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Stereoselective Syntheses of Both Enantiomers of Ketoconazole from (*R*)- and (*S*)-Epichlorohydrin

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Abstract: Stereoselective syntheses of both enantiomers of ketoconazole (**1**) from commercially available (*R*)- or (*S*)-epichlorohydrin has been developed. The key-step of these syntheses involves the selective substitution of the methylene chlorine atom by benzoate on a mixture of (2*S*,4*R*)-**14a** and (2*R*,4*R*)-**15a** or of their enantiomers, followed by crystallization of the corresponding *cis*-benzoates, (2*R*,4*R*)-**18** or (2*S*,4*S*)-**18**, from which (+)- or (-)-**1** were obtained as described for (±)-**1**. The ee's of (+)- and (-)-ketoconazole were determined by HPLC on the CSP Chiralcel OD-H.

Ketoconazole is a potent orally active, broad-spectrum antifungal azolic agent[1,2] which is marketed as a racemic mixture of *cis*-1-acetyl-4-[4-[[2-(2,4-dichlorophenyl)-2-[(1*H*-imidazol-1-yl)methyl]-1,3-dioxolan-4-yl]methoxy] phenyl]piperazine, (±)-**1**, which are more potent than the *trans* stereoisomers. The configuration of both enantiomers of ketoconazole is shown in Figure 1, the (-)-stereoisomer being (2*S*,4*R*)-**1**[3]. Ketoconazole, like other azole derivatives, impairs the synthesis of ergosterol, which is the principal sterol of fungal cell membranes. This probably increases the membrane permeability with loss of intracellular content. Most of these compounds, including ketoconazole, share adverse effects such as nausea, vomiting, anemia, thrombocytosis, hypersensitivity reactions, hepatotoxicity and some central nervous system toxicity[4, 5, 6].

Recently, Rotstein et al.[3] prepared both enantiomers of ketoconazole and the corresponding *trans*-derivatives in a stereocontrolled way from the optically active precursors (*R*)- and (*S*)-solketal tosylate. When tested against mammalian enzymes involved in steroid metabolism, the two *cis*-enantiomers were found to have varying relative potencies as inhibitors depending on the particular enzyme. The authors concluded that, for hormone dependent prostate cancer, there was no apparent advantage to the use of the enantiomerically pure *cis*-compound. On the contrary, Gray[6] claimed the use of the enantiomerically pure compounds (+)-**1** and (-)-**1** as more effective than (±)-**1** for treating local and systemic fungal, yeast and dermatophyte infections in a human. Thus, in a near future, methods to prepare (+)- and (-)-**1** on an industrial scale, will be required.

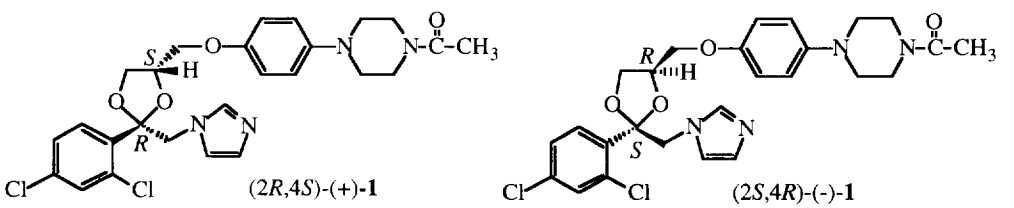
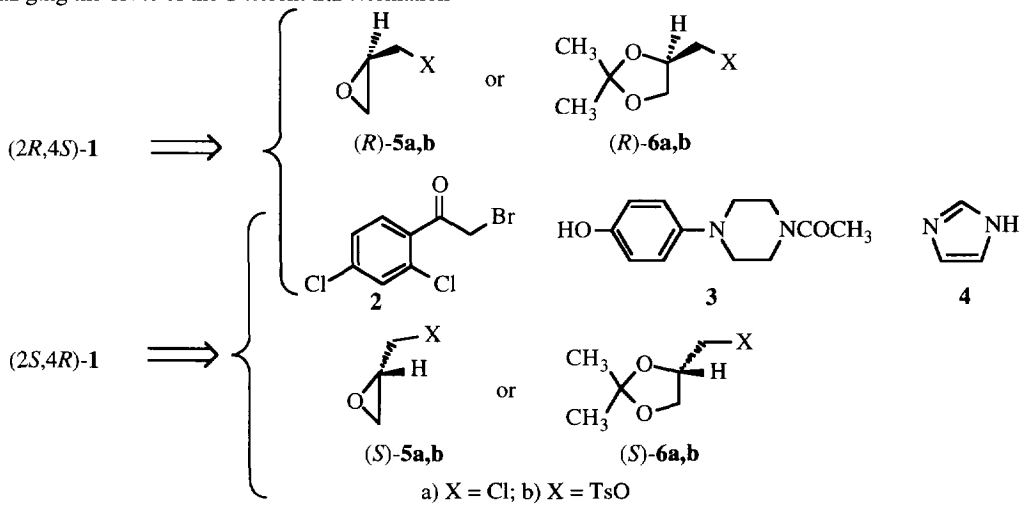


Figure 1

The described syntheses from (*R*)- and (*S*)-solketal tosylate[3] suffer from several drawbacks: a) the chiral reagents are very expensive and, to the best of our knowledge, they are only available on a laboratory scale, b) after the acetal formation, separation of the *cis* and *trans*-diastereomers is carried out by flash column chromatography, as it is the case for the purification of most intermediates and final products. Separation of a racemic mixture of (±)-**1** or of a close synthetic intermediate would not be a good method, if only one of the enantiomers is required, since at least half of the product will be lost, while recovery of the unwanted enantiomer will be a difficult matter. On the other hand, both enantiomers of epichlorohydrin are available at a reasonable cost on an industrial scale[7]. Consequently, we studied the possible use of (+)- and (-)-epichlorohydrin to prepare both enantiomers of ketoconazole.

Retrosynthetic analysis of (+)- and (-)-ketoconazole (Scheme 1) led to an α-halo ketone **2**, the commercially available phenol **3**, imidazole **4**, and a chiral C3 synthon such as (+)- or (-)-**5**/(+)- or (-)-**6**. As stated before, the use of the corresponding chloro-derivatives was preferred. Known bromo ketone **2**[3] was chosen over the corresponding α-chloro derivative due to its greater reactivity towards nucleophilic displacement by imidazole[8]. Several syntheses of (+)- or (-)-ketoconazole from these starting compounds can be envisaged by changing the order of the different transformations.

