[2 + 2] Cycloaddition of Ethyl Propiolate and Silyl Enol Ethers

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The [2 + 2] cycloaddition of ethyl propiolate and silyl enol ethers with titanium tetrachloride catalysis gives cyclobutene adducts. Yields are generally high using *tert*-butyldimethylsilyl ($BuMe_2Si$) ethers, and correspondingly lower yields were obtained with trimethylsilyl (Me_3Si) ethers. The cycloadducts can be opened either thermally or by treatment with acid or base. The overall sequence provides a two-carbon ring expansion which is complimentary to the analogous ring expansion utilizing enamines.

The two-carbon ring expansion which utilizes the [2 + 2] cycloaddition of an acetylenic ester with the enamine of a cyclic ketone followed by opening of the resulting cyclobutene is a useful method in organic synthesis.[2-10] This sequence has been utilized in the syntheses of the natural products steganacin[11] and muscone,[12] as well as in the construction of the ophibolin nucleus.[13] There are two major problems inherent in the use of enamines for this synthetic application. Enamines of many hindered ketones are not readily accessible, and there is little control over the regiochemistry in enamine formation.[2] For these reasons, we have developed a similar two-carbon ring expansion based on the use of silyl enol ethers, which are more readily accessible by a variety of procedures and can be obtained with greater regiospecificity.[14-17]

Preparation of Trimethylsilyl and *tert*-Butyldimethylsilyl Enol Ethers. The silyl enol ethers used in the subsequent cycloaddition studies were all obtained by trapping of the kinetic enolates (deprotonation of the ketones with lithium diisopropylamide, THF, −70 °C) with the requisite silyl chloride.[16,17] In most cases, the silyl enol ethers prepared would have been derived from either the kinetic or thermodynamic enolates. The silyl enol ether **7** from 2-methylcyclopentanone was contaminated with ca. 5% of its isomer **8**. A mixture of *E* and *Z* isomers was obtained from cyclododecanone, with the *E* isomer **21** predominating (ca. 75% of the mixture). These were separated by silica gel chromatography, and the assignments of structure are based partially on their NMR spectra. The vinyl proton of *E* isomer **21** (δ 4.47) is slightly downfield from that of **24** (δ 4.40), a general trend in such cases.[17] Further evidence for these assignments derives from the subsequent cycloaddition studies. A mixture of isomers was obtained also from 4-heptanone, which was 65% *E* isomer **28** (vinyl proton at δ 4.50) and 35% *Z* isomer **29** (vinyl proton at δ 4.33).

Cycloaddition of Ethyl Propiolate and Trimethylsilyl Enol Ethers. Our initial investigations were prompted by reports of the aluminum chloride catalyzed [2 + 2] cycloaddition of propiolate esters with mono- and 1,2-disubstituted alkenes.[18] The reaction of (trimethylsilyloxy)cyclopentene (**1**) and ethyl propiolate under similar conditions ($AlCl_3$, benzene, 0 °C)[18] gave the cycloadduct **2** in 46% yield along with a minor amount of the corresponding silyl ether. Comparable yields of **2** were obtained with other Lewis acid catalysts ($SnCl_4$ and $TiCl_4$), with $TiCl_4$ in methylene chloride at −78 °C providing the best results. Although the cycloaddition reaction had been realized, the yields were relatively low (20–50%). It was found that competitive cleavage of the trimethylsilyl (Me_3Si) group in the starting material **1** had occurred, prior to cycloaddition. Even lower yields were obtained with several other trimethylsilyl enol ethers, e.g., **3**, which directly gave the ring expansion product **4** in only 22% yield.[19]

Cycloadditions with *tert*-Butyldimethylsilyl Enol Ethers. In light of the relatively low yields obtained with trimethylsilyl enol ethers, the *tert*-butyldimethylsilyl ($BuMe_2Si$)[16] ethers were evaluated. These generally proved to give good yields of cycloadducts since the $BuMe_2Si$ group is less susceptible to cleavage by the $TiCl_4$ catalyst. Typically, the reaction is carried out by the dropwise addition of a CH_2Cl_2 solution of the silyl enol ether to a −70 °C solution of $TiCl_4$ (1 equiv). As ascertained by TLC analysis, the cycloaddition is complete within several minutes at −70 °C. The results of this investigation are listed in Table I.

As is evident from the table, the cycloaddition reaction is general and gives acceptable yields in most cases. In all cases examined, the structure of the cycloadducts reflects both the regiochemistry and the stereochemistry of the initial enol ether, which demonstrates that the cycloaddition is significantly faster than double-bond isomerization.

Several examples require further comment. Silyl ether **7** gave the stereoisomeric adducts **9** and **10** in a 70:30 ratio. The stereochemistry of these products was ascertained by the use of the $Eu(fod)_3$ NMR shift reagent on the derived alcohols which are available by hydrolysis of the silyl ethers **9** and **10**. The shift reagent studies showed that in the major alcohol isomer the 7-methyl group is shifted to a much greater extent that that of the minor isomer and thus establish structure **9** as the major cycloadduct (cf., Experimental Section). It is noted also that silyl ether **8**, present in 5% of the starting mixture, gave the adduct **11** in a corresponding amount, i.e., ca. 5% of the total yield as determined by NMR. This finding supports the conclusion that the cycloadditions occur regioselectively and stereospecifically.

The $BuMe_2Si$ enol ether from cyclohexanone (**14**) gave the dienol ether **16** in addition to a modest yield of cycloadduct **15**. The formation of **16** may be explained by isomerization of the initially formed ene adduct **36**. Similar ene adducts have been observed by Snider in the aluminum chloride catalyzed reaction of ethyl propiolate with 2,2-disubstituted olefins.[18] We also observed a small amount of ene adduct **23** from the *E* silyl enol ether **21**. In this case the ene adduct did not isomerize.

Another type of product was observed in the case of the silyl ether from 2-octanone (**25**), which gave, in addition to cyclobutene **26**, 1-(*tert*-butyldimethylsilyl)-2-octanone, (**27**). Formation of **27** can be explained by $TiCl_4$ cleavage of **25** to the enolate (and $BuMe_2SiCl$), followed by carbon silylation.

