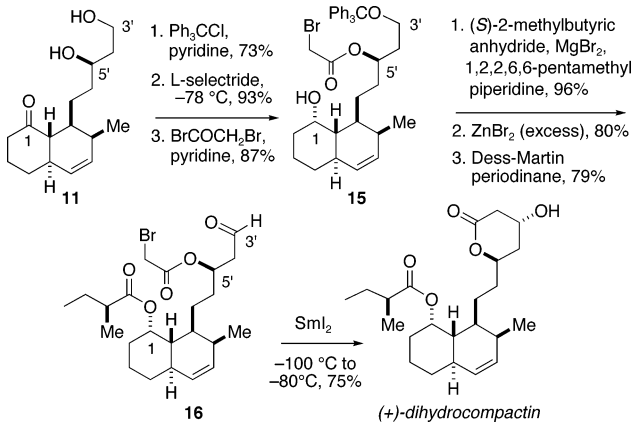
(Figure 1). This seemingly contrasteric result can be understood by considering the preferred conformation of the cyclic oxocarbenium ion. The lowest energy conformation of this intermediate was determined via a Monte Carlo conformational search using the AM1 method.[8] The four sp^2 centers within the seven-membered ring are nearly coplanar, while the remaining three sp^3 atoms adopt a more staggered conformation. The alkyl substituent on the ring splays outward from the periphery of the molecule and does not interfere with the incoming diene. However, the three sp^3 hybridized atoms contain three pseudoaxial hydrogens (Ha, Hb, and Hc in Figure 1) that could potentially interfere with the approach of the diene. Of these, Ha and Hb point toward the top face of the structure as depicted, and Hc points toward the bottom. We hypothesize that Ha and Hb more effectively block the top face of the molecule and thereby dictate that the diene approach from the bottom face.[9]

To probe for the intermediacy of an oxocarbenium ion, we studied the corresponding bis-TIPS ether (**12**), which cannot form an oxocarbenium ion under our optimized reaction conditions ($Al(OTf)_3$/TfOH, CH_2Cl_2, −20 °C, eq 2). Under these conditions, this compound provides an 85:15 mixture of the *trans*-alkene **14** with both TIPS ethers intact and the Diels−Alder adducts **13** as a mixture of diastereomers. At 0 °C, a 10:90 mixture of **14** and **13**, again as a mixture of diastereomers, is observed. The decreased reactivity and selectivity of **12** as compared to that of **5** suggests that these compounds react via different mechanisms and that **5** reacts via the corresponding oxocarbenium ion.



Completion of the synthesis was accomplished as described in Scheme 3. The primary alcohol of compound **11** was selectively protected as the trityl ether (73%) and the ketone at C-1 reduced with L-selectride to the hindered axial alcohol (93%).[1] The less hindered hydroxyl group at C-5′ was then acylated with bromoacetyl bromide (87%) to provide compound **15**, and the hindered alcohol at C-1 was acylated with (*S*)-2-methylbutyric anhydride using Vedejs' conditions (96%).[10] Deprotection of the trityl ether with excess zinc bromide[11] provided the primary alcohol at C-3 (80%), which was oxidized with the Dess−Martin periodinane[12] to aldehyde **16** (79%). Compound **16** then underwent a SmI_2 promoted intramolecular Reformatsky reaction as described by Molander[13] to provide (+)-dihydrocompactin in 75% yield as a 7:1 mixture of isomers at C-3′, which was crystallized to homogeneity.[14]

Scheme 3



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Supporting Information Available: Experimental procedures for the synthesis and characterization of all new compounds as well as ^1H and ^{13}C spectra for selected compounds, and X-ray crystallography data for compound **11**. This material is available free of charge via the Internet at http://pubs.acs.org.

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