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Preparation of some deuterium labelled 9- and/or 10-oxygenated derivatives of geraniol, geranial, nerol, and neral[1]

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The preparation of various deuterium labelled 9- and/or 10-oxygenated derivatives of geraniol, geranial, nerol, and neral is described. Wittig reaction of the tetrahydropyranyl ethers of (*E*)- and (*Z*)-1,1-dideutero-6-(triphenylphosphonium)-3-methyl-2-hexen-1-ol iodides (**23** and **24**) with the tetrahydropyranyl ethers of hydroxyacetone and 1,3-dihydroxyacetone afforded, after deprotection, C-1 dideuterated 9-hydroxygeraniol, 9-hydroxynerol, 9,10-dihydroxygeraniol, and 9,10-dihydroxynerol of high isomeric purity. Selective oxidation of these products allowed for the preparation of the corresponding derivatives possessing an aldehyde functionality at C-9 or C-1 and C-9. Wittig reaction of **23** and **24** with pyruvaldehyde dimethyl acetal followed by acidic hydrolysis afforded C-1 dideuterated 10-oxogeraniol and 10-oxonerol, oxidation of which yielded C-1 deuterated 10-oxogeranial and 10-oxoneral. Wittig reaction of (*E*)- and (*Z*)-1,1-dideutero-6-(triphenylphosphonium)-3-methyl-2-hexen-1-ol iodides (**49** and **50**) with 1,1,3,3-tetraethoxyacetone afforded C-1 dideuterated 9,9,10,10-tetraethoxygeraniol and 9,9,10,10-tetraethoxynerol, oxidation of which provided C-1 deuterated 9,9,10,10-tetraethoxygeranial and 9,9,10,10-tetraethoxyneral.

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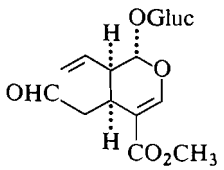
On décrit la préparation de plusieurs dérivés oxygénés en position 9 et/ou 10 du géraniol, du géranial, du nérol et du néral marqués au deutérium. Une réaction de Wittig des éthers tétrahydropyrannyles des iodures du dideutéro-1,1 (triphénylphosphonium)-6 méthyl-3 hexène-2 ol-1 (*E*) et (*Z*) (**23** et **24**) avec les éthers tétrahydropyrannyles de l'hydroxyacétone et de la dihydroxy-1,3 acétone conduit, après déprotection, aux hydroxy-9 géraniol, hydroxy-9 nérol, dihydroxy-9,10 géraniol et dihydroxy-9,10 nérol dideutérés en C-1 en une grane pureté isomérique. L'oxydation sélective de ces produits permet de préparer les dérivés correspondants ayant une fonction aldéhyde en C-9 ou en C-1 et en C-9. La réaction de Wittig des composés **23** et **24** avec le diméthyle acétal de la pyruvaldéhyde, suivie d'une hydrolyse acide, conduit à l'oxo-10 géraniol et à l'oxo-10 nérol dideutérés en C-1. Par oxydation, ces composés donnent l'oxo-10 géranial et l'oxo-10 néral dideutérés en C-1. La réaction de Wittig des iodures de dideutéro-1,1 (triphénylphosphonium)-6 méthyl-3 hexène-2 ol-1 (*E*) et (*Z*) (**49** et **50**) avec la tétraéthoxy-1,1,3,3 acétone permet d'obtenir le tétraéthoxy-9,9,10,10 géraniol et le tétraéthoxy-9,9,10,10 nérol dideutérés en C-1 qui, par oxydation fournissent le tétraéthoxy-9,9,10,10 géranial et le tétraéthoxy-9,9,10,10 néral deutérés en C-1.

[Traduit par le journal]

In the biosynthesis of monoterpene indole alkaloids, the "monoterpene portion" of the alkaloids has been shown to arise from the seco-iridoid glucoside secologanin (**1**) (1, 2) which in turn arises, via the cyclopentanoid derivative loganin (**2**) (3), from the acyclic monoterpenes geraniol (**3**) and nerol (**4**)



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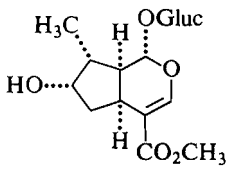

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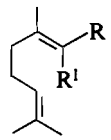
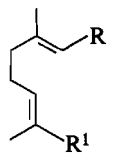
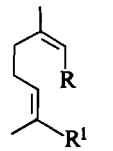


3 R = CH_2OH, R^1 = H
4 R = H, R^1 = CH_2OH

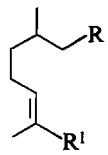
(4–6). The exact pathway between geraniol/nerol and loganin, however, remains uncertain. Previously, tracer studies had established that 10-hydroxygeraniol (**5**) and 10-hydroxynerol (**6**) were incorporated into loganin and indole alkaloids in *Cathar-*



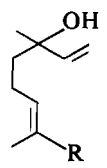
5 R = R^1 = CH_2OH
7 R = CH_2OH, R^1 = CHO
9 R = CHO, R^1 = CH_2OH
11 R = R^1 = CHO



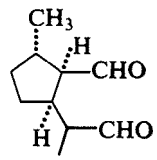
6 R = R^1 = CH_2OH
8 R = CH_2OH, R^1 = CHO
10 R = CHO, R^1 = CH_2OH
12 R = R^1 = CHO



13 R = R^1, = CH_2OH
14 R = CHO, R^1 = CH_2OH
15 R = CH_2OH, R^1 = CHO
16 R = CH_2OH, R^1 = CH_3
17 R = CHO, R^1 = CH_3



18 R = CH_3
19 R = CH_2OH



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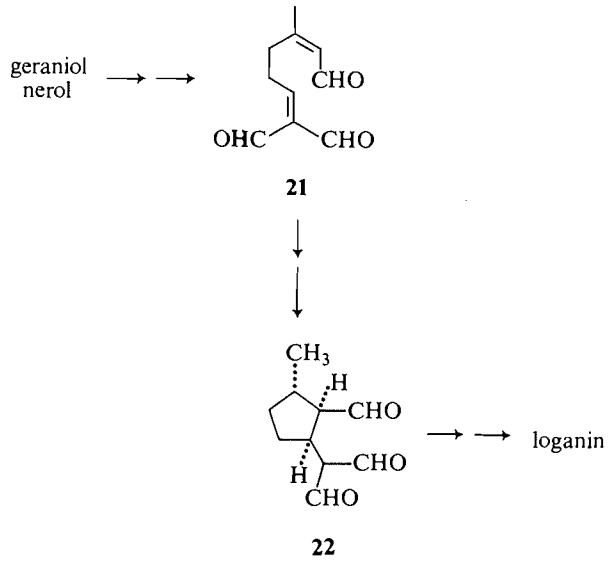
[1]NRCC No. 20574.