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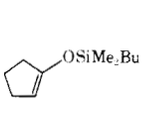
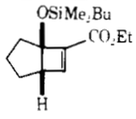
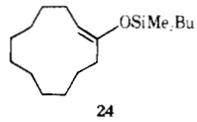
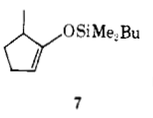
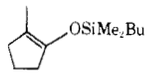
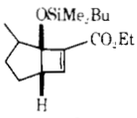
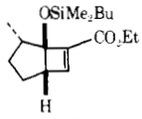
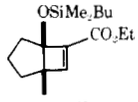
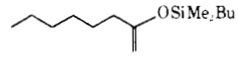
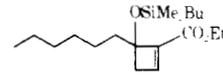
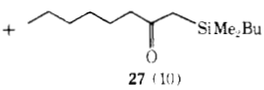
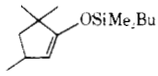
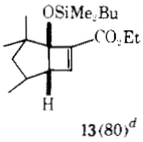
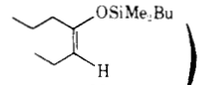
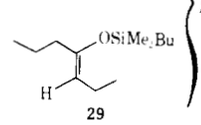
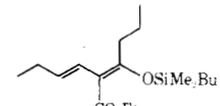
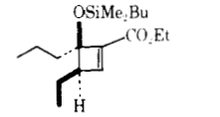
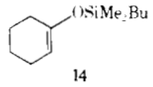
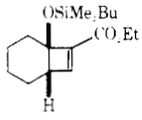
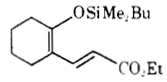
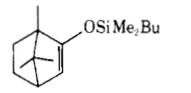
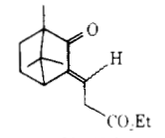
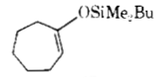
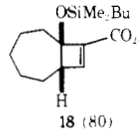
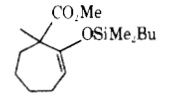
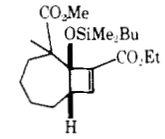
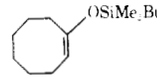
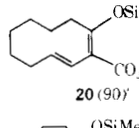
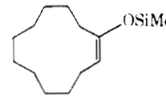
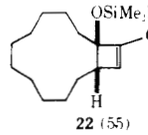
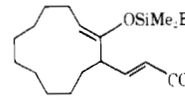
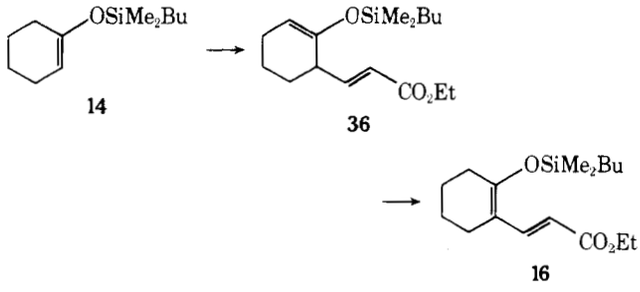
Table I. Reaction of *tert*-Butyldimethylsilyl (BuMe$_2$Si) Enol Ethers with Ethyl Propiolate

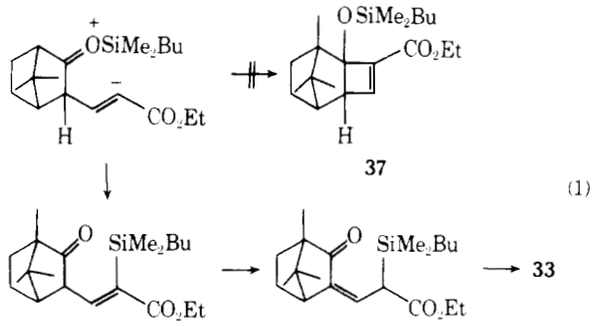
enol ether	cycloadduct (% yield)[a]	enol ether	cycloadduct (% yield)[a]
 5	 6 (57)	 24	none
 7  8 [b]	 9  10  11 [87]	 25	 26 (35) +  27 (10)
 12	 13 (80)[d]	 28  29 [f]	 30  31 [84][g]
 14	 15 (37) +  16 (10)	 32	 33 (25)[h]
 17	 18 (80)	 34	 35 (4)
 19	 20 (90)[e]		
 21	 22 (55) +  23 (5)		

[a] Products in all cases were isolated by silica gel chromatography, and yields refer to analytically pure materials. [b] A 95:5 mixture of **7** and **8**. [c] A 67:29:4 mixture of **9**, **10**, and **11**. See Experimental Section for assignments of stereochemistry. [d] The product appears to be one isomer, which is assigned this structure based solely on addition from the less hindered side. [e] The cycloadduct opens at room temperature. [f] A 65:35 mixture of **28** and **29**. [g] A 58:42 mixture of **30** and **31**. [h] A 84:16 mixture of *E* and *Z* isomers.



In no other instance was this type of product observed.

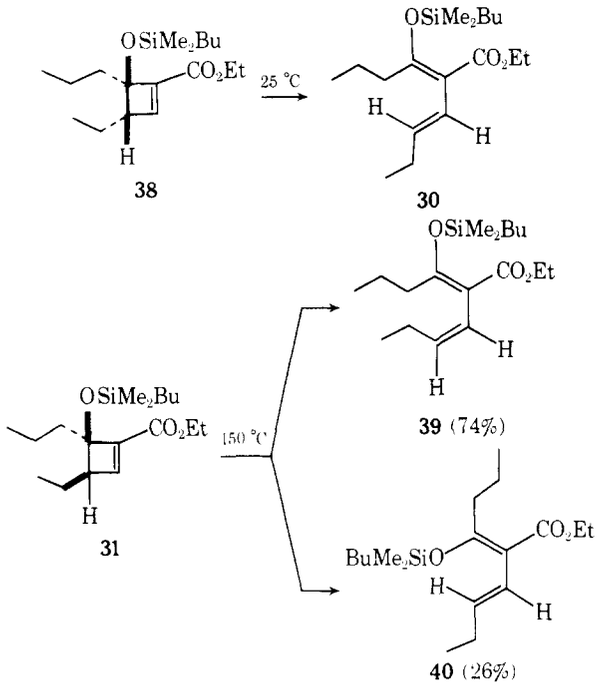
The silyl ether from camphor (**32**) gave the carboethoxyethylidine derivatives **33** in 25% yield with the remainder of the product being recovered camphor. The formation of these anomalous products may be explained by the failure of the initially formed zwitterionic intermediate to close to the cyclobutene **37**.[20,21] This ring closure would involve the development of severe steric interactions between the *tert*-butyldimethylsilyloxy group and the 7-methyl group.[22] A possible explanation for the observed products is shown in eq 1.



