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Double Michael Addition Reaction of Oxophorone and Its Derivatives Leading to Bicyclo[2.2.2]octane Compounds

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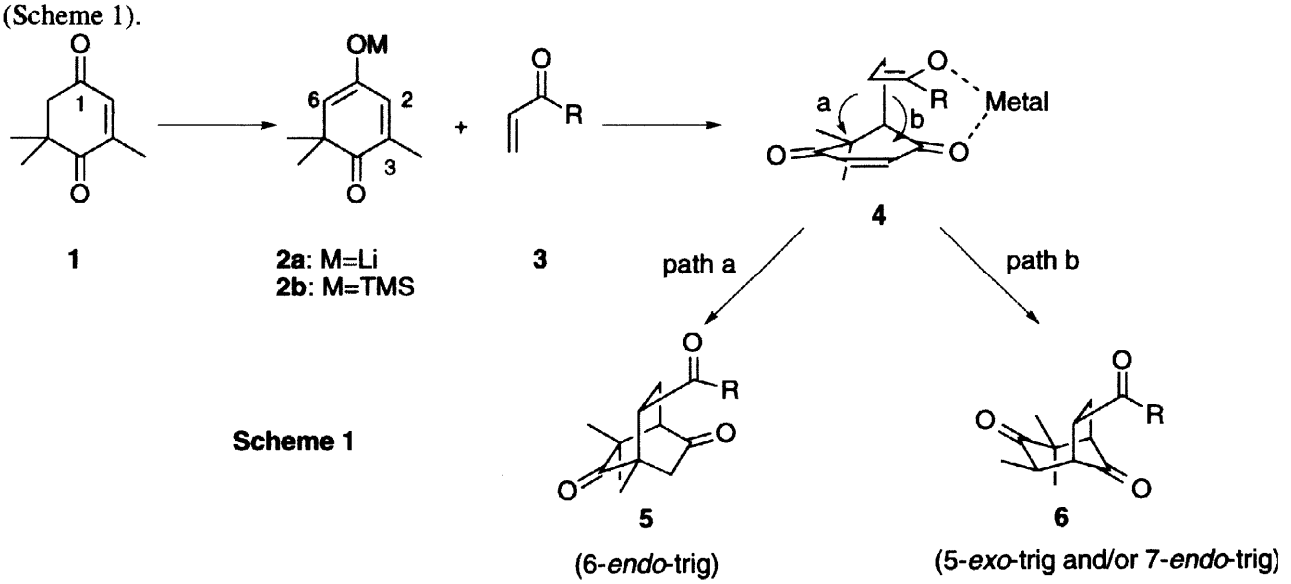
Abstract: Trimethylsilylenol ethers of oxophorone **1** and its derivatives provided bicyclo[2.2.2]octane compounds **5** in a selective way.

Bicyclo[2.2.2]- or a bicyclo[3.2.1]octane system forms an integral part of several natural products.[1] Normally, bicyclo[2.2.2]octane framework is derived through a successive double Michael addition reaction involving the kinetic enolate of 2-cyclohexenone and an α,β-unsaturated carbonyl compound. This procedure has turned out as a popular synthetic tool to prepare such bicyclic systems,[2] since an alternative procedure employing the Diels-Alder reaction involving cyclohexadiene and an electron deficient dienophile sometimes lacks regio as well as endo/exo selectivities.[3]

As a part of our ongoing research program directed towards the synthesis of polycyclic molecules via a single pot operation by employing nucleophilic domino reactions,[4] we investigated the reaction of trimethylsilylenol ether of oxophorone **1**[5] and its derivatives with α,β-unsaturated carbonyl compounds **3** (Scheme 1).



Scheme 1

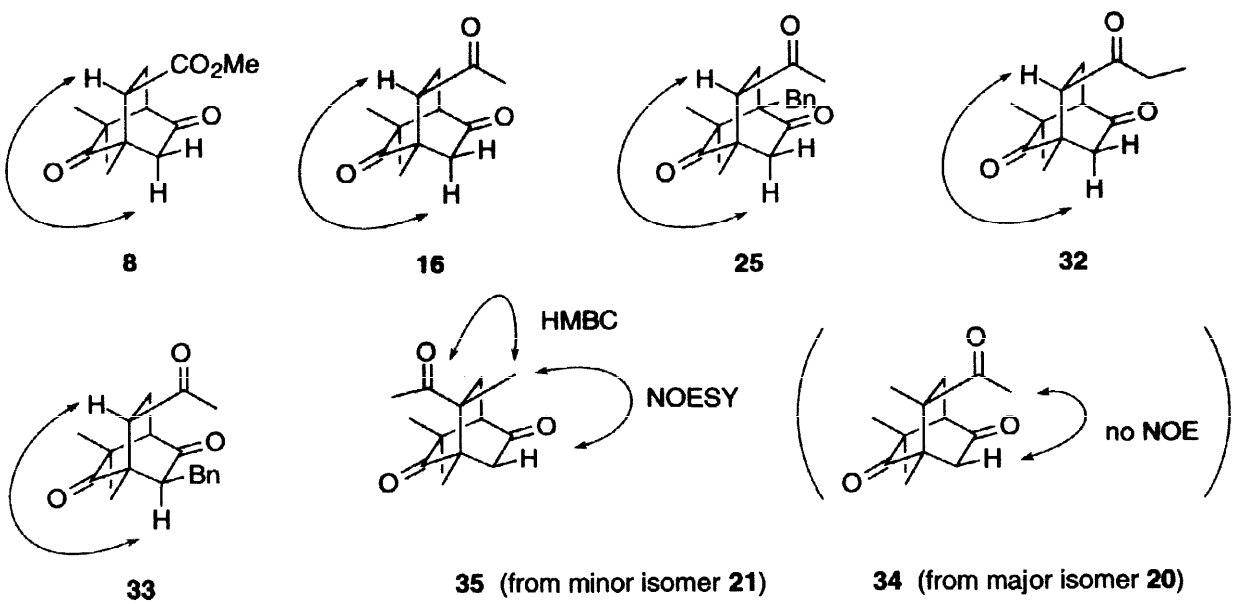
PII: S0040-4020(98)00646-2

In this direction, we wish to report herein, the synthesis of bicyclo[2.2.2]octane derivatives formed *via* a double Michael addition reaction of **1** with the respective α,β-unsaturated compounds **3**. The advantage of the present reported procedure lies in the fact that only bicyclo[2.2.2]octane derivatives **5** were obtained selectively though there were two options available for the intermediate adduct **4** before it undergoes the successive second addition reaction to provide either **5** or **6** (path a or b).