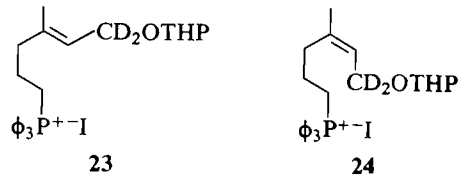


SCHEME 1

anthus roseus plants (7, 8). More recently, mixtures consisting of 10-oxogeraniol (**7**)/10-oxonerol (**8**), 10-hydroxygeranial (**9**)/10-hydroxyneral (**10**), and 10-oxogeranial (**11**)/10-oxoneral (**12**) were also shown to be incorporated (9), while such derivatives as 10-hydroxycitronellol (**13**), 10-hydroxycitronellal (**14**), 10-oxocitronellol (**15**), citronellol (**16**), citronellal (**17**), linalool (**18**), 10-hydroxylinalool (**19**), and iridodial (**20**) were not (7, 8, 10). These results coupled with the observation that an isotopic label at C-9 of geraniol becomes scrambled between C-9 and C-10 on conversion to loganin (3, 7, 11, 12) led to the hypothesis that the biosynthesis of loganin involves conversion of geraniol and nerol via several oxidative steps (and appropriate isomerizations) to 9,10-dioxoneral (**21**). Cyclization of **21** (to afford **22**) followed by further elaboration would then lead to loganin (Scheme 1) (7, 13).

In spite of the obtained evidence, however, definitive information regarding the importance of double bond geometries or direct evidence supporting the role of 9,10-oxygenated geraniol (nerol) derivatives is lacking. With the development of tissue culture methodology (which offers such advantages over the use of intact plants as having fewer problems associated with metabolite transport as well as greater control of experimental conditions) it was deemed that such questions could be resolved. Recently, it had been determined that 10-hydroxygeraniol and 10-hydroxynerol (labelled with deuterium) could be incorporated into indole alkaloids to the extent of 80% when a cell suspension culture of *C. roseus* was used for the tracer experiments (14). This incorporation was two orders of magnitude greater than that previously observed using intact plants, and augered well for further studies; however, a number of geraniol, geranial, nerol, and neral derivatives oxygenated at the 9 and/or 10 positions (i.e. hypothetical alkaloid precursors or analogs thereof) were required. Accordingly, the synthesis of these derivatives, possessing a deuterium label, was undertaken and the results presented here.

It was envisioned that the target compound could be conveniently prepared by Wittig reaction of isomerically pure phosphonium salts **23** and **24** with appropriately oxygenated derivatives of acetone (followed by deprotection and further functional group manipulation as required). To this end, 5-chloro-2-pentanone was coupled by Wittig–Horner reaction



with trimethylphosphonoacetate to yield a mixture of (*E*)- and (*Z*)-methyl 6-chloro-3-methyl-2-hexenoates (**25** and **26**, *E*/*Z* = 1.8:1) in 91% yield. The assignments of stereochemistry were achieved by examination of the proton magnetic resonance spectra which exhibited characteristic signals for the olefinic methyl groups at δ 2.16 for the (*E*)-isomer **25** and δ 1.87 for the (*Z*)-isomer **26** (7). Separation, by spinning band distillation, afforded the individual esters in >98% isomeric purity as determined by glc analysis. Reduction of **25** and **26**

25 R = CO_2CH_3
27 R = CD_2OH
29 R = CD_2OTHP

26 R = CO_2CH_3
28 R = CD_2OH
30 R = CD_2OTHP

with lithium aluminum deuteride furnished the allylic alcohols **27** and **28** in 96% and 93% yields respectively. Alcohols **27** and **28** were converted to the tetrahydropyranyl ethers **29** (98% yield) and **30** (95% yield) via standard means and then treated with triphenylphosphine and sodium iodide in refluxing acetonitrile to afford the desired phosphonium salts **23** (86% yield) and **24** (89% yield) as crystalline solids.

Having the desired phosphonium salts in hand, their Wittig reactions with various substrates were examined. Wittig reaction of **23** with the tetrahydropyranyl ether of hydroxyacetone under "salt free conditions" (15) yielded, after removal of the protecting groups, 1,1-dideutero-9-hydroxygeraniol (**31**) in 85% yield. Correspondingly, **24** yielded 1,1-dideutero-9-hydroxynerol (**32**) in 91% yield. The Wittig reactions were highly stereoselective with only 3% contamination by the 10-hydroxy isomers.

Oxidation of **31** and **32** with manganese dioxide gave, after purification by thin-layer chromatography, 1,1-dideutero-9-oxogeraniol (**33**) and 1,1-dideutero-9-oxonerol (**34**) contaminated with ca. 5% of the 10-oxo isomers. The chemical shifts of the aldehyde protons of **33** and **34** (δ 10.13 and δ 10.09)

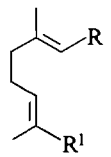
31 R = CD_2OH, R' = CH_2OH
33 R = CD_2OH, R' = CHO
35 R = CDO, R' = CHO

32 R = CD_2OH, R' = CH_2OH
34 R = CD_2OH, R' = CHO
36 R = CDO, R' = CHO

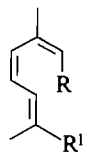
were consistent with the 9-oxo assignments (8). The observed preference for oxidation of the C-9 over the C-1 hydroxy groups was likely the result of the deuterium isotope effect wherein the rate-determining step of the oxidation would be the breaking of the C—H (C—D) bond.

Further oxidation of **33** and **34** using barium manganate afforded dialdehydes **35** and **36** in 71% and 75% yields respectively. In the case of **35**, no significant isomerization was noted during this oxidation. In the case of **36** a small amount (ca. 2%) of isomerization of the 2,3 double bond was observed.

For the preparation of some 10-oxygenated derivatives, the phosphonium salts **23** and **24** were coupled by Wittig reaction with the dimethyl acetal of pyruvaldehyde. Although the 9-acetal derivatives were formed initially, acidic hydrolysis of the protecting groups was accompanied by isomerization to



37 R = CD_2OH, R' = CHO
39 R = CDO, R' = CHO

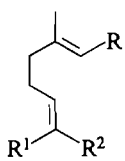


38 R = CD_2OH, R' = CHO
40 R = CDO, R' = CHO

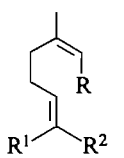
afford 1,1-dideutero-10-oxogeraniol (**37**) contaminated with 2% of the 9-oxo isomer and 1,1-dideutero-10-oxonerol (**38**) contaminated with 7% of the 9-oxo isomer. The chemical shifts of the aldehyde protons of **37** and **38** (δ 9.36 and δ 9.38) were consistent with the 10-oxo assignments (8).

