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Asymmetric C–C bond forming reactions with chiral crown catalysts derived from D-glucose and D-galactose

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Abstract

New chiral monoaza-15-crown-5 derivatives anellated to methyl-4,6-*O*-benzylidene-α-D-glucopyranoside **2a**, **2e**, **2g**–**i** and to methyl-4,6-*O*-benzylidene-α-D-galactopyranoside **3a**, **3e**, **3i** have been synthesized. These crown ethers showed significant asymmetric induction as phase transfer catalysts in the Michael addition of 2-nitropropane to chalcone (87% ee), in the Darzens condensation of phenacyl chloride with benzaldehyde (71% ee) and in the self-condensation of phenacyl chloride (64% ee) to give **14**. The absolute configurations of (−)-(2*R*,3*S*)-epoxy-3-(4-chlorophenyl)-1-phenyl-1-propanone **12** and (−)-4-chloro-(2*R*,3*S*)-epoxy-1,3-diphenyl-1-butanone **14** have also been determined by X-ray diffraction.

1. Introduction

Phase-transfer catalysis has been recognized as a practical methodology for organic synthesis due to its operational simplicity, mild reaction conditions, safety considerations, and environmental concerns. In addition, the development of novel phase-transfer catalyzed asymmetric reactions is of considerable industrial interest. One of the most up-to-date and interesting techniques of catalytic asymmetric synthesis is a phase-transfer reaction in which the enantioselectivity is generated by a chiral crown-ether catalyst.[1] A special group of optically active crown ethers are compounds whose carbohydrate moieties function as carriers of chirality. In the past two decades numerous macrocycles built up of one or more monosaccaride units have been synthesized.[2] Cheap natural sugars are attractive starting materials for organic syntheses. However, so far, only a limited number of asymmetric reactions have been demonstrated in which a sugar-based crown-ether catalyst produced a good enantiomeric excess.[1]

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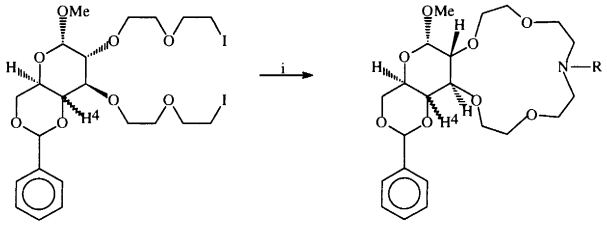
A synthesis of a new monoaza-15-crown-5 type macrocycle, containing D-glucopyranoside- and D-galactopyranoside units, respectively, has been recently reported.[3] Until now we have carefully examined two important reaction types, the Michael addition to an electrophilic double bond and the Darzens condensation, in which these crown ethers proved to be effective catalysts.[4] It was shown that the flexibility of the chiral macrocycle, the type of carbohydrate building blocks, the type of the substituents in the carbohydrate unit and at the nitrogen atom of the macrocycle play the most important roles in the generation of asymmetric induction. Furthermore, the so-called lariat ethers, in which the *N*-substituent contains an electron donating heteroatom (O, P) in the proper place, have also been studied.[5]

In the present paper, the synthesis of the crown ethers, the study of relationships between the catalysts' structure and their effect in the above mentioned reactions is disclosed with a more detailed experimental. Also included are experiments on the self-condensation of the phenacyl chloride reagent giving Darzens type products in a diastereoselective and enantioselective process.

2. Results and discussion

2.1. Synthesis

The new 15-crown-5 type compounds incorporating methyl-4,6-*O*-benzylidene-α-D-glucopyranoside and galactopyranoside as well as a nitrogen atom in the macrocycle, **2** and **3**, respectively, were synthesized using the same route as described by us previously.[3] The glucopyranoside based bis-iodo compound **1a** was cyclized with various primary amines, such as *n*-butylamine, 2-phenylethylamine, 3-hydroxypropylamine, 4-hydroxybutylamine and 2-methoxyethylamine (Scheme 1). The method requires dry sodium carbonate in acetonitrile solvent (reflux, 24–48 h). In dilute solutions (1–3%) polycondensation side reactions are suppressed and the desired intramolecular cyclization reaction takes place preferentially. After the usual work-up procedure and chromatographic purification, macrocycles **2a**–**i** were obtained in 44–64% yields. By the same method **3a**, **3e** monoaza-crown ethers and **3i** lariat ether were synthesized in 49–75% yields, starting from galactose-based bis-iodo compound **1b** and the corresponding primary amines. The structures of the ligands were confirmed via the analysis of their respective ^{1}H NMR, ^{13}C NMR spectra and by CIMS and FABMS. The $[M+H]^+$ fragment was present in all cases in the CIMS and FABMS spectra, the most intense in the CIMS spectra being *m/z* 452 fragment characteristic of the [crown-*N*-CH_2]$^+$ ion (see Experimental).



