

ISOPRENOID HOMOLOGATION

A SYNTHESIS OF ISOPRENOID ALCOHOLS USING TERPENE BUILDING BLOCKS

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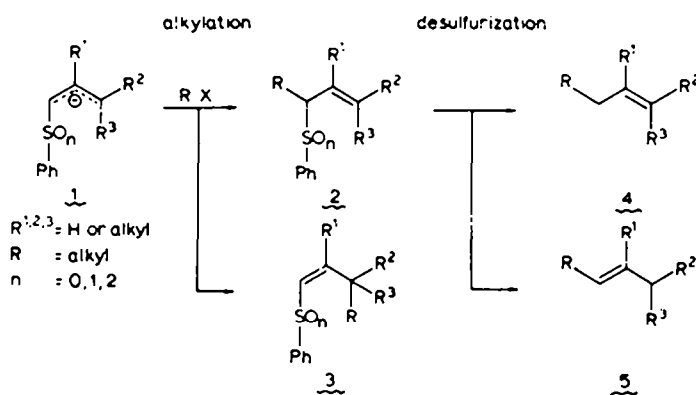
Abstract—This paper describes the synthesis of linalool and nerolidol by means of a regioselective coupling of the hydroxy-sulfoxide **6a** with prenyl- and geranyl bromide, followed by reductive desulfurization.

The structural elucidation of insect juvenile hormones and insect pheromones has considerably stimulated the search for poly-isoprenoid synthesis.

Many isoprenoids have been synthesized by the coupling of a sulfur-stabilized, allylic carbanion 1 with an appropriate halide RX. However, this method has an intrinsic limitation: the ambident character of the allylic anion causes the formation of double bond isomers during both the alkylation and desulfurization procedure.¹ The yield of γ -alkylated product 3 frequently exceeds 25%.² After the reductive desulfurization of 2, the ratio of 4/5 may even become smaller than unity.³

and can not exhibit any isomerization. The utility of this building block is illustrated by the stepwise building up of the nerolidol skeleton. The dithio derivative **6b** is easily prepared by treatment of a THF solution of **6a** with butyllithium in hexane. Addition of prenylbromide to **6b**, followed by quenching with one equivalent of dilute sulfuric acid, leads to the formation of the alpha-alkylated product **7**. The introduction of the third asymmetric centre proceeds in a highly stereoselective manner. The two possible diastereomers are formed in a 95/5 ratio.[†] No trace of O-alkylated product has ever been detected.

The reductive desulfurization of **7** is carried out with



Scheme 1.

As part of a broader investigation into improved homologations of functionalized isoprenoids, we wish to report a synthesis which excludes the formation of positional isomers of the double bond during alkylation and reductive desulfurization. The poly-isoprenoids are built up by a stepwise addition of the five-carbon unit **6a**, which is prepared in one single operation from isoprene.⁴

RESULTS AND DISCUSSION

The coupling reaction is performed with the dilithiated sulfoxide **6b**. This anionic species is not stabilized by allylic delocalization. For this reason it is very reactive

lithium in ethylamine and gives the corresponding terpene alcohol, linalool, in 80% yield after column chromatography. Depending on the reaction conditions, some terminal double bond reduction is observed. We have not tried to suppress this side reaction.

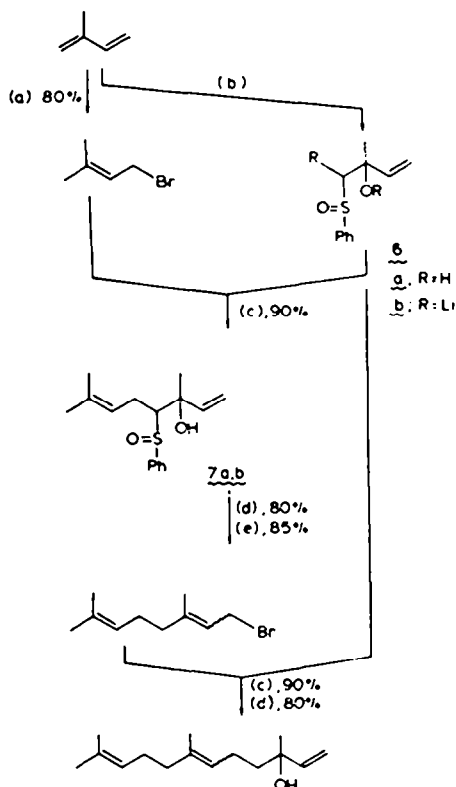
Before the addition of another C-5 unit can take place, the conversion of linalool into a geranylhalide is required. Although this rearrangement is well documented in the literature,⁷ we found this conversion to be most troublesome. Methods claimed for conversion of linalool into geranylbromide⁸ led in our hands to considerable amounts of the (Z)-isomer nervylbromide.

A 75/25 mixture of geranyl- and nerylbromide was prepared by a phosphorus tribromide promoted allylic rearrangement.⁷ The coupling of **6b** with this halide mixture was performed as described above for prenylbromide. Reductive desulfurization again led to the sulfur free alcohol. After column chromatography, nerolidol

†This hydroxy sulfoxide **6a** is a racemic mixture of the configurations *RR* and *SS*.

†Comparable results have been obtained starting from the racemic hydroxy sulfoxide with the *RS/SR* configuration.

was isolated in 72% yield as a 75/25 mixture of its (E)- and (Z)-isomers.



Scheme 2. (a): aq. HBr, CuBr, (b) PhSH-O₂, (c) BuLi, THF. (d): Li, EtNH₃, (e) PBr₃, pyridine.

