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A new synthesis of carboxyterfenadine (fexofenadine) and its bioisosteric tetrazole analogs

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Abstract

A new synthesis of carboxyterfenadine (**4**), based on the conversion of a α-halo-alkylarylketone into the corresponding substituted 2-arylalkanoic ester, is described. The enantioselective synthesis of its two bioisosteric tetrazole analogs together with preliminary biological results are reported.

Keywords: Antihistamine; Tetrazole; Enantioselective reduction

1. Introduction

The development of non-sedating histamine H1-receptor antagonists has provided the physician with valuable tools for the treatment of histamine mediated disorders with a marked decrease of side effects related to central nervous system (CNS). Terfenadine (**1**), 1-(*p*-*tert*-butylphenyl)-4-[4′-(α-hydroxydiphenylmethyl)-1′-piperidyl] butanol (Teldane®, Merrel Dow Pharmaceuticals, Inc.), the first non-sedating antihistamine introduced in therapy is a specific H1-receptor antagonist having no significant affinity for histamine H2-receptors, also devoid of anticholinergic and antiserotoninergic activity [1,2]. Terfenadine (**1**) is a well tolerated drug and a 60 mg dose, administered twice a day, is effective in providing relief for histamine-induced disorders such as seasonal and perennial allergic rhinitis and allergic dermatological conditions (especially chronic urticaria). Analogously to loratadine and acrivastine, moreover, terfenadine does not potentiate the central depressant effects of alcohol or diazepam. Recently, however, there has been an increasing concern on the cardiotoxic effects of terfenadine, especially those due to torsades de pointes, a form of polymorphic ventricular tachycardia [3]. Terfenadine undergoes cytochrome P-450 3A4 (CYP3A4) mediated extensive first pass metabolism (over 99% of absorbed dose) [4] resulting in extremely low plasma concentrations and undetectable urinary levels [5,6]. The first pass metabolism leads to two metabolites: a carboxylate derivative arising from the oxidation of a *tert*-butyl group to an isobutyrate group in the liver [carboxyterfenadine (fexofenadine), **4**] which is the major biotransformation product formed in urine and feces of animal species and man and azacyclonol (α,α,-diphenyl-4-piperidine-methanol) [5–7]. In 1991, thermospray liquid chromatography-mass spectroscopy (TSP LC-MS) was used to determine human urinary metabolites of terfenadine after oral administration of terfenadine tablets [7]. In addition to the two above reported, three additional metabolites have been detected and identified with the alcohol metabolite (**2**) and the 'aldehyde' and 'ketone-acid' metabolites **3** and **5**, respectively. A proposed metabolic pathway for terfenadine metabolism is represented in Fig. 1.

2. Antihistaminic activity of carboxyterfenadine (4) in humans

Between the two major metabolites of terfenadine (**1**), the carboxylic acid derivative **4** is endowed with

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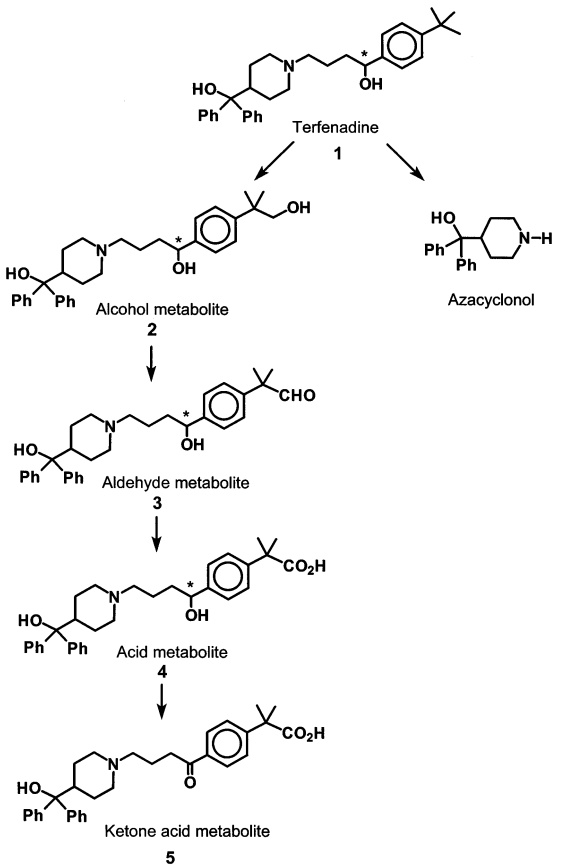


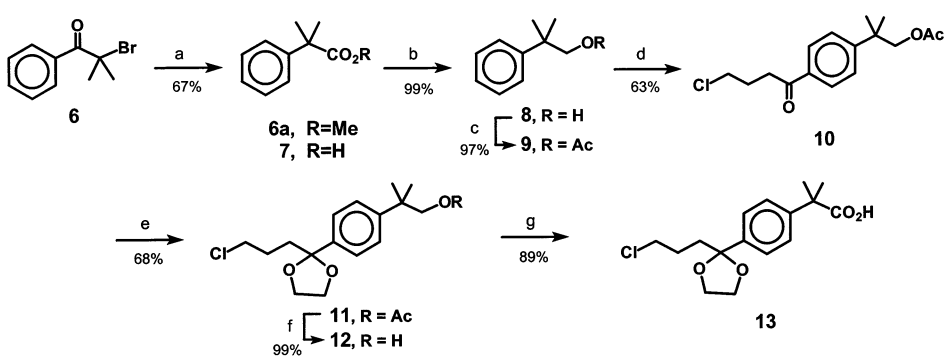
Fig. 1. Terfenadine metabolic pathway. The asterisk indicates the asymmetric carbon atom.

antihistaminic activity and is responsible for the activity of terfenadine in vivo [6], while azacyclonol is apparently devoid of antihistaminic activity. Carboxyterfenadine (**4**) is detectable in plasma after 30 min from the administration of a single oral terfenadine 60 mg dose and peak plasma concentrations are reached after approximately 3 h. While terfenadine is extensively (97%) bound to human serum proteins, **4** is only 70% bound. Following administration of single oral 60, 120 and 180 mg terfenadine doses, peak plasma concentrations and AUC values of **4** increased linearly with the dose [8]. While the terminal elimination half life of **4** determined from single and multiple dose studies was approximately 17 h, its plasma concentrations are not affected by food and are similar in elder and young adults [9]. The mean serum-elimination half-life of carboxyterfenadine (**4**) has been shown to be 8.7–3.7 h, while the mean serum-elimination half life of another H1-antagonist, chlorpheniramine, has been shown to be 22.6–11 h [10]. Interestingly, **4** has been reported to be devoid of the fatal abnormal heart rhythm induced by terfenadine in some patients with liver disease or who also take the antifungal drug ketoconazole or the antibiotic erythromycin. As above reported, cytochrome P-450 3A4 (CYP 3A4) is involved in the metabolism of terfenadine to two of its metabolites. Inhibition of CYP 3A4 by drugs such as erythromycin, ketoconazole and itaconazole would result in terfenadine accumulation and toxicity [11–14].