1a $H^4 = \beta$ **2** $H^4 = \beta$

1b $H^4 = \alpha$ **3** $H^4 = \alpha$

Scheme 1. Cyclization with amines. Glucose-based **2** and galactose-based crown ether **3**. Reagents and conditions: (i) CH_3CN, reflux, 28–36 h, RNH_2, R=butyl **2a**, **3a**, 2-phenylethyl **2e**, **3e**, 3-hydroxypropyl **2g**, 4-hydroxybutyl **2h**, 2-methoxyethyl **2i**, **3i**

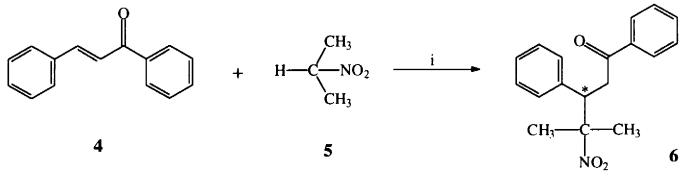
2.2. Asymmetric induction in Michael additions

The Michael addition of carbon nucleophiles to conjugated enones is one of the most powerful methods for carbon–carbon bond formation. Due to its relevance in the synthesis of biologically active compounds, much effort has been centered on carrying out this reaction in a stereoselective way.[6a] 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.[6b,c] To the best of our knowledge, only one reaction is known in which significant asymmetric induction has been achieved with sugar-based crown-ether catalysts, and that is the Michael addition of methylphenylacetate to methylacrylate.[7] Now we describe our results with another Michael reaction, in which the new catalysts are also effective: the Michael addition of 2-nitropropane **5** to the chalcone **4** that was performed with 60–82% enantiomeric excess in a solid–liquid phase-transfer system[4] (Scheme 2). The addition was carried out in dry toluene, in the presence of a chiral catalyst (5 mol%) and solid sodium tertiary butoxide as base (35 mol%) at room temperature. After the usual work-up procedure, the adduct **6** was isolated by preparative TLC; the enantiomeric excess (ee%), was monitored by measuring the optical rotation of the product **6** and comparing the specifications with literature data for the preferred pure enantiomer and by ^{1}H NMR spectroscopy using (+)-Eu(hfc)$_3$ as a chiral shift reagent. For comparison purposes, our earlier results[4a,b] with **2b**–**d** and **2f** are also incorporated in Table 1. The results show that the type of the monosaccharide and the substituent at the nitrogen atom of the catalyst have the most significant influence on both the chemical yield and the enantiomeric excess.

Table 1
Addition of 2-nitropropane to chalcone catalyzed by chiral crown ethers[a]

Entry	Catalyst	R	Time (h)	Yield (%)[b]	ee (%)[c]
1	**2a**	$CH_3(CH_2)_3$	40	41	58
2[e]	**2b**	C_6H_{11}	22	42	47
3[e]	**2c**	C_6H_5	30	21	10
4[e]	**2d**	$C_6H_5CH_2$	22	39	46
5	**2e**	$C_6H_5CH_2CH_2$	36	44	61
6[e]	**2f**	$HOCH_2CH_2$	20	51	62 (63[d])
7	**2g**	$HO(CH_2)_3$	28	53	85
8	**2h**	$HO(CH_2)_4$	48	52	85
9	**2i**	$CH_3OCH_2CH_2$	40	45	87 (88[d])
10	**3a**	$CH_3(CH_2)_3$	41	34	47
11	**3e**	$C_6H_5CH_2CH_2$	40	41	49
12	**3i**	$CH_3OCH_2CH_2$	38	34	52

[a] (+)-(*S*) enantiomer is always in excess; [b] Based on substance isolated by preparative TLC; [c] Determined by optical rotation; [d] Determined by ^{1}H NMR spectroscopy; [e] Lit. 4a, b



Scheme 2. Michael addition of 2-nitropropane to chalcone. Reagents and conditions: (i) catalyst **2** or **3**, NaOBu^t, toluene, 20°C

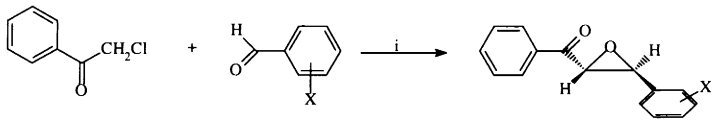
Among the glucopyranose derivatives **2a**–**i** it was the crown **2c** (phenyl group at the nitrogen) which gave the worst result (21% chemical yield, 10% ee). The catalytic effect was better with *N*-cyclohexyl and *N*-benzyl derivatives (**2b**, 47% ee; **2d**, 46% ee), and further increased with *N*-butyl (**2a**, 58% ee), and *N*-phenylethyl derivatives (**2e**, 61% ee). When the side arm cooperation in the complexation could operate (lariat ethers) again an increase in the ee value was detected: in the case of the *N*-2-hydroxyethyl derivative **2f** it was 62%, with the *N*-3-hydroxypropyl crown **2g** the ee value was 85%. However, further increase in the chain length did not increase the ee% value (**2h** has 85% ee). Interestingly we observed that the **2i** methylether derivative induced a higher enantioselectivity (87% ee) than its analogue containing a free hydroxyl group (61% ee). It can be seen that the chain length of the substituents is of crucial importance. In the case of the galactopyranose derivatives **3a**, **3e**, and **3i** the ee% observed were lower than those for the corresponding **2a**, **2e**, and **2i** (Table 1) in spite of the fact that the stability constants of the galactose containing crown ethers with sodium ion were found to be higher than those for the glucose derivatives.[3]

