

198. A Short Stereoselective Total Synthesis of Racemic Patchouli Alcohol

Preliminary Communication

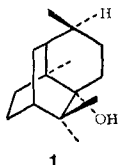
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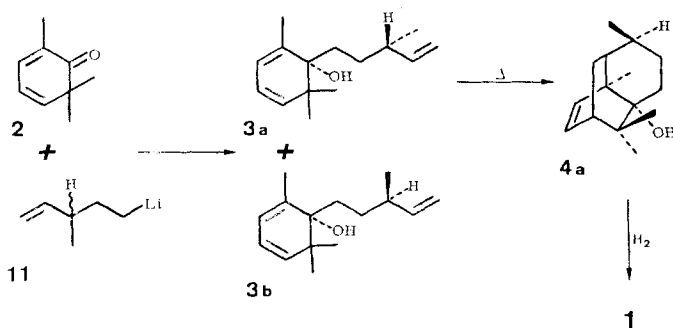
Summary. A stereoselective four-step synthesis of racemic patchouli alcohol starting from the known 2,6,6-trimethyl-2,4-cyclohexadien-1-one [1] and 3-methylpent-4-en-1-ol [2] is described.

Patchouli alcohol (**1**) is the major component of patchouli oil, an important raw material for the perfume industry. The structure of patchouli alcohol (**1**) has been definitely established by X-ray analysis of the corresponding chromate ester [3].



There already exist three fairly long syntheses [4]–[6] of patchouli alcohol. We here present a short route leading stereoselectively and in only four steps to racemic patchouli alcohol¹⁾, involving an intramolecular *Diels-Alder* reaction as a key step.

Our synthesis starts from 2,6,6-trimethyl-2,4-cyclohexadien-1-one (**2**) [1] which upon reaction with 3-methylpent-4-enyl-lithium (**11**) yielded a ~1:1-mixture (~59%



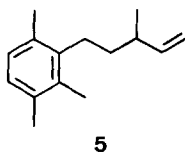
based on **2**) of the diastereoisomeric dienols **3a** and **3b**. Of these isomers only **3a** possesses the correct configuration. Both alcohols **3a** and **3b** are very labile towards acid and decompose even on silica gel. The 60-MHz-NMR. spectrum (in CDCl_3) of the bulb distilled (at 80–91°/0.03 Torr) diastereomeric mixture **3a/3b** (ratio ~1:1)

¹⁾ A way to the optically pure (+)- and (–)-enantiomers will be described in the full paper [7].

was in good accord with the structure given (*sec*-CH₃ at δ 0.95 ppm, *d*, $J \sim 5.5$ Hz; two *tert*-CH₃ at δ 1.0 ppm, *s*; =C-CH₃ at δ 1.81 ppm; two *gem* vinyl protons at δ 4.75 and 4.98 ppm; four olefinic protons at δ 5.2–6.0 ppm, superimposed complex *m*).

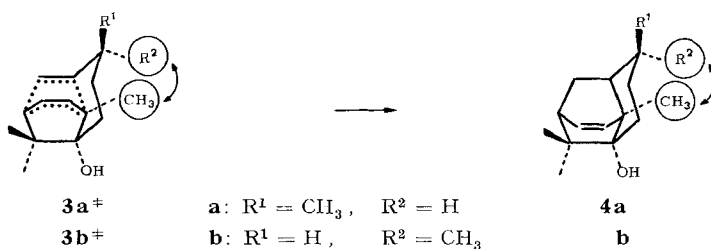
When a degassed solution of these alcohols (**3a/3b**, 1:1 ratio) in decalin was heated in the presence of 5% potassium *t*-butoxide for 24 h at 280° in a sealed glass tube, a stereoselective intramolecular *Diels-Alder* reaction took place to give the racemic, tricyclic alcohol **4a** (yield $\sim 30\%$ based on **3a** + **3b**; or $\sim 60\%$ based on **3a**) which was isolated in pure form by preparative gas chromatography (5% silicon 5 mm \times 2.5 m column; 190°). Apart from **4a** several, more volatile, unknown by-products were also formed.

