NHAc group. A parent peak (m/e 227) was observed in the mass spectrum of **2a**.

The yield of **2a** decreased and that of **3** increased gradually by increasing current density. Dimethyl 2,3-dimethyl-2,3-bis(2,2,2-trifluoroethyl)succinate (**4a**) was also isolated in about 3% yield and identified by comparison with an authentic sample.[7] Most of the other products were unidentified because of their volatility.

It must be pointed out that Renaud has reported the formation of **4a** (9.8% yield) as the only isolated product in the electrolysis of MMA in methanol or acetic acid, but no formation of the corresponding trifluoromethyl-methoxylated or acetoxylated compound is reported.[7] In sharp contrast to MMA, the electrochemical trifluoromethylation of methyl acrylate[8] afforded dimer **4b** formed from the trifluoromethylated radical **5b**, and the corresponding acetamide **2b** was not isolated. We also observed the preferential dimer **4b** formation (40–50% yield) on the electrolysis of methyl acrylate under our experimental conditions.

The formation of different products can be rationalized as follows. The addition of the electrochemically generated trifluoromethyl radical to MMA leads to radical **5a**, which would suffer further one-electron oxidation and the successive acetamidation leading to **2a**. Alternatively, the formation of the intermediate **6**[9] by dehydrogenation from the methyl group of **5a** followed by addition of another CF_3 radical, one-electron oxidation, and acetamidation at the final stage would result in the formation of **3**. The use of a 2:1 ratio of MMA to TFA results in the decreased formation of **3** and the increase of **4a** as indicated by VPC. On the other hand, electrolysis of methyl α-phenylacrylate under similar conditions failed to produce the desired acetamide **2c** because substrate **1c** was electrooxidized much faster than TFA. In fact, the cyclic voltammogram of **1c** in MeCN–Et_4NClO_4–TFA reveals a sharp anodic current at around 1.7 V vs Ag/Ag^+, while the currents of **1a** and **1b** were observed at around 2.5 V, quite close to that of TFA in MeCN–Et_4NClO_4.

The four types of reaction modes on the electrochemical trifluoromethylation of olefins so far known are (1) addition of the CF_3 group to the carbon–carbon double bond followed by dimerization,[7-11] (2) addition of the CF_3 group followed by hydrogen abstraction,[7-10,12] (3) 1,2-addition of two CF_3 groups to olefin,[7-11] and (4) addition of the CF_3 group followed by elimination of hydrogen leading to trifluoromethylated olefin (substitution of hydrogen on sp^2 carbon with the CF_3 group).[7-10] The present electrochemical trifluoromethyl–acetamidation is the first example of 1,2–addition of a CF_3 group and a nucleophile to a carbon–carbon double bond.

Experimental Section

All reagents were commercially available and were used without further purification. Melting points were uncorrected. Infrared spectra were taken on a Hitachi 270–30 spectrometer. ^1H, ^{13}C, and ^{19}F NMR spectra were measured on a Varian VXR-500 instrument using TMS for ^1H and ^{13}C and C_6F_6 for ^{19}F NMR as internal standards. Mass spectra (MS) were obtained with a Hitachi-M80A instrument (20 eV).

Electrolysis of TFA in the Presence of MMA. (a) Excess of TFA. MMA (200 mg, 2 mmol), TFA (0.46 mL, 6 mmol), and sodium hydroxide (24 mg, 0.6 mmol) were dissolved a mixture of acetonitrile (20 mL) and water (3 mL) in a cylindrical electrolysis cell. Two platinum foils were used as an electrode, and the mixture was electrolyzed under a constant current of 24 mA (1 mA/cm^2) at 0–5 °C for 8 h and 55 min (4 F/mol based on MMA). The solution was neutralized with saturated $NaHCO_3$, the organic layer was separated, and the aqueous layer was extracted with ethyl acetate (3 × 4 mL). The combined organic extracts were washed with saturated NaCl, dried (Na_2SO_4), and concentrated in vacuo. The residue was submitted to flash column chromatography, affording 91 mg (20%) of **2a** and 30 mg (5%) of **3**.

Methyl 2-(acetylamino)-2-methyl-4,4,4-trifluorobutyrate (2a): mp 95–97 °C; IR (KBr) 3258 (NH), 1738 (C=O), 1652 (NHC=O), 1568, 1460, 1378, 1263, 1176, 1104, 1056 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.45 (1 H, s, NH), 3.80 (3 H, s, OCH_3), 3.43 (1 H, dq, J_1 = 15.6 Hz, J_2 = 10.7 Hz, CH_2CF_3), 2.82 (1 H, dq, J_1 = 15.6 Hz, J_2 = 10.7 Hz, CH_2CF_3), 2.01 (3 H, s, Ac), 1.67 (3 H, s, CH_3); ^{13}C NMR ($CDCl_3$) δ 24.0 (s, CH_3), 24.1 (s, CH_3), 38.0 (q, J = 27.5 Hz, CH_2), 53.6 (s, OCH_3), 56.6 (q, J = 2.3 Hz, CNH), 125.8 (q, J = 278.5 Hz, CF_3), 170.3 (s, C=O), 173.6 (s, C=O); ^{19}F NMR ($CDCl_3$) δ 99.2 (t, J = 10.3 Hz); MS, m/e (relative intensity) 227 (1), 196 (1), 184 (1), 168 (32), 126 (100), 102 (8), 43 (42). Anal. Calcd for $C_8H_{12}F_3O_3N$: C, 42.29; H, 5.32; N, 6.17. Found: c, 42.50; H, 5.45; N, 6.23.