2.3. Darzens condensation

The Darzens reaction, which allows the generation of new stereocenters with complete diastereocontrol, is one of the most powerful methodologies for the synthesis of α,β-epoxy carbonyl and related compounds, and therefore has been recognized as one of most significant C–C bond forming processes in synthetic organic chemistry. Although many trials have been performed aimed at developing an asymmetric variant of the section in recent decades, many of them require a stoichiometric amount of a chiral source[8] and only a few examples which proceed catalytically are known.[9] The special attention paid to the Darzens reactions is justified by their pharmaceutical significance, e.g.: diltiazem is a widely prescribed cardiovascular drug.[10]

As already described in our preliminary report,[4a] the previously discussed chiral crown ethers proved to be effective asymmetric catalysts in the condensation of phenacyl chloride **7** with benzaldehyde **8a** (Scheme 3). This reaction was studied by many researchers, and in the presence of one of the most frequently used chiral phase-transfer catalysts benzyl quininium chloride 8% ee was achieved,[9a] while *N*-(4-trifluoromethylbenzyl)cinchoninium bromide resulted in 42% ee.[9d]

We performed the above reaction in both a liquid–liquid (LL) and solid–liquid (SL) system. Since our catalysts were more effective in LL phase-transfer conditions, this technique was studied thoroughly. Solvent, base, reaction time and temperature were varied until optimal reaction conditions were established. Reagents and the catalyst (5 mol%) were dissolved in toluene and reaction was initiated by adding 30% sodium hydroxide (volume ratio: 3:1, reaction time: 1–4 h). Following the usual work-up procedure, the pure epoxy ketone was separated by preparative TLC. The diastereomeric ratio of the product was determined by ^{1}H NMR spectroscopy, enantiomeric excess (ee%) by rotatory power measurements or by ^{1}H NMR in the presence of a chiral shift reagent. In each case the *trans*-epoxy ketone **9** was formed (de >98%) and its levorotatory enantiomer was found to be in excess. This corresponds to an absolute configuration of 2*R*,3*S*.[11] The most important results and reaction conditions are shown in Table 2. From



7 **8a** X = H **9** X = H

8b X = o-NO_2 **10** X = o-NO_2

8c X = p-NO_2 **11** X = p-NO_2

8d X = p-Cl **12** X = p-Cl

8e X = p-OMe **13** X = p-OMe

Scheme 3. Darzens condensation of phenacylchloride with benzaldehyde. Reagents and conditions: (i) crown-ether catalyst, 30% NaOH, toluene

Table 2
Asymmetric Darzens condensation of phenacyl chloride with benzaldehyde in the presence of chiral crown ethers[a]

Entry	Catalyst	Temperature (°C)	Time (h)	Yield (%)[b]	ee (%)[c]
1	**2a**	22	4	74	21
2	**2c**	22	1	43	4
3	**2d**	22	1	67	13
4	**2e**	22	6	54	31
5	**2f**	22	1	90	42 (41[d])
6	**2f**	-5	2	88	59 (59[d])
7	**2f**	-20	4	76	64 (65[d])
8	**2g**	22	1	74	62
9	**2g**	-20	1	49	71 (72[d])
10	**2h**	22	1	65	26
11	**2i**	22	1	59	19
12[e]	**2f**	-20	3	44	39

[a] (-)-(2*R*,3*S*) enantiomer is always in excess; [b] Based on isolation by preparative TLC; [c] Determined by optical rotation; [d] Determined by ^{1}H NMR spectroscopy; [e] In SL system.

Table 2 it is obvious that, concerning asymmetric induction, the worst catalysts are **2c** (*N*-phenyl, 4% ee) and **2d** (*N*-benzyl, 13% ee). The compounds **2a** and **2e** possessing butyl and 2-phenylethyl side arms, respectively, were somewhat better catalysts (21% ee and 31% ee, respectively). The effect of the terminal hydroxyl groups was advantageous: 42% ee was achieved with 2-hydroxyethyl containing **2f**, and 62% ee with 3-hydroxypropyl substituted **2g**. However, further increases in chain length did not result in higher ees: in the presence of catalyst **2h** containing 4-hydroxybutyl substituent, the ee value of the epoxy ketone **9** dropped to 26%, there is an optimum in the chain length of the *N*-substituent.

The hydrophilic terminal group was found to have an important role in the toluene–water phase-transfer system: the free OH-group at the end of the substituent significantly decreased the catalytic effect, e.g. **2i** methylether derivative resulted in only 19% ee. Furthermore, from Table 2 it is obvious (entries 5–7 and 8–9) that a drop in the temperature increased the enantioselectivity: e.g. at room temperature with crown ether **2f** 42% ee was achieved, compared to 64% ee at −20°C. Maximum enantioselectivity (71% ee) was achieved with catalyst **2g** (having a 3-hydroxypropyl side arm) at −20°C. At temperatures lower than −20°C the reaction mixture solidified. An experiment carried out in a SL system (Table 2, entry 12), in the presence of NaOBu^t base, **2f** (possessing a 2-hydroxyethyl side arm) gave 39% ee.

