and heated for 3 h at reflux under Ar. Analysis of the solution by ^{1}H NMR indicated quantitative reaction. Upon cooling to ambient temperature, the product separated as white needles (0.23 g, 74%): mp >180 °C dec; IR (KBr) 1330 (B–O–B); ^{1}H NMR (CD$_2$Cl$_2$ vs. Me$_4$Si) δ 7.70 (d of d, 2, β-H); 8.21 (d, 2, J = 8 Hz, γ-H); 8.44 (d, 2, J = 7 Hz, α-H); ^{11}B NMR (CD$_2$Cl$_2$ vs. BF$_3$OEt$_2$) +41.5; mass spectrum, m/z 234 (M$^+$). Anal. Calcd for C$_{10}$H$_6$B$_2$Cl$_2$O: C, 51.18; H, 2.58; B, 9.21. Found: C, 51.40; H, 2.76; B, 9.48.

1,3-Dimethyl-1*H***,3***H***-naphth[1,8-***cd***][1,2,6]oxadiborin (2d).** Crude diester **2b** (1.5 g) was dissolved in 100 mL of (CH$_2$)$_4$O. An aliquot of MeMgBr (32.6 mmol, 5 equiv) in Et$_2$O was added and the mixture was stirred for 3 h under Ar. The anions were quenched with BF$_3$·OEt$_2$ (4.0 mL, 32.5 mmol), the solvents were evaporated, and the residue was extracted with 2 × 60 mL of petroleum ether. The extracts were filtered, concentrated, and crystallized from minimal petroleum ether. The yield was 0.83 g (64%) of beige needles: mp 97–99 °C; UV max (CH$_2$Cl$_2$) 323 nm (ϵ 9300), 311 (10 500), 232 (25 000); IR (KBr) 1307 (B–O–B); ^{1}H NMR (CD$_2$Cl$_2$ vs. Me$_4$Si) δ 1.06 (s, 6, CH$_3$); 7.64 (d of d, 2, β-H), 8.09 (d of d, 2, $J_{\alpha\gamma}$ = 1.2 Hz, $J_{\beta\gamma}$ = 8.2 Hz, γ-H); 8.31 (d of d, 2, $J_{\alpha\gamma}$ = 1.2 Hz, $J_{\alpha\beta}$ = 6.6 Hz, α-H); ^{13}C NMR (CD$_2$Cl$_2$ vs. Me$_4$Si) 3.5, 126.2, 131.6, 133.5, 138.1, 138.8; ^{11}B NMR (CD$_2$Cl$_2$ vs. BF$_3$·OEt$_2$) 50.7; mass spectrum, m/z 194 (M$^+$). Anal. Calcd for C$_{12}$H$_{12}$B$_2$O: C, 74.35; H, 6.24; B, 11.15. Found: C, 74.19; H, 6.46; B, 10.93.

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Organic Reactions at High Pressure. The Preparative Scale Synthesis of Cantharidin[1]

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The benefits of applying high pressure (1–20 kbar; 0.1–2.0 GPa) to organic reactions which have a $-\Delta V^*$ are readily seen by considering the variety of synthetic organic reactions recently found to be accelerated under elevated pressures.[2] One example which is of possible commercial interest is the synthesis of the potent vesicant cantharidin which is used in the removal of benign epithelial growths (warts). This synthesis proceeds via the Diels–Alder reaction of the dihydrothiophene anhydride **1**[3] with furan, a reaction which proceeds at pressures in the 4–15 kbar range and yields the adducts **2** and **3**.[4] Subsequent hydrogenation and desulfurization of the mixture of isomeric adducts and selective recrystallization affords the desired

Table I. Optimization of the Preparative Scale Diels–Alder Reaction of 1 with Furan at High Pressure[a]

entry	1, mmol (g)	mmol of furan/ mmol of 1	time, h	conversn,[c] %
1	65 (10.07)	26	24	95
2	45 (7.0)	34	29	100
3	97 (15.09)	15	26	67
4	98 (15.26)	16	48	97
5	90 (14.02)	16	74	100
6	0.7 (0.103)	62	144[b]	95

