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Synthesis of D-mannose-based azacrown ethers and their application in enantioselective reactions

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Abstract—New chiral monoaza-15-crown-5 compounds anellated to methyl-4,6-*O*-benzylidene-α-D-mannopyranosides **2a**–**f** have been synthesized. These crown ethers showed significant asymmetric induction as phase-transfer catalysts in the Michael addition of 2-nitropropane to chalcone (92% ee), in the Darzens condensation of phenacyl chloride with benzaldehyde (45% ee) and in the epoxidation of chalcones with *tert*-butyl-hydroperoxide (82% ee). The enantioselectivity was effected by the substituents at the nitrogen atom of the crown ring. The absolute configurations of epoxyketones **10** were determined by CD spectroscopy.

1. Introduction

The development of new methodologies for efficient asymmetric synthesis is of tremendous importance due to the increasing demand for optically active compounds.[1] One of the techniques of catalytic asymmetric synthesis currently generating great interest is phase-transfer catalysis, in which the enantioselectivity is induced by a chiral crown ether.[2] Crown ethers with carbohydrate moieties form a special group of optically active crown ethers. Over the past two decades numerous macrocycles made up of one or more monosaccharide units have been synthesized.[3] Inexpensive natural sugars are attractive starting materials in organic syntheses. Until now, only a limited number of asymmetric reactions have, however, been explored, in which the application of a sugar-based crown catalyst resulted in a good enantioselectivity.[4] Recently Itoh and Shirakami introduced a variety of α-D-glucose-based chiral macrocycles that gave high enantioselectivities in a Michael addition.[5] Chiral monoaza-15-crown-5 macrocycles incorporating α-methyl-glucopyranoside **1** were synthesized in our laboratory,[6] which proved to be efficient catalysts in a few asymmetric reactions.[7] Herein we report the synthesis of analogous azacrown ethers anellated to α-D-mannopyranoside **2** and their applications in enantioselective reactions. Our main purpose was to compare the catalytic effects of sugar based azacrown ethers with different configurations at C-2.

2. Results and discussion

2.1. Synthesis

The vicinal hydroxy groups of the 4,6-*O*-benzylidene-α-D-mannopyranoside **3** were alkylated with bis(2-chloroethyl) ether in the presence of tetrabutylammonium hydrogen sulfate and 50% aq NaOH in a liquid–liquid two-phase system to give intermediate **4**, which was purified by chromatography.[8] The exchange of chlorine to iodine in **4** was accomplished by NaI in acetone, at the boiling point resulting in bis-iodo derivative **5**. Compound **5** was then cyclized with various primary amines, namely with ethanolamine, propanolamine, butanolamine and 3-methoxypropylamine in boiling acetonitrile, in the presence of dry sodium carbonate yielding azacrowns **2a**, **2b**, **2c** and **2d**, respectively. This protocol is the extension of our previously described method.[6] After purification by column chromatography, the 15-membered macrocycles **2a**–**d** was obtained in yields between 44% and 53%.

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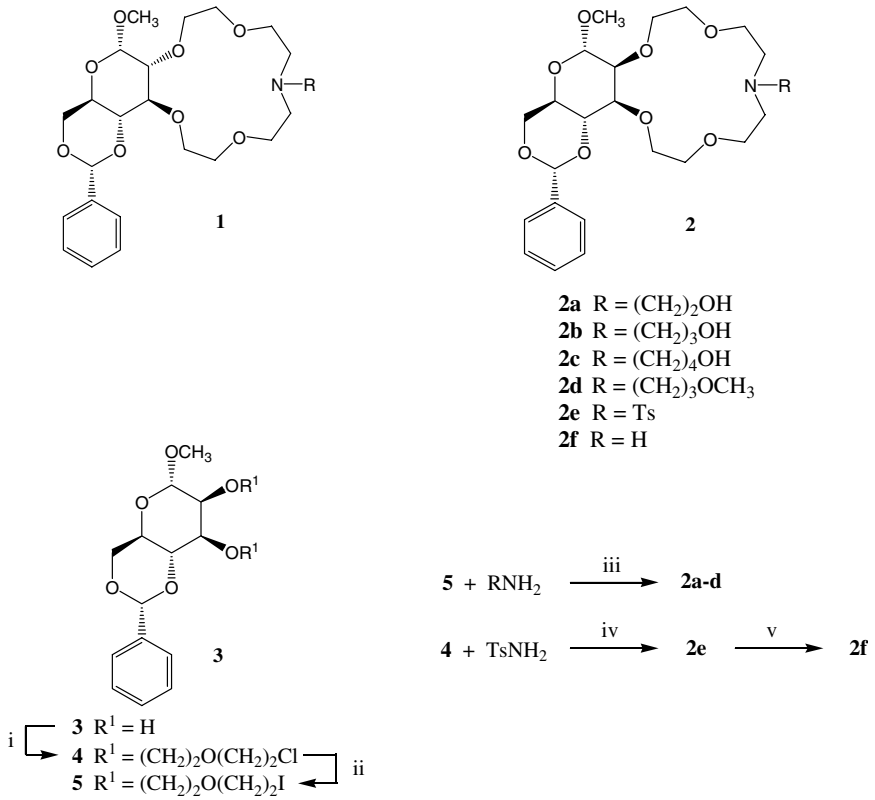


Scheme 1. Reagents and conditions: (i) $O(CH_2CH_2Cl)_2$, 50% aq NaOH, NBu_4HSO_4, 89%; (ii) NaI, acetone, reflux, 92%; (iii) Na_2CO_3, CH_3CN, reflux, 44–53%; (iv) K_2CO_3, DMF, reflux, 52%; (v) 4% Na/Hg_x, Na_2HPO_4, MeOH, reflux, 85%.

The *N*-tosyl macrocycle **2e** needed for the preparation of the unsubstituted derivative **2f** was obtained from the dichloro intermediate **4** by treatment with 1 equiv of *p*-toluene-sulfonamide in the presence of dry potassium carbonate, in DMF at boiling point. After work-up, **2e** was obtained in 52% yield. The tosyl group of **2e** was removed then by 4% sodium amalgam in methanol to give **2f** in a yield of 85% (Scheme 1). All intermediates and new products were characterized by ^{1}H NMR and mass spectroscopy.

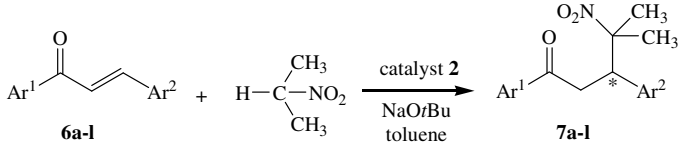
2.2. Asymmetric induction

Chiral crown ethers **2a**–**d** and **2f** were tested in a Michael addition, a Darzens condensation and in an epoxidation reaction. In all cases, the products were isolated by preparative TLC after the usual work-up procedure. The enantiomeric excess (ee) was determined by measuring the specific rotation of the products or by ^{1}H NMR spectroscopy using (+)-Eu(hfc)$_3$ as a chiral shift reagent.

2.2.1. Michael addition of 2-nitropropane to chalcone. The stereoselective variants of the addition of enolates or their analogues to the carbon–carbon double-bond of the α,β-unsaturated ketones or aldehydes have been extensively investigated in recent years.[9] Perhaps, the most frequently studied model reaction is the Michael addition of methyl phenylacetate to methyl acrylate carried out in the presence of a sugar-based crown ether, where enantioselectivities between 53% and 70% were achieved.[10]

Asymmetric induction due to glucose-based azacrown ethers **1** in the Michael addition of 2-nitropropane to chalcone has already been observed earlier.[7,11] Herein, the effect of mannose-based macrocycles **2a**–**d** and **2f** was studied in the same reaction. The solid–liquid phase-transfer reaction was carried out in dry toluene, in the presence of a chiral catalyst (7 mol %) and solid sodium tertiary butoxide (35 mol %) as base, at room temperature (Scheme 2). The experimental results are summarized in Table 1. It can be seen that the substituent at the nitrogen atom of the catalyst has a significant influence on the enantiomeric excess.

