JOC*Note*

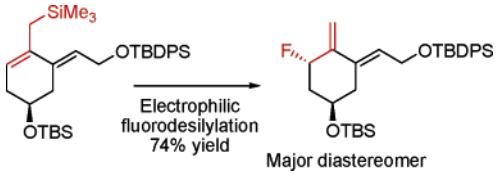
Enantioselective Synthesis of a Key "A-Ring" Intermediate for the Preparation of 1α-Fluoro Vitamin D_3 Analogues

Guy Giuffredi, Carla Bobbio, and Véronique Gouverneur*

University of Oxford, Chemistry Research Laboratory, 12 Mansfield Road, Oxford OX1 3TA, U.K.

veronique.gouverneur@chemistry.oxford.ac.uk

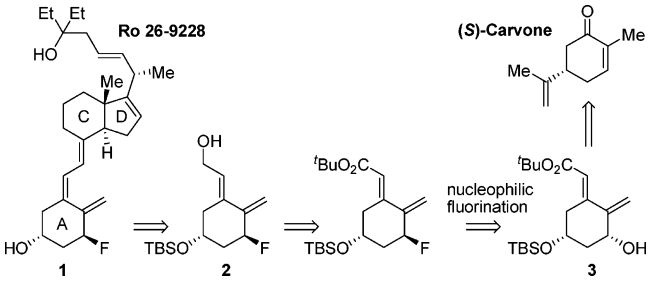
Received March 9, 2006



1α-Fluoro A-ring dienol **2**, a useful building block for the preparation of fluorinated vitamin D_3 analogues, was synthesized in eight steps from 4-{[*tert*-butyldimethylsilyl]oxy}-cyclohexanone. The most distinctive synthetic development to emerge from this new synthesis is an unprecedented substrate-controlled diastereoselective fluorodesilylation of an advanced dienylsilane intermediate. This is the first enantioselective route to compound **2** relying on the use of an electrophilic fluorinating reagent.

Fluorinated analogues of vitamin D have been used extensively as molecular probes to determine the structure−function relationship of vitamin D metabolites and their target molecules.[1−5] Early work on the synthesis and biological activity of 1α-fluoro-25-hydroxy vitamin D_3 revealed that the addition of this compound to human leukemia cells resulted in strong phagocytic activity.[6,7] Since then, Hoffmann-La Roche has invested a great deal of effort on the synthesis, chemical reactivity, and biological activity of numerous 1α-fluoro-25-hydroxy vitamin D_3 analogues, including compound **1**, known as Ro 26-9228 (Scheme 1).[8−12] This molecule is of particular interest as it was reported to restore bone mineral density without inducing hypercalcemia in osteopenic rats.[4] An essential component of this research program was the availability of robust synthetic routes to the 1α-fluorosubstituted A-ring fragment

SCHEME 1. Structure of Ro 26-9228 and Known Retrosynthesis from (*S*)-Carvone



featuring a functional group that will allow easy coupling with the C−D ring system.[12] In this context, the fluorinated dienol **2** emerged as a key intermediate for interactive chemical and biological investigations.[9] From a strictly chemical perspective, this compound presents unusual synthetic challenges with the construction of a fluorinated carbocycle featuring two adjacent exocyclic double bonds and two stereogenic centers, one of them being a fluorinated allylic carbon. Not surprisingly, compound **2** has stimulated the search of several inventive synthetic routes, which are based on the use of (*S*)-carvone, an optically active starting material provided by nature in abundance. Most of the syntheses reported to date relied on the nucleophilic fluorinating reagent DAST (dimethylaminosulfur trifluoride)[6,9,11,12] or structurally related sulfur trifluorides for the introduction of the fluorine atom. The nucleophilic substitution on the precursor dienol **3** proved to be particularly tricky, as it must be carried out at low temperature and consistently gave a mixture of S_N2 and S_N2' products that must be separated prior to further functional manipulations. Alternative methods of fluorination were also studied and include the nucleophilic displacement of the corresponding mesylate with fluoride as well as substitutions with perfluoro-1-butanesulfonyl fluoride/DBU or *N*,*N*-diisopropyl-1-fluoro-2-methylpropenamine. None of these methods proved fruitful (Scheme 1).[9] A different route featured a successful ring opening of an epoxide with $Bu_4NH_2F_3$, but the introduction of fluorine at an early stage of the synthesis caused difficulties in the subsequent transformations.[10]

