Optically Active Antifungal Azoles. XI.[1] An Alternative Synthetic Route for 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-(1*H*-1-tetrazolyl)phenyl]-2-imidazolidinone (TAK-456) and Its Analog

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Received July 3, 2000; accepted August 28, 2000

New routes for the synthesis of the optically active antifungal triazoles 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-(1*H*-1-tetrazolyl)phenyl]-2-imidazolidinone (1b) and the 3-[4-(1*H*-1,2,3-triazol-1-yl)phenyl]-2-imidazolidinone analog (1a) that possess an imidazolidine nucleus were established. The key synthetic intermediates, (2*R*,3*R*)-3-(2,2-diethoxyethyl)amino-2-(2,4-difluorophenyl)-1-(1*H*-1,2,4-triazol-1-yl)-2-butanol (8) and (2*R*,3*R*)-2-(2,4-difluorophenyl)-3-(2-hydroxyethyl)amino-1-(1*H*-1,2,4-triazol-1-yl)-2-butanol (14), were prepared by the ring-opening reaction of the oxirane (2) with the corresponding 2-substituted ethylamines. The acetal (8) was converted to the imidazolidinones (1a, b) by condensation with the carbamates (10a, b) followed by treatment with hydrochloric acid and subsequent catalytic hydrogenation. The candidate selected for the clinical trials, 1b (TAK-456), was alternatively prepared from the hydroxyethylamino intermediate (14) *via* two reaction steps: condensation with the carbamate (10b) to the urea (15) and subsequent cyclization to the imidazolidinones. This newly developed synthetic route could be applied to a large scale preparation of 1b.

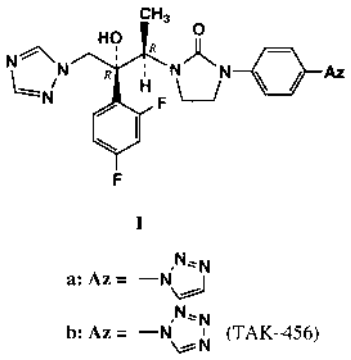
Key words TAK-456; optically active antifungal azoles; 1,2,3-trisubstituted-2-butanol; imidazolidinone; practical synthesis

We have recently reported the synthesis and antifungal activity of imidazolidinone derivatives with the general formula **1** (Chart 1).[1] These compounds exhibited strong growth inhibitory activity against not only yeasts such as *Candida albicans* and *Cryptococcus neoformans* but also against molds such as *Aspergillus fumigatus*, as well as potent protective effects against candidiasis and aspergillosis in mice. From these imidazolidinones, 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-(1*H*-1,2,3-triazol-1-yl)phenyl]-2-imidazolidinone (**1a**) and 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-(1*H*-1-tetrazolyl)phenyl]-2-imidazolidinone (**1b**) were selected for further biological evaluation to determine a candidate for clinical trials.

As we have previously described,[1] compounds **1a** and **1b** were prepared from the optically active synthetic intermediates, **2**, **4** and **5**, which were derived from (*R*)- and (*S*)-lactic acid esters as shown in Chart 2. Compound **1a** was obtained in an overall yield of 33% from the oxirane **2** by ring opening with **7a** followed by catalytic reduction, and **1b** was obtained *via* S_N2 displacement with the anion derived from **7b** in either four steps from the oxiranylethanol **4** or seven steps from the hydroxypropiophenone **5** in overall yields of 1.7% and 0.9%, respectively. Although these procedures were useful for the synthesis of a wide variety of optically active 1,2,3-trisubstituted-2-butanols,[1—3] the overall yields for the synthesis of **1a** and **1b** by these routes are low. We therefore needed to develop a higher-yielding synthetic procedure to supply sufficient quantities required for the detailed biological evaluation of **1a** and **1b**. In this paper we describe a new route for the efficient synthesis of the novel antifungal agents, **1a** and **1b**, starting from the oxirane **2**.

The main cause of the low yield in our previous synthesis was considered to be the low reactivity of the anion of the imidazolones **7a** and **7b** to nucleophilic substitution. Therefore, we devised an alternative retrosynthetic pathway, in which the imidazolone- or imidazolidinone ring is formed by intramolecular cyclization after introduction of the appropriate functionality into the butanol framework (Chart 3). Thus the 2-substituted ethylamine moiety is first introduced into the 3-position of the oxirane **2** to give the aminoalcohol III whose secondary amino group is sufficiently basic to allow addition of an *N*-substituted carbamoyl group to give the urea II. Intramolecular cyclization utilizing the functional groups (R^1 and R^2) then allows synthesis of the desired skeleton I.

The synthetic routes initially investigated are shown in Chart 4. The oxirane **2** was allowed to react with 2,2-diethoxyethylamine [$H_2NCH_2CH(OEt)_2$] in the presence of titanium tetraisopropoxide [$Ti(O\text{-}isoPr)_4$][4] in propanol (PrOH)



I

a: Az =

b: Az = (TAK-456)

Chart 1

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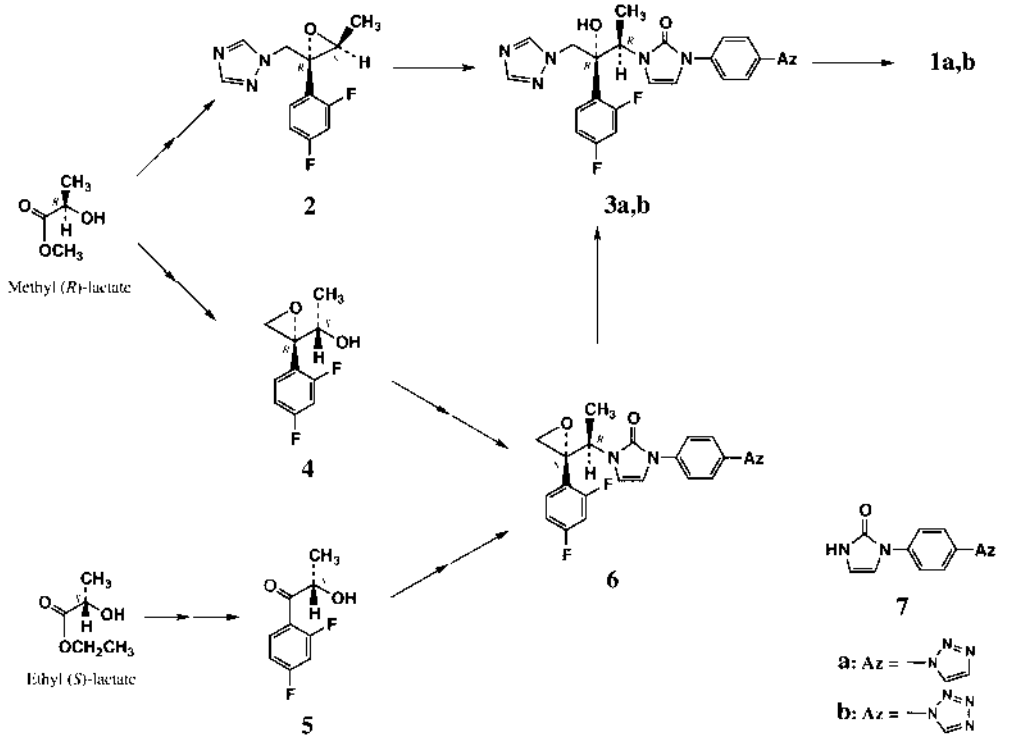