The Michael addition carried out in the presence of the unsubstituted catalyst **2f** led to an ee of 61% (entry 1). Comparing the results obtained by azacrowns **2a**–**c**,



Scheme 2. Michael addition of 2-nitropropane to chalcones, Ar^1 and Ar^2 listed in Tables 1 and 2.

Table 1. The effect of the side arm in crown catalyst **2** in the addition of 2-nitropropane to chalcone at room temperature (Scheme 2, $Ar^1 = Ar^2 = Ph$)

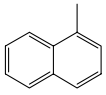
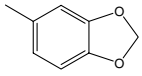
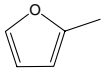
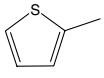
Entry	Catalyst	R substituent on catalyst **2**	Time (h)	Yield[a] (%)	ee[b] (%)
1	**2f**	H	50	34	61 (*S*)
2	**2a**	CH_2CH_2OH	44	32	70 (*S*)
3	**2b**	$(CH_2)_3OH$	52	37	92 (*S*)
4	**2c**	$(CH_2)_4OH$	58	40	63 (*S*)
5	**2d**	$(CH_2)_3OCH_3$	50	37	77 (*S*)

[a] Based on isolation by preparative TLC.
[b] Determined by ^1H NMR spectroscopy in the presence of $Eu(hfc)_3$ as chiral shift reagent.

the importance of the length of the side arm can be seen. The best result of 92% ee was obtained with catalyst **2b**, which incorporates three carbon atoms between the heteroatoms (entry 3). Replacement of the hydroxy group of **2b** by a methoxy substituent (as in **2d**) led to a decrease in the enantioselectivity (77% ee, entry 5). Using azacrowns with shorter and longer side arms (**2a** and **2c**), ee values of 70% and 63%, respectively, were detected (entries 2 and 4). Then, lariat ether **2b**, which gave the best results among the model compounds **2a–d** and **2f** studied was tested as a phase-transfer catalyst in the Michael reactions of substituted chalcones **6a–g** and of the heteroaromatic analogues of chalcones **6h–l**. The results are shown in Table 2. It can be seen that any kind of substitution in one or both phenyl groups of **6a** led to products **7b–g** with much lower enantioselectivities (21–49%, entries 2–7), when compared to the result of the reference reaction involving **6a** as the starting material (92%, entry 1). Substitution of the β-phenyl ring of **6a** decreased the ee values to a high extent. In the case of the 4-nitro- and 4-methyl-substituted starting materials **6b** and **6c**, the products **7b** and **7c** were obtained with enantioselectivities of 21% and 30%, respectively (entries 2 and 3). Substitution of the keto-aryl ring (as in starting materials **6d–f**) led to ee values of 44–49% (entries 4–6). A comparison of the results obtained using chalcones **6f** and **6g** suggests that the simultaneous substitution of both phenyl rings reduces the enantioselectivity further (ee values of 48% and 40%, respectively). Catalytic hydrogenation of Michael adducts **7f** and **7g** led to a product that was fully identical with **7a**. The negative specific rotations of the products obtained by reduction suggested that the absolute configuration of **7f** and **7g** was identical with that of **7a**, that is, *S*.

The change of the phenyl ring to a naphthyl group in chalcone **6a** resulted in a dramatically decreased asymmetric induction: product **7h** was formed with an ee value of only 20% (entry 8). Product **7i** with a piperonyl substituent was obtained with a somewhat higher enantioselectivity (47%). As the naphthyl and piperonyl groups are sterically demanding, the decrease in the enantioselectivity in these cases may be the consequence of steric effects. In the case of heteroaromatic chalcones **6j–l**, products **7j–l** were obtained with enantioselectivities between 51% and 57% (entries 10–12). Relatively the best result (ee of 57%) was achieved with the pyridyl-substituted model compound (entry 10). The furyl- and thienyl-products **7k** and **7l** were obtained with similar enantioselectivities, 53% and 51%, respectively. The absolute configuration of Michael adduct **7k** is based on

Table 2. Asymmetric Michael reaction of 2-nitropropane with chalcones and heteroaromatic chalcone analogues mediated by chiral azacrown ethers **2b** (Scheme 2)

Entry	Starting material	Ar^1	Ar^2	Time (h)	Product and yield[a] (%)	$[\alpha]_D$[b]	ee[c] (%)
1	**6a**	Ph	Ph	52	**7a**, 37	−74.8	92 (*S*)
2	**6b**	Ph	4-NO_2–Ph	51	**7b**, 28	−8.5	21
3	**6c**	Ph	4-CH_3–Ph	58	**7c**, 38	−33.1	30
4	**6d**	4-CH_3–Ph	Ph	70	**7d**, 42	−48.2	44
5	**6e**	4-OCH_3–Ph	Ph	160	**7e**, 27	−46.3	49
6	**6f**	4-Cl–Ph	Ph	40	**7f**, 42	−51.7	48 (*S*)
7	**6g**	4-Cl–Ph	4-Cl–Ph	67	**7g**, 54	−51.6	40 (*S*)
8	**6h**	Ph		167	**7h**, 28	−67.5	20
9	**6i**	Ph		72	**7i**, 54	−35.4	47
10	**6j**	Ph		20	**7j**, 72	−84.8	57
11	**6k**	Ph		48	**7k**, 48	−33.3	53 (*R*)
12	**6l**	Ph		49	**7l**, 36	−56.7	51

[a] Based on product quantity isolated by preparative TLC.
[b] In CH_2Cl_2 at 22 °C.
[c] Determined by ^1H NMR spectroscopy.

the sign of its specific rotation.[12] It is noteworthy that using glucose-based azacrowns **1** products **7** had positive specific rotation signs,[11] whereas the mannose-based catalysts **2** led to products **7** with negative specific rotations.

2.2.2. Darzens condensation. The mannose-based crown ethers induced a moderate asymmetric induction in the condensation of phenacyl chloride **8** with benzaldehyde **9** (Scheme 3). This reaction was studied by a number of other groups. The best results were obtained using *N*-(4-trifluoromethylbenzyl)cinchoninium bromide (42% ee)[13] or a crown ether incorporating a glucopyranoside unit (72% ee)[4] as phase-transfer catalysts. We performed the above reaction in a liquid–liquid (LL) as well as in a solid–liquid (SL) system and our catalysts were found to be more efficient under LL phase-transfer conditions. The reagents and catalyst **2** (7 mol %) were dissolved in toluene and the reaction initiated by adding 30% sodium hydroxide. After a reaction time of 1–4 h the *trans*-epoxyketone **10a** was formed (de >98%) in each case and its enantiomer with positive specific rotation was found to be in excess. This corresponds to an absolute configuration of (2*S*,3*R*).[13] The highest enantiomeric excess was achieved in the presence of crown catalyst **2b**; where product **10a** was obtained with an enantioselectivity of 45% after 2 h of stirring at −10 °C.

2.2.3. Asymmetric epoxidation of chalcones. A significant enantioselectivity was generated by the mannose-based crown ethers **2** in the epoxidation of chalcones and chalcone analogues under phase-transfer conditions (Scheme 4).

The enantioselective epoxidation of α,β-unsaturated ketones employing chiral catalysts has received considerable attention in recent years.[14] A variety of methods have been developed including the use of polyphasic systems involving hydrogen peroxide in the presence of polyamino acids,[15] alkylperoxides in conjuction with lanthanoid–binaphthol complexes,[16] tartrate-modified metal *tert*-butyl peroxides[17] and hydrogen peroxide in the presence of chiral platinum(II) complexes.[18] Good enantioselectivities were also achieved using non-catalytic systems, such as molecular oxygen in the presence of diethylzinc/chiral amino alcohols.[19] The use of chiral quaternary ammonium salts as phase-transfer catalyst for this transformation has also been investigated,[20] to date, results have been, however, disappointing.