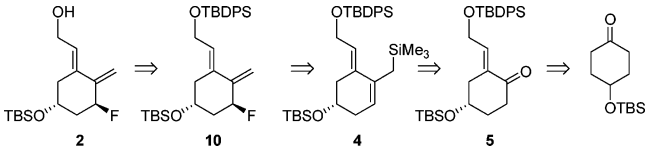
In this note, we present a new enantioselective synthesis of **2** that differs significantly from all the syntheses reported to date. We decided to commit ourselves to the pursuit of a conceptually novel strategy that did not use (*S*)-carvone as the starting material (Scheme 2). We elected an electrophilic fluorodesilylation reaction for the introduction of the fluorine atom in order to avoid the inherent difficulties associated with DAST chemistry. On the basis of relevant precedents from our laboratory,[13−15] it was anticipated that the allylic fluoride could be constructed at a late stage of the synthesis from the corresponding allylsilane upon treatment with an electrophilic

* Corresponding author. Fax and Tel: + 44 (0) 1865 275644.

(1) Nagpal, S.; Na, S.; Rathnachalam, R. *Endocr. Rev.* **2005**, *26*, 662.
(2) Crescioli, C.; Ferruzzi, P.; Caporali, A.; Scaltriti, M.; Bettuzzi, S.; Mancina, R.; Gelmini, S.; Serio, M.; Villari, D.; Vannelli, G. B.; Colli, E.; Adorini, L.; Maggi, M. *Eur. J. Endocrinol.* **2004**, *150*, 591.
(3) Ismail, A.; Nguyen, C. V.; Ahene, A.; Fleet, J. C.; Uskoković, M. R.; Peleg, S. *Mol. Endocrinol.* **2004**, *18*, 874.
(4) Peleg, S.; Ismail, A.; Uskokoviæ, M. R.; Avnur, Z. *J. Cell. Biochem.* **2003**, *88*, 267.
(5) Posner, G. H.; Kahraman, M. *Eur. J. Org. Chem.* **2003**, 3889.
(6) Ohshima, E.; Takatsuto, S.; Ikekawa, N.; DeLuca, H. F. *Chem. Pharm. Bull.* **1984**, *32*, 3518.
(7) Ohshima, E.; Sai, H.; Takatsuto, S.; Ikekawa, N.; Kobayashi, Y.; Tanaka, Y.; DeLuca, H. F. *Chem. Pharm. Bull.* **1984**, *32*, 3525.
(8) Daniewski, A. R.; Garofalo, L. M.; Kabat, M. M. *Synth. Commun.* **2002**, *32*, 3031.
(9) Kabat, M. M.; Garofalo, L. M.; Daniewski, A. R.; Hutchings, S. D.; Liu, W.; Okabe, M.; Radinov, R.; Zhou, Y. *J. Org. Chem.* **2001**, *66*, 6141.
(10) Barbier, P.; Mohr, P.; Muller, M.; Masciadri, R. *J. Org. Chem.* **1998**, *63*, 6984.
(11) Kiegiel, J.; Wovkulich, P. M.; Uskoković, M. R. *Tetrahedron Lett.* **1991**, *32*, 6057.
(12) Shiuey, S.-J.; Kulesha, I.; Baggiolini, E. G.; Uskoković, M. R. *J. Org. Chem.* **1990**, *55*, 243.

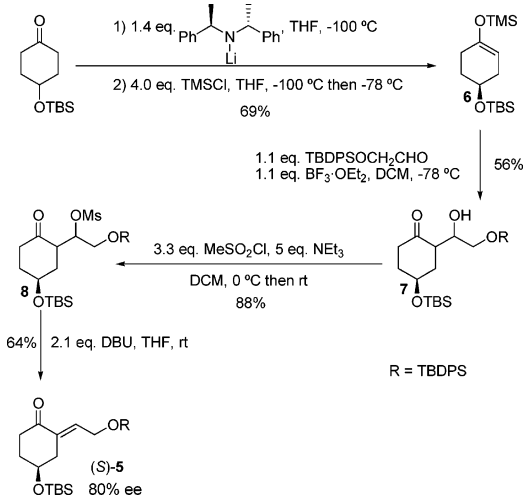
10.1021/jo060516m CCC: $33.50
Published on Web 06/16/2006