We were also studying the Darzens condensation of phenacyl chloride with various substituted benzaldehydes under the same reaction conditions as previously described. Results of the reactions performed with catalyst **2g** at ambient temperature are summarized in Table 3. Reactions below room temperature could not be performed due to solubility problems. In the reaction with *o*-nitro-benzaldehyde (entry 1) the best chemical yield (71%) was obtained along with the lowest enantioselectivity (29% ee). One possible explanation is that the presence of an electron attracting group near the reaction center is advantageous regarding the chemical reaction itself, but its steric position is disadvantageous regarding the formation of a stereogenic carbon atom. Furthermore, it was observed that in the case of benzaldehydes with *para* electron attracting substituents the corresponding epoxy ketones[12] were obtained with approximately the same enantiomeric excess (*p*-NO_2 **11** 61% ee and *p*-Cl **12** 59% ee) as in the case of the unsubstituted benzaldehyde (62% ee). A methoxy group in the *para* position drastically decreased both the chemical yield (31%) and the enantioselectivity (12% ee). After repeated crystallization we managed to obtain pure levorotatory enantiomers of *trans*-*p*-NO_2 substituted **11** and *trans*-*p*-Cl substituted **12** epoxy ketones, and their specific rotatory power was determined. Their absolute configuration has not been studied so far, and is only assumed to be 2*R*,3*S*.[13] We have succeeded in obtaining a single crystal from the pure levorotatory enantiomer of *trans*-*p*-Cl substituted **12** epoxy ketone, and the subsequent X-ray studies (Fig. 1) confirmed its absolute configuration as 2*R*,3*S*.

Table 3
Asymmetric Darzens condensation of phenacyl chloride with substituted benzaldehyde in the presence of catalyst **2g**[a]

Entry	X	Yield (%)[b]	$[\alpha]_D$[c]	ee (%)[d]
1	o-NO_2	71	-48,7	29
2	p-NO_2	63	-161	61
3	p-Cl	54	-127	59
4	p-OMe	31	-16	12
5[e]	p-NO_2	29	-31	11

[a] At room temperature; [b] Based isolation by preparative TLC; [c] 20 °C, c=1, CH_2Cl_2; [d] Determined by ^{1}H NMR spectroscopy; [e] In SL system.

Scheme 4 describes a possible reaction path for the mechanism. Under the influence of the crown ether the sodium enolate gets solubilized in toluene thereby ensuring the chiral environment for the next step, in which the *Si* face of the enolate attacks the *Re* face of the aldehyde. The stereochemistry of the reaction is probably decided in this first, possibly slowest step, in which an intermediate with the 2*S*,3*S*

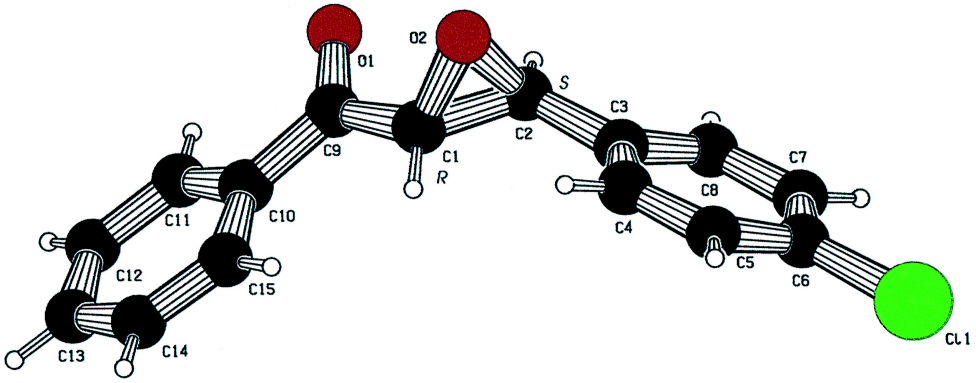
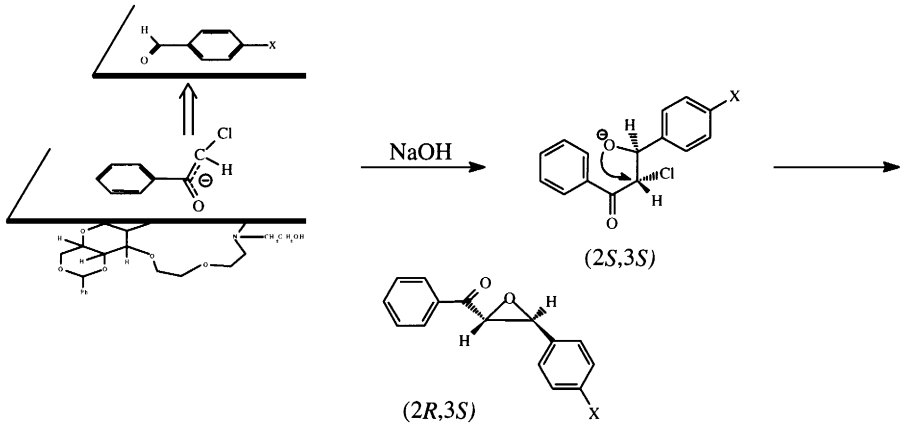


