Optically Active Antifungal Azoles. IX.[1] An Alternative Synthetic Route for 2-[(1*R*,2*R*)-2-(2,4-Difluorophenyl)-2-hydroxy-1-methyl-3-(1*H*-1,2,4-triazol-1-yl)propyl]-4-[4-(2,2,3,3-tetrafluoropropoxy)phenyl]-3(2*H*,4*H*)-1,2,4-triazolone and Its Analogs

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Received October 7, 1998; accepted December 9, 1998

A new route for the synthesis of the optically active antifungal azole TAK-187, 2-[(1*R*,2*R*)-2-(2,4-difluorophenyl)-2-hydroxy-1-methyl-3-(1*H*-1,2,4-triazol-1-yl)propyl]-4-[4-(2,2,3,3-tetrafluoropropoxy)phenyl]-3(2*H*,4*H*)-1,2,4-triazolone, was established. The key synthetic intermediate, 2-[(1*R*)-2-(2,4-difluorophenyl)-2-oxo-1-methylethyl]-4-[4-(2,2,3,3-tetrafluoropropoxy)phenyl]-3(2*H*,4*H*)-1,2,4-triazolone (8), was prepared starting from the esters (11a, b) of (*S*)-lactic acid in a stereocontrolled manner. This optically active propiophenone derivative 8 was converted to the one carbon-elongated (1*R*,2*S*)-diol 7, which was then reacted with 1*H*-1,2,4-triazole to yield TAK-187. This newly developed route was applied to the synthesis of the analogs (25a, b—28a, b) containing an imidazolone or imidazolidinone nucleus.

Key words TAK-187; antifungal azole; triazolone; imidazolone; imidazolidinone; chiral synthesis

We have recently reported the synthesis and antifungal activity of triazolone and tetrazolone derivatives with the general formula I (Chart 1).[2] Among these azolones, 2-[(1*R*,2*R*)-2-(2,4-difluorophenyl)-2-hydroxy-1-methyl-3-(1*H*-1,2,4-triazol-1-yl)propyl]-4-[4-(2,2,3,3-tetrafluoropropoxy)phenyl]-3(2*H*,4*H*)-1,2,4-triazolone (TAK-187) was selected as a candidate for clinical trials.[3] We subsequently extended our study of the azolone-based antifungal azoles to the analogs with carbon substitutions in the azolone moiety: *i.e.*, the imidazolone (II) and imidazolidinone (III) derivatives depicted in Chart 1. In the preceding report, we described the stereocontrolled synthesis of II and III as well as their potent antifungal activity and broad antifungal spectrum.[1]

As reported previously, compounds I were prepared starting from methyl (*R*)-lactate (**1**) as a chiral synthon *via* the route involving *SN*2 displacement of the triflate **5** with an azolone anion followed by the oxirane ring-opening reaction with 1*H*-1,2,4-tiazole, as exemplified in Chart 2 for the synthesis of TAK-187 (**1**→**2**→**3**→**4**→**5**→**6**→TAK-187).[2] The imidazolones II were synthesized *via* substantially the same sequence of reactions as above, and the imidazolidinones III could be obtained from II by catalytic hydrogenation.[1] The procedure shown in Chart 2 was useful for the preparation of a wide variety of optically active 1,2,3-trisubstituted-2-butanols such as I—III, since the triflate **5** is highly reactive toward nucleophiles and all reaction steps are fully stereocontrolled. This method, however, is composed of several reactions and involves the labile synthetic intermediate **5**[4] which tends to decompose and, hence, there was a need to develop a more practical and efficient route for the synthesis of azolones I—III. In this paper, we describe an alternative route starting from (*S*)-lactic acid derivatives for the synthesis of TAK-187 and its congeners (II, III).

Our protocol for the new synthetic route to TAK-187 is illustrated in Chart 3 by a retrosynthetic formula. The final step is the introduction of 1*H*-1,2,4-triazole into the oxirane **6** or the diol **7**. For the synthesis of **6** and **7**, the optically active propiophenone derivative **8** with the (*R*)-configuration could be used as the precursor, since several synthetic procedures have been reported for the preparation of one-carbon-elongated diols or oxiranes from the corresponding carbonyl compounds,[5] although asymmetric induction at the carbon in the 2-position must be controlled. It was considered that **8** would be obtained from the (*S*)-lactic acid derivative **11** *via* an *SN*2 reaction, *i.e.*, **11**→**9**→**8** or **11**→**10**→**8**. We, therefore, focused our initial efforts on the preparation of **8** from **11**.

The synthetic routes investigated are illustrated in Chart 4. Firstly, we examined the synthesis of **8** *via* a route involving *SN*2 displacement of the (*S*)-lactic acid derivative followed by Friedel–Crafts (F.-C.) acylation (route A). Benzyl (*S*)-lactate (**11a**) was converted to the triflate **12** using trifluoromethanesulfonic anhydride (Tf_2O) in the presence of diisopropylethylamine (iso-Pr_2NEt). The resulting triflate **12** was isolated as an oil, which was stable during isolation by chromatography, followed by evaporation of the eluate under ordinary conditions.[4] The substitution reaction of **12** with an anion of 4-[4-(2,2,3,3-tetrafluoropropoxy)phenyl]-3(2*H*,4*H*)-1,2,4-triazolone (H-TAZ)[2] in a mixture of *N*,*N*-dimethylformamide (DMF) and tetrahydrofuran (THF) gave a single product in 82% yield. The IR spectrum of the product showed two strong absorption bands centered at 1746 and 1707 cm^{-1} due to the stretching vibration of two sorts of carbonyl groups and, hence, the structure was determined to be the desired *N*-substituted isomer **13a**, not the *O*-substituted isomer **13b**. The optical purity of **13a** was assessed by HPLC using a chiral column and the enantiomer excess (ee) was determined to be 93%. Removal of the benzyl group of **13a** by catalytic hydrogenolysis afforded the corresponding carboxylic acid **9** in 90% yield. Conversion of **9** to the chloride **14** was performed using oxalyl chloride [$(COCl)_2$]. The ee of **14** was checked by HPLC after converting to the corresponding methyl ester

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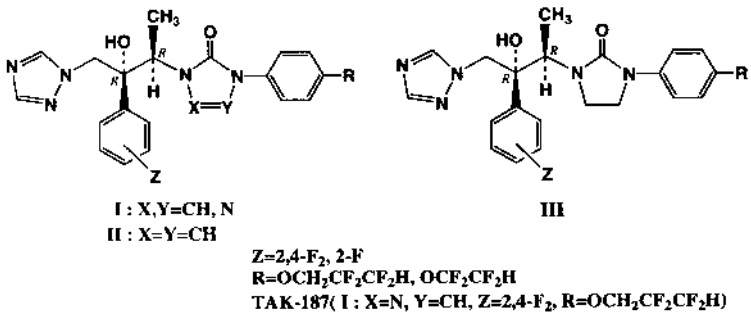

Chart 1

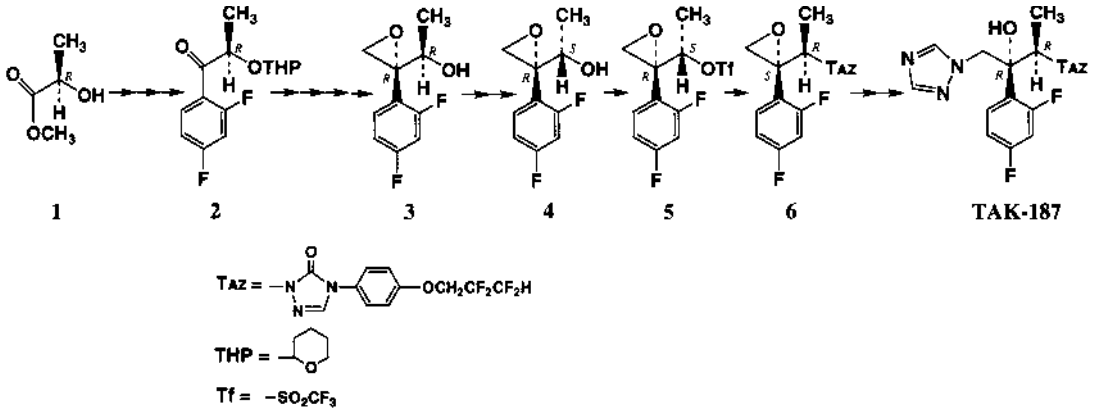

Chart 2

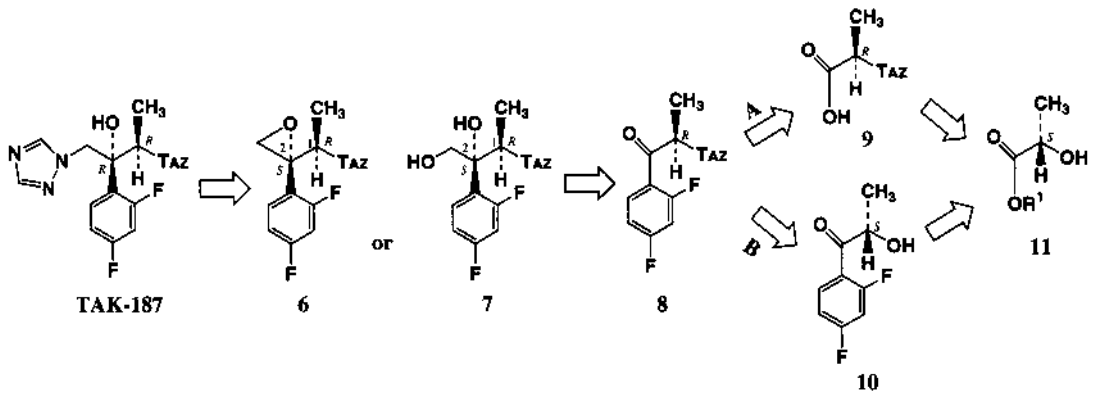

Chart 3

15 and confirmed to be maintained at 93%. Compound **14** was allowed to react with 1,3-difluorobenzene in the presence of aluminum chloride ($AlCl_3$) to give the propiophenone derivative **8**. It was expected that the proton (Ha) on the α-carbon of the carbonyl moiety in **8** would be somewhat acidic and liable to cause racemization. In fact, the value of the optical rotation ($[\alpha]_D$) of **8** was observed to decrease through purification by silica gel column chromatography using an ordinary eluent, such as a mixture of ethyl acetate (AcOEt) and hexane. We suspect that silica gel works as a base to cause this racemization.[6] Thus we carried out silica gel column chromatography using a weakly acidic eluent, *i.e.*, a mixture of AcOEt and hexane (1 : 2) containing a small amount (1%) of acetic acid (AcOH). The optically active propiophenone **8** could consequently be obtained as a viscous oil in 61% yield based on **9**. The ee of **8** was measured by HPLC and determined to be 93%.

