Table I. Reductions of Prochiral Ketones with Neat *B*-3-Pinanyl-9-borabicyclo[3.3.1]nonane at 6000 atm (92% ee (+)-α-Pinene)

ketone	reaction time, days: 6000 atm[a]	reaction time, days: 1 atm[b]	%ee[c]: 6000 atm	%ee[c]: (corrected[d])	%ee[c]: 1 atm	isolated yield	abs config[e]
acetophenone	1	7[4a]	92	(100)	78[4a]	80	*S*
acetophenone	1		98.4[f]			83	*S*
3-acetylpyridine	1.5[g]	2	92	(100)	90	67	*S*
2,2-dimethyl-5-(trimethylsilyl)-4-pentyn-3-one	2.5[h]	NR[i]	92	(100)	*i*		(*R*)[j]
3-methyl-2-butanone	1	14[4a]	83	(90)	57[4a]	47	*S*
α-tetralone	3	29	82	(89)	52	43	*S*
cyclopropyl methyl ketone	5.5	NR[i]	69	(75)	*i*	65	(*S*)[j]
trans-4-phenyl-3-buten-2-one	<1	3	65	(71)	58		*S*
2-octanone	<1	7[4a]	58	(63)	44[4a]	63	*S*

[a] Reaction carried to >97% completion. [b] Reaction typically carried to 60–75% completion except as noted in ref 4a. [c] %ee determined by proton chiral shift study at 200 MHz with $Eu(hfc)_3$. [d] Corrected for 92% ee (+)-α-pinene. [e] Determined by sign of rotation. [f] 98.5% ee (+)-α-pinene was used. [g] 1.0 mL of THF added per 10.0 mmol of borane. [h] Reaction was 83% complete. [i] Reaction at 1 atm too slow to be useful. [j] Configuration based on proposed mechanism.

selectivity is largely due to a 1,3-diaxial repulsion of the 3-methyl group of the pinane skeleton and the larger group of the approaching ketone. In all cases thus far observed, this model predicts the proper stereochemistry of the product alcohols. From the data in Table I and other data,[2-4] one may group the substituents according to steric bulk into categories of very small (acetylene, nitrile, hydrogen), small (methyl, carbomethoxy), medium (*n*-alkyl, vinyl), medium-large (trifluoromethyl), large (aryl, isopropyl), and very large (*tert*-butyl). Ketones containing substituents from the same or two adjacent categories will be reduced with low selectivity while ketones with substituents from two nonadjacent categories will provide alcohols in higher ee's.

The use of high pressure allows one to achieve reductions of moderately bulky ketones such as 2,2-dimethyl-5-(trimethylsilyl)-4-pentyn-3-one, cyclopropyl methyl ketone, and α-tetralone. These ketones are reduced only sluggishly or not at all at atmospheric pressure. Only 3,3-dimethyl-2-butanone failed to react at high pressure (9 days, 6000 atm). This compound is slowly reduced at atmospheric pressure (70% in 40 days)[4a] to racemic product, presumably by the dissociative process. Our results thus indicate that even at 2000 atm the dehydroboration process is essentially stopped.

In a typical procedure, Alpine-Borane is first formed as a 0.5 M THF solution.[1,3] The solvent is then removed under reduced pressure at 30 °C;[4] 0.5 equiv of a prochiral ketone is then added, and the mixture is transfered to a disposable syringe and placed in the high-pressure apparatus. After the reaction is deemed complete (>97% reduction), the sample is quenched with an aldehyde (i.e., 1.0 equiv of propionaldehyde, room temperature 1 h). The chiral alcohol product is isolated after either oxidative workup[3b] (1 equiv of 3 N NaOH followed by 3 equiv of 30% hydrogen peroxide, 40–50 °C in THF for 2 h) or ethanolamine complexation of the borane[2] (1.1 equiv of ethanolamine in ether, 0 °C) followed by chromatography and/or Kügelrohr distillation.