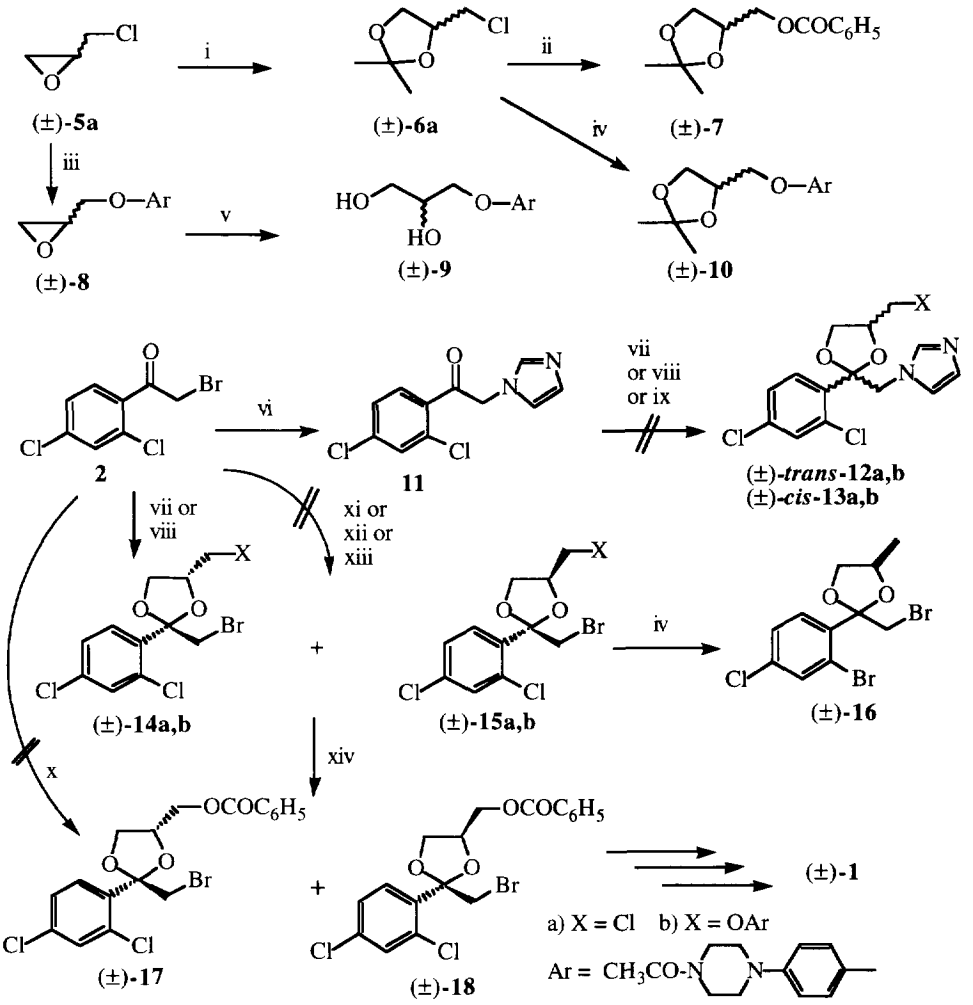


Scheme 1. Retrosynthetic Analysis of (+)- and (-)-Ketoconazole.

Initial studies were carried out with racemic epichlorohydrin, (±)-**5a** (Scheme 2). Reaction of (±)-**5a** with phenol **3**, under phase transfer catalysis conditions, gave (±)-**8** in good yield, which on acidic hydrolysis yielded the corresponding diol (±)-**9**. The chloro acetal (±)-**6a**[9] was obtained by reaction of (±)-**5a** with acetone catalyzed by boron trifluoride etherate as described starting from enantiomerically pure epichlorohydrin[10]. Reaction of (±)-**6a** with sodium benzoate gave the corresponding benzoate (±)-**7** in good yield, while reaction with the sodium phenolate derived from **3** afforded acetal (±)-**10** in moderate yield.

On the other hand, bromo ketone **2** was reacted with imidazole under mild conditions[11] to give the known compound[12] **11**, which failed to react with (±)-**5a** or (±)-**6a** under acid catalysis to give the mixture of acetals (±)-**12a** and (±)-**13a**, the starting ketone being recovered unchanged. Also, attempts to acetalize **11** with (±)-**8** and **2** with (±)-**9** or (±)-**10** failed. The failure of all of these acetalizations could be related to the presence of

basic nitrogen atoms in at least one of the starting compounds, which neutralize the acid catalyst. In fact, the separation of insoluble oily products after the addition of the acid catalalyst was always observed in these reactions. In accord with this hypothesis, reaction of **2** with (±)-**6a** gave in good yield a mixture of the corresponding *trans* and *cis* acetals (±)-**14a** and (±)-**15a**, in which the *cis* racemate was slightly predominant (^{1}H-NMR). A similar mixture was obtained, although in very low yield, by reaction of **2** with (±)-**5a**.



i) $CO(CH_3)_2$, $BF_3.OEt_2$, 40 °C, 4 h; ii) $NaOCOC_6H_5$, DMSO, 160-165 °C, 4 h; iii) **3**, KOH, $Bu_4N^+Br^-$, toluene, Δ, 2 h; iv) NaOAr (from **3** and NaH), DMSO, 80 °C, 3 h; v) H_2O, MsOH, r.t., 24 h; vi) imidazole, $CHCl_3$, 0-5 °C, 3 h; vii) (±)-**5a**, $BF_3.OEt_2$, CH_2Cl_2, 40 °C, 4 h; viii) (±)-**6a**, toluene / BuOH, *p*-TsOH.H_2O, reflux, 24 h; ix) (±)-**8**, $SnCl_4$, CH_2Cl_2, 25-30 °C, 18 h; x) (±)-**7**, toluene / BuOH, *p*-TsOH.H_2O, reflux,12 h; xi) (±)-**10**, toluene / BuOH, *p*-TsOH.H_2O, reflux, 24 h; xii) (±)-**9**, $CH(OMe)_3$, MsOH, 120-130 °C, 6 h; xiii) (±)-**9**, toluene / BuOH, *p*-TsOH.H_2O, reflux, 24 h; xiv) $NaOCOC_6H_5$, DMF, 160-165 °C, 6 h.

Scheme 2. Transformations related to the synthesis of (±)-Ketoconazole.

