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STRUCTURE AND SYNTHESIS OF GASTROLACTONE

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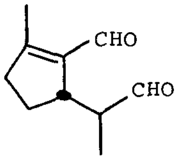
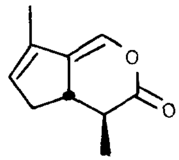
Summary The novel cyclopentenoid monoterpene, gastrolactone (4), was synthesized from carvenolide (5), and the synthetic material was found to be identical to the natural product by direct comparison. This synthesis confirmed structure 4 which had been suggested earlier on the basis of spectral data.

The iridoid monoterpene, chrysomelidial (1), was first identified as a component of the larval defensive secretion of the chrysomelid beetles *Plagiodera versicolora*[1] and *Gastrophysa cyanea*.[2] More recently, it has been found in a number of other chrysomelid larvae.[3] In *P. versicolora*, 1 is accompanied by plagiolactone (2) whose structure was confirmed by synthesis.[4] The larval secretion of *G. cyanea* was found to contain a diene lactone isomeric with 2 that had a mass spectrum almost identical to that of 2.[2] GLC analysis using polar liquid phases (OV-225, SP-1000) has shown that the *G. cyanea* lactone (gastrolactone) elutes earlier than 1, while plagiolactone (2) elutes later than 1. Structure 3 was initially proposed for gastrolactone, but this was revised after synthesis of 3 and nmr studies of the natural material suggested that the correct structure might be 4.[5] We now wish to report the preparation of 4 which confirms it as the structure of gastrolactone.



1



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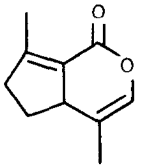

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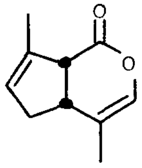

4

The *cis* ring junction and the nonconjugated double bond of carvenolide (5), which can be prepared from carvone in ca. 30% yield, make it an attractive starting material for gastrolactone.[6] Thus the crude diol from lithium aluminum hydride reduction of 5 could be converted by heating to reflux with acetic anhydride to a diacetate in which the tertiary acetate could be selectively eliminated by continued heating. Following distillation of the

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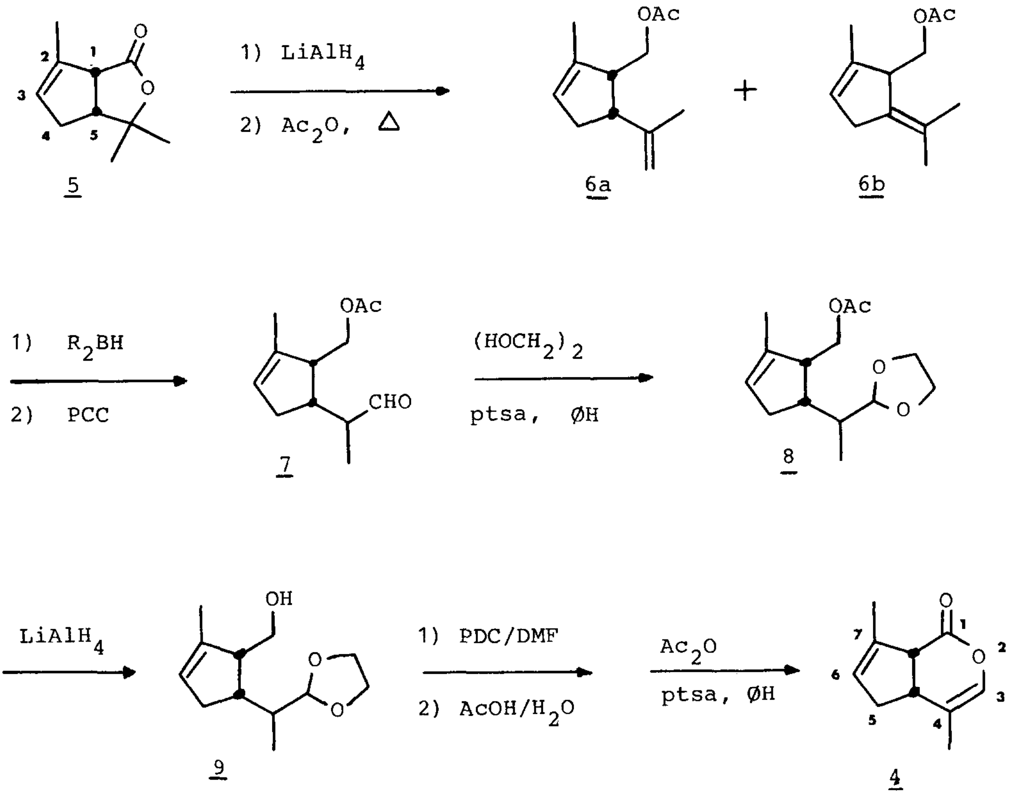
solvent under atmospheric pressure, the isomeric diene acetates 6a and 6b were obtained in 70% yield as a 4:1 mixture of 6a and 6b respectively (bp 70-80^{0}/0.5 mm Hg) by GLC and nmr analysis (nmr: δ=5.40, $\underline{H}C$=C (6a and 6b); 4.78, $C\underline{H}_2$=C (6a only)). This is analogous to the selective elimination of the diacetate derived from pugenolide, the saturated homologue of



5,[8] and the single olefinic signal at 5.40 ppm indicates that the ring double bond is uneffected by these conditions.

