Asymmetric Synthesis and Structural Analysis of 5-*O*-Benzoyl-2,3-dideoxy-3-fluoro-α,β-D-ribofuranose and -xylofuranose from Homochiral 1-Fluoro-3-sulfinylacetone

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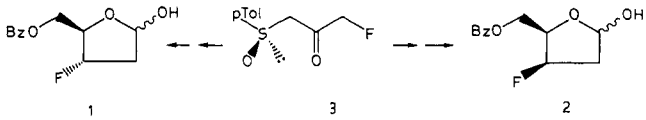
The use of (*R*)-1-fluoro-3-[(4-methylphenyl)sulfinyl]acetone (**3**) as a chiral fluorinated synthon in the preparation of fluorodideoxyfuranoses is reported. The dilithium derivative of the homochiral **3**, alkylated with allyl bromide and reduced with diisobutylaluminum hydride, gave the (2*S*,3*S*,R_S)-3-fluoro-1-sulfinyl-5-hexen-2-ol **5** and its 2*S*,3R,R_S epimer. Diastereoisomerically pure (2*S*,3*S*,R_S)-**5**, obtained by flash chromatography, afforded 5-*O*-benzoyl-2,3-dideoxy-3-fluoro-α,β-D-ribofuranose (**1**) by removal of the auxiliary sulfinyl group through a Pummerer rearrangement followed by a reductive workup and by oxidative cleavage (osmium tetroxide/sodium metaperiodate) of the carbon–carbon double bond. Starting from (2*S*,3*R*,R_S)-**5** the same reaction sequence afforded 5-*O*-benzoyl-2,3-dideoxy-3-fluoro-α,β-D-xylofuranose (**2**). A detailed ^{1}H NMR analysis of the two fluoro sugars **1** and **2** allowed assignment of the configuration and the preferred conformation in solution.

The increasing need for optically pure regio- and stereoselectively fluorinated compounds in both academic and industrial laboratories has made their synthesis an important focus of current research.[1]

At the present, fluorocarbohydrates and their derivatives having a single fluorine atom that replaces a specific hydroxyl group are one of the most extensively studied classes of fluorinated compounds[2] as a consequence of their interesting biological and pharmacological properties.[3]

The most commonly used approach to the synthesis of fluorocarbohydrates and their derivatives resorts to the fluorination of the preformed sugar molecule in an advanced stage of the synthetic sequence toward the target structure.[2]

We are studying a different approach to the synthesis of fluoro sugars and fluoro nucleosides in which the chiral carbohydrate moiety is built up around a chiral fluorinated C_3 synthon.[4] In this paper we describe how starting from (*R*)-1-fluoro-3-[(4-methylphenyl)sulfinyl]propan-2-one (**3**),



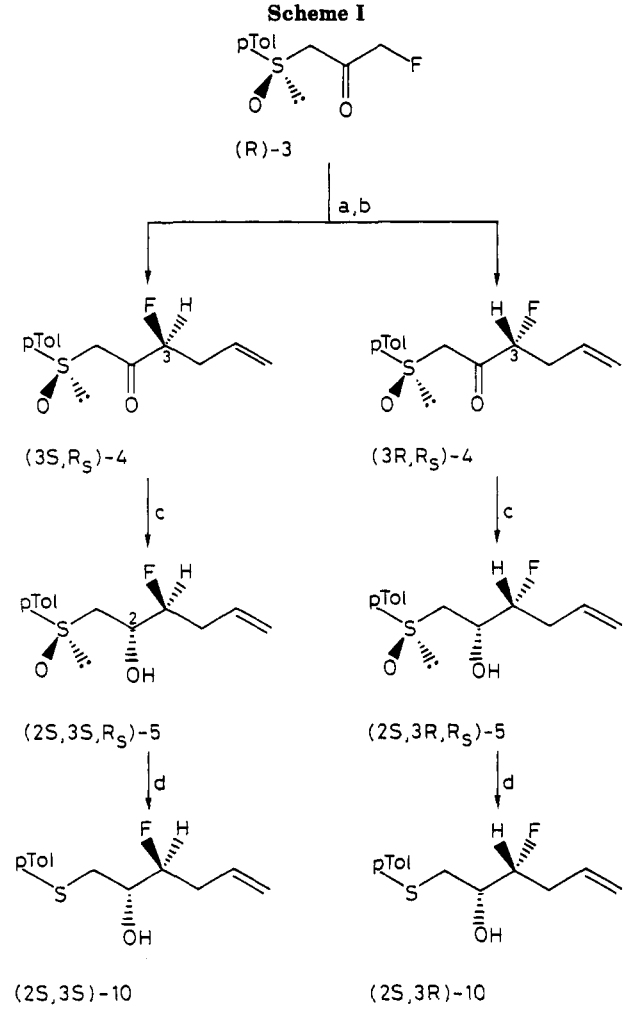
1 3 2

it has been possible to realize an asymmetric synthesis of 5-*O*-benzoyl-2,3-dideoxy-3-fluoro-α,β-D-ribofuranose (**1**) and of 5-*O*-benzoyl-2,3-dideoxy-3-fluoro-α,β-D-xylofuranose (**2**). Both these fluoro sugars are the carbohydrate constituents of anti-HIV nucleosides that have been synthesized following the classical semisynthetic approach. A detailed conformational study of these fluoro sugars **1** and **2** has also been conducted.

Results and Discussion

Synthesis of Fluoro Sugars 1 and 2. The 1,3-dilithium derivative[5] of the (*R*)-3-fluoro-1-sulfinyl-2-propanone **3** (obtained in quantitative yields through condensation of (+)-(*R*)-methyl 4-methylphenyl sulfoxide on ethyl fluoroacetate) was formed with lithium diisopropyl amide (LDA) and monoalkylated on the fluorinated carbon with allyl bromide (Scheme I). (3*S*)-3-Fluoro-1(*R*)-[(4-methylphenyl)sulfinyl]-5-hexen-2-one (**4**) and the 3*R*,R_S diastereoisomer of **4** were produced (65% yield, 6:4 mixture), and single epimers were isolated in pure form through flash chromatography. Diisobutylaluminum hy-