Next, the route involving *SN*2 displacement of the (2*S*)-2-hydroxypropiophenone derivative **10** with H-TAZ (route B) was investigated for the synthesis of **8**. We had already established a method for the synthesis of the (2*S*)-alcohol **10** starting from ethyl (*S*)-lactate (**11b**), *i.e.*, **11b**→**16**→**17**→**18**→**10**.[7] The alcohol **10** was converted to the corresponding triflate **19** by treatment with Tf_2O in the presence of iso-Pr_2NEt. The resulting triflate **19** was found to be stable enough to be isolated as an oil by evaporation of the eluate obtained from silica gel chromatography.[4] Compound **19** was then allowed to react with the sodium salt of H-TAZ at −30——−50 °C in a mixture of 1-methyl-2-pyrrolidone (MP) and THF to give the two isomeric products, in a ratio of 4 : 1 on HPLC, which were separated by silica gel column chromatography using AcOEt–hexane–AcOH (1 : 3 : 0.04). The major product (more polar, 62% isolated yield based on H-TAZ) was identical to the *N*-substituted isomer **8** prepared *via*

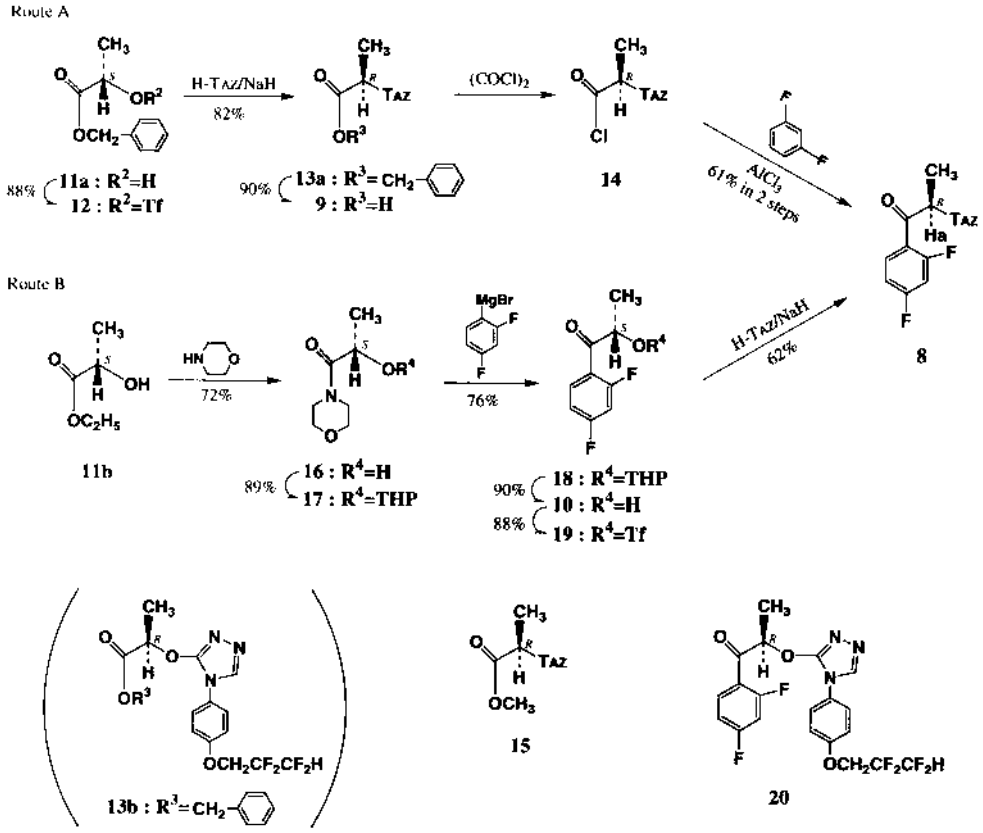

Chart 4

route A described above. Therefore, the minor product (less polar) was determined to be the *O*-substituted isomer **20**. The ee of **8** obtained *via* route B was assessed by HPLC and determined to be 96%.

The optical purity of **8** obtained *via* routes A and B could be increased to 97—98% by removal of a small amount of the crystalline racemate which precipitated out of a solution of **8** in diisopropyl ether (iso-Pr_2O) upon standing.

Both routes, A and B, described above for the synthesis of **8** were thus shown to proceed in a stereoselective manner as well as to give a good overall yield. We then studied routes for converting **8** to TAK-187. The three routes (methods a, b, c) shown in Chart 5 were applicable to this conversion.[8] Compound **8** was reacted with vinylmagnesium bromide to give the vinyl derivative **21** (66% yield), which was obtained as a single diastereomer. This result indicates that reactions involving a Grignard's reagent and **8** proceed in a stereoselective manner.[9] The carbon–carbon double bond in **21** was cleaved using sodium periodate ($NaIO_4$) in the presence of a catalytic amount of osmium tetroxide (OsO_4), and the subsequent reduction with sodium borohydride ($NaBH_4$) gave the desired (1*R*,2*S*)-diol **7** (method a).[10] The isolated yield, however, was inadequate (12% from **21**) to warrant further study of the reaction conditions. We next examined ozonolysis of **21**. Bubbling ozone (O_3) into a solution of **21** followed by the addition of dimethylsulfide (Me_2S) gave the aldehyde **22** in 76% yield, and subsequent reduction with $NaBH_4$ afforded **7** in 55% yield (method b). For the practical synthesis of TAK-187, it was desired to obtain **7** in a greater isolated yield as well as to adopt the easiest and safest procedure.

Compound **8** was reacted with (dimethylisopropoxysilyl)-methylmagnesium chloride [iso-PrOSi(Me_2)CH_2MgCl].[5c—e] The silylalcohol **23** was obtained stereoselectively as crystals with >99% ee in 82% isolated yield. Oxidative desilylation of **23** with hydrogen peroxide (H_2O_2)[5c—e] in the presence of sodium bicarbonate ($NaHCO_3$) afforded **7** in high yield (94% from **23**: method c). Compound **7** prepared by this method was identical to that obtained by methods a and b. Furthermore, the optical purity of **7** obtained *via* each of the three routes (methods a, b and c) was assessed by HPLC and confirmed to be high enough (>99% ee) for use in the subsequent synthetic step. On the basis of the results described above, we chose method c for the preparation of **7**. The highly optically pure diol **7** was converted to the corresponding mesylate **24** followed by treatment with 1*H*-1,2,4-triazole in the presence of potassium carbonate (K_2CO_3)[11] to give TAK-187 with >99% ee in 80% isolated yield. This was identical to our authentic sample.[2]

The synthetic method established as described above was then applied to the preparation of the imidazolone (II) and imidazolidinone (III) derivatives depicted in Chart 1. Among these congeners, the 2,4-difluorophenyl (**25a**, **b**, **27a**, **b**) and 2-fluorophenyl (**26a**, **b**, **28a**, **b**) derivatives, which exhibit strong antifungal activity,[1] were chosen as the synthetic targets (Chart 6).

We first attempted the synthesis of the propiophenone derivative **31a** by route A involving F.-C. acylation. The triflate of benzyl (*S*)-lactate **12** was allowed to react with an anion of 1-[4-(2,2,3,3-tetrafluoropropoxy)phenyl]-2(1*H*,3*H*)-imidazolone (H-Imz: R=$OCH_2CF_2CF_2H$)[1] to prepare the imidazolone-*N*-substituted lactate derivative **29**, which was obtained as crystals in 85% yield. The IR spectrum of **29**

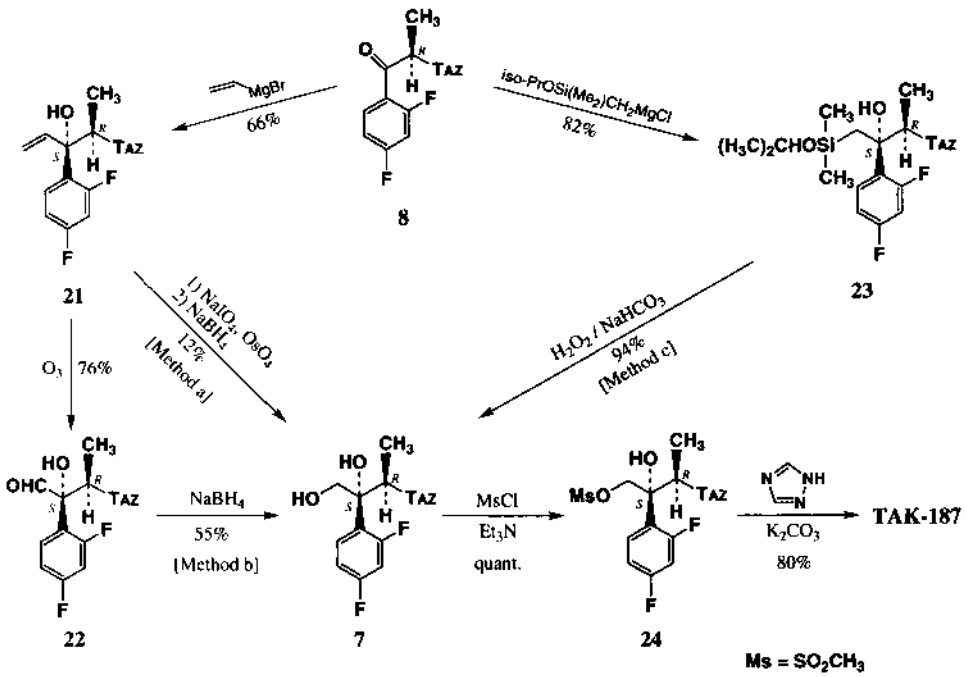

Chart 5

showed two strong absorption bands ($\nu_{C=O}$) at 1742 and 1692 cm^{-1}, similar to **13a**. The benzyl group of **29** was removed by catalytic hydrogenolysis to give the lactic acid derivative **30** in 81% yield. Compound **30** was then converted to the corresponding chloride by treatment with $(COCl)_2$ and subsequently subjected to F.-C. acylation as described for the synthesis of **8** to obtain **31a**. However, considerable decomposition occurred during the course of the reaction, and the isolated yield for **31a** was low (13%). We, therefore, turned to route B for the synthesis of **31a**. *SN*2 reaction of the 2,4-difluorophenyl-triflate **19** with an anion of H-IMZ (R=$OCH_2CF_2CF_2H$) gave a mixture of two products in a ratio of 5 : 1 on HPLC, similar to the synthesis of **8**. The more polar product on TLC (major component) was identical to the *N*-substituted derivative **31a** prepared by the above F.-C. reaction and, hence, the less polar product (minor component) was assumed to be the *O*-substituted by-product **33a**. These products were separated by chromatography on silica gel using AcOEt–hexane–AcOH (1 : 2 : 0.03) as the eluent, and **31a** was isolated as a solid in 49% yield based on H-IMZ. The ee of **31a** after recrystallization was 99% on HPLC. The congener **31b** containing the 4-(1,1,2,2-tetrafluoroethoxy)-phenyl moiety was prepared using an anion of H-IMZ (R=OCF_2CF_2H)[1] as described above, and **31b** was obtained as crystals with 99% ee in 23% isolated yield.