Our results thus indicate that pressures as low as 2000 atm can provide the rather unique ability to accelerate a desired process while stopping an undersired reaction. Increases of pressure above 2000 atm serve to further accelerate the rate of reduction. As the wide variety of ketones studied indicate, good to excellent enantiomeric excesses may be obtained with Alpine-Borane if the steric differences between the two substituents of the prochiral ketone are large enough. The enantiomeric alcohols should be readily available through the use of (−)-α-pinene or nopol.[10] We are currently exploring further applications of this novel use of high-pressure chemistry.

Acknowledgment. We thank the National Institutes of Health (GM-24517) for support of this work and Professor R. C. Neuman for helpful discussions and for the use of the high-pressure apparatus.

Registry No. $Me_3SiC{\equiv}CC(O)C(CH_3)_3$, 53723-94-7; (*S*)-$PhCH(OH)CH_3$, 1445-91-6; (*R*)-$Me_3SiC{\equiv}CCH(OH)C(CH_3)$, 89017-38-9; acetophenone, 98-86-2; 3-acetylpyridine, 350-03-8; 3-methyl-2-butanone, 563-80-4; α-tetralone, 529-34-0; cyclopropyl methyl ketone, 765-43-5; *trans*-4-phenyl-3-buten-2-one, 1896-62-4; 2-octanone, 111-13-7; *B*-(3-pinanyl)-9-borabicyclo[3.3.1]nonane, 64106-79-2; (*S*)-3-(1-hydroxyethyl)pyridine, 5096-11-7; (*S*)-3-methyl-2-butanol, 1517-66-4; (*S*)-α-tetralol, 53732-47-1; (*S*)-1-cyclopropylethanol, 55637-37-1; (*S*)-*trans*-4-phenyl-3-buten-2-ol, 81176-43-4; (*S*)-2-octanol, 6169-06-8.

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Silicon in Organic Synthesis. 23. Chloro[(trimethylsilyl)methyl]ketene as a Useful Intermediate for the Elaboration of α-Methylenecyclobutanones and -cyclopentanones[1]

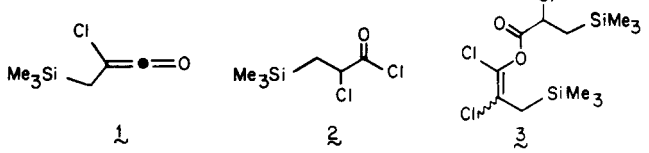
Summary: The title ketene, which is readily available by dehydrohalogention of the α-chloro acid chloride, adds to cyclopentadiene, vinyl ethers, and silyl enol ethers to give cyclobutanones with complete stereocontrol (and regiocontrol where relevant). These products enter regiospecifically into ring expansion with diazomethane. Both sets of molecules experience desilylative elimination with introduction of an α-methylene group on reaction with fluoride ion in an anhydrous dipolar solvent at room temperature.

Sir: Although methyleneketene ($CH_2{=}C{=}C{=}O$) could well service several synthetic objectives, the elusiveness and instability of this substance[2] preclude its widespread

(1) Part 22: DeLucca, G.; Paquette, L. A. *Tetrahedron Lett.* **1983**, *24*, 4931.

0022-3263/84/1949-1317$01.50/0

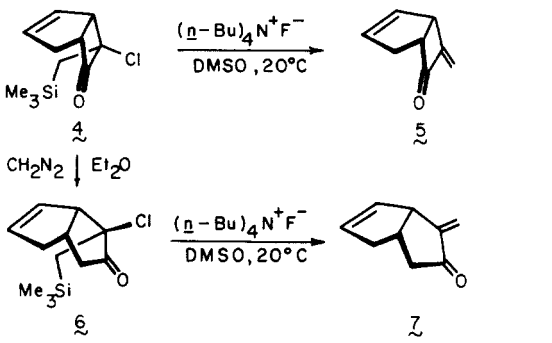
use. Consequently, interest has arisen in the development of a conveniently accessible synthon for this reactive species. Hassner[3] and Agawa[4] have shown that methylchloroketene and methyl[(phenylthio)methyl]ketene enter satisfactorily into [2 + 2] cycloaddition. Unfortunately, subsequent introduction of the desired double bond suffers in both cases from conditions sufficiently vigorous to discourage their implementation with polyfunctional molecules. The need to achieve this overall chemical conversion in connection with a synthetic program underway in these laboratories led to the search for a more mild and generally useful method. This communication records the fact that chloro[(trimethylsilyl)methyl]ketene (1) represents a practical solution to this problem.