(1)

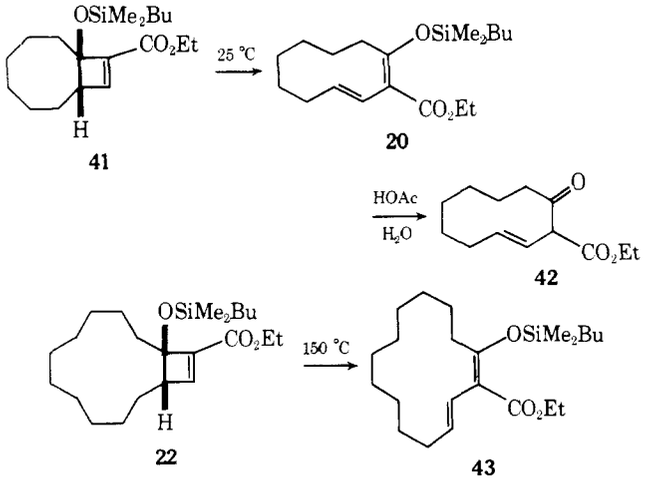
Opening of (*tert*-Butyldimethylsilyloxy)cyclobutenes. Two of the products listed in Table I are the result of the cycloadducts having undergone ring opening at room temperature. The diene **30** (J_{vinyl} = 16 Hz) is formed from the labile

cyclobutene **38**, which was observable by TLC but rapidly underwent ring opening during workup. The isomeric cyclobutene **31**, however, required heating at 150 °C for 10 min to effect ring opening. In this case, dienes **39** (J_{vinyl} = 11 Hz) and **40** (J_{vinyl} = 16 Hz) were produced in a 74:26 ratio.



The structure assigned to cyclobutene **31** is supported by the chemical shift of the allylic proton (H-4, δ 2.43), which is at higher field than the corresponding proton in any of the eight other cyclobutenes (see Table I) examined (δ 2.63–2.80) in which H-4 is cis to the *tert*-butyldimethylsilyloxy group. The structures of the three isomeric dienes follow from their conrotatory mode of formation[23] and are supported by their NMR spectra. The vinyl proton splitting patterns of the (*Z*,*E*)-**30** and (*E*,*E*)-**40** isomers are identical, but the protons in **40** are shifted to lower field (Δ = 0.23–0.27 ppm). This downfield shift can be attributed to 1,3 and 1,4 steric effects of both the *tert*-butyldimethylsilyloxy and carbethoxy groups on the vinyl protons of **40**.

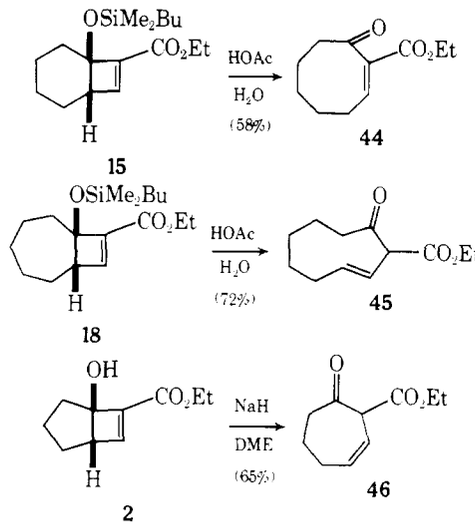
The second ring-opened product listed in Table I, diene **20**, results from cyclobutene **41**. Adduct **41** was isolated as the crude product, but readily underwent ring opening during column chromatography. The structure of **20** follows from the spectral data (J_{vinyl} = 16 Hz) and from its hydrolysis to the known β-keto ester **42**.[7] In contrast to **41**, cyclobutene **22** was opened only upon heating neat at 150 °C for 10 min to give a single product **43** in quantitative yield.



From examples **22**, **31**, **38**, and **41**, the highly preferred, if not exclusive, mode of conrotatory ring opening is that in which the *tert*-butyldimethylsilyloxy group rotates away from the center of the developing dienic system (e.g., preferred formation of **39** instead of **40**). The disparity between the thermal labilities of **31** and **38** and of **41** and **22** suggests that secondary factors such as substituents and ring fusions significantly influence the ease of cyclobutene opening.

As one might anticipate, the cyclobutenes **6**, **15**, and **18** are not thermally labile. No ring opening occurred up to 200 °C, where these compounds begin to decompose. This is in contrast to the corresponding dialkylaminocyclobutenes, which undergo ring opening at temperatures between 30–90 °C.[5-8] This indicates that participation by the nitrogen in the latter cases would afford an ionic mechanism for the ring opening. The thermal stability of the cyclobutenes **6**, **15**, and **18** is easily understood since conrotatory opening would require formation of a trans double bond in the product cyclic dienes.

However, both **15** and **18** are smoothly opened by hydrolysis in aqueous acetic acid to the corresponding alcohols, which are labile and open to the β-keto esters **44** and **45**, respectively.[24] Alcohol **2** is stable under the same acidic conditions. However, it is opened readily at room temperature by conversion to its alkoxide to give the known ketone **46**.[4]



Several examples in Table I point out some limitations of the cycloaddition reaction. The *Z* isomer of (*tert*-butyldimethylsilyloxy)cyclododecene (**24**) fails to give a cycloadduct as it is converted back to cyclododecanone under the reaction conditions. Similarly, silyl enol ether **34** gives only a 4% yield of cycloadduct **35** with the remainder of the material being recovered ketone. As in the case of the silyl ether from camphor, **32**, steric hindrance in **34** allows the cleavage of the silyl group to become the predominant reaction pathway.

We have demonstrated that the cycloaddition of ethyl propiolate and silyl enol ethers followed by subsequent ring opening of the cycloadducts offers in many cases a viable alternative to the enamine ring expansion. The use of the enol ether route is indicated in cases where regiospecificity is required as well as in certain cases where the enamine may be inaccessible. Furthermore, the silyloxycyclobutene adducts themselves may be of inherent interest as synthetic intermediates.

Experimental Section

Infrared (IR) spectra were recorded on a Perkin-Elmer 137 or a 237B grating spectrometer. Nuclear magnetic resonance (NMR) spectra were obtained with Varian A-60 and HA-100 instruments, and with a Brucker WH-90 spectrometer with Me_4Si as an internal standard. NMR spectra were recorded in carbon tetrachloride solution

unless otherwise specified. Mass spectra were recorded on an Atlas CH 4 instrument. Combustion analyses were performed by our microanalytical laboratory. Thin-layer chromatography (TLC) was carried out on Analtech (Uniplate) glass plates precoated with silica gel GF (250 μm).

Ethyl 1-Hydroxybicyclo[3.2.0]hept-6-ene-7-carboxylate (2). To a −70 °C solution of ethyl propiolate (490 mg, 5 mmol) and titanium tetrachloride (948.5 mg, 5 mmol) in 10 mL of methylene chloride was added a solution of (trimethylsilyloxy)cyclopentene (1; 780 mg, 5 mmol) in 5 mL of methylene chloride dropwise over a period of 5 min. After an additional 20 min at −70 °C, ether was added and the mixture was washed with water and brine, dried, and evaporated to a colorless oil. Chromatography on silica gel (35 g) with 30% ether–hexane afforded 444 mg (48.8%) of alcohol **2** as a colorless oil: IR (film) 3300, 1710, 1605 cm^{-1}; ^1H NMR δ 1.30 (t, 3, J = 6.5 Hz), 2.63 (s, 1, OH), 2.83 (m, 1, H-5), 4.23 (quartet, 2, J = 6.5 Hz), 6.76 (s, 1). Anal. Calcd for $C_{10}H_{14}O_3$: C, 65.91; H, 7.74. Found: C, 65.57; H, 7.72.

