Enantioselective Synthesis of a Fluorinated Analogue of the Orsellinic Acid-Type Twelve-Membered Lactone Lasiodiplodin

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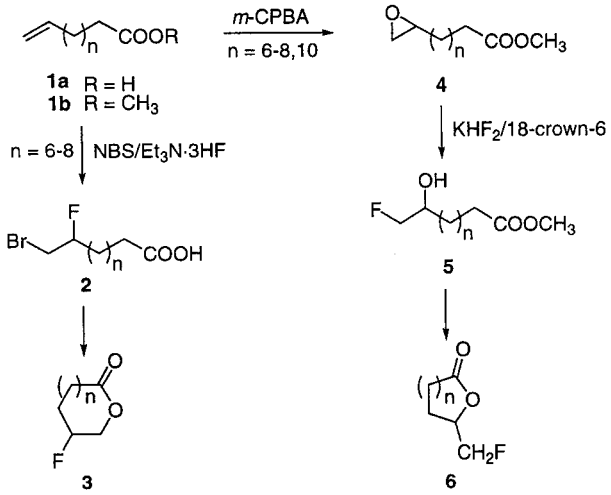
Received August 15, 2000

The chemoenzymatic synthesis of the racemate and the one enantiomer of the fluorinated analogue **8** of the natural cyclooxygenase inhibitor lasiodiplodin is decribed. A lipase-mediated deracemization of the fluorohydrin **18** provided the chiral, nonracemic building block for the enantioselective synthesis of the title compound. The key step was the formation of the 12-membered lactone by a ring-closing metathesis.

Introduction

The development of methods[1] to synthesize particularly optically active new fluorinated organic compounds[2] has advanced progress in biochemistry and medicine during the past decades.[3a] By exchanging hydrogen for fluorine, the chemical and biological behavior of modified natural compounds can be changed dramatically. The sterically nondemanding fluorine atom does not significantly change the geometry of a molecule, but has a strong influence on the electron density of neighboring groups and results in a lower polarizability.[3]

Monofluorinated lactones with medium to large ring-size can easily be synthesized by two general synthetic pathways. In a convenient two-step procedure by bromofluorination of terminal unsaturated fatty acids **1a** with NBS/Et_3N·3HF bromofluorides bearing a secondary fluoride have been formed which were subsequently cyclized under basic conditions.[4] Fluoromethyl substituted macrolides on the other hand have been synthesized in a five-step sequence starting with the unsaturated fatty acids **1a**.[4b,5] The key step was the regioselective opening[6] of the epoxides derived from unsaturated fatty acid esters **1b**, resulting in the formation of fluorohydrins **5** bearing a primary fluorine substituent. After hydrolysis, final cyclization using Yamaguchi's method[7] of mixed anhydrides and high dilution resulted in the fluoromethyl-substituted macrolides.



This methodology has already been applied successfully to the synthesis of both enantiomers of fluorophoracantholide I, namely (9*S*)-10-fluorodecan-9-olide and its (9*R*)-enantiomer, which are fluorinated analogues of the metasternal gland secretion of the eucalypt longicorn (*Phoracantha synonyma*).[8] This synthesis was based on a lipase-catalyzed resolution by way of the acetylation of 10-fluoro-9-hydroxydecanoate.[5,9]

This paper reports the synthesis of a monofluorinated analogue of the 12-membered orsellinic acid type lactone lasiodiplodin **7a**, a constituent of the fungus *Lasiodiplodia theobromae*[10a] and of the wood of *Euphorbia splendens*[10b] and *Euphorbia fidjiana*.[10c] Its de-*O*-methyl derivative **7b** is also a secondary metabolite of *Arnebia euchroma*, a plant used in traditional Chinese medicine.[10d]

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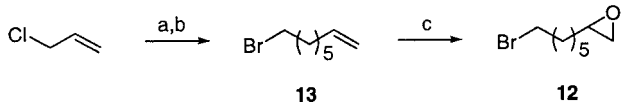
10.1021/jo0012445 CCC: $19.00 © 2000 American Chemical Society
Published on Web 11/14/2000

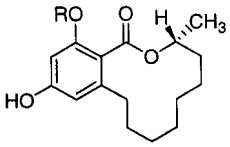
Scheme 1[a]



13 12

[a] Reagents and conditions: (a) 1. Mg, Et_2O, 2. Extraction with Et_2O [58%]; (b) 1,5-dibromopentane, Li_2CuCl_4 (cat.), THF, −20 °C, 2.5 h, [50 %]; (c) *m*-CPBA, CH_2Cl_2, 0 °C → rt, 19 h, [85 %].

Both naturally occurring lactones were found to be efficient inhibitors of prostaglandin biosynthesis and both exhibit significant antileukemic activity.[10b,10d] Thus, several total syntheses of these compounds have been published.[11]



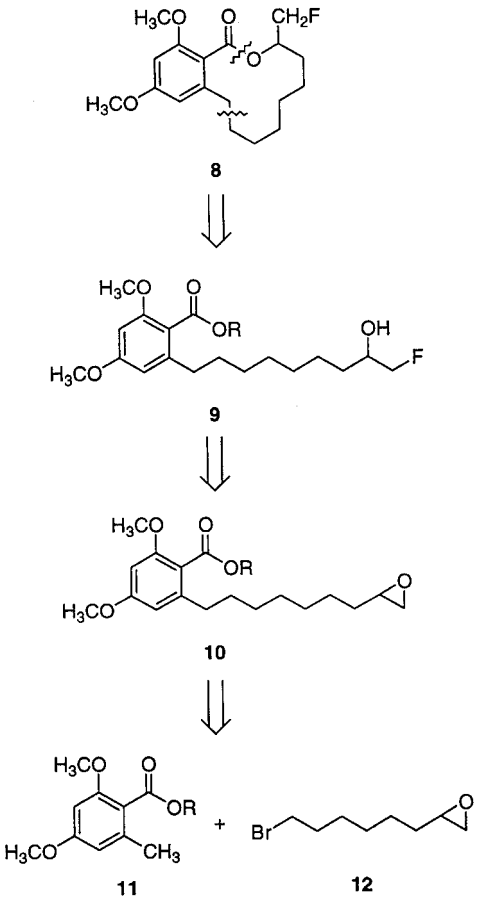
R = CH_3 **7a**
R = H **7b**

Results and Discussion

According to our experience in the synthesis of monofluorinated macrolides, we intended to construct the title compound **8** analogously to the fluoro-phoracantholides.[5,9] Retrosynthetic analysis of **8** led to the benzoic ester **9** bearing a 9-fluoro-8-hydroxynonane as a side-chain in the *ortho*-position. This compound should be available by regioselective hydrofluorination of the oxirane formed by alkylation of the methyl group of benzoic acid **11** with the bromide **12**.

