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Organic Reactions at High Pressure. Conversion of Cyclic Alkanones and Enones to 1,3-Dioxolanes[1]

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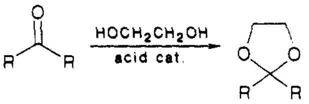
Cycloalkenones and α,α-disubstituted cycloalkanones were allowed to react under 15 kbar (1.5 GPa) pressure by employing either the protic conditions of ethylene glycol, triethyl orthoformate, and p-toluenesulfonic acid in benzene/toluene (7:3 mol ratio) at 40 °C for 48 h or the aprotic conditions of 1,2-bis[(trimethylsilyl)oxy]ethane and TMSOTf in dichloromethane at 20 °C for 24 h. Both the protic and aprotic high-pressure methods brought about the formation of 1,3-dioxolanes 8–14 as a result of enhanced reaction rates promoted by the application of pressure.

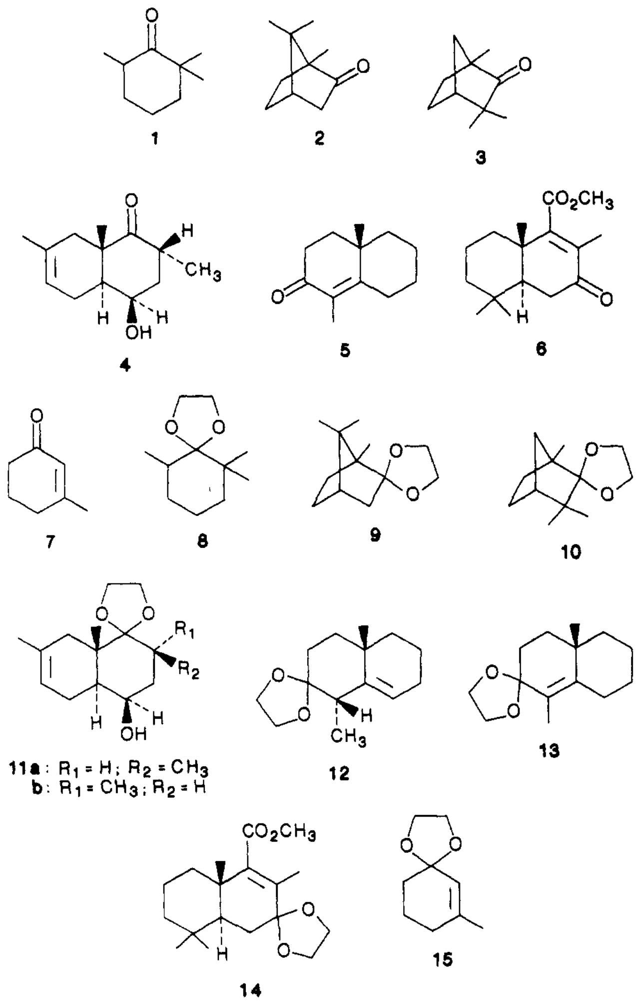
The ketone functionality often plays an important role during the course of the synthesis of complex natural products since this functionality may undergo a variety of useful functional group interconversions. For those synthetic strategies which evolve by having the carbonyl moiety present in the molecule at an early stage of the synthesis, this functional group is often masked such that the remaining portion of the molecule may be manipulated by utilizing a variety of reaction conditions. The most widely used ketone protecting group is the 1,3-dioxolane[3] which is readily synthesized from the corresponding ketone.



Not only are ketals versatile carbonyl protecting groups,[3] but when the glycol unit of the ketal contains chiral carbon centers, the resulting chiral ketals are of considerable value. The chiral 1,3-dioxolanes may aid in the assignment of stereochemistries of parent prochiral ketones and also serve as useful chiral auxiliaries for subsequent reaction.[4]

When planning a synthesis which employs the preparation of a 1,3-dioxolane, attention must be given to the reactivity of the ketone substrate. It is well-known[3b] that cyclic ketones which are α,β-unsaturated and/or contain an α,α-disubstituted pattern show low reactivity toward ketalization, and the use of forcing conditions often leads to decomposition of the starting ketone and/or formation of undesirable side products. The present research efforts have been focused toward developing a new synthetic method to overcome these ketone substrate limitations which hinder ketal production.

Chart I



The utilization of pressure as a variable parameter[5] appeared to be a logical choice with regard to a method which would effect ketalization upon the less reactive ketone substrates. This choice was based on the following considerations dealing with the use of high pressure in synthesis.[5,6] First, the formation of the structurally related

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[3] For reviews dealing with the formation and chemistry of ketals, see: (a) Alexahis, A.; Commercon, A.; Coulentianos, C.; Norman, J. F. *Pure Appl. Chem.* **1983**, *55*, 1759. (b) Greene, T. W. *Protective Groups in Organic Synthesis*; Wiley-Interscience: New York, 1981; Chapter 4, pp 116–128. (c) Meskens, F. A. J. *Synthesis* **1981**, 501. (d) Bergstrom, R. G. In *The Chemistry of Ethers, Crown Ethers, Hydroxyl Groups and Their Sulphur Analogues, Supplement E, Part 2*; Patai, S., Ed.; Wiley: New York, 1980; Chapter 20. (e) Schnitz, E.; Eichhorn, I. In *The Chemistry of the Ether Linkage*; Patai, S., Ed.; Wiley: New York, 1967; Chapter 7.

[4] (a) Hiemstra, H.; Wynberg, H. *Tetrahedron Lett.* **1977**, 2183. (b) van Leusen, D.; Rouwette, P. H. F. M.; van Leusen, A. M. *J. Org. Chem.* **1981**, *46*, 5159. (c) Fukatani, Y.; Maruoka, K.; Yamamoto, H. *Tetrahedron Lett.* **1984**, *25*, 5911.

[5] For selected reviews of high pressure chemistry see: (a) Matsumoto, K.; Sera, A.; Uchida, T. *Synthesis* **1985**, *1*. (b) le Noble, W. J. *Chem. Unserer Zeit* **1983**, *17*, 152. (c) Isaacs, N. S. *Liquid Phase High Pressure Chemistry*; Wiley-Interscience: New York, 1981. (d) Asano, T.; le Noble, W. J. *Chem. Rev.* **1978**, *78*, 407. (e) le Noble, W. J. *Prog. Phys. Org. Chem.* **1967**, *5*, 207.

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acetals has been noted to possess a negative volume of activation $(-\Delta V^{\ddagger})$.[5d] Such processes should be enhanced with pressure. Secondly, bimolecular acid-catalyzed processes have been shown to be accelerated with pressure.[5c,d] And lastly, several types of reactions which utilize sterically hindered substrates often experience reaction rate acceleration with the application of pressure.[5a,c] Therefore, a study was performed to evaluate the effects of applying 15-kbar (1.5-GPa) pressure to the acid-catalyzed protic and aprotic ketalization methods[3] when cyclic α,β-unsaturated and α,α-disubstituted ketones are used as substrates.

