

Unusual Diastereoselectivity in Intramolecular Diels–Alder Reactions of Substituted 3,5-Hexadienyl Acrylates. Preference for a Boatlike Structure of the Six-Atom Tether Due to Ester Overlap

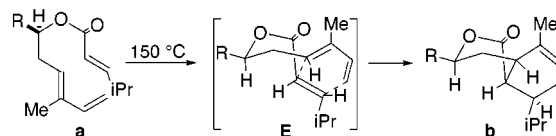
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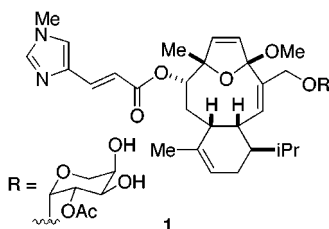
Received April 21, 2000

ABSTRACT



Thermolysis of the 3,5-hexadienyl acrylates (a) proceeds via the transition state E in which the connecting chain adopts a boatlike conformation due to a preference for maintaining ester overlap to afford the products b with good diastereoselectivity.

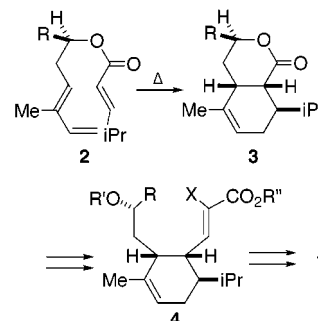
Eleutherobin **1**, a novel diterpene isolated from a sea sponge, exhibits potent cytotoxicity against a wide variety of cancer cells (IC₅₀ 10–15 nM).¹



In an approach to the total synthesis of eleutherobin, we postulated that the cyclohexene ring of **1** could possibly be constructed by an intramolecular Diels–Alder reaction of a substituted hexadienyl crotonate as shown in Scheme 1. We hoped to utilize the one stereocenter α to the oxygen in ester **2** to set the additional three stereocenters required in

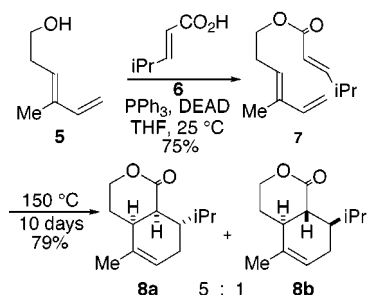
substructure **3** which could then be converted by reduction and Wittig reaction into compound **4** and then into eleutherobin **1**. We first determined that the isopropyl substituent would not undermine the preference of this type of cycloaddition for the cis ring juncture which was shown by Martin et al. for the parent case.² Mitsunobu reaction³ of alcohol **5**⁴

Scheme 1

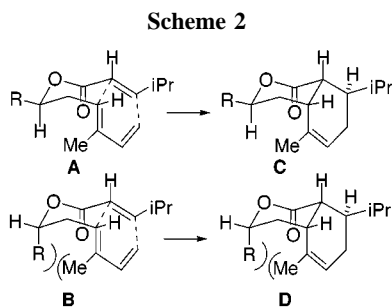


(1) Lindel, T.; Jensen, P. R.; Fenical, W.; Long, B. H.; Casazza, A. M.; Carboni, J.; Fairchild, C. R. *J. Am. Chem. Soc.* **1997**, *119*, 8744.

with carboxylic acid **6**⁵ gave ester **7** in good yield. A variety of conditions were examined to optimize the yield and diastereoselectivity of this and the later Diels–Alder reactions. Lewis acids did catalyze the Diels–Alder reaction but also gave a significant amount of undesired side products as did various polar solvents. However, heating triene **7** at 150 °C for 10 days in 1,2-dichlorobenzene gave the endo and exo lactones **8a** and **8b** in a 5:1 ratio in 79% yield.⁶ Thus, as Martin had found, the reaction is quite sluggish but affords primarily the cis-fused isomer.



We postulated that the intramolecular Diels–Alder reaction of an ester such as **2** might occur with the required diastereoselectivity to provide the relative stereochemistry found in eleutherobin. Of the two possible diastereomeric chairlike endo transition states **A** and **B**, the former would be greatly favored over the latter due to the severe steric interaction between the vinylic methyl and the R group in **B** and thus **C** should be formed preferentially (Scheme 2).