The starting material **11** (R = H) was obtained from orcinol in a three-step reaction pathway according to reference[11e] while 8-bromoct-1-ene oxide (**12**) was synthesized analogously to known procedures[12] in three steps from allyl chloride and 1,5-dibromopentane via **13** (Scheme 1).

Alkylation of benzoic acid **11** with the bromide **12** gave **10a** which had to be protected as the methyl ester prior to the hydrofluorination of the oxirane ring. There are many different methods for the synthesis of fluorohydrins from epoxides.[13] To obtain selectively the regioisomer **9** in a high yield, we employed potassium hydrogen difluoride (KHF_2) and 18-crown-6 in DMF under refluxing conditions according to the method applied for other epoxides.[6,14] A 90:10 mixture of regioisomers was formed



from which **9** was isolated by column chromatography (Scheme 2).

For the final cyclization, the methyl ester **9** had to be first hydrolyzed. However, all attempts to hydrolyze *o,o′*-disubstituted benzoic esters **9** (R = Me, *t*-Bu, $CHPh_2$) under various conditions, including enzymatic hydrolysis by *Candida rugosa* lipase or porcine pancreatic lipase, failed. Using mildly basic conditions, only the methyl ester **9** (R = Me) was reisolated, while under forcing conditions (60 °C), the fluorohydrin moiety was not stable and gave partially the epoxide, besides other products. The hydrolysis with sulfuric acid of the methyl ester or with trifluorocetic acid of the *tert*-butyl ester (**9**, R = *t*-Bu) resulted in partial defluorination without hydrolysis of the ester function. Under the conditions of benzhydryl ester synthesis the side chain was cleaved partially, and a mixture of compounds was formed.

Consequently, we planned an alternative synthetic strategy for "fluoro-lasiodiplodin" **8** which was based on ring-closing metathesis as the key step to form the macrocyclic ring. Since this methodology is evolving into a mature preparative method, it was applied to several

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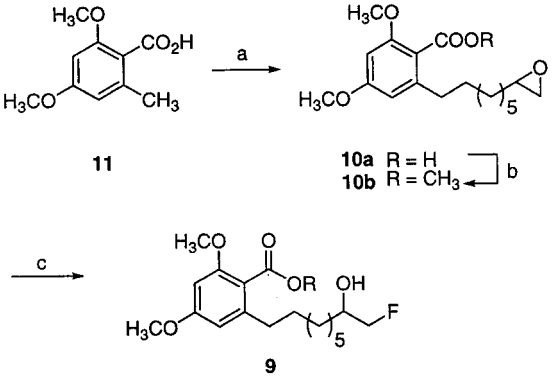
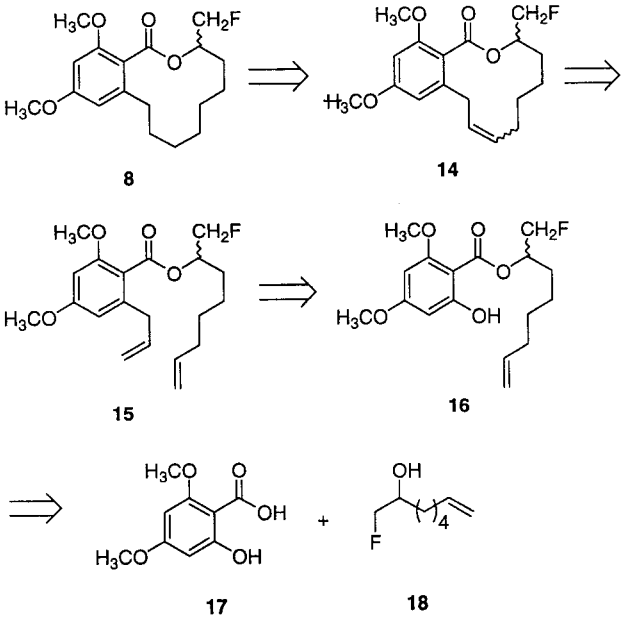
Scheme 2[a]



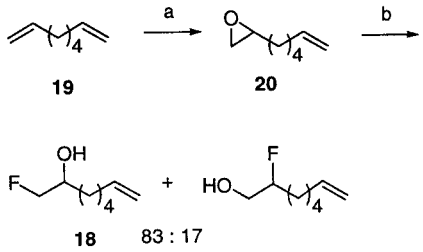
[a] Reagents and conditions: (a) 1. LDA, THF, −78 °C → −15 °C, 3 h 2. 8-bromooct-1-ene oxide **12**, THF, −30 °C, 12 h → rt [55%]; (b) DCC, DMAP, CH_3OH, CH_2Cl_2 [67%]; (c) KHF_2, 18-crown-6, DMF, reflux, 36 h, chromatography [50%].

natural product total syntheses and was also the crucial step in the synthesis of (*R*)-(+)-lasiodiplodin.[11i] The target compound **8** should be formed from diene **15** by ring-closing metathesis and subsequent hydrogenation. Compound **15** should be available from the phenol **16** which could be formed from the known salicylic acid derivative **17** by esterification with 1-fluoro-oct-7-en-2-ol (**18**). The fluorohydrin **18** should be available from 1,7-octadiene (**19**).