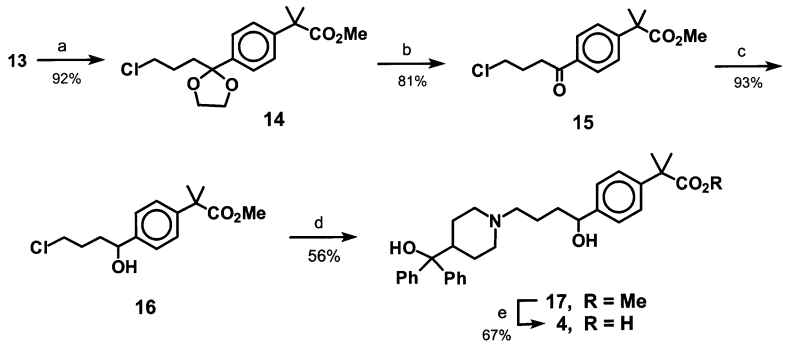
As a part of a research program directed to the design and preparation of new, non-sedative antiallergic agents, we have considered synthetically interesting to report an alternative [15–17] route to carboxyterfenadine (**4**), and to point out a new, enantioselective synthesis of its epimeric tetrazole analogs in order to assess the pharmacokinetic and metabolic profile of these bioisosteric derivatives. The new chiral synthetic approach could be also applied to the preparation of optically active carboxyterfenadine.

3. Results and discussion

The preparation of carboxyterfenadine is depicted in Schemes 1 and 2. Key step in this sequence is the conversion by the Giordano's procedure [18] of an

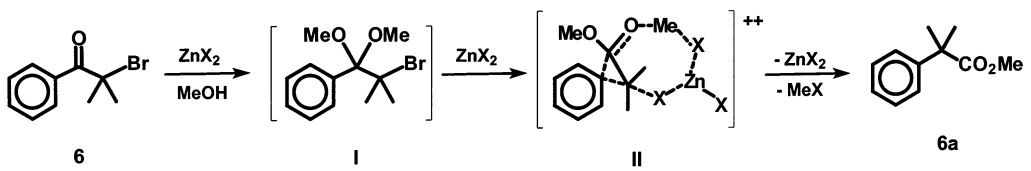


Scheme 1. (a) (i) $ZnBr_2$, MeOH, 115°C, 5 h; (ii) 0.4 N NaOH, MeOH–H_2O (2:1, v/v), 80°C, 12 h; (b) $LiAlH_4$, Et_2O; (c) Ac_2O, Et_3N, 4-PPy, r.t., 20 min; (d) 4-Cl-butyryl chloride, $AlCl_3$, CS_2, 0°C, 1.5 h; (e) ethylene glycol, pTsOH, PhH, reflux, 24 h; (f) NaOH, MeOH, r.t., 30 min; (g) Jones oxn.

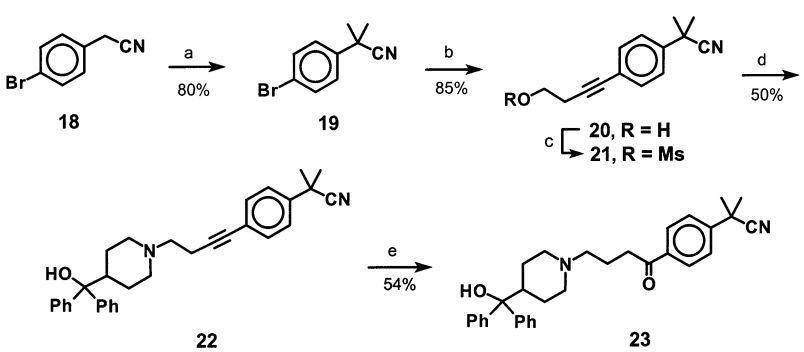


Scheme 2. (a) CH_2N_2, Et_2O, 0°C; (b) 2% HCl, THF, r.t., 1.5 h; (c) $NaBH_4$, MeOH/THF, 0°C, 30 min; (d) azacyclonol, K_2CO_3, KI, PhMe–DMF (8:2, v/v), reflux, 7 h; (e) 10% NaOH, MeOH, reflux, 2 h.

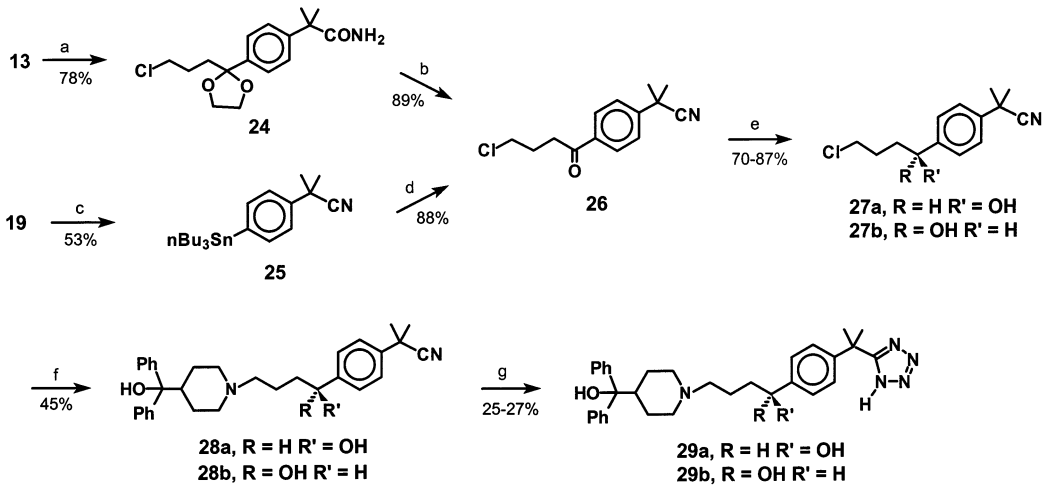
α-halo-alkylarylketone into the corresponding substituted 2-arylalkanoic ester. Accordingly, commercially available 2-bromo-*iso*-butyrophenone (**6**) was converted into the corresponding methyl α,α-dimethyl-phenylacetate (**6a**) readily hydrolyzed to the acid **7** in 67% yield. A possible mechanism for this transposition is shown in Scheme 3. The reaction proceeds via $ZnBr_2$ catalysis with formation of an acetalic intermediate (I) and polarization of the carbon-halogen bond. Transposition of the hemiacetalic intermediate (II) and 1,2-migration of the phenyl moiety affords the phenylalkanoic ester **6a**. The nature of the halogen in the α-halo-alkylarylketone influences the rate of conversion: the rank order is Br > Cl, thus suggesting the heterolytic cleavage of the C–X bond as the rate determining step. Attempts to convert the methyl ester **6a** into the ketone **15** via direct acylation with 4-chlorobutyryl chloride, however, resulted in the formation of a mixture of *para*- and *meta*-acylated isomers which were difficult to resolve. To circumvent this, the carboxylic moiety of **7** was reduced with $LiAlH_4$ (**8**, 99%) and the resulting alcoholic function acetylated to give **9** in 97% yield. When the acetate **9** was submitted to Friedel–Crafts acylation with 4-chlorobutyryl chloride the corresponding ketone **10** was regioisomerically formed in 63.5% yield. Protection of the carbonyl group (**11**, 68%) followed by alkaline hydrolysis of the acetate moiety (**12**, 99%) and Jones oxidation of the alcoholic function thus obtained afforded the corresponding acid **13** in 89% yield. Esterification of **13** with diazomethane (Scheme 2) afforded



Scheme 3.



