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Diverging Stereochemical Pathways in an Intramolecular Diels–Alder Reaction Determined by Dienophile Structure

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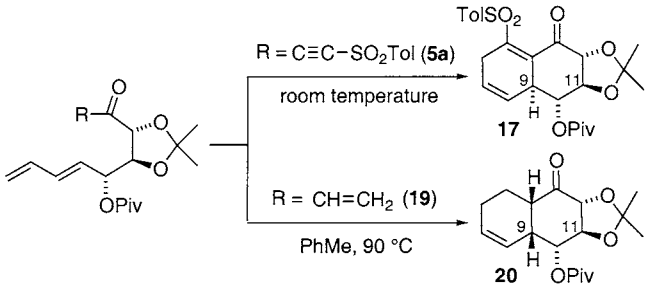
ABSTRACT



Intramolecular Diels–Alder cycloaddition of tolylsulfonyl alkynone 5a and vinyl ketone 19 led to single isomers with opposite diastereoselectivity. Decalin 20 incorporates the correct C(9)–C(11) stereochemical array for a projected synthesis of HMP-Y1 (1).

Hibarimicins A, B, C, D, and G are among the most complex aromatic polyketide dimeric microbial secondary metabolites isolated (Figure 1).[1,2] In addition to unique structural features, the hibarimicins possess important biological activity, specifically inhibiting protein tyrosine kinase activity with little effect on protein kinases A and C. In an effort to elucidate details of the biosynthetic pathway leading to the hibarimicins, Kajiura and co-workers subjected the producing strain, *Microbispora rosea* subsp. *hibaria* TP-A0121, to random mutagenesis.[3] Several of the resulting blocked mutants were cultured and found to produce a series of novel metabolites related to the biogenesis of the hibarimicins

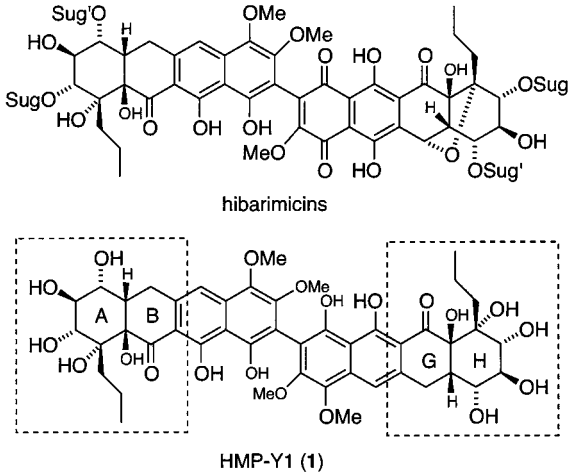


Figure 1. Structure of hibarimicins and HMP-Y1 (**1**).

(1) (a) The structure of Hibarimicin B is identical with that of angelmicin B, see: Uehara, Y.; Li, P.-M.; Fukazawa, H.; Mizuno, S.; Nihei, Y.; Nishio, M.; Hanada, M.; Yamamot, C.; Furumai, T.; Oki, T. *J. Antibiot.* **1993**, *46*, 1306−1308. (b) Hori, H.; Higashi, K.; Ishiyama, T.; Uramoto, M.; Uehara, Y.; Oki, T. *Tetrahedron Lett.* **1996**, *37*, 2785−2788.

(2) (a) Kajiura, T.; Furumai, T.; Igarashi, Y.; Hori, H.; Higashi, K.; Ishiyama, T.; Uramoto, M.; Uehara, Y.; Oki, T. *J. Antibiot.* **1998**, *51*, 394−401. (b) Hori, H.; Igarashi, Y.; Kajiura, T.; Furumai, T.; Higashi, K.; Ishiyama, T.; Uramoto, M.; Uehara, Y.; Oki, T. *J. Antibiot.* **1998**, *51*, 402−417.