Methyl 2-(acetylamino)-2-(2,2,2-trifluoroethyl)-4,4,4-trifluorobutyrate (3): mp 58–59 °C; IR (KBr) 3436, 3388 (NH), 1754 (C=O), 1690 (NHC=O), 1512, 1376, 1354, 1256, 1212, 1166, 1100, 1048 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.68 (1 H, s, NH), 3.87 (3 H, s, OCH_3), 3.69 (2 H, dq, J_1 = 15.6 Hz, J_2 = 10.7 Hz, CH_2CF_3), 3.48 (2 H, dq, J_1 = 15.6 Hz, J_2 = 10.7 Hz, CH_2CF_3), 2.02 (3 H, s, Ac); ^{13}C NMR ($CDCl_3$) δ 23.9 (s, CH_3), 38.2 (q, J = 28.2 Hz, CH_2), 54.2 (s, OCH_3), 56.3 (q, J = 3.0 Hz, CNH), 124.9 (q, J = 278.3 Hz, CF_3), 170.7 (s, C=O), 171.1 (s, C=O); ^{19}F NMR ($CDCl_3$) δ 99.1 (t, J = 9.6 Hz); MS, m/e (relative intensity) 295 (4), 253 (1) 236 (1), 194 (78), 174 (6), 170 (10), 110 (10), 59 (4), 43 (100). Anal. Calcd for $C_9H_{11}F_6O_3N$: C, 36.62; H, 3.76; N, 4.75. Found: C, 36.90; H, 3.43; N, 4.40.

(b) Equivalent of TFA and MMA. MMA (0.22 mL, 2 mmol), TFA (228 mg, 2 mmol), and sodium hydroxide (16 mg, 0.4 mmol) were dissolved in a mixture of acetonitrile (14 mL) and water (2 mL) in a cylindrical electrolysis cell. The mixture was electrolyzed under a constant current of 60 mA (20 mA/cm^2) at 0–5 °C for 86 min (1.6 F/mol based on TFA). The residue was submitted to flash column chromatography, affording 80 mg (18%) of **2a**, a trace amount of **3**, and 20 mg (3%) of **4a**. MMA was recovered in ca. 20% yield (by VPC analysis).

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Absolute Configuration of L-659,699, a Novel Inhibitor of Cholesterol Biosynthesis

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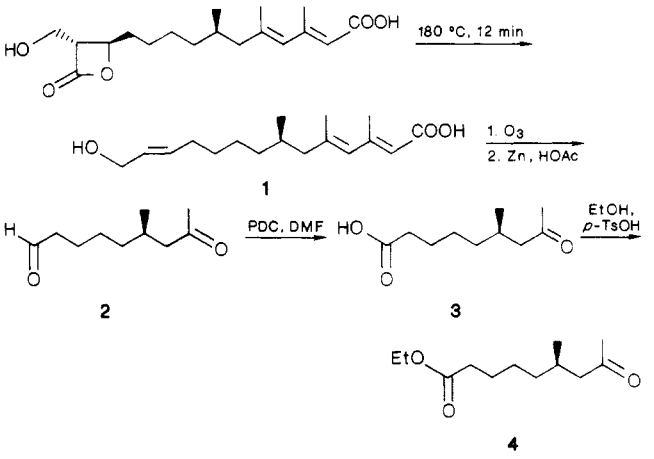
L-659,699, a naturally occurring β-lactone isolated from *Fusarium* sp.[1] and *Scopulariopsis* sp.,[2] is a potent, specific

(1) Greenspan, M. D.; Yudkovitz, J. B.; Lo, C. L.; Chen, J. S.; Alberts, A. W.; Hunt, V. M.; Chang, M. N.; Yang, S. S.; Thompson, K. L.; Chiang, Y. P.; Chabala, J. C.; Monaghan, R. L.; Schwartz, R. E. *Proc. Natl. Acad. Sci. U.S.A.* **1987**, *84*, 7488.

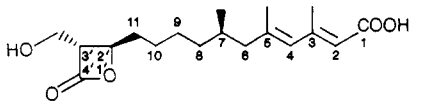
0022-3263/88/1953-4599$01.50/0

Scheme I



inhibitor of the enzyme 3-hydroxy-3-methylglutaryl coenzyme A synthase (HMG-CoA synthase) and cholesterol biosynthesis in cell culture.[1,2] This compound, also known as 1233A, was first isolated from *Cephalosporin* sp. in 1971 by Turner et al. and was reported to possess weak antibacterial activity.[3] The compound was identified by Turner as (*E*,*E*)-11-[3′-(hydroxymethyl)-4′-oxo-2′-oxetanyl]-3,5,7-trimethyl-2,4-undecadienoic acid, with the hydroxymethyl group and alkyl chain in a trans relationship on the β-lactone ring. However, the absolute stereochemistry at C-7 and the ring carbons of this compound remained undetermined.

As this compound is the first specific inhibitor of HMG-CoA synthase, knowledge of its absolute configuration is important for the understanding of the mechanism of inhibition and essential for the design of more potent inhibitors. The small needles of L-659,699 were found unsuitable for X-ray diffraction study. A number of derivatives of L-659,699 were prepared but no crystals adequate for X-ray diffraction studies were obtained. In this paper, we report the determination of the stereochemistry of L-659,699 by a combination of chemical degradation and NMR spectroscopic methods.



