

## SYNTHESIS OF GERANIOL-9-<sup>14</sup>C. METHODS FOR OBTAINING LABELED GERANIOLS FREE OF CITRONELLOL

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### SUMMARY

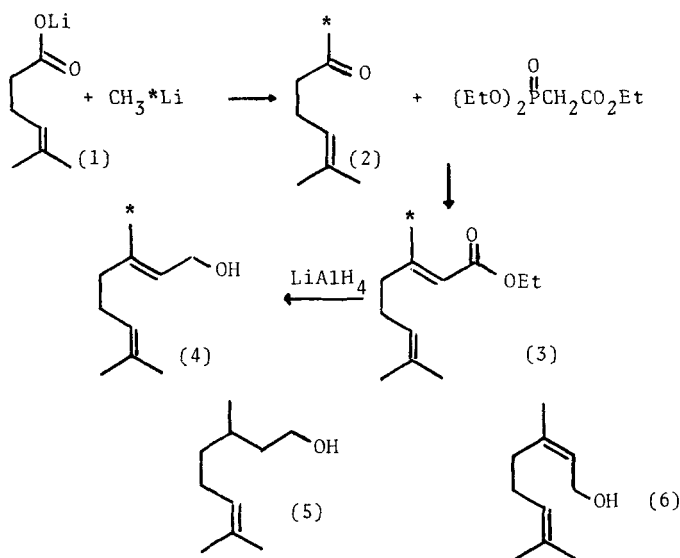
*Geraniol-9-<sup>14</sup>C has been prepared starting with methyl lithium-<sup>14</sup>C. Methods have been developed for obtaining radiolabeled geraniol free of citronellol and other by-products.*

### INTRODUCTION

Geraniol (4) labeled with <sup>14</sup>C or <sup>3</sup>H has been used extensively in biosynthetic studies on terpenes and steroids. Methods for the preparation of geraniol-2-<sup>14</sup>C (1,2,3) geraniol-3-<sup>14</sup>C (4) and geraniol-7-<sup>14</sup>C (5) are known. Here we report the synthesis of geraniol-9-<sup>14</sup>C. Labeling of the 9-methyl group would be useful in biosynthetic studies since geraniol-9-<sup>14</sup>C will lead to terpene or steroid metabolites that are labeled at methyl or methylene positions in the natural product. Such groups present in complex terpenes or steroids are more accessible and easy to isolate in a chemical degradation procedure used to determine the specific location of the label in the biosynthesized natural product.

The starting material in our synthesis of geraniol-9-<sup>14</sup>C was 5-methyl-4-hexenoic acid which was prepared by decarboxylation of 2-carboxy-5-methyl-4-hexenoic acid (6). In addition to the lactone by-product reported to be formed in this reaction (7) we also obtained

a second by-product which is believed to be 5-methyl-5-hexenoic acid (vinyl protons at  $\delta$ 4.68, broad singlet). The 5-methyl-4-hexenoic acid was purified by preparing its *p*-chlorophenacyl ester derivative followed by base hydrolysis of the ester. The lithium salt (1) of 5-methyl-4-hexenoic acid was prepared in anhydrous ether by allowing 1 equivalent of unlabeled methyl lithium to react with the acid. Methyl lithium  $^{14}\text{C}$  (0.1 equivalent) followed by carrier methyl lithium (0.5 equivalent) were then added to the freshly prepared (1) (7). The resulting 6-methyl-5-hepten-2-one-1- $^{14}\text{C}$  (2) was converted to ethyl *trans*-3,7-dimethyl-2,6-octadienoate-9- $^{14}\text{C}$  (3) with triethylphosphonoacetate in the presence of sodium hydride<sup>(4,5)</sup>



Ethyl *trans*-3,7-dimethyl-2,6-octadienoate-9- $^{14}\text{C}$  was reduced to geraniol-9- $^{14}\text{C}$  (4) using excess lithium aluminum hydride in ether at  $-70^\circ$  for 1 hr followed by 15 min at room temperature. We obtained about 10% citronellol (5) but no nerol (6) in this reaction. The formation of the citronellol by-product has been a recurring problem in the synthesis of labeled geraniols. Battersby, Laing and Ramage<sup>(8)</sup>

