

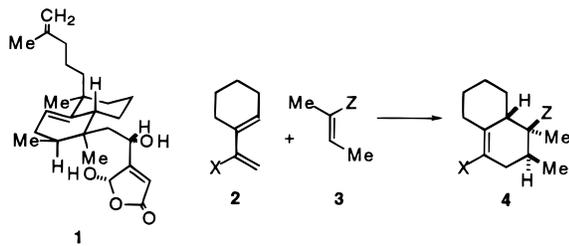
Communications to the Editor

Stereoselective Formation of Formal Exo Diels–Alder Adducts of Silyloxydienes and Allenecarboxylates

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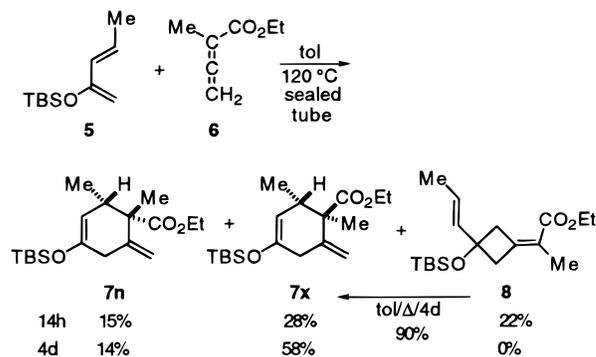
For a projected total synthesis of the novel naturally occurring phosphatase inhibitor, dysidiolide **1**,² we envisioned an intermolecular Diels–Alder cycloaddition of the vinylcyclohexene **2** with a highly substituted dienophile **3** which could be forced to occur in the normally less favorable exo mode to give an adduct such as **4**. This compound would possess many of the structural and



stereochemical features of the desired natural products and thereby perhaps simplify its total synthesis.³ However, all attempts at carrying out such a cycloaddition with **2** using Fisher carbene complexes⁴ **3** [Z = C(OMe)=Cr(CO)₅], which would have given the exo adducts, or the simple acid chloride **3** (Z = COCl), which would have given more of the endo adducts, unfortunately gave only starting material, presumably due to the steric hindrance of these dienophiles. We proposed using α -methyl allenecarboxylates as the dienophiles in order to decrease this steric hindrance with a subsequent reduction of the exocyclic double bond to give compounds such as **4**. We report herein the thermal cycloaddition of silyloxydienes **2** (X = OSiR₃) and allenecarboxylates which ultimately afford the formal exo Diels–Alder adducts **4**.

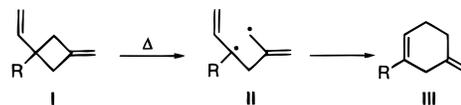
Heating a solution of *E*-4-methyl-2-silyloxybutadiene **5**⁵ with ethyl 2-methylbuta-2,3-dienoate **6** in toluene at 120 °C (sealed tube) for 14 h afforded, after chromatographic separation, a mixture of three compounds, the endo Diels–Alder product **7n** (18%), the exo Diels–Alder product **7x** (28%), and the [2 + 2] cycloadduct **8** (22%) (Scheme 1). The isolation of [2 + 2] cycloadducts from dienes and allenes was preceded in our own

Scheme 1



work and that of others.⁶ However, we have now shown that thermolysis of the purified cyclobutane **8** in toluene at 120 °C for 4 d gave only the exo cycloadduct **7x**. Thus heating the diene **5** and dienophile **6** in toluene for 4 d gave only the two [4 + 2] cycloadducts **7n** and **7x** in 14 and 58% yields, respectively. Although we had observed the thermal rearrangement of a [2 + 2] cycloadduct into a [4 + 2] cycloadduct before,^{6ab} this is the first case where the stereochemical course of this process could be determined.

The mechanism of the rearrangement of simple 3-ethenylmethylcyclobutanes **I** has been proposed to involve an initial bond homolysis to give a bis(allylic) diradical **II** which then recombines at the termini to give the 4-methylenecyclohexene **III**.⁷ Indeed it was shown that the divinyl compound **I** (R = CH=CH₂) had a lower activation energy for this reaction (E_a = 27.3 kcal/mol) than did the parent **I** (R = H) (E_a = 35.7 kcal/mol).^{7a} We believe that the substitution in our case may cause the reaction to proceed through a zwitterionic rather than a diradical pathway although the latter can certainly not be ruled out.



The reasons for the interesting stereochemical course of the reaction are not known. However, we suggest the following hypothesis: cleavage of the strained C–C bond of the cyclobutane syn to the ester⁸ in **IV** would generate the zwitterion **V**, rotation about the indicated C–C bond would give a different conformer of the zwitterion **VI**, and final coupling of the zwitterion at the termini would then give the product **VII** (which corresponds to the exo cycloadduct **7x**). We are currently trying to lend some computational evidence to this hypothesis.⁹

(6) (a) Jung, M. E.; Node, M.; Pfluger, R.; Lyster, M. A.; Lowe, J. A., III. *J. Org. Chem.* **1982**, *47*, 1150. (b) Jung, M. E.; Lowe, J. A., III; Lyster, M. A.; Node, M.; Pfluger, R.; Brown, R. W. *Tetrahedron* **1984**, *40*, 4751. (c) Spitzner, D.; Klein, I. *Liebigs Ann. Chem.* **1990**, *63*. (d) *Angew. Chem.* **1982**, *94*, 639. In reference c, Spitzner and Klein report that their [2 + 2] cycloadduct does not rearrange to the [4 + 2] cycloadduct on heating.

