Syntheses of the Branched Nine-Carbon Unit of the Type A Streptogramins and Other Antibiotics

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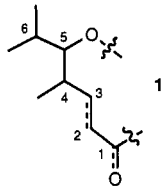
The nine-carbon unit **1** is seen as a structural unit in several important naturally occurring compounds. Within these compounds, the degree of unsaturation (i.e., with or without a 2,3-double bond), the oxidation state at C-1, and the stereochemistry at C-4 and C-5 differ.



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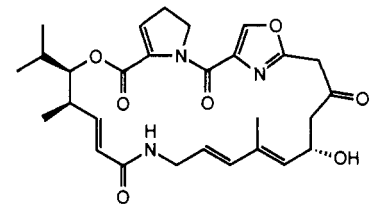
One particular form of this unit is seen in five out of the six type A streptogramin antibiotics for which structures are presently known, with virginiamycin M_1 (**2**) being a representative example. These antibiotics are among the world's most heavily used antibacterial products[1] and have been the subject of synthetic studies in several laboratories,[2] including our own.[3] Other forms of the nine-carbon unit are seen in the polyene antibiotics mycoticin A (**3**)[4] and roflamycoin (**4**), although the stereochemistry of the latter compound has yet to be established.[5]

Chiral syntheses have been reported previously for various derivatives of **1**,[2d,e,h–j,5a] but we recognized the need for both chiral and racemic routes that would be sufficiently flexible to permit the synthesis of not only the natural products discussed above but also analogues in which the relative and absolute stereochemistry and the level of saturation are altered. A side benefit would be access to any of the possible stereoisomers of the roflamycoin fragment. We now report simple pathways that meet these needs.



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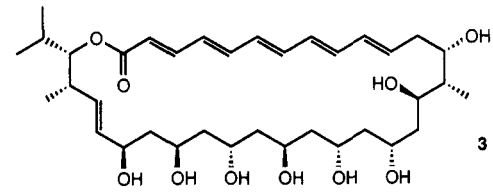

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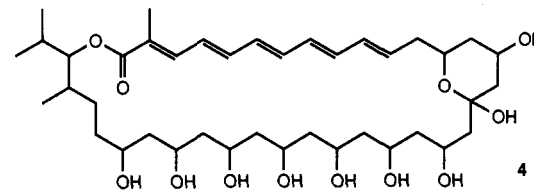

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Our first route is shown in Scheme I. Most of the steps are rather straightforward and do not require further comment. The key stereochemical determining step is the hydrogenation of the disubstituted cyclopentenone **6**. Despite the problems that have been reported in the hydrogenation of other hindered, tetrasubstituted alkenes,[6] **6** undergoes hydrogenation smoothly under Paquette's conditions[7] to give the disubstituted cylopentanone **7** in up to a 44:1 ratio of the desired cis isomer to the undesired trans isomer **11** (vide infra). Baeyer–Villiger oxidation of **7**, lactone ring-opening, hydroxyl protection, and introduction of the 2,3-unsaturation then complete the synthesis of the desired ester **10** as a protected derivative of the nine-carbon fragment **1**.

Of interest in our synthesis of streptogramin analogues and of the possible stereoisomers of roflamycoin (**4**), the cyclopentanone **7**, as expected, undergoes facile epimerization to provide the more stable trans isomer **11** in ca. a 30:1 ratio relative to the initial cis isomer **7**. This compound may then be converted into the nine-carbon derivative **12** (eq 1) through use of the steps employed for the conversion of **6** to **10** in Scheme I (see Experimental Section for details). Also of further interest is the reduction of the saturated ester **9** to the aldehyde **13** (eq 2). This compound, or its stereoisomers, may be regarded as a suitable intermediate for the synthesis of roflamycoin (**4**). A straightforward chiral synthesis of (4*R*,5*R*)-**10** was also accomplished (Scheme II). This synthesis is closely analogous to routes reported previously,[2d,h,i] but it employs the chiral aldol methodology developed by Miller.[8] Most importantly for our present purposes, the product is identical in all respects, except optical activity, with the racemic **10** obtained above. The enantiomeric excess of the final product (4*R*,5*R*)-**10** was found to be at least 99%.

In conclusion, we have developed straightforward syntheses of a key fragment of several important antibiotics. Our routes are amenable to the synthesis of ster-

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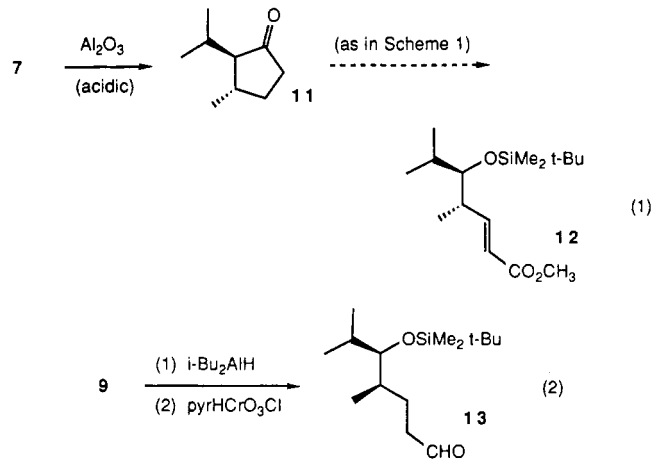


eoisomeric analogues of these compounds for use in our planned studies of structure–activity relationships. These pathways are also sufficiently flexible to permit the synthesis of this unit in roflamycoin (4), regardless of the stereochemistry that is ultimately determined for this compound.

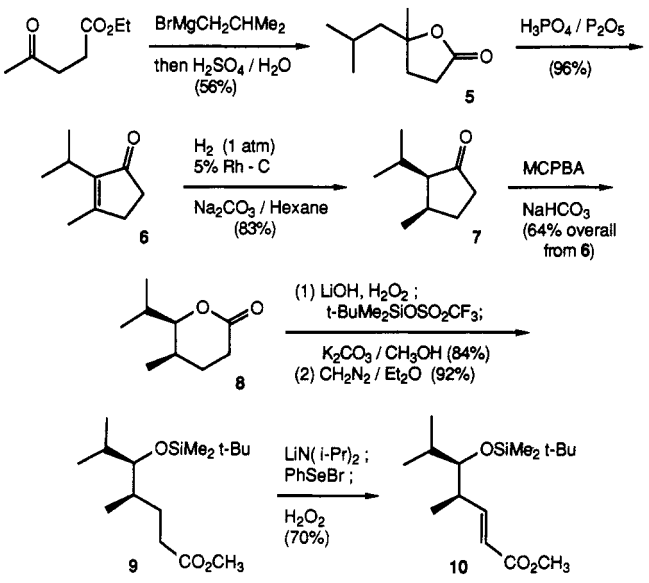
Experimental Section

General Remarks. All reactions of air-sensitive compounds were performed under a nitrogen atmosphere. Solutions of air- and/or water-sensitive compounds were transferred with double-ended needles (cannulas) or hypodermic syringes. NMR spectra were obtained with Magnachem A-200 (200 MHz) Nicolet NT-300 (300 MHz) and General Electric GN-300 (300 MHz) spectrometers. The IR spectra were obtained on a Perkin-Elmer Model 1420 spectrometer using a polystyrene standard. Mass spectral data were obtained on a Finnigan MAT Model 8430 spectrometer. Elemental analyses were performed by M-H-W Laboratories (Phoenix, AZ).