Significantly, in the *absence* of *t*-butoxide, a catalyst which proved decisive for the success of this approach, only the undesired aromatized compound **5** was obtained.



The effect of potassium *t*-butoxide is not yet sufficiently understood. It might merely act as a stabilizer and prevent elimination of water from alcohol **3**. Alternatively, this particular *Diels-Alder* reaction may also be *catalyzed via* homoconjugation of the oxyanion with the diene system.

The structure of **4a** was established by NMR. (90-MHz, in CDCl₃: *sec*-CH₃ at δ 0.82 ppm, *d*, $J \sim 6.5$ Hz; a *tert*-CH₃ at δ 0.91 ppm, *s*; two *tert*-CH₃ δ 1.18, *s*; =CH- at δ 5.81 ppm, *d*, $J \sim 8$ Hz, with fine splitting; =CH- at δ 6.35 ppm, *d* \times *d*, $J \sim 8$ Hz, $J' \sim 7$ Hz) and by direct comparison (retention time on GC., IR., NMR. and MS.) with an authentic sample of the (–)-enantiomer of **4a** [4]²).

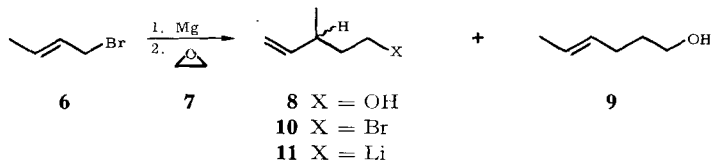


Predilection of the *Diels-Alder* reaction for the desired alcohol **4a** is readily understood by comparing the two transition states **3a[‡]** (leading to **4a**) and **3b[‡]** (leading to **4b**). A severe 1,3-diaxial methyl-methyl interaction is present in **3b[‡]**, operating against formation of **4b**.

The racemic 3-methyl-4-pentenyl side chain was prepared from crotyl bromide by way of *Grignard* reaction with ethylene oxide. Crotylmagnesium bromide is known to react with electrophilic substrates preferentially at the secondary carbon [8] and was therefore expected to give the branched 3-methyl-4-pentenol (**8**) rather than the

²) We are indebted to Professor G. Büchi, M.I.T. Cambridge, USA, for a sample of alcohol **4a**.

linear 4-hexenol (**9**). A 3:1 mixture of **8** and **9** was indeed obtained in 90% yield, and the desired isomer **8** was easily separated by fractional distillation on a *Fischer* column (type MS 300, ~40 plates). This preparation of alcohol **8** was much easier than the one described earlier [2]. Bromination of alcohol **8** using PBr_3 and pyridine gave in 68% yield bromide **10** which on reaction with lithium (containing 1.5% Na) in ether at -8° led to the organolithium reagent **11**.



Hydrogenation of the tricyclic alcohol **4a** as described by *Büchi & Erickson* [4a] gave racemic patchouli alcohol whose retention time on GC. (5% silicon 5 mm \times 2.5 m column) and spectra (90-MHz-NMR., IR. and MS.) were identical with those of natural patchouli alcohol.

Epilogue. - Although the plan of this synthesis is straightforward and can be visualized without the aid of a computer³⁾, it has never been carried out before. A computer may well be able to find many dazzling potential solutions but it often fails to take account of the inherent difficulties (*viz* *Diels-Alder* step p. 1869, and ref. [10]). Until computers are 'smarter' and less expensive, a chemist with some intuition, perseverance and luck would still seem to have a role. Nevertheless, we would not wish to discourage those who think travelling hopefully with a computer is better than arriving.

We are indebted to Mr. *Philippe Lang* and Miss *Therese Manz* for skilful technical assistance.

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³⁾ For a computer analysis of patchouli alcohol see [9].