Syntheses of α-agarofuran and isodihydroagarofuran

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A new synthesis of α-agarofuran (**1**) has been realized in four steps from ketol **3** and a stereospecific synthesis of isodihydroagarofuran (dihydro-α-agarofuran) has been achieved in four steps.

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Bhattacharyya and co-workers (1) isolated dihydroagarofuran, α-, and β-agarofuran from agarwood oil. Their proposed stereo-structures with a 7-α-isopropyl configuration for the agarofurans has been corrected to a 7-β-isopropyl configuration. This correction was achieved by Barrett and Büchi (2) who showed that (−)epi-α-cyperone (**2**) can be used for the synthesis of α-agarofuran (**1**). Recently, a new synthesis of α-agarofuran (**1**) has been reported by Marshall and Pike (3) starting also with (−)epi-α-cyperone (**2**). Furthermore, a total synthesis of norketoagarofuran (4) has been communicated by Heathcock and Kelly (5).

These recent reports (3, 5) prompt us to disclose a very simple four-step synthesis of α-agarofuran (**1**) starting with ketol **3** (6), which is the precursor of (−)epi-α-cyperone (**2**). We wish also to describe a stereospecific synthesis of isodihydroagarofuran (**9**), an epimer of natural dihydroagarofuran (**11**). Thus, the complete stereo-structure of natural dihydroagarofuran is also clarified.

Oxymercuration of crystalline ketol **3** (7) gave a 75% yield of keto–diol **4**. This keto–diol **4** has been previously reported in 40% yield, using the same general procedure (3). By refluxing compound **4** with sodium methoxide in methanol for four days and then utilizing chromatography, an 81% yield of the crystalline enone–alcohol **5** was obtained.

Reduction of compound **5** with lithium aluminium tri-*t*-butoxy hydride in ether yielded quantitatively the crystalline diols mixture **6**. A similar diols mixture, presumably in a different ratio, has been prepared by Marshall and Pike (3) using a different method. According to the reduction of similar compounds with the same reducing agent (8), the major compound in the diols mixture **6** should possess the OH grouping in the α-quasi-equatorial orientation.

Treatment of the diols mixture **6** in benzene with a small amount of *p*-toluenesulfonic acid at room temperature for 1 h gave quantitatively α-agarofuran (**1**, 80% yield) and the new crystalline diene–alcohol **7** (20% yield) which were easily separated by chromatography.[2] The identity of compound **1** was established by comparison of its infrared and nuclear magnetic resonance spectra with the published spectra of α-agarofuran (**1**). The structure of the diene–alcohol **7** was assigned on the basis of its spectral properties.

Since the diene–alcohol **7** is a minor product, this work constitutes the shortest and the most efficient synthesis of α-agarofuran (**1**).

Treatment of the enone–alcohol **5** with benzene and *p*-toluenesulfonic acid at room temperature for 24 h and chromatography, gave the starting material **5** in 70% yield and the new crystalline keto–oxide **8** in 30% yield. This keto–oxide **8** was also isolated in a low yield (6%) during the basic dehydration of keto–diol **4** leading to the enone–alcohol **5**. Thus, the secondary methyl group in compound **8** is clearly equatorial.

Reduction of keto–oxide **8** with the tosylhydrazide – sodium borohydride method (9) gave the crystalline isodihydroagarofuran **9** as the only isolable product. Thus, this work constitutes a four-step stereospecific synthesis of isodihydroagarofuran **9**.

Natural dihydroagarofuran, although being an oil, has been claimed to be isolated in the pure form and its published spectra (1) are different

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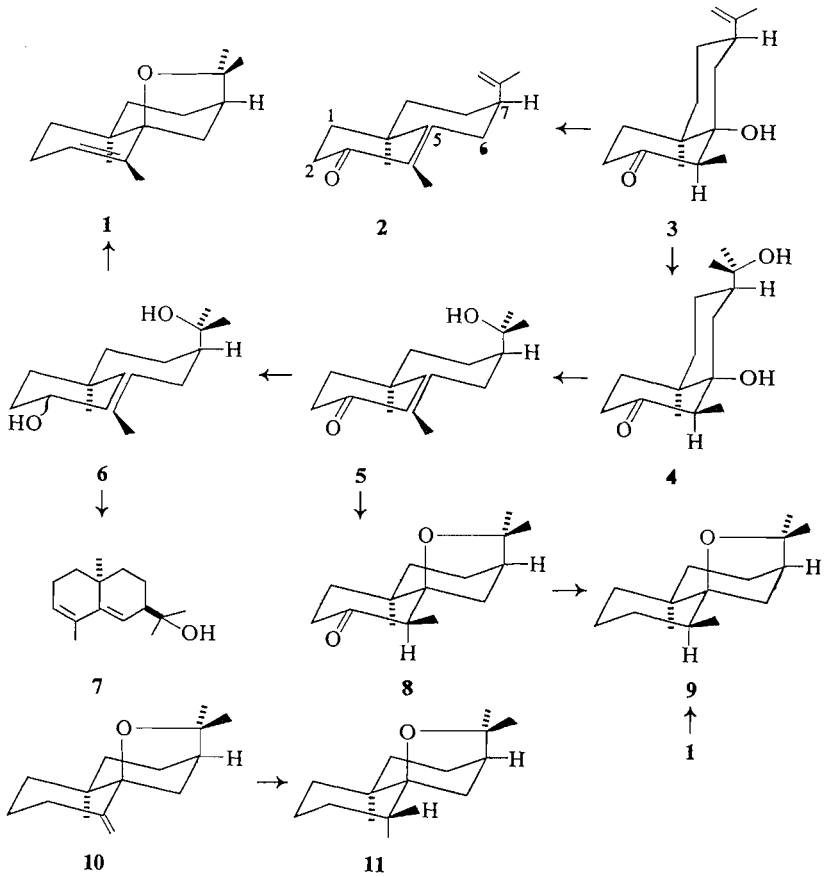
[2]Work is now directed toward the purification of both epimeric alcohols from the diols mixture (**6**). This is done in an effort to find out if there is a stereospecific conversion of the major epimeric alcohol (α-quasi-equatorial isomer) to α-agarofuran (**1**) and the other into diene–alcohol **7**.