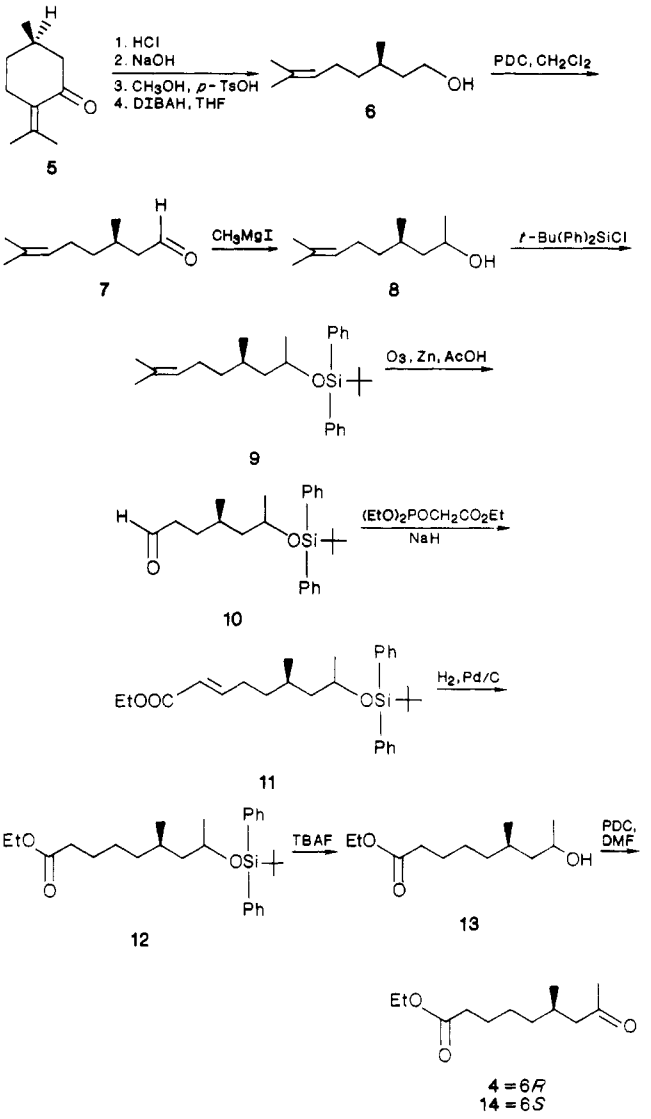
L-659,699

Results and Discussion

The absolute configuration of the side-chain center was determined by correlation of a degradation product with natural products of known structure. A four-step sequence detailed in Scheme I transformed L-659,699 to **4**, which contains only the C-7 stereogenic center. Pyrolysis of the natural product effected extrusion of carbon dioxide affording olefin **1**. Ozonolysis of **1** followed by oxidation with pyridinium dichromate in DMF produced the acid **3**. Subsequent esterification of **3** with ethanol afforded the target compound **4**.

Compound **4** was prepared from (*R*)-(+)-pulegone (**5**) by the synthetic sequence show in Scheme II. (*R*)-(+)-β-Citronellol (**6**) ([α]$_D$ +4.48° (*c* 3.26, MeOH)) was obtained from (*R*)-(+)-pulegone (**5**) according to the procedure of

Scheme II



Overberger.[4] Oxidation of (*R*)-(+)-β-citronellol (**6**) with pyridinium dichromate produced the (*R*)-(+)-citronellal (**7**). Treatment of **7** with methylmagnesium iodide gave the alcohol **8**. Protection of the hydroxy group of **8** with *tert*-butylchlorodiphenylsilane followed by ozonolysis yielded the aldehyde **10**. Exposure of **10** to triethyl phosphonoacetate afforded **11**. Hydrogenation of **11** followed by deprotection with tetrabutylammonium fluoride gave the alcohol **13**, which was converted to compound **4** by PDC oxidation in DMF.

The optical rotation of the degradation product **4** was found to be [α]$_D$ +7.99° (*c* 2.18, MeOH), whereas that observed for the synthetic compound **4** was [α]$_D$ +7.94° (*c* 2.45, MeOH). The near-identity of these two values leads to the conclusion that these two compounds have the same absolute configuration. As the synthetic compound **4** has the *R* configuration at C-6, the absolute configuration at C-7 of L-659,699 is assigned 7*R*. This is confirmed by the synthesis of enantiomer **14** from (*S*)-(−)-β-citronellol by the same synthetic sequence used to prepare **4**. The optical rotation of this compound was found to be [α]$_D$ −5.74° (*c* 2.18, MeOH),[5] which is opposite in sign to the

(2) Omura, S.; Toma, H.; Kumagai, H.; Greenspan, M. D.; Yudkovitz, J. B.; Chen, J.; Alberts, A. W.; Martin, I.; Mochales, S.; Monaghan, R. L.; Chabala, J. C.; Schwartz, R. E.; Patchett, A. A. *J. Antibiot.* **1987**, *40*, 1356.
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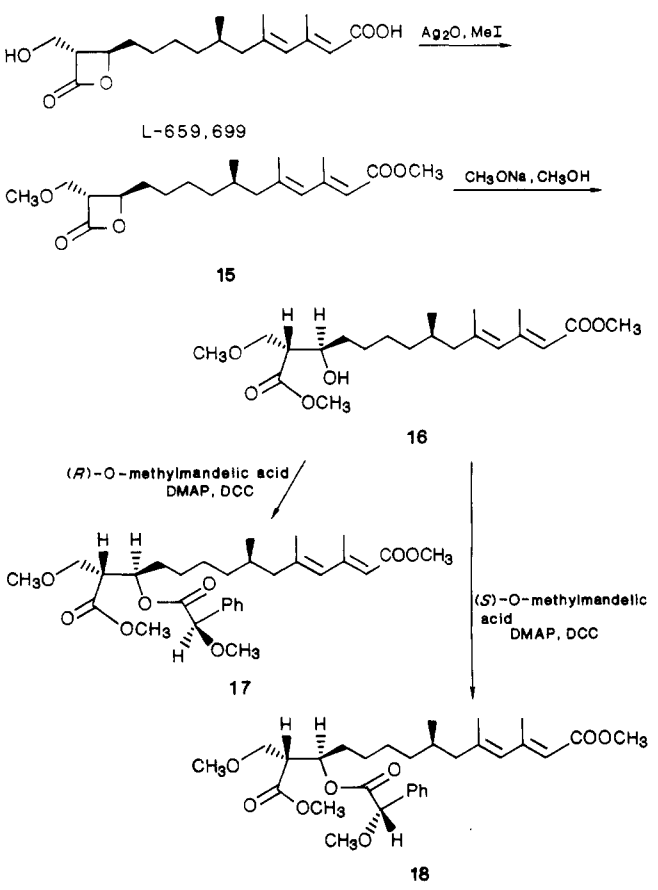
(5) The difference in optical rotation between **14** and **4** is due to the low enantiomeric excess of the starting material, (*S*)-(−)-β-citronellol, which has 68% enantiomeric excess by comparison to literature data.

