Neighboring Group Participation in a Regio- and Stereoselective Chlorination of a Bicyclo[2.2.2]octanone

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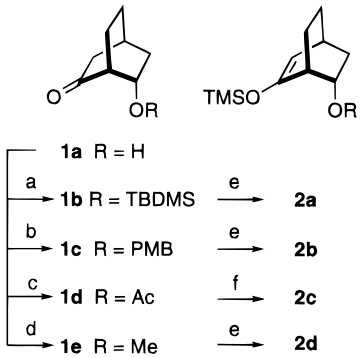
The zinc chloride-mediated acetylation of the optically active silyl enol ether **2a** gave the β-diketone **3a** (48%) together with the regio- and stereoselectively chlorinated compound **4** (27%). The yield of **4** increased to 70% by starting from the O-acetyl derivative **2c**. The chlorination most likely occurs *via* neighboring group participation by the *endo* acetoxy group.

Optically active bicyclo[2.2.2]octane derivatives have attracted attention as rigid templates for regio- and stereocontrolled transformations toward natural products.[1−3] Several other synthetic applications of optically active bicyclo[2.2.2]octane derivatives have been reported,[4−8] and very recently racemic analogs were used in combinatorial chemistry.[9] We would also like to point out the use of a racemic bicyclo[2.2.2]octane derivative for the intentional construction of taxanes.[10] Our initial aim was to prepare optically active bicyclo[2.2.2]octane derivatives, e.g. β-diketones **3** (Scheme 2), for further development into ligands for asymmetric synthesis.[11] During this work we encountered an unexpected stereo- and regioselective chlorination during acetylation attempts of the bicyclo[2.2.2]octane enol ethers **2a**−**c**, which is reported here as well as its probable mechanism.

Our attempts to acetylate directly the enolate of ketone **1b** (Scheme 1), generated by LDA treatment, using acetylating agents such as acetyl chloride or *N*-acetylimidazole were unsuccessful; only starting material was recovered. This sluggishness was also observed for another class of reagents namely, diphenyl disulfide and phenylsulfenyl chloride, with the same ketone enolate.[12] Silyl enol ethers seem to be better choices for synthesis of 1,3-diketones but still O-acylation may be the major reaction.[13] In order to avoid this complication, Rathke et al.[14] recommended a zinc chloride/acetyl chloride mixture for C-acetylation of silyl enol ethers. These conditions were reported to give good yields of 1,3-diketones with formation of only minor amounts of the O-acetylated product. We applied these and other conditions to the TMS-enol ethers **2a**−**d**, prepared according to Scheme 1, and our experiments are shown in Table 1 and Scheme 2.

Scheme 1[a]



[a] (a) TBDMSCl, imidazole, DMF, 97%; (b) *p*-methoxybenzyl trichloroacetimidate, $BF_3{\cdot}OEt_2$, 0 °C to rt, 87%; (c) Ac_2O, pyr, 95%; (d) MeI, Ag_2O, MeCN, reflux, 81%; (e) LDA, TMSCl, −72 °C, >90%; (f) LiBr, TMSCl, NEt_3, −20 to +40 °C, 84%.

Results and Discussion

Treatment of **2a** with the zinc chloride/acetyl chloride mixture gave **3a** as the major product (entry 1). This was the desired product although the protecting group at O-6 was exchanged for an acetyl group. Also some **1d** was isolated. Since chlorination has not been reported previously with this reagent mixture, we were surprised to find that chloro enone **4** was formed in considerable amounts (27%). When the zinc chloride was used directly as delivered (i.e. without drying), the only product was **1d** (entry 2). In order to circumvent the chlorination, we tried other Lewis acids containing no halogens. Zinc tosylate gave only **1d** (entry 3) without any C-acetylated product. C-acetylation did occur, albeit with the TBDMS group exchanged for an acetyl group, by application of the zinc triflate/acetyl chloride mixture (entry 4). But here also a trace of the chlorinated derivative **4** was detected together with a substantial amount of **1d**.