[a] All reactions were carried out at 20 °C and except where noted under 7-kbar pressure. [b] 1-kbar pressure. [c] Conversion of anhydride 1 was determined by ^{1}H NMR (90-MHz) spectroscopy. All of the reactions afforded approximately a 20:80 ratio of isomers 2/3.

cantharidin (**4**). The efficiency of this high pressure procedure has prompted the study of a preparative scale synthesis of **4**.
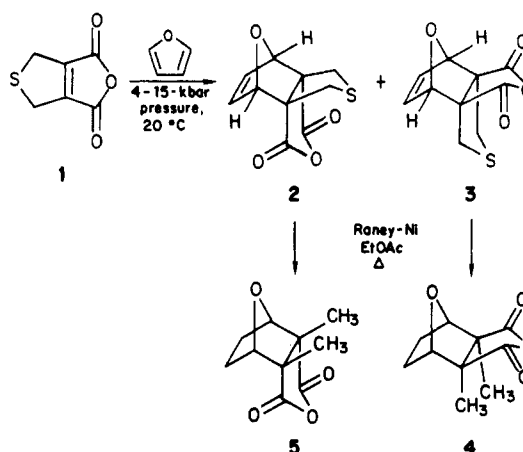
Performing large-scale (>100 mL) reactions at pressures greater than 7 kbar is limited by the engineering problems associated with the scaling-up of the pressure apparatus.[5] Reaction vessels of the piston-and-cylinder design which operate at pressures greater than 7 kbar require a costly conical inner liner so that the vessel can withstand very high pressures.[5] The construction of such a reaction vessel with a piston having a diameter greater than 1 in. so as to allow larger scale preparative reactions is impractical due to the mass of the vessel required. The construction of a reaction vessel having a wide bore (>2 in.) which can be used at pressures less than 7 kbar can be achieved by a reaction cylinder devoid of the extra inner linear.[6,7] This pressure restriction as related to large scale preparative reactions requires a study of reaction conditions to see if lower pressures can be utilized in the desired reaction. The ease by which preparative scale reactions (0.065 mol) can be carried out at the lower pressure (7 kbar) is reported in this study of the optimization of the [4 + 2] cycloaddition synthesis of cantharidin.

In our earlier study,[4] it was found that the cycloaddition reaction proceeded at a pressure of 7 kbar in solvents such as methylene chloride, acetone, or acetonitrile. The time required for 80% conversion at 8-kbar pressure (42 h) was increased 2–4-fold as compared to that needed at 15-kbar

(1) This work was supported by National Science Foundation Grant No. CHE-8401434.

(2) For recent high-pressure applications. (a) Quaternization of triphenylphosphine: Dauben, W. G.; Gerdes, J. M.; Bunce, R. A. *J. Org. Chem.* **1984**, *49*, 4293. (b) Asymmetric reduction: Midland, M. M.; McLoughlin, J. I. *J. Org. Chem.* **1984**, *49*, 1317. (c) 1,4-Addition reactions: Yamamoto, Y.; Maruyama, K.; Matsumoto, K. *Tetrahedron Lett.* **1984**, *25*, 1075. (d) Alcohol protection: Dauben, W. G.; Bunce, R. A.; Gerdes, J. M.; Henegar, K. E.; Cunningham, A. C.; Ottoboni, T. B. *Tetrahedron Lett.* **1983**, *24*, 5709. (e) Wittig reactions: Nonnemacker, A.; Mayer, R.; Plieniger, H. *Liebigs Ann. Chem.* **1983**, 2135. (f) Diels-Alder reactions: Jurczak, J.; Bauer, T.; Filipek, S.; Tkacz, M.; Zygo, K. *J. Chem. Soc., Chem. Commun.* **1983**, 540.

(3) The synthesis of anhydride 1 from methyl 4-oxotetrahydrothiophene-3-carboxylate has been described by; Baker, B. R.; Querry, M. V.; Kadish, A. F. *J. Org. Chem.* **1948**, *13*, 128.

(4) Dauben, W. G.; Kessel, C. R.; Takemura, K. H. *J. Am. Chem. Soc.* **1980**, *102*, 6893.

