those of more manageable proximate chirality (cf. **13** → **14**). Applications of these findings to the total synthesis of other natural products are currently being pursued.

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Simple, Efficient Total Synthesis of Cantharidin via a High-Pressure Diels–Alder Reaction[1]

Sir:

Cantharidin (**1**) is the active principle of *Cantharis vesicatoria* which, notwithstanding its notoriety as the putative aphrodisiac in "Spanish fly", has found commercial applications in the removal of benign epithelial growths (warts) and as a vesicant.[2] We now report a simple, efficient total synthesis of **1** by a [4 + 2] cycloaddition reaction at high pressure.

Historically, the relative simplicity of the structure and the absence of enantiomeric forms have made cantharidin an enticing but elusive target for total synthesis. The obvious [4 + 2] cycloaddition between dimethylmaleic anhydride and furan was investigated as early as the 1920's, but such a direct synthetic approach failed.[3,4] The synthesis of **1** has been achieved;[5] however, the length and the complexity of these efforts stand in sharp contrast to the uncomplicated structure of **1**.

Earlier studies in these laboratories[6] suggested that the failure of dimethylmaleic anhydride to add to furan was a result of both electronic and steric factors. The electron-donating methyl groups of dimethylmaleic anhydride decrease its dienophilicity, and the extra crowding in the transition state given by these same methyl groups should further reduce its reactivity. Furthermore, furan is a poor Diels–Alder diene due to its aromaticity, and the cycloaddition products derived from it are generally susceptible to thermal cycloreversion,[4] so high reaction temperatures cannot be used.

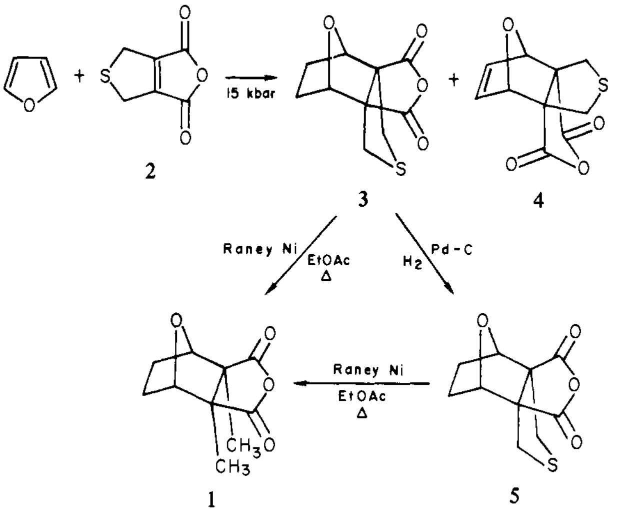
It has previously been reported from these laboratories[6] that pressures in the range of 10–20 kbars (1 kbar = 986.9 atm) greatly facilitate Diels–Alder reactions of furan. Although dimethylmaleic anhydride, itself, will not add to furan even at pressures up to 40 kbars,[7] the earlier studies indicated that a suitable dienophile which overcomes the electronic and/or the steric problems might undergo [4 + 2] cycloaddition with furan. The target dienophile was 2,5-dihydrothiophene-3,4-dicarboxylic anhydride (**2**), a known compound which could be synthesized readily on a large scale.[8] The presence of the sulfur-containing methylene bridge in place of the dimethyl substituents on the maleic anhydride nucleus was anticipated to reduce or eliminate the electron-donating character of these two alkyl substituents, and it was anticipated that this new ring would reduce the steric demands of the disubstituted maleic anhydride.

Table I. Reaction of 2 with 1.2 equiv of Furan at High Pressure

solvent	concn of 2, mol/L	pressure, kbar	time, h	conversion,[a] %	product ratio[a,b] (3:4)
CH_2Cl_2	0.26	15	6	100	85:15
	0.26	8	42	79	85:15
	0.26	4	88	41	80:20
CH_3COCH_3	0.45	15	24	*c*	
	0.45	8	42	81	85:15
	0.45	4	88	49	85:15
CH_3CN	0.45	15	24	*c*	
	0.45	8	42	64[d]	85:15
	0.45	4	88	57	85:15

[a] Determined by NMR spectroscopy. [b] Unless otherwise noted, no other products were observable by NMR spectroscopy. [c] Quantitative analysis of reaction mixture not possible by NMR spectroscopy due to poly-Diels–Alder products; see text. [d] Some diacid formed; see text.

