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THE ACETATE OF (Z)-4-CHLORO-2-METHYL-2-BUTEN-1-OL STEREOSELECTIVE WITTIG SYNTHESIS OF A NEW HEMITERPENOID SYNTHON

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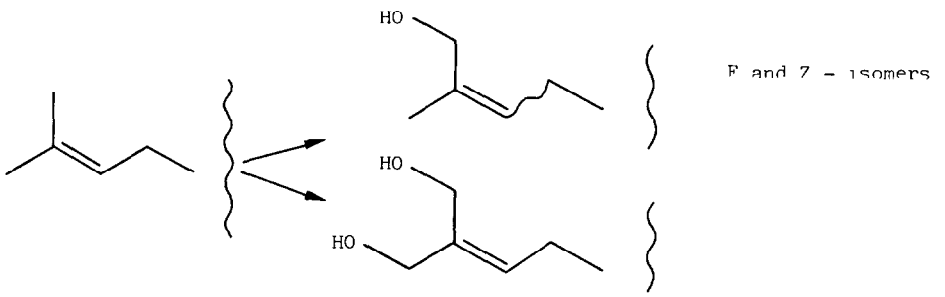
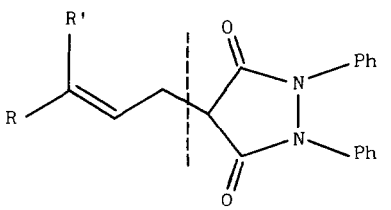
Summary a synthetic method for the preparation of the acetate of (Z)-4-chloro-2-methyl-2-buten-1-ol, a precursor of the (Z)-hydroxy prenyl synthon is described The use of such synthon in the preparation of a metabolite of a prenyl-containing substance is also illustrated

The hemiterpenoid group (isopentenyl, prenyl) present in various natural substances[1,2] as well as in synthetic compounds of medicinal interest[3,4] is well known to undergo oxidative attack during metabolic biotransformation in mammals



Recently, in our studies on the metabolism of feprazone (1)[5] an antiinflammatory drug containing a prenyl side-chain, three urinary metabolites in rat were isolated having the following structures



1 R = R' = Me

2 R = Me R' = CH_2OH

3 R = CH_2OH R' = Me

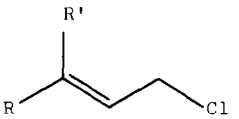
4 R = R' = CH_2OH

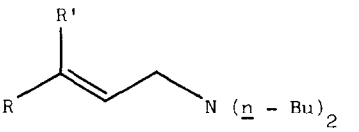
The synthetic strategy for a preparation of these substances (2, 3, and 4) poses some challenges Without considering problems connected with stereoselectivity for 2 and 3, chemoselective oxidation[6] of the terminal methyl groups of the prenyl part of the molecule is clearly

unpractical owing to the sensitivity of 1 to oxidizing agents On the other hand, the use of a Wittig reaction for double bond generation[6] requires the synthesis of the suitable carbonyl compound of the rather complex 3,5-pyrazolidinedione molecule

A synthon approach (represented by the bond dissection) was thought reasonable in view of the favourable nucleophilic character of the anion of the 3,5-pyrazolidinedione nucleus and of the foreseeable reactivity of the allylic substituent

The trisubstituted functionalized olefin synthons (4a-6a) were then envisaged suitable tools for our approach

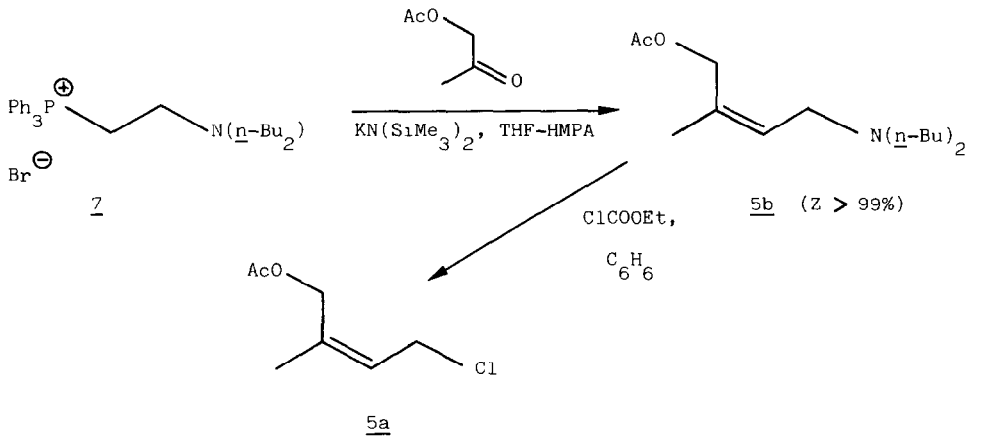




4a	R = CH_2OAc	R' = Me (E)	4b	R = CH_2OAc	R' = Me (E)
5a	R = Me	R' = CH_2OAc (Z)	5b	R = Me	R' = CH_2OAc (Z)
6a	R = R' = CH_2OAc		6b	R = R' = CH_2OAc	

