Efficient Fluorination with Tetrabutylammonium Dihydrogen Trifluoride in a Novel Approach toward 1-α-Fluoro-25-hydroxy-vitamin D_3 Analogues

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The known, but hardly accessible, A-ring phosphine oxide **20**, a building block for 1-α-fluoro-25-hydroxy-vitamin D_3, was prepared by a new route in gram amounts from (*S*)-(+)-carvone in 20 steps and 0.6% overall yield. Fluorine was introduced at an early stage by the completely regio- and stereoselective *trans*-diaxial opening of key-epoxide **5** with neat tetrabutylammonium dihydrogen trifluoride at 95 °C. The required 2-carbon chain extension of cyclohexanol **13** was accomplished in moderate yield via S_N' substitution with cesium phenylselanyl acetate followed by Ireland−Claisen rearrangement of the resulting ester **15**. Spontaneous elimination of the derived phenyl selenoxide led stereorandomly to a 1:1 mixture of dienoates *E*/*Z*-**17**, which was transformed into **20** as previously described.

Introduction and Plans

De novo construction of so-called A-ring phosphine oxides, crucial intermediates in the countless vitamin D syntheses, is a long-standing topic in this area, and many ingenious solutions have been provided by leading laboratories over the last two decades.[1] We required building block **20** (Scheme 1) for our current medicinal chemistry program aimed at novel vitamin D derivatives as antipsoriatics. We intended to design an approach that would allow us to make optimal use of previous work in the area and, at the same time, to overcome some limitations. In planning so, we realized that easy mode of operation and potential for scale-up would play a decisive role, since the number of synthetic steps would be in the range of 15−20, thus reducing the overall yield to ca. 1%, assuming a mean efficiency of 80% for each step. The 17-step synthesis of **20** by Uscocovíc[2] harbors the advantage of starting from readily available and cheap (*S*)-(+)-carvone, but suffers from the use of rather exotic reagents such as Martin's sulfurane and (diethylamino)sulfur trifluoride (DAST). We planned to introduce fluorine via *trans*-diaxial opening of epoxide **5** (Scheme 1), in analogy to the pioneering synthesis of 1-α-fluoro-25-hydroxy-vitamin D_3 by DeLuca,[3,4] which in turn would be accessible from (*S*)-(+)-carvone (**1**), thus combining advantageous features of the DeLuca and the Uskokovíc approach, respectively. Regio- and stereoselective opening of epoxides with fluoride is an extremely valuable process,[5−8] facilitated by the introduction of tetrabutylammonium dihydrogen trifluoride ($NBu_4H_2F_3$),[9] a powerful and safe source of fluoride, compatible with standard glassware. Our second key transformation was adapted from Takano's highly efficient synthesis of the A-ring phosphine oxide precursor of 1α,25-dihydroxy-vitamin D_3, where an epoxide similar to **12** is rearranged to the corresponding allylic alcohol.[10] We speculated that this process should be applicable to the 1α-fluoro analogue. Third, the missing 2-carbon fragment would be installed via Ireland−Caisen rearrangement of ester **15**, in analogy with a strategy devised by Posner.[11]

Results and Discussion

Our synthesis of key phosphine oxide **20** started from (*S*)-(+)-carvone (**1**) (Scheme 1): Diastereoselective reduction with sodium dihydridobis(2-methoxyethoxy)aluminate (REDAL) in THF at −70 °C afforded an inseparable 8:1 mixture of (+)-*cis*-carveol (**2a**)[12] and (+)-*trans*-carveol (**2b**) in 95% combined yield. Regioselective syn-epoxidation of the allylic double bond of mixture **2a,b** was achieved with m-CPBA in CH_2Cl_2 at −40 °C producing quantitatively a crude mixture of epoxides containing 85% of the desired compound **3**.[13] Mitsunobu reaction of this crude epoxide mixture with 4-nitrobenzoic acid and DEAD/TPP in toluene occurred with inversion of configuration at C-1 of **3** affording crude nitrobenzoate **4**, which was conveniently purified by filtration over silica gel followed by crystallization, thus removing all stereo- and regioisomeric impurities generated in the two preceding steps. Nitrobenzoate **4** was cleaved with LiOH in THF/H_2O at 0 °C (strict temperature control mandatory) yielding the crystalline epoxide **5** in 80% yield over

(1) Zhu, G.-D.; Okamura, W. *Chem. Rev.* **1995**, *95*, 1877.
(2) Baggiolini, E. G.; Kulesha, I.; Shiuey, S. J.; Uskokovic, M. R. *J. Org. Chem.* **1990**, *55*, 243.
(3) DeLuca, H. F.; Ikekawa, N.; Takazuto, S.; Oschima, E. *Chem. Pharm. Bull.* **1984**, *32*, 3518.
(4) DeLuca, H. F.; Ikekawa, N.; Takazuto, S.; Oschima, E.; Hiroshi, S.; Kobayashi, Y.; Tanaka, J. *Chem. Pharm. Bull.* **1984**, *32*, 3525.
(5) Alvernhe, G.; Laurent, A. *J. Fluorine Chem.* **1986**, *34*, 147.
(6) Armi, H.; El Gaied, M. M. *J. Fluorine Chem.* **1990**, *46*, 75.
(7) Landini, D.; Albanese, D.; Penso, M. *Tetrahedron* **1992**, *48*, 4163.
(8) Giannini, G. *Gazz. Chim. Ital.* **1996**, *126*, 771.
(9) Landini, D.; Molinari, H.; Penso, M.; Rampoldi, A. *Synthesis* **1988**, 953.
(10) Hatakeyama, S.; Numata, H.; Osanai, K.; Takano, S. *J. Org. Chem.* **1989**, *54*, 3515.
(11) Posner, G. H.; Crouch, D. R.; Kinter, C. M.; Carry, J.-C. *J. Org. Chem.* **1991**, *56*, 6981.
(12) Nozaki, H.; Yamamoto, H.; Yasuda, A. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1757.
(13) Kover, B. W.; Jones, J. J. *Synth. Commun.* **1995**, *25*, 3907.

