

THE SYNTHESIS OF CARBON-14 LABELED 1-(4,8-DIMETHYL-8-METHOXYNONYL)-4-(1-METHYLETHYL)BENZENE.

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SUMMARY

The title compound, uniformly labeled with carbon-14 in the benzene ring, was prepared by Wittig reaction of 4-isopropylbenzaldehyde- ^{14}C ring (U) with 3,7-dimethyl-7-methoxyoctylidene-triphenylphosphorane followed by catalytic hydrogenation of the resulting mixture of olefins. A second route to the title compound, based on alkyllithium chemistry, was demonstrated using unlabeled intermediates. Attempted preparation of the title compound via the Horner-Emmons modification of the Wittig reaction was unsuccessful.

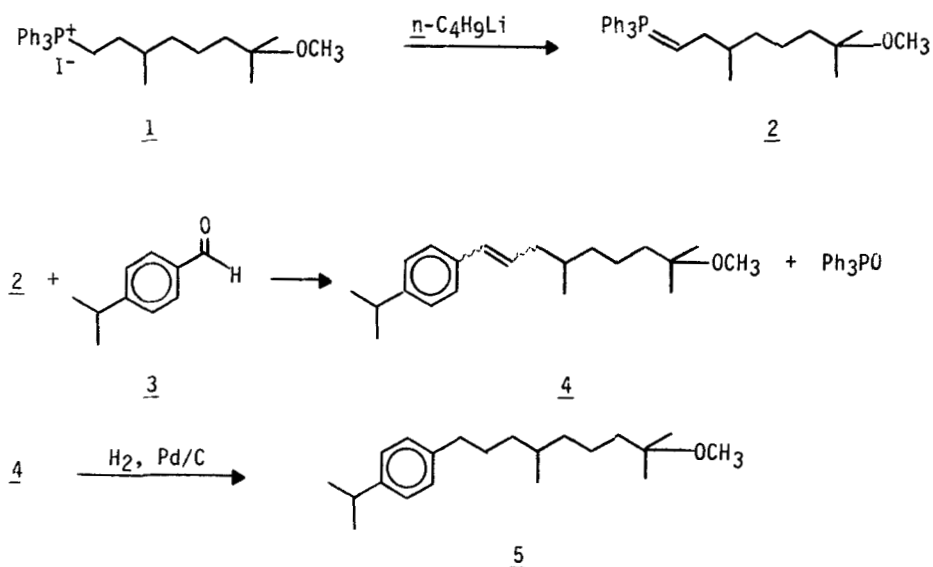
Key Words: 1-(4,8-dimethyl-8-methoxynonyl)-4-(1-methylethyl)benzene, Pro-DroneTM, Wittig reaction, 4-isopropylbenzaldehyde, hydrogenation

INTRODUCTION

The commercial insect growth regulator, Pro-Drone,TM is a member of a new generation of environmentally non-persistent and highly specific products for insect control. It was developed as an alternative to older, ineffective or environmentally unsafe products for control of the red imported fire ant (*Solenopsis invicta*), which infests over 230 million acres of the southern United States. By inhibiting the natural development of the worker ants responsible for gathering food, Pro-DroneTM causes the death of the entire ant colony over a period of several months. In support of the registration program for Pro-Drone,TM the active ingredient, 1-(4,8-dimethyl-8-methoxynonyl)-4-(1-methylethyl)benzene, 5, uniformly labeled with carbon-14 in the benzene ring, was prepared for metabolic and toxicological studies.

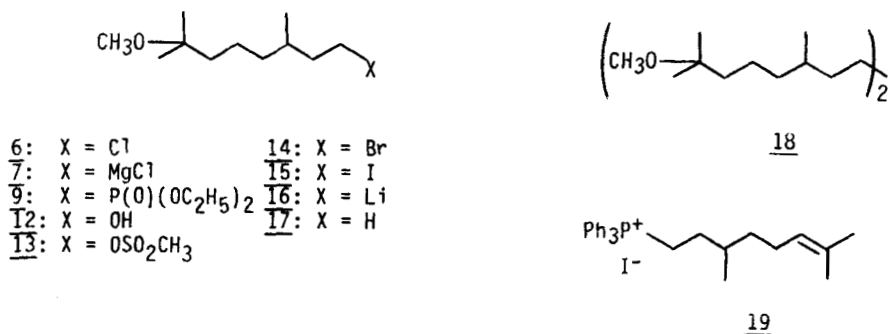
Carbon-14 labeled 5 was prepared, as shown in Scheme 1, by treatment of 4-isopropylbenzaldehyde- ^{14}C ring (U) with 3,7-dimethyl-7-methoxyoctylidene-triphenylphosphorane 2 followed by catalytic hydrogenation of the resulting mixture of *cis*- and *trans*-4,8-dimethyl-8-methoxy-1-(4-isopropylphenyl)-1-nonene- ^{14}C ring (U).

