

A SYNTHESIS OF JAPANESE HOP ETHER *

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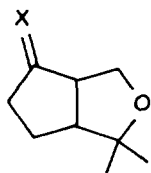
(Received December 1st, 1986)

Summary

Reaction of 2,5-dihydro-2,2-dimethylfuran with ethynehexacarbonyldicobalt lacks significant regioselectivity, but nevertheless makes possible the synthesis of (\pm)-hop ether (*cis*-hexahydro-1,1-dimethyl-4-methylene-1*H*-cyclopenta[*c*]furan) in five steps from *cis*-4-methylpent-2-ene-1,4-diol.

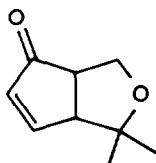
Introduction

The iridoid terpene ether **1** was first characterised in 1967 [1] and is regarded as a hop constituent which markedly affects the aroma [2] and taste [3] of beer. The published syntheses [4,5] employ methylenation of the intermediate **2** as the final step(s). We describe here an alternative approach to this ketone (**2**) and hence a formal total synthesis of both the racemic and optically active forms of the ether **1**.



(**1**, X = CH₂ ;

2, X = O)



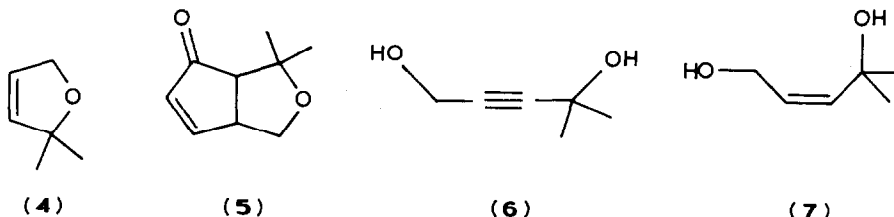
(**3**)

* Dedicated to Professor J. Tirouflet on the occasion of his retirement and in recognition of his stimulating contributions.

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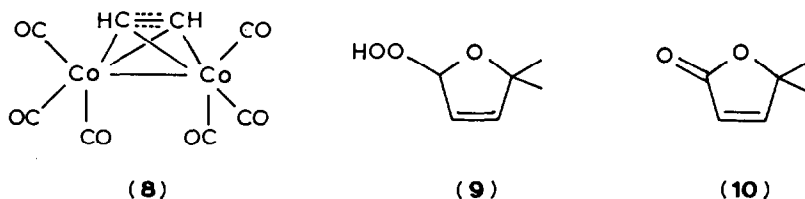
Results and discussion

Our route involves the construction of the ketone **2** via the enone **3** itself formed in a single step from 2,5-dihydro-2,2-dimethylfuran (**4**) by the Khand reaction. Unfortunately this reaction proves to be less regioselective in this case than for other related examples recently examined by us [6,7]; the required compound **3** is formed along with its regioisomer **5** in a 3/2 ratio [8]. This ratio was not significantly solvent-dependent in contrast to the Khand reaction of allyl 2-tetrahydropyranyl ether [6].



We were able to obtain the required alkene **4** in excellent yield by catalytic reduction of the readily available alkyne-diol [9] (**6**). Our procedure is similar to but not identical with that previously described [10]. Cyclodehydration of the diol **7** proved unexpectedly difficult. Our best yield, 58%, was obtained by use of toluene-*p*-sulphonyl chloride and quinoline. Acidic dehydrating agents appeared to cause extensive polymerisation of the dihydrofuran.

Reaction of the resultant dihydrofuran **4** with an equimolar amount of ethyne-hexacarbonyldicobalt (**8**) was studied in four solvents and over the temperature range 60–130 °C. The best combined yield (22%) of the bicyclic ketones **3** and **5** was obtained by use of benzene at 60 °C, while the ratio of these ketones varied only between 56/44 and 62/38. The yield based on complex **8** was increased to 53% when a large excess of alkene **4** and a 1:1 carbon monoxide-acetylene atmosphere were used, despite the fact that adventitious presence of a small amount of oxygen in the system resulted in the simultaneous production of the lactone **10**, apparently by the rapid autoxidation of the alkene followed by (Co catalysed) decomposition of the hydroperoxide **9**.



