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The reaction of epoxyisophorone with ethyl acetoacetate under basic conditions

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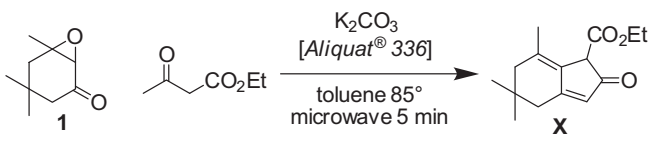
ABSTRACT

Treatment of epoxyisophorone (**1**) with ethyl acetoacetate under basic conditions resulted in the stereoselective formation of dihydroxybenzofuran **2** in moderate yield. This result is in contradiction to previous work where similar conditions were reported to afford a bicyclo [4.3.0]nonadienone via a putative *Robinson* annulation reaction.

1. Introduction

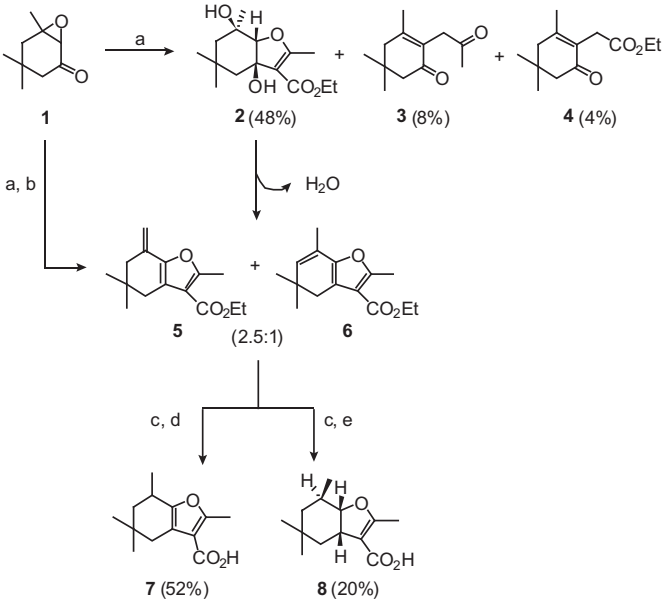
In 2001,[1] a publication describing the formation of bicyclo [4.3.0] nonadienone **X** in 89% yield from epoxyisophorone (**1**), by treatment with ethyl acetoacetate under basic conditions using microwave radiation, attracted our attention as a potential cost-effective access to substituted perhydro-2-indanones (Scheme 1).



Scheme 1. Reported formation of compound X from **1**.[1]

2. Results and discussion

Not having ready access to microwave equipment, we decided to carry out the published experimental procedure using toluene at reflux as a substitute for the microwave treatment, expecting to form **X** to some extent. However, to our surprise, after 32 h at reflux the major product (48% yield), isolated by chromatography and recrystallisation, was the *cis*-fused dihydroxybenzofuran **2**. The stereochemistry of **2** was unambiguously assigned by extensive NMR and MS spectroscopy. Minor products, also identified by spectral analysis, were the known diketone **3**[2] (8% yield) and keto ester **4**[3] (4% yield) (Scheme 2). Neither **X** nor compounds structurally related to **X** were detected in the product mixture.



Scheme 2. Reagents and conditions: (a) Ethyl acetoacetate K_2CO_3, [Aliquat®336], toluene, reflux, 32 h; (b) [$TsOH \cdot H_2O$], cyclohexane, reflux, 2 h (41% over two steps); (c) KOH, EtOH rt, 4 h; (d) H_2, [10% Pd–C] (10% by wgt), MeOH, rt, 48 h; (e) H_2, [10% Pd–C] (25% by wgt), MeOH, rt, 84 h.

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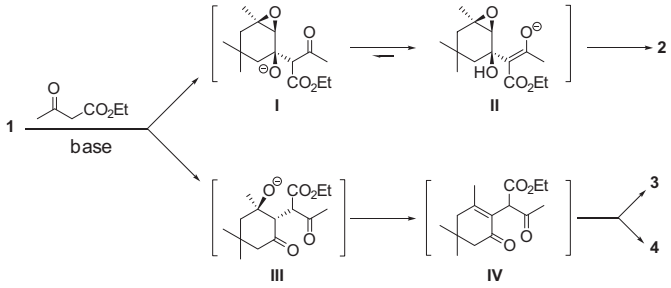
We believe that the principal reaction pathway (**1**→**2**) proceeds via stereoselective 1,2-addition of the enolate derived from ethyl acetoacetate to the carbonyl group of **1** on the face opposite to the epoxy group. The resultant alkoxide **I** then isomerizes to enolate **II**, which undergoes cyclisation via *trans*-ring opening of the epoxide. The minor reaction pathway (**1**→**3**, **4**) is a consequence of initial epoxide opening by the same enolate to form alkoxide **III**. Subsequent dehydration can then lead to diketo ester **IV**, which undergoes either decarboethoxylation to **3** or a retro-Claisen condensation reaction to afford **4** (Scheme 3).