Further oxidation of **37** and **38** employing barium manganate afforded the dialdehydes **39** and **40**. The isomeric purity of these derivatives was essentially unchanged.

For the preparation of some 9,10-oxygenated derivatives two approaches were utilized. In the first, phosphonium salts **23** and **24** were coupled by Wittig reaction with ditetra-



41 R = CD_2OH, R' = R^2 = CH_2OH
43 R = CD_2OH, R' = CHO, R^2 = CH_2OH
45 R = CD_2OH, R' = CH_2OH, R^2 = CHO

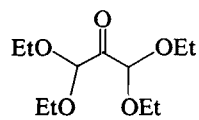


42 R = CD_2OH, R' = R^2 = CH_2OH
44 R = CD_2OH, R' = CHO, R^2 = CH_2OH
46 R = CD_2OH, R' = CH_2OH, R^2 = CHO

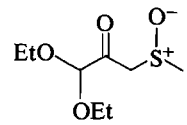
hydropyranyl ether of 1,3-dihydroxyacetone. After removal of the protecting groups 1,1-dideutero-9,10-dihydroxygeraniol (**41**) and 1,1-dideutero-9,10-dihydroxynerol (**42**) were obtained in 56% and 63% yields respectively.

Oxidation of triols **41** and **42** with manganese dioxide in tetrahydrofuran at 0°C was reasonably regioselective yielding 1,1-dideutero-9-oxo-10-hydroxygeraniol (**43**) contaminated with 12% of the 9-hydroxy-10-oxo isomer **45** and 1,1-dideutero-9-oxo-10-hydroxynerol (**44**) contaminated with 14% of the isomer **46**. The assignments of stereochemistry were based on the chemical shifts of the aldehyde protons. The major components of the two oxidations (i.e. **43** and **44**) exhibited resonances at δ 10.10 and δ 10.02 while the minor components (**45** and **46**) exhibited resonances at δ 9.41 and δ 9.37 (8). The yields of the oxidations were 72% and 66% respectively. Interestingly, when manganese dioxide in dichloromethane at ambient temperatures was used, poorer yields and lower regioselectivity were observed.

Attempted oxidation of **43** with barium manganate gave poor recovery of a complex mixture of products and was not further pursued, rather an alternative approach to other 9,10 oxygenated derivatives was employed. The second approach involved preparation of 1,1,3,3-tetraethoxyacetone (**47**) (16, 17) as the

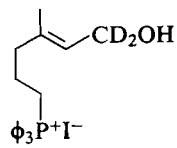


47

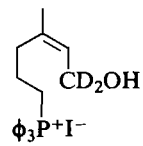


48

ketonic substrate for the Wittig reaction. Accordingly, ethyl diethoxyacetate was reacted with dimsyl sodium in dimethyl sulfoxide to furnish β-ketosulfoxide **48**. Treatment of **48** with mercuric oxide and boron trifluoride in refluxing ethanol effected Pummerer rearrangement and ethanolysis to yield **47**.[2]

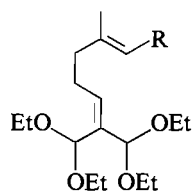


49

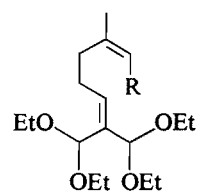


50

Wittig reaction of **47** (18) with phosphonium salts **49** and **50** (prepared from the chloroalcohols **27** and **28** by reaction with triphenylphosphine and sodium iodide in refluxing acetonitrile as before) furnished 1,1-dideutero-9,9,10,10-tetraethoxygeraniol (**51**) in 71% yield and 1,1-dideutero-9,9,10,10-tetraethoxynerol (**52**) in 55% yield.



51 R = CH_2OH
53 R = CDO



52 R = CH_2OH
54 R = CDO

Oxidation of **51** and **52** with barium manganate yielded the corresponding aldehydes **53** and **54**. Attempts to hydrolyse compounds **51** to **54** to afford the corresponding 9,10 dialdehydes were not successful, likely due to the instability of the vinyl dialdehyde system. This result, however, does not preclude the use of these derivatives for tracer experiments as the possibility of in vitro generation of the 9,10-dialdehyde functionality remains.

[2]The previous preparation of **47** (16, 17) involves reaction of pyruvaldehyde diethylacetal with ethyl nitrite in the presence of ethanolic hydrogen chloride, however, the product is generally contaminated with 5–10% of the corresponding ketal. The procedure employed gave essentially pure **47**.

Experimental

Melting points (mp) were obtained on a Koffler block and are uncorrected. Gas–liquid chromatography (glc) was carried out with a Hewlett–Packard model 5710A gas chromatograph equipped with an 8.6 meter capillary glass column containing OV-101. Ultraviolet (uv) spectra were obtained with samples in 95% ethanol using a Beckman model 35 spectrophotometer; absorption maxima are quoted in nanometers with log ϵ values in brackets. Infrared (ir) spectra were obtained with samples as neat films on sodium chloride plates using a Varian model 257B spectrophotometer; absorption maxima are quoted in centimeters^{-1}. Proton magnetic resonance (^{1}Hmr) spectra were obtained with samples in deuterochloroform (unless otherwise noted) using a Varian model EM-390 spectrometer. The position of peaks is listed in the δ scale relative to tetramethylsilane which was used as internal standard. Low resolution mass spectra (ms) were obtained on a Finnegan model 4000 spectrometer run at 70 eV. Microanalyses were performed by the Spang Microanalytical Laboratory, Eagle Harbor, Michigan, U.S.A. For thin-layer chromatography, Whatman PLK5F precoated silica gel plates were employed. For column chromatography, Aldrich silica gel, grade 12, 28–200 mesh was used.

Lithium aluminum deuteride and n-butyllithium were obtained from the Alfa Chemical Co. Manganese dioxide, barium manganate, and phenyllithium were obtained from the Aldrich Chemical Co. Potassium hexamethyldisilazide was prepared by the reaction of potassium hydride with hexamethyldisilazane in tetrahydrofuran. The tetrahydropyranyl ethers of hydroxyacetone (acetol) and 1,3-dihydroxyacetone were prepared from the alcohols via standard means. Anhydrous tetrahydrofuran was obtained by distillation from the sodium ketyl of benzophenone. Spinning band distillation was carried out with a Kontes model K-500400 spinning band micro still. Isomeric purities were determined from glc analyses or ^{1}Hmr spectra.