Scheme 1

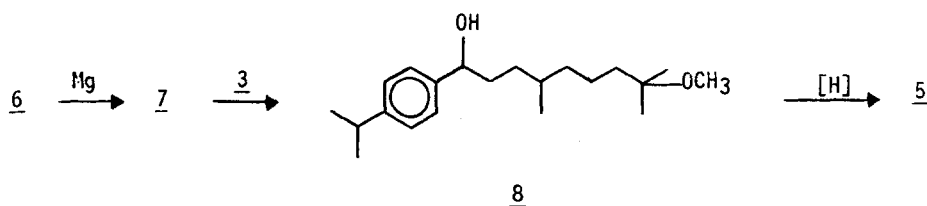


RESULTS AND DISCUSSION

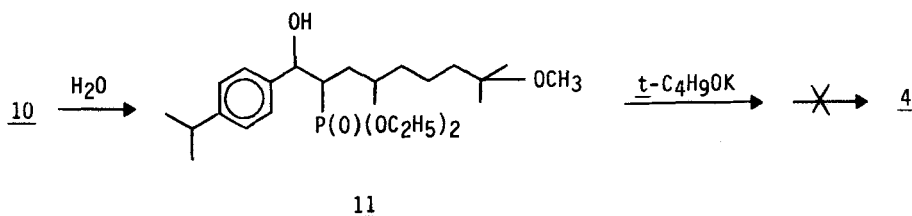
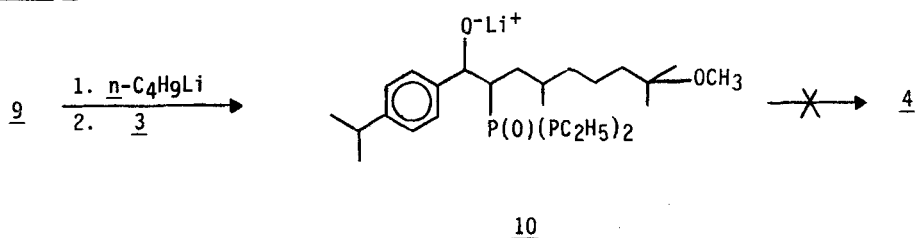
Several routes were investigated prior to the selection of a method for the preparation of radiolabeled 5. Although some work had been done earlier on the route outlined in Scheme 2,¹ erratic results observed with the key Grignard reaction to form alcohol 8 led us to prefer a route based on the Horner-Emmons modification² of the Wittig reaction as outlined in Scheme 3. Initially, we avoided the standard Wittig³ reaction because of anticipated difficulty in separating olefin mixture 4 from by-product triphenylphosphine oxide.



Scheme 2



Scheme 3



Application of the Horner-Emmons method required the preparation of phosphonate 9, which was accomplished via the Arbuzov⁴ reaction of triethyl phosphite and bromide 14. Bromide 14 was prepared via mesylate 13 from commercially available 3,7-dimethyl-7-methoxyoctanol, 12. Attempts to prepare 9 using commercially available 1-chloro-3,7-dimethyl-7-methoxyoctane, 6, in place of 14 were unsuccessful.

Reaction of the lithium salt of phosphonate 9 (prepared in THF at -78°C by treatment of 9 with *n*-butyllithium) with cuminaldehyde, 3, afforded betaine 10, but thermal decomposition of 10 to olefin mixture 4 was unsuccessful. A high yield of hydroxyphosphonate 11 was obtained on quenching the reaction mixture with water. Although betaines derived from certain unactivated phosphonates have been reported to eliminate the phosphate moiety more readily when the counterion is potassium than when it is lithium,⁵ the potassium salt

prepared by reaction of 11 in THF with potassium *t*-butoxide did not undergo thermal decomposition to 4 either.

We next decided to look at a modification of the route shown in Scheme 2 in which an alkyllithium reagent was substituted for the Grignard reagent. Lithium alkyl 16 was readily prepared from bromide 14 and lithium metal in ether at 0°C. Side reactions leading to reduction product 17 and coupling product 18 could be minimized by adding bromide 14 to lithium metal over a period of at least 3 hours. Subsequent condensation of 16 with cuminaldehyde afforded alcohol 8. To completely consume aldehyde 3, it was necessary to use 16 freshly prepared from 1.5 equivalents of bromide 14. Although 17 and 18 could not be completely eliminated, their formation would not consume any radiolabeled material, and they were easily separated from alcohol 8 by preparative TLC. Hydrogenolysis of alcohol 8 afforded the desired product, 5, but required reaction times several hours longer than did reduction of olefin mixture 4 (*vide infra*).