Scheme 3. Proposed reaction mechanism for the conversion of **1** to **2**, **3** and **4**.

Confirmation of the benzofuran structure of **2** was obtained by further transformations (Scheme 2). Accordingly, the crude reaction mixture from the first step was submitted to acid-catalysed dehydration conditions using *para*-toluenesulfonic acid in cyclohexane at reflux to afford a 2.5:1 mixture of benzofurans **5** and **6**, in 41% yield over two steps. Saponification to the corresponding carboxylic acids was followed by catalytic hydrogenation to **7** (52% yield over two steps). Hydrogenation under more stringent conditions resulted in the stereoselective formation of benzofuran **8**, whose structure was determined by X-ray diffraction[4] (Fig. 1).

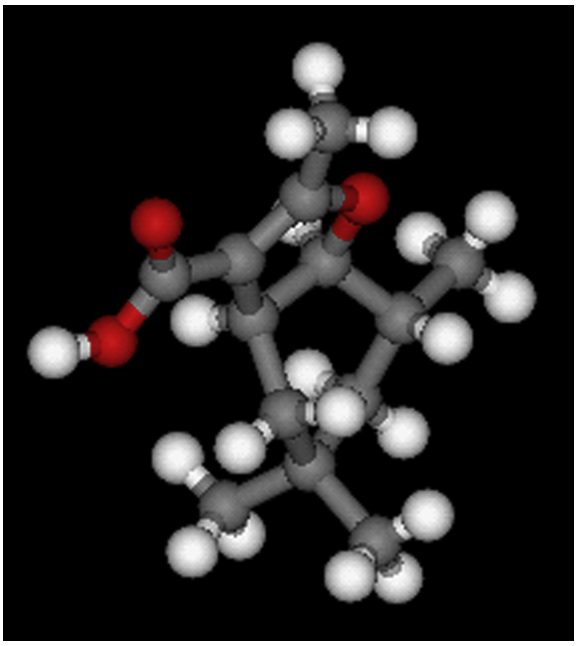


Figure 1. Perspective view of the crystal structure of **8**.

Having firmly established that the major product from the reaction of **1** with ethyl acetoacetate under the aforementioned basic conditions is **2**, the question was why this latter compound, or the dehydration products **5** and **6**, had not been isolated in the previous work using microwave irradiation. For clarification, we closely inspected the reported ^{1}H and ^{13}C NMR data for structure **X**. Our conclusion is that these data are not consistent with this structure and that the structural assignment is erroneous.[5]

3. Conclusion

We have demonstrated that treatment of epoxyisophorone (**1**) with ethyl acetoacetate under basic conditions principally leads to a furannulation reaction, with stereoselective formation of dihydroxybenzofuran **2**. This compound undergoes ready dehydration to a mixture of isomeric benzofurans **5** and **6**, which can be converted to benzofuran **7** after saponification and mono-hydrogenation. Further hydrogenation affords benzofuran **8**. These results are in contradiction to previous work, where similar conditions in the first step were reported to give a bicyclo [4.3.0] nonadienone structure via a putative *Robinson* annulation reaction.[6]

4. Experimental

4.1. General

All reactions were carried out in anhydrous solvents under an atmosphere of nitrogen except where noted, in oven-dried glassware. Workup refers to filtration and concentration in vacuo of the filtrate. TLC was performed on glass-backed plates coated with silica gel 60 with F_{254} indicator. Column chromatography was carried out on silica gel 60 (230–240 mesh). ^{1}H NMR (360 MHz) and ^{13}C NMR (90 MHz) were recorded in $CDCl_3$ as solvent and chemical shifts are expressed in parts per million downfield from tetramethylsilane (δ=0.00). ^{1}H NMR data are presented as follows: chemical shift, multiplicity (s=singlet, br s=broad singlet, d=doublet, dd=doublet of doublet, t=triplet, q=quadruplet, m=multiplet), *J* coupling constant in Hz (hertz), number of protons.

