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An Example of the Influence of Stereochemistry of a Proximate Methyl Substituent on Keto-Enol Tautomerism

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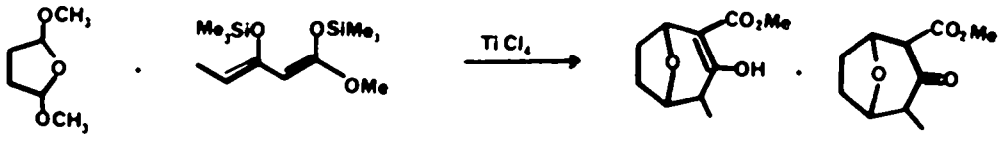
Abstract: The keto-enol equilibrium of 2-methoxycarbonyl-3-oxo-4-methyl-8-oxabicyclo[3,2,1]-octane is dramatically affected by the stereochemistry of the 4-methyl group.

The equilibrium between a keto compound and its enol tautomer depends on a number of structural features. These may include the formation of an intramolecular hydrogen bond, conjugation of the double bond, the extent of substitution on the double bond, the electronegativity of the substituents and the ring size if the enol double bond is part of a ring (exo or endo). We wish to report an example where the stereochemistry of a proximate methyl group has a dramatic effect on the keto-enol equilibrium.

Because of our interest in the chemistry of enol silyl ethers[1], we examined the condensation of 1,3-bis(trimethylsiloxy)-1-methoxy-1,3-pentadiene (1)[2] and 2,5-dimethoxy-tetrahydrofuran (2) with titanium tetrachloride as Lewis acid. It was found that when 2 equivalents of $TiCl_4$ were used, a mixture of 3 and 4 was obtained in the ratio of 2:1 in an overall yield of 57%.

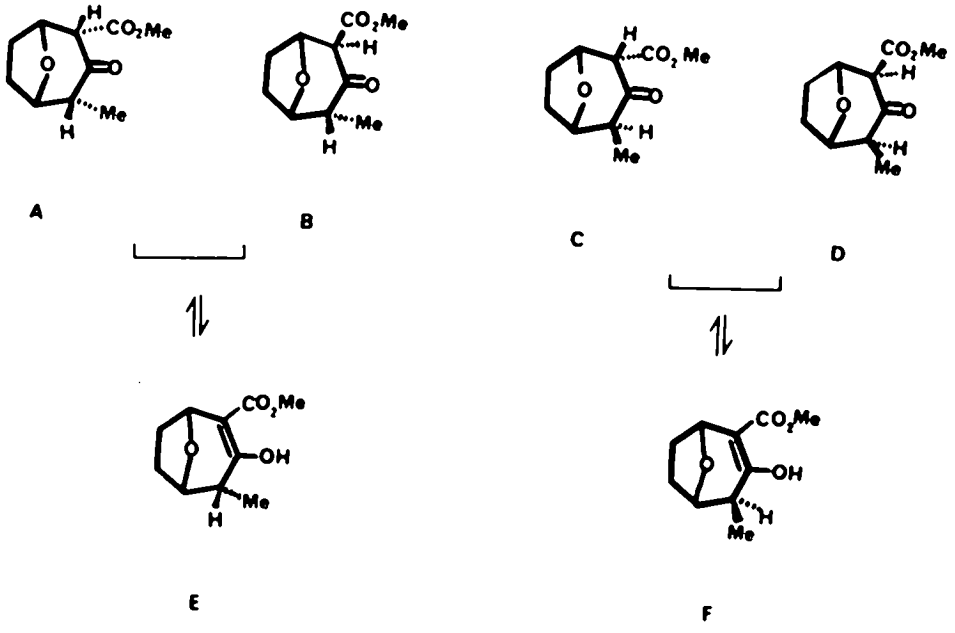


2 1 3 4

Compounds 3 and 4 could be separated by TLC-mesh column chromatography[3]. According to their mass spectra ($C_{10}H_{14}O_4$ by exact mass measurements), 3 and 4 are isomers. The distinction between 3 and 4 was quite apparent in their spectroscopic data. The ^1H nmr peak of the enolic proton of 3 appeared at 11.68 ppm. In the ir spectrum, enolic O-H, C=C and C=O (ester) stretching frequencies appeared at 3600 ~ 3300 cm^{-1} (br), 1615 cm^{-1} and 1660 cm^{-1} respectively. On the other hand, compound 4 seems to be two isomers (2 spots on TLC) which could not be separated in our hands. Its ^1H nmr spectrum showed resolved signals at 3.76, 3.73 ppm (s, each OMe) for the methoxy groups and at 1.01, 0.98 ppm (d each, J=6.8 Hz) for the methyl groups respectively; carbonyl stretching frequencies for ketone and ester appeared at 1715 and 1740 cm^{-1} in the ir spectrum.

