Synthesis of Elvirol Methyl Ether

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Elvirol methyl ether has been synthesized from *p*-cresol via 2-(2-cyclopentenyl)-4-methylphenyl methyl ether by ozonolysis, dithioacetalization, reduction, and Wittig reaction. The overall yield was 18.8%.

Elvirol (**1a**), a metabolite of *Elvira biflora* DC. (family Compositae),[1] possesses a carbon skeleton which does not conform to the "isoprene rule", and is likely to arise in nature from α-curcumene by undergoing *Ar*-epoxidation and subsequent 1,2-alkyl shift. The structure **1a** was confirmed by several syntheses.[2,3,4] Our interest in phenolic sesquiterpenes[5] has led us to develop a different approach to elvirol.

A retrosynthetic analysis indicated the trisnor-aldehyde (**2**) as a viable precursor. Considering atom economy, the only sensible structure for generating **2** is that based on an internal association of the trigonal carbon atom to the secondary methyl group. Thus, a 3-arylcyclopentene emerged as our choice. Owing to the proximity of an oxygen substituent in the aromatic ring to one end of the disubstituted double bond we hoped that the oxidative cleavage of such a structure may give rise to differentiable functionalities by some manipulation exploiting neighboring group participation.[6]

2-(2-Cyclopentenyl)-4-methylphenol **3a** is conveniently prepared by alkylation of *p*-cresol with cyclopentadiene in the presence of phosphoric acid.[7] When this phenol was ozonolyzed the product appeared to be a tautomeric mixture of **4** and **5**. Unfortunately, the Wittig reaction of this mixture with isopropylidenetriphenylphosphorane was found to be totally nonregioselective. Both **6** and **7** were generated (together with recovered starting material) even when only one equivalent of the Wittig reagent was employed. As an attempted formation of the methoxydihydrobenzofuran derivative failed, we turned our attention to the ozonolysis of the aryl methyl ether[8] **3b** in methanol and followed by treatment with acetic anhydride and triethylamine.[9] By this protocol the aldehydo-ester **8** was obtained in approximately 50% yield and the regioisomer **9** (slightly impure) in 25% yield. More importantly, these isomers could be separated by silica gel column chromatography. The aldhyde group of **8** was transformed into a dithiane (**10**) almost quantitatively which was then desulfurized with Raney nickel. The resulting ester **11** was reduced with diisobutylaluminum hydride to give **2** and a small amount of the primary alcohol due to overreduction, and finally a Wittig reaction completed the synthesis of elvirol methyl ether (**1b**). Since **1b** has been converted to elvirol by reaction with sodium ethanethiolate in *N,N*-dimethylformamide, our work constitutes a formal synthesis of the phenolic terpene.

The 2:1 selectivity for the transformation of the ozonide derived from **3b** is still quite interesting. Apparently, the aryl group in the cyclic peroxide intermediate exerted some steric hindrance to the base for deprotonation at the proximal anomeric center.

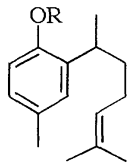
EXPERIMENTAL SECTION

2-(2-Cyclopentenyl)-4-methylphenyl Methyl Ether (3b)

The reaction of *p*-cresol with freshly distilled cyclopentadiene in the presence of a catalytic amount of 80% phosphoric acid into luene at room temperature for 18 h gave phenol **3a** in 70% yield. Methylation of this phenol (1.0 g, 5.75 mmol) in refluxing acetone (10 mL) with dimethyl sulfate (1.45 g, 115 mmol) and potassium carbonate (2.38 g, 17.25 mmol) for 36 h afforded, after cooling, washing with NH_4OH, extraction with dichloromethane and silica gel chromatography, the methyl ether **3b** (1.0 g, 92.6%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.28 (3H, s), 2.36-2.48 (4H, m), 3.82 (3H, s), 4.24-4.26 (1H, m), 5.74-5.94 (2H, m), 6.71-6.95 (3H, m); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 20.7 (q), 32.4 (t), 32.5 (t), 43.8 (d), 55.6 (q), 110.3 (d), 127.1 (d), 128.0 (d), 129.6 (s), 131.7(d), 134.1 (d), 134.5 (s), 154.9 (s).