The propiophenone derivatives **31a**, **b** were converted to the corresponding diols **36a**, **b** according to method c as shown in Chart 6. Thus, **31a**, **b** were allowed to react with iso-PrOSi(Me_2)CH_2MgCl to give **34a**, **b** in 60—66% yield, and the subsequent oxidative cleavage with H_2O_2 afforded **36a**, **b** in 69—78% yield. Compounds **36a**, **b** were converted to the corresponding mesylates **38a**, **b** in 91—99% yield, followed by treatment with 1*H*-1,2,4-triazole in the presence of K_2CO_3 to obtain the imidazolones **25a**, **b** in 46—47% isolated yield.

We then undertook the synthesis of 2-fluorophenyl analogs (**26a**, **b**) using to substantially the same method as above, *i.e.*, **42**→**32a**, **b**[12]→**35a**, **b**→**37a**, **b**→**39a**, **b**→**26a**, **b**. In this synthesis, the starting triflate **42** was prepared from the corresponding (*S*)-2-hydroxypropiophenone derivative **40**[13] as follows: **40**→**41**→**42**.

All imidazolones, **25a**, **b** and **26a**, **b**, were subjected to catalytic hydrogenation over palladium carbon (Pd–C) as described in our previous report[1] to obtain the corresponding imidazolidinones, **27a**, **b** and **28a**, **b**. Furthermore, the imidazolidinones could be prepared by hydrogenation of the diols followed by mesylation and subsequent reaction with 1*H*-1,2,4-triazole, as exemplified by the synthesis of **28a**, *i.e.*, **37a**→**43**→**44**→**28a**.

The imidazolone (**25a**, **b**, **26a**, **b**) and imidazolidinone (**27a**, **b**, **28a**, **b**) derivatives obtained above were identical to our authentic samples.[1]

In conclusion, we established an efficient and practical route for the synthesis of the optically active antifungal triazole, TAK-187, starting from the esters of (*S*)-lactic acid. Furthermore, this stereocontrolled synthesis could be applied to the preparation of other azolone-based antifungal triazoles such as the imidazolones (**25a**, **b**, **26a**, **b**) and imidazolidinones (**27a**, **b**, **28a**, **b**).

Experimental

Melting points were determined using a Yanagimoto melting point apparatus and are uncorrected. IR spectra were measured with a JASCO IR-810 spectrometer. ^{1}H-NMR spectra were recorded on a Varian Gemini-200 spectrometer with tetramethylsilane as an internal standard. The following abbreviations are used: s=singlet, d=doublet, t=triplet, m=multiplet, br=broad. The secondary ion mass spectra (SI-MS) were measured with a Hitachi M-80A mass spectrometer. The optical rotations were recorded with a JASCO DIP-181 or DIP-370 digital polarimeter.

Reactions were run at room temperature unless otherwise noted and followed by TLC on Silica gel 60 F_{254} precoated TLC plates (E. Merck) or by HPLC using an octadecyl silica (ODS) column (A-303, 4.6 mm i.d.× 250 mm, YMC Co., Ltd.). Standard work-up procedures were as follows. The reaction mixture was partitioned between the indicated solvent and water. Organic extracts were combined and washed in the indicated order

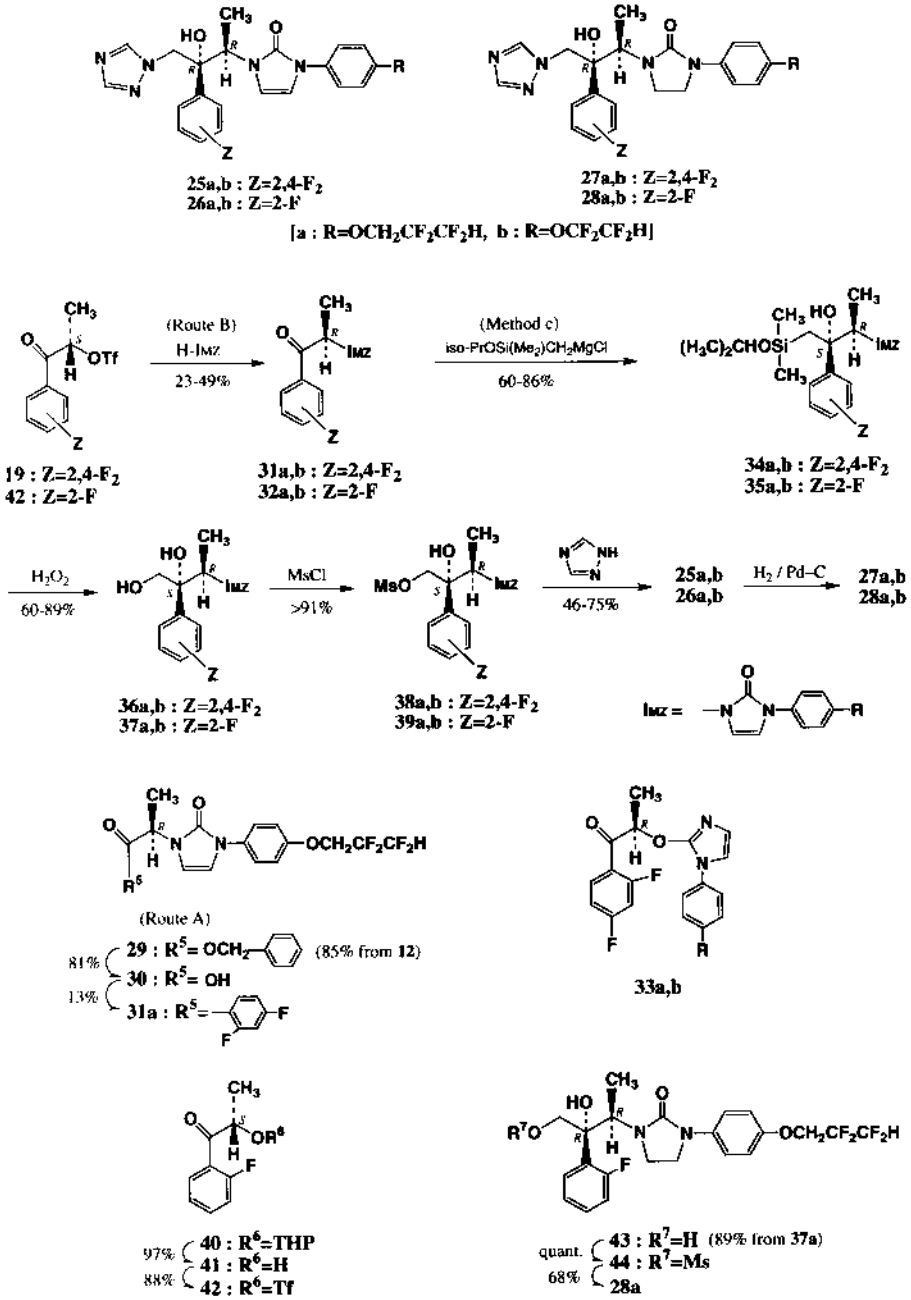

Chart 6

using the following aqueous solutions; water, hydrochloric acid (HCl), 5% aqueous sodium bicarbonate solution (aqueous $NaHCO_3$) and saturated NaCl solution (brine). Extracts were dried over $MgSO_4$, filtered and evaporated *in vacuo*.

Chromatographic separations were carried out on Silica gel 60 (0.063—0.200 mm, E. Merck) using the indicated eluents.

The ee of the compounds prepared was determined by HPLC using a chiral column (Chiralcel OF, Chiralcel OB and Chiralpak AD, 4.6 mm i.d.× 250 mm, Daicel Chemical Industries, Tokyo, Japan) under the indicated conditions [column; mobile phase; flow rate; detection]. The corresponding racemate used in this analysis was prepared independently.

Benzyl (2*S*)-2-Trifluoromethanesulfonyloxypropanoate (12) Tf_2O (50 g) was added dropwise to a stirred solution of **11a** (29 g)[14] and iso-Pr_2NEt (22.8 g) in dichloromethane (CH_2Cl_2, 300 ml) over a period of 15 min at around −55 °C. The resulting mixture was stirred for 10 min at around −25 °C, and then diluted with CH_2Cl_2 (200 ml). The whole was worked up (CH_2Cl_2; water, aqueous $NaHCO_3$, brine) and purified by silica gel column chromatography (CH_2Cl_2–hexane, 1 : 1, v/v) to give **12** (44.2 g, 88%) as a colorless oil. ^{1}H-NMR ($CDCl_3$) δ: 1.70 (3H, d, J=7 Hz), 5.26 (1H, q, J=7 Hz), 5.26 (2H, s), 7.31 (5H, s).

Benzyl (2*R*)-2-[4-[4-(2,2,3,3-Tetrafluoropropoxy)phenyl]-4,5-dihydro-5-oxo-1*H*-1,2,4-triazol-1-yl]propanoate (13a) A mixture of H-Taz (18 g), sodium hydride (NaH, 60% in oil, 2.52 g) and DMF (180 ml) was stirred for 40 min. The resulting solution was added dropwise to a solution of **12** (20 g) in THF (240 ml) over a period of 40 min at around −35 °C under a nitrogen atmosphere. After the mixture had been stirred for 10 min at around −30 °C, AcOH (10 ml) was added. The whole was worked up [AcOEt–iso-Pr_2O; water, 2 N HCl, brine] and purified by silica gel column chromatography (AcOEt–hexane, 1 : 2, v/v) to give **13a** (24 g, 82%) as a colorless oil. ^{1}H-NMR ($CDCl_3$) δ: 1.76 (3H, d, J=7.4 Hz), 4.38 (2H, tt, J=11.8, 1.4 Hz), 5.08 (1H, q, J=7.4 Hz), 5.20 (2H, s), 6.06 (1H, tt, J=53, 4.6 Hz), 7.02 (2H, dt, J=9, 2.2 Hz), 7.33 (5H, s), 7.47 (2H, dt, J=9, 2.2 Hz), 7.66 (1H, s). $[\alpha]_D^{23}$ +63.0° [c=1.43, methanol (MeOH)]. IR (neat): 1746, 1707, 1557, 1516, 1456, 1225 cm^{-1}. The ee was determined to be 93% [column, Chiralcel OF; mobile phase, hexane-isopropyl alcohol (iso-PrOH), 4 : 1; flow rate, 1 ml/min; detection, UV at 262 nm].

