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STEREOSELECTIVE APPROACH TO THE NORPATCHOULENE UNIT - TOTALSYNTHESIS OF (±)-ISO AND DEOXYNORPATCHOULENOL.

Jean-Louis GRAS
Laboratoire Associé au C.N.R.S. n° 109 - Université d'AIX-MARSEILLE III -
Rue H. POINCARE - 13397 MARSEILLE CEDEX 4

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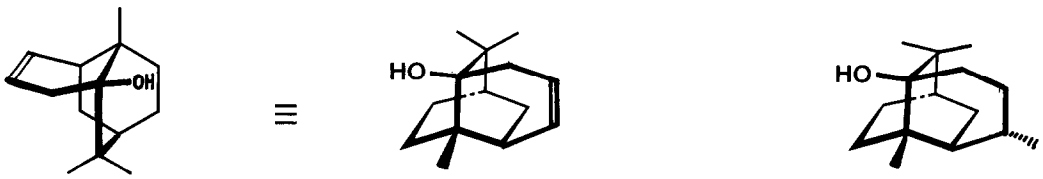
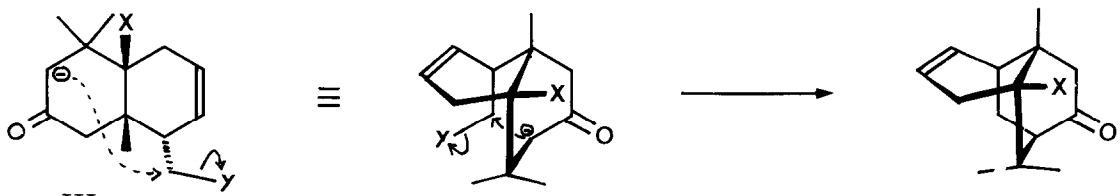
The contribution to the study of commercial patchouli oil derived from *pogostemon cablin benth,* led to the isolation of a minor compound which is the real carrier of the scent of this natural product (1). The structure and absolute configuration have been assigned as shown in I (2).



I II

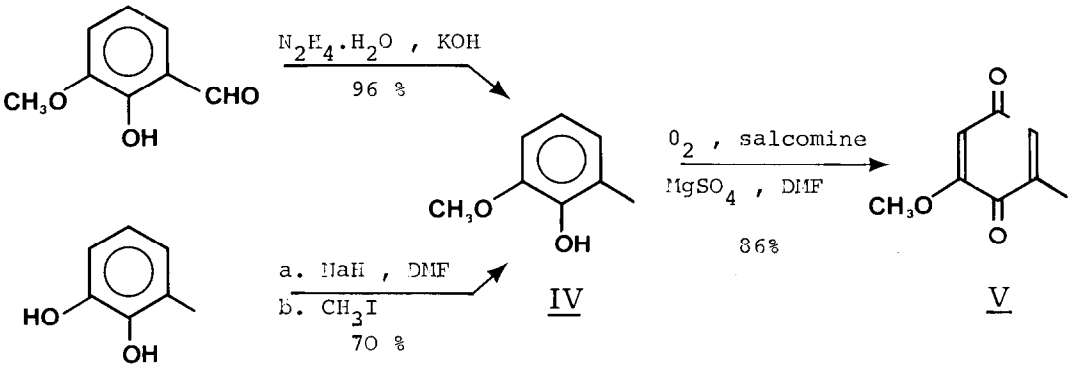
This norsesquiterpenoid alcohol (formaly norpatchoulenol) is closely related to the well-known patchouli alcohol II from which it can be derived by biological oxidation and degradation (3). The structure assigned to I was confirmed by a total synthesis. However, several steps led to an undesired mixture of isomers (4). An efficient stereoselective route to the tricyclic norpatchoulene skeleton is reported here.

This approach involves an intramolecular alkylation (5) of the substituted decalone III. The reaction product would be a ketonorpatchoulene from which several derivatives may arise.

