Enolate Reactions of Bicyclo[4.2.0]octan-7-ones[1]

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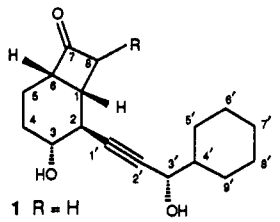
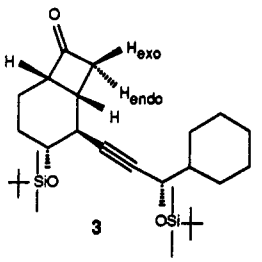
Under kinetic conditions, the lithium enolate formed from the bicyclo[4.2.0]octan-7-one **3** undergoes reaction with MeI, EtI, and dimethyl disulfide to give *6-substituted* compounds **7–9** in 65%, 43%, and 70% yield, respectively, rather than the anticipated 8-substituted isomers. Similarly, fluorination of the silyl enol ether gives the 6-fluoro compound **10** in 40% yield. Using a TMSCl trapping technique it was shown that kinetic deprotonation takes place at *both* the 6- and 8-positions in bicyclo[4.2.0]octan-7-ones, whereas the thermodynamic product is the expected 6-enolate. Generation of the enolate from a mixture of 6- and 7-silyl enol ethers (57:43) results in 6- and 8-alkylated products. The kinetic enolate from bicyclo[4.2.0]oct-2-en-7-one is the 7-enol derivative.

During work on the synthesis of novel bicyclo[4.2.0]octane analogs of prostacyclin,[2] we required an efficient preparation of the 8-methyl analogue **2** of the bicyclic ketone **1**. We expected that this might be accessible by alkylation of a kinetic enolate of the hydroxyl protected compound **3**, although literature precedent was not encouraging. Thus far only two synthetic applications of



1 R = H
2 R = Me



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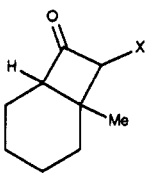
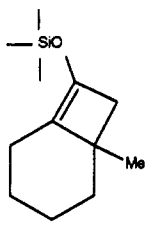
enolate chemistry in this ring system have been described. Clark et al.[3] were unsuccessful in generating the enolate from the 1-methyl compound **4** using an amide base and had to resort to reaction of the chloro ketone **5** with dimethylcopperlithium, followed by trapping with chlorotrimethylsilane and generation of the lithium enolate with methyllithium. Cohen et al.[4] were able to generate the silyl enol ether **6** from **4** under equilibrating conditions using $(Me_3Si)_2NH/Me_3SiI$ as a precursor to the corresponding α-phenylthio ketone.



4 X = H
5 X = Cl



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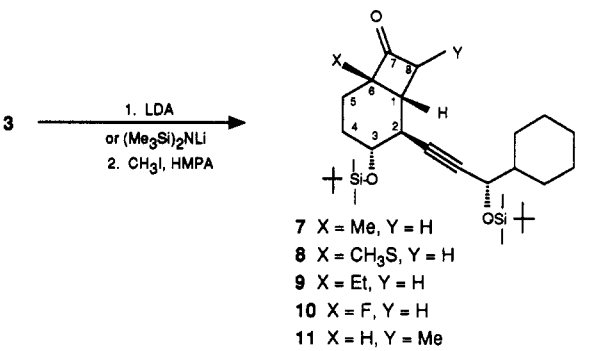
On the basis of steric factors, ketone **3** was expected to undergo alkylation at the less hindered 8-position under kinetic deprotonation conditions. To our surprise, slow addition of the *tert*-butyldimethylsilyl-protected bicyclo[4.2.0]octanone **3** to 1.2 equiv of lithium diisopropylamide (LDA) or lithium hexamethyldisilazide (LiHMDS) in THF at −78 °C, followed by addition of methyl iodide at −78 °C and warming to room temperature, gave a 65% yield of a methyl ketone, shown to be the 6-methyl ketone **7** rather than the desired 8-methyl compound **11**. Similarly, quenching the enolate with dimethyl disulfide or ethyl iodide, or the silyl enol ethers (vide infra) with xenon difluoride, gave the 6-substituted products **8** (43%), **9** (70%), and **10** (40%), respectively. The structural assignments of **7–10** were based on the ^1H NMR spectra, which retained the H-8 resonances between 2.80 and 3.47 ppm, comprising the AB portion of an ABC spin system, with loss of the H-6 resonance at 3.27 ppm in **3**. Additionally, the C-6 methyl resonance in **7** appears as a singlet at 1.24 ppm. The ^{13}C NMR spectra further confirmed the assignments, showing replacement of the C-6 doublet at 55.76 ppm in **3** by an additional singlet carbon in the range 59–64 ppm in **7–10** while the triplet carbon assigned to C-8 remained in the 49–53 ppm range. The results of NOE difference experiments were also consistent with structure **7** (Table I).

Table I. Nuclear Overhauser Enhancements of C6-Me Compound 7

resonance saturated	NOE observed
C6-Me	H-1
H1	C6-Me, H-2, H-8β[a]
H2	H-1, H-3, H-8α[b]

[a] Upfield H-8. [b] Downfield H-8.



7 X = Me, Y = H
8 X = CH_3S, Y = H
9 X = Et, Y = H
10 X = F, Y = H
11 X = H, Y = Me

Because alkylation at the hindered 6-position was unexpected under kinetic conditions, additional experiments were conducted in an attempt to determine whether a particularly rapid equilibration takes place during the reaction, or if indeed, removal of the C-6 proton is kinetically favored. In an attempt to determine whether the products arise from the kinetic or thermodynamic enolate, the TMSCl trapping technique was used to form tri-

(1) Contribution No. 784 from the Institute of Organic Chemistry.
(2) Kluge, A. F.; Kertesz, D. J.; O-Yang, C.; Wu, H. Y. *J. Org. Chem.* **1987**, *52*, 2860.
(3) Clark, G. R.; Lin, J.; Nikaido, M. *Tetrahedron Lett.* **1984**, *25*, 2645.
(4) Cohen, T.; Yu, L.-C.; Daniewski, W. M. *J. Org. Chem.* **1985**, *50*, 4596.