To start with, the kinetically derived enolate of oxophorone **1** was reacted with methyl acrylate **7** to provide the bicyclo[2.2.2]octane derivative **8** in 23% yield (Table 1, entry 1). No bicyclo[3.2.1]octane derivative **6** was formed under the reaction conditions employed. All attempts to optimize the yield of **8** under the basic conditions employed proved futile in providing any better results and hence the reaction was repeated by following the reaction conditions reported by Fukumoto and Ihara.[6] It was observed that under the reaction conditions, the reaction proceeded to furnish **8** in 42% yield along with the corresponding TMS enol ether **10**, a product derived from single Michael addition reaction, which was reacted further on prolonged heating (entry 3).

The relative stereochemistry of the bicyclo[2.2.2]octane derivative **8** was determined as depicted in Fig. 1 by the W-type long range coupling (*J* 1.3 Hz) between a proton on a carbon bearing methoxycarbonyl group and an *endo* -proton of methylene protons α to carbonyl group.

Fig. 1 Determination of relative stereochemistries by W-type long range coupling

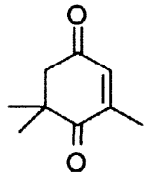
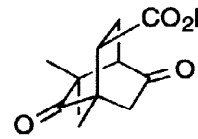
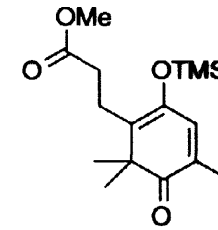
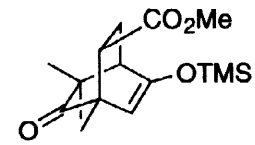
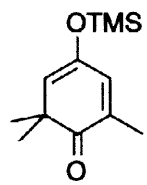
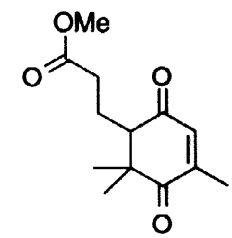


8 **16** **25** **32**

33 **35** (from minor isomer **21**) **34** (from major isomer **20**)

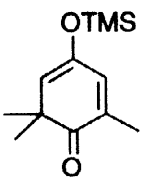
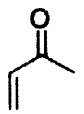
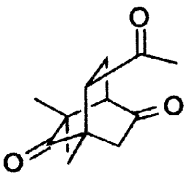
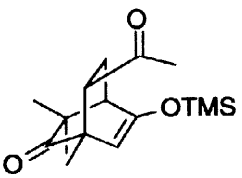
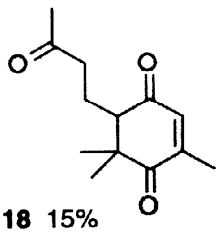
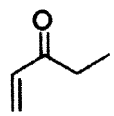
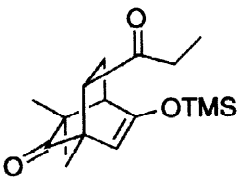
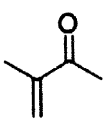
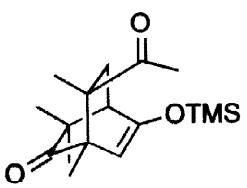
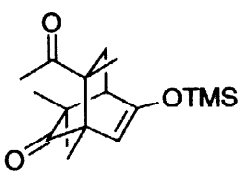
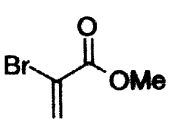
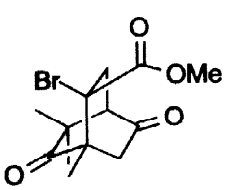
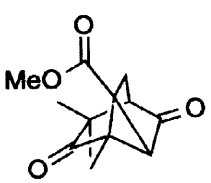
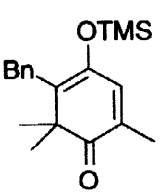
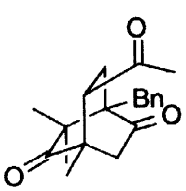
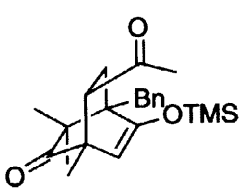
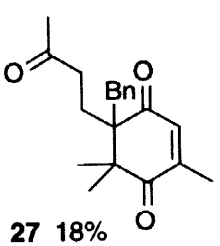
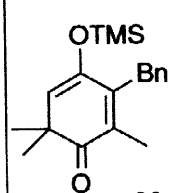
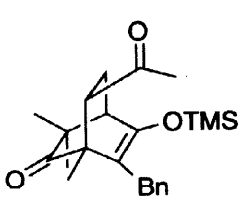
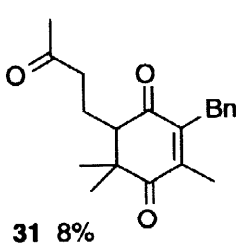
In an attempt to use mild reaction conditions, the TMS enol ether **2b** of oxophorone **1** was prepared with TMSI and $(TMS)_2NH$[6,7] since an attempt to prepare trimethylsilylenol ether of oxophorone **2b** with LDA/TMSCl failed and provided a complex mixture. The TMS enol ether **2b** was made to react with methyl acrylate **7** employing Et_2AlCl catalyst[8] to afford stereoselectively, the bicyclic compounds **8**, **9** and single Michael addition adduct **10** (Table 1, entry 4). Other Lewis acid catalyst such as titanium tetrachloride[8] resulted in decomposition of **2b**.

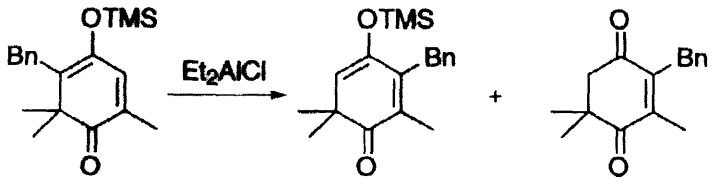
Table 1. Optimization of the Reaction Condition of Double Michael Addition Reactions of Oxophorone with Methyl Acrylate 7.