(3) (a) Kajiura, T.; Furumai, T.; Igarashi, Y.; Hori, H.; Higashi, K.; Ishiyama, T.; Uramoto, M.; Uehara, Y.; Oki, T. *J. Antibiot.* **2002**, *55*, 53−60. (b) Igarashi, Y.; Kajiura, T.; Furumai, T.; Hori, H.; Higashi, K.; Ishiyama, T.; Uramoto, M.; Uehara, Y.; Oki, T. *J. Antibiot.* **2002**, *55*, 61−70. (c) Hori, H.; Kajiura, T.; Igarashi, Y.; Furumai, T.; Higashi, K.; Ishiyama, T.; Uramoto, M.; Uehara, Y.; Oki, T. *J. Antibiot.* **2002**, *55*, 46−52.

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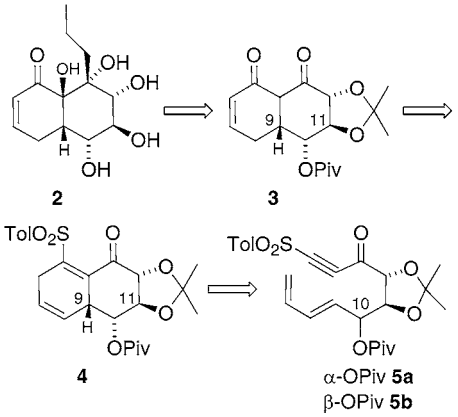
including the symmetrical aglycon HMP-Y1 (**1**) (hibarimicin-mutant product Y1). A common structural feature shared by HMP-Y1 (**1**) and the more complex hibarimicins is the highly substituted AB and GH ring systems (Figure 1). In contemplating the development of a synthetic program directed toward the hibarimicins and related metabolites such as HMP-Y1 (**1**) we considered the development of a stereocontrolled synthesis of the AB and GH ring systems a major sub-goal. To this end, we have investigated the intramolecular Diels−Alder cycloaddition of tolylsulfonyl alkynones **5a** and **5b** (Scheme 1). We anticipated that hydrolysis of cycloadduct

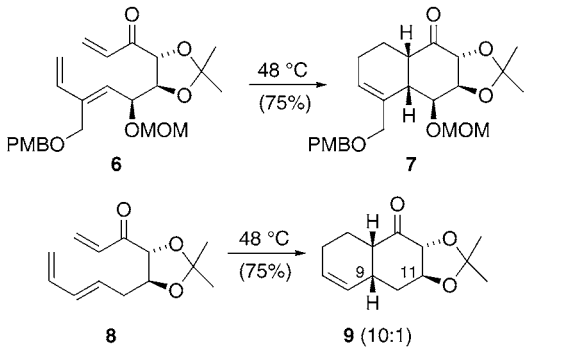
Scheme 1



4 would produce diketone **3**, an intermediate that in principle could be manipulated to ketone **2** based on earlier investigations on the hibarimicins reported from our group.[4] *An important consideration in our proposed Diels−Alder cycloaddition was the emergence of the C(9) stereocenter in the configuration shown.*

Among the factors to be taken into account to obtain excellent stereoselectivity in intramolecular Diels−Alder reactions are the incorporation of steric and rigidifying structural features within the tether joining the diene and dienophile. In earlier work Fallis demonstrated that the incorporation of a trans isopropylidene acetal β to both the diene and dienophiles serves to limit the flexibility of the side chain. This added rigidity results in an enhancement of the interaction between the reacting diene and dienophile and induces excellent diastereoselectivity for the production of substituted Decalins.[5] For example, heating triene **6** in refluxing dichloromethane resulted in exclusive production of endo adduct **7** (Scheme 2). In this case $A_{1,3}$ interaction between the MOM ether and PMB carbinol ether groups may contribute to the observed diastereoselectivity. Of greater significance to our planned approach to the AB and GH ring system of HMP-Y1 was the cycloaddition of triene **8** to give

Scheme 2



cis Decalin **9** with the desired sense of asymmetric induction between the acetonide group and ring fusion hydrogen (cf. C(9) and C(11) in **3** and **9**). We also planned to evaluate the effect of the configuration of the neighboring C(10) allylic oxygen on the stereoselectivity of the cycloaddition process (**5a** and **5b**). An intramolecular Diels−Alder reaction reported by Hirama and Uei leading to a substituted Decalin en route to compactin showed that an allylic oxygen adjacent to the diene component of the Diels−Alder reaction induced the C(9)−C(10) relative stereochemistry shown in **4**.[6] We thus anticipated that isomer **5a** would constitute a matched case and give higher selectivity for the desired cycloadduct (**4**). Finally, our synthetic plan will also serve to evaluate for the first time an arylsulfonyl alkynone as a dienophile in a Diels−Alder reaction.[7]

