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# TERPENOID SYNTHESIS. III[1]. CHLOROMETHYL ETHERS IN THE HYDROXYMETHYLATION OF OLEFINS AND THE SYNTHESIS OF SIRENIN

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Methyl perillate (1) is preferentially attacked by electrophilic reagents at C-9.[1] However, its conversion with formaldehyde (Prins reaction)[3] under a variety of conditions into the hydroxymethylated product (2), a useful intermediate in the synthesis of e.g. juvabione and sirenin,[4] proceeded in poor yield (<5%). By employing halomethyl ethers a hydroxymethylation procedure for olefins was elaborated and successfully applied to a short synthesis of sirenin (3).

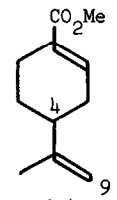
Chloromethyl ethers are used extensively in both base and acid catalysed alkylations.[5] We employed allylchloromethyl ether and benzylchloromethyl ether in addition reactions to olefins, and subsequently cleaved[6] the resulting allyl and benzyl ethers to effect hydroxymethylation of the olefins; for example addition of the ether (4) to the olefins (7) - (9) proceeded in good to practically quantitative isolated yields to give the chloro-ethers (10) - (12) [See Table]. Treatment of the resulting chloro-ethers with $Ac_2O/BF_3$ gave the corresponding chloro-acetates: In a typical experiment the ether (10) (20g) in $Ac_2O$ (50 ml) was mixed with $BF_3$-etherate (1 ml) in $Ac_2O$ (5 ml) and left at room temperature for 1h to yield the chloro-ester (13) (12g, b.p. $80^{o}$/10 mm;77%) and benzyl acetate. Dehydrochlorination prior to the ether cleavage reaction gave the alkenyl ethers. The condensation with olefin (9) presents a new approach for the construction of the lavandulyl skeleton.[7] Dehydrochlorination of the ether (12) followed by reductive cleavage ($Na/NH_3$) gave the lavandulols (15). Alternatively hydroxymethylation may also be effected by condensation with the ether (6) to give ethers of type (14),[8] which may be cleaved in various ways e.g. by dehydrobromination (t-BuOK/DMSO) to give vinyl ethers (16) and (17), which on hydrolysis, yield hydroxymethylated olefins**.

Methyl perillate (1) similarly reacted with ethers (4) and (5). Treatment of ester (1) with allylchloromethyl ether in the presence of $BF_3$-etherate gave the intermediate chloro-ether (18), which was directly cyclised by treatment with base (t-BuOK/THF; r.t.; 2.5 hr) to a mixture of the *exo*- and

TABLE

| Ether | Olefin | Product | Yield (%)† |
|---|---|---|---|
| $Ph\cdot CH_2OCH_2Cl$ | $Me_2C:CH_2$ | 10 | 76 |
| $Ph\cdot CH_2OCH_2Cl$ | $Me_2C:CH\cdot Me$ | 11 | 76 |
| $Ph\cdot CH_2OCH_2Cl$ | $Me_2C:CH\cdot(CH_2)_2C(Me_2)Cl$ | 12 | 61 |
| $Br(CH_2)_2OCH_2Br$ | $Me_2C:CH_2$ | 14 | 72 |

† Figures refer to lowest isolated yields. Yields not optimised. $TiCl_4$ was employed as Lewis acid. Solvent: $CH_2Cl_2$.

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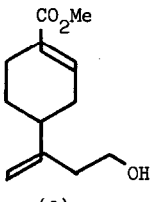


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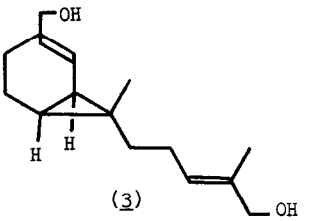


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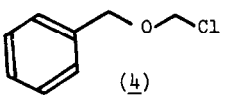


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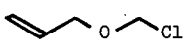


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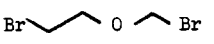


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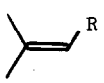
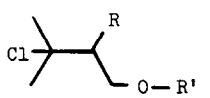
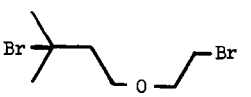



(7) : R=H
(8) : R=Me
(9) : R= $-CH_2-CH_2-C(Cl)Me_2$




(10) : R=H; R'=Benzyl
(11) : R=Me; R'=Benzyl
(12) : R= $-CH_2-CH_2-C(Cl)Me_2$; R'=Benzyl
(13) : R=H; R'=MeCO-