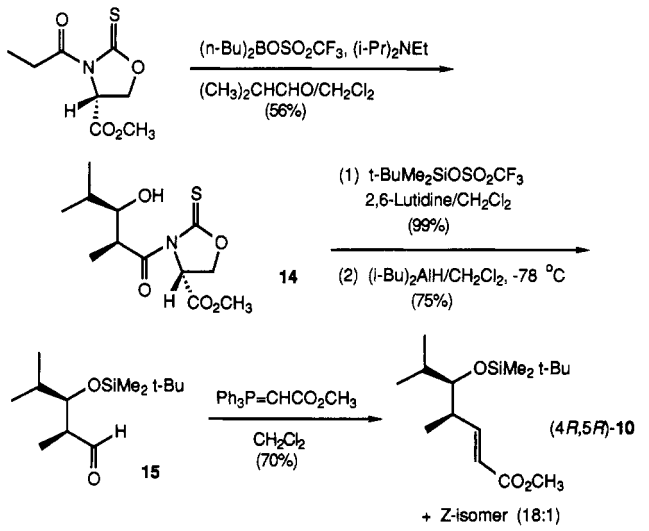
γ-Methyl-γ-isobutyl-γ-butyrolactone (5).[9] To magnesium turnings (1.025 g, 42 mmol) in diethyl ether (10 mL) was added dropwise a solution of isobutyl bromide (4.58 mL, 42.0 mmol, dried over calcium chloride and freshly distilled) in diethyl ether (10 mL) under nitrogen. After formation of the Grignard reagent, ca. two-thirds of the ether was distilled from the mixture under nitrogen, and the oily-gray solution was diluted with anhydrous benzene (10 mL). This solution was added dropwise over 45 min to a stirred solution of ethyl levulinate (5.3 g, 37 mmol, dried over potassium carbonate and freshly distilled, bp 95–97 °C, 15 Torr) in dry benzene (15 mL) at 0 °C. The nearly colorless solution was stirred for an additional 15 min at −5 to 0 °C and was then poured into a mixture of concentrated H_2SO_4 (10 mL) and ice (ca. 300 g). The mixture was extracted with ether (3 × 150 mL), and the extracts were washed with water (200 mL) and 5% aqueous $NaHCO_3$ (200 mL), dried over anhydrous Na_2SO_4, and concentrated in vacuo to give 4.224 g of a nearly colorless oil. Vacuum distillation (bp 110 °C, 0.15 Torr) gave 3.57 g of a colorless oil, which was further purified by column chromatography on silica gel (60:40 hexane/ether). Obtained was 3.24 g (56% yield) of **5** as a clear, colorless oil exhibiting spectral data identical with the literature data.[10]

3-Methyl-2-isopropyl-2-cyclopenten-1-one (6).[11] To a solution of P_2O_5 (6.1 g) in 85% H_3PO_4 (4 mL) at 60–70 °C was added **5** (0.850 g, 5.44 mmol). Stirring of the mixture at 60–70 °C for 2 min resulted in a change of color from colorless to yellow-brown. The mixture was then stirred at 98 °C under nitrogen for 4–6 h, after which the hot, dark red-brown mixture was poured onto ice (ca. 150 g). The mixture was extracted with ether (4 × 100 mL), and the combined extracts were washed with water (100 mL), dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was purified by flash chromatography on silica gel (90:10 hexane/ether) to give 0.722 g (96%) of **6** as a clear, colorless oil exhibiting spectral data identical with the literature data.[10]

Scheme I



Scheme II



3(*R)-Methyl-2(*R**)-isopropylcyclopentanone (7).** Compound **6** (0.101 g, 0.73 mmol) was dissolved in pentane (30 mL), and to this solution were added powdered sodium carbonate (0.258 g, 2.43 mmol) and 5% rhodium on carbon (0.050 g; Aldrich Chemical Co.).[7] The mixture was shaken vigorously under hydrogen (14 psi) in a Parr apparatus at 25 °C. The reaction progress was monitored by GC (OV-1, 100–200 °C), and the reaction was complete after 3 h. The mixture was filtered, and the filtrate was concentrated under reduced pressure at 25 °C to give 0.085 g (83% yield) of a colorless oil consisting of a 37:1 to 44:1 mixture of the cis and trans isomers **7** and **11**, respectively (GC analysis; batches of the catalyst obtained from Aldrich have been of various activities and in some cases have resulted in longer reaction times and isomers ratios of only 20:1): IR (film) 2950, 2920, 2860, 1735 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.45 (qddd, 1 H, J = 7.1, 6.9, 6.9, 1.5 Hz), 2.14 (dd, 2 H, J = 8.2, 7.8 Hz), 1.95 (dt, 1 H, J = 12.0, 3.4 Hz), 1.87 (dd, 1 H, J = 9.3, 6.9 Hz), 1.72 (dq, 1 H, J = 11.0, 6.5 Hz), 1.63 (dt, 1 H, J = 12.1, 3.4 Hz), 1.08 (d, 3 H, J = 6.4 Hz), 0.88 (d, 3 H, J = 6.6 Hz), 0.84 (d, 3 H, J = 7.1 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 219.49, 60.58, 35.32, 33.19, 27.72, 25.35, 21.80, 21.14, 14.62; EIMS, m/z (rel intensity) 140 (64, M^+), 125 (22, $M^+ - CH_3$), 111 (36, $M^+ - C_2H_5$), 96 (78, $M^+ - C_3H_7 - H$), 83 (100, $M^+ - C_3H_7 - CH_2$). Anal. Calcd for $C_9H_{16}O$: C, 77.09; H, 11.50. Found: C, 77.02; H, 11.56.