have attempted to avoid this problem by using an ethoxy aluminum hydride reducing agent. However, they still obtained 4% citronellol (5) and 6% nerol (6). We have found that the citronellol by-product can be easily removed by thin layer chromatography on silver nitrate impregnated silica gel. We have also examined the reduction reaction more closely with the intention of finding a method that would give geraniol cleanly - free of citronellol or other impurities. In this connection we have investigated the effect of temperature, solvent, and reaction time on the amount of citronellol by-product formed in this reaction. The data in Table I suggests that ether is a more suitable solvent for this reaction than the more polar tetrahydrofuran solvent. The temperature of the reaction is critical. Greater amounts of citronellol are formed as the temperature of reaction is increased while at very low temperatures (-70°) the reduction of the ester function proceeds only slowly. Thus the ideal temperature appears to be -35°. At this temperature very little if any of the citronellol by-product is formed and reduction of the ester to geraniol is complete within 2 hrs when a large excess of lithium aluminum hydride reagent is used. We found no advantage in using an ethoxy lithium aluminum hydride reagent following the reported procedure (8). The corresponding isopropoxy lithium aluminum hydride reagent was also not useful. It has been reported (9) that cinnamyl alcohol is reduced to 3-phenyl-1-propanol using lithium aluminum hydride, however, in our studies geraniol was not reduced to citronellol even with excess lithium aluminum hydride in refluxing tetrahydrofuran. It is probable that citronellol formation occurs by reduction of the conjugated double bond in (3) for which there is precedent (10) followed by reduction of the ester function. Nerol was not obtained as a by-product in any of the reduction experiments that we carried out using pure *trans* (3). Finally it is recommended that the reduction reaction be quenched with ethanol (at -70°) rather than with methyl acetate.

Table I. Reduction of ethyl *trans*-3,7-dimethyl-2,6-octadienoate (3) with excess lithium aluminum hydride in ether or tetrahydrofuran<sup>(a)</sup>.

exp.	solvent	temp	time (hr)	unreacted ester (3)	geraniol(4)	citronellol (5)
1.	ether	-70°	2	98%	2%	0
2.	"	-60°	2	96	4	0
3.	"	-50°	2	64	36	0
4.	"	-35°	2	0	>99.8	<0.2%
5.	"	0°	2	0	94	6
6.	"	25°	2	0	83	17
7.	"	-35°	1	23	77	0.2
8. <sup>b</sup>	"	-35°	8	0	99.6	0.4
9. <sup>c</sup>	"	5°	4	0	88	12
10. <sup>d</sup>	"	5°	4	0	87	13
11.	THF	-35°	2	0	50	50

- (a) The percent of monoterpenes listed represent the amounts determined by analytical gas chromatography using the two chromatography systems described in the experimental section.
- (b) Geraniol was not reduced to citronellol after refluxing in ether saturated with LiAlH<sub>4</sub> for 8 hrs or refluxing in tetrahydrofuran saturated with LiAlH<sub>4</sub> for 21 hrs.
- (c) Experiment 9 was carried out with added ethanol using the reported procedure<sup>(8)</sup>.
- (d) Experiment 10 was carried out in the same manner as experiment 9 but replacing ethanol with isopropanol.

## EXPERIMENTAL

Analytical gas chromatography was carried out on a Hewlett Packard F + M model 700 instrument. Ethyl *trans*-3,7-dimethyl-2,6-octadienoate, geraniol<sup>(11)</sup>, citronellol<sup>(11)</sup> and nerol<sup>(12)</sup> were identified using two different chromatography systems. Aluminum columns (1/8" O.D. by 6') were packed with 15% carbowax 20M on 80-100 mesh chromosorb W-NAW (system I) and 15% diethylene glycol-succinate on 80-100 mesh chromosorb W-NAW (system II). In both systems the oven temperature was maintained at 110° with a helium gas flow rate of 30 ml per min. Injection port and detector temperatures were maintained at 145° and 165° respectively. Radioactivity measurements were carried out in a Packard model

3320 Tri-Carb liquid scintillation counter using toluene solvent and a PPO-POPOP scintillator system (13).

#### 5-Methyl-4-hexenoic acid

Crude 5-methyl-4-hexenoic acid (6) was converted to its *p*-chlorophenacyl ester (mp 71-72°, recrystallized from ethanol) using the procedure of Rather and Reid (14). Base hydrolysis of the ester with refluxing 5% sodium hydroxide followed by careful acidification (6), ether extraction and short path distillation of the oil obtained following evaporation of the ether gave essentially pure 5-methyl-4-hexenoic acid:  $n_D^{23^\circ}$  1.4458 (reported (15)  $n_D^{20^\circ}$  1.4470); nmr (CCl<sub>4</sub>, TMS):  $\delta$  11.53 (s, 1H), 5.09 (broad triplet, 1H), 2.30 (m, 4H), 1.70 (s, 3H), 1.63 (s, 3H).

#### 6-Methyl-5-hepten-2-one-1-<sup>14</sup>C (2)

Unlabeled methyl iodide (3.55g, 25mmol) in anhydrous ether (20ml) was added at a rate that would maintain gentle refluxing to excess lithium metal (0.52g) suspended in ether (5ml) under nitrogen atmosphere. This resulted in the formation of a solution of unlabeled methyl lithium. In a second flask lithium metal (80mg), in ether (2ml) was allowed to react with methyl iodide-<sup>14</sup>C (16) (1.0mc, 0.5mmol - transferred to the flask by means of a vacuum line). In a third flask was placed 5-methyl-4-hexenoic acid (640mg, 5.0mmol) in ether (15ml) under nitrogen. Unlabeled methyl lithium was added to 5-methyl-4-hexenoic acid to form the lithium salt. After the addition of 5 mls of the unlabeled methyl lithium - ether solution (approximately 5mmol), methane gas was no longer evolved and a white precipitate of the lithium salt (1) of 5-methyl-4-hexenoic acid was formed. Additional unlabeled methyl lithium (approximately 1mmol) in ether (1ml) was added to insure conversion of all of the acid to the lithium salt. Methyl lithium-<sup>14</sup>C (0.5mmol) in ether (2ml) from the second flask was then added to the lithium

