

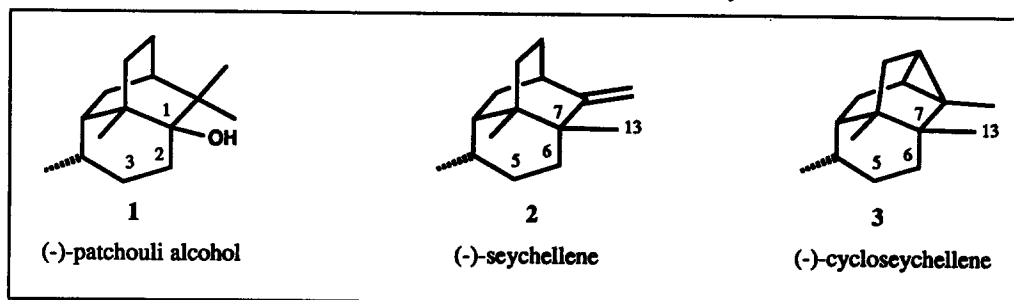
A Divergent Approach to Patchouli Sesquiterpenes: Synthesis of 3-Oxopatchouli Alcohol, 5-Oxo-7-hydroxy-13-norcycloseychellene, 6-Methoxy-4,12-dehydro-13-norcycloseychellene And Patchouli Alcohol

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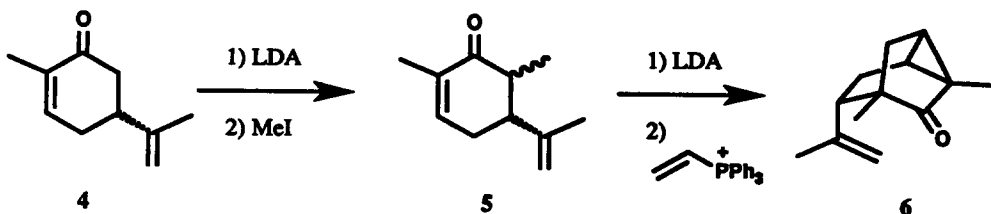
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Summary: α -Methylation of (-)-carvone followed by bicycloannulation with vinyltriphenylphosphonium bromide gives a 59% yield of a tricyclo[3.2.1.0^{2,7}]octan-6-one which can be converted to precursors of (-)-patchouli alcohol, (-)-seychellene and (-)-cycloseychellene.

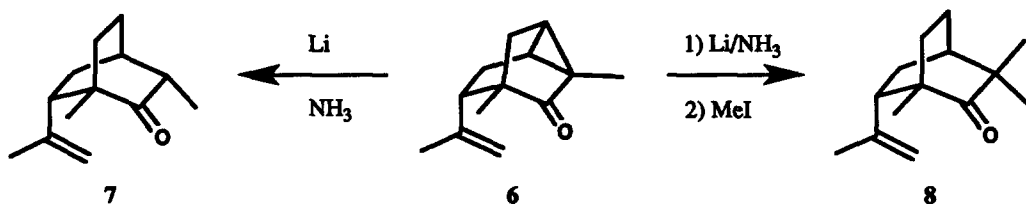
Among the many terpenes which have been isolated from patchouli oil, the tricyclic sesquiterpenes (-)-patchouli alcohol (1) and (-)-seychellene (2) and the tetracyclic sesquiterpene (-)-cycloseychellene (3) have attracted particularly strong attention. Considerable synthetic interest in these compounds has resulted in several total syntheses.¹ We now report a *unified* approach to these ring systems which reduces the number of required synthetic operations by employing a one-pot conversion of a monocyclic substrate to a tricyclic intermediate.