(9) By analogy with the preparation of γ-methyl-γ-propyl-γ-butyrolactone: Cason, J.; Adams, C. A.; Bennett, L. L., Jr.; Register, U. D. *J. Am. Chem. Soc.* **1944**, *66*, 1764.

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(11) Based upon the preparation of 3-methyl-2-alkylcyclopenten-1-one: Rai, C.; Dev. S. *J. Indian Chem. Soc.* **1957**, *34*, 178.

5(*R)-Methyl-6(*R**)-isopropyl-δ-valerolactone (8) from 3-Methyl-2-isopropyl-2-cyclopenten-1-one (6) without Isolation of 3(*R**)-Methyl-2(*R**)-isopropylcyclopentanone (7).** Compound **6** (0.750 g, 5.43 mmol) was dissolved in hexane (120 mL), and to this solution were added powdered sodium carbonate (2.0 g, 19 mmol) and 5% rhodium on carbon (0.310 g). The mixture was shaken vigorously under hydrogen (21 psi) in a Parr apparatus. The reaction was monitored by GC (OV-1, 100–200 °C) and was complete after 4 h. The mixture was filtered, and the filter was washed with hexane (30 mL). To the combined filtrates was added powdered sodium bicarbonate (3.19 g, 38 mmol). The mixture was stirred at −8 °C, and a solution of *m*-chloroperoxybenzoic acid (2.81 g, 16.28 mmol)[12] in CH_2Cl_2 (30 mL) was added over 20 min. The temperature was gradually increased to 0 °C, and the mixture was stirred at 0 °C for 7 h and at 25 °C for 3 days. The mixture was filtered, and the solid was washed with hexane (30 mL). The combined filtrates were concentrated in vacuo, and the oily residue was purified by flash chromatography on silica gel (9:1 hexane/Et_2O) to give 0.545 g (64% overall yield based on **6**) of **8** as a colorless, viscous oil: IR (film) 2970, 2950, 2885, 1740 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.75 (dd, 1 H, *J* = 9.8, 2.4 Hz, H-6), 2.46 (dd, 2 H, *J* = 8.6, 6.3 Hz, H-3), 2.13 (qddd, 1 H, *J* = 7.1, 5.9, 2.7, 2.4 Hz, H-5), 1.98 (ddd, 1 H, *J* = 13.4, 6.3, 5.9 Hz, H-4), 1.79 (dqq, 1 H, *J* = 9.8, 6.6, 6.6 Hz, C*H*$(CH_3)_2$), 1.61 (ddd, 1 H, *J* = 13.4, 6.3, 2.7 Hz, H-4), 1.02 (d, 3 H, *J* = 6.6 Hz, CH(C*H*$_3$)CH_3), 0.89 (d, 3 H, *J* = 7.1 Hz, CHC*H*$_3$), 0.83 (d, 3 H, *J* = 6.6 Hz, CH(CH_3)C*H*$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.04, 88.25, 29.74, 26.79, 26.58, 26.09, 19.68, 17.97, 11.41; EIMS, *m*/*z* 156 (26, M^+), 128 (13, $M^+ - CO$), 113 (100, $M^+ - CO - CH_3$). Anal. Calcd for $C_9H_{16}O_2$: C, 69.19; H, 10.33. Found: C, 69.37; H, 10.48. Attempts were also made to use the more reactive peroxytrifluoroacetic acid in the Baeyer–Villiger reaction, but substantial epimerization resulted.

Methyl (4*R,5*R**)-4,6-Dimethyl-5-((*tert*-butyldimethylsilyl)oxy)heptanoate (9).**[13-15] A solution of **8** (0.0968 g, 0.620 mmol) dissolved in THF (2.20 mL) was added to a solution of LiOH (0.016 g, 0.68 mmol) in H_2O (0.33 mL) at 25 °C. To this solution was added 30% hydrogen peroxide (1.64 mL). The solution was stirred at 25 °C for 2.5 h, and after being cooled to 0 °C, the solution was acidified with 1 N aqueous hydrochloric acid to pH 1–2. It was extracted with CH_2Cl_2 (4 × 10 mL), and the combined extracts were washed with brine (10 mL), dried over anhydrous $MgSO_4$, concentrated to ca. 5 mL, and cooled to 0 °C. The solution was stirred under nitrogen, and 2,6-lutidine (0.288 mL, 2.456 mmol) was added. After 10 min, *tert*-butyldimethylsilyl triflate (0.424 mL, 1.844 mmol) was added dropwise. The mixture was stirred at 25 °C for 45 min, and distilled water (5 mL) was added dropwise. After 5 min of stirring, the mixture was extracted with CH_2Cl_2 (3 × 20 mL). The combined extracts were cooled to 0 °C, washed with ice-cold 1 N hydrochloric acid (20 mL) and brine (20 mL), dried over anhydrous $MgSO_4$, and concentrated under reduced pressure, leaving a pale yellow oil (0.516 g). A major component of this oil was *tert*-butyldimethylsilyl (4*R**,5*R**)-4,6-dimethyl-5-((*tert*-butyldimethylsilyl)oxy)heptanoate: EIMS, *m*/*z* 402 (M^+); HRMS *m*/*z* calcd for $C_{17}H_{37}O_3Si_2$ ($M^+ - C_4H_9$) 345.228, found 345.227. Isolation by silica gel chromatography was unsuccessful. The oil was dissolved in a mixture of methanol (12 mL) and THF (4 mL), and the solution was treated with a 4-mL portion of a solution of potassium carbonate (1 g) in water (10 mL). The mixture was stirred at 25 °C for 45 min, concentrated in vacuo to one-quarter volume, and diluted with brine (10 mL). The mixture was cooled to 0 °C and was acidified to pH 3–4 with 1 M aqueous potassium bisulfate. It was extracted with CH_2Cl_2 (4 × 20 mL), and the combined extracts were washed with brine (20 mL), dried over anhydrous $MgSO_4$, and concentrated in vacuo, leaving 0.295 g of an oily residue. The product was isolated by flash chromatography on acidic silica gel (99:1 hexane/EtOAc) to give 0.151 g (84% overall yield based on **8**) of 4(*R**)-methyl-5(*R**)-isopropyl-5-((*tert*-butyldimethylsilyl)oxy)pentanoic acid as a colorless, viscous oil of 98% purity (GC, OV-1, 100–250 °C): ^1H NMR (300 MHz, $CDCl_3$) δ 10.5 (br s, 1 H, CO_2H), 3.25 (dd, 1 H, *J* = 5.52, 3.20 Hz, C*H*OSi), 2.33 (ddd, 2 H, *J* = 18.15, 9.41, 8.95 Hz, CH_2CO_2H), 1.73 (dqq, 1 H, *J* = 6.93, 6.77, 5.52 Hz, C*H*$(CH_3)_2$), 1.58 (qddd, 1 H, *J* = 6.82, 6.20, 6.17, 3.20 Hz, C*H*CH_3), 1.47 (ddd, 2 H, *J* = 12.96, 6.20, 6.17 Hz, $CH_2CH_2CO_2H$), 0.88 (s, 9 H, C(C*H*$_3$)$_3$), 0.95 (d, 3 H, *J* = 5.52 Hz, CH(C*H*$_3$)CH_3), 0.85 (d, 3 H, *J* = 6.82 Hz, CHC*H*$_3$), 0.85 (d, 3 H, *J* = 6.77 Hz, CH(CH_3)C*H*$_3$), 0.02 (s, 6 H, Si(C*H*$_3$)$_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 179.81 (*C*=O), 80.39, 36.19, 32.38, 31.87, 29.52, 26.15, 20.19, 18.97, 18.46, 14.41, −3.71 (SiC*H*$_3$), −3.78 (SiC*H*$_3$); EIMS, *m*/*z* (rel intensity) 288 (1, M^+), 287 (0.5, $M^+ - 1$), 273 (1, $M^+ - CH_3$), 245 (68, $M^+ - C_3H_7$), 231 (56, $M^+ - C_4H_9$), 213 (88, $M^+ - C_4H_9 - H_2O$), 187 (100, $M^+ - C_4H_9 - C_3H_7 - H$); CIMS (isobutane), *m*/*z* (rel intensity) 289 (16, $M^+ + 1$); HRMS *m*/*z* calcd for $C_{11}H_{23}O_3Si$ ($M^+ - C_4H_9$) 231.142, found 231.141.

