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Reaction of Isoeugenol with Formaldehyde in Basic Medium: Formation of *trans*-4-(4-Hydroxy-3-hydroxymethyl-5-methoxy)-5-methyl-1,3-dioxane and its Transformation into the Tricyclo[5.2.2.$0^{2,6}$]undecane System†

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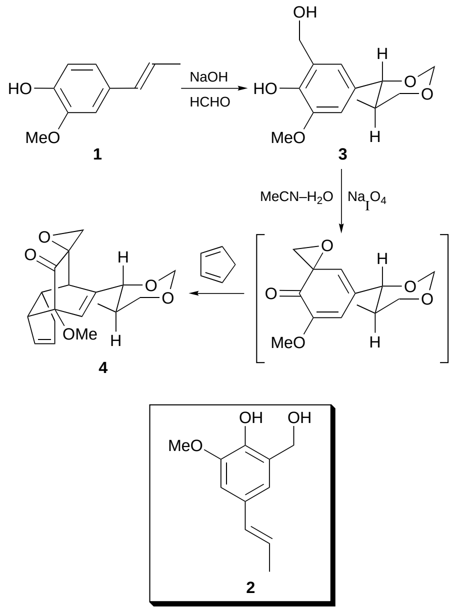
Formation of the title compound **3**, *via* an unusual Prins-type reaction on isoeugenol with formaldehyde in alkaline medium, and its conversion into a tricyclo[5.2.2.$0^{2,6}$]undecane system **4** is described.

In the context of a synthetic endeavour we needed to prepare the phenol **2** which was thought to be obtainable *via* hydroxymethylation of isoeugenol **1**. However, the hydroxymethylation of **1** with formaldehyde in basic medium furnished a highly unusual product **3** as a result of the hydroxymethylation being followed by a Prins reaction across the double bond. The Prins reaction generally occurs under acidic conditions[1–3] and such type of reaction in alkali has not, to the best of our knowledge, been reported earlier. We now report the structure of the compound **3** and its transformation to the tricyclic system **4**.

Treatment of isoeugenol with an excess of formaldehyde (aqueous, *ca.* 30%) in basic medium for *ca.* 7 h followed by acidification gave a product in good yield (60%) to which we assigned the structure **3** based on high-field ^{1}H NMR (500 MHz), ^{13}C NMR and other data.

A plausible mechanism for the formation of the product **3** it outlined in Scheme 2. The conjugation of the phenolic group with the double bond of the side chain *via* the aromatic ring appears to be responsible for the Prins-type reactions. The product **3** may be obtained either from isoeugenol **1** or its hydroxymethylated derivative **2** *via* a quinonoid species of type **5** and/or **6** respectively. Thus, the quinonoid species **6** may undergo hydroxymethylation to give **7** which upon addition of one more mole of formaldehyde either directly or *via* the oxetane intermediate **8**, leads to the formation of **9**. Intramolecular cyclisation of the species **9** finally gives the product **3** as shown in Scheme 1. Alternatively, the species **5** may also undergo hydroxymethylation[4] in an analogous fashion to give the intermediate **10** which upon subsequent hydroxymethylation at the *ortho* position of the aromatic ring finally gives the product **3**. In this context, it may be mentioned that the intermediacy of oxetanes has been proposed during the acid-catalysed Prins reaction of alkenes.[5] It may also be noted that the hydroxymethylation of eugenol **11**, wherein the double bond in the side chain is not conjugated, smoothly furnished the usual compound **12** (Scheme 3) upon treatment with formaldehyde and base.