1 2 3

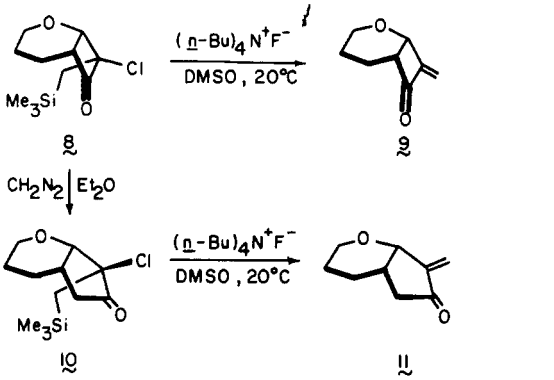
Synthesis of the key reagent 2 was readily achieved via reaction of β-(trimethylsilyl)propionic acid[5] with oxalyl or thionyl chloride, followed by treatment with *N*-chlorosuccinimide in thionyl chloride solution under nitrogen at 70 °C[6] (56% overall after distillation). Dehydrochlorination of 2 with triethylamine *in the absence of an acceptor olefin* affords 3 in line with limited precedent.[7] Because of the competing formation of 3 during cycloadditions involving 1 and lesser reactive acceptor olefins,[8] it proved advisable to utilize more than one equivalent of the ketene in these circumstances.

Exposure of cyclopentadiene to 1 in dry pentane solution at 0 °C resulted in isolation of the single homogeneous adduct 4 in 67% yield after chromatography.[9] The stereochemical assignment to 4 is predicated upon previously recognized[10] steric control criteria and supported by ^{1}H NMR chemical shift data. Despite the relatively hindered nature of the trimethylsilyl substituent, elimination proceeds smoothly at 20 °C in dry dimethyl sulfoxide solution containing tetra-*n*-butylammonium fluoride to furnish 5[4] (34%). Regiocontrolled ring expansion[11] of 4 to 6 is also possible (66%) and serves as a prelude to the elaboration of 7 (89%).



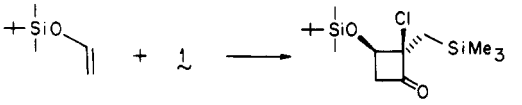
4 5 6 7

Analogously, cyclobutanone 8 was obtained from dihydropyran (93%)[12] and transformed into 9[4] (30%) and 11 (73%).



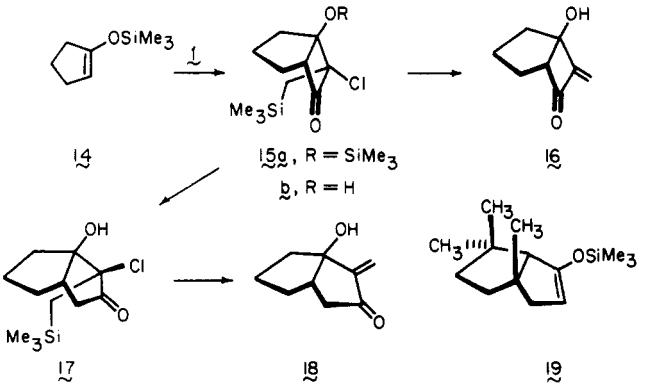
8 9 10 11

A study of the reactivity of silyl enol ethers began with the use of 12[13] as the test substrate. Conversion to 13 was effected cleanly and very efficiently (94%) in the presence of 2 molar equiv of the ketene. The stereo- and regioselectivity of this cycloaddition are particularly noteworthy.