Scheme I



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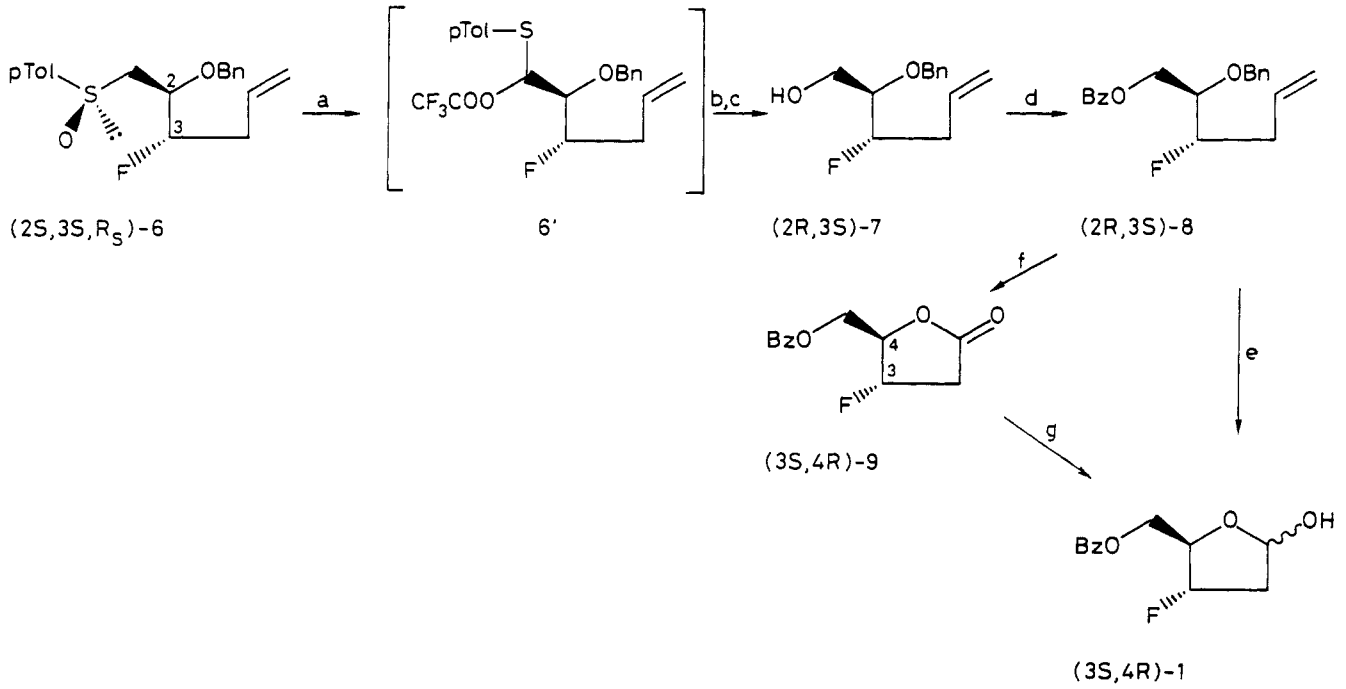
Scheme II



(2S,3S,R_S)-6 6' (2R,3S)-7 (2R,3S)-8 (3S,4R)-9 (3S,4R)-1

dride (DIBAH) reduction of the carbonyl group of both diastereoisomeric ketones (3*S*,R_S)-4 and (3*R*,R_S)-4 occurred with high asymmetric induction under the control of the chirality of the sulfinyl auxiliary group as expected.[6] In fact, independent of the configuration at the fluorinated

Table I. ^{1}H and ^{19}F NMR Data of the 5-*O*-Benzoyl-2,3-dideoxy-3-fluoro-D-ribo- and -D-xylofuranoses 1 and 2[a]

	1α	1β[b]	2α	2β
H-1	5.67	5.26	5.83	5.59
H-2	2.30	1.87	2.53	2.43
H-2′	2.36	2.00	2.26	2.27
H-3	5.24	4.82	5.33	5.33
H-4	4.79	4.36	*c*	4.37
H-5	4.38	4.25	*c*	4.70
H-5′	4.41	4.11	*c*	4.63
F-3	−173.6	−179.3	−193.9	−192.4
J(1,2)	5.2	3.5	5.7	<0.3
J(1,2′)	<0.3	5.5	3.3	5.0
J(2,2′)	15.0	14.7	15.2	14.2
J(2,3)	5.5	6.0	1.0	<0.3
J(2′,3)	<0.9	2.5	5.5	4.1
J(3,4)	1.2	2.0	*c*	3.5
J(4,5)	5.0	5.5	*c*	5.4
J(4,5′)	4.5	6.5	*c*	7.0
J(5,5′)	11.6	11.6	*c*	11.5
J(2,F)	39.0	28.0	29.0	21.0
J(2′,F)	23.0	27.5	31.8	42.6
J(3,F)	55.0	55.0	54.0	54.0
J(4,F)	25.1	23.9	25.5	28.5

[a] ^{1}H and ^{19}F NMR chemical shifts in ppm from internal TMS and from internal C_6F_6, respectively. Coupling constants in hertz. Solvent $CDCl_3$, except otherwise indicated. [b] Solvent C_6D_6. [c] Not detected.

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carbon, nearly quantitative yields of the 3-fluoro-1-sulfinyl-5-hexen-2-ols **5** having the *S* absolute configuration at the alcoholic stereocenter formed.

The chirality at C-2 and C-3 in these two epimeric fluorosulfinyl alcohols **5** corresponds to that required for the carbons C-3 and C-4 of the desired fluoro sugars **1** and **2**. The stereocontrolled functional group elaboration utilized to transform the (2*S*,3*S*,R_S)-fluorosulfinyl alcohol **5** into the final fluoro sugars **1** is described in the Scheme II. (2*S*,3*S*)-2-(Benzyloxy)-3-fluoro-1-(*R*)-[(4-methylphenyl)sulfinyl]-5-hexene (**6**) obtained in quantitative yields from (2*S*,3*S*,R_S)-**5** by treatment with benzyl bromide and sodium hydride was treated with trifluoroacetic anhydride and 2,4,6-trimethylpyridine.[7] A clean Pummerer rearrangement occurred and gave the 1-((trifluoroacetyl)oxy)-1-*p*-toluenesulfenyl derivative **6'**. This masked aldehyde was treated with copper(II) chloride in basic medium, and the crude free aldehyde was directly reduced with sodium borohydride to give (2*R*,3*S*)-2-(benzyloxy)-3-fluoro-5-hexen-1-ol (**7**) in 70% overall yield. This alcohol was treated with benzoyl chloride and pyridine to afford doubly protected (2*R*,3*S*)-1-(benzoyloxy)-2-(benzyloxy)-3-fluoro-5-hexene (**8**).

Cleavage of the double bond of the olefin (2*R*,3*S*)-**8** with sodium metaperiodate and catalytic amounts of osmium tetroxide[8] followed by the hydrogenolysis with Raney nickel of the benzyl group afforded 1-*O*-benzoyl-2,3-dideoxy-3-fluoro-α,β-D-ribofuranose (**1**). Alternatively, when catalytic ruthenium tetroxide[9] was used instead of osmium in the sodium metaperiodate oxidation of the double bond of (2*R*,3*S*)-**8**, the corresponding 4-(benzyloxy)-5-(benzoyloxy)-3-fluoropentanoic acid was formed. This acid gave (3*S*,4*R*)-5-(benzyloxy)-3-fluoro-4-pentanolide (**9**) on debenzylation and spontaneous lactonization. Reduction with DIBAH of the lactone produced the desired dideoxyfluororibose **1**. The latter three-step sequence used to transform **8** into **1** gave higher overall yields (48%) than the two-step procedure described above (23%).