(2*R*)-2-[4-[4-(2,2,3,3-Tetrafluoropropoxy)phenyl]-4,5-dihydro-5-oxo-1*H*-1,2,4-triazol-1-yl]propanoic Acid (9) A solution of **13a** (24 g) in

ethanol (EtOH, 500 ml) was hydrogenated over 10% Pd–C (50% wet, 2.5 g) under atmospheric pressure. After absorption of hydrogen stopped, the catalyst was removed by filtration and the filtrate was evaporated *in vacuo*. The residue was crystallized from EtOH–iso-Pr_2O to give **9** (17.3 g, 90%) as colorless prisms. mp 162—165 °C. *Anal*. Calcd for $C_{14}H_{13}F_4N_3O_4$: C, 46.29; H, 3.61; N, 11.57. Found: C, 46.37; H, 3.67; N, 11.53. ^{1}H-NMR (DMSO-d_6) δ: 1.56 (3H, d, J=7.4 Hz), 4.65 (2H, tt, J=13.4, 1.6 Hz), 4.85 (1H, q, J=7.4 Hz), 6.69 (1H, tt, J=52, 5.5 Hz), 7.20 (2H, dt, J=9, 2.2 Hz), 7.64 (2H, dt, J=9, 2.2 Hz), 8.45 (1H, s). $[\alpha]_D^{23}$ +59.3° (c=1.0, MeOH).

(2*S*)-2′4′-Difluoro-2-trifluoromethanesulfonyloxypropiophenone (19) Tf_2O (25.9 ml) was added dropwise to a stirred solution of (2*S*)-2′,4′-difluoro-2-hydroxypropiophenone (**10**: 26.01 g)[7] and iso-Pr_2NEt (19.9 g) in CH_2Cl_2 (300 ml) over a period of 20 min at −60 °C under a nitrogen atmosphere. The resulting mixture was stirred for 30 min at −30°C. The whole was chromatographed on silica gel. Elution with CH_2Cl_2–hexane (1 : 1, v/v) gave **19** (39.21 g, 88%) as a pale yellow oil. ^{1}H-NMR ($CDCl_3$) δ: 1.73 (3H, dd, J=7, 1.6 Hz), 5.93 (1H, q, J=7 Hz), 6.90—7.12 (2H, m), 8.03 (1H, dt, J=6.4, 8.6 Hz). $[\alpha]_D^{23}$ +29.2° (c=1.12, MeOH).

2-[(1*R*)-2-(2,4-Difluorophenyl)-2-oxo-1-methylethyl]-4-[4-(2,2,3,3-tetrafluoropropoxy)phenyl]-3(2*H*,4*H*)-1,2,4-triazolone (8) [Route A] Five drops of DMF were added to a solution of **9** (1 g) and $(COCl)_2$ (2.5 ml) in CH_2Cl_2 (20 ml). The resulting mixture was stirred for 2 h and then evaporated *in vacuo* to give the chloride **14** as a pale yellow oil. To a solution of this oil in CH_2Cl_2 (20 ml) were added 1,3-difluorobenzene (2.5 ml) and $AlCl_3$ (powder, 1.5 g). The resulting mixture was heated under reflux for 8 h with stirring. After cooling, the whole was added to ice-water (50 ml) and worked up (AcOEt–iso-Pr_2O; 1 N HCl, brine). The residue was chromatographed on silica gel using AcOEt–hexane–AcOH (1 : 2 : 0.03, v/v) as an eluent. The eluate was washed with water, dried over $MgSO_4$ and evaporated *in vacuo* to give **8** (0.77 g, 61% based on **9**) as a pale yellow oil with 93% ee [column, Chiralpak AD; mobile phase, hexane–iso-PrOH, 1 : 1; flow rate, 1 ml/min; detection, UV at 262 nm].

The optical purity of the chloride **14** was checked by the following method: compound **14** was converted to the corresponding methyl ester **15** by reaction with MeOH. Compound **15**: ^{1}H-NMR ($CDCl_3$) δ: 1.75 (3H, d, J=7.2 Hz), 3.77 (3H, s), 4.38 (2H, tt, J=11.8, 1.4 Hz), 5.05 (1H, q, J=7.2 Hz), 6.07 (1H, tt, J=53, 4.8 Hz), 7.04 (2H, dt, J=9, 2.2 Hz), 7.53 (2H, dt, J=9, 2.2 Hz), 7.69 (1H, s). The ee of **15** was determined to be 93% [column, Chiralpak AD; mobile phase, hexane–iso-PrOH, 1 : 1; flow rate, 1 ml/min; detection, UV at 262 nm].

[Route B] A mixture of H-Taz (6.12 g), NaH (60% in oil, 0.8 g) and MP (60 ml) was stirred for 3 h. The resulting solution was cooled in an ice bath and added dropwise to a solution of **19** (7.32 g) in THF (180 ml) over a period of 25 min at −50 °C under a nitrogen atmosphere. After stirring for 30 min at −30 °C, the whole was diluted with a mixture of AcOH (10 ml) and AcOEt (500 ml) and worked up (AcOEt; water, 0.5 N HCl, brine). The residue was purified by silica gel column chromatography (AcOEt–hexane–AcOH, 1 : 3 : 0.04, v/v). The eluate containing the more polar product was washed with water, dried over $MgSO_4$ and evaporated *in vacuo* to give **8** (6.01 g, 62% based on H-Taz) as a pale yellow oil with 96% ee [column, Chiralpak AD; mobile phase, hexane–iso-PrOH, 1 : 1; flow rate, 1 ml/min; detection, UV at 262 nm].

The eluate containing the less polar product was washed with water, dried over $MgSO_4$ and evaporated *in vacuo* to give **20** as colorless crystals. mp 130—132 °C. *Anal*. Calcd for $C_{20}H_{15}F_6N_3O_3$: C, 52.30; H, 3.29; N, 9.15. Found: C, 52.52; H, 3.27; N, 9.13. ^{1}H-NMR ($CDCl_3$) δ: 1.24 (3H, d, J=5.4 Hz), 4.37 (2H, tt, J=11.8, 1.4 Hz), 4.52 (1H, q, J=5.4 Hz), 6.06 (1H, tt, J=53, 4.8 Hz), 6.79—7.05 (2H, m), 7.02 (2H, dt, J=9, 2.2 Hz), 7.45 (2H, dt, J=9, 2.2 Hz), 7.62 (1H, s), 7.68 (1H, dt, J=6.4, 8.6 Hz). SI-MS (m/z): 460 (MH^+).

Compound **8**, obtained *via* routes A and B, was dissolved in twice the amount (v/w) of iso-Pr_2O and cooled in an ice-bath. The crystalline precipitate was removed by filtration and the filtrate was evaporated *in vacuo* to give **8** with higher optical purity, 97—98% ee [column, Chiralpak AD; mobile phase, hexane–iso-PrOH, 1 : 1; flow rate, 1 ml/min; detection, UV at 262 nm]. *Anal*. Calcd for $C_{20}H_{15}F_6N_3O_3$: C, 52.30; H, 3.29; N, 9.15. Found: C, 52.41; H, 3.48; N, 8.89. IR (neat): 1710, 1610, 1560, 1520, 1240, 1100 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.75 (3H, d, J=7 Hz), 4.38 (2H, tt, J=11.8, 1.4 Hz), 5.70 (1H, q, J=7 Hz), 6.06 (1H, tt, J=53, 4.8 Hz), 6.85—7.05 (2H, m), 7.02 (2H, dt, J=9, 2.4 Hz), 7.49 (2H, dt, J=9, 2.4 Hz), 7.68 (1H, s), 7.94 (1H, dt, J=6.4, 8.6 Hz). $[\alpha]_D^{23}$ +69.8° (c=1.2, MeOH).

2-[(1*R*,2*S*)-2-(2,4-Difluorophenyl)-2-hydroxy-1-methyl-3-butenyl]-4-[4-(2,2,3,3-tetrafluoropropoxy)phenyl]-3(2*H*,4*H*)-1,2,4-triazolone (21) A solution of vinylmagnesium bromide in THF (1 M solution, 5 ml) was added dropwise to a solution of **8** (1.16 g, 98% ee) in THF (20 ml) over a period of 13 min at −60 °C. After stirring the mixture for 2 h at −30 °C, a saturated aqueous solution (5 ml) of ammonium chloride (NH_4Cl) was added. The whole was worked up (AcOEt–iso-Pr_2O; water, brine) and purified by silica gel column chromatography (AcOEt–hexane, 1 : 3→1 : 2, v/v) to give **21**, which was crystallized from iso-Pr_2O–hexane to obtain colorless needles (0.81 g, 66%). mp 104—106 °C. *Anal*. Calcd for $C_{22}H_{19}F_6N_3O_3$: C, 54.21; H, 3.93; N, 8.62. Found: C, 54.24; H, 3.91; N, 8.47. ^{1}H-NMR ($CDCl_3$) δ: 1.26 (3H, d, J=7 Hz), 4.39 (2H, tt, J=11.8, 1.4 Hz), 4.93 (1H, s), 5.03 (1H, d, J=9.5 Hz), 5.11 (1H, q, J=7 Hz), 5.43 (1H, dt, J=17.2, 1.6 Hz), 6.06 (1H, tt, J=53, 4.8 Hz), 6.45—6.58 (1H, m), 6.75—6.96 (2H, m), 7.04 (2H, dt, J=9, 2.8 Hz), 7.48 (2H, dt, J=9, 2.8 Hz), 7.66 (1H, s), 7.75—7.88 (1H, m). $[\alpha]_D^{23}$ −26.0° (c=0.54, MeOH).

2-[(1*R*,2*S*)-2-(2,4-Difluorophenyl)-2-formyl-2-hydroxy-1-methylethyl]-4-[4-(2,2,3,3-tetrafluoropropoxy)phenyl]-3(2*H*,4*H*)-1,2,4-triazolone (22) O_3 was bubbled through a solution of **21** (0.6 g) in CH_2Cl_2 (20 ml) for 20 min at −60 °C, and then nitrogen gas was bubbled for 10 min. Me_2S (0.6 ml) was added to the mixture and the whole was stirred until the temperature of the mixture reached to 0 °C, and then worked up (AcOEt; water, brine). The residue was crystallized from iso-Pr_2O–hexane to give **22** as colorless prisms (0.46 g, 76%). mp 134—136 °C. *Anal*. Calcd for $C_{21}H_{17}F_6N_3O_4$: C, 51.54; H, 3.50; N, 8.59. Found: C, 51.39; H, 3.50; N, 8.42. ^{1}H-NMR ($CDCl_3$) δ: 1.35 (3H, d, J=7 Hz), 4.38 (2H, tt, J=11.8, 1.4 Hz), 4.81 (1H, s), 5.42 (1H, q, J=7 Hz), 6.06 (1H, tt, J=53, 4.8 Hz), 6.84—7.10 (2H, m), 7.03 (2H, dt, J=9, 2.2 Hz), 7.47 (2H, dt, J=9, 2.2 Hz), 7.66 (1H, s), 7.73—7.85 (1H, m), 9.97 (1H, m).