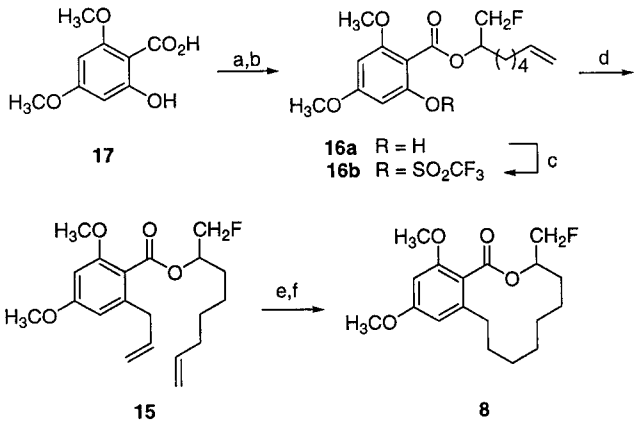
The starting material, 2,4-dimethoxysalicylic acid (**17**), was prepared from 3,5-dimethoxyphenol by a four-step procedure[15−18] in 38% overall yield. The synthesis of **18** started from 1,7-octadiene (**19**), which was transformed into the mono-epoxide **20**. Refluxing of **20** with KHF_2/18-crown-6 in DMF according to the literature[6,19] led to

Scheme 3[a]



[a] Reagents and conditions: (a) *m*-CPBA, CH_2Cl_2, 12 h to give **20** [58%]; (b) KHF_2, 18-crown-6, DMF, reflux, 36 h, chromatography [83%].

Scheme 4[a]



[a] Reagents and conditions: (a) 2,4,6-trichlorobenzoyl chloride, Et_3N, THF, 12 h, rt; (b) 1-fluoro-oct-7-en-2-ol (18), toluene, DMAP, 100 °C, 2.5 h [64%]; (c) $(CF_3SO_2)_2O$, pyridine, 0 °C → rt, 24 h [80%]; (d) allyltributylstannane, $Pd_2(dba)_3$, TFP, LiCl, NMP, 40 °C, 41 h [65%]; (e) $(PCy_3)_2Cl_2Ru{=}CHPh$, CH_2Cl_2, 45 °C, 36 h [65%]; (f) H_2, Pd/C, MeOH, rt, 12 h [83 %].

1-fluoro-oct-7-en-2-ol (**18**) as the main regioisomer (83%), which was purified by flash chromatography (Scheme 3).

Esterification of **17** with the fluorinated alcohol **18** under Yamaguchi's conditions[7] resulted in the formation of **16a**. After activation of **16a** with $(CF_3SO_2)_2O$ in pyridine,[20] the corresponding aryltriflate **16b** was subjected to a Stille reaction with allyltributylstannane and $Pd_2(dba)_3$/tris(2-furyl)phosphane (TFP) as catalyst in the presence of LiCl in *N*-methylpyrrolidone (NMP) analogously to ref 21. In this way the cross-coupling product **15** was obtained as a precursor for cyclization. The macrocyclization was achieved by ring-closing metathesis in high dilution in dichloromethane catalyzed with benzylidenebis(tricyclohexylphosphine)dichlororuthenium ($Cl_2(PCy_3)_2Ru{=}CHPh$),[22] a catalyst introduced to metathesis reactions by Grubbs et al.[23] The resulting unsaturated macrolide **14**, formed as an 81:19 mixture of (*E*)- and (*Z*)-isomers, was hydrogenated in the presence of palladium on carbon to give the racemic "fluoro-lasiodiplodin" **8** in 18% overall yield (Scheme 4).

The synthesis of the (*S*)-enantiomer of compound **8** was accomplished by enzymatic resolution of 1-fluoro-oct-7-en-2-ol (**18**), as the key step. Compound **18** was derace-

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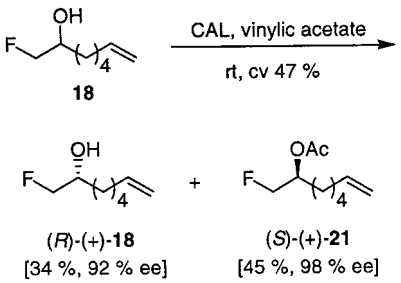
mized by a lipase-catalyzed acetylation with *Candida antarctica* lipase (CAL, Novozym435) and vinyl acetate in cyclohexane according to a procedure which we have successfully used for other fluorinated alcohols,[9,24] to obtain the chiral nonracemic (*R*)-(+)-**18** and (*S*)-(−)-**18** with very high ee's after separation of (*R*)-(+)-**18** and (*S*)-(+)-**21** by chromatography and hydrolysis of acetate **21** (eq 1).



The enantiomer (*S*)-(−)-**18** was used as a functional building block for the synthesis of (*S*)-(+)-**8** as described above for the racemate without loss of optical activity. Unfortunately the enantiomeric excess of the final product could neither be determined by chiral GC, nor using chiral HPLC, nor with the chiral shift reagent Eu(hfc)$_3$ in ^{19}F or ^{1}H NMR spectroscopy.[25]

Conclusion

The monofluorinated analogue **8** of lasiodiplodin has been synthesized using a ring-closing metathesis as the key step. After preparation of the acid **17** in an overall yield of 38% in four steps and synthesis of the fluorohydrin **18** in 48% yield in two steps, the racemic target molecule **8** was prepared in five steps in 18% overall yield. The enantioselective synthesis was achieved by lipase-mediated acetylation of fluorohydrin **18** with Novozym435 and vinyl acetate resulting in obtaining both enantiomers of the desired building block. After hydrolysis of the acetate (*S*)-(+)-**21**, the enantiomer (*S*)-(+)-**8** was obtained analogously to the preparation of the racemate.

Experimental Section

General. Melting/boiling points: uncorrected values. ^{1}H NMR (300 MHz), ^{13}C NMR (75.5 MHz) and ^{19}F NMR (282.4 MHz), about 20% solutions in $CDCl_3$, TMS for ^{1}H, $CDCl_3$ for ^{13}C, and $CFCl_3$ for ^{19}F as internal standards. The multiplicity of ^{13}C signals was determined by DEPT technique. Mass spectra (70 eV): GLC/MS coupling. Gas liquid chromatography: Quartz capillary column, Hewlett-Packard, HP-1 (0.52 μm), dimensions: 25 m, ∅ 0.33 mm. The ee's were determined by GLC analysis on a β-cyclodextrin phase, Sulpelco, Beta-Dex 120 (0.25 μm), dimensions: 30 m, ∅ 0.25 mm. Thin-layer chromatography: Merck silica gel DC 60 F_{254}. Flash chromatography: Merck silica gel 60. Chiral HPLC: Chira OJ (Grom Co., 250 × 2 mm, cellulose-tris-4-methylbenzoate, heptane/ethanol, 9:1 containing 0.1% H_2O and 0.01% TFA). Elemental analyses: Mikroanalytisches Laboratorium, Universität Münster.