salt. The second flask was washed with carrier methyl lithium (approximately 1mmol) in ether (1ml) and these washings were also added to the lithium salt. The reaction was allowed to stir at room temperature under nitrogen for 1 hr before additional carrier methyl lithium (approximately 1.5mmol) in ether (1.5ml) was added. The reaction was stirred at room temperature for two additional hours before work up by dropwise addition of the reaction mixture with stirring to ice water <sup>(17)</sup>. The product was extracted into ether (4x25mls), the combined ether extracts were dried (Na<sub>2</sub>SO<sub>4</sub>), and concentrated to give 6-methyl-5-hepten-2-one-1-<sup>14</sup>C (450mg, 3.56mmol, 0.15mc/mmol) which was used in the next step without further purification.

Ethyl *trans*-3,7-dimethyl-2,6-octadienoate-9-<sup>14</sup>C (3)

A 57% dispersion of sodium hydride in mineral oil (257mg, 6.1mmol) was washed with n-hexane (3x3ml) under nitrogen atmosphere and anhydrous dimethoxyethane (5ml) was added. Triethylphosphonoacetate (1.34gm, 6.0mmol) in dimethoxyethane (10ml) was then added over a 30 min period with cooling. When hydrogen was no longer evolved 6-methyl-5-hepten-2-one-1-<sup>14</sup>C (450mg, 0.15mc/mmol) in dimethoxyethane (5ml) was added and the mixture was allowed to stir overnight at room temperature. After stirring 24 hrs the reaction was warmed to 50° and stirred an additional hr. Excess water was added to the reaction at 0°C and the product was extracted into ether (3x50ml), dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated to give a mixture of triethyl phosphonoacetate and *cis* and *trans* ethyl 3,7-dimethyl-2,6-octadienoates-9-<sup>14</sup>C. This mixture was separated by chromatography on four Merck silica gel GF254 thin layer plates (8"x8" - 2mm thick) which were developed 6 times with benzene-hexane (4:6). Elution of the lower zone with 5% methanol in chloroform gave after evaporation of the solvents ethyl *trans*-3,7-dimethyl-2,6-octadienoate-9-<sup>14</sup>C (381mg, 1.94mmol, 55%, 0.15mc/mmol). This

material did not contain any of the *cis* isomer. Elution of the upper zone gave ethyl *cis*-3,7-dimethyl-2,6-octadienoate (88mg, 0.45mmol, 13%, 0.15mc/mmol).

#### Geraniol-9-<sup>14</sup>C (4)

A saturated solution of lithium aluminum hydride in ether (20ml) was added to ethyl *trans*-3,7-dimethyl-2,6-octadienoate-9-<sup>14</sup>C (381mg, 0.15mc/mmol) in ether (10ml) at -70° under nitrogen atmosphere. The reaction was stirred for 1 hr at -70° and then warmed to room temperature where it was stirred for 15 min before cooling again to -70° where it was quenched with alcohol. Water was added at room temperature and the ether layer was separated. The water was extracted with ether (2x25mls), the combined ether extracts were dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated to give geraniol-9-<sup>14</sup>C (241mg, 1.57 mmol, 81%, 0.15mc/mmol). This material contained approximately 10% citronellol but was free of nerol. The geraniol was purified by chromatography on three thin layer plates (8"x8" - 2mm thick) impregnated with silver nitrate. The silica gel was prepared by adding a 5% aqueous silver nitrate solution (50ml) to Merck silica gel GF254 (75g). The plates were developed 3 times with 5% ethyl acetate in benzene. The lower zone was eluted with 5% methanol in chloroform to give pure geraniol-9-<sup>14</sup>C (189mg, 0.15mc/mmol).

#### Reduction of ethyl *trans*-3,7-dimethyl-2,6-octadienoate (3) with excess lithium aluminum hydride

The following procedure was used in experiments 1-8 (table 1). Ether (0.5ml) saturated with lithium aluminum hydride was added to ethyl *trans*-3,7-dimethyl-2,6-octadienoate (25mg) in ether (2.5ml) under nitrogen at -70°. The reaction was warmed to the appropriate temperature where it was maintained for the indicated time (table I). It was then cooled to -70° and ethanol (0.25ml) in ether (1.0ml) followed by distilled water (5ml) were added. After warming

to room temperature 5% HCl was added and the product was extracted with ether (3x3ml). The combined ether extracts were dried ( $\text{Na}_2\text{SO}_4$ ) and concentrated and the residual oil was analyzed by gas chromatography using both systems I and II.

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