Fig. 1. Molecular structure of **12** with atomic labeling used in the X-ray analysis

configuration is formed. Following this, the configuration at C-2 is inverted to *R* by an S^{i}_{N} process, thus giving the end-product with 2*R*,3*S* stereochemistry.

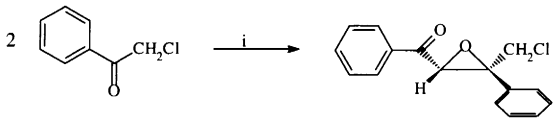


Scheme 4. Presumed reaction mechanism of the enantioselective Darzens condensation

2.4. Self-condensation of phenacyl chloride

During analysis of the by-products of the Darzens condensation, we have isolated an optically active by-product, which was found to be the base initiated self-condensation product of phenacyl chloride: 4-chloro-2,3-epoxy-1,3-diphenyl-butan-1-one (Scheme 5). This product has already been reported as a mixture of the racemic diastereomers.[14,15] The self-condensation of phenacyl chloride was then studied under the previously described conditions (toluene, 30% sodium hydroxide) in the presence of **2g** sugar-based crown-ether catalyst. By ^{1}H NMR spectroscopy we have shown that the ratio of *cis:trans* isomers was 23:77 in the condensation product, and these isomers were chromatographically separated. It was found that in the *trans* isomer the levorotatory enantiomer was in excess (64% ee). By repeated crystallization we have managed to isolate the pure levorotatory enantiomer, and obtained a single crystal. Crystal structure determinations of **12** and **14** showed that the stereogenic asymmetric carbons in both compounds (Figs. 1 and 2) have the respective 2*R*,3*S* configuration. The structures have normal bonding geometry. Intermolecular distances in the crystalline environment have only two peculiarities. One is that

in **12** there is a short H···H contact ($d_{H1\cdots H15}$=2.06 Å). The other is that both structures exhibit signs of the *chloro* effect.[16] The chloro substituted aromatic group in **12** probably causes the characteristic short *a* axis (~4.4 Å), while the chloromethyl moiety in **14** gives rise to numerous Cl···X (X=H, C, O) contacts, some of which are appreciably shorter than the sum of their van der Waals radii.



7 **14**

Scheme 5. Self-condensation of phenacyl chloride. Reagents and conditions: (i) crown-ether catalyst **2g**, 30% NaOH, toluene

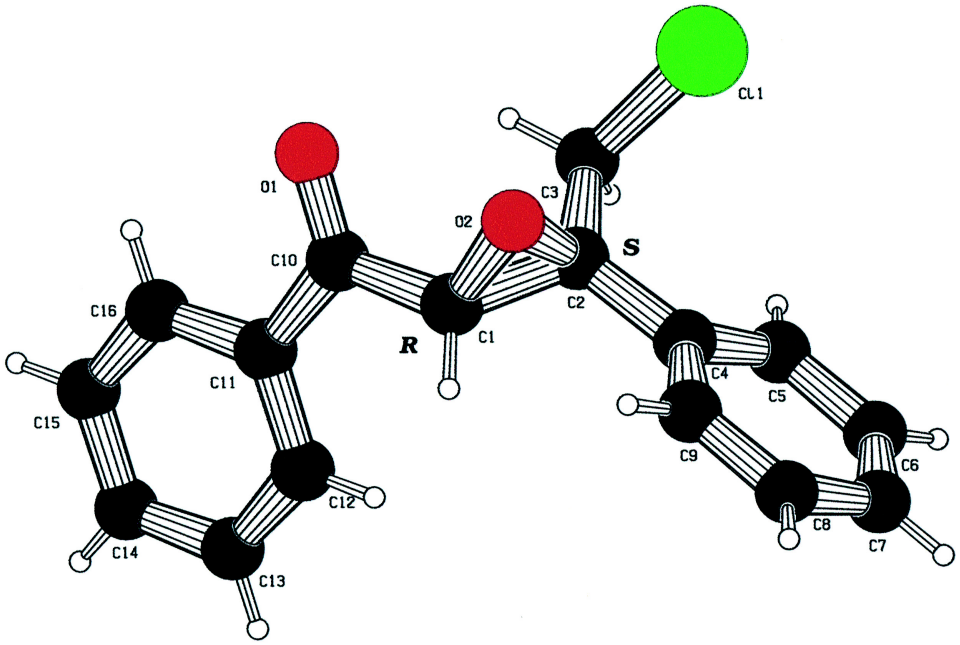


Fig. 2. Molecular structure of **14** with atomic labeling used in the X-ray analysis

Our research activity is being continued in field of the self-condensation of phenacyl chloride: the effect of other chiral catalysts in this reaction is being studied.