Entry	Starting Material	Reaction Condition	Products		
1	 1	LDA/THF −78 °C/45 min	 **8** 23%		
2		$ZnCl_2$/TMSCl Et_3N/Toluene 180 °C/7.5 hr	**8** 42%		 **10** 12%
3		$ZnCl_2$/TMSCl Et_3N/Toluene 180 °C/43 hr	**8** 38%	 **9** 34%	
4	 **2b**	Et_2AlCl/CH_2Cl_2 0 °C→rt/23 hr	**8** 10%	**9** 35%	**10** 20%
5		Et_2AlCl/CH_2Cl_2 −78→0 °C/8 hr			 **11** 66%

In order to probe further, the synthetic utility of this procedure, the reaction of **2b** and its derivatives such as **24** and **28**[9] with various Michael addition partners **12~15** were investigated and the results obtained are summarized in Table 2. It is noteworthy that the α,β-unsaturated ketones **12~14** reacted smoothly with **2b**, **24** or **28** to afford the corresponding bicyclo[2.2.2]octane derivatives, since such substrates are known to be fragile double Michael partners during the reaction with cyclohexenone enolates resulting in either decomposition or forming aldol condensation products. The isomeric silylenol ether **28** was prepared by Lewis acid promoted rearrangement of the silylenol ether **24** (Scheme 2, see Experimental section). The mechanistic aspects of this rearrangement is under investigation and will be reported elsewhere. In the reaction of methyl α-bromoacrylate **15**, cyclopropane derivative **23** was obtained (entry 4) as a result of double Michael-alkylation reaction.[9]

Table 2. Et_2AlCl Promoted Double Michael Addition Reactions of Oxophorone Trimethylsilylenol Ether **2b** and its Derivatives **24** and **27** with Other α,β-Unsaturated Carbonyl Compounds.

Entry	Silylenol ether	Michael Partner	Products		
1	 **2b**	 **12**	 **16** 48%	 **17** 30%	 **18** 15%
2		 **13**	 **19** 93%		
3		 **14**	 **20**	 **21**	
			Total 43% (6 : 1)		
4		 **15**	 **22** 15%	 **23** 28%	
5	 **24**	**12**	 **25** 5%	 **26** 65%	 **27** 18%
6	 **28**	**12**	 **30** 76%		 **31** 8%



Scheme 2

Since single Michael addition adduct **11** was formed at low temperature conditions (Table 1, entry 5), the present reaction seems to proceed *via* two successive silyl transfer Michael pathway. Isolation of a mixture of diastereomers **20** and **21** in the reaction of 3-methyl-3-penten-2-one **14** (Table 2, entry 3) also supports such pathway. Relative stereochemistries of the bicyclo[2.2.2]octanes **16**, **17**, **19**, **25**, **26** and **30** were confirmed as depicted in Table 2 by the W-type long range couplings between bridge and *endo*-protons of the corresponding triketones **16**, **32**, **25**, and **33** (Fig 1) derived by acid catalyzed hydrolyses. The relative stereochemistry of **21** was determined by NOESY experiment utilizing triketone **35** formed after acid catalyzed hydrolysis (Fig 1).

Preferential formation of bicyclo[2.2.2]octane derivatives (*via* path a) rather than bicyclo[3.2.1]octane derivative (*via* path b) could be explained on the basis of a larger HOMO coefficient at C-3 than at C-2 (MOPAC, AM1) in case of the silylenol ether **2b**, thereby providing for the second Michael addition to occur concurrently.[10] In the case of the lithium enolate **2a**, the sign of LUMO coefficients of methyl acrylate matches only with those of HOMO at C-3 and C-6. The resultant stereochemical aspect of bicyclo[2.2.2]octane derivatives may be explained by chelation of metal with carbonyl oxygen of Michael partner and oxygen of enolate or enol ether.[4]

In summary, we have demonstrated that the double Michael addition reactions of oxophorone **1**, its trimethylsilylenol ether **2b** and other derivatives **24** and **28** furnished selectively the bicyclo[2.2.2]octane derivatives in single pot operation.

Acknowledgement.
We thank Soda Aromatics Co. Ltd. for measurement of mass spectral data.

Experimental

All m.p.s were determined with a Yanaco MP hot-stage apparatus and are uncorrected. IR spectra were recorded on a Shimadzu FT/IR-4200 spectrophotometer for solutions in carbon tetrachloride unless otherwise indicated. ^{1}H-NMR spectra were obtained for solutions in deuteriochloroform with Varian Gemini 200H (200 MHz) and Unity 500 (500 MHz) instruments with tetramethylsilane as internal standard. ^{13}C-NMR spectra were measured with Varian Gemini 200H (50 MHz) or Unity 500 (125 MHz) instruments. Mass spectral data were run on a Hitachi M-80B spectrometer with M0101 data system. Medium-pressure liquid chromatography (MPLC) were carried out on a JASCO PRC-50 instrument with a silica gel packed column. Microanalyses were carried out in the microanalytical laboratory of Institute for Chemical Reaction Science, Tohoku University.

Methyl (2S*)-*1,5,5-Trimethyl-6,8-dioxobicyclo[2.2.2]octane-2-carboxylate* **8**.— To a stirred solution of diisopropylamine (158 μl, 1.2 mmol) in THF (5 ml) was added a solution of n-BuLi (730 μl, 1.2 mmol, 1.6 M solution in n-hexane) at 0 °C under nitrogen atmosphere. After being cooled at −78 °C, a solution of oxophorone **1** (102 μl, 1 mmol) in THF (5 ml) was added and the resulting solution was stirred for 5 min. Subsequently, methyl acrylate (120 μl., 1 mmol) was added and stirring was continued for 45 min. The reaction was quenched by addition of aq. NH_4Cl and extracted with chloroform twice. The combined organic layers were washed with brine and dried over anhydrous Na_2SO_4. Evaporation of the solvent *in vacuo* followed by MPLC purification afforded bicyclic compound **8** (54 mg, 23%) as white needles which had; mp 72-75 °C; ν_{max}/cm^{-1} 2973, 1742, 1730, 1203 and 1177; ^{1}H-NMR δ (200 MHz) 1.07 (s, 3H), 1.08 (s, 3H), 1.23 (s, 3H), 2.10 (dd, 1H, *J* 19.8, 1.6 Hz), 2.18 (ddd, 1H, *J* 15.4, 7.3, 2.9 Hz), 2.43 (ddd, 1H, *J* 15.4, 10.5, 3.8 Hz), 2.45 (dd, 1H, *J* 7.0, 3.8 Hz), 2.74 (ddd, 1H, *J* 10.5, 7.3, 1.6 Hz), 3.07 (d, 1H, *J* 19.8 Hz) and 3.73 (s, 3H); ^{13}C-NMR (50MHz) δ (ppm) 17.1 (q), 23.1 (q), 23.7 (t), 25.1 (q), 41.3 (t), 41.8 (d), 44.1 (q), 48.0 (d), 52.1 (s), 55.8 (s), 173.2 (s) and 209.9 (s) (Anal. Calc. for $C_{13}H_{18}O_4$: C, 65.53 %; H, 7.6 %. Found: C, 65.27 %; H, 7.41%).