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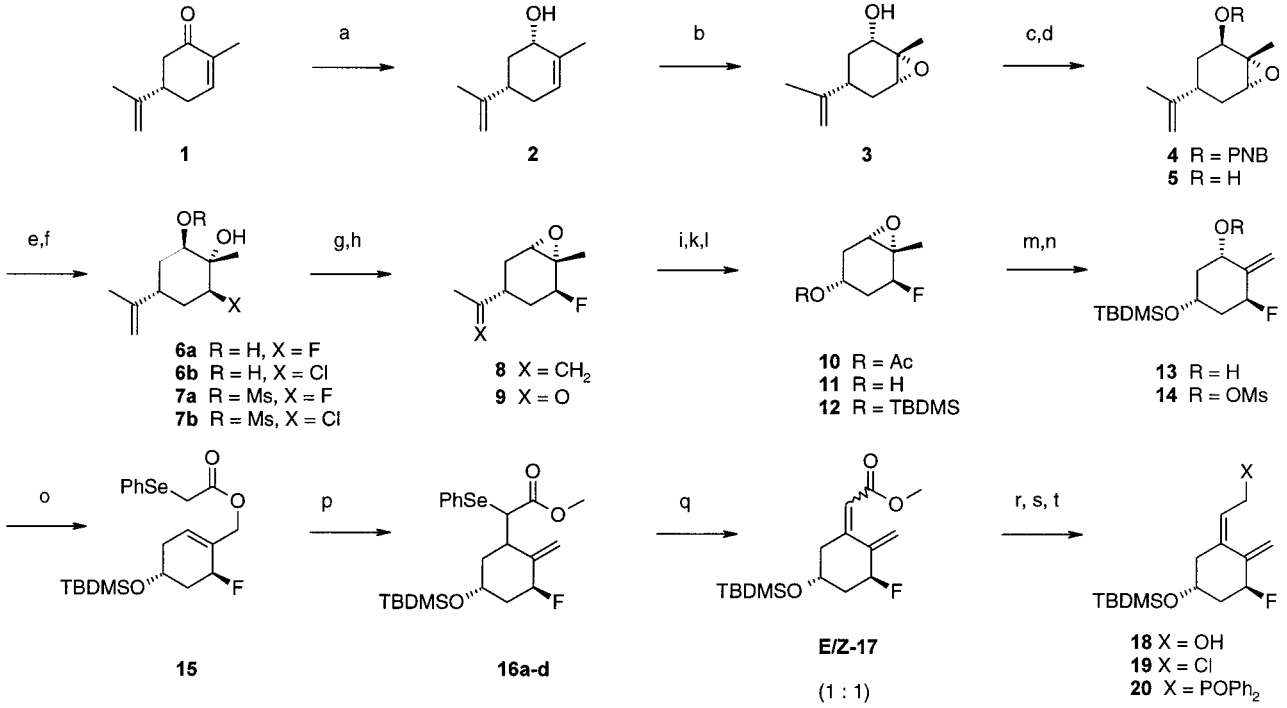
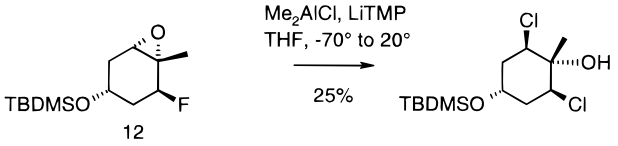
Scheme 1[a]



[a] Legend for reaction conditions: (a) $NaAlH_2(OCH_2CH_2OMe)_2$, THF, −70 °C (80%); (b) m-CPBA, CH_2Cl_2, −40 °C (99%); (c) TPP/DEAD, PNBA, toluene, (82%); (d) LiOH, 1:1 THF/H_2O, 0 °C (99%); (e) neat $Bu_4NH_2F_3$, 95 °C (99%); (f) MsCl, pyridine, CH_2Cl_2 (99%); (g) K_2CO_3, MeOH (85%); (h) $OsCl_3$, $NaIO_4$, 1:1 THF/ H_2O (83%); (i) m-CPBA, CH_2Cl_2 (94%); (k) K_2CO_3, MeOH (79%); (l) (TBDMS)Cl, imidazole, DMF (91%); (m) EtMgTMP, THF (72%); (n) DIEA, MsCl, CH_2Cl_2 (99%); (o) $PhSeCH_2CO_2Cs$, cat. NBu_4I, DMF, 50 °C (32%); (p) (1) DIEA, TBSOTf, CH_2Cl_2, (2) NaOH, THF, (3) MeOH, DCC/DMAP, CH_2Cl_2 (44%); (q) $NaIO_4$, THF/H_2O/MeOH (87%); (r) DIBALH, THF, −70 °C (72%); (s) NCS, Me_2S, CH_2Cl_2 (65%); (t) (1) $LiPPh_2$, THF, −70 °C, (2) H_2O_2 (51%).

these two steps. Small-scale fluorination of epoxide **5** with 2 equiv of $NBu_4H_2F_3$ in 1,2-dichloroethane at reflux gave rise to the desired fluoro diol **6a** in 80% yield. A minor byproduct was isolated and identified as **6b**, which resulted from incorporation of chlorine instead of fluorine into the molecule. The diols **6a,b** were fully characterized as the corresponding crystalline mesylates **7a,b**. Since the solvent 1,2-dichloroethane was the only possible source of chlorine, and byproduct formation became even more substantial (15−20%) on scale-up, we performed the fluorination of epoxide **5** in neat $NBu_4H_2F_3$ (prepared by a slight modification of Landini's procedure)[9] at 95 °C, affording exclusively the fluoro diol **6a** in quantitative yield. Our safety laboratory recommended a maximal process temperature of 100 °C on the basis of thermal decomposition studies, which indicated no exothermic decomposition of $NBu_4H_2F_3$ up to 360 °C but a slight rise in pressure (180 mbar/h) in a closed vessel. Transformation of the crude fluoro diol **6a** to the epoxide **8** was achieved by regioselective mesylation of the secondary hydroxyl group in the presence of pyridine as weak base, followed by ring closure with K_2CO_3/MeOH in 83% yield. Oxidative degradation of the isopropenyl group of **8** was attempted by two well-established literature procedures, first by ozonolysis in MeOH to an α-methoxy hydroperoxide which upon treatment with acetic anhydride and triethylamine underwent in situ Criegee rearrangement affording epoxy alcohol **11** in only 40% yield.[14] We therefore switched to the higher yielding two-step procedure encompassing Lemieux−Johnson oxidation of **8** with 0.5 mol % of OsO_4 (prepared in situ from nonvolatile $OsCl_3$) and 2 equiv of $NaIO_4$ (83% yield) followed by Baeyer−Villiger oxidation of **9** with m-CPBA (94% yield). At this stage the protective group on the secondary hydroxyl had to be exchanged for TBDMS. The acetate **10** was cleaved with K_2CO_3/MeOH affording in 79% yield the somewhat water-soluble, crystalline alcohol **11**, which was silylated in 91% yield. Silyl ether **12** was then exposed to the complex prepared in situ from Me_2AlCl and LiTMP. Unexpectedly, we obtained a symmetrical dichloride (Scheme 2).

