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A new Enantiospecific Route toward Monocarbocyclic Terpenoids: Synthesis of (-)- Caparrapi Oxide

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Abstract:

A new and efficient strategy is described for carrying out the enantiospecific synthesis of monocarbocyclic terpenoids from (-)-sclareol (**1**). The key steps are the Grob scission of 11-*p*-toluenesulphonyloxydriman-7α-ol (**2**) to give the tobacco seco-sesquiterpene **3** and the Baeyer-Villiger oxidation of 4-[(*1'S, 2'S*)-2'-formyl-2',6',6'-trimethylcyclohexyl]-2-butanone (**4**), derived from **3**. The first enantiospecific synthesis of (-)-caparrapi oxide (**8**) based on this methodology is reported.

Keywords: Terpenoids; enantiospecifity; Baeyer-Villiger reactions.

Monocarbocyclic di- and triterpenoids are interesting metabolites because of their unusual structural features and biological activity. However, these compounds are scarce owing to biosynthetic processes often involving polycyclization.

Over the last few years the isolation of some of these metabolites has been reported. Caparrapi oxide (**8**) [1], 8-epicaparrapi oxide (**9**) [2], **14** [3] and trixagol (**15**) [4] are representative compounds.

In this paper the enantiospecific synthesis of **8** and **9** from (-)-sclareol (**1**) is reported. These compounds have been previously obtained in low yield by electrophilic cyclization of nerolidol [5, 6]. Lombardi et al reported a synthesis of the same terpenoids from dihydro-β-ionone [7]. The sequence starts with the drimanic tosyl derivative **2** [8], which undergoes Grob scission by treating with NaH in dimethoxyethane, to give **3** in quantitative yield. An efficient synthesis of this seco-sesquiterpene, isolated from *Nicotiana tabacum* L. [9], has not previously been reported. Ozonolysis of **3** and subsequent reduction with PPh_3 yielded the aldehyde **4**, which underwent Baeyer-Villiger rearrangement by treating with *m*-chloroperbenzoic acid to afford in high yield the formate **5**.[1] Regioselective elimination took place when **5** was refluxed with collidine, affording a 8:1 mixture of **10** and **11**. **10**[2] is a suitable synthon to prepare compounds as **15**. Reaction of **5** with vinylmagnesium bromide and further hydrolysis with KOH-MeOH gave the diol **6** as a 7:3 mixture of diastereoisomers.[3] Acetylation of **6** yielded a 6:4 mixture of **7** and **12**.

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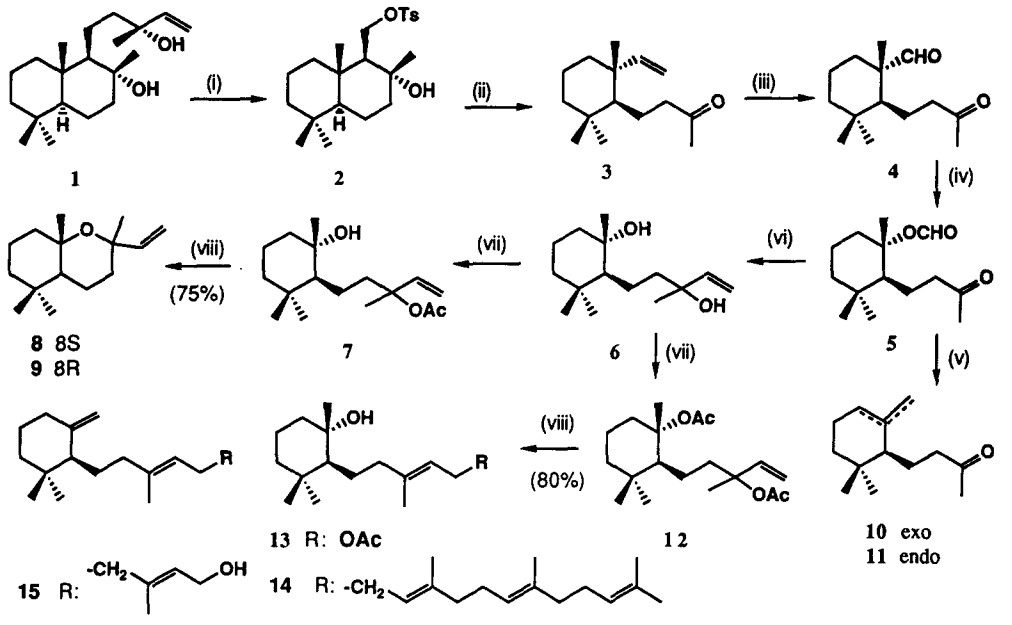
Treatment of **12** with $PdCl_2(CH_3CN)_2$ afforded the rearranged ester **13** (*E*/*Z* 9:1),[4] which is an appropriate synthon for preparing terpenoids such as **14**. Under the same reaction conditions the monoacetate **7** gave (-)-caparrapi oxide (**8**) and its 8-epimer (**9**) (ratio 2:1) in 75% yield. The physical properties of **8** and **9** were identical to those reported in the literature [1,2,10].



(i) Ref.8. (ii) NaH, DME, reflux, 2.5 h (95%). (iii) O_3, CH_2Cl_2, -78°C, 20 min; Ph_3P, -78°C--rt.14 h (75%). (iv) MCPBA, CH_2Cl_2, rt, 5 days (93%). (v) Collidine, reflux, 2.5 h (90%). (vi) CH_2=CHMgBr, Et_2O, 0°C; rt, 20 min; 2 N KOH-MeOH, rt, 4 h (90%). (vii) Ac_2O, DMAP, Et_3N, THF, reflux, 4 days. (viii) $PdCl_2(CH_3CN)_2$, THF, rt, 12 h.

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Significant ^1H- and ^{13}C-NMR data:

1 -OC<u>H</u>O: δ 8.05 ppm, s; -O<u>C</u>HO: δ 160.5 ppm.

2 =C<u>H</u>$_2$: δ 4.52 ppm, d, J = 2.2 Hz and 4.78 ppm, bs; =<u>C</u>H$_2$: δ 109.5 ppm.

3 C<u>H</u>=CH$_2$: δ 5.91 and 5.96 ppm, dd, J= 17.4 and 10.7 Hz; CH=C<u>H</u>$_2$: δ 5.24 and 5.27 ppm, d, J = 17.4 Hz; CH=C<u>H</u>$_2$: δ 5.05 and 5.09 ppm, d, J =10.7 Hz. <u>C</u>H=CH$_2$: δ 145.3 and 146.0 ppm; CH=<u>C</u>H$_2$: δ 111.3 and 111.9 ppm.

4 C<u>H</u>$_2$OAc: δ 4.59 ppm, d, J = 7.1 Hz; <u>C</u>H$_2$OAc: δ 61.4 and 61.5 ppm.