Preparation of *tert*-Butyldimethylsilyl Enol Ethers. The silyl enol ethers were prepared by quenching the kinetic enolates (LDA, THF, −70 °C) with *tert*-butyldimethylsilyl chloride and were purified by distillation.[16,17] Compounds **25** and **32** have been reported previously.[22] Spectral characteristics of the other silyl ethers follow.

1-(*tert*-Butyldimethylsilyloxy)cyclopentene (5): 80% yield; IR (film) 1640, 1240, 940, 835, 780 cm^{-1}; ^1H NMR δ 0.08 (s, 6), 0.87 (s, 9), 4.47 (m, 1).

2-(*tert*-Butyldimethylsilyloxy)-3-methylcyclopentene (7): 84% yield; IR (film) 1640, 1230, 860, 835 cm^{-1}; ^1H NMR δ 0.06 (s, 6), 0.87 (s, 9), 0.95 (d, 3, methyl), 4.40 (m, 1). A small amount of isomer **8** (ca. 5%) was also present: IR (film) 1680 cm^{-1}.

2-(*tert*-Butyldimethylsilyloxy)-3,3,5-trimethylcyclopentene (12): 84% yield; IR (film) 1630, 1240, 1220, 840 cm^{-1}; ^1H NMR δ 0.10 (s, 6), 0.88 (s, 9), 0.93 (s, 3), 0.96 (s, 3), 2.50 (m, 1), 4.23 (m, 1).

1-(*tert*-Butyldimethylsilyloxy)cyclohexene (14): 86% yield; IR (film) 1655, 1180, 890, 835 cm^{-1}; ^1H NMR δ 0.10 (s, 6), 0.89 (s, 9), 4.60 (m, 1).

1-(*tert*-Butyldimethylsilyloxy)cycloheptene (17): 75% yield; IR (film) 1650, 1240, 1220, 1160, 840 cm^{-1}; ^1H NMR δ 0.13 (s, 6), 0.93 (s, 9), 1.63 (m, 6), 2.10 (m, 4), 4.95 (t, 1, J = 6 Hz).

1-(*tert*-Butyldimethylsilyloxy)cyclooctene (19): 76% yield; IR (film) 1650, 1240, 1160, 960, 840 cm^{-1}; ^1H NMR δ 0.11 (s, 6), 0.90 (s, 9), 1.50 (m, 8), 2.10 (m, 4), 4.63 (t, 1, J = 8 Hz).

1-(*tert*-Butyldimethylsilyloxy)cyclododecene (21 and 24). This material was obtained as a mixture of *E* and *Z* isomers, predominantly the *Z* isomer (ca. 75–80%), in 57.3% yield. In one instance the two isomers were separated by silica gel chromatography (hexane), although this was not reproducible. The first isomer eluted has been assigned structure **21:** IR (film) 1645, 1240, 830, 770 cm^{-1}; ^1H NMR δ 0.10 (s, 6), 0.95 (s, 9), 4.47 (t, 1, J = 7 Hz). The second isomer eluted was **24:** IR (film) 1645, 1240, 1220, 930, 830, 780 cm^{-1}; ^1H NMR δ 0.10 (s, 6), 0.90 (s, 9), 4.40 (t, 1, J = 7.5 Hz).

(*E*)- and (*Z*)-4-(*tert*-Butyldimethylsilyloxy)hept-3-ene (28 and 29). A mixture of **28** and **29** was obtained in a ratio of 65:35 (^1H NMR analysis) in 78% yield: IR (film) 1650, 1240, 1190, 950, 830, 775 cm^{-1}. **28:** ^1H NMR δ 0.08 (s, 6), 0.93 (s, 9), 4.50 (t, 1, J = 7 Hz). **29:** ^1H NMR 0.08 (s, 6), 0.90 (s, 9), 4.33 (t, 1, J = 7 Hz).

7-(Carbomethoxy)-7-methyl-1-(*tert*-butyldimethylsilyloxy)cycloheptene (34): 93% yield; IR (film) 1735, 1650, 1240, 1160, 1100 cm^{-1}; ^1H NMR δ 0.08 (s, 6), 0.82 (s, 9), 1.25 (s, 3), 3.56 (s, 3), 4.80 (t, 1, J = 6 Hz).

General Procedure for Reaction of *tert*-Butyldimethylsilyl Enol Ethers with Ethyl Propiolate. Ethyl 1-(*tert*-Butyldimethylsilyloxy)bicyclo[5.2.0]non-8-ene-9-carboxylate (18). A solution of silyl ether **17** (1.13 g, 5 mmol) in 10 mL of methylene chloride was added dropwise to a −70 °C solution of ethyl propiolate (735 mg, 7.5 mmol) and titanium tetrachloride (948 mg, 5 mmol) in 15 mL of methylene chloride. The addition was carried out at such a rate (ca. 15 min) as to maintain the internal temperature below −65 °C. After an additional 20 min, the mixture was diluted with ether, washed with water and brine, dried over sodium sulfate, filtered, and evaporated to a colorless oil (1.54 g). Chromatography on silica gel (70 g) with ether–hexane (8%) gave **18** (1.30 g, 80.2%) as a colorless oil: IR (film) 1705, 1605, 832, 770 cm^{-1}; ^1H NMR δ 0.00 (s, 6), 0.85 (s, 9), 1.28 (t, 3, J = 7 Hz), 2.70 (m, 1, H-7), 4.13 (quartet, 2, J = 7 Hz), 6.76 (d, 1, J = 1 Hz). Anal. Calcd for $C_{18}H_{32}O_3Si$: C, 66.62; H, 9.94. Found: C, 66.54; H, 10.14.

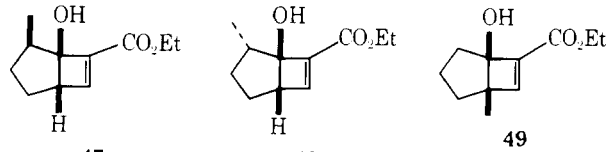
Ethyl 1-(*tert*-Butyldimethylsilyloxy)bicyclo[3.2.0]hept-6-ene-7-carboxylate (6). A yield of 60% of **6** was realized after silica gel chromatography (10% ether–hexane): IR (film) 1710, 1600, 880, 850 cm^{-1}; ^1H NMR δ 0.05 (s, 6), 0.86 (s, 9), 1.30 (t, 3, J = 7 Hz), 2.78 (m, 1), 4.16 (quartet, 2, J = 7 Hz), 6.60 (s, 1). Anal. Calcd for $C_{16}H_{28}O_3Si$: C, 64.82; H, 9.52. Found: C, 65.04; H, 9.41.