Our route to arylsulfonyl alkynones **5a** and **5b** started with aldehyde **10**, which was prepared in four steps from L-tartaric acid following a slight modification of a procedure reported by Kibayashi.[8] Addition of 1-lithio-1,3-butadiene[9] to **10** gave a 70:30 mixture of allylic alcohols **11** and **12**, a ratio of stereoisomers in accord with related aldehyde addition reactions.[10] We elected to first pursue the synthesis of arylsulfonyl alkynone **5b**, with the expectation that we would observe the desired sense of asymmetric induction in the key intramolecular Diels−Alder reaction based on the earlier report from the Fallis group on a related Diels−Alder substrate (**6** → **7**, Scheme 2). Allylic alcohol **11** was converted to aldehyde **13** by a standard three-step procedure. A key transformation was the addition of the ethynyl *p*-tolyl sulfone anion to aldehyde **13**. Ethynyl *p*-tolyl sulfone has served as an excellent Michael acceptor and dienophile on numerous occasions.[11] However, there are no examples of the derived anion adding to carbonyl compounds. We

(4) Lee, C. S.; Audelo, M. Q.; Reibenspies, J.; Sulikowski, G. A. *Tetrahedron* **2002**, *58*, 4403−4409.

(5) (a) Millan, D. S.; Pham, T. T.; Lavers, J. A.; Fallis, A. G. *Tetrahedron Lett.* **1997**, *38*, 795−798. (b) Wong, T.; Wilson, P. D.; Woo, S.; Fallis, A. G. *Tetrahedron Lett.* **1997**, *38*, 7045−7048. (c) Melekhov, A.; Forgione, P.; Legoupy, S.; Fallis, A. G. *Org. Lett.* **2000**, *2*, 2793−2796.

(6) Hirama, M.; Uei, M. *J. Am. Chem. Soc.* **1982**, *104*, 4251−4253.

(7) Arylsulfonyl alkynoates: (a) Shen, M.; Schultz, A. G. *Tetrahedron Lett.* **1981**, *22*, 3347−3350. (b) Corey, E. J.; Jardine, P. D.; Rohloff, J. C. *J. Am. Chem. Soc.* **1988**, *110*, 3672−3673. (c) Pangka, V. R.; Morgan, A. R.; Dolphin, D. *J. Org. Chem.* **1986**, *51*, 1094−1100.

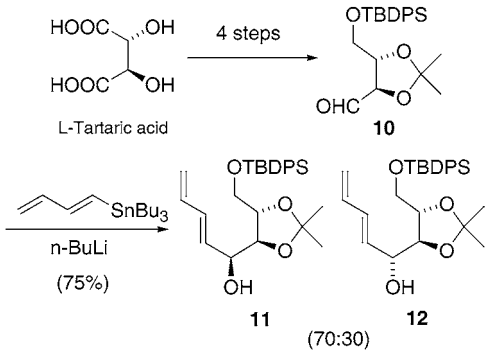
(8) Iida, H.; Yamazaki, N.; Kibayashi, C. *J. Org. Chem.* **1987**, *52*, 3337−3342.

(9) Wender, P. A.; Sieburth, S. M.; Petraitis, J. J.; Singh, S. K. *Tetrahedron* **1981**, *37*, 3967−3975.

(10) (a) Schneider, C.; Kazmaier, U. *Synthesis* **1998**, 1314−1320. (b) Martin, S. F.; Chen, H. J.; Lynch, V. M. *J. Org. Chem.* **1995**, *60*, 276−278.