Preparation of synthon 4a of (E)-configuration was available from the literature[7], while a procedure for the symmetric 6a was recently described by us[8] Their synthesis is based on the preparation of the pre-target allylic amines 4b and 6b, respectively, from which the desired synthons are obtained by preferentia. splitting with ethyl chloroformate Nothing is instead reported in the literature concerning the (Z)-synthon 5a A correspondingly simple preparation of this synthon was therefore deemed of interest in view also of the potential utility of such intermediates in the field of substances containing the isoprene unit

In this letter, we wish to report the stereoselective synthesis of the acetate of (Z)-4--chloro-2-methyl-2-buten-1-ol (5a) via the corresponding key-intermediate 5b, and illustrate its synthetic usefulness in the preparation of metabolite 2



7 5b (Z > 99%) 5a

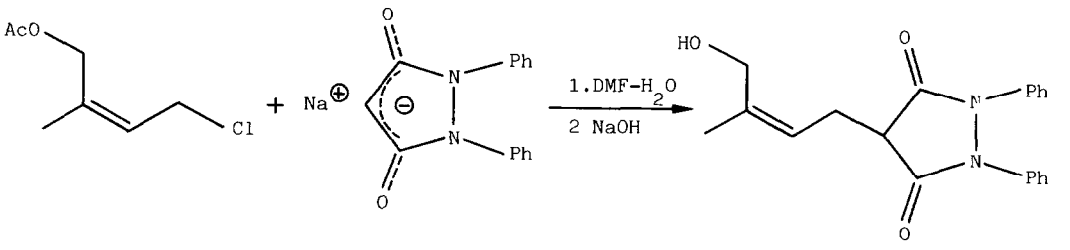
When acetoxyacetone[9] (0.21 mole) was allowed to react with the unstabilized ylide obtained from the β-dialkylamino phosphonium salt 7[10] (0 3 mole) and potassium hexamethyldisilazide (0 28 mole) under the conditions described by Sreekumar et al[11] (10% HMPA/THF), the allylic acetate 5b (51% yield, $bp_{0\ 1}$ 85-87°) of high stereoisomeric purity was obtained [7-isomer > 99% by vpc, DC 550 column, temp 170°C Retention time for 5b (Z-isomer) 1227 sec in comparison with the corresponding 4b (E-isomer)[7] 1311 sec.] Splitting of the allylic substituent from 5b by ethyl chloroformate (1 5 eq) in refluxing benzene for 2 hr gave, after distillation to effect separation from ethyl di-n-butyl-carbamate produced as a by-product, the stereoselectively pure Z-synthon 5a [74% yield, bp_{15} 98-101°, vpc analysis DC 550 column, temp 130°C Retention time 565 sec for 5a, in comparison with the corresponding 4a (E-isomer)[7] 611 sec]

The structure of these hemiterpenoids follow from microanalysis, ir and nmr spectral data

5b ir (film) 1740 cm^{-1}, nmr (CCl_4) δ 5 42 (t, 1H, $CH_2 = CH$), 4 53 (s, 2H, $AcOCH_2$), 3 02 (d, 2H, $CH = CH_2-N$), 2 33 (t, 4H, CH_2CH_2N), 2 (s, 3H, CH_3CO), 1 77 (s, 3H, $CH_3-C =$), 1 13-1 5 (m, 8H, CH_2-CH_2), 0 9 (t, 6H, CH_3CH_2)

5a ir (film) 1740 cm^{-1}, nmr ($CDCl_3$) δ 5 66 (t, 1H, $CH_2 = CH$), 4 66 (s, 2H, $AcOCH_2$), 4 15 (d, 2H, $CH = CH_2Cl$), 2.08 (s, 3H, CH_3CO), 1 83 (s, 3H, $CH_3 - C =$) Double bond geometry (Z) was confirmed, in addition to vpc information, by comparison of the nmr spectral data of 5a with those of the corresponding E-isomer (4a)[7] In particular, 5a exhibited different relative shifts for the $AcOCH_2$ and $CH_3 - C =$ singlets, which are downfield with respect to those of the corresponding E-isomer (4a) δ 4.43 and 1.73, respectively

By utilizing the (Z)-synthon 5a, the feprazone metabolite 2 could be synthesized according to the following scheme



5a 8 2

Reaction of 5a with the sodium salt of 1,2-diphenyl-3,5-dioxopyrazolidine (8)[12] in aqueous dimethylformamide at room temperature for 12 hr gave the acetate of the desired 2 along with some unreacted 8 Direct saponification of this mixture with 5% sodium hydroxide (2 hr, room temperature) furnished after acidification and chromatography on silica-gel [dichloromethane--methanol (9 1, v/v)] the desired metabolite 2 as a colourless solid [31% overall yield, mp 141°], ir (nujol) 3400, 3200, 1750, 1720, 1590, 750, and 705 cm^{-1}, nmr ($CDCl_3$) δ 7 23 (s, 10H, arom protons), 5 27 (t, 1H, CH_2 = C<u>H</u>), 4.02 (s, 2H, $C\underline{H}_2OH$), 3 48 (t, 1H, COCHCO), 2 92 (m, 2H, = $CHC\underline{H}_2CH$), 1.73 (s, 3H, CH_3C), 1,56 (brs, 1H, OH)

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