SCHEME 2. Retrosynthetic Analysis of 2 Featuring the Key Electrophilic Fluorodesilylation Step



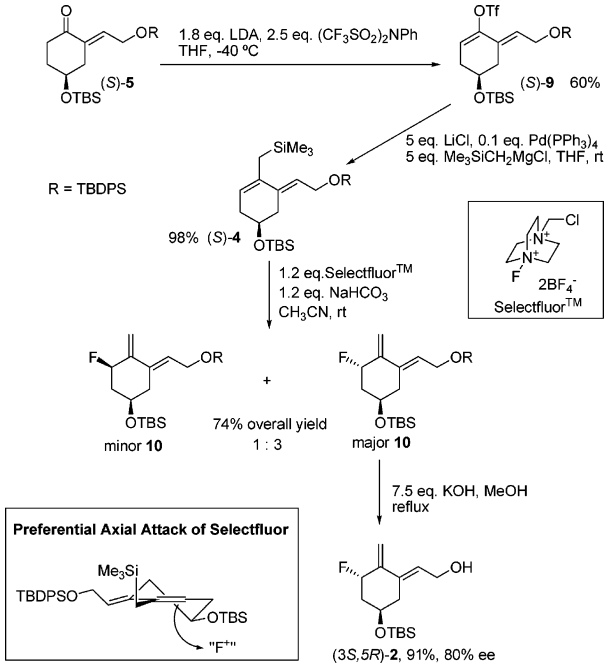
source of fluorine. This retrosynthetic analysis revealed the silylated diene **4**, which could be formed upon C−C coupling of the triflate derived from ketone **5** with trimethylsilylmethylmagnesium chloride. It remained to conceive an enantioselective synthesis of the α,*β*-unsaturated ketone **5** from a readily available starting material. We opted for a well-precedented desymmetrization reaction of 4-{[*tert*-butyldimethylsilyl]oxy}-cyclohexanone with a chiral base to form an intermediate silyl enol ether,[16−20] followed by a sequential aldolization−crotonization. For differential deprotection at the end of the synthesis, the *tert*-butyldimethylsilyl- and the *tert*-butyldiphenylsilyl groups were chosen to protect the secondary and the primary alcohol, respectively.[9,21]

SCHEME 3. Enantioselective Synthesis of the α,*β*-Unsaturated Ketone 5



The overall synthesis of the chiral ketone **5** is illustrated in Scheme 3. The requisite chiral trimethylsilyl enol ether (*S*)-**6** was prepared as reported in the literature.[17] Asymmetric deprotonation of 4-{[*tert*-butyldimethylsilyl]oxy}cyclohexanone using the lithium amide derived from (+)-bis(α-methylbenzyl)-amine and silylation of the resulting lithium enolate afforded the silyl enol ether (*S*)-**6** in 69% yield. A subsequent classic

SCHEME 4. Final Stages of the Synthesis of 2



Mukaiyama aldol reaction of **6** with {[*tert*-butyldiphenylsilyl]-oxy}acetaldehyde[23] employing a stoichiometric amount of $BF_3 \cdot Et_2O$ afforded the aldol product **7** as a mixture of diastereomers.[24] The selectivity of this transformation was not critical, as the two newly generated stereogenic centers are destroyed during the course of the next steps through dehydration. This elimination was best performed at room temperature by treatment of the mixture of the corresponding mesylated aldol products **8** with DBU in THF.[25] This sequence of steps afforded the desired ketone (*S*)-**5** as the single geometrical *E*-isomer in 80% enantiomeric excess (ee).[26]