Results and Discussion

The cyclic ketones chosen for this study are shown in Chart I. The cycloalkanone substrates used were those which are known to be sterically congested,[7] such as 2,2,6-trimethylcyclohexanone (**1**), camphor (**2**), and fenchone (**3**). The fourth cycloalkanone, bicyclic ketol **4**,[8] was chosen because of the hindered carbonyl moiety and also because of the sensitive hydroxyl and olefin functionalities. The three cycloalkenones employed as starting materials included enones **5**, **6**, and **7**. Since the conversion of enones to ketals can often be slow,[3b,e] they are also appropriate substrates for the pressure study.

In order to evaluate which method[3] would be best to convert ketones **1**–**7** to their corresponding ketals, the first experiments run were those which employed the classical protic conditions[3b] of ethylene glycol and *p*-toluenesulfonic acid (*p*-TsOH). Since the 15-kbar pressure technique is a static process, triethyl orthoformate was chosen as the in situ water trap.[9] Therefore, ketones **1**–**7** were allowed to react with ethylene glycol, triethyl orthoformate, and *p*-TsOH in benzene/toluene at 15-kbar pressure[10] (1.5 GPa) at 40 °C for 48 h, and the results from these runs are summarized in Table I. Indeed, treatment of these sterically hindered ketones using the protic condition under 15-kbar pressure at 40 °C yielded all of the desired ketals (**8**–**14**) except for 1,3-dioxolane **15**. The substituted alkanones **1**–**3** readily afforded their respective ketals **8** (83%), **9** (74%), and **10** (82%). When the more highly functionalized and sensitive ketone **4** was allowed to react, the methyl epimer ketals **11a** (53%) and **11b** (3%) and also starting material **4** (18%) were obtained.

The assignments of the stereochemistry of the C-2 methyl groups in ketals **11a** and **11b** were based on their ^{1}H NMR spectra.[11] Noteworthy is the ratio of **11a**/**11b** (17/1) whereby the ketal assigned the axially oriented methyl grouping (**11a**) predominates. Finally, when 1,3-dioxolanes **11a** and **11b** were individually subjected to the protic pressure reaction conditions (ethylene glycol, triethyl orthoformate, and *p*-TsOH in benzene/toluene, 15-kbar pressure for 48 h at 40 °C), analyses of these reactions revealed that ketals **11a** and **11b** did not interconvert and were stable to the reaction conditions.

Table I. Formation of 1,3-Dioxolanes from Sterically Congested Cyclic Ketones Using Ethylene Glycol and Triethyl Orthoformate under 15-kbar Pressure

entry	ketone	15-kbar pressure yields[a,b] ketal product, % (recovered ketone, %)	1-bar pressure yields[b,c] ketal product, % (recovered ketone, %)
1	**1**	**8**, 83 (**1**, 0)	
2	**2**	**9**, 74 (**2**, 0)	
3	**3**	**10**, 82 (**3**, 0)	**10**, 24 (**3**, 72)
4	**4**	**11a**, 53; **11b**, 3 (**4**, 18)[d]	
5	**5**	**12**, 32; **13**, 38 (**5**, 25)	**12**, 14; **13**, 0 (**5**, 73)
6	**6**	**14**, 82 (**6**, 0)	
7	**7**	**15**, 0[e] (**7**, 0)	

[a] The reactions were run by using molar ratios of ketone/ethylene glycol/triethyl orthoformate/*p*-TsOH equal to 1.0 mmol/10.7 mmol/1.5 mmol/0.05 mmol in 3.5 mL of benzene/toluene (7.3 mol ratio) under 15-kbar pressure at 40 °C for 48 h. [b] Yields for products and recovered ketones are isolated yields. [c] The reactions were run by using molar ratios of ketone/ethylene glycol/triethyl orthoformate/*p*-TsOH equal to 1.0 mmol/10.7 mmol/1.5 mmol/0.05 mmol in 20 mL of benzene under 1-bar pressure at 40 °C for 48 h. [d] Remainder of material is elimination products. [e] A complex mixture resulted as detected by ^{1}H NMR and HPLC.

Table II. 1-bar Pressure Control Reactions of the Protic Ethylene Glycol Ketalizations of Ketones 1–7 Carried Out Using Refluxing Conditions with a Water Separator

entry	ketone	1-bar pressure yield,[a,b] ketal product, % (recovered ketone, %)
1	**1**	**8**, 78 (**1**, 7)
2	**2**	**9**, 71 (**2**, 28)
3	**3**	**10**, 30 (**3**, 62)
4	**4**	**11a**, 0; **11b**, 38 (**4**, 9)
5	**5**	**12**, 22; **13**, 20 (**5**, 56)
6	**6**	**14**, 0 (**6**, 96)
7	**7**	**15**, 0[c] (**7**, 0)

[a] The 1-bar pressure control reactions were performed by using molar ratios of ketone/ethylene glycol/*p*-TsOH of 1.0 mmol/10.7 mmol/1.5 mmol in 20 mL of benzene and were maintained at reflux for 48 h with continuous water removal. [b] Ketal product and recovered ketone yields are isolated. [c] A complex mixture resulted as detected by ^{1}H NMR and HPLC.

Enone **5** also underwent ketalization using the protic pressure method (Table I) to afford the olefin-isomerized 1,3-dioxolane **12** (32%), the unisomerized ketal **13** (38%), and also unreacted enone starting material **5** (24%). The formation of ketal **12** was not unexpected since olefins of 3-keto-4-ene steroids are known to isomerize during the ketalization process.[12] The stereochemistry of **12** follows from ^{1}H NMR analysis and structural assignments of **12** and **13** follow from ^{1}H NMR analysis[13] and crossover experiments.[14-16]

Enone-ester **6** was readily converted to the corresponding ketal **14** (82%). Finally, enone **7**, when treated

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(6) Commercial high pressure equipment is available from several sources. Semipreparative and preparative high-pressure apparati which operate between 5 and 10 kbar pressures are available from Harwood Engineering Co., Inc., South Street, Walpole, MA 02081, and Tem-Pres Division, Leco Corp., Bellefonte, PA 16823.

(7) Corey, E. J.; Tius, M. A. *Tetrahedron Lett.* **1980**, *21*, 3535.

(8) For a discussion regarding compounds of the type **4** see: Henegar, K. E. Ph.D. Dissertation, University of California, Berkeley, 1984.

(9) Caserio, F. F.; Roberts, J. D. *J. Am. Chem. Soc.* **1958**, *80*, 5837.

(10) For a description of the 15-kbar pressure apparatus and the associated methodologies see: Dauben, W. G.; Krabbenhoft, H. O. *J. Org. Chem.* **1977**, *42*, 280.

(11) The C-2 hydrogen atom of **11b** should resonate at lower field than the same hydrogen atom of **11a** due to the well-established axial–axial interaction between the C-2 hydrogen and C-4 hydroxyl group. From COSY experiments such was found to be the case, and from NOESY experiments a large NOE effect was found between the axial C-2 hydrogen and the axial angular methyl group in **11b**.

(12) For a discussion of the mechanism of olefin isomerization during ketalization of 3-keto-4-ene steroids, see: (a) Djerassi, C.; Gorman, M. *J. Am. Chem. Soc.* **1953**, *75*, 3704. (b) Brown, J. J.; Lenhard, R. H.; Bernstein, S. *Experientia* **1962**, *18*, 309. (c) Brown, J. J.; Lenhard, R. H.; Bernstein, S. *J. Am. Chem. Soc.* **1964**, *86*, 2183.

