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HIGHER TERPENES FROM LOWER TERPENES:
A SHORT, SIMPLE AND VERSATILE ROUTE TO BISABOLANE SESQUITERPENOIDS[1]

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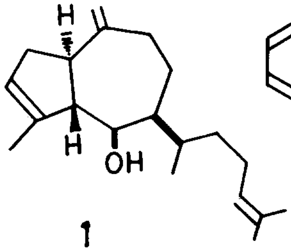
Summary: An efficient procedure for the elaboration of abundantly available monoterpenes to bisabolane sesquiterpenes utilising catalysed ene addition as the key reaction is described.

Recently, structures of several novel terpenoids have been elucidated[2], particularly from marine sources, whose carbocyclic skeleton resembles that of the lower terpene but which carry an additional isopentane unit in the side chain. For example, diterpenoids pachydictyol-A 1[2a], dictyolene 2[2b] and dihydroxyserrulatic acid 3[2c] bear the basic carbocyclic framework of corresponding sesquiterpenes of guaiane, eudesmane and cadinane types, respectively, with a 5C unit attached to the isopropyl side chain. A common example of this type of structural relationship is to be found between the monoterpenes of the menthane group (e.g. +-limonene 4) and the sesquiterpenes of the bisabolane group (e.g. β-bisabolene 5). Since, biosynthetic pathway endows many terpenes with a side chain isopropenyl group, we considered the 5 carbon homologation of this functionality (6 → 7) as an attractive and viable method of synthesising higher terpenes from abundantly available lower terpenes. In this letter, we delineate a simple and general approach, utilising ene reaction, through which menthane derived monoterpenes are elaborated into the sesquiterpenes of the bisabolane family.



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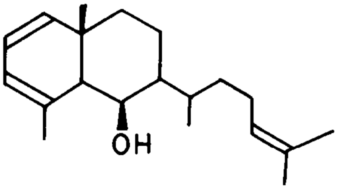

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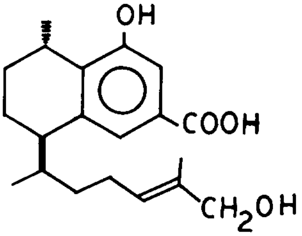

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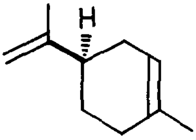
We have found that (+)-limonene 4 and many of its derivatives like



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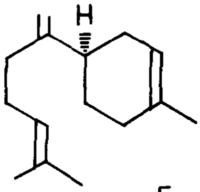

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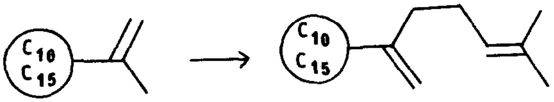

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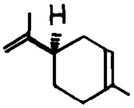
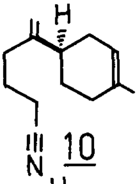
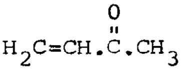
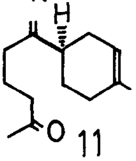
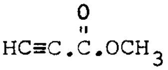
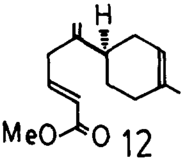
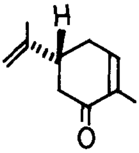
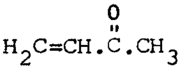
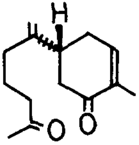
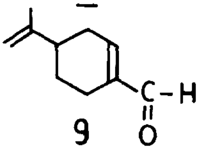
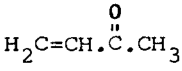
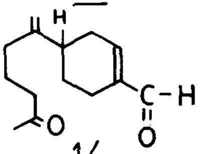
7

(-) carvone 8 and (±)-perillaldehyde 9 readily enter into a Lewis acid catalysed[3] ene reaction, at room temp. with a variety of enophiles (acrylonitrile, propio-

Table 1. Ene Addition to Menthane Based Monoterpenes

Substrate	Enophile	Reaction[c,d] conditions	Product[a]	Yield[b]
 4	$CH_2{=}CH.CN$	c, 200°, 24hr	 10	25%
4	 $H_2C{=}CH.\overset{O}{\overset{\|}{C}}.CH_3$	c, 200°, 12hr d, 12hr	 11	45%[c] 60-75%
4	 $HC{\equiv}C.\overset{O}{\overset{\|}{C}}.OCH_3$	c, 160°, 24hr	 12	70-80%
 8	 $H_2C{=}CH.\overset{O}{\overset{\|}{C}}.CH_3$	d, 12hr	 13	80-95%
 9	 $H_2C{=}CH.\overset{O}{\overset{\|}{C}}.CH_3$	d, 12hr	 14	70%

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a. All new compounds gave satisfactory analytical and spectral data.