Scheme 2



This result confirms the exceedingly high affinity of aluminum for fluorine, which in this case could not be exploited in a constructive manner.[15] No reaction of **12** was observed under Noyori's conditions with TMS−OTf/DBU.[16] Next, we explored a series of magnesium amides[17] which were prepared form the corresponding lithium amides (LDA, LiN(*c*-hex)(i-Pr), LiTMP) and ethylmagnesium chloride, and obtained the desired allylic alcohol **13** in 20%, 53%, and 72%, respectively. This rearrangement proceeded slowly and incompletely at room tem-

(14) Brabander, J. D. M.; Vandewalle, M.; Kulkarni, A.; Garcia-Lopez, R. *Tetrahedron: Asymmetry* **1997**, *8*, 1721.

(15) Ooi, T.; Kagoshima, N.; Maruoka, K. *J. Am. Chem. Soc.* **1997**, *119*, 5754.

(16) Noyori, R.; Murata, S.; Suzuki, M. *Tetrahedron* **1981**, *37*, 3899.

(17) Mosset, P.; Manna, S.; Viala, J.; Falk, J. R. *Tetrahedron Lett.* **1986**, *27*, 299.

perature, but longer reaction times led to extensive decomposition, revealing the instability of **13**. 1,3-Transposition of the secondary allylic alcohol **13** was attempted in several ways: Pd-catalyzed isomerization of the corresponding acetate failed.[18] Mitsunobu reaction with phenylselanyl acetic acid produced the unrearranged ester.[19] Attempted (trimethylsilyl)trioxorhenium-catalyzed isomerization led to clean removal of the TBDMS group but left the allylic moiety untouched.[20] Treatment with $SOCl_2$/pyridine in *tert*-butyl methyl ether afforded a mixture which contained only 30% of the desired chloride.[21] Exposure to chlorodiphenylphosphine/imidazole/iodine[22] or MsCl/DMAP/NaI[10] produced again mixtures of iodides and elimination products. Finally, we managed to transform mesylate **14** directly in one pot to the rearranged ester **15** in 33% overall yield using a catalytic amount of tetrabutylammonium iodide and an excess of crystalline cesium phenylselanyl acetate in DMF at 50 °C.[23,24] Again, elimination products and unrearranged ester were concomitantly formed at the expense of **15**. Thermally induced Ireland−Claisen rearrangement of ester **15** with an excess of Hünig's base and fresh TBDMSOTf in CH_2Cl_2, cleavage of the intermediary silyl ester with NaOH, and reesterification with DCC/DMAP/MeOH lead to a crude, inseparable mixture of diastereomeric α-phenylselanyl esters **16a**−**d**. Ensuing oxidation with $NaIO_4$ in THF/H_2O/MeOH afforded directly a 1:1 mixture of *Z*/*E*-**17** in 38% overall yield from **15**. This finding stood in contrast to our unpublished results in the classical series (1α,25-dihydroxy-vitamin D_3), where we had obtained a *Z*/*E* = 9:1 ratio. Although the mixture of *Z*/*E*-**17** is normally photochemically isomerized[25] to *Z*-**17**, we performed a silica gel separation, characterized both compounds, and found that *Z*-**17** was stable and amenable to further manipulation whereas pure *E*-**17** rapidly polymerized in our hands thus precluding its photoisomerization. Since the ethyl ester analogue of *E*-**17** has been previously successfully isomerized to the *Z*-isomer,[2] one may conclude that the slightly increased steric bulk of the ethyl ester group contributes to the stability of the corresponding *E*-isomer. Reduction of *Z*-**17** with DIBALH in THF at −70 °C afforded in 72% yield the known allylic alcohol **18**,[2] which was converted uneventfully into the desired phosphine oxide **20** as previously reported.[2]

Conclusions

The first 11 steps of this approach to phosphine oxide **20** represent a very robust and high yielding route. Except for one silica gel filtration, chromatographic separations could be avoided, and most reactions worked well with crude intermediates. However, as soon as the allylic fluoride moiety was generated, several transformations proceeded with moderate yield due to inherent compound instability. We suspect from our work that the allylic fluoride substructure common to compounds **13**−**20** is particularly sensitive to S_N' nucleophilic displacement, limiting thereby the overall efficiency of our process.

Experimental Section

Materials and Methods. All reagents and solvents were commercially available and used as received, unless otherwise stated. Small-scale fluorinations were performed with 50−55% weight solution of $NBu_4H_2F_3$ in 1,2-dichloroethane available from ACROS. All reactions, including the fluorination step, were run in normal glassware, except for the preparation of $NBu_4H_2F_3$[9] (see below). All organic extracts were dried over Na_2SO_4, filtered, and evaporated under vacuum. All chromatographic separations were performed on Flash 40 or 150M cartridges (40 g, 90 g, 2.5 kg), KP-Sil silica, 32−63 μm, 6 nm, unless otherwise stated. Chemical yields are corrected for the purity (GC or HPLC) of starting material and product. ^{13}C NMR spectra (100 MHz) were measured in $CDCl_3$.

(1*S*,5*S*)- and (1*R*,5*S*)-5-Isopropenyl-2-methylcyclohex-2-enol (2a,b). A 3.5 M solution of sodium dihydridobis(2-methoxyethoxy)aluminate in toluene (880 mL, 3.1 mol) was added under argon to THF (3 L) at −70 °C. Then (*S*)-(+)-carvone (**1**) (810 mL, 5.2 mol) was added dropwise over 4 h at −70 °C. Stirring was continued for 1 h at −70 °C. Excess reagent was destroyed by slow addition of AcOEt (500 mL, 5 mol) over 1 h at −70 °C and allowing the solution to warm to 0 °C. Finally, the yellow solution was poured into cold 3 N HCl, stirred for 15 min (check pH 2−3), and extracted with AcOEt. The organic layer was washed with saturated NaCl. The crude oil (821 g) was distilled at 75 °C/0.4 mbar (bath-*T*: 100 °C) affording a colorless oil (751 g, yield 80%, GC-purity 84% + 10% (1*R*)-epimer).

