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GUAIOL, A SYNTHESIS IN WHICH THE C-10 CENTER IS INDUCED STEREOSPECIFICALLY

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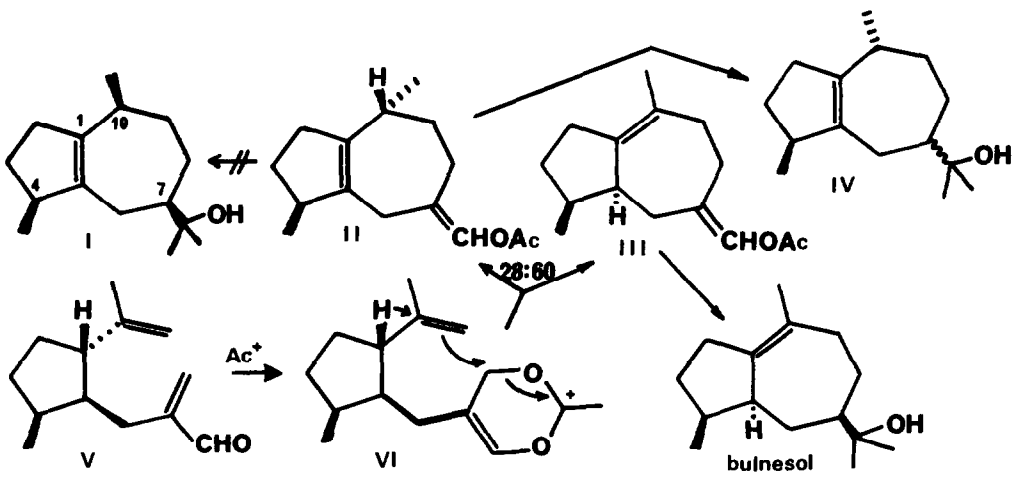
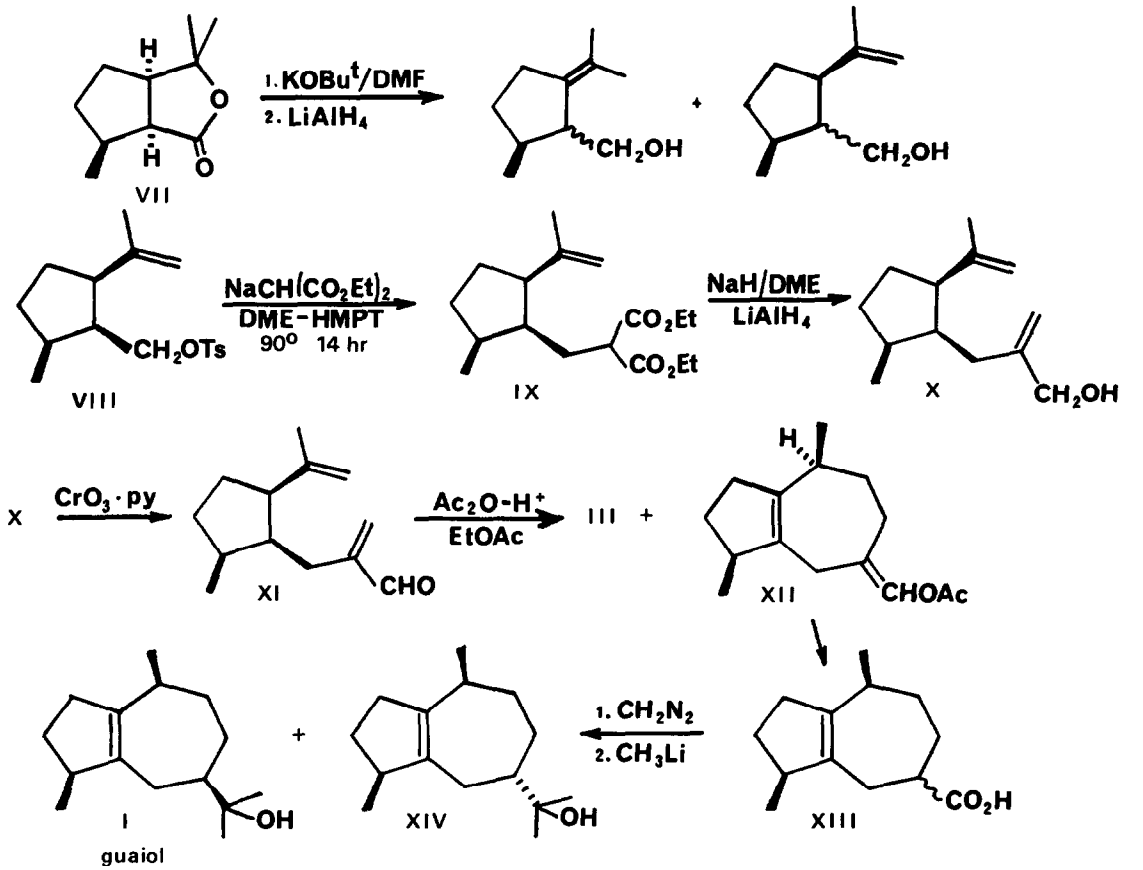
The hydroazulenic sesquiterpenes have, of late been the subject of a number of synthetic efforts. The ambiguities of conformational analysis of cycloheptanes[1] and the difficulties associated with the introduction of stereochemistry have dictated approaches in which stereochemistry is elaborated in decalinic intermediates. Guaiol (I), as an example, has been synthesized either by non-stereospecific methods[2] or via decalin intermediates.[3] We recently completed a synthesis of bulnesol[4] which employed as the key step the acetylation of aldehyde V. The major product of this reaction, enol acetate III, was used in the synthesis of bulnesol. The minor product (II) clearly had a 1,5-olefinic linkage but did not afford guaiol by the steps that had produced bulnesol and its 7-epimer from III. The two products obtained must thus be IV. The cyclization of aldehyde V apparently proceeds with a stereospecific hydride shift as indicated in VI. This suggested that a guaiol synthesis would be possible via an aldehyde of inverted (relative to V) stereochemistry at the isopropenyl junction