Chart 2

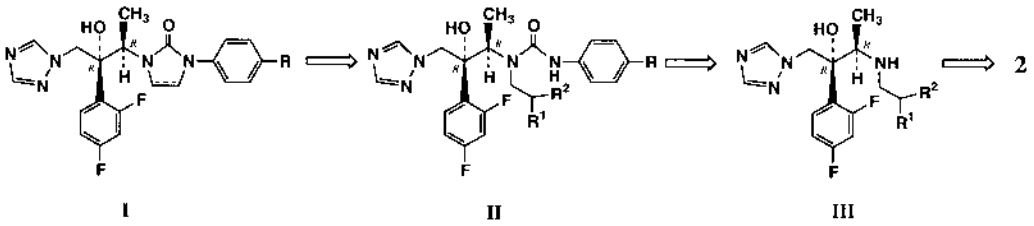

Chart 3

to give the ring-opened product **8**, which is the key intermediate in this synthetic route, as an oil in 81% yield. For the synthesis of **1a**, compound **8** was reacted with phenyl 4-(1*H*-1,2,3-triazol-1-yl)phenylcarbamate (**10a**) at 110 °C in *N*,*N*-dimethylformamide (DMF) to give the urea **9a** (94% isolated yield). Intramolecular cyclization was achieved by heating **9a** in the presence of methanolic hydrochloric acid (HCl–MeOH) to form the imidazolone **3a** in 84% yield. The synthesis could also be carried out without purification of the intermediate **9a**, resulting in a slightly improved overall yield of **3a** from **8** (83%). Catalytic hydrogenation of **3a** over palladium on carbon (Pd–C) in acetic acid (AcOH) using the conditions described in our preceding report afforded **1a**. This synthetic route, which allowed the preparation of **1a** in 58% overall yield from the starting material **2**, was then applied to the synthesis of the 1-tetrazolylphenylimidazolone derivative **1b**. Thus compound **8** was reacted with phenyl 4-(1*H*-1-tetrazolyl)phenylcarbamate (**10b**) and then cyclized and hydrogenated as described above to give **1b** in 40% overall yield from **2**.

The synthesis of **1b** was also carried out by an alternative route using commercially available 4-nitrophenyl isocyanate (4-NO_2PhNCO) instead of **10b**. Room temperature reaction of **8** with 4-NO_2PhNCO gave the nitrophenylurea **11** in 81% isolated yield, which was then cyclized to the imidazolone **12** (86%). When the synthesis was carried out without purification of **11**, the overall yield of **12** from **8** was improved slightly to 80%. The nitro group and the double bond were simultaneously reduced by catalytic hydrogenation on Pd–C to afford the aminophenylimidazolidinone **13** in a moderate yield (52%). The amino group of **13** was converted into a tetrazole ring in 55% isolated yield by reaction with sodium azide (NaN_3) and ethyl orthoformate [$CH(OEt)_3$] in the presence of AcOH. Using this route, **1b** was obtained in 19% overall yield from **2**.

On the basis of results of detailed biological studies carried out on compounds **1a** and **1b**, compound **1b** (TAK-456) was selected as the candidate for clinical trials. Therefore, a more practical pathway for the large scale synthesis of **1b** was now required, since the previous synthetic routes involved a moderate yielding conversion of imidazolone to imdazolidinone, *i.e.*, **3b**→**1b** (64%) and **12**→**13** (52%), by catalytic hydrogenation. Thus we devised an alternative route to synthesize the imidazolidinone ring by direct cyclization of the hydroxyethyl precursor II (R^1=H, R^2=OH: Chart 3).