(1*S*,2*S*,3*R*,5*R*)-2,3-Epoxy-5-isopropenyl-2-methylcyclohex-2-enol (3).[13] Alcohols **2a,b** (367 g, 2.4 mol) were dissolved in CH_2Cl_2 (4 L) and cooled under argon at −40 °C (bath-*T*: −50 °C). Then m-CPBA (594 g, 2.4 mol) was added in 3 portions (30 min of stirring after each addition) and stirring continued for 5 h at −40 to −30 °C. The reaction was monitored by GC of a sample having been extracted with saturated Na_2CO_3. The cold reaction mixture (−30 °C) was poured into the extraction vessel on ice and then slowly mixed while stirring with an aqueous solution of $Na_2CO_3 \cdot 10H_2O$ (3 mol). The layers did separate, but a voluminous white precipitate remained in the upper aqueous layer, which was back-extracted with CH_2Cl_2. The organic layers were again extracted with an aqueous solution of $Na_2CO_3 \cdot 10H_2O$ (3 mol) and finally with a saturated solution of NaCl. One obtained a yellowish oil (397 g, yield 99%, GC purity 85%). ^{13}C NMR: δ 19.2, 20.2, 29.1, 34.0, 40.5, 60.4, 62.3, 72.3, 109.7, 147.6.

4-Nitrobenzoic Acid (1*R*,2*R*,4*S*,6*R*)-4-Isopropenyl-1-methyl-7-oxabicyclo[4.1.0]hept-2-yl Ester (4). Alcohol **3** (379 g, 2.25 mol), 4-nitrobenzoic acid (376.5 g, 2.25 mol), and triphenylphosphine (590 g, 2.25 mol) were dissolved under argon in toluene (5 L) and cooled in ice. Then DEAD (368 mL, 2.25 mol) was added dropwise over 1 h (slightly exothermic) while keeping the temperature below 10 °C. Stirring without cooling was continued for 2 h. The reaction mixture was filtered through a pad of toluene-wetted silica gel (2 kg) in a porcelain funnel (35 × 10 cm), and the filter cake was washed with more toluene (10 L). The yellow filtrate was evaporated, and the resulting solid was crystallized from hot ethanol (4 L). After stirring of the mixture for 1 h in ice, the crystals were filtered off and dried at 50 °C/0.1mbar for 24 h. One obtained white crystals (518 g, yield 77%, HPLC purity 90%). The mother liquor was concentrated to ca. 1 L and allowed to crystallize once more at 4 °C over the weekend. One obtained white crystals (40 g, yield 5%, HPLC purity 86%), mp 130 °C: ^1H NMR (250 MHz, $CDCl_3$) δ 1.38 (s, 3H), 1.68 (s, 3H), 1.70−1.93 (m, 3H), 2.13−2.43 (m, 2H), 3.22 (d, *J* = 5 Hz, 1H), 4.69

(18) Sulikowski, M. M.; Ellis Davies, G. E. R.; Smith, A. B., III. *J. Chem. Soc., Perkin Trans. 1* **1992**, 979.
(19) Burke, S. D.; Pacofsky, G. J.; Piscopio, A. D. *Tetrahedron Lett.* **1986**, *27*, 3345.
(20) Osborn, J. A.; Bellemin-Laponnaz, S.; Gisie, H.; Le Ny, J.-P. *Angew. Chem.* **1997**, *109*, 1011.
(21) Wong, G.; Fraser-Reid, B. *Can. J. Chem.* **1994**, *72*, 69.
(22) Ioannidis, P.; Soederman, P.; Samuelsson, B.; Classon, B. *Tetrahedron Lett.* **1993**, *34*, 2993.
(23) Reich, H. J.; Chow, F.; Shah, S. K. *J. Am. Chem. Soc.* **1979**, *101*, 6638.
(24) Kruizinga, H.; Strijtveen, B.; Kellogg, R. M. *J. Org. Chem.* **1981**, *46*, 4321.
(25) Baggiolini, E. G.; Iacobelli, J. A.; Hennessy, B. M.; Uscokovíc, M. R. *J. Am. Chem. Soc.* **1982**, *104*, 2945.

(m, 2H), 5.59 (m, 1H), 8.28 (m, 4H); ^{13}C NMR δ 19.3, 20.3, 28.8, 29.7, 34.2, 56.8, 59.8, 73.4, 110.0, 123.7, 130.8, 135.5, 147.6, 150.7, 163.9; TSP/MS *m/z* (%) 318 (M^+, 1), 299 (1), 259 (10), 150 (100). Anal. Calcd for $C_{17}H_{19}NO_5$ (317.345): C, 64.34; H, 6.04; N, 4.41. Found: C, 64.15; H, 6.03; N, 4.31. $[\alpha]^{20}_D = +121.2$ (*c* 0.5, $CHCl_3$).

(1*R*,2*S*,3*R*,5*R*)-2,3-Epoxy-5-isopropenyl-2-methylcyclohex-2-enol (5). Ester **4** (580 g, 1.83 mol) was dissolved in THF (2 L) under argon and cooled to 0 °C. Then a solution of $LiOH \cdot H_2O$ (306 g, 7.3 mol) in H_2O (2 L) was added over ca. 1 h while the temperature was kept below 5 °C. Stirring was continued for 3 h at 5 °C. Extraction: Et_2O, 10% Na_2CO_3, saturated NaCl. One obtained a crude solid (300 g, yield 99%, GC purity 91%), mp 46 °C: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.42 (s, 3H), 1.52 (ddd, $J_1 = 13.8$ Hz, $J_2 = 5.0$ Hz, $J_3 = 2.6$ Hz, 1H), 1.66 (d, $J = 5$ Hz, 1H), 1.69 (s, 3H), 1.71 (dd, $J_1 = 13.8$, $J_2 = 3.4$ Hz, 1H), 1.76 (ddd, $J_1 = 13.8$ Hz, $J_2 = 13.6$ Hz, $J_3 = 3.0$ Hz, 1H), 2.07 (dddd, $J_1 = 15.3$ Hz, $J_2 = 6.8$ Hz, $J_3 = 5.0$ Hz, $J_4 = 2.0$ Hz, 1H), 2.39 (dddd, 1H), 3.11 (d, $J = 5.2$ Hz, 1H), 4.18 (br, 1H), 4.70 (m, 2H); ^{13}C NMR δ 19.5, 20.3, 29.0, 32.9, 33.0, 58.6, 60.0, 69.6, 109.6, 148.5; TSP/MS *m/z* (%) 153 (5), 135 (23), 125 (28), 109 (100). Anal. Calcd for $C_{10}H_{16}O_2$ (168.238): C, 71.39; H, 9.59. Found: C, 71.29, H, 9.62. $[\alpha]^{20}_D = +84.2$ (*c* 0.5, $CHCl_3$).