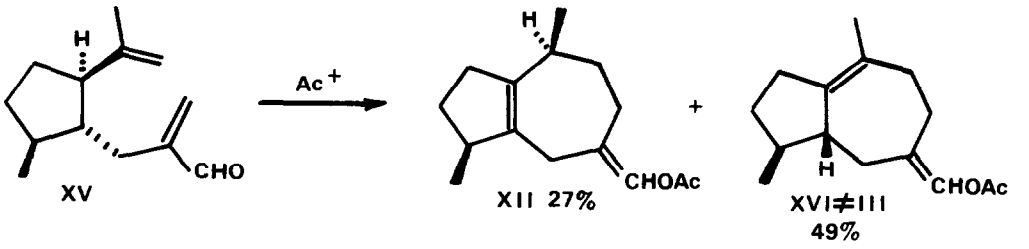


Lactone VII appeared as an ideal entry into this stereochemical series. Lactone VII has been prepared by the Favorskii rearrangement of the tribromide of (-)-carvone,[5] or alternatively, the enantiomer (cis,cis-puleganolide) has been prepared in good yield from (+)-pulegone or (+)-carvone.[6] Further, Wolinsky and Eustace report that lactone VII affords primarily the all cis isopropenyl carboxylate on heating with an equivalent of KOtBu in DMF.[7] When, in our hands, lactone VII[8] was subjected to elimination and then immediate reduction with excess ethereal $LiAlH_4$, a mixture of alcohols was obtained in 77% yield after distillation. Apparently we had failed to duplicate the elimination conditions as the mixture contained ca. 25% each of the α-epimeric isopropenyl alcohols and both epimeric isopropylidene alcohols. The cis,cis-alcohol was separated by preparative gc and identified by its nmr spectrum.[6]



Following the sequence developed previously,[4] malonate IX [δ_{TMS} 1.67, 4.72 ($CH_3C=CH_2$); 1.27, 4.19 (protodiastereomeric OEt groups $\Delta\delta \approx 0.03$); 3.40 (malonate methine, J = 7.5 Hz), and 1.02 ppm (CH_3, d., 5.2 Hz)] was obtained in 84% yield from the cis, cis-alcohol via tosylate VIII. Once again the use of a 1:1 mixture of dimethoxyethane and hexamethyl phosphoric triamide (HMPT) was essential for a successful displacement reaction. Reduction of the sodiomalonate[9] afforded allylic alcohol X as the major product. Oxidation with Collins' reagent in the presence of celite[4] gave aldehyde XI — δ_{TMS} 0.94 (CH_3 d, 4.5 Hz) 1.64, 4.64 ($CH_3C=CH_2$) 5.90, 6.18, and 9.50 ppm ($H_2C=C-CHO$, all singlets) — as a colorless oil. When 110 mg of XI in 1 ml of EtOAc was added to 10 ml of a solution of acetic anhydride (1.33 M), and $HClO_4$ (2.5 mM) in EtOAc,[10] the reaction was complete in 5 min. at room temperature. Gas chromatography revealed the previously obtained III (57%), two isomeric (at the double bond) enol acetates of structure XII (16%), and the absence of isomer II (< 1%): confirming the proposed hydride shift. The crude product was dissolved in 24 ml of 50% aq. EtOH containing 800 mg of $AgNO_3$. Dropwise addition of 8 ml of water containing 800 mg of NaOH with stirring in an ice bath followed by 16 hr of stirring at room temperature, effected hydrolysis and oxidation affording the mixture of acids (containing XIII). Treatment with ethereal CH_2N_2 followed by bulb-to-bulb distillation (@ 0.1 torr) gave 80 mg of ester mixture (66% yield from aldehyde XI). Glc analysis indicated that the mixture consists of the ester precursors of bulnesol (44%), 7-epibulnesol (17%), 7-epiguaiol (14%), and guaiol (11%). Treatment with excess ethereal CH_3Li afforded the alcohols in essentially quantitative yield. The individual isomers were isolated by preparative gc and proved identical to the previously synthesized samples in the case of bulnesol,[4] 7-epi-bulnesol,[4] and 7-epi-guaiol (XIV),[11] and identical to natural guaiol by nmr, ir, and glc in the case of guaiol.[12]

Finally, the other product from VII has been converted to aldehyde XV. Cyclization afforded guaiol precursor XII and a new $\Delta^{1,10}$-isomer (XVI) as shown below. This reaction was also stereospecific: gc analysis indicated less than 0.5% of isomer II.



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8. The kind gift of 2 g of the enantiomer of lactone VII from Prof. Wolinsky is acknowledged. All experiments were in the enantiomeric series, but are shown as leading to natural guaiol in order to show the relationships between the different series more directly.
9. J. A. Marshall, N. H. Andersen, and A. R. Hochstetter, J. Org. Chem., 32, 113 (1967).
10. This reagent is very nearly that recommended by B. E. Edwards and P. N. Rao [J. Org. Chem., 31, 324 (1960)] for the conversion of cyclic ketones to enol acetates.
11. Authentic 7-epiguaiol[3b] was kindly supplied by Prof. J. A. Marshall (Northwestern U.).
12. From Guaiacwood oil (Givaudan Corp.).

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+ This work is taken in part from the Ph.D. thesis of H.S.U., University of Washington (1973).