Scheme III



observed rotation of the degradation product **4**.

The absolute configuration of the ring carbons was determined by NMR spectroscopic methods.[6] A secondary alcohol **16** derived from L-659,699 was converted to the two diastereomeric *O*-methylmandelates **17** and **18**. Scheme III outlines the preparation of the diastereomeric mandelates **17** and **18**. The hydroxyl and carboxyl groups on the side chains of L-659,699 were protected by methylation with methyl iodide in the presence of silver oxide. The lactone ring of **15** was opened to the β-hydroxy ester **16** by reaction with a catalytic amount of sodium methoxide in MeOH, which effected the acyl cleavage while maintaining the integrity of the C-2′ center. Independent treatment of **16** with (*R*)- and (*S*)-*O*-methylmandelic acid in the presence of DMAP and DCC gave the diastereomeric esters **17** and **18**, respectively.

The diastereomers **17** and **18** have known configuration at the mandelic acid moiety but unknown configuration at the carbinyl center. On the basis of a NMR-configurational correlation model proposed by Dale and Mosher,[6] the nonequivalence of the chemical shifts of the proton resonances from the groups attached to the carbinyl carbon can be used to assign the absolute configuration of that stereogenic center. The assumed low-energy conformation upon which this model depends is illustrated by the structures **17B** and **18B** in Figure 1. The protons of the substituent that is eclipsed by the phenyl ring always show an upfield shift presumably due to the shielding effect of the phenyl ring. In structure **17B**, which was derived from (*R*)-*O*-methylmandelic acid, this group is L^3. In structure

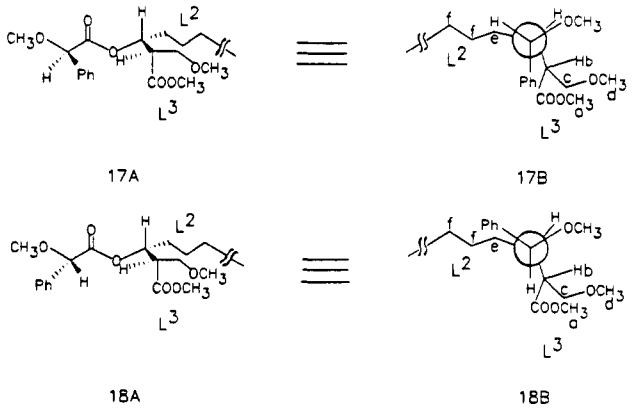


Figure 1. Configuration correlation model.

Table I. Nonequivalent ^{1}H NMR Chemical Shifts for Selected Protons of (*R*)- and (*S*)-*O*-Methylmandelates 17 and 18

	proton	17 (*R*)	18 (*S*)
L^3	H_a	3.49	3.68
	H_b	2.81	2.90
	H_c	3.15, 3.33	3.47, 3.61
	H_d	3.12	3.30
L^2	H_e	1.62	1.47
	H_f	1.08, 1.26	0.88, 1.06

18B, which was derived from (*S*)-*O*-methylmandelic acid, this group is L^2.

Table I summarizes the nonequivalent chemical shifts for the diastereomers **17** and **18**. The data of Table I show that the protons H_a, H_b, H_c, and H_d in the (*R*)-mandelate resonate at higher field than the corresponding protons in the (*S*)-mandelate. The reverse is true for the protons H_e and H_f, which resonate at higher field in the *S* isomer than in the *R* isomer. As illustrated by the correlation model in Figure 1, the shift data are consistent with the assignment of an *R* configuration at the center bearing the mandelate residue. This carbinyl center corresponds to C-2′ of L-659,699.

The trans disposition of the two substituents on the oxetanone ring of L-659,699 was established by spectroscopic methods.[3] Since the C-2′ configuration was determined to be *R*, the absolute configuration at C-3′ of L-659,699 is then assigned as 3′*R*, resulting in an overall assignment of 2′*R*,3′*R*,7*R*.

Experimental Section

General. Proton nuclear magnetic resonance spectra were recorded at 200 or 300 MHz. Preparative TLC plates were purchased from Analtech, Newark, DE. Silica gel 60 (230–400 mesh, EM Reagents) was used for flash chromatography.

(*E*,*E*,*E*)-14-Hydroxy-3,5,7-trimethyl-2,4,12-tetradecatrienoic Acid (1). L-659,699 (561 mg, 1.73 mmol) was heated at 180 °C for 12 min under an N_2 atmosphere. After cooling to room temperature, the residue was purified by preparative TLC on silica gel (R_f 0.40, 8% MeOH in CH_2Cl_2) to yield 318 mg (66%) of **1**: NMR ($CDCl_3$, δ) 0.83 (d, 3 H, J = 7 Hz), 1.02–1.18 (m, 1 H), 1.19–1.50 (m, 5 H), 1.54–1.74 (m, 1 H), 1.75–1.96 (s + m, 4 H), 1.98–2.18 (m, 3 H), 2.18–2.40 (s + m, 4 H), 4.11 (d, 2 H, J = 4 Hz), 5.54–5.84 (m, 4 H); mass spectrum, m/e 263 (M^+ − 17). Anal. Calcd for $C_{17}H_{28}O_3 \cdot {}^1/_3H_2O$: C, 71.44; H, 10.09. Found: C, 71.16; H, 9.91.

