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Studies in Bicyclo[3.1.0]hexane Methanolysis. Ring Opening of Activated Cyclopropanes under Acidic and Basic Conditions

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Abstract: A bicyclo[3.1.0]hexane, with one cyclopropane carbon flanked by a ketone and an ester or an aldehyde, undergoes methanolysis with cleavage of one of the two activated cyclopropane bonds, depending on the reaction conditions. Acidic conditions yield primarily or exclusively a 4-methoxycyclohexane, while basic conditions yield a 3-methoxymethylcyclopentanone.

Cyclopropanes are key intermediates in many synthetic strategies because of their ready availability and high reactivity,[1] and methods for asymmetric synthesis of cyclopropanes have enhanced their importance.[2] Among the useful reactivities of cyclopropanes is ring opening by nucleophiles when the cyclopropane is activated by one or more electron-withdrawing groups.[3] The stereoelectronic predictability of this reaction and its selective stereochemical result account for its utility in a broad set of syntheses.[4]

As part of an ongoing investigation,[5] we required enantiomerically pure pyridone **1** and anticipated that the retrosynthetic approach in Scheme 1 would generate it expeditiously from cyclopropane **3**. The attractive attributes of this approach included carbonyls properly positioned for a standard pyridone annulation[6] and stereochemistry derived from an asymmetric intramolecular cyclopropanation of **4**, which can be prepared in two steps from acetoacetate. Despite ample precedent for production of molecules such as **2** from **3**, we report here that the cyclopropane bond of **3** that is cleaved during methanolysis is highly dependent on the reaction conditions and the nature of the attached functional group.

SCHEME 1. Retrosynthetic Approach to Optically Active Pyridone 1

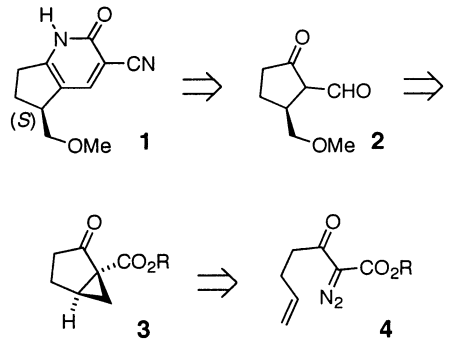
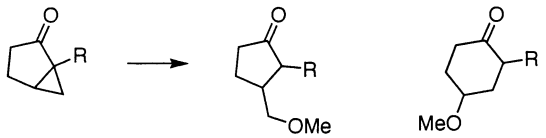


TABLE 1. Methanolysis of Bicyclo[3.1.0]hexane Derivatives



entry	conditions	ratio (yield)
	5 R = CO_2Me	**6** **7**
1	methanol TsOH, reflux	0.9 : 1 (78%)
2	NaOMe methanol	8.6 : 1 (44%)
3	$Mg(OMe)_2$ methanol, reflux	8.8 : 1 (84%)
	8 R = CHO	**9** R = $CH(OMe)_2$ **10**
4	methanol TsOH, reflux	– : 1[a] (65%)
5	cyanoacetamide AcOH, piperidine methanol, reflux	only **11** (23%)
	12 R = $CH(OMe)_2$	**9** **10**
6	methanol TsOH, reflux	– : 1[b] (80%)

[a] Cis:trans ratio = 1.7:1. [b] Cis:trans ratio = 1.3:1.

Our studies began with methyl ester **5** and the use of acidic conditions (Table 1, entry 1). Reflux of **5** in methanol with catalytic *p*-toluenesulfonic acid gave not one but two methanolysis products in nearly equal quantities. These were readily identified as **6** and **7** by NMR spectroscopy, particularly the ^1H and DEPT spectra. The expected chemical shifts of the methylene and methine carbons were distinctive in the DEPT; the proton

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NMR spectrum of **6** has a two-proton ABX pattern for the methylene ether protons, whereas a single methine ether proton is found in the ^{1}H spectrum of **7**. IR spectroscopy was also supportive, with ketone absorbances at 1757 and 1717 cm^{-1} for **6** and **7**, respectively. Both **6** and **7** were single isomers. Compound **7** exists primarily as the enol, partly on the basis of the presence of a well-defined single proton at 12 ppm in the ^{1}H NMR spectrum. In contrast, cyclopentanone **6** is a ketone with a methine doublet between the carbonyls clearly visible in the ^{1}H NMR spectrum. The coupling constant for this doublet (10 Hz) does not allow for determination of the stereochemistry, however, which is assumed to be trans.