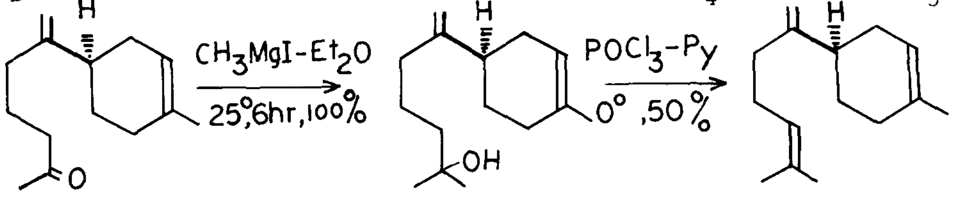
b. Yields correspond to the actual product isolated by chromatography (SiO_2gel) of the crude reaction mixture and are based on recovered substrate.

c. Reaction carried out thermally in a sealed tube.

d. Reaction carried out in presence of 0.8-1 mol. $AlCl_3$ in dry benzene at room temperature. Generally, excess (2-3 moles) of the enophile was used.

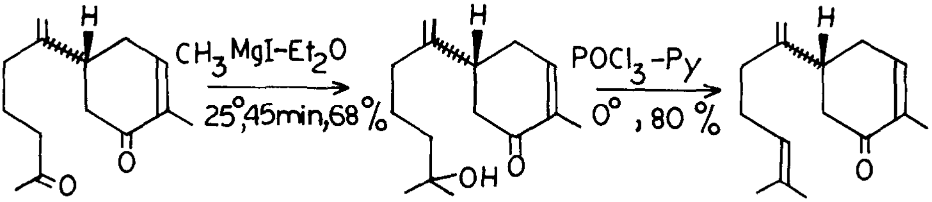
lic ester, methylvinyl ketone-MVK etc.) to furnish addition products with 3 or 4 carbon homologation. A few examples from many such additions studied by us are depicted in Table 1. A truly remarkable aspect of these catalysed ene additions is that 8 & MVK, both bearing sensitive functionalities, furnish clean addition product 13 in presence of anhydrous $AlCl_3$. Furthermore, 8 does not give the expected ene product under usual thermal conditions[4].

The (+)-limonene-MVK ene addition product 11 was transformed into β-bisabolene 5 in two steps. Reaction of 11 with CH_3MgI furnished 15, bp 135-140°/0.1mm, α_D= +35.1, ir(neat):3400, 1650, 895cm^{-1}, pmr(CCl_4):δ1.2(6H,s,$CH_3-\underset{CH_3}{\overset{|}{C}}-OH$);



11 15 5

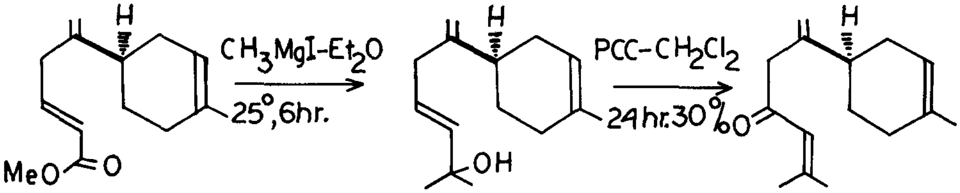
which was dehydrated with $POCl_3$-py reagent to 5, α_D+47.2, identical (IR,PMR) with the natural product. In a similar manner the (-)-carvone-MVK adduct 13 was treated with excess of CH_3MgI to furnish 16, bp,150-160/0.04mm, α_D= -18.7 ir(neat):3400, 1680, 890cm^{-1}, pmr ($CDCl_3$):δ1.15 (6H,s,$CH_3-\underset{CH_3}{\overset{|}{C}}-OH$). The Grignard addition, as expected, occurred regioselectively at the side chain carbonyl group. Dehydration of 16 with $POCl_3$-py reagent yielded (-)-cryptomerion 17, α_D= -34.6 identical with natural product[5] in just three steps from 8.



13 16 17

Lastly, the (+)-limonene-propiolic ester adduct 12 was elaborated to (+)-β-atlantone 19 and (+)-α-atlantone 20. Grignard reaction with 12 using two moles of the reagent furnished 18 (α_D +29.5, ir (neat): 3400, 1650, 990cm^{-1}

pmr ($CDCl_3$):δ1.25 (6H,s,$CH_3\text{-}\overset{CH_3}{\overset{|}{C}}\text{-}OH$) which on oxidation with pyridinium-chlorochromate[6], gave (+)-β-atlantone 19 identical (IR, PMR) to the one reported in literature[7]. Isomerisation of 19 to the cross conjugated isomer has been accomplished earlier and thus completes a formal synthesis of (+)-α-atlantone 20[8].



12 18 19

In summary, we have demonstrated a very simple strategy by which lower terpenes can be homologated in just three steps and with retention of chirality. The ability to perform catalysed ene reaction with the isolated double bond in presence of other functionalities makes the present route highly versatile for 5 carbon homologation. Further applications will shortly follow.

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