3. Experimental

3.1. General procedures

Melting points were determined with Büchi 510 apparatus and are uncorrected. Specific rotation was measured on a Perkin–Elmer 241 polarimeter at 20°C, and IR spectra were recorded on a Perkin–Elmer 237 spectrophotometer. NMR spectra were recorded on a Bruker WM 250 instrument in $CDCl_3$. The

mass spectra were obtained on a Jeol JMS-01 SG-2 instrument. Chemical ionization was applied as the ionization technique. Elemental analysis was performed on a Perkin–Elmer 240 automatic analyzer. Analytical and preparative thin layer chromatography was performed on silica gel (60 GF-254, Merck), column chromatography was carried out using 70–230 mesh silica gel (Merck).

3.2. General method for preparation of crown ethers

Dry Na_2CO_3 (3.84 g, 36.2 mmol) was suspended in a solution of 4.60 mmol of the corresponding primary amine and 3.45 g (4.6 mmol) of bis-iodo compound **1** in 110 mL of dry acetonitrile under argon. The stirred reaction mixture was refluxed for 24–48 h and monitored by TLC until the disappearance of the bis-iodo compound. After cooling, the precipitate was filtered and washed with acetonitrile. The combined acetonitrile solution was concentrated at reduced pressure. The residue oil was dissolved in $CHCl_3$, washed with water and dried over Na_2SO_4 and the solvent evaporated under vacuum. The corresponding monoaza-crown ether was isolated by column chromatography.

3.2.1. *Methyl-4,6-*O*-benzylidene-2,3-dideoxy-α-*D*-glucopyranosido[2,3-*h*]-*N*-butyl-1,4,7,10-tetraoxa-13-azacyclopentadecane* ***2a***

The column chromatography was carried out with eluent dichloromethane:methanol (100:5) on silica gel. Yield 64% (yellow oil); $[\alpha]_D^{20}$ +32 (c 1, $CHCl_3$); IR (neat) 2926, 2869, 1600, 1491, 1368, 1228, 1093, 1031, 749, 693 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.91 (t, J=7.3 Hz, 3H, CH_3), 1.28–1.76 (m, 4H, $CH_3CH_2CH_2$), 2.65–2.88 (m, 6H, $3NCH_2$), 3.40 (s, 3H, OCH_3), 3.48–4.07 (m, 16H, CH and CH_2 groups), 4.33 (dd, J=10.5 Hz, 1H, H-6), 4.77 (d, J=3.6 Hz, 1H, anomeric-H), 5.48 (s, 1H, PhCH), 7.18–7.53 (m, 5H, Ph); ^{13}C NMR ($CDCl_3$) δ 14.0, 20.6, 29.6, ($CH_3CH_2CH_2$), 54.0, 54.5 (CH_2NCH_2), 55.0 (OCH_3), 56.5 (NCH_2), 66.1 (C-5), 68.7 (C-6), 69.2, 69.3, 70.3, 70.4, 72.4, 72.5 ($6OCH_2$ of the macrocycle), 81.0, 81.5 (C-3, C-4), 81.7 (C-2), 96.9 (C-1), 100.9 (PhCH), 125.9 (PhC-*o*), 128.2 (PhC-*m*), 129.0 (PhC-*p*), 137.3 (PhC-*ipso*); FABMS *m/z* 496 (M+H). Anal. calcd for $C_{26}H_{41}NO_8$: C, 63.03; H, 8.28; N, 2.83%. Found: C, 62.98; H, 8.25; N, 2.81%.

3.2.2. *Methyl-4,6-*O*-benzylidene-2,3-dideoxy-α-*D*-glucopyranosido[2,3-*h*]-*N*-(2-phenyl)ethyl-1,4,7,10-tetraoxa-13-azacyclopentadecane* ***2e***

The purification was carried out by column chromatograpy with eluent chloroform:methanol (10:1) on silica gel. Yield 48% (yellow crystals); mp 73–75°C (ether); $[\alpha]_D^{20}$ +32.4 (c 1, $CHCl_3$); IR (KBr) 2913, 2866, 1600, 1492, 1368, 1230, 1127, 1092, 751, 694 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.76–2.88 (m, 8H, $3NCH_2$ and CH_2Ph), 3.43 (s, 3H, OCH_3), 3.48–3.86 (m, 17H, CH and CH_2 groups), 4.23 (dd, J=10.5 Hz, 1H, H-6), 4.76 (d, J=3.6 Hz, 1H, anomeric-H), 5.47 (s, 1H, PhCH), 7.12–7.53 (m, 10H, 2Ph); ^{13}C NMR ($CDCl_3$) δ 34.0 (NCH_2CH_2Ph), 54.1, 54.3 (CH_2NCH_2), 58.7 (NCH_2CH_2Ph), 66.1 (C-5), 68.7 (C-6), 69.2, 69.3, 70.3, 70.4, 72.4, 72.5 ($6OCH_2$ of the macrocycle), 81.0, 81.5 (C-3, C-4), 81.7 (C-2), 96.9 (C-1), 100.9 (PhCH), 125.9 (PhC-*o*), 126.0 (PhC-*o*), 128.2 (PhC-*m*), 128.3 (PhC-*m*), 129.0 (PhC-*p*), 129.6 (PhC-*p*), 137.3 (PhC-*ipso*), 140.5 (PhC-*ipso*); ClMS *m/z* (rel. int.) 544 (M+H, 29), 512 (72), 452 (100). Anal. calcd for $C_{30}H_{41}O_8N$: C, 66.29; H, 7.55; N, 2.58; Found: C, 66.31; H, 7.52; N, 2.57%.