The product (0.028 g, 0.097 mmol) was dissolved in diethyl ether (1 mL), and excess diazomethane in ether was added. The solution was stirred at 25 °C for 2.5 h in the dark. The solvent was evaporated under reduced pressure, leaving an oily residue. The product was purified by flash chromatography on silica gel (99.5:0.5 hexane/EtOAc) to give 0.027 g (92% yield) of **9** as a colorless oil: IR (film) 2965, 2940, 2900, 2865, 1747 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.65 (s, 3 H, CO_2CH_3), 3.23 (dd, 1 H, *J* = 5.46, 3.12 Hz, C*H*OSi), 2.30 (ddd, 2 H, *J* = 18.7, 9.45, 7.01 Hz, $CH_2CO_2CH_3$), 1.72 (qdq, 1 H, *J* = 5.50, 5.46, 4.72 Hz, C*H*$(CH_3)_2$), 1.55 (dddq, 1 H, *J* = 6.34, 5.81, 4.72, 3.11 Hz, C*H*CH_3), 1.47 (ddd, 2 H, *J* = 12.84, 6.34, 5.81 Hz, $CH_2CH_2CO_2CH_3$), 0.95 (d, 3 H, *J* = 4.72, C*H*$_3$), 0.88 (s, 9 H, C(C*H*$_3$)$_3$), 0.85 (d, 3 H, *J* = 5.50 Hz, C*H*$_3$), 0.85 (d, 3 H, *J* = 4.72 Hz, C*H*$_3$), 0.02 (s, 6 H, Si(C*H*$_3$)$_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.32 (*C*=O), 80.44, 51.45, 36.18, 32.47, 31.91, 30.91, 26.16, 20.16, 18.95, 18.48, 14.40, −3.69 (SiC*H*$_3$), −3.372 (SiC*H*$_3$); EIMS, *m*/*z* (rel intensity) 302 (≪1, M^+), 271 (14, $M^+ - CH_2 - OH$), 259 (58, $M^+ - C_3H_7$), 245 (100, $M^+ - C_4H_9$), 227 (16, $M^+ - C_3H_7 - CH_2 - H_2O$), 213 (36, $M^+ - C_4H_9 - CH_2 - H_2O$), 187 (70, $M^+ - C_4H_9 - C_3H_7 - CH_3$); CIMS (isobutane), *m*/*z* (rel intensity) 303 (40, $M^+ + H$); HRMS *m*/*z* calcd for $C_{12}H_{25}O_3Si$ ($M^+ - 57$) 245.157, found 245.157.

Methyl (4*R,5*R**)-4,6-Dimethyl-5-((*tert*-butyldimethylsilyl)oxy)-2(*E*)-heptenoate (10).**[16,17] To a stirred solution of diisopropylamine (0.028 mL, 0.020 g, 0.20 mmol) in anhydrous THF (1 mL) cooled to −78 °C under argon was added dropwise a 2.05 M solution of *n*-butyllithium (0.097 mL, 0.20 mmol) in hexane. After 30 min, a solution of **9** (0.050 g, 0.165 mmol) in THF (1.5 mL) was added dropwise over 15 min. The temperature of the reaction mixture was slowly increased to −20 °C (1 h) and was again decreased to −78 °C. Then a benzeneselenenyl bromide solution (0.215 mmol, prepared from 0.0506 g of diphenyl diselenide and 0.0171 g of bromine) in THF (0.5 mL) was added dropwise. After being stirred for 5–10 min at −78 °C, the mixture was quenched with a 1:1 mixture of saturated aqueous NH_4Cl and brine (4 mL). The mixture was extracted at 25 °C with CH_2Cl_2 (3 × 20 mL), and the combined extracts were washed with brine (20 mL), dried over anhydrous $MgSO_4$, and concentrated in vacuo, leaving 0.178 g of a yellow brown oil. The product was isolated by flash chromatography on silica gel (1:1 hexane/CH_2Cl_2). Obtained was 0.065 g (86%) of the selenide as a mixture of diastereoisomers: IR (film) 3060, 2960, 2930, 2860, 1735 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.62 and 7.32 (m, 5 H), 3.73 (dd, 1 H, *J* = 5.6, 4.7 Hz), 3.65 (2 s, 3 H), 3.23 (2 dd, 1 H, *J* = 4.1, 2.2 Hz), 2.0 (dd, 1 H, *J* = 10.2, 9.5 Hz), 1.84 (m, 1 H), 1.74 (qd, 1 H, *J* = 6.7, 4.1 Hz), 1.65 (ddd, 1 H, *J* = 8.1, 5.4, 4.7 Hz), 0.92 (2 s, 9 H), 0.89 (d, 3 H, *J* = 6.8 Hz), 0.87 (2 d, 6 H, *J* = 6.9, 6.7 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.72, 173.26, 135.74, 135.63, 128.97, 128.48, 127.90, 127.85, 80.61, 80.12, 51.89, 42.52, 41.57, 37.55, 36.55, 35.12, 32.12, 26.18, 19.60, 19.29, 19.07, 18.47, 14.29, 13.87, −3.70, −3.76; CIMS (ammonia), *m*/*z* (rel intensity) 459 (20, $M^+ + H$); HRMS *m*/*z* calcd for $C_{22}H_{38}O_3SeSi$ (M^+) 458.175, found 458.174.