Ethyl 1-(*tert*-Butyldimethylsilyloxy)-2-methylbicyclo[3.2.0]hept-6-ene-7-carboxylate (9 and 10). Reaction of silyl ether **8** gave a colorless oil (yield 87.3%) after chromatography on silica gel (20% ether–hexane) which showed a single spot on TLC (R_f 0.74, 25% ether–hexane): IR (film) 1705, 1605, 1080, 890, 830 cm^{-1}. ^1H NMR showed the presence of isomers **9** and **10** in an ca. 70:30 ratio with approximately 5% of **11** also present: δ 0.00 (s, 6), 0.83 (s, 9), 1.25 (t, 3, J = 7 Hz), 2.78 (m, 1), 4.16 (quartet, 2, J = 7 Hz), 6.52 (s, 1, vinyl H, isomer **11**), 6.58 (s, 1, vinyl H, isomer **10**), 6.63 (s, 1 vinyl H, isomer **9**). Anal. Calcd for $C_{17}H_{30}O_3Si$: C, 65.76; H, 9.74. Found: C, 65.75; H, 9.60.

Hydrolysis of the above mixture of silyl ethers **9**, **10**, and **11** (2.03 g, 6.5 mmol) in 5 mL of acetic acid, 2.5 mL of water, and 7 mL of THF containing 3 drops of 85% phosphoric acid at reflux for 20 h afforded a colorless oil after ether extraction. TLC showed two spots, R_f 0.24 and 0.32 (50% ether–hexane). Chromatography on 100 g of silica gel (40% ether–hexane) gave a fraction (215 mg) containing only the less polar component, a fraction (201 mg) which was a mixture, and a fraction (382 mg) of the more polar component. The total yield was 798 mg (63.3%).

The less polar component was assigned structure **48** and contained ca. 20% of isomer **49:** IR (film) 3300, 1710, 1600 cm^{-1}; ^1H NMR δ 0.96 (d, 3, J = 7 Hz), 1.16 (s, 3, Me of **49**), 1.26 (t, 3, J = 7 Hz), 2.50 (s, 1, OH), 2.85 (m, 1, H-5), 4.18 (quartet, 2, J = 7 Hz), 6.73 (d, 1, J = 1 Hz), 6.68 (1, s, vinyl of **49**); ^{13}C NMR ($CDCl_3$) δ 161.6 (CO_2–), 147.8 (C-6), 140.7 (C-7), 88.1 (C-1), 60.3 (OCH_2), 52.9 (C-5), 34.3 (C-2), 31.9 and 22.4 (C-3 and -4), 14.3 (CH_2CH_3), 13.4 (2-CH_3). Anal. Calcd for $C_{11}H_{16}O_3$: C, 67.32; H, 8.22. Found: C, 67.13; H, 8.14.

The more polar alcohol was assigned structure **47:** IR (film) 3300, 1710, 1600 cm^{-1}; ^1H NMR δ 1.02 (d, 3, J = 6 Hz), 1.27 (t, 3, J = 7 Hz), 2.83 (m, 1), 4.18 (2 quartets, 2, J = 7 Hz), 6.83 (s, 1); ^{13}C NMR ($CDCl_3$) δ 162.0 (CO_2–), 148.2 (C-6), 138.6 (C-7), 88.8 (C-1), 60.2 (OCH_2), 53.9



47 48 49

(C-5), 41.0 (C-2), 32.4 and 24.3 (C-3 and -4), 14.4 and 14.2 (CH_2CH_3 and 2-CH_3). Anal. Calcd for $C_{11}H_{16}O_3$: C, 67.32; H, 8.22. Found: C, 67.37; H, 8.49.

The stereochemistry of alcohols **47** and **48** was determined by measuring the ^1H NMR spectra in $CDCl_3$ in the presence of the Eu(fod)$_3$ shift reagent[25] over a concentration range of 0–2.0 mg of Eu(fod)$_3$/mg of alcohol.[26] Plots of Δδ (Hz) for the 2-methyl groups of **47** and **48** vs. mg of Eu(fod)$_3$ reagent were linear. Isomer **47** gave a slope of 155 Hz/mg of Eu(fod)$_3$ compared to a slope of 54.5 units for **48**. According to the usual angular and distance dependences for this shift reagent,[27,28] the structures are assigned as shown.

Ethyl 1-(*tert*-Butyldimethylsilyloxy)-2,2,4-trimethylbicyclo[3.2.0]hept-6-ene-7-carboxylate (13). An 80% yield of **13** was realized after silica gel chromatography (2.5% ether–hexane): IR (film) 1705, 1605, 1100, 900, 835 cm^{-1}; ^1H NMR δ −0.03 (s, 3), 0.02 (s, 3), 0.83 (s, 9), 0.94 (s, 3), 1.04 (s, 3), 1.11 (d, 3, J = 6 Hz), 1.23 (t, 3, J = 7 Hz), 2.67 (m, 1), 4.10 (quartet, 2, J = 7 Hz), 6.76 (d, 1, J = Hz). Anal. Calcd for $C_{19}H_{34}O_3Si$: C, 67.40; H, 10.12. Found: C, 67.40; H, 10.21.

Ethyl 1-(*tert*-Butyldimethylsilyloxy)bicyclo[4.2.0]oct-7-ene-8-carboxylate (15). Reaction of silyl ether **14** (1.06 g, 5 mmol) under the usual conditions gave a light yellow oil (1.33 g) which displayed two prominent spots on TLC (R_f 0.83 and 0.73, 5% ether–hexane) as well as minor more polar impurities. Chromatography on 60 g of silica gel with 5% ether–hexane gave compound **15** (575 mg, 37.1%) as the less polar component: IR (film) 1705, 1600, 1260 cm^{-1}; ^1H NMR δ 0.00 (s, 6), 0.83 (s, 9), 1.27 (t, 3, J = 7 Hz), 2.63 (broad t, 1), 4.13 (quartet, 2, J = 7 Hz), 6.78 (d, 1, J = 1 Hz). Anal. Calcd for $C_{17}H_{30}O_3Si$: C, 65.76; H, 9.74. Found: C, 65.72; H, 9.90.

The more polar component was **16** (163 mg, 10.5%): IR (film) 1700, 1600 (s), 1140, 930, 825 cm^{-1}; ^1H NMR δ 0.15 (s, 6), 0.98 (s, 9), 1.25 (t, 3, J = 7 Hz), 1.67 (broad m, 4), 2.16 (broad m, 4), 4.10 (quartet, 2, J = 7 Hz); UV (methanol) λ_{max} 280 nm (ε 565); MS (70 eV) *m/e* (relative intensity) 310 (8, M^+), 281 (3, $M^+ - C_2H_5$), 265 (5), 253 (25, $M^+ - C_7H_9$), 225 (10, $M^+ - C_2H_5 - C_7H_8$), 75 (100), 73 (21).