In order to synthesize the tricyclic system **4**, a solution of the compound **3** in acetonitrile was oxidized with aqueous sodium metaperiodate and the resulting spiroepoxycyclohexa-2,4-dienone was trapped with cyclopentadiene.[6] Usual work-up and chromatography of the crude product furnished the adduct **4** as a solid (mp 132 °C) in very good yield (72%). The structure of the adduct **4** was deduced from its spectral and analytical data.[7] The IR spectrum showed a strong absorption band at 1742 cm^{-1} for the carbonyl group. The ^{1}H NMR spectrum exhibited characteristic signals at δ 5.93 (br s, 1 H, β-proton of β,γ-enone moiety) and 5.77 (m, 1 H), 5.6 (m, 1 H) olefinic protons. It further exhibited signals at δ 5.02 (d, J 6 Hz, 1 H), and 4.64 (d, J 6 Hz, 1 H) due to the equatorial and axial protons of the O—CH$_2$—O group. In addition it showed signals at δ 4.06 (dd, J_1 11 Hz, $J_2 \approx 4$ Hz, 1 H), 3.72 (d, J 10 Hz, 1 H), corresponding to the equatorial proton of the O—CH$_2$—C group and the methine proton of the O—CH—C=C group. The methoxy signal appeared at δ 3.60 (s, 3 H). Furthermore, signals were observed at δ 3.5 (br d, $J \approx 6$ Hz, 1 H, methine proton) and at 3.28 (superimposed dd, $J_1 = J_2 = 11$ Hz, 1 H, axial proton of O—CH$_2$—C group). Other resonances were observed at δ 3.06 (d overlapped with other signal, total 2 H, methine and 1 H of O—CH$_2$ of oxirane group), 2.88 (d, 1 H, $J \approx 6.5$ Hz, 1 H, OCH$_2$ of oxirane moiety), 2.72 (s, 1 H, methine H at the bridgehead), 2.69 (m, 1 H, allylic methylene of cyclopentene ring), 2.05 (d, J 18 Hz, 1 H, of allylic methylene) and 1.95 (m, 1 H, methine proton of the H—C—CH$_3$ group). The methyl signal appeared at δ 0.67 (d, J 3.5 Hz, 3 H). Comparison of the above spectral features with that of the compound **3** and other adducts of type **4** clearly revealed the structure of the adduct which was also supported by its ^{13}C NMR spectrum. Thus, the ^{13}C NMR spectrum of **4** displayed characteristic resonances at δ 204.9 for the carbonyl carbon and at 141.2, 135.0, 128.3, 127.4 for the four olefinic carbons. It further exhibited signals at δ 93.7, 88.2, 84.2, 72.5, 59.0, 53.9, 53.7, 53.0, 44.1, 38.8, 36.7, 32.4 and 12.8 for the other quaternary, methine, methylene and methyl carbons. The transformation of compound **3** into the tricyclic system **4** provided further mutual chemical support for their structures.



Scheme 1

We have thus described an unusual Prins-type reaction of potential use in functionalisation–homologation across a

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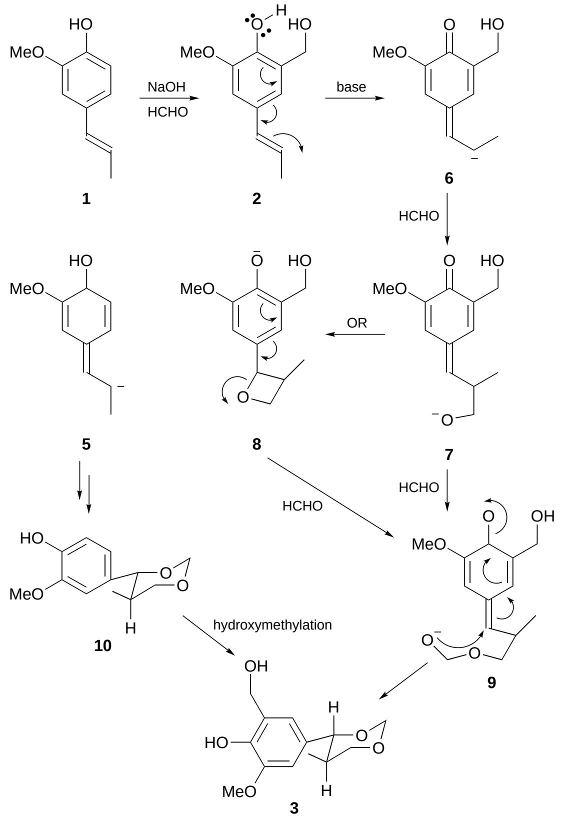
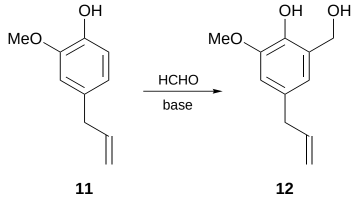


Scheme 2



Scheme 3

double bond and also described the transformation of the Prins-type product into a tricyclic system having a β,γ-enone chromophore of synthetic utility.