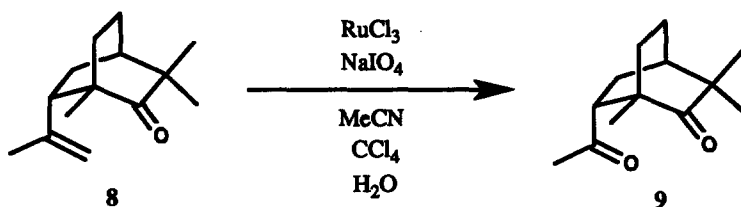
The synthesis of this key intermediate proceeded as follows. Methylation of (-)-carvone (4) via its kinetic enolate (LDA, THF, hexane, 0 °C; MeI) gave methyl carvone 5 as a mixture of diastereomers in 91% yield, a significant improvement over previously published yields.² The key tricyclic intermediate was then constructed in one step by vinyl phosphonium bicycloannulation³ of 5 (LDA, THF, hexane, 0 °C; CH₂=CHPPh₃Br, pyridine, reflux, 3 h)⁴ to give, stereoselectively, tricyclo-octanone 6^{2,3} in 65% yield. This intermediate is the cornerstone for planned syntheses of all three of the above-mentioned patchouli sesquiterpenes.



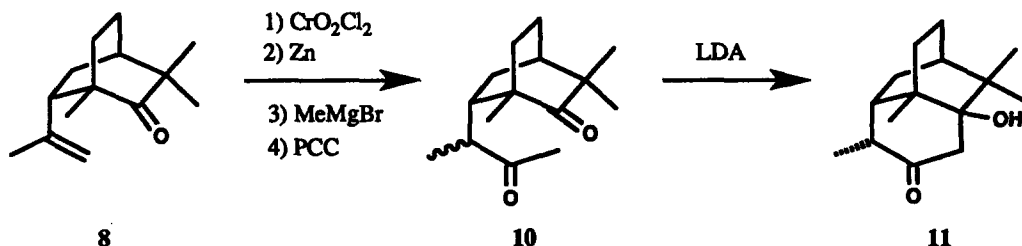
Reductive cleavage⁵ of the cyclopropyl ketone moiety of **6** (Li, NH₃, THF) was both regioselective and stereoselective, giving rise to bicyclo-octanone **7**, a potential precursor of (-)-seychellene (**2**). Reductive cleavage-alkylation (Li, NH₃, THF, *t*-BuOH; MeI) of **6** gave bicyclo-octanone **8** in 90% yield. Oxidative cleavage⁶ of **8** afforded



enantiomerically pure diketone **9** in 94% yield (mp 74-75 °C; racemic mp 51-52 °C⁷). The overall yield of **9** from commercially available (-)-carvone was 50% over four steps. In view of the two previous conversions of the *racemic* modification of **9** to *racemic* patchouli alcohol,^{7,8} the synthesis of this homochiral diketone constitutes a formal synthesis of (-)-patchouli alcohol (**1**). Furthermore, racemic **9** is a useful intermediate in the manufacture of perfume components and is the subject of at least two patents.⁹ Since both enantiomers of carvone are commercially available and inexpensive, both **9** and its enantiomer are now readily available without resolution.

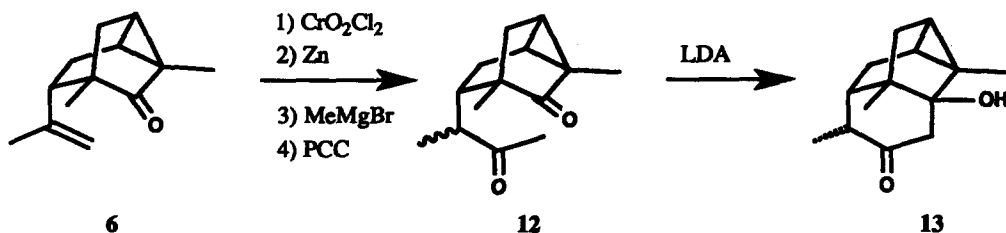


Alternatively, chromyl chloride oxidation of the olefinic moiety of **8** (CrO₂Cl₂, CH₂Cl₂, 0 °C; Zn, H₂O)¹⁵ followed by Grignard reaction of the resulting keto-aldehyde (MeMgI, Et₂O, inverse addition) and oxidation (PCC, NaOAc, CH₂Cl₂) afforded diketone **10**, as a single diastereomer of unknown configuration, in 46% overall yield. Closure of the remaining ring of the patchouli alcohol system was accomplished by intramolecular aldol condensation (LDA, THF, hexane, 0 °C, 1 h), resulting in a 75% yield of 3-oxopatchouli alcohol (**11**).¹⁰