(*Z,E*)-Ethyl 1-(*tert*-Butyldimethylsilyloxy)cyclodeca-1,3-diene-2-carboxylate (20). Reaction of silyl ether **19** (1.20 g, 5 mmol) gave 1.63 g of crude product (TLC R_f 0.7, 10% ether–hexane) which was apparently the cyclobutene adduct. After chromatography on 70 g of silica gel (10% ether–hexane) and remaining at 25 °C overnight, the cyclodecadiene **20** was obtained (1.52 g, 90.1%): TLC R_f 0.6; IR

(film) 1705, 1575 (s) cm^{-1}; ^1H NMR δ 0.08 (s, 6), 0.83 (s, 9), 1.15 (t, 3, J = 7 Hz), 2.10 (m, 4), 3.98 (quartet, 2, J = 7 Hz), 5.35 (dt, 1, J = 16, 6 Hz, H-4), 5.75 (d, 1, J = 16 Hz, H-3); UV (hexane) λ_{max} 241 nm (ϵ 8150). Anal. Calcd for $C_{19}H_{34}O_3Si$: C, 67.40; H, 10.12. Found: C, 67.18; H, 10.23.

Hydrolysis of silyl enol ether **20** (157 mg, 0.46 mmol) to the known keto ester **42**[7] was carried out in 3 mL of acetic acid, 1 mL of H_2O, and 3 mL of THF at reflux for 2 h. Ether extraction gave 90 mg (86.5%) of **42** as a colorless oil: IR (film) 1730, 1705 cm^{-1}; ^1H NMR δ 1.26 (t, 3, J = 7 Hz), 3.86 (m, 1, H-2), 4.15 (quartet, 2, J = 7 Hz), 5.63 (m, 2, H-3,4).

Ethyl 1-(*tert*-Butyldimethylsilyloxy)bicyclo[10.2.0]tetradec-13-ene-14-carboxylate (22). The E silyl ether **21** (1.48 g, 5 mmol) was reacted with ethyl propiolate to give 1.58 g of crude product which was chromatographed on 75 g of silica gel (4% ether–hexane) to give cyclobutene **22** (1.08 g, 55%) as a colorless oil which slowly crystallized: mp 43–45 °C; IR (film) 1710, 1605, 1220, 835, 785 cm^{-1}; ^1H NMR δ −0.11 (s, 3), 0.13 (s, 3), 0.83 (s, 9), 1.23 (t, 3, J = 7 Hz), 2.80 (m, 1), 4.10 (2 quartets, 2, J = 7 Hz), 6.70 (d, 1, J = 1 Hz). Anal. Calcd for $C_{23}H_{42}O_3Si$: C, 70.00; H, 10.73. Found: C, 70.13; H, 11.10.

In addition, the more polar **23** also was obtained as a mixture of stereoisomers (98.5 mg, 5%): IR (film) 1715, 1645 (s), 1600 (w), 830, 775 cm^{-1}; ^1H NMR δ 0.13 (s, 6), 0.88 and 0.91 (s, 9), 3.33 (m, 1), 4.08 (quartet, 2, J = 7 Hz), 4.50 (t, 1, J = 7 Hz, silyl enol ether H), 5.68 (d, 1, J = 16 Hz), 6.75 (dd, 1, J = 16, 7.5 Hz, vinyl H, one isomer), 6.82 (dd, 1, J = 16, 7 Hz, vinyl, other isomer).

Ethyl 2-(*tert*-Butyldimethylsilyloxy)-2-hexylcyclobut-4-ene-1-carboxylate 26. Under the usual conditions, silyl ether **25** gave a colorless oil which was chromatographed on silica gel (2% ether–hexane to give as the less polar component 1-*tert*-butyldimethylsilyl)-2-octanone (**27**; 10%): IR (film) 1710, 1220, 830, 770 cm^{-1}. The more polar component was **26** (35%): IR (film) 1710, 1605, 835, 780 cm^{-1}; ^1H NMR δ 0.00 (s, 6), 0.83 (s, 9), 1.26 (t, 3, J = 7 Hz), 2.45 (m, 2), 4.11 (quartet, 2, J = 7 Hz), 6.78 (t, 1, J = 1 Hz). Anal. Calcd for $C_{19}H_{36}O_3Si$: C, 67.01; H, 10.65. Found: C, 66.84; H, 10.56.

Ethyl 3-Ethyl-4-(*tert*-butyldimethylsilyloxy)-4-propylcyclobut-1-ene-1-carboxylate (31) and (*E,Z*)-Ethyl 6-(*tert*-Butyldimethylsilyloxy)nona-3,5-diene-5-carboxylate (30). Reaction of the silyl ether mixture **28** and **29** (ratio ca. 65:35; 1.14 g, 5 mmol) with ethyl propiolate in the usual manner afforded 1.57 g of crude product which was a mixture of two components by TLC (R_f 0.35 and 0.50, 5% ether–hexane). TLC of the crude ether extract before evaporation had shown an additional component, R_f 0.6, which was converted to the lower R_f spot during workup. Chromatography on 70 g of silica gel (5% ether–hexane) gave cyclobutene **31** (571 mg, 35.0%) as a colorless oil: IR (film) 1705, 1600, 1220, 1060, 920, 835, 775 cm^{-1}; ^1H NMR δ −0.12 (s, 3), 0.10 (s, 3), 0.80 (s, 9), 1.23 (t, 3, J = 7 Hz), 2.43 (td, 1, J = 7, 1.5 Hz, H-3), 4.12 (two quartets, 2, J = 7 Hz, diastereotopic $-OCH_2CH_3$), 6.78 (d, 1, J = 1 Hz). Anal. Calcd for $C_{18}H_{34}O_3Si$: C, 66.21; H, 10.50. Found: C, 66.09; H, 10.65.

The second component eluted was diene **30** (800 mg, 49.1%), a colorless oil: IR (film) 1710, 1635 (w), 1605, 1200, 1170, 840, 825 cm^{-1}; ^1H NMR δ 0.06 (s, 6), 0.85 (s, 9), 1.23 (t, 3, J = 7 Hz), 4.08 (quartet, 2, J = 7 Hz), 5.26 (dt, 1, J = 16, 6 Hz, H-3), 5.90 (dt, 1, J = 15.5, 1.3 Hz, H-4); UV (methanol) λ_{max} 242 nm (ϵ 13 390); MS (70 eV) m/e (relative intensity) 326 (5, M^+), 281 (5), 269 (50, $M^+ - C_4H_9$), 241 (7), 199 (19), 75 (100), 73 (48). Anal. Calcd for $C_{18}H_{34}O_3Si$: C, 66.21; H, 10.50. Found: C, 66.22; H, 10.45.