Experimental

IR spectra were recorded on a Nicolet Impact 400 FT-IR instrument. Mass spectra were recorded on a Hewlett Packard GCD 1800-A instrument. ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were recorded on a Varian VXR 300S instrument. Some ^{13}C NMR (125 MHz) spectra were also taken on a GE NMR Omega instrument. All the samples were dilute solutions in CDCl$_3$ with SiMe$_4$ as internal standard. Melting points were taken on a Buchi-type apparatus and are uncorrected. All the organic extracts were dried over anhydrous Na$_2$SO$_4$. Reactions were monitored with TLC and spots visualized with iodine vapour. Chromatographic separations were performed on silica gel–light petroleum.

trans-4-(4-*Hydroxy*-3-*hydroxymethyl*-5-*methoxy*)-5-*methyl*-1,3-*dioxane* (**3**).—To a solution of compound **2** (3 g, 18.3 mmol) in water (15 ml) and formaldehyde [aqueous 37–41%; 10 ml (excess)] was added NaOH (0.6 g) and the mixture was stirred at room temperature. After stirring had continued for 7 h, the reaction mixture was acidified with HCl (50%) and extracted with diethyl ether (3 × 30 ml). The combined ether layer was washed with brine (15 ml) and dried over anhydrous sodium sulfate. The solvent was removed under vacuum and the residue was chromatographed. Elution with light petroleum–ethyl acetate (60:40) gave the *dioxane* **3** (2.8 g, 60%) as a solid which was recrystallized from light petroleum–ethyl acetate (65:35), mp 108 °C; ν_{max}/cm^{-1} (KBr) 3418, 1611; δ_H (500 MHz) 6.86 (s, 1 H, aromatic), 6.81 (s, 1 H, aromatic), 6.35 (s, 1 H, OH), 5.16 (d, *J* 6.30 Hz, 1 H, equatorial proton of O—CH$_2$—O), 4.80 (d, *J* 6.3 Hz, 1 H, axial proton of O—CH$_2$—O), 4.70 (s, 2 H, C*H*$_2$OH), 4.10 (dd, J_1 10 Hz, $J_2 \approx 4$ Hz, 1 H, equatorial proton of —CH$_2$—O), 4.02 (d, *J* 10 Hz, 1 H, benzylic methine), 3.88 (s, 3 H, OCH$_3$), 3.40 (superimposed dd, $J_1 = J_2 \approx 10$ Hz, 1 H, axial proton of CH$_2$O), 2.65 (s, 1 H, OH), 2.08 (m, 1 H, methine H), 0.60 (d, *J* 7 Hz, 3 H, CH$_3$); δ_C (125 MHz) 146.9, 143.9, 131.2, 126.2, 120.1, 109.3 (aromatic carbons), 94.3, 86.3, 73.2, 61.9, 56.3, 36.5 and 12.8; *m*/*z* 254 (M$^+$) (Found: C, 61.46; H, 7.48. C$_{13}$H$_{18}$O$_5$ requires C, 61.41; H, 7.08%).

