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ON THE STRUCTURE OF A NOVEL ETHER FROM *ARTEMISIA TRIDENTATA*

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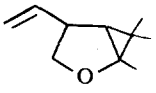
Key Word Index—*Artemisia tridentata*; Compositae; irregular monoterpene; cyclic ether; structure; synthesis.

Abstract—1,6,6-Trimethyl-4-ethenyl-2-oxabicyclo-[3.1.0]hexane was unambiguously synthesized in seven steps from 4,5-dihydro-2-methylfuran. The product possessed IR, ^{1}H NMR and MS which differed from those of a compound isolated from *Artemisia tridentata*. This compound has been assigned the above structure on the basis of spectral evidence: consequently the proposed structure is erroneous.

A monoterpene ether from *Artemisia tridentata* (sagebrush) grown in the U.S.A. was initially assigned the structure **1** [2], but this was not fully consistent with the observed 1H NMR spectrum and detailed analysis of this spectrum and of the MS led to the proposal [2] that the so-called sagebrush ether was 1,6,6-trimethyl-4-ethenyl-exo-2-oxabicyclo-[3.1.0]hexane (**2**). However, **2** is not a known monoterpenoid skeleton and it is also irregular (i.e. not obeying the biogenetic isoprene rule). In addition, the biogenetic pathway to the skeleton is not obvious: hence the validity of the newer assignment is of considerable interest.

Examination of the GC–MS patterns of oils from a large number of *Artemisia* species grown in England [3] did not reveal the occurrence of such a compound as a source for further structural analysis and so we set out to synthesize **2**. After the work was under way, a further study by ^{13}C NMR spectroscopy led to the proposal of the alternative structure **3** for the ether [4]. This structure is also irregular but now biogenetic routes are easy to visualize.

1



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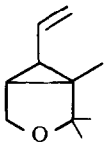

3

RESULTS AND DISCUSSION

Compound **2** was synthesized in seven steps from 4,5-dihydro-2-methylfuran (**4**) which is commercially available (Fig. 1). Each step was unambiguous and the expected products were confirmed by ^{1}H NMR, IR and mass spectra. Yields of the steps ranged between 28 and 80%, and the overall yield was 0.3%. Of particular interest are the selective reduction of a conjugated bond (**7**→**8**) and the need to conduct the elimination (**9**→**2a**) under basic conditions in order to avoid scission of the cyclopropane ring. GLC analysis of the final product showed a mixture of two partially resolvable compounds (65:35) but these could not be separated on a preparative scale. These must be the *endo* and *exo*-isomers of **2a** which are epimeric at C-4.

Compound **2a** has a ^{1}H NMR spectrum in total agreement with the structure expected (letters refer to hydrogens in **2a**): δ 0.5 (1H, *d* J = 6 Hz, g), 0.6 (6H, *s*, f), 0.8 (3H, *s*, e), 1.65 (1H, *m*, c), 3.45 (2H, *dd*, d), 4.8 (2H, *m*, b), 6.0 (1H, *m*, a). This spectrum differs very significantly from that reported [2] for the natural product: viz. δ 1.15 (1H, *d*), 1.20 (9H, *s*), 1.52 (1H, *q*), 3.66 (2H, *q*), 5.0 (1H, *m*), 5.53 (1H, *quintet*). With hindsight the latter assignment can be seen to rely on a reasonable, but nevertheless, special assumption that all three methyls resonante (as singlets) at the same frequency despite the long-range influence of the oxygen on one if structure **2a** were valid.

The IR spectrum of our synthetic product had medium and strong bands at ν(cm^{-1}) 3010, 1660, 1455, 1300, 1025, 865, 725 and this differed completely from that of the natural product: ν(cm^{-1}) 3075, 3020, 1635, 985, 940. Also, the MS for the synthetic product [*m/e*: 152 (M^+, 20%); 137 (15); 109 (25); 97 (10); 65 (35); 55 (55); 43 (100)] differed significantly from that reported [2] for the naturally-occurring compound [*m/e*: 152 (M^+, 22%) 137 (18); 109(8); 95 (60); 79 (58); 67 (51); 43 (100)].

In summary, our work rules out structure **2** for the naturally-occurring ether, and strengthens the claim [4] that the latter is indeed **3**.