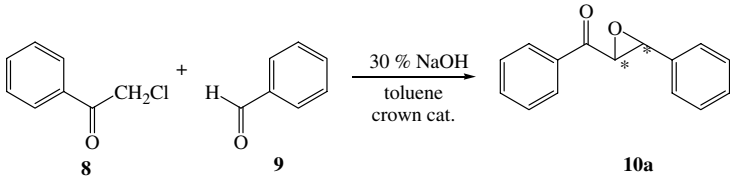
In our experiments, the epoxidation of chalcones **6** was carried out with *tert*-butyl hydroperoxide (TBHP, 2 equiv) in toluene, in a liquid–liquid two-phase system, employing 20% aq NaOH (3.5 equiv) as base and 7 mol % of lariat ethers having mannopyranoside unit **2a–d** at a temperature of between 0 and 4 °C (Scheme 4). The *trans*-epoxyketone **10** was obtained in all experiments. Table 3 summarizes the results obtained in the epoxidation of chalcones in the presence of chiral crown catalysts. It can be seen that the yields and the enantioselectivities are significantly affected by the N-substituent of the crown ring.

Table 3. Effect of chiral crown catalysts **2a–f** on the asymmetric epoxidation of chalcone **6a** by *t*-BuOOH, at 0–4 °C (Scheme 3)

Entry	Catalyst		Time (h)	Yield[a] (%)	ee (%)[b]
	Compound	R			
1	**2f**	H	9	25	9
2	**2a**	CH_2CH_2OH	3	50	72
3	**2b**	$(CH_2)_3OH$	8	47	82 (81)[c]
4	**2c**	$(CH_2)_4OH$	3	61	51
5	**2d**	$(CH_2)_3OCH_3$	6	67	31

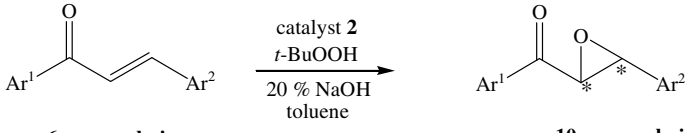
[a] Based on the isolation by preparative TLC.
[b] Determined by specific rotation.
[c] Determined by ^1H NMR spectroscopy.

The lowest enantiomer excess (9%) was observed using catalyst **2f** containing no substituent at the nitrogen (entry 1). The best result (82% ee) was obtained applying catalyst **2b** with γ-hydroxypropyl substituent on the nitrogen atom (entry 3). In the presence of azacrown **2a** with β-hydroxyethyl group, an ee of 72%, while using the δ-hydroxybutyl derivative **2c**, an ee of 51% was observed (entries 2 and 4). It can be seen that the length of the chain connecting the hydroxy group to the nitrogen



8 **9** **10a**

Scheme 3. Darzens condensation of phenacyl chloride and benzaldehyde.



6a, c-e, g, h, j, m **10a, c-e, g, h, j, m**

Scheme 4. Asymmetric epoxidation of chalcones, Ar^1 and Ar^2 listed in Table 4.

atom plays an important role in the asymmetric induction: the chain with three carbon atoms is the optimum length, as in **2b**. It is noteworthy that the methylation of the hydroxy group in **2b** results in a dramatic decrease in the enantioselectivity, as indicated by the ee value of 31% obtained in the presence of **2d**. It has been clearly demonstrated that the hydrophilic substituents improve the transport of the catalyst between the two phases (toluene and water), while the lipophilic $-(CH_2)_3OMe$ substituents have the opposite effect. The discrimination between the prochiral planes of the chalcone is the most efficient, when catalyst **2b** assists the formation of the transient complex.

It is worth noting that the earlier described glucopyranoside-based catalysts **1** promoted the formation of the (2*R*,3*S*) isomer of epoxyketone **10a** (with negative specific rotation).[21] In contrast, the lariat ethers incorporating a mannose unit **2** used as catalysts favoured the formation of the opposite antipodes—(2*S*,3*R*)—of the epoxyketones **10a**–**g** and **10j** with positive rotations.

Finally, we studied the asymmetric epoxidation of substituted chalcones **6c**–**e**, **6g** and **6m**, as well as their naphthyl- and pyridyl-analogues **6h** and **6j** using the *tert*-butylperoxide base in the presence of lariat ether **2b**, which produced the best results in the epoxidation of chalcone (see above). The experimental results are presented in Table 4. Due to the poor solubility of chalcones **6e**, **6m** and **6j**, the epoxidation of these starting materials had to be carried out at a somewhat elevated temperature (24 °C). The reference reaction, the epoxidation of chalcone **6a** was accomplished both at 0–4 °C and at 24 °C, yielding the product **10a** with enantiomeric excesses of 82% and 60%, respectively (entries 2 and 1). It can be seen that the substitution of the phenyl rings resulted in lower enantioselectivities, 50–54% at room temperature (entries 5 and 6) when compared to the values of 55–64% obtained at 0–4 °C (entries 3, 4 and 7). Modest enantioselectivities of 42% and 32% were obtained with the naphthyl- and the pyridyl-substituted model compounds **6h** and **6j** (entries 8 and 9). As can be seen, all the products, with the exception of **10h**, displayed positive specific rotations, suggesting the excess of the same enantiomer configuration in them. The impact of a naphthyl group as the Ar^2 unit in **10h** on the specific rotation will be clarified at a later stage.

The efficiency of the chiral crown ether in this oxidation can be explained by assuming a mechanism, in which the *t*-$BuOO^-$ anion accompanied by the crown-complexed sodium cation attacks the electron-deficient alkene. The efficiency of the azacrown ether in the asymmetric induction suggests that the substituent on the nitrogen atom assists the complexation of the cation of the salt in the third dimension. The complexing interaction may be optimal in case of a hydroxypropyl substituent. The role of the side arm of the lariat ethers in the asymmetric induction will be the subject of further investigation.

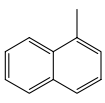
In conclusion, both in the Michael addition and in the epoxidation of chalcone, the asymmetric induction strongly depends on the nature of the aryl substituents. The optimum value was observed with the unsubstituted model compound. It is uncertain whether the steric or the electronic effects of the substituents have a larger impact on the asymmetric induction. The situation may be complicated by the possible retro-Michael addition reaction and by deracemization, both modifying the outcome of the asymmetric induction.

2.3. CD spectra of chalcone epoxides

As has been pointed out in our previous paper,[21] the CD spectra of *trans*-chalcone epoxide samples give a reliable indication of which enantiomer—whether it be (2*R*,3*S*) or (2*S*,3*R*)—they contain in excess. The identification of the dominant component is based on the 'octant rule', which predicts the sign of CD signal belonging to the $n \rightarrow \pi^*$ transition of C=O groups from the arrangement of the atoms around the carbonyl unit.[22]

The CD spectra of the chalcone epoxides obtained herein from substituted chalcones in the presence of the lariat ether **2b** are illustrated in Figure 1, where the spectra

Table 4. Epoxidation of substituted chalcones by *t*-BuOOH in the presence catalyst **2b** (Scheme 4)

Entry	Starting compd	Ar^1	Ar^2	Temperature (°C)	Time (h)	Yield[a] (%)	$[\alpha]_D$[b]	ee[c] (%)
1	**6a**	Ph	Ph	24	5	**10a**, 70	+128	60
2	**6a**	Ph	Ph	0–4	8	**10a**, 47	+171.4	82
3	**6c**	Ph	4-CH_3–Ph	0–4	7	**10c**, 37	+81.6	55
4	**6d**	4-CH_3–Ph	Ph	0–4	7	**10d**, 40	+120.4	61
5	**6e**	4-OCH_3–Ph	Ph	24	3	**10e**, 37	+142.9	54
6	**6m**	4-CH_3–Ph	4-CH_3–Ph	24	5	**10m**, 40	+122.8	50
7	**6g**	4-Cl–Ph	4-Cl–Ph	0–4	4	**10g**, 38	+124.8	64
8	**6h**	Ph		0–4	11	**10h**, 49	−46.5	42
9	**6j**	Ph		24	6	**10j**, 55	+81	32

[a] Based on product quantity isolated by preparative TLC.
[b] In CH_2Cl_2 at 22 °C.
[c] Determined by ^1H NMR spectroscopy in the presence of $Eu(hfc)_3$ as the chiral shift reagent.