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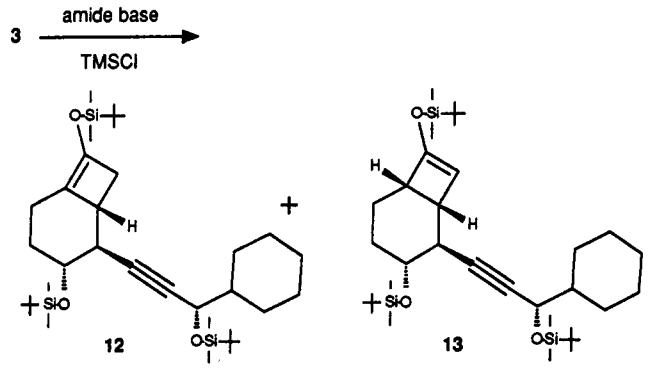
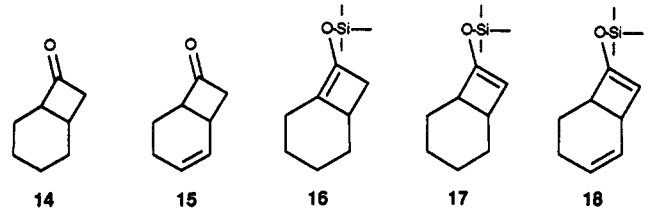
methylsilyl enol ethers under different kinetic[5] and thermodynamic[6] conditions.



Slow addition of ketone **3** to an excess of LDA or LiHMDS in THF or DME at −78 °C in the presence of TMSCl (kinetic conditions) and isolation of the resulting silyl enol ether within 15 min gave a 57:43 ratio of **12**:**13** in the case of LDA and a ratio of 85:15 using LiHMDS, according to ^{1}H NMR and GC/MS. The ratio of **12** to **13** was estimated by comparing the integrals of the H-8 resonances in the ^{1}H NMR spectrum. The ratios of enol silyl ethers were consistent in repeated experiments and are probably representative of the initial ratio of enolates.

To investigate the role of the cyclohexyl side chain at C-2 and the OSiBu^{t}Me$_2$ group at C-3 in the kinetic process, we repeated the kinetic deprotonation conditions with the parent bicyclo[4.2.0]octan-7-one, **14**. Deprotonation of **14** with LDA and in situ trapping with TMSCl gave **16** and **17** in a ratio of 46:54, whereas with LiHMDS the ratio was 75:25 (Table II). This finding suggests that the substituents at C-2 and C-3 may present a certain degree of steric hindrance at the 8-position relative to the 6-position, or may change the conformation of the ring system.



Kinetic enolate formation from bicyclo[4.2.0]oct-2-en-7-one (**15**) was also studied for comparison. Treatment of **15** with LiHMDS in THF at −78 °C in the presence of TMSCl under the same conditions as above gave the 7-silyl enol ether **18** as the sole product, according to ^{1}H NMR spectroscopy and GC/MS (Table II). This probably reflects the difficulty of introducing a double bond *exo* to the unsaturated six-membered ring.

The thermodynamic trimethylsilyl enol ethers were also generated from **3** and **14** using Me_3SiI and the base hexamethyldisilazane $(Me_3Si)_2NH$.[6] Whereas the 6-silyl enol ether **12** was the exclusive product from **3**, silyl enol ether **11** contained traces of **17**. These results confirm the expectation that the 6-enol is thermodynamically more stable and agree with the findings of Hanack and Auchter[7] for the thermodynamic enol nonaflate of **14**.

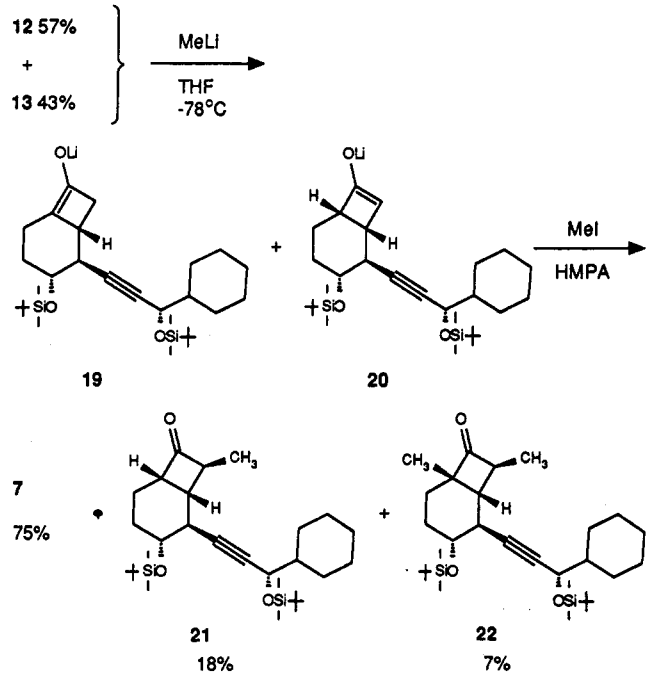
Table II. Preparation of Trimethylsilyl Enol Ethers under Kinetic Conditions

entry	ketones	base	solvent	ratio of silyl enol ethers 6-	7-
1	3	$(Me_3Si)_2NLI$	THF	85	15
2	3	$(Me_3Si)_2NLi$	DME	83	17
3	3	LDA	THF	57	43
4	14	LDA	THF	46	54
5	14	$(Me_3Si)_2NLi$	THF	75	25
6	15	$(Me_3Si)_2NLi$	THF	0	>99

Table III. Nuclear Overhauser Enhancements of C-6, C-8 Dimethyl Compound 22

resonance saturated	NOE observed	
C-8αH	2α-H	
C-8 methyl	1β-H	no NOE on H-2
C-6 methyl	1β-H	