(13) The chemical shift (see ref 11) for the C-1 methyl group and the vinyl proton clearly establish an equatorial methyl group and an 8,8a-olefinic double bond for **12**. The chemical shift for the C-1 methyl singlet and the absence of a vinyl proton signal supports the structural assignment for **13**.

(14) In crossover experiments, treatment of the unisomerized **13** under reaction conditions (ethylene glycol, triethyl orthoformate, and *p*-TsOH in benzene–toluene, 15-kbar pressure, 48 h, 40 °C) afforded a mixture of **12** and **13** in ratios of 1.05–1.0, respectively. Similar treatment of **12** to the reaction conditions provided only recovered starting 1,3-dioxolane **12**.

(15) Similar interconversion of ketal products have been previously performed; see ref 12.

(16) The 15-kbar pressure control reaction of **12** afforded only recovered starting material. The potential products of this reaction, ketals **12** and **13**, were not detected by ^{1}H NMR and HPLC.

under the protic ketalization conditions, failed to provide the desired 1,3-dioxolane **15**. Analysis of the reaction mixture (^{1}H NMR and HPLC) revealed a complex array of products (>10) and a complete absence of starting material **7**. Enone **7** is considered to be a more reactive substrate, thereby allowing side reactions to compete effectively with the desired ketalization process under 15-kbar pressure. Possible side reactions include those which involve the 1,4-additions of alcohols to enones in the presence of an acid catalyst while under pressure.[17]

In order to evaluate the 15-kbar reactions with regard to the similar reaction at 1-bar pressure, a direct comparison of ketones **3** and **5** was undertaken (see Table I).[18] In both cases, the 1-bar reaction afforded less of the desired 1,3-dioxolane: for compound **3**, 24% as compared to 82%, and for compound **5**, 13% as compared to 70%. These experiments clearly demonstrate that rate enhancement of the protic ketalization process occurs with the application of high pressure.

The evaluation of an alternate 1-bar protic ketalization method devoid of triethyl orthoformate which could be conducted at a temperature higher than 40 °C was undertaken. The standard method of using ethylene glycol and *p*-TsOH in benzene with water removed by continuous azeotropic distillation[19] for 48 h was studied with ketones **1**–**7**. The results for these higher temperature experiments are summarized in Table II. It was found that yields of the ketals from ketones **1** and **2** were equivalent to the high-pressure procedure, but the conversion for ketone **3** was much lower (82% vs. 30%). The yields of ketals from ketones **4** and **5** was less than half that obtained at high pressure, and the ratios of the ketal isomers were quite different. The enone **6** did not react, and the enone **7** yielded a complex mixture of products. In summary, a comparison of the 15-kbar pressure syntheses to both 1-bar experiments clearly shows the enhanced product yields are a result of ketalization rate acceleration promoted by the application of pressure.

Efforts were directed next toward evaluating the effects of changing the parameters of solvent, temperature, time, and *in situ* drying agent upon the protic ketalization product yields.[20] A solvent study is necessary when one considers that the ketalization process is undoubtedly occurring by acid catalysis[3c] which involves participation of a charged species along the reaction coordinate.[3] Since the electrostriction phenomenon can be critical to rate enhancement under pressure and also since electrostriction can be effected by solvent polarity,[5] the solvents chosen for study were the less polar hexane and the more polar acetonitrile and dichloromethane. Using the ketalization of fenchone (Table I) as the test reaction, the experiment was performed by subjecting **3** to the same reagents under 15-kbar pressure for 48 h at 40 °C in the three solvents mentioned above. The product yields obtained for the formation of ketal **10** were 55% (hexane), 85% (CH_2Cl_2), and 82% (CH_3CN) (data not shown).

Table III. Ketalization of Ketones 3 and 5 Employing the Protic Ethylene Glycol Method under 15-kbar Pressure at the Lower Temperature of 20 °C[a]

entry	ketone	*T*, °C	*t*, h	yields ketal product, % (recovered ketone, %)
1[b]	3	20	48	**10**, 22 (**3**, 78)[b]
2[b]	3	20	168	**10**, 62 (**3**, 38)[b]
3[c]	5	20	48	**12**, 5; **13**, 16 (**5**, 71)[c]
4[d]	5	20	168	**12**, 27; **13**, 34 (**5**, 25)[d]

[a] The reactions were carried out by subjecting a mixture of ketone (1.0 mmol), ethylene glycol (10.7 mmol), triethyl orthoformate (1.5 mmol), and *p*-toluenesulfonic acid (0.05 mmol) in 3.5 mL of benzene/toluene to 15-kbar pressure at 20 °C for the time indicated. [b] Gas chromatography yields. [c] Isolated yields. [d] The yields of 1,3-dioxolanes **11a** and **13** were determined by ^{1}H NMR. The yield of **5** is an isolated yield.

The decreased production of ketal **10** in hexane relative to the other solvents studied is significant since solvents of lower dielectric constant normally aid the electrostriction phenomenon most.[5c] The implication is that those steps of the ketalization process which are enhanced by pressure are most likely those in which there are no new charges created. Thus, for the protic ketalization reaction it seems that the electrostriction phenomenon is of lesser importance than originally thought, which would account for the similar yields obtained with benzene/toluene, CH_2Cl_2, and CH_3CN.

For minimization of the thermal requirements to optimally effect ketalization, cycloalkanone **3** and cycloenone **5** were allowed to react with ethylene glycol, triethyl orthoformate, and *p*-toluenesulfonic acid under 15-kbar pressure at a lower temperature (20 °C) for both 48 and 168 h. The results of these ketalization runs are summarized in Table III. Allowing fenchone (**3**) to react for 48 h at 20 °C provided ketal **10** in 22% yield (entry 1). Extending the reaction time to 168 h increased the yield of **10** to 62% (entry 2). When enone **5** was allowed to react for 48 h at 20 °C, ketals **12** and **13** were obtained in 5% and 16% yields, respectively. When the duration of reaction is extended to 168 h, increased yields of 1,3-dioxolane formation (**12**, 27%; **13**, 34%) were observed. Comparison of the product yields obtained under pressure at 20 °C (Table III, entries 1 and 3) to those at 40 °C (Table I, entries 3 and 5) show that during the constant time period of 48 h superior yields are obtained with the use of elevated temperature. Even by allowing the 20 °C reactions to proceed for 168 h (Table III, entries 2 and 4) did not afford ketal yields equal to those obtained at 40 °C for 48 h (Table I, entries 3 and 5). Thus, the shorter time (48 h) and higher temperature (40 °C) condition is the better method to effect the protic ketalizations while under pressure.