Methyl 3-(2,2,4-Trimethyl-3,6-dioxo-4-cyclohexenyl) propanoate **11**.— To a stirred solution of oxophorone trimethylsilylenol ether **2b** (59 mg, 0.26 mmol) in dichloromethane (5 ml) was successively added methyl acrylate (32 μl, 0.32 mmol) and diethylaluminum chloride (356 μl, 0.32 mmol, 0.9 M solution in n-hexane) at −78 °C under nitrogen atmosphere. The resulting solution was allowed to warm to 0 °C over 6 hr and the reaction was quenched by addition of aq. $NaHCO_3$. After extraction with chloroform twice, the organic layer was washed with brine and dried over anhydrous Na_2SO_4. Evaporation of the solvent followed by MPLC purification provided single Michael adduct **11** (31 mg, 66%) along with recovered oxophorone **1** (15 mg, 25%).

The single Michael adduct **11** had; mp 90-92 °C; ν_{max}/cm^{-1} 2773, 1755, 1714, 1682, 1437, 1267 and 1181; ^{1}H-NMR δ (200MHz) 1.86 (d, 3H, *J* 1.4 Hz), 1.98 (t, 3H, *J* 14.1 Hz), 2.33-2.53 (m 2H), 3.34 (t, 1H, *J* 8 Hz), 3.7 (s, 3H) and 5.88 (q, 1H, *J* 1.4 Hz) (Anal. Calc. for $C_{13}H_{18}O_4$: C, 65.53 %; H, 7.61 %. Found: C, 65.30 %; H, 7.47 %).

Methyl (2S*)-*3,5,5-Trimethyl-7-trimethylsiloxy-4-oxobicyclo[2.2.2]oct-7-ene-2-carboxylate* **9**.— A solution of oxophorone **1** (20 μl, 0.2 mmol), zinc chloride (273 mg, 2 mmol), triethylamine (446 μl, 3.2 mmol) and methyl acrylate (39 μl, 0.8 mmol) in toluene (2 ml) was heated in a sealed glass tube at 180 °C for 43 hr. After cooling to room temperature, the resulting solution was poured into 1N HCl and extracted with ethyl acetate twice. The organic layer was washed with water and brine and dried over anhydrous Na_2SO_4. Evaporation of the solvent followed by MPLC purification provided trimethylsilylenol ether of bicyclic compound **9** (21 mg, 34 %) and bicyclic product **8** (18 mg, 38 %).

The trimethylsilylenol ether **9** had; mp 63-66 °C; ν_{max}/cm^{-1} 2973, 1744, 1731, 1368, 1240 and 1204; ^{1}H-NMR δ (200MHz) 0.27 (s, 9H), 1.05 (s, 3H), 1.14 (d, 3H, *J* 1.7 Hz), 1.15 (s, 3H), 1.87 (ddd, 1H, *J* 13.2, 7.0, 2,7 Hz), 2.27 (ddd, 1H, *J* 13.2, 9.4, 2.7 Hz), 2.33 (dd, 1H, *J* 5.5, 2.7 Hz), 2.57 (dd, 1H, *J* 9.4, 7.0 Hz), 2.67 (s, 3H) and 4.41 (d, 1H, *J* 1.7 Hz).

2,6,6-Trimethyl-4-trimethylsiloxy2-cyclohexene-1-one **2b**.— To a stirred solution of 3,5,5-trimethyl-2-cyclohexene-1,4-dione (oxophorone) **2a** (204 µl, 2 mmol) in 1,2-dichloromethane (10 ml) was added hexamethyldisilazane (630 µl, 3 mmol) and trimethylsilyliodide (345 µl, 2.4 mmol) at 0 °C under nitrogen atmosphere. The resulting solution was stirred at room temperature for 1 hr and poured into aq. $NaHCO_3$. After extraction with chloroform twice, the organic layer was washed with brine and dried over anhydrous Na_2SO_4. Evaporation of the solvent *in vacuo* followed by purification with MPLC provided the trimethylsilylenol ether of oxophorone **2b** (298 mg, 67%).
The silylenol ether **2b** had; ν_{max}/cm^{-1} 2965, 1692, 1651, 1372, 1254 and 1150; ^{1}H-NMR δ (200 MHz) 0.23 (s, 9H), 1.19 (s, 6H), 1.87 (s, 3H), 5.28 (s, 1H) and 6.63 (s, 1H).

Methyl (2S*)-*1,5,5-Trimethyl-6,8-dioxobicyclo[2.2.2]octane-2-carboxylate* **8**, *Methyl* (2S*)-*3,5,5-Trimethyl-7-trimethylsiloxy-4-oxobicyclo[2.2.2]oct-7-ene-2-carboxylate* **9**, and *Methyl 3-(2,2,4-Trimethyl-4-trimethylsiloxy-3-oxo-4,6-cyclohexa dienyl) propanoate* **10**.— To a stirred solution of oxophorone trimethylsilylenol ether **2b** (50 mg, 0.22 mmol) in dichloromethane (4.4 ml) was successively added methyl acrylate (26 µl, 0.26 mmol) and diethylaluminum chloride (295 µl, 0.26 mmol, 0.9M solution in n-hexane) at –78 °C under nitrogen atmosphere. The resulting solution was stirred at –78 °C for 30 min, 0 °C for 2 hr and then room temperature for 21 hr. The reaction was quenched by addition of aq. $NaHCO_3$. After extraction with chloroform twice, the organic layer was washed with brine and dried over anhydrous Na_2SO_4. Evaporation of the solvent *in vacuo* followed by MPLC purification gave silylenol ether of bicyclic compound **9** (24 mg, 35%), silylenol ether of single Michael adduct **10** (11 mg, 20%) and bicyclic compound **8** (5 mg, 10%) in the order of elution.
The silylenol ether of single Michael adduct **10** had;mp 88-92 °C; ν_{max}/cm^{-1} 2955, 1745, 1682, 1253, 1203, 1034 and 914; ^{1}H-NMR δ (200 MHz) 0.27 (s, 9H), 0.92 (s, 3H), 1.07 (s, 3H), 1.86 (d, 3H, *J* 1.5 Hz), 1.91-2.03 (m, 2H), 2.31-2.48 (m, 1H), 3.36-3.47 (m, 1H), 3.70 (s, 3H) and 5.88 (q, 1H, *J* 1.5 Hz).