From intermediate **5**, the completion of the synthesis required four additional steps: the formation of the triflate, the C−C coupling to generate the dienylsilane **4**, the electrophilic fluorodesilylation, and the final monodeprotection step (Scheme 4). Regioselective proton abstraction of (*S*)-**5** was performed with LDA at −40 °C in THF, and treatment of the resulting enolate with *N*-phenyltrifluoromethanesulfonimide gave the vinyl triflate (*S*)-**9** in 60% yield. The preparation of the dienylsilane (*S*)-**4** was remarkably efficient upon treatment of triflate (*S*)-**9** with an excess of LiCl and trimethylsilylmethylmagnesium chloride in the presence of a catalytic amount of $Pd(PPh_3)_4$.[14,27] This reaction resulted in the formation of the dienylsilane (*S*)-**4** in 98% isolated yield. We were now in a position to study the feasibility of the key fluorination process. The introduction of the secondary fluorine atom, and thus the second stereocenter, was performed by treating the dienylsilane (*S*)-**4** with 1.2 equiv of Selectfluor [1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate)][27] and 1.2

(13) Tredwell, M.; Tenza, K.; Pacheco, M. C.; Gouverneur, V. *Org. Lett.* **2005**, 4891.
(14) Greedy, B.; Paris, J.-M.; Vidal, T.; Gouverneur, V. *Angew. Chem., Int. Ed.* **2003**, *7*, 3291.
(15) Thibaudeau, S.; Gouverneur, V. *Org. Lett.* **2003**, *5*, 4891.
(16) Rodeschini, V.; Van de Weghe, P.; Salomon, E.; Tarnus, C.; Eustache, J. *J. Org. Chem.* **2005**, *70*, 2409.
(17) Poupon, J.-C.; Demont, E.; Prunet, J.; Férézou, J.-P. *J. Org. Chem.* **2003**, *68*, 4700.
(18) Aggarwal, V. K.; Olofsson, B. *Angew. Chem., Int. Ed.* **2005**, *44*, 5516.
(19) Parker, K. A.; Dermatakis, A. *J. Org. Chem.* **1997**, *62*, 6692.
(20) Majewski, M.; Irvine, N. M.; MacKinnon, J. *Tetrahedron: Asymmetry* **1995**, *6*, 1837.
(21) Kabat, M. M.; Lange, M.; Wovkulich, P. M.; Uskoković, M. R. *Tetrahedron Lett.* **1992**, *33*, 7701.
(22) Nelson, T. D.; Crouch, R. D. *Synthesis* **1996**, 1031.
(23) Marshall, J. A.; Garofalo, A. W. *J. Org. Chem.* **1996**, *61*, 8732.
(24) The diastereomeric ratio of the crude product could not be determined. One diastereomer could be isolated and was assigned as (*S,S,R*)-**7** by NOESY analysis.
(25) Clive, D. L. J.; Huang, X. *Tetrahedron* **2001**, *57*, 3845.
(26) For determination of ee and NMR assignments, see the Experimental Section and Supporting Information.
(27) Kamikawa, T.; Hayashi, T. *J. Org. Chem.* **1998**, *63*, 8922.

equiv of $NaHCO_3$ in acetonitrile. The fluorodesilylation proceeded smoothly with full transposition of the double bond, as expected for an S_E2' process.[13−15,29] The reaction was completed within 1.5 h at room temperature to afford the doubly protected fluorinated dienes **10** with an overall yield of 74%. The crude mixture revealed that two diastereomers were formed in a 3:1 ratio, and these were separated by preparative thin-layer chromatography. The major isomer was fully characterized by NMR studies[26] and was unambiguously identified as the desired anti product, (3*R*,5*S*)-**10**, resulting from a preferential axial attack of Selectfluor on the endocyclic double bond (Scheme 4). The completion of the synthesis required a final deprotection step to release the primary alcohol. This deprotection took place in the presence of an excess of KOH in methanol under reflux. Under these conditions, the target compound (3*R*,5*S*)-**2** was remarkably stable and was isolated after purification in 91% yield and with 80% enantiomeric excess. This ee was measured unambiguously by chiral HPLC by comparison with HPLC data of the structurally identical racemic compound (±)-**2**, which was prepared independently using the exact synthetic sequence starting with the racemic silyl enol ether (±)-**6**.[26]

In summary, we have developed a conceptually novel process for the preparation of 1α-fluoro A-ring dienol **2**, which is a known key intermediate for the synthesis of numerous vitamin D analogues bearing the same A-ring fragment.[9,30] This first enantioselective route comprises three crucial steps: an enantioselective desymmetrization for the creation of the first stereogenic center, a Pd-mediated C−C coupling for the preparation of the dienylsilane, and a most synthetically useful electrophilic fluorodesilylation for the substrate-controlled diastereoselective introduction of the fluorine atom. With the preparation of compound **2**, this recently developed fluorination process bodes well for future applications of this reaction to the total synthesis of other biologically active fluorinated targets.