2,4-Dimethoxy-6-methyl benzoic acid (**11**) was prepared from orcinol as described in ref 11g. Allyl chloride, 1,5-dibromopentane, 3,5-dimethoxyphenol, and 1,7-octadiene were purchased from Acros chemicals. Benzylidenebis(tricyclohexylphosphine)dichlororuthenium was obtained from Fluka chemicals while all other applied reagents were obtained from Acros and Aldrich chemicals. All solvents were purified by distillation and stored over molecular sieves. CH_2Cl_2 was dried by distillation from P_2O_5 and stored over molecular sieves (0.4 nm). THF was dried by distillation from Na/K alloy. Lipase Novozym435 was kindly donated by Novo Nordisk A/S.

8-Bromo-oct-1-ene (13). According to procedures given in ref 12 (allylmagnesium chloride[12a] was used instead of allylmagnesium bromide[12b]), treatment of magnesium **(**25.0 g, 1.03 mol) in Et_2O (250 mL) with allyl chloride (23.6 g, 0.31 mol) at −15 °C gave an ethereal solution of allylmagnesium chloride (180 mmol, 58%). After filtration under an argon atmosphere the ethereal solution of this Grignard reagent (77 mmol) was added dropwise to a suspension of dibromopentane (19.48 g, 84.7 mmol), $CuCl_2$ (1.65 g, 12.3 mmol) and LiCl (1.04 g, 24.5 mmol) in THF (100 mL) at −20 °C and stirred for 2 h at this temperature. After warming to room temperature and the usual workup, **13** was isolated as a colorless liquid by distillation using a spinning band column. Yield: 7.47 g (50%), bp 84 °C/20 mmHg (lit.:[12b] Yield: 33%, bp 98−99 °C/24 mmHg). The spectroscopic data agree with published ones.[12b]

Epoxidation with *m*-CPBA. A solution of the olefins (**13** or **19**) in CH_2Cl_2 was dropped into a solution of *m*-CPBA in CH_2Cl_2 at 0 °C. The reaction mixture was stirred for another 20 h at room temperature (reaction monitored by TLC). After separating the formed *m*-CBA by filtration, the filtrate was treated with aqueous solutions of 10% Na_2SO_3, 10% $NaHCO_3$, and saturated aqueous NaCl. After drying with Na_2SO_4, evaporating the solvent, and purifying by column chromatography (silica gel, cyclohexane/ethyl acetate, 3:1), the oxiranes were obtained.

8-Bromo-1,2-epoxyoctane (12). From **13** (11.01 g, 62 mmol) in CH_2Cl_2 (60 mL) and *m*-CPBA (17.36 g, 74 mmol) in CH_2Cl_2 (150 mL) was formed **12** and isolated as described above. Yield: 10.98 g (85%). ^{1}H NMR: δ 1.27−1.60 (m, 8H), 1.80 (tt, J = 6.7 Hz, 2H), 2.41 (dd, J = 5.1 Hz, J = 2.7 Hz, 1H), 2.69 (dd, J = 5.1 Hz, J = 4.1 Hz, 1H), 2.81−2.89 (m, 1H), 3.37 (t, J = 6.7 Hz, 2H); ^{13}C NMR: δ 25.7 (t), 28.0 (t), 28.5 (t), 31.8 (t), 32.2 (t), 33.7 (t), 46.9 (t), 52.1 (d); MS *m*/*z*: 205/207 (0.2), 176/178 (1), 162/164 (1), 148/150 (8), 127 (4), 95 (100), 71 (83), 67 (24). Anal. Calcd for $C_8H_{15}OBr$ (207.1): C, 46.39; H, 7.31. Found: C, 46.39; H, 7.42.

7,8-Epoxyoct-1-ene (20). From **19** (5.50 g, 50 mmol) in CH_2Cl_2 (50 mL) and *m*-CPBA (9.38 g, 40 mmol) in CH_2Cl_2 (100 mL) was formed **20** and purified by column chromatography (silica gel, CH_2Cl_2). Yield: 3.65 g (58%). ^{1}H NMR: δ 1.40−1.60 (m, 6H), 2.03−2.13 (m, 2H), 2.45 (dd, J = 5.0 Hz, J = 2.6 Hz, 1H), 2.73 (dd, J = 5.0 Hz, J = 4.06 Hz, 1H), 2.87−2.92 (m, 1H), 4.92−5.05 (m, 2H), 5.80 (ddt, J = 17.2 Hz, J = 10.3 Hz, J = 6.7 Hz, 1H); ^{13}C NMR: δ 25.4−33.6 (4t), 47.0 (d), 52.2 (t), 114.5 (t), 138.6 (d); MS *m*/*z*: 127 (2), 125 (2), 97 (6), 83 (25), 71 (16), 67 (75). ^{1}H NMR spectroscopic data agree with published data.[26]

6-(8′,9′-Epoxynon-1′-yl)-2,4-dimethoxybenzoic Acid (10a). Under an argon atmosphere, a THF-solution of LDA was prepared by adding 1.6 M *n*-butyllithium (9.3 mL, 15 mmol) in diisopropylamine (2.1 mL, 15 mmol) dissolved in THF (18 mL) at −78 °C. Under an argon atmosphere this solution was injected slowly into a stirred solution of 2,4-dimethoxy-6-methylbenzoic acid (**11**) (1.30 g, 7.1 mmol) in THF (18 mL) at −78 °C and allowed to warm to −15 °C. After stirring at −15 °C to −10 °C for 3 h, the reaction mixture was cooled to −30 °C, and 8-bromo-1,2-epoxyoctane (**12**) (1.46 g, 7.1 mmol)

(24) (a) Goj, O.; Burchardt, A.; Haufe, G. *Tetrahedron: Asymmetry* **1997**, *8*, 399−408. (b) Skupin, R.; Cooper, T. G.; Fröhlich, R.; Prigge, J.; Haufe, G. *Tetrahedron: Asymmetry* **1997**, *8*, 2453−2464. (c) Takahashi, T.; Fukushima, A.; Tanaka, Y.; Segawa, M.; Hori, H.; Takeuchi, Y.; Burchardt, A.; Haufe, G. *Chirality* **2000**, *12*, 458−463.