Starting from (2*S*,3*R*)-3-fluoro-1-(*R*)-sulfinyl-5-hexen-2-ol (**5**), the reaction sequences described above for the diastereoisomeric (2*S*,3*S*,R_S)-**5** gave 1-*O*-benzoyl-2,3-dideoxy-3-fluoro-α,β-D-xylose (**2**) (Table I). The route employing the ruthenium-catalyzed oxidation gave the target fluoro sugar (3*R*,4*R*)-**2** in higher overall yields than the sequence employing osmium tetraoxide (48% with respect to 29%; see the Experimental Section).

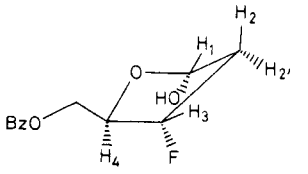
Also the two enantiomers of the fluoro sugars **1** and **2** here described may be made available through the same reaction sequence simply by starting from (−)-(*S*)-(**3**), which is available in two steps from (1*S*,2*R*,5*S*)-(+)-menthyl (*R*)-*p*-toluenesulfinate.[5]

Configuration and Conformation of Fluoro Sugars 1 and 2. The absolute configurations at C-2 of all the open-chain products, which correspond to C-4 in the cyclic compounds, was derived from the configurations, determined by spectroscopic techniques, of the two diastereoisomeric 3-fluoro-1-sulfenyl-5-hexen-2-ols **10**. These products were easily obtained through deoxygenation of the sulfinyl group of the corresponding alcohols **5** (Scheme I). The *S* absolute configuration at the C-2 was assigned through the chemical shift differences in the ^{1}H NMR spectra of their (*S*)- and (*R*)-2-phenylpropionic esters **12**.[10]

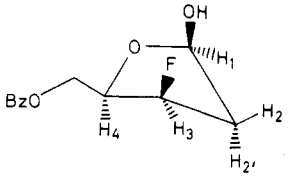
The relative configuration of the fluorohydrin moiety of **10** was established through the analyses of their ^{1}H and ^{19}F NMR spectra. The syn[11] relative stereochemistry was assigned to the diastereoisomer that showed a higher value for $^3J_{C(O)-H,C-F}$. This trend has been already shown to be diagnostic for the syn relative configuration of the fluorohydrin grouping.[10a] It was observed, among other cases, in diprotected fluorodiols **8** and was also in agreement with the relative stereochemistries established for the furanoses **1** and **2**. The ^{1}H and ^{19}F chemical shifts and the coupling constants of both these products, which have been isolated as mixtures of anomers, are collected in Table I.

In general, the conformational behavior of the furanose ring can be described in terms of 10 possible envelope (*E*) and 10 possible twist (*T*) conformations, which undergo a rapid mutual exchange in the so-called pseudorotational cycle.[12] Previous studies[13] led to the conclusion that vicinal coupling constants less than about 4 Hz can be ascribed to neighboring trans-pseudoequatorial hydrogens.[14] Inspection of Table I reveals that the α anomer of **1** displays three small coupling constants $J(1,2')$, $J(3,2')$, and $J(3,4)$ of ca. 0.0, 0.0, and 1.2 Hz, respectively. Thus only a limited segment of the pseudorotational cycle must be populated for this isomer to accommodate such low values of the observed ^3J's. The most probable conformations are the envelope ^2E(D) or the twist $^2T_3$(D) conformations. For both conformations protons H-1, H-2', H-3, and H-4 are in a trans-quasi-equatorial orientation with dihedral angles in the range 80–100°, thus confirming the D-*ribo* configuration of **1**.

For compound **2**β the vicinal coupling constant $J(1,2)$

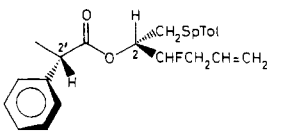


1α, ^{2}E(D)

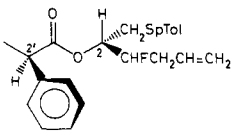


2β, E_2(D)

(10) The (*S*)- and (*R*)-2-phenylpropionic acids **11** are chiral derivatizing agents that have been employed for the assignment of the absolute configuration of the following: (a) Alcohols: Bravo, P.; Ganazzoli, F.; Resnati, G.; De Munari, S.; Albinati, A. *J. Chem. Res.* **1988**, *216*(S), 1701 (M). Raban, M.; Mislow, K. *Tetrahedron Lett.* **1965**, 4249. Helmchen, G. *Tetrahedron Lett.* **1974**, 1527. (b) Amides: Helmchen, G.; Volter, H.; Schule, W. *Tetrahedron Lett.* **1977**, 1417. (c) Thiols: Helmchen, G.; Schmierer, R. *Angew. Chem.* **1976**, *88*, 770; *Angew. Chem., Int. Ed. Engl.* **1976**, *15*, 703. In the esters **12** obtained from the acid (*R*)-**11** the proton chemical shift of the fluorinated residue ($CHFCH_2CH{=}CH_2$) of the carbinol carbon were at higher fields than in the corresponding esters **12** obtained from the acid (*S*)-**11**, and the opposite was true for the sulfur-substituted residue ($CH_2SC_6H_4pCH_3$):



(2S,2'S)-12



(2S,2'R)-12

This was due to the shielding effect that the phenyl ring of the esterifying acid exerts on the facing protons of the secondary alcohols according to the reported conformations. The validity of the conformational model was supported by the high esterification shift of the carbinol proton (H-2).

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Table II. Selected ^{19}F and ^{13}C NMR Chemical Shifts (δ, ppm) and ^{13}C–^{19}F Coupling Constants (hertz) for Compounds 1–10

compd	C-1	C-2	C-3	C-4	C-5	C-6	CH_2(Bn)	^{19}F NMR
(2*S*,3*R*,R_S)-**5**	59.90 (3.1)	66.35 (21.2)	94.46 (177.0)	35.04 (21.3)	132.63 (6.3)	118.48		−196.2
(2*S*,3*S*)-**10**	37.96 (4.3)	70.05 (20.0)	93.05 (175.8)	35.50 (22.0)	132.67 (6.3)	118.30		−198.9
(2*S*,3*R*,R_S)-**6**	60.45 (3.5)	73.77 (21.0)	93.92 (178.5)	35.16 (22.0)	132.38 (5.66)	118.51	74.55	−192.5
(2*R*,3*R*)-**7**	61.22 (7.0)	79.83 (19.0)	93.23 (174.5)	35.47 (21.0)	132.67 (3.1)	118.29	73.50	−193.9
(2*R*,3*R*)-**8**	63.38 (6.3)	76.70 (19.5)	92.25 (177.4)	35.24 (22.0)	132.69 (5.6)	118.42	73.27	−195.2
(3*R*,4*R*)-**9**		36.50 (25.0)	88.77 (186.0)	80.95 (20.0)	61.66 (14.0)			−195.9
(3*R*,4*R*)-**2**α[a]	98.02	41.45 (22.0)	93.17 (182.40)	78.37 (18.9)	62.35 (12.6)			−193.9
(3*R*,4*R*)-**2**β[a]	98.72	40.85 (19.5)	92.80 (181.2)	80.65 (19.50)	63.61 (13.8)			−192.4
(2*S*,3*S*,R_S)-**5**	58.02 (3.0)	67.22 (24.3)	94.23 (175.0)	35.52 (21.0)	132.52 (3.7)	118.42		−192.3
(2*S*,3*S*)-**10**	38.38 (4.8)	69.98 (24.5)	93.92 (173.5)	35.53 (21.0)	132.76 (4.4)	118.15		−192.4
(2*S*,3*S*,R_S)-**6**	60.16 (5.6)	74.64 (21.6)	93.22 (178.1)	35.16 (21.2)	132.33 (4.4)	118.60	73.69	−189.5
(2*R*,3*S*)-**7**	60.63 (6.5)	79.79 (23.2)	91.66 (173.0)	35.53 (20.8)	132.97 (3.2)	118.18	72.71	−190.7
(2*R*,3*S*)-**8**	62.87 (7.0)	77.74 (24.0)	91.73 (174.0)	35.50 (21.0)	132.74 (3.2)	118.46	72.72	−191.3
(3*S*,4*R*)-**9**	173.24	35.80 (23.9)	89.99 (182.4)	82.49 (27.0)	63.13 (10.7)			
(3*S*,4*R*)-**1**α	99.09	40.32 (20.7)	94.48 (177.4)	82.20 (25.8)	63.79 (10.0)			−173.6
(3*S*,4*R*)-**1**β	99.39	40.60 (20.7)	94.42 (180.5)	82.19 (23.9)	64.56 (10.7)			−179.3