(E)-*and* (Z)-*Methyl 3-methyl-6-chloro-2-hexenoates (25 and 26)*

A suspension of sodium hydride (4.7 g of 50% NaH/mineral oil, 0.098 mol) in anhydrous tetrahydrofuran (150 mL) at 0°C was treated with a solution of trimethylphosphonoacetate (18.2 g, 0.099 mol) in dimethyl sulfoxide (25 mL) at a dropwise rate over 20 min. After a further 20 min 5-chloro-2-pentanone (10 mL, 0.087 mol) was added. The reaction mixture was stirred for 24 h at ambient temperature, diluted with petroleum ether (100 mL), and washed with 5% sodium bicarbonate solution (5 × 50 mL). The combined aqueous portion was back-extracted with petroleum ether (1 × 50 mL). The combined organic portion was dried (Na_2SO_4) and the solvent removed *in vacuo*. The residue was distilled at 10 Torr to afford a mixture of **25** and **26** (1.8:1, 13.92 g, 91%) as a colorless liquid; bp 112–119°C at 10 Torr. The two isomers were separated by spinning band distillation at 0.5 Torr (3×) yielding **25** and **26** in greater than 98% isomeric purity. (*E*)-Methyl 3-methyl-6-chloro-2-hexenoate (**25**); bp: 65°C at 0.5 Torr; glc retention time (80°C): 3.97 min; uv λ_{max}: 218 (4.41); ir ν_{max}: 1718, 1650, 1432, 1224, 1151, 1144; ^{1}Hmr δ: 5.67 (1H, bs), 3.65 (3H, s), 3.48 (2H, t, J = 6 Hz), 2.29 (2H, m), 2.16 (3H, d, J = 1.3 Hz), 1.96 (2H, m); ms *m/e*: 178 (^{37}Cl, M$^+$, 5%), 176 (^{35}Cl, M$^+$, 16%), 145 (39%), 127 (69%), 114 (100%), 95 (44%). (*Z*)-Methyl 3-methyl-6-chloro-2-hexenoate (**26**); bp: 61°C at 0.5 Torr; glc retention time (80°C): 3.07 min; uv λ_{max}: 217 (4.20); ir ν_{max}: 1716, 1648, 1430, 1224, 1152; ^{1}Hmr δ: 5.70 (1H, bs), 3.64 (3H, s), 3.52 (2H, t, J = 6 Hz), 2.73 (2H, m), 1.93 (2H, m), 1.87 (3H, d, J = 1.4 Hz); ms *m/e*: 178 (^{37}Cl, M$^+$, 7%), 176 (^{35}Cl, M$^+$, 20%), 145 (33%), 127 (100%), 114 (55%), 95 (72%). *Anal.* (mixture of *E* and *Z* isomers) calcd. for $C_8H_{13}O_2Cl$: C 54.39, H 7.42, Cl 20.07; found: C 54.43, H 7.42, Cl 20.10.

(E)-*1,1-Dideutero-3-methyl-6-chloro-2-hexen-1-ol (27)*

A solution of ester **25** (18 g, 0.10 mol) in anhydrous ether (150 mL) was treated with small portions of lithium aluminum deuteride (4.2 g, 0.10 mol) over a period of 30 min. After stirring for a further 4 h at ambient temperature, water (20 mL) was cautiously added over a period of 30 min. The reaction mixture was filtered and the solvent removed *in vacuo* to give **27** as a colorless liquid (14.5 g, 96%); ir ν_{max}: 3350, 2190, 2085, 1664, 1078; ^{1}Hmr δ: 5.44 (1H, bs), 3.51 (3H, t, J = 6 Hz), 2.3–1.7 (4H, m), 1.66 (3H, d, J = 1.3 Hz); ms *m/e*: 152 (^{37}Cl, M$^+$, 1.4%), 150 (^{35}Cl, M$^+$, 5.5%), 135 (15%), 133 (36%), 97 (15%), 83 (18%), 73 (100%). *Anal.* (of nondeuterated analog) calcd. for $C_7H_{13}OCl$: C 56.57, H 8.82, Cl, 23.85; found: C 56.32, H 8.77, Cl 23.75.

(Z)-*1,1-Dideutero-3-methyl-6-chloro-2-hexen-1-ol (28)*

A solution of ester **26** (13 g, 0.07 mol) in anhydrous ether (130 mL) was treated with lithium aluminum deuteride (3 g, 0.07 mol) as above to afford alcohol **28** as a colorless liquid (10.2 g, 93%); ir ν_{max}: 3350, 2190, 2082, 1664, 1078; ^{1}Hmr δ: 5.42 (1H, bs), 3.45 (3H, t, J = 6 Hz), 2.4–1.7 (4H, m), 1.71 (3H, d, J = 1.3 Hz); ms *m/e*: 152 (^{35}Cl, m$^+$, 0.9%), 150 (^{35}Cl, m$^+$, 3.1%), 135 (7%), 133 (13%), 97 (15%), 83 (30%), 73 (100%). *Anal.* calcd. for $C_7H_{11}D_2OCl$: C 55.83, Cl 23.54; found: C 55.11, Cl 23.25.

(E)-*Tetrahydropyranyl ether 29*

A solution of alcohol **27** (14.5 g, 0.096 mol) and *p*-toluenesulfonic acid monohydrate (300 mg, 1.6 mmol) in ether (100 mL) was treated with dihydropyran (11 mL, 0.13 mol) at a dropwise rate over a period of 2 h. The reaction mixture was stirred for a further 18 h at ambient temperature and then washed with 1 *N* sodium hydroxide solution (3 × 30 mL) and brine (2 × 30 mL). After drying (Na_2SO_4) the solvent was removed *in vacuo* to afford **29** as a colorless liquid (22 g, 98%); ir ν_{max}: 2155, 2075, 1662, 1020, 724; ^{1}Hmr δ: 5.39 (1H, bs), 4.59 (1H, t, J = 3 Hz), 3.9 (1H, m), 3.5 (1H, m), 3.49 (2H, t, J = 6 Hz), 2.4–1.4 (10H, m), 1.67 (3H, bs); ms *m/e*: 234 (M$^+$, 0.1%), 133 (33%), 85 (100%).

(Z)-*Tetrahydropyranyl ether 30*

A solution of alcohol **28** (9.5 g, 0.06 mol) and *p*-toluenesulfonic acid monohydrate (200 mg, 1.1 mmol) in ether (70 mL) was treated with dihydropyran (7.3 mL, 0.09 mol) as above to afford **30** as a colorless liquid (14 g, 95%); ir ν_{max}: 2158, 2074, 1661, 1020; ^{1}Hmr δ: 5.43 (1H, bs), 3.49 (1H, t, J = 6 Hz), 2.5–1.4 (10H, m), 1.75 (3H, bs); ms *m/e*: 234 (M$^+$, 0.1%), 133 (24%), 85 (100%). *Anal.* calcd. for $C_{12}H_{19}D_2O_2Cl$: C 61.39, Cl 15.12; found: C 61.73, Cl 15.02.