2-[(1*R*,2*S*)-2-(2,4-Difluorophenyl)-2-hydroxy-3-(isopropoxydimethylsilyl)-1-methylpropyl]-4-[4-(2,2,3,3-tetrafluoropropoxy)phenyl]-3(2*H*,4*H*)-1,2,4-triazolone (23) A mixture of chloromethylisopropoxydimethylsilane [iso-PrOSi(Me_2)CH_2Cl, 18.1 g], magnesium (Mg, turnings, 2.65 g) and THF (100 ml) was heated at 45—50 °C. A few chips of Mg activated with methyl iodide (CH_3I) were added, and the resulting mixture was heated for 3 h at 45—50 °C and then cooled in an ice bath. To this ice-cooled mixture was added dropwise a solution of **8** (10.5 g, 97% ee) in THF (50 ml) over the period of 20 min. After stirring for 20 min, the mixture was diluted with saturated aqueous NH_4Cl (50 ml) and water (50 ml) at 0 °C. The whole was worked up (AcOEt–iso-Pr_2O; brine) and the residue was purified by silica gel column chromatography (AcOEt–hexane, 1 : 2, v/v), followed by recrystallization from iso-Pr_2O–hexane to give **23** (11.03 g, 82%) as colorless needles. The ee of compound **23** was determined to be >99% [column, Chiralpak AD; mobile phase, hexane–iso-PrOH, 1 : 1; flow rate; 1 ml/min; detection, UV at 262 nm]. mp 125—126 °C. *Anal*. Calcd for $C_{26}H_{31}F_6N_3O_4Si$: C, 52.78; H, 5.28; N, 7.10. Found: C, 52.82; H, 5.30; N, 6.96. ^{1}H-NMR (DMSO-d_6) δ: −0.35 (3H, s), −0.16 (3H, s), 0.93 (3H, d, J=6 Hz), 0.96 (3H, d, J=6 Hz), 1.03—1.11 (4H, m), 1.62 (1H, dd, J=15, 2 Hz), 3.79 (1H, quintet, J=6 Hz), 4.62 (1H, q, J=7 Hz), 4.66 (2H, t, J=13.4 Hz), 5.00 (1H, s), 6.69 (1H, tt, J=52, 5 Hz), 7.07—7.22 (2H, m), 7.22 (2H, d, J=9 Hz), 7.66 (2H, d, J=9 Hz), 7.72 (1H, dt, J=0.8, 9 Hz), 8.50 (1H, s). IR (KBr): 3400, 1710, 1618, 1560, 1517, 1498 cm^{-1}. $[\alpha]_D^{23}$ +2.8° (c=1.0, MeOH).

2-[(1*R*,2*S*)-2-(2,4-Difluorophenyl)-2,3-dihydroxy-1-methylpropyl]-4-[4-(2,2,3,3-tetrafluoropropoxy)phenyl]-3(2*H*,4*H*)-1,2,4-triazolone (7) (Method a) A solution of $NaIO_4$ (321 mg) in water (2 ml) and OsO_4 (3 mg) were added to a solution of **21** (244 mg) in MeOH (5.7 ml). The resulting mixture was stirred for 18 h and worked up (AcOEt; water, brine). The residue was dissolved in MeOH (8 ml), and then $NaBH_4$ (20 mg) was added to the solution. After stirring for 30 min, the whole was worked up (AcOEt; water, brine). The residue was chromatographed on silica gel and elution with AcOEt–hexane (1 : 2→1 : 1, v/v) gave **7** (29 mg, 12%) as colorless powder.

(Method b) $NaBH_4$ (74 mg) was added to an ice-cooled solution of **22** (300 mg) in MeOH (9 ml). After stirring for 30 min, the whole was worked up (AcOEt; 1 N HCl, water, brine). The residue was purified by silica gel column chromatography (AcOEt–hexane, 1 : 1, v/v) to give **7** as colorless prisms (165 mg, 55%).

(Method c) A 30% aqueous solution of H_2O_2 (19.2 ml) and $NaHCO_3$ (1.57 g) were added to a solution of **23** (11 g) in MeOH–THF (1 : 1, v/v, 90 ml). The mixture was heated for 90 min at 70—80 °C and, after cooling, the whole was worked up (AcOEt–iso-Pr_2O; water, aqueous solution of $Na_2S_2O_3$, brine). The residue was crystallized from iso-Pr_2O to give **7** as colorless prisms (8.27 g, 90%). The mother liquor of the above crystallization was evaporated and the residue was purified by silica gel column chromatography (AcOEt–hexane, 1 : 1, v/v) to obtain an additional amount of **7** as colorless prisms (0.33 g, 4%).

Compound **7**: mp 144—145 °C. *Anal*. Calcd for $C_{21}H_{19}F_6N_3O_4$: C, 51.33;

H, 3.90; N, 8.55. Found: C, 51.15; H, 3.76; N, 8.52. ^{1}H-NMR ($CDCl_3$) δ: 1.29 (3H, d, J=7 Hz), 2.09—2.21 (1H, m), 3.82—4.00 (2H, m), 4.40 (2H, tt, J=11.8, 1.4 Hz), 4.80 (1H, s), 5.04 (1H, q, J=7 Hz), 6.06 (1H, tt, J=53, 4.6 Hz), 6.75—7.00 (2H, m), 7.05 (2H, dt, J=9, 2.2 Hz), 7.50 (2H, dt, J=9, 2.2 Hz), 7.71 (1H, s), 7.73—7.84 (1H, m). IR (KBr): 3480, 1695, 1619, 1560, 1519, 1504 cm^{-1}. $[\alpha]_D^{23}$ −6.3° (c=1.0, MeOH). SI-MS (m/z): 492 (MH^+).

The ee of compound **7** was determined to be >99% [column, Chiralpak AD; mobile phase, hexane–iso-PrOH, 1 : 1; flow rate, 1 ml/min; detection, UV at 262 nm].

2-[(1*R*,2*S*)-2-(2,4-Difluorophenyl)-2-hydroxy-3-methanesulfonyloxy-1-methylpropyl]-4-[4-(2,2,3,3-tetrafluoropropoxy)phenyl]-3(2*H*,4*H*)-1,2,4-triazolone (24) Methanesulfonyl chloride (MsCl, 2.89 g) and triethylamine (Et_3N, 2.54 g) were added to a stirred solution of **7** (8.26 g) in AcOEt (100 ml) at 0 °C. The resulting mixture was stirred for 30 min at 0 °C and then worked up (AcOEt; water, brine) to give **24** (10 g, quantitative) as a colorless oil. ^{1}H-NMR ($CDCl_3$) δ: 1.27 (3H, d, J=7 Hz), 2.91 (3H, s), 4.40 (2H, tt, J=11.8, 1.6 Hz), 4.49—4.59 (2H, m), 5.05 (1H, q, J=7 Hz), 5.34 (1H, s), 6.06 (1H, tt, J=53, 4.8 Hz), 6.80—7.05 (2H, m), 7.06 (2H, d, J=9.2 Hz), 7.53 (2H, d, J=9.2 Hz), 7.72 (1H, s), 7.78—7.92 (1H, m).

2-[(1*R*,2*R*)-2-(2,4-Difluorophenyl)-2-hydroxy-1-methyl-3-(1*H*-1,2,4-triazol-1-yl)propyl]-4-[4-(2,2,3,3-tetrafluoropropoxy)phenyl]-3(2*H*,4*H*)-1,2,4-triazolone (TAK-187) 1*H*-1,2,4-Triazole (5.7 g) and K_2CO_3 (23.2 g) were added to a solution of **24** (10 g) in DMF (180 ml). The resulting mixture was stirred for 5 h at 90 °C and then concentrated to a volume of *ca*. 100 ml *in vacuo*. The whole was worked up (AcOEt–iso-Pr_2O; water, 1 N HCl, brine) and the residue was chromatographed on silica gel (hexane–AcOEt; 3 : 4→AcOEt, v/v) to give TAK-187 as a colorless solid, which was recrystallized from AcOEt–iso-Pr_2O to afford colorless powdery crystals (7.3 g, 80%) with >99% ee [column, Chiralpak AD; mobile phase, hexane–iso-PrOH, 1 : 1; flow rate; 1 ml/min; detection, UV at 262 nm]. This product was identical to TAK-187 prepared from methyl (*R*)-lactate (**1**) in our preceding report[2] upon direct comparison with the authentic sample.

Benzyl (2*R*)-2-[3-[4-(2,2,3,3-Tetrafluoropropoxy)phenyl]-2,3-dihydro-2-oxo-1*H*-imidazol-1-yl]propanoate (29) A mixture of H-Imz (R=$OCH_2CF_2CF_2H$, 4 g), NaH (60% in oil, 0.55 g) and MP (30 ml) was stirred for 30 min. The resulting solution was added dropwise to a solution of **12** (5.2 g) in THF (80 ml) over a period of 10 min at around −45 °C under a nitrogen atmosphere. After stirring the mixture for 50 min at around −30 °C, AcOH (9.6 ml) was added. The whole was worked up (AcOEt; water, 1 N HCl, brine) and the residue was purified by silica gel column chromatography (AcOEt–hexane, 3 : 2, v/v) to give **29** (5.3 g, 85%) as colorless powdery crystals. mp 75—76 °C (recrystallized from AcOEt–hexane). *Anal*. Calcd for $C_{22}H_{20}F_4N_2O_4$: C, 58.41; H, 4.46; N, 6.19. Found: C, 58.16; H, 4.42; N, 6.24. ^{1}H-NMR ($CDCl_3$) δ: 1.63 (3H, d, J=7.4 Hz), 4.38 (2H, tt, J=11.8, 1.4 Hz), 5.09 (1H, q, J=7.4 Hz), 5.20 (2H, s), 6.07 (1H, tt, J=53, 4.6 Hz), 6.50 (1H, d, J=3 Hz), 6.57 (1H, d, J=3 Hz), 6.97 (2H, dt, J=9, 2.2 Hz), 7.35 (5H, s), 7.53 (2H, dt, J=9, 2.2 Hz). IR (KBr): 1742, 1692, 1609, 1516, 1464, 1441, 1271 cm^{-1}.