(25) To proof the stereoconservation of the esterification step, we hydrolyzed (2′*S*)-**16a** with KOH/MeOH. No loss of optical purity was found in the formed fluorohydrin (*S*)-**18** by chiral GLC. With 20−50 mol % of the shift reagent, the ortho methoxy groups of **14**, **15**, and **8** were broadened showing a shoulder. No exact determination of the ee was possible.

(26) Byrom, N. T.; Grigg, R.; Kongkathip, B.; Reimer, G.; Wade, A. R. *J. Chem. Soc., Perkin Trans. 1* **1984**, *8*, 1643−1653.

dissolved in THF (3.5 mL) was added. The resulting solution was allowed to warm to room temperature over a period of 12 h. The reaction mixture was hydrolyzed with saturated aqueous NH_4Cl (80 mL), and the pH was adjusted to pH 3 with 2 N HCl. The volume of the mixture was reduced to 100 mL by evaporation and extracted with CH_2Cl_2. The organic layer was dried with Na_2SO_4 and evaporated. Purification of the crude product by column chromatography (silica gel, ethyl acetate) gave **10a** (1.25 g, 55%). ^{1}H NMR: δ 1.20−1.60 (br m, 12H), 2.45 (dd, J = 4.8 Hz, J = 2.9 Hz, 1H), 2.73 (dd, J = 4.8 Hz, J = 4.5 Hz, 1H), 2.79 (t, 2H), 2.87−2.93 (m, 1H), 3.81, 3.87 (2s, 6H), 6.34, 6.39 (2d, J = 2.4 Hz, 2H); ^{13}C NMR: δ 25.8 (t), 29.0 (t), 29.2 (t), 31.1 (t), 32.2 (t), 34.5 (t), 47.0 (t), 52.4 (d), 55.3 (q), 56.1 (q), 96.2 (d), 107.2 (d), 113.8 (s), 146.0 (s), 161.8 (s), 169.6 (s) 171.1 (s); MS (silylated **10a**) *m*/*z*: 396 (5), 395 (17), 394 (58), 379 (16), 377 (16), 349 (4), 305 (17), 304 (41), 279 (35); 268 (56), 267 (33), 224 (39); 191 (100), 178 (39), 177 (31), 152 (74), 151 (27), 135 (17), 91 (3), 89 (22), 77 (11), 73 (99).

Methyl 6-(8′,9′-Epoxynon-1′-yl)-2,4-dimethoxy-6-methylbenzoate (10b). Under argon, **10a** (2.04 g, 6.3 mmol), DCC (2.69 g, 10 mmol), methanol (1.5 mL, 50 mmol), and DMAP (0.16 g, 1.3 mmol) were dissolved in CH_2Cl_2 (30 mL) and stirred at room temperature for 12 h until esterification was complete (monitored by TLC). *N*,*N*-Dicyclohexylurea was filtered off, the filtrate was washed with water, 5% acetic acid solution, and again with water and dried ($MgSO_4$), and the solvent was evaporated in vacuo to give the ester **10b** (1.42 g, 67%) after column chromatography (silica gel, pentane/Et_2O, 1:1). ^{1}H NMR: δ 1.22−1.59 (br m, 12H,), 2.42 (dd, J = 4.9 Hz, J = 2.6 Hz, 1H), 2.52 (t, 2H), 2.71 (dd, J = 4.9 Hz, J = 4.1 Hz, 1H), 2.82−2.88 (m, 1H), 3.75, 3.79 (2s, 6H), 3.84 (s, 3H), 6.25−6.30 (m, 2H), ^{13}C NMR: δ 25.8 (t), 29.3 (t), 29.4 (t), 31.0 (t), 32.3 (t), 33.8 (t), 46.9 (t), 51.9 (q), 52.2 (d), 55.2 (q), 55.8 (q), 96.0 (d), 105.8 (d) 157.9 (s), 161.2 (s), 168.7 (s); MS *m*/*z*: 337 (6), 336 (25), 306 (3), 305 (14), 304 (10); 289 (10), 277 (4), 210 (100), 191 (39), 179 (8), 152 (9), 151 (24), 121 (4), 91 (5), 77 (4).

Oxirane Ring Opening with KHF_2/18-Crown-6.[5] To an argon-covered solution of 18-crown-6 (10.6 g, 40 mmol) and KHF_2 (7.8 g, 100 mmol) in refluxing dry DMF (120 mL) was added the relevant epoxide (25 mmol). The solution was refluxed for additional 36 h. After cooling, the solution was poured into ice−water, and the mixture was extracted with CH_2Cl_2. The combined organic layer was repeatedly washed with water and dried with Na_2SO_4. Evaporation of the solvent gave the respective secondary β-fluorohydrins together with about 10% of their regioisomers. The isomers were separated by flash chromatography (silica gel, cyclohexane/ethyl acetate, 3:1).

Methyl 6-(9′-Fluoro-8′-hydroxynon-1′-yl)-2,4-dimethoxybenzoate (9). Synthesized from the oxirane **10b** (0.87 g, 2.6 mmol). Yield: 0.46 g (50%). ^{1}H NMR: δ 1.20−1.60 (m, 10H), 1.90−2.10 (m, 2H), 2.52 (m, 3H, 1′-H_2), 3.77, 3.79, 3.85 (3s), 3.78−3.80 (m, 1H), 4.26 (ddd, $J_{H,F}$ = 48.2 Hz, J = 9.3 Hz, J = 6.7 Hz, 1H), 4.40 (ddd, $J_{H,F}$ = 47.0 Hz, J = 9.5 Hz, J = 3.1 Hz, 1H), 6.28−6.32 (m, 2H); ^{13}C NMR: δ 25.3 (t), 29.2 (t), 29.4 (t), 31.1 (t), 31.8 (dt), 33.9 (t), 52.0 (q), 55.4 (q), 55.9 (q), 70.7 (dd, J_{CF} = 17.4 Hz), 87.1 (dt, J_{CF} = 165.3 Hz), 96.2 (d), 105.9 (d), 116.3 (s,), 143.0 (s,), 158.1 (s), 175.9 (s), 192 (s); ^{19}F NMR: δ −228.6 (dt, J = 47.7 Hz, J = 19.1 Hz); MS *m*/*z*: 356 (0.5), 355 (1), 325 (10), 324 (7), 307 (4), 305 (1), 291 (24), 210 (100), 191 (51), 179 (22), 151 (35); 121 (10); 91 (14), 77 (14), 63 (19). Anal. Calcd for $C_{19}H_{29}O_5F$ (356.5): C, 64.02; H, 8.21. Found: C, 64.34; H, 8.19.