(E)-*Phosphonium salt 23*

A mixture of **29** (21.5 g, 0.092 mol), triphenylphosphine (25 g, 0.095 mol), and sodium iodide (27 g, 0.18 mol) in acetonitrile (60 mL) was heated at reflux. After 27 h the reaction mixture was cooled to 0°C, diluted with dichloromethane (130 mL), and filtered. The solvent was removed *in vacuo* and the resultant gum was washed with ether (3 × 50 mL), dissolved in acetone (50 mL), treated with ether (130 mL), and allowed to stand at 0°C for several days whereupon crystallization occurred. The solid mass was pulverized, filtered, further washed with ether and water, and dried *in vacuo* at 100°C to afford **23** as an off-white crystalline solid (48 g, 86%), mp 149–151°C (crystals soften at 119°C); ^{1}Hmr δ: 7.8 (15H, m), 5.35 (1H, bs), 4.55 (1H, m), 4.0–3.3 (4H, m), 2.73 (2H, t, J = 7.5 Hz), 2.2–1.3 (8H, m), 1.54 (3H, bs). *Anal.* calcd. for $C_{30}H_{37}D_2IOP$: C 61.23, I 21.57; found: C 61.40, I, 21.65.

(Z)-*Phosphonium salt 24*

A mixture of **30** (8 g, 0.034 mol), triphenylphosphine (9.4 g, 0.036 mol) and sodium iodide (10.2 g, 0.068 mol) in acetonitrile (25 mL) was heated at reflux. After 27 h the reaction mixture was cooled to 0°C, diluted with dichloromethane (100 mL), and filtered. The solvent was removed *in vacuo* and the resultant gum washed with ether (3 × 4 mL). The residue was treated with acetone (40 mL) and let stand at 0°C for 4 h whereupon cyrstallization occurred. The solid mass was pulverized, filtered, washed with ether, and dried *in vacuo* at 100°C to afford **24** as a white crystalline solid (17.8 g, 89%), mp 187–188°C; ^{1}Hmr δ: 7.8 (15H, m), 5.45 (1H, bs), 4.57 (1H, m), 4.0–3.2 (4H, m), 2.43 (2H, t, J = 7.5 Hz), 2.0–1.2 (8H, m), 1.59 (3H, bs). *Anal.* calcd. for $C_{30}H_{37}D_2IOP$: C 61.23, I 21.57; found: C 61.27, I 21.48.

1,1-Dideutero-9-hydroxygeraniol (31)

A suspension of phosphonium salt **23** (2.8 g, 4.76 mmol) in anhydrous tetrahydrofuran/hexamethylphosphoramide (10 mL/1 mL) under a nitrogen atmosphere was treated with a solution of potassium hexamethyldisilylazide in tetrahydrofuran (4.8 mL of 1 *M* solution, 4.8 mmol). After 15 min at ambient temperature the reaction mixture was cooled to −78°C and treated with the tetrahydropyranyl ether of hydroxyacetone (0.7 g, 4.7 mmol). The cooling bath was removed and the reaction mixture allowed to warm to ambient temperature. After a further 3 h at ambient temperature the reaction mixture was diluted with petroleum ether (10 mL) and filtered through a short column of silica gel using petroleum ether as eluent. After evaporation of the solvent, the residue was dissolved in methanol (50 mL), treated with *p*-toluenesulfonic acid monohydrate (80 mg), and stirred at ambient temperature for 18 h. Sodium hydroxide solution (2 *M*, 0.25 mL) was added and the solvent removed *in vacuo*. The residue was chromatographed on silica gel using ether as eluent to afford **31** (contaminated with 3% of the 10-hydroxy isomer) as a colorless liquid (690 mg, 85%); ir ν_{max}: 3340, 2180, 2090, 1080; ^{1}Hmr δ: 5.37 (1H, bs), 5.22 (1H, t, J = 7 Hz), 4.04 (2H, s), 2.70 (1H, bs), 2.2 (4H, m), 1.76 (3H, bs), 1.65 (3H, bs); ms m/e: 154 (M^+ − 18, 0.5%), 136 (3.2%), 121 (15%), 84 (28%), 70 (35%), 43 (100%). *Anal.* calcd. for $C_{10}H_{16}D_2O_2$: C 69.74; found: C 69.75.

1,1-Dideutero-9-hydroxynerol (32)

Reaction of phosphonium salt **24** (2 g, 3.4 mmol) with potassium hexamethyldisilazide (3.4 mL of 1 *M* solution in THF) and the tetrahydropyranyl ether of hydroxyacetone (0.5 g, 3.4 mmol) as above afforded **32** (contaminated with 3% of the 10-hydroxy isomer) as a colorless liquid (530 mg, 91%); ir ν_{max}: 3340, 2160, 2078, 1662, 1080; ^{1}Hmr δ: 5.40 (1H, bs), 5.26 (1H, t, J = 6.5 Hz), 4.02 (2H, s), 2.1 (4H, m), 1.77 (3H, bs), 1.71 (3H, bs); ms m/e: 154 (M^+ − 18, 0.3%), 139 (5%), 136 (5%), 121 (16%), 84 (27%), 70 (40%), 43 (100%).

1,1-Dideutero-9-oxogeraniol (33)

A solution of diol **31** (200 mg, 1.16 mmol) in dichloromethane (18 mL) at ambient temperature was treated with manganese dioxide (2.4 g). The resultant suspension was stirred for 1.5 h and filtered through Celite. The filtrate was concentrated *in vacuo* and the residue chromatographed on silica gel using ether/petroleum ether (1:1, v/v) as eluent to yield **33** (contaminated with 5% of the 10-oxo isomer) as a pale yellow oil (141 mg, 71%); uv λ_{max}: 237 nm (4.09); ir ν_{max}: 3420, 2180, 2078, 1672; ^{1}Hmr δ: 10.13 (1H, s), 6.48 (1H, t, J = 7 Hz), 5.43 (1H, bs), 2.71 (2H, q, J = 7 Hz), 2.18 (2H, t, J = 7 Hz), 1.88 (1H, s), 1.75 (3H, bs), 1.68 (3H, bs); ms m/e: 152 (M^+ − 18, 5%), 137 (9%), 123 (13%), 109 (11%), 95 (16%), 84 (35%), 82 (43%), 41 (100%).