Scheme 4. (a) NaH, MeI, THF, r.t., 15 h; (b) 3-butyn-l-ol, $(Ph_3P)_4Pd$, CuBr, Et_3N, reflux, 3 h; (c) MsCl, Py, CH_2Cl_2, r.t., 20 h; (d) azacyclonol, K_2CO_3, MeCN, reflux, 15 h; (e) (i) HgO, H_2SO_4 (4%, w/v), MeOH, 55°C, 3 h.



Scheme 5. a) (i) Oxalyl chloride, r.t., 2.5 h; (ii) 30% NH_4OH, THF, 0°C, 0.5 h; (b) $POCl_3$, Na_2CO_3, MeCN, reflux, 2.5 h; (c) $(Bu_3Sn)_2$, $(Ph_3P)_4Pd$, PhMe, 65°C, 50 h; (d) 4-Cl-butyryl chloride, $(Ph_3P)_2PdCl_2$, PhMe, 70°C, 8 h; (e) (−)- or (+)-DIP-Cl, THF, −25°C, then r.t., 24 h; (f) azacyclonol, KI, K_2CO_3, DMF, PhMe, reflux, 8 h; (g) (i) Bu_3SnN_3, xylene, reflux 24 h; (ii) 1.25 N NaOH, r.t., 12 h.

14 (92%) which was submitted to ketal deprotection (**15**, 89%) and reduction to give alcohol **16** (95%). When **16** was reacted with azacyclonol terfenadine methyl carboxylate **17** was obtained in 44% yield [19]. Finally, alkaline hydrolysis of **17** afforded carboxyterfenadine (**4**) in 67.6% yield.

The introduction of the tetrazole moiety as bioisosteric replacement of the carboxylic one could be envisaged as proceeding from a nitrile precursor. Moreover, it seemed of interest to devise an enantioselective synthesis of tetrazolyl-terfenadine in order to obtain both the epimeric alcoholic functions useful for a better biological characterization. A first attempt was experienced through the synthesis of ketone-nitrile **23** by utilizing Kawai's method [15] applied to *p*-bromophenylacetonitrile (**18**), chosen as suitable starting product (Scheme 4). Thus, methylation of the benzylic carbon of **18** afforded **19** (80%) which was submitted to $Pd(0)/Cu_2Br_2$-catalyzed coupling with 3-butyn-1-ol to give the alkyne **20** in 85% yield. Mesylation of the hydroxy group followed by reaction of the protected alkyne (**21**) thus formed with azacyclonol afforded the tertiary amine **22** in 52% yield (from **20**). Mercury-catalyzed hydration gave the benzylic ketone **23** in 54% yield. Unfortunately, attempts to selectively reduce the carbonyl function of **23** with chiral reducing agents such as (−)- or (+)-B-chlorodiisopino-campheylborane [(−)- or (+)-DIP-chloride] failed and the conventional reduction with $NaBH_4$ afforded an unseparable racemic mixture of alcohols. Successful efforts were then made with the enantioselective reduction using chiral DIP-Cl [20] of the nitrile **26** (Scheme 5), either synthetized from acid **13**, via its conversion into the corresponding amide **24** (78%) followed by reaction with $POCl_3$ (89%), or prepared in a shorter way by Pd(0)-catalyzed reaction of **19** with bis-(tributyltin) followed by Pd(II)-catalyzed acylation of the stannyl derivative (**25**) thus formed with 4-chlorobutyryl chloride. In this case, reduction of **26** with (−)-DIP-Cl afforded *S*-(−)-2-[4-(1-hydroxy-4-chlorobutyl)-phenyl]-2,2-dimethyl acetonitrile (**27a**) in 87% yield. Condensation of **27a** with azacyclonol yielded nitrile **28a** (45%) which was reacted with tris-*n*-butyltin azide followed by alkaline cleavage of the stannyl moiety to give (*S*)-tetrazolyl-terfenadine (**29a**) in 27% yield. An analogous sequence applied to the epimeric alcohol **27b**, obtained via reduction of **26** with (+)-DIP-Cl, afforded (*R*)-tetrazolyl-terfenadine (**29b**). However, when the racemic mixture of alcohols obtained from $NaBH_4$ reduction of **23** was reacted with tris-*n*-butyltin azide followed by alkaline cleavage of the stannyl moiety, (±)-tetrazolyl-terfenadine (**30**) was obtained in 25% yield.

Preliminary biological tests have been made on racemic tetrazolyl-terfenadine [(±)-TFZ, **30**] and on both enantiomers [(−)-TFZ (**29a**) and (+)-TFZ (**29b**)]. When tested for binding affinity for the H1-receptors of both the guinea-pig cerebellum [21,22] and

Table 1
IC_{50} values (M) from displacement of [^{3}H]mepyramine as the radioligand

	Cerebellum	Ileum
TER (**1**)	7×10^{-9}	8×10^{-10}
CARB (**4**)	5×10^{-8}	5×10^{-8}
(±)-TFZ (**30**)	8×10^{-8}	3×10^{-7}
(−)-TFZ (**29a**)	2×10^{-8}	
(+)-TFZ (**29b**)	5×10^{-7}	

ileum [23] in comparison with carboxyterfenadine (**4**) and terfenadine (**1**) itself, (±)-tetrazolyl-terfenadine (**30**) showed affinity values similar to those of **4**, with the *S*-(−) enantiomer (**29a**) displaying IC_{50} values higher than that of the *R*-(+) enantiomer (**29b**) (Table 1). Moreover, functional activity studies on isolated guinea-pig ileum indicated that **30** is devoid of any H1-agonist activity and cholinergic antagonism as well. Further studies are in progress on the separated enantiomers (**29a** and **29b**) in order to evaluate the presence of stereoselective processes involving metabolism, distribution and/or excretion [24].

4. Conclusions

We have devised a new synthetic way to carboxyterfenadine (**4**) along with the enantioselective synthesis of its bioisosteric tetrazole analogs (**29a** and **29b**). The preliminary biological characterization of these new compounds indicates that *S*-(−)-tetrazolyl-terfenadine (**29a**) is endowed with good antihistaminic activity, superimposable to that of **4.**

5. Experimental

Melting points were determined by the capillary method on a Büchi 535 electrothermal apparatus and are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were taken on a Bruker AC 200 spectrometer as solutions in $CDCl_3$ unless otherwise indicated. Proton chemical shifts are reported in ppm downfield from tetramethylsilane. Carbon chemical shifts are reported in ppm. using $CDCl_3$ (δ 77.0) or MeOH (δ 49.0) as internal standards. Flash chromatography was performed on Merck silica gel (0.040–0.063 mm). Specific rotations were recorded on a Jasco Dip-360 digital polarimeter.