1-Fluorooct-7-en-2-ol (18).[27] Synthesized from the oxirane **20** (3.15 g, 25 mmol). Yield: 3.03 g (83%). ^{1}H NMR: δ 1.30−1.55 (m, 6H), 1.80−1.95 (br s, 1H), 2.02−2.12 (m, 2H), 3.82−3.91 (m, 1H), 4.27 (ddd, $J_{H,F}$ = 48.2 Hz, J = 9.3 Hz, J = 6.7 Hz, 1H), 4.42 (ddd, $J_{H,F}$ = 47.0 Hz, J = 9.3 Hz, J = 3.1 Hz, 1H), 4.91−5.05 (m, 2H), 5.80 (ddt, J = 16.9 Hz, J = 10.3 Hz, J = 6.7 Hz, 1H); ^{13}C NMR: δ 24.7 (t), 28.8 (t), 31.7 (dt, $J_{C,F}$ = 7.6 Hz), 33.5 (t); 70.4 (dd, $J_{C,F}$ = 17.8 Hz), 87.0 (dt, $J_{C,F}$ = 167.9 Hz), 114.5 (t), 138.6 (d); ^{19}F NMR: δ −228.9 (dt, J = 47.7 Hz, J = 19.1 Hz); MS *m*/*z*: 146 (<0.1), 128 (8), 113 (22), 95 (76), 67 (61).

Enzymatic Resolution of 1-Fluoro-oct-7-en-2-ol (18). Racemic **18** (146 mg, 1 mmol) and vinylic acetate (129 mg, 1.5 mmol) were dissolved in cyclohexane (5 mL). After addition of Novozym435 (73.6 mg), the resulting suspension was stirred at room temperature until 50% conversion was reached. For reaction monitoring, a 0.2 mL aliquot of the suspension was filtered through silica gel (addition of 2 mL of ethyl acetate as eluent) and submitted to GLC analysis. After completion of the reaction (about 12 h), the whole suspension was treated in the same manner. Column chromatography (silica gel, cyclohexane/ethyl acetate, 3:1) provided the acetate (*S*)-(+)-**21** and the fluorohydrin (*R*)-(+)-**18**.

(2*R*)-(+)-1-Fluoro-oct-7-en-2-ol ((2*R*)-(+)-18). Yield: 49.6 mg (34%); $[\alpha]^{20}_D$ = +6.9 (*c* 1.04, CH_2Cl_2), 92% ee (GLC).

(7*S*)-(+)-7-Acetoxy-8-fluoro-oct-1-ene ((7*S*)-(+)-21). Yield: 99.6 mg (45%); $[\alpha]^{20}_D$ = +7.7 (c 1.31, CH_2Cl_2), 98% ee (GLC). ^{1}H NMR: δ 1.20−1.50 (m, 4H), 1.55−1.57 (m), 1.95−2.10 (m, 2H), 2.07 (s, 3H), 4.39 (ddd, $J_{H,F}$ = 47.2 Hz, J = 10.0 Hz, J = 4.8 Hz, 1H), 4.47 (ddd, $J_{H,F}$ = 47.5 Hz, J = 10.3 Hz, J = 3.3 Hz, 1H), 4.96 (m, 2H), 4.97−5.11 (m, 1H), 5.78 (ddt, J = 16.9 Hz, J = 10.2 Hz, J = 6.7 Hz, 1H); ^{13}C NMR: δ 20.9 (q), 24.5 (t), 28.5 (t), 29.3 (dt, $J_{C,F}$ = 5.9 Hz), 33.4 (t), 72.2 (dd, $J_{C,F}$ = 17.8 Hz), 83.5 (dt, $J_{C,F}$ = 172.9 Hz), 114.6 (t), 138.4 (d), 170.4 (s); ^{19}F NMR: δ −231.1 (dt, J = 47.7 Hz, J = 21.0 Hz); MS *m*/*z*: 188 (<1), 173 (1), 146 (1), 128 (30), 113 (15), 95 (100), 86 (30), 81 (34), 68 (91), 67 (70). Anal. Calcd for $C_{10}H_{17}O_2F$ (188.3): C, 63.80; H, 9.11. Found: C, 64.09; H, 9.22.

(2*S*)-(−)-1-Fluoro-oct-7-en-2-ol ((2*S*)-(−)-18). (*S*)-(+)-**21** (188 mg, 1 mmol) dissolved in methanol (10 mL) was treated with KOH (80 mg, 2 mmol) and stirred for 2 h at room temperature. The solvent was removed in vacuo, and the residue was diluted with water and extracted with ethyl acetate. Drying the combined organic layers ($MgSO_4$) and evaporating the solvent gave (2*S*)-(−)-**18** (139 mg, 95%): $[\alpha]^{20}_D$ = −7.1 (*c* 1.03, CH_2Cl_2), >98% ee (GLC).