Treatment of the isomeric mixture 6 with disiamylborane, followed by oxidation of the reaction mixture with pyridinium chlorochromate[9] provided 80% of a 1:4 mixture of unreacted 6b and acetoxyaldehyde 7 (nmr: δ=9.75 (1, d, J=3Hz, $C\underline{H}O$), 5.53 (1, s, $\underline{H}C$=C), 4.38 (1, d of d, J=12.5, 4.3, -$C\underline{H}_2$-OAc), 4.03 (1, d of d, J=12.5, 4.8, $C\underline{H}_2$OAc), 2.7-2.1 (5, m), 2.07 (3, s, $OCOCH_3$), 1.77 (3, br s, $C\underline{H}_3C$=C), 1.18 (3, d, J=6Hz, CH-$C\underline{H}_3$)). The ethylene acetal 8 could be prepared from 7 in the usual manner (ethylene glycol, ptsa, refluxing benzene) and at this point, the diene acetate 6a could be removed by vacuum distillation to provide essentially pure 8 (nmr: δ=5.52 (1, s, $\underline{H}C=C$), 4.93 (1, d, J=2.4Hz, $-C\underline{H}(OCH_2)_2$), 4.38 (1, d of d, J=12.5, 5.3, $-C\underline{H}_2-OAc$), 3.95 (5, m, $OC\underline{H}_2C\underline{H}_2O$ and $C\underline{H}_2OAc$), 2.6-2.1 (5, m), 2.05 (3, s, $OCOCH_3$), 1.76 (3, br s, $CH_3C=C$), 1.01 (3, d, J=6Hz, $CH-C\underline{H}_3$)).[7] Lithium aluminum hydride reduction, followed by a non-acidic work-up,[10] provided the hydroxy-acetal (9) almost quantitatively. (nmr: δ=5.66 (1, s, $\underline{H}C=C$), 4.92 (1, d, J=2.5Hz, $-C\underline{H}(OCH_2)_2$), 4.95 (4, m, $OC\underline{H}_2CH_2O$), 4.78 (2, br s, $C\underline{H}_2OH$), 2.6-2.1 (6, m), 1.8 (3 br s, $C\underline{H}_3C=C$), 1.01 (3, d, J=6Hz, $CH-C\underline{H}_3$)).[7]

Conversion of 9 to gastrolactone 4 was accomplished by oxidation with seven equiv. of freshly prepared pyridinium dichromate in DMF.[11] The resulting mixture was diluted with ten volumes of water and continuously extracted with ether for 3 days. The free carboxylic acid was purified by extraction into 5%. NaOH, acidification with dil. HCl, and reextraction with ether. The ethylene acetal group was removed with refluxing 50% acetic acid,[12] and the enol lactone was formed using acetic anhydride with a trace of p-toluenesulfonic acid in benzene,[4] to provide 4 as the major volatile product in ca. 25% yield from 9.[13] (nmr: δ= 6.28 (1, br s, $C=C\underline{H}-O$), 5.60 (1, br s, $C=C\underline{H}-CH_2$), 3.53 (1, br d, J=9.7Hz, $-C\underline{H}CO_2-$), 3.07 (1, d of d of d, J=9.7, 9.7, 6.0 Hz, $-C\underline{H}-C=C-O-$), 2.83-2.30 (2, complex m, $C\underline{H}_2-CH=C$), 1.95 (3, br s, $CH_2-CH=C(C\underline{H}_3)$), and 1.68 (3, s, $C\underline{H}_3C=C-O$)). The assignment of the signal at 3.07 ppm to the C_{4a} proton was confirmed by irradiation of the C_6 olefinic signal at 5.60 ppm which collapsed the complex multiplet at 2.3-2.8 ppm and left the 3.07 ppm signal unchanged. The cis-fused ring system of 4 is indicated by the broad doublet at 3.53 ppm (J=9.5 Hz) arising from the C_{7a} proton and identical in appearance to the doublet arising from the proton α to the carbonyl in 5.[6] This nmr spectrum is essentially identical to the spectrum obtained previously from a crude sample of the natural lactone. Synthetic 4 had gas chromatographic retention times (SP-1000, OV-25, SE-30) and a mass spectrum[13] identical to those of the early eluting component of the secretion from freshly milked *G. cyanea* larvae.[14]

Significantly, whereas plagiolactone (2) or its epimer have been identified as larval defensive compounds of six of 12 species of chrysomelids, gastrolactone has only been detected in *G. cyanea*. That (4) is not a characteristic product of *Gastrophysa* species is demonstrated by the fact that it is absent from the larval exudates of two other species in this genus.[3] These results point to the presence of idiosyncratic selection pressures that have resulted in the evolution of this novel cyclopentenoid monoterpene by *G. cyanea*. The relative potencies of 1, 2, and 4 as feeding deterrents are currently being investigated.

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7. GLC analyses and preparations were carried out using a column packed with 10% SE-30 on Chromosorb W. NMR spectra were obtained at 90 MHz using a Varian EM-390 spectrometer.

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13. Gastrolactone (4) could be isolated by preparative GLC (10% SE-30); ir (neat liquid) 3040, 1748, 1690, 1650, 1380, 1347, 1195, 1155, 1120, 1080, and 1000 cm^{-1}; ms (70 eV) m/z (rel. %) 165(7), 164(60, M+), 149(5), 136(53), 135(20), 121(44), 109(10), 108(12), 107(100), 105(20), 103(9), 95(6), 93(50), 91(86), 82(10), 80(87), 79(50), 78(47), 77(48), 67(20), 65(24), 55(12), 53(28), 51(29), 44(25), 43(48), and 41(36). $[\alpha]^{24}_{D}$= -32.5° in benzene, when the synthesis started with (-)-R-carvone.

14. Although this synthesis began with (-)-(R)-carvone to give (1R, 5R)-5 and thus (4aR, 7aR)-4, there was insufficient natural 4 available to carry out optical rotation measurements and establish its absolute configuration by comparison.

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