(5) For a discussion of high-pressure equipment see: Isaacs, J. S. "Liquid Phase High Pressure Chemistry"; Wiley Interscience: New York, 1981; Chapter 1.

(6) Semipreparative and preparative high-pressure apparatus are available from Harwood Engineering Co., Inc., South Street, Walpole, MA 02081, and Tem-Pres Division, Leco Corp., Bellefonte, PA 16823.

(7) Plans for a simple pressure apparatus devoid of the cylinder inner linear have been described in: DeShong, P.; Dicken, C. M.; Perez, J. J.; Shoff, R. M. *Org. Prep. Proceed. Int.* **1982**, 369.

pressure (6–24 h). To carry out the reaction to completion at 8-kbar pressure would therefore require at least double the aready increased times. An increase of the amount of 1 to aid the bimolecular rate was not permitted due to the limited solubility of 1 in the above solvents (0.26–0.45 M). However, the other reactant, furan, was found to be an excellent solvent[8] for anhydride 1 allowing reaction of a 0.5 M solution of 1 in neat furan. A high pressure reaction using such a solution occurs in the liquid phase since the temperature of freezing for furan is –16 °C at 9.14-kbar pressure (see ref 5, p 113).

The preparative-scale cycloaddition reaction was studied by combining the anhydride 1 and neat furan in an annularly bellowed copper tube[9] of 115-mL volume,[10] as compared to the 20-mL volume of the 15-kbar reactor, and then placing the tube in the preparative scale press,[11,12] followed by pressurization to a modest 7-kbar pressure. These reactions were carried out at 20 °C at various concentrations and for different lengths of time, and the results are summarized in Table I. The conversion of anhydride 1 to adducts 2 and 3 and also the endo/exo ratios (2:3) were determined by ^{1}H NMR (90 MHz) integration.[13]

The most favorable conditions found were those of entry 1, which maximized the initial amount of anhydride 1, minimized the time required for conversion to isomers 2 and 3, optimized the relative ratio of 1 to furan, and afforded a significant amount of adducts 2 and 3. Reduction of the initial amount of anhydride 1 (entry 2) and pressurization for the longer duration of 29 h afforded a quantitative yield of mixture 2 and 3. When larger amounts of 1 were used (entries 3–5), a much longer time (74 h, entry 5) was necessary for quantitative conversion. It was also of interest to demonstrate that the Diels–Alder cycloaddition was feasible at the minimized 1-kbar pressure for 144 h as shown by entry 6. Finally, preparative-scale Raney nickel desulfurization[4] was performed by using 14.4 g (11 mmol) of the adduct mixture (2 + 3). Selective recrystallization from ethyl acetate afforded pure cantharidin (4; 51%). Chromatography of the recrystallization residue afforded pure *epi*-cantharidin (5; 8%).

In conclusion, a wide-bore piston-and-cylinder apparatus operating at lower pressures (<8 kbar) overcomes the smaller reaction volume limitation associated with a 15-kbar press and therefore permits preparative-scale high-pressure reactions. The employment of lower pressures (<15 kbar), however, requires that reaction conditions be evaluated. The best conditions for cycloaddition of anhydride 1 with neat furan on a 10–15 g scale at 20 °C under

7-kbar pressure were found by adjusting the relative concentrations of reactants and reaction time. This is the first example of a dramatic reaction rate increase with the concentration change of a reactant for a bimolecular reaction in a high-pressure synthetic operation.

Experimental Section

General Methods. Furan was distilled under a nitrogen atmosphere from sodium. IR spectra were recorded on a Perkin-Elmer Model 281 spectrometer as solutions (NaCl cells). ^{1}H NMR data were recorded on a Varian EM-390 (90 MHz) spectrometer. Melting points were determined on a Büchi melting point apparatus and are uncorrected. Elemental analyses were performed by the Microanalytical Laboratory, operating by the College of Chemistry, University of California, Berkeley.

The four step preparative scale synthesis of dihydrothiophene anhydride 1 followed the route of Baker et al.[3] starting from the readily available methyl 4-oxotetrahydrothiophene-3-carboxylate[14] (6) in an overall yield of 53%. Several experimental modifications of the existing synthetic procedures[3] for the large-scale production of 1 are noteworthy.