The route for the alternative synthesis for **1b** is shown in

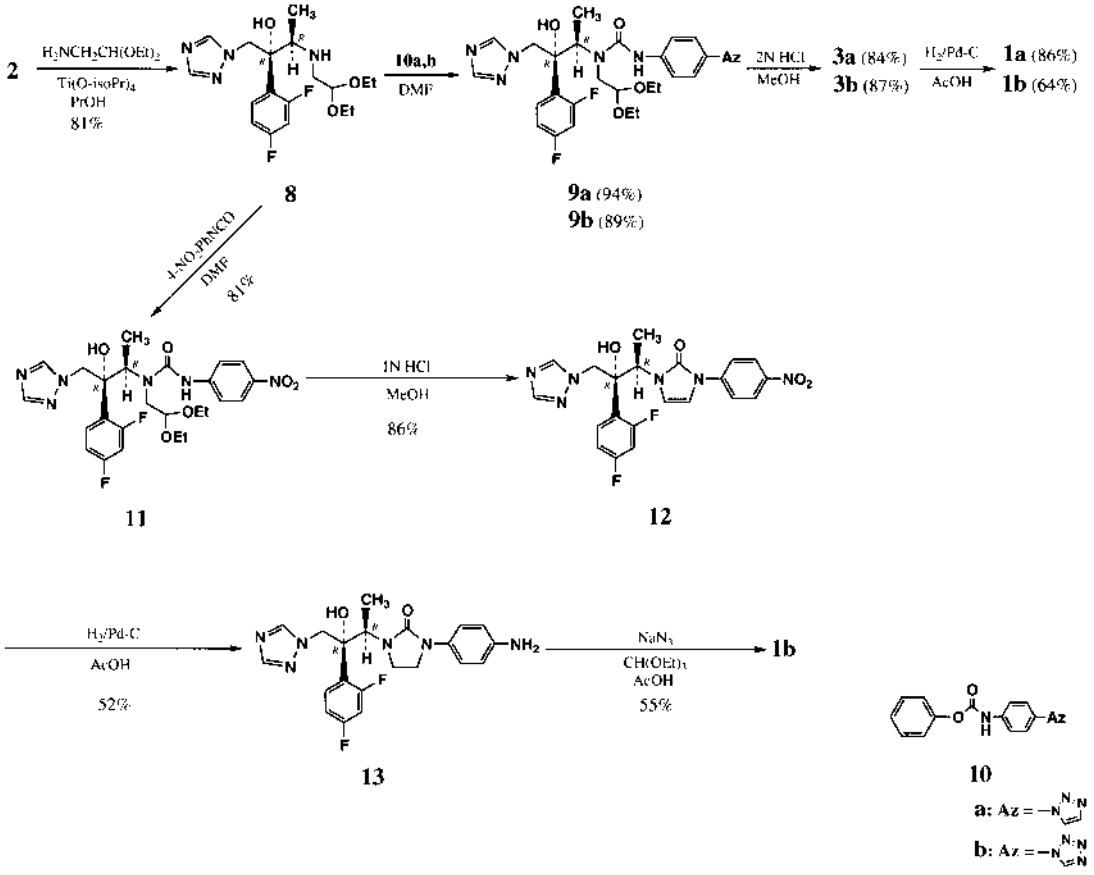

Chart 4

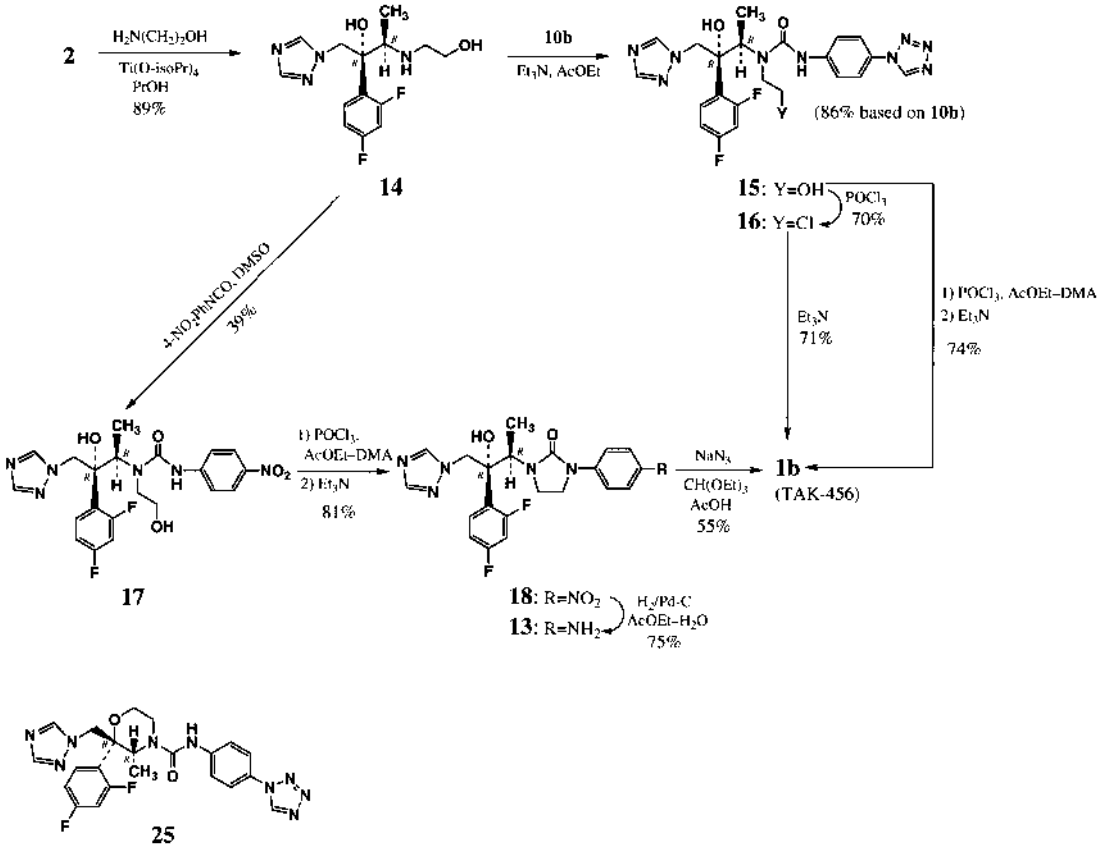

Chart 5

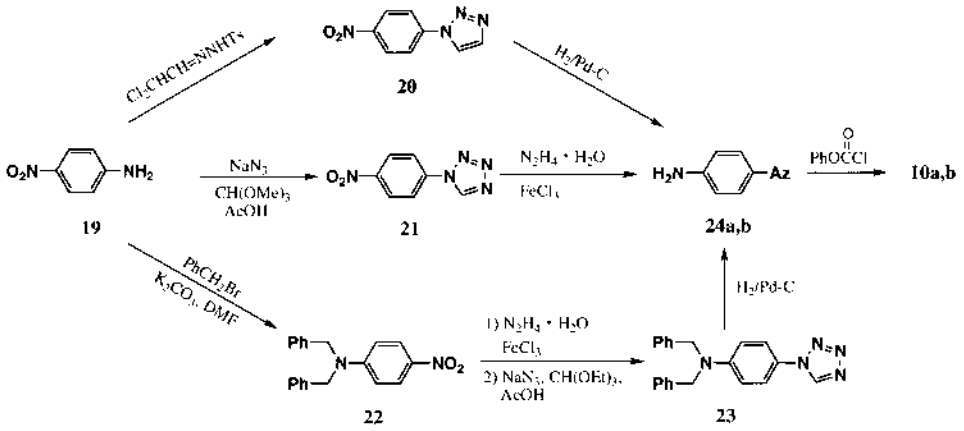

Chart 6

Chart 5. The oxirane ring-opening reaction of **2** with 2-aminoethanol [$H_2N(CH_2)_2OH$] was successfully carried out using similar reaction conditions to those used in the synthesis of **8**, to give the hydroxyethylaminobutanol **14** as an oil in 89% yield. Condensation of **14** with the carbamate **10b** (0.8 eq) in the presence of triethylamine (Et_3N) in ethyl acetate (AcOEt) at reflux resulted in the precipitation of **15** from the reaction mixture (86% yield from **10b**). Several reaction conditions were examined for the ring closure of **15** to give the imidazolidinone and initially it seemed that the Mitsunobu reaction[5] using diethyl azodicarboxylate (DEAD) and triphenylphosphine (Ph_3P) would be able to affect direct ring closure. However, this reaction was found to proceed *via* 2 pathways, which in addition to giving the desired product **1b** (67% yield), also produced the undesired morpholine derivative **25**[6] (12% yield) as a byproduct. We next examined a 2-step cyclization *via* initial conversion of **15** to the chloride **16** followed by dehydrochlorination with base to give **1b**. Treatment of **15** with thionyl chloride ($SOCl_2$) afforded the chloride **16** in 43% yield, but an improved isolated yield (70%) was obtained by using phosphorous oxychloride ($POCl_3$), and dehydrochlorination of **16** with Et_3N gave the imidazolidinone **1b** in 71% yield. Furthermore, this two-step cyclization reaction could be carried out as a one-pot process. Thus $POCl_3$ was added to a solution of **15** in AcOEt and *N*,*N*-dimethylacetamide (DMA), and the subsequent addition of Et_3N gave the product **1b** in 74% overall yield from **15**.

As described above (Chart 4), **1b** was also obtained by tetrazole ring formation at the amino group of **13**, although the yield of the preceding hydrogenation step to synthesize **13** was moderate (52%). Therefore, in order to improve the yield of **13**, we investigated its synthesis from **14** *via* the imidazolidinone cyclization route we have established. Ring closure of **17** using $POCl_3$–Et_3N to give **18** and subsequent catalytic hydrogenation to give **13** proceeded successfully in 81% yield and in 75% yield, respectively. However the initial step to synthesize **17** by introduction of the *N*-nitrophenylcarbamoyl moiety onto the secondary amino group of **14** proceeded in a poor yield (39%), probably due to the competing reaction of the primary hydroxyl group of **14** with the isocyanate.