(2*R*)-2-[3-[4-(2,2,3,3-Tetrafluoropropoxy)phenyl]-2,3-dihydro-2-oxo-1*H*-imidazol-1-yl]propanoic Acid (30) Hydrogenolysis of **29** (5.1 g) was carried out as described in the synthesis of **9** to give **30**, which was recrystallized from EtOH–iso-Pr_2O to obtain colorless prisms (3.3 g, 81%). mp 149—151 °C. *Anal*. Calcd for $C_{15}H_{14}F_4N_2O_4$: C, 49.73; H, 3.90; N, 7.73. Found: C, 49.64; H, 3.93; N, 7.72. ^{1}H-NMR (DMSO-d_6) δ: 1.54 (3H, d, J=7.2 Hz), 4.55—4.77 (3H, m), 6.69 (1H, tt, J=52, 5.5 Hz), 6.84 (1H, d, J=3 Hz), 7.02 (1H, d, J=3 Hz), 7.13 (2H, d, J=9 Hz), 7.66 (2H, d, J=9 Hz).

(2*S*)-2′-Fluoro-2-hydroxypropiophenone (41) Pyridinium *p*-toluenesulfonate (1.28 g) was added to a solution of (2*S*)-2′-fluoro-2-(3,4,5,6-tetrahydro-2*H*-pyran-2-yloxy)propiophenone (**40**, 25.5 g)[13] in EtOH (200 ml). The resulting mixture was stirred for 2.5 h at 55 °C and then concentrated *in vacuo*. The residue was purified by silica gel column chromatography (AcOEt–hexane, 1 : 9→1 : 5, v/v) to give **41** (16.4 g, 97%) as a colorless oil with 98% ee [column, Chiralcel OB; mobile phase, hexane–iso-PrOH, 4 : 1; flow rate; 1 ml/min; detection, UV at 262 nm]. ^{1}H-NMR ($CDCl_3$) δ: 1.41 (3H, dd, J=7, 1.4 Hz), 3.78 (1H, d, J=6 Hz), 4.98—5.15 (1H, m), 7.12—7.36 (2H, m), 7.54—7.68 (1H, m), 7.90—8.00 (1H, m). IR (neat): 1690 cm^{-1}.

(2S)-2′-Fluoro-2-trifluoromethanesulfonyloxypropiophenone (42) Compound **41** (3.36 g) was allowed to react with Tf_2O (4.03 ml) as described in the synthesis of **19** to give the triflate **42** (5.3 g, 88%) as a pale yellow oil. ^{1}H-NMR ($CDCl_3$) δ: 1.73 (3H, dd, J=7, 1.6 Hz), 6.49 (1H, q, J=7 Hz), 7.15—7.38 (2H, m), 7.58—7.72 (1H, m), 7.97 (1H, dt, J=7.6, 1.8 Hz).

1-[(1*R*)-2-(2,4-Difluorophenyl)-2-oxo-1-methylethyl]-3-[4-(2,2,3,3-tetrafluoropropoxy)phenyl]-2(1*H*,3*H*)-imidazolone (31a) [Route A] Compound **30** (1.5 g) was converted to the chloride and then allowed to react with 1,3-difluorobenzene in the presence of $AlCl_3$ in a manner similar to that described in the synthesis of **8**. The product was purified by silica gel column chromatography (AcOEt–hexane–AcOH, 1 : 2 : 0.03, v/v) and the eluate was washed with water, dried over $MgSO_4$ and evaporated *in vacuo*. The residue was crystallized from iso-Pr_2O to give **31a** as colorless crystals (0.25 g, 13%).

[Route B] A mixture of H-Imz (R=$OCH_2CF_2CF_2H$, 6.58 g), NaH (60% in oil, 0.86 g) and MP (45 ml) was stirred for 15 min. The resulting solution was cooled in an ice bath and added dropwise to a solution of **19** (7.98 g) in THF (150 ml) over a period of 15 min at −40 °C under a nitrogen atmosphere. Then, the mixture was stirred for 10 min at −20 °C. AcOH (16 ml) and AcOEt (200 ml) were added to the mixture and the whole was worked up (AcOEt; water, 0.5 N HCl, brine). The residue was purified by silica gel column chromatography (AcOEt–hexane–AcOH, 1 : 2 : 0.08, v/v) and the eluate containing the more polar product was washed with water, dried over $MgSO_4$ and evaporated *in vacuo* to give **31a** (4.7 g, 49% based on H-Imz) as a solid, which was recrystallized from iso-Pr_2O to obtain colorless crystals (3.5 g) with 99% ee [column, Chiralpak AD; mobile phase, hexane–iso-PrOH, 1 : 1; flow rate, 1 ml/min; detection, UV at 262 nm]. mp 70—71 °C. *Anal*. Calcd for $C_{21}H_{16}F_6N_2O_3$: C, 55.03; H, 3.52; N, 6.11. Found: C, 54.90; H, 3.65; N, 6.13. IR (KBr): 1690, 1670, 1610, 1520, 1370, 1100, 980, 830 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.62 (3H, d, J=7 Hz), 4.35 (2H, tt, J=11.8, 1.4 Hz), 5.74 (1H, q, J=7 Hz), 6.07 (1H, tt, J=53, 4.8 Hz), 6.56 (2H, s), 6.57—7.05 (2H, m), 6.96 (2H, dt, J=9, 2.4 Hz), 7.52 (2H, dt, J=9, 2.4 Hz), 7.94—8.05 (1H, m). $[\alpha]_D^{20}$ +10.5° (c=1.0, MeOH).

Compound **31b** and the 2-fluoro analogs **32a**, **b** were prepared from **19** and **42**, respectively, by reaction with H-Imz (R=$OCH_2CF_2CF_2H$ or OCF_2CF_2H) as described above. Compound **31b** (23% yield): mp 71—72 °C (recrystallized from hexane–iso-Pr_2O). Optical purity, 99% ee [column, Chiralpak AD; mobile phase, hexane–iso-PrOH, 1 : 1; flow rate; 1 ml/min; detection, UV at 262 nm]. *Anal*. Calcd for $C_{20}H_{14}F_6N_2O_3$: C, 54.06; H, 3.18; N, 6.30. Found: C, 53.81; H, 3.19; N, 6.41. ^{1}H-NMR ($CDCl_3$) δ: 1.63 (3H, d, J=7 Hz), 5.74 (1H, q, J=7 Hz), 5.90 (1H, tt, J=53, 2.8 Hz), 6.58 (1H, d, J=3 Hz), 6.62 (1H, d, J=3 Hz), 6.86—7.05 (2H, m), 7.26 (2H, dt, J=9, 2.4 Hz), 7.53 (2H, dt, J=9, 2.4 Hz), 7.93—8.05 (1H, m). IR (KBr): 1690, 1670, 1610, 1510, 1370, 1100, 980, 850 cm^{-1}. $[\alpha]_D^{25}$ +6.9° (c=1.0, MeOH). Compound **32a** (41% yield): mp 71—73 °C (recrystallized from iso-Pr_2O). Optical purity, 98.8% ee [column, Chiralpak AD; mobile phase, hexane–iso-PrOH, 1 : 1; flow rate; 1 ml/min; detection, UV at 262 nm]. *Anal*. Calcd for $C_{21}H_{17}F_5N_2O_3$: C, 57.28; H, 3.89; N, 6.36. Found: C, 57.34; H, 3.78; N, 6.12. ^{1}H-NMR ($CDCl_3$) δ: 1.63 (3H, d, J=7.2 Hz), 4.35 (2H, tt, J=11.8, 1.4 Hz), 5.80 (1H, q, J=7.2 Hz), 6.07 (1H, tt, J=53, 4.6 Hz), 6.57 (2H, s), 6.97 (2H, d, J=9 Hz), 7.13—7.30 (2H, m), 7.48—7.64 (1H, m), 7.53 (2H, d, J=9 Hz), 7.93 (1H, dt, J=7.6, 1.8 Hz). IR (KBr): 1712, 1679, 1608, 1519, 1438, 1267 cm^{-1}. $[\alpha]_D^{23}$ +8.5° (c=1.0, MeOH). Compound **32b** (34% yield): mp 78—79 °C (recrystallized from iso-Pr_2O). Optical purity, 99.9% ee [column, Chiralpak AD; mobile phase, hexane–iso-PrOH, 1 : 1; flow rate; 1 ml/min; detection, UV at 262 nm]. *Anal*. Calcd for $C_{20}H_{15}F_5N_2O_3$: C, 56.34; H, 3.55; N, 6.57. Found: C, 56.20; H, 3.61; N, 6.41. ^{1}H-NMR ($CDCl_3$) δ: 1.63 (3H, d, J=7 Hz), 5.79 (1H, q, J=7 Hz), 5.92 (1H, tt, J=53, 3 Hz), 6.60 (1H, d, J=3 Hz), 6.63 (1H, d, J=3 Hz), 7.13—7.30 (2H, m), 7.26 (2H, d, J=9 Hz), 7.51—7.64 (1H, m), 7.63 (2H, d, J=9 Hz), 7.93 (1H, dt, J=8, 2 Hz). IR (KBr): 1690, 1673, 1608, 1512, 1450, 1438 cm^{-1}. $[\alpha]_D^{23}$ +4.6° (c=1.0, MeOH).

For the synthesis of both **31a** and **31b**, the eluate containing the less polar product was washed with water, dried over $MgSO_4$ and evaporated *in vacuo* to give the *O*-substituted isomers, **33a** and **33b**, as a pale yellow oil. Compound **33a**: ^{1}H-NMR ($CDCl_3$) δ: 1.48 (3H, d, J=5.4 Hz), 3.59 (1H, q, J=5.4 Hz), 4.34 (2H, t, J=12 Hz), 6.05 (1H, tt, J=53, 4.8 Hz), 6.55 (1H, d, J=3 Hz), 6.67 (1H, d, J=3 Hz), 6.76—7.02 (2H, m), 6.95 (2H, d, J=8.8 Hz), 7.50 (2H, d, J=8.8 Hz), 7.58—7.70 (1H, m). Compound **33b**: ^{1}H-NMR ($CDCl_3$) δ: 1.48 (3H, d, J=4.8 Hz), 3.60 (1H, q, J=4.8 Hz), 5.90 (1H, tt, J=53, 2.6 Hz), 6.60 (1H, d, J=3.2 Hz), 6.70 (1H, d, J=3.2 Hz), 6.77—7.05 (2H, m), 7.24 (2H, d, J=9 Hz), 7.60 (2H, d, J=9 Hz), 7.48—7.69 (1H, m).