than those of compound **9**. It has also been reported (1) that catalytic reduction of β-agarofuran (**10**) gave a compound identical to natural dihydroagarofuran while catalytic reduction of α-agarofuran yielded a different oily dihydro derivative.

We have repeated the catalytic reduction with synthetic α-agarofuran (**1**) and have obtained a crystalline dihydro compound which was found to be identical to compound **9**, obtained from keto–oxide **8**.

Thus, it is clear that natural dihydroagarofuran (dihydro-β-agarofuran) possesses structure **11** with the secondary methyl group in the α-axial configuration while dihydro-α-agarofuran (iso-dihydroagarofuran) has structure **9** with the methyl group in the β-equatorial orientation.

Experimental

Melting points are not corrected. Ultraviolet (u.v.) spectra (λ_{max}) were measured on a Cary model 14 spectrophotometer and infrared (i.r.) spectra (ν_{max}) were recorded on Perkin–Elmer Infracord, model 137 spectrophotometer. Nuclear magnetic resonance spectra (n.m.r., τ values) were taken on a Varian A60 spectrometer with tetramethylsilane as an internal standard. Thin-layer chromatograms (t.l.c.) were developed with iodine. Anhydrous magnesium sulfate was used as the drying agent in working up reactions. Fisher Florisil 100–200 mesh was used for preparing all column chromatograms.

The ketol **3** was prepared according to the method of Howe and McQuillin (6) using (+)-dihydrocarvone.

Keto–Diol (4)

Ketol **3** (11.8 g, 0.05 mole) was added to a well-stirred suspension of tetrahydrofuran (100 ml), water (100 ml), and mercuric acetate (32 g, 0.1 mole) cooled with an ice-bath. After 5 min, aqueous sodium hydroxide (3 *M*, 100 ml) was added, followed by a solution of sodium borohydride (0.5 *M*, 82 ml) in aqueous sodium hydroxide (3 *M*). Acetone (15 ml) was added and the mixture was filtered through Celite. After saturation with sodium chloride, the reaction mixture was thoroughly extracted with ethyl acetate. Evaporation of the dried extract yielded a white crystalline solid (11 g) which was crystallized with ethyl acetate (9.3 g, m.p. 190–193 °C). Further recrystallization

gave an analytically pure sample, m.p. 195–197 °C (lit. m.p. 195–196 °C (3)). Infrared: ν_{max} ($CHCl_3$) 3600, 3400, and 1700 cm^{-1}; n.m.r.: τ (acetone-d_6) 8.77 (3H, singlet), 8.92 (6H, singlet), and 9.03 (3H, doublet, J = 6.5 c.p.s.).

Enone–Alcohol (5)

Keto-diol **4** (5.0 g, 19.7 mmole) was dissolved in methanol (60 ml) containing sodium methoxide (2.5 g). The mixture was refluxed for 4 days. Water (500 ml) was added and the mixture was extracted with ether. The dried organic phase was evaporated to dryness. The resulting product (4.7 g) was purified by column chromatography. The fractions were analyzed by t.l.c. (silica gel, ether–benzene (1:1)).

Elution with petroleum ether (b.p. 30–60 °C) gave a trace of material. Elution with benzene gave a mixture of compounds **5** and **8** (700 mg, R_f value: 0.7 and 0.9). Elution with ether–benzene (5%) gave pure enone–alcohol **5** (3.4 g). The mixture (700 mg) was again submitted to column chromatography yielding keto–oxide **8** (303 mg) and enone–alcohol **5** (340 mg).

Enone–alcohol **5** was recrystallized with ether–pentane to give the analytical sample, m.p. 56–56.5 °C. Infrared: ν_{max} ($CHCl_3$) 3500, 3400, 1650, and 1620 cm^{-1}; u.v.: λ_{max} (EtOH) 254 m (ε 14 800); n.m.r.: τ ($CDCl_3$) 8.18 (3H, singlet), 8.78 (6H, singlet), and 8.81 (3H, singlet).