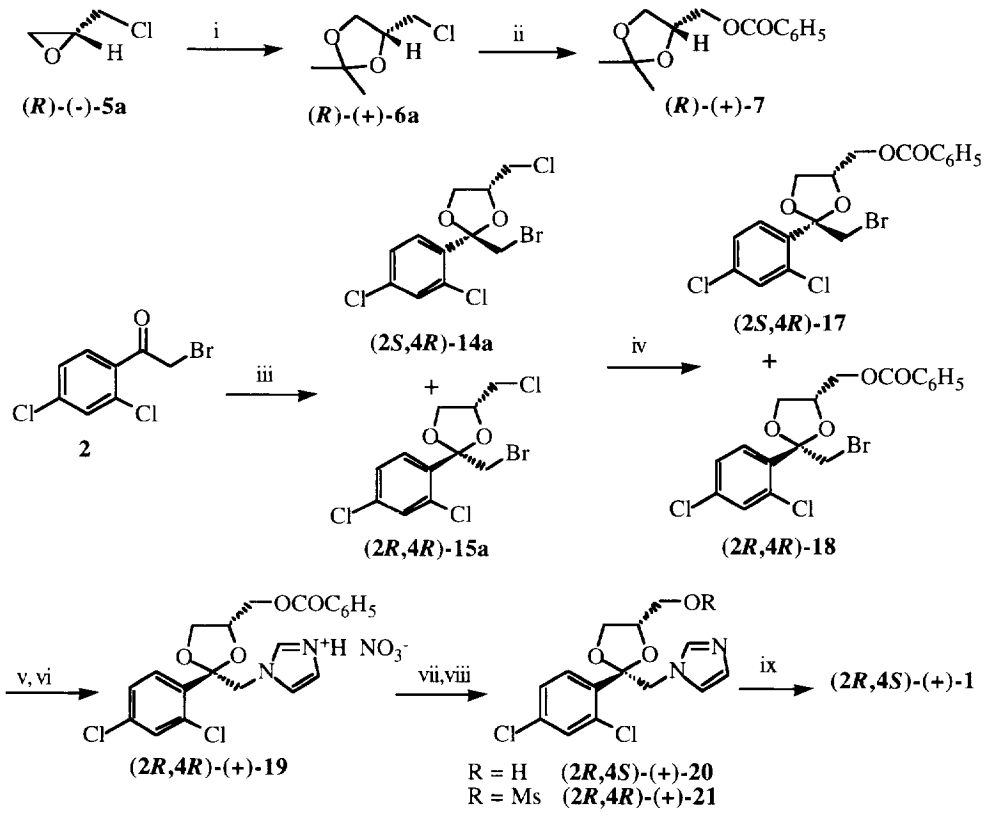
Attempted substitution of the less hindered chlorine atom of a mixture of (±)-**14a** and (±)-**15a** by the phenoxide anion derived from **3** gave mainly the elimination product (±)-**16**, as an unstable oil that could be isolated by column chromatography and characterized spectroscopically. Reaction of the above mixture with the less basic sodium benzoate gave in medium yield the corresponding mixture of benzoates (±)-**17** and (±)-**18**. This mixture could not be obtained by acetalization of **2** with (±)-**7**, under the conditions used to obtain the mixture of (±)-**14a** and (±)-**15a** (toluene/butanol/p-TsOH), the formation of butyl tosylate and butyl benzoate being observed. As described[2,8], crystallization of the mixture of *trans* and *cis* benzoates (±)-**17** and (±)-**18** from methanol gave pure (±)-**18** from which the synthesis of (±)-ketoconazole had been previously carried out[2]. The preparation of (±)-**18** herein described, constitutes a total formal synthesis of (±)-ketoconazole from (±)-epichlorohydrin.

Application of this procedure to the synthesis of both enantiomers of ketoconazole was straightforward. (*R*)-(-)-**5a** was transformed into (*R*)-(+)-**6a** in 76% yield as described[10]. Since this transformation takes place at the chiral center of (*R*)-(-)-**5a**, the enantiomeric excess (ee) of the product could be lower than that of the starting compound. In order to establish the ee, (*R*)-(+)-**6a** was transformed into the known acetal ester[13] (*R*)-(+)-**7**, by reaction with sodium benzoate. The ee of this product was established to be only 90%, by chiral HPLC using cellulose tris(3,5-dimethylphenyl carbamate (Chiralcel OD-H) as chiral stationary phase (CSP) and a mixture of hexane/isopropanol in a ratio of 97/3 as eluent (Conditions A). Kodali[13] had resolved previously the enantiomers of **7** by using cellulose tribenzoate (Chiralcel OB) as CSP.

Transacetalization of (*R*)-(+)-**6a** with **2** gave in 76% yield after column chromatography a mixture of the *trans* and *cis* acetals, (2*S*,4*R*)-**14a** and (2*R*,4*R*)-**15a**, in which the *cis*-diastereomer was sligthly predominant (500 MHz ^{1}H-NMR). The ^{1}H- (Table 1) and ^{13}C-NMR data (experimental) of each diastereomer could be obtained from the spectra of the mixture with the aid of COSY ^{1}H/^{1}H and ^{1}H/^{13}C experiments. Reaction of the above mixture with sodium benzoate in DMF gave the corresponding diastereomeric mixture of (2*S*,4*R*)-**17** and (2*R*,4*R*)-**18**, which on crystallization from methanol and recrystallization from a mixture isopropanol/diisopropyl ether afforded (2*R*,4*R*)-(+)-**18** in 29% overall yield [58% approximate yield from the starting (2*R*,4*R*)-**15a**]. When the above two transformations were performed in a one-pot manner, thus avoiding the column chromatography, (2*R*,4*R*)-(+)-**18** was obtained in 22% overall yield from **2**.

From this compound, following the procedures[2,8,14] described for (±)-**18**, (2*R*,4*S*)-(+)-**1** was obtained in comparable yields. Thus, reaction of (2*R*,4*R*)-(+)-**18** with imidazole in dimethylacetamide (DMA) followed by reaction with concd. HNO_3 in ethereal solution gave (2*R*,4*R*)-(+)-**19**.HNO_3, which on alkaline hydrolysis gave the corresponding alcohol (2*R*,4*S*)-(+)-**20**. Esterification of this alcohol with methanesulfonyl chloride gave the corresponding mesylate (2*R*,4*R*)-(+)-**21** which on reaction with the sodium phenolate derived from **3** in DMSO afforded (+)-ketoconazole, (2*R*,4*S*)-(+)-**1**. The melting point of this compound coincides with that described[3], but the optical rotation is slightly higher, $[\alpha]_D^{20}$ = + 8.99 (c = 0.4, $CHCl_3$), Lit.[3] $[\alpha]_D^{20}$ = + 8.22 (c = 0.4, $CHCl_3$).

The ee of (2*R*,4*S*)-(+)-**1** was established to be > 99% by chiral HPLC, using the CSP Chiralcel OD-H and a mixture of hexane/ethanol in a ratio of 1/1 containing 0.1% of diethylamine as eluent (conditions B). Other CSP such as β-cyclodextrin naphthylethyl carbamate (Cyclobond SN) or β-cyclodextrin hydroxypropyl ether (Cyclobond RSP) failed or gave poor resolutions of both enantiomers of ketoconazole. Thus, in spite of the low ee (90%) of the starting (*R*)-(+)-**6a**, the (+)-ketoconazole obtained by the above procedure shows a high ee (> 99%), which must be due to enrichment during the crystallization of the different intermediates.



i) $CO(CH_3)_2$, $BF_3.OEt_2$, 40 °C, 4 h; ii) $NaOCOC_6H_5$, DMSO, 160-165 °C, 4 h; iii) **(*R*)-(+)-6a**, toluene / BuOH, *p*-TsOH.H_2O, reflux, 24 h; iv) $NaOCOC_6H_5$, DMF, 160-165 °C, 6 h; v) Crystallization from MeOH; vi) Imidazole, DMA, reflux, 4 d; vii) Dioxane, H_2O, NaOH 50 %, Δ, 0.5 h; viii) MsCl, pyridine, 0 °C, 16 h; ix) CH_3CO-N⟨⟩N-⟨⟩-O^- Na^+, DMSO, 80 °C, 5 h.

Scheme 3. Synthesis of (+)-Ketoconazole.

In a similar way, from (*S*)-(+)-**5a**, (*S*)-(-)-**6a** (ee = 94%, established by conversion to (*S*)-(-)-**7** and chiral HPLC analysis under conditions A) was obtained in 71% yield. After transacetalization with **2**, reaction with sodium benzoate, crystallization from methanol and recrystallization from a mixture isopropanol/diisopropyl ether, (2*S*,4*S*)-(-)-**18** was obtained. The same sequence of reactions described above let us transform this compound into (-)-ketoconazole, which shows essentially the same melting point and specific rotation described by Rotstein[3]. The ee of (2*S*,4*R*)-(-)-**1** was established to be > 99% by chiral HPLC, under conditions B.