On treatment of **2a** with acetyl chloride in the presence of the strong Lewis acids $TiCl_4$ and $SnCl_4$ (entries 5 and 6) only deprotection of the TBDMS-ether and restoration of the keto function occurred. It is likely that the keto group was restored during the aqueous workup. With the milder Lewis acids, silver triflate and $MgCl_2$, the OTBDMS-protecting group survived but C-acetylated or -chlorinated products were not detected in any of these cases (entries 7, 8). It should be mentioned that the most substituted TMS-enol ether of 2-methylcyclohexanone

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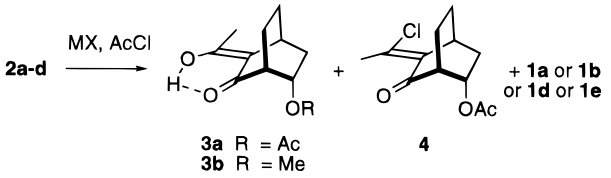
Table 1. Results of the Lewis Acid−Acetyl Chloride Treatment of 2a−d

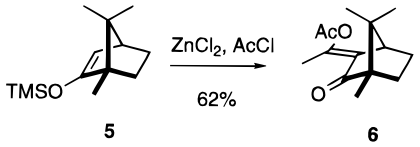
				Isolated yields (%)		
entry	silyl enol ether	MX	conditions	**3**	**4**	**1**
1	**2a**	$ZnCl_2$[a]	0 °C → rt	**3a** 48	27	**1d** 16
2	**2a**	$ZnCl_2$[b]	0 °C → rt	−	−	**1d** 78
3	**2a**	$Zn(tosylate)_2$	0 °C → rt	−	−	**1d** 74
4	**2a**	$Zn(OTf)_2$	0 °C → rt	**3a** 50	traces	**1d** 38
5	**2a**	$TiCl_4$	−72 °C → rt	−	−	**1a** 74
6	**2a**	$SnCl_4$	−72 °C → rt	−	−	**1a** 68
7	**2a**	AgOTf	0 °C → rt	−	−	**1b** 70, **1a** 10
8	**2a**	$MgCl_2$	0 °C → rt	−	−	**1b** 64, **1a** 12
9	**2c**	$ZnCl_2$[a]	0 °C → rt	**3a** 2	70	**1d** 24
10	**2d**	$ZnCl_2$[a]	0 °C → rt	**3b** 13	−	**1e** 27
11	**2b**	$ZnCl_2$[a]	0 °C → rt	**3a** 44	21	**1d** 11

[a] Dried (see Experimental Section). [b] The commercial quality was used as delivered.

Scheme 2



Scheme 3



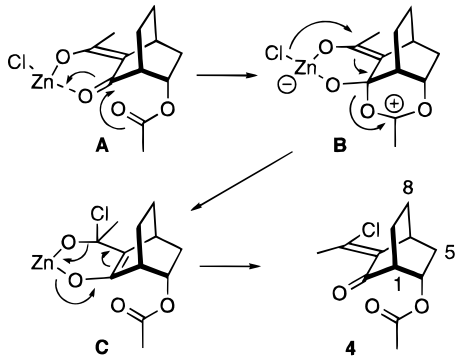
was reported to give a very high yield of the 1,3-diketone on treatment with $TiCl_4$/acetyl chloride.[15,16]

The PMB-ether **2b** (entry 11) behaved essentially as the TBDMS-ether in entry 1. Both gave exchange of the protecting groups and very similar product distributions. On the other hand, the methyl ether derivative **2d** did not result in any chlorinated compounds (entry 10) at the expected interval of retention times as judged by GC-mass spectroscopy. For unknown reasons, **2d** gave a large number of products of which only **3b** and **1e** were isolated. Since the protecting group at O-6 was exchanged in several reactions, we simply applied compound **2c**, having an O-6 acetyl group already in place, as a substrate. This gave, on treatment with the dry $ZnCl_2$/acetyl chloride mixture, a quite high yield of **4** (70%) and a small amount of **1d** (entry 9).

From the above experiments it is obvious that the acetyl group at O-6 is necessary for an efficient conversion into the chloro enone **4**. It also seems necessary to maintain a high chloride concentration since neither zinc triflate nor zinc tosylate gave much chlorinated product, despite the presence of acetyl chloride. In some of the reactions of **2a** we observed that some of the C-acetylated product was formed, which still carried the O-TBDMS group. Thus, it seems possible that the C-acetylation is competing with the deprotective acetylation at O-6 (unless the O-6 carries an acetyl group already). The next event should be the chlorination of some intermediate, which is likely to be a zinc enolate of the 1,3-diketone. Acetyl group participation is indicated from the experiment in entry 10, which does not result in any chlorination but does give some C-acetylation, and the high yield when the O-6 acetate is present from the beginning (entry 9). Moreover, compound **5**, lacking a participating group, gives only the *O*-acetyl enolate **6** (Scheme 3) in good yield.