(2S*)-*2-Acetyl-1,5,5-trimethyl-6,8-dioxobicyclo[2.2.2]octane* **16**, (2S*)-*2-Acetyl-1,5,5-trimethyl-8-trimethylsiloxy-6-oxobicyclo[2.2.2]oct-7-ene* **17** and *2,2,6-Trimethyl-3-(3-oxobutyl)-5-cyclohexene-1,4-dione* **18**.— To a stirred solution of oxophorone trimethylsilylenol ether **2b** (62 mg, 0.27 mmol) in dichloromethane (5.5 ml) was successively added 3-pentene-2-one (28 µl, 0.34 mmol) and diethylaluminum chloride (370 µl, 0.33 mmol, 0.9 M solution in n-hexane) at 0 °C under nitrogen atmosphere. The resulting solution was stirred at 0 °C for 30 min and then room temperature for 40 hr and poured into aq. $NaHCO_3$. The products were extracted with chloroform twice, and the organic layer was washed with brine and dried over anhydrous Na_2SO_4. Evaporation of the solvent *in vacuo* followed by MPLC purification afforded bicyclic compound **16** (29 mg, 48%), bicyclic silylenol ether **17** (25 mg, 30%), and Michael product **18** (9.3 mg, 15%) in the order of elution.
The bicyclic compound **16** had; mp 67-68 °C; ν_{max}/cm^{-1} 2973, 1734, 1458, 1359, 1153 and 1051; ^{1}H-NMR δ (200 MHz) 1.06 (s, 3H), 1.13 (s, 3H), 1.26 (s, 3H), 2.04 (d, 1H, *J* 19.9 Hz), 2.07 (dt, 1H, *J* 3.7, 2.1 Hz), 2.23 (s, 3H), 2.33 (ddd, 1H, *J* 14.1, 10.2, 3.7 Hz), 2.44 (ddd, 1H, *J* 3.7, 2.1, 0.6 Hz), 2.93 (ddd, 1H, *J* 10.2, 7.4, 1.2 Hz) and 3.03 (dd, 1H, *J* 19.9, 0.6 Hz) (Anal. Calc. for $C_{13}H_{18}O_3$: C, 70.25; H, 8.16. Found: C, 70.13; H, 8.05).
The bicyclic silylenol ether **17** had; ν_{max}/cm^{-1} 2968, 1721, 1634, 1475, 1356, 1255, 1161 and 878; ^{1}H-NMR δ (200 MHz) 0.27 (s, 9H), 1.06 (s, 3H), 1.14 (s, 3H), 1.18 (s, 3H), 1.75 (ddd, 1H, *J* 13.1, 7.2, 2.5 Hz), 2.15 (s, 3H), 2.25 (ddd, 1H, *J* 13.1, 9.5, 3.4 Hz), 2.36 (dd, 1H, *J* 5.7, 2.5 Hz), 2.69 (dd, 1H, *J* 9.5, 7.2 Hz) and 4.42 (d, 1H, *J* 2.5 Hz).

The Michael product **18**; ν_{max}/cm^{-1} 2986, 1718, 1699, 1682, 1624, 1462, 1358, 1259 and 868; ^{1}H-NMR δ (200 MHz) 0.92 (s, 3H), 0.98 (s, 3H), 2.04 (d, 3H, *J* 1.6 Hz), 1.99-2.18 (m, 1H), 2.25 (s, 3H), 2.35 (dt, 2H, *J* 12.3, 6.4 Hz), 2.54 (dd, 1H, *J* 7.2, 1.9 Hz), 2.76 (dd, 1H, *J* 12.3, 6.4 Hz) and 5.76 (q, 1H, *J* 1.6 Hz); *m/z* 222 (M^+, 12), 151 (49), 123 (38), 109 (47), 83 (31), 81 (36), 43 (100) and 41 (58) (Found:M^+, 222.1221. $C_{13}H_{18}O_3$ requires *m/z*, 222.1256).

(2S*)-*3-[1,5,5-Trimethyl-8-trimethylsiloxy-6-oxo-2-(1-oxopropyl)]bicyclo[2.2.2]oct-7-ene* **19**.— To a stirred solution of oxophorone trimethylsilylenol ether **2b** (50 mg, 0.22 mmol) in dichloromethane (4.5 ml) was successively added 4-pentene-3-one (36 µl, 0.27 mmol) and diethylaluminum chloride (300 µl, 0.27 mmol, 0.9 M solution in n-hexane) at 0 °C under nitrogen atmosphere. The resulting solution was stirred at 0 °C for 10 min and then room temperature for 2 hr and poured into aq. $NaHCO_3$. The products were extracted with chloroform twice, and the organic layer was washed with brine and dried over anhydrous Na_2SO_4. Evaporation of the solvent *in vacuo* followed by MPLC purification afforded bicyclic silylenol ether **19** (64 mg, 93%); ν_{max}/cm^{-1} 2871, 1724, 1712, 1634, 1458, 1254, 1145 and 879; ^{1}H-NMR δ (200 MHz) 0.27 (s, 9H), 1.03 (t, 3H, *J* 7.3 Hz), 1.07 (s, 3H), 1.13 (s, 6H), 1.72 (ddd, 1H, *J* 13.0, 7.2, 2.4 Hz), 2.22 (ddd, 1H, *J* 13.0, 9.5, 3.4 Hz), 2.34 (m, 1H), 2.42 (q, 2H, *J* 7.3 Hz), 2.70 (dd, 1H, *J* 9.5, 7.2 Hz) and 4.41 (d, 1H, *J* 2.4 Hz).

(2S*)-*2-Propionyl-1,5,5-trimethyl-6,8-dioxabicyclo[2.2.2]octane* **32**.— To a stirred solution of trimethylsilylenol ether **19** (62 mg, 0.20 mmol) in MeOH (2.0 ml) and H_2O (36 µl, 2.0 mmol) was added PTSA-H_2O (37.9 mg, 0.20 mmol) and stirring was continued at room temperature for 2.5 hr. The resulting solution was poured into aq. $NaHCO_3$ and extracted with ethyl acetate twice. The organic layer was washed with water, brine and dried over anhydrous Na_2SO_4. Evaporation of the solvent followed by MPLC (EtOAc/Hexane=1/3) purification afforded triketone **32** (34 mg, 65 %) which had; ν_{max}/cm^{-1} 2975, 1744, 1726, 1714, 1458 and 1111; ^{1}H-NMR δ (500 MHz) 1.05 (t, 3H, *J* 7.3 Hz), 1.06 (s, 6H), 2.02 (dt, 1H, *J* 7.2, 2.2 Hz), 2.03 (dd, 1H, *J* 19.9, 1.4 Hz), 2.32 (ddd, 1H, *J* 14.4, 10.6, 3.8 Hz), 2.44 (m, 1H), 2.49 (q, 2H, *J* 7.3 Hz), 2.89 (ddd, 1H, *J* 10.6, 7.2, 1.4 Hz) and 3.12 (d, 1H, *J* 19.9 Hz); ^{13}C-NMR δ (125 MHz) 7.3 (q), 17.1 (q), 23.2 (q), 23.9 (t), 25.0 (q), 39.2 (t), 40.9 (t), 44 (s), 45.8 (d), 48.5 (s), 56.2 (d), 210 (s), 211.5 (s) and 215.1 (s) (Anal. Calc. for $C_{14}H_{20}O_3$: C, 71.16 %; H, 8.53 %. Found: C, 71.11 %; H, 8.44 %).