3.2.3. *Methyl-4,6-*O*-benzylidene-2,3-dideoxy-α-*D*-glucopyranosido[2,3-*h*]-*N*-3-hydroxypropyl-1,4,7,10-tetraoxa-13-azacyclopentadecane* ***2g***

The purification was carried out by column chromatography with eluent dichloromethane:methanol (100:5→100:10) on silica gel. Yield: 58% (yellow crystals); mp 58–60°C; $[\alpha]_D^{20}$ +52.4 (c 1, $CHCl_3$); IR (neat) 3120–3600, 2920, 2875, 1600, 1491, 1236, 1093, 756, 692 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.67–1.98

(m, 2H, $NCH_2CH_2CH_2$), 2.25–2.43 (m, 2H, CH_2), 2.73–3.01 (m, 6H, $3NCH_2$), 3.43 (s, 3H, OCH_3), 3.52–3.90 (m, 13H, CH and CH_2 groups), 4.01–4.10 (m, 4H, $2OCH_2$), 4.26 (dd, *J*=10.5 Hz, 1H, H-6), 4.83 (d, *J*=3.6 Hz, 1H, anomeric-H), 5.0 (s, 1H, OH), 5.50 (s, 1H, Ph*CH*), 7.27–7.43 (m, 5H, Ph); ^{13}C NMR ($CDCl_3$) δ 28.4 ($NCH_2CH_2CH_2$), 54.3 (CH_2NCH_2), 56.4 ($NCH_2CH_2CH_2$), 64.0 ($NCH_2CH_2CH_2$), 66.1 (C-5), 68.7 (C-6), 68.8, 68.9, 70.2, 70.3, 72.3, 72.5 ($6OCH_2$ of the macrocycle), 80.9, 81.4 (C-3, C-4), 81.7 (C-2), 101.2 (PhCH), 102.1 (C-1), 125.9 (PhC-*o*), 128.2 (PhC-*m*), 129.0 (PhC-*p*), 137.3 (PhC-*ipso*); FABMS *m/z* 498 (M+H, 100). Anal. calcd for $C_{25}H_{39}O_9N$: C, 60.36; H, 7.85; N, 2.82%. Found: C, 60.30; H, 7.79; N, 2.80%.

*3.2.4. Methyl-4,6-*O*-benzylidene-2,3-dideoxy-α-*D*-glucopyranosido[2,3-*h*]-*N*-4-hydroxybutyl-1,4,7,10-tetraoxa-13-azacyclopentadecane* ***2h***

The purification was carried out by column chromatography with eluent dichloromethane:methanol (100:1→100:5) on silica gel. Yield: 51% (yellow oil); $[\alpha]_D^{20}$ +38.4 (c 1, CH_2Cl_2); IR (neat) 3120–3600, 2920, 2875, 1600, 1491, 1236, 1093, 756, 692 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.54–1.70 (m, 4H, $2CH_2$), 2.47–2.91 (m, 6H, $3NCH_2$), 3.37 (s, 3H, OCH_3), 3.46–3.93 (m, 20H, CH and CH_2 groups), 4.24 (dd, *J*=10.5 Hz, 1H, H-6), 4.80 (d, *J*=3.6 Hz, 1H, anomeric-H), 5.48 (s, 1H, Ph*CH*), 7.23–7.46 (m, 5H, Ph); FABMS *m/z* 512 (M+H). Anal. calcd for $C_{26}H_{41}O_9N$: C, 61.05; H, 8.02; N, 2.73%. Found: C, 61.15; H, 8.10; N, 2.70%.