7′-*Methoxy*-10′-(5-*methoxy*-1,3-*dioxan*-4-*yl*)*spiro*[*oxirane*-2,9′-endo-*tricyclo*[5.2.2.0^{2,6}]*undeca*-4′,10′-*dien*]-8′-*one* **4**.—To a solution of compound **3** (2 g, 7.87 mmol) in acetonitrile (30 ml) was added freshly cracked cyclopentadiene (8 ml, excess) and the reaction mixture was cooled in an ice bath (~0 °C). A solution of NaIO$_4$ (6 g, 28.1 mmol) in water (50 ml) was then added dropwise to the reaction mixture with stirring. After stirring for 8 h, the reaction mixture was filtered and extracted with diethyl ether (3 × 25 ml). The organic layer was washed with brine (10 ml) and dried over anhydrous sodium sulfate. Removal of solvent followed by chromatography [light petroleum–ethyl acetate (85:15)] of the residue on silica gel furnished *spiro compound* **4** (1.8 g, 72%) as a solid, which was recrystallised from light petroleum–ethyl acetate (80:20), mp 132 °C. ν_{max}/cm^{-1} (KBr) 3063, 2939, 2849, 1743; δ_H (500 MHz) 5.93 (br s, 1 H, β-proton of β,γ-enone), 5.77 (m, 1 H, olefinic H), 5.6 (m, 1 H, olefinic H), 5.02 (d, *J* 6 Hz, 1 H, equatorial proton of O—CH$_2$—O), 4.64 (d, *J* 6 Hz, 1 H, axial proton of O—CH$_2$—O), 4.06 (dd, J_1 11 Hz, $J_2 \approx 4$ Hz, 1 H, equatorial proton of OCH$_2$), 3.72 (d, *J* 10 Hz, 1 H, methine H), 3.6 (s, 3 H, OCH$_3$), 3.5 (br d, $J \approx 6$ Hz, 1 H, methine H), 3.28 (superimposed dd, $J_1 = J_2 = 11$ Hz, 1 H, axial proton of OCH$_2$—C), 3.06 (d, overlapped with other signal, total 2 H, methine and 1 H, OCH$_2$ of oxirane), 2.88 (d, 1 H, $J \approx 6.5$ Hz, O—CH$_2$ of oxirane group), 2.72 (s, 1 H, methine H at the bridgehead), 2.69 (m, 1 H, allylic methylene of cyclopentene ring), 2.05 (d, *J* 18 Hz, 1 H, allylic methylene), 1.95 (m, 1 H, methine H) and 0.67 (d, *J* 3.5 Hz, 3 H, CH$_3$); δ_C (125 MHz) 204.9 (CO), 141.2, 135.0, 128.3, 127.4 (olefinic carbons), 93.7, 88.2, 84.2, 72.5, 59.0, 53.9, 53.7, 53.0, 44.1, 38.8, 36.7, 32.4 and 12.8; *m*/*z* 318 (M$^+$) (Found: C, 68.37; H, 7.15. C$_{18}$H$_{22}$O$_5$ requires C, 67.91; H, 6.97%).

5-*Allyl*-2-*hydroxy*-3-*methoxybenzyl Alcohol* (**12**).—To a solution of eugenol **11** (1 g, 6.1 mmol) in water (5 ml) and formalin (37–41%; 3 ml) was added NaOH (0.2 g) with stirring at room temperature. After stirring for 5 h, the reaction mixture was acidified with HCl (50%) and extracted with diethyl ether (3 × 20 ml). The ether layer was washed with brine (10 ml) and dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure and the residue was chromatographed on silica gel. Elution with light petroleum–ethyl acetate (70:30) furnished the *alcohol* **12** (0.98 g, 83%) as a liquid; ν_{max}/cm^{-1} (KBr) 3400, 1640, 1615; δ_H ^{1}H NMR (300 MHz) 6.66 (m, 2 H, aromatic protons), 6.03 (br s, 1 H, ArOH), 5.94 (m, 1 H, olefinic H), 5.07 (m, 2 H, olefinic H), 4.66 (br s, 2 H, ArCH$_2$), 3.87 (s, 3 H, OCH$_3$), 3.30 (d, $J \approx 7$ Hz, 2 H, Ar—CH$_2$—O—), 2.44 (s, 1 H, Ar—CH$_2$—OH); *m*/*z* 194 (M$^+$).

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