All of the new compounds have been fully characterized through their spectroscopic data [500 MHz ^{1}H-NMR (Table 1), 75.4 or 50.3 MHz ^{13}C-NMR (Table 2) and IR (Table 3)] and elemental analysis (Table 4). The NMR spectra of each pair of enantiomers and the corresponding racemic mixture are identical, so only the values for one of them have been collected in the tables. The ^{1}H-NMR spectra of these compounds have been fully assigned on the basis of COSY ^{1}H/^{1}H and ^{1}H/^{13}C experiments, except for the pairs of diastereotopic protons 5-H_2, 4-CH_2 and 2-CH_2. Most of the coupling constant values have been measured and are also collected in Table 1. It is worthy of note the lower value of the *geminal* coupling contant for the 5-H_2 pair of protons as compared

with the 4-CH_2 pair, in epoxide (±)-**8** and all acetals, which allowed us easily distinguish these protons. Due to the hindered rotation around the amide bond, four kinds of methylenic protons are seen for the piperazine part in compounds (±)-**8**, (±)-**9**, (±)-**10** and (+)-**1**. Assignment of these protons has been made by assuming the carbon atom *syn* to the carbonyl group to be more shielded than the *anti* one as it is the case in piperidine derivatives[15]. Moreover, the ^{13}C-NMR spectra of these compounds (Table 2) have been fully assigned on the basis of COSY ^{1}H/^{13}C experiments using HMQC and HMBC sequences, which let us detect several mistakes in the previously described assignment for the 2,4-dichlorophenyl ring of compounds (±)-**18**, (±)-**19**, (±)-**20**, (±)-**21**, (+)- and (-)-**1**, based on additivity rules[8,14,16].

In conclusion, stereoselective syntheses of both enantiomers of ketoconazole from commercially available (R)- or (S)-epichlorohydrin, that could be applied on an industrial scale, have been developed. The merits of these procedures as compared with the previously described[3] are: 1) the use of the less expensive and industrially available (R)- or (S)-epichlorohydrin instead of (R)- or (S)-solketal tosylate as chiral reagents, and 2) the avoidance of column chromatography for the purification of most of the intermediates and final product. Moreover, to establish the optical purity of (+)- and (-)-ketoconazole, an HPLC protocol using the CSP Chiralcel OD-H has been developed.

EXPERIMENTAL

Melting points were determined on a Gallenkamp melting-point apparatus, model MFB 595010M. IR spectra were recorded on a FT/IR Perkin-Elmer spectrometer, model 1600. NMR spectra were taken on Varian Gemini 200, 300 and VXR 500 spectrometers. The chemical shifts are given in ppm (δ scale) relative to internal TMS. COSY ^{1}H/^{1}H experiments were performed using standard procedures while for COSY ^{1}H/^{13}C experiments the HMQC and HMBC sequences with an indirect detection probe were used. Coupling constants are expressed in Hertz. Optical rotations were measured in a 1-dm cell on a Perkin-Elmer, model 241 polarimeter. HPLC analyses were carried out on a Hewlett Packard, model 1090 series II liquid chromatograph, provided with variable λ Diode array detector, using the chiral column Chiracel OD-H (25 x 0.46 cm; Daicel Chem. Ind., Ltd.). Conditions A: hexane/isopropanol in a ratio of 97/3 as eluent, flow 0.8 ml/min, λ = 210 nm, temp. 25 °C; Conditions B: ethanol/hexane in a ratio of 1/1, containing 0.1% diethylamine as eluent, flow 0.2 ml/min, λ = 235 nm, temp 25 °C. Column chromatography was carried out by using silica gel SDS 60 A CC (70-230 mesh), 50 g silica gel per gram of product. (S)- and (R)-epichlorohydrin > 98% e.e., were obtained from DAISO Co., Ltd. and α-bromo-2,4-dichloroacetophenone (97% content by GLC) was prepared by bromination of 2,4-dichloroacetophenone following the method of Rotstein et al.[3]. Microanalyses were carried at the Microanalysis Service of the Centro de Investigación y Desarrollo, CID, Barcelona, Spain. Spectral and analytical data are collected in Tables. ^{1}H-NMR, Tab. 1; ^{13}C-NMR, Tab. 2; Yields, melting points, boiling points, optical rotations and IR spectra, Tab. 3; Elemental analyses, Tab. 4.

(±)-(2,2-Dimethyl-1,3-dioxolan-4-yl)methyl benzoate[13] (±)-**7.** A mixture of (±)-**6a** (3.00 g, 19.9 mmol) and sodium benzoate (5.70 g, 39.6 mmol) in anhydrous DMSO (50 ml) was heated at 160-165 °C for 4 h. The mixture was allowed to cool to room temp., diluted with 10% aqueous Na_2CO_3 solution (150 ml) and extracted with CH_2Cl_2 (3 x 50 ml). The dried (Na_2SO_4) organic extracts were concentrated in vacuo and the oily residue was distilled at reduced pressure to afford (±)-**7** (3.90 g, 83% yield) as an oil, b.p. 120-130 °C/0.5 Torr.

(±)-1-Acetyl-4-(2,3-epoxypropoxy)phenyl]piperazine (±)-**8**. A mixture of **3** (5.00 g, 22.7 mmol), tetrabutyl ammonium bromide (120 mg, 0.37 mmol), 85% powdered potassium hydroxide (1.73 g, 26.2 mmol) and (±)-epichlorohydrin (2.7 ml, 34 mmol) in toluene (25 ml) was heated at the reflux temp. for 2 h. The reaction mixture was allowed to cool to room temperature, water (28 ml) and toluene (25 ml) were then added and the mixture was

stirred for 15 minutes. The organic phase was separated, and the aqueous one was extracted with toluene (3 x 25 ml). The combined organic phases were dried with Na_2SO_4 and concentrated to dryness and the residue was crystallized from toluene to afford (±)-**8** as a white solid (5.5 g).

(±)-1-Acetyl-4-[4-(2,3-dihydroxypropoxy)phenyl]piperazine (±)-**9**. A mixture of (±)-**8** (2.00 g, 7.25 mmol), water (36 ml) and methanesulfonic acid (0.70 ml, 10.8 mmol) was stirred at room temp. for 24 h. The mixture was made alkaline with 10% aqueous $NaHCO_3$ solution and was extracted with CH_2Cl_2 (4 x 30 ml). The combined organic extracts were washed with water (3 x 30 ml), dried with Na_2SO_4 and concentrated in vacuo. The residue was crystallized from a mixture of acetonitrile/ether to afford (±)-**9** (1.86 g) as a white solid.

Table 1. 500 MHz ^{1}H NMR data of the new compounds[a].