6-Methyl-8-oxononanal (2). A solution of 297 mg (1.1 mmol) of **1** in 50 mL of CH_2Cl_2 was ozonized at −78 °C until the solution turned slightly blue. The resulting mixture was stirred at −78 °C for $^1/_2$ h, then at room temperature for 2 h. To the solution was added 3 mL of acetic acid followed by 0.5 g of zinc dust. After having been stirred at room temperature for $^1/_2$ h, the solution was filtered and concentrated. The residue was purified by flash chromatography on silica gel (R_f 0.72, 20% EtOAc in hexane) to

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afford 110 mg (61%) of the air-sensitive product **2**: NMR ($CDCl_3$, δ) 0.89 (d, 3 H, J = 7 Hz), 1.06–1.44 (m, 4 H), 1.54–1.72 (m, 2 H) 1.90–2.06 (m, 1 H), 2.13 (s, 3 H), 2.26–2.50 (m, 4 H), 9.75 (t, 1 H).

6-Methyl-8-oxononanoic Acid (3). To a solution of 100 mg (0.59 mmol) of **2** in 5 mL of DMF was added 660 mg (1.75 mmol) of pyridinium dichromate. The solution was stirred at room temperature for 20 h, diluted with 20 mL of CH_2Cl_2, filtered, and concentrated to give 50 mg of the crude product **3**, which was used for the next step without further purification.

Ethyl 6-Methyl-8-oxononanoate (4). A solution of 50 mg (0.26 mmol) of the crude product **3** in 12 mL of absolute ethanol containing 10 mg (0.05 mmol) of *p*-toluenesulfonic acid monohydrate was boiled under reflux for 1.5 h and then concentrated. The product was purified by preparative TLC on silica gel (R_f 0.40, 20% EtOAc in hexane to yield 34 mg (61%) of **4**: NMR ($CDCl_3$, δ) 0.89 (d, 3 H, J = 7 Hz), 1.12–2.04 (t + m, 6 H), 1.53–1.70 (m, 2 H), 1.94–2.08 (m, 1 H), 2.13 (s, 3 H), 2.17–2.47 (m, 5 H), 4.15 (q, 2 H); FAB mass spectrum, m/e 215 (M^+ + 1); $[\alpha]_D$ +7.99° (c 2.18, MeOH). Anal. Calcd for $C_{12}H_{22}O_3$: C, 67.26; H, 10.35. Found: C, 67.45; H, 10.54.

(*R*)-(+)-Citronellal (7). The starting material, (*R*)-(+)-β-citronellol [$[\alpha]_D$ +4.48° (c 3.26, MeOH)] was prepared from (*R*)-(+)-pulegone [purchased from Aldrich, purified by chromatography on silica gel before use, $[\alpha]_D$ +23.68° (c 7.7, $CHCl_3$)] according to a literature procedure.[4] A mixture of 4.8 g (30.7 mmol) of (*R*)-(+)-β-citronellol and 20.2 g (53.7 mmol) of pyridinium dichromate in 30 mL of CH_2Cl_2 was stirred at room temperature for 19 h, diluted with 60 mL of ether, filtered, and concentrated. The residue was purified by flash chromatography on silica gel (R_f 0.61, 8% EtOAc in hexane) to yield 2.8 g (59%) of **7**, sensitive to air oxidation, which was subjected to the next reaction immediately: NMR ($CDCl_3$, δ) 0.96 (d, 3 H, J = 7 Hz), 1.17–1.43 (m, 2 H), 1.60 (s, 3 H), 1.68 (s, 3 H), 1.89–2.13 (m, 3 H), 2.14–2.49 (m, 2 H), 5.09 (td, 1 H), 9.74 (t, 1 H).

(6*R*)-2,6-Dimethyl-2-nonen-8-ol (8). A solution of 0.89 g (5.8 mmol) of **7** in 15 mL of ether was added dropwise to a solution of 3.2 mL (7.0 mmol) of 2.2 M methylmagnesium iodide in 15 mL of ether at 0 °C. The mixture was stirred at 0 °C for 10 min, then poured into 200 mL of ice water, and extracted with 3 × 30 mL of ether. The ether phases were combined, dried and concentrated. The residue was purified by flash chromatography on silica gel (R_f 0.46, 22% EtOAc in hexane) to afford 0.83 g (84%) of **8**: NMR ($CDCl_3$, δ) 0.90 (d, 3 H, J = 7 Hz), 1.06–1.20 (d + m, 4 H), 1.22–1.45 (m, 4 H), 1.46–1.60 (m + s, 4 H), 1.68 (s, 3 H), 1.84–2.06 (m, 2 H), 3.82–3.94 (m, 1 H), 5.05–5.10 (m, 1 H); mass spectrum, m/e 170 (M^+). Anal. Calcd for $C_{11}H_{22}O$: C, 77.58; H, 13.02. Found: C, 77.66; H, 12.79.