To a stirred solution of the selenide (0.060 g, 0.13 mmol) in THF (2 mL) at 0 °C were successively added acetic acid (500 μL) and 30% aqueous hydrogen peroxide (200 μL). The mixture was

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stirred for 2 h at 0 °C, and then the solution was brought to slightly basic pH with saturated aqueous sodium bicarbonate. The mixture was extracted with CH_2Cl_2 (3 × 20 mL), and the combined extracts were washed with brine (20 mL), dried over anhydrous $MgSO_4$, and concentrated under reduced pressure, leaving 0.068 g of a pale yellow oil. The product was isolated by flash chromatography on silica gel (95:5 hexane/CH_2Cl_2). Obtained was 0.038 g (96%) of **10** as a colorless oil: IR (film) 2950, 2920, 2845, 1715, 1640 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.98 (dd, 1 H, J = 15.78, 7.85 Hz, C*H*=CHCO$_2$CH$_3$), 5.78 (dd, 1 H, J = 15.78, 1.32 Hz, CH=C*H*CO$_2$CH$_3$), 3.72 (s, 3 H, CO$_2$C*H*$_3$), 3.37 (dd, 1 H, J = 5.39, 4.43 Hz, C*H*OSi), 2.50 (qddd, 1 H, J = 7.85, 6.67, 4.43, 1.32 Hz, C*H*CH$_3$), 1.72 (qqd, 1 H, J = 6.83, 6.83, 5.39 Hz, C*H*(CH$_3$)$_2$), 1.04 (d, 3 H, J = 6.81 Hz, C*H*$_3$), 0.92 (s, 9 H, C(C*H*$_3$)$_3$), 0.88 (d, 3 H, J = 6.84 Hz, C*H*$_3$), 0.83 (d, 3 H, J = 6.76 Hz, C*H*$_3$), 0.037 (s, 3 H, Si(C*H*$_3$)CH$_3$), 0.023 (s, 3 H, Si(CH$_3$)C*H*$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.20 (*C*=O), 153.25 (*C*=C), 119.70 (C=*C*), 80.08, 51.37, 40.99, 32.01, 26.11, 20.34, 18.44, 17.55, 15.08, -3.74 (Si(*C*H$_3$)CH$_3$), -3.84 (Si(CH$_3$)*C*H$_3$); CIMS (isobutane), m/z (rel intensity) 301 (6, M^+ + H); HRMS m/z calcd for $C_{12}H_{23}O_3Si$ (M^+ - C_4H_9) 243.1416, found 243.1412.

