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Alicyclic Terpenoids from Cyclocitryl Phenyl Sulfides. VI.[1] Syntheses of β-Ionone Derivatives

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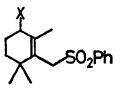
Synopsis. 4-(2,6,6-Trimethyl-3-oxo-1-cyclohexenyl)-3-buten-2-one and 4-(2,6,6-trimethyl-1,3-cyclohexadienyl)-3-buten-2-one were efficiently synthesized by alkylation of 2,4,4-trimethyl-3-(phenylsulfonylmethyl)-2-cyclohexen-1-ol and 1-(phenylsulfonylmethyl)-2,6,6-trimethyl-1,3-cyclohexadiene with propylene oxide followed by oxidation and elimination of sulfonyl group, respectively.

In connection with studies on the synthesis of terpenoids, we demonstrated a simple preparation of cyclocitryl phenyl sulfone (**1**) and its use as a synthon for cyclocitral.[2] The sulfone **1** was also converetd to β-ionone, deoxytrisporone,[3] and vitamin A acid methyl esters.[4] Here, we describe a convenient preparation of 1-phenylsulfonylmethyl-2,6,6-trimethylcyclohexa-1,3-diene (**4**) from **1**, as well as syntheses of 4-(2,6,6-trimethyl-3-oxo-1-cyclohexenyl)-3-buten-2-one (**5**), a tea aroma substance[5,6] and 4-(2,6,6-trimethyl-1,3-cyclohexadienyl)-3-buten-2-one (**6**), a tobacco flavor constituent,[7,8] from **2** and **4**, respectively.

Oxidation of **1** with 1.5 equiv of SeO_2 in dioxane at 80 °C for 1.5 h gave the alcohol **2** (74%) and the starting material **1** (23%). On treatment of **2** with PBr_3 in dry ether at 0 °C,[9] the alcohol **2** was converted smoothly to the corresponding bromo compound **3**, which was dehydrobrominated by the action of 1.5 equiv of LiCl in DMF at 100 °C for 2 h, affording **4** in 92% yield.

The reaction of **2** with 2 equiv. of BuLi in THF at −70 °C, followed by reaction with propylene oxide at room temperature for 20 hours, provided the diol **7** in 86% yield. The alcohol **7** was easily purified by column chromatography (SiO_2) and was homogeneous by TLC, but the NMR was unexpectedly complex, presumably due to intramolecular hydrogen bonding between the hydroxyl group and sulfonyl oxygen and/or the presence of diastereomers on C-2 and C-4. On oxidation with Jones reagent, **7** was converted to the corresponding diketone in 92% yield, whose NMR spectrum was in agreement with the structure **8**.

Treatment of **8** with MeONa in *t*-BuOH-EtOH at room temperature afforded **5** in 78% yield.[11]



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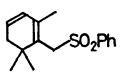
2 X=OH
3 X=Br



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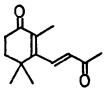

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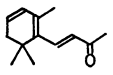

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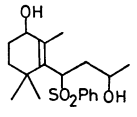

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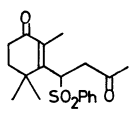

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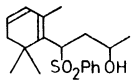

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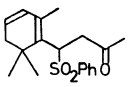

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Alkylation of **4** with propylene oxide was performed similarly with 1 equiv. of BuLi, affording **9** in 95% yield. Oxidation of **9** was attempted with both Jones and Collins reagents, but the yield of the ketone **10** was unsatisfactory. However, when **9** was oxidized with pyridinium chlorochromate in anhydrous dichloromethane at room temperature as described by Corey,[12] the ketone **10** was obtained in 82% yield. Then, **10** was subjected to the base-promoted elimination of sulfonyl group with MeONa in *t*-BuOH–EtOH at room temperature to give **6** in 88% yield. The IR and NMR spectra of **6** are consistent with those reported.[7]

Experimental

Melting points are uncorrected. IR spectra were determined with a Jasco IRA-1 infrared spectrometer. NMR spectra were obtained at 60 MHz with a Hitachi R-24 spectrometer and the chemical shift values are expressed in δ value (ppm) relative to Me_4Si in $CDCl_3$.

2,4,4-Trimethyl-3-phenylsulfonylmethyl-2-cyclohexen-1-ol (2). A mixture of **1** (102 mg, 0.37 mmol) and SeO_2 (62 mg, 0.56 mmol) in 1 ml of dioxane was stirred at 80 °C for 1.5 h. After removing the precipitate with centrifuge and evaporating the solvent *in vacuo*, the residue was chromatographed (SiO_2, benzene/hexane=5/1) to give **2** (82 mg, 74%) together with **1**(24 mg, 23%): Mp 94—95 °C (benzene/hexane =1/10); IR (Nujol) 3500 (OH), 1632 (C=C), 1302, 1137 (SO_2) cm^{-1}; NMR ($CDCl_3$) δ 8.02—7.42 (5H, m, ArH), 3.98 (2H, s, CH_2SO_2), 3.80—4.10 (1H, m, CHOH), 2.98 (1H, s, OH), 1.84 (3H, s, CH_3C=), 1.12—2.22 (4H, m, CH_2), 1.08 (3H, s, CH_3), 1.01 (3H, s, CH_3).