[a] The assignments of the α and β anomers may be interchanged.

and $J(2,3)$ show values that are nearly zero, indicating that the H-1, H-2, and H-3 protons are pseudoequatorial. This arrangement is well represented by the E_2(D) conformation, which should be one of the most populated. For this conformation the dihedral angles between protons H-3 and H-4 are ca. 150° for the trans and ca. 30° for the cis orientation of the substituents. The calculated values of $J(3,4)$ obtained through a generalized Karplus equation[14] are 8.0 and 4.4 Hz, respectively. The latter value, corresponding to the 3,4-cis (D-*xylo*) configuration of the furanose ring, is in reasonable agreement with the observed value of 3.5 Hz for $J(3,4)$ in **2**.

In the case of anomers 1β and 2α the change of the configuration of C-1 induces strong variations of the ring conformations with respect to 1α and 2β discussed above. The increase of $J(2',3)$ and $J(3,4)$ in 1β with respect to 1α and of $J(2,3)$ in 2α with respect to 2β suggests that a flattening of the ring or an equilibrium between opposite conformations occurs. This observation is also confirmed by the values of the vicinal proton–fluorine coupling constants. In fact, $^3J(F,H_{2,2'})$'s can be clearly distinguished for compounds 1α and 2β in the case of trans-quasi-axial C–F, C–H arrangement (39–42 Hz) and cis-axial–equatorial (21–23 Hz) orientation. On the contrary, the values of $^3J(F,H_{2,2'})$ become very similar (27.5–31.8 Hz) for the anomers 2α and 1β.

Experimental Section

^1H and ^{13}C NMR spectra were recorded with a Bruker CXP 300, a Bruker AM 500, or a Bruker WP 80 spectrometer; $CDCl_3$ was used as solvent unless otherwise stated; $\delta_{H,C}$ values are in ppm. The same instruments were used for ^{19}F NMR spectra; δ_F values are ppm upfield from $CFCl_3$, and C_6F_6 was used as internal standard (δ_F = −162.9) and $CDCl_3$ as solvent. $[\alpha]_D$ values are obtained on a Jasco DIP-181 polarimeter. Mass spectra were registered on a Hitachi–Perkin-Elmer RMU 6D or on a VGMM ZAB 2F instrument. IR spectra were taken on a Perkin-Elmer 177 spectrophotometer. Melting points are uncorrected and were obtained on a capillary apparatus. TLC were run on silica gel 60 F_{254} Merck; column chromatographies were performed with silica gel 60 (60–200 μm, Merck). Tetrahydrofuran (THF) was freshly distilled from lithium aluminum hydride; diisopropylamine was distilled from calcium hydride and stored over molecular sieves (4 Å); dimethylformamide was stored over molecular sieves (4 and 13 Å); in other cases commercially available reagent-grade solvents were employed without purification. ^{13}C and ^{19}F NMR data of compounds 1–10 are reported in Table II.

(3*S*)-3-Fluoro-1(*R*)-[(4-methylphenyl)sulfinyl]-5-hexen-2-one (4) and (3*R*,R_S)-4. Allyl bromide (3.39 g, 28.05 mmol) was added dropwise at −78 °C to a solution of the dilithium derivative (generated with LDA (41.15 mmol) in THF (55 mL) of (+)-(*R*)-1-fluoro-3-[(4-methylphenyl)sulfinyl]-2-propanone (**3**, 4.00 g, 73.17 mmol) stirred under argon. After 5 min at the same temperature, an excess of a saturated aqueous solution of ammonium chloride was added, the layers were separated, and the aqueous phase was extracted with ethyl acetate (3 × 300 mL). The combined organic extracts were dried over anhydrous sodium sulfate, the solvent was removed under reduced pressure, and the residue was flash chromatographed (*n*-pentane/diethyl ether 4:6) to give (3*S*,R_S)-**4** (7.63 g, 41% yield) and (3*R*,R_S)-**4** (4.49 g, 24% yield) as pure compounds. (3*S*,R_S)-**4**: R_f (*n*-pentane/diethyl ether 4:6) 0.35; $[\alpha]^{20}_D$ +175° (*c* 1.0, $CHCl_3$); IR (Nujol) 1720, 1510, 1045 cm^{-1}; mp 45–47 °C (diisopropyl ether); ^1H NMR (90 MHz) δ 2.57 (m, 2 H, CH_2CHF), 4.06 (d, 2 H, $^4H_{H,F}$ = 4 Hz, CH_2S), 4.78 (dt, 1 H, CHF), 5.1–5.2 (m, 2 H, CH=CH_2), 5.7 (m, 1 H, C*H*=CH_2). Anal. Calcd for $C_{13}H_{15}FO_2S$: C, 61.39; H, 5.94. Found: C, 61.50; H, 6.06. (3*R*,R_S)-**4**: R_f (*n*-pentane/ethyl ether 4:6) 0.28; $[\alpha]^{20}_D$ +230° (*c* 1.0, $CHCl_3$); IR (film) 2930, 1730, 1480, 1050 cm^{-1}; ^1H NMR (250 MHz) δ 2.54 (m, 2 H, CH_2CHF), 3.91 and 4.17 (AB system, 2 H, CH_2S), 4.78 (m, 1 H, $^2J_{H,F}$ = 49 Hz, CHF), 5.1–5.2 (m, 2 H, CH=CH_2), 5.7 (m, 1 H, C*H*=CH_2). Anal. Calcd for $C_{13}H_{15}FO_2S$: C, 61.39; H, 5.94. Found: C, 61.68; H, 6.14.