1,1-Dideutero-9-oxonerol (34)

A solution of diol **32** (150 mg, 0.87 mmol) in dichloromethane (15 mL) was treated with manganese dioxide (1.5 g) as above to yield **34** (contaminated with 5% of the 10-oxo isomer) as a pale yellow oil (98 mg, 65%); uv λ_{max}: 237 (4.08); ir ν_{max}: 3420, 1674; ^{1}Hmr δ: 10.09 (1H, s), 6.46 (1H, t, J = 7 Hz), 5.47 (1H, bs), 1.74 (6H, bs); ms m/e: 170 (M^+, 0.1%), 152 (8%), 137 (12%), 109 (15%), 95 (30%), 84 (52%), 82 (94%), 42 (100%). *Anal.* calcd. for $C_{10}H_{14}D_2O_2$: C 70.55; found: C 70.05.

1-Dieutero-9-oxogeranial (35)

A solution of **33** (180 mg, 1.08 mmol) in dichloromethane (11 mL) was treated with barium manganate (1.9 g). The resultant suspension was stirred at ambient temperature for 2.5 days and filtered through Celite. The filtrate was concentrated *in vacuo* and the residue chromatographed on silica gel using ether/petroleum ether (1:1, v/v) as eluent to afford **35** as a pale yellow liquid (130 mg, 71%); uv λ_{max}: 237 (4.38); ir ν_{max}: 2100, 1663; ^{1}Hmr δ: 10.15 (1H, s), 6.43 (1H, t, J = 8 Hz), 5.89 (1H, bs), 3.0–2.2 (4H, m), 2.21 (3H, bs), 1.78 (3H, bs); ms m/e: 167 (M^+, 0.5%), 152 (7%), 149 (4%), 95 (36%), 82 (96%), 42 (100%). *Anal.* calcd. for $C_{10}H_{13}DO_2$: C 71.83; found: C 71.55.

1-Deutero-9-oxoneral (36)

A solution of **34** (120 mg, 0.71 mmol) in dichloromethane (8 mL) was treated with barium manganate (1.3 g) as above to afford **36** as a pale yellow liquid (88 mg, 75%); uv λ_{max}: 236 (4.35); ir ν_{max}: 2100, 1667, 1636; ^{1}Hmr δ: 10.11 (1H, s), 6.44 (1H, t, J = 7 Hz), 5.93 (1H, bs), 2.9–2.6 (4H, m), 2.00 (3H, bs), 1.77 (3H, bs); ms m/e: 167 (M^+, 0.4%), 152 (6%), 149 (4%), 95 (38%), 82 (96%), 42 (100%).

1,1-Dideutero-10-oxogeraniol (37)

A suspension of the (*E*)-phosphonium salt **23** (5.4 g, 9.2 mmol) in anhydrous tetrahydrofuran/hexamethylphosphoramide (30 mL/3 mL) under a nitrogen atmosphere was treated with a 1.9 *M* solution of phenyllithium in ether (5 mL, 9.5 mmol). After stirring for 10 min at ambient temperature the reaction mixture was cooled to −78°C and treated with pyruvaldehyde dimethyl acetal (1.05 g, 8.9 mmol). The reaction was allowed to warm to ambient temperature (ca. 30 min) and stirred for a further 3 h. Petroleum ether (30 mL) was added and the resultant mixture filtered through a short column of silica gel using ether/petroleum ether (1:1) as eluent. The filtrate was concentrated *in vacuo* and the residue dissolved in methanol (60 mL) containing *p*-toluenesulfonic acid monohydrate (50 mg). After stirring for 18 h at ambient temperature, water (70 mL) was added and stirring continued. After 30 min, the reaction mixture was concentrated *in vacuo* (to ca. one-half the original volume, made basic with 1 *N* sodium hydroxide, and extracted with ether (3 × 40 mL). The combined ether extract was dried and the solvent removed *in vacuo* to afford **37** (contaminated with 2% of the 9-oxo isomer) as a pale yellow oil (980 mg, 65%); uv λ_{max}: 229 (4.20); ir ν_{max}: 3400, 1683, 1640; ^{1}Hmr δ: 9.36 (1H, s), 6.46 (1H, t, J = 7 Hz), 5.43 (1H, bs), 2.7–2.0 (4H, m), 1.73 (3H, bs), 1.68 (3H, bs); ms m/e: 152 (M^+ − H_2O, 11%), 137 (26%), 123 (26%), 84 (60%), 42 (100%).

1,1-Deutero-10-oxonerol (38)

A suspension of the (*Z*)-phosphonium salt **24** (2.5 g, 4.3 mmol) in anhydrous tetrahydrofuran/hexamethylphosphoramide (13 mL/1.3 mL) under a nitrogen atmosphere was treated with a 1.9 *M* solution of phenyllithium in ether (2.4 mL, 4.6 mmol) as above to afford **38** (contaminated with 7% of the 9-oxo isomer) as a pale yellow oil (500 mg, 69%); uv λ_{max}: 229 (4.29); ir ν_{max}: 3400, 1672, 1644; ^{1}Hmr δ: 9.38 (1H, s), 6.48 (1H, t, J = 7 Hz), 5.48 (1H, bs), 2.4 (4H, m), 1.76 (6H, bs); ms m/e: 152 (M^+ − 18, 5%), 151 (6%), 137 (11%), 123 (16%), 109 (11%), 98 (26%), 95 (19%), 84 (76%), 55 (60%), 42 (100%). *Anal.* calcd. for $C_{10}H_{14}D_2O_2$: C 70.55; found: C 70.48.

1-Deutero-10-oxogeranial (39)

A solution of **37** (350 mg, 2.06 mmol) in dichloromethane (25 mL) was treated with barium manganate (3.3 g). The resultant suspension was stirred at ambient temperature for 3 days and then filtered through Celite. The solvent was removed *in vacuo* to give the dialdehyde **39** as a pale yellow liquid (272 mg, 80%); uv λ_{max}: 234 (4.42); ir ν_{max}: 2100, 1682, 1660, 1640; ^{1}Hmr δ: 9.39 (1H, s), 6.44 (1H, t, J = 7 Hz), 5.89 (1H, bs), 2.7–2.22 (4H, m), 2.22 (3H, bs), 1.76 (3H, bs); ms m/e: 167 (M^+, 0.2%, 166 (0.5%), 149 (8%), 121 (13%), 110 (33%), 82 (44%), 55 (100%). *Anal.* calcd. for $C_{10}H_{13}DO_2$: C 71.83; found: C 71.39.