Compounds **3**[2] and **4**[3] have been previously described.

*4.1.1. 2,3-Epoxy-3,5,5-trimethylcyclohexan-1-one (epoxyisophorone) (**1**).* Compound **1** was prepared from 3,5,5-trimethyl-2-cyclohexen-1-one (isophorone) using the reported procedure.[1]

*4.1.2. Ethyl (3aRS,7RS,7aRS)-3a,7a-dihydroxy-2,5,5,7-tetramethyl-3a,4,5,6,7,7a-hexahydro-benzo[b]furan-3-carboxylate (**2**).* A mixture of **1** (8.9 g, 58 mmol), ethyl acetoacetate (11.7 g, 90 mmol), anhydrous K_2CO_3 (16 g, 116 mmol) and Aliquat®336 (1.33 g, 3.5 mmol) in toluene (50 ml) was heated at 100–110 °C during 32 h. The cooled dark-red mixture was filtered through a column of silica gel (20 g) (eluent: cyclohexane/EtOAc 60:40) and the filtrate was concentrated in vacuo to afford a semi-crystalline oil (21.3 g). Silica gel column chromatography (cyclohexane/EtOAc 70:30) and recrystallisation from pentane afforded **2** (7.9 g, 48% yield) as white crystals. Mp 118–120 °C. R_f=0.13 (cyclohexane/EtOAc 70:30). ^{1}H NMR: δ 4.15–4.33 (m, 3H); 2.18 (s, 3H); 2.12 (d, *J*=13.9 Hz, 1H); 2.03 (d, *J*=13.9 Hz, 1H); 1.44 (dd, *J*=14.7, 1.8 Hz, 1H); 1.31 (t, *J*=7.2 Hz, 3H); 1.30 (s, 3H); 1.14 (d, *J*=14.7 Hz, 1H); 1.10 (s, 3H); 0.82 (s, 3H). ^{13}C NMR: δ 169.1 (C); 165.6 (C); 109.1 (C); 92.3 (CH); 81.9 (C); 72.9 (C); 59.7 (CH_2); 43.1 (CH_2); 42.7 (CH_2); 34.1 (CH_3); 32.1 (CH_3); 29.1 (C); 27.7 (CH_3); 14.8 (CH_3); 14.5 (CH_3). HRMS calcd for $C_{15}H_{24}O_5$: 280.13107, found 280.12931. Also isolated from the chromatographic purification were *3,5,5-trimethyl-2-(2-oxopropyl)-2-cyclohexen-1-one* (**3**) (0.95 g, 8% yield) as a viscous colourless oil and *ethyl 2,4,4-trimethyl-6-oxo-1-cyclohexene*-1-*acetate* (**4**) (0.52 g, 4% yield) as a viscous colourless oil. For **3**: ^{1}H NMR: δ 3.45 (d, *J*=3 Hz, 2H); 2.30 (s, 2H); 2.28 (s, 2H); 2.17 (s, 3H); 1.88 (s, 3H); 1.04 (s, 6H). ^{13}C NMR: δ 205.9 (C); 198.2 (C); 156.4 (C); 128.6 (C); 61.4 (CH_2); 50.7 (CH_2); 46.9 (CH_2); 40.0 (CH_2); 32.8 (C); 28.2 (2×CH_3); 21.9 (CH_3);

14.1 (CH_3). MS *m*/*z* (%) 194 ([M^+], 37), 152 (60), 96 (100). HRMS calcd for $C_{12}H_{18}O_2$: 194.13068, found: 194.12994. For **4**: ^{1}H NMR: δ 1.05 (s, 6H); 1.23 (t, *J*=7 Hz, 3H); 1.92 (s, 3H); 2.29 (s, 2H); 2.30 (s, 2H); 3.37 (s, 2H); 4.11 (q, *J*=7 Hz, 2H). ^{13}C NMR: δ 198.0 (C); 171.4 (C); 155.9 (C); 128.3 (C); 60.6 (CH_2); 50.7 (CH_2); 46.9 (CH_2); 32.8 (C); 30.6 (CH_2); 28.1 (2×CH_3); 21.8 (CH_3); 14.2 (CH_3). MS *m*/*z* (%) 224 ([M^+], 15), 178 (100), 163 (15), 150 (28). HRMS calcd for $C_{13}H_2O_3$: 224.14124, found: 224.14078.