(2*S*,3*S*)-3-Fluoro-1(*R*)-[(4-methylphenyl)sulfinyl]-5-hexen-2-ol (5) and (2*S*,3*R*,R_S)-(5). A 1.0 N solution of DIBAH in *n*-hexane (24.0 mL) was dropped into a solution of (3*S*,R_S)-**4** (5.09 g, 20.0 mmol) in THF (freshly distilled from lithium aluminum hydride, 80 mL) with stirring at −78 °C under an argon atmosphere. After 30 min at the same temperature an excess of a saturated aqueous solution of sodium hydrogen carbonate was added, the resulting mixture was stirred for 30 min, and then a 10 N solution of hydrochloric acid was dropped until pH 5 was reached. Organic products were extracted with ethyl acetate (3 × 300 mL). The collected organic phases were dried with anhydrous sodium sulfate, and the solvent was removed under reduced pressure to give crude (2*S*,3*S*,R_S)-**5** in nearly pure form and quantitative yields. An analytical sample was obtained through flash chromatography (*n*-hexane/ethyl acetate 1:1) and crystallization. $[\alpha]^{20}_D$ +258° (*c* 1.15, $CHCl_3$); IR (Nujol) 3300, 1450, 1050, 1030, 1010 cm^{-1}; mp 98–100 °C (diisopropyl ether); ^1H NMR (250 MHz) δ 2.45 (m, 2 H, CH_2CHF), 2.85 (ddd, $^2J_{H,H}$ = 12 Hz, $^3J_{H,H}$ = $^4J_{H,F}$ = 1.5 Hz, 1 H, CHS), 3.16 (dd, $^3J_{H,H}$ = 9 Hz, 1 H, CHS), 4.16 (m, 1 H, CHO), 4.47 (m, $^2J_{H,F}$ = 47 Hz, 1 H, CHF), 5.05, 5.12 (m, 2 H, CH=CH_2), 5.75 (m, 1 H, C*H*=CH_2). Anal. Calcd for $C_{13}H_{17}FO_2S$: C, 60.91; H, 6.69. Found: C, 60.75; H, 6.88.

When (3*R*,R_S)-**4** was similarly reacted, the alcohol (2*S*,3*R*,R_S)-**5** formed in nearly quantitative yields: $[\alpha]^{20}_D$ +270° (*c* 1.2, $CHCl_3$); IR (Nujol) 3300, 1460, 1040, 1030, 1010 cm^{-1}; mp 143–145 °C (diisopropyl ether); ^1H NMR (250 MHz) δ 2.49 (m, 2 H, CH_2CHF), 2.73 (dd, $^2J_{H,H}$ = 13 Hz, $^3J_{H,H}$ = 2.0 Hz, 1 H, CHS), 3.21 (dd, $^3J_{H,H}$ = 10 Hz, 1 H, CHS), 4.2–4.4 (m, 2 H, C*H*OC*H*F), 5.0–5.2 (m, 2 H, CH=CH_2), 5.75 (m, 1 H, C*H*=CH_2). Anal. Calcd for $C_{13}H_{17}FO_2S$: C, 60.91; H, 6.69. Found: C, 60.80; H, 6.83.

(2*S*,3*S*)-2-(Benzyloxy)-3-fluoro-1(*R*)-[(4-methylphenyl)-sulfinyl]-5-hexene (6) and (2*S*,3*R*,R_S)-6. A solution of (2*S*,3*S*,R_S)-**5** (4.74 g, 18.5 mmol) in DMF (15 mL) was dropped

into a suspension of oil-free sodium hydride (672 mg, 28.0 mmol) in THF (15 mL) with stirring under argon at 0 °C. Benzyl bromide (3.33 mL, 28.0 mmol) was then added at the same temperature, and after 0.5 h at 25 °C diluted hydrochloric acid was added. The usual workup and flash chromatography (*n*-hexane/ethyl acetate 7:3) gave the (2*S*,3*S*,R_S)-**6** in 93% yield. $[\alpha]^{20}_D$ +164° (*c* 0.95, $CHCl_3$); ^{1}H NMR (250 MHz) δ 2.2–2.6 (m, 2 H, CH_2CHF), 2.93 (m, 2 H, CH_2S), 4.21 (m, 1 H, CHO), 4.65 (m, $^2J_{H,F}$ = 47.5 Hz, 1 H, CHF), 4.78, 4.82 (AB system, 2 H, $CH_2C_6H_5$), 5.13 (m, 2 H, CH=CH_2), 5.8 (m, 1 H, CHCH$_2$). Anal. Calcd for $C_{20}H_{23}FO_2S$: C, 69.33; H, 6.69. Found: C, 69.06; H, 6.48.

When (2*S*,3*R*,R_S)-**5** was similarly reacted, the flash chromatography (*n*-hexane/ethyl acetate 7:3) of the crude reaction mixture afforded the (2*S*,3*R*,R_S)-**6** in 91% yield: ^{1}H NMR (250 MHz) δ 2.3–2.5 (m, 2 H, CH_2CHF), 2.94, 2.99 (m, 2 H, CH_2S), 4.21 (m, 1 H, CHO), 4.47 (m, $^2J_{H,F}$ = 47 Hz, 1 H, CHF), 4.78, 4.90 (AB system, 2 H, $CH_2C_6H_5$), 5.10, 5.14 (m, 2 H, CH=CH_2), 5.77 (m, 1 H, CH=CH$_2$). Anal. Calcd for $C_{20}H_{23}FO_2S$: C, 69.33; H, 6.69. Found: C, 68.09; H, 6.69.

(2*R*,3*S*)-2-(Benzyloxy)-3-fluoro-5-hexen-1-ol (7) and (2*R*,3*R*)-7. A solution of trifluoroacetic anhydride (2.82 mL, 20.0 mmol) in acetonitrile (80 mL) was added dropwise into a solution of (2*S*,3*S*,R_S)-**6** (3.46 g, 10.0 mmol) and of 2,4,6-trimethylpyridine (3.97 mL, 30.0 mmol) in the same solvent (200 mL) with stirring at 0 °C under argon. After 30 min at room temperature a solution of copper(II) chloride (2.02 g, 15.0 mmol) and of potassium carbonate (2.07 g, 15.0 mmol) in water (75 mL) was added. The resulting mixture was stirred at room temperature for 2.0 h and then evaporated under reduced pressure. The resulting solution was diluted with water (50 mL) and extracted with ethyl acetate (3 × 100 mL), and the collected organic phases were dried with anhydrous sodium sulfate and evaporated under reduced pressure. The crude product mixture was dissolved in acetonitrile (20 mL) and isopropyl alcohol (20 mL), and sodium borohydride (378 mg, 10.0 mmol) was added portionwise with stirring at 0 °C. After 10 min at 25 °C diluted hydrochloric acid was dropped into the resulting brown suspension until pH 4 was reached. The organic solvents were removed under reduced pressure, and the aqueous layer was extracted with ethyl acetate (3 × 150 mL). The collected organic phases were dried with anhydrous sodium sulfate and evaporated under reduced pressure to give, after flash chromatography (*n*-hexane/ethyl acetate 35:10), 1.57 g (70% global yield) of (2*R*,3*S*)-**7**: $[\alpha]^{20}_{435}$ −9.44° (*c* 1.9, $CHCl_3$); ^{1}H NMR (250 MHz) δ 2.50 (m, 2 H, CH_2CHF), 3.55–3.85 (m, 3 H, CHOCH_2OH), 4.63 (m, $^2J_{H,F}$ = 47 Hz, 1 H, CHF), 4.65 (d, 2 H, *J* = 3 Hz, $CH_2C_6H_5$), 5.12 (m, 2 H, CH=CH_2), 5.83 (m, 1 H, CH=CH$_2$). Anal. Calcd for $C_{13}H_{17}FO_2$: C, 69.62; H, 7.64: Found: C, 69.54; H, 7.58.