Finally, since enone **7** appeared to be highly reactive to both the 15-kbar and 1-bar pressure conditions (Tables I and II, entry 7) and in view of the result that methanol undergoes a 1,4-addition to mesityl oxide in the presence of acid while under pressure,[17b] it was of interest to examine the ketal product distribution as a function of the type of in situ drying agent used. The experiment was performed by changing the reagent from triethyl to trimethyl orthoformate and allowing the new water trap to react with enones **5** and **7** in the presence of ethylene glycol and *p*-toluenesulfonic acid in benzene/toluene under 15-kbar pressure for 48 h at 40 °C. Enone **5** afforded the expected ketals **12** and **13** in the combined yield of 71%. When the more reactive **7** was subjected to the trimethyl orthoformate condition, the novel methoxy adduct **16** (60%) was obtained. Since cycloalkanones are known to

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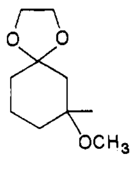
(17) Side reactions of this type have precedence. (a) The 1,4-addition of methanol occurring under 1-bar pressure: Rabiller, C.; Martin, G. *Tetrahedron* **1978**, *34*, 3281. (b) Methanol has been shown to add cleanly to mesityl oxide in the presence of acid while under pressure: Scott, J. J.; Brower, K. R. *J. Am. Chem. Soc.* **1967**, *89*, 2682.

(18) A literature search (1920–present) revealed that the formation of ketals **8**–**15** have yet to be reported.

(19) Daignault, R. A.; Eliel, E. L. *Organic Synthesis*; Wiley: New York, 1973; Collect. Vol. V, p 303.

(20) It should be noted that an additional optimization study was performed by varying the pressure (1–15 kbar) upon the protic ketalization of fenchone. This study revealed that for those pressures studied, thee conditions of 15 kbar, 40 °C, and 48 h produced the greatest amount of the desired ketal **10**. A full account of this experiment may be found in: Dauben, W. G.; Gerdes, J. M.; Look, G. C. *Synthesis* **1986**, 532.



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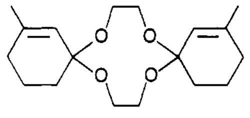
be more easily converted to 1,3-dioxolanes than enones[3b] and also realizing how feasible the 1,4-addition reaction of methanol is under pressure,[17b] it is postulated that the formation of **16** is occurring by first the 1,4-addition of methanol followed by ketalization of the resulting methoxycycloalkanone. The absence of methanol addition products associated with bicyclic enone **5** demonstrates the reactivity difference between ketone substrates **5** and **7**. It appears that the β-accepting end of the olefin in **5** is sufficiently hindered to make the 1,4-addition of methanol a less competitive process relative to ketalization of the enone carbonyl.

Complementary to the protic ketalization conditions employing ethylene glycol and *p*-toluenesulfonic acid[9,19] is the aprotic ketalization method recently reported by Noyori[21] to be highly efficient at low temperatures. More recently, Hwu[22] has shown that this reaction is highly affected by steric congestion. The question arose as to whether this more recent aprotic methodology would also bring about ketalization of hindered alkanones **1–3** and enones **5–7** under 15-kbar and 1-bar pressures.[23] Ketones **1–7** were allowed to react with 1,2-bis[(trimethylsilyl)oxy]ethane (**17**)[24] and the catalyst trimethylsilyl trifluoromethanesulfonate (TMSOTf) in dichloromethane under 15-kbar pressure at 20 °C for 24 h. The results for these aprotic high-pressure ketalizations are shown in Table IV. As revealed by entries 1, 2, and 3, hindered cycloalkanones **1**, **2**, and **3** underwent ketalization to the extents of 81% (**8**), 48% (**9**), and 91% (**10**) yields, respectively. The three enones **5–7** also underwent reaction. Enone **5** gave rise to ketals **12** and **13** in 24% and 45% yields, respectively, and keto-ester **6** provided the expected 1,3-dioxolane **14** in 59% yield. Finally, when 3-methylcyclohexenone was subjected to the aprotic pressure conditions, dimer **18** (30%) was obtained and not the monomer ketal **15**.



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Comparison of the 15-kbar pressure yields afforded using the protic method (Table I) to those obtained with the aprotic conditions (Table IV) show that the formation of ketals **8** and **10** are almost equivalent. Camphor (**2**), however, afforded only a 48% yield of **9** (Table IV) as compared to the protic process yield of **9** of 74% (Table I). It should be noted that enone **5** afforded a smaller ratio of **12**/**13** using the aprotic method (Table IV, entry 6) than that obtained with the protic conditions (Table I). The increased amounts of unisomerized olefin ketal **13** using the Noyori reagents were not unexpected.[21] The formation of dimer **18** (Table IV, entry 9) is of value since **18** may undergo further chemical transformation as compared to the complex mixture obtained when enone **7** is treated under the protic pressure ketalization conditions (Table I, entry 7). In summary, application of 15-kbar pressure using either the aprotic or protic methods will give rise to nearly all of the desired 1,3-dioxolanes.

Since the Noyori method under pressure afforded acceptable amounts of the desired ketals, two different aprotic 1-bar pressure control experiments were conducted. The first experiment followed the thermal conditions noted previously,[21] whereby the selected ketones **2**, **3**, and **5** (Table IV, entries 3, 5, and 7, method B) were allowed to react with **17** and TMSOTf at −78 °C for 5 h and quenched with pyridine (−78 °C). Subsequent processing and analysis revealed that all three ketones *failed* to undergo ketalization and only starting materials were recovered. On the basis of these results, a second aprotic 1-bar pressure control experiment was performed which allowed the ketalization temperature to be raised from −78 to 20 °C. These control reactions were carried out by treating ketones **1–3** and **5–7** with **17** and TMSOTf in CH_2Cl_2 first at −78 °C for 30 min and then at 20 °C for 48 h. The reactions were quenched (20 °C, pyridine), worked up, and then analyzed to afford the data in Table IV, entries 1, 2, 4, 6, 8, and 9 (method A, 1-bar pressure). As shown by entries 1, 6, and 9, only ketones **1**, **5**, and **7** were observed to react at 20 °C to yield 1,3-dioxolanes **8** (48%), **13** (23%), and dimer ketal **17** (57%), respectively.

Comparison of the aprotic 1-bar pressure yields to those obtained under 15-kbar pressure (Table IV) indicates that the formation of ketals **8–14** are greatly accelerated with pressure. This claim is substantiated by the failure of bicyclic alkanones **2** and **3** to form their respective ketals even at 20 °C and 1-bar pressure. Furthermore, the reaction of enone **5** which gave rise to both ketals **12** and **13** at 15-kbar pressure, only afforded the 1,3-dioxolane **13** at 1-bar pressure and 20 °C. Further evidence of the dramatic difference of product yields between 1-bar and 15-kbar pressure is demonstrated by enone **6** (entry 8). Finally, the fact that dimer **18** was obtained in much greater yield at 1-bar pressure than at 15-kbar pressure (entry 9) could be a result of the labile nature of enone **7** and a change of reactivity of **17** and TMSOTf under pressure.[25] This reasoning could account for the observations that under 15-kbar pressure no starting material (**7**) is recovered, whereas under 1 bar pressure a significant balance of starting material is obtained.

These studies have shown that α,α-disubstituted cycloalkanones and highly substituted cycloalkenones which react slowly, if at all, under normal ketalization reaction conditions do react under 15-kbar pressure using protic or aprotic conditions. These findings offer a new dimension to the use of ketals as blocking groups.