*4.1.3. Ethyl 2,5,5-trimethyl-7-methylene-4,5,6,7-tetrahydro-1-benzofuran-3-carboxylate (**5**) and ethyl 2,5,5,7-tetramethyl-4,5-dihydro-1-benzofuran-3-carboxylate (**6**) (2.5:1 mixture).* The aforementioned experiment was repeated to afford crude **2** as a semi-crystalline oil (21.1 g), which was taken up into cyclohexane (200 ml), TsOH·H_2O (150 mg) added, and the mixture heated under reflux during 2 h with continual removal of H_2O using a *Dean–Stark* apparatus. The cooled solution was then washed with 10% aqueous $NaHCO_3$ solution and then dried (Na_2 SO_4). Workup, silica gel column chromatography (cyclohexane/EtOAc 95:5), and bulb-to-bulb distillation in vacuo afforded a 2.5:1 mixture of **5** and **6** (5.92 g, 41% yield over two steps) as a pale-yellow oil. Bp 160–180 °C (oven temperature)/0.1 mm Hg. For **5**: ^{1}H NMR: δ 5.23 (br s, 1H); 4.75 (br s, 1H); 4.28 (q, *J*=7.1 Hz, 2H); 2.58 (s, 3H); 2.54 (br s, 2H); 2.20 (br s, 2H); 1.35 (t, *J*=7.1 Hz, 3H); 0.99 (s, 6H). ^{13}C NMR: δ 164.6 (C); 159.4 (C); 147.7 (C); 132.2 (C); 120.5 (C); 113.9 (C); 104.5 (CH_2); 59.9 (CH_2); 45.1 (CH_2); 36.8 (CH_2); 32.2 (C); 28.1 (2×CH_3); 14.4 (CH_3); 14.3 (CH_3). HRMS calcd for $C_{15}H_{20}O_3$: 248.1412, found: 248.1407. MS 248 (M^+, 100), 233 (8), 219 (41), 203 (20), 201(16), 187(15), 159(10), 43(7). For **6**: ^{1}H NMR: δ 5.12 (q, *J*=1.6 Hz, 1H); 4.28 (q, *J*=7.1 Hz, 2H); 2.69 (s, 2H); 2.57 (s, 3H); 1.91 (d, *J*=1.6 Hz, 2H); 1.35 (t, *J*=7.1 Hz, 3H); 1.06 (s, 3H). ^{13}C NMR: δ 164.9 (C); 157.5 (C); 149.6 (C); 133.0 (C); 122.5 (C); 115.8 (C); 113.7 (C); 59.8 (CH_2); 35.6 (CH_2); 33.6 (C); 29.0 (2×CH_3); 15.7 (CH_3); 14.4 (CH_3); 14.2 (CH_3). HRMS calcd for $C_{15}H_{20}O_3$: 248.1412, found: 248.1418. MS 248 (M^+, 64), 233 (98), 205 (35), 203 (29), 187 (100), 161 (36), 133 (24), 115 (11), 43 (10).

*4.1.4. 2,5,5,7-Tetramethyl-4,5,6,7-tetrahydro-1-benzofuran-3-carboxylic acid (**7**).* A solution of the foregoing 2.5:1 mixture of **5** and **6** (2 g, 9 mmol) in 40% ethanolic KOH solution (10 ml) was stirred at room temperature during 4 h. The reaction mixture was poured into cold H_2O (50 ml) and extracted with Et_2O. The aqueous phase was then acidified using 10% aqueous HCl solution. Extraction with EtOAc afforded an organic phase, which was successively washed with H_2O, 10% aqueous $NaHCO_3$ solution, and brine and then dried (Na_2SO_4). Workup gave a yellow solid (1.2 g), 0.93 g of which were taken up into MeOH (15 ml). 10% Pd–C (0.09 g) was then added and the mixture was hydrogenated at atmospheric pressure at room temperature during 48 h. Filtration through Celite, concentration in vacuo of the filtrate, silica gel column chromatography (cyclohexane/EtOAc 70:30), and recrystallisation from EtOH afforded **7** (0.8 g, 52% yield over two steps) as white crystals. Mp 125–127 °C. ^{1}H NMR: δ 2.73 (m, 1H); 2.57 (s, 3H); 2.52 (d, *J*=16.8 Hz, 1H); 2.36 (dd, *J*=16.8, 3.1 Hz, 1H); 1.60 (ddd, *J*=12.9, 5.6, 1.6 Hz, 1H); 1.24 (dd, *J*=12.9, 11.0 Hz, 1H); 1.21 (d, *J*=6.7 Hz, 3H); 1.06 (s, 3H); 0.90 (s, 3H). ^{13}C NMR: δ 171.1 (C); 160.0 (C); 152.2 (C); 116.6 (C); 112.5 (C); 46.0 (CH_2); 36.3 (CH_2); 31.4 (CH_3); 31.0 (C); 26.6 (CH); 25.2 (CH_3); 18.3 (CH_3); 14.4 (CH_3). HRMS calcd for $C_{13}H_{18}O_3$: 222.12559, found: 222.12532. Also detected in the crude product prior to chromatography was **8** (ca. 10% by GC analysis). For the isolation and spectral data of **8**, see below.