Our synthesis of **1a** and **1b** above used the carbamate **10a** and **10b** as key synthetic intermediates. In our preceding report, **10a** and **10b** were prepared from the corresponding anilines **24a** and **24b**, which in turn were synthesized by reduction of the corresponding 4-azolylnitrobenzenes prepared by nucleophilic substitution of 4-fluoronitrobenzene with the appropriate azoles, *i.e.*, 1,2,3-triazole and tetrazole. However, in both cases, an isomeric mixture of 1-substituted and 2-substituted azoles were obtained, which required separation at either the 4-azolylnitrobenzene or the 4-azolylaniline stage.[1] Clearly for the efficient large scale synthesis of **1a** and **1b**, we needed a method to selectively prepare the 1-substituted azole isomer. Thus a new route was devised for the synthesis of the carbamates **10a** and **10b** using *p*-nitroaniline (**19**) as the starting material (Chart 6), in which the 1-substituted 1,2,3-triazole derivative **20** was selectively synthesized by reaction with chloroacetaldehyde tosylhydrazone ($ClCH_2$-CH=NNHTs) according to the method described in a patent.[7] This enabled **20** to be obtained as crystals in 67% yield from the hydrazone, after which **10a** could be obtained by reduction to **24a** followed by treatment with phenyl chlorocarbonate (PhOCOCl) [overall yield from **20**, 80%]. For the synthesis of the 1-substituted tetrazole derivative **10b**, compound **19** was first converted quantitatively to **21** according to the method reported by Gaponik *et al*.[8] Subsequent reduction of **21** to **24b** with hydrazine hydrate ($N_2H_4 \cdot H_2O$) in the presence of ferric chloride ($FeCl_3$) followed by treatment with PhOCOCl afforded the carbamate **10b**, in 82% overall yield from **19**. In alternative approach, compound **19** was dibenzylated with benzyl bromide ($PhCH_2Br$) in the presence of potassium carbonate (K_2CO_3) to give **22** (82% yield), and the nitro group was reduced to amino group and then reacted with NaN_3 and $CH(OEt)_3$ to form the 1-substituted tetrazole **23** (63% yield). The dibenzyl group was removed by catalytic hydrogenolysis, and the resulting aniline **24b** was converted to the carbamate **10b** in 91% yield from **23**.

In conclusion, we have established an efficient and practical route for the synthesis of the imidazolidinone-based antifungal triazoles, **1a** and **1b**. This route is suitable for application to large-scale production, since each reaction step proceeded in a good yield under mild conditions, and in addition all the synthetic intermediates were stable and easily purified. Pre-clinical studies on the selected candidate **1b** (TAK-456) are currently in progress and detailed profiles of the biological activity of **1b** will be reported in due course.

Experimental

Melting points were determined using a Yanagimoto melting point apparatus and are uncorrected. IR spectra were measured with 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, q=quartet, m=multiplet and 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 carried out 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 nm, 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 using the following aqueous solutions: water, 5% aqueous sodium carbonate solution (aqueous $NaHCO_3$), saturated sodium chloride (NaCl) solution (brine), 1 N aqueous sodium hydroxide solution (1 N NaOH), 1 N hydrochloric acid (1 N HCl) and 5% aqueous phosphoric acid solution (5% H_3PO_4). Extracts were dried over anhydrous magnesium sulfate ($MgSO_4$), 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.

(2*R*,3*R*)-3-(2,2-Diethoxyethyl)amino-2-(2,4-difluorophenyl)-1-(1*H*-1,2,4-triazol-1-yl)-2-butanol (8) A mixture of **2** (40 g), Ti(O-isoPr)$_4$ (68 g), $H_2NCH_2CH(OEt)_2$ (464 ml) and PrOH (400 ml) was stirred under reflux for 24 h under a nitrogen atmosphere. The solvent and $H_2NCH_2CH(OEt)_2$ were distilled off under reduced pressure. The residue was diluted with AcOEt (800 ml). 1 N NaOH–brine (1 : 1, v/v, 520 ml) was added and the resulting mixture was stirred for 1 h. A milky precipitate was filtered off and washed with AcOEt (250 ml). The filtrate and the washing were combined. The organic layer was extracted with 1 N HCl (150 ml×4). The aqueous extracts were combined and neutralized with 2 N NaOH (300 ml) at 0 °C. The whole was worked up (AcOEt; 1 N NaOH, brine). Compound **8** (49.4 g, 81%) was obtained as a pale yellow oil. *Anal*. Calcd for $C_{18}H_{26}F_2N_4O_3$: C, 56.24; H, 6.82; N, 14.57. Found: C, 55.88; H, 6.74; N, 14.50. ^{1}H-NMR ($CDCl_3$) δ: 0.91 (3H, d, J=6.6 Hz), 1.0—1.2 (1H, br), 1.23 (6H, t, J=7 Hz), 2.66 (1H, dd, J=12 Hz, 4.6 Hz), 2.95 (1H, dd, J=12, 6.4 Hz), 3.14 (1H, q, J=6.6 Hz), 3.48—3.81 (4H, m), 4.56 (1H, dd, J=6.4, 4.6 Hz), 4.75 (1H, d, J=14 Hz), 4.88 (1H, s), 4.89 (1H, d, J=14 Hz), 6.69—6.80(2H, m), 7.33—7.45 (1H, m), 7.76 (1H, s), 7.93 (1H, s). IR (neat): 2976, 1617, 1501, 1273, 1136, 1100, 1063, 964 cm^{-1}. $[\alpha]_D^{20}$: −60.4° (c=0.28, MeOH). SI-MS (*m/z*): 385 (MH^+).

1-(2,2-Diethoxyethyl)-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-(1*H*-1,2,3-triazol-1-yl)-phenyl]urea (9a) A mixture of **8** (188 mg), **10a** (137 mg) and DMF (2 ml) was stirred for 2 h at 110 °C under an argon atmosphere. The reaction mixture was cooled and worked up (AcOEt; water, brine). The residue was purified by silica gel column chromatography (AcOEt–hexane, 3 : 1, v/v→AcOEt) to give **9a** (262 mg, 94%) as a white powder. *Anal*. Calcd for $C_{27}H_{32}F_2N_8O_4$: C, 56.83; H, 5.65; N, 19.64. Found: C, 56.71; H, 5.76; N, 14.44. ^{1}H-NMR ($CDCl_3$) δ: 1.07 (1.2H, d, J=7 Hz), 1.23 (1.8H, d, J=7 Hz), 1.34 (6H, t, J=7 Hz), 3.51—4.07 (7H, m), 4.39 (0.4H, d, J=14 Hz), 4.54 (0.6H, d, J=14 Hz), 4.74 (0.6H, m), 4.94—5.01 (1H, m), 5.24—5.41 (1.4H, m), 6.72—6.82 (2H, m), 7.37—7.84 (8.2H, m), 7.95 (0.6H, s), 8.24 (0.4H, s), 8.75 (0.4H, br), 9.05 (0.4H, s). IR (KBr): 3350, 3160, 2970, 1630, 1540, 1510, 1460, 1220, 1150 cm^{-1}. $[\alpha]_D^{20}$: −107.1° (c=1.0, MeOH).

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-(1*H*-1,2,3-triazol-1-yl)phenyl]-2-(1*H*,3*H*)-imidazolone (3a) 1) 2 N HCl (2.4 ml) was added to a solution of **9a** (228 mg) in MeOH (2.4 ml). The mixture was stirred for 4 h at 60 °C and cooled. After having been neutralized with 1 N NaOH (4.8 ml), the whole was concentrated *in vacuo* and worked up (AcOEt; water, brine). The residue was crystallized from AcOEt–diisopropyl ether (isoPr$_2$O) to give **3a** (161 mg, 84%) as white powdery crystals.