	(±)-**8**	(±)-**9**	(±)-**10**	**14a** (2*S*,4*R*)	**15a** (2*R*,4*R*)	(+)-**18** (2*R*,4*R*)	(+)-**19**[b] (2*R*,4*R*)	(+)-**20** (2*R*,4*S*)	(+)-**21** (2*R*,4*R*)	(+)-**1** (2*R*,4*S*)
1,3-Dioxolane or C3 fragment										
$C(CH_3)_2$			1.37 1.43							
4-H[c]	3.31	4.05	4.42	4.65	4.32	4.43	4.36	4.09	4.29	4.34
5-H_A[c]	2.72	3.70	3.85	3.82	3.95	4.02	3.75	3.65	3.69	3.73
5-H_B[c]	2.87	3.79	4.12	4.44	4.12	4.12	3.96	3.78	3.81	3.86
4-CH_A[c]	3.90	3.95	3.87	3.30	3.69	4.55	4.15	3.27	3.62	3.27
4-CH_B[c]	4.15	3.97	3.99	3.58	3.74	4.56	4.30	3.42	3.83	3.70
2-CH_A				3.85	3.82	3.86	4.68	4.38	4.39	4.40
2-CH_B				3.85	3.93	3.95	4.69	4.48	4.48	5.00
J4-H,5-H_A	2.5	6.0	6.0	6.5	6.5	6.5	6.0	5.0	4.5	5.0
J4-H,5-H_B	4.0	3.5	6.5	6.0	5.0	6.0	7.0	4.0	7.0	6.5
J4-H,4-CH_A	5.5	6.5	6.5	8.0	8.0	5.0	5.5	6.0	6.0	7.0
J4-H,4-CH_B	3.0	4.5	5.5	5.0	5.0	5.0	4.0	7.0	6.0	5.0
J4-CH_A,4-CH_B	11.0	11.5	9.5	11.0	11.0	12.0	12.0	12.0	11.0	9.5
J5-H_A,5-H_B	5.0	11.5	8.5	8.5	8.5	8.5	8.5	8.0	8.5	8.0
J2-CH_A,2-CH_B					11.5	11.5	15.0	14.5	14.5	15.0
Imidazole										
2-H							8.75	7.55	7.53	7.53
4-H							7.14*	7.00	7.01	6.99
5-H							7.15*	6.98	6.98	6.96
2,4-Dichlorophenyl										
3-H				7.416	7.423	7.43	7.48	7.44	7.45	7.46
5-H				7.27	7.27	7.27	7.29	7.24	7.24	7.25
6-H				7.60	7.60	7.64	7.55	7.56	7.52	7.57
J3-H,5-H				2.0	2.0	2.0	2.0	2.0	2.0	2.0
J5-H,6-H				8.5	8.5	8.5	8.5	8.5	8.5	8.5
O-Aryl-N or benzoate										
2(6)-H	6.85	6.84	6.84			8.08	7.95			6.76
3(5)-H	6.85	6.84	6.84			7.46	7.48			6.88
4-H						7.59	7.60			
J2-H,3-H							8.5			9.0
Piperazine										
2-H	3.74	3.72	3.73							3.76
3-H	3.00	2.98	3.00							3.02
5-H	3.04	3.02	3.03							3.05
6-H	3.58	3.57	3.58							3.60
Other signals										
N^+H							1.1-1.9			
OH		1.87 2.60						2.2		
CH_3	2.11	2.10	2.10						3.01	2.13

[a]All spectra have been taken in $CDCl_3$. Values from the same column marked with * can be interchanged. Due to restricted rotation around the amide bond, four kind of methylene groups are observed for the piperazine part of these compounds, numbering assigns the lowest value to the carbon atom closest to the carbonyl oxygen atom. [b]This spectrum corresponds to the nitrate. [c]In compounds (±)-**8** and (±)-**9**, 4-H, 5-H and 4-CH_2 of the dioxolane correspond to 2-H, 3-H and 1-H of the C3 fragment, respectively

Table 2. ^{13}C NMR data of the new compounds[a].

	(±)-**8**[b]	(±)-**9**[b]	(±)-**10**[b]	**14a** (2*S*,4*R*)	**15a** (2*R*,4*R*)	(+)-**18** (2*R*,4*R*)	(+)-**19**[c] (2*R*,4*R*)	(+)-**20** (2*R*,4*S*)	(+)-**21** (2*R*,4*R*)	(+)-**1**[b] (2*R*,4*S*)
1,3-Dioxolane or C3 fragment										
C2			109.6	108.0	108.2	107.8	106.9	107.5	108.3	108.0
C4[d]	50.1	70.4	74.0	77.4	76.0	74.3	74.2	77.0	73.8	74.7
C5[d]	44.5	63.7	66.8	69.2	68.5	67.5	66.7	66.9	66.3	67.6
2-CH_2				36.1	35.1	35.2	52.4	51.3	50.9	51.2
4-CH_2[d]	69.1	69.6	69.2	43.3	43.7	64.0	63.2	61.7	67.6	67.6
C(CH_3)$_2$			25.3							
			26.7							
Imidazole										
C2							137.6	138.7	138.7	138.8
C4							122.6	128.0	128.4	128.5
C5							119.7	121.1	121.1	121.2
CO	168.8	169.1	168.9			166.2	165.9			168.9
CH_3	21.2	21.3	21.3						37.4	21.3
2,4-Dichlorophenyl										
C1				135.3	134.3	134.5	132.9*	134.7	133.8	134.6
C2				132.9	132.8	132.9	132.6*	132.9	132.8	133.0
C3				131.1	131.3	131.3	131.5	131.2	131.3	131.3
C4				135.6	135.7	135.6	136.5	135.7	136.0	135.8
C5				127.0	127.0	126.9	127.5	127.2	127.2	127.2
C6				129.6	129.8	129.9	129.9	129.5	129.3	129.5
O-Aryl-N or benzoate										
C1	145.5	145.6	145.5			129.5	129.1			145.6
C2(6)	115.3	115.3	115.2			129.7	129.5			115.2
C3(5)	118.6	118.6	118.7			128.4	128.5			118.8
C4	153.0	153.2	153.2			133.3	133.5			152.8
Piperazine										
C2	41.3	41.5	41.4							41.4
C3	50.5	50.7	50.6							50.6
C5	50.9	51.1	51.0							51.0
C6	46.2	46.4	46.3							46.3

[a]All spectra have been taken at 50.3 MHz in $CDCl_3$, except where otherwise stated. Values from the same column marked with * can be interchanged. Due to restricted rotation around the amide bond, four kind of methylene groups are observed for the piperazine part of these compounds, numbering assignes the lowest value to the carbon atom closest to the carbonyl oxygen atom. [b]This spectrum was taken at 75.4 MHz. [c]This spectrum corresponds to the nitrate. [d]In compounds (±)-**8** and (±)-**9**, C4, C5 and 4-CH_2 of the 1,3-dioxolane correspond to C2, C3 and C1, of the C3 fragment, respectively.

Table 3. Yields, melting points, solvent of crystallization, specific rotations[a] and IR data of the new compounds.

Compound	Yield (%)	m.p. (°C)	Solvent of crystallization	$[\alpha]_D^{20}$	IR (cm^{-1}) (KBr) OH / NH^+	CO	SO_3
(±)-**8**	88	106-107	toluene			1621	
(±)-**9**	87	116-117	acetonitrile/ether		3354, 3118	1613	
(±)-**10**	50	73-75	ethyl acetate			1621	
(2*R*,4*R*)-(+)-**18**	23[b]	138-139	*i*-PrOH/*i*-Pr2O	+23.8		1711	
(2*S*,4*S*)-(-)-**18**	22[b]	138-139	*i*-PrOH/*i*-Pr2O	-27.8		1711	
(2*R*,4*R*)-(+)-**19**.HNO_3	53	155-156	ethanol/toluene	+25.0	2800, 2450	1728	
(2*S*,4*S*)-(-)-**19**.HNO_3	53	154-155	ethanol/toluene	-26.2	2800, 2450	1728	
(2*R*,4*S*)-(+)-**20**	89	129-130	ethyl acetate	+17.0	3138		
(2*S*,4*R*)-(-)-**20**	90	129-131	ethyl acetate	-18.5	3125		
(2*R*,4*R*)-(+)-**21**[a]	81	91-93	ethyl acetate	+16.2			1366,1180
(2*S*,4*S*)-(-)-**21**[a]	97	93-94	ethyl acetate	-17.7			1366,1180

[a]In $CHCl_3$, c = 0.5. [b]Overall yield from **2**. [c]The IR spectrum of this compound was registered in $CHCl_3$.