3-Cyano-4-carbomethoxy-2,5-dihydrothiophene (7). Transformation of keto ester 6[14] (126.63 g, 0.77 mol) to cyano ester 7 was carried out in a fashion similar to that reported previously.[3] It has been found the use of a commercially available liquid HCN[15] (and taking necessary laboratory precautions) greatly facilitates the preparation of the cyanohydrin. The crude cyanohydrin was dehydrated[3] to afford 108.15 g (0.639 mol) of cyanoester 7 (83%): bp 93–96 °C (0.1 torr); ^{1}H NMR (CDCl₃) δ 3.8 (s, 3), 4.0 (s, 4) [lit.[3] 0.924-mol scale, distilled yield 82%, bp 120–125 °C (1 torr)].

2,5-Dihydrothiophene-3,4-dicarboxylic Acid (8). Hydrolysis of 7 on a preparative scale was effected by allowing 35.38 g (0.209 mol) of 7 to react with glacial acetic acid (103 mL) and concentrated HCl (172 mL) at reflux for 20 h.[3] The crude product was purified by Soxhlet extraction[16] (acetone, 10–20 cycles) to afford 33.85 g (0.195 mol) of diacid 8 (93%); mp 168–172 °C [lit.[3] 0.0296-mol scale, 77%, mp 183–184 °C]. Diacid 8 was used without further purification.

2,5-Dihydrothiophene-3,4-dicarboxylic Acid Anhydride (1). The large-scale dehydration of diacid 8 to anhydride 1 was performed by treating 41.92 g (0.241 mol) of 8 with SOCl₂ (89 mL) at reflux.[3] The resultant crude solid was recrystallized[17] first from benene then from acetonitrile to provide 26.38 g (0.169 mol) of pure 1 (70%): mp 165–170 °C; ^{1}H NMR (CDCl₃) δ 4.03 (s, 4) [lit.[3] 0.0029-mol scale, 78%, mp 164–166 °C].

Cycloaddition of Anhydride 1 with Furan at 7-kbar Pressure. An annularly bellowed copper tube[10] with a volume of 115 mL was charged with 10.07 g (0.065 mol) of dihydrothiophene anhydride 1 and ~115 mL (1.69 mol) of freshly distilled furan. The tube was sealed with a lead washer and a brass hexagon nut and placed in the reaction cylinder[11,12] bore, followed by air-driven hydraulic pressurization to 7 kbar. After 24 h the sample was depressurized and the excess furan was removed under reduced pressure to afford 14.4 g of a white solid. Analysis by ^{1}H NMR (CDCl₃) revealed[13] a mixture of stereoisomers, *endo*-anhydride 2 [δ 3.9 (q, 4, *J* = 12.0 Hz), 5.2 (s, 2), 6.95 (s, 2)], *exo*-anhydride 3 [δ 3.3 (q, 4, *J* = 12.0 Hz), 5.0 (s, 2) 6.70 (s, 2)], and also anhydride 1 [δ 4.03 (s, 4)]. ^{1}H NMR analysis of the reaction mixture which contained only 1, 2 and 3 showed the composition of the mixture to be 5% of 1, 19% of 2, and 76% of 3. The mixture was subsequently subjected to Raney nickel desulfurization without further purification.

(8) The solubility of anhydride 1 in furan was approximately 80 mg/mL.

(9) The annularly bellowed copper tube 1.5-in. o.d. by 6.75-in. length (sealed volume of 115 mL) was obtained by expanding a 1.5-in. o.d. by 3.86-in. length (sealed volume of 52 mL) in a vacuum oven (CCl₄, 120 °C, 1.5 h).

(10) As noted in ref 4, the reported total working volume of the reaction cylinder bore at 15-kbar pressure is 70 mL. The actual reaction volume (20 mL) is smaller than the total working volume (70 mL) due to the type of reaction vessel used and also due to the requisite void space in the bore needed for pressure transfer fluid. A similar volume differential (reaction volume, 115 mL; total working volume, 300 mL) exists with the 7-kbar reactor.