Experimental Section

***tert*-Butyl [((2*E*)-2-{(5S)-5-{[*tert*-butyldimethylsilyl]oxy}-2-[(trimethylsilyl)methyl]cyclohex-2-en-1-ylidene}ethyl)oxy]diphenylsilane (4).** Tetrakis(triphenyphosphine)palladium(0) (0.12 g, 0.10 mmol, 0.10 equiv) was added to a suspension of vinyl triflate **9** (0.65 g, 1.0 mmol, 1.0 equiv) and lithium chloride (0.22 g, 5.0 mmol, 5.0 equiv) in THF (4.0 mL). After 30 min, a solution of trimethylsilylmethylmagnesium chloride, prepared from chlorotrimethylsilylmethane (0.70 mL, 5.0 mmol, 5.0 equiv) and magnesium (0.18 g, 7.5 mmol, 7.5 equiv) in THF (5.0 mL) was added dropwise over 10 min. After being stirred for 2 h, the reaction mixture was quenched with a saturated aqueous solution of sodium bicarbonate (7.0 mL), and the phases were separated. The aqueous phase was extracted with diethyl ether (3 × 5.0 mL) and the combined organic layers were washed with water (15 mL) and brine (15 mL), dried over magnesium sulfate, and filtered, and the solvents were removed in vacuo. By column chromatography on silica gel (hexane/ethyl acetate, 33:1) pure allylsilane **4** was obtained (0.58 g, 98%). R_f = 0.29. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.02 (brs, 12H), 0.04 (s, 3H), 0.88 (s, 9H), 1.08 (s, 9H), 1.60 (d, J = 14.0 Hz, 1H), 1.71 (d, J = 14.0 Hz, 1H), 2.00 (t, J = 12.6 Hz, 1H), 2.12 (dd, J = 16.9, 8.9 Hz, 1H), 2.33 (dt, J = 17.0, 5.4 Hz, 1H), 2.49 (dd, J = 14.3, 3.8 Hz, 1H), 3.75−3.84 (m, 1H), 4.33 (dd, J = 13.3, 5.8 Hz, 1H), 4.41 (dd, J = 13.3, 6.5 Hz, 1H), 5.35 (dd, J = 5.5, 2.6 Hz, 1H), 5.59 (t, J = 5.6 Hz, 1H), 7.37−7.47 (m, 6H), 7.71−7.75 (m, 4H). ^{13}C NMR ($CDCl_3$, 101 MHz): δ −4.6, −4.6, −0.9, 18.1, 19.2, 22.1, 25.9, 26.8, 35.9, 36.1, 61.0, 68.1, 122.2, 124.8, 127.7, 127.7, 129.6, 129.6, 133.9, 134.9, 135.3, 135.6. IR (neat): 3072, 2955, 2857, 1642, 1472, 1375 cm^{-1}. HRMS: calculated for $C_{34}H_{54}NaO_2Si_3$ *m*/*z* 601.3324, found *m*/*z* 601.3322. $[\alpha]^{23}_D$ = −17.5 (*c* 1, $CHCl_3$).

***tert*-Butyl{[(2*E*)-2-((3*S*,5*R*)-5-{[*tert*-butyldimethylsilyl]oxy}-3-fluoro-2-methylenecyclohexylidene)ethyl]oxy}diphenylsilane (10).** Sodium bicarbonate (82 mg, 1.0 mmol, 1.2 equiv) and Selectfluor (0.35 g, 1.0 mmol, 1.2 equiv) were consecutively added to a solution of allylsilane **4** (0.47 g, 0.80 mmol, 1.0 equiv) in acetonitrile (8.0 mL). The mixture was stirred for 1.5 h at room temperature, before being quenched with water (8.0 mL). After extracting the aqueous phase with diethyl ether (3 × 8.0 mL), the combined organic layers were washed with brine (20 mL), dried over magnesium sulfate, and filtered, and the solvents were removed in vacuo. ^{1}H NMR analysis of the crude mixture indicated the formation of two diastereomers in a 3:1 ratio. Purification by preparative TLC (3 × hexane/diethyl ether, 45:1) afforded minor-**10** (71.7 mg, 17%) and major-**10** (201 mg, 47%) as colorless oils. R_f^{minor} = 0.30, R_f^{major} = 0.23. The configuration of the major diastereomer was identified by NOESY as (3*S*,5*R*)-**10**.