Tetrabutylammonium Dihydrogen Trifluoride.[9] In a polymethylpentene (TPX) 5 L beaker with mechanical stirrer, tetrabutylammonium hydrogen sulfate (339.5 g, 1 mol) in chloroform (3 L) was treated with a solution of $KHCO_3$ (100.1 g, 1 mol) in water (300 mL) and stirred for 10 min at 20 °C. Then solid KHF_2 (390.5 g, 5 mol) was added and stirring continued for 1 h at 20 °C. The suspension was filtered through a glass microfiber filter (Whatman) in a Buchner funnel with suction, the salts were washed with chloroform (200 mL), the filtrate was poured into a separatory funnel, the lower clear organic layer was separated, and the filtrate was concentrated to ca. 500 mL. The resulting solution, containing still some solid, was filtered through normal paper in a funnel, evaporated, and dried while stirred magnetically for 1 day at 20 °C/0.1 mbar. The resulting *solvent-free* colorless oil (296 g, 98%) was used directly in the next step.

(1*S*,2*R*,4*R*,6*S*)-6-Fluoro-4-isopropenyl-1-methylcyclohexane-1,2-diol (6a). Epoxide **5** (173.5 g, 1.03 mol) and $NBu_4H_2F_3$ (602 g, 2 mol) were heated at 95 °C for 24 h. Extraction: AcOEt, ice/H_2O. One obtained a crude brown oil (194 g, yield 99%, GC purity 90%), which was used without further purification in the next step: ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.44 (d, $J = 2$ Hz, 3H), 1.59 (d, $J = 4.3$, 1H), 1.76 (s, 3H), 1.75−2.18 (m, 5H), 2.51 (m, 1H), 3.66 (m, 1H), 4.55 (dt, $J_{HF} = 48$ Hz, $J_2 = 6$ Hz, 1H), 4.81 (m, 2H); ^{13}C NMR δ 19.7, 21.3, 31.2, 31.3, 32.3, 33.0, 73.7, 94.8, 96.5, 110.0, 147.4; TSP/MS *m/z* (%) 170 (10), 168(8), 155 (18), 152 (36), 107 (100), 71 (100).

Methanesulfonic Acid (1*R*,2*S*,3*S*,5*R*)-3-Fluoro-2-hydroxy-5-isopropenyl-2-methylcyclohexyl Ester (7a). Diol **6a** (194 g, 1.02 mol) was dissolved in CH_2Cl_2 (900 mL) and cooled to 15 °C. Then pyridine (123 mL, 1.53 mol) and MsCl (119 mL, 1.53 mol) were added while holding the temperature between 15° and 25 °C and stirring continued for 40 h at 20 °C. Extraction: CH_2Cl_2, cold 1 N HCl, 10% NaCl. The crude brown oil (280 g, yield 99%, GC purity 88%), which crystallized spontaneously upon refrigeration, was used without further purification in the next step, mp 82 °C: ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.43 (d, 3H, $J = 2$ Hz), 1.77 (s, 3H), 1.80 (s, 1H), 1.83−2.25 (m, 4H), 2.59 (br, 1H), 3.08 (s, 3H), 4.46 (ddd, 1H, $J_{HF} = 48$ Hz, $J_2 = 6$ Hz, $J_3 = 4$ Hz), 4.67 (dd, 1H), 4.86 (m, 2H); ^{13}C NMR δ 20.3, 21.3, 31.0, 31.2, 31.8, 32.9, 38.6, 71.5, 71.8, 81.7, 92.4, 94.2, 110.8, 146.2; EI/MS *m/z* (%) 248 (2), 246 (2), 170 (100), 155 (60). Anal. Calcd for $C_{11}H_{19}FO_4S$ (266.334): C, 49.61; H, 7.19; S, 12.04; F, 7.13. Found: C, 49.53; H, 7.04; S, 11.95; F, 7.21. $[\alpha]^{20}_D = -12.2$ (*c* 0.5, $CHCl_3$).

Mixture of (1*S*,2*R*,4*R*,6*S*)-6-Fluoro-4-isopropenyl-1-methylcyclohexane-1,2-diol (6a) and (1*S*,2*R*,4*R*,6*S*)-6-Chloro-4-isopropenyl-1-methylcyclohexane-1,2-diol (6b). Epoxide **5** (47.4 g, 0.28 mol) and $NBu_4H_2F_3$ (180 g, 0.6 mol) were dissolved in 1,2-dichloroethane (150 mL) and heated at 90 °C bath-*T* for 24 h. Extraction: AcOEt, H_2O. Chromatography: 2:1 CH_2Cl_2/AcOEt. One obtained an inseparable fluoro:chloro = 74:20 mixture as a colorless oil (43 g, 81%). Separation of the corresponding mesylates was feasible.

Methanesulfonic Acid (1*R*,2*S*,3*S*,5*R*)-3-Chloro-2-hydroxy-5-isopropenyl-2-methylcyclohexyl Ester (7b). Mixture **6a,b** (43 g, 228 mmol) and pyridine (55 mL, 685 mmol) were dissolved in CH_2Cl_2 (500 mL) and cooled in ice. Then MsCl (53 mL, 685 mmol) was added and stirring continued for 24 h at 20 °C. Extraction: 1 N HCl, H_2O. Chromatography: 2:1 CH_2Cl_2/TBME. **7b** was eluted first yielding white crystals (12 g, 18%), mp 73 °C: ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.59 (d, 3H), 1.79 (s, 3H), 1.82−1.96 (m, 4H), 2.30 (s, 1H), 2.32−2.46 (m, 2H), 2.58 (br, 1H), 3.11 (s, 3H), 4.02 (dd, 1H, $J_1 = 8$ Hz, $J_2 = 4$ Hz), 4.61 (dd, 1H, $J_1 = 8$ Hz, $J_2 = 4$ Hz), 4.99 (s, 1H), 5.01 (s, 1H); ^{13}C NMR δ 16.6, 22.1, 31.2, 34.8, 37.0, 38.3, 64.3, 75.5, 82.4, 112.2, 144.0; EI/MS *m/z* (%) 282 (2), 246 (8), 186 (50), 151 (85), 133 (100). Anal. Calcd for $C_{11}H_{19}ClO_4S$ (282.789): C, 46.72; H, 6.77; S, 11.34; Cl, 12.54. Found: C, 46.80; H, 6.79; S, 11.36; Cl, 12.37.

