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Studies into the Stereoselectivity of Tartrate-Derived Dienophiles

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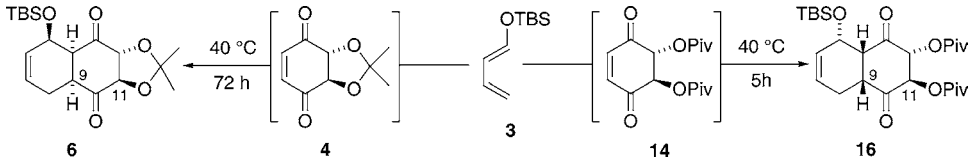
ABSTRACT



Diels−Alder reactions of 1-(*tert*-butyldimethylsiloxy)-1,3-butadiene (3) with three C2 symmetric dienophiles derived from tartaric acid have been examined. Complementary diastereoselectivity is observed depending on the nature of the 1,2-diol protecting group incorporated in these dienophiles.

The Diels−Alder reaction has enjoyed immense popularity as a synthetic method since its discovery over 75 years ago.[1] A major reason for this extraordinary level of interest from the synthetic community is the seemingly endless possibilities of inter- and intramolecular variations of this reaction in addition to the high levels of stereoselectivity often achieved in this reaction.[2] Even relatively remote stereocenters have been shown to induce high levels of stereoselectivity.[3] Despite extensive investigations into this reaction process, unexpected and/or unpredictable cases of Diels−Alder stereoselectivity have been occasionally encountered due to seemingly subtle balances of steric and electronic effects dictating overall stereoselectively. In this communication, we describe a study of such a Diels−Alder cycloaddition in connection with our ongoing efforts toward the total synthesis of members of the hibarimicin group of antitumor antibiotics.

During the course of designing a synthetic approach toward the AB and GH ring systems of hibarimicin and congeners such as HMP−Y1 (**1**), we proposed a stereoselective intermolecular Diels−Alder reaction between tartrate-derived dienophile **4** and 1-(*tert*-butyldimethylsiloxy)-1,3-butadiene (**3**)[4] as the key ring-forming step.[5] In this cycloaddition process we required bond formation to occur with good stereocontrol leading to the desired relative stereochemistry between C(9) and C(11) as indicated in cis Decalin **2**. Examination of molecular models shows enedione **4** to be locked in a half-chair conformation with the two hydrogens located at the ring fusion of the bicyclic system occupying axial positions (**4**, Figure 2). The Diels−Alder

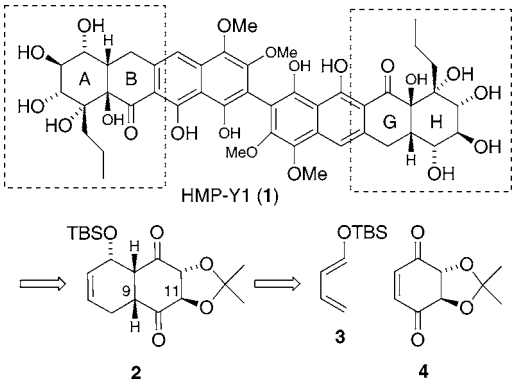


Figure 1. Retrosynthetic analysis of the AB/GH ring system of HMP−Y1 (**1**).

(1) Reviews: (a) Nicolaou, K. C.; Snyder, S. A.; Montagnon, T.; Vassilikogiannakis *Angew. Chem., Int. Ed.* **2002**, *41*, 1668−1698. (b) Corey, E. J *Angew. Chem., Int. Ed.* **2002**, *41*, 1650−1667.

(2) (a) Intramolecular Diels−Alder reactions: Roush, W. R. In *Comprehensive Organic Synthesis*; Trost B. E., Ed.; Pergamon Press: Elmsford, NY, 1991; Vol. 5, pp 513−550. (b) Intermolecular Diels−Alder reactions: Oppolzer, W. In *Comprehensive Organic Synthesis*; Trost B. E., Ed.; Pergamon Press: Elmsford, NY, 1991; Vol. 5, pp 316−399.

(3) (a) Angell, E. C., Fringuelli, F.; Minuti, L.; Pizzo, F.; Porter, B.; Taticchi, A.; Wenkert, E. *J. Org. Chem.* **1985**, *50*, 4686−4690. (b) Angell, E. C., Fringuelli, F.; Pizzo, F.; Porter, B.; Taticchi, A.; Wenkert, E. *J. Org. Chem.* **1986**, *51*, 2642−2649.