(6*R*)-2,6-Dimethyl-8-[(*tert*-butyldiphenylsilyl)oxy]-2-nonene (9). A solution of 1.46 g (8.6 mmol) of **8**, 0.93 g (13.7 mmol) of imidazole, and 2.60 g (9.5 mmol) of *tert*-butylchlorodiphenylsilane in 14 mL of DMF was stirred at room temperature for 18 h. After addition ether (100 mL) and water (200 mL), the aqueous phase was separated and extracted with 3 × 50 mL of ether, and the combined extracts were dried and concentrated. The residue was purified by flash chromatography on silica gel (R_f 0.62, 2% EtOAc in hexane) to yield 2.70 g (77%) of **9**: NMR ($CDCl_3$, δ) 0.68 (t, 3 H), 0.86–1.28 (s + m, 15 H), 1.38 (m, 1 H), 1.48–1.72 (2 s + m, 7 H), 1.92 (q, 2 H), 3.89 (q, 1 H), 5.05 (td, 1 H), 7.40 (m, 6 H), 7.69 (m, 4 H); mass spectrum, m/e 408 (M^+). Anal. Calcd for $C_{27}H_{40}OSi$: C, 79.35; H, 9.86. Found: C, 79.32; H, 9.86.

(4*R*)-4-Methyl-6-[(*tert*-butyldiphenylsilyl)oxy]heptanal (10). The air-sensitive compound was prepared from **9** according to the method described for **2**. Spectral data are as follows: NMR ($CDCl_3$, δ) 0.70 (t, 3 H), 0.85–1.20 (s + m, 13 H), 1.20–1.68 (m, 5 H), 2.28 (td, 1 H), 3.88 (m, 1 H), 7.30–7.48 (m, 6 H), 7.62–7.76 (m, 4 H), 9.66 (m, 1 H).

(6*R*)-Ethyl 6-Methyl-8-[(*tert*-butyldiphenylsilyl)oxy]-2-nonenoate (11). To a suspension of 0.094 g (3.8 mmol) of sodium hydride in 20 mL of dry THF was added a solution of 0.71 g (0.70 mL, 3.5 mmol) of triethyl phosphonoacetate in 2 mL of THF dropwise was stirring. During the addition period, the temperature was maintained at <20 °C and vigorous evolution of hydrogen was noted. The mixture was stirred for 10 min until the solution turned clear. To the clear solution was added 1.35 g (3.5 mmol) of **10** in 4 mL of THF slowly, and stirring was continued for 4 h at room temperature. The solvent was removed in vacuo and the residue was purified by preparative TLC on silica gel (R_f 0.53, 10% EtOAc in hexane) to give 0.69 g (40%) of **11** [0.45 g (33%) of the starting material **10** was recovered]: NMR ($CDCl_3$, δ) 0.68 (t, 3 H), 0.86–1.20 (s + m, 13 H), 1.20–1.40 (t + m, 5 H), 1.42–1.66 (m, 2 H), 2.01–2.16 (m, 2 H), 3.86 (q, 1 H), 4.19 (q, 2 H), 5.76 (dd, 1 H, J = 16, 2 Hz), 6.90 (m, 1 H), 7.30–7.44 (m, 6 H), 7.62–7.76 (m, 4 H); FAB mass spectrum, m/e 453 (M^+ + 1). Anal. Calcd for $C_{28}H_{40}O_3Si$: C, 74.29; H, 8.91. Found: C, 74.26; H, 8.88.

(6*R*)-Ethyl 6-Methyl-8-[(*tert*-butyldiphenylsilyl)oxy]nonanoate (12). A solution of 0.6 g (1.32 mmol) of **11** in 20 mL of ethyl acetate was hydrogenated (40 psi, room temperature) for 3 h in the presence of 0.06 g of 10% palladium on carbon. The solution was filtered and concentrated. The residue was purified by preparative TLC on silica gel (R_f 0.50, 8% EtOAc in hexane) to yield 0.59 g (98%) of **12**: NMR ($CDCl_3$, δ) 0.66 (t, 3 H), 0.84–1.42 (s + t + m, 20 H), 1.42–1.66 (m, 4 H), 2.26 (t, 2 H), 3.88 (q, 1 H), 4.14 (q, 2 H), 7.30–7.45 (m, 6 H), 7.62–7.78 (m, 4 H); FAB mass spectrum, m/e 454 (M^+ + 1). Anal. Calcd for $C_{28}H_{42}O_3Si$: C, 73.96; H, 9.31. Found: C, 74.14; H, 9.12.

(6*R*)-Ethyl 6-Methyl-8-hydroxynonanoate (13). A solution of 0.53 g (1.16 mmol) of **12** and 0.85 mg (2.68 mmol) of tetrabutylammonium fluoride trihydrate in 8 mL of THF was stirred for 18 h at room temperature. The solution was concentrated and the product was purified by flash chromatography on silica gel (R_f 0.50, 5% MeOH in CH_2Cl_2) to afford 0.20 g (80%) of **13**: NMR ($CDCl_3$, δ) 0.89 (d, 3 H, J = 7 Hz), 1.04–1.44 (m, 11 H), 1.46–1.74 (m, 4 H), 1.82 (s, 1 H), 2.30 (t, 2 H), 3.89 (q, 1 H), 4.14 (q, 2 H); FAB mass spectrum, m/e 172 (M^+ – 44). Anal. Calcd for $C_{12}H_{24}O_3$: C, 66.63; H, 11.18. Found: C, 66.64; H, 11.35.