Methyl (4*R,5*S**)-4,6-Dimethyl-5-((*tert*-butyldimethylsilyl)oxy)-2(*E*)-heptenoate (12).** Cyclopentenone **6** (0.622 g, 4.50 mmol, 92% purity by GC) was subjected to hydrogenation as described above for the preparation of **7**. The product mixture, with **7** again greatly predominating over **11**, was subjected to column chromatography using acidic alumina (activity grade I, Aldrich; 4:1 ether/hexane, then ether only) to give a mixture of **11** and **7** in a ratio varying from 26:1 to 32:1 (capillary GC), respectively, for a series of experiments. In one case, this mixture was subjected to the Baeyer–Villiger oxidation as reported above for the preparation of **8**. Obtained was 0.384 g (60% overall yield) of a 26:1 mixture of products in which the trans isomer of lactone **8** predominated over the previously obtained cis isomer. *trans*-**8**: IR (film) 2970, 2940, 2880, 1740 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.76 (dd, 1 H, J = 10.1, 2.4 Hz, H-6), 2.55 (ddd, 1 H, J = 17.5, 8.8, 5.6 Hz, H-3), 2.39 (ddd, 1 H, J = 17.5, 7.5, 6.3 Hz, H-3), 1.87 (dqq, 1 H, J = 6.9, 6.9, 2.4 Hz, C*H*(CH$_3$)$_2$), 1.82 (dddd, 1 H, J = 10.2, 8.8, 5.6, 4.5 Hz, H-4), 1.77 (dqdd, 1 H, J = 10.1, 6.5, 4.5, 4.5 Hz, H-5), 1.47 (dddd, 1 H, J = 10.2, 7.5, 6.3, 4.5 Hz, H-4), 1.01 (d, 3 H, J = 6.9 Hz, CH(C*H*$_3$)CH$_3$), 0.92 (d, 3 H, J = 6.5 Hz, CHC*H*$_3$), 0.85 (d, 3 H, J = 6.9 Hz, CH(CH$_3$)C*H*$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.01 (*C*=O), 89.64 (*C*HO), 29.89 (*C*HCH$_3$), 29.40 (O=C*C*H$_2$), 29.13 (O=CCH$_2$*C*H$_2$), 27.67 (*C*H(CH$_3$)$_2$), 19.68 (CH(*C*H$_3$)CH$_3$), 17.06 (CH(CH$_3$)*C*H$_3$), 14.14 (CH*C*H$_3$); EIMS, m/z (rel intensity) 156 (17, M^+), 128 (12, M^+ - CO), 113 (100, M^+ - CO - CH_3), 85 (54, M^+ - CO - C_3H_7); HRMS m/z calcd for $C_9H_{16}O_2$ (M^+) 156.1150, found 156.1149. This mixture enriched in *trans*-**8** (0.288 g, 1.84 mmol) was then subjected to the same lactone hydrolysis, silylation, and esterification sequence as reported above for the preparation of **9**. Obtained was 0.420 g (75% overall from *trans*-**8**) of the anti isomer of ester **9**: IR (film) 2960, 2940, 2890, 2860, 1745 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.65 (s, 3 H, CO$_2$C*H*$_3$), 3.22 (dd, 1 H, J = 4.59, 4.59 Hz, C*H*OSi), 2.37 (m, 1 H, C*H*CO$_2$CH$_3$), 2.23 (m, 1 H, C*H*CO$_2$CH$_3$), 1.86 (m, 1 H, C*H*CH$_2$CO$_2$CH$_3$), 1.75 (m, 1 H, C*H*(CH$_3$)$_2$), 1.58 (m, 1 H, C*H*CH$_3$), 1.37 (m, 1 H, C*H*CH$_2$CO$_2$CH$_3$), 0.89 (s, 9 H, C(C*H*$_3$)$_3$), 0.87 (d, 3 H, J = 4.45 Hz, CHC*H*$_3$), 0.87 (d, 3 H, J = 4.45 Hz, CH(C*H*$_3$)CH$_3$), 0.85 (d, 3 H, J = 4.65 Hz, CH(CH$_3$)C*H*$_3$), 0.24 (s, 6 H, Si(C*H*$_3$)$_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.38 (*C*=O), 81.27 (*C*HOSi), 51.37 (*C*O$_2$CH$_3$), 36.74 (*C*H$_2$CO$_2$CH$_3$), 32.41 (*C*HCH$_3$), 31.26 (*C*H$_2$CH$_2$CO$_2$CH$_3$), 27.39 (*C*H(CH$_3$)$_2$), 26.14 (C(*C*H$_3$)$_3$), 20.66 (CH(*C*H$_3$)CH$_3$), 18.42 (*C*(CH$_3$)$_3$), 18.32 (CH(CH$_3$)*C*H$_3$), 16.73 (CH*C*H$_3$), -3.77 (OSi(*C*H$_3$)CH$_3$), -3.88 (OSi(CH$_3$)*C*H$_3$); EIMS, m/z (rel intensity) 302 (0.5 M^+), 245 (22, M^+ - C_4H_9); HRMS m/z calcd for $C_{12}H_{25}O_3Si$ (M^+ - C_4H_9) 245.1573, found 245.1572. A portion of this compound (0.0055 g, 0.018 mmol) was subjected to the selenylation and oxidative elimination sequence as used in the preparation of **10** above but using sodium bis(trimethylsilyl)amide and *m*-chloroperbenzoic acid in place of LDA and H_2O_2, respectively. Obtained by flash chromatography on silica gel (95:5 hexane/CH_2Cl_2) was 0.0035 g (64%) of the unsaturated ester **12** as a colorless oil: ^1H NMR (300 MHz, $CDCl_3$) δ 7.05 (dd, J = 15.80, 8.24 Hz, 1 H, C*H*=CHCO$_2$CH$_3$), 5.90 (dd, J = 15.80, 1.08 Hz, 1 H, CH=C*H*CO$_2$CH$_3$), 3.73 (s, 3 H, CO$_2$C*H*$_3$), 3.30 (dd, J = 4.67, 4.67 Hz, 1 H, C*H*OSi), 2.53 (dqdd, J = 8.24, 6.92, 4.67, 1.08 Hz, 1 H, C*H*CH$_3$), 1.73 (qqd, J = 5.07, 4.88, 4.67 Hz, 1 H, C*H*(CH$_3$)$_2$), 1.05 (d, J = 6.92 Hz, 3 H, CHC*H*$_3$), 0.91 (s, 9 H, C(C*H*$_3$)$_3$), 0.88 (d, J = 4.88 Hz, 3 H, CH(C*H*$_3$)CH$_3$), 0.85 (d, J = 5.07 Hz, 3 H, CH(CH$_3$)C*H*$_3$), 0.04 (s, 3 H, Si(C*H*$_3$)CH$_3$), 0.03 (s, 3 H, Si(CH$_3$)C*H*$_3$); ^{13}C NMR (75 MHz, $CDCl_3$ δ 167.19 (*C*=O), 152.79 (*C*H=CHCO$_2$CH$_3$), 120.08 (CH=*C*HCO$_2$CH$_3$), 80.47 (*C*HOSi), 52.52 (CO$_2$*C*H$_3$), 40.78 (*C*HCH$_3$), 32.36 (*C*H(CH$_3$)$_2$), 26.09 (C(*C*H$_3$)$_3$), 23.71 (*C*(CH$_3$)$_3$), 19.74 (CH(*C*H$_3$)CH$_3$), 18.13 (CH(CH$_3$)*C*H$_3$), 17.39 (CH*C*H$_3$), -3.78 (OSi(*C*H$_3$)CH$_3$), -3.84 (OSi(CH$_3$)*C*H$_3$); CIMS (ammonia), m/z (rel intensity) 318 (100, M^+ + 18), 243 (4, M^+ - C_4H_9); HRMS m/z calcd for $C_{16}H_{31}O_3Si$ (M^+ - 1) 299.2042, found 299.2045.