Experimental Section

General Methods. Benzene, toluene, dichloromethane, and acetonitrile were distilled from CaH_2 and stored over 4-Å molecular sieves. Diethyl ether was distilled from sodium benzophenone ketyl. Pyridine, triethyl orthoformate, and trimethyl orthoformate

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[21] (a) Tsunoda, T.; Suzuki, M.; Noyori, R. *Tetrahedron Lett.* **1980**, *21*, 1357. (b) Noyori, R.; Murata, S.; Suzuki, M. *Tetrahedron* **1981**, *37*, 3899.

[22] Hwu, J. R.; Wetzel, J. M. *J. Org. Chem.* **1985**, *50*, 3948.

[23] As discussed in ref 3, there are a variety of procedures to effect 1,3-dioxolane formation. Besides the protic and aprotic methods discussed in the text, several other methods were tried under 15-kbar pressure; however, all failed to provide the desired ketals. The procedures tried were as follows. (a) Ethylene glycol, $BF_3 \cdot Et_2O$, and HOAc: Fieser, L. F.; Stevenson, R. *J. Am. Chem. Soc.* **1954**, *76*, 1728. (b) Ethylene glycol and 2,4,6-collidinium *p*-toluenesulfonate: Nitz, T. J.; Paquette, L. A. *Tetrahedron Lett.* **1984**, *25*, 3047. (c) Methanol and pyridinium *p*-toluenesulfonate: Sterzycki, R. *Synthesis* **1979**, 724. (d) Ethylene glycol, 2-methyl-2-ethyl-1,3-dioxolane, and *p*-TsOH: Bauduin, G.; Pietrasanta, Y. *Tetrahedron* **1973**, *29*, 4225.

[24] Available from Aldrich Chemical Co.

[25] It is possible that the acidic properties of TMSOTf are enhanced under pressure. For a discussion of increased acid and base strengths with pressure, see ref 5c.

Table IV. Formation of 1,3-Dioxolanes Using 1,2-Bis[(trimethylsilyl)oxy]ethane and Trimethylsilyl Trifluoromethanesulfonate under 15-kbar and 1-bar Pressures

		15-kbar pressure[a]	1-bar pressure[b]	
entry	ketone	yields[c], ketal, % (recovered ketone, %)	method[d]	yield[c] ketal, % (recovered ketone, %)
1	1	8, 81 (1, 0)	A	8, 48 (1, 22)
2	2	9, 48 (2, 47)	A	9, 0 (2, 98)
3	2		B	9, 0, (2, 100)
4	3	10, 91 (3, 7)	A	10, 0 (3, 97)
5	3		B	10, 0 (3, 100)
6	5	12, 24; 13, 45 (5, 0)	A	12, 0; 13, 23 (5, 35)
7	5		B	12 + 13, 0 (5, 100)
8	6	14, 59 (6, 31)	A	14, 0 (6, 87)
9	7	15, 0; 18, 30 (7, 0)	A	18, 57 (7, 35)

[a] The reaction were performed by using molar ratios of ketone/$(TMSOCH_2)_2$/TMSOTf equal to 1.0 mmol/1.1 mmol/0.001 mmol in 3.5 mL of CH_2Cl_2 under 15-kbar pressure at 20 °C for 24 h. [b] The 1-bar pressure control reactions were run by using the same molar ratios of reactants and solvent as the 15-kbar pressure entries. [c] Yields are isolated. [d] Method: A, −78 °C for 30 min and then 20 °C for 48 h; B, −78 °C for 5 h.

were distilled from Na. Ethylene glycol was purified by drying over $MgSO_4$ followed by distillation and then a second distillation from Na. The second distillate was stored over 4-Å molecular sieves.

Analytical gas chromatography was performed with a Hewlett-Packard 5880A level four integrating recorder which also employed a capillary column (30 m × 0.25 mn) packed with J & W Scientific Durabond-1 (film thickness = 0125 μm). Preparative gas chromatography was carried out on a Varian Aerograph Model A-90-P gas chromatograph affixed with a 10 ft × 0.25 in. column packed with 5% SE-30 on Chromosorb W. High performance liquid chromatography (HPLC) was carried out with a Waters Associates 6000A pumping system and an R401 differential refractometer coupled with a Rheodyne injector and a Whatman M9-partisil 10/50 semipreparative column. The solvents employed, hexane and ethyl acetate, were glass distilled, and their mixtures were reported as volume/volume ratios. Flash chromatography was carried out by using EM silica gel (230–400 mesh).

The ^1H NMR spectra were recorded with a Varian EM-390 spectrometer (90 MHz). Chemical shifts are expressed in δ (ppm) downfield from tetramethylsilane. Infrared (IR) spectra were obtained by using a Perkin-Elmer Model 281 spectrometer as thin films (NaCl plates). Ultraviolet (UV) spectra were run in 95% ethanol by using a Hewlett-Packard 8450A spectrophotometer and recorded with a Hewlett-Packard Model 7225B printer-plotter; results are expressed as λ_{max} in nanometers (ϵ). Melting points reported are uncorrected and were obtained with a Mel-Temp melting point apparatus. Elemental analyses were performed by the Microanalytical Laboratory, operated by the College of Chemistry, University of California, Berleley. Mass spectra were obtained by using a Kratos MS-50 high-resolution mass spectrometer operated by the College of Chemistry, University of California, Berkeley.

The high-pressure reactions were executed by using the 15-kbar pressure technology described previously.[10]

General Procedure for the Conversion of Cycloalkanones and Cycloalkenones to 1,3-Dioxolane Using Ethylene Glycol and Triethyl Orthoformate at 15-kbar Pressure (Table I). A 3.5-mL benzene/toluene (7:3 mol ratio) solution of ketone (1.0 mmol), ethylene glycol (10.7 mmol), triethyl orthoformate (1.5 mmol), and p-toluenesulfonic acid (anhydrous, 0.05 mmol) in a 4.0 cm × 1.0 cm Teflon tube clamped at both ends was pressurized at 15-kbar (1.5-GPa) pressure for 48 h at 40 °C (see the following experimental details for the exact amount of starting material used for each reaction). The reactions were cooled, depressurized, and poured into saturated $NaHCO_3$ (50 mL). The mixture was extracted with ether (50 mL) and washed with water (25 mL) and brine (50 mL). The ether portion was dried (Na_2SO_4/Na_2CO_3 [anhydrous], 1:1) and filtered, and the solvent was removed on a rotary evaporator. The resulting crude product mixtures were purified and characterized as described below.

1-(1,3-Dioxolan-2-yl)-2,2,6-trimethylcyclohexane (8) (Table I, Entry 1). Ketone 1 (140 mg, 1.0 mmol) was subjected to the conditions described above and the resulting crude oil was chromatographed (HPLC, 1:19 ethyl acetate/hexane). The solvent was removed on a rotary evaporator to provide only ketal 8 (151 mg, 83%): IR (thin film) 1100 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 4.03 (s, 4), 2.0 (m, 1), 1.8–1.1 (complex, 6), 1.0 (s, 3), 0.83 (s, 3), 0.80 (d, 3, J = 3 Hz). The analytical sample was afforded by preparative gas chromatography. Anal. Calcd for $C_{11}H_{20}O_2$: C, 71.70; H, 10.94. Found: C, 71.78; H, 11.05.