On the basis of these observations, we propose the mechanism shown in Scheme 4. Thus, the C- and O-6 acetylated primary intermediate forms a zinc enolate (possibly a chelate), which is triggered to lose a chloride

Scheme 4. Tentative Mechanism Showing the Neighboring Group Participation of the 6-OAc Group



ion by participation of the endo-positioned acetoxy group (A → B). It is then possible that the chloride migrates to the exo-methylene carbon without becoming entirely free (B → C). During this migration, the acetoxy group at C-6 is restored to give C, which then decomposes to give **4**. Whether the stereoselectivity originates from kinetic or thermodynamic control is unclear. A mixutre of the (*E*)- and (*Z*)-isomers may be formed initially which then equilibrates to give only the (*E*)-derivative under the reaction conditions. We have not been able to validate this since the (*Z*)-derivatives were not available, and the literature does not seem to give any leads. However, *ab initio* (STO-3G) calculations[17] confirmed that the (*E*)-isomer is 4.4 kcal/mol lower in energy than the (*Z*)-isomer and thus would dominate under thermodynamic control. It should be noted that in all cases where there is a hetero substituent at the exo-methylene position (**4**, **6**, **8**,**10**) the (*E*)-configuration is obtained except for OH, which stabilizes the (*Z*)-configuration via hydrogen bonding (**3a**−**c**, **9**).

Structural proof for **4** was obtained from its spectroscopic data. The presence of one chlorine atom as well as the absence of the TBDMS group was obvious from its mass spectrum. The ^1H NMR data show a large downfield shift of H-4 in **4** as compared with H-4 in **3a**

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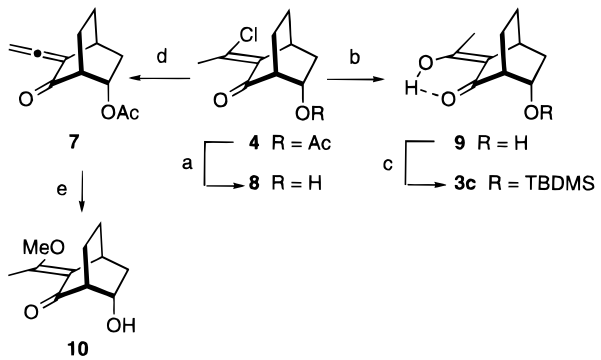
Scheme 5[a]



[a] (a) 1 M HCl:EtOH, 50 °C, 5 h, 91%; (b) 1 M HCl:EtOH, reflux, 14 h, 83%; (c) TBDMSCl, imidazole, DMF, 84%; (d) KOtBu, THF, −50 °C, quant; (e) K_2CO_3, MeOH:H_2O, quant.

(3.43 ppm versus 2.85 ppm), which indicates that the chlorine atom and H-4 are positioned close in space. A differential NOE experiment further confirmed this observation. A strong NOE between the ethylidene methyl protons and H-4 would be expected for the (*Z*)-isomer but not for the corresponding (*E*)-isomer. The experiment showed the H-4→H-5 and H-4→H-8 NOE effects, but none was detected between H-4 and the ethylidene methyl protons. The (*E*)-configuration of **6** was determined similarly.

β-Chloro-α,*β*-unsaturated ketones synthesized from α-allenones and $SnCl_4$ were reported to have the (*E*)-configuration,[18] in agreement with our results. Other methods such as the sodium acetate-induced elimination of HCl from α-(1,1-dichloroethyl)cyclohexanone gave a 77/23 mixture of the (*E*)- and (*Z*)-products.[19] Still, the (*E*)-isomer dominated. On the other hand, treatment of α-acetylcyclohexanone with oxalyl chloride was reported to give the (*Z*)-isomer as the major product, together with the isomer having the chlorine atom at the ring position.[20] The structure of the (*Z*)-isomer was not rigorously proven, however.

