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SYNTHESIS OF THE DIACETATE OF 4-CHLORO-2-HYDROXYMETHYL-2--BUTEN-1-OL. A USEFUL SYNTHON IN THE CHEMISTRY OF THE ISOPRENE UNIT

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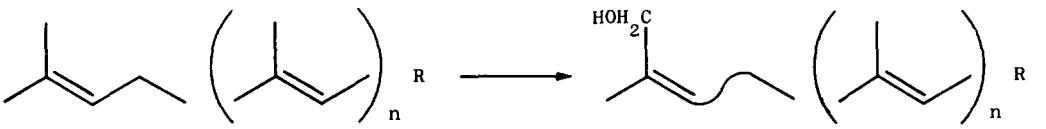
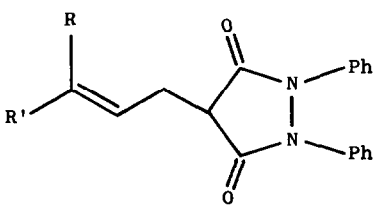
Summary: a versatile procedure for the synthesis of the diacetate of 4-chloro-2-hydroxymethyl-2-buten-1-ol, a precursor of the dihydroxyprenyl synthon, is described. Its application to the synthesis of an unusual metabolite of a prenyl-containing drug is illustrated.

The hydroxylation of one of the terminal methyl groups of the isoprene unit of prenyl or poly-prenyl compounds is a common metabolic pathway in most mammalian species



Many natural substances[1,2] such as dihydromyrcene, geraniol, citral, etc., and compounds of medicinal interest (e.g., pentazocine[3], galegine[4]) have been found to undergo such metabolic transformation, which, depending on the relative position of the oxidative attack, may give rise to cis- and trans-hydroxylated derivatives.

Recently, during a study of the metabolism in rats of feprazone (1)[5], a non-steroidal antiinflammatory drug containing a prenyl side-chain, besides the expected cis- and trans--monohydroxylated metabolites 2 and 3, respectively, a urinary metabolite was isolated having the gem-dihydroxylated structure 4[6].



1 R = R' = Me

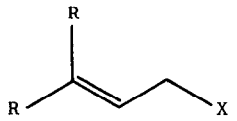
2 R = CH_2OH R' = Me

3 R = Me R' = CH_2OH

4 R = CH_2OH R' = CH_2OH

Whereas sufficient methodology exists for the preparation of cis- and trans-monohydroxylated prenyl synthons or their precursors[7-11], the literature records no examples concerning the corresponding dihydroxylated derivatives[12].

We wish to report here the preparation of the diacetate of 4-chloro-2-hydroxymethyl-2-buten-1-ol (5a) and illustrate its synthetic usefulness in the preparation of feprazone metabolite 4.