While the mixture of **6** and **7** was understandable as a balance of steric effects favoring **6** and carbocation stability favoring **7**, the formation of substantial amounts of the latter was surprising. The overlap of cyclopropane bonds with the ketone π-bonds would be expected to strongly favor **6**. To account for this outcome, we reasoned that the ester of **5** is the strongest Lewis base and that its conformational freedom might be the determining factor in the cyclopropane bond cleavage. We therefore reduced ketoester **5** to keto aldehyde **8**, anticipating that this would have two desirable effects: the ketone would be the stronger Lewis base and would thereby direct the methanolysis, and the product **9** would be at the proper oxidation state for subsequent pyridone annulation.

Treatment of keto aldehyde **8** with acidic methanol also led to two products, entry 4, neither of which were cyclopentanones! Each had a single methine ether proton in their ^{1}H NMR spectra and IR absorptions of 1716 and 1713 cm^{-1}. Under these reaction conditions, the aldehyde was simultaneously converted to an acetal, and it appeared that the rate of acetal formation was competitive with cyclopropane ring cleavage. To separate these two processes, we converted aldehyde **8** to the acetal **12** using trimethylorthoformate and then subjected this adduct to acidic methanolysis conditions. Use of acetal **12** improved the methanolysis yield, but again led only to a mixture of cis and trans isomers of **10**, entry 6. This selectivity is inconsistent with involvement of the ketone in **12** and is likely driven by a carbocation derived from the acetal. The cis and trans isomers of **10**, designated as **10a** and **10b**, are presumably kinetically derived isomers.

One additional attempt to bias the orbital alignment of the free-rotating carbonyl was to condense **8** with cyanoacetamide, entry 5. Condensation of acetamide with the aldehyde and ketone before cyclopropane cleavage would form an aza-analogue of the CC-1065 cyclopropane, a structure known to open with methanol to give a methoxymethyl-substituted cyclopentane in high yield.[7] Unfortunately, this condensation/methanolysis combination gave tetrahydroquinolone **11** as the only identifiable product.

The use of basic conditions proved to be much more selective for the desired **6**. Treatment of ester **5** with sodium methoxide led to a rapid ring opening, entry 2; however, the yield for this transformation was modest. In an effort to employ milder conditions, we turned to the use of magnesium methoxide, entry 3. The use of this base is simplifying, as methanol is usually dried by heating to reflux over magnesium turnings. Following the dissolution of magnesium metal in methanol at reflux, addition of **5** directly to this mixture led to the most favorable results. After a 30 min reaction time, the starting **5** was fully consumed and the methanolysis products were isolated in 84% yield, with a nearly 90% selectivity for **6**.

The selectivity of the ring opening by the alkoxides is likely due to the need for both ketone and ester π-orbitals to align with the breaking cyclopropane bond. Only one cyclopropane bond can easily align with the ketone π-bond. Nevertheless, the bond selectivity is not complete, even under the basic cleavage conditions.

Stereoelectronics are expected to dominate in the bond cleavage of activated cyclopropanes. For bicyclo[3.1.0]-hexanes, we are only aware of two studies reporting competitive cleavage of the central bond.[8] Both cases involve acidic conditions and a halogen nucleophile (pyridinium halides and TMSBr), but the selectivities for the internal bond cleavage are not as high as that reported here. Tricyclic ring systems provide additional examples of ring cleavage diversity.[9] The role played by conformation in the stereoelectronic bias for cyclopropane bond cleavage can most clearly be found in the work of Caine et al.[10]

The ability to select for either a five- or six-membered ring product from bicyclo[3.1.0]hexane should enhance the value of these readily available cyclopropane intermediates. Additional studies are in progress.