Found: C, 65.42; H, 7.53%. Calcd for $C_{16}H_{22}O_3S$: C, 65.29; H, 7.53%.

2,6,6-Trimethyl-1-(phenylsulfonylmethyl)-3-bromocyclohexene (3). Into a solution of **2** (372 mg, 1.26 mmol) in 1.2 ml of dry ether and 0.8 ml of dry THF was added dropwise phosphorus tribromide (344 mg, 1.27 mmol) at 0 °C and the mixture was stirred for 2.5 h. After addition of saturated $NaHCO_3$, the organic substances were extracted with AcOEt. The extracts were washed with brine, dried (Na_2SO_4), and concentrated *in vacuo* to give **3** as pale colored crystals (450 mg, 100%): Mp 129—130 °C (AcOEt/hexane=1/10); IR(Nujol)

1305, 1145 (SO_2) cm^{-1}; NMR ($CDCl_3$) δ 7.45—8.02 (5H, m, ArH), 4.58—4.75 (1H, m, CHBr), 3.96 (2H, s, CH_2SO_2), 2.07—2.26 (2H, m, CH_2), 1.86 (3H, s, CH_3), 1.27—1.68 (2H, m, CH_2), 1.06 (3H, s, CH_3), 1.03 (3H, s, CH_3).

Found: C, 53.68; H, 5.99%. Calcd for $C_{16}H_{21}O_2SBr$: C, 53.79; H, 5.93%.

*2,6,6-Trimethyl-1-(phenylsulfonylmethyl)-1,3-cyclohexadiene (**4**).* A mixture of **3** (450 mg, 1.26 mmol) and LiCl (80 mg, 1.89 mmol) in dry DMF was stirred under N_2 at 100 °C for 2 h. After addition of 5 ml of water, the organic substances were extracted with ether. The extracts were washed with brine, dried (Na_2SO_4), and concentrated *in vacuo* to yield 351 mg of crystals, which was chromatographed (SiO_2, AcOEt/hexane=1/5) to give **4** (323 mg, 93%): Mp 58—60 °C (benzene/hexane=1/10); IR (Nujol) 1305, 1145 (SO_2) cm^{-1}; NMR ($CDCl_3$) δ 7.38—8.04 (5H, m, ArH), 5.78 (2H, br s, CH=CH), 4.01 (2H, s, CH_2SO_2), 2.07 (2H, d, J=4 Hz, CH_2C=), 1.62 (3H, s, CH_3C=), 1.11 (6H, s, CH_3).

Found: C, 69.43; H, 7.42%. Calcd for $C_{16}H_{20}O_2S$: C, 69.55; H, 7.30%.

*4-Phenylsulfonyl-4-(2,6,6-trimethyl-3-hydroxy-1-cyclohexenyl)-2-butanol (**7**).* Into a solution of **2** (103 mg, 0.35 mmol) in 1.5 ml of dry THF, was added ethereal solution of BuLi (0.8 mmol) at −50 °C under N_2. After stirring for 15 min, propylene oxide (0.2 ml) was added to the mixture, which was stirred at room temperature for additional 20 h. The reaction mixture was quenched with saturated NH_4Cl and extracted with AcOEt. The extracts were washed with brine, dried (Na_2SO_4), and concentrated *in vacuo* to yield a viscous liquid, which was chromatographed (SiO_2, benzene/AcOEt=1/1) to give **7** (106 mg, 86%): IR (neat) 3407 (OH), 1291, 1137 (SO_2) cm^{-1}; NMR ($CDCl_3$) δ 7.34—8.00 (5H, m, ArH), 3.39—4.46 (3H, m, CHOH, $CHSO_2$), 2.42—3.00 (2H, m, OH), 2.08 (3H, s, CH_3C=), 1.39—2.40 (6H, m, CH_2), 0.67—1.32 (9H, m, CH_3).

Found: C, 64.92; H, 8.09%. Calcd for $C_{19}H_{28}O_4S$: C, 64.75; H, 8.01%.