2) A mixture of **8** (16 g), **10a** (11.66 g) and DMF (160 ml) was stirred for 2 h at 110 °C under an argon atmosphere. The mixture was cooled and worked up (AcOEt; water, brine). The residue was dissolved in MeOH (210 ml), and then 2 N HCl (210 ml) was added to the solution. The mixture was stirred for 6 h at 60 °C and cooled. After having been concentrated *in vacuo*, the remaining aqueous solution was washed with isoPr$_2$O (200 ml) and neutralized with 1 N NaOH (420 ml). The whole was extracted with AcOEt and the extract was washed with brine. The organic layer was dried over $MgSO_4$ and concentrated *in vacuo*. The residue was crystallized from AcOEt–isoPr$_2$O to give **3a** (18 g), which was then recrystallized from AcOEt to give white powdery crystals (16.5 g, 83% from **8**).

Compound **3a** was hydrogenated to **1a** in the same manner as that described in our preceding report.[1)] Compounds **3a** and **1a** were identical to the authentic sample[1)] upon direct comparison.

1-(2,2-Diethoxyethyl)-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-(1*H*-1-tetrazolyl)phenyl]-urea (9b) A mixture of **8** (30 g), **10b** (21.9 g) and DMF (300 ml) was stirred for 5 h at 80 °C. The reaction mixture was cooled and worked up (AcOEt; water). The residue was crystallized from AcOEt–isoPr$_2$O to give **9b** (35.7 g) as white powdery crystals. The mother liquor was concentrated *in vacuo* and the residue was purified by silica gel column chromatography (AcOEt–hexane, 3 : 1, v/v→AcOEt) to obtain an additional amount of **9b** (4 g). Yield: 39.7 g (89%). mp 180—182 °C. *Anal*. Calcd for $C_{26}H_{31}F_2N_9O_4$: C, 54.63; H, 5.47; N, 22.05. Found: C, 54.58; H, 5.37; N, 21.61. ^{1}H-NMR ($CDCl_3$) δ: 1.08 (1.5H, d, J=7 Hz), 1.24 (1.5H, d, J=7 Hz), 1.31—1.38 (6H, m), 3.50—4.06 (7H, m), 4.39 (0.5H, d, J=14 Hz), 4.59 (0.5H, d, J=14 Hz), 4.76 (0.5H, m), 4.93—5.08 (1.5H, m), 5.25—5.48 (1H, m), 6.73—6.83 (2H, m), 7.31—7.69 (5.5H, m), 7.79 (0.5H, s), 7.82 (0.5H, s), 8.24 (0.5H, s), 8.85 (0.5H, br), 8.94 (0.5H, s), 8.96 (0.5H, s), 9.16 (0.5H, s). IR (KBr): 3340, 3140, 2970, 1640, 1530, 1500, 1460, 1200, 1140 cm^{-1}. $[\alpha]_D^{20}$: −106.9° (c=1.0, MeOH).

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-(1*H*-1-tetrazolyl)phenyl]-2-(1*H*,3*H*)-imidazolone (3b) 2 N HCl (342 ml) was added to a solution of **9b** (39 g) in MeOH (342 ml). The mixture was stirred for 17 h at 50—55 °C and cooled. After having been neutralized with 2 N NaOH (342 ml), the whole was concentrated *in vacuo* and worked up (AcOEt; water, brine). The residue was crystallized from AcOEt–isoPr$_2$O to give **3b** (28.6 g, 87%) as white powdery crystals. This product was identical to **3b** prepared in our preceding report[1)] upon direct comparison with the authentic sample.

1-(2,2-Diethoxyethyl)-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-nitrophenyl)urea (11) A mixture of **8** (0.25 g), 4-NO_2PhNCO (0.11 g) and DMF (2 ml) was stirred for 2 h. The reaction mixture was worked up (AcOEt; water, brine). The residue was purified by silica gel column chromatography (AcOEt–hexane, 1 : 3→1 : 2, v/v) to give **11** (0.29 g, 81%) as a pale yellow powder. *Anal*. Calcd for $C_{25}H_{30}F_2N_6O_6$: C, 54.74; H, 5.51; N, 15.32. Found: C, 54.61; H, 5.29; N, 15.29. ^{1}H-NMR ($CDCl_3$) δ: 1.07 (1.5H, d, J=7 Hz), 1.23 (1.5H, d, J=7 Hz), 1.30—1.38 (6H, m), 3.50—4.10 (6.5H, m), 4.36 (0.5H, d, J=14 Hz), 4.53 (0.5H, d, J=14 Hz), 4.72—4.77 (0.5H, m), 4.91—5.01 (1H, m), 5.26—5.42 (2H, m), 6.70—6.84 (2H, m), 7.31—7.64 (3.5H, m), 7.78 (0.5H, s), 7.81 (0.5H, s), 8.16—8.23 (2.5H, m), 9.02 (0.5H, br), 9.37 (0.5H, s). IR (KBr): 3283, 2978, 1557, 1505, 1331, 1304, 1244, 1113 cm^{-1}. $[\alpha]_D^{20}$: −120.9° (c=0.44, MeOH). SI-MS (*m/z*): 549 (MH^+).

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-nitrophenyl)-2-(1*H*,3*H*)-imidazolone (12) 1) 1 N HCl (2.8 ml) was added to a solution of **11** (0.15 g) in MeOH (3 ml). The mixture was stirred under reflux for 2 h and cooled. After having been neutralized by addition of $NaHCO_3$ (0.24 g) at 0 °C, the whole was worked up (AcOEt; water, brine) to give **12** (0.11 g, 86%) as a pale yellow powder. *Anal*. Calcd for $C_{21}H_{18}F_2N_6O_4 \cdot 1/2H_2O$: C, 54.19; H, 4.11; N, 18.06. Found : C, 54.53; H, 4.05; N, 18.13. ^{1}H-NMR ($CDCl_3$) δ: 1.20 (3H, d, J=7 Hz), 4.19 (1H, d, J=14 Hz), 5.02 (1H, q, J=7 Hz), 5.11 (1H, d, J=14 Hz), 5.41 (1H, br), 6.76—6.90 (4H, m), 7.41—7.53 (1H, m), 7.76 (1H, s), 7.82 (1H, s), 7.94 (2H, d, J=9.2 Hz), 8.34 (2H, d, J=9.2 Hz). IR (KBr): 1692, 1597, 1503, 1426, 1334, 1252, 855 cm^{-1}. $[\alpha]_D^{20}$: −11.4° (c=1.0, MeOH). SI-MS (*m/z*): 457 (MH^+).

2) A mixture of **8** (8.9 g), 4-NO_2PhNCO (4.2 g) and dimethyl sulfoxide (DMSO, 30 ml) was stirred for 2 h, and the whole was worked up (AcOEt; water; brine). The residue was dissolved in MeOH (180 ml) and treated with 2 N HCl (115 ml) in a manner similar to that described above. The precipitate was filtered off, and the filtrate was neutralized by addition of $NaHCO_3$ (19.3 g). The whole was concentrated *in vacuo* and worked up (AcOEt; water, brine). The residue was purified by silica gel column chromatography (AcOEt–hexane, 2 : 1, v/v) to give **12** (8.6 g, 80% from **8**) as a pale yellow powder.