(1*S*,2*S*,4*R*,6*S*)-2-Fluoro-4-isopropenyl-1-methyl-7-oxabicyclo[4.1.0]heptane (8). Crude mesylate **7a** (290 g, 0.96 mol) was dissolved in MeOH (1.7 L), treated with K_2CO_3 (200 g, 1.45 mol), and stirred at 20 °C for 17 h. Extraction: hexane, ice/water, 10% NaCl. Careful evaporation gave a crude oil (136 g, 85% yield, GC purity 90%), which was used without further purification in the next step: ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.43 (d, 3H, $J = 2$ Hz), 1.55−1.82 (m, 3H), 1.69 (s, 3H), 2.05−2.16 (m, 1H), 2.27−2.38 (m, 1H), 3.17 (d, 1H, $J = 5.2$ Hz), 4.71 (m, 2H), 4.86 (d, 1H, $J_{HF} = 48$ Hz); ^{13}C NMR δ 18.8, 20.3, 28.8, 30.5, 30.7, 33.4, 56.3, 56.6, 60.2, 90.1, 91.8, 109.9, 147.8; EI/MS *m/z* (%) 155 (12), 137 (18), 112 (100). Anal. Calcd for $C_{10}H_{15}FO$ (170.229): C, 70.56; H, 8.88; F, 11.16. Found: C, 70.43; H, 8.81; F, 11.28. $[\alpha]^{20}_D = -74.9$ (*c* 0.71, $CHCl_3$).

(1*S*,3*R*,5*S*,6*S*)-1-(5-Fluoro-6-methyl-7-oxabicyclo[4.1.0]-hept-3-yl)ethanone (9). Epoxide **8** (136 g, 0.8 mol), $NaIO_4$ (409 g, 1.9 mol), and $OsCl_3$ (1.2 g, 4 mmol) were stirred under argon in 1:1 THF/H_2O (1.8 L). The reaction temperature was increased to 35 °C in order to initiate the process, which then proceeded exothermally reaching a maximum of 44 °C after 1 h. The reaction was completed after 4 h in total. Extraction: AcOEt, H_2O, 10% $Na_2S_2O_5$, $NaHCO_3$, saturated NaCl. One obtained a brownish oil (114 g, 83% yield, GC purity 90%): ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.44 (d, 3H, $J = 2$ Hz), 1.62−2.25 (m, 4H), 2.15 (s, 3H), 2.70 (m, 1H), 2.27−2.38 (m, 1H), 3.18 (d, $J = 4.6$ Hz, 1H), 4.91 (dt, 1H, $J_{HF} = 48$ Hz, $J_2 = 2$ Hz); ^{13}C NMR δ 18.6, 24.9, 27.7, 27.9, 28.1, 40.0, 56.3, 56.6, 59.0, 89.1, 90.8, 209.2; EI/MS *m/z* (%) 139 (4), 131 (15), 112 (32), 97 (28), 43 (100). Anal. Calcd for $C_9H_{13}FO_2$ (172.201): C, 62.78; H, 7.61; F, 11.03. Found: C, 62.73; H, 7.54; F, 11.17. $[\alpha]^{20}_D = -101.4$ (*c* 1.0, $CHCl_3$).

Acetic Acid (1*S*,3*R*,5*S*,6*S*)-5-Fluoro-6-methyl-7-oxabicyclo-[4.1.0]hept-3-yl Ester (10). Methyl ketone **9** (114 g, 0.66 mol) was dissolved in CH_2Cl_2 (1.1 L) and stirred with m-CPBA (328 g, 1.33 mol, purity 70%) for 4 days at 20 °C yielding eventually a suspension. GC analysis: 74% product, 14% starting material. More m-CPBA (74 g, 0.3 mol) was added and stirring continued for 2 days at 20 °C. GC analysis: 82% product, 4% starting material. Extraction: CH_2Cl_2, cold 10% $Na_2S_2O_5$, Na_2CO_3, 50% saturated NaCl. One obtained a yellow oil (106 g, yield 94%, GC purity 95%): ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.43 (d, $J = 2$ Hz, 3H), 1.72−2.14 (m, 3H), 2.03 (s, 3H), 2.46−2.59 (m, 1H), 3.10 (d, $J = 15$ Hz,1H), 4.93 (dt, 1H, $J_{HF} = 48$ Hz, $J_2 = 2$ Hz), 4.90−5.10 (m, 1H); ^{13}C NMR δ 18.4, 21.1, 29.4, 31.0, 31.2, 56.3, 56.6, 58.4, 64.1, 89.8, 91.5, 170.3; EI/MS *m/z* (%) 145 (5), 128 (20), 82 (64), 43 (100). Anal. Calcd for $C_9H_{13}FO_3$ (188.201): C, 57.44; H, 6.96; F, 10.10. Found: C, 57.44; H, 0.90; F, 9.85. $[\alpha]^{20}_D = -85.4$ (*c* 1.0, $CHCl_3$).

(1*S*,3*R*,5*S*,6*S*)-5-Fluoro-6-methyl-7-oxabicyclo[4.1.0]-heptan-3-ol (11). Acetate **10** (204 g, 1.08 mol) and K_2CO_3 (182 g, 1.32 mol) were stirred in MeOH (1.1 L) at 20 °C for 2.5 h. Extraction: AcOEt, 1:1 saturated NaCl/ice, attention:

product is water-soluble). Chromatography of the crude product (151 g) in 2:1 hexane/AcOEt afforded a purified oil (129 g) which was suspended in hexane (500 mL), cooled, and seeded. One obtained white crystals (109 g, yield 79%, GC purity 99%), mp 53 °C: ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.43 (d, 3H, J = 2 Hz), 1.77 (d, J = 6.8 Hz, 1H), 1.86−2.10 (m, 3H), 2.26−2.40 (m, 1H), 2.27−2.38 (m, 1H), 3.14 (d, J = 5.2 Hz, 1H), 4.00 (sx, 1H), 4.91 (dt, 1H, J_{HF} = 48 Hz, J_2 = 4 Hz); ^{13}C NMR δ 18.4, 32.6, 34.9, 35.1, 57.1, 57.4, 59.4, 62.0, 89.5, 91.2; EI/MS *m*/*z* (%) 146 (5), 129 (5), 102 (30), 76 (56), 43 (100). Anal. Calcd for $C_7H_{11}FO_2$ (146.163): C, 57.52; H, 7.59; F, 13.00. Found: C, 57.40; H, 7.45; F, 12.82. $[\alpha]^{20}_D$ = −52.7 (*c* 1.0, $CHCl_3$).