As a test of the stability of the 8-enolate, the mixture of silyl enol ethers **12** and **13** from the initial LDA–TMSCl trapping experiment [ratio of 57:43 of **12** to **13**] was converted to the lithium enolate using methyllithium and then quenched with MeI and HMPA. The reaction mixture contained 75% of 6-Me compound **7**, 18% of 8-exo Me compound **21**, 7% of the 6,8-dimethyl compound **22**, and none of the unreacted ketone according to GC/MS and ^{1}H NMR spectroscopy. This result demonstrates that some equilibration of the enolates can take place during alkylation. However, the finding of 8-alkylated products



in this experiment contrasts with the exclusive formation of the 6-alkylated product when the enolate is generated directly from the ketone, and indicates that most, if not all, of the equilibration of enolates takes place during enolate formation.[8] In the case of alkylations using

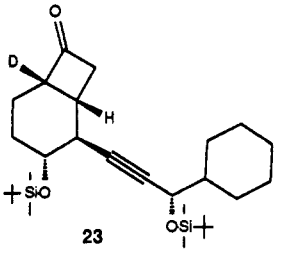
(5) (a) Krueger, C. R.; Rochow, E. G. *J. Organomet. Chem.* **1964**, *1*, 476. (b) Bourhis, R.; Frainnet, E. *Bull. Soc. Chim. Fr.* **1967**, 3552. (c) Stork, G.; Hudrlik, P. F. *J. Am. Chem. Soc.* **1968**, *90*, 4462 and 4464. (d) Danishefsky, S.; Kitahara, T. *J. Am. Chem. Soc.* **1974**, *96*, 7807. (e) Stork, G.; Singh, J. *J. Am. Chem. Soc.* **1974**, *96*, 6181. (f) Kirzan, T. D.; Martin, J. C. *J. Am. Chem. Soc.* **1983**, *105*, 6155. (g) Ireland, R. E.; Mueller, R. H.; Willard, A. K. *J. Am. Chem. Soc.* **1976**, *98*, 2868. (h) House, H. O.; Czuba, L. J.; Gall, M.; Olmstead, H. D. *J. Org. Chem.* **1969**, *36*, 2324. (i) House, H. O.; Gall, M.; Olmstead, H. D. *J. Org. Chem.* **1971**, *36*, 2361. (j) Brownbridge, P. *Synthesis* **1983**, 1–28, 85–104. (k) Rasmussen, J. K. *Synthesis* **1977**, 91–110. (l) Fleming, I.; Paterson, I. *Synthesis* **1979**, 736. (m) Colvin, E. W. *Chem. Soc. Rev.* **1978**, *7*, 15. (n) Corey, E. J.; Gross, A. W. *Tetrahedron Lett.* **1984**, *25*, 495. (o) Jung, M. E.; McCombs, C. A. *Tetrahedron Lett.* **1976**, 2935; *Org. Synth.* **1978**, *58*, 163. (p) Carter, M. J.; Fleming, I.; Percival, A. *J. Chem. Soc., Perkin Trans. 1* **1981**, 2415.

(6) Miller, R. D.; McKean, R. D. *Synthesis* **1979**, 730. Miller, R. D.; McKean, D. R. *Synth. Commun.* **1982**, *12*, 319.

(7) Hanack, M.; Auchter, G. *J. Am. Chem. Soc.* **1985**, *107*, 5238.

LiHMDS, the greater acidity of $(Me_3Si)_2NH$[9] would further facilitate equilibration at this point. Compound **22** could also be generated directly in 76% yield by treatment of **7** with 1.5 equiv of LDA or LiHMDS followed by CH_3I. The results of NOE difference experiments were used to confirm the stereochemistry of the C-6 and C-8 Me's (Table III).

Deuteration studies were also carried out to study the regiochemistry of enolate formation. The enolate ions were prepared by reaction of the ketone with excess LiHMDS in THF at −78 °C and quenched with DCl in D_2O, D_2O, CD_3COOD, or CD_3COOD in MeOD. All deuteration observed occurred solely at the C-6 position to give compound **23**; no 8-D compound **24** was detected by integration of the ^1H NMR spectrum, although, repeated deuteration studies gave highly varying yields of 6-D incorporation.



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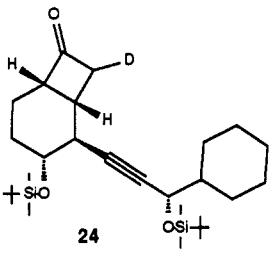

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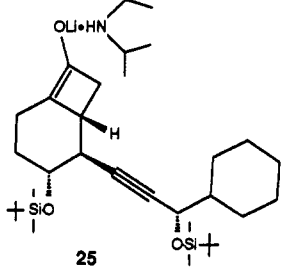
In light of the results obtained using TMSCl trapping, these experiments indicate that we were not able to deuterate the same enolate mixture as was trapped with TMSCl. We believe that rapid equilibration occurs during quenching, or during enolate formation when the enolate is not removed by silyl enol ether formation. The relatively low deuterium incorporation (30–70% by NMR) is consistent with previous observations.[10,11] It has been suggested[11] that the mechanism underlying low deuterium incorporation may be an H-bonded complex between the amine and the enol lithium derivative, as shown below, wherein quenching may cause protonation from the amine to compete with deuteration.



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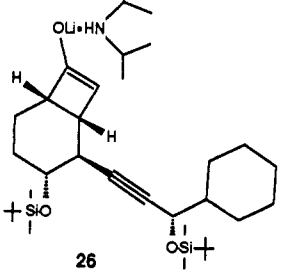

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To remedy this problem, we modified our deuterium trapping experiment, as Laube et al.[11] had done, by using 1 equiv of *n*-BuLi to break up the H-bonded complex. As expected, incorporation of deuterium rose to 97%, but the result of this modified deuterium trapping experiment was the same as before, with all of the deuterium appearing at the 6-position. LDA was also used for deuterium incorporation studies; however, in all experiments performed, no 8-D compound **24** was detected. The maximum incorporation obtained using LDA was 85%; however, these results were also highly variable.