Experimental Section

2-Diazo-3-oxo-6-heptenoic Acid Methyl Ester (4, R = methyl).[11] To a solution of methyl 3-oxo-6-heptenoate[12] (870 mg, 5.6 mmol) in acetonitrile (28 mL) was added triethylamine (1.01 mL, 7.3 mmol) followed by the addition of *p*-acetamidobenzenesulfonyl azide[13] (1.74 g, 7.3 mmol). A white precipitate formed within 5 min. After stirring for 2 h, the reaction mixture was washed with saturated NH_4Cl, and the aqueous layer was extracted with ether. The combined organics were washed with 10% KOH, saturated $NaHCO_3$, and saturated NaCl, dried over anhydrous $MgSO_4$, concentrated in vacuo to give **4** (993 mg, 98%) as a clear liquid, and used without purification. ^{1}H NMR ($CDCl_3$): δ 5.76 (ddt, J = 17.1, 10.5, 6.0 Hz, 1H), 5.02−4.89 (m, 2H), 3.77 (s, 3H), 2.88 (t, J = 6.0 Hz, 2H), 2.31 (dd, J = 14.4, 6.6 Hz, 2H). ^{13}C NMR ($CDCl_3$): δ 191.8, 161.5, 136.7, 115.2, 52.0, 39.1, 28.0.

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2-Oxo-bicyclo[3.1.0]hexane-1-carboxylic Acid Methyl Ester (5).[14] To a −15 °C solution of **4** (663 mg, 3.64 mmol) in methylene chloride (2 mL) was added $Rh_2(AcO)_4$ (6.43 mg, 0.15 mmol), and the green reaction mixture was allowed to stir overnight. The solution was concentrated in vacuo and purified over silica gel (1:1 ethyl acetate/hexanes) to yield **5** (550 mg, 98%) as a tan oil. R_f = 0.5 (1:1 ethyl acetate/hexanes). ^{1}H NMR ($CDCl_3$): δ 3.70 (s, 3H), 2.59−2.53 (m, 1H), 2.39−2.11 (m, 3H), 2.03−1.93 (m, 2H), 1.36 (t, J = 5.1 Hz, 1H). ^{13}C NMR ($CDCl_3$): δ 206.9, 168.8, 52.2, 37.5, 33.5, 33.0, 22.2, 20.8.

1-Hydroxymethyl-bicyclo[3.1.0]hexan-2-ol. To a −20 °C suspension of $LiAlH_4$ (2.29 g, 57.2 mmol) in ether (102 mL) was added dropwise a solution of **5** (2.205 g, 14.3 mmol) in ether (3 mL). After 3 h, the reaction was brought to room temperature for 1 h. Ethyl acetate (2 mL) was carefully added, followed by water (2 mL), 15% NaOH (2 mL), and then water (3 mL). The mixture was filtered and the residue washed with ether. The combined organic phases were washed with water and brine solution, dried over anhydrous $MgSO_4$, and concentrated in vacuo. Flash chromatography (1:19 methanol/methylene chloride) gave the title compound (1.68 g, 92%) as a clear liquid. R_f = 0.2 (2:98 methanol/methylene chloride). ^{1}H NMR ($CDCl_3$): δ 4.48 (t, J = 8.3 Hz, 1H), 3.76 (d, J = 11.4 Hz, 1H), 3.50 (d, J = 11.4 Hz, 1H), 3.47 (bs, 2H), 1.85 (m, 1H), 1.69 (m, 2H), 1.14 (m, 2H), 0.80 (t, J = 4.6 Hz, 1H), 0.39 (dd, J = 7.9, 5.3 Hz, 1H). ^{13}C NMR ($CDCl_3$): δ 75.8, 66.8, 33.6, 28.7, 23.7, 20.8, 8.64.