*4-Phenylsulfonyl-4-(2,6,6-trimethyl-3-oxo-1-cyclohexenyl)-2-butanone (**8**).* Into a solution of **7** (46 mg, 0.13 mmol) in 0.5 ml of CH_2Cl_2, was added Jones reagent[13] (0.2 ml, 0.52 mmol) under ice-cooling and the mixture was stirred at 5 °C for 1 h. After addition of 0.5 ml of water, the organic substances were extracted with $CHCl_3$. The extracts were washed with saturated $NaHCO_3$ and water, dried (Na_2SO_4), and concentrated *in vacuo* to yield 45 mg of dark brown crystals, which were chromatographed (SiO_2, benzene/AcOEt=2/1) to give **8** (41 mg, 92%): Mp 128—129 °C (benzene/hexane=1/10); IR (Nujol) 1717 (C=O), 1658 (C=C), 1297, 1148 (SO_2) cm^{-1}; NMR ($CDCl_3$) δ 7.35—7.93 (5H, m, ArH), 4.95 (1H, dd J=6.6 and 2.4 Hz, $CHSO_2$), 3.91 (1H, dd J=6.6 and 19.2 Hz, CH_2CSO_2), 2.73 (1H, dd J=2.4 and 19.2 Hz, CH_2CSO_2), 2.28—2.52 (2H, m, CH_2), 2.10 (3H, s, CH_3), 2.07 (3H, s, CH_3), 1.64—2.00 (2H, m, CH_2), 1.17 (3H, s, CH_3), 0.97 (3H, s, CH_3).

Found: C, 65.59; H, 7.04%. Calcd for $C_{19}H_{24}O_4S$: C, 65.50; H, 6.94%.

*4-Phenylsulfonyl-4-(2,6,6-trimethyl-1,3-cyclohexadienyl)-2-butanol (**9**).* The alcohol **9** could be prepared in 95% yield under similar reaction conditions to the procedure described for **7**: IR (neat) 3493 (OH), 1303, 1143 (SO_2) cm^{-1}; NMR ($CDCl_3$) δ 7.31—8.02 (5H, m, ArH), 5.62—5.86 (2H, m, CH=CH), 4.21—4.56 (1H, m, $CHSO_2$), 3.46—4.06 (1H, m, CHOH), 1.56—2.36 (7H, m, CH_2, OH), 1.99 (3H, s, CH_3), 0.78—1.40 (9H, m, CH_3).

Found: C, 68.37; H, 7.98%. Calcd for $C_{19}H_{26}O_3S$: C, 68.24; H, 7.84%.

*4-Phenylsulfonyl-4-(2,6,6-trimethyl-1,3-cyclohexadienyl)-2-butanone (**10**).* Into a solution of pyridinium chlorochromate (74 mg, 0.34 mmol) in 1 ml of dry CH_2Cl_2, was added the alcohol **9** (58 mg, 0.17 mmol) dissolved in 0.5 ml of dry CH_2Cl_2 under N_2 and the mixture was stirred at room temperature for 8 h. After addition of 1 ml of water, the organic substances were extracted with $CHCl_3$. The extracts were washed with brine, dried (Na_2SO_4), and concentrated *in vacuo* to yield a dark brown oil, which was chromatographed (SiO_2, benzene/AcOEt=10/1) to give **10** (47 mg, 82%) as a colorless liquid: IR (CCl_4) 1721 (C=O), 1646 (C=C), 1302, 1145 (SO_2) cm^{-1}; NMR ($CDCl_3$) δ 7.35—8.00 (5H, m, ArH), 5.74 (2H, br s, CH=CH), 4.95 (1H, dd J=6.6 and 4.8 Hz, $CHSO_2$), 3.71 (1H, dd J=6.6 and 18.6 Hz, CH_2CSO_2), 2.79 (1H, dd J=4.8 and 18.6 Hz, CH_2CSO_2), 2.05 (3H, s, CH_3), 2.01 (3H, s, CH_3), 1.80—2.20 (2H, m, CH_2), 0.94 (3H, s, CH_3), 0.82 (3H, s, CH_3).

Found: C, 68.88; H, 7.37%. Calcd for $C_{19}H_{24}O_3S$: C, 68.66; H, 7.28%.

*4-(2,6,6-Trimethyl-3-oxo-1-cyclohexenyl)-3-buten-2-one (**5**).* A solution of **8** (74 mg, 0.21 mmol) in 4 ml of dry *t*-BuOH was added into 50 mg of MeONa under N_2 and the mixture was stirred at room temperature for 5 h. The reaction mixture was quenched with saturated NH_4Cl and extracted with ether. The ether extracts were washed with brine, dried (Na_2SO_4), and concentrated *in vacuo* to yield a dark brown oil, which was chromatographed (SiO_2, benzene/AcOEt=7/1) to give **5** (34 mg, 78%) as crystals.

*4-(2,6,6-Trimethyl-1,3-cyclohexadienyl)-3-buten-2-one (**6**).* The compound **6** could be prepared in 78% yield under similar reaction conditions to the procedure described for **5**.

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