We have thus shown that lithium enolates can be generated from bicyclo[4.2.0]octan-7-ones under standard conditions and that trapping with electrophiles occurs unexpectedly at the 6-position to give synthetically useful yields. Enolate trapping experiments suggest that the kinetic enolate is a mixture of 6- and 8-enolates with the former predominating and that the 8-enolate rapidly equilibrates to the more stable 6-enolate during the enol-forming reaction unless the enolates are trapped in situ with trimethylchlorosilane. The thermodynamic enolate was shown to be the 6-enol isomer.

Although we were not able to prepare the desired 8-mono-substituted analogues of **2** through this enolate chemistry, several of the 6-substituted compounds led to interesting biologically active prostacyclin analogues.[12] Analogues with 8-substituents were prepared using other methodology.[13]

Experimental Section

General. All reactions were performed under argon. Melting points are uncorrected. Thin-layer chromatograms (TLC) were run on glass supported silica gel 60 plates (0.25-mm layer, F-254, E. Merck). Flash chromatography[14] was performed with 40–63-mm silica gel 60 (E. Merck). Mixtures of silyl enol ethers were isolated by extraction with dry pentane and submitted directly to NMR analysis to determine the ratios of possible regioisomers.

Tetrahydrofuran (THF) was freshly distilled from sodium and benzophenone, and trimethylsilyl chloride was distilled from calcium hydride. Methyllithium and *n*-butyllithium were purchased from Aldrich Chemical Co. and were titrated periodically when necessary.

(3′*S*,1*R*,2*S*,3*R*,6*S*)-2-(3′-((*tert*-Butyldimethylsilyl)oxy)-3′-cyclohexylprop-1′-ynyl)-3-((*tert*-butyldimethylsilyl)oxy)bicyclo[4.2.0]octan-7-one (3). To a solution of **1** (500 mg, 1.81 mmol) in dry DMF (15 mL) was added *tert*-butyldimethylsilyl chloride (681 mg, 4.52 mmol) and imidazole (615 mg, 9.05 mmol). After being stirred for 16 h at 24 °C, the reaction mixture was poured into brine (20 mL), and the product was isolated by extraction with ethyl acetate (2 × 20 mL). The combined extracts were dried (Na_2SO_4) and evaporated. The residue was purified by flash chromatography[14] on silica gel to give **3** (850 mg, 93%): mp 67–68 °C; $[\alpha]_D$ = −12.30° (*c* 0.439, $CHCl_3$); IR (KBr) 1778 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.45 (m, 1 H, H-4′), 2.31 (ddd, 1 H, J = 1.4, 7.9, 8.1 Hz, H-2), 2.57 (dddd, 1 H, J = 3.9, 7.9, 8.1, 8.5 Hz, H-1), 2.88 (ddd, 1 H, J = 1.8, 3.9, 16.5 Hz, H-8β), 3.21 (ddd, 1 H, J = 3.1, 8.1, 16.5 Hz, H-8α), 3.27 (m, 1 H, H-6), 4.07 (dd, 1 H, J = 1.4, 6.4 Hz, H-3′); ^{13}C NMR ($CDCl_3$, 125.8 MHz) δ −4.36 (q), −4.55 (q), −4.55 (q), −5.04 (q, 2 $SiMe_2$), 18.07 (s), 18.29 (s), 25.83 (q), 25.86 (q) (2 *t*-Bu), 18.41 (t, C-5), 25.55 (t, C-7′), 26.01 (t), 26.07 (t, C-6′, C-8′), 28.64 (t), 28.90 (t, C-5′, C-9′), 29.60 (d, C-1), 30.33 (t, C-4), 40.64 (d, C-2), 44.90 (d, C-4′), 52.28 (t, C-8), 55.76 (d, C-6), 67.91 (d, C-3′), 71.10 (d, C-3), 83.46 (s, C-2′), 85.71 (s, C-1′), 208.59 (s, C-7); MS *m*/*z* 504 (M^+). Anal. Calcd for $C_{29}H_{52}O_3Si_2$: C, 68.99; H, 10.38. Found: C, 68.77; H, 10.32.

(3′*S*,1*R*,2*S*,3*R*,6*S*)-2-(3′-((*tert*-Butyldimethylsilyl)oxy)-3′-cyclohexylprop-1′-ynyl)-3-((*tert*-butyldimethylsilyl)oxy)-6-methylbicyclo[4.2.0]octan-7-one (7). (a) Using LDA as the Base. A solution of LDA in THF was prepared by addition of *n*-BuLi (0.92 mL of 1.25 M in hexane, 1.15 mmol) in hexane to diisopropylamine (170 μL, 1.20 mmol) in THF (4.5 mL)

(8) GC/MS analysis of reaction mixtures formed by generating the enolate from **3** with lithium bis(trimethylsilyl)amide or freshly prepared LDA followed by quenching with methyl iodide showed the following composition of volatile products after 2 h at −78 °C: $(Me_3Si)_2NLi$ (no HMPA) **22** 1.1%, **21** 0%, **7** 97.9%, **3** 1.0%; $(Me_3Si)_2NLi$ (HMPA added) **22** 1.9%, **21** 0%, **7** 97.2%, **3** 0.9%; LDA (no HMPA) **22** 0%, **21** 0%, **7** 73.6%, **3** 26.4%; LDA (HMPA added) **22** 3.5%, **21** 0.8%, **7** 71.8%, **3** 23.8% confirming that formation of 8-alkylated products is minimal under these conditions.

(9) Fraser, R. R.; Mansour, T. S. *J. Org. Chem.* **1984**, *49*, 3442.

(10) Seebach, D.; Boes, M.; Naef, R.; Schweizer, W. B. *J. Am. Chem. Soc.* **1983**, *105*, 5390.

(11) Laube, T.; Dunitz, J. D.; Seebach, D. *Helv. Chim. Acta* **1985**, *68* 1373.

(12) Wu, H. Y.; Kurz, W. U.S. Patent 4,735,966, 1988; *Chem. Abstr.* **1988**, *109*, 190117h.