2-Oxo-bicyclo[3.1.0]hexane-1-carbaldehyde (8). To a −78 °C solution of oxalyl chloride (860.7 μL, 9.86 mmol) in methylene chloride (25 mL) was added over 10 min a solution of DMSO (1.4 mL, 19.7 mmol) in methylene chloride (1 mL), and the mixture was stirred for an additional 10 min. A solution of 1-hydroxymethyl-bicyclo[3.1.0]hexan-2-ol (632.3 mg, 4.93 mmol) in DMSO (3 mL) was added. After the mixture was stirred for 25 min, triethylamine was added dropwise. After an additional 15 min at −78 °C, the mixture was warmed to room temperature. Following addition of water, the organic phase was washed successively with 1% HCl and 5% $NaHCO_3$. The aqueous phase was extracted with methylene chloride. The combined organics were dried over anhydrous $MgSO_4$, concentrated in vacuo, and purified by flash chromatography (2:98 methanol/methylene chloride) to give **8** (441.8 mg, 72%). R_f = 0.13 (1:5 ethyl acetate/hexane). ^{1}H NMR ($CDCl_3$): δ 10.1 (s, 1H), 2.70 (m, 1H), 2.26−2.21 (m, 3H), 2.04−2.01 (m, 2H), 1.60 (t, J = 10 Hz, 1H). ^{13}C NMR ($CDCl_3$): δ 215.7, 197.1, 169.8, 35.1, 33.8, 27.2, 21.9.

2-Methoxymethyl-5-oxo-cyclopentanecarboxylic Acid Methyl Ester (6) and 2-Hydroxy-5-methoxy-cyclohex-1-enecarboxylic Acid Methyl Ester (7). To a solution of **5** (110.4 mg, 0.716 mmol) in methanol (10 mL) was added *p*-toluenesulfonic acid (133 mg, 0.716 mmol), and the mixture was heated to reflux for 5 h. After cooling to room temperature, the mixture was concentrated on a rotary evaporator and diluted with ethyl acetate and water, and the resulting aqueous phase was extracted with ether. The combined organic phases were dried over anhydrous $MgSO_4$, concentrated, and purified by flash chromatography (1:5 ethyl acetate/hexane) to give **6** (49.3 mg) and **7** (54.1 mg). **Compound 6:** R_f = 0.2 (1:5 ethyl acetate/hexane). ^{1}H NMR ($CDCl_3$): δ 3.69 (s, 3H), 3.38 (m, 2H), 3.27 (s, 3H), 3.05−3.03 (d, J = 10.0 Hz, 1H), 2.81 (m, 1H), 2.35 (m, 1H), 2.27 (m, 1H), 2.09 (m, 1H), 1.65 (m, 1H). ^{13}C NMR ($CDCl_3$): δ 211.7, 169.8, 74.5, 59.4, 58.5, 52.8, 41.5, 38.0, 24.2. IR (KBr mull): 2953, 2881, 2360, 1757, 1729, 1437, 1114 cm^{-1}. MS (DCI) *m*/*z* (%): 187 (M + H, 50), 155 (100), 99 (55). Exact mass calcd for $C_9H_{15}O_4$ (M + H): 187.0970. Found: 187.0968. **Compound 7:** R_f = 0.5 (1:5 ethyl acetate/hexane). ^{1}H NMR ($CDCl_3$): δ 12.0 (s, 1H), 3.75 (s, 3H), 3.50 (m, 1H), 3.36 (s, 3H), 2.50 (dd, J = 4.7, 1.0 Hz, 1H), 2.35 (m, 1H), 2.23 (m, 1H), 2.18 (m, 1H), 1.79 (m, 1H), 1.76 (m, 1H). ^{13}C NMR ($CDCl_3$): δ 206.0, 170.8, 94.9, 74.5, 56.5, 52.5, 28.2, 26.5, 26.3. IR (KBr mull): 2951, 1746, 1717, 1659, 1618, 1443, 1281, 1206, 736 cm^{-1}. MS (DCI) *m*/*z* (%): 187 (M + H, 60), 155 (100). Exact mass calcd for $C_9H_{14}O_4$: 186.0892. Found: 186.0888.