(2S*)-*2-Acetyl-1,2,5,5-tetramethyl-8-trimethylsiloxy-6-oxobicyclo[2.2.2]oct-7-ene* **20** and (2R*)-*2-Acetyl-1,2,5,5-tetramethyl-8-trimethylsiloxy-6-oxobicyclo[2.2.2]oct-7-ene* **21**.— To a stirred solution of oxophorone trimethylsilylenol ether **2b** (50 mg, 0.22 mmol) in dichloromethane (4.5 ml) was successively added 3-methyl-3-buten-2-one (26 µl, 0.27 mmol) and diethylaluminum chloride (300 µl, 0.27 mmol, 0.9 M solution in n-hexane) at 0 °C under nitrogen atmosphere. The resulting solution was sitrred at 0 °C for 10 min and then room temperature for 6 hr and poured into aq. $NaHCO_3$. The products were extracted with chloroform twice, and the organic layer was washed with brine and dried over anhydrous Na_2SO_4. Evaporation of the solvent *in vacuo* followed by MPLC purification afforded bicyclic silylenol ether **20** (25 mg, 37%) and its diastereomer **21** (4 mg, 6%).

The bicyclic silylenol ether **20** had; ν_{max}/cm^{-1} 2980, 1746, 1725, 1642, 1455, 1256, 1229 and 1159; ^{1}H-NMR δ (200 MHz) 0.24 (s, 9H), 1.13 (s, 6H), 1.14 (s, 3H), 1.17 (s, 3H), 1.88 (dd, 1H, *J* 13.9, 2.7 Hz), 2.14 (s, 3H), 2.18 (dd, 1H, *J* 13.9, 3.1 Hz), 2.30 (t, 1H, *J* 3.1 Hz) and 4.52 (d, 1H, *J* 2.7 Hz).

The diastereomer **21** had; ν_{max}/cm^{-1} 2970, 1730, 1712, 1459, 1356, 1236, 1151 and 1086; ^{1}H-NMR δ (200 MHz) 0.25 (s, 9H), 1.00 (s, 3H), 1.12 (s, 3H), 1.17 (s, 3H), 1.33 (s, 3H), 1.49 (dd, 1H, *J* 13.7, 2.8 Hz), 2.17 (s, 3H), 2.08-2.21 (m, 1H), 2.29 (dd, 1H, *J* 13.7, 2.8 Hz) and 4.33 (d, 1H, *J* 2.7 Hz).

(2S*)-*2-Acetyl-1,2,5,5-tetramethyl-6,8-dioxabicyclo[2.2.2]octane* **34**.— To a stirred solution of trimethylsilylenol ether **20** (25 mg, 0.08 mmol) in MeOH (2 ml) and H_2O (15 µl, 0.83 mmol) was added PTSA-H_2O (152 mg, 0.8 mmol) and stirring was continued at room temperature for 2.5 hr. The resulting solution was poured into aq. $NaHCO_3$ and extracted with ethyl acetate twice. The organic layer was washed with water, brine and dried over anhydrous Na_2SO_4. Evaporation of the solvent followed by MPLC (EtOAc/Hexane=1/2) purification afforded triketone **34** (16 mg, 77 %) which had ν_{max}/cm^{-1} 2980, 1746, 1726, 1706, 1455, 1354 and 1228; ^{1}H-NMR δ (500 MHz) 1.07 (s, 3H), 1.10 (s, 3H), 1.24 (s, 3H), 1.29 (s, 3H), 1.88 (dd, 1H, *J* 14.7, 2.9 Hz), 2.09 (d, 1H, *J* 20.0 Hz), 2.19 (s, 3H), 2.42 (t, 1H, *J* 2.9 Hz), 2.48 (dd, 1H, *J* 14.7, 2.9 Hz) and 2.75 (d, 1H, *J* 20.0 Hz); ^{13}C-NMRδ (125 MHz) 15.2 (q), 22.6 (q), 23.8 (q), 26.5 (q), 28.5 (q), 32.1 (t), 42.5 (t), 44.1 (s), 49.2 (s), 52.3 (s), 56.6 (d), 210.1 (s), 210.6 (s) and 215.8 (s) (Anal. Calc. for $C_{14}H_{20}O_3$: C, 71.16; H, 8.53. Found: C, 71.01; H, 8.48).

(2R*)-*2-Acetyl-1,2,5,5-tetramethyl-6,8-dioxabicyclo[2.2.2]octane* **35**.— To a stirred solution of trimethylsilylenol ether **21** (41 mg, 0.13 mmol) in MeOH (2 ml) and H_2O (47 µl, 2.6 mmol) was added PTSA-H_2O (247 mg, 1.3 mmol) and stirring was continued at room temperature for 4hr. The resulting solution was poured into aq. $NaHCO_3$ and extracted with ethyl acetate twice. The organic layer was washed with water, brine and dried over anhydrous Na_2SO_4. Evaporation of the solvent followed by MPLC (EtOAc/Hexane=1/2) purification afforded triketone **35** (28 mg, 83 %) which had; ν_{max}/cm^{-1} 2980, 1747, 1730, 1712, 1452, 1356 and 1236; ^{1}H-NMR δ (500 MHz) 1.02 (s, 3H), 1.09 (s, 3H), 1.23 (s, 3H), 1.42 (s, 3H), 1.61 (dd, 1H, *J* 14.9, 3.2 Hz), 2.11 (d, 1H, *J* 19.8 Hz), 2.20 (s, 3H), 2.35 (t, 1H, *J* 3.2 Hz), 2.53 (dd, 1H, *J* 14.9, 3.2 Hz) and 2.57 (d, 1H, *J* 19.8 Hz); ^{13}C-NMRδ (125 MHz) 15.1 (q), 21.0 (q), 22.9 (q), 27.0 (q), 27.6 (q), 33.3 (t), 43.5 (t), 43.7 (s), 51.6 (s), 51.7 (s), 56.1 (d), 211.2 (s), 211.4 (s) and 215.1 (s) ; *m/z* 236 (M^+, 18), 137 (30), 95 (33), 83 (42), 43 (100) and 41 (65) (Found:M^+, 236.1373. $C_{14}H_{20}O_3$ requires *m/z*, 236.1412).