2-(1,3-Dioxolan-2-yl)-1,7,7-trimethylbicyclo[2.2.1]heptane (9) (Table I, Entry 2). Ketone 2 (152 mg, 1.0 mmol) was subjected to the conditions described above, and the resulting crude oil was chromatographed (HPLC, 1:19 ethyl acetate/hexane). The solvent was removed under reduced pressure to afford only ketal 9 (145 mg, 74%): IR (thin film) 1125 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 3.8 (m, 4), 2.2–1.1 (complex 7), 1.03 (s, 3), 0.83 (s, 3), 0.80 (s, 3). Preparative gas chromatography was used to obtain the analytical sample. Anal. Calcd for $C_{12}H_{20}O_2$: C, 71.64; H, 10.93. Found: C, 71.42; H, 10.69.

2-(1,3-Dioxolan-2-yl)-1,3,3-trimethylbicyclo[2.2.1]heptane (10) (Table I, Entry 3). Fenchone 3 (152 mg, 1.0 mmol) was treated under the reaction conditions noted above, and the resultant oil was analyzed by using analytical gas chromatography which indicated only the single component ketal 10 (160 mg, 82%): IR (thin film) 1160 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 3.86 (m, 4), 1.85–1.1 (complex, 7), 1.0 (s, 3), 0.98 (s, 3), 0.97 (s, 3). The mass spectra sample was obtained by preparative gas chromatography; exact mass calcd for $C_{12}H_{20}O_2$ 196.1464; found 196.1459.

trans-(2S*,4R*,4aS*,8aS*)- and trans-(2R*,4R*,4aS*,8aS*)-1-(1,3-Dioxolan-2-yl)-4-hydroxy-2,7,8a-trimethyl-1,2,3,4,4a,5,8,8a-octahydronaphthalene, 11a and 11b (Table I, Entry 4). Ketone 4 (300 mg, 1.44 mmol) was treated under the reaction conditions described above, and the resultant crude semisolid was chromatographed (HPLC, 1.0:3.00 ethyl acetate/hexane). Many fast-moving elimination products appeared first, and then three compounds were obtained in the following elution order. They were the less polar ketal 11a, isolated as an oil (192 mg, 53%), the more polar ketal 11b, isolated as a solid (11 mg, 3%), and finally the recovered starting material ketone 4 (54 mg, 18%). The oil 11a properties were as follows: IR (thin film) 3500, 1100 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 5.34 (br s, 1), 3.85 (m, 5), 1.75 (m, 1), 1.61 (br s, 3), 1.25 (d, 3, J = 7.5 Hz), 1.20 (s, 3); exact mass calcd for $C_{15}H_{24}O_3$ 252.1756; found 252.1729. The solid 11b was recrystallized from ether/hexane: mp 81–83 °C; IR (thin film) 3420, 1110, 1080 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 5.4 (br s, 1), 4.0 (m, 4), 3.79 (m, 1), 2.45 (m, 1), 1.62 (br s, 3), 1.12 (s, 3), 0.84 (d, 3, J = 7.5 Hz); exact mass calcd for $C_{15}H_{24}O_3$ 252.1726; found 252.1719.

(1S*,4aS*)-2-(1,3-Dioxolan-2-yl)-1,4a-dimethyl-1,2,3,4,4a,5,6,7-octahydronaphthalene, 12, and (4aS*)-2-(1,3-Dioxolan-2-yl)-1,4a-dimethyl-2,3,4,4a,5,6,7,8-octahydronaphthalene, 13 (Table I, Entry 5). Enone 5 (178 mg, 1.0 mmol) was subjected to the reaction conditions noted above, and the crude yellow oil was chromatographed (HPLC, 1.0:5.86 ethyl acetate/hexane, recycle and shave). Three compounds were obtained, and the order of their elution was the less polar olefin isomerized ketal 12 (71 mg, 32%), the more polar ketal 13 (85 mg, 38%), and recovered starting material enone 5 (43 mg, 24%).

The ketal 12 was rechromatographed (seven recycles) to reveal that only one compound (12) was present (also note the ^{1}H NMR spectra described below). The properties of ketal 12 were as follows: IR (thin film) 1620, 1465, 1020, 975 cm^{-1}; ^{1}H NMR (90 MHz, CDCl$_3$) δ 5.43 (m, 1), 3.9 (m, 4), 1.05 (s, 3), 0.92 (d, 3, J = 7.5 Hz); exact mass calcd for $C_{14}H_{22}O_2$ 222.1621; found 222.1617. The properties of 13 were as follows: IR (thin film) 1650, 1450, 1175, 1080 cm^{-1}; ^{1}H NMR (90 MHz, CDCl$_3$) δ 4.3 (m, 4), 1.58 (s, 3), 1.1 (s, 3); exact mass calcd for $C_{14}H_{22}O_2$ 222.1621; found 222.1622.

***trans*-(4a*S**,8a*S**)-1-Carbomethoxy-3-(1,3-dioxolan-2-yl)-2,5,5,8a-tetramethyl-3,4,4a,8a,5,6,7,8-octahydronaphthalene, 14 (Table I, Entry 6).** Enone 6 (61 mg, 0.23 mmol) was treated under the reaction conditions described above. The resulting crude oil was chromatographed (HPLC, 1.0:5.66 ethyl acetate/hexane) to reveal one new component and also the complete absence of starting material enone 6. The solvent was removed under reduced pressure to afford ketal 14 (58 mg, 82%): IR (thin film) 1735, 1650, 1250, 1060 cm^{-1}; ^{1}H NMR (90 MHz, CDCl$_3$) δ 4.03 (m, 4), 3.7 (s, 3), 1.56 (s, 3), 1.23 (s, 3), 0.9 (s, 3), 0.86 (s, 3); UV (95% EtOH) λ_{max} 267 (ϵ 9806); exact mass calcd for $C_{18}H_{28}O_4$ 308.1988; found 308.1995.

Ketalization of 3-Methylcyclohex-2-en-1-one, 7 (Table I, Entry 7). Enone 7 (110 mg, 1.0 mmol) was subjected to the reaction conditions described above. The crude yellow oil was chromatographed (HPLC, ethyl acetate/hexane, 1:1.86) to reveal a complex mixture consisting of 11 components. Due to the complexity of this mixture, further separation and characterization was not pursued. Starting material enone was not detected by HPLC or ^{1}H NMR.

Ketalization of Ketones 3 and 5 Employing Ethylene Glycol and Triethyl Orthoformate under 15-kbar Pressure at 20 °C (Table III). The procedure used was similar to that employed at 15-kbar pressure and 40 °C. A 3.5-mL benzene/toluene (7:3 mol ratio) solution of ketone (1.0 mmol), ethylene glycol (10.7 mmol), triethyl orthoformate (1.5 mmol), and *p*-toluenesulfonic acid (0.05 mmol) was pressurized to 15 kbar at 20 °C for either 48 or 168 h (see the experimental details in the supplementary material and also Table II). The reactions were depressurized and processed with saturated NaHCO$_3$, water, brine, andd Na$_2$SO$_4$/Na$_2$CO$_3$ as described earlier for the 15-kbar, 40 °C runs. The resulting crude reaction product mixtures were purified and characterized as noted in prior studies. The results are listed in Table III.