1-Deutero-10-oxoneral (40)

A solution of **38** (114 mg, 0.67 mmol) in dichloromethane (8 mL) was treated with barium manganate (1 g) as above to afford the dialdehyde **40** as a pale yellow liquid (93 mg, 82%); uv λ_{max}: 229 (4.32), 235 sh (4.29); ir ν_{max}: 2100, 1681, 1662, 1638; ^{1}Hmr δ: 9.40 (1H, s), 6.45 (1H, t, J = 7 Hz), 5.93 (1H, bs), 3.0–2.4 (4H, m), 2.02 (3H, bs), 1.75 (3H, bs); ms m/e: 167 (M^+, 1%), 152 (3%), 149 (6%), 138 (12%), 122 (14%), 109 (27%), 95 (63%), 85 (66%), 82 (76%), 55 (100%).

1,1-Dideutero-9,10-dihydroxygeraniol (41)

A suspension of the (*E*)-phosphonium salt **23** (5.36 g, 9.1 mmol) in anhydrous tetrahydrofuran/hexamethylphosphoramide (30 mL/3 mL) under a nitrogen atmosphere was treated with a 1.9 *M* solution of

phenyllithium in ether/hexane (4.7 mL, 8.9 mmol). After stirring at ambient temperature for 15 min the reaction mixture was cooled to −78°C and treated with a solution of the ditetrahydropyranyl ether of 1,3-dihydroxyacetone (2.3 g, 8.9 mmol) in ether (3 mL). The reaction mixture was allowed to warm to ambient temperature and stirred for a further 3 h. Petroleum ether (20 mL) was added and the resultant mixture filtered through a short column of silica gel using petroleum ether/ether as eluent. The filtrate was concentrated *in vacuo* and the residue was dissolved in methanol (230 mL) containing *p*-toluenesulfonic acid monohydrate (150 mg). After standing at ambient temperature for 17 h, sodium hydroxide (50 mg) was added and the solvent removed *in vacuo*. The residue was chromatographed on silica gel using ether/methanol (20:1 then 10:1) as eluent to afford **41** as a colorless oil (940 mg, 56%); ir ν_{max}: 3340, 1005; ^{1}Hmr δ: 5.47 (1H, t, J = 7 Hz), 5.30 (1H, bs), 4.22 (2H, s), 4.14 (2H, s), 2.4–2.0 (4H, m), 1.66 (3H, bs). *Anal.* calcd. for $C_{10}H_{16}D_2O_3$: C 63.80; found: C 63.75.

1,1-Dideutero-9,10-dihydroxynerol (42)

A suspension of the (*Z*)-phosphonium salt **24** (3.4 g, 5.8 mmol) in anhydrous tetrahydrofuran/hexamethylphosphoramide (20 mL/2 mL) was treated with phenyllithium (3 mL of 1.9 *M* solution, 5.7 mmol) and the tetrahydropyranyl ether of 1,3-dihydroxyacetone (1.5 g, 5.7 mmol) as above to afford **42** as a colorless oil (680 mg, 63%); ir ν_{max}: 3340, 1008; ^{1}Hmr δ: 5.53 (1H, t, J = 7 Hz), 5.39 (1H, bs), 4.16 (2H, s), 4.10 (2H, s), 2.2–1.9 (4H, m), 1.73 (3H, bs).

*Oxidation of **41** with manganese dioxide*

A solution of **41** (100 mg, 0.53 mmol) in tetrahydrofuran (14 mL) at 0°C was treated with manganese dioxide (1 g). After 30 min at 0°C the reaction mixture was filtered through Celite and the filtrate concentrated *in vacuo* to afford 1,1-dideutero-9-oxo-10-hydroxygeraniol (**43**), contaminated with 12% of the 9-hydroxy-10-oxo isomer **45**, as a pale yellow liquid (72 mg, 72%); uv λ_{max}: 233 (4.04); ir ν_{max}: 3368, 1670; ^{1}Hmr δ: 10.10 (1H, s), 6.69 (1H, t, J = 7 Hz), 5.41 (1H, bs), 4.21 (2H, s), 2.75 (2H, q, J = 7 Hz), 2.23 (2H, t, J = 7 Hz), 1.67 (3H, bs).

*Oxidation of **42** with manganese dioxide*

A solution of **42** (150 mg, 0.81 mmol) in tetrahydrofuran (20 mL) at 0°C was treated with manganese dioxide as above to afford 1,1-dideutero-9-oxo-10-hydroxynerol (**44**), contaminated with 14% of the 9-hydroxy-10-oxo isomer **46**, as a pale yellow liquid (98 mg, 66%); uv λ_{max}: 234 (4.01); ir ν_{max}: 3380, 1668; ^{1}Hmr δ: 10.02 (1H, s), 6.70 (1H, t, J = 7 Hz), 5.44 (1H, bs), 4.19 (2H, bs), 2.71 (2H, q, J = 7 Hz), 2.32 (2H, t, J = 7 Hz), 1.73 (3H, bs). *Anal.* calcd. for $C_{10}H_{14}D_2O_3$: C 64.49; found: C 63.94.

*β-Ketosulfoxide **48***

A suspension of sodium hydride (4 g of 50% NaH/mineral oil, 83 mmol) in dimethyl sulfoxide (80 mL) was heated at 70°C for 1 h, cooled to ambient temperature, and treated with a solution of ethyl 1,1-diethoxyacetate (7 g, 39.8 mmol) in ether (5 mL) at a dropwise rate over 2 h. The reaction mixture was stirred for a further 17 h, diluted with water (50 mL), and washed with petroleum ether (3 × 50 mL). The aqueous portion was made neutral with acetic acid (5 mL) and extracted with dichloromethane (4 × 50 mL). The combined dichloromethane extract was dried (Na_2SO_4) and the solvent removed *in vacuo*. The residue was chromatographed on silica gel (250 g) using ethyl acetate/ethanol (100:1 then 10:1) as eluent to afford **48** as a yellow liquid (5 g, 60%); ir ν_{max}: 1729, 1110; ^{1}Hmr δ: 4.60 (1H, s), 4.00 (2H, AB quartet), 3.6 (4H, m), 2.,67 (3H, s), 1.23 (6H, t, J = 7 Hz). *Anal.* calcd. for $C_8H_{16}O_4S$: C 46.13, H 7.74, S 15.39; found: C 46.19, H 7.66, S 15.38.