(13) Kluge, A. F.; Wu, H. Y. U.S. Patent 4,678,805, 1987; *Chem. Abstr.* **1988**, *109*, 109905u.

(14) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

at −78 °C followed by stirring at −78 °C for 30 min, and at 0 °C for 30 min. After the solution was recooled to −78 °C, **3** (484 mg, 0.96 mmol) in THF (1.5 mL) was added slowly with stirring, and the reaction mixture was maintained at −78 °C for 30 min before rapid addition of iodomethane (0.6 mL, 9.6 mmol). Following the addition, the reaction mixture was stirred at −78 °C for 1 h and then allowed to warm slowly to room temperature. After being stirred at room temperature for 2 h, the reaction mixture was treated with a saturated solution of aqueous NH_4Cl (3 mL), and the product was extracted with EtOAc (3 × 5 mL). The extracts were dried (Na_2SO_4), and the solvent was evaporated. The residue was purified by flash chromatography on silica gel to give **7** (299 mg, 60%) as a colorless syrup: $[\alpha]_D$ = −6.57° (*c* 0.335, $CHCl_3$); IR (neat) 1780 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.24 (s, 3 H, C6-Me), 1.50 (m, 1 H, H-4′), 2.23 (ddd, 1 H, *J* = 2.9, 8.7, 8.9 Hz, H-1), 2.73 (m, 1 H, H-2), 2.99 (dd, 1 H, *J* = 8.9, 16.7 Hz, H-8β), 3.51 (dd, 1 H, *J* = 8.7, 16.7 Hz, H-8α), 4.05 (ddd, 1 H, *J* = 1.8, 3.0, 4.7 Hz, H-3), 4.08 (dd, 1 H, *J* = 1.8, 6.2 Hz, H-3′); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ −4.41 (q), −4.41 (q), −4.92 (q), −4.92 (q, 2 $SiMe_2$), 17.99 (s), 18.30 (s), 25.80 (q), 25.86 (q, 2 *t*-Bu), 21.38 (q, 6-Me), 23.03 (t, C-5), 25.43 (t, C-4), 26.04 (t), 26.04 (t, C-6′, C-8′), 26.60 (t, C-7), 28.72 (t), 28.69 (t, C-5′, C-9′), 34.85 (d, C-2), 35.30 (d, C-1), 45.13 (d, C-4′), 49.32 (t, C-8), 59.08 (s, C-6), 67.81, (d, C-3′), 70.19 (d, C-3), 83.16 (s, C-2′), 86.02 (s, C-1′), 212.26 (s, C-7); MS *m/z* 518 (M^+). Anal. Calcd for $C_{30}H_{54}O_3Si_2$: C, 69.44; H, 10.49. Found: C, 69.31; H, 10.43.

(b) Using LiHMDS as the Base. To a solution of LiHMDS (1.4 mL of 0.5 M in THF, 0.7 mmol) at −78 °C was added slowly ketone **3** (291 mg, 0.58 mmol) in THF (1.0 mL) with stirring. After 30 min at −78 °C, iodomethane (0.36 mL, 5.8 mmol) was added rapidly. Workup as above gave **7** (200 mg, 0.38 mmol, 65%).

(3′*S*,1*R*,2*S*,3*R*,6*R*)-2-(3′-((*tert*-Butyldimethylsilyl)oxy)-3′-cyclohexylprop-1′-ynyl)-3-((*tert*-butyldimethylsilyl)oxy)-6-(methylthio)bicyclo[4.2.0]octan-7-one (8) was prepared as in b above using **3** (1.0 g, 1.98 mmol, in 4.0 mL of THF), LiHMDS (4.8 mL of 0.5 M solution in THF, 2.4 mmol), $(CH_3)_2S_2$ (2.0 mL, 22 mmol), to give **8** (470 mg, 0.85 mmol, 43%) as a colorless gum: $[\alpha]_D$ = −78.44° (*c* 0.561, $CHCl_3$); IR (neat) 1780 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.48 (m, 1 H, H-4′), 2.11 (s, 3 H, SMe), 2.34 (obscured by other resonances, 1 H, H-1), 2.59 (ddd, 1 H, *J* = 1.5, 5.8, 5.8 Hz, H-2), 3.24 (dd, 1 H, *J* = 6.0, 17.1 Hz, H-8β), 3.47 (dd, 1 H, *J* = 9.1, 17.1 Hz, H-8α), 3.95 (ddd, 1 H, *J* = 3.5, 5.5, 5.8 Hz, H-3), 4.07 (dd, 1 H, *J* = 1.5, 6.3 Hz, H-3′); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ −4.36 (q), −4.73 (q), −4.73 (q), −4.98 (q, 2 $SiMe_2$), 12.21 (q, 6-SMe), 18.01 (s), 18.01 (s), 21.81 (q), 25.87 (q, (2 *t*-Bu), 22.43 (t, C-5), 26.05 (t), 26.05 (t, C-6′, C-9′), 26.57 (t, C-7′), 27.45 (t, C-4), 28.68 (t), 28.74 (t, (C-5′, C-8′), 34.49 (d, C-1), 37.78 (d, C-2), 45.05 (d, C-4′), 50.21 (t, C-8), 63.89 (s, C-6), 67.86 (d, C-3′), 70.33 (d, C-3), 83.72 (s, C-2′), 85.00 (s, C-2′), 204.62 (s, C-7); MS *m/z* 550 (M^+). Anal. Calcd for $C_{30}H_{54}O_3Si_2S$: C, 65.40; H, 9.88; S, 5.82. Found: C, 65.11; H, 9.94; S, 5.88. This experiment was repeated with 0.5 mmol of **3** and 1.2 equiv of LDA which gave **8** (110 mg, 0.2 mmol) in 40% yield.