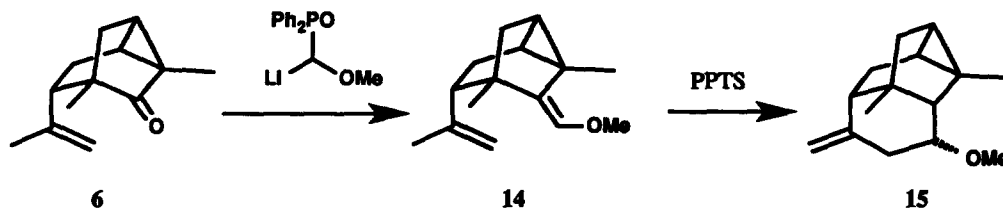


The key intermediate in this divergent approach, keto-olefin **6**, is also the branch point for projected syntheses of (-)-cycloseychellene (**3**). Modification of the isopropenyl group of **6** (in the same manner as in the preparation of diketone **10**) provided diketone **12** as a mixture of diastereomers in 83% overall yield. Aldol cyclization as described above gave, quantitatively, 5-oxo-7-hydroxy-13-norcycloseychellene (**13**) as a *single* diastereomer (the secondary methyl group is assumed to have the more stable equatorial orientation).¹⁰

Alternatively, a Horner-Wittig olefination¹¹ of **6** (Ph₂POCHLiOMe, THF, 17 h) provided enol ether **14** in 85%



yield. Surprisingly, attempted hydrolysis of 14 to the corresponding aldehyde (*t*-BuOH or wet acetone, PPTS, reflux 3-24 h)¹² led instead to 6-methoxy-4,12-dehydro-13-norcycloescyhellene (15)¹⁰ by intramolecular trapping of the intermediate carbocation resulting from protonation of the enol ether moiety. This apparently unprecedented reaction may be mechanistically related to the intramolecular Prins (ene) reaction.¹³ In any case, this serendipitous availability of a precursor possessing the complete ring system of (-)-cycloescyhellene in only four steps from (-)-carvone offers the possibility of an extremely concise synthesis of this structurally complex sesquiterpene.¹⁴



Acknowledgement: We wish to express our thanks to Professor Marcel Bertrand for providing us with a copy of an ¹H NMR spectrum of the racemic modification of diketone 9. Financial support of this work by the Natural Sciences and Engineering Research Council of Canada is gratefully acknowledged.

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10. ^1H NMR (200 MHz, CDCl_3):
 - 11: δ 2.75 (d, 1H, $J = 15$ Hz), 2.69 (m, 1H), 2.40 (d, 1H, $J = 15$ Hz), 1.15-1.98 (m, 9H), 1.10 (s, 3H), 1.07 (s, 3H), 1.03 (d, 3H, $J = 6$ Hz), 0.92 (s, 3H).
 - 13: δ 2.74 (d, 1H, $J = 14$ Hz), 2.68 (m, 1H), 2.45 (d, 1H, $J = 14$ Hz), 1.85 (dd, 1H, $J = 12, 4$ Hz), 1.78 (m, 2H), 1.60 (d, 1H, $J = 12$ Hz), 1.46 (m, 2H), 1.17 (s, 3H), 1.14 (m, 1H), 1.10 (s, 3H), 0.89 (d, 3H, $J = 6.5$ Hz), 0.76 (dd, 1H, $J = 8, 4$ Hz).
 - 15: δ 4.57 (m, 1H), 4.50 (m, 1H), 3.39 (s, 3H), 3.37 (dd, 1H, $J = 8, 4$ Hz), 2.40 (m, 2H), 2.15 (dd, 1H, $J = 14, 10$ Hz), 2.02 (d, 1H, $J = 4$ Hz), 1.81 (d, 1H, $J = 10$ Hz), 1.63 (dd, 1H, $J = 14, 4$ Hz), 1.57 (d, 2H, $J = 1$ Hz), 1.26 (s, 3H), 0.81 (s, 3H), 0.79 (dt, 1H, $J = 8, 1$ Hz), 0.72 (dd, 1H, $J = 8, 4$ Hz).
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