Anal. Calcd. for $C_{15}H_{24}O_2$: C, 76.23; H, 10.23. Found: C, 76.58; H, 10.46.

Keto–oxide **8** was recrystallized with ether–pentane to give the analytical sample, m.p. 124 °C. Infrared: ν_{max} ($CHCl_3$) 1715 cm^{-1}; n.m.r.: τ ($CDCl_3$) 7.39 (1H, quadruplet, J = 6.5 c.p.s.), 8.70 (3H, singlet), 8.75 (3H, singlet), 8.85 (3H, singlet), and 8.90 (3H, doublet, J = 6.5 c.p.s.).

Anal. Calcd. for $C_{15}H_{24}O_2$: C, 76.23; H, 10.23. Found: C, 76.02; H, 10.02.

Diols Mixture (6)

An ethereal solution (10 ml) of enone–alcohol **5** (90 mg, 0.38 mmole) was slowly added to lithium aluminium tri-*t*-butoxy hydride (460 mg, 4 mmole) in ether (20 ml) at 0 °C. After stirring at room temperature for 4 h, the excess hydride was destroyed by the addition of brine and the organic phase was separated. Evaporation of the dried organic solution yielded a crystalline mixture (90 mg), m.p. 70–103 °C. Infrared: ν_{max} ($CHCl_3$) 3700 and 3500 cm^{-1}, no carbonyl absorption.

Agarofuran (1) and Diene–Alcohol (7)

The diols mixture **6** (25 mg, 0.105 mmole) was dissolved in benzene (10 ml) and treated with *p*-toluenesulfonic acid (6 mg) at room temperature for 1 h. Brine was added and the mixture extracted with ether. The dried organic phase was evaporated to dryness yielding a mixture of two compounds. This mixture was separated by column chromatography using pentane and ether–pentane mixtures. The fractions were analyzed by t.l.c. (alumina, ether–pentane (10%)). The first material obtained (21 mg, 80% yield, R_f value: 0.8) had i.r. and n.m.r. spectra identical with the published spectra (1) of α-agarofuran derived from agarwood oil.

The second fraction (5 mg, 20% yield, R_f value: 0.2) was crystalline and structure **7** was assigned on the basis of its spectral properties. This compound was recrystallized from ether–pentane but was not sent for microanalysis because of its slow decomposition at room temperature, m.p. 67.5–68 °C. Infrared: ν_{max} ($CHCl_3$) 3600, 3400 cm^{-1}; u.v.: λ_{max} (EtOH) 233, 241, and 248 mμ (ε 18 000, 20 000, and 12 800); n.m.r.: τ($CDCl_3$) 4.40(2H, multiplet), 8.12 (3H, ~quadruplet, J = 1 c.p.s.), 8.79 (6H, singlet), and 9.05 (3H, singlet).

Keto–Oxide (8)

Enone–alcohol **5** (75 mg, 0.31 mmole) was dissolved in benzene (20 ml) containing *p*-toluenesulfonic acid (32 mg). After 24 h at room temperature, the reaction mixture was mixed with brine and extracted with ether. The dried organic phase was evaporated to dryness yielding a mixture of compound **5** and keto–oxide **8** which were separated by column chromatography using ether–hexane as eluent. The fractions were analyzed by t.l.c. (alumina, ether–hexane (1:1)).

The first compound was obtained crystalline (19 mg, R_f value: 0.3) and was identical with keto–oxide **8** obtained during the basic dehydration of keto–diol **4**.

The second product (51 mg, R_f value: 0.7) was identified as the starting enone–alcohol **5**.

Isodihydroagarofuran (9)

(a) From Keto–Oxide (8)

Keto–oxide **8** (80 mg, 0.34 mmole) was dissolved in methanol (5 ml) containing *p*-toluenesulfonyl hydrazine (100 mg, 0.56 mmole), and the mixture was refluxed for 30 min. The mixture was cooled at room temperature, sodium borohydride (100 mg, 2.6 mmole) was added, and the mixture was refluxed for 1 h. Brine was added and the mixture was extracted with ether. The dried organic phase was evaporated to dryness and the product obtained was purified by column chromatography. Elution with pentane gave crystalline isodihydroagarofuran **9** (20 mg). A t.l.c. analysis was performed (alumina, pentane, R_f value: 0.6). The analytical sample was prepared by sublimation, m.p. 35.5 °C. Nuclear magnetic resonance: τ ($CDCl_3$) 8.61 (3H, singlet), 8.82 (3H, singlet), 9.00 (3H, singlet), and 9.11 (3H, doublet, J = 6 c.p.s.).

Anal. Calcd. for $C_{15}H_{26}O$: C, 81.02; H, 11.79. Found: C, 81.02; H, 11.96.

(b) From α-Agarofuran (1)

α-Agarofuran **1** (200 mg, 0.91 mmole) was hydrogenated in acetic acid (5 ml) with prereduced platinum oxide (10 mg) for 1.5 h. The catalyst was removed by filtration and the filtrate evaporated to dryness. The resulting product was purified by column chromatography. Elution with pentane yielded a crystalline material (110 mg) which had physical and spectral properties identical with those of isodihydroagarofuran **9** (obtained from procedure *a*).

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