(2*R*,3*R*)-2-(2,4-Difluorophenyl)-3-(2-hydroxyethyl)amino-1-(1*H*-1,2,4-triazol-1-yl)-2-butanol (14) A mixture of **2** (30 g), Ti(O-isoPr)$_4$ (51 g), $H_2N(CH_2)_2OH$ (109.4 g) and PrOH (300 ml) was refluxed for 7.5 h under a nitrogen atmosphere. After having been cooled, the mixture was diluted with AcOEt (500 ml) and 2 N NaOH (98 ml) saturated with NaCl. The resulting mixture was stirred for 30 min, diluted with brine (195 ml) and stirred for a further 10 min. The supernatant was separated by decantation. AcOEt (400 ml) was added to the aqueous layer, and the mixture was stirred vigorously for 3 min. The supernatant was separated again by decantation. Addition of

AcOEt (300 ml each) followed by separation of the supernatant was repeated two more times. The supernatants were combined, washed with brine (250 ml) and extracted with 1 N HCl (225 ml×2). The acidic aqueous extracts were combined and neutralized at 0 °C with 2 N NaOH (230 ml) saturated with NaCl. The whole was extracted with AcOEt and the extract was washed with brine. The organic layer was dried over $MgSO_4$ and concentrated *in vacuo* to give **14** (34.2 g, 89%) as a pale yellow oil. *Anal*. Calcd for $C_{14}H_{18}F_2N_4O_2 \cdot 1/2H_2O$: C, 52.33; H, 5.96; N, 17.44. Found : C, 52.76; H, 6.06; N, 17.06. ^{1}H-NMR ($CDCl_3$) δ: 0.92 (3H, d, J=6.6 Hz), 1.60—1.80 (2H, br), 2.61—2.73 (1H, m), 2.98—3.16 (2H, m), 3.65—3.71 (2H, m), 4.81 (1H, d, J=14 Hz), 4.96 (1H, d, J=14 Hz), 4.77—4.99 (1H, br), 6.70—6.80 (2H, m), 7.36—7.48 (1H, m), 7.78 (1H, s), 7.87 (1H, s). IR (neat): 3320, 1617, 1597, 1501, 1422, 1273, 1136, 1101 cm^{-1}. $[\alpha]_D^{20}$: −66.4° (c=1.0, MeOH). SI-MS (*m/z*): 313 (MH^+).

1-[(1*R*,2*R*)-2-(2,4-Difluorophenyl)-2-hydroxy-1-methyl-3-(1*H*-1,2,4-triazol-1-yl)propyl]-1-(2-hydroxyethyl)-3-[4-(1*H*-1-tetrazolyl)phenyl]urea (15) A mixture of **14** (34.2 g), **10b** (23.7 g), Et_3N (17.6 ml) and AcOEt (600 ml) was stirred under reflux for 1.5 h. After having been cooled, the mixture was stirred for 2 h at 0 °C. The precipitate was collected by filtration, washed with AcOEt (50 ml) and dried at 40 °C *in vacuo* to give **15** (37.9 g, 86% based on **10b**) as white powdery crystals. mp 172—175 °C. *Anal*. Calcd for $C_{22}H_{23}F_2N_9O_3 \cdot 1/4$AcOEt: C, 52.97; H, 4.83; N, 24.17. Found: C, 53.01; H, 4.81; N, 24.19. ^{1}H-NMR (d_6-DMSO) δ: 0.93, 1.16 (3H, d, J=7.0 Hz), 3.47—4.09 (4.5H, m), 4.56 (1H, d, J=14 Hz), 4.91—5.03 (1H, m), 5.30 (0.5H, q, J=7 Hz), 5.79, 6.12, 6.21 (2H, br), 6.87—6.96 (1H, m), 7.13—7.45 (2H, m), 7.59—7.88 (5H, m), 8.21, 8.32 (1H, s), 9.41, 9.49 (1H, s), 10.02, 10.05 (1H, s). IR (KBr): 3240, 3136, 1649, 1524, 1473, 1338, 1207, 1138 cm^{-1}. $[\alpha]_D^{20}$: −100.9° (c=0.94, MeOH). SI-MS (*m/z*): 500 (MH^+).

1-(2-Chloroethyl)-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-(1*H*-1-tetrazolyl)phenyl]-urea (16) A solution of $POCl_3$ (0.51 ml) in AcOEt (6 ml) was added dropwise to a solution of **15** (2 g) in DMA–AcOEt (1 : 1, v/v, 20 ml) over a period of 1 h at around 22 °C. The mixture was stirred for 16 h and worked up (AcOEt; water). The residue was crystallized from diethyl ether (Et_2O, 30 ml) to give **16** (1.44 g, 70%) as a white powder. *Anal*. Calcd for $C_{22}H_{22}ClF_2N_9O_2 \cdot H_2O$: C, 49.30; H, 4.51; N, 23.52. Found: C, 49.38; H, 4.50; N, 23.14. ^{1}H-NMR (d_6-DMSO) δ: 1.02, 1.16 (3H, d, J=7 Hz), 3.61—4.09 (4.5H, m), 4.43, 4.57 (1H, d, J=14 Hz), 4.87, 4.97 (1H, d, J=14 Hz), 5.20 (0.5H, q, J=7 Hz), 5.98 (1H, br), 6.89—6.98 (1H, m), 7.13—7.48 (2H, m), 7.64—7.85 (5H, m), 8.31 (1H, s), 9.02, 9.22 (1H, s), 10.02 (1H, s). IR (KBr): 3125, 1657, 1524, 1473, 1309, 1257, 1179 cm^{-1}. SI-MS (*m/z*): 518 (MH^+).

1-[(1*R*,2*R*)-2-(2,4-Difluorophenyl)-2-hydroxy-1-methyl-3-(1*H*-1,2,4-triazol-1-yl)propyl]-1-(2-hydroxyethyl)-3-(4-nitrophenyl)urea (17) A mixture of **14** (10 g), 4-NO_2PhNCO (5.25 g) and DMSO (50 ml) was stirred for 1 h. The whole was worked up (AcOEt; water, brine). The residue was crystallized from AcOEt to give **17** (5.9 g, 39%) as yellow powdery crystals. mp 122—125 °C. *Anal*. Calcd for $C_{21}H_{22}F_2N_6O_5 \cdot 1/2H_2O$: C, 51.96; H, 4.78; N, 17.31. Found: C, 51.72; H, 5.05; N, 17.14. ^{1}H-NMR (d_6-DMSO) δ: 0.94 (1.8H, d, J=7 Hz), 1.13 (1.2H, d, J=7 Hz), 3.40—4.05 (4.4H, m), 4.54, 4.58 (1H, d, J=14 Hz), 4.94, 4.97 (1H, d, J=14 Hz), 5.28 (0.6H, q, J=7 Hz), 6.08, 6.25 (2H, br), 6.87—6.96 (1H, m), 7.12—7.46 (2H, m), 7.59—7.72 (3.4H, m), 8.17—8.30 (3H, m), 9.90 (0.6H, br). IR (KBr): 1618, 1599, 1568, 1503, 1331, 1304, 1258 cm^{-1}. SI-MS (*m/z*): 477 (MH^+). $[\alpha]_D^{20}$: −111.1° (c=1.0, MeOH).