5.1. 2-Phenyl-isobutyric acid (7)

MeOH (130 ml) was carefully added to dry $ZnBr_2$ (300.0 g, 1.3 mol) kept in a argon atmosphere; after the strong exothermic reaction subsided, the resulting solution was heated under stirring at 115°C and 2-bromoisobutyrophenone (**6**, 25.65 g, 112.9 mmol) was added dropwise in 20 min. Stirring was continued for 5 h at 115°C after which the reaction mixture was diluted with ice-cold water (300 ml) and extracted with CH_2Cl_2 (3 × 150 ml). The combined organic phases were dried over anhydrous Na_2SO_4 and, after evaporation of the solvent, the residue was dissolved in a solution of 0.4 N NaOH in MeOH-H_2O (240 ml, 2:1, v/v) and heated at 80°C for 12 h. The reaction mixture was then diluted with ice-cold water (200 ml), acidified with 3 N HCl and extracted with CH_2Cl_2 (3 × 200 ml). The combined organic phases were successively extracted with saturated $NaHCO_3$ (4 × 200 ml) and the resulting combined aqueous phases were acidified with 3 N HCl to give **7** as a white solid (12.4 g, 67%), m.p. 80°C; ^{1}H NMR ($CDCl_3$) δ 1.60 (6H, s, 2 × Me), 7.30 (5H, m, Ar); ^{13}C NMR ($CDCl_3$) δ 26.14 (Me), 46.24 (*C*–Me), 125.73, 126.88, 128.38, 143.76 (Ar), 183.35 (CO).

5.2. 2-Phenyl-isobutanol (8)

A solution of **7** (11.0 g, 67.0 mmol) in dry ether (400 ml) was added dropwise in 20 min to a stirred suspension of $LiAlH_4$ (28.9 g, 497 mmol) in dry ether (200 ml) in a argon atmosphere. Excess of hydride was then removed by adding a MeOH–ether mixture (570 ml, 3:15, v/v) and the resulting solid was dissolved with 5% H_2SO_4 (1400 ml). The reaction mixture was extracted with ether (4 × 400 ml) and the combined organic phases were washed with 5% $NaHCO_3$ (500 ml), brine (500 ml) and dried over anhydrous Na_2SO_4. Evaporation of the solvent yielded **8** (10.0 g, 99%); ^{1}H NMR ($CDCl_3$) δ 1.30 (6H, s, 2 × Me), 1.50 (1H, br s, OH), 3.60 (2H, s, CH_2), 7.30 (5H, m, Ar).

5.3. 2-Phenyl-isobutyl acetate (9)

Acetic anhydride (32.46 g, 318 mmol), triethylamine (32.67 g, 323 mmol) and 4-pyrrolidinopyridine (0.30 g, 2.0 mmol) were added to a solution of **8** (16.0 g, 106.7 mmol) and the resulting mixture was stirred at room temperature for 20 min. Evaporation of the solvent gave a residue which was diluted with ether (500 ml), washed with water (4 × 300 ml), brine (300 ml) and dried (Na_2SO_4). Evaporation of the solvent gave **9** (19.9 g, 97%); ^{1}H NMR ($CDCl_3$) δ 1.40 (6H, s, 2 × Me), 2.00 (3H, s, MeCO), 4.10 (2H, s, CH_2), 7.25 (5H, m, Ar).

5.4. 2-[4-(4-Chlorobutyryl)-phenyl]-isobutyl acetate (10)

4-Chlorobutyryl chloride (9.58 g, 67.9 mmol) was added to a stirred suspension of $AlCl_3$ (14.0 g, 105.0 mmol) in CS_2 (14 ml) and the resulting mixture was cooled to 0°C. After 15 min, a solution of **9** (10.0 g, 52.0 mmol) in CS_2 (50 ml) was added dropwise in 20 min and the resulting mixture was maintained under stirring at 0°C for 30 min. An additional amount of $AlCl_3$ (7.0 g, 52.5 mmol) in CS_2 (7 ml) was then added and stirring was continued for 1 h at 0–5°C. The reaction mixture was poured into ice-cold water (400 ml) and stirred for 2 h; the organic phase was then separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 200 ml). The combined organic phases were washed with saturated $NaHCO_3$ (3 × 200 ml),

brine (200 ml) and dried (Na_2SO_4). Evaporation of the solvent yielded a residue (14 g) which was submitted to flash chromatography: elution with light petroleum–ether (8:2) afforded a product (**10**, 9.8 g, 63.5%) which contained traces of isomers; ^{1}H NMR ($CDCl_3$) δ 1.40 (6H, s, 2 × Me), 2.00 (3H, s, MeCO), 2.20 (2H, m, $ClCH_2CH_2$), 3.20 (2H, t, CH_2CO), 3.70 (2H, t, $ClCH_2$), 4.20 (2H, s, CH_2OAc), 7.70 (4H, 2 × d, $J = 8.5$ Hz, Ar).

5.5. 2-[4-(1-Ethylendioxo-4-chlorobutyl)-phenyl]-isobutyl acetate (**11**)

Ethylene glycol (5.56 g, 89.6 mmol) and *p*-toluenesulfonic acid monohydrate (0.40 g, 2.1 mmol) were added to a solution of **10** (18.0 g, 60.6 mmol) in anhydrous benzene (700 ml) and the resulting mixture was refluxed 24 h in a argon atmosphere taking care of removing the reaction water by a Dean–Stark trap. After cooling and evaporation of the solvent, the residue was diluted with AcOEt (350 ml), washed with water (4 × 200 ml), brine (200 ml) and dried (Na_2SO_4). Evaporation of the solvent gave a residue which was submitted to flash chromatography: elution with light petroleum–ether (8:2) afforded **11** (14.0 g, 68%); ^{1}H NMR ($CDCl_3$) δ 1.40 (6H, s, 2 × Me), 1.85 (2H, m, $ClCH_2CH_2$), 1.95 (2H, m, $ClCH_2CH_2CH_2$), 2.00 (3H, s, MeCO), 3.50 (2H, m, $ClCH_2$), 3.70–4.00 (4H, 2 × m, –OCH_2CH_2O–), 4.10 (2H, s, CH_2OAc), 7.35 (4H, m, Ar).

5.6. 2-[4-(1-Ethylendioxo-4-chlorobutyl)-phenyl]-isobutanol (**12**)

A solution of **11** (14.0 g, 41.1 mmol) in 2% methanolic NaOH (300 ml) was stirred at room temperature for 30 min. The reaction mixture was then diluted with water (200 ml) and extracted with AcOEt (3 × 300 ml). The combined organic phases were washed with brine (200 ml) and dried (Na_2SO_4). Evaporation of the solvent afforded **12** (12.2 g, 99%); ^{1}H NMR ($CDCl_3$) δ 1.35 (6H, s, 2 × Me), 1.85 (2H, m, $ClCH_2CH_2$), 2.00 (2H, m, $ClCH_2CH_2CH_2$), 3.50 (2H, t, $ClCH_2$), 3.60 (2H, s, CH_2OH), 3.70–4.00 (4H, 2 × m, –OCH_2-CH_2O–), 7.35 (4H, m, Ar).