EXPERIMENTAL

All intermediates had satisfactory ^{1}H NMR (60 MHz), MS, IR and UV spectra and elemental analysis. Analytical GLC was on columns (6 mm × 2 m) of Carbowax 20M (15%) on Diatomite C-NAW (60–80 mesh).

4,5-Dihydro-2-methylfuran (**4**; 25 g ex Aldrich Chem. Co.) in dioxan (100 ml) and H_2O (10 ml) was oxidized with freshly-prepared SeO_2 (33.1 g) at reflux (8 hr) [5, 6]. After work-up, distillation yielded a mixture of **5** and **6** (80:20 deduced from ^{1}H NMR; 9 g) at 80–7°/769 mm. This mixture was coupled to carbomethoxymethylenetriphenylphosphorane in a Wittig reaction at 20° for 4 days [cf. 7] following which chromatography on Al_2O_3 with petrol (bp 40–60°) yielded on oil **7** (4.3 g). **7** (2.9 g) in EtOH (50 ml) was refluxed (5 hr) with freshly-pre-

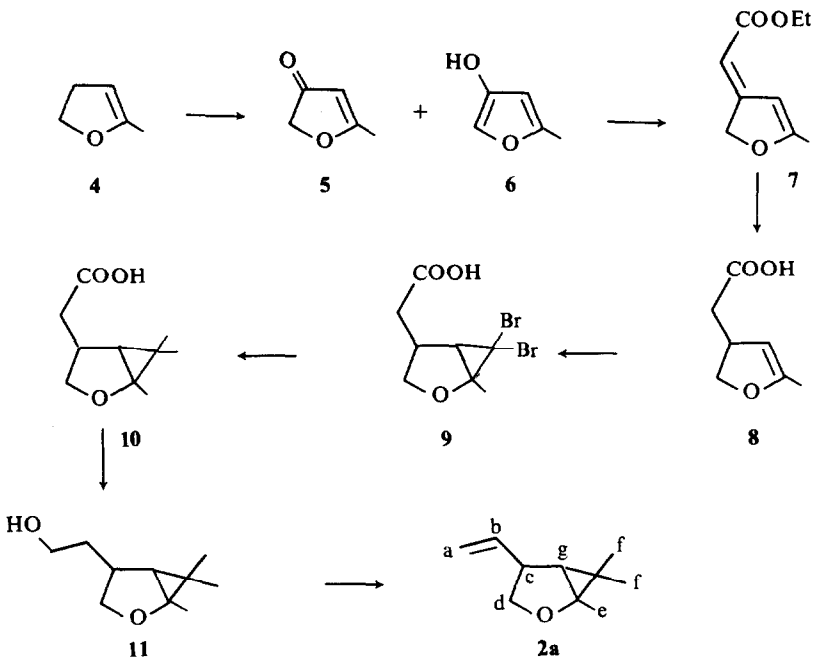

Fig. 1. Synthesis of compound **2a** (see Experimental for details).

pared Raney nickel (1.5 g) [8]. After removal of the catalyst, KOH (3 g) in H_2O (50 ml) was added and the mixture was further refluxed under N_2 (3 hr). On work-up and distillation an oil (0.8 g; **8**) resulted. This was converted into its Na salt and dibromocarbene added [9, 10] using cetyltrimethylammonium chloride (0.2 g) as a phase-transfer catalyst. After reaction, the acid was regenerated by addition of NH_4Cl, and an oil (**9**; 0.8 g) was recovered by careful distillation. **9** was converted into **10** (0.22 g) by treatment with a 10-fold excess of dimethylcopper/lithium in Et_2O [11, 12] (0° for 2 hr; then 20° for 12 hr), and the product was reduced to **11** with B_2H_6 [13] prepared by a standard procedure [14], and the product (0.15 g) recovered by distillation at *ca* 15 mm. **11** (0.15 mg) was treated with $POCl_3$ in Py [14] (0° for 1 hr, followed by 20° for 24 hr) and distilled (49–51°/3–6 mm) to yield a product (0.06 g) that on analytical GLC contained a mixture (>99%) of two compounds 65:35, RR_t's 4.00 and 4.05: Et_2O = 1.00). Assay on a variety of TLC systems showed that <1.0% of other compounds were present. The product (4-*endo* and 4-*exo* isomers of **2a**) had MS, IR and ^1H NMR spectra as described in the previous section.

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