Methyl (2R*)-*2-Bromo-1,5,5-trimethyl-6,8-dioxobicyclo[2.2.2]octane-2-carboxylate* **22** and *Methyl 2,4,4-Trimethyl-3,6,dioxotricyclo[3.2.1.0^{2,7}]octane-1-carboxylate* **23**.— To a stirred solution of oxophorone trimethylsilylenol ether **2b** (112 mg, 0.5 mmol) in dichloromethane (10 ml) was successively added methyl α-bromoacrylate **15** (65 µl, 0.65 mmol) and diethylaluminum chloride (670 µl, 0.6 mmol, 0.9M solution in n-hexane) at 0 °C under nitrogen atmosphere. The resulting solution was stirred at 0 °C for 30 min and then room temperature for 30 hr. After addition of diethylaluminum chloride (670 µl, 0.6 mmol, 0.9M solution in n-hexane), the resulting solution was stirred for 85 hr. The reaction was quenched by addition of aq. $NaHCO_3$. After extraction with chloroform twice, the organic layer was washed with brine and dried over anhydrous Na_2SO_4. Evaporation of the solvent *in vacuo* followed by MPLC purification gave bicyclic compound **22** (23 mg, 15%) and tricyclic compound **23** (33 mg, 28%) in the order of elution.
The bicyclic compound **22** had; ν_{max}/cm^{-1} ($CHCl_3$) 2980, 1744, 1728, 1456, 1400, 1279 and 1197; ^{1}H-NMR δ (200 MHz) 1.13 (s, 3H), 1.21 (s, 3H), 1.27 (s, 3H), 2.28 (d, 1H, *J* 19.7 Hz), 2.41 (m, 1H), 2.75 (dd, 1H, *J* 16.5,

3.5 Hz), 3.07 (d, 1H, *J* 19.7 Hz), 3.39 (dd, 2H, *J* 16.5, 2.6 Hz) and 3.80 (s, 3H) (Anal. Calc. for $C_{13}H_{17}O_4Br$: C, 49.23 %; H, 5.40 %; Br, 20.18 %. Found: C, 48.99 %; H, 5.27 %; Br, 20.40 %).

The tricyclic compound **23** had; ν_{max}/cm^{-1} ($CHCl_3$) 2980, 1738, 1709, 1464, 1439 and 1244; ^{1}H-NMR δ (200 MHz) 1.04 (s, 3H), 1.15 (s, 3H), 1.39 (s, 3H), 2.10 (dd, 1H, *J* 5.4, 1.8 Hz), 2.38 (d, 1H, *J* 13.2 Hz), 2.44 (dd, 1H, *J* 13.2, 5.4 Hz), 2.53 (d, 1H, *J* 1.8 Hz) and 3.79 (s, 3H); ^{13}C-NMR (50 MHz, $CDCl_3$) δ (ppm) 12.5 (q), 22.6 (q), 24.2 (q), 26.6 (s), 41.7 (s), 41.9 (s), 46.2 (s), 47.9 (s), 51.3 (d), 52.7 (q), 168.2 (s), 205.9 (s) and 208.2 (s); *m/z* 236 (M^+, 44), 121 (60), 70 (59), 41 (100) and 39 (82) (Found:M^+, 236.0998. $C_{13}H_{16}O_4$ requires *m/z*, 236.1049).

(2S*)-*2-Acetyl-4-benzyl-1,5,5-trimethyl-8-trimethylsiloxy-6-oxobicyclo[2.2.2]oct-7-ene* **25**, *3-Benzyl-2,2,6-trimethyl-3-(3-oxoproryl)-5-cyclohexene-1,4-dione* **26** *and 2-Benzyl-2,2,6-trimethyl-3-(3-oxopropyl)-5-cyclohexene-1,4-dione* **27**.— To a stirred solution of α-benzyloxophorone trimethylsilylenol ether **24** (115 mg, 0.37 mmol) in dichloromethane (3.7 ml) was successively added 3-penten-2-one (37 μl, 0.44 mmol) and diethylaluminum chloride (490 μl, 0.44 mmol, 0.9M solution in n-hexane) at 0 °C under nitrogen atmosphere. The resulting solution was stirred at 0 °C for 2.5 hr and then at room temperature for 3.5 hr. The reaction was quenched by addition of aq. $NaHCO_3$. After extraction with chloroform twice, the organic layer was washed with brine and dried over anhydrous Na_2SO_4. Evaporation of the solvent *in vacuo* followed by MPLC purification gave trimethylsilylenol ether of bicyclic compound **26** (91 mg, 65%), bicyclic compound **25** (5 mg, 5%) and single Michael product **27** (20 mg, 18%) in the order of elution.

The trimethylsilylenol ether bicyclic compound **25** had; mp 184-185 °C; ν_{max}/cm^{-1} ($CHCl_3$) 3048, 1725, 1718, 1495, 1456, 1386, 1363 and 1165; ^{1}H-NMR δ (200 MHz) 1.02 (s, 3H), 1.08 (s, 3H), 1.32 (s, 3H), 1.47 (dd, 1H, *J* 14.9, 8.5 Hz), 1.97 (dd, 1H, *J* 14.9, 10.5 Hz), 1.98 (dd, 1H, *J* 19.6, 1.2 Hz), 2.14 (s, 3H), 2.36 (d, 1H, *J* 13.5 Hz), 2.88 (ddd, 1H, *J* 10.5, 8.5, 1.2 Hz), 3.15 (d, 1H, *J* 19.6 Hz), 3.53 (d, 1H, *J* 13.5 Hz) and 7.13-7.29 (m, 5H).

The bicyclic compound **26** had; mp 134-136 °C; ν_{max}/cm^{-1} 2975, 1150, 1717, 1626, 1456, 1256, 864, 849 and 704; ^{1}H-NMR δ (200 MHz) 0.32 (s, 9H), 1.09 (s, 3H), 1.15 (s, 6H), 1.26 (dd, 1H, *J* 13.6, 7.3 Hz), 1.96 (dd, 1H, *J* 13.6, 9.5 Hz), 2.00 (s, 3H), 2.58 (d, 1H, *J* 13.9 Hz), 2.59 (dd, 1H, *J* 9.5, 7.3 Hz), 3.39 (d, 1H, *J* 13.9 Hz), 4.47 (s, 1H) and 7.14-7.33 (m, 5H).

The single Michael product **27** had; mp 163-165 °C; ν_{max}/cm^{-1} ($CHCl_3$) 2939, 1709, 1669, 1495, 1454, 1358, 874 and 689; ^{1}H-NMR δ (200 MHz) 0.66 (s, 3H), 1.21 (s, 3H), 1.76 (dd, 2H, *J* 12.4, 6.7 Hz), 1.89 (d, 3H, *J* 1.5 Hz), 1.96-2.28 (m, 1H), 2.17 (s, 3H), 2.98 (d, 1H, *J* 14.0 Hz), 3.13 (d, 1H, *J* 14.0 Hz), 3.27 (dd, 1H, *J* 10.4, 6.7 Hz), 5.96 (d, 1H, *J* 1.5 Hz) and 7.14-7.24 (m, 5H).