Because the alkyllithium sequence was quite time consuming, we decided to investigate the Wittig route (Scheme 1) before choosing the most efficient method for the preparation of radiolabeled 5. Iodide 15 was prepared by treatment of chloride 6 with lithium iodide in methyl ethyl ketone at reflux. Phosphonium iodide 1 was prepared by heating a methanolic solution of 15 and triphenylphosphine at reflux for approximately three days. An attempt to accelerate the formation of 1 by substituting mixed xylenes as solvent failed. Although iodide 15 was completely consumed in 28 hours at reflux, the product was a 1:5 mixture of the desired salt, 1, and salt 19 (resulting from elimination of methanol), as determined by reaction of the phosphorane mixture prepared from the mixed salts with cuminaldehyde, and analysis of the resulting olefin mixture by GC.

Reaction of phosphorane 2 (prepared at -78°C by treatment of 1 with *n*-butyllithium) with cuminaldehyde cleanly afforded the desired olefin mixture, but aqueous ethereal work up left the product contaminated with much triphenylphosphine oxide. Removal of the triphenylphosphine oxide required a

tedious partitioning of the mixture between mixed hexanes, methanol and water which would be impractical with radiolabeled material. Subsequently, we found that removal of the THF after the reaction was done allowed extraction of the olefin mixture from the pasty residue by simply stirring the residue vigorously with pentane. Stripping the pentane then afforded 4 sufficiently free of triphenylphosphine oxide that subsequent catalytic hydrogenation to 5 could be accomplished. Hydrogenation proceeded substantially faster, however, if olefin mixture 4 was first purified by preparative TLC. When 4 was so treated, subsequent purification of 5 was unnecessary.

Having solved the problem of separation of triphenylphosphine oxide from the intermediate olefin mixture, we chose the Wittig route over the alkyllithium route for preparation of radiolabeled 5 and elected to purify the intermediate olefin mixture by preparative TLC before hydrogenation. Thus, a 10% molar excess of phosphorane 2 treated with 4-isopropylbenzaldehyde-¹⁴C ring (U) afforded, after purification, a mixture of cis- and trans-4,8-dimethyl-8-methoxy-1-(4-isopropylphenyl)-1-nonene-¹⁴C ring (U) in an overall yield of 74.7% based on the starting aldehyde. Hydrogenation of the olefin mixture in methanol over 10% palladium on carbon afforded 1-(4,8-dimethyl-8-methoxynonyl)-4-(1-methylethyl)benzene-¹⁴C ring (U) in 97.6% yield with a radiochemical purity greater than 97%.

EXPERIMENTAL

Unless noted otherwise all unlabeled chemicals and solvents are available from several suppliers and were used as received. Samples of authentic unlabeled 4 and 5 were obtained from Stauffer Chemical Company. Unlabeled cuminaldehyde was obtained from Fluka Chemical Corporation and distilled before use. The material, before and after distillation, was a mixture of the ortho, meta and para isomers in the approximate ratio of 8:2:89. Tetrahydrofuran (THF) and pyridine were dried at least 16 hours over 3A molecular sieves before use.

Gas chromatography was carried out on two different systems. Cold work was done on a Hewlett-Packard Model 5711 using a 4 ft by 2 mm i.d. Pyrex

column packed with 5% SP-2100 on 100/120 mesh Supelcoport. The column oven was temperature programmed as follows: 125°C (2 min) then 16°C/min to 230°C (8 min). Analysis of radiolabeled intermediates was done on a Varian Model 3700 using a 6 ft by 2 mm i.d. Pyrex column packed with 3% OV-1 on 60/80 mesh Chromosorb W HP. The column oven was temperature programmed as follows: 100°C (3 min) then 16°C/min to 230°C (8 min). The effluent of the column was split into two streams. One stream was conducted to a flame-ionization detector (FID) and the other was conducted to a Cary Model 5010 ion chamber connected to a Cary Model 401 vibrating-reed electrometer (VRE). The FID detects all components, radioactive or not, while the VRE detects only the radioactive components. The electrical signals from the two detectors were recorded on a dual-pen recorder allowing facile determination of which peaks correspond to radioactive components. Unless noted otherwise, reported percentage compositions were simple area ratios, not true weight percents.

Thin layer chromatography (TLC) was carried out using Merck analytical (0.2mm layer) and preparative (2.0 mm layer) plates coated with silica gel F-254. Compounds were visualized on the plates using a UV lamp.