(4*R,5*R**)-4,6-Dimethyl-5-((*tert*-butyldimethylsilyl)oxy)heptanal (13).** To a solution of ester **9** (0.012 g, 0.040 mmol) in anhydrous CH_2Cl_2 (1 mL) at -78 °C under nitrogen was added dropwise a 1 M solution of diisobutylaluminum hydride (0.20 mL, 0.20 mmol) in THF. After being stirred for 15 min at -78 °C, the mixture was warmed to 0 °C over 45 min. The solution was recooled to -78 °C, quenched with a 1:1 mixture (2 mL) of saturated aqueous NH_4Cl and brine, and extracted with CH_2Cl_2. The extracts were washed with brine, dried ($MgSO_4$), and concentrated in vacuo to a volume of 5 mL. GC (HP1 capillary column, 100–250 °C) indicated complete conversion of **9** to a single product, which was identified by GCMS as the desired alcohol: CIMS (isobutane) m/z (rel intensity) 273 (2, M^+ - 1), 231 (7, M^+ - C_3H_7), 217 (11, M^+ - C_4H_9); HRMS m/z calcd for $C_{12}H_{27}O_2Si$ (M^+ - C_3H_7) 231.1780, found 231.1780. The solution containing the intermediate alcohol was added dropwise to a suspension of pyridinium chlorochromate (0.017 g, 0.079 mmol) in CH_2Cl_2 (2 mL) at 25 °C. The mixture was stirred for 1 h and then was filtered through a pad of silica gel. The colorless filtrate was concentrated in vacuo to give 0.0093 g (86% overall yield from **9**) of **13** as a colorless oil: GC (HP1 capillary column, 100–250 °C) >98% purity; IR (film) 2940, 2910, 2840, 2790, 2690, 1730 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.77 (dd, 1 H, J = 1.78, 1.66 Hz, C*H*O), 3.27 (dd, 1 H, J = 5.50, 3.20 Hz, C*H*OSi), 2.43 (ddddd, 2 H, J = 16.40, 9.25, 9.18, 1.78, 1.66 Hz, C*H*$_2$CHO), 1.75 (qqd, J = 6.85, 6.85, 5.50 Hz, 1 H, C*H*(CH$_3$)$_2$), 1.75 (qddd, 1 H, J = 6.85, 3.76, 3.20, 3.11 Hz, C*H*CH$_3$), 1.59 (ddd, 1 H, J = 12.18, 9.25, 3.76 Hz, C*H*HCH$_2$CHO), 1.49 (ddd, 1 H, J = 12.18, 9.18, 3.11 Hz, CH*H*CH$_2$CHO), 0.90 (s, 9 H, C(C*H*$_3$)$_3$), 0.89 (d, 3 H, J = 6.85, CHC*H*$_3$), 0.87 (d, 6 H, J = 6.85 Hz, CH(C*H*$_3$)$_2$), 0.048 (s, 3 H, Si(C*H*$_3$)CH$_3$), 0.037 (s, 3 H, Si(CH$_3$)C*H*$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.66 (*C*HO), 80.47 (*C*HOSi), 42.40 (*C*H$_2$CHO), 36.36 (*C*HCH$_3$), 31.88 (*C*H$_2$CH$_2$CHO), 29.55 (*C*H(CH$_3$)$_2$), 26.15 (SiC(*C*H$_3$)$_3$), 22.65 (Si*C*(CH$_3$)$_3$), 20.20 (CH(*C*H$_3$)CH$_3$), 18.98 (CH(CH$_3$)*C*H$_3$), 14.53 (CH*C*H$_3$), -3.67 (Si(*C*H$_3$)CH$_3$), -3.69 (Si(CH$_3$)*C*H$_3$); CIMS (isobutane), m/z (rel intensity) 329 (36, M^+ + C_4H_9), 315 (14, M^+ + C_3H_7), 273 (34, M^+ + H), 229 (18, M^+ - C_3H_7), 215 (75, M^+ - C_4H_9); HRMS m/z calcd for $C_{11}H_{23}O_2Si$ (M^+ - C_4H_9) 215.1467, found 215.1488.

Methyl (4*R*,5*R*)-4,6-Dimethyl-5-((*tert*-butyldimethylsilyl)oxy)-2(*E*)-heptenoate ((4*R*,5*R*)-10). Following its preparation by an asymmetric aldol condensation as reported by Miller,[8] compound **14**, $[\alpha]^{25}_D$ + 7.96° (*c* 1.88, CH_2Cl_2), was converted in 99% yield to its (*tert*-butyldimethylsilyl)oxy derivative, $[\alpha]^{25}_D$ +22.9° (*c* 3.18, CH_2Cl_2), by the procedure used above for the preparation of **9**. To a solution of this *O*-silyl derivative (0.023 g, 0.057 mmol) in CH_2Cl_2 (1 mL) at -78 °c was added dropwise a 1 M solution of diisobutylaluminum hydride (0.11 mL, 0.11 mmol) in toluene. The mixture was stirred for 5 min at -78 °C, saturated aqueous ammonium chloride (2 mL) was added dropwise, the mixture was stirred at 25 °C for 15 min and extracted with CH_2Cl_2 (3 × 10 mL), and the combined extracts were washed with brine (10 mL), dried ($MgSO_4$), and concentrated in vacuo. The yellow residue (0.086 g) was purified by flash chromatography on silica gel (97.5:2.5 hexane/ethyl acetate) to give 0.0105 g (75%) of **15** as a colorless oil: ^1H NMR (300 MHz, $CDCl_3$) δ 9.78 (d, J = 0.76 Hz, 1 H, C(=O)*H*), 3.90 (dd, J = 5.45, 3.88 Hz, 1 H, H-3), 2.50 (qdd, J = 7.09, 3.88, 0.76 Hz, 1 H, H-2), 1.81 (qqd, J = 6.94, 6.80, 5.45 Hz, 1 H, C*H*(CH$_3$)$_2$), 1.09 (d, J = 7.09 Hz, 3 H, CHC*H*$_3$), 0.92 (d, J = 6.94 Hz, 3 H, CH(C*H*$_3$)CH$_3$), 0.89 (d, J = 6.80 Hz, 3 H, CH(CH$_3$)C*H*$_3$), 0.88 (s, 9 H, C(C*H*$_3$)$_3$), 0.07 (s, 3 H, Si(C*H*$_3$)CH$_3$), 0.01 (s, 3 H, Si(CH$_3$)C*H*$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 205.46 (*C*=O), 76.41 (*C*—O—), 50.64 (C-2), 32.21 (*C*(CH$_3$)$_2$), 29.70 (*C*(CH$_3$)$_3$), 25.95 (C(*C*H$_3$)$_3$), 19.71 (C(*C*H$_3$)CH$_3$), 18.28 (C(CH$_3$)*C*H$_3$), 8.61 (CHCH$_3$), -4.02 (Si(*C*H$_3$)CH$_3$), -4.19 (Si(CH$_3$)*C*H$_3$);

CIMS (isobutane), m/z (rel intensity) 245 (19, $M^+ + H$); HRMS m/z calcd for $C_9H_{19}O_2Si$ ($M^+ - C_4H_9$) 187.1154, found 187.1154; $[\alpha]^{25}_D$ +40.0 (c 1.27, CH_2Cl_2). Also isolated by the chromatographic purification was the corresponding alcohol as an overreduction product (6% yield). To a solution of **15** (0.019 g, 0.078 mmol) in CH_2Cl_2 (2.5 mL) at 25 °C under nitrogen was added a solution of methyl (triphenylphosphoranylidene)acetate (0.026 g, 0.078 mmol; Aldrich) in CH_2Cl_2 (2.5 mL). The solution was then heated at reflux for 4 weeks. The mixture was poured into brine (5 mL), and the resulting mixture was extracted with CH_2Cl_2 (3 × 10 mL), dried ($MgSO_4$), and concentrated in vacuo, leaving a yellow oil. The *E*:*Z* ratio in the crude reaction mixture was 18:1 under these conditions. Flash chromatography on silica gel (99.5:0.5 hexane/ethyl acetate) gave 0.016 g (70%) of pure (2*E*)-(4*R*,5*R*)-**10** as a colorless oil having spectroscopic data identical with that of the racemic material prepared above but having $[\alpha]^{25}_D$ +25.0 (c 0.58, CH_2Cl_2). Through use of the chiral NMR shift reagent tris(3-((heptafluoropropyl)hydroxymethylene)-(+)-camphorato)europium(III) (Eu(hfc)$_3$, Aldrich), none of the 4*S*,5*S* enantiomer could be detected. By addition of Eu(hfc)$_3$ to samples of racemic **10**, (4*R*,5*R*)-**10**, and mixtures of racemic **10** and (4*R*,5*R*)-**10**, the minimum detection limit for (4*S*,5*S*)-**10** was found to be 0.5%, and therefore, an enantiomeric excess of at least 99% can be claimed for (4*R*,5*R*)-**10**.