12 13

The capture of 14 proceeds similarly to give **15a**, which was routinely hydrolyzed with 1% hydrochloric acid in methanol and isolated in the form of the analytically pure hydroxy derivative (94–96% overall). Although both **15a**



14 15a, R = SiMe$_3$ 16
15b, R = H
17 18 19

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(8) The cycloaddition of 1 to norbornene delivers a [2 + 2] adduct in approximately 5% yield amidst considerable amounts of 3. With cyclopentene, no adduct was found.

(9) All new compounds exhibited compatible infrared, proton/carbon magnetic resonance, and mass spectroscopic or combustion analysis data. Yields refer to isolated chromatographically homogeneous materials.

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(12) A typical cycloaddition procedure follows: Freshly distilled 2 (1.0 g, 5.0 mmol) in 20 mL of pentane (freshly distilled from CaH_2) was added via syringe pump over 3 h to a cold (0 °C) solution of dihydropyran (420 mg, 0.92 mmol) and triethylamine (1.0 mL, 5.1 mmol) in pentane (20 mL). A white precipitate formed immediately, and the slurry was stirred under nitrogen for 1 h prior to filtration through 80 g of Florisil. Elution with pentane afforded 1.14 g (93%) of 8 as a faintly yellow oil; IR (CCl_4, cm^{-1}) 1800; ^{1}H NMR ($CDCl_3$) δ 4.2 (d, J = 5.8 Hz, 1 H), 3.8 (m, 2 H), 3.2 (m, 1 H), 2.1 (d, J = 14 Hz, 1 H), 1.6–1.4 (m, 3 H), 1.4 (d, J = 15 Hz, 1 H), 1.2 (d, J = 15 Hz, 1 H), 0.1 (s, 9 H).

(13) Jung, M. E.; Blum, R. B. *Tetrahedron Lett.* **1977**, 3794.

and **15b** are susceptible to ring expansion with diazomethane, the direct conversion of **15b** to the colorless crystalline cyclopentanone **17** (mp 52.5–53 °C; 87%) is a particularly attractive laboratory protocol. The desilylative elimination of **15b** and **17** to produce the labile, synthetically attractive hydroxy ketones **16** and **18** was achieved in excellent yield through use of Bu_4NF or KF in a variety of strictly anhydrous aprotic solvents (Me_2SO, THF, or CH_3CN).

While the above data demonstrate the useful features of **1**, two drawbacks to its application in other contexts have been noted. The ketene, which is a relatively bulky reagent in its own right, is sensitive to the level of steric congestion in its reaction partner. As an illustration, **1** happens to be unreactive toward **19**. Also, although the high level of C_α substitution in cyclobutanones such as **4**, **8**, and **15** does not discourage attack by diazomethane, ring expansion to the corresponding lactones by peracids does not proceed at a rate sufficiently rapid to preclude the incursion of unwanted side reactions.

Nevertheless, the particular juxtaposition of functional groups found in **1** offers an opportunity for achieving simply the annulation of highly unsaturated four- and 5-membered rings under conditions customarily tolerant to a broad range of substituents.[14]

Registry No. **1**, 89121-60-8; **2**, 89121-61-9; **3**, 89121-62-0; **4**, 89121-63-1; **5**, 66977-61-5; **6**, 89121-64-2; **7**, 89121-65-3; **8**, 89121-66-4; **9**, 66977-62-6; **10**, 89121-67-5; **11**, 89121-68-6; **12**, 66031-93-4; **13**, 89144-56-9; **14**, 19980-43-9; **15a**, 89121-69-7; **15b**, 89121-59-5; **16**, 89121-70-0; **17**, 89121-71-1; **18**, 89121-72-2; **19**, 89121-73-3; $(n\text{-}Bu)_4N^+F^-$, 429-41-4; $CH_2{=}C{=}C{=}O$, 61244-93-7; β-(trimethylsilyl)propionic acid, 5683-30-7.

(14) We acknowledge with appreciation the financial support of this research effort by the National Institutes of Health (Grant GM-28468).