(3*S*,5*R*)-10. ^{1}H NMR ($CDCl_3$, 500 MHz): δ −0.02 (s, 3H), −0.01 (s, 3H), 0.84 (s, 9H), 1.06 (s, 9H), 1.87 (dddd, J = 31.0, 13.4, 8.6, 3.4 Hz, 1H), 1.97 (dd, J = 13.9, 8.4 Hz, 1H), 2.10−2.17 (m, 1H), 2.36 (dd, J = 13.9, 4.0 Hz, 1H), 4.05 (ddd, J = 12.0, 7.9, 3.5 Hz, 1H), 4.24−4.33 (m, 2H), 5.02 (s, 1H), 5.15 (d, J = 1.2 Hz, 1H), 5.15 (ddd, J = 50.3, 6.0, 3.3 Hz, 1H), 5.84 (t, J = 6.1 Hz, 1H), 7.36−7.45 (m, 6H), 7.68−7.72 (m, 4H). ^{13}C NMR ($CDCl_3$, 126 MHz): δ −4.9, −4.9, 18.0, 19.2, 25.7, 26.8, 37.2, 40.7 (d, J = 20.6 Hz), 60.7, 66.0 (d, J = 5.4 Hz), 91.7 (d, J = 169.3 Hz), 112.3 (d, J = 10.0 Hz), 127.6, 127.6, 127.8, 129.6, 133.7, 133.8, 135.1 (d, J = 2.1 Hz), 135.6, 135.6, 146.7 (d, J = 16.5 Hz). ^{19}F NMR ($CDCl_3$, 375 MHz): δ −171.7 (ddd, J = 50.2, 31.0, 9.9 Hz). IR (neat): 3072, 2955, 2857, 1651, 1472, 1023 cm^{-1}. HRMS: calculated for $C_{31}H_{45}FNaO_2Si_2$ *m*/*z* 547.2834, found *m*/*z* 547.2836. $[\alpha]^{23}_D$ = −13.9 (*c* 1, $CHCl_3$).

(3*R*,5*R*)-10. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.01 (s, 3H), 0.04 (s, 3H), 0.87 (s, 9H), 1.07 (s, 9H), 1.70 (quint, J = 11.2 Hz, 1H), 1.74−1.83 (m, 1H), 2.35−2.44 (m, 1H), 2.51 (dm, J = 13.7 Hz, 1H), 3.56−3.65 (m, 1H), 4.24 (ddd, J = 13.5, 5.5, 1.5 Hz, 1H), 4.32 (ddd, J = 13.4, 7.0, 0.9 Hz, 1H), 4.88 (dddt, J = 50.0, 11.3, 5.4, 2.1 Hz, 1H), 5.04 (brs, 1H), 5.07 (m, 1H), 5.82−5.87 (m, 1H), 7.38−7.48 (m, 6H), 7.68−7.73 (m, 4H). ^{13}C NMR ($CDCl_3$, 101 MHz): δ −4.8, −4.7, 18.0, 19.2, 25.8, 26.8, 37.7, 42.2 (d, J = 17.1 Hz), 60.8, 66.7 (d, J = 13.5 Hz), 88.0 (d, J = 182.9 Hz), 107.3 (d, J = 10.2 Hz), 127.7, 127.7, 128.0 (d, J = 2.7 Hz), 129.7, 129.7, 133.6, 133.7, 134.2 (d, J = 5.0 Hz), 135.6, 135.6, 147.5 (d, J = 15.5 Hz). ^{19}F NMR ($CDCl_3$, 375 MHz): δ −180.1 (dm, J = 50.0). IR (neat): 3072, 2957, 2858, 1651, 1472, 1042 cm^{-1}. HRMS: calculated for $C_{31}H_{45}FNaO_2Si_2$ *m*/*z* 547.2834, found *m*/*z* 547.2829. $[\alpha]^{23}_D$ = −34.3 (*c* 1, $CHCl_3$).