In view of the limitation to the efficiency of our route imposed by the formation of substantial quantities of the bicyclic ketone **5** and the relative difficulty of separating this from the required isomer **3**, no further attempts were made to improve the yield of the Khand reaction (e.g. with additives). A small scale separation of the ketones **3** and **5** was readily effected by preparative GLC, and a sample of the former ketone so obtained was quantitatively hydrogenated (Pd/C) to the saturated precursor **2**. We completed our five-step synthesis of (±)-hop ether from the diol **6** by repeating one of the known [4] methylenation procedures.

Experimental

(*Z*)-4-Methylpent-2-en-1,4-diol (7)

Following Montijn et al. [9], reaction of propargyl alcohol (100 g, 1.78 mol) with 2,3-dihydropyran (180 g, 2.14 mol) and toluene-*p*-sulphonic acid (30 mg) below 60 °C yielded tetrahydro-2-(2-propynyloxy)-2*H*-pyran (242 g, 97%) as a colourless liquid, b.p. 66–70 °C/15 torr (lit. [9,11] b.p. 71–74 °C/12 torr; 78 °C/25 torr) having IR and NMR spectra in agreement with lit. [12] data. This was converted [9], by treatment with ethylmagnesium bromide, followed by dry acetone, to 2-methyl-5-[(tetrahydro-2*H*-pyran-2-yl)-oxy]-3-pentyn-2-ol, b.p. 115–118 °C/0.15 torr (lit. [9] b.p. 105–108 °C/0.01 torr), also having spectra in agreement with lit. [13] data. Methanolysis [9] afforded the free diol, 4-methyl-2-pentyn-1,4-diol (**6**) (97%), b.p. 76–80 °C/0.01 torr (lit. [9] b.p. 91–93 °C/0.08 torr), ν_{\max} (film) 3350, 2985, 2940, 2870, 1450, 1380, 1360, 1235, 1165, 1060, 1002, 947, 853 cm⁻¹, δ (CDCl₃) 1.54 (s, 6H, CH₃), 4.00 (br.s., 2H, OH), 4.30 ppm (br.s., 2H, CH₂).

This diol (93.5 g, 820 mmol) in ethanol (95 ml) was added to poisoned P-2 nickel catalyst prepared [14] from 25.5 g (102.5 mmol) nickel(II) acetate tetrahydrate in ethanol (250 ml). The mixture was stirred under hydrogen until uptake ceased (~ 5 d), then filtered. The residue was washed with ethanol and the combined filtrates were diluted with water (300 ml) and extracted with ether (2 × 125 ml). The aqueous layer was then saturated with sodium chloride and extracted exhaustively (TLC) with ether (total 5 l). The combined extracts were dried (MgSO₄) and evaporated under reduced pressure to leave the product **7** (78.7 g, 83%), b.p. 77–80 °C/0.13 torr (lit. [10] b.p. 119–120 °C/14 torr); ν_{\max} (film) (cf. [15]) 3320, 3020, 2980, 2935, 2880, 1650, 1460, 1375, 1360, 1270, 1202, 1165, 1150, 1020, 958, 922, 890, 761, 710 cm⁻¹; δ (CDCl₃; 250 MHz) 1.36 (s, 6H, CH₃), 4.30 (d, 2H, *J* 4.2 Hz; CH₂), 4.73 (br.s., 2H, OH; disappears in contact with D₂O), 5.54 ppm (m, 2H, -CH=).

2,5-Dihydro-2,2-dimethylfuran (4)

In a 250 ml flask were placed toluene-*p*-sulphonyl chloride (40.85 g, 210 mmol) and dry quinoline (136 g, 1.05 mol, freshly distilled from KOH). After dissolution (stirring) the diol **7** (24.4 g, 210 mmol) was added over 30 min. After stirring for a further 1 h, the product **4** (12.0 g, 58%) was distilled out at 75–85 °C (Lit. [16] b.p. 82 °C). After drying over calcium chloride and filtration this was pure enough for further work; ν_{\max} (film) (cf. [17]): 3075, 2972, 2915, 2860, 2845, 2665, 1633, 1458, 1373, 1357, 1343, 1332, 1232, 1193, 1172, 1085, 1040, 937, 865, 808, 761, 716 cm⁻¹; δ (CDCl₃) (cf. [16]) 1.30 (s, 6H, CH₃), 4.63 (s, 2H, CH₂), 5.75 ppm (s, 2H, -CH=); ¹³C NMR: δ (C₆D₆) 27.72 (q, CH₃), 74.14 (t, C(5)), 87.73 (s, C(2)), 125.04 (d, C(3)), 135.78 ppm (d, C(4)).