(11) Acknowledgement is made to Mr. John Holthuis for the use of the preparative scale press, Materials and Molecular Research Division, Lawrence Berkeley Laboratory, Berkeley, CA 94720.

(12) The preparative scale reaction cyclinder used was devoid of an inner linear and is similar in design to that described in ref 7. The bore of the cylinder measured 2.02 in. i.d. by 12 in. length. The overall working volume is approximately 300 mL. The press frame and hydraulic pumping system used are similar to those discussed in, Dauben, W. G.; Krabbenhoft, H. O. *J. Org. Chem.* 1977, 42, 282.

(13) It was noted that little (<4%) or not formation of extraneous side products occurred by using an excess of neat furan for the cycloaddition reaction, as determined by ^{1}H NMR (90 MHz).

(14) (a) Woodward, R. B.; Eastman, R. H. *J. Am. Chem. Soc.* 1946, 68, 2232. (b) For a more recent synthesis, see: Hromatka, O.; Binder, D.; Eichinger, K. *Montash. Chem.* 1973, 104, 520.

(15) The 40-lb tank of liquid HCN was purchased from Fumico Chemical Company, Amarillo, Texas. The liquid HCN was easily transferred from the tank to the reaction flask by using tygon tubing at 20 °C.

(16) Soxhlet extraction is a sufficient enough method for obtaining diacid 8. By omitting the recrystallization step,[3] 8 is obtained in an improved yield of +15%.

(17) It was noted that large scale purification by double recrystallization (benzene then acetonitrile) was superior to the trituration (petroleum ether) method as described in ref 3.

The other high-pressure runs were performed and analyzed as described above employing the concentrations and reaction times as shown in Table I.

Cantharidin (4) and *epi*-Cantharidin (5). A slurry of freshly prepared Raney nickel[18] in ethyl acetate (200 mL) was added to a solution of cycloaddition adducts 2 and 3 (14.4 g) in ethyl acetate (600 mL) under a nitrogen atmosphere. The mixture was stirred at reflux for 3 h and cooled slightly, and then the catalyst was removed by hot filtration. The collected catalyst residue was rinsed with warm acetone (500 mL), the acetone washings were combined with the early acetate portion, and the solvent was removed under reduced pressure to afford 12.94 g of a crude white solid. Selective recrystallization from ethyl acetate afforded 6.55 g (51%) of pure cantharidin (4): mp 210-211 °C; IR (CHCl$_3$) 1835, 1780 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 1.20 (s, 6), 1.76 (m, 4), 4.70 (m, 2). Anal. Calcd for C$_{10}$H$_{12}$O$_3$: C, 61.22; H, 6.16. Found: C, 61.40; H, 6.23.

Medium-pressure chromatography (silica, ether/hexane, 1:1) of the mother liquor afforded 0.647 g (8%) of pure *epi*-cantharidin (5): mp 193-194 °C; IR (CHCl$_3$) 1860, 1790 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 1.38 (s, 6), 1.88 (m, 4), 4.66 (m, 2). Anal. Calcd for C$_{10}$H$_{12}$O$_3$: C, 61.22; H, 6.16. Found: C, 61.26; H, 6.35.

Registry No. 1, 75532-25-1; 2, 75558-06-4; 3, 75532-26-2; 4, 56-25-7; 5, 80558-50-5; 7, 96307-21-0; 8, 20688-07-7; furan, 110-00-9.

(18) The W-6 Raney nickel was prepared according to Fieser: L. F.; Fieser, M. "Reagents for Organic Synthesis"; Wiley: New York, 1967; Vol. 1, p 729.

Relative Reactivities of Representative Aldehydes and Ketones toward Trimethylsilyl-Substituted Propargylic Boranes

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We recently reported that borane 1 reacts with representative aldehydes and ketones to form trimethylsilyl-substituted α-allenic alcohols with high regioselectivity and in excellent isolated yields (Scheme I).[1] Such allenes have recently been found to be useful for a variety of chemical reactions.[2] The bifunctional adduct 1 thus provides opportunities for achieving a wide array of transformations. This prompted us to investigate the relative reactivities of aldehydes and ketones toward 1.