(1*S*,3*R*,5*S*,6*S*)-*tert*-Butyl((5-fluoro-6-methyl-7-oxabicyclo-[4.1.0]hept-3-yl)oxy)dimethylsilane (12). Alcohol **11** (42 g, 0.287 mol) and imidazole (45 g, 0.66 mol) were dissolved under argon in DMF (60 mL) and treated in portions with (TBDMS)-Cl (46 g, 0.31 mol). The reaction mixture was stirred for 16 h at 20 °C. Extraction: Et_2O, cold 3 N HCl, 50% saturated NaCl. The crude oil (72 g, 91% yield, GC purity 94%) was used without further purification: ^{1}H NMR (250 MHz, $CDCl_3$) δ −0.01 (s, 6H), 0.82 (s, 9H), 1.34 (d, 3H, J = 2 Hz), 1.5−1.9 (m, 3H), 2.14−2.29 (m, 1H), 3.00 (d, J = 5.2, 1H), 3.90 (m, 1H), 4.83 (dt, 1H, J_{HF} = 48 Hz, J_2 = 4 Hz);^{13}C NMR δ −4.8, −4.7, 18.0, 18.5, 25.8, 33.6, 35.1, 35.3, 56.1, 56.4, 59.0, 61.8, 91.0, 92.6; EI/MS *m*/*z* (%) 203 (40), 183 (6), 161 (50), 129 (100). Anal. Calcd for $C_{13}H_{25}FO_2Si$ (260.427): C, 59.96; H, 9.68; F, 7.30. Found: C, 59.68; H, 9.67; F, 7.48. $[\alpha]^{20}_D$ = −49.2 (*c* 0.5, $CHCl_3$).

(1*S*,3*S*,5*R*)-5-((*tert*-Butyldimethylsilanyl)oxy)-3-fluoro-2-methylenecyclohexanol (13). Method A. *N*-Cyclohexylisopropylamine (134.5 mL, 0.8 mol) was dissolved in THF (1 L) under argon and cooled to −70 °C. Then a 1.6 M solution of *n*-BuLi in hexane (500 mL, 0.8 mol) was added dropwise and stirring continued for 15 min at −70 °C. Then a 2.8 M solution of ethylmagnesium chloride in THF (286 mL, 0.8 mol) was added dropwise and stirring continued for 15 min at −70 °C. Finally a solution of epoxide **12** (52 g, 0.2 mol) in THF (100 mL) was added at −70 °C, the temperature was allowed to rise to 20 °C, and stirring was continued for 5 h at 20 °C. The reaction mixture was poured on ice/3 N HCl and extracted twice with AcOEt. Chromatography of the crude oil (55 g) in 5:1 hexane/AcOEt gave a yellow oil (27.5 g, 53%).

Method B. This was analogous to method A, using 2,2,6,6-tetramethylpiperidine instead of *N*-cyclohexylisopropylamine, yield 72% and GC purity 95%. Compound **13** should be stored in the freezer because of limited stability: ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.115 (s, 3H), 0.120 (s, 3H), 0.90 (s, 9H), 1.78−2.22 (m, 4H), 3.27 (d, J = 8, 1H), 4.34 (br, 1H), 4.43 (br, 1H), 5.13 (s, 2H), 5.45 (dq, 1H, J_{HF} = 48 Hz, J_2 = 4 Hz); ^{13}C NMR δ −5.0, −4.7, 17.9, 25.7, 41.5, 41.6, 68.4, 71.7, 88.6, 90.3, 109.0, 147.9; EI/MS *m*/*z* (%) 243 (3), 203 (40), 185 (45) 183 (75), 165 (34), 111 (100). Anal. Calcd for $C_{13}H_{25}FO_2Si$ (260.427): C, 59.96; H, 9.68; F, 7.3. Found: C, 59.90; H, 9.69; F, 7.1. $[\alpha]^{20}_D$ = +48.6 (*c* 0.8, $CHCl_3$).

Phenylselanyl Acetic Acid.[23] Diphenyl diselenide (90 g, 0.288 mol) was dissolved in EtOH (900 mL) by heating at 50 °C and then cooled again to 25 °C. Sodium hydroxymethyl sulfoxylate (46.7 g, 0.3 mol) was added, and the resulting suspension was treated with a solution of NaOH (31 g, 0.78 mol) in H_2O (300 mL) over 20 min. The mixture was heated at 50 °C for 15 min, and then a solution of bromoacetic acid (80.5 g, 0.58 mol) in EtOH (300 mL) was added dropwise over 20 min and stirring at 50 °C was continued for 20 h. After cooling, a saturated solution of $NaHCO_3$ was added dropwise. The resulting mixture was poured on ice and extracted with toluene. The aqueous layer was washed with toluene, acidified to pH 2 with 25% HCl, and extracted twice with toluene. The toluene layers were washed with water and brine. One obtained a yellow oil (86 g, 69%), which crystallized upon refrigeration. Anal. Calcd for $C_8H_8O_2Se$ (215.112): C, 27.69; H, 2.03. Found: C, 27.42; H, 2.19.

Cesium Phenylselanyl Acetate.[24] Cesium carbonate (65 g, 0.2 mol) was suspended in MeOH (200 mL) and mixed with a solution of phenylselanyl acetic acid (86 g, 0.4 mol) in MeOH (200 mL) by addition over 30 min. Stirring at 20 °C was continued for 1 h. The reaction mixture was evaporated and the residue redissolved in MeOH (200 mL) and *i*-PrOH (1.6 L) at 60 °C. The hot solution was filtered and concentrated to ca. 500 mL. Crystallization was allowed to proceed first at 20 °C and then in ice. One obtained white, nonhygroscopic crystals in two fractions (111 g + 10 g, 87%), mp > 240 °C.