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-nitrophenyl)-2-imidazolidinone (18) A solution of $POCl_3$ (0.88 ml) in AcOEt (10 ml) was added dropwise to a solution of 17 (3 g) in DMA–AcOEt (1 : 1, v/v, 30 ml) over a period of 20 min at around 21 °C. The mixture was stirred for 16 h, and then Et_3N (8.8 ml) was added dropwise over a period of 20 min at −5 °C. The whole was stirred for 2 h and worked up (AcOEt; water, 5% H_3PO_4, aqueous $NaHCO_3$, brine). The residue was purified by silica gel column chromatography (AcOEt–hexane, 6 : 1, v/v) to give **18** (2.3 g, 81%) as a pale yellow powder. *Anal*. Calcd for $C_{21}H_{20}F_2N_6O_4$: C, 55.02; H, 4.40; N, 18.33. Found: C, 54.70; H, 4.44; N, 17.95. ^{1}H-NMR ($CDCl_3$) δ: 1.07 (3H, d, J=7 Hz), 3.70—4.18 (4H, m), 4.48 (1H, d, J=14 Hz), 4.68—4.80 (1H, m), 5.11 (1H, d, J=14 Hz), 5.30 (1H, br), 6.73—6.85 (2H, m), 7.35—7.48 (1H, m), 7.75 (2H, d, J=9 Hz), 7.77 (1H, s), 7.84 (1H, s), 8.24 (2H, d, J=9 Hz). IR (KBr): 1701, 1597, 1501, 1426, 1329, 1267, 1113, 849 cm^{-1}. SI-MS (*m/z*): 459 (MH^+). $[\alpha]_D^{20}$: −69.0° (c=1.0, MeOH).

1-(4-Aminophenyl)-3-[(1*R*,2*R*)-2-(2,4-Difluorophenyl)-2-hydroxy-1-methyl-3-(1*H*-1,2,4-triazol-1-yl)propyl]-2-imidazolidinone (13) 1) A solution of **12** (1 g) in AcOH (15 ml) was hydrogenated over 10% Pd–C (1 g) for 7 h at 40—45 °C. The catalyst was filtered off and washed with AcOH (30 ml). The filtrate and the washing were combined and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (AcOEt–hexane, 9 : 1, v/v→AcOEt) and crystallized from AcOEt to give **13** (0.48 g, 52%) as white powdery crystals. mp 192—193 °C. *Anal*. Calcd for $C_{21}H_{22}F_2N_6O_2$: C, 58.87; H, 5.18; N, 19.62. Found: C, 58.87; H, 5.08; N, 19.54. ^{1}H-NMR ($CDCl_3$) δ: 1.06 (3H, d, J=7 Hz), 3.58—3.87 (6H, m), 4.46 (1H, br), 4.54 (1H, d, J=14 Hz), 5.07 (1H, d, J=14 Hz), 5.80 (1H, br), 6.69—6.81 (4H, m), 7.31 (2H, d, J=9 Hz), 7.35—7.52 (1H, m), 7.72 (1H, s), 7.92 (1H, s). IR (KBr): 3356, 1647, 1518, 1510, 1489, 1448, 1437, 1271 cm^{-1}. $[\alpha]_D^{20}$: −62.5° (c=1.0, MeOH).

2) A mixture of **18** (1 g), AcOEt (18 ml) and water (2 ml) was hydrogenated over 10% Pd–C (0.5 g) for 3 h. The catalyst was filtered off and washed with AcOEt (50 ml). The filtrate and the washing were combined and concentrated *in vacuo*. The residue was crystallized from AcOEt to give **13** (0.35 g) as white powdery crystals. The mother liquor was concentrated *in vacuo*, and the residue was purified by silica gel column chromatography (AcOEt–acetone, 3 : 1, v/v) to give an additional amount of **13** (0.35 g). Yield: 0.7 g (75%).

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-(1*H*-1-tetrazolyl)phenyl]-2-imidazolidinone (1b: TAK-456) 1) A solution of **3b** (27 g) in AcOH (500 ml) was hydrogenated over 10% Pd–C (27 g) for 48 h at 40 °C under a pressure of 50 kg/cm^2. The catalyst was filtered off and washed with AcOH (100 ml). The filtrate and the washing were combined and concentrated *in vacuo*. The concentrate was worked up (AcOEt; brine), and the residue was crystallized from EtOH (1000 ml) to give **1b** (17.45 g, 64%) as colorless powdery crystals.

2) NaN_3 (0.18 g) and AcOH (2 ml) were added successively to a mixture of **13** (1 g) and $CH(OEt)_3$ (1.16 ml). The mixture was stirred for 20 min and for further 1.5 h at 80—85 °C under an argon atmosphere. After having been cooled, the mixture was diluted with water (2 ml) and 6 N HCl (0.85 ml). A 25% aqueous solution of sodium nitrite (25% $NaNO_2$, 0.3 ml) was added, and the resulting mixture was cooled in an ice bath. The precipitate was collected by filtration, washed with water and recrystallized from EtOH to give **1b** (0.62 g, 55%) as colorless crystals.

3) A solution of **15** (0.2 g) in tetrahydrofuran (THF, 6 ml) was added dropwise over a period of 5 min to a mixture of Ph_3P (0.145 g), a 40% solution of DEAD in toluene (0.24 g) and THF (6 ml) at −20 °C. The resulting mixture was stirred for 2 h. The solvent was distilled off *in vacuo*, and the residue was chromatographed on silica gel (hexane–AcOEt–acetone, 4 : 3 : 3, v/v→AcOEt). From the first eluate, **1b** was obtained as colorless powdery crystals (0.118 g, 67%). From the second eluate, the morpholine derivative **25** (0.021 g, 12%) was obtained as a white powder. Compound **25**: ^{1}H-NMR ($CDCl_3$) δ: 1.19 (3H, d, J=6.8 Hz), 3.80—4.02 (2H, m), 4.50—4.58 (3H, m), 4.68 (1H, d, J=14.5 Hz), 5.04 (1H, d, J=14.5 Hz), 6.74—6.84 (2H, m), 7.32 (2H, d, J=8.8 Hz), 7.57 (2H, d, J=8.8 Hz), 7.50—7.88 (3H, m), 8.03 (1H, br), 8.93 (1H, s). SI-MS (*m/z*): 482 (MH^+).

4) A solution of Et_3N (0.96 ml) in AcOEt (2 ml) was added dropwise to a solution of **16** (1.2 g) in DMA–AcOEt (3 : 5, v/v, 16 ml) over a period of 15 min at an internal temperature of 0—2 °C. After having been stirred for 3 h, the mixture was diluted with ice-water (20 ml) and worked up (AcOEt; water, 5% H_3PO_4, aqueous $NaHCO_3$, brine). The residue was crystallized from AcOEt to give a white powder, which was then recrystallized from EtOH to give **1b** (0.765 g, 71%) as colorless crystals.

5) A solution of $POCl_3$ (1.41 ml) in AcOEt (15 ml) was added dropwise to a solution of **15** (5 g) in DMA–AcOEt (1 : 1,v/v, 50 ml) over a period of 1.7 h at 22—25 °C. The mixture was stirred for 16 h, and then Et_3N (12.8 ml) was added dropwise over a period of 20 min at around −4 °C. After having been stirred for 5 h, the whole was diluted with ice-water (20 ml) and worked up (AcOEt; water, 5% H_3PO_4, aqueous $NaHCO_3$, brine). The AcOEt layer was treated with activated carbon and concentrated *in vacuo*. The residue was crystallized from AcOEt to give a white powder, which was then recrystallized from EtOH to give **1b** (3.4 g, 74%) as colorless crystals.