3-Benzyl-2,6,6-trimethyl-4-trimethylsiloxy-2,4-cyclohexadienone **28** *and 2-benzyl-3,5,5-trimethyl-2-cyclohexene-1,4-dione* **29**.— To a solution of trimethylsilylenol ether **24** (678 mg, 2.2 mmol) in dichloromethane (22 ml) was added a solution of diethyl aluminumchloride (2.7 ml, 2.7 mmol, 1M in n-hexane) at 0 °C under nitrogen atmosphere. After stirring for 30 min at 0 °C and then 8 hr at room temperature, the resulting solution was added to aq. $NaHCO_3$. Extraction with chloroform three times followed by evaporation of solvent gave a residue which was purified by MPLC to provide trimethylsilylenol ether **28** (370 mg, 55%) and 1,4-dione **29** (184 mg, 35%) in the order of elution.

The trimethylsilylenol ether **28** had; ν_{max}/cm^{-1} 2967, 1715, 1682, 1495, 1454, 1381, 1257, 1151, 1084, 845 and 700; ^{1}H-NMR δ (200 MHz) 0.07 (s, 9H), 1.22 (s, 6H), 1.95 (s, 3H), 3.82 (s, 2H), 5.25 (s, 1H) and 7.08-7.32 (m, 5H).
The 1,4-dione **29** had; ν_{max}/cm^{-1} (neat) 2980, 1678, 1495, 1455, 1277, 727 and 700; ^{1}H-NMR δ (200 MHz) 1.23 (s, 6H), 2.05 (s, 3H), 2.75 (s, 2H), 3.82 (s, 2H) and 7.08-7.31 (m, 5H); ^{13}C-NMRδ (50 MHz) 14.2 (q), 26.7 (q), 32.9 (t), 45.8 (s), 52.4 (t), 127.0 (d), 129.0 (d), 129.2 (d), 138.4 (s), 145.2 (s), 147.5 (s), 198.0 (s) and 204.0 (s); *m/z* 242 (M^+, 84), 227 (75), 130 (53), 129 (92), 128 (62), 115 (100), 91 (77), 41 (66) and 39 (59) (Found:M^+, 242.1277. $C_{16}H_{18}O_2$ requires *m/z*, 242.1307).

(2S*)-*2-Acetyl-7-benzyl-1,5,5-trimethyl-8-trimethylsiloxy-6-oxobicyclo[2.2.2]oct-7-ene* **30** and *5-Benzyl-2,2,6-trimethyl-3-(3-oxoproryl)-5-cyclohexene-1,4-dione* **31**.— To a stirred solution of benzyloxophorone trimethylsilylenol ether **28** (72 mg, 0.23 mmol) in dichloromethane (2.3 ml) was successively added 3-penten-2-one (23 µl, 0.28 mmol) and diethylaluminum chloride (290 µl, 0.28 mmol, 0.9M solution in n-hexane) at 0 °C under nitrogen atmosphere. The resulting solution was stirred at 0 °C for 2 hr and then at room temperature for 30 min. The reaction was quenched by addition of aq. $NaHCO_3$. After extraction with chloroform twice, the organic layer was washed with brine and dried over anhydrous Na_2SO_4. Evaporation of the solvent *in vacuo* followed by MPLC purification gave trimethylsilylenol ether of bicyclic compound **30** (67 mg, 76%) and single Michael product **31** (6 mg, 8%) in the order of elution.
The trimethylsilylenol ether of bicyclic compound **30** had;ν_{max}/cm^{-1} 2969, 1717, 1657, 1495, 1455, 1354, 1159, 847 and 696; ^{1}H-NMR δ (200 MHz) 0.26 (s, 9H), 1.07 (s, 6H), 1.21 (s, 3H), 1.70 (ddd, 1H, *J* 13.0, 7.0, 2.7 Hz), 2.13 (s, 3H), 2.28 (ddd, 1H, *J* 13.0, 9.7, 3.2 Hz), 2.44 (dd, 1H, *J* 3.2, 2.7 Hz), 2.70 (dd, 1H, *J* 9.7, 7.0 Hz), 3.02 (d, 1H, *J* 15.4 Hz), 3.88 (d, 1H, *J* 15.4 Hz) and 6.99-7.26 (m, 5H).
The single Michael product **31** had; ν_{max}/cm^{-1} 2961, 1694, 1667, 1433, 1358, 1183 and 1154; ^{1}H-NMR δ (200 MHz) 0.90 (s, 3H), 0.91 (s, 3H), 1.95-2.20 (m, 2H), 2.07 (s, 3H), 2.23 (s, 3H), 2.37 (dd, 1H, *J* 14.4, 7.0 Hz), 2.66 (dd, 2H, *J* 11.8, 7.0 Hz), 3.58 (d, 1H, *J* 14.7 Hz), 3.67 (d, 1H, *J* 14.7 Hz) and 7.09-7.29 (m, 5H); *m/z* 312 (M^+, 23), 227 (21), 91 (77), 55 (20), 43 (100) and 41 (29) (Found:M^+, 312.1686. $C_{20}H_{24}O_3$ requires *m/z*, 312.1725).

(2S*)-*2-Acetyl-7-benzyl-1,5,5-trimethyl-6,8-dioxobicyclo[2.2.2]octane* **33**.— To a stirred solution of trimethylsilylenol ether **30** (47 mg, 0.12 mmol) in acetone (1.2 ml) and H_2O (22 µl, 1.2 mmol) was added PTSA-H_2O (23 mg, 0.12 mmol) and stirring was continued at room temperature for 3 hr. The resulting solution was poured into aq. $NaHCO_3$ and extracted with ethyl acetate twice. The organic layer was washed with water, brine and dried over anhydrous Na_2SO_4. Evaporation of the solvent followed by MPLC (EtOAc/Hexane=1/2) purification afforded triketone **33** (16 mg, 44 %) which had; ν_{max}/cm^{-1} ($CHCl_3$) 2970, 1779, 1742, 1721, 1456, 1387, 1109 and 1024; ^{1}H-NMR (500 MHz) δ 1.17 (s, 3H), 1.24 (s, 3H), 1.43 (s, 3H), 1.57 (s, 3H), 1.74-1.79 (m, 1H), 1.84 (ddd, 1H, *J* 14.6, 12.2, 4.0 Hz), 2.00 (dd, 1H, *J* 10.8, 2.7 Hz), 2.32 (ddd, 1H, *J* 14.6, 10.8, 2.0 Hz), 2.49 (dd, 1H, *J* 4.0, 2.0 Hz), 2.57 (d, 1H, *J* 15.3 Hz), 2.93 (d, 1H, *J* 15.3 Hz) and 7.13-7.31 (m, 5H).

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