Thus, not many examples of *exo*-chloroethylidene ketones or analogues appear to be reported in the literature, despite their seemingly high potential as reactive intermediates in organic synthesis. Examples of some useful transformations are shown in Scheme 5. Compound **4** could be almost quantitatively transformed into the chiral allene **7** on treatment with potassium *tert*-butylate. Hydrolysis of **7** in methanol/water was not selective; the acetyl group was removed but methanol added to the allenic moiety. On the other hand, the acetyl group of **4** could be selectively removed under hydrolytic conditions to give **8**, and under more forcing conditions also the vinylic chloride function was hydrolyzed to generate the nonprotected **9**, the 6-OH group of which could be selectively protected after acidic work up to give **3c**. Thus a host of optically active compounds can be obtained by selective manipulation of the functionalities of **4**. Since the reactions used in this work do not allow racemization, we assume that the optical purities of all compounds are at least as high as the starting material **1a** (97% ee). Some obvious aspects of this chemistry is now under active investigation in our laboratories.

In conclusion, we found that the use of the $ZnCl_2$/acetyl chloride mixture in the case of **2c** gave the chlorinated product **4** in high yield (70%). Also **2a** gave a considerable amount of **4** with this reagent. The mechanism of the chlorination most likely occurs *via* neighboring group participation by the *endo* acetoxy group. The chlorination could be avoided by the use of zinc triflate/acetyl chloride, which is the reagent of choice for the direct synthesis of **3a** from silyl enol ether **2a**. Compound **4** can be transformed into various optically active compounds such as **7**, **8**, **9**, **10**, and **3c**, suitable for further development.

Experimental Section

General. GC analyses were performed with a SPB-5 (Supelco) capillary column (30 m, 0.25 mm i.d., 0.25 *μ*m stationary phase). NMR spectra were recorded at 300 or 400 MHz using $CDCl_3$ ($CHCl_3$ *δ* 7.26 (^{1}H) and 77.0 (^{13}C)) as solvent. Chromatographic separations were performed on Matrex Amicon normal phase silica gel 60 (0.035−0.070 mm), and for TLC we used Merck precoated plates (silica gel 60 F-254, 0.25 mm). All solvents were dried and distilled according to standard procedures,[21] and the reactions were performed in septum-capped, oven-dried flasks under an atmospheric pressure of argon. Organic extracts were dried using Na_2SO_4 throughout. Optical rotations were measured at rt at the sodium D-line.

Dry $ZnCl_2$ was prepared as follows: $ZnCl_2$ was added to a flame-dried, weighed roundbottomed flask followed by $SOCl_2$. The mixture was heated at reflux temperature for 4 h, and then the $SOCl_2$ was evaporated at reduced pressure under argon. The flask was placed in a desiccator over KOH pellets and kept at reduced pressure overnight. The flask was weighed and the amount of dry $ZnCl_2$ was determined.

(1*R*,4*S*,6*S*)-6-[(*tert*-Butyldimethylsilyl)oxy]bicyclo[2.2.2]-octan-2-one (1b) was prepared according to published procedures.[12]

(1*R*,4*S*,6*S*)-6-[(*p*-Methoxybenzyl)oxy]bicyclo[2.2.2]octan-2-one (1c). Hydroxy ketone (−)-**1a**[22,23] (610 mg, 4.35 mmol) in CH_2Cl_2 (5.0 mL) was added to a solution of *p*-methoxybenzyl trichloroacetimidate[24] (1.84 g, 6.51 mmol) in cyclohexane (10.5 mL) followed by addition of BF_3·OEt_2 (8 *μ*L) at 0 °C. After 30 min the cooling bath was removed, and after 12 h the resultant nonhomogenous mixture was filtered through a pad of Hyflo-Supercel. The pad was rinsed several times with CH_2Cl_2:cyclohexane 1:2, and the combined solution was washed with aqueous saturated $NaHCO_3$ and dried. Concentration at reduced pressure followed by chromatography (SiO_2, heptane:EtOAc 70:30) gave **1c** as an oil (987 mg, 87%): [α] −27° (*c* 0.7, $CHCl_3$); IR (neat) 3020, 2930, 1715, 1605, 1505 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 7.21 (d, *J* = 8.4 Hz, 2H) 6.85 (d, *J* = 8.4 Hz, 2H) 4.52 (d, *J* = 11.4 Hz, 1H) 4.34 (d, *J* = 11.4 Hz, 1H) 3.87 (m, 1H) 3.79 (d, *J* = 0.7 Hz, 3H) 2.72 (m, 1H) 2.35 (dm, *J* = 18.2 Hz, 1H) 2.15−2.26 (m, 2H) 2.05 (m, 1H) 1.82 (m, 1H) 1.47−1.74 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 214.71, 159.09, 130.10, 129.27, 113.73, 75.01, 69.26, 55.23, 46.69, 44.40, 34.21, 27.63, 24.18, 19.90; HRCIMS (CH_4) calcd for $C_{16}H_{20}O_3$ 260.1412, observed 260.1411.