The relative reactivities of representative aldehydes and ketones toward 1 were studied by mixing 5 mmol of two carbonyl compounds in 10 mL of tetrahydrofuran and then introducing 5 mmol of 1 to the mixture. The amounts of the two products were determined by GLC and the relative reactivity was calculated according to the Ingold-Shaw equation.[3] The results summarized in Table I reveal an interesting chemoselectivity of 1. Aldehydes are much more reactive than ketones; even pivalaldehyde is 40 times more reactive than cyclohexanone. Cyclohexanone is about 30 times more reactive than cyclopentanone; 2-pentanone, a methyl ketone, is about 9 times more reactive than 3-pentanone and cyclopentanone.

(1) Wang, K. K.; Nikam, S. S.; Ho, C. D. *J. Org. Chem.* **1983**, *48*, 5376-5377.

(2) (a) Danheiser, R. L.; Carini, D, J.; Fink, D. M.; Basak, A. *Tetrahedron* **1983**, *39*, 935-947. (b) Danheiser, R. L.; Carini, D. J. *J. Org. Chem.* **1980**, *45*, 3925-3927.

(3) Ingold, C. K.; Shaw, F. R. *J. Chem. Soc.* **1927**, 2918-2926.
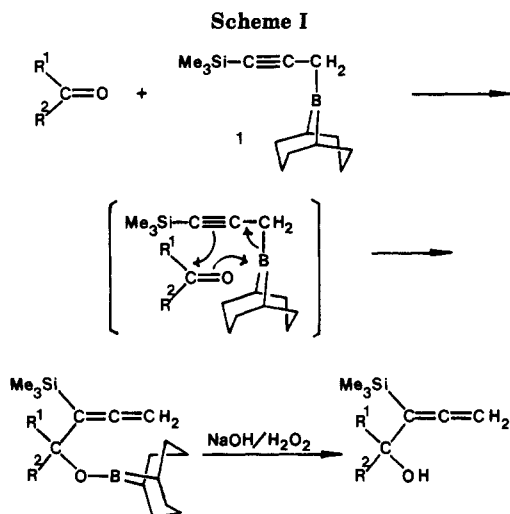
Scheme I

Table I. Relative Reactivities of Representative Aldehydes and Ketones toward Trimethylsilyl-Substituted Propargylic Borane 1 in THF at 25 °C

| aldehyde or ketone	relative reactivity[a]
hexanal	100
isobutyraldehyde	87
benzaldehyde	37
crotonaldehyde	31
pivalaldehyde	3.0
cyclohexanone	7.3×10^{-2}
2-methylcyclohexanone	5.2×10^{-2}
acetone	4.4×10^{-2}
2-pentanone	2.1×10^{-2}
acetophenone	1.8×10^{-2}
cyclopentanone	2.5×10^{-3}
3-pentanone	2.4×10^{-3}
2-methylcyclopentanone	1.0×10^{-3}
butyrophenone	5.9×10^{-4}

[a] Normalized; hexanal = 100.

Table II. Relative Reactivities of Representative Ketones toward Trimethylsilyl-Substituted Propargylic Borane 2 in THF at 25 °C

ketone	relative reactivity[a] 2	relative reactivity[a] 1
cyclohexanone	100	100
2-pentanone	28	29
acetophenone	17	25
cyclopentanone	9.4	3.5
3-pentanone	2.8	3.2

[a] Normalized; cyclohexanone = 100.

We also investigated the relative reactivities of ketones toward 2 (Table II). Similar results were observed when compared with 1.
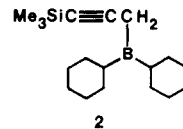
The data in Table I indicate that 1 will selectively react with an aldehyde group in the presence of a keto group. Indeed, this selectivity was observed with 3 (eq 1), and the hemiketal 4 was obtained. The hemiketal as the preferred tautomer had also been observed for 2-(3-hydroxypropyl)cyclohexanone.[4]

(4) Cazaux, M.; De Jeso, B. *C. R. Hebd. Seances Acad. Sci., Ser. C* **1980**, *290*(2), 49-51.