(3′*S*,1*R*,2*S*,3*R*,6*S*)-2-(3′-((*tert*-Butyldimethylsilyl)oxy)-3′-cyclohexylprop-1′-ynyl)-3-((*tert*-butyldimethylsilyl)oxy)-6-ethylbicyclo[4.2.0]octan-7-one (9) was prepared as in b above using **3** (671.3 mg, 1.33 mmol, in 3.0 mL of THF), LiHMDS (3.2 mL of 0.5 M solution in THF, 1.6 mmol), EtI (1.0 mL, 12.5 mmol), and HMPA (0.3 mL, 2.4 mmol) to give **9** (495 mg, 0.95 mmol, 70%) as a colorless gum: $[\alpha]_D$ = −66.64° (*c* 0.317, $CHCl_3$); IR (neat) 1780 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.95 (t, 3 H, *J* = 7.4 Hz, C6-Et), 1.45 (m, 1 H, H-4′), 1.64 (q, 2 H, *J* = 7.4 Hz, C6-Et), 2.40 (ddd, 1 H, *J* = 3.5, 8.0, 9.0 Hz, H-1), 2.73 (nm, 1 H, H-2), 2.98 (dd, *J* = 9.0, 17.5 Hz, H-8β), 3.39 (dd, 1 H, *J* = 8.0, 17.5 Hz, H-8α), 4.02 (m, 1 H, H-3), 4.06 (dd, *J* = 2.0, 6.5 Hz, H-3′); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ −4.43 (q), −4.88 (q), −4.88 (q), −4.99 (q, 2 $SiMe_2$), 9.30 (q, 6-Et), 18.00 (s), 18.31 (s), 25.81 (q), 25.86 (q, 2 *t*-Bu), 21.82 (t, C-5), 26.05 (t), 26.05 (t, C-6′, C-9′), 26.16 (t, C-4), 26.58 (t, C-7′), 28.27 (t, 6-Et), 28.72 (t), 28.72 (t, C-5′, C-8′), 34.85 (d, C-2), 35.30 (d, C-1), 45.13 (d, C-4′), 49.32 (t, C-8), 59.08 (s, C-6), 67.81 (d, C-3′), 70.19 (d, C-3), 83.16 (s, C-2′), 86.02 (s, C-1′), 212.26 (s, C-7); MS *m/z* 532 (M^+); HRMS *m/z* 532.379 010 ($C_{31}H_{56}O_3Si_2$ requires 532.376 803).

(3′*S*,1*R*,2*S*,3*R*,6*R*)-2-(3′-((*tert*-Butyldimethylsilyl)oxy)-3′-cyclohexylprop-1′-ynyl)-3-((*tert*-butyldimethylsilyl)oxy)-6-fluorobicyclo[4.2.0]octan-7-one (10). To a solution of LiHMDS (400 μL of 1.0M solution in THF, 0.40 mmol) and chlorotrimethylsilane (200 μL, *d* = 0.856, 1.6 mmol) at −78 °C under argon was added ketone **3** (101 mg, 0.2 mmol) in THF (1.0 mL) dropwise. The resulting mixture was stirred under argon at −78 °C for 15 min. The solvent was evaporated under vacuum, and the residue was extracted with dry hexane. The hexane extract was filtered, and the solvent was removed under vacuum to give silyl enol ethers **12** and **13** in a ratio of 85:15 according to ^1H NMR and GC/MS. The mixture of **12** and **13** was dissolved in CH_2Cl_2 (1.5 mL) and added to a solution of XeF_2 (169 mg, 1.0 mmol) in CH_2Cl_2 (1.5 mL) (containing 2 drops of HF·pyridine) at 0 °C. The reaction mixture was stirred at 0 °C for 2 h, poured into ice water, and extracted with CH_2Cl_2. The organic phase was separated, dried (Na_2SO_4), evaporated, and purified by flash chromatography (5% ethyl acetate in hexane) to give **10** (48 mg, 40%) as a colorless oil: IR (neat) 1780 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.46 (m, 1 H, H-4′), 2.71 (m, 1 H, H-1), 2.80 (ddd, 1 H, *J* = 8.5, 11.0, 16.0 Hz, H-8β), 2.88 (m, 1 H, H-2), 3.24 (ddd, 1 H, *J* = 3.5, 10.5, 16.0 Hz, H-8α), 4.07 (dd, 1 H, *J* = 2.1, 6.3 Hz, H-3′), 4.18 (m, 1 H, H-3); MS *m/z* 532 (MH^+), 540 (MNH_4)$^+$; HRMS *m/z* 465.265 282 ($C_{25}H_{42}O_3FSi_2 - C_4H_9$ requires 465.265 653).

Bicyclo[4.2.0]octan-7-one (14).[15] A mixture of bicyclo[4.2.0]oct-2-en-7-one (**15**)[16] (10.0 g, 81.8 mmol), 5% Pd/C (2.0 g), and ethyl acetate (500 mL) was stirred under H_2 at 24 °C for 24 h. The reaction mixture was filtered, the solvent was removed by evaporation, and the residue was purified by Kugelrohr distillation (100 °C, 0.1 mmHg) to give 8.0 g (79%) of **14** as an oil: IR (neat) 1774 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.48 (m, 1 H, H-1), 2.50 (m, 1 H, H-8β), 3.13 (m, 1 H, H-8α), 3.27 (br dd, *J* = 8.0, 8.0 Hz, 1 H, H-6); MS *m/z* 124 (M^+); HRMS *m/z* 124.088 691 ($C_8H_{12}O$ requires 124.088 815).

General Trapping Procedure under Kinetic Conditions.[5]

(a) Using LDA as the Base. To a solution of LDA [prepared in situ by addition of *n*-BuLi (440 μL of a 1.25 M solution in hexane, 0.55 mmol) to diisopropylamine (84 μL, 0.60 mmol) in freshly distilled THF (2.0 mL) at −78 °C] and chlorotrimethylsilane (250 μL, 2.0 mmol) was added the bicyclo[4.2.0]octan-7-one **3** (252.5 mg, 0.5 mmol) in THF (0.2 mL under argon at −78 °C) over 5 min. The resulting mixture was stirred under argon at −78 °C for 15 min. The solvent was evaporated under vacuum, and the residue was extracted with dry pentane. The reaction mixture was centrifuged (or filtered), and the solvent was evaporated to give silyl enol ethers **12** and **13** in a ratio of 57:43. The kinetic enol ether **18** (>99%) and the kinetic enol ethers **16** and **17** (in a ratio of 46:54) were prepared similarly.