Reaction of 32 with Ethyl Propiolate. Under the usual reaction conditions, the silyl ether **32** from camphor gave a mixture which was chromatographed on silica gel (20% ether–hexane) to give, as the first components eluted, the isomeric keto esters **33** (ca. 25% yield), which were not separable under these conditions: IR (film) 1730, 1665, 1170 cm^{-1}; ^1H NMR (from the spectra of the mixture, the ratio of E/Z isomers is 84:16) (E) δ 1.23 (t, 3, J = 7 Hz), 2.68 (d, 1, J = 4 Hz, CHC=C), 3.12 (d, 2, J = 7.5 Hz, CH_2CO_2Et), 4.13 (quartet, 2, J = 7 Hz), 6.45 (t, 1, J = 7.5 Hz); ^1H NMR (Z) δ 1.23 (t, 3, J = 7 Hz), 2.48 (d, 1, J = 4 Hz), 3.71 (dd, 2, J = 7, 3.5 Hz), 4.13 (quartet, 2, J = 7 Hz), 5.93 (t, 1, J = 7 Hz); UV (methanol) λ_{max} 238 nm (ϵ 10 150). Anal. Calcd for $C_{15}H_{22}O_3$: C, 71.97; H, 8.86. Found: C, 71.96; H, 8.84.

Ethyl 1-(*tert*-Butyldimethylsilyloxy)-2-carbomethoxy-2-methylbicyclo[5.2.0]non-8-ene-9-carboxylate (35). A 4% yield of **35** was realized after chromatography on silica gel (8% ether–hexane): IR (film) 1710, 1600, 1240 cm^{-1}. ^1H NMR showed two isomers in a 4:1 ratio. Major isomer: δ 0.18 (s, 6), 0.80 (s, 9), 1.36 (s, 3), 3.16 (m, 1), 3.56 (s, 3), 6.90 (d, J = 1 Hz, 1). Minor isomer: δ 0.11 (s, 6), 0.86 (s, 9), 2.75 (m, 1), 3.50 (s, 1), 6.67 (d, J = 1 Hz, 1).

(*E,E*)- and (*Z,Z*)-Ethyl 6-(*tert*-Butyldimethylsilyloxy)-nona-3,5-diene-5-carboxylate (39 and 40). Cyclobutene **31** (260 mg, 0.8 mmol) was heated neat at 160 °C under nitrogen for 10 min. ^1H NMR analysis showed isomers **39** and **40** in a ratio of 74:26. Chromatography on 25 g of silica gel (2% ether–hexane) gave the less polar isomer **39** (105 mg, 40.4%): IR (film) 1710, 1600, 1200, 840, 780 cm^{-1}; ^1H NMR δ 0.08 (s, 6), 0.86 (s, 9), 1.17 (t, 3, J = 7 Hz), 4.00 (quartet, 2, J = 7 Hz), 5.28 (dt, 1, J = 7, 11 Hz, H-3), 5.75 (dt, 1, J = 1, 11 Hz, H-4); UV (methanol) λ_{max} 243 nm (ϵ 11 620); MS (70 eV) m/e (relative intensity) 326 (3, M^+), 281 (3), 269 (25, $M^+ - C_7H_9$), 199 (9), 93 (18), 75 (100), 73 (18). Anal. Calcd for $C_{18}H_{34}O_3Si$: C, 66.21; H, 10.50. Found: C, 66.21; H, 10.30.

A fraction enriched in the more polar isomer **40** was also obtained (44 mg, 17%): ^1H NMR δ 0.13 (s, 6), 0.93 (s, 9), 1.25 (t, 3, J = 7 Hz), 4.13 (quartet, 2, J = 7 Hz), 5.53 (dt, 1, J = 16,6 Hz, H-3), 6.13 (dt, 1, J = 16, 1 Hz, H-4). Anal. Calcd for $C_{18}H_{34}O_3Si$: C, 66.21; H, 10.50. Found: C, 66.09; H, 10.52.

(*Z,E*)-Ethyl 1-(*tert*-Butyldimethylsilyloxy)cyclotetradeca-1,3-diene-2-carboxylate (43). Cyclobutene **22** (563 mg, 1.43 mmol) was heated neat at 160 °C under nitrogen for 10 min. Chromatography on 20 g of silica gel (5% ether–hexane) gave diene **43** (560 mg, 99.5%) as a colorless oil: IR (film) 1710, 1585 (s), 1125, 830, 780 cm^{-1}; ^1H NMR δ 0.15 (s, 6), 0.96 (s, 9), 1.28 (t, 3, J = 7 Hz), 4.16 (quartet, 2, J = 7 Hz), 5.50 (ddd, 1, J = 16, 10, 4 Hz, H-4), 6.23 (dd, 1, J = 16, 1 Hz, H-3); UV (hexane) λ_{max} 257 nm (ϵ 10 070). Anal. Calcd for $C_{23}H_{42}O_3Si$: C, 70.00; H, 10.73. Found: C, 69.80; H, 10.90.

Ethyl 3-Oxocyclooct-1-ene-2-carboxylate (44). A. From Cyclohexanone Trimethylsilyl Enol Ether. Silyl ether **3** (850 mg, 5 mmol) was reacted with ethyl propiolate under the described conditions to give 830 mg of crude product. TLC (50% ether–hexane) showed a mixture of several components. Chromatography on 40 g of silica gel gave **44** as the major product (212 mg, 21.6%): IR (film) 1700, 1680, 1625, 1060 cm^{-1}; ^1H NMR δ 1.23 (t, 3, J = 7 Hz), 1.65 (broad m, 4), 2.40 (m, 4), 4.12 (quartet, 2, J = 7 Hz), 7.02 (t, 1, J = 5 Hz); ^{13}C NMR ($CDCl_3$) δ 209.0 (C-3), 164.6 (CO_2Et), 146.5 (C-2), 132.0 (C-1), 61.2 (OCH_2), 44.6, 30.2, 29.2, 22.2, 21.8, 14.1 (CH_3); MS (70 eV) m/e 196 (M^+), 108 (100). Anal. Calcd for $C_{11}H_{16}O_3$: C, 67.32; H, 8.22. Found: C, 66.97; H, 8.31.

B. From Cyclobutene 15. Silyl ether **15** (929 mg, 3 mmol) in 4 mL of acetic acid, 2 mL of water, and 6 mL of THF with 5 drops of 85% phosphoric acid was refluxed for 20 h. The mixture was diluted with water and extracted with ether. The ether was washed with sodium bicarbonate solution and brine, dried, and evaporated. Chromatography of the residue on 50 g of silica gel (15% ether–hexane) gave the keto ester **44** (343 mg, 58.4%).