2-Dimethoxymethyl-4-methoxy-cyclohexanones (10a and 10b). Following a procedure identical to that described for **6** and **7** from **5** with *p*-toluenesulfonic acid, aldehyde **8** (73.2 mg, 0.58 mmol) gave a mixture that was purified by flash chromatography (1:3 ethyl acetate/hexane) to give **10a** (47.6 mg) and **10b** (28.5 mg). Compound **10a:** R_f = 0.2 (1:3 ethyl acetate/hexane). ^{1}H NMR ($CDCl_3$): δ 4.79 (d, J = 6 Hz, 1H), 3.52 (m, 1H), 3.35 (s, 3H), 3.34 (s, 3H), 3.33 (s, 3H), 2.58 (m, 1H), 2.39 (m, 1H), 2.23 (m, 2H), 2.10 (m, 1H), 1.69−1.74 (m, 2H). ^{13}C NMR ($CDCl_3$): δ 211.7, 104.1, 56.9, 55.8, 48.8, 38.6, 32.2, 31.7, 30.6, 30.3. IR (KBr mull): 2930, 1716, 1456, 1374, 1104, 1070 cm^{-1}. MS (DCI) *m*/*z* (%): 187 (M + H, 50), 155 (100), 99 (55). MS (CI+) *m*/*z* (%): 202.1 (M), 171.1 (M − OCH_3, 100). Exact mass calcd for $C_{10}H_{18}O_4$: 202.1204. Found: 202.1210. Compound **10b:** R_f = 0.5 (1:5 ethyl acetate/hexane). ^{1}H NMR ($CDCl_3$): δ 4.7 (d, J = 4 Hz, 1H), 3.68 (bs, 1H), 3.37 (s, 3H), 3.35 (s, 3H), 3.33 (s, 3H), 3.25 (m, 1H), 2.88 (m, 1H), 2.52 (m, 1H), 2.26 (m, 1H), 2.19−2.11 (m, 2H), 1.70 (m, 1H). ^{13}C NMR ($CDCl_3$): δ 206.0, 105.1, 56.5, 52.5, 39.6, 33.1, 32.7, 30.1, 28.2, 26.5. IR (KBr mull): 2933, 1713, 1268, 1071, 737 cm^{-1}. MS (CI+) *m*/*z* (%): 202.1 (M), 171.1 (M − OCH_3, 100). Exact mass calcd for $C_{10}H_{18}O_4$: 202.1204. Found: 202.1209.

1-Dimethoxymethyl-bicyclo[3.1.0]hexan-2-one (12). To a solution of keto aldehyde **8** (87 mg, 0.708 mmol) in methanol (1.5 mL) was added trimethyl orthoformate (116 mg, 1.06 mmol) and *p*-toluenesulfonic acid (14 mg, 0.071 mmol) at room temperature. After 30 min, the mixture was poured into a mixture of saturated $NaHCO_3$ and ether. The organic phase was washed with saturated NaCl, dried $MgSO_4$, and concentrated in vacuo. Purification by flash chromatography (1:199 methanol/methylene chloride) gave **12** (88 mg, 73%) as a colorless oil. R_f = 0.6 (1:99 methanol/methylene chloride). ^{1}H NMR ($CDCl_3$): δ 4.85 (s, 1H), 3.33 (s, 3H), 3.28 (s, 3H), 2.18 (m, 1H), 2.07 (m, 2H), 2.03 (m, 1H), 1.89 (m, 1H), 1.37 (m, 1H), 0.90 (t, J = 9 Hz, 1H). ^{13}C NMR ($CDCl_3$): δ 206.7, 56.8, 55.8, 52.2, 37.5, 33.5, 33.0, 22.2, 20.8.