3,7-Dimethyl-7-methoxyoctyl Methanesulfonate (13): The procedure was adapted from a similar one reported by Photis and Paquette.⁶ A solution of 94.2 g (500 mmoles) of 7-methoxycitronellol, 12, (SCM Terpene Products) in 100 mL of dry pyridine was added to a cooled solution of 58 mL (85.8 g, 749 mmoles) of methanesulfonyl chloride in 600 mL of dry pyridine at such a rate that the temperature was maintained at $-5 \pm 2^\circ\text{C}$. Addition took 35 min after which the mixture was allowed to stir at $0-5^\circ\text{C}$ for an additional 2 hr. A cold solution of 3.1 moles of hydrochloric acid in 1 L of water was then added at such a rate that the temperature remained below 10°C . The mixture was extracted with a solution of 50 mL of dichloromethane in 500 mL of mixed hexanes followed by extraction with two more 500 mL portions of hexanes. The combined hexane solutions were washed with one 150 mL portion each of 1 M hydrochloric acid, water and saturated sodium chloride and were then dried over anhydrous magnesium sulfate, filtered and concentrated on the rotary

evaporator. The residue was held in vacuo at a pressure of 0.30 mm Hg to remove the last traces of solvent. The product, a viscous, yellow oil (129.7 g; technical yield, 97%), was converted directly to bromide 14.

1-Bromo-3,7-dimethyl-7-methoxyoctane (14): The procedure was adapted from a similar one reported by Finkelstein.⁷ Crude mesylate 13 was dissolved in 600 mL of acetone. Solid lithium bromide (65.1 g, 750 mmoles) was added in one portion, and the mixture was heated to reflux. The reaction was followed by GC, completion being determined by the disappearance of 13 (approximately 3 hr). The mixture was then cooled to -5°C, filtered to remove solid lithium salts, and concentrated on the rotary evaporator. The cloudy residue was diluted with 500 mL of mixed hexanes, slurried with a little diatomaceous earth, filtered and concentrated on the rotary evaporator to yield 111.5 g of crude 14 as a pale yellow oil. Vacuum distillation of the crude product afforded a main fraction of 105.2 g (83.8% yield based on 12) of colorless liquid 14: bp, 73-80°C (0.03-0.05 mm Hg).

Diethyl 3,7-Dimethyl-7-methoxyoctylphosphonate (9): Triethyl phosphite (13.5 mL, 13.1 g, 78.7 mmoles) was heated to reflux, and 17.1 g (68.1 mmoles) of neat bromide 14 was added over 15 min. The pot temperature rose slowly from 152°C to 165°C during the addition and then fell to 145°C over the next hour. The reflux condenser was replaced with a distillation head, and approximately 1 mL of colorless liquid, bp 38°C, was collected as the pot temperature rose to 192°C. The mixture was allowed to stir an additional 2 hr at 175-195°C and was then distilled in vacuo to afford a main fraction of 11.1 g (technical yield, 53%) of colorless oily 9: bp, 121-130°C (0.50-0.2 mm Hg).

3,7-Dimethyl-1-iodo-7-methoxyoctane (15): The procedure was similar to that reported above for 14. A mixture of 62.0 g (300 mmoles) of 7-methoxy-citronellyl chloride, 6, (SCM Terpene Products) and 49.5 g (330 mmoles) of sodium iodide in 600 mL of methyl ethyl ketone was heated at reflux. Analysis after 36 hrs of an aliquot of the reaction mixture by GC showed the mixture to contain 95% iodide 15 and 5% unreacted 6. The mixture was concentrated on the rotary evaporator, and the dark orange-yellow residue was slurried with 600 mL

of ether and filtered. Removal of the ether on the rotary evaporator afforded 89.2 g (quantitative technical yield) of crude 15 as a dark orange oil. The crude liquid was purified by vacuum distillation to afford a main fraction of 69.9 g (recovery, 78%) of 15 as an amber liquid: bp, 86-91°C (0.05 mm Hg). Purified 15 still contained 1.7% of unreacted 6 by GC analysis. The product was stored over copper wire, the color disappearing over a few days.