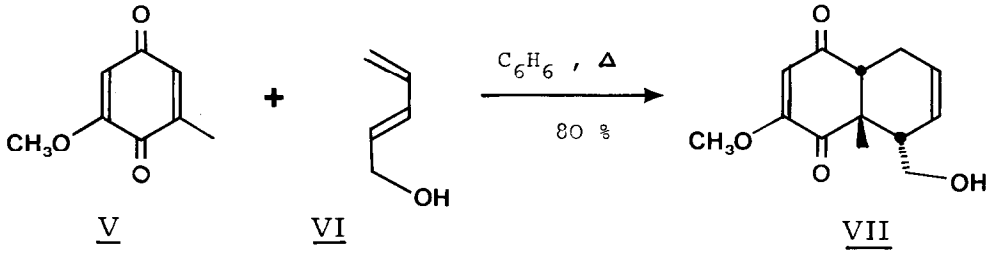


III

The starting material may be either the commercially available 3-methyl-o-cresol methylated to give IV, or o-vanillin which efficiently is reduced to IV (6). Oxydation of this phenol by O_2 catalysed by salcomine (7) led to the known p-quinone V, in much better yield than previously reported (8).



We have determined that 2-methoxy-6-methyl-p-bensoquinone V undergoes a DIELS-ALDER addition with trans penta-2,4-dienol VI to give, under controlled conditions, stereospecifically the crystalline (±) 4a, 5, 8, 8a-tetrahydro-5-hydroxymethyl-3-methoxy-4a-methyl-1,4-naphtoquinone VII.



The side of addition and the relative orientation of the substituents were predicted on the basis of several investigations on the DIELS-ALDER reaction between 1-substituted dienes and unsymmetrically substituted p-quinones (9).

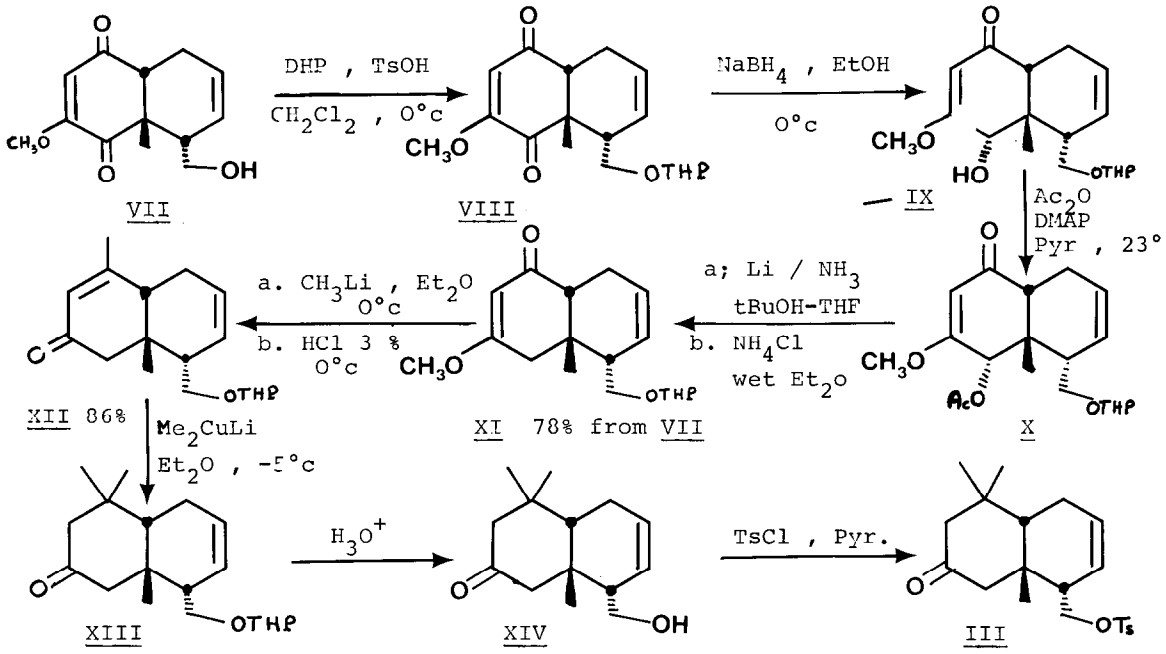
The electron-donating properties of the methoxy group in dienophile V are exposed to the mechanistic challenge of the nearly neutral methyl group and its hyperconjugative effect. Therefore, addition of diene VI occurs at the more electron dificient methylethene-linkage of p-quinone V. Moreover, the deactivating effect of the methoxy group will preclude further addition of adduct VII.