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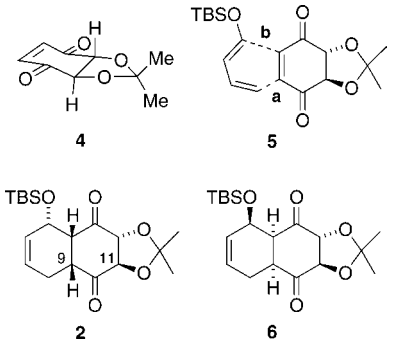


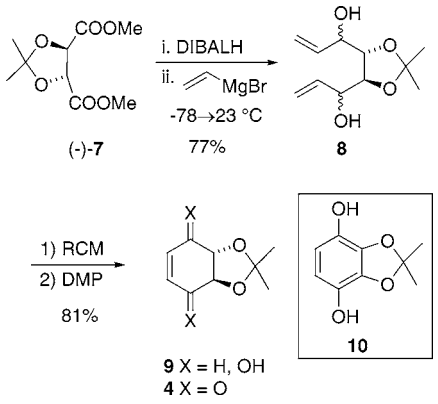
Figure 2. Stereochemical analysis of Diels−Alder reaction between **3** and **4**.

cycloaddition between **3** and **4** may proceed by way of four different transition state structures, two endo and two exo structures. Initially, we considered only the endo approach to be viable, and our rationale leading to the prediction that diastereomer **2** would be the major reaction product was as follows. First, on the basis of considerations of frontier molecular orbitals, we anticipated that the transition-state structure leading to the cycloaddition product would be asynchronous with bond **a** further developed relative to bond **b** (cf. **5**).[6] Next, we anticipated, on the basis of stereoelectronic considerations, that the first formed bond (bond **a**) would favor a pseudoaxial approach, leading us to predict formation of the desired cycloadduct (**2**) instead of the diastereomeric product **6**.[7] A second major concern was the questionable stability of diketone **4** since tautomerization could readily lead to the corresponding, thermodynamically more stable dihydroquinone.[8]

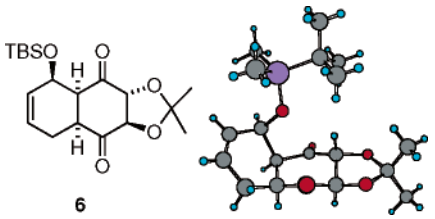
Following the procedure of Fürstner and co-workers, we converted dimethyl tartrate (−)-**7** to diol **8** starting with a one-pot reduction/vinyl Grignard addition to afford diol **8** in 77% yield.[9] As reported earlier, diol **8** underwent a ring-closing metathesis reaction mediated by Grubbs second-generation catalyst to afford cyclohexene **9** in 90−95% yield. Next, we examined the oxidation of **9** to enedione **4** under Swern oxidation conditions.[10] In this case, we were disappointed to observe exclusive production of hydroquinone **10** (45% yield). Fortunately, oxidation of **9** with Dess−Martin periodinane proceeded smoothly to give enedione **4** in 84% yield.[11] Enedione **4** proved to be stable to silica gel chromatography and could be stored at −20 °C for several months without any sign of isomerization to **10** observed.

The Diels−Alder reaction of enedione **4** with 1-(*tert*-butyldimethylsiloxy)-1,3-butadiene (**3**) was examined using several different solvent and temperature conditions. Optimal conditions reacted enedione **4** with 1.5 equiv of diene **3** in dichloromethane at 40 °C for 3 days to afford a single (>95:5) crystalline (mp 185−187°) cycloadduct in 60−68% yield. The stereochemistry of this adduct was unambiguously assigned by single-crystal X-ray analysis and much to our surprise proved to be the unanticipated diastereomer **6** (Scheme 2). It was later determined that microwave irradiation (100 W) of a neat mixture of enedione **4** and siloxydiene **3** (4 equiv) heated to 70 °C reduced the reaction time to 10 h and increased the chemical yield to 84%.[12]

Scheme 1



Scheme 2



The [4 + 2] cycloaddition of diene **3** and dienophile **4** proceeded with anticipated endo selectivity; however, the observed *facial* selectivity was the reverse of that anticipated on the basis of our earlier discussion of stereoelectronic control (Figure 2) and required for the synthesis of the AB/GH ring system of the hibarimicins. We therefore elected to examine alternate diol protecting groups in hope of altering the course of the facial selectivity of the Diels−Alder reaction. Toward this end, we prepared dienophiles **11** and **14**,[13] where the diol was protected as a bis-TBS ether and