When (2*S*,3*R*,R_S)-**6** was similarly reacted, the (2*R*,3*R*)-**7** was obtained in 66% yield: $[\alpha]^{20}_D$ +11.6° (*c* 2.0, $CHCl_3$); ^{1}H NMR (250 MHz) δ 2.45 (m, 2 H, CH_2CHF), 3.5–3.8 (m, 3 H, CHOCH_2OH), 4.68 (m, 1 H, $^2J_{H,F}$ = 47.5 Hz, CHF), 4.70 (m, 2 H, $CH_2C_6H_5$), 5.1–5.2 (m, 2 H, CH=CH_2), 5.80 (m, 1 H, CH=CH$_2$).

(2*R*,3*S*)-1-(Benzoyloxy)-2-(benzyloxy)-3-fluoro-5-hexene (8) and (2*R*,3*R*)-8. Benzoyl chloride (0.35 mL, 3.0 mmol) and pyridine (0.24 mL, 3.0 mmol) were added dropwise into a solution of (2*R*,3*S*)-**7** (448 mg, 2.0 mmol) in THF (10 mL) with stirring at 0 °C. After 1.5 h at room temperature and the usual workup, flash chromatography (*n*-hexane/ethyl acetate 95:5) gave (2*R*,3*S*)-**8** in 87% yield as a yellowish oil: $[\alpha]^{20}_D$ −16.7° (*c* 2.1, $CHCl_3$); ^{1}H NMR (250 MHz) δ 2.55 (m, 2 H, CH_2CHF), 3.88 (m, 1 H, CHOCHF), 4.39, 4.70 (ddd each, 2 H, CH_2OCO), 4.66, 4.78 (AB system, 2 H, $CH_2C_6H_5$), 4.71 (m, 1 H, CHF), 5.16, 5.19 (m, 2 H, CH=CH_2), 5.87 (m, 1 H, CH=CH$_2$). Anal. Calcd for $C_{20}H_{21}FO_3$: C, 73.15; H, 6.45. Found: C, 73.31; H, 6.36.

When (2*R*,3*R*)-**7** was reacted in a similar manner, the benzoic ester (2*R*,3*R*)-**8** was obtained in 78% yield: $[\alpha]^{20}_D$ +12.3° (*c* 2.4, $CHCl_3$); ^{1}H NMR (250 MHz) δ 2.55 (m, 2 H, CH_2CHF), 3.84 (m, $^3J_{H,F}$ = 20.5 Hz, 1 H, CHO), 4.55, 4.57 (m, 2 H), 4.69, 4.81 (AB system, 2 H), 4.71 (m, 1 H, CHF), 5.10, 5.16 (m, 2 H, CH=CH_2), 5.80 (m, 1 H, CH=CH$_2$). Anal. Calcd for $C_{20}H_{21}FO_3$: C, 73.15; H, 6.45. Found: C, 73.31; H, 6.36.

(3*S*,4*R*)-5-(Benzoyloxy)-3-fluoropentan-4-olide (9) and (3*R*,4*R*)-9. Sodium metaperiodate (2.14 g, 10.0 mmol) and ruthenium(IV) oxide hydrate (7.3 mg, 0.055 mmol) were added into a solution (20 mL) of (2*R*,3*S*)-**8** (821 mg, 2.50 mmol) in a 1:1:1.4 mixture of carbon tetrachloride/acetonitrile/water. After 2.0 h at room temperature, the brown suspension turned to black. Dichloromethane was added, and the aqueous phase was separated and extracted with dichloromethane (3 × 20 mL). The collected organic phases were dried with anhydrous sodium sulfate and evaporated under reduced pressure. The so-obtained (3*S*,4*R*)-5-(benzoyloxy)-4-(benzyloxy)-3-fluoropentanoic acid could be isolated in pure form through flash chromatography (toluene/ethyl acetate/acetic acid 50:10:1): ^{1}H NMR (250 MHz) δ 2.85 (m, 2 H, CH_2CHF), 3.93 (m, 1 H, CHO), 4.38, 4.68 (ddd, 2 H), 4.66, 4.78 (AB system, 2 H), 5.13 (m, $^2J_{H,F}$ = 47 Hz, 1 H, CHF); ^{13}C NMR (62.9 MHz) δ 36.30 (C-2, $J_{C,F}$ = 23.0 Hz), 72.76 (C-5, $J_{C,F}$ = 6.5 Hz), 76.70 (C-4, $J_{C,F}$ = 24.0 Hz), 88.70 (C-3, $J_{C,F}$ = 174.8 Hz). Anal. Calcd for $C_{19}H_{19}FO_5$: C, 65.89; H, 5.53. Found: C, 66.09; H, 5.65. The crude product was directly dissolved in trifluoroacetic acid (15 mL), and palladium on activated charcoal (50 mg) was added. The mixture was shaken under hydrogen for 20 min and then filtered, and the solvent was evaporated under reduced pressure. The residue was treated with an excess of a saturated aqueous solution of sodium hydrogen carbonate, the aqueous phase was extracted with diethyl ether (3 × 50 mL), and the collected organic phases were dried over anhydrous sodium sulfate and evaporated under reduced pressure. The residue was flash chromatographed (*n*-hexane/ethyl acetate 2:1) to give 0.43 g (72% yield) of pure (3*S*,4*R*)-**9**: $[\alpha]^{20}_D$ −20.0° (*c* 0.8, $CHCl_3$); ^{1}H NMR (250 MHz) δ 2.84 (ddd, $^2J_{H,H}$ = 19.0 Hz, $^3J_{H,H}$ = 1.4 Hz, $^3J_{H,F}$ = 27.0, 1 H, $CHCO_2$), 3.00 (ddd, $^3J_{H,H}$ 5.8 Hz, $^3J_{H,F}$ = 33.0 Hz, 1 H, $CHCO_2$), 4.52 (ddd, $^4J_{H,F}$ = 1.5 Hz, $^2J_{H,H}$ = 12.5 Hz, $^3J_{H,H}$ = 3.9 Hz, 1 H, CHOCO), 4.65 (dd, $^3J_{H,H}$ = 3.1 Hz, 1 H, CHOCO), 5.01 (ddd, 1 H, C-4), 5.36 (dddd, $^3J_{H,H}$ = 1.3 Hz, $^2J_{H,F}$ = 53.0 Hz, 1 H, CHF). Anal. Calcd for $C_{12}H_{11}FO_4$: C, 60.50; H, 4.65. Found: C, 60.38; H, 4.65.