Table 4. Molecular formula, molecular mass, and elemental analyses of the new compounds

Compound	Molecular Formula	Molecular Mass		Elemental Analysis C	H	N	Cl	Br or S
(±)-**8**	$C_{15}H_{20}N_2O_3$	276.34	Calc.	65.19	7.30	10.14		
			Found	65.05	7.16	10.04		
(±)-**9**	$C_{15}H_{22}N_2O_4$	294.35	Calc.	61.21	7.53	9.52		
			Found	61.31	7.49	9.59		
(±)-**10**	$C_{18}H_{26}N_2O_4$	334.41	Calc.	64.65	7.84	8.38		
			Found	64.54	7.90	8.45		
(2*R*,4*R*)-(+)-**18**	$C_{18}H_{15}BrCl_2O_4$	446.12	Calc.	48.46	3.39		15.89	17.91
			Found	48.45	3.37		15.84	17.55
(2*S*,4*S*)-(-)-**18**	$C_{18}H_{15}BrCl_2O_4$	446.12	Calc.	48.46	3.39		15.89	17.91
			Found	48.41	3.36		15.76	17.78
(2*R*,4*R*)-(+)-**19**.HNO_3	$C_{21}H_{19}Cl_2N_3O_7$	496.31	Calc.	50.82	3.86	8.47	14.29	
			Found	50.78	3.87	8.60	14.29	
(2*S*,4*S*)-(-)-**19**.HNO_3	$C_{21}H_{19}Cl_2N_3O_7$	496.31	Calc.	50.82	3.86	8.47	14.29	
			Found	50.75	3.85	8.52	14.30	
(2*R*,4*S*)-(+)-**20**	$C_{14}H_{14}Cl_2N_2O_3$	329.19	Calc.	51.08	4.29	8.51	21.54	
			Found	51.10	4.37	8.38	21.30	
(2*S*,4*R*)-(-)-**20**	$C_{14}H_{14}Cl_2N_2O_3$	329.19	Calc.	51.08	4.29	8.51	21.54	
			Found	51.03	4.23	8.49	21.46	
(2*R*,4*R*)-(+)-**21**	$C_{15}H_{16}Cl_2N_2O_5S$	407.29	Calc.	44.24	3.96	6.88	17.41	7.87
			Found	44.03	3.91	6.81	17.33	7.70
(2*S*,4*S*)-(-)-**21**	$C_{15}H_{16}Cl_2N_2O_5S$	407.29	Calc.	44.24	3.96	6.88	17.41	7.87
			Found	44.24	3.93	6.71	17.33	7.60

(±)-1-Acetyl-4-[4-[2,2-dimethyl-1,3-dioxolan-4-yl)methoxy]phenyl]piperazine (±)-**10.** To a suspension of sodium hydride (420 mg, 60-65% dispersion in mineral oil, 10 mmol) anhydrous DMSO (30 ml), phenol **3** (2.20 g, 10.0 mmol) was added, and the mixture was stirred for 1 h at room temp. Then, a solution of (±)-**6a** (1.54 g, 10.2 mmol) in anhydrous DMSO (5 ml) was added and the mixture was heated at 80 °C for 5 h with stirring. The mixture was allowed to cool to room temp., diluted with water (75 ml) and extracted with CH_2Cl_2 (5 x 50 ml). The combined organic extracts were washed with water (3 x 100 ml), dried with Na_2SO_4 and concentrated at reduced pressure. The residue was crystallized from ethyl acetate to give solid (±)-**10** (1.65 g).

Mixture of (±)-*trans* and (±)-*cis*-2-(bromomethyl)-4-(chloromethyl)-2-(2,4-dichlorophenyl)-1,3-dioxolane, (±)-**14a** and (±)-**15a.** A solution of bromoketone **2** (2.70 g, 9.80 mmol), (±)-**6a** (2.30 g, 15.3 mmol) and *p*-TsOH.H_2O (3.00 g, 15.8 mmol) in a mixture of toluene (45 ml) and butanol (21 ml) was heated at the reflux temp. for 24 h with continuous removal of water by means of a Dean-Stark equipment. The mixture was allowed to cool to room temp., poured into a 10% aqueous $NaHCO_3$ solution (100 ml) and extracted with ether (3 x 50 ml). The combined organic extracts were washed with water (3 x 100 ml), dried with Na_2SO_4 and concentrated at reduced pressure to dryness. The residue was purified by column chromatography (silica gel, hexane/CH_2Cl_2: 8/2, as eluent) to give a mixture of (±)-**14a** and (±)-**15a** (2.85 g, 81% yield) in which (±)-**15a** slightly predominated (^{1}H-NMR). The NMR data of this mixture coincide with that of the mixture of (2S,4R)-**14a** and (2R,4R)-**15a**. IR (NaCl) not significative. Elemental analysis: calcd. for $C_{11}H_{10}BrCl_3O_2$: C, 36.65; H, 2.80; Cl, 29.51. Found: C, 36.37; H, 2.88; Cl, 29.29.

Reaction of the mixture of (±)-14a and (±)-15a with 3: Isolation of (±)-2-(2,4-dichlorophenyl)-2-(2-bromomethyl)-4-methylene-1,3-dioxolane (±)-**16.** To a suspension of sodium hydride (60-65% dispersion in mineral oil, 34 mg, 0.85 mmol) in anhydrous DMSO (5 ml), **3** (190 mg, 0.86 mmol) was added. After stirring for 1 h at room temp. in an argon atmosphere, a solution of a mixture of (±)-**14a** and (±)-**15a** (260 mg, 0.72 mmol) in anhydrous DMSO (5 ml) was added and the mixture was heated at 80 °C for 5 h with stirring. The reaction mixture was allowed to cool, diluted with water (30 ml) and extracted with CH_2Cl_2 (3 x 30 ml). The combined organic phases were washed with water (3 x 50 ml), dried with Na_2SO_4 and concentrated in vacuo. The oily residue was submitted to column chromatography (silica gel, mixtures hexane/ethyl acetate as eluent) to give

in order of elution **3** (30 mg, 16% yield) and (±)-**16** (55 mg, 21% yield) as an unstable oil. ^{1}H-NMR (200 MHz, $CDCl_3$), δ: 3.89 (s, 2H, CH_2-Br), 3.94 (m, 1H) and 4.47 (m, 1H) (4=CH_2), 4.30 (dm, J = 12.0 Hz, 1H) and 4.65 (dm, J = 12.0 Hz, 1H) (5-H_2), 7.21 (dd, J = 8.5 Hz, J' = 2.0 Hz, 1H, 5'-H), 7.37 (d, J = 2.0 Hz, 1H, 3'-H), 7.53 (d, J = 8.5 Hz, 1H, 6'-H). ^{13}C NMR (50.3 MHz, $CDCl_3$), δ: 34.8 (CH_2, CH_2-Br), 67.2 (CH_2, C5), 80.2 (CH_2, 4=CH_2), 109.1 (C, C2), 127.0 (CH), 129.9 (CH) and 131.2 (CH) (C3', C5' and C6'), 132.8 (C), 133.5 (C), 136.0 (C) (C1', C2' and C4'), 154.7 (C, C4).