1′-Fluoroct-7′-en-2′-yl 2-Hydroxy-4,6-dimethoxybenzoate (16a). Under an argon atmosphere, 2,4,6-trichlorobenzoyl chloride (0.91 mL, 5.7 mmol) was added to a stirred mixture of **17** (1.13 g, 5.7 mmol) and Et_3N (0.85 mL, 6.3 mmol) in THF (57 mL). After stirring at room temperature for 12 h and removing the triethylamine hydrochloride under argon, the resulting anhydride was diluted with toluene (60 mL) and treated with **18** (0.88 g, 6.3 mmol) and DMAP (1.51 g, 12.4 mmol) and refluxed for 2.5 h. Subsequently, the reaction mixture was washed successively with water, 3% aqueous HCl, water, 10% aqueous $NaHCO_3$ solution, and water again and dried. The solvent was removed, and the residue was purified by column chromatography (silica gel, CH_2Cl_2) to give **16a**. Yield: 1.19 g (64%). ^{1}H NMR: δ 1.40−1.53 (m, 4H), 1.70−1.90 (m, 2H), 2.03 (m, 2H), 3.80, 3.79 (2s, 6H), 4.43−4.66 (dm, $J_{H,F}$ = 47.2 Hz, 2H), 4.91−5.04 (m, 2H), 5.20−5.36 (m, 1H), 5.80 (ddt, J = 16.9 Hz, J = 10.2 Hz, J = 6.7 Hz, 1H), 5.96, 6.10 (2d, J = 2.4 Hz); ^{13}C NMR: δ 24.4 (t), 28.6 (t), 29.6 (t), 33.5 (t), 55.4 (q),. 55.9 (q) 72.9 (dd, $J_{C,F}$ = 20.4 Hz), 83.5 (dt, $J_{C,F}$ = 172.9 Hz), 91.7 (d), 93.4 (d), 114.6 (t), 138.5 (d), 162.5 (s), 165.5 (s), 165.8 (s), 170.6 (s); ^{19}F NMR: δ −230.3 (dt, J = 47.7 Hz, J = 19.1 Hz); MS *m*/*z*: 326 (0), 325 (0.2), 199 (4), 180 (100), 152 (20), 137 (10), 109 (2), 95 (5), 79 (2), 67 (4), 55 (6), 41 (11), 39 (12). Anal. Calcd for $C_{17}H_{23}O_5F$ (326.4): C, 62.55; H, 7.11. Found: C, 62.07; H, 7.16.

(2′*S*)-(−)-16a: Yield 1.24 g (67%); $[\alpha]^{20}_D$ = −27.4 (*c* 1.06, CH_2Cl_2).

1′-Fluorooct-7′-en-2′-yl2,4-Dimethoxy-6-trifluoromethanesulfonatebenzoate (16b). To a solution of **16a** (0.74 g, 2.3 mmol) in pyridine (1.2 mL) was slowly added trifluoromethanesulfonic anhydride (0.71 g, 0.42 mL, 2.5 mmol) at 0 °C. The resulting mixture was stirred for 24 h while allowing it to warm to room temperature. The resulting mixture was poured into water and extracted with Et_2O. The ethereal extract was washed sequentially with water, 10% aqueous HCl, and concentrated aqueous NaCl solution and dried ($MgSO_4$). Evaporation of the solvent gave the trifluoromethanesulfonate

(27) First synthesized by Ishihara, J.; Hanafusa, T. *J. Chem. Soc., Chem. Commun.* **1989**, 1848−1850, no spectroscopic data given.

16b. Yield: 0.84 g (80%). ^{1}H NMR: δ 1.40−1.58 (m, 4H), 1.70−1.85 (m, 2H), 2.02−2.13 (m, 2H), 3.84 (s, 6H), 4.51 (ddd, $J_{H,F}$ = 47.4 Hz, J = 10.3 Hz, $^3J_{H,H}$ = 3.6 Hz, 1H, 1′-H); 4.59 (ddd, $^2J_{H,F}$ = 47.4 Hz, $^2J_{H,H}$ = 10.3 Hz, $^3J_{H,H}$ = 3.3 Hz, 1H), 4.90−5.05 (m, 2H), 5.20−5.33 (m, 1H), 5.80 (ddt, J = 17.2 Hz, J = 10.3 Hz, J = 6.7 Hz, 1H), 6.44−6.48 (m, 2H); ^{13}C NMR: δ 24.5 (t), 29.1 (t), 29.4 (dt, J_{CF} = 4.9 Hz), 33.5 (t), 55.9 (q), 56.4 (q), 74.1 (dd, $J_{C,F}$ = 22.6 Hz), 83.2 (dt, $J_{C,F}$ = 175.1 Hz), 98.5 (d), 99.0 (d), 110.2 (t), 120.7 (t, $J_{C,F}$ = 361.5 Hz), 138.6 (d), 148.0 (s), 159.5 (s), 162.5 (s), 162.8 (s), 176.3 (s); ^{19}F NMR: δ −231.3 (dt, J = 22.7 Hz, J = 47.7 Hz, 1F), −73.8 (s, CF_3).

(2′*S*)-(−)-16b: Yield 0.79 g (75%); $[\alpha]^{20}_D$ = −10.8 (*c* 0.97, CH_2Cl_2).

1′-Fluorooct-7′-en-2′-yl 2-Ally-4,6-dimethoxybenzoate (15). The triflate **16b** (0.38 g, 0.83 mmol) was dissolved in *N*-methylpyrrolidone (5 mL) and treated with anhydrous LiCl 106 mg, 2.5 mmol), trifurylphosphine (23.1 mg, 12 mol %), and $Pd_2(dba)_3$ (11.4 mg, 3 mol %). After 10 min at room temperature, the solution was treated with allyltributyltin (0.14 mL, 0.97 mmol), and the mixture was stirred at 40 °C for 40 h. Dilution with saturated KF solution was followed by extraction with ethyl acetate, drying ($MgSO_4$), and evaporation. Column chromatography (silica gel, cyclohexane/ethyl acetate, 3:1) gave **15**. Yield: 190 mg (65%). ^{1}H NMR: δ 1.40−1.54 (m, 4H), 1.65−1.80 (m, 2H), 2.03−2.11 (m, 2H), 3.37 (d, J = 6.4 Hz, 2H), 3.79, 3.80 (2s, 6H), 4.48 (ddd, $J_{H,F}$ = 47.2 Hz, J = 10.0 Hz, J = 5.0 Hz, 1H), 4.56 (ddd, $J_{H,F}$ = 47.7 Hz, J = 7.4 Hz, J = 3.3 Hz, 1H); 4.90−5.10 (m, 4H), 5.20−5.34 (m, 1H), 5.72−5.99 (m, 2H), 6.34 (m 2H); ^{13}C NMR: δ 24.6 (t), 26.9 (t), 29.5 (dt, $J_{C,F}$ = 5.1 Hz), 33.6 (t), 37.7 (t), 55.4 (q), 55.8 (q), 72.9 (dd, $J_{C,F}$ = 20.3 Hz), 83.6 (dt, $J_{C,F}$ = 175.5 Hz), 96.8 (d), 106.1 (d), 114.5 (t), 116.3 (t), 136.3 (d), 138.6 (d), 140.2 (s), 158.3 (s), 161.6 (s), 162.6 (s), 167.6 (s); ^{19}F NMR: δ −230.3 (dt, J = 49.6 Hz, ^3J = 19.1 Hz); MS *m*/*z*: 351 (4), 350 (15), 222 (19), 207 (100), 205 (90), 177 (34), 146 (13), 115 (12), 91 (12), 41 (22); HRMS calcd for $C_{20}H_{27}O_4F$ 350.1893, found 350.1861.