When the double bond of (2*R*,3*R*)-**8** was oxidized as described above, the corresponding (3*R*,4*R*)-5-(benzoyloxy)-4-(benzyloxy)-3-fluoropentanoic acid could be isolated in pure form [^{1}H NMR (250 MHz) δ 2.70, 2.90 (m, 2 H, CH_2CHF), 3.90 (m, 1 H, $^3J_{H,F}$ = 21 Hz, CHOH), 4.53 (d, 2 H), 4.63, 4.79 (AB system, 2 H), 5.13 (m, 1 H, $^2J_{H,F}$ = 46 Hz, CHF)]; however, direct hydrogenolysis of the benzyl group as described above afforded in this case too pure (3*R*,4*R*)-**9** in 67% yield: mp 123–125 °C (*n*-pentane/ethyl acetate); $[\alpha]^{20}_D$ +65.3° (*c* 0.53, $CHCl_3$); ^{1}H NMR (250 MHz) δ 2.91 (m, 2 H, CH_2CHF), 4.62 (m, 1 H, CHOCOC$_6$H$_5$), 4.80 (m, 1 H, CHOCOC$_6$H$_5$), 4.85 (m, 1 H, CHOCOCH$_2$), 5.48 (m, 1 H, $^2J_{H,F}$ = 53 Hz, CHF). Anal. Calcd for $C_{12}H_{11}FO_4$: C, 60.50; H, 4.65. Found: C, 60.70; H, 4.80.

5-*O*-Benzoyl-2,3-dideoxy-3-fluoro-α,β-D-ribofuranose (1) and 5-*O*-Benzoyl-2,3-dideoxy-3-fluoro-α,β-D-xylofuranose (2). With OsO_4/$NaIO_4$ from 8. Osmium tetraoxide (41 mg, 0.16 mmol) was added to a solution of (2*R*,3*S*)-**8** (300 mg, 0.91 mmol) in dioxane (6 mL). After this stirred in the dark for 15 min, a solution of sodium metaperiodate (456 mg, 2.13 mmol) in water (4.0 mL) was added dropwise, and stirring was continued for 30 min, during which time the mixture turned to light yellow. The reaction was poured into saturated aqueous sodium sulfite and cracked ice. The aqueous phase was extracted with diethyl ether (4 × 50 mL), and the collected organic phases were dried with anhydrous sodium sulfate. The crude (3*S*,4*R*)-5-(benzoyloxy)-4-(benzyloxy)-3-fluoropentanal was directly dissolved in trifluoroacetic acid (2.0 mL) and shaken under hydrogen in the presence of palladium on activated charcoal (20 mg). After 10 min at room temperature, the mixture was filtered, the solvent was removed under reduced pressure, and the residue was treated with aqueous saturated hydrogen carbonate (15 mL). The products were extracted with diethyl ether, the collected organic phases were dried with anhydrous sodium sulfate, and the solvent was removed under reduced pressure. Flash chromatography (*n*-hexane/diethyl ether 1:1) of the residue afforded 41 mg (19% yield) of pure (3*S*,4*R*)-**9** and 50 mg (23% yield) of pure (3*S*,4*R*)-**1** as a white oil: $[\alpha]^{20}_D$ +13.2° (*c* 1.03, $CHCl_3$); ^{1}H NMR data are reported in Table I.

When (2*R*,3*R*)-**8** (343 mg, 1.04 mmol) was similarly reacted, 73 mg (29% yield) of pure (3*R*,4*R*)-**2** was isolated: $[\alpha]^{20}_D$ +31.0° (*c* 0.7, $CHCl_3$); ^{1}H NMR data are reported in Table I. Anal. Calcd for $C_{12}H_{13}FO_4$: C, 60.00; H, 5.45. Found: 59.88; H, 5.40.

With DIBAH from 9. DIBAH (2.4 mL, 1 N solution in toluene) was dropped into a solution of (3*S*,4*R*)-**9** (100 mg, 0.42

mmol) in THF (10 mL) with stirring under argon at -78 °C. After 30 min at that temperature, the solution was stirred at -50 °C for 10 h, and then an excess of a saturated aqueous solution of ammonium chloride was added. Hydrochloric acid (10 N) was added dropwise until pH 3 was reached. The aqueous phase was extracted with diethyl ether (4 × 30 mL), and the collected organic phases were dried with anhydrous sodium sulfate. Evaporation of the solvent under reduced pressure and flash chromatography of the residue afforded 67 mg (67% yield) of pure (3*S*,4*R*)-**1** with physical and spectral data identical with those reported above and 14 mg (14% recovery) of starting lactone (3*S*,4*R*)-**9**.

When (3*R*,4*R*)-**9** (108 mg, 0.45 mmol) was similarly reacted, (3*R*,4*R*)-**2** was isolated in 71% yield along with a 18% of starting lactone (3*R*,4*R*)-**9**.

(2*S*,3*S*)-3-Fluoro-1-[(4-methylphenyl)sulfenyl]-5-hexen-2-ol (10) and (2*S*,3*R*)-10. Trifluoroacetic anhydride (0.35 mL, 2.50 mmol) was added to a mixture of (2*S*,3*S*,R_S)-**5** (128 mg, 0.50 mmol) and of sodium iodide (240 mg, 1.60 mmol) in acetone (15 mL) with stirring at -40 °C under argon. After 10 min at the same temperature the reaction was quenched with an excess of a saturated aqueous solution of sodium sulfite and of a saturated aqueous solution of sodium hydrogen carbonate. Acetone was removed under reduced pressure and the aqueous layer was extracted with ethyl ether (3 × 20 mL). The combined organic phases were dried over anhydrous sodium sulfate, and the solvent was removed to give (2*S*,3*S*)-**10** as a pure compound in 96% yield. An analytical sample was obtained through flash chromatography (*n*-hexane/diethyl ether 85:25); $[\alpha]^{20}_D$ +46° (*c* 0.62, $CHCl_3$); ^1H NMR (250 MHz) δ 2.48 (m, 2 H, CH_2CF), 2.90 (dd, $^2J_{H,H}$ = 14 Hz, $^3J_{H,H}$ = 9 Hz, $^4J_{H,F}$ = 1.0 Hz, CHS), 3.30 (ddd, 1 H, CHS), 3.71 (m, $^3J_{H,F}$ = 10.5, $^3J_{H,H}$ = 6.0 Hz, 1 H, CHO), 4.47 (m, 1 H, CHF), 5.13 (m, 2 H, CH=CH_2), 5.82 (m, 1 H, CH=CH_2). Anal. Calcd for $C_{13}H_{17}FOS$: C, 64.96; H, 7.13. Found: C, 65.14; H, 7.32.