[(4*R*,6*S*)-Phenylselanyl]acetic Acid [4-((*tert*-Butyldimethylsilanyl)oxy)-6-fluorocyclohex-1-enyl]methyl Ester (15). Allylic alcohol **13** (47 g, 0.18 mol) was dissolved under argon in CH_2Cl_2 (470 mL) and cooled to −70 °C. Then *N*-ethyldiisopropylamine (39.4 mL, 0.23 mol) was added, and finally a solution of MsCl (17 mL, 0.22 mol) in CH_2Cl_2 (10 mL) was added slowly over 20 min at −70 °C. The mixture was allowed to warm, stirring at 20 °C was continued for 3 h, and then the mixture was poured on ice/water and extracted: Et_2O, 1 M citric acid, saturated NaCl. The resulting labile mesylate **14** was dissolved under argon in DMF (600 mL) and treated with cesium phenylselanyl acetate (76 g, 0.22 mol) and a catalytic amount of Bu_4NI (11 g, 30 mmol) at 50 °C for 15 h. The reaction mixture was poured on ice/water and extracted: Et_2O, H_2O, saturated NaCl. Chromatography of the crude oil (74 g) in 95:5 to 9:1 hexane/AcOEt gave a yellow oil (25.8 g, yield 32%, GC purity 95%): ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.07 (s, 3H), 0.08 (s, 3H), 0.89 (s, 9H), 1.45−2.45 (m, 4H), 3.53 (s, 2H), 4.02 (br, 1H), 4.60 (br, 2H), 4.93 (dt, 1H, J_{HF} = 48 Hz, J_2 = 4 Hz), 5.88 (br, 1H), 7.27 (m, 3H), 7.5 (m, 2H); ^{13}C NMR δ −4.74, −4.72, 18.1, 25.8, 27.4, 35.1, 38.3, 38.5, 63.8, 65.5, 85.7, 87.3, 127.9, 129.1, 129.2, 130.3, 130.5, 131.4, 131.5, 133.4, 133.5, 170.6; EI/MS *m*/*z* (%) 438.5 (3), 401 (20), 273 (100), 271 (50), 111 (95).

(1′*RS*,2*RS*,3′*S*,5′*R*)-[5′-((*tert*-Butyldimethylsilanyl)oxy)-3′-fluoro-2′-methylenecyclohexyl](phenylselanyl)-acetic Acid Methyl Ester (16a−d). Ester **15** (28 g, 61 mmol) was dissolved under argon in CH_2Cl_2 (280 mL), molecular sieves (0.4 nm) were added, and the mixture was cooled in ice. Finally, *N*-ethyldiisopropylamine (51 mL, 0.3 mol) and a solution of fresh TBDMSOTf (28 mL, 0.12 mol) in CH_2Cl_2 (20 mL) was added slowly over 20 min at 5 °C. The reaction mixture was stirred at 20 °C for 15 h. The resulting solution was poured on 1 M citric acid/ice and extracted: CH_2Cl_2, ice water. The resulting residue was dissolved in THF (600 mL), cooled to 10 °C, and treated with 1 N NaOH (160 mL) for 3 h at 20 °C. The resulting solution was poured on 1 M citric acid/ice and extracted: AcOEt, ice/water, saturated NaCl. The resulting residue was dissolved under argon in CH_2Cl_2 (300 mL), 4-DMAP (36.6 g, 0.3 mol), DCC (25.1 g, 0.12 mol), and MeOH (15 mL) were added, and stirring was continued for 15 h at 20 °C. The resulting solution was poured on 1 M citric acid/ice and extracted: CH_2Cl_2, ice water, saturated NaCl. Chromatography in 20:1 to 9:1 hexane/AcOEt gave a partially purified yellow oil (17.2 g, yield 44%, GC purity 70%): ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.09 (s, 3H), 0.11(s, 3H), 0.90 (s, 9H), 1.00−2.30 (m, 6H), 2.80−3.00 (m, 1H), 3.54 (s, 3H), 3.88 and 3.96 (d, J = 12, 1H), 4.21 (br, 1H), 4.7−5.3 (m, 3H), 5.88 (br, 1H), 7.28 (m, 3H), 7.58 (m, 2H); EI/MS *m*/*z* (%) 472 (3), 415 (95), 73 (100).

(*E*,3*S*,5*R*)-[5-((*tert*-Butyldimethylsilanyl)oxy)-3-fluoro-2-methylenecyclohexylidene]acetic Acid Methyl Ester (*E*-17) and (*Z*,3*S*,5*R*)-[5-((*tert*-Butyldimethylsilanyl)oxy)-3-fluoro-2-methylenecyclohexylidene]acetic Acid Methyl Ester (*Z*-17). Diastereomeric mixture **16a−d** (10 g, 21.2 mmol) was dissolved in THF (150 mL) and cooled in ice. Then a solution of $NaIO_4$ (13.5 g, 63.6 mmol) in 1:1 MeOH/H_2O (120 mL) was added dropwise keeping the temperature below 15 °C. Stirring at 20 °C was continued overnight. The reaction mixture was filtered and the filtrate diluted with water and then extracted: Et_2O, saturated NaCl. Chromatography of the crude product (6 g) in 8:1 hexane/ethyl acetate eluted first *E*-**17** (2.1 g, 44%) and then *Z*-**17** (2 g, 43%), both as colorless oils. The former was apparently less stable on the shelf. *E*-**17**: ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.08 (s, 3H), 0.81 (s, 3H), 0.88 (s, 9H), 1.60−2.30 (m, 3H), 2.98 (dd, J_1 = 8 Hz, J_2 = 14 Hz, 1H),

3.14 (dd, $J_1 = 4$ Hz, $J_2 = 14$ Hz, 1H), 3.71 (s, 3H), 4.24 (sept, 1H), 5.19 (s, 1H), 5.24 (dt, $J_{HF} = 48$ Hz, $J_2 = 6$ Hz, 1H), 5.99 (m, 1H); ^{13}C NMR δ −4.66, −4.55, 18.4, 26.2, 37.8, 40.8, 41.0, 51.5, 66.8, 90.4, 92.1, 114.0, 117.5, 147.0, 147.2, 155.0, 167.0; EI/MS *m*/*z* (%) 299 (2), 283 (3), 257 (100), 151 (30), 89 (45); $[\alpha]^{20}_D = +15.3$ (*c* 0.4, $CHCl_3$). *Z*-**17**: ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.08 (s, 3H), 0.81 (s, 3H), 0.88 (s, 9H), 1.84−2.24 (m, 3H), 2.30 (dd, $J_1 = 8$ Hz, $J_2 = 12$ Hz, 1H), 2.51 (dd, $J_1 = 4$ Hz, $J_2 = 12$ Hz, 1H), 3.68 (s, 3H), 4.22 (sept, 1H), 5.22 (dm, $J_1 = 48$ Hz, 1H), 5.27 (s, 1H), 5.37 (m, 1H); ^{13}C NMR δ −4.84, −4.80, 18.0, 25.7, 41.4, 41.6, 46.1, 51.2, 67.0, 90.8, 92.5, 115.5, 118.6, 142.0, 142.2, 150.9, 166.1; EI/MS *m*/*z* (%) 314 (M^+, 3), 299 (2), 257 (100), 151 (65), 89(88). Anal. Calcd for $C_{16}H_{27}FO_3Si$ (314.47): C, 61.11; H, 8.65; F, 6.04. Found: C, 61.00; H, 8.78; F, 6.03. $[\alpha]^{20}_D = +15.4$ (*c* 0.4, $CHCl_3$).

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