(2*E*)-2-((3*S*,5*R*)-5-{[*tert*-butyldimethylsilyl]oxy}-3-fluoro-2-methylenecyclohexylidene)ethanol (2).[22] Potassium hydroxide (68 mg, 1.2 mmol, 7.5 equiv) and (3*S*,5*R*)-**10** (86 mg, 0.16 mmol, 1.0 equiv) in methanol (8.0 mL) were stirred at 70 °C for 19 h. At room temperature, an aqueous saturated solution of ammonium chloride (3.0 mL) and diethyl ether (20 mL) was added, and the phases were separated. The aqueous phase was washed with diethyl ether (3 × 10 mL), and the combined organic layers were washed with a saturated aqueous solution of ammonium chloride (30 mL) and brine (30 mL). After drying over magnesium sulfate, filtration, and removal of the solvents in vacuo, the crude mixture was purified by column chromatography on silica gel (hexane/ethyl acetate, 3:1). The pure alcohol **2** was obtained as colorless oil in 91% yield (43 mg) and 80% ee. The ee was determined by HPLC analysis (CHIRACEL OD, hexane/ethanol 99:1, flow rate = 0.7 mL/min^{-1}, t_R^{major} = 15.4, t_R^{minor} = 17.1). R_f = 0.32. ^{1}H NMR ($CDCl_3$, 400

(28) Nyffeler, P. T.; Durón, S. G.; Burkart, M. D.; Vincent, S. P.; Wong, C.-H. *Angew. Chem., Int. Ed.* **2005**, *44*, 192.
(29) Tredwell, M.; Gouverneur, V. *Org. Biomol. Chem.* **2006**, *4*, 26.
(30) Zhu, G.-D.; Okamura, W. H. *Chem. Rev.* **1995**, *95*, 1877.

MHz): δ 0.09 (s, 6H), 0.89 (s, 9H), 1.96 (dddd, J = 27.7, 13.3, 8.0, 3.7 Hz, 1H), 2.08−2.18 (m, 1H), 2.24 (dd, J = 13.9, 7.7, 1H), 2.54 (dd, J = 13.9, 3.8 Hz, 1H), 4.14−4.21 (m, 1H), 4.21 (s, 1H), 4.23 (s, 1H), 5.06 (brs, 1H), 5.18 (ddd, J = 50.2, 6.7, 3.7 Hz, 1H), 5.19 (s, 1H), 5.87 (t, J = 6.8, 1H). ^{13}C NMR ($CDCl_3$, 101 MHz): δ −4.8, −4.8, 18.0, 25.8, 37.0, 40.8 (d, J = 20.2 Hz), 58.9, 66.2 (d, J = 6.3 Hz), 91.4 (d, J = 170.7 Hz), 112.0 (d, J = 10.1 Hz), 126.9, 137.6 (d, J = 2.4 Hz), 146.9 (d, J = 16.3 Hz). ^{19}F NMR ($CDCl_3$, 375 MHz): δ −173.8 (ddd, J = 50.1, 27.7, 9.9 Hz). IR (neat): 3356, 2955, 2858, 1651, 1023 cm^{-1}. $[\alpha]^{23}_D$ = −19.6 (*c* 1, $CHCl_3$).

Acknowledgment. We sincerely thank the Royal Society of Chemistry (2005/R1), the Swiss National Science Foundation (Fellowship for Perspective Researchers FBEL$_2$-106159, to C.B.), and the EPSRC (GR/S79268/01, to C.B.) for generous financial support. We also thank Prof. Jacques Eustache (Ecole Nationale Supérieure de Chimie de Mulhouse, France), Dr. Jean-Christophe Poupon (Université de Montreal, Canada), and Dr. Joëlle Prunet (Ecole Polytechnique de Palaiseau, France) for helpful advice on the preparation of the enantiopure silyl enol ether **6**.

Supporting Information Available: Detailed description of experimental procedures and NMR spectra of compounds **2**−**10**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO060516M