5.7. 2-[4-(1-Ethylendioxo-4-chlorobutyl)-phenyl]-isobutyric acid (**13**)

Jones reagent (30 ml) was added dropwise in 15 min to a solution of **12** (14.0 g, 46.8 mmol) in acetone (1000 ml) kept under stirring at 0°C. The reaction mixture was then filtered the filtrate was diluted with AcOEt (1000 ml), washed with water (5 × 300 ml), brine (300 ml) and dried (Na_2SO_4). Evaporation of the solvent yielded **13** (13.0 g, 89%); ^{1}H NMR ($CDCl_3$) δ 1.60 (6H, s, 2 × Me), 1.85 (2H, m, $ClCH_2CH_2$), 2.00 (2H, m, $ClCH_2CH_2CH_2$), 3.50 (2H, t, $ClCH_2$), 3.70–4.00 (4H, 2 × m, –OCH_2CH_2O–), 7.35 (4H, m, Ar), 10.08 (1H, br s, CO_2H).

5.8. Methyl 2-[4-(1-ethylendioxo-4-chlorobutyl)-phenyl]-isobutyrate (**14**)

An ethereal solution of diazomethane (150 ml, from 21 g of Diazald®) was added dropwise (10 min) to a cold (0°C) solution of **13** (13.0 g, 39 mmol) in anhydrous ether (100 ml). The resulting yellow solution was carefully evaporated to dryness to give **14** (12.5 g, 92%); ^{1}H NMR ($CDCl_3$) δ 1.55 (6H, s, 2 × Me), 1.85 (2H, m, $ClCH_2CH_2$), 2.00 (2H, m, $ClCH_2CH_2CH_2$), 3.50 (2H, t, $ClCH_2$), 3.65 (3H, s, OMe), 3.70–4.00 (4H, 2 × m, –OCH_2CH_2O–), 7.35 (4H, m, Ar).

5.9. Methyl 2-[4-(4-chlorobutyryl)-phenyl]-isobutyrate (**15**)

A 2 N HCl solution in THF (76 ml) was added to a solution of **14** (12.0 g, 36.7 mmol) in THF (74 ml) and the resulting mixture was magnetically stirred for 15 h at room temperature. The reaction mixture was then diluted with water (100 ml) and extracted with AcOEt (3 × 50 ml). The combined organic phases were washed with water (50 ml), brine (50 ml) and dried over anhydrous Na_2SO_4. After evaporation of the solvent, the residue (10 g) was submitted to flash chromatography: elution with light petroleum–ether (8:2) yielded **15** (9.26 g, 89%); ^{1}H NMR ($CDCl_3$) δ 1.60 (6H, s, 2 × Me), 2.20 (2H, m, $ClCH_2CH_2$), 3.15 (2H, t, CH_2CO), 3.68 (2H, t, $ClCH_2$), 3.70 (3H, s, OMe), 7.45 and 7.95 (4H, 2 × d, $J = 8.5$ Hz, Ar); ^{13}C NMR ($CDCl_3$) δ 26.34, 26.80, 35.20, 44.53, 46.82, 52.26, 126.00, 128.17, 135.28, 150.11, 176.46, 198.35.

5.10. Methyl 2-[4-(1-hydroxy-4-chlorobutyl)-phenyl]-isobutyrate (**16**)

A suspension of $NaBH_4$ (5.0 g, 133 mmol) in MeOH (300 ml) was added to a cold (0°C), magnetically stirred solution of **15** (9.26 g, 32.7 mmol) in THF (600 ml). Stirring was continued at 0°C for 30 min after which pH was adjusted to 7 (3 N HCl) and the solvent evaporated off. The residue was taken up in AcOEt (80 ml), washed with water (2 × 20 ml), brine (20 ml) and dried over anhydrous Na_2SO_4. Evaporation of the solvent and flash chromatography of the residue (light petroleum–AcOEt, 8:2) afforded **16** (8.9 g, 95%); ^{1}H NMR ($CDCl_3$) δ 1.55 (6H, s, 2 × Me), 1.85 (4H, m, CH_2CH_2CHOH), 2.45 (1H, br s, OH), 3.50 (2H, m, $ClCH_2$), 3.60 (3H, s, OMe), 4.65 (1H, t, $CHOH$), 7.30 (4H, m, Ar).

5.11. Methyl 2-[4-(1-hydroxy-4-(4-hydroxydiphenyl-methyl-1-piperidyl)-butyl)-phenyl]-isobutyrate (17)

Diphenyl-(4-piperidyl)-methanol (azacyclonol, 9.55 g, 36 mmol), anhydrous K_2CO_3 (11 g, 79 mmol) and KI (0.493 g, 2.97 mmol) were added to a solution of **16** (8.55 g, 30 mmol) in toluene (173 ml) and DMF (43 ml) and the resulting mixture was refluxed under argon for 7 h. The water formed during the reaction was removed by a Dean–Stark trap. After cooling, the reaction mixture was filtered and the filtrate evaporated to give a residue which was dissolved in $CHCl_3$ (500 ml), washed with water (3×200 ml), brine (200 ml) and dried over anhydrous Na_2SO_4. Evaporation of the solvent and flash chromatography of the residue (17.8 g) with dichloromethane containing 2% methanol afforded **17** (6.84 g, 44%); ^{1}H NMR ($CDCl_3$) δ 1.40–2.10 (8H, m, $CH_2CH\mathit{CH_2}$ and $\mathit{CH_2CH_2}CHOH$), 1.55 (6H, s, $2 \times$ Me), 2.35 (3H, m, CHCOH and CH_2N), 3.00 (4H, m, CH_2NCH_2), 3.60 (3H, s, OMe), 4.50 (1H, m, *CH*OH), 7.00–7.50 (14H, m, Ar); ^{13}C NMR ($CDCl_3$) δ 23.93, 25.81, 26.47, 39.48, 44.09, 46.15, 51.92, 53.23, 54.56, 58.68, 73.13, 79.12, 125.66, 126.23, 127.97, 142.83, 144.00, 146.10, 177.21.

5.12. 2-[4-(1-Hydroxy-4-(4-hydroxydiphenylmethyl-1-piperidyl)-butyl)-phenyl]-isobutyric acid (carboxy-terfenadine) (4)

A solution of **17** (6.84 g, 13.3 mmol) in a 2.5 N methanolic solution of NaOH (181 ml) was refluxed for 2 h under vigorous magnetic stirring. After neutralization with 3 N HCl and evaporation of the solvent, the residue was taken up in water (100 ml) and washed with chloroform (20 ml). The organic phase was filtered and the solid thus obtained was collected with the one resulted from concentration and filtration of the aqueous layer. After drying in high vacuum, **4** was obtained as a white solid (4.5 g, 67.6%), m.p. 215–216°C; ^{1}H NMR (DMSO-d_6) δ 1.15–1.65 (9H, m, $\mathit{CH_2CH_2}CHOH$ and $\mathit{CH_2CHCH_2}$), 1.40 (6H, s, $2 \times$ Me), 1.93. 2.30 and 2.90 (6H, $3 \times$ m, $3 \times CH_2N$), 4.50 (1H, m, *CH*OH), 7.10–7.60 (14H, m, Ar); ^{13}C NMR ($CDCl_3$) δ 22.25, 24.11, 26.75, 27.01, 37.46, 43.16, 46.79, 52.47, 53.34, 57.04, 73.07, 78.89, 125.67, 125.70, 126.41, 128.13, 142.44, 145.56, 146.05, 181.34.