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(5) For an earlier approach to this ring system, see: Kim, K.; Maharoof, U. S. M.; Raushel, J.; Sulikowski, G. A. *Org. Lett.* **2003**, *5*, 2777−2780.
(6) Dewar, M. J. S. *J. Am. Chem. Soc.* **1984**, *106*, 209−215.
(7) (a) Capaccio, C. A. I.; Varela, O. *J. Org. Chem.* **2002**, *67*, 7839−7846. (b) Primeau, J. L.; Anderson, R. C.; Fraser-Reid, B. *J. Am. Chem. Soc.* **1983**, *105*, 5874−5879.
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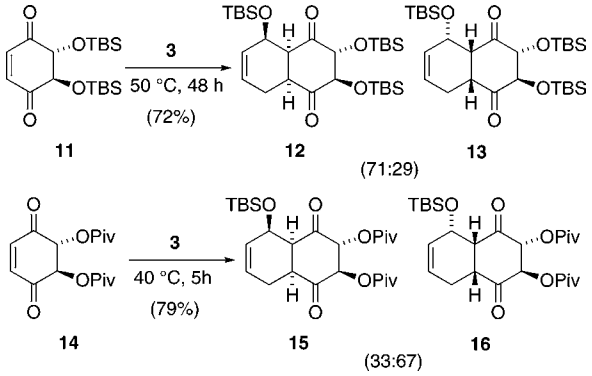
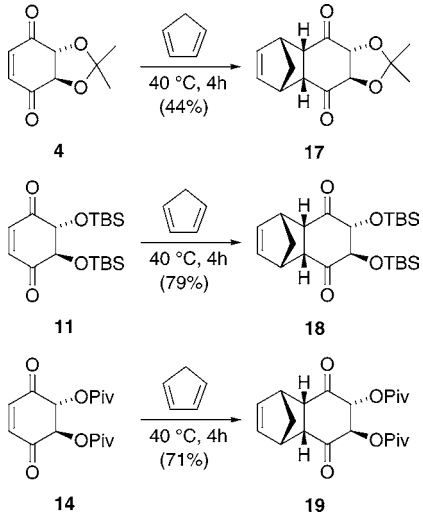
(11) (a) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155−4156. (b) Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 7277−7287.
(12) Kappe, C. O. *Angew. Chem., Int. Ed.* **2004**, *43*, 6250−6284.

Scheme 3



bis-pivaloate, respectively (Scheme 3). Reaction of enedione **11** with diene **3** resulted in a 71:29 ratio of Diels−Alder adducts **12** and **13**, again favoring production of the undesired relative stereochemistry between C9 and C11 (**12**). *In contrast, heating a solution of enedione **14** and diene **3** in dichloromethane for 5 h produced a 33:67 mixture of diastereomers, now favoring the desired stereoisomer **16**.* The stereochemistry of cycloadducts **12** and **15** was assigned by chemical correlation with Diels−Alder adduct **6**. The second Diels−Alder adduct produced in each reaction (i.e., adducts **13** and **16**) was assumed to be the diastereomeric *endo*. While there existed a probability that the second isomer may be one of two *exo* adducts, we discounted this possibility on the basis of the observed propensity for endo addition of cyclopentadiene to all three dienophiles **4**, **11**, and **14** (Scheme 4).[14]

Scheme 4



The observed reversal of stereoselectivity of dienophiles **4** (Scheme 2) and **14** (Scheme 3) led to a unique solution to the stereochemical problem of establishing the correct relative stereochemistry between C9 and C11 posed by HMP−Y1 (**1**) and the hibarimicins (Figure 1). To arrive at an explanation for the differences in stereoselectivity of the two dienophiles we examined molecular models. Dienophile **4** is a rigid bicyclic system, and assuming a highly asynchronous transition state we arrived at two possible diastereomeric transition-state structures (**20** and **21**, Figure 3). Transition

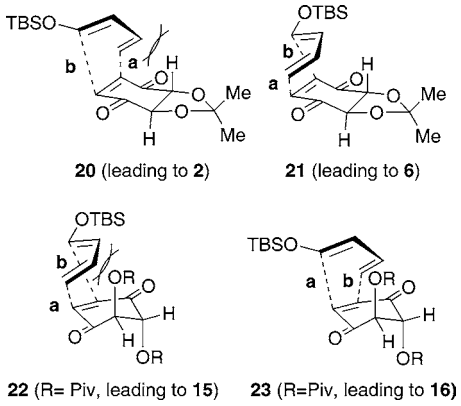


Figure 3. Transition-state structures.

state **20** (leading to the minor adduct **2**) apparently suffers, due to the asymmetry of bond formation, from a steric interaction between the C2 diene carbon and ring fusion hydrogen. In the case of transition state **21**, the asymmetry of bond formation matches the chirality of the C2 dienophile resulting in reduction of steric interactions relative to structure **20**. Dienophile **14** may favor the two-ester groups occupying axial positions, as this conformation reduces gauche interactions.[15] Then, following an analysis parallel to transition states **20** and **21**, we may conclude that structure **23** is favored leading to cycloadduct **16** as the major product.

In summary, we have observed complementary facial selectivity in the addition of diene **3** to C2 symmetric dienophiles **4** and **14**. Capitalizing on these results, progress on the total synthesis of HMP−Y1 (**1**) will be reported in due course.

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Supporting Information Available: Full characterization data and select experimental procedures for **4**, **6**, **8**, **9**, and **11**−**19**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(13) Preparation of **11** and **14** starting from enedione **4** is described in Supporting Information.

(14) Stereochemical assignments of **17**−**19** based on NOESY analysis.

(15) Hosoya, T.; Ohashi, Y.; Matumoto, T.; Suzuki, K. *Tetrahedron Lett.* **1996**, *37*, 663−666.