(6*R*)-Ethyl 6-Methyl-8-oxononanoate (4). A solution of 130 mg (0.60 mmol) of **13** and 0.60 g (1.60 mmol) of pyridinium dichromate in 4 mL of DMF was stirred at room temperature for 2 h, diluted with 20 mL of CH_2Cl_2, filtered, and concentrated. The product was purified by preparative TLC on silica gel (R_f 0.40, 20% EtOAc in hexane) to produce 114 mg (89%) of **4**: NMR ($CDCl_3$, δ) 0.89 (d, 3 H, J = 7 Hz), 1.12–1.42 (t + m, 7 H), 1.52–1.70 (m, 2 H), 1.92–2.10 (m, 1 H), 2.13 (s, 3 H), 2.16–2.47 (m, 4 H), 4.15 (q, 2 H); FAB mass spectrum, m/e 215 (M^+ + 1); $[\alpha]_D$ + 7.94° (c 2.45, MeOH). Anal. Calcd for $C_{12}H_{22}O_3$: C, 67.26; H, 10.35. Found: C, 67.45; H, 10.54.

(2′*R*,3′*R*,7*R*)-(*E*,*E*)-Methyl 11-[3′-(Hydroxymethyl)-4′-oxo-2′-oxetanyl]-3,5,7-trimethyl-2,4-undecadienoate (15). To a solution of 310 mg (0.96 mmol) of L-659,699 in 8 mL of ether was added 5 mL (80 mmol) of iodomethane and 600 mg (4.3 mmol) of silver oxide. The suspension was heated at 49 °C for 18 h and filtered, and the filtrate was concentrated. The residue was purified by preparative TLC on silica gel (R_f 0.35, 20% EtOAc in hexane) to give 190 mg (56%) of **15**: NMR ($CDCl_3$, δ) 0.84 (d, 3 H, J = 7 Hz), 1.02–1.50 (m, 6 H), 1.60–1.96 (s + m, 7 H), 2.03–2.13 (dd, 1 H, J = 6, 13 Hz), 2.24 (s, 3 H), 3.34–3.45 (s + m, 4 H), 3.60–3.76 (s + m, 5 H), 4.45–4.55 (m, 1 H), 5.68 (d, 2 H, J = 8 Hz); FAB mass spectrum, m/e 353 (M^+ + 1). Anal. Calcd for $C_{20}H_{32}O_5$: C, 68.15; H, 9.15. Found: C, 68.21; H, 9.15.

(7*R*,12*R*,13*R*)-(*E*,*E*)-Methyl 12-Hydroxy-14-methoxy-13-(methoxycarbonyl)-3,5,7-trimethyl-2,4-tetradecadienoate (16). A solution of 200 mg (0.57 mmol) of **15** in 5 mL of methanol containing a catalytic amount of sodium methoxide (24 μL, 25 wt %) was kept for 20 min at room temperature and evaporated. The residue was concentrated and purified by preparative TLC on silica gel (R_f 0.35, 30% EtOAc in hexane) to yield 189 mg (87%) of **16**: NMR ($CDCl_3$, δ) 0.82 (d, 3 H, J = 7 Hz), 1.00–1.16 (m, 1 H), 1.16–1.52 (m, 7 H), 1.54–1.68 (m, 1 H), 1.70–1.86 (s + m, 4 H), 2.08 (dd, 1 H, J = 6, 13 Hz), 2.24 (s, 3 H), 2.56–2.82 (q + m, 2 H), 3.35 (s, 3 H), 3.56–3.90 (2 s + 2 m, 9 H), 5.69 (d, 2 H, J = 6 Hz); FAB mass spectrum, m/e 385 (M^+ + 1). Anal. Calcd for $C_{21}H_{36}O_6$: C, 65.60; H, 9.44. Found: C, 65.32; H, 9.37.

(7*R*,12*R*,13*R*)-(*E*,*E*)-Methyl 12-[(*R*)-α-Methoxyphenylacetoxy]-14-methoxy-13-(methoxycarbonyl)-3,5,7-trimethyl-2,4-tetradecadienoate (17). To a solution of 40 mg (0.10 mmol) of **16**, 20 mg (0.12 mmol) of (*R*)-(–)-α-methoxyphenylacetic acid, and 214 mg (1.04 mmol) of DCC in 4 mL of CH_2Cl_2 was added 13 mg (0.11 mmol) of 4-(dimethylamino)pyridine. The resulting mixture was stirred for 17 h at room temperature. The solution was concentrated, and the product was purified by preparative TLC on silica gel (R_f 0.35, 20% EtOAc in hexane)

to afford 50.5 mg (91%) of **17** and 5.0 mg (9%) of **18**. Spectral data of **17** were as follows: NMR ($CDCl_3$, δ) 0.81 (d, 3 H, J = 7 Hz), 0.98–1.42 (m, 6 H), 1.52–2.00 (s + m, 7 H), 2.08 (dd, 1 H, J = 6, 13 Hz), 2.24 (s, 3 H), 2.81 (m, 1 H), 3.06–3.20 (s + m, 4 H), 3.28–3.44 (s + m, 4 H), 3.49 (s, 3 H), 3.71 (s, 3 H), 4.75 (s, 1 H), 5.21 (q, 1 H), 5.69 (d, 2 H, J = 6 Hz), 7.30–7.50 (m, 5 H); FAB mass spectrum, m/e 533 ($M^+ + 1$). Anal. Calcd for $C_{30}H_{44}O_8$: C, 67.64; H, 8.32. Found: C, 67.70; H, 8.44.

(7*R*,12*R*,13*R*)-(*E*,*E*)-Methyl 12-[(*S*)-α-Methoxyphenylacetoxy]-14-methoxy-13-(methoxycarbonyl)-3,5,7-trimethyl-2,4-tetradecadienoate (18). The compound was prepared from **16** and (*S*)-(+)-α-methoxyphenylacetic acid according to the method described for **17**. Spectral data were as follows: NMR ($CDCl_3$, δ) 0.75 (d, 3 H, J = 7 Hz), 0.76–0.94 (m, 3 H), 0.96–1.12 (m, 3 H), 1.38–1.54 (m, 3 H), 1.67–1.79 (s + m, 4 H), 2.00 (dd, 1 H, J = 6, 12 Hz), 2.23 (s, 3 H), 2.90 (m, 1 H), 3.30 (s, 3 H), 3.38–3.50 (s + m, 4 H), 3.56–3.74 (2 s + m, 7 H), 4.74 (s, 1 H), 5.21 (q, 1 H), 5.68 (s, 2 H), 7.30–7.50 (m, 5 H); FAB mass spectrum, m/e 533 ($M^+ + 1$). Anal. Calcd for $C_{30}H_{44}O_8$: C, 67.64; H, 8.32. Found: C, 67.66; H, 8.31.