In light of these spectroscopic data, and our previous work on the condensation of 2 with 1,3-bis(trimethylsiloxy)-1-methoxy-1,3-butadiene[1], 3 and 4 are assigned to have the bicyclo[3.2.1]-structure. Since the relative stereochemistry at C-1 and C-5 are already fixed, four stereoisomers (A-D) in the keto-form are expected from the bicyclic structure. Actually, only three products

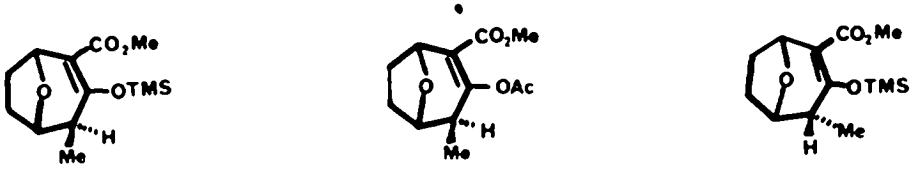
appeared on TLC, one of them being 3 which, because of the enol form, must have either structure E or F (Scheme 1). Compound 4 must have the keto structure. Furthermore, because 3 and 4 could be separated, they most likely have different configurations at the C-4 positions.



Scheme 1

^{1}H nmr spectra of 3 and 4 are sufficiently complicated so that confirmation concerning the stereochemistry at C-4 is not readily apparent.

Their O-silylation and O-acylation derivatives were examined with a view to simplify the interpretation of the spectra. O-Silylation product 5 was obtained in quantitative yield by the reaction of 3 and TMSCl in the presence of Et_3N. Similarly, O-acylation product 6 was obtained by the reaction of 3 and acetyl chloride in the presence of pyridine. The configuration at C-4 was deduced from the ^{1}H nmr spectra of 5 and 6. As shown in Fig. 1 for 5, a quartet for H-4 is found at ~ 1.8 ppm. Irradiation of the methyl doublet of 5 at 1.28 ppm (Fig. 1) caused the collapse of the quarter at 1.80 ppm to a broad singlet. Lack of residual coupling of H-4 to H-5 suggests that the coupling constant between them is close to zero indicating a dihedral angle between H-4 and H-5 of approximately



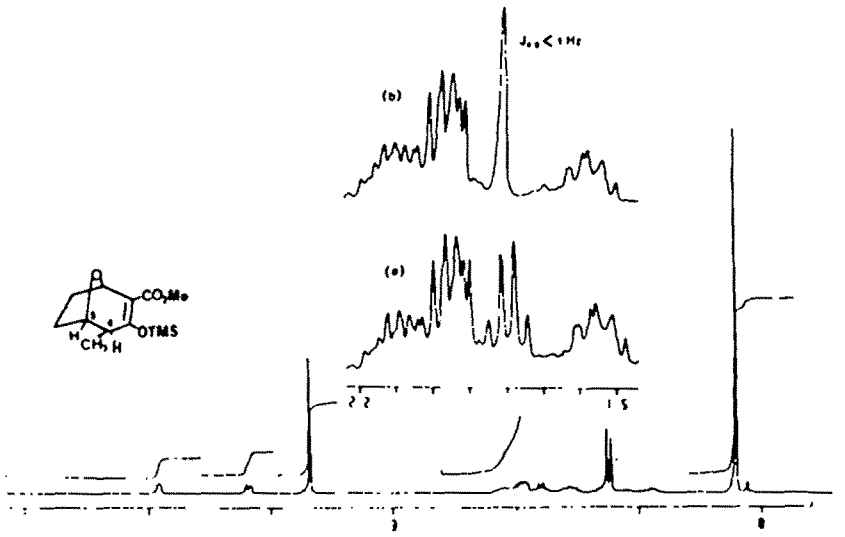


Fig. 1: 200 MHz ^{1}H nmr and related decoupled spectra of 5
(a) expanded spectrum between 2.2 and 1.5 ppm
(b) decoupled spectrum on irradiation of methyl group at C-4