1-[(1*R*,2*S*)-2-(2,4-Difluorophenyl)-2-hydroxy-3-(isopropoxydimethylsilyl)-1-methylpropyl]-3-[4-(2,2,3,3-tetrafluoropropoxy)phenyl]-2(1*H*,3*H*)-imidazolone (34a) Compound **31a** (3.9 g) was allowed to react with iso-PrOSi(Me_2)CH_2MgCl as described in the synthesis of **23** to give **34a**, which was recrystallized from hexane–iso-Pr_2O to obtain colorless needles (1.42 g, 66%). mp 131—132 °C. *Anal*. Calcd for $C_{27}H_{32}F_6N_2O_4Si$: C, 54.91; H, 5.46; N, 4.74. Found: C, 54.65; H, 5.32; N, 4.74. ^{1}H-NMR (DMSO-d_6) δ: −0.23 (6H, s), 1.02 (6H, d, J=6 Hz), 1.00—1.09 (4H, m), 1.59 (1H, dd, J=15,

2 Hz), 3.84 (1H, quintet, J=6 Hz), 4.61—4.74 (3H, m), 5.32 (1H, br), 6.75 (1H, tt, J=53, 6 Hz), 6.84 (1H, d, J=3 Hz), 7.09 (1H, d, J=3 Hz), 7.15—7.32 (2H, m), 7.20 (2H, d, J=9 Hz), 7.68—7.81 (1H, m), 7.75 (2H, d, J=9 Hz). IR (KBr): 3400, 1670, 1510, 1430, 1250, 1110, 1010, 830 cm^{-1}. $[\alpha]_D^{20}$ +14.5° (c=1.0, MeOH).

Compound **34b** and the 2-fluoro analogs **35a**, **b** were prepared from **31b** and **32a**, **b**, respectively, as described above. Compound **34b** (60% yield): mp 123—125 °C (recrystallized from hexane–iso-Pr_2O). *Anal*. Calcd for $C_{26}H_{30}F_6N_2O_4Si$: C, 54.16; H, 5.24; N, 4.86. Found: C, 54.06; H, 5.29; N, 4.90. ^{1}H-NMR (DMSO-d_6) δ: −0.29 (3H, s), −0.27 (3H, s), 0.96 (6H, d, J=6 Hz), 0.83—1.25 (4H, m), 1.53 (1H, dd, J=15, 2 Hz), 3.79 (1H, quintet, J=6 Hz), 4.67 (1H, q, J=7 Hz), 5.26 (1H, br), 6.82 (1H, tt, J=52, 3 Hz), 6.83 (1H, d, J=3 Hz), 7.16 (1H, d, J=3 Hz), 7.08—7.29 (2H, m), 7.38 (2H, d, J=9 Hz), 7.65—7.77 (1H, m), 7.89 (2H, d, J=9 Hz). IR (KBr): 3400, 1680, 1510, 1430, 1260, 1110, 1010, 830 cm^{-1}. $[\alpha]_D^{20}$ +0.3° (c=1.0, MeOH). Compound **35a** (70% yield): mp 151—152 °C (recrystallized from hexane–iso-Pr_2O). *Anal*. Calcd for $C_{27}H_{33}F_5N_2O_4Si$: C, 56.63; H, 5.81; N, 4.89. Found: C, 56.51; H, 5.91; N, 5.02. ^{1}H-NMR ($CDCl_3$) δ: −0.62 (3H, s), −0.02 (3H, s), 1.0—1.25 (10H, m), 1.69 (1H, dd, J=15, 2 Hz), 3.82 (1H, quintet, J=6 Hz), 4.37 (2H, tt, J=11.8, 1.6 Hz), 4.89 (1H, q, J=6 Hz), 4.89 (1H, br), 6.09 (1H, tt, J=53, 5 Hz), 6.57 (1H, d, J=3 Hz), 6.81 (1H, d, J=3 Hz), 6.99 (2H, d, J=9 Hz), 7.00—7.35 (3H, m), 7.65 (2H, d, J=9 Hz), 7.73 (1H, dt, J=2, 7.8 Hz). IR (KBr): 3471, 1680, 1670, 1519, 1430, 1249, 1010, 830 cm^{-1}. $[\alpha]_D^{22}$ +13.1° (c=1.0, MeOH). Compound **35b** (86% yield): Oil [SI-MS (m/z): 559 (MH^+)]. ^{1}H-NMR (DMSO-d_6) δ: −0.35 (3H, s), −0.30 (3H, s), 0.94—1.09 (4H, m), 0.98 (6H, d, J=6 Hz), 1.56 (1H, dd, J=15, 2 Hz), 3.79 (1H, septet, J=6 Hz), 4.73 (1H, q, J=7 Hz), 5.16 (1H, br), 6.82 (1H, tt, J=52, 3 Hz), 6.85 (1H, d, J=3 Hz), 7.14 (1H, d, J=3 Hz), 7.17—7.56 (3H, m), 7.38 (2H, d, J=9 Hz), 7.69 (1H, t, J=8 Hz), 7.89 (2H, d, J=9 Hz). IR (neat): 3420, 2960, 2890, 1680, 1610, 1510 cm^{-1}. $[\alpha]_D^{22}$ +14.8° (c=1.0, MeOH).

1-[(1*R*,2*S*)-2-(2,4-Difluorophenyl)-2,3-dihydroxy-1-methylpropyl]-3-[4-(2,2,3,3-tetrafluoropropoxy)phenyl]-2(1*H*,3*H*)-imidazolone (36a) Compound **34a** was converted to **36a** by treatment with H_2O_2 as described in the synthesis of **7**. Yield 78%. mp 151—152 °C (recrystallized from iso-Pr_2O). *Anal*. Calcd for $C_{22}H_{20}F_6N_2O_4$: C, 53.88; H, 4.11; N, 5.71. Found: C, 53.69; H, 3.99; N, 5.74. ^{1}H-NMR ($CDCl_3$) δ: 1.26 (3H, d, J=7 Hz), 2.68 (1H, br s), 3.77—3.99 (2H, m), 4.37 (2H, t, J=11.8 Hz), 4.76 (1H, q, J=7 Hz), 4.85 (1H, br s), 6.07 (1H, tt, J=53, 4.6 Hz), 6.46 (1H, d, J=3 Hz), 6.54 (1H, d, J=3 Hz), 6.76—7.00 (2H, m), 6.99 (2H, dt, J=9, 2.4 Hz), 7.53 (2H, dt, J=9, 2.4 Hz), 7.68—7.84 (1H, m). IR (KBr): 3500, 3400, 1640, 1520, 1260, 1120 cm^{-1}. $[\alpha]_D^{20}$ +2.2° (c=1.0, MeOH).

Compound **36b** and the 2-fluoro analogs **37a**, **b** were prepared similarly from **34b** and **35a**, **b**, respectively. Compound **36b** (69% yield): mp 177—179 °C (recrystallized from iso-Pr_2O). *Anal*. Calcd for $C_{21}H_{18}F_6N_2O_4$: C, 52.95; H, 3.81; N, 5.88. Found: C, 52.72; H, 3.74; N, 5.72. ^{1}H-NMR ($CDCl_3$) δ: 1.26 (3H, d, J=7 Hz), 2.57 (1H, br s), 3.76—3.99 (2H, m), 4.79 (1H, q, J=7 Hz), 5.92 (1H, tt, J=53, 2.8 Hz), 6.50 (1H, d, J=3 Hz), 6.59 (1H, d, J=3 Hz), 6.79—6.97 (2H, m), 7.29 (2H, d, J=9 Hz), 7.69 (2H, d, J=9 Hz), 7.68—7.85 (1H, m). IR (KBr): 3500, 3400, 1650, 1515, 1260, 1110 cm^{-1}. $[\alpha]_D^{20}$ +0.3° (c=1.0, MeOH). Compound **37a** (89% yield): mp 166—167 °C (recrystallized from MeOH–iso-Pr_2O). *Anal*. Calcd for $C_{22}H_{21}F_5N_2O_4$: C, 55.93; H, 4.48; N, 5.93. Found: C, 55.77; H, 4.41; N, 6.16. ^{1}H-NMR ($CDCl_3$) δ: 1.28 (3H, d, J=7.2 Hz), 2.61 (1H, br), 3.78—4.00 (2H, m), 4.38 (2H, tt, J=11.8, 1.4 Hz), 4.80 (1H, br), 4.85 (1H, q, J=7.2 Hz), 6.08 (1H, tt, J=53, 4.8 Hz), 6.49 (1H, d, J=3 Hz), 6.55 (1H, d, J=3 Hz), 7.01 (2H, dt, J=9, 1.8 Hz), 7.02—7.40 (3H, m), 7.55 (2H, dt, J=9, 1.8 Hz), 7.76 (1H, dt, J=8, 1.8 Hz). IR (KBr): 3430, 3284, 1650, 1519, 1448, 1255 cm^{-1}. $[\alpha]_D^{22}$ +2.0° (c=1.0, MeOH). Compound **37b** (60% yield): mp 175—176 °C (recrystallized from MeOH–iso-Pr_2O). *Anal*. Calcd for $C_{21}H_{19}F_5N_2O_4$: C, 55.03; H, 4.18; N, 6.11. Found: C, 54.84; H, 4.12; N, 6.24. ^{1}H-NMR ($CDCl_3$) δ: 1.26 (3H, d, J=7 Hz), 2.60 (1H, br), 3.75—3.88 (1H, m), 3.88—4.02 (1H, m), 4.68 (1H, br), 4.88 (1H, q, J=7 Hz), 5.94 (1H, tt, J=53, 3 Hz), 6.55 (1H, d, J=3 Hz), 6.60 (1H, d, J=3 Hz), 7.01—7.40 (3H, m), 7.29 (2H, d, J=9 Hz), 7.65 (2H, d, J=9 Hz), 7.75 (1H, t, J=8 Hz). IR (KBr): 3485, 3400, 1642, 1510, 1436, 1252 cm^{-1}. $[\alpha]_D^{23}$ +0.58° (c=1.0, MeOH).

1-[(1*R*,2*S*)-2-(2,4-Difluorophenyl)-2-hydroxy-3-methanesulfonyloxy-1-methylpropyl]-3-[4-(2,2,3,3-tetrafluoropropoxy)phenyl]-2(1*H*,3*H*)imidazolone (38a) Compound **36a** was reacted with MsCl as described in the synthesis of **24** to give **38a** in 91% yield. ^{1}H-NMR ($CDCl_3$) δ: 1.27 (3H, d, J=7 Hz), 2.91 (3H, s), 4.43 (2H, t, J=11.8 Hz), 4.46—4.71 (3H, m), 6.07 (1H, tt, J=53, 4.8 Hz), 6.44 (1H, d, J=3 Hz), 6.57 (1H, d, J=3 Hz), 6.80—7.05 (2H, m), 7.00 (2H, d, J=9.2 Hz), 7.54 (2H, d, J=9.2 Hz), 7.78—7.92 (1H, m). *Anal*. Calcd for $C_{23}H_{22}F_6N_2O_6S$: C, 48.59; H, 3.90; N, 4.93. Found: C, 48.57; H, 3.84; N, 4.89.