Methyl 4-(2-Methoxy-5-methylphenyl)-5-oxopentanoate (8)

Ozone was passed through a mixture of **3b** (1.0 g, 5.32 mmol) and sodium bicarbonate (0.14 g, 1.33 mmol) in dichloromethane (20 mL) and methanol (4 mL) at -78° until the liquid phase became blue. Diluted with more dichloromethane (20 mL) the reaction mixture was brought to 0°, treated with triethylamine (1.11 mL, 7.98 mmol) and acetic anhydride (1.5 mL, 15.96 mmol), and stirred for 15 min. Removal of the ice bath to allow the decomposition of the



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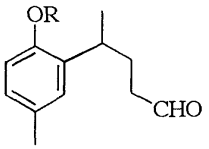
(1b) R = CH_3



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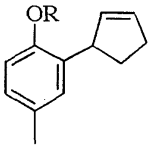
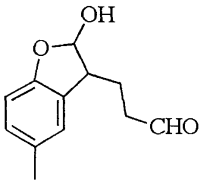


(3a) R = H
(3b) R = CH_3



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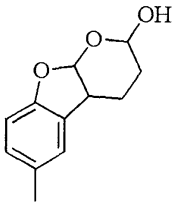

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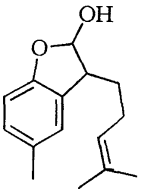

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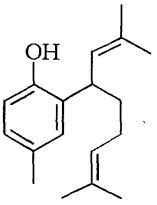

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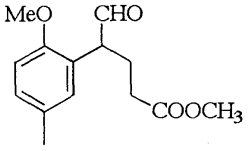

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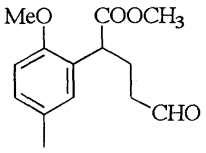

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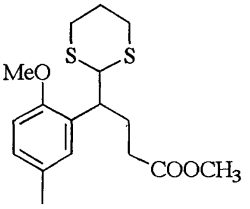

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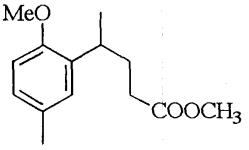

(11)

ozonide at room tem per a ture for 4 h, the prod uct **8** (0.66 g, 49.6%) was then iso lated by wash ing with HCl, NaOH, and wa ter, dry ing over Na_2SO_4, evap o ra tion in vacuo, and sil ica gel chro ma tog ra phy us ing a 4:6 mix ture of EtOAc and hexane as eluent. The iso meric arylacetate es ter **9** was ob tained in im pure form from later frac tions. For **8**: IR (film) ν 1737, 1729 cm^{-1}; ^1H NMR δ 1.83-1.96 (2H, m), 2.16 (3H, s), 2.26-2.35 (2H, m), 3.43 (3H, s), 3.71-3.73 (1H, m), 3.72 (3H, s), 6.65-6.75 (2H, m), 6.97 (1H, dd, *J* = 6.9, 1.5 Hz), 9.52 (1H, d, *J* = 3.6 Hz); ^{13}C NMR δ 20.2 (q), 23.5 (t), 31.1 (t), 51.0 (q), 51.9 (d), 55.1 (q), 110.6 (d), 124.0 (s), 129.1 (d), 129.9 (s), 130.5 (d), 155.1 (s), 173.0 (s), 199.8 (d); HRMS (*m/z*) 250.1205 (250.1209 calcd. for $C_{14}H_{18}O_4$).

Methyl 4-(1,3-Dithian-2-yl)-4-(2-methoxy-5-methylphenyl)butanoate (10)

Boron tri fluor ide etherate (0.2 mL) was added to a stirred mix ture of **8** (0.56 g, 2.24 mmol) and 1,3- pro panedithiol (0.24 g, 2.24 mmol) at -25°. Af ter the ad di tion was com plete the mix ture was warmed to room tem per a ture, kept for 15 h and dis solved in di chloro methane. Af ter al ka line wash, dry ing (Na_2SO_4) and evap o ra tion, the crude prod uct was chromatographed (SiO_2/1:9 EtOAc-hexane) to fur nish **10** (0.76 g, 99%). IR (film) ν 1715 cm^{-1}; ^1H NMR δ 1.95-2.08 (4H, m), 2.24 (3H, s), 2.36-2.70 (2H, m), 2.70-2.87 (4H, m), 3.56 (3H, s), 3.75-3.78 (1H, m), 3.76 (3H, s), 4.28 (1H, d, *J* = 8.7 Hz), 6.69-6.97 (3H, m); ^{13}C NMR δ 20.7 (q), 25.9 (t), 26.9 (t), 29.8 (t), 30.0 (t), 32.3 (t), 51.2 (q), 52.0 (d), 55.5 (q), 110.7 (d), 128.0 (s), 128.3 (d), 128.4 (d), 129.3 (d), 129.4 (s), 155.8 (s), 173.4 (s); HRMS (*m/z*) 340.1159 (340.1161 calcd. for $C_{17}H_{24}O_3S_2$).