3,7-Dimethyl-7-methoxyoctyltriphenylphosphonium Iodide (1): A solution of 26.8 g (100 mmoles) of triphenylphosphine and 29.8 g (100 mmoles) of distilled iodide 15 in 200 mL of methanol was heated at reflux. Although formation of 1 could not be monitored by GC, both of the starting materials could still be detected after three days at reflux. Less than 7% of the original triphenylphosphine charged remained unreacted. The reaction mixture was cooled and diluted with 500 mL of pentane whereupon it separated into two phases. The lower, methanolic phase was washed with two 500 mL portions of pentane. The combined pentane phases were washed with 200 mL of fresh methanol. The methanol phases were combined, whereupon a small, upper phase separated. It was removed, and the combined methanol phases were concentrated on the rotary evaporator to afford 1 as a pale yellow, taffy-like material. Traces of solvent were removed from this material by exposing it to lower and lower vacuum until no further foaming was observed. A final pressure of 0.3 mm Hg was held for one hour. A total of 52.5 g (technical yield, 94%) of 1 was obtained. For ease of handling, the product could be dissolved in a known amount of dry THF to concentrations of up to about 30% by weight.

Cis- and Trans-4,8-dimethyl-8-methoxy-1-(4-isopropylphenyl)-1-nonene-¹⁴C ring (U): A solution of phosphonium salt 1 in THF (18.3% 1 by weight, 14.4 g, 4.71 mmoles) was diluted with 5.0 mL of dry THF under an argon atmosphere and cooled to -78°C. An aliquot of 10.5 M n-butyllithium in hexanes (Aldrich Chemical Co., 0.45 mL, 4.7 mmoles) was added over 30 sec to afford a bright orange solution of phosphorane 2. After 15 min, a solution of 4-isopropylbenzaldehyde-¹⁴C ring (U) (New England Nuclear, 52.0 mCi, specific activity 12.2 mCi/mole, 4.26 mmoles, 0.632 g) in 2.0 mL of dry THF was siphoned in

over 10 min via a Teflon capillary tube. The reservoir and siphon tube were rinsed with two fresh 2.0 mL portions of THF which were added to the reaction mixture. The mixture was allowed to warm to ambient temperature over 1 hr and was then concentrated over 50 min in a moving stream of argon. During concentration, the reaction flask was immersed in a water bath maintained at 40-45°C. The pasty yellow residue was slurried vigorously by magnetic stirring for 5 min with each of three 25 mL portions of pentane. The combined pentane extracts were filtered and concentrated in a moving argon stream at 40-45°C and then held in vacuo for 10 min at a pressure of less than 1 mm Hg to afford 1.11 g (86% technical yield) of crude radiolabeled 4. The crude product was divided into four portions and applied to four 20 cm by 20 cm preparative TLC plates. The plates were developed in 1:4 (v/v) ether:pentane and air dried. The combined UV active bands at R_f 0.66 on the plates were extracted thoroughly with four 40 mL portions of ether. The combined ether extracts were dried over anhydrous magnesium sulfate, filtered and concentrated as before to afford 0.963 g (3.18 mmoles, 74.7% yield) of radiolabeled 4. Analysis of this material by GC showed the same two peaks obtained by analysis of authentic unlabeled 4.

1-(4,8-Dimethyl-8-methoxynonyl)-4-(1-methylethyl)benzene-¹⁴C ring (U): A mixture of 0.963 g (3.18 mmoles) of radiolabeled 4, 0.103 g of 10% Pd/C catalyst and 25 mL of methanol in a 50 mL 3-neck round bottom flask equipped with a reflux condenser capped with a three-way stopcock was stirred magnetically while the apparatus was slowly evacuated. When the methanol just started to boil, evacuation was stopped, and the apparatus was filled with hydrogen from a gas buret. The evacuation/filling cycle was repeated twice more, and the apparatus was left open to the gas buret. After 35 min, 86 mL (3.55 mmoles at 22.5°C and 762 mm Hg) of hydrogen had been absorbed. The apparatus was purged with argon, and the reaction mixture was filtered to remove the catalyst. The filtrate was concentrated as previously described to afford 0.946 g (3.11 mmoles, 37.9 mCi, 97.6% yield) of radiolabeled 5 as a pale yellow oil. The mass spectrum of this material was as expected from

comparison with that of authentic unlabeled material. The radiochemical purity of the product was determined by GC. Two peaks, both corresponding to radioactive components, were observed. The one corresponding to 5 accounted for 97.1% of the total peak area. An aliquot of the product was spotted on an analytical TLC plate which was developed with 1:9 (v/v) ether:pentane. The region of the plate containing the single UV-detectable spot (R_f 0.66) corresponding to 5 was carefully scraped off, and its radioactivity was determined by liquid scintillation counting. The rest of the silica gel in the path of the removed spot from the baseline to the solvent front was scraped from the plate and counted separately. The results of the scintillation counting showed that 98.5% of the radioactivity in the sample was associated with the spot corresponding to 5. The results of the two analyses indicate that the radiochemical purity of the sample is at least 97%.

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