5.13. 2-(4-Bromophenyl)-isobutyronitrile (19)

Sodium hydride (6.0 g, 150 mmol, 60% mineral oil dispersion) was placed in a three necked, round bottomed flask equipped with condenser and washed three times with THF (30 ml) by swirling under argon allowing the hydride to settle and decanting the liquid portion in order to remove the mineral oil. Fresh THF (30 ml) was then added and a solution of 4-bromophenyl acetonitrile (**18**, 9.20 g, 46.9 mmol) in THF (45 ml) was added dropwise in 10 min to the resulting suspension. Once the addition was completed methyl iodide (16.1 g, 113.4 mmol) was carefully added dropwise (20 min) and the resulting mixture was stirred at room temperature for 15 h in an argon atmosphere. The reaction mixture was filtered, the solid washed with AcOEt (100 ml), the filtrate concentrated in vacuo and the residue was extracted with pentane (3×30 ml) and AcOEt (2×50 ml). The combined organic phases were then concentrated to give a crude product (11 g) which was submitted to flash chromatography: elution with light petroleum–AcOEt (9:1) afforded **19** (8.40 g, 80%); ^{1}H NMR ($CDCl_3$) δ 1.67 (6H, s, $2 \times$ Me), 7.40 (4H, $2 \times$ d, Ar).

5.14. 2-[4-(4-Hydroxy-1-butynyl)-phenyl]-isobutyronitrile (20)

Tetrakis(triphenylphosphine)palladium (0.17 g, 0.144 mmol) and cuprous bromide (0.06 g, 0.43 mmol) were added to a stirred solution of **19** (0.81 g, 3.62 mmol) and 3-butyn-1-ol (0.51 g, 7.28 mmol) in freshly distilled triethylamine (15 ml) and the resulting solution was refluxed for 3 h in an argon atmosphere. After cooling, the reaction mixture was concentrated in vacuo and the residue extracted with ether (3×40 ml). The combined organic phases were washed with saturated NH_4Cl (2×100 ml) and dried over anhydrous Na_2SO_4. Evaporation of the solvent gave a residue (0.9 g) which was submitted to flash chromatography: elution with light petroleum containing 20–50% of AcOEt afforded **20** (0.66 g, 85%); ^{1}H NMR ($CDCl_3$) δ 1.72 (6H, s, $2 \times$ Me), 2.70 (2H, t, $J = 6.4$ Hz, $CH_2C\equiv$), 3.82 (2H, t, $J = 6.4$ Hz, $\mathit{CH_2}OH$), 7.41 (4H, m, Ar).

5.15. 2-[4-(4-Methanesulfonyloxy-1-butynyl)phenyl]-isobutyronitrile (21)

Methanesulfonyl chloride (0.71 g, 6.16 mmol) was added to a stirred solution of **20** (0.66 g, 3.08 mmol) in dry CH_2Cl_2 (8 ml) containing pyridine (0.5 ml) and the resulting solution was stirred for 20 h at room temperature in an argon atmosphere. The reaction mixture was then diluted with CH_2Cl_2 (100 ml) and washed with 1% H_2SO_4 (100 ml) and brine (100 ml). The combined organic phases were dried over anhydrous Na_2SO_4 and, after evaporation of the solvent, **21** was obtained (1.28 g) and used in the next step without any further purification.

5.16. 2-[4-(4-(4-Hydroxydiphenylmethyl-1-piperidyl)-1-butynyl)-phenyl]-isobutyronitrile (22)

A solution of the mesylate **21** (1.20 g, 4.1 mmol), diphenyl-(4-piperidyl)-methanol (azacyclonol, 1.28 g,

4.8 mmol) and anhydrous K_2CO_3 (1.8 g) in dry MeCN (20 ml) was refluxed for 15 h in an argon atmosphere. After cooling, the reaction mixture was filtered and the filtrate was evaporated in vacuo to give a residue (2 g) which was submitted to flash chromatography: elution with light petroleum containing 20–50% of AcOEt yielded **22** (0.70 g, 52% from **20**); ^{1}H NMR ($CDCl_3$) δ 1.54 (4H, m, 3- and 5-CH_2), 1.70 (6H, s, 2 × Me), 2.10–2.70 (8H, m, 3 × CH_2N, *CH*-C*OH*)), 3.02 (2H, d, $J = 12$ Hz, CH_2-C≡), 7.15–7.55 (14H, m, Ar).

5.17. 2-[4-(4-(4-Hydroxydiphenylmethyl-1-piperidyl)-butyryl)-phenyl]-isobutyronitrile (**23**)

A solution of HgO (0.07 g, 0.35 mmol) in 4% H_2SO_4 (12 ml, w/v) was added to a stirred suspension of **22** (0.70 g, 1.51 mmol) in MeOH (4 ml) and the resulting mixture was heated for 3 h at 55°C. After cooling, the reaction mixture was diluted with saturated $NaHCO_3$ solution (50 ml) and extracted with CH_2Cl_2 (4 × 50 ml). The combined organic phases were then washed with brine (80 ml) and dried over anhydrous Na_2SO_4. Evaporation of the solvent yielded an oil (1 g) which was submitted to flash chromatography: elution with CH_2Cl_2 containing 2–5% MeOH afforded **23** (0.391 g, 54%); ν_{max} ($CHCl_3$) 2230 (CN), 1690 cm^{-1} (CO); ^{1}H NMR ($CDCl_3$) δ 1.45 (4H, m, 3- and 5-CH_2), 1.72 (6H, s, 2 × Me), 2.00 (4H, m, *CH*$_2$CH$_2$CO, *CH*-C*OH*), 2.45 (4H, t, $J = 7.0$ Hz, 2- and 6-CH_2), 2.98 (4H, t, $J = 7.0$ Hz, N*CH*$_2$CH$_2$*CH*$_2$CO), 7.10–7.60 and 7.92 (14H, m, Ar).