It was found that reaction of **2** with 1.2 equiv of furan in methylene chloride at room temperature for 6 h under 15 kbar pressure effected quantitative conversion to 1:1 cycloadducts as a 85:15 mixture of isomers. The two adducts could be separated by chromatography on silica gel and were characterized as isomers **3** (mp 112–113 °C, acetone–hexane) and **4** (mp 125–126 °C, chromatograph).[9] The major isomer **3** was hydrogenated over 10 mol % of 10% Pd-C to give **5** (mp 154–155 °C, acetone–hexane) in a quantitative yield. The exo-anhydride stereochemistry was assigned on the basis of the 0.3-ppm downfield shift of one of the two proton doublets for the protons α to the sulfur atom in the NMR spectrum of **5** relative to **3**. Confirmation of this stereochemical assignment was provided by Raney nickel[10] desulfurization of **5** which gave **1**, identical by NMR and IR spectrometry and mixed melting point with a sample of natural cantharidin.[11] More efficiently, the mixture of isomers obtained



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(1) This work was supported by the National Science Foundation under Grant 78-04811.

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(7) (a) Gladysz, J. A. *CHEMTECH* **1979**, 372. (b) Dauben, W. G.; Kozikowski, A. P., unpublished results, 1974.

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(9) All new compounds reported were characterized by NMR and IR spectroscopy and possessed the proper elemental analysis.

(10) Fieser, L. F.; Fieser, M. "Reagents for Organic Synthesis", Wiley: New York, 1967; Vol. 1, p 729.

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directly from the high-pressure cycloaddition was reduced and desulfurized in one step over Raney nickel in refluxing ethyl acetate, and cantharidin was isolated in 63% from **2** by one recrystallization (EtOAc).

Not surprisingly, in view of the previously cited thermal instability of furan Diels–Alder reaction products, this present reaction sequence could not be achieved by thermal activation. The heating of furan and dienophile **2** at 110 °C led to no reaction, while heating to 200 °C resulted in decomposition of **2** to give a black tar with a strong sulfur odor. The adduct **3** also decomposed in less than 15 min at 200 °C. Therefore, it must be concluded that the production of adduct **3** is only possible at elevated pressures.

The scale on which this cycloaddition can be performed is limited by the solubility of **2** (less than 60 mg/mL in CH_2Cl_2) and the size of the high-pressure apparatus. The Berkeley apparatus is capable of holding a 70-mL volume at 15 kbar; however, the employment of lower pressures allows the use of equipment with much larger usable volume. Furthermore, the solubility of **2** is approximately twice as great in acetonitrile and in acetone as it is in methylene chloride. A survey of the high-pressure cycloaddition of **2** and furan in three solvents at three pressures was made, and the results are given in Table I.

The reaction proceeded cleanly at all pressures in methylene chloride which is still liquid at 15 kbar.[12] The reaction is also clean in acetone at 4 and 8 kbar; however, at 15 kbar, the NMR spectrum of the crude reaction mixture could not be interpreted quantitatively, due to large amounts of unidentified reaction products. In acetonitrile, the same unidentified products were produced at 15 kbar, and, in addition, 12% of the dicarboxylic acid of **2** was formed at 8 kbar. This same diacid was formed in many of the reactions run in acetonitrile, and this hydrolysis, accelerated by pressure, is ascribed to traces of water which are difficult to remove from the solvent. The unidentified products formed at the higher pressures may be the result of the addition of furan to the initially formed adducts **3** and **4**; analogous results have been observed in the high-pressure reaction of furan with quinones.[13] Since both pure acetone and acetonitrile are solid at 15 kbar,[12] the formation of the products may be due to reaction in the solid state.

This work represents the first total synthesis of cantharidin which would be feasible on a large scale. Forty years after the first synthesis, the utilization of high-pressure acceleration of reactions which possess a $-\Delta V^{*}$ combined with careful selection of reactants and reaction conditions to achieve maximum utilization of the volume parameter has allowed the achievement of a simple synthesis of cantharidin in accord with its simple structure.

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(11) An authentic sample of cantharidin was kindly supplied by Dr. J. Muchowski.

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(13) Dauben, W. G.; Moreland, D. W., unpublished results.

(14) NIH Postdoctoral Fellow, 1979–present.

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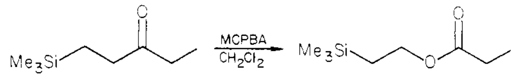
Silicon-Directed Baeyer–Villiger Reactions. Stereospecific Synthesis of Olefinic Acids and Esters[1]

Sir:

A considerable body of evidence indicates that cations β to silicon in organosilicon compounds are considerably stabilized by the silicon.[2,3] We have been interested in the possibility that this stabilization can be used to direct some types of carbon–carbon bond cleavage reactions. We have therefore been investigating the Baeyer–Villiger reactions of β-silyl ketones (γ-ketosilanes), as the migratory aptitude in Baeyer–Villiger reactions appears to be related to the ability of a group to bear a positive charge.[4] Here we report that Baeyer–Villiger reactions of a number of β-trimethylsilyl ketones are directed by the trimethylsilyl group to give esters of β-hydroxysilanes in accord with this rationale, and that this reaction is useful for the synthesis of olefinic acids and esters.