The angular methyl group and the diene substituent were found ortho to each other in the new ring formed. No detectable amount of meta isomer was found. Furthermore, the side chain can be assigned trans to the angular methyl group as a consequence of the endo-cis addition principle of DIELS-ALDER reactions. Finally, evidence for the ring juncture stereochemistry was obtained by isomerisation of a sample of VII cis to VII' trans. This could be carried out by treatment of VII with NEt_3 in methanol.

Spectroscopic data fully corroborate the assigned structure (10).

VII containing the correct stereochimistry and manageable functionality was efficiently converted to the key intermediate III, precursor of the

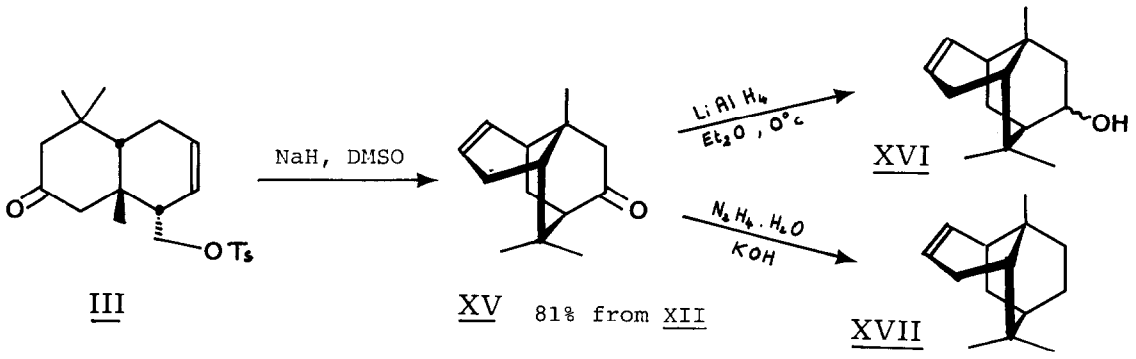
desired tricyclic system, according to the following sequence :



Protection of the hydroxyl group VII was necessary to preclude intramolecular addition to other functionality (11). Interaction with the methoxy function through the double bond, allowed one of the two carbonyl groups to be much less susceptible to reduction than the other. Thus, $NaBH_4$ reduction of VIII afforded stereoselectively alcohol IX (12). This later was readily converted to the corresponding acetate X by the hypernycleophilic acylation catalyst N,N-dimethylaminopyridine (13). Reduction of acetate X with lithium in liquid NH_3 using tBuOH under controlled conditions, yielded primarily the non-conjugated enone XI'. Conjugation was operated directly under appropriate work-up to afford enone XI in 78% overall yield from VII after chromatographic purification (14).

Treatment of XI with CH_3Li in ether followed by *in situ* smooth solvolysis of the resulting tertiary alcohol, afforded enone XII in 86% yield. Lithium-dimethylcopper added in 1-4 position to give exclusively the saturated cyclohexanone XIII. The key keto-tosylate III was achieved by THP removal from XIII, followed by treatment of the resulting alcohol with toluene-p-sulphonyl chloride in dry pyridine. The keto-tosylate was then treated with an excess of methylsulphinyl carbanion in DMSO (15) to give the desired tricyclic ketone XV in 81% overall yield from XII.

Finally, this ketone was quantitatively reduced to the tricyclic alcohol XVI (isonorpatchoulenol) or to the tricyclic hydrocarbure XVII (deoxynorpatchoulenol).



III XV 81% from XII XVI XVII

Total synthesis of norpatchoulenol I using this stereoselective approach is in progress in this laboratory.

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10) The DIELS-ALDER reaction thus described, gives two products which are mirror images. Only one stereoisomer of VII is drawn, but the reaction sequence reported below will produce both stereoisomers of the endproducts.
11) Since the THP protecting group cannot be introduced stereoselectively, compound VIII exits as a mixture of two diastereoisomers. For the sake of simplicity, mixtures of isomers resulting from the asymmetry of the THP group will be refered to as one compound.
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14) The sequence V XI was basicaly inaugurated during a post-doctoral stage at HARVARD University, E.J. Corey et al., unpublished results.
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