Methods utilizing basic conditions for the protection according to standard procedures[25] were unsuccessful.

(1*R*,4*S*,6*S*)-6-Acetoxybicyclo[2.2.2]octan-2-one (1d). Acetic anhydride (0.20 mL, 2.13 mmol) was added dropwise to a solution of (−)-**1a** (100 mg, 0.71 mmol) in pyridine (3.0 mL) at rt. The mixture was kept at this temperature for 8 h when

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aqueous saturated $NaHCO_3$ (10.0 mL) was added, and the resultant mixture was extracted with EtOAc. The combined organic phase was washed in sequence with aqueous saturated $CuSO_4$ and brine and dried. Concentration at reduced pressure and chromatography (SiO_2, heptane:EtOAc 1:2) gave **1d** as an oil (123 mg, 95%); [α] −30° (*c* 3.1, $CHCl_3$) (lit.[23] $[\alpha]^{20.0}_D$ −27.6° (*c* 1.4, $CHCl_3$)); IR and NMR data were as reported.[23]

(1*R*,4*S*,6*S*)-6-Methoxybicyclo[2.2.2]octan-2-one (1e). Iodomethane (1.1 mL, 17.7 mmol) was added dropwise to a solution of (−)-**1a** (200 mg, 1.43 mmol) in acetonitrile (2.5 mL) under argon at rt. After 5 min Ag_2O (460 mg, 1.98 mmol) was added in portions, and the mixture was heated at reflux for 36 h and then filtered through a pad of Hyflo-Supercel. The pad was washed with CH_2Cl_2, and the combined solution was concentrated at reduced pressure. Chromatography (SiO_2, heptane:EtOAc 1:1) gave **1e** as an oil (178 mg, 81%): [α] −26° (*c* 1.9, $CHCl_3$); IR (neat) 2940, 2870, 2820, 1725, 1100 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.67 (ddd, *J* = 8.9, 3.7, 2.5 Hz, 1H) 3.26 (s, 3H) 2.65 (m, 1H) 2.27 (dm, *J* = 18.3 Hz, 1H) 2.22 (m, 1H) 2.15 (dm, *J* = 18.3 Hz, 1H) 2.04 (m, 1H) 1.80 (m, 1H) 1.45−1.68 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 214.39, 77.84, 55.67, 46.39, 44.31, 33.98, 27.56, 24.06, 19.78; HRCIMS (CH_4) calcd for $C_9H_{15}O_2$ 155.1072, observed 155.1075.

Methods utilizing basic conditions for the protection according to standard procedures[25] were unsuccessful.

General Procedure for the Preparation of the TMS-Enol Ethers 2a−d and 5. The silyl enol ethers **2a**, **2b**, **2d**, and **5** were prepared according to a literature procedure[12] in over 90% yields. Silyl enol ether **2c** was synthesized by applying a method developed for the preparation of silyloxy dienes as follows.[26] TMSCl (0.52 mL, 4.10 mmol), **1d** (748 mg, 4.10 mmol), and NEt_3 (0.57 mL, 4.38 mmol) were added in sequence to a solution of dry LiBr (714 mg, 8.22 mmol) in THF (3 mL) at −20 °C. After 1 h at −20 °C, the temperature was raised to 40 °C, and the mixture was kept at that temperature for 48 h. The solvent was then removed at reduced pressure and replaced with cold pentane. The resulting mixture was filtered through Hyflo-Supercel, and then the solvent was removed at reduced pressure to give an oil which was diluted with heptane:EtOAc 3:1, and the solution was filtered through a pad of silica. The solvent was removed at reduced pressure to give **2c** as a pale yellow oil (877 mg, 84%). Due to their sensibility toward hydrolysis, all the TMS-enol ethers were used directly in the next step without further purification. The purity of the TMS-enol ethers was generally ≥90% according to GC; NMR data were as reported for **2a**[12] and **5**.[27]