Compounds **38b** and **39a**, **b** were prepared similarly from **36b** and **37a**, **b**, respectively. Compound **38b** (99% yield): ^{1}H-NMR ($CDCl_3$) δ: 1.27 (3H, d, J=7 Hz), 2.90 (3H, s), 4.45—4.72 (3H, m), 5.93 (1H, tt, J=53, 2.8 Hz), 6.49 (1H, d, J=3 Hz), 6.62 (1H, d, J=3 Hz), 6.81—7.00 (2H, m), 7.30 (2H, d, J=9.2 Hz), 7.64 (2H, d, J=9.2 Hz), 7.78—7.92 (1H, m). Compound **39a** (quantitative yield): ^{1}H-NMR ($CDCl_3$) δ: 1.28 (3H, d, J=7 Hz), 2.89 (3H, s), 4.38 (2H, tt, J=11.8, 1.6 Hz), 4.53 (1H, dd, J=11, 1.8 Hz), 4.68 (1H, q, J=7 Hz), 4.73 (1H, d, J=11 Hz), 6.08 (1H, tt, J=53, 5 Hz), 6.47 (1H, d, J=3 Hz), 6.58 (1H, d, J=3 Hz), 7.02 (2H, d, J=9 Hz), 7.05—7.43 (3H, m), 7.55 (2H, d, J=9 Hz), 7.81 (1H, dt, J=8, 1.8 Hz). Compound **39b** (quantitative yield): ^{1}H-NMR ($CDCl_3$) δ: 1.26 (3H, d, J=7 Hz), 2.87 (3H, s), 4.52 (1H, dd, J=11, 1.8 Hz), 4.68—4.78 (2H, m), 5.93 (1H, tt, J=53, 2.8 Hz), 6.52 (1H, d, J=3.2 Hz), 6.62 (1H, d, J=3.2 Hz), 7.01—7.40 (5H, m), 7.65 (2H, d, J=9 Hz), 7.79 (1H, dt, J=8, 1.6 Hz).

1-[(1*R*,2*R*)-2-(2,4-Difluorophenyl)-2-hydroxy-1-methyl-3-(1*H*-1,2,4-triazol-1-yl)propyl]-3-[4-(2,2,3,3-tetrafluoropropoxy)phenyl]-2(1*H*,3*H*)-imidazolone (25a) The mesylate **38a** was allowed to react with 1*H*-1,2,4-triazole as described in the synthesis of TAK-187 to obtain **25a** (47% yield). The optical purity of **25a** was confirmed to be >99% ee [column, Chiralpak AD; mobile phase, hexane–iso-PrOH, 1 : 1; flow rate; 1 ml/min; detection, UV at 262 nm]. This product was identical to **25a**, prepared starting from methyl (*R*)-lactate in our previous report,[1] on direct comparison with the authentic sample.

Compound **25b** and the 2-fluoro analogs **26a**, **b** were prepared similarly from the corresponding mesylates, **38b** and **39a**, **b**, in 46%, 75% and 69% yields, respectively. These products were also identical with those prepared in our previous report[1] on direct comparison with the authentic sample.

1-[(1*R*,2*R*)-2-(2-Fluorophenyl)-2-hydroxy-1-methyl-3-(1*H*-1,2,4-triazol-1-yl)propyl]-3-[4-(2,2,3,3-tetrafluoropropoxy)phenyl]-2-imidazolidinone (28a) A solution of **37a** (1.0 g) in AcOH (15 ml) was hydrogenated over 10% Pd–C (50% wet, 0.25 g) for 5 h at room temperature and then for 3 h at 50 °C under atmospheric pressure. The catalyst was removed by filtration and the filtrate was concentrated *in vacuo*. The residue was crystallized from iso-Pr_2O to give 1-[(1*R*,2*S*)-2-(2-fluorophenyl)-2,3-dihydroxy-1-methylpropyl]-3-[4-(2,2,3,3-tetrafluoropropoxy)phenyl]-2-imidazolidinone (**43**, 0.69 g, 69%) as colorless crystals. The mother liquor of the above crystallization was evaporated *in vacuo*. The residue was purified by silica gel column chromatography (AcOEt–hexane, 1 : 2, v/v) followed by crystallization from iso-Pr_2O–hexane to obtain an additional amount of **43** (0.20 g, 20%). mp 139—140 °C. *Anal*. Calcd for $C_{22}H_{23}F_5N_2O_4$: C, 55.70; H, 4.89; N, 5.90. Found: C, 55.54; H, 4.84; N, 5.76. IR (KBr): 3430, 2940, 1675, 1640, 1510, 1480, 1460 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.13 (3H, d, J=7.4 Hz), 2.20 (1H, br), 3.56—4.45 (7H, m), 4.33 (2H, t, J=11.9 Hz), 4.98 (1H, br), 6.07 (1H, tt, J=53.2, 4.8 Hz), 6.93 (2H, d, J=8.8 Hz), 6.95—7.40 (3H, m), 7.47 (2H, d, J=8.8 Hz), 7.74 (1H, dt, J=8.2, 1.8 Hz). $[\alpha]_D^{20}$ −27.4° (c=1.0, MeOH).

Compound **43** (5.85 g) was reacted with MsCl as described in the synthesis of **24** to give 1-[(1*R*,2*S*)-2-(2-fluorophenyl)-2-hydroxy-3-methanesulfonyloxy-1-methylpropyl]-3-[4-(2,2,3,3-tetrafluoropropoxy)phenyl]-2-imidazolidinone **44** (6.8 g, quantitative yield) as a colorless oil. ^{1}H-NMR ($CDCl_3$) δ: 1.12 (3H, d, J=7 Hz), 2.89 (3H, s), 3.60—3.69 (2H, m), 3.85—3.95 (2H, m), 4.10—4.29 (1H, br), 4.34 (2H, tt, J=12, 1.4 Hz), 4.68 (1H, dd, J=11, 1.6 Hz), 4.80 (1H, d, J=11 Hz), 6.07 (1H, tt, J=53, 5 Hz), 6.94 (2H, d, J=9 Hz), 7.00—7.39 (3H, m), 7.47 (2H, d, J=9 Hz), 7.79 (1H, dt, J=8, 1.8 Hz).

The mesylate **44** (6.8 g) was allowed to react with 1*H*-1,2,4-triazole as described in the synthesis of TAK-187 to obtain **28a** (4.4 g, 68% yield) as colorless prisms. This product was identical with **28a** prepared starting from methyl (*R*)-lactate in our previous report[1] on direct comparison with the authentic sample.

Acknowledgments We thank Dr. S. Kishimoto and Dr. A. Miyake for their encouragement throughout this work.

References and Notes

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4) We attempted to isolate triflate **5** by evaporation of the eluate obtained from silica gel column chromatography. Considerable decomposition was observed and, therefore, the concentrated eluate containing the triflate was used immediately in the subsequent nucleophilic displacement reaction.

5) *a*) Wulfman D. S., Linstrumelle G., Cooper C. F., "Synthetic Application of Diazoalkanes, Diazocyclopentadienes and Diazoazacyclopentadienes. The Chemistry of Diazonium and Diazo Groups," ed. by Patai S., John Wiley & Sons Inc., New York, 1978, p.821—976; *b*) Corey E. J., Chaykovsky M., *J. Am. Chem. Soc*., **87**, 1353—1364 (1965); *c*) Tamao K., Ishida N., *Tetrahedron Lett*., **25**, 4245—4248 (1984); *d*) Konosu T., Tajima Y., Takeda N., Miyaoka T., Kasahara M., Yasuda H., Oida S., *Chem. Pharm. Bull*., **38**, 2476—2486 (1990); *e*) Konosu T., Miyaoka T., Tajima Y., Oida S., *ibid*., **39**, 2241—2246 (1991); *f*) Konosu T., Miyaoka T., Tajima Y., Oida S., *ibid*., **40**, 562—564 (1992); *g*) Mooto D. R., Fraser-Reid B., *J. Chem. Soc*., *Perkin Trans. 1*, **1990**, 739—746; *h*) Cainelli G., Ronchi A. U., Bertini F., Grasselli P., Zubiani G., *Tetrahedron*, **27**, 6109—6114 (1971); *i*) Ohta H., Kimura Y., Sugano Y., Sugai T., *ibid*., **45**, 5469—5476 (1989); *j*) Park J., Pedersen S. F., *ibid*., **48**, 2069—2080 (1992); *k*) Clerici A., Porta O., *J. Org. Chem*., **54**, 3872—3878 (1989); *l*) Imamoto T., Takeyama T., Yokoyama M., *Tetrahedron Lett*., **25**, 3225—3226 (1984); *m*) Schroder M., *Chem. Rev*., **80**, 187—213 (1980).

6) A similar incident was observed in our previous study on the synthesis of HIV-1 protease inhibitors; The chiral methine carbon adjacent to the dioxoethylene moiety was epimerized during silica gel column chromatography using ordinary eluent (AcOEt : CH_2Cl_2 : MeOH = 5 : 5 : 1): Kitazaki T., Asano T., Kato K., Kishimoto S., Itoh K., *Chem. Pharm. Bull*., **42**, 2636—2640 (1994).

7) Tasaka A., Tamura N., Matsushita Y., Teranishi K., Hayashi R., Okonogi K., Itoh K., *Chem. Pharm. Bull*., **41**, 1035—1042 (1993).

8) We attempted the synthesis of the oxirane **6** from **8** by Corey's method.[5b] However, the reaction proceeded without stereoselectivity to give **6** as a diastereomeric mixture with low optical purity.

9) It has been reported that reaction of a Grignard's reagent and the 2-hydroxypropiophenone derivative (**18**) proceeds with high stereoselectivity to give a single diastereomer.[5d—f]

10) The stereochemistry of **7** was confirmed to be (1*R*,2*S*) after converting to the oxirane **6**, which was identical to (1*R*,2*S*)-**6** prepared in our previous study on direct comparison with an authentic sample.[2]

11) The TLC analysis of the reaction mixture at the initial stage indicated the formation of the oxirane **6**, which diminished with increasing reaction time to produce TAK-187.

12) The formation of the *O*-substituted by-product was detected by HPLC analysis of the reaction mixture. This by-product was unstable and decomposed during the work-up using aqueous solutions.

13) Tasaka A., Tsuchimori N., Kitazaki T., Hiroe K., Hayashi R., Okonogi K., Itoh K., *Chem. Pharm. Bull*., **43**, 441—449 (1995).

14) Radddatz P., Minck K.-O., Rippmann F., Schmitges C.-J., *J. Med. Chem*., **37**, 486—497 (1994).