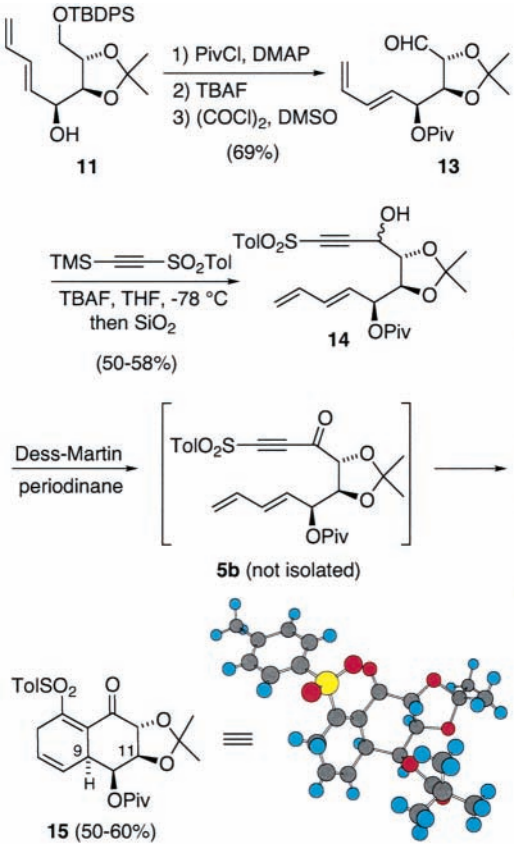
(11) Back, T. G. *Tetrahedron* **2001**, *57*, 5263−5301.

Scheme 3



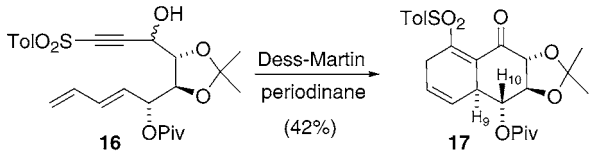
succeeded in adding the lithium salt derived from ethynyl *p*-tolyl sulfone to several aldehydes; however, attempts to add the corresponding anion to aldehyde **13** proceeded in poor yield. In contrast, addition of trimethylsilylethynyl *p*-tolyl sulfone[12] to aldehyde **13** catalyzed by tetrabutylammonium fluoride (Kuwajima conditions) provided **14** in 50−58% yield.[13] Oxidation of **14** with Dess−Martin periodinane in dichloromethane produced ketone **5b**, which spontaneously underwent Diels−Alder cycloaddition at room temperature to afford a single cycloadduct **15** in 50−60% yield. The stereochemistry of **15** was assigned following single-crystal X-ray analysis and surprisingly proved to possess the undesired C(9) stereochemical configuration.

Scheme 4



We next considered the possibility that the opposite C(10) configuration may favor the desired cycloadduct stereoisomer. To this end, we converted allylic alcohol **12** to alkynyl sulfone **16** (Scheme 5) following a synthetic route identical

Scheme 5



with the reaction sequence shown in Scheme 4. Oxidation of **16** with Dess−Martin periodinane in dichloromethane led to the production of a single Diels−Alder cycloadduct (**17**) via arylsulfonyl alkynone **5a**. The stereochemistry of **17** was assigned based on an observed 10.5-Hz coupling constant between H_9 and H_{10}. Thus, once again we observed exclusive formation of the undesired configuration at C(9).

Our results initially appeared to contradict the intramolecular Diels−Alder cycloadditions reported by Fallis (Scheme 2). The two substrates we examined (**5a** and **5b**) upon oxidation led to a Diels−Alder cycloaddition in which the C(9) and C(11) hydrogens emerged in a cis relationship. In contrast, intramolecular cyclization of **6** and **8** led to the corresponding trans isomer as the major product. The major difference between substrates was the reacting dienophile. To determine if simply changing the nature of the dienophile did indeed lead to a reversal of diastereoselectivity we prepared triene **19** (Scheme 6). Heating **19** at 90 °C in toluene for 40 h led to the isolation of a single cycloadduct. Single-crystal X-ray analysis revealed the cycloadduct indeed possessed the trans relative stereochemistry between C(9) and C(11) in accord with earlier results by Fallis.

There have been many documented examples of cycloaddition reactions reported in the literature in which the dienophile activating group and/or substituents within the connecting chain can have a major effect on the stereochemical outcome of an intramolecular Diels−Alder reaction.[14−16] For example, the position of the electron-withdrawing group on the dienophile component can have a significant effect on the stereoselectivity of an IMDA reaction (vis á vis internal versus external activation) by inducing variation in the asynchronicity of the reacting transition state.[15] In the case of Diels−Alder substrates **5a**, **5b**, and **19**, the trans

(12) (a) Bhattach, S. N.; Josiah, B. M.; Walton, D. R. M. *Organomet. Chem. Synth.* **1971**, *1*, 145−149. (b) Waykole, L.; Paquette, L. A. *Org. Synth.* **1988**, *67*, 149−156.