1,1,3,3-Tetraethoxyacetone (47)

A suspension of red mercuric oxide (6.5 g, 0.03 mol) in ethanol (60 mL) was treated with boron trifluoride etherate (3.6 mL, 0.03 mol). After stirring for 5 min, a solution of **48** (4.4 g, 0.021 mol) in ether (5 mL) was added. The resultant mixture was heated at reflux for 45 min, cooled to ambient temperature, and stirred for a further 2 h. Petroleum ether (50 mL) was added and the mixture filtered through Celite. The filtrate was washed with 1 *N* sodium hydroxide (4 × 50 mL). The combined aqueous portion was back-extracted with petroleum ether (2 × 40 mL) and the combined organic portion dried (Na_2SO_4). The solvent was removed *in vacuo* and the residue distilled at 0.7 Torr to give **50** as a colorless liquid (3.5 g, 71%); bp 82°C at 0.7 Torr; ir ν_{max}: 1763, 1070; ^{1}Hmr δ: 5.02 (2H, s), 3.65 (8H, m), 1.24 (12H, t, J = 7 Hz).

*Phosphonium salt **49***

A mixture of the (*E*)-chloroalcohol **27** (5.2 g, 34.6 mmol), triphenylphosphine (9.2 g, 35.1 mmol), and sodium iodide (6 g, 40 mmol) in acetonitrile (80 mL) was heated at reflux. After 30 h, the reaction mixture was cooled to 0°C, diluted with dichloromethane (60 mL), and filtered. The filtrate was concentrated *in vacuo*, treated with ether (100 mL), and allowed to stand until crystallization was complete. The solid mass was pulverized, washed with ether, recrystallized from aqueous ethanol, and dried *in vacuo* at 100°C to give **49** as a white crystalline solid (14.4 g, 83%); mp 180–181°C; ^{1}Hmr δ: 7.8 (15H, m), 5.50 (1H, bs), 3.48 (2H, m), 2.28 (2H, t, J = 7 Hz), 1.8 (2H, m), 1.50 (3H, bs). *Anal.* (of nondeuterated analog) calcd. for $C_{25}H_{28}IPO$: C 59.77, H 5.62, I 25.26; found: C 59.91, H 5.62, I 25.32.

*Phosphonium salt **50***

A mixture of the (*Z*)-chloroalcohol **28** (7.3 g, 48.5 mmol), triphenylphosphine (13.1 g, 50 mmol), and sodium iodide (9 g, 60 mmol) in acetonitrile (100 mL) was treated as above to give **50** as a white crystalline solid (20.3 g, 83%); mp 149–150°C; ^{1}Hmr δ: 7.8 (15H, m), 5.59 (1H, bs), 3.57 (2H, m), 2.44 (2H, t, J = 7 Hz), 1.8 (2H, m), 1.49 (3H, bs). *Anal.* calcd. for $C_{25}H_{26}D_2IPO$: C 59.53, I 25.16; found: C 59.64, I 25.22.

1,1-Dideutero-9,9,10,10-tetraethoxygeraniol (51)

A suspension of phosphonium salt **49** (2.2 g, 4.38 mmol) in anhydrous tetrahydrofuran/hexamethylphosphoramide (15 mL/1.5 mL) under a nitrogen atmosphere was treated with a 2 *M* solution of n-butyllithium in hexane (4.4 mL, 8.8 mmol). After stirring for 15 min at ambient temperature the reaction was cooled to −78°C and treated with a solution of 1,1,3,3-tetraethoxyacetone (1 g, 4.27 mmol) in ether (2 mL). The reaction was allowed to warm to ambient temperature and stirred for a further 3 h. Water (5 drops) and petroleum ether (20 mL) were added, and the resultant mixture filtered through Celite. The filtrate was concentrated *in vacuo* and the residue chromatographed on silica gel using ether/petroleum ether (1:1) as eluent to give **51** as a colorless liquid (1 g, 71%); ir ν_{max}: 3450, 1056; ^{1}Hmr δ: 5.79 (1H, t, J = 7 Hz), 5.40 (1H, bs), 5.01 (1H, s), 4.77 (1H, s), 4.0–3.3 (8H, m), 2.7–2.0 (4H, m), 1.67 (3H, bs), 1.19 (12H, t, J = 7 Hz).

1,1-Dideutero-9,9,10,10-tetraethoxynerol (52)

A suspension of phosphonium salt **50** (2.2 g, 4.38 mmol) in tetrahydrofuran/hexamethylphosphoramide (15 mL/1 mL) was treated with a 2 *M* solution of n-butyllithium in hexane (4.4 mL, 8.8 mmol) and a solution of 1,1,3,3-tetraethoxyacetone (1 g, 4.27 mmol) in ether (2 mL) as above to afford **52** as a colorless oil (780 mg, 55%); ir ν_{max}: 3450, 1060; ^{1}Hmr δ: 5.81 (1H, t, J = 7 Hz), 5.43 (1H, bs), 5.00 (1H, s), 4.78 (1H, s), 4.0–3.3 (8H, m), 2.6–2.0 (5H, m), 1.72 (3H, bs), 1.18 (12H, t, J = 7 Hz). *Anal.* calcd. for $C_{18}H_{32}D_2O_5$: C 65.03; found: C 64.95.

1-Deutero-9,9,10,10-tetraethoxygeranial (53)

A solution of **51** (180 mg, 0.54 mmol) in dichloromethane (15 mL) was treated with barium manganate (1.7 g). The resultant suspension was stirred at ambient temperature for 3 days, filtered through Celite, and concentrated *in vacuo*. The residue was chromatographed on silica gel using ether/petroleum ether (1:1) as eluent to give **53** (86 mg, 48%) as a colorless liquid; uv λ_{max}: 238 (4.06); ir ν_{max}: 2096, 1665, 1064; ^{1}Hmr (CCl_4) δ: 5.74 (1H, bs), 5.53 (1H, t, J = 7 Hz), 4.79 (1H,

s), 4.53 (1H, s), 3.4 (8H, m), 2.8–2.1 (4H, m), 2.13 (3H, bs), 1.14 (6H, t, J = 7 Hz), 1.11 (6H, t, J = 7 Hz). *Anal.* calcd. for $C_{18}H_{31}DO_5$: C 65.62; found: C 65.56.

*1-Deutero-9,9,10,10-tetraethoxyneral (**54**)*

A solution of **52** (200 mg, 0.60 mmol) in dichloromethane (18 mL) was treated with barium manganate (1.9 g) as above to afford **54** as a colorless liquid (89 mg, 45%); uv λ_{max}: 237 (4.07); ir ν_{max}: 2092, 1663, 1062; ^{1}Hmr (CCl_4) δ: 5.74 (1H, bs), 5.60 (1H, t, J = 7 Hz), 4.81 (1H, s), 4.56 (1H, s), 3.4 (8H, m), 2.9–2.1 (4H, m), 1.95 (3H, bs), 1.15 (6H, t, J = 7 Hz), 1.12 (6H, t, J = 7 Hz).

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