When (2*S*,3*R*,R_S)-**5** was similarly reacted, the sulfenyl alcohol (2*S*,3*R*)-**10** was obtained in 94% yield through flash chromatography (*n*-hexanediethyl ether 85:25); $[\alpha]^{20}_D$ +17.7° (*c* 0.61, $CHCl_3$); ^1H NMR (250 MHz) δ 2.52 (m, 2 H, CH_2CF), 3.04, 3.09 (m, 2 H, CH_2S), 3.66 (m, $^3J_{H,F}$ = 22.0 Hz, $^3J_{H,H}$ = 2.9 Hz, 1 H, CHO), 4.60 (m, $^2J_{H,F}$ = 47.4 Hz, 1 H, CHF), 5.14 (m, 2 H, CH=CH_2), 5.80 (m, 1 H, CH=CH_2). Anal. Calcd for $C_{13}H_{17}FOS$: C, 64.96; H, 7.13. Found: C, 65.03; H, 7.24.

2-Phenylpropionic Esters 12 of (2*S*,3*S*)-10 and of (2*S*,3*R*)-10. 4-(Dimethylamino)pyridine (1.2 mg, 0.01 mmol) was added to a dichloromethane solution (0.5 mL) containing the sulfenyl alcohol (2*S*,3*S*)-**10** (24 mg, 0.10 mmol), the (+)-(*S*)-2-phenylpropionic acid (**11**, 17 mg, 0.11 mmol), and dicyclohexylcarbodiimide (25 mg, 0.12 mmol). After 4 h at room temperature the dicyclohexylurea was removed by filtration and washed with *n*-hexane. The collected organic phases were dried over anhydrous sodium sulfate, the solvent was removed under reduced pressure, and the residue was flash chromatographed (*n*-hexane/diethyl ether 98:2) to give the desired (*S*)-2-phenylpropionate **12** of the alcohol (2*S*,3*S*)-**10**: ^1H NMR (250 MHz) δ 1.51 (d, 3 H, CH_3CH), 2.30 (s, 3 H, $CH_3C_6H_4$), 2.28 (m, 2 H, CH_2CHF), 3.02, 3.07 (m, 2 H, CH_2S), 3.72 (q, 1 H, $CHCH_3$), 4.66 (m, 1 H, CHF), 5.0-5.1 (m, 3 H, CHO and CH=CH_2), 5.72 (m, 1 H, CH=CH_2). Similarly, by use of (-)-(*R*)-**11** and (2*S*,3*S*)-**10** the corresponding (*R*)-2-phenylpropionate **12** of the alcohol (2*S*,3*S*)-**10** was obtained: ^1H NMR (250 MHz) δ 1.37 (d, 3 H, CH_3CH), 1.96 (m, 2 H, CH_2CHF), 2.26 (s, 3 H, $CH_3C_6H_4$), 3.02, 3.14 (m, 2 H, CH_2S), 3.41 (q, 1 H, $CHCH_3$), 4.47 (m, 1 H, CHF), 4.7-5.0 (m, 3 H, CHO and CH=CH_2), 5.53 (m, 1 H, CH=CH_2). When (2*S*,3*R*)-**10** was esterifyied with (+)-(*S*)-**11**, the obtained ester **12** showed the following spectrum: ^1H NMR (250 MHz) δ 1.53 (d, 3 H, CH_3CH), 2.25 (m, 2 H, CH_2CF), 2.30 (s, 3 H, $CH_3C_6H_4$), 3.01 (d, 2 H, CH_2S), 3.78 (q, 1 H, $CHCH_3$), 4.80-4.95 (m, 2 H, CHFCHO), 5.01, 5.06 (m, 2 H, CH=CH_2), 5.70 (m, 1 H, CH=CH_2). Similarly the ester **12** obtained from (-)-(*R*)-**11** and the alcohol (2*S*,3*R*)-**10** showed the following spectrum: ^1H NMR (250 MHz) δ 1.52 (d, 3 H, CH_3CH); 1.99 (m, 2 H, CH_2CF), 2.31 (s, 3 H, $CH_3C_6H_4$), 3.09, 3.18 (m, 2 H, CH_2S), 3.71 (q, 1 H, $CHCH_3$), 4.73 (m, 1 H, CHF), 4.7-5.0 (m, 3 H, CHO and CH=CH_2), 5.53 (m, 1 H, CH=CH_2).

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Registry No. α-(3*S*,4*R*)-**1**, 122333-24-8; β-(3*S*,4*R*)-**1**, 122333-25-9; α-(3*R*,4*R*)-**2**, 122333-26-0; β-(3*R*,4*R*)-**2**, 122333-27-1; (*R*)-**3**, 105984-80-3; (3*R*,R_s)-**4**, 121911-10-2; (3*S*,R_s)-**4**, 121911-11-3; (2*S*,3*R*,R_s)-**5**, 121911-13-5; (2*S*,3*S*,R_s)-**5**, 121961-08-8; (2*S*,3*R*,R_s)-**6**, 122406-16-0; (2*S*,3*S*,R_s)-**6**, 122333-15-7; (2*R*,3*R*)-**7**, 122333-16-8; (2*R*,3*S*)-**7**, 122356-68-7; (2*R*,3*R*)-**8**, 122333-18-0; (2*R*,3*S*)-**8**, 122333-17-9; (3*R*,4*R*)-**9**, 122333-22-6; (3*R*,4*R*)-**9** ring opened acid deriv), 122333-21-5; (3*S*,4*R*)-**9**, 122333-20-4; (3*S*,4*R*)-**9** (ring opened acid deriv), 122333-19-1; (2*S*,3*R*)-**10**, 121911-12-4; (2*S*,3*S*)-**10**, 12233-28-2; (*R*)-**11**, 7782-26-5; (*S*)-**11**, 7782-24-3; (2*S*,2′*R*,3*R*)-**12**, 122406-19-3; (2*S*,2′*R*,3*S*)-**12**, 122406-17-1; (2*S*,2′*S*,3*R*)-**12**, 122406-18-2; (2*S*,2′*S*,3*S*)-**12**, 122333-29-3; allyl bromide, 106-95-6; (3*S*,4*R*)-5-(benzoyloxy)-4-(benzyloxy)-3-fluoropentanal, 122333-23-7.

Notes

On the Synthesis of Diarylnitrones

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Compounds containing the imine *N*-oxide moiety are most commonly called nitrones and were first described nearly 100 years ago.[1] Interest in nitrones stems from their photochemical reactivity,[2] as well as from their utility in the synthesis of heterocycles by 1,3-dipolar cycloaddition reactions.[3] Nitrones are also well-known as radical spin-trapping reagents,[4] which has led to their use as antioxidants.[5] Our own interest in nitrones grew out of a new imaging technology we recently introduced for the field of microlithography.[6]

We required for our microlithography programs diarylnitrones with absorption maxima above 400 nm. Nitrones with substituent combinations that provided the requisite absorption maxima proved difficult to synthesize by conventional techniques. In fact few such compounds

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