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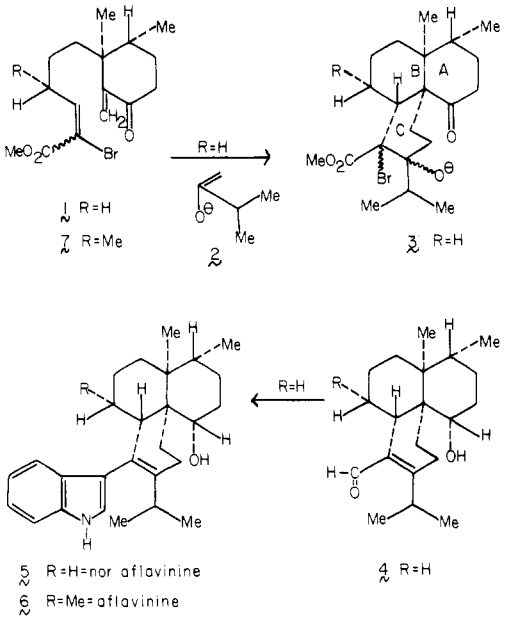
A Notable Stereochemical Variation in the 2 + 2 + 2 Annulation Reaction

Summary: A rapid entry to the epiaflavinine ring system is described.

Sir: Recently a new 2 + 2 + 2 annulation was described.[1] The reaction of compound **1** and lithium enolate **2** in dimethoxyethane gives rise to a group of bromoalkoxides, **3**. Three products, differing only in their configurations at the carbon–bromine and carbon–oxygen bonds, are obtained from **3**. The carbon–carbon backbone stereochemistry is the same in all of these compounds and corresponds to that which pertains in the novel indolic diterpene aflavinine[2] **6**. Indeed, in subsequent experiments, the bromohydrin and the two epoxides derived from **3** have been converted to noraflavinine (**5**) via the hydroxy enal **4**.[3]



It was of interest to study the extendability of this scheme to the methyl homologue **7**. If the pathway followed in the "nor" series would be operative in the case of substrate **7**, a route to aflavinine itself could be developed. In this communication, the realization of the 2 + 2 + 2 annulation with bis electrophile **7** is described. However, the inclusion of the additional methyl group brings about a major change in the stereochemical outcome relative to that observed for the reaction of **1** and **2**. While this divergence complicates the solution to the aflavinine synthesis, *it provides a rare opportunity for insight into the conformations of transients that emerge in this new annulation process.* An account of these findings is given below.

The coupling of subunits of appropriately matched chirality provided a solution to the problem of relating the remotely disposed centers of dissymmetry in structure **7**. Grignard reagent **8a** was prepared from bromide **8**, which was synthesized from (*S*)-citronellol[4] according to Ireland.[5] The preparation of (*R*)-4-methylcyclohex-2-ene-1-one (**9**) from (*R*)-pulegone was recently described from our laboratory.[6] Reaction of **9** with lithium dimethylcuprate (Et_2O, 0 °C) was followed by trapping of the metallo enolate with chlorotrimethylsilane. The resultant silyl enol ether was converted by reaction with palladium acetate into **10** (60% overall), according to the procedure of Saegusa and Ito.[7]

Treatment of Grignard reagent **8a** with enone **10** under the influence of cuprous iodide–dimethyl sulfide complex in ether (0 °C) produced a metallo enolate which was quenched (0 °C) with excess methyl chloroformate to provide a 70% yield of enol carbonate **11** (Scheme I). Reaction of **11** with 3.3 equiv of methyllithium in THF generated the corresponding lithium enolate, which reacted with 4.4 equiv of dimethylmethyleneammonium chloride,[8] to afford crude Mannich base **12**.[9] Ozonolysis of this

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(3) Danishefsky, S.; Chackalamannil, S., unpublished results, Yale University, 1983.
(4) (*S*)-(−)-Citronellol was obtained from the Fluka Chemical Corp.
(5) Following the procedure by which Ireland prepares the enantiomeric bromide: Ireland, R. E.; Anderson, R. C.; Badoud, R.; Fitzsimmons, B. J.; McGarvey, G. J.; Thaisrivongs, S.; Wilcox, C. S. *J. Am. Chem. Soc.* **1983**, *105*, 1988.
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