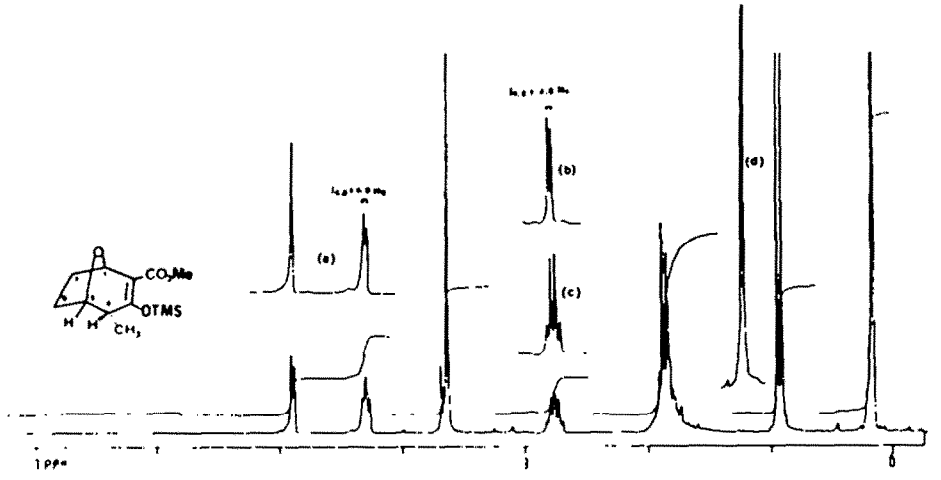


Fig. 2: 200 MHz ^{1}H nmr and related decoupled spectra of 7
(a) on irradiation of H-6 and H-7,
(b) on irradiation of methyl group at C-4
(c) on irradiation of H-5
(d) on irradiation of H-4

90°. This conclusion is consistent with that of the decoupled spectrum of 6, since irradiation of the methyl doublet at 1.23 ppm reduced the quartet at 2.06 ppm to a singlet. With the aid of a molecular model, we concluded that the methyl group at C-4 in 5 and 6 is exo.

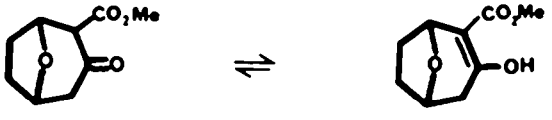
On the other hand, the enol silyl ether 7 (Fig. 2) was obtained from 4 by $Et_3N/ZnCl_2/Me_3SiCl$. The high yield (92%) of the single product 7 from the mixture of two components in 4 suggests that the two isomers of 4 are isomeric at C-2. On the basis of ^1H nmr, compound 7 is distinct from 5 and therefore isomeric at C-4.

The ^1H nmr spectrum of 7 shows a singlet for methoxy at 3.63 ppm and a doublet for the C-4 methyl group at 0.93 ppm. Carbon-carbon double bond stretching was evident at 1615 cm^{-1} in the ir spectrum of 7. Irradiation of H-5 at 4.31 ppm caused the multiplet at 2.76 ppm, assigned to C-4, to collapse to a quartet. The methyl doublet at 0.93 pp, collapsed to a singlet when H-4 was irradiated. Inversely, the methine multiplet at 2.76 ppm changed to a doublet, on irradiation of the methyl group at C-4. Finally, when both methylene groups at 1.83 ppm were irradiated, the bridgehead proton (H-1) peak at 4.9 ppm collapsed to a singlet and another bridgehead proton (H-5) peak at 4.31 ppm to a doublet. From these experiments, the coupling constant between H-4 and H-5, $J_{4,5}$ = 4.8 Hz, was deduced suggesting a dihedral angle between H-4 and H-5 of about 45°. We concluded that the methyl group at C-4 in 7 was endo.

The fact that only 5 was obtained from 3 and only 7 was obtained from 4 suggests that under silylation reaction conditions, stereochemistry at C-4 remains intact. We can therefore conclude that 3 has the methyl at C-4 exo (F of scheme 1), whereas 4 has the methyl at C-4 endo (A and B of scheme 1).

In terms of the keto-enol tautomerism between C,D ⇌ F, the enol tautomer F is the major component when the methyl group is exo. On the other hand, when the methyl is endo, the keto tautomers A and B dominate in the equilibrium between A,B ⇌ E.

These observations should be compared with the degree of enolization for the parent compound 8 which has an enol content of about 30% in $CDCl_3$ according to ^1H nmr[1,8,9].