*4.1.5. (3aRS,7SR,7aRS)-2,5,5,7-Tetramethyl-3a,4,5,6,7,7a hexahydro-1-benzofuran-3-carboxylic acid (**8**).* Treatment of **5**/**6** (2.5:1) (5.6 g, 25 mmol) with 40% ethanolic KOH solution was effected using the experimental procedure described in Section 4.1.4, affording a yellow solid (3.4 g), which was taken up into MeOH (50 ml). 10% Pd–C (0.8 g) was then added and the mixture was hydrogenated at atmosphere pressure at room temperature during 84 h. Filtration through Celite and concentration in vacuo afforded a white solid, shown by GC analysis to be a 1.35:1 mixture of **8** and **7**. Silica gel column chromatography (cyclohexane/EtOAc 70:30) and recrystallisation from EtOH afforded **8** (1.1 g, 20% yield) as white crystals. Mp 143–145 °C. ^{1}H NMR: δ 4.18 (t, *J*=9.7 Hz, 1H); 3.12 (m, 1H); 2.21 (br s, 3H); 1.79 (m, 1H); 1.72 (dd, *J*=13.6, 4.6 Hz, 1H); 1.19–1.32 (m, 2H); 1.04 (d, *J*=6.4 Hz, 3H); 0.95 (s, 3H); 0.94 (s, 3H); 0.85 (t, *J*=13.8 Hz, 1H). ^{13}C NMR: δ 172.4 (C); 171.2 (C); 106.3 (C); 90.3 (CH); 42.9 (CH_2); 39.0 (CH); 38.5 (CH_2); 30.9 (CH_3); 30.4 (CH); 30.3 (CH_3); 28.8 (C); 19.5 (CH_3); 14.7 (CH_3). HRMS calcd for $C_{13}H_2O_3$: 224.14124, found: 224.14077.

References and notes

1. Rissafi, B.; Rachiqi, N.; El Louzi, A.; Loupy, A.; Petit, A.; Fkih-Tétouani, S. *Tetrahedron* **2001**, *57*, 2761.
2. Valenta, Z.; Liu, H. J. *Org. Synth.* **1977**, *57*, 113.
3. See Ref. 1. It is to be noted however that the reported attribution for the chemical shifts in the ^{13}C NMR spectrum is incorrect for C(α) and C(6); the chemical shifts (δ ppm) for these two carbon atoms are 30.6 and 50.7, respectively.
4. Crystallographic data for **8** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 734083. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (Fax. +44 (0) 1223 336033 or e-mail. deposit@ccdc.cam.ac.uk).
5. It is worth remarking that the published ^{1}H NMR data of structure **X** corresponds exactly with those for **5**. In contrast, the ^{13}C NMR data are only in partial correspondence. In addition, the reported MS data of **X** are consistent with those of **5**, as are the CH elemental analysis results, **X** and **5** being constitutional isomers of molecular formula $C_{15}H_{20}O_3$.
6. Following the advice of one of the referees, we attempted to repeat the published experimental procedure with the aid of microwave equipment. Accordingly, using an Initiator® Microwave Synthesizer commercialized by Biotage, we added **1** (1.23 g, 8 mmol) to a mixture of anhydrous K_2CO_3 (2.21 g, 16 mmol), Aliquat® 336 (160 mg, 0.4 mmol), ethyl acetoacetate (1.56 g, 12 mmol) and toluene (8 ml), prior to microwave irradiation (2.45 GHz) under magnetic stirring during 5 min at 85 °C. Workup and GC–MS analysis showed the resulting product to be a complex mixture containing unreacted **1** (69%), **2** (14%), **3** (4%), **4** (2%), **5** (3%), **6** (1%), together with unidentified trace components (7%). There was no evidence for the presence of **X**. This experiment was repeated without toluene with essentially the same result.