(b) Using LiHMDS as the Base. Procedure and workup were the same as in a except lithium bis(trimethylsilyl)amide instead of LDA was used.

(3′*S*,1*S*,2*S*,3*R*,6*S*)-2-(3′-((*tert*-Butyldimethylsilyl)oxy)-3′-cyclohexylprop-1′-ynyl)-3-((*tert*-butyldimethylsilyl)oxy)-7-((trimethylsilyl)oxy)bicyclo[4.2.0]oct-7-ene (13). NMR resonances for **13** were identified from a 57:43 mixture of **12** and **13**. In addition to the resonances for **12** (below) the following resonances were observed: ^1H NMR ($CDCl_3$, 300 MHz) δ 1.48 (m, 1 H, H-4′), 2.37 (m, 1 H, H-2), 2.39 (m, 1 H, H-1), 2.86 (m, 1 H, H-6), 3.81 (m, 1 H, H-3), 4.06 (dd, 1 H, *J* = 1.3, 5.9 Hz, H-3′), 4.80 (br s, 1 H, H-8); GC/MS *m/z* 576 (M^+).

(±)-7-((Trimethylsilyl)oxy)bicyclo[4.2.0]oct-7-ene (17). NMR resonances for **17** were identified from a 46:54 mixture of **16** and **17**. In addition to the resonances for **16** (see below) the following resonances were observed: ^1H NMR ($CDCl_3$, 300 MHz) δ 2.44 (dddd, *J* = 5.0, 5.0, 4.5, 0.8 Hz, 1 H, H-1), 2.86 (ddd, *J* = 5.0, 5.0, 5.5 Hz, 1 H, H-6), 4.62 (d, *J* = 0.8 Hz, 1 H, H-8); GC/MS *m/z* 196 (M^+).

(±)-7-((Trimethylsilyl)oxy)bicyclo[4.2.0]octa-2,7-diene (18) as a colorless oil: ^1H NMR ($CDCl_3$, 300 MHz) δ 0.18 (s, 9 H, $SiMe_3$), 2.79 (dd, 1 H, *J* = 5.0, 5.0 Hz, H-1), 3.16 (br ddd, 1 H, *J* = 2.0, 5.0, 5.0 Hz, H-6), 4.55 (s, 1 H, H-8), 5.77 (m, 1 H, H-3), 5.89 (ddd, 1 H, *J* = 1.5, 5.0, 10.5 Hz, H-2); MS *m/z* 194 (M^+).

General Trapping Procedure under Thermodynamic Conditions.[6] Freshly prepared iodotrimethylsilane[17] (0.4 mmol)

(15) Blomquist, A. T.; Kwiatek, J. *J. Am. Chem. Soc.* **1951**, *73*, 2098.
(16) Ghosez, L.; Montaigne, R.; Roussel, A.; Vanlierde, H.; Mollet, P. *Tetrahedron* **1971**, *27*, 615.

was added slowly with stirring to a solution of **3** (101 mg, 0.20 mmol) and hexamethyldisilazane (100 μL, 0.47 mmol) in dry pentane (3.0 mL) at −20 °C. The reaction mixture was stirred at −20 °C for 20 min and then at 24 °C for 6 h. The solid was removed by centrifugation, and the solvent was removed under vacuum. The 6-silyl enol ether **12** as a colorless oil was the exclusive product, accompanied by 10% of starting ketone **3**.

(3′*S*,1*R*,2*S*,3*R*)-2-(3′-((*tert*-Butyldimethylsilyl)oxy)-3′-cyclohexylprop-1′-ynyl)-3-((*tert*-butyldimethylsilyl)oxy)-7-((trimethylsilyl)oxy)bicyclo[4.2.0]oct-6-ene (12): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.48 (m, 1 H, H-4′), 1.98 (m, 1 H, H-1), 2.0 (m, 1 H, H-2), 2.21 (dd, 1 H, *J* = 2.0, 12.5 Hz, H-8β), 2.66 (ddd, 1 H, *J* = 3.2, 3.2, 12.5 Hz, H-8α), 3.54 (br dd, 1 H, *J* = 9.0, 9.0 Hz, H-3), 4.08 (dd, 1 H, *J* = 1.3, 5.9 Hz, H-3′); GC/MS *m/z* 576 (M^+).

(±)-7-((Trimethylsilyl)oxy)bicyclo[4.2.0]oct-6-ene (16) as a colorless oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.07 (s, 6 H, $SiMe_2$), 0.20 (s, 3 H, SiMe), 1.93 (m, 1 H, H-1), 2.10 (br dd, 1 H, *J* = 1.9, 12.3 Hz, H-8β), 2.62 (ddd, 1 H, *J* = 3.7, 3.7, 12.3 Hz, H-8α); GC/MS *m/z* 196 (M^+).