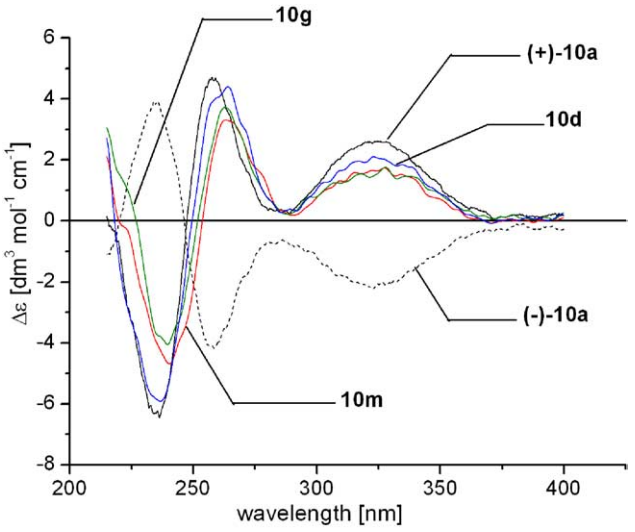


Figure 1. CD spectra of the enantiomers of unsubstituted *trans*-chalcone epoxide (+)-**10a** and (−)-**10a** and of the substituted derivatives **10d**, **10m** and **10g** [5×10^{-5} M solutions in acetonitrile, ee values (+)-**10a** 82%, (−)-**10a** 80%, **10d** 61%, **10m** 50%, **10g** 64%].

of **10a** [denoted as (+)-**10a**], **10d**,**10m** and **10g** are displayed. For comparison, the spectrum of the antipode of **10a** [denoted as (−)-**10a**] is also shown. The positive CD signals around 320 nm belong to the $n \rightarrow \pi^*$ transitions of the C=O units. The positive bands around 260 nm and the negative bands around 240 nm arise probably from exciton couplings between the $\pi \rightarrow \pi^*$ transitions of the phenyl and benzoyl moieties.

The steric structures of the two enantiomers of **10a** were determined by quantum chemical calculations: their molecular geometries were optimized with the aid of density functional theory (DFT) using the Becke 3-parameter–Lee–Yang–Parr (B3LYP)] functional[23] and the correlation consistent valence double-zeta (cc-pVDZ) basis set.[24] All calculations were carried out by the Gaussian 98 suite of quantum chemical programs.[25] The octant projection diagrams of the two isomers of **10a** were created then using the atomic coordinates obtained in the calculations.

The diagram obtained for (2*S*,3*R*)-**10a** is shown in Figure 2. The octant rule for such an arrangement predicts a positive Cotton-effect, since the chiral disturbance of the carbonyl group arises primarily from the atoms lying in the upper back left octant. Thus, the positive sign of the $n \rightarrow \pi^*$ band in the CD spectrum of **10a** is a clear evidence that the (2*S*,3*R*) isomer being dominant in the sample. This is in accordance with the result of Marsman and Wynberg, who proved by chemical correlation that the antipode (−)-**10a** has a (2*R*,3*S*)-configuration.[26] The spectra of the substituted chalcone epoxides **10c**, **10d**, **10e**, **10m**, **10g** also exhibit a positive $n \rightarrow \pi^*$ Cotton-effect. Providing that the substitutions in the 4-positions of the benzene rings do not lead to substantial conformational changes, one concludes that the (2*S*,3*R*)-isomers are in excess in all these products.

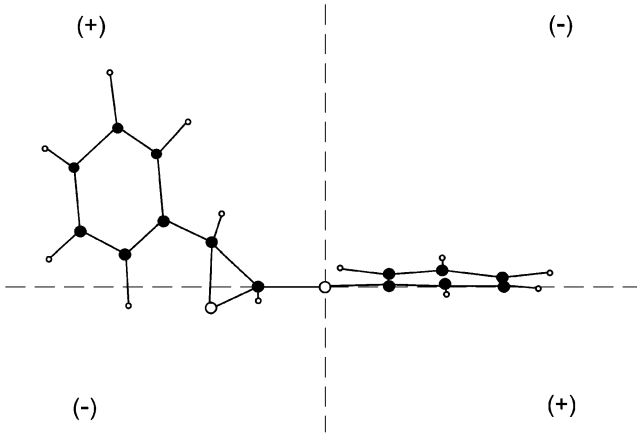


Figure 2. Octant projection diagram for the (2*S*,3*R*)-isomer of chalcone epoxide **10a**. The atomic positions were determined by quantum chemical geometry optimization.

Likewise the carbonyl bands, the exciton couplets also show a similar pattern in the spectra of the compounds studied. In general, these couplets are very sensitive to the conformation[27] and in the spectra of some other *trans*-chalcone epoxides this range exhibits completely different features.[28] Consequently, the appearance of similar positive couplets in the CD spectra of our chalcone epoxides confirms that these molecules have very similar conformations in solvent phase and the employment of the projection diagram of **10a** for the determination of the absolute configuration of the substituted derivatives was correct.

3. Experimental

3.1. General procedures

Melting points were determined using a Büchi 510 apparatus and are uncorrected. The specific rotation was measured with the help of a Perkin–Elmer 241 polarimeter at 22 °C, the IR spectra were recorded on a Perkin–Elmer 237 spectrophotometer. CD spectra were taken on a Jasco 810 spectropolarimeter. NMR spectra were obtained in $CDCl_3$ on a Brucker DRX-500 instrument. Mass spectra were obtained on a Varian MAT312 instrument. Elemental analyses were carried out using a Perkin–Elmer 240 automatic analyzer. Analytical and preparative thin layer chromatography was performed on silica gel plates (60 GF-254, Merck), while column chromatography was carried out using 70–230 mesh silica gel (Merck). The shift reagent was $Eu(hfc)_3$ (Aldrich Chem. Co.).

3.1.1. Methyl-4,6-*O*-benzylidene-2,3-bis[(2-chloroethoxy)ethyl]-α-D-mannopyranoside, 4. A solution of compound **3** (12.3 g, 43.8 mmol) and tetrabutylammonium hydrogensulfate (12.5 g, 36.9 mmol) in bis(2-chloroethyl)ether (93 mL, 650.3 mmol) was vigorously stirred with 50% NaOH solution (93 mL) at room temperature for 18 h. A mixture of CH_2Cl_2 (160 mL) and water (160 mL) was added to the reaction mixture. The organic layer was decanted and the aqueous phase washed with

CH_2Cl_2. The organic phases were combined and washed with water, dried over $MgSO_4$, filtered and concentrated under vacuum. After removal of the solvent and excess of the bis(2-chloroethyl)ether, the product was purified by column chromatography on silica gel using CH_2Cl_2–MeOH (100:1 → 100:7) as the eluant to give **4** (19.3 g, 89%) in the form of a gum; $[\alpha]_D^{20} = +22.9$ (*c* 1, $CHCl_3$); lit.[8] $[\alpha]_D^{20} = +23.2$ (*c* 1.13, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 3.36 (s, 3H, OCH_3), 3.52–3.88 (m, 19H, CH and CH_2 groups), 3.93–3.97 (tt, 1H, H-6), 4.05 (t, 1H, H-4), 4.21–4.24 (dd, 1H, H-6), 4.77 (s, 1H, anomer-H), 5.57 (s, 1H, PhCH), 7.33–7.46 (m, 5H, Ar).