However, on closer examination of these transition structures using molecular models, we realized that the overlap between the carbonyl and oxygen of the ester group is poor in both transition states **A** and **B**. Since such overlap is worth 10–13 kcal/mol,⁷ other normally less-favored boatlike transition states which retain this overlap may well be favored since the boat-chair difference is roughly 4.7–6.2 kcal/mol.⁷ Thus,

(2) Martin, S. F.; Williamson, S. A.; Gist, R. P.; Smith, K. M. *J. Org. Chem.* **1983**, *48*, 5170.

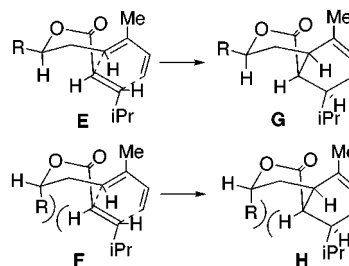
(3) Mitsunobu, O. *Synthesis* **1981**, 1.

(4) Buss, A. D.; Hirst, G. C.; Parson, P. J. *J. Chem. Soc., Chem. Commun.* **1987**, 1836. (b) For the preparation of the corresponding ester, which can be reduced to the alcohol using lithium aluminum hydride, see: Shing, K. M.; Tang, Y. *Tetrahedron* **1990**, *46*, 2187.

(5) Pirrung, M. C.; Han, H.; Ludwig, R. T. *J. Org. Chem.* **1994**, *59*, 2430.

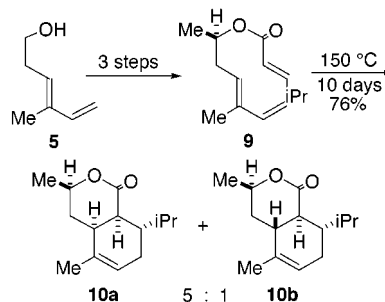
one must consider two other diastereomeric endo transition states, **E** and **F** (Scheme 3), in which the tether adopts a

Scheme 3

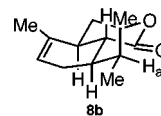


boatlike conformation in order to allow the ester group to retain coplanarity during the cycloaddition. Of these two transition structures, one would expect **E** to be greatly favored over **F** due to a strong steric interaction between the vinylic hydrogen and the axial group 1,4 to it (a flagpole–flagpole interaction).⁷ Thus, one would expect compound **G** to be the major diastereomer formed. It should be pointed out that certain intramolecular Diels–Alder reactions, e.g., those of substituted 1,7,9-decatrien-3-ones, have been shown to proceed predominately through a boatlike conformation of the connecting chain.⁸

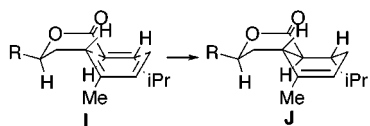
The substrate used to test these mechanistic ideas, **9**, was prepared from alcohol **5** by oxidation, addition of methylmagnesium bromide, and Mitsunobu reaction with acid **6**. Heating **9** in 1,2-dichlorobenzene at 150 °C for 10 days gave a 76% yield of a 5:1 ratio of the two diastereomeric lactones **10a** and **10b**. The structures of both **10a** and **10b** were



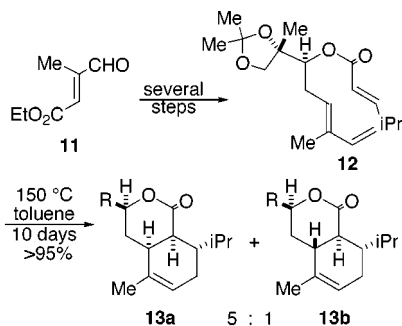
(6) The structures were determined by a combination of NMR techniques, both NOE experiments and simple coupling data (obtained by double irradiation). In particular, there is an interesting effect on chemical shift due to interaction of the isopropyl methine proton H_a with the carbonyl group in **8b**. This proton appears at quite low field (δ 2.8–3.4, depending on solvent) as a doublet of septets due to this interaction, which is possible only in this half chair-chair trans conformation. For a similar argument in the xestobergsterol class of antihistamines, see: Jung, M. E.; Johnson, T. W. *J. Am. Chem. Soc.* **1997**, *119*, 12412.



conclusively shown by proton NMR data, especially NOESY experiments, which showed a strong correlation between the proton α to the lactone oxygen and both ring juncture protons in **10a** and with only the proton α to the carbonyl in **10b**.⁹ Thus, the Diels–Alder reaction presumably proceeds via endo transition state **E**, namely, with the tether in a boatlike conformation that maximizes ester overlap. It is interesting to note that minor isomer **10b** must be formed from the other possible transition state in which the tether adopts a boatlike conformation, namely, the exo transition structure **I**, which would then give rise to **J** as the cycloadduct.