For **2b**: ^1H NMR (300 MHz, $CDCl_3$) δ 7.27 (d, *J* = 8.6 Hz, 2H) 6.86 (d, *J* = 8.6 Hz, 2H) 5.17 (dd, *J* = 7.3, 2.2 Hz, 1H) 4.51 (d, *J* = 11.7 Hz, 1H) 4.40 (d, *J* = 11.6 Hz, 1H) 3.80 (s, 3H) 3.65 (m, 1H) 2.69 (m, 1H) 2.53 (m, 1H) 1.78 (ddd, *J* = 13.0, 8.2, 2.4 Hz, 1H) 1.46 (m, 1H) 1.12−1.38 (m, 4H) 0.21 (s, 9H).

For **2c**: ^1H NMR (300 MHz, $CDCl_3$) δ 5.1 (dd, *J* = 7.2, 2.3 Hz, 1H) 4.88 (m, 1H) 2.53 (m, 1H) 1.97 (s, 3H) 1.89−1.99 (m, 1H) 1.40-1.50 (m, 2H) 1.12−1.36 (m, 3H) 0.19 (s, 9H).

For **2d**: ^1H NMR (400 MHz, $CDCl_3$) δ 5.16 (dd, *J* = 7.2, 2.3 Hz, 1H) 3.48 (m, 1H) 3.28 (s, 3H) 2.64 (m, 1H) 2.53 (m, 1H) 1.77 (dd, *J* = 12.9, 7.9, 2.4 Hz, 1H) 1.46 (m, 1H) 1.14−1.38 (m, 4H) 0.19 (s, 9H).

General Procedure for the Acetylation of the TMS-Enol Ethers 2a−d and 5. Acetyl chloride (2.7 mmol) was added to a slurry of Lewis acid (2.3 mmol) in CH_2Cl_2 (1.2 mL) and diethyl ether (0.2 mL) at 0 °C (−72 °C when $TiCl_4$ or $SnCl_4$ were used). After 5 min the TMS-enol ether (1.0 mmol) was added. The mixture was kept at 0 °C for 1 h and then allowed to reach rt within 45 min. After 30 min at rt ice was added, and then the mixture was extracted with CH_2Cl_2. The combined organic phase was washed with saturated aqueous $NaHCO_3$ and dried. Concentration at reduced pressure gave a crude oil which was purified by chromatography (SiO_2, heptane:EtOAc 70:30).

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2a and dry $ZnCl_2$ gave **3a** (48%), **4** (27%), and **1d** (16%). For **3a**: mp 84.5−85.5 °C; [α] −55° (*c* 9.9, $CHCl_3$); IR (neat) 2960, 2880, 1740, 1650, 1610, 1245 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 14.24 (s, 1H) 5.06 (dm, *J* = 9.2 Hz, 1H) 2.85 (m, 1H) 2.69 (m, 1H) 2.20 (ddd, *J* = 14.0, 9.2, 2.6 Hz, 1H) 2.04 (s, 3H) 1.98 (s, 3H) 1.70 (m, 2H) 1.57 (m, 1H) 1.46 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.05, 174.59, 170.41, 112.54, 71.29, 44.89, 36.10, 29.38, 25.09, 21.13, 19.97, 18.78; HRCIMS (CH_4) calcd for $C_{12}H_{16}O_4$ 224.1049, observed 224.1047.

For **4**: [α] −40° (*c* 3.9, $CHCl_3$); IR (neat) 2930, 2860, 1730, 1695, 1600 1225 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.10 (dm, *J* = 9.5 Hz, 1H) 3.43 (m, 1H) 2.65 (d, *J* = 0.8 Hz, 3H) 2.65 (m, 1H) 2.26 (m, 1H) 1.99 (d, *J* = 1.0 Hz, 3H) 1.71−1.87 (m, 2H) 1.58−1.68 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.14, 170.19, 143.99, 134.77, 70.81, 48.40, 34.13, 33.33, 25.06, 23.18, 21.06, 19.73; HRCIMS (CH_4) calcd for $C_{12}H_{15}O_3Cl$ 242.0710, observed 242.0710.