3.1.2. Methyl-4,6-*O*-benzylidene-2,3-bis[(2-iodoethoxy)ethyl]-α-D-mannopyranoside, 5. A mixture of bis-chloro derivative **4** (18.0 g, 36.4 mmol) and dry NaI (21.8 g, 145.3 mmol) in dry acetone (360 mL) was stirred under reflux for 22 h. After cooling, the precipitate was filtered off and washed with acetone. The combined acetone solutions were evaporated under vacuum. The residue was dissolved in CH_2Cl_2 (200 mL), washed with water and dried over Na_2SO_4 to give **5** (22.6 g, 91.5%) as a syrup. $[\alpha]_D^{20} = +18.0$ (*c* 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 3.26 (t, 4H, ICH_2), 3.38 (s, 3H, OCH_3), 3.66–4.0 (m, 15H, CH and CH_2 groups), 3.95–3.97 (tt, 1H, H-6), 4.06 (t, $J = 9.6$ Hz, 1H, H-4), 4.23–4.26 (dd, 1H, H-6), 4.78 (s, 1H, anomer-H), 5.59 (s, 1H, PhCH), 7.47 (d, 2H, ArH), 7.36 (t, 3H, ArH). Anal. Calcd for $C_{22}H_{32}I_2O_8$: C, 38.96; H, 4.76; I, 37.42; Found: C, 39.05; H, 4.82; I, 37.48.

3.1.3. General method for preparation of crown ethers 2a–d. Dry Na_2CO_3 (3.84 g, 36.2 mmol) was suspended in a solution of the corresponding primary amine (4.60 mmol) and bis-iodo compound **5** (3.45 g, 4.60 mmol) in dry acetonitrile (100 mL) under argon. The stirred reaction mixture was refluxed for 24–48 h and monitored by TLC. After cooling, the precipitate was filtered off and washed with acetonitrile. The combined organic solutions were concentrated at reduced pressure. The residual oil was dissolved in $CHCl_3$, washed with water, dried over Na_2SO_4 and the solvent evaporated under vacuum. The corresponding monoaza-crown ether was isolated by column chromatography on silica gel using $CHCl_3$–MeOH (100:2 → 100:7) as eluant.

3.1.4. Methyl-4,6-*O*-benzylidene-2,3-dideoxy-α-D-mannopyranosido(2,3-h)-*N*-hydroxy-ethyl-1,4,7,10-tetraoxa-13-azacyclopentadecane, 2a. Yield: 44%; $[\alpha]_D^{20} = +16.0$ (*c* 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 2.78 (t, 6H, CH_2N), 3.37 (s, 3H, OCH_3), 3.55–3.98 (m, 19H, CH and CH_2 groups), 4.11 (t, 1H, $J = 9.6$ Hz, H-6), 4.24 (q, $J = 10.1$ Hz, 1H, H-6), 4.75 (s, 1H, anomer-H), 5.30 (s, 1H, PhCH), 7.48 (d, 2H, ArH), 7.35 (t, 3H, ArH); FAB-MS: (M^++H) 484, (M^++Na) 506. Anal. Calcd for $C_{24}H_{37}NO_9$: C, 59.61; H, 7.71; N, 2.90. Found: C, 59.70; H, 7.79; N, 2.97.

3.1.5. Methyl-4,6-*O*-benzylidene-2,3-dideoxy-α-D-mannopyranosido(2,3-h)-*N*-hydroxy-propyl-1,4,7,10-tetraoxa-13-azacyclopentadecane, 2b. Yield: 53%; $[\alpha]_D^{20} = +15.0$ (*c* 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 2.78 (t, 6H, CH_2N), 3.37 (s, 3H, OCH_3), 3.55–3.98 (m, 20H, CH and CH_2 groups), 4.11 (t, $J = 9.6$ Hz, 1H, H-6), 4.24 (q, $J = 10.1$ Hz, 1H, H-6), 4.75 (s, 1H, anomer-H), 5.30 (s, 1H, PhCH), 7.48 (d, 2H, ArH), 7.35 (t, 3H, ArH); FAB-MS: (M^++H) 498, (M^++Na) 520. Anal. Calcd for $C_{25}H_{39}NO_9$: C, 60.35; H, 7.90; N, 2.81. Found: C, 60.44; H, 7.68; N, 2.88.

3.1.6. Methyl-4,6-*O*-benzylidene-2,3-dideoxy-α-D-mannopyranosido(2,3-h)-*N*-hydroxybuty1-1,4,7,10-tetraoxa-13-azacyclopentadecane, 2c. Yield: 50%; $[\alpha]_D^{20} = +13.6$ (*c* 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 2.78 (t, 6H, CH_2N), 3.37 (s, 3H, OCH_3), 3.55–3.98 (m, 22H, CH and CH_2 groups), 4.11 (t, $J = 9.6$ Hz, 1H, H-6), 4.24 (q, $J = 10.1$ Hz, 1H, H-6), 4.75 (s, 1H, anomer-H), 5.30 (s, 1H, PhCH), 7.48 (d, 2H, ArH), 7.35 (t, 3H, ArH); FAB-MS: (M^++H) 512, (M^++Na) 534. Anal. Calcd for $C_{26}H_{41}NO_9$: C, 61.04; H, 8.08; N, 2.74. Found: C, 61.15; H, 8.12; N, 2.82.

3.1.7. Methyl-4,6-*O*-benzylidene-2,3-dideoxy-α-D-mannopyranosido(2,3-h)-*N*-methoxy-propyl-1,4,7,10-tetraoxa-13-azacyclopentadecane, 2d. Yield: 49%; $[\alpha]_D^{20} = +19.6$ (*c* 1, $CHCl_3$), ^{1}H NMR ($CDCl_3$) δ 1.69 (m, 2H, CH_2), 2.56 (t, 2H, CH_2N), 2.72 (t, 4H, CH_2N), 3.24 (s, 3H, OCH_3), 3.31 (s, 3H, OCH_3), 3.45–3.95 (m, 18H, CH and CH_2 groups), 4.02 (t, 1H, $J = 9.6$ Hz, H-4), 4.16 (q, 1H, $J = 10.1$ Hz, H-6), 4.67 (s, 1H, anomer-H), 5.52 (s, 1H, PhCH), 7.27 (t, 3H, ArH), 7.39 (d, 2H, ArH); FAB-MS: (M^++H) 512, (M^++Na) 534. Anal. Calcd for $C_{26}H_{341}NO_9$: C, 61.04; H, 8.08; N, 2.74. Found: C, 61.10; H, 8.11; N, 2.78.

3.1.8. Methyl-4,6-*O*-benzylidene-2,3-dideoxy-α-D-mannopyranosido(2,3-h)-*N*-tosyl-1,4,7,10-tetraoxa-13-azacyclopentadecane, 2e. A mixture of bis-chloro compound **4** (2.6 g, 5.0 mmol), toluene-*p*-sulfonamide (0.86 g, 5.0 mmol) and anhydrous K_2CO_3 (3.5 g, 25.3 mmol) was stirred and refluxed in dry DMF (150 mL) for 32 h. When the reaction was complete, the precipitate was filtered off and washed with chloroform. The combined filtrates and washings were evaporated under reduced pressure and the residue was dissolved in chloroform, washed with water and dried ($MgSO_4$). After removal of the solvent, column chromatography of the residue on silica gel using CH_2Cl_2–MeOH (100:2) as eluant gave the *N*-tosyl macrocycle **2e** as a yellow solid (1.6 g, 52%); mp 52–54 °C; $[\alpha]_D^{20} = +18.8$ (*c* 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 2.44 (s, 3H, $ArCH_3$), 3.20–3.26 (m, 4H, CH_2N), 3.40 (s, 3H, OCH_3), 3.51–4.00 (m, 16H, CH and CH_2 groups), 4.12 (t, 1H, $J = 9.6$ Hz, H-6), 4.26 (q, 1H, $J = 10.1$ Hz, H-6), 7.71 (d, 2H, tosyl-ArH), 4.74 (s, 1H, anomer-H), 5.62 (s, 1H, PhCH), 7.32 (t, 3H, ArH), 7.49 (d, 2H, tosyl-ArH), 7.38 (d, 2H, ArH); FAB-MS: (M^++H) 594, (M^++Na) 616. Anal. Calcd for $C_{29}H_{39}NO_{10}S$: C, 58.67; H, 6.62; N, 2.36. Found: C, 58.60; H, 6.61; N, 2.38.