5.18. 2-[4-(1-Ethylendioxo-4-chlorobutyl)-phenyl]-isobutyryl amide (**24**)

13 (17.0 g, 54.3 mmol) was dissolved in oxalyl chloride (14.0 g, 110 mmol) and the resulting mixture was stirred at room temperature for 2.5 h in an argon atmosphere. Excess of oxalyl chloride was removed, the residue (18.0 g) was dried in high vacuum and then dissolved in THF (18 ml). This solution was added dropwise in 15 min to a cool (0°C), stirred solution of 30% NH_4OH (122 ml). Stirring was continued for 30 min after which water (45 ml) and $CHCl_3$ (400 ml) were added. The organic phase was then separated and the aqueous layer was extracted with $CHCl_3$ (3 × 70 ml); the combined organic phases were washed with brine (2 × 200 ml) and dried (Na_2SO_4). Evaporation of the solvent gave a residue which was triturated with light petroleum; removal of the solvent afforded **24** (13.3 g, 78%); ^{1}H NMR ($CDCl_3$) δ 1.60 (6H, s, 2 × Me), 1.80–2.10 (4H, m, ClCH$_2$*CH*$_2$*CH*$_2$), 3.55 (2H, t, ClCH$_2$), 3.70–4.10 (4H, 2 × m, –OCH$_2$CH$_2$O–), 5.40 (2H, br s, NH_2), 7.40 (4H, m, Ar).

5.19. 2-[4-(4-Chlorobutyryl)-phenyl]-isobutyronitrile (**26**) (from **24**)

A mixture of **24** (24.2 g, 77.6 mmol), Na_2CO_3 (6.05 g, 157.1 mmol) and $POCl_3$ (18.65 g, 121.7 mmol) in anhydrous MeCN (108 ml) was refluxed under stirring in an argon atmosphere for 2.5 h. After cooling, the reaction mixture was filtered and evaporated to give a residue which was redissolved in CH_2Cl_2 (200 ml), washed with water (100 ml), saturated $NaHCO_3$ (100 ml), brine (100 ml) and dried (Na_2SO_4). After evaporation of the solvent, the residue was dissolved in THF (290 ml), acidified with 12 N HCl (20 ml) and the resulting mixture was stirred for 1.5 h. The reaction mixture was then diluted with water, extracted with AcOEt (3 × 200 ml) and dried (Na_2SO_4). Evaporation of the solvent yielded a residue which was submitted to flash chromatography: elution with light petroleum–AcOEt (8:2) afforded **26** as white crystals (17.3 g, 89%), m.p. 80.5–81.5°C; ^{1}H NMR ($CDCl_3$) δ 1.75 (6H, s, 2 × Me), 2.20 (2H, quint., $J = 6$ Hz, CH$_2$*CH*$_2$CH$_2$), 3.20 (2H, t, $J = 6$ Hz, CH$_2$CO), 3.70 (2H, t, $J = 6$ Hz, CH$_2$Cl), 7.80 (4H, 2 × d, $J = 8$ Hz, Ar).

5.20. 2-(4-Tributyltin-phenyl)-isobutyronitrile (**25**)

A mixture of bis(tributyltin) (5.03 g, 8.67 mmol), **19** (1.50 g, 6.69 mmol) and tetrakis(triphenylphosphine)-palladium (0.08 g, 0.07 mmol) in toluene (5 ml) was stirred at 65°C in an argon atmosphere for 50 h. The reaction mixture was diluted with ether (50 ml) and filtered, the filtrate was washed with water (2 × 30 ml), brine (50 ml) and dried over anhydrous Na_2SO_4. After evaporation of the solvent, the residue (2.3 g) was submitted to flash chromatography: elution with light petroleum–ether (98:2) yielded **25** (1.52 g, 52.3%); ^{1}H NMR ($CDCl_3$) δ 0.95 (9H, t, $J = 8$ Hz, 3 × CH$_2$*CH*$_3$), 1.05–1.70 (18H, m, 9 × CH_2), 1.75 (6H, s, 2 × Me), 7.42 (4H, m, Ar).

5.21. 2-[4-(4-Chlorobutyryl)-phenyl]-isobutyronitrile (**26**) (from **25**)

4-Chlorobutyryl chloride (0.34 g, 2.40 mmol) and bis(triphenylphosphine)palladium(II)chloride (0.11 g, 0.15 mmol) were added to a solution of **25** (0.95 g, 2.18 mmol) in toluene (15 ml) and the resulting mixture was stirred at 70°C in an argon atmosphere for 8 h. The reaction mixture was then concentrated at reduced pressure and the residue was submitted to flash chromatography: elution with light petroleum–ether (9:1) gave **26** as white crystals (0.48 g, 88%).

*5.22. S-(−) 2-[4-(1-Hydroxy-4-chlorobutyl)-phenyl]isobutyronitrile (**27a**)*

A solution of ketone **26** (6.20 g, 24.82 mmol) in THF (100 ml) was added dropwise in 45 min to a cold (−25°C), magnetically stirred solution of (−)-B-chlorodiisopino-campheylborane [(−)-DIP-chloride] (11.90 g, 37.10 mmol) in THF (110 ml) in an argon atmosphere. Stirring was continued for 2 h at −25°C and then 24 h at room temperature. After evaporation of the solvent, the oily residue was dried in high vacuum overnight and then dissolved in ether (200 ml). Diethanolamine (8.5 g, 80.8 mmol) was added to this solution and the resulting mixture was stirred for 3 h at room temperature. After filtration, the solid residue was washed with ether (30 ml) and pentane (2 × 30 ml). The combined liquid phases were concentrated to give a residue (11 g) which was submitted to flash chromatography: elution with light petroleum–AcOEt (8:2) yielded **27a** (5.43 g, 87%), m.p. 79–80°C; ^{1}H NMR ($CDCl_3$) δ 1.75 (3H, s, –CMe_2), 1.90 (4H, m, CH_2CH_2CHOH), 2.20 (1H, br s, OH), 3.55 (2H, t, $J = 6$ Hz, CH_2Cl), 4.72 (1H, br s, *CH*OH), 7.40 (4H, 2 × d, $J = 8$ Hz, Ar); $[\alpha]_D^{20} = -31.4$ ($c = 1$, $CHCl_3$).

*5.23. S-(−) 2-[4-(1-Hydroxy-4-(4-hydroxydiphenyl-methyl-1-piperidyl)-butyl)-phenyl]-isobutyronitrile (**28a**)*

Diphenyl-(4-piperidyl)-methanol (azacyclonol, 5.60 g, 20.94 mmol), anhydrous K_2CO_3 (7.28 g, 52.7 mmol) and KI (0.312 g, 1.88 mmol) were added to a solution of **27a** (5.20 g, 20.65 mmol) in toluene (130 ml) and DMF (21 ml) and the resulting mixture was refluxed under argon for 8 h. The water formed during the reaction was removed by a Dean–Stark trap. After cooling, the reaction mixture was filtered and the filtrate evaporated to give a residue which was dissolved in $CHCl_3$ (400 ml), washed with water (3 × 200 ml), brine (200 ml) and dried over anhydrous Na_2SO_4. Evaporation of the solvent and flash chromatography of the residue (10 g) with dichloromethane containing 2–5% methanol afforded **28a** (4.50 g, 45%), m.p. 174–176°C; ^{1}H NMR ($CDCl_3$) δ 1.40–2.20 (15H, m, 2 × Me, 4 × CH_2, *CH*CPh_2OH), 2.50 (4H, m, CH_2–N–CH_2), 3.05 (2H, 2 × d, $J = 12$ Hz, CH_2CH_2N), 4.60 (1H, m, *CH*OH), 7.10–7.55 (14H, m, Ar); $[\alpha]_D^{20} = -53.4$ ($c = 2$, $CHCl_3$).