2-Dimethoxymethyl-4-methoxy-cyclohexanones (10a and 10b). Following a procedure identical to that described for **6** and **7**, acetal **12** (99.2 mg, 0.58 mmol) gave a mixture that was purified by flash chromatography (1:3 ethyl acetate/hexane) to give **10a** (52.0 mg) and **10b** (41.6 mg).

6-Methoxy-2-oxo-1,2,5,6,7,8-hexahydro-quinoline-3-carbonitrile (11). To a solution of **8** (52 mg, 0.42 mmol) in methanol (4 mL) was added cyanoacetamide (38 mg, 0.45 mmol), a mixture of acetic acid and piperidine in methanol (180 μL, 0.18 mmol), and *p*-toluenesulfonic acid (79.7 mg, 0.42 mmol). The mixture was heated to reflux for 3 h. The resulting red wine mixture was cooled to 0 °C, and glacial acetic acid was added until the solution was pH 5.5. The reaction mixture was diluted with methylene chloride and water. The organic phase was washed with saturated NaCl, dried over $MgSO_4$, concentrated in vacuo, and purified by flash chromatography (1:19 methanol/methylene chloride) to give **11** (22 mg, 23%). R_f = 0.5 (1:19 methanol/methylene chloride). ^{1}H NMR ($CDCl_3$): δ 13.5 (bs, N-1H), 7.64 (s, 1H), 3.71 (m, 1H), 3.39 (s, 3H), 2.91 (m, 1H), 2.80 (m, 1H), 2.76 (d, J = 3.6 Hz, 1H), 2.66−2.61 (m, 1H), 2.08 (m, 1H), 1.94 (m, 1H). ^{13}C NMR ($CDCl_3$): δ 162.7, 150.8, 150.3, 116.1, 113.1, 101.8, 73.4, 56.4, 31.7, 24.9, 24.2. IR (KBr mull): 3853, 3649, 2922, 2831, 2226, 1652, 1265, 1095, 736 cm^{-1}. MS (FAB+) *m*/*z* (%): 205 (M + H, 100), 154.2 (35). Exact mass calcd for $C_{11}H_{13}N_2O_2$ (M + H): 205.0977. Found: 205.077.

2-Methoxymethyl-5-oxo-cyclopentanecarboxylic Acid Methyl Ester (6) and 2-Hydroxy-5-methoxy-cyclohex-1-enecarboxylic Acid Methyl Ester (7). To a room temperature solution of sodium methoxide, prepared from sodium (290 mg, 12.1 mmol) and methanol (11 mL), was added **5** (233 mg, 1.51 mmol) in methanol (1 mL). After 30 min, the reaction mixture was poured into saturated NH_4Cl and the aqueous phase was extracted with ether. The combined organic phases were washed with saturated NaCl, dried over $MgSO_4$, filtered, concentrated,

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and purified by flash chromatography (1:5 ethyl acetate/hexane) to give **6** (112 mg, 40%) and **7** (13 mg, 4.6%).

2-Methoxymethyl-5-oxo-cyclopentanecarboxylic Acid Methyl Ester (6) and 2-Hydroxy-5-methoxy-cyclohex-1-enecarboxylic Acid Methyl Ester (7). Mg turnings (1.90 g, 0.078 g atom) in methanol (56 mL) were heated to reflux for 1 h, and the resulting white suspension was cooled to room temperature. Ketone **5** (1.2 g, 7.8 mmol) in methanol (3 mL) was added dropwise. After 30 min, 10% HCl was added and the aqueous phase was extracted with ether. The combined organic phases were washed with saturated NaCl, dried over $MgSO_4$, filtered, concentrated, and purified by flash chromatography (1:5 ethyl acetate/hexanes) to give **6** (1.09 g, 75%) and **7** (122 mg, 8.4%).

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Supporting Information Available: Proton NMR spectra for all new products. This material is available free of charge via the Internet at http://pubs.acs.org.

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