(3′*S*,1*S*,2*S*,3*R*,6*S*)-2-(3′-((*tert*-Butyldimethylsilyl)oxy)-3′-cyclohexylprop-1′-ynyl)-3-((*tert*-butyldimethylsilyl)-oxy)-6-methyl-8-*exo*-methylbicyclo[4.2.0]octan-7-one (22). A 1.0 M solution of LiHMDS (0.87 mL) in THF was cooled to −78 °C, and a solution of **7** (300 mg, 0.58 mmol) in THF (10 mL) was added dropwise. The reaction mixture was stirred at −78 °C for 30 min, and then methyl iodide (1.0 mL, 16 mmol) in HMPA (0.5 mL) was added in one portion. The reaction conditions and workup were the same as described for the synthesis of compound **7**, and the residue was chromatographed on silica gel, eluting with 2% ethyl acetate in hexane, to give **22** as a colorless gum (235 mg, 76%): $[\alpha]_D$ = −19.78° (*c* 0.425, $CHCl_3$), IR (neat) 1780 (C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ [0.06 (s, 3 H), 0.08 (s, 6 H), 0.11 (s, 3 H)] (4 SiMe), 0.88, 0.91 (2 s, 18 H, tBu), 1.11 (d, *J* = 7.1 Hz, 3 H, C8-Me), 1.24 (s, 3 H, C6-Me), 1.74 (br d, *J* = 9 Hz, 1 H, H-1), 2.84 (br s, 1 H, H-2), 4.13 (m, 1 H, H-3), 3.96 (dq, *J* = 9.0, 7.1 Hz, 1 H, H-8), 4.06 (dd, *J* = 6.2, 1.9 Hz, 1 H, H-3′); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ −4.46, −5.03 (s), −5.03 (s), −5.03 (s, 2 $SiMe_2$), 12.54 (q, 8-Me), 17.94 (s), 18.33 (s), 25.72 (q), 25.86 (q), (2 *t*-Bu), 20.80 (q, 6-Me), 22.32 (t, C-5), 23.80 (t, C-4), 26.03 (t), 26.03 (t, C-6′, C-8′), 26.59 (t, C-7′) 28.62 (t), 28.76 (t, C-5′, C-9′), 31.83 (d, C-2), 43.40 (d, C-1), 45.15 (d, C-4′), 55.26 (d, C-8), 56.52 (s, C-6), 67.79 (d, C-3′), 69.80 (d, C-3), 82.83 (s, C-2′), 86.04 (s, C-1′), 214.65 (s, C-7); MS *m/z* 532 (M^+); HRMS *m/z* 532.378 493 ($C_{31}H_{56}O_3Si_2$ requires 532.376 803). Anal. Calcd for $C_{31}H_{56}O_3Si_2$: C, 69.86; H, 10.59. Found: C, 69.67; H, 10.42.

(17) Sakurai, H.; Shirahata, A.; Sasaki, K.; Hosomi, A. *Synthesis* **1979**, 740.

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Supplementary Material Available: ^{13}C and/or ^{1}H NMR spectra for compounds **9**, **10**, **12**, (**12** + **13**), **16**, (**16** + **17**), and **18** (20 pages). Ordering information is given on any current masthead page.

1,3-Benzodithiolium Cation Mediated Cyclization Reactions

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General protocols for the construction of various ring systems employing cation olefin cyclizations initiated by the readily accessible 1,3-benzodithiolium ion are described. Several substituted tetralones and tetralins can be rapidly assembled by this methodology as can a variety of substituted bicyclo[3.2.1]octane and tricyclic ring systems. The products of these transformations are amenable to interconversion into a range of functionalized species.

Introduction

The readily available 1,3-benzodithiole heterocycle (**1**)[1] exhibits a number of interesting properties which, if properly harnessed, offer considerable appeal in terms of application to rapid and versatile carbon–carbon bond formation. Of particular note is the relative ease with which both the corresponding carbanionic **2** and carbocationic **3** forms can be expressed. The former is generated by simple deprotonation at the C_2 position with a strong base such as *n*-butyllithium. This species can be viewed as a convenient acyl anion equivalent and has been shown to react accordingly.[2] The alternative 1,3-benzodithiolium carbocation (**3**) exhibits considerable stability and can be produced, among other ways, by a hydride exchange with triphenylmethyl fluoroborate.[1,3] Several studies attesting to the useful electrophilicity of **3** have appeared recently.[4] The unique stability of carbocation **3** has been attributed to the presence of a cyclic 10π electron array that renders the system aromatic in character. Indeed, ^{13}C NMR studies on **3** and related sulfur stabilized carbocations have been cited in support of this contention.[5] Experimental evidence places the stability of the 1,3-benzodithiolium ion **3** somewhere between that of the tropylium and trityl carbocations.[1,3]

The notion of combining this dichotomy of reactivity into a sequence in which the nucleophilic and electrophilic

(1) For a recent review of 1,3-benzodithiole chemistry, see: Lozach, N.; Stavaux, M. *Adv. Heterocycl. Chem.* **1980**, *27*, 152.

(2) (a) Ncube, S.; Pelter, A.; Smith, K. *Tetrahedron Lett.* **1979**, 1893, 1895. (b) Ncube, S.; Pelter, A.; Smith, K.; Blatcher, P.; Warren, S. *Ibid.* **1978**, 2345. (c) Brown, C. A.; Miller, R. D.; Lindsay, C. M.; Smith, K. *Ibid.* **1984**, *25*, 991.

(3) Prinzbach, H.; Futterer, E. *Adv. Heterocycl. Chem.* **1966**, *7*, 39.

(4) (a) Nakayama, J. *Synthesis* **1975**, 170. (b) Nakayama, J.; Fujiwara, K.; Hoshino, M. *Bull. Chem. Soc. Jpn.* **1976**, *49*, 3567. (c) Degani, I.; Fochi, R. *Synthesis* **1976**, 759. (d) Degani, I.; Fochi, R. *Ibid.* **1977**, 263. (e) Degani, I.; Fochi, R. *J. Chem. Soc., Perkin Trans. 1* **1978**, 1133. (f) Degani, I.; Fochi, R.; Regondi, V. *Tetrahedron Lett.* **1981**, *22*, 1821. (g) Ncube, S.; Pelter, A.; Smith, K. *Ibid.* **1977**, 255. (h) Pelter, A.; Rupani, P.; Stewart, P. *J. Chem. Soc., Chem. Commun.* **1981**, 164.

(5) (a) Sakamoto, K.; Nakamura, N.; Oki, M.; Nakayama, J. *Chem. Lett.* **1977**, 1133. (b) Hirai, K. *Tetrahedron* **1971**, *27*, 4003. (c) Olah, G. A.; Grant, J. L. *J. Org. Chem.* **1977**, *42*, 2237.

0022-3263/90/1955-5078$02.50/0