With shorter reaction times and with benzene as the solvent instead of CH_2Cl_2 in the final condensation step with the phosphonium ylide, significantly larger amounts of the 2*Z* isomer of (4*R*,5*R*)-**10** were obtained. In an extreme case, when the condensation of **15** was done with trimethyl phosphonoacetate and potassium *tert*-butoxide in THF at −78 °C rather than with the ylide used above, the *E* and *Z* isomers were isolated in 18% and 47% yields, respectively. (2*Z*)-(4*R*,5*R*)-**10**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.12 (dd, 1 H, J = 11.60, 10.43 Hz, C*H*=CHCO$_2$CH$_3$), 5.70 (dd, 1 H, J = 11.60, 0.85 Hz, CH=C*H*CO$_2$CH$_3$), 3.71 (s, 3 H, CO$_2$C*H*$_3$), ca. 3.7 (m, difficult to detect, overlapped with the strong CO$_2$C*H*$_3$ singlet, and probably strongly deshielded by the carbomethoxy group, 1 H, C*H*CH$_3$), 3.32 (dd, 1 H, J = 5.13, 5.13 Hz, C*H*OSi), 1.71 (qqd, 1 H, J = 6.80, 6.76, 5.13 Hz, C*H*(CH$_3$)$_2$), 1.05 (d, 3 H, J = 6.95 Hz, CH$_3$), 0.91 (s, 9 H, C(C*H*$_3$)$_3$), 0.87 (d, 3 H, J = 6.80 Hz, CH(C*H*$_3$)CH$_3$), 0.82 (d, 3 H, J = 6.76 Hz, CH(CH$_3$)C*H*$_3$), 0.036 (s, 3 H, Si(C*H*$_3$)CH$_3$), 0.023 (s, 3 H, Si(CH$_3$)C*H*$_3$); EIMS, m/z (rel intensity) 300 (1, M^+), 285 (4, $M^+ - CH_3$), 257 (36, $M^+ - C_3H_7$), 243 (100, $M^+ - C_4H_9$); HRMS m/z calcd for $C_{12}H_{23}O_3Si$ ($M^+ - C_4H_9$) 243.1416, found 243.1414.

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Alkaline Hydrolysis of 1,3-Dibromo-1,1-difluoroalkanes: A Two-Step Vinyl Carboxylation

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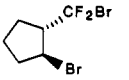
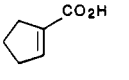
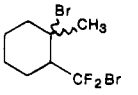
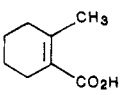
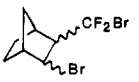
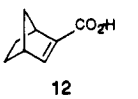
In a recent attempt to prepare 3-(difluoromethylene)-cyclohexene, **1**, we found that refluxing 1-(bromodifluoromethyl)-2-bromocyclohexanes, **2**, with aqueous potassium hydroxide followed by acidic workup produced 1-cyclohexene-1-carboxylic acid, **3**. Subsequent investigations showed that diene **1** is an intermediate but is converted to **3** under the reaction conditions.[1] Inasmuch as dibromides **2** were obtained from addition of CF_2Br_2 to cyclohexene, this reaction sequence amounts to a two-step vinyl carboxylation strategy. We therefore sought to demonstrate the generality of these conversions.

Table I. Dibromodifluoromethane-Alkene Adducts and Their Alkaline Hydrolysis Products

CF_2Br_2–alkene adduct	unsaturated acid	% yield[a]
2	**3**	93[b]
$CH_3(CH_2)_3CHBrCH_2CF_2Br$	$CH_3(CH_2)_3CH{=}CHCO_2H$	96
4	**9**	
		69
5	**10**	
		53
6	**11**	
		73
7	**12**	
$PhCH_2CHBrCH_2CF_2Br$	$PhCH{=}CHCH_2CO_2H$	72
8	**13**	

[a] Based on unrecovered haloalkane. [b] Reference 1.

Scheme I

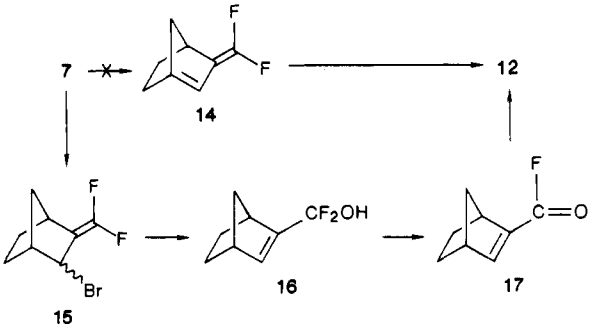


Table I summarizes the results of this study. Mono-, di-, and trisubstituted alkenes all give CuCl-initiated free-radical addition products with CF_2Br_2. When the adducts were refluxed with aqueous potassium hydroxide and then acidified, α,β-unsaturated carboxylic acids were produced in good yield.

One noteworthy exception is 1,3-dibromo-1,1-difluoro-4-phenylbutane, **8**, which gave 4-phenyl-3-butenoic acid, **13**, upon alkaline hydrolysis. This presumably reflects a thermodynamic advantage for the alkene to be conjugated with the aryl ring rather than the carboxy carbonyl.[2]

The mechanistically significant observation that **7** is converted to **12** suggests the existence of an alternative pathway which does *not* involve a diene intermediate.[3]

(1) Elsheimer, S.; Michael, M.; Landavazo, A.; Slattery, D. K.; Weeks, J. *J. Org. Chem.* **1988**, *53*, 6151.

(2) The isomerization of (*E*)-4-phenyl-2-butenoic acid to (*E*)-4-phenyl-3-butenoic acid was estimated to be exothermic by 1.64 kcal/mol at 150 °C. ASTM Chemical Thermodynamics and Energy Release Evaluation Program.

(3) Elsheimer, S.; Slattery, D. K.; Weeks, J. *J. Chem. Soc., Chem. Commun.*, submitted for publication.

(4) Burton, D. J.; Kehoe, L. J. *Tetrahedron Lett.* **1966**, 5163.

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