*5.24. S-(−) 4-[1-Hydroxy-4-(4-hydroxydiphenyl-methyl-1-piperidyl)-butyl]-1′-(tetrazol-5-yl)-isopropyl-benzene (**29a**)*

A suspension of **28a** (3.70 g, 7.67 mmol) and tri-*n*-butyltin azide (5.10 g, 15.36 mmol) in xylene (8 ml) was refluxed in an argon atmosphere for 24 h. After cooling, the solvent was removed in vacuo and the residue which contains traces of tri-*n*-butyltin azide was dissolved in hot ether (40 ml) containing 10% light petroleum. The solution was stored in the refrigerator until a solid precipitated. After filtration, the solid thus obtained was carefully washed with hot ether (30 ml) to afford a solid (4.4 g) which was then dissolved in 1.25 N NaOH in MeOH (30 ml) and stirred at room temperature in an argon atmosphere overnight. After evaporation of the solvent, the residue (4.5 g) was dissolved in water (150 ml) and washed with ether (2 × 80 ml). The aqueous layer was neutralized with 3 N HCl and extracted with $CHCl_3$–MeOH (9:1, 4 × 80 ml). The combined organic phases were dried over anhydrous Na_2SO_4 and, after evaporation of the solvent, the solid thus obtained (3.1 g) was submitted to flash chromatography on deactivated silica gel, obtained by passing through the column three volumes of MeOH: elution with $CHCl_3$–MeOH–hexane (55:25:20) afforded **29a** (1.10 g, 27%), m.p. 169°C (dec); ^{1}H NMR ($CDCl_3$ + CD_3OD) δ 1.40–1.90 (15H, m, 2 × Me, CH_2CH-(CPh_2OH)CH_2, CH_2CH_2CHOH), 2.58 (4H, m, piperidyl CH_2NCH_2), 3.20 (2H, m, CH_2N), 4.36 (1H, m, *CH*OH), 6.98–7.40 (14H, m, Ar); ^{13}C NMR (CD_3OD) δ 21.72, 25.36, 30.07, 36.85, 39.42, 42.75, 53.76, 57.78, 73.72, 79.84, 126.71, 127.03, 127.50, 129.16, 143.35, 147.13, 149.11, 169.78; $[\alpha]_D^{20} = -12.4$ ($c = 1$, MeOH).

*5.25. R-(+) 2-[4-(1-Hydroxy-4-chlorobutyl)-phenyl]isobutyronitrile (**27b**)*

A solution of ketone **26** (1.00 g, 4.00 mmol) in THF (10 ml) was added dropwise in 20 min to a cold (−25°C), magnetically stirred solution of (+)-B-chlorodiisopino-campheylborane [(+)-DIP-chloride] (1.93 g, 6.02 mmol) in THF (21 ml) in an argon atmosphere. Stirring was continued for 30 min at −25°C and then 48 h at room temperature. After evaporation of the solvent, the oily residue was dried in high vacuum overnight and then dissolved in ether (50 ml). Diethanolamine (1.37 g, 13.04 mmol) was added to this solution and the resulting mixture was stirred for 3 h at room temperature. After filtration, the solid residue was washed with ether (10 ml) and pentane (2 × 10 ml). The combined liquid phases were concentrated to give a residue (3 g) which was submitted to flash chromatography: elution with light petroleum–ethyl acetate (8:2) yielded **27b** (0.70 g, 70%); $[\alpha]_D^{20} = +27.5$ ($c = 1$, $CHCl_3$).

*5.26. R-(+) 2-[4-(1-Hydroxy-4-(4-hydroxydiphenyl-methyl-1-piperidyl)-butyl)-phenyl]-isobutyronitrile (**28b**)*

2-(4-Piperidyl)-2,2-diphenylmethanol (azacyclonol, 0.65 g, 2.43 mmol), anhydrous potassium carbonate (0.84 g, 6.08 mmol) and potassium iodide (0.04 g, 0.22

mmol) were added to a solution of **27b** (0.57 g, 2.26 mmol) in toluene (20 ml) and DMF (2.58 ml) and the resulting mixture was refluxed under argon for 9 h. The water formed during the reaction was removed by a Dean–Stark trap. After cooling, the reaction mixture was filtered and the filtrate evaporated to give a residue which was dissolved in chloroform (50 ml), washed with water (3×20 ml), brine (20 ml) and dried over anhydrous sodium sulfate. Evaporation of the solvent and flash chromatography of the residue (3 g) with dichloromethane containing 2–5% methanol afforded **28b** (0.49 g, 45%), m.p. 182°C; $[\alpha]_D^{20} = +56.9$ ($c = 2$, $CHCl_3$).

5.27. *R-(+) 4-[1-Hydroxy-4-(4-hydroxydiphenylmethyl-1-piperidyl)-butyl]-1′-(tetrazol-5-yl)-isopropylbenzene (**29b**)*

A suspension of **28b** (2.80 g, 5.80 mmol) and tri-*n*-butyltin azide (3.86 g, 11.62 mmol) in xylene (6 ml) was refluxed in an argon atmosphere for 24 h. After cooling, the solvent was removed in vacuo and the residue which contains traces of tri-*n*-butyltin azide was dissolved in hot ether (30 ml) containing 10% light petroleum. The solution was stored in the refrigerator until a solid precipitated. After filtration, the solid thus obtained was carefully washed with hot ether (30 ml) to afford a solid (3.5 g) which was then dissolved in 1.25 N NaOH in MeOH (30 ml) and stirred at room temperature in an argon atmosphere overnight. After evaporation of the solvent, the residue (3 g) was dissolved in water (100 ml) and washed with ether (2×50 ml). The aqueous layer was neutralized with 3 N HCl and extracted with $CHCl_3$–MeOH (9:1, 4×50 ml). The combined organic phases were dried over anhydrous Na_2SO_4 and, after evaporation of the solvent, the solid thus obtained (2 g) was submitted to flash chromatography on the above described, deactivated silica gel: elution with $CHCl_3$–MeOH–hexane (55:25:20) afforded **29b** (0.76 g, 25%), m.p. 170°C (dec); $[\alpha]_D^{20} = +11.4$ ($c = 2$, MeOH).

5.28. *Inhibition of [3H]mepyramine binding to guinea pig cerebellum membranes*

Guinea pigs (200–500 g) cerebellum was homogenized in phosphate buffer (50 mM, pH 7.5) and centrifuged at 4°C for 10 min ($35\,000 \times g$). The pellet was subsequently washed twice and resuspended in the phosphate buffer. In the displacement experiment the membrane suspension (600 μg of protein/ml) was incubated with increasing concentrations of the antagonist (1 nM, 31.2 Ci/mM specific activity) at 25°C for 30 min. The radioactivity was measured after centrifugation and non specific binding was assessed in the presence of promethazine (200 μg). Each experiment was performed in triplicate.

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