Synthesis of a Tritium-Labeled Photoaffinity Analogue of the Tussock Moth Pheromone: Tritium NMR of Vinyl Tritons of (*E*)- and (*Z*)-Alkene Isomers

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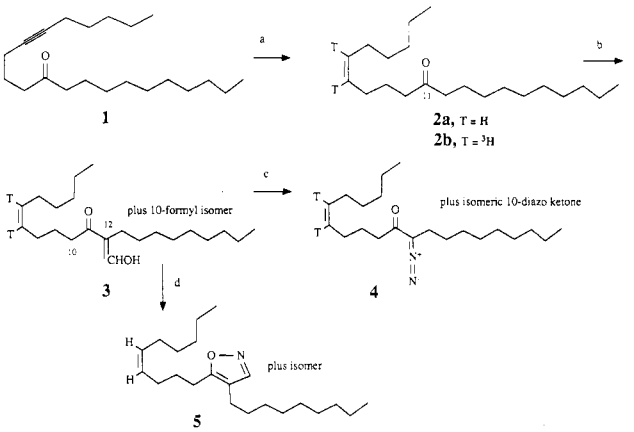
Introduction

The molecular mechanisms of pheromone perception[1] and degradation in insect olfactory sensilla can be examined in detail by using high specific activity tritium-labeled pheromones and pheromone analogues.[2] We recently identified pheromone binding proteins and putative pheromone receptors in the wild silkmoth, *Antheraea polyphemus*, using tritium-labeled (*E*,*Z*)-6,11-hexadecadienyl diazoacetate, a photoaffinity analogue of the natural hexadecadienyl acetate pheromone.[3] Many lepidopteran forest pests belong to the family Lymantriidae, which includes the gypsy moth and the tussock moths. We were intrigued by the unique ketonic pheromone of the Douglas fir tussock moth, *Orgyia pseudotsugata*, as a model system to examine the use of diazo ketone photoaffinity labels in this economically important group of insects.

The major pheromone component for *O. pseudotsugata* was identified in 1975 as (*Z*)-6-heneicosen-11-one,[4] and its occurrence in other tussock moths and the activity of several isomers and analogues have been briefly investigated.[5] Two syntheses[6] of this alkenone have been described in which the Eschenmoser fragmentation of an epoxy ketone is used to produce an acetylenic intermediate; the pheromone is obtained by semihydrogenation of an alkynone. These two schemes were most suitable for the introduction of tritium at high specific activity, i.e., by semitritiation with carrier-free tritium gas.

Scheme I. Synthesis of Labeled and Unlabeled Pheromone Photoaffinity Labels[a]



[a] Reagents: (a) 1 atm of $^nH_2$ (n = 1 or 3), 5% $Pd/BaSO_4$, THF, quinoline, 1 h, 20 °C; (b) NaH, $HCO_2C_2H_5$, ether, EtOH, 10 h, 30 °C; (c) TsN_3, CH_2Cl_2, Et_3N, 3 h, 0–20 °C; 1 N KOH, 0.5 h, 20 °C; (d) NH_2OH·HCl, EtOH, K_2CO_3, 80 °C.

The unlabeled mixture of diazo ketones **4a** was obtained as shown in Scheme I. Thus, alkynone **1** was obtained by using either the Kocienski[6a] or Mori[6b] procedures and was semihydrogenated in THF using 5% $Pd/BaSO_4$ poisoned with quinoline to give TLC- and GC-homogeneous enone **2a**. Formylation with sodium hydride and ethyl formate[7] provided a mixture of the 10- and 12-formylated ketones **3a** in a ratio of approximately 2:1 based on the ratios of enolic carbon resonances. In deuteriochloroform, approximately 10% of the β-dicarbonyl form was detectable by proton NMR; however, the formyl compounds decomposed during extended data acquisition. Thus, the crude formyl ketones **3a** were subjected to the diazo transfer reaction with tosyl azide[8] to provide the mixed 10- and 12-diazo ketones **4a** in 54% overall yield. The diazo ketone mixture induces upwind flight behavior at 20 ng and shows approximately 40% of the electroantennogram response[5] relative to the actual pheromone (at a 2000-ng dose) in male tussock moths (G. E. Daterman, personal communication).

The mixture of formyl compounds was converted in 81% yield to a complex mixture of the isoxazoles **5** by treatment with hydroxylamine hydrochloride to obtain thermally stable derivatives of the 10 and 12 isomers. Capillary GC analysis showed eight peaks, consistent with the presence of both (*E*)- and (*Z*)-alkenes (see below), the 10- and 12-formylated species, and two modes of addition of the hydroxylamine. Nonetheless, the high resolution mass spectroscopy confirmed the elemental composition of this mixture of isoxazole isomers.

The tritium-labeled pheromone **2b** and its derivatives were produced similarly. Catalytic tritiation of 10 mg of alkynone **1** using carrier-free tritium gas furnished 1.73 Ci of [^{3}H]-**2b**, specific activity 50–58 Ci/mmol. A 156-mCi fraction of purified [^{3}H]alkenone **2b** was formylated and

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