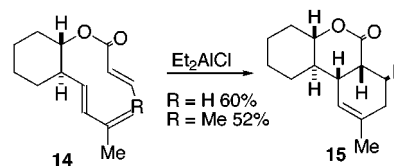
The size of the group α to the oxygen is not a significant factor in terms of diastereocontrol. Thus, commercially available aldehyde **11** was converted in several steps (the key enantioselective step being a Sharpless asymmetric dihydroxylation)¹⁰ into the late intermediate **12** for the synthesis of eleutherobin. Cycloaddition occurred on heating **12** in toluene in a sealed tube at 150 °C for 10 days to give in quantitative yield a 5:1 ratio of the two diastereomer lactones, **13a** and **13b**, in which again the product formed via transition state **E** was the major product. The structures were proven by NMR experiments, especially NOESY, which again showed correlation between the proton α to the lactone oxygen and the ring juncture protons.¹¹



The closest analogy to this work in the literature is that of Alexakis who reported that the trans 1,2-disubstituted cyclohexyl analogues **14** (R = H, Me) afforded the analogous products **15** in good yield.¹² However, although they

(7) For a discussion of these conformational and/or stereochemical issues and for the references to the energies quoted, see: Eliel, E. L.; Wilen, S. H. *Stereochemistry of Organic Compounds*; Wiley-Interscience: New York, 1994; pp 619, 689, and 1193.

(8) See for example: (a) Coe, J. W.; Roush, W. R. *J. Org. Chem.* **1989**, *54*, 915. (b) Roush, W. R. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon: Oxford, 1991; Vol. 5, Chapter 4.4, pp 513–550.



postulated that the reaction proceeded via a similar boatlike conformation of the connecting chain, they ascribed its stability to the presence of the Lewis acid in their case. Thus, we are the first to use the argument of ester overlap energetics to explain such diastereoselectivity in trienes linked by an ester tether.^{13,14}

In conclusion, we have shown that the thermal intramolecular Diels–Alder cycloaddition of substituted 3,5-hexadienyl acrylates proceeds via a novel transition structure in which the tether adopts a boatlike conformation to maximize overlap of the ester group. The application of this process to the total synthesis of eleutherobin is currently underway in our laboratories.

Acknowledgment. We thank the National Institutes of Health for financial support and Dean Tantillo and Ken Houk for helpful discussions.

Supporting Information Available: Proton and carbon NMR data for all the cycloadducts **8ab**, **10ab**, and **13ab** and procedures for their preparation. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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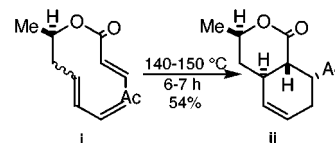
(9) Two other pieces of data in the proton NMR spectra were helpful in assigning structure **10b** for the minor isomer, namely, the proton α to the carbonyl is a large dd ($J = \sim 12$ Hz) and again the isopropyl methine proton appears at very low field.⁶

(10) Kolb, H. C.; Van Nieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483.

(11) There is a very small amount of another minor isomer (accounting for about 20% of the minor product **13b**) which was not isolated in pure form but most likely is the other cis ring juncture compound, C, e.g., that produced from the endo chairlike transition state **A**.

(12) Alexakis, A.; Jachiet, D.; Toupet, L. *Tetrahedron* **1989**, *45*, 6203.

(13) Mori reported that the analogue having an acetyl group on the distal carbon of the enoate **i** afforded the trans-fused product **ii** as the only crystalline product isolated in 54% yield. However, it is well-known that activating groups at the distal end of alkenes often dominate the stereocontrol of intramolecular Diels–Alder reactions and therefore these systems are not directly comparable. Mori, K.; Gupta, A. K. *Tetrahedron* **1985**, *41*, 5295. The structural assignment of **ii** indicates that an equilibration of one of the two carbonyl functions must have occurred since the stereochemistry of the alkene is not retained in the Diels–Alder reaction, i.e., either the proton α to the acetyl group or α to the lactone carbonyl has been epimerized in the product.



(14) After the original submission of this manuscript, we learned of a very similar study by Kurth, et al., who recently presented a poster on this work. Kurth, M. J.; Kim, P.; Olmstead, M. M.; Nantz, M. H. 219th National Meeting of the American Chemical Society, San Francisco, March 26–30, 2000; ORGN 343.