(±)-*cis*-[2-(Bromomethyl)-2-(2,4-dichlorophenyl)-1,3-dioxolan-4-yl]methyl benzoate (±)-**18.** A mixture of (±)-**14a** and (±)-**15a** in which the last compound was slightly predominant (1.80 g, 5.00 mmol), and sodium benzoate (1.44 g, 10.0 mmol) in anhydrous DMF (20 ml), was heated at 160-165 °C for 6 h. The mixture was allowed to cool to room temp., diluted with water (60 ml) and extracted with ether (4 x 50 ml). The combined organic phases were washed with water (3 x 50 ml), dried with Na_2SO_4 and concentrated at reduced pressure to give an oily residue. Upon addition of methanol a solid precipitated which was filtered and recrystallized from a mixture isopropanol/diisopropyl ether to afford (±)-**18** as a white solid (610 mg, 54% yield), m.p. 114-115 °C (Described[2] 118.3 °C). The spectral data [IR(KBr) ^{1}H and ^{13}C NMR] coincide with those of (2*R*,4*R*)-**18**.

(*R*)-(+)-(2,2-Dimethyl-1,3-dioxolan-4-yl)methyl benzoate[13] (*R*)-(+)-**7.** It was prepared as described above for (±)-**7**. From (*R*)-(+)-**6a**[10] (1.16 g, 7.70 mmol) and sodium benzoate (2.00 g, 13.8 mmol) in anhydrous DMSO (15 ml), (*R*)-(+)-**7** (1.25 g, 69% yield) was obtained, b.p. 120-130 °C/0.5 Torr, $[\alpha]_D^{20}$ = + 7,35 (c = 1.0, $CHCl_3$). The ee was established to be 90% by chiral HPLC under conditions A: r.t. 9.22 min.

Mixture of (2*S*,4*R*)- and (2*R*,4*R*)-2-(bromomethyl)-4-(chloromethyl)-2-(2,4-dichlorophenyl)-1,3-dioxolane, (2*S*,4*R*)-**14a and** (2*R*,4*R*)-**15a.** This mixture was prepared as described above for the mixture of (±)-**14a** and (±)-**15a**. From bromoketone **2** (5.00 g, 18.1 mmol), (*R*)-(+)-**6a** (3.90 g, 25.9 mmol) and *p*-TsOH.H_2O (4.18 g, 22.0 mmol), a mixture of (2*S*,4*R*)-**14a** and (2*R*,4*R*)-**15a** (4.97 g, 76% yield) was obtained after purification by column chromatography. IR (NaCl) not significative. Elemental analysis: calcd. for $C_{11}H_{10}BrCl_3O_2$: C, 36.65; H, 2.80; Cl, 29.51. Found: C, 36.80; H, 2.72; Cl, 29.30.

(2*R*,4*R*)-(+)-[2-(Bromomethyl)-2-(2,4-dichlorophenyl)-1,3-dioxolan-4-yl]methyl benzoate (2*R*,4*R*)-(+)-**18.** It was prepared as described for (±)-**18**. From a mixture of (2*S*,4*R*)-**14a** and (2*R*,4*R*)-**15a** (2.06 g, 5.70 mmol) and sodium benzoate (1.65 g, 11.4 mmol), after crystallization from methanol and recrystallization from a mixture isopropanol/diisopropyl ether, (2*R*,4*R*)-(+)-**18** (740 mg) was isolated as a white solid. In a one-pot procedure, starting from bromoketone **2** (2.50 g, 9.05 mmol) and (*R*)-(+)-**6a** (2.00 g, 13.3 mmol), the non-chromatographed mixture of (2*S*,4*R*)-**14a** and (2*R*,4*R*)-**15a** was reacted directly with sodium benzoate (2.60 g, 18.1 mmol) to give after crystallization from methanol and recrystallization as before (2*R*,4*R*)-(+)-**18** (930 mg).

(2*R*,4*R*)-(+)-[2-(2,4-Dichlorophenyl)-2-[(1*H*-imidazol-1-yl)methyl]-1,3-dioxolan-4-yl]methyl benzoate nitrate (2*R*,4*R*)-(+)-**19**.HNO_3**.** A solution of (2*R*,4*R*)-(+)-**18** (1.10 g, 2.46 mmol) and imidazole (560 mg, 8.23 mmol) in anhydrous DMA (8 ml) was heated at the reflux temp. for 5 d. The mixture was allowed to cool to room temp., diluted with water (50 ml) and extracted with ether (4 x 50 ml). The combined organic extracts were concentrated to a final volume of approximately 20 ml, and treated with a small excess of 65% HNO_3 (0.20 ml, 2.90 mmol), an orange oil being separated from the solution. The oil was isolated from the solution by decantation, washed with ether, dried in vacuo and crystallized from a mixture of ethanol/toluene affording (2*R*,4*R*)-(+)-**19**.HNO_3 (640 mg) as a white solid.

(2*R*,4*S*)-(+)-2-(2,4-Dichlorophenyl)-2-[(1*H*-imidazol-1-yl)methyl]-1,3-dioxolane-4-methanol (2*R*,4*S*)-(+)-**20.** To a solution of (2*R*,4*R*)-(+)-**19**.HNO_3 (690 mg, 1.39 mmol) in a mixture of dioxane (4.6 ml) and water (1 ml), a 50% aqueous solution of NaOH (1 ml) was added, and the mixture was heated at the reflux temp. for 0.5 h. The mixture was allowed to cool to room temp., diluted with water (30 ml) and extracted with ethyl acetate (3 x 30 ml). The combined organic extracts were dried with Na_2SO_4, concentrated at reduced pressure to dryness and the solid residue was crystallized from ethyl acetate to give pure (2*R*,4*S*)-(+)-**20** (410 mg).

(2*R*,4*R*)-(+)-[2-(2,4-Dichlorophenyl)-2-[(1*H*-imidazol-1-yl)methyl]-1,3-dioxolan-4-yl]methyl methanesulfonate (2*R*,4*R*)-(+)-**21.** To a cold (ice-bath) solution of (2*R*,4*S*)-(+)-**20** (276 mg, 0.84 mmol) in

anhydrous pyridine (5 ml), methanesulfonyl chloride (78 µl, 1.0 mmol) was added and the mixture was stirred for 16 h allowing the reaction mixture to warm slowly to room temp. The mixture was diluted with water (20 ml) and extracted with CH_2Cl_2 (3 x 25 ml). The combined organic phases were washed with water (3 x 30 ml), dried with Na_2SO_4, concentrated at reduced pressure to dryness and the oily residue was crystallized from ethyl acetate affording (2*R*,4*R*)-(+)-**21** (275 mg) as a white solid.