3.1.9. Methyl-4,6-*O*-benzylidene-2,3-dideoxy-α-D-mannopyranosido(2,3-h)-1,4,7,10-tetraoxa-13-azacyclopentadecane, 2f. Compound **2e** (1.4 g, 2.27 mmol), anhydrous disodium hydogenphosphate (1.3 g, 9.10 mmol) and 4% sodium amalgam (11.0 g, 19.1 mmol) were placed

in dry methanol (20 mL). The mixture was heated at reflux under a nitrogen atmosphere for 20 h, while being stirred intensely. After cooling to room temperature, the resulting slurry was decanted into water (80 mL) and extracted with chloroform (4 × 30 mL). The organic layers were combined, dried over $MgSO_4$ and evaporated under reduced pressure to yield compound **2f** (0.89 g, 85%) as a yellow oil. $[\alpha]_D^{20} = +26.3$ (*c* 1, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 2.55 (m, 1H, NH), 2.76 (t, 2H, CH_2N), 2.85 (t, 2H, CH_2N), 3.39 (s, 3H, OCH_3), 3.55–4.08 (m, 16H, CH and CH_2 groups), 4.14 (t, 1H, $J = 9.6$ Hz, H-6), 4.25 (q, 1H, $J = 10.1$ Hz, H-6), 4.78 (s, 1H, anomer-H), 5.60 (s, 1H, PhCH), 7.35 (t, 3H, ArH), 7.47 (d, 2H, ArH); FAB-MS: (M^++H) 440, (M^++Na) 462. Anal. Calcd for $C_{22}H_{33}NO_8$: C, 60.12; H, 7.57; N, 3.19; Found: C, 60.19; H, 7.64; N, 3.12.

3.2. General procedure for the Michael addition of 2-nitropropane to chalcones

The corresponding azacrown ether (0.1 mmol) and sodium *tert*-butoxide (0.05 g, 0.5 mmol) was added to a solution of chalcone (1.44 mmol) and 2-nitropropane (0.3 mL, 3.36 mmol) in dry toluene (3 mL). The mixture was stirred under argon at room temperature. After a reaction time of 20–168 h, a new portion of toluene (7 mL) was added and the mixture stirred with water (10 mL). The organic phase was washed with water and dried Na_2SO_4. The crude product obtained after evaporating the solvent was purified by preparative TLC (silica gel, hexane–ethyl acetate; 10:1, eluant) to give pure adducts **7a**–**l**.

3.2.1. 3-(*S*)-4-Methyl-4-nitro-1,3-diphenylpentan-1-one, 7a. Yield: 37%, mp: 140–146 °C; $[\alpha]_D^{20} = -74.8$ (*c* 1, CH_2Cl_2), 92% ee; ^1H NMR ($CDCl_3$) δ 1.54 (s, 3H), 1.63 (s, 3H), 3.70 (dd, 1H; $J_{gem} = 17.6$, 3.1 Hz); 4.09 (dd, 1H, $J_{gem} = 17.6$, 10.0 Hz), 4.15 (dd, 1H), 7.18–7.32 (m, 5H, CHPhH), 7.42 (t, 2H, COPhH-*m*), 7.53 (t, 1H, COPhH-*p*), 7.85 (d, 2H, COPhH-*o*); HRMS calcd for $C_{18}H_{19}NO_3$ (M^+) 297.1365, found 297.1361.

3.2.2. 4-Methyl-4-nitro-3-(4-nitrophenyl)-1-phenylpentan-1-one, 7b. Yield: 28%; mp: 92–96 °C; $[\alpha]_D^{20} = -8.5$ (*c* 1, CH_2Cl_2), 21% ee. IR (KBr), *v* 2929, 1680, 1532, 1449, 1370, 1335, 1214, 820; 746, 680 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.60 (s, 3H), 1.65 (s, 3H), 3.40 (dd, $J_{gem} = 17.7$, 3.2 Hz, 1H), 3.71 (dd, $J_{gem} = 17.7$, 10.6 Hz, 1H), 4.25 (dd, 1H), 7.43 (d, 2H, COPhH-*m*), 7.46 (d, 2H, CHPhH-*o*), 7.58 (t, 1H, COPhH-*p*); 7.87 (d, 2H, COPhH-*o*), 8.16 (d, 2H, CHPhH-*m*); HRMS calcd for $C_{18}H_{18}N_2O_5$ (M^+) 342.1216, found 342.1212.

3.2.3. 4-Methyl-4-nitro-3-(4-tolyl)-1-phenylpentan-1-one, 7c. Yield: 38%; mp 109–110 °C; $[\alpha]_D^{20} = -33.1$ (*c* 1, CH_2Cl_2); 30% ee. IR (KBr), *v* 2921, 1686, 1532, 1449, 1372, 1334, 1216; 814, 748, 686 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.55 (s, 3H), 1.63 (s, 3H), 2.29 (s, 3H), 3.25 (dd, $J_{gem} = 17.3$, 3.3 Hz, 1H), 3.66 (dd, $J_{gem} = 17.3$, 10.6 Hz, 1H), 4.12 (dd, 1H), 7.09 (d, 2H, CHPhH-*m*), 7.13 (d, 2H, CHPhH-*o*), 7.43 (t, 2H, COPhH-*m*), 7.55 (t, 1H, COPhH-*p*), 7.87 (d, 2H, COPhH-*o*); HRMS calcd for $C_{19}H_{21}NO_3$ (M^+) 311.1521, found 311.1526.

3.2.4. 1-(4-Tolyl)-4-methyl-4-nitro-3-phenylpentan-1-one, 7d. Yield: 42%; mp 111–115 °C; $[\alpha]_D^{20} = -48.2$ (*c* 1, CH_2Cl_2); 44% ee. IR (KBr), *v* 2999, 1680, 1606, 1537, 1453, 1397, 1346, 1232, 818, 723 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.55 (s, 3H), 1.64 (s, 3H), 2.40 (s, 3H), 3.25 (dd, $J_{gem} = 17.2$, 3.7 Hz, 1H), 3.65 (dd, $J_{gem} = 17.2$, 10.4 Hz, 1H), 4.15 (dd, 1H), 7.22–7.25 (m, 5H, CHPhH), 7.28 (d, 2H, COPhH-*m*), 7.78 (d, 2H, COPhH-*o*); HRMS: calcd for $C_{19}H_{21}NO_3$ (M^+): 311.1521, found 311.1529.

3.2.5. 1-(4-Methoxyphenyl)-4-methyl-4-nitro-3-phenylpentan-1-one, 7e. Yield: 27%; mp 102–104 °C; $[\alpha]_D^{20} = -46.3$ (*c* 1, CH_2Cl_2); 49% ee. IR (KBr), *v* 2998, 1662, 1601, 1535, 1454, 1344, 1267, 1245, 1175, 1027, 833, 762, 705 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.55 (s, 3H), 1.63 (s, 3H), 3.23 (dd, $J_{gem} = 16.8$, 3.2 Hz, 1H), 3.63 (dd, $J_{gem} = 16.8$, 10.4 Hz, 1H), 3.85 (s, 3H), 4.15 (dd, 1H), 6.90 (d, 2H, COPhH-*m*), 7.22–7.29 (m, 5H, CHPhH), 7.86 (d, 2H, COPhH-*o*); HRMS calcd for $C_{19}H_{21}NO_4$ (M^+): 327.1471, found 327.1478.

3.2.6. 3-(*S*)-1-(4-Chlorophenyl)-4-methyl-4-nitro-3-phenylpentan-1-one, 7f. Yield: 48% (colourless crystals); mp 112–117 °C; $[\alpha]_D^{20} = -51.7$ (*c* 1, CH_2Cl_2), 48% ee, (*S*); IR (KBr), *v* 2997, 1689, 1589, 1529, 1452, 1344, 1231, 1094, 797, 703 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.46 (s, 3H), 1.55 (s, 3H), 3.16 (dd, $J_{gem} = 17.3$, 3.1 Hz, 1H), 3.55 (dd, $J_{gem} = 17.3$, 10.4 Hz, 1H), 4.04 (dd, 1H), 7.13–7.21 (m, 5H, CHPhH), 7.32 (d, 2H, COPhH-*o*), 7.72 (d, 2H, COPhH-*m*); HRMS calcd for $C_{18}H_{18}ClNO_3$ (M^+): 331.0975, found 331.0972.