EXPERIMENTAL

All alkylations and reductions were carried out under N₂. The *n*-BuLi (Merck, Darmstadt) was a 19.2% soln in *n*-hexane. THF was freshly distilled from LAH prior to use. Satisfactory elemental analyses were obtained for all new compounds. IR and NMR (TMS, $\delta = 0$) were recorded on a Unicam SP200 spectrometer and a Varian associates model HA-100 instrument, respectively. GLC-analyses were performed on an all glass modified, Varian Aerograph series 1700 apparatus, using a 3 ft Carbowax 20M column at 150°C.

Preparation of the dithiosulfoxide 6b. 1.04 ml of the hexane soln of *n*-BuLi (2 mmol) was added dropwise to a soln of 210 mg (1 mmol) of the sulfoxides 6a in 15 ml THF at -78°. The so formed yellow-orange soln was stirred for an additional 15 min.

Prenylbromide.⁹ 10 g (0.07 mol) CuBr was dissolved in 500 ml 47% aqueous HBr. This soln was vigorously shaken for 5 min with 50 ml (0.5 mol) isoprene in a separatory funnel. The layers were separated and the organic layer was dried by filtration over MgSO₄. The prenylbromide was isolated by distillation from K₂CO₃, yield: 58.3 g (78%).

Alkylation of the sulfoxide 6a with prenylbromide. To the THF soln of the dithiated sulfoxide 6b, prepared as described above, was added 149 mg (1 mmol) prenylbromide. The temp. was

maintained at -60° for 30 min and then allowed to rise to 0°. The mixture was poured into water, to which 1 eq H₂SO₄ had been added previously. The product was isolated by extraction with ether. The combined extracts were dried over MgSO₄ and the solvents were removed *in vacuo*. The crude sulfoxide 7 (240–260 mg, 90–95%) was used without purification in the reductive desulfurization.[†] ¹H NMR (CCl₄): 7.30–7.55 and 7.55–7.75 (m, phenyl), 4.90–5.90 (m, C₁-H and C₂-H), 4.55–4.75 (t, C₃-H), 2.73–2.84 (m, C₄-H), 2.05–2.15 (broad t, C₅-H), 1.49 (s, C₆-Me and C₇-Me or C₈-H), 1.41 (s, C₉-H or C₁₀-Me): IR (CHCl₃): 3380 and 995 cm⁻¹ (OH and SO).

Reductive desulfurization of the coupled sulfoxide 7. The coupled product (278 mg, 1 mmol) was dissolved in 10 ml ethylamine and the temp. of the soln was lowered to -78° using an alcohol-dry ice bath. Li wire (210 mg, 30 mmol) was added and the soln was stirred until a blue colour appeared. The excess of Li was removed and solid NH₄Cl (800 mg) was added. The ethylamine was carefully evaporated under reduced pressure. The residue was dissolved in water and extracted four times with ether. The combined organic fractions were dried over MgSO₄, filtered and evaporated, affording a clear residue. Chromatography on silicagel (benzene) yielded 125 mg linalool (82%) identical in all respects to the autentic material. 15 mg (10%) dihydrolinalool was isolated, originating from overreduction of the coupled product.

Conversion of linalool into a 75/25-geranyl neryl bromide mixture. The conversion of linalool into the bromide-mixture was essentially performed according to the method described by Babler.⁷ To a cooled soln (-70°) of 770 mg (5 mmol) linalool and 0.5 ml pyridine in anhydrous ether was added a soln of 475 μ l PBr₃ (5 mmol) in dry pentane. The mixture was stirred for 1 hr at -70°, poured into ice water and extracted with pentane. The extracts were washed with 5% H₂SO₄ aq and dried over CaCl₂, to give 920 mg (85%) of the bromide-mixture.

Alkylation of sulfoxide 6a with geranyl neryl bromide mixture. 217 mg (1 mmol) of bromide mixture was added to the THF soln of the dithiated sulfoxide 6b, prepared as described above. The mixture was stirred at -20° overnight and worked up as described for 7. Evaporation provided a clear oil. Chromatography on silicagel (CH₂Cl₂/EtOAc 25:1) gave the pure coupled product (245 mg, 86%). ¹H NMR (CCl₄): 7.30–7.55 and 7.55–7.80 (m, phenyl), 4.80–5.90 (m, C₁-H, C₂-H, C₁₀-H), 4.50–4.75 (t, C₃-H), 2.67–2.80 (t, C₄-H), 2.05–2.25 (t, C₅-H), 1.76 (broad s, C₆-H), 1.45 (s, C₇-Me), 1.58, 1.50 and 1.38 (s, remaining methyl). IR: (liq): 3400, 1428, 1010 cm⁻¹ (OH, CH, SO).

Reductive desulfurization of the C₁₅-coupled sulfoxide. The reductive desulfurization of 330 mg (1 mmol) of the C₁₅-coupled sulfoxide was carried out as described above for the C₁₀-coupled sulfoxide 7. Pure nerolidol was obtained (160 mg, 75%) upon chromatography (benzene/silicagel) preceded by dihydronerolidol (40 mg, 20%) [(E)/(Z) = 75/25].

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[†]Purified products (columnchromatography, silicagel, CH₂Cl₂) gave slightly higher yields in the reduction.

[‡]To our surprise addition of the sulfoxide to a previously prepared solution of Li in ethylamine led to the reduction of the sulfoxide grouping to the sulfide only.