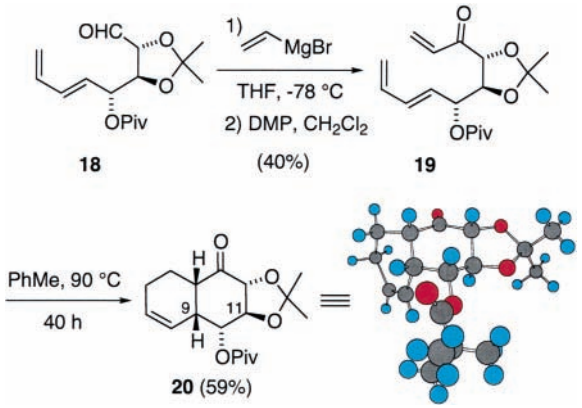
(13) Kuwajima, I.; Nakamura, E.; Hashimoto, K. *Tetrahedron* **1983**, *39*, 975−982.

(14) (a) Brown, F. K.; Houk, K. N. *Tetrahedron Lett.* **1985**, *26*, 2297−2300. (b) Boeckman, R. K.; Ko, S. S. *J. Am. Chem. Soc.* **1982**, *104*, 1033−1041. (c) White, J. D.; Sheldon, B. G. *J. Org. Chem.* **1981**, *46*, 2273−2280.

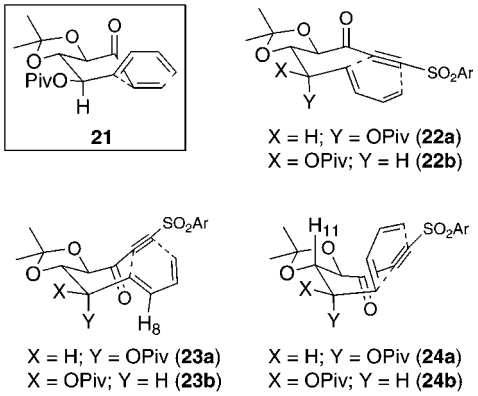
(15) (a) Taber, D. F.; Campbell, C.; Gunn, B. P.; Chiu, I. C. *Tetrahedron Lett.* **1981**, *22*, 5141−5144. (b) Roush, W. R.; Peseckis, S. M. *J. Am. Chem. Soc.* **1981**, *103*, 6696−6704.

(16) Coe, J. W.; Roush, W. R. *J. Org. Chem.* **1989**, *54*, 915−930.

Scheme 6



Scheme 7



acetonide group located within the connecting side chain significantly restricts the number of possible transtion states leading to the observed products. In the case of triene **19** the chair transition state **21** (Scheme 7) best accounts for the observed stereoselectivity.[5] In contrast, chair (**22**) and boat (**23** and **24**) transition states can be proposed for the cyclization of arylsulfonyl alkynones **5a** and **5b** to provide cycloadducts **15** and **17**. Inspection of molecular models suggests a boat transition state provides optimal overlap of the reacting diene and acetylenic dienophile.[16] Furthermore, boat transition state **23** should be favored over **24** based on consideration of nonbonded interactions between C(8) and C(11) hydrogens. Thus we conclude arylsulfonyl alkynones **5a** and **5b** favor boat transition state **23** and vinyl ketone **19** cyclizes by way of chair transition state **21** accounting for the opposite stereoselectivity of these Diels−Alder substrates.

In conclusion we have observed opposite diastereoselectivity for two Diels−Alder substrates that differ only in dienophile structure. Notably, both substrates give a single isomeric product. One cycloadduct (**20**) possesses an array of four stereocenters common to the aglycon of hibarimicin and various congeners. Finally, we also demonstrated the excellent reactivity of arylsulfonyl alkynones as dienophiles. Further progress on the total synthesis of hibarimicin and related aromatic polyketide dimeric natural products will be reported in due course.

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Supporting Information Available: Full characterization data for **10**−**20**. This material is available free of charge via the Internet at http://pubs.acs.org.

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