3.2.7. 3-(*S*)-4-Methyl-4-nitro-3-(4-chlorophenyl)-1-(4-chlorophenyl)pentan-1-one, 7g. Yield: 54%; mp 109– 110 °C; $[\alpha]_D^{20} = -51.6$ (*c* 1, CH_2Cl_2); 40% ee; IR (KBr), *v* 2996, 1682, 1590, 1533, 1398, 1345, 1231, 1095, 821, 770 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.55 (s, 3H), 1.61 (s, 3H), 3.25 (dd, $J_{gem} = 17.2$, 3.1 Hz, 1H), 3.58 (dd, $J_{gem} = 17.2$, 10.5 Hz, 1H), 4.09 (dd, 1H), 7.16 (d, 2H, CHPhH-*m*), 7.27 (d, 2H, CHPhH-*o*), 7.41 (d, 2H, COPhH-*m*), 7.80 (d, 2H, COPhH-*o*); HRMS calcd for $C_{18}H_{17}Cl_2NO_3$ (M^+): 365.0586, found 365.0590.

3.2.8. 4-Methyl-3-naphthalen-2-yl-4-nitro-1-phenylpentan-1-one, 7h. Yield: 28%; $[\alpha]_D^{20} = -67.5$ (*c* 1, CH_2Cl_2), 20% ee. IR (KBr), *v* 3000, 1689, 1590, 1531, 1454, 1341, 1238, 765, 698 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.47 (s, 3H), 1.66 (s, 3H), 3.45 (dd, $J_{gem} = 17.4$, 3.2 Hz, 1H), 3.86 (dd, $J_{gem} = 17.4$, 10.2 Hz, 1H), 5.28 (dd, 1H), 7.33–7.38 (m, 5H, naphthalene-CH), 7.50 (t, 2H, COPhH-*m*), 7.61 (t, 1H, COPhH-*p*), 7.76 (d, 1H, naphthalene-CH), 7.82 (d, 2H, COPhH-*o*), 8.47 (d, 1H, naphthalene-CH); HRMS calcd for $C_{22}H_{21}NO_3$ (M^+): 347.1521, found 347.1530.

3.2.9. 3-Benzo[1,3]dioxol-5-y1-4-methyl-4-nitro-1-phenylpentan-1-one, 7i. Yield: 54%; mp 92 °C; $[\alpha]_D^{20} = -35.4$ (*c* 1, CH_2Cl_2), 47% ee. IR (KBr), *v* 3441, 1687, 1597, 1580, 1534, 1489, 1448, 1345, 1253, 1039, 748, 689 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.47 (s, 3H), 1.55 (s, 3H), 3.14 (dd, $J_{gem} = 17.1$, 3:2 Hz, 1H), 3.53 (dd, $J_{gem} = 17.1$, 10.6 Hz, 1H), 3.98 (dd, 1H), 5.83 (s, 2H),

6.58–6.63 (m, 3H, CHPhH), 7.35 (t, 2H, CO PhH-*m*), 7.47 (t, 114, COPhH-*p*), 7.79 (d, 2H, COPhH-*o*); HRMS calcd for $C_{19}H_{19}NO_5$ (M^+): 341.1263, found 341.1268.

3.2.10. 4-Methyl-4-nitro-1-phenyl-3-pyridin-2-yl-pentan-1-one, 7j. Yield: 72%; $[\alpha]_D^{20} = -84.8$ (*c* 1, CH_2Cl_2), 57% ee. IR (KBr), *v* 3448, 1680, 1594, 1535, 1447, 1400, 1374, 1341, 1238, 1001, 846, 760, 694 cm^{-1}; ^1H NMR ($CDCl_3$) 5 1.55 (s, 3H), 1.77 (s, 3H), 3.11 (dd, J_{gem} = 17.3, 2.0 Hz, 1H), 4.24 (dd, J_{gem} = 17.3, 10.7 Hz, 1H), 4.35 (dd, 1H), 7.15 (t, 1H, pyridine-CH), 7.38 (d, 1H, pyridine-CH), 7.44 (t, 2H, COPhH-*m*), 7.55 (t, 1H, pyridine-CH), 7.64 (t, 1H, COPhH-*p*), 7.91 (d, 2H, COPhH-*o*), 8.48 (d, 1H, pyridine-CH); HRMS calcd for $C_{17}H_{18}N_2O$ (M^+): 298.1317, found 298.1322.

3.2.11. (*R*)-3-Furan-2-yl-4-methyl-4-nitro-1-phenylpentan-1-one, 7k. Yield: 48%; mp 79–80 °C; $[\alpha]_D^{20} = -33.3$ (*c* 1, CH_2Cl_2), 53% ee. IR (KBr), *v* 3447, 1681, 1596, 1539, 1450, 1397, 1380, 1346, 1231, 1149, 1016, 766, 750, 691 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.57 (s, 3H), 1.67 (s, 3H), 3.05 (dd, J_{gem} = 17.0, 2.9 Hz, 1H), 3.69 (dd, J_{gem} = 17.0, 10.8 Hz, 1H), 4.34 (dd, 1H), 6.19 (d, 1H, furane-CH), 6.27 (t, 1H, furane-CH), 7.29 (d, 1H, furane-CH),7.44 (t, 2H, COPhH-*m*), 7.55 (t, 1H, COPhH-*p*), 7.89 (d, 2H, COPhH-*o*); HRMS calcd for$C_{16}H_{17}NO_4$ (M^+): 287.1158, found 287.1162.

3.2.12. 4-Methyl-4-nitro-1-phenyl-3-thiophen-2-yl-pentan-1-one, 7l. Yield: 36%; mp 107–109 °C; $[\alpha]_D^{20} = -56.7$ (*c* 1, CH_2Cl_2), 51% ee. IR (KBr), *v* 3447, 1680,1596, 1528; 1447, 1399, 1380, 1348, 1233, 848, 743, 710, 684 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.60 (s, 3H), 1.71 (s, 3H), 3.18 (dd, J_{gem} = 17.1, 2.8 Hz, 1H), 3.63 (dd, J_{gem} = 17.1, 10.6 Hz, 1H), 4.54 (dd, 1H), 6.92 (m, 2H, thiophene-CH), 7.16 (d, 1H, thiophene-CH), 7.44 (t, 2H, COPhH-*m*), 7.55 (t, 1H, COPhH-*p*), 7.87 (d, 2H, COPhH-*o*); HRMS calcd for $C_{16}H_{17}NO_3S$ (M^+): 303.0929, found 303.0930.

3.2.13. Catalytic hydrogenation of compound 7f and 7g. A solution of chloro-compound **7f** or **7g** (0.3 g, 0.9 mmol), sodium acetate (0.1 g, 1.22 mmol) and 10% Pd/C (100 mg) in methanol (5 mL) was stirred under an atmosphere of H_2 (1 atm), at room temperature for 14 h. The reaction mixture was filtered and concentrated. The residue was purified by crystallization to give **7a** as a solid (0.24 g, 80%); $[\alpha]_D^{20} = -45.2$ (*c* 1, CH_2Cl_2); 56% ee; mp 146–148 °C {$[\alpha]_D^{20} = -80.8$ (*c* 1, CH_2Cl_2) for pure (−)-(*S*) enantiomer}.[4] The data are identical with those of **7a**.