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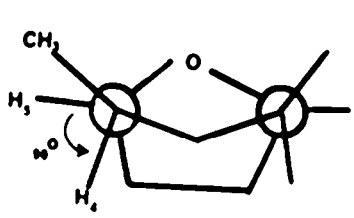
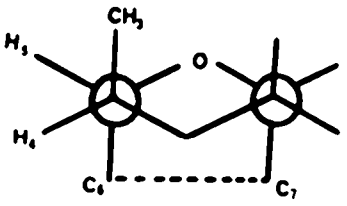
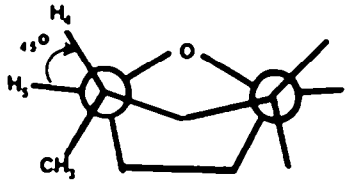
The methyl substituent at C-4, though removed from the site of enolization, has an important effect on the extent of enolization[10]. A possible explanation for this effect of the proximate methyl group is to consider the conformation of the bicyclo[3.2.1] system. It has been suggested that in the 8-oxa-bicyclo[3.2.1]-oct-6-en-one system, the six-membered ring adopts a half-chair conformation due to the tying back of the C-6 and C-7 bond[10]. We can apply this concept to compound 3 (scheme 2). In 3A, the six-membered ring is represented in the normal chair conformation. Because of the bond linking C-6 and C-7 together, the chair flattens to a half chair as in 3B, giving a dihedral angle between H-5 and H-4 of about ~90° as deduced in ^1H nmr. In the half chair conformation, the enol tautomer F is favoured because the planarity of the enol form can be accommodated readily. For compound 4, the flattening of the chair (from 4A to 4B) is less pronounced because of the gauche interaction of the methyl group with the C_5-C_6 bond. This in turn leads to a higher percentage of the keto tautomers.



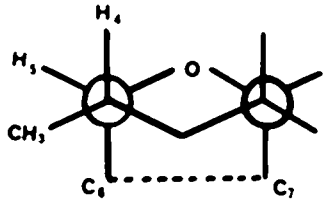
3B



3A



4B



4A

Scheme 2

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Experimental

Mass spectra (ms) were obtained on DuPont 21-492B mass spectrometer, with the direct insertion probe or the batch inlet. Proton magnetic resonance (^{1}H nmr) spectra were recorded on Varian T-60, T-60A and XL-200 spectrometers, using TMS or chloroform as internal standard. Infrared spectra(ir) were obtained on a Perkin-Elmer 297 spectrophotometer. Analytical thin layer chromatography(tlc) was performed on Merck Silica Gel 60 F_{254} aluminum-backed plates and was visualized by dipping into a solution of ammonium molybdate (2.5g) and ceric sulfate (1g) in H_2SO_4/H_2O (10 mL/90 mL) and heating on a hot plate. Kieselgel 60 HF_{254} was used for TLC-mesh chromatography.[3] Merck Silica (Kieselgel 60, 40-63μ) was used for flash column chromatography.[7] Hexane and CH_2Cl_2 were dried over P_2O_5, diisopropylamine and triethylamine over CaH_2, and benzene over Na.

The reaction of 1 with 2,5-dimethoxy-THF to give 3 and 4

To a solution of 2,5-dimethoxy-THF (2) (5 mmol, 0.66 g) in dry methylene chloride (15 mL) at -78°C under N_2 atmosphere was added titanium tetrachloride (10 mmol, 1.9 g) dropwise. A solution of 1 (5 mmol, 1.37 g) in dry CH_2Cl_2 (25 mL) was added over 20 mins. The mixture was stirred at -78°C for 3 hrs and then allowed to warm to 0°C. To the dark red solution was then added excess 5% aqueous sodium bicarbonate solution (2 mL). The mixture was extracted with ether, dried over anhydrous magnesium sulfate, and evaporated. The residue was separated by TLC-mesh column chromatography on silica gel using hexane-ethylacetate (7:3) as eluent to give the bicyclic enol 3 (38%) and two isomeric ketones 4 (20%).

2-carbomethoxy-3-hydroxy-4-methyl-8-oxabicyclo-[3.2.1]-2- octene (3): R_f = 0.51; ^{1}H nmr ($CDCl_3$), δ: 11.68 (s, 1H), 4.88 (m,1H), 4.28 (m, 1H), 3.76 (s, 3H), 1.95 (m, 5H), 1.32 (d, 3H); ms, m/z = 198.0890 (M^+, Calcd for $C_{10}H_{14}O_4$ 198.0892); ir (neat): 3600~3300 (b, OH), 3040~2800, 1660, 1615 cm^{-1}.