Methyl 4-(2-Methoxy-5-methylphenyl)pentanoate (11)

Raney nickel (ca. 1 mL) was washed with and suspended in eth a nol (5 mL) and heated with the dithiane **10** (0.1 g, 0.3 mmol) at re flux for 17 h. On cool ing to room tem per ature the solid was re moved by fil tra tion, and the fil trate was evap o rated. The res i due was pu ri fied by sil ica gel chro ma-

tography to give **11** (0.06 g, 90%). IR (film) ν 1729 cm^{-1}; ^1H NMR δ 1.16 (3H, d, *J* = 5.1 Hz), 1.83-1.91 (2H, m), 2.14-2.22 (2H, m), 2.26 (3H, s), 3.14-3.17 (1H, m), 3.58 (3H, s), 3.76 (3H, s), 6.68-6.91 (3H, m); ^{13}C NMR δ 20.8 (q), 20.9 (q), 31.5 (d), 32.3 (t), 51.3 (q), 55.4 (q), 110.4 (d), 127.2 (d), 127.6 (d), 129.6 (s), 134.0 (s), 155.0 (s), 174.1 (s); HRMS (*m/z*) 236.1406 (236.1413 calcd. for $C_{17}H_{20}O_3$).

4-(2-Methoxy-5-methylphenyl)pentanal (12)

To a stirred solution of ester **11** (0.07 g, 0.3 mmol) in dry toluene (2 mL) at -78° was added diisobutylaluminum hydride (1 M in hexane, 0.26 mL, 0.39 mmol). The reaction was maintained at -70° for 4 h, quenched with saturated NH_4Cl solution, warmed to room temperature and separated into layers after adding dichloromethane. The crude product was treated with pyridinium chlorochromate (0.1 g, 0.45 mmol) to reoxidize the overreduced material for 0.5 h. Solvent removal and chromatography gave the aldehyde **12** (0.056 g, 91.7%). IR (film) ν 1708 cm^{-1}; ^1H NMR δ 1.15 (3H, d, *J* = 7.5 Hz), 1.82-1.94 (2H, m), 2.20-2.36 (2H, m), 2.27 (3H, s), 3.14-3.21 (1H, m), 3.76 (3H, s), 6.69-6.93 (3H, m), 9.66 (1H, t); ^{13}C NMR δ 20.7 (q), 20.9 (q), 29.6 (t), 31.4 (d), 42.2 (t), 55.4 (q), 110.5 (d), 127.3 (d), 127.6 (d), 129.7 (s), 133.8 (s), 154.9 (s), 202.1 (d); HRMS (*m/z*) 206.1309 (206.1307 calcd. for $C_{13}H_{18}O_2$).

2-(1,5-Dimethyl-4-hexenyl)-4-methylphenyl Methyl Ether {Elvirol methyl ether} (1b)

n-Butyllithium (1.6 M in hexane, 0.12 mL, 0.2 mmol) was added to a stirred suspension of isopropyltriphenylphosphonium iodide (80 mg, 0.2 mmol) in tetrahydrofuran (2 mL) at 0°. After 10 min, a solution of the aldehyde **12** (20 mg, 0.1 mmol) in dry tetrahydrofuran (1 mL) was introduced dropwise via a syringe. After 2 h the reaction mixture was quenched with methanol (1 mL) and chromatographed over silica gel to give **1b** (16.1 mg, 71.6%). IR (film) ν 1610 cm^{-1}; ^1H NMR δ 1.33 (3H, d, *J* = 7.2 Hz), 1.59 (3H, s), 1.68-1.76 (2H, m), 1.85 (3H, s), 2.04 (2H, m), 2.42 (3H, s), 3.28 (1H, m), 3.88 (3H, s), 5.24 (1H, t, *J* = 6.9 Hz), 6.80-7.43 (3H, m); ^{13}C NMR δ 17.6 (q), 20.7 (q), 21.2 (q), 25.8 (q), 26.4 (t), 31.5 (d), 37.2 (t), 55.3 (q), 110.4 (d), 125.1 (d), 126.7 (d), 127.5 (d), 129.4 (s), 130.8 (s), 135.5 (s), 157.5 (s); HRMS (*m/z*) 232.1820 (232.1828 calcd. for $C_{16}H_{24}O$).

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Key Words

Sesquiterpenes; Ozonolysis; Wittig reaction; Elvirol methyl ether.

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