3.3. General procedure for Darzens condensation

A toluene solution (3 mL) of 1.3 mmol of phenacyl chloride was treated with 1.9 mmol of benzaldehyde and 0.1 mmol of catalyst in 1.0 mL of 30% NaOH solution. The mixture was stirred under an argon atmosphere. After completing the reaction, 7 mL of toluene was added, the organic phase washed with water, dried over $MgSO_4$ and the solvent evaporated. Product **10a** was isolated by preparative TLC using CH_2Cl_2 as eluant. Yield: 56%, mp: 64–66 °C; $[\alpha]_D^{20} = +97$ (*c* l, CH_2Cl_2), 45% ee for (2*S*,3*R*)-enantiomer. ^1H NMR ($CDCl_3$) δ 4.09 (d, J = 1.9 Hz, 1H, PhCH), 4.30 (d, J = 1.9 Hz, 1H, COCH), 7.38–7.44 (m, 5H, Ph), 7.50 (t, 2H, COPhH-*m*), 7.63 (t, 1H, COPhH-*p*), 8.02 (d, 2H, COPhH-*o*); HRMS calcd for $C_{15}H_{12}O_2$ (M^+): 224.0837, found 224.0830.

3.4. General procedure for the epoxidation of chalcones

A solution of chalcone (1.44 mmol) and the appropriate catalyst (0.1 mmol) in toluene (3 mL) containing sodium hydroxide (1 mL 20% aq) was treated with 50% *tert*-butyl hydroperoxide in decane (0.5 mL, 2.88 mmol) and the mixture stirred at 0–4 °C. After a reaction time of 1–10 h, a new portion of toluene (7 mL) was added and the mixture was stirred with water (10 mL). The organic phase was washed with 10% aq hydrochloridic acid (10 mL) twice and then with (10 mL) water. The organic phase was dried (Na_2CO_3). The crude product obtained after evaporating the solvent was purified by preparative TLC (silica gel, hexane–ethylacetate, 10:1, eluant) to give adduct **10a**–**j** in a pure form.

3.4.1. (2*S*,3*R*)-2,3-Epoxy-1,3-diphenyl-3-propan-1-one, 10a. Yield: 47%, mp: 65–67 °C; $[\alpha]_D^{20} = +171.4$ (*c* 1, CH_2Cl_2), 82% ee; ^1H NMR spectra see before.

3.4.2. (2*S*,3*R*)-2,3-Epoxy-1-phenyl-3-(4-tolyl)-propan-1-one, l0c. Yield: 37% (white crystals); mp 76 °C (lit.[29] 77–78 °C); $[\alpha]_D^{20} = +81.6$ (*c* 1, CH_2Cl_2); 55% ee. ^1H NMR ($CDCl_3$) δ 2.37. (s, 3H, CH_3), 4.04 (d, J = 1.3 Hz, 1H), 4.28 (d, J = 1.6 Hz, 1H), 7.21 (d, 2H, CHPhH-*o*), 7.26 (d, 2H, CHPhH-*m*), 7.48 (t, 2H, COPhH-*m*), 7.61 (t, 1H, COPhH-*p*), 8.00 (d, 2H, COPhH-*o*); HRMS calcd for $C_{16}H_{14}O_2$ (M^+): 238.0998, found 238.0994.

3.4.3. (2*S*,3*R*)-2,3-Epoxy-1-(4-tolyl)-3-phenylpropan-1-one, l0d. Yield: 40% (white crystals); mp 58–60 °C (lit.[30] 59–60 °C); $[\alpha]_D^{20} = +120.4$ (*c* 1, CH_2Cl_2); 61% ee; ^1H NMR ($CDCl_3$) δ 2.42 (s, 3H, CH_3), 4.07 (d, J = 1.2 Hz, 1H), 4.27 (d, J = 1.7 Hz, 1H), 7.28 (d, 2H, COPhH-*m*), 7.39 (m, 5H, CHPhH), 7.91 (d, 2H, COPhH-*o*); HRMS calcd for $C_{16}H_{14}O_2$ (M^+): 238.0998, found 238.0995.

3.4.4. (2*S*,3*R*)-2,3-Epoxy-1-(4-methoxyphenyl)-3-phenyl-propan-1-one, l0e. Yield: 37% (white crystals); mp 69–73 °C; $[\alpha]_D^{20} = +142.9$ (*c* 1, CH_2Cl_2); 54% ee; ^1H NMR ($CDCl_3$) δ 3.87 (s, 3H, CH_3), 4.07 (d, J = 1.3 Hz, 1H), 4.25 (d, J = 1.7 Hz, 1H), 6.95 (d,2H, COPhH-*m*), 7.39 (m, 5H, CHPhH), 8.01 (d, 2H, COPhH-*o*); HRMS calcd for $C_{16}H_{14}O_3$ (M^+): 254.0943, found 254.0948.

3.4.5. (2*S*,3*R*)-2,3-Epoxy-1-(4-tolyl)-3-(4-tolyl)-propan-1-one, 10m. Yield: 40% (white crystals); mp 97–100 °C; $[\alpha]_D^{20} = +122.8$ (*c* 1, CH_2Cl_2); 50% ee; ^1H NMR ($CDCl_3$) δ ppm: 2.37 (s, 3H, CH_3), 2.42 (s, 3H, CH_3), 4.03 (d, J = 1.4 Hz, 1H), 4.27 (d, J = 1.8 Hz, 1H), 7.20 (d, 2H, CHPhH-*o*), 7.26 (m, 4H, PhCH), 7.91 (d, 2H, COPhH-*o*); HRMS calcd for $C_{17}H_{16}O_2$ (M^+) 252.1150, found 252.1145.

3.4.6. (2*S*,3*R*)-2,3-Epoxy-1-(4-chlorophenyl)-3-(4-chlorophenyl)-propan-1-one, l0g. Yield: 38% (yellow crystals); mp 112–118 °C; $[\alpha]_D^{20} = +124.6$ (*c* 1, CH_2Cl_2); 64% ee; ^1H NMR ($CDCl_3$) δ ppm: 4.09 (d, $J = 1.3$ Hz, 1H), 4.24 (d, $J = 1.6$ Hz, 1H), 7.40 (d, 2H, CHPhH-*o*), 7.44 (d, 2H, CHPhH-*m*), 7.47 (d, 2H, COPhH-*o*), 7.98 (d, 2H, COPhH-*m*); HRMS calcd for $C_{15}H_{10}Cl_2O_2$ (M^+): 292.0058, found 292.0057.

3.4.7. (2*S*,3*R*)-2,3-Epoxy-1-phenyl-3-(1-naphthyl)-propan-1-one, l0h. Yield: 49%; $[\alpha]_D^{20} = -46.5$ (*c* 1, CH_2Cl_2), 42% ee; ^1H NMR ($CDCl_3$) δ 4.24 (d, $J = 0.6$ Hz, 1H), 4.66 (d, $J = 0.5$ Hz, 1H), 7.41–7.48 (m, 5H, naphthalene-CH), 7.57 (t, 2H, COPhH-*m*), 7.81 (d, 1H, naphthalene-CH), 7.86 (t, 1H, COPhH-*p*), 7.93 (d, 1H, naphthalene-CH), 8.01 (d, 2H, COPhH-*o*); HRMS calcd for $C_{19}H_{14}O_2$ (M^+): 274.0994, found 274.0998.

3.4.8. (2*S*,3*R*)-2,3-Epoxy-1-phenyl-3-(1-pyridyl)-propan-1-one, l0j. Yield: 55%; $[\alpha]_D^{20} = +81.0$ (*c* 1, CH_2Cl_2), 32% ee. ^1H NMR ($CDCl_3$) δ 4.23 (d, $J = 0.2$ Hz, 1H), 4.60 (d, $J = 0{,}4$ Hz, 1H), 7.32 (t, 1H, pyridine-CH), 7.42 (d, 1H, pyridine-CH), 7.51 (t, 2H, COPhH-*m*), 7.63 (t, 1H, pyridine-CH), 7.77 (t, I H, COPhH-*p*), 8.06 (d, 2H, COPhH-*o*), 8.65 (d, 1H, pyridine-CH); HRMS calcd for $C_{14}H_{11}NO_2$ (M^+): 225.0790, found 225.0794.

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