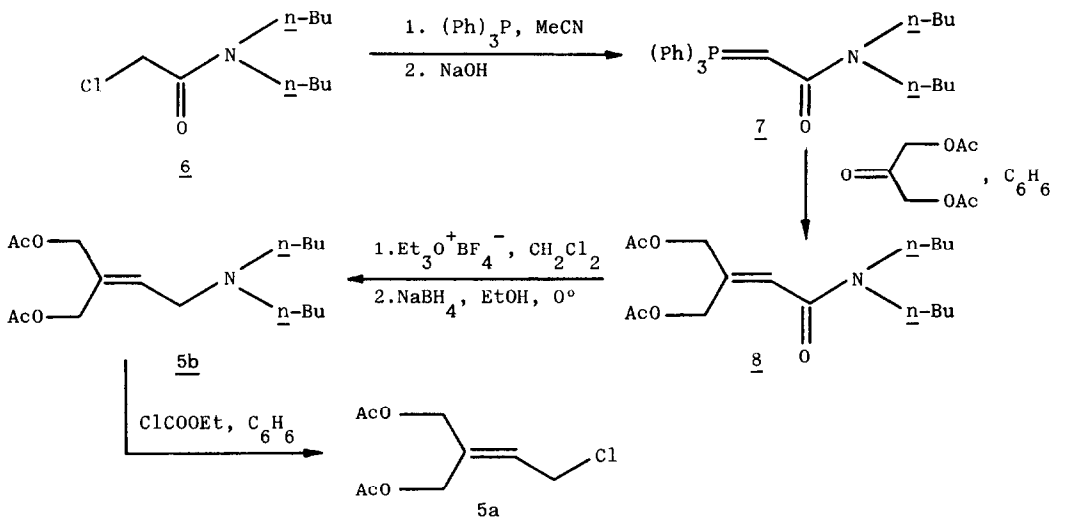


5a R = $AcOH_2C$ X = Cl

5b R = $AcOH_2C$ X = N (n-Bu)$_2$

5c R = EtOOC X = H

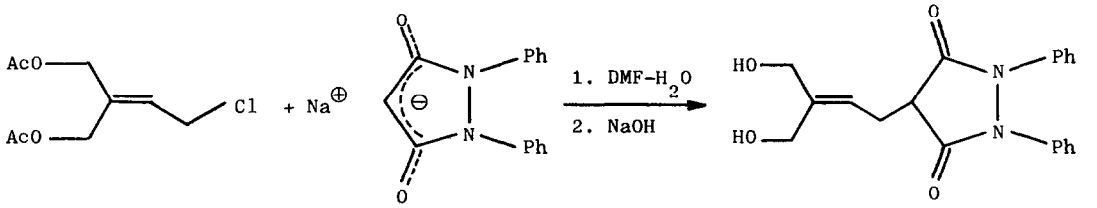
As a strategy, the allylic tertiary amine 5b was envisaged as a pre-target structure in view of the possibility of di-n-butylamino/halogen interchange by preferential splitting of the allylic substituent by ethyl chloroformate[11-13]. Structures having R = EtOOC as precursors of the alcoholic groups were considered unsuitable owing to extensive double bond saturation which occurred on attempted reductions of the model compound 5c.



Reaction of the chloroacetamido derivative 6 with triphenylphosphine in acetonitrile at reflux for 18 hr gave the corresponding phosphonium salt [81%; mp 217°]. Treatment of this salt with 2.5% aqueous sodium hydroxide furnished the crystalline phosphorane 7 [95%; mp 125°; nmr ($CDCl_3$) δ 0.90 (t, 6H, CH_3), 1.06-1.86 (m, 8H, CH_2-CH_2), 3.26 (t, 4H, CH_2N), 7.20-7.93 (m, 16H, arom protons and HC = P)]. Wittig reaction of 7 with one eq of 1,3-diacetoxyacetone[14] in refluxing benzene for 18 hr afforded the diacetoxybutenamide 8 purified by distillation [72%; $bp_{0.06}$ 140-142°; ir (film) 1750, 1640, and 1230 cm^{-1}; nmr ($CDCl_3$) δ 0.9 (t, 6H, CH_3CH_2), 1.05-1.80 (m, 8H, CH_2-CH_2), 2.03 (s, 6H, CH_3CO), 3.23 (q, 4H, CH_2N),

4.63, 4.90 (2s, 4H, CH_2-C =), 6.23 (s, 1H, HC = C)]. Reduction of the amide 8 to the amine 5b was performed according to Borch[15] by a two-step sequence utilizing triethyloxonium fluoborate and sodium borohydride. The reaction proved highly selective without affecting either the ester groups or the conjugate double bond[16]. Thus, treatment of the amide 8 in dry dichloromethane with 1.3 eq of triethyloxonium fluoborate at 25° for 20 hr gave, after evaporation of the solvent, an oily residue which was immediately reacted with 2.5 eq of sodium borohydride in ethanol at 0° for 3 hr, to give the crude amine 5b purified by distillation [71%; $bp_{0.7}$ 148-150°; ir (film) 3000-2800, 1750, and 1230 cm^{-1}; nmr ($CDCl_3$) δ 0.9 (t, 6H, CH_3-CH_2), 1.03-1.67 (m, 8H, CH_2-CH_2), 2.05 (s, 6H, CH_3CO), 2.4 (t, 4H, CH_2CH_2N), 3.18 (d, 2H, HC = CH_2-N), 4.60, 4.66 (2s, 4H, CH_2O Ac), 5.85 (t, 1H, H_2C = CH)]. Treatment of 5b with 1.5 eq of ethyl chloroformate in refluxing benzene for 2 hr afforded selective cleavage to give, after distillation to effect separation from ethyl di-n-butylcarbamate produced as a by-product, the desired allylic synthon 5a [74%; $bp_{0.7}$ 115-116°; ir (film) 1750 and 1230 cm^{-1}; nmr ($CDCl_3$) δ 2.10 (s, 6H, CH_3CO), 4.20 (d, 2H, CH_2Cl), 4.63, 4.70 (2s, 4H, CH_2OH), 5.97 (t, 1H, HC = C).

By utilizing the isoprenic synthon 5a, the dihydroxylated feprazone metabolite 4 could be synthesized according to the following scheme.



5a 9 4

Reaction of 5a with the sodium salt of 1,2-diphenyl-3,5-dioxopyrazolidine (9)[17] in aqueous dimethylformamide at room temperature for 12 hr gave the diacetate of the desired 4 along with some amount of the starting material 9. Direct saponification of this mixture with 5% sodium hydroxide at room temperature for 2 hr furnished after acidification and chromatography on silica gel [dichloromethane-methanol (9:1, v/v)]the desired metabolite 4 as a white solid [26% overall yield; mp 131-132°; ir (nujol) 3400, 1750, 1720, 1600, 750, and 700 cm^{-1}; nmr ($CDCl_3$) δ 2.11 (brs, 1H, OH), 2.95 (m, 2H, = CH-CH_2-CH), 3.55 (t, 1H, COCHCO), 4.11 4.20 (2s, 4H, CH_2OH), 5.60 (t, 1H, = CH-CH_2), 7.28 (s, 10H, arom protons).

This dihydroxylation of the terminal methyl groups of a prenyl compound represents a novel biotransformation pathway in the field of substances containing the isoprene unit. The present preparation makes available a synthon of potential utility in the chemistry of these substances and of their biotransformation products.

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