2d and dry $ZnCl_2$ gave **3b** (13%) and **1e** (27%). For **3b**: [α] −36° (*c* 0.15, $CHCl_3$); IR (neat) 2930, 2860, 1640, 1590, 1255 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 14.27 (s, 1H) 3.66 (dm, *J* = 9.4 Hz, 1H) 3.32 (s, 3H) 2.87 (m, 1H) 2.84 (m, 1H) 2.02−2.10 (m, 1H) 2.03 (s, 3H) 1.71 (m, 1H) 1.42−1.76 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.17, 173.87, 112.67, 78.45, 55.94, 44.41, 36.12, 29.52, 25.72, 19.81, 18.68; HRCIMS (CH_4) calcd for $C_{11}H_{17}O_3$ 197.1177, observed 197.1177.

5 and dry $ZnCl_2$ gave **6** (62%) as an oil: [α] +141° (*c* 1.40, $CHCl_3$); IR (neat) 2960, 2920, 2870, 1755, 1730, 1665, 1370, 1200, 1175 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.59 (d, *J* = 4.2 Hz, 1H) 2.28 (s, 3H) 2.17 (s, 3H) 1.92 (m, 1H) 1.64 (m, 1H) 1.42 (m, 2H) 0.94 (s, 3H) 0.91 (s, 3H) 0.80 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 207.55, 168.06, 151.24, 130.21, 58.82, 47.95, 46.10, 30.31, 25.65, 20.86, 20.27, 18.30, 17.20, 9.35; HRCIMS (CH_4) calcd for $C_{14}H_{20}O_3$ 237.1491, observed 237.1490.

(1*R*,4*S*,6*S*)-6-Acetoxy-3-vinylidenebicyclo[2.2.2]octan-2-one (7). Potassium *tert*-butoxide (180 mg, 1.61 mmol) was added in one portion under a stream of argon to a solution of **4** (300 mg, 1.24 mmol) in THF (55 mL) at −50 °C. After 90 min at this temperature aqueous saturated NH_4Cl was added cautiously, and the mixture was extracted with EtOAc and dried. Concentration at reduced pressure followed by chromatography (SiO_2, heptane:EtOAc 70:30) gave **7** (255 mg, 100%): mp 131−132 °C; [α] −39° (*c* 0.7, $CHCl_3$); IR (KBr) 2950, 2880, 1960, 1930, 1735, 1680, 1240 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.24 (s, 2H) 5.15 (dm, *J* = 9.6 Hz, 1H) 2.86 (m, 1H) 2.69 (m, 1H) 2.30 (m, 1H) 2.00 (s, 3H) 1.62−1.92 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 206.57, 200.23, 170.29, 106.88, 79.86, 70.74, 46.67, 34.89, 33.48, 24.08, 21.11, 19.62; HRMS calcd for $C_{12}H_{14}O_3$ 206.0943, observed 206.0946.

(1*R*,4*S*,6*S*)-(*E*)-3-(1-Chloroethylidene)-6-hydroxybicyclo-[2.2.2]octan-2-one (8). Compound **4** (614 mg, 2.54 mmol) was diluted with EtOH (14 mL) and 1 M HCl (43 mL). After 6 h at 50 °C ice was added, and the mixture was extracted with EtOAc. The combined organic phase was washed with saturated aqueous $NaHCO_3$ and dried. Concentration at reduced pressure followed by chromatography (SiO_2, heptane:EtOAc 1:2) gave **8** (462 mg, 91%): mp 83−84 °C; [α] −0.4° (*c* 7.7, $CHCl_3$); IR (KBr) 3420, 1690, 1600, 635 cm^{-1} ^1H NMR (400 MHz, $CDCl_3$) δ 4.16 (dm, *J* = 9.0 Hz, 1H) 3.38 (m, 1H) 2.81−3.06 (s, 1H) 2.60 (d, *J* = 1.2 Hz, 3H) 2.56 (m, 1H) 2.15 (m, 1H) 1.52−1.81 (m, 5H) ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.33, 143.61, 135.09, 68.68, 52.14, 36.10, 33.42, 25.09, 23.22, 19.58; HRCIMS (CH_4) calcd for $C_{10}H_{12}OCl$ 183.0576, observed 183.0577.