In a preliminary observation, we found that the Baeyer–Villiger reaction of 1-(trimethylsilyl)-3-pentanone[5] with *m*-chloroperbenzoic acid (MCPBA) in CH_2Cl_2 produced what appeared (by NMR) to be β-(trimethylsilyl)ethyl propionate,[6] the ester of a β-hydroxysilane (eq 1). Since β-hydroxysilanes are readily convertible to olefins by β-elimination reactions,[3,7] the silicon-substituted lactones resulting from Baeyer–Villiger reactions of *cyclic* β-silyl ketones should be useful precursors to olefinic acids and, in principle, other olefinic compounds. We have therefore studied the Baeyer–Villiger reactions of silyl ketones **1**, **5a**, and **5b**.



(1)

Silyl ketone **1**[8] was prepared from the cyclohexylamine imine of cyclohexanone by alkylation of the bromomagnesium salt[9] with Me_3SiCH_2Cl followed by hydrolysis of the product with aqueous acetic acid. Silyl ketones **5a** and **5b** were prepared from cyclohexenone by reaction with Me_3SiLi, followed by protonation (MeOH) or alkylation (MeI), respectively, as reported by Still.[10,11]

Treatment of silyl ketones **1** and **5a** with MCPBA in CH_2Cl_2 in the presence of Na_2HPO_4 buffer produced the silyl lactones **2**[8] and **6a**[8] in yields of 96% and 99%, respectively (Scheme I). The structures of the lactones were assigned from their spectra and from their conversion to olefinic acids and esters as discussed below. It should be noted that, in the absence of any directive effect of silicon, a mixture of two lactones would have been expected from silyl ketone **5a**. Only one lactone (**6a**) was obtained; the virtual absence of its regioisomer was shown by its conversion to silicon-free products as discussed below.

Saponification of the lactones yielded β-hydroxysilane acids **3a**[8a] (from **2**) and **7a**[8a] (from **6a**), which were treated (without

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(1) Portions of this work were presented at the 12th Organosilicon Symposium, Ames, IA, March 1978, and at the 178th National Meeting of the American Chemical Society, Washington, DC, September 1979, Abstr. ORGN 244.

(2) (a) A. W. P. Jarvie, *Organomet. Chem. Rev., Sect. A*, **6**, 153–207 (1970). (b) Cations β to other electropositive atoms in organometallic compounds also appear to be stabilized. The effectiveness of this stabilization is presumably related to the ability of the carbon–metal bond to overlap with the empty orbital of the cationic center—see T. G. Traylor, W. Hanstein, H. J. Berwin, N. A. Clinton, and R. S. Brown, *J. Am. Chem. Soc.*, **93**, 5715–5725 (1971), and references cited therein.

(3) For recent reviews on the properties of organosilicon compounds and their use in organic synthesis, see (a) P. F. Hudrlik in "New Applications of Organometallic Reagents in Organic Synthesis", D. Seyferth, Ed., Elsevier, Amsterdam, 1976, pp 127–159; (b) E. W. Colvin, *Chem. Soc. Rev.*, **7**, 15–64 (1978); (c) P. F. Hudrlik and A. M. Hudrlik, "Silicon Compounds—Register and Review", Petrarch Systems, Inc., Levittown, PA, 1979, pp 25–32; (d) I. Fleming, "Comprehensive Organic Chemistry", Vol. 3, D. H. R. Barton, Ed., Pergamon Press, Oxford, 1979, pp 541–686.

(4) Reviews of the Baeyer–Villiger reaction: (a) C. H. Hassall, *Org. React.* (N.Y.), 73–106 (1957); (b) P. A. S. Smith, "Molecular Rearrangements", Part 1, P. de Mays, Ed., Wiley-Interscience, New York, 1963, pp 577–589. Strongly electronegative groups γ to carbonyl have recently been found to partially direct the Baeyer–Villiger reaction: R. Noyori, T. Sato, and H. Kobayashi, *Tetrahedron Lett.*, 2569–2572 (1980).

(5) P. F. Hudrlik and G. P. Withers, *Tetrahedron Lett.*, 29–32 (1976).

(6) The pertinent features of the NMR spectrum (CH_2Cl_2) were a triplet at δ 4.13 (J = 7 Hz, $-CH_2-O$) and a quartet at δ 2.25 (J = 7 Hz, $-CH_2CO$).

(7) P. F. Hudrlik and D. Peterson, *J. Am. Chem. Soc.*, **97**, 1464–1468 (1975); P. F. Hudrlik, D. Peterson, and R. J. Rona, *J. Org. Chem.*, **40**, 2263–2264 (1975).

(8) The (a) IR and NMR spectra and (b) high-resolution mass spectrum were in agreement with the proposed structure.

(9) For the alkylation of imine salts, see G. Stork and S. R. Dowd, *J. Am. Chem. Soc.*, **85**, 2178–2180 (1963). See also P. F. Hudrlik and C.-N. Wan, *J. Org. Chem.*, **40**, 2963–2965 (1975).

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