2-carbomethoxy-3-oxo-4-methyl-8-oxabicyclo-[3.2.1]-octane (4): (mixture of two isomers); R_f = 0.4 and 0.31 (without separation); ^{1}H nmr ($CDCl_3$), δ: 5.05 and 4.84 (m, each H-1), 1H), 4.49 (m, 1H, H-5), 3.76 and 3.73 (s, each OMe, 3H), 3.0 (m each H-2 and H-4, 1H), 1.8 (m, 4H), 1.01 and 0.98 (d, J = 6.8 Hz, each CH_3 at C-4, 3H); ir (neat): 3040~2820, 1740, 1715 cm^{-1}; ms, m/z = 198.0884 (M^+, Calcd for $C_{10}H_{14}O_4$ 198.0892). Attempts to separate the two isomers by preparative TLC gave the same mixture after purification.

O-Silylation of bicyclic enol 3 to give 2-carbomethoxy-3-trimethylsiloxy-4-methyl-8-oxabicyclo[3.2.1]-2-octene (5)

To a solution of bicyclic enol 3 (4.3 mmol, 0.85 g) in dry ether (30 mL) was added triethylamine (6 mmol, 0.84 mL) dropwise followed by TMSCl (8 mmol, 1 mL) under N_2 atmosphere. After 1 hr, the mixture was filtered and the filtrate was evaporated in vacuo to give the enol silyl ether 5 quantitatively. ^{1}H nmr ($CDCl_3$), δ: 4.95 (m, 1H), 4.21 (m, 1H), 3.7 (s, 3H), 1.93 (m,4H), 1.80 (q, 1H), 1.28 (d, 3H), 0.22 (s, 9H); ir (neat): 3020 ~ 2860, 1720 and 1680 (CO_2Me), 1620 (olefin), 880 and 850 cm^{-1} ($OSiMe_3$); ms, m/z (rel. intensity), 270 (M^+, 7.9).

O-Acylation of bicyclic enol 3 to give 2-carbomethoxy-3-acetoxy-4-methyl-8-oxabicyclo[3.2.1]-2-octene (6)

To the mixture of bicyclic enol 3 (2 mmol, 0.4 g) and acetyl chloride (2.2 mmol, 0.17 mL) was slowly added 2 mL of pyridine at 0°C. The reaction mixture was allowed to warm to room temperature. After 5 hrs, ice-hydrochloric acid solution was added dropwise to the mixture to achieve pH 5. The mixture was extracted with ether (3 x 15 mL), dried over anhydrous magnesium sulfate, filtered, and evaporated in vacuo. The crude product was purified by flash column chromatography[7] using ethylacetate-hexane (3:7) as eluent to give 6; R_f = 0.38, in 81% yield. ^{1}H nmr ($CDCl_3$), δ: 4.97 (m, 1H), 4.27 (m, 1H), 3.72 (s, 3H), 2.21 (s, 3H), 2.10 ~ 1.70 (m, 5H), 1.23 (d, 3H); ir (neat): 3040 ~ 2820, 1765 ($C=C-OCOCH_3$), 1650 cm^{-1} (olefin); ms, m/z (rel. intensity), 240 (M^+, 1.6).

Preparation of 3-trimethylsiloxy-8-oxabicyclo[3.2.1]-2-octene derivative 7

Dry triethylamine (11 mmol, 1.55 g) and zinc chloride (50 g) were stirred vigorously under N_2 atmosphere for 1 hr, giving a fine suspension. A solution of 4 (5 mmol, 1 g) in dry benzene (10 mL) was added, followed by TMSCl (10 mmol, 1.3 mL). The mixture was stirred overnight and 25 mL of anhydrous ether was added, filtered and concentrated. The residue was diluted with dry hexane (30 mL), cooled to precipitate any remaining solids, filtered and concentrated to give the enol silyl ether 7 in 92% yield. ^{1}H nmr ($CDCl_3$), δ: 4.9 (bd, 1H), 4.31 (m, 1H), 3.63 (s, 3H), 2.76 (m, 1H), 1.83 (m, 4H), 0.93 (d, 3H), 0.16 (s, 9H); ir (neat): 3020 ~ 2820, 1720 and 1690 (CO_2Me), 1615 cm^{-1} (olefin), 880 and 845 (OTMS); ms, m/z (rel. intensity), 270 (M^+, 9.7).

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