(1*R*,4*S*,6*S*)-(*Z*)-6-Hydroxy-3-(1-hydroxyethylidene)-bicyclo[2.2.2]octan-2-one (9). Compound **4** (218 mg, 0.90 mmol) was diluted with EtOH (5 mL) and 1 M HCl (15 mL). After 14 h at reflux ice was added, and the mixture was extracted with EtOAc. The combined organic phase was washed with saturated aqueous $NaHCO_3$ and dried. Concentration at reduced pressure followed by chromatography (SiO_2, heptane:EtOAc 1:3) gave **9** (136 mg, 83%): mp 137−143 °C; [α] −24° (*c* 0.3, $CHCl_3$); IR (KBr) 3400, 1630, 1585, 705 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.18 (dm, *J* = 8.7 Hz, 1H) 2.85 (m, 1H) 2.63 (m, 1H) 2.15 (ddd, *J* = 13.7, 8.9, 2.6 Hz, 1H) 2.04 (s, 3H) 1.39−1.91 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ

201.21, 174.44, 112.70, 69.43, 48.83, 38.31, 29.42, 25.15, 19.90, 15.91; HRCIMS (CH_4) calcd for $C_{10}H_{15}O_3$ 183.1021, observed 183.1023.

(1*R*,4*S*,6*S*)-(*Z*)-3-(1-Hydroxyethylidene)-6-[(*tert*-butyldimethylsilyl)oxy]bicyclo[2.2.2]octan-2-one (3c). A solution of **9** (79 mg, 0.43 mmol), imidazole (88 mg, 1.29 mmol), and TBDMSCl (131 mg, 0.87 mmol) in DMF (1 mL) was kept at rt for 12 h. A mixture of diethyl ether and EtOAc (1:1) was then added, and the mixture was washed in sequence with water, cold 1.5 M HCl (several times), saturated aqueous $NaHCO_3$, and water. The organic phase was dried, the solvent was removed at reduced pressure, and the residue was chromatographed (SiO_2, heptane:EtOAc 85:15) to give **3c** (107 mg, 84%): [α] −36° (*c* 1.3, $CHCl_3$); IR (KBr) 1705, 1640, 1605, 1250, 1095 cm^{-1} ^1H NMR (400 MHz, $CDCl_3$) δ 14.31 (s, 1H) 4.07 (dm, J = 8.7 Hz, 1H) 2.78 (m, 1H) 2.52 (m, 1H) 2.06 (ddd, J = 13.2, 8.7, 2.6 Hz, 1H) 2.02 (s, 3H) 1.36−1.69 (m, 5H) 0.84 (s, 9H) 0.04 (s, 3H) 0.02 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.54, 173.16, 112.76, 69.90, 48.88, 39.60, 29.54, 25.74, 25.34, 20.00, 18.62, 18.01, −4.67, −4.82; HRCIMS (CH_4) calcd for $C_{16}H_{29}O_3Si$ 297.1886, observed 297.1891.

(1*R*,4*S*,6*S*)-(*E*)-6-Hydroxy-3-(1-methoxyethylidene)-bicyclo[2.2.2]octan-2-one (10). K_2CO_3 (84 mg, 0.61 mmol) was added to a solution of **7** (29 mg, 0.11 mmol) in MeOH and water (6 mL, 9:1). After 2 h at rt the mixture was concentrated to approximately 1 mL, and brine was added. The mixture was extracted with EtOAc and dried. Concentration at reduced pressure followed by chromatography (SiO_2, EtOAc) gave **10** (26 mg, quant): mp 184−186 °C; [α] −0.4° (*c* 0.1, $CHCl_3$); IR (KBr) 3360, 1650, 1570 cm^{-1} ^1H NMR (400 MHz, $CDCl_3$) δ 4.14 (dm, J = 8.9 Hz, 1H) 3.72 (s, 3H) 3.31 (m, 1H) 2.49 (s, 3H) 2.49 (m, 1H) 2.29 (s, 1H) 2.08 (ddd, J = 14.0, 9.1, 2.7 Hz) 1.72 (m, 1H) 1.59 (m, 1H) 1.40−49 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.80, 162.38, 117.87, 69.62, 54.35, 52.36, 37.28, 27.45, 24.29, 20.24, 14.31; HRCIMS (CH_4) calcd for $C_{11}H_{17}O_3$ 197.1178, observed 197.1180.

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Supporting Information Available: Copies of the ^{13}C NMR spectra for those compounds for which elemental analysis data are given as HRMS data (11 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of this journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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