Reaction of 2,5-dihydro-2,2-dimethylfuran (4) with ethynehexacarbonyldicobalt (8)

The alkene **4** (980 mg, 10 mmol) and the complex **8** (3.12 g, 10 mmol) were heated in benzene (50 ml) at 60 °C (bath temp.) under nitrogen until no more of the initial complex could be detected by TLC (4 d). After cooling, the mixture was filtered through Kieselguhr, the residue washed with chloroform and the combined filtrates evaporated in vacuo. The residue was chromatographed on alumina eluting with chloroform and the ketonic fraction further purified by 'flash' silica chromatography using ether as solvent and/or distillation at 95–100 °C/100 torr, using

a Kugelrohr apparatus. The isomeric ketones (combined yield 328 mg, 22%) were separated on a 10'' 'flash'-silica column or by GLC using a 20% FFAP on diatomite S-AW column (2 m; 6 mm i.d.) at 140 °C (injection temp. 170 °C). Analytical separations were effected on a 5% FFAP column at 100–120 °C or on 5% carbowax at 125 °C (retention times: 5 8.8 min; 3 10.8 min].

The more mobile isomer on flash silica, but less mobile on GLC (retention time 140–175 min) was identified as *cis*-1,3,3*a*,6*a*-tetrahydro-1,1-dimethyl-4*H*-cyclopenta[*c*]furan-4-one (**3**) by its ¹H NMR spectrum: δ (CDCl₃; 250 MHz) 1.296 (s, 3H, CH₃), 1.301 (s, 3H, CH₃), 2.97 (m, 1H, H(3*a*)), 3.23 (m, 1H, H(6*a*)), 3.99 (m, 2H, H(3)), 6.21 (dd, 1H, *J*_{5,6*a*} 1.83 Hz, H(5)), 7.61 ppm (dd, 1H, *J*_{6,6*a*} 2.74, *J*_{5,6} 5.67 Hz, H(6)) assignments being confirmed by decoupling using irradiation at 2.97, 3.23, 6.21 and 7.61 ppm. IR: ν_{max} (CHCl₃) 2970, 2930, 2880, 1700, 1591, 1465, 1385, 1370, 1355, 1300, 1270, 1173, 1142, 1093, 1049, 1028, 988, 973, 949, 873, 837 cm⁻¹. Found: C, 70.05; H, 8.1. C₉H₁₂O₂ calc: C, 71.0; H, 7.95%.

The second isomer (retention time 105–138 min) showed spectral characteristics in harmony with its formulation as *cis*-1,3,3*a*,6*a*-tetrahydro-3,3-dimethyl-4*H*-cyclopenta[*c*]furan-4-one (**5**): ¹H NMR: δ (CDCl₃, 250 MHz) 1.298 (s, 3H, CH₃), 1.311 (s, 3H, CH₃), 2.58 (d, 1H, *J*_{3*a*,6*a*} 6.03 Hz, H(3*a*)), 3.61 (m, 1H, H(6*a*)), 3.84 (dd, 1H, *J*_{1*α*,6*a*} 2.01, *J*_{1*α*,1*β*} 9.50 Hz), 3.98 (dd, 1H, *J*_{1*β*,6*a*} 7.04 Hz, H(1*β*)), 6.16 (dd, 1H, *J*_{5,6*a*} 1.83, H(5)), 7.57 ppm (dd, 1H, *J*_{6,6*a*} 2.65, *J*_{5,6} 5.67 Hz, H(6)) (The H(1) *trans* to H(6) being labelled α). Decoupling experiments used irradiation at 2.58, 3.61, 3.84, 3.98, 6.16 and 7.57 ppm. IR: ν_{max} (CHCl₃) 2.970, 2.940, 2.870, 1700, 1592, 1460, 1388, 1370, 1359, 1337, 1304, 1265, 1171, 1135, 1091, 1079, 1050, 970, 960, 902, 887, 854 cm⁻¹. Found: C, 71.05; H, 7.9. C₉H₁₂O₂ calc: C, 71.0; H, 7.95%.