(2*R*,4*S*)-(+)-1-Acetyl-4-[4-[[2-(2,4-diclorophenyl)-2-[(1H-imidazol-1-yl)methyl]-1,3-dioxolan-4-yl] methoxy]phenyl]piperazine (2*R*,4*S*)-(+)-**1.** To a suspension of NaH (60-65% dispersion in mineral oil, 19.2 mg, 0.48 mmol) in anhydrous DMSO (3 ml), phenol **3** (102 mg, 0.46 mol) was added and the mixture was stirred for 1 h at room temp.. Then, a solution of (2*R*,4*R*)-(+)-**21** (160 mg, 0.39 mmol) in anhydrous DMSO (5 ml) was added and the mixture was heated at 80 °C for 4 h with stirring. The reaction mixture was allowed to cool to room temp., diluted with water (20 ml) and extracted with CH_2Cl_2 (3 x 25 ml). The combined organic extracts were washed with water (3 x 30 ml), dried with Na_2SO_4 and concentrated at reduced pressure to dryness. The oily residue was crystallized from a mixture acetone/ethyl acetate affording (2*R*,4*S*)-(+)-**1** (110 mg, 53% yield) as a solid m.p. 155-156 °C (Lit.[3] 154-156 °C), $[\alpha]_D^{20}$ = + 8.99 (c = 0.4, $CHCl_3$) (Lit.[3] $[\alpha]_D^{25}$ = + 8.22, c = 0.4, $CHCl_3$). The ee was shown to be > 99% by chiral HPLC (conditions B) r.t. 73.28 min.

(*S*)-(-)-(2,2-Dimethyl-1,3-dioxolan-4-yl)methyl benzoate[13] (*S*)-(-)-**7.** It was prepared as described above for (±)-**7**. From (*S*)-(-)-**6a**[10] (1.23 g, 8.17 mmol) and sodium benzoate (2.10 g, 14.6 mmol) in anhydrous DMSO (15 ml), (*S*)-(-)-**7** (1.17 g, 61% yield) was obtained, b.p. 120-130 °C/0.5 Torr, $[\alpha]_D^{20}$ = - 7,55 (c = 1.0, $CHCl_3$) (Lit.[13] $[\alpha]_D^{22}$ = - 9.9, c = 10, $CHCl_3$). The ee was established to be 94% by Chiral HPLC under conditions A, r.t. 9.70 min.).

Mixture of (2*R*,4*S*)- and (2*S*,4*S*)-2-(bromomethyl)-4-(chloromethyl)-2-(2,4-dichlorophenyl)-1,3-dioxolane, (2*R*,4*S*)-**14a and** (2*S*,4*S*)-**15a.** This mixture was prepared as described above for the mixture of (±)-**14a** and (±)-**15a**. From bromoketone **2** (2.50 g, 9.05 mmol), (*S*)-(-)-**6a** (2.00 g, 13.3 mmol) and *p*-TsOH.H_2O (2.60 g, 13.7 mmol), a mixture of (2*R*,4*S*)-**14a** and (2*S*,4*S*)-**15a** (2.36 g, 72% yield) was obtained after purification by column chromatography. The spectral data of this mixture (IR and NMR) coincide with those of the corresponding enantiomeric mixture (2S,4R)-**14a** and (2R,4R)-**15a**. Elemental analysis: calcd. for $C_{11}H_{10}BrCl_3O_2$: C, 36.65; H, 2.80; Cl, 29.51. Found: C, 36.80; H, 2.72; Cl, 29.32.

(2*S*,4*S*)-(-)-[2-(Bromomethyl)-2-(2,4-dichlorophenyl)-1,3-dioxolan-4-yl]methyl benzoate (2*S*,4*S*)-(-)-**18.** It was prepared as described for (±)-**18**. From a mixture of (2*R*,4*S*)-**14a** and (2*S*,4*S*)-**15a** (2.10 g, 5.82 mmol) and sodium benzoate (1.70 g, 11.8 mmol), after crystallization from methanol and recrystallization from a mixture isopropanol/diisopropyl ether, (2*S*,4*S*)-(-)-**18** (730 mg) was isolated as a white solid. The spectral data are identical to those of its enantiomer. As before, in a one-pot procedure, starting from bromoketone **2** (2.50 g, 9.05 mmol) and (*S*)-(-)-**6a** (2.00 g, 13.3 mmol), the non-chromatographed mixture of (2*R*,4*S*)-**14a** and (2*S*,4*S*)-**15a** was reacted directly with sodium benzoate (2.60 g, 18.1 mmol) to give after crystallization from methanol and recrystallization (2*S*,4*S*)-(-)-**18** (890 mg).

(2*S*,4*S*)-(-)-[2-(2,4-Dichlorophenyl)-2-[(1*H*-imidazol-1-yl)methy]-1,3-dioxolan-4-yl]methyl benzoate nitrate, (2*S*,4*S*)-(-)-**19**.HNO_3. It was prepared as described above for (2*R*,4*R*)-(+)-**19**.HNO_3. From (2*S*,4*S*)-(-)-**18** (1.07 g, 2.39 mmol) and imidazole (550 mg, 8.10 mmol), (2*S*,4*S*)-(-)-**19**.HNO_3 (625 mg) was obtained as a white solid, after crystallization from a mixture of ethanol/toluene.

(2*S*,4*R*)-(-)-2-(2,4-Dichlorophenyl)-2-[(1*H*-imidazol-1-yl)methyl]-1,3-dioxolane-4-methanol (2*S*,4*R*)-(-)-**20.** It was prepared as described above for (2*R*,4*S*)-(+)-**20**. From (2*S*,4*S*)-(-)-**19** (386 mg, 0.78 mmol), dioxane (2.5 ml), water (0.5 ml) and 50% aqueous solution of NaOH (0.5 ml), after crystallization from ethyl acetate, (2*S*,4*R*)-(-)-**20** (230 mg) was obtained as a white solid.

(2*S*,4*S*)-(-)-[2-(2,4-Dichlorophenyl)-2-[(1*H*-imidazol-1-yl)methyl]-1,3-dioxolan-4-yl]methyl methanesulfonate (2*S*,4*S*)-(-)-**21.** It was prepared as described above for (2*R*,4*R*)-(+)-**21**. From (2*S*,4*R*)-(-)-**20** (200 mg, 0.61 mmol) and methanesulfonyl chloride (56 µl, 0.72 mmol) in anhydrous pyridine (3 ml), after crystallization from ethyl acetate, (2*S*,4*S*)-(-)-**21** (240 mg) was obtained as a white solid.

(2*S*,4*R*)-(-)-1-Acetyl-4-[4-[[2-(2,4-diclorophenyl)-2-[(1*H*-imidazol-1-yl)methyl]-1,3-dioxolan-4-yl] methoxy]phenyl]piperazine (2*S*,4*R*)-(-)-**1.** It was prepared as described above for (2*R*,4*S*)-(+)-**1**. From NaH (60-65% dispersion in mineral oil, 32 mg, 0.80 mmol), phenol **3** (153 mg, 0.69 mol) and (2*S*,4*S*)-(-)-**21** (250 mg, 0.61 mmol), after crystallization from a mixture acetone/ethyl acetate, (2*S*,4*R*)-(-)-**1** (196 mg, 61% yield) was obtained as a solid m.p. 153-155 °C (Lit.[3] 155-157 °C); $[\alpha]_D^{20}$ = -10.50 (c = 0.4, $CHCl_3$) (Lit.[3] $[\alpha]_D^{25}$ = -10.58, c = 0.4, $CHCl_3$). The ee was shown to be > 99% by Chiral HPLC (conditions B) r.t. 79.06 min.

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