(2′*S*)-(−)-15: Yield 0.18 g (62%); $[\alpha]^{20}_D$ = −20.7 (*c* 0.65, CH_2Cl_2).

7-Fluoromethyl-2,4-dimethoxy-7,8,9,10,11,14-hexahydro-6-oxabenzocyclododecen-5-on (14). Solutions of the diene **15** (0.16 g, 0.46 mmol) and of benzylidenebis(tricyclohexylphosphine)dichlororuthenium (16 mg, 0.02 mmol, 4.3 mol %) in CH_2Cl_2 each (27 mL) were simultaneously added dropwise to CH_2Cl_2 (27 mL) over a period of 12 h at reflux. After stirring for another 24 h at that temperature, the solvent was removed in vacuo, and the residue was purified by flash chromatography (silica gel, cyclohexane/ethyl acetate 3:1) to give **14**. Yield: 90 mg (65%) as a mixture of *E*/*Z*-isomers (81:19): ^{1}H NMR: δ 1.23−1.85 (m, 6H), 2.11−2.25 (m, 2H), 3.04−3.12 (m, 2H), 3.78, 3.80 (2s, 6H), 4.43 (ddd, $J_{H,F}$ = 47.7 Hz, J = 9.5 Hz, J = 4.1 Hz, 1H), 4.59 (ddd, $J_{H,F}$ = 47.7 Hz, J = 10.3 Hz, J = 4.0 Hz, 1H), 5.14−5.46 (m, 3H), 6.33, 6.34 (2d, J = 2.1 Hz, 2H); ^{13}C NMR: δ 19.7 (t), 24.8 (t), 32.5 (dt, $J_{C,F}$ = 2.5 Hz), 38.3 (t), 55.3 (q), 56.1 (q), 70.0 (dd, $J_{C,F}$ = 20.4 Hz), 84.1 (dt, $J_{C,F}$ = 172.9 Hz), 97.1 (d), 107.3 (d), 116.8 (t), 128.7 (d), 132.9 (d), 141.1 (s), 158.8 (s), 161.4 (s), 167.9 (s); ^{19}F NMR: δ −230.8 (dt, J = 47.7 Hz, J = 19.1 Hz); MS *m*/*z*: 323 (12), 322 (63), 289 (10), 217 (39), 207 (100), 204 (66), 178 (24), 158 (8), 115 (10), 91 (8), 77 (8); HMRS calcd for $C_{18}H_{23}O_4F$ 322.1580, found 322.1569.

(7*S*)-(+)-14: Yield 98 mg (66%); $[\alpha]^{20}_D$ = +59.7 (*c* 0.49, CH_2Cl_2).

7-Fluoromethyl-2,4-dimethoxy-7,8,9,10,11,12,13,14-octahydro-6-oxabenzocyclodo-decan-5-one (8). Compound **14** (70 mg, 0.22 mmol) was dissolved in methanol (5 mL) and hydrogenated over Pd/C. Stirring the suspension for 12 h under a hydrogen atmosphere gave **8**. Yield: 58 mg (83%). ^{1}H NMR: δ 1.22−1.49 (m, 8H) 1.57−1.72 (m, 2H), 1.75−1.86 (m, 1H), 1.92−2.02 (m, 1H), 2.52−2.75 (m, 2H), 3.79, 3.80 (2s, 6H), 4.49 (ddd, $J_{H,F}$ = 47.2 Hz, J = 9.8 Hz, J = 4.8 Hz, 1H), 4.57 (ddd, $J_{H,F}$ = 47.2 Hz, J = 9.8 Hz, J = 5.5 Hz, 1H), 527−5.40 (m, 1H), 6.30−6.34 (m, 2H); ^{13}C NMR: δ 21.7 (t), 24.1 (t), 25.5 (t), 26.4 (t), 27.1 (dt, $J_{C,F}$ = 5.1 Hz), 30.0 (t), 30.6 (t); 55.3 (q), 56.0 (q), 73.2 (dd, $J_{C,F}$ = 20.4 Hz), 83.4 (dt, $J_{C,F}$ = 172.9 Hz), 96.4 (d), 106.1 (d), 117.3 (s), 143.0 (s), 158.1 (s), 161.5 (s), 168.2 (s); ^{19}F NMR: δ −229.5 (dt, J = 47.7 Hz, J = 19.1 Hz); MS *m*/*z*: 324 (2), 323 (14), 322 (66), 289 (12), 277 (5), 260 (14), 233 (5), 217 (36), 207 (100), 204 (68), 189 (34), 178 (27), 161 (8), 145 (5), 128 (5), 115 (10), 91 (8), 77 (8), 67 (5); HMRS calcd for $C_{18}H_{25}O_4F$ 324.1737, found 324.1773.

(7*S*)-(+)-8. Yield 60 mg (85%); $[\alpha]^{20}_D$ = +11.6 (*c* 0.57, CH_2Cl_2).

Acknowledgment. The authors are grateful to the "Deutsche Forschungsgemeinschaft" and the "Fonds der Chemischen Industrie" for generous support. M.R. would like to thank the Graduiertenkolleg "Hochreaktive Mehrfachbindungssysteme" for a stipend. The kind donation of chemicals and enzymes by Bayer AG, Leverkusen, Hüls AG, Marl and Novo Nordisk A/S, Denmark, are gratefully acknowledged.

Supporting Information Available: Synthesis of **17** from 3,5-dimethoxyphenol, spectroscopic data of compounds **17** and its precursors, and copies of ^{1}H, ^{13}C, and ^{19}F NMR spectra of compounds **8**, **14**, **15**, **16a**, **16b**, and **18**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO0012445