Ketalization of Enones 5 and 7 Using Trimethyl Orthoformate and Ethylene Glycol at 15-kbar Pressure. A similar procedure to that described previously using triethyl orthoformate at 15-kbar pressure (Table I) was employed. A 3.5-mL benzene/toluene (7:3 mol ratio) solution of enone (1.0 mmol), ethylene glycol (10.7 mmol), trimethyl orthoformate (1.5 mmol), and *p*-toluene sulfonic acid (anhydrous, 0.05 mmol) was pressurized under 15-kbar pressure for 48 h at 40 °C (see the following experimental details for exact amounts of starting materials used). The reactions were processed with ether, saturated NaHCO$_3$, water, and brine as described earlier. The resulting crude product mixtures were purified and characterized as described below.

Ketalization of Enone 5. Enone 5 (178 mg, 1.0 mmol) was treated with trimethyl orthoformate by using the reaction conditions described above. The resulting crude oil was chromatographed (HPLC, 1.0:5.66 ethyl acetate/hexane), and the solvent was removed from the two fractions collected to afford 157 mg of the ketal mixture 12 and 13 (71%) and 43 mg of recovered starting material enone 5 (25%). Adducts resulting from the acid-catalyzed 1,4-addition of methanol to enone 5 were not detected by ^{1}H NMR and HPLC analyses. The ketal mixture was shown by ^{1}H NMR integration (vinyl proton of 12 and ketal protons of 12 and 13) to consist of an 11a/12 ratio equal to 1:1.19.

Ketalization of Enone 7: 1-(1,3-Dioxolan-2-yl)-3-methoxy-3-methylcyclohexane, 16. Enone 7 (110 mg, 1.0 mmol) was treated with trimethyl orthoformate under reaction conditions described above. The resulting bright yellow crude oil was flash chromatographed (silica gel, 20 cm × 2.5 cm, ether/hexane, 1.5:1), and the solvent was removed under reduced pressure to afford only the methoxy ketal 16 (110 mg, 60%): IR (thin film) 1460, 1100, 1030 cm^{-1}; ^{1}H NMR (90 MHz, CDCl$_3$) δ 3.83 (s, 4), 3.15 (s, 3), 2.0–1.3 (complex, 8), 1.2 (s, 3); mass spectrum, exact mass calcd for $C_{10}H_{18}O_3$ 186.1256; found 186.1262.

General Procedure for the 15-kbar Pressure Ketalization Reactions Using 1,2-Bis[(trimethylsilyl)oxy]ethane and Aprotic Conditions (Table IV). A similar procedure to that described by Noyori[21] was employed. A solution of CH$_2$Cl$_2$ (1 mL) was cooled to −78 °C under argon and then charged with trimethylsilyl trifluoromethanesulfonate (TMSOTf, 0.001 mmol).[24] To this mixture was added (−78 °C) 1,2-bis[(trimethylsilyl)oxy]ethane[24] (1.1 mmol) in CH$_2$Cl$_2$ (1 mL) followed by the ketone (1.0 mmol) in CH$_2$Cl$_2$ (1.5 mL). The solution was maintained at −78 °C for 30 min and warmed to 20 °C (30 min). The colored solutions were transferred (argon) to a Teflon tube (argon) which was sealed and pressurized to 15 kbar at 20 °C for 24 h. The samples were depressurized and quenched with dry pyridine (3 drops). The solution was poured into saturated NaHCO$_3$ (20 mL) and extracted with ether (50 mL). The ether portion was washed with water (20 mL) and brine (20 mL) followed by drying over Na$_2$SO$_4$/Na$_2$CO$_3$, 1:1. The solutions were filtered and concentrated under reduced pressure to afford the crude reaction mixtures which were purified and analyzed as described below.

Ketone 1 (Table IV, Entry 1). Ketone 1 (139 mg, 1.0 mmol) was treated to the conditions above. The crude reaction mixture oil was purified by preparative gas chromatography to afford ketal 8 (148 mg, 81%) and recovered ketone 1 (11 mg, 8%).

Ketone 2 (Table IV, Entry 2). Ketone 2 (154 mg, 1.0 mmol) was subjected to the conditions described above. The crude oil obtained was purified and separated by preparative gas chromatography to provide 94 mg of ketal 9 (48%) and 72 mg of ketone 2 (47%).

Ketone 3 (Table IV, Entry 4). Ketone 3 (152 mg, 1.0 mmol) was treated under the conditions described above. The resulting crude oil was chromatographed (HPLC, 1.0:1.19 ethyl acetate/hexane), and the solvent was removed under reduced pressure to afford ketal 10 (178 mg, 91%) and also recovered fenchone 3 (11 mg, 7%).

Enone 5 (Table IV, Entry 6). Enone 5 (178 mg, 1.0 mmol) was subjected to the reagents and conditions cited above. The crude oil was chromatographed (HPLC, 1.0:1.86 ethyl acetate/hexane), and the solvent was removed under reduced pressure to afford 153 mg of a mixture of ketals 12 and 13. The mixture was analyzed by ^{1}H NMR (integration of the vinyl proton of 12, relative to the ketal protons of 12 and 13) and showed the ketal 12 (24%) and the ketal 13 (45%). No starting material enone 5 was detected (HPLC, ^{1}H NMR).

Enone 6 (Table IV, Entry 8). Keto ester 6 (150 mg, 0.56 mmol) was allowed to react under the conditions noted above. The resulting oil was chromatographed (HPLC, 1.5:5.66 ethyl acetate/hexane), and the solvent was removed under reduced pressure from the two fractions collected. The residues were analyzed by ^{1}H NMR and showed ketal 14 (101 mg, 59%) and enone 13 (47 mg, 31%).

Enone 7 (Table IV, Entry 9). Enone 7 (110 mg, 1.0 mmol) was subjected to the reaction conditions given above. Flash chromatography of the resulting crude oil (silica gel, 20 cm × 1.5 cm, 2:1 ether/hexane) afforded only dimer 17 (46 mg, 30%): IR (thin film) 1675, 1190, 1090, 1035 cm^{-1}; ^{1}H NMR (90 MHz, CDCl$_3$) δ 5.2 (s, 1), 3.86 (s, 4), 1.66 (s, 3); exact mass calcd for $C_{18}H_{28}O_4$ 308.1998; found 308.1983.

General Procedures for the 1-bar Pressure Ketalizations Using Aprotic Conditions (Table III). Method A. A 1-mL solution of CH$_2$Cl$_2$ was cooled to −78 °C under argon and charged with trimethylsilyl trifluoromethanesulfonate (0.001 mmol). To this solution was added (−78 °C), 1,2-bis[(trimethylsilyl)oxy]ethane (1.1 mmol) in CH$_2$Cl$_2$ (1.0 mL) followed by the ketone (1.0 mmol) in CH$_2$Cl$_2$ (1.5 mL). The solution was maintained at −78 °C for 30 min, warmed to 20 °C, and stirred for 48 h. The reaction was quenched with dry pyridine (three drops) and poured into saturated NaHCO$_3$ and extracted with ether (20 mL). The ether portion was washed with water (20 mL) with wine brine (20 mL) followed by drying over Na$_2$SO$_4$/Na$_2$CO$_3$ (1:1). The solution was filtered and concentrated under reduced pressure to affford the crude residues which were purified and analyzed as described below.