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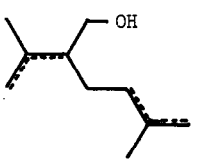


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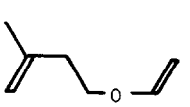
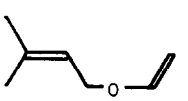



(16)

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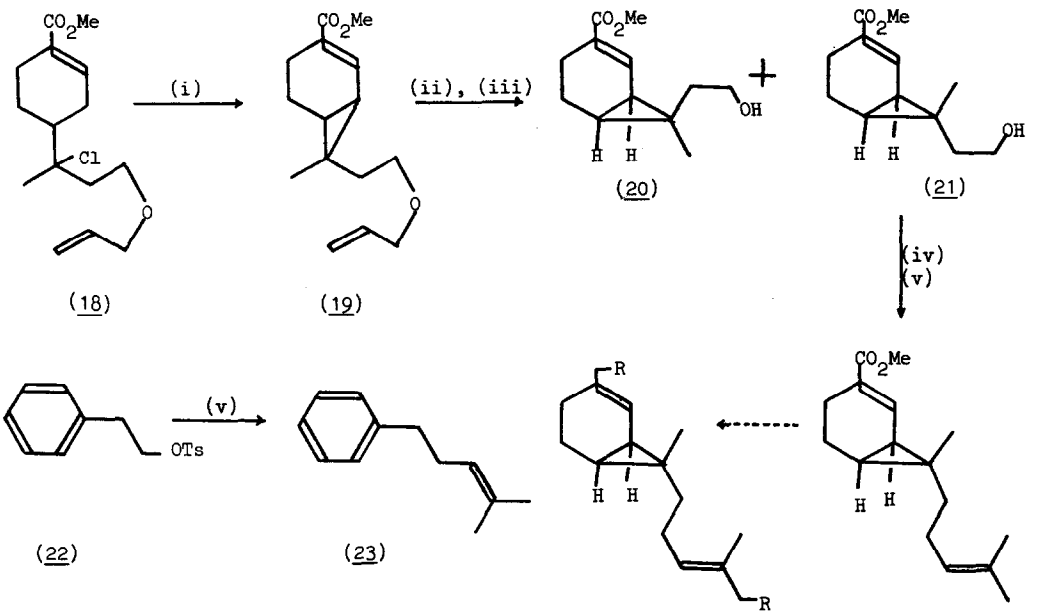


(i) t-BuOK, THF (ii) $Ac_2O/BF_3$ (iii) MeONa/MeOH (iv) $TsCl/C_5H_5N$ (v) lithium-di-*iso*-butenylcuprate

*endo*-methyl isomers (19) (30% based on 1, yield not optimised), with the latter isomer predominating (ca. 40:60). Cleavage of the ether linkage ($Ac_2O/BF_3$; 0°; 90 m.) in product (19), followed by trans-esterification with MeOH (MeONa/MeOH; reflux temp.; 60 m.) gave the corresponding alcohols ( >90%, based on 19) from which the *exo*-methyl isomer (20) [$\tau$(C-$CH_3$) 8.84 in $CDCl_3$] and the *endo*-methyl isomer (21) [$\tau$(C-$CH_3$) 9.11] were isolated severally by liquid chromatography.[9]***

Selective conversion of the tosylate (22) to hydrocarbon (23) in the presence of methyl perillate (1) with excess lithium di-*iso*-butenylcuprate[10] (5 mol/mol; ether; 2h; -5°) was effected in high yield. Consequently the *endo*-methyl alcohol (21) was converted into its tosylate[11] (95%) and treated with lithium di-*iso*-butenylcuprate to give the ester (24) (87%). Alternatively, the mixture of alcohols (20) and (21) was similarly converted into a mixture of ester (24) and its *exo*-methyl isomer, which was then separated by chromatography on alumina. The conversion of ester (24) into sirenin (3)[12a,b] and sesquicarene (25)[13a] in two steps, has already been described.

The bicyclo[4.1.0]heptane skeleton of sirenin and sesquicarene has previously been constructed by the intramolecular carbene insertion reaction[12,13] or by base catalysed opening of methyl

5,9-epoxyperillate.[14] Since *l*-methyl perillate is acylated with isovaleric anhydride at C-9 with retention of configuration at C-4,[1] the procedure outlined above, could probably be applied to the conversion of *l*-methyl perillate to *l*-sirenin and *l*-isosirenin.

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