The ratio of ketones **3/5** under the above conditions was 60/40. Lower yields but very similar ratios resulted at higher temperature using benzene, toluene, isooctane or 1,2-dimethoxyethane as solvents. A higher yield based on complex **8** was obtained under the following conditions: The alkene **4** (1.96 g, 20 mmol) and the complex **8** (312 mg, 1 mmol) in benzene (50 ml) were stirred under acetylene/carbon monoxide (1/1) at 65 °C for 6 d. The product was worked up as above to yield the mixed ketones **3** and **5** (80 mg; 53%; ratio 62/38). The more mobile by-product (~ 40 mg) was identified as the lactone **10** [18]; δ(CDCl₃) 1.47 (s, 6H, CH₃), 5.95 (d, 1H, H(3)), 7.42 ppm (d, 1H, H(4)); ν_{max} (CDCl₃) 2960, 2930, 2865, 1750, 1605, 1460, 1365, 1270, 1130, 960, 945 cm⁻¹.

cis-Hexahydro-1,1-dimethyl-4*H*-cyclopenta[*c*]furan-4-one (**2**)

The unsaturated ketone **3** (152 mg) in ethanol (5 ml) was stirred with 10% palladium on charcoal (10 mg) under hydrogen until the gas uptake ceased. The filtered (Kieselguhr) solution was evaporated under reduced pressure, the residue taken up in chloroform, dried (MgSO₄) and the filtered solution again evaporated in vacuo to leave the product **2** (154 mg, 100%). TLC (*R*_f in ether: 0.40) and GLC (5% carbowax; retention time 7.6 min at 125 °C) showed homogeneity. The product [1] had ν_{max} (CHCl₃) 2968, 2880, 1730, 1453, 1405, 1382, 1368, 1260, 1160, 1145, 1102, 1040, 1000, 970, 933, 907, 830 cm⁻¹; δ (CDCl₃; 250 MHz), 1.21 (s, 3H, CH₃), 1.30 (s, 3H, CH₃), 1.80 (m, 1H, H(6*β*)), 2.01 (m, 1H, H(6*α*)), 2.33 (m, 2H, H(5)), 2.66 (br. q; 1H, *J*_{6,6*a*} ≈ 8.0 Hz, H(6*a*)), 2.99 (td, 1H, *J*_{3*a*,6*a*} 9.1, *J*_{3*β*,3*a*} 9.1, *J*_{3*α*,3*a*} ≈ 4.3 Hz, H(3*a*)), 3.91 (dd, 1H, *J*_{3*α*,3*β*} 9.5 Hz, H(3*α*)), 4.01 ppm (t, 1H, H(3*β*)). ¹³C NMR: δ (CDCl₃) 22.71 (q, CH₃), 23.20 (t, C(6)), 26.85 (q, CH₃), 39.48 (t, C(5)), 50.52 (d,

C(6a)), 52.80 (d, C(3a)), 67.47 (t, C(3)), 83.36 (s, C(1)), 219.53 ppm (s, C(4)), all in good agreement with literature data [1,4]. The above ^1H NMR assignments were based on decoupling experiments using irradiation at 1.80, 2.01, 2.33, 2.66, 2.99, 3.91 and 4.01 ppm.

The identity of this compound is further confirmed by methylenation of a sample (154 mg) using the reagent prepared from zinc (196 mg), dibromomethane (261 mg) and titanium tetrachloride (1.1 ml of a 1 M solution in CH_2Cl_2) in tetrahydrofuran (5 ml). Although this single attempt gave a poor yield (19 mg, 12.5%) of product, this was readily separated on a 'flash' silica column from unreacted ketone **2** (16 mg, 10%) and showed spectral characteristics in good agreement with the published values [1] for (\pm) hop ether (**1**); ν_{max} (CHCl_3) 2957, 2925, 2855, 1600, 1458, 1380, 1367, 1269, 1090, 1010, 911, 887 cm^{-1} ; δ (CDCl_3 ; 250 MHz) 1.24 (s, 3H, CH_3), 1.255 (s, 3H, CH_3), 1.67 (m, 2H, H(6)), 2.34 (m, 3H, H(5) and H(6a)), 3.26 (m, 1H, H(3a)), 3.65 (dd, 1H, $J_{3a,3\alpha}$ 4.75, $J_{3\alpha,3\beta}$ 8.77 Hz, H(3 α)), 4.07 (t, 1H, $J_{3a,3\beta} \approx 8.77$ Hz; H(3 β)), 4.76 and 4.82 ppm (ea. br.s, ea. 1H, $=\text{CH}_2$).

Acknowledgements

We thank Dr. P. Bladon and his staff for spectroscopic measurements. W.J.K. thanks the SERC for a research studentship.

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