Method B. The reactions were carried out by using the identical molar ratios of reactants and amounts of solvent as noted for method A. The reactions were stirred at −78 °C for 5 h and quenched (-78 °C) with dry pyridine (three drops). The solutions were processed with saturated $NaHCO_3$, ether, water, brine, and drying agent as described above (method A). The resulting crude reaction mixtures were purified and analyzed as described below.

Ketone 1 (Table IV, Entry 1). Method A. Ketone 1 (139 mg, 1.0 mmol) afforded, after flash chromatography (silica gel, 20 cm × 1 cm, 1.9 ether/hexane), ketal 8 (85 mg, 47%) and ketone 1 (39 mg, 28%).

Ketone 2 (Table IV, Entries 2 and 3). Method A. Ketone 2 (152 mg, 1.0 mmol) yielded only recovered camphor 2 (150 mg, 98%). **Method B.** Ketone 2 (152 mg, 1.0 mmol) afforded, after chromatography (HPLC, 1:19 ethyl acetate/hexane), starting material 2 (152 mg, 100%).

Ketone 3 (Table IV, Entries 4 and 5). Method A. Fenchone 3 (152 mg, 1.0 mmol) afforded after distillation only recovered fenchone 3 (147 mg, 97%). **Method B.** Ketone 3 (152 mg, 1.0 mmol) yielded, after chromatography (HPLC, 1:19 ethyl acetate/hexane), recovered fenchone 3 (152 mg, 100%).

Ketone 5 (Table IV, Entries 6 and 7). Method A. Enone 5 (178 mg, 1.0 mmol) provided, after chromatography (HPLC, 1.0:1.86 ethyl acetate/hexane) ketal 13 (51 mg, 23%) and recovered enone 5 (62 mg, 35%). The formation of ketal 11a was not detected (HPLC, ^1H NMR). **Method B.** Enone 5 (178 mg, 1.0 mmol) yielded, after chromatography (HPLC, 1.0:1.86 ethyl acetate/hexane), only recovered ketone 5 (178 mg, 100%).

Ketone 6 (Table IV, Entry 8). Enone 6 (84 mg, 0.38 mmol) afforded, after chromatography (HPLC, 1.0:1.86 ethyl acetate/hexane), only recovered starting material 6 (73 mg, 87%).

Ketone 7 (Table IV, Entry 9). Enone 7 (110 mg, 1.0 mmol) yielded, after flash chromatography (silica gel, 1:1 ether/hexane), the dimer 18 (87 mg, 57%) and recovered enone 7 (39 mg, 35%).

Registry No. 1, 2408-37-9; 2, 76-22-2; 3, 1195-79-5; 4, 105018-93-7; 5, 878-55-7; 6, 105018-96-0; 7, 1193-18-6; 8, 71018-58-1; 9, 18501-53-6; 10, 105018-92-6; 11a, 105018-94-8; 11b, 105087-93-2; 12, 105018-95-9; 13, 65898-56-8; 14, 105087-94-3; 15, 105018-99-3; 16, 105018-97-1; 18, 105018-98-2; ethylene glycol, 107-21-1; 1,2-bis[(trimethylsilyl)oxy]ethane, 7381-30-8.

Supplementary Material Available: Experimental details for the crossover experiments, 1-bar control experiments referred to in Tables I and II, the effect of solvent in the formation of ketal 10, and 15-kbar experiments using triethyl orthoformate at 20 °C (7 pages). Ordering information is given on any current masthead page.

Complete Structural Analysis of Cyclic Polyhalogenated Monoterpenes. A Force Field 2D NMR Study

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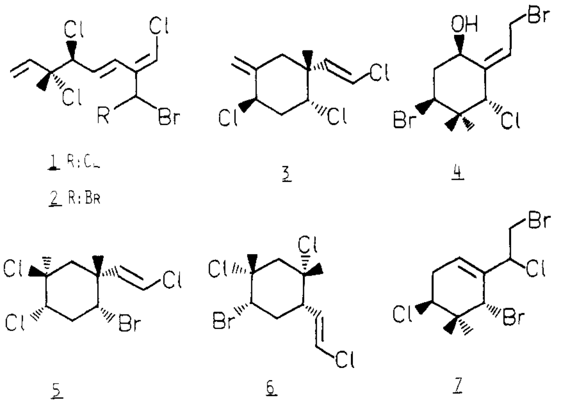
The information obtained from two-dimensional NMR and NOED spectroscopy led to the complete structural analysis of five cyclic monoterpenes of marine origin. Correlated 2D spectra allowed the establishment of the gross structural features, the final stereochemical assignments being made by NOEDS. The use of ^{13}C NMR shifts in defining the regio- and stereochemistry of monoterpenes 17-21 is criticized in terms of the inappropriateness of the models used. Force field calculations show that models 8-16 do not accurately reproduce the structural features of the cyclic terpenes 17-21, thus precluding the straightforward application of ^{13}C additive effects. The calculated minimum energy conformers of 17-21 agree well with the geometries deduced experimentally by using a generalized Karplus equation.

The complete structural analysis of natural products is a topic of continuing interest among chemists. One of the important characteristics of the molecules obtained from natural sources is the wide variety of the structures exhibited by them, which has served as a permanent stimulus for the development of spectroscopic techniques of increasing power and sophistication.

The analysis of ^{13}C shift data in terms of substituent effects has led to the structural elucidation of many natural products.[1,2] The approach used is to determine a series of additive substituent shift effects from the study of suitable model compounds and to apply them to the molecules of interest. This technique has been extensively used in the field of marine natural products, a recent example of this being represented by the excellent work of P. Crews and co-workers[3] who identified the structures of three newly isolated polyhalogenated monoterpenes 1-3 and proposed corrected structures for the other four compounds 4-7 (Chart I) by using additive effects taken from simple models (Chart II).

Chart I



Unsuspectedly, a few months later the proposed structure 5 was revised as its epimer 19 by a low-temperature X-ray analysis.[4] This finding prompted us to investigate this issue further and to develop a more reliable spectro-

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(1) Maciel, G. E. *Topics in C-13 NMR Spectroscopy*; Levy, G. C., Ed.; Wiley: New York, 1974; Vol. I, p 53.

(2) (a) Wenkert, E.; Buckwalter, B. L.; Burfit, I. R.; Gasic, M. J.; Gottlieb, H. E.; Hagaman, E. W.; Schell, F. M.; Wovkulich, P. M. *Topics in C-13 NMR Spectroscopy*; Levy, G. C., Ed.; Wiley: New York, 1976; Vol. II, p 81. (b) Wehrli, F. W.; Nishida, T. *Prog. Chem. Org. Nat. Prod.* 1979, *36*, 1.

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