(7) (a) Dolbier, W. R., Jr.; Mancini, G. J. *Tetrahedron Lett.* **1975**, 2141. (b) Dolbier, W. R., Jr.; Piedrahita, C. A.; Al-Sader, B. H. *Tetrahedron Lett.* **1979**, 2957.

(8) We believe that the anion syn to the ester should be more stable than that syn to the methyl group, and thus, this determines which of the otherwise symmetrical C–C bonds of the cyclobutane ring is broken preferentially. Weiler showed several years ago that deprotonation of 3-methylbut-2-enoic acid salts with butyllithium in THF/HMPA gave nearly exclusively the anion syn to the acid. Harris, F. L.; Weiler, L. *Tetrahedron Lett.* **1985**, *26*, 1939.

(9) Jung, M. E.; Houk, K. N., unpublished results.

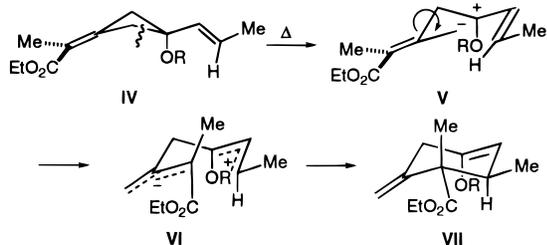
(1) Recipient of the Award for Excellence in First Year Graduate Study, University of California, Los Angeles, CA, 1997.

(2) Gunasekera, S. P.; McCarthy, P. J.; Kelly-Borges, M.; Lobkovsky, E.; Clardy, J. *J. Am. Chem. Soc.* **1996**, *118*, 8759.

(3) (a) Corey, E. J.; Roberts, B. E. *J. Am. Chem. Soc.* **1997**, *119*, 12425. (b) Boukouvalas, J.; Cheng, Y. X.; Robichaud, J. *J. Org. Chem.* **1998**, *63*, 228. (c) Magnuson, S. R.; Sepp-Lorenzino, L.; Rosen, N.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1998**, *120*, 1615. (d) Brohm, D.; Waldmann, H. *Tetrahedron Lett.* **1998**, *39*, 3998.

(4) Wulff, W. D.; Bauta, W. E.; Kaesler, R. W.; Lankford, P. J.; Miller, R. A.; Murray, C. K.; Yang, D. C. *J. Am. Chem. Soc.* **1990**, *112*, 3642.

(5) This diene was prepared by silylation of the kinetic enolate of *E*-3-penten-2-one.

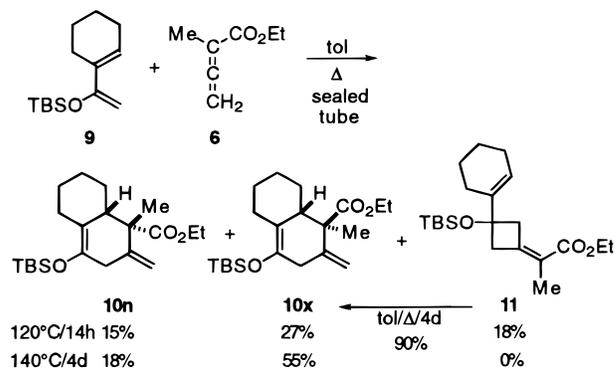


As a closer model for the synthesis of dysidiolide, we carried out the cycloaddition of the (silyloxyvinyl)cyclohexene **9** with the allenecarboxylate **6** under similar conditions and obtained analogous results, namely, the formation of the endo and exo [4 + 2] cycloadducts **10n** and **10x** in 15 and 27% yield, respectively, along with 18% of the [2 + 2] cycloadduct **11** (Scheme 2). Thermolysis of **11** for several days afforded **10x** exclusively in good yield. As before, when the diene and dienophile were heated in a sealed tube for an extended period, only the [4 + 2] cycloadducts **10n** and **10x** were isolated in 18 and 55% yield, respectively. Thus, one can obtain a reasonable yield of the desired exo adduct **10x** by this reaction.

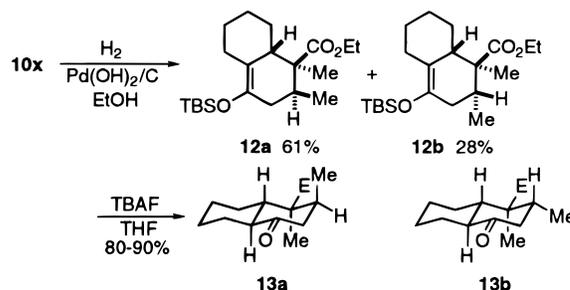
Hydrogenation of **10x** over Pd(OH)₂/C gave in 89% yield an approximate 2:1 mixture of the dihydro compounds **12ab**¹⁰ which were separated by chromatography and converted to the two trans decalones **13ab** in 80–90% yield (Scheme 3).¹⁰ Compounds **12a** and **13a** have the required stereochemistry at the ring juncture and two methyl-bearing carbons for dysidiolide. Further work on this project is under way in our laboratories.

(10) The structures of all of the products were assigned by careful analysis of the high field proton NMR spectra, using coupling constants, 2D and nOe techniques heavily. Hydrolysis of the minor Diels–Alder adduct, **10n**, afforded a crystalline enone, the structure of which was confirmed by single-crystal X-ray analysis. We thank Dr. Kenneth Hardcastle of the California State University, Northridge for that data.

Scheme 2



Scheme 3



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Supporting Information Available: Experimental procedures and spectral data for all new compounds (PDF). This material is available free of charge via the Internet at <http://pubs.acs.org>.

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