Ethyl 2-Oxocyclonon-8-ene-1-carboxylate (45). A solution of silyl ether **18** (537 mg, 1.6 mmol) in 4 mL of THF, 4 mL of acetic acid, and 2 mL of water containing 3 drops of 85% phosphoric acid was refluxed for 5 h. Ether extraction gave a colorless oil which was chromatographed on 25 g of silica gel (25% ether–hexane) to give 338 mg of crystalline material. Recrystallization from pentane at −78 °C gave 248 mg (71.6%) of **45**: mp 43.5–44.0 °C; IR (CCl_4) 1735, 1710, 1180 cm^{-1}; ^1H NMR δ 1.26 (t, 3, J = 7 Hz), 2.83 (triplet of doublets, 1, J = 13, 3 Hz, H-3), 4.10 (d, 1, J = 9 Hz, H-1), 4.21 (quartet, 2, J = 7 Hz), 5.58 (dd, 1, J = 9, 16 Hz, H-9), 5.84 (ddd, 1, J = 4, 10, 16 Hz, H-8). Anal. Calcd for $C_{12}H_{18}O_3$: C, 68.57; H, 8.57. Found: C, 68.36; H, 8.72.

Hydrolysis of Silyl Ether 6. Hydrolysis of **6** (634 mg, 2.14 mmol) in 4:2:6 v/v acetic acid–water–THF at reflux for 20 h followed by workup with ether extraction gave a yellow oil. Chromatography on silica gel gave the pure alcohol **2** (222 mg, 56.8%), identical with that obtained from the Me_3Si ether **1**.

Ethyl 2-Oxocyclohept-6-ene-1-carboxylate (46). Alcohol **2** (207 mg, 1.23 mmol) in 22.3 mL of potassium *tert*-butoxide in *tert*-butyl alcohol (0.06 M) was stirred at room temperature for 1 h. The mixture was acidified with acetic acid and diluted with water. Extraction with ether afforded the known keto ester **46** (130 mg, 62.8%), identical (IR, NMR) with that reported in the literature.[4]

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Registry No.—**1**, 19980-43-9; **2**, 68081-37-8; **5**, 68081-15-2; **6**, 68081-25-4; **7**, 68081-16-3; **8**, 68081-17-4; **9**, 68081-26-5; **10**, 68127-29-7; **11**, 68081-27-6; **12**, 68081-18-5; **13**, 68081-28-7; **14**, 62791-22-4; **15**, 68081-29-8; **16**, 68081-30-1; **17**, 68081-19-6; **18**, 68081-31-2; **19**, 67788-03-8; **20**, 68091-85-0; **21**, 68081-20-9; **22**, 68081-32-3; **23**, 68081-38-9; **24**, 68081-21-0; **25**, 54251-60-4; **26**, 68081-33-4; **27**, 68081-34-5; **28**, 68081-22-1; **29**, 68081-23-2; **30**, 68081-36-6; **31**, 68081-36-7; **32**, 54251-61-5; (*E*)-**33**, 68081-39-0; (*Z*)-**33**, 68081-40-3; **34**, 68081-24-3; **35** (isomer 1), 68128-56-3; **35** (isomer 2), 68081-41-4; **39**, 68081-42-5; **40**, 68081-43-6; **41**, 68081-44-7; **42**, 68081-45-8; **43**, 68081-46-9; **44**, 57205-18-2; **45**, 68081-47-0; **46**, 68081-48-1; **47**,

68081-49-2; **48**, 68127-30-0; **49**, 68081-37-8; ethyl propiolate, 623-47-2; *tert*-butyldimethylsilyl chloride, 18162-48-6; cyclopentanone, 120-92-3; 2-methylcyclopentanone, 1120-72-5; 2,2,4-trimethylcyclopentanone, 28056-54-4; cyclohexanone, 108-94-1; cycloheptanone, 502-42-1; cyclooctanone, 502-49-8; cyclododecanone, 830-13-7; 2-octanone, 111-13-7; 4-heptanone, 123-19-3; camphor, 76-22-2; methyl 1-methyl-2-oxocycloheptanecarboxylate, 68081-50-5.

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[2 + 2] Cycloadditions of Silyl Enol Ethers and Dimethyl Acetylenedicarboxylate, Dimethyl Fumarate, and Methyl Crotonate

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[2 + 2] cycloadditions of silyl enol ethers with dimethyl acetylenedicarboxylate, dimethyl fumarate, and methyl crotonate using titanium tetrachloride catalysis are reported. The cyclobutene adducts undergo a two-carbon ring expansion during acid hydrolysis.

We have shown previously that silyl enol ethers undergo [2 + 2] cycloaddition with ethyl propiolate under titanium tetrachloride catalysis and that in the case of cyclic enol ethers the derived silyloxycyclobutenes can be opened to afford two-carbon ring-expanded products.[2] We now report that a similar cycloaddition–ring expansion can also be accomplished with dimethyl acetylene dicarboxylate. Furthermore, we have found that certain α,β-unsaturated esters will also undergo cycloaddition with silyl enol ethers to afford cyclobutane adducts.

The results of the $TiCl_4$-catalyzed cycloaddition of trimethylsilyl (Me_3Si) and *tert*-butyldimethylsilyl ($BuMe_2Si$) enol ethers with dimethyl acetylenedicarboxylate are listed in Table I. Typically, the reaction is carried out by addition of the silyl ether to a −78 °C CH_2Cl_2 solution of $TiCl_4$ (1 equiv) and dimethylacetylenedicarboxylate (1.5 equiv). The reaction is virtually instantaneous, and after several minutes at −78 °C the product is isolated by ether extraction. The $BuMe_2Si$ group is relatively stable to the reaction conditions and is retained in the cycloadduct, whereas the Me_3Si group is usually cleaved. Since the Me_3Si group is also rapidly cleaved from the starting enol ether, the yields are significantly better with the corresponding $BuMe_2Si$ ethers. However, some cleavage of the $BuMe_2Si$ enol ether does occur, and the yields are generally lower than in the corresponding cycloadditions with ethyl propiolate.[3]

Also listed in Table I are the products from the aqueous acetic acid hydrolysis of the cycloadducts. Silyl ethers **9** and **14** are converted to the known ring expansion products **10**[4] and **15**,[4e] which have been prepared previously from the corresponding enamines. Compound **15** results from decarboxylation of **12**,[4c,e] which is the direct product from Me_3Si ether **11**. The cycloadduct from the silyloxycyclooctene **16** opens at room temperature to afford cyclodecadiene **17**, which is converted by hydrolysis to the known keto diester **18**.[4c,e]

The bicyclo[3.2.0]heptenyl alcohols **2** and **7** are stable under the hydrolysis conditions. Treatment with sodium hydride in *tert*-butyl alcohol (or THF) affords the cleavage products **19** (57%) and **20** (40%) rather than ring-expanded materials.[5] The formation of **19** and **20** may involve Michael addition of alkoxide at C-6 followed by fragmentation of the $C_{1,7}$ bond with loss of alkoxide to generate the β,γ-unsaturated isomer which isomerizes to the observed product.[6]

Cycloadditions with dimethyl fumarate (**21**) and methyl crotonate (**23**) were also investigated, and modest yields of cyclobutane adducts **22** and **24** and **25** were obtained (yields

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