The product **1b** prepared by the methods described above was identical to the authentic sample[1)] upon direct comparison.

Phenyl 4-(1*H*-1,2,3-Triazol-1-yl)phenylcarbamate (10a) A mixture of **19** (14.75 g), $Cl_2CHCH{=}NNHTs$ (10 g) and MeOH (400 ml) was stirred for 1 h at around −3 °C. After having been stirred overnight, the mixture was concentrated *in vacuo* to a volume of about 170 ml. The concentrate was allowed to stand in an ice-bath for 30 min. The precipitate was collected by filtration to give **20** (4.04 g) as pale yellow crystals. The mother liquor was concentrated *in vacuo*, and the residue was dissolved in AcOEt–THF (1 : 1, v/v, 400 ml). The solution was washed with 1 N HCl, 1 N NaOH, water and brine, successively. The organic layer was dried over $MgSO_4$ and evaporated

in vacuo. The residue was crystallized from Et_2O to give an additional amount of **20** (0.47 g). Yield 4.51 g (67% based on the hydrazone).

A mixture of **20** (33.33 g), EtOH (200 ml) and THF (200 ml) was hydrogenated over 10% Pd–C (50% wet, 4 g) at 50 °C for 6 h. The catalyst was removed by filtration, and the filtrate was concentrated *in vacuo*. The residue was crystallized from $isoPr_2O$ to give **24a** (27.45 g, 94%) as pale yellow powdery crystals.

PhOCOCl (28.5 g) was added dropwise over a period of 15 min to an ice-cooled solution of **24a** (26.45 g) in acetone (550 ml) containing pyridine (14.4 g). After having been stirred for 1 h, the mixture was concentrated *in vacuo*. The concentrate was worked up (AcOEt–THF, 2 : 1, v/v; water, brine). The residue was crystallized from $isoPr_2O$ to give **10a** (39.68 g, 85%). Compounds **20**, **24a** and **10a** were identical to the authentic samples[1] upon direct comparison.

***N*,*N*-Dibenzyl-*p*-nitroaniline (22)** A mixture of **19** (10 g), $PhCH_2Br$ (49.5 g), K_2CO_3 (22 g) and DMF (50 ml) was stirred for 32 h at 160 °C. After having been cooled, the mixture was worked up (AcOEt; water, brine). The residue was crystallized from $isoPr_2O$–hexane to give **22** (19 g, 82%) as pale yellow crystals. ^{1}H-NMR ($CDCl_3$) δ: 4.76 (4H, s), 6.70 (2H, d, J=9.2 Hz), 7.81—7.41 (10H, m), 8.07 (2H, d, J=9.2 Hz).

1-[4-(*N*,*N*-Dibenzylamino)phenyl]-1*H*-tetrazole (23) A mixture of **22** (18 g), $FeCl_3$ (0.55 g), activated carbon (2.2 g) and MeOH (120 ml) was stirred under reflux for 30 min. $N_2H_4 \cdot H_2O$ (27.4 ml) was added dropwise under reflux over a period of 1 h. The resulting mixture was stirred under reflux for 24 h and cooled. Activated carbon (2.2 g) and $FeCl_3$ (0.55 g) were added, and the mixture was refluxed for 10 min. $N_2H_4 \cdot H_2O$ (27.4 ml) was added dropwise under reflux over a period of 1 h. The resulting mixture was stirred under reflux for further 24 h. After having been cooled, the whole was filtered to remove the activated carbon, and the filtrate was concentrated *in vacuo*. The concentrate was worked up (AcOEt; water, brine) and crystallized from hexane–$isoPr_2O$ to give *N*,*N*-dibenzyl-*p*-phenylenediamine (15 g, 92%) as purple crystals. ^{1}H-NMR ($CDCl_3$) δ: 3.29 (2H, br), 4.51 (4H, s), 6.57 (2H, d, J=8.4 Hz), 6.64 (2H, d, J=8.4 Hz), 7.18—7.34 (10H, m).

AcOH (40 ml) was added dropwise over a period of 10 min to a mixture of *N*,*N*-dibenzyl-*p*-phenylenediamine (15 g) prepared above, $CH(OEt)_3$ (25.5 ml) and NaN_3 (4 g). The mixture was stirred for 5 min and for further 4 h at 90 °C under a nitrogen atmosphere. After having been cooled, the mixture was diluted with water (50 ml) and 6 N HCl (18 ml). A solution of $NaNO_2$ (2 g) in water (8.4 ml) was added, and the whole was cooled in an ice-bath. The precipitate was collected by filtration and recrystallized from EtOH–MeOH–THF to give **23** (12.4 g, 68%) as brown scaly crystals. ^{1}H-NMR ($CDCl_3$) δ: 4.74 (4H, s), 6.82 (2H, d, J=9.2 Hz), 7.23—7.43 (12H, m), 8.80 (1H, s).

Phenyl 4-(1*H*-1-Tetrazolyl)phenylcarbamate (10b) 1) Methyl orthoformate [$CH(OMe)_3$, 2.74 ml] was added to a mixture of **19** (3 g) and AcOH (18 ml). The mixture was stirred for 30 min, and then NaN_3 (2.35 g) was added. The resulting mixture was stirred for 2 h at 83 °C. After having been cooled, the mixture was diluted with water (18 ml) and 6 N HCl (5 ml). A solution of $NaNO_2$ (1.2 g) in water (3.6 ml) was added dropwise over a period of 5 min. The whole was stirred for 1 h in an ice-bath. The precipitate was collected by filtration and washed with water to obtain **21** as a wet solid. This solid was dissolved in THF (60 ml) at 60 °C. $FeCl_3$ (39.1 mg) and activated carbon (413 mg) were added to the solution, and then $N_2H_3 \cdot H_2O$ (3.79 ml) was added dropwise over a period of 30 min under reflux. The resulting mixture was stirred under reflux for 2.5 h and cooled. The activated carbon was removed by filtration and washed with AcOEt (30 ml). The filtrate and the washing were combined and washed with brine. The organic layer containing **24b** was dried over $MgSO_4$. The solution was cooled in an ice-bath, and pyridine (2.06 g) was added. PhOCOCl (4.08 g) was added dropwise to the solution over a period of 5 min. After having been stirred for 1h, the whole was worked up (AcOEt; brine, water, brine). The residue was crystallized from $isoPr_2O$ to give **10b** (5.05 g, 83% over all yield from **19**).

2) A mixture of **23** (2 g), MeOH–THF (2 : 1, v/v, 30 ml) and 6 N HCl (1 ml) was hydrogenated over 10% Pd–C (0.5 g) for 25 min. The catalyst was removed by filtration, and the filtrate was concentrated *in vacuo*. The residue was dissolved in a mixture of AcOEt–THF (2 : 1, v/v, 45 ml) and water (5 ml), and a solution of $NaHCO_3$ (1.3 g) in water (20 ml) was added dropwise under ice-cooling over a period of 5 min. PhOCOCl (0.89 g) was added dropwise to the solution over a period of 5 min. Water (10 ml) was added, and the resulting mixture was stirred for 30 min. The organic layer was worked up (brine). The residue was crystallized from $isoPr_2O$ to give **10b** (1.5 g, 91%).

The product **10b** obtained above was identical to the authentic sample[1] upon direct comparison.

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

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