*3.2.5. Methyl-4,6-*O*-benzylidene-2,3-dideoxy-α-*D*-glucopyranosido[2,3-*h*]-*N*-2-methoxyethyl-1,4,7,10-tetraoxa-13-azacyclopentadecane* ***2i***

The purification was carried out by column chromatography with eluent dichloromethane:methanol (10:2) on silica gel. Yield: 44% (yellow crystals); mp 78–79°C (ether); $[\alpha]_D^{20}$ +41.6 (c 1.2, $CHCl_3$); IR (KBr) 2920, 2876, 1600, 1496, 1388, 1239, 1093, 749, 695 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.71–2.92 (m, 6H, $3NCH_2$), 3.31 (s, 3H, OCH_3), 3.40 (s, 3H, OCH_3), 3.46–3.90 (m, 19H, CH and CH_2 groups), 4.23 (dd, 1H, *J*=10.5 Hz, H-6), 4.82 (d, *J*=3.6 Hz, 1H, anomeric-H), 5.50 (s, 1H, Ph*CH*), 7.23–7.46 (m, 5H, Ph); CIMS *m/z* (rel. int.) 498 (M+H, 15), 452 (100); FABMS *m/z* 498 (M+H). Anal. calcd for $C_{25}H_{39}O_9N$: C, 60.36; H, 7.85; N, 2.82%. Found: C, 60.28; H, 7.80; N, 2.78%.

*3.2.6. Methyl-4,6-*O*-benzylidene-2,3-dideoxy-α-*D*-galactopyranosido[2,3-*h*]-*N*-butyl-1,4,7,10-tetraoxa-13-aza-cyclopentadecane* ***3a***

The purification was carried out by column chromatography with eluent dichloromethane:methanol (100:1→100:5) on silica gel. Yield: 61% (yellow oil); $[\alpha]_D^{20}$ +91.8 (c 1, $CHCl_3$); IR (KBr) 2926, 2869, 1600, 1491, 1368, 1228, 1093, 1031, 749, 693 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.90 (t, *J*=7.3 Hz, 3H, CH_3), 1.27–1.74 (m, 4H, CH_2), 2.65–2.88 (m, 6H, $3NCH_2$), 3.40 (s, 3H, OCH_3), 3.48–4.14 (m, 18H, CH and CH_2 groups), 4.36 (dd, *J*=2.8 Hz, 1H, H-6), 4.86 (d, *J*=2.6 Hz, 1H, anomeric-H), 5.52 (s, 1H, Ph*CH*), 7.18–7.52 (m, 5H, Ph); ^{13}C NMR ($CDCl_3$) δ 14.0, 20.6, 29.6 ($CH_3CH_2CH_2$), 54.0, 54.5 (CH_2NCH_2), 55.0 (OCH_3), 56.5 (NCH_2), 66.1 (C-5), 68.6 (C-6), 69.2, 69.3, 70.3, 70.4, 72.4, 72.5 ($6OCH_2$ of the macrocycle), 81.1, 81.6 (C-3, C-4), 81.6 (C-2), 100.0 (C-1), 100.9 (PhCH), 125.9 (PhC-*o*), 128.2 (PhC-*m*), 129.0 (PhC-*p*), 137.2 (PhC-*ipso*); FABMS *m/z* 496 (M+H). Anal. calcd for $C_{26}H_{41}NO_8$: C, 63.03; H, 8.28; N, 2.83%. Found: C, 63.07; H, 8.25; N, 2.80%.

*3.2.7. Methyl-4,6-*O*-benzylidene-2,3-dideoxy-α-*D*-galactopyranosido-[2,3-*h*]-*N*-(2-phenyl)ethyl-1,4,7,10-tetraoxa-13-azacyclopentadecane* ***3e***

The purification was carried out by column chromatography with eluent dichloromethane:methanol (100:5→100:10) on silica gel. Yield: 49% (yellow syrup) $[\alpha]_D^{20}$ +103 (c 1, $CHCl_3$); IR (KBr) 2913,

2866, 1600, 1492, 1368, 1230, 1127, 1092, 751, 694 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.73–2.87 (m, 8H, $3NCH_2$ and *CH_2*Ph), 3.40 (s, 3H, OCH_3), 3.53–4.16 (m, 17H, CH and CH_2 groups), 4.26 (dd, *J*=2.8 Hz, 1H, H-6), 4.92 (d, *J*=2.6 Hz, 1H, anomeric-H), 5.46 (s, 1H, Ph*CH*), 7.18–7.51 (m, 10H, 2Ph); EI-MS *m/z* 544 (M+H, 17), 512 (80), 452 (100). Anal. calcd for $C_{30}H_{41}O_8N$: C, 66.30; H, 7.55; N, 2.58%. Found: C, 66.35; H, 7.51; N, 2.53%.

*3.2.8. Methyl-4,6-*O*-benzylidene-2,3-dideoxy-α-*D*-galactopyranosido[2,3-*h*]-*N*-2-methoxyethyl-1,4,7, 10-tetraoxa-13-azacyclopentadecane* ***3i***

The purification was carried out by column chromatography with eluent dichloromethane:methanol (100:1→100:10) on silica gel. Yield: 75% (yellow oil); $[\alpha]_D^{20}$ +85.1 (c 1, $CHCl_3$); IR (neat) 2920, 2876, 1600, 1496, 1388, 1239, 1093, 749, 695 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.71–2.92 (m, 6H, $3NCH_2$), 3.32 (s, 3H, OCH_3), 3.40 (s, 3H, OCH_3), 3.51–3.93 (m, 19H, CH and CH_2 groups), 4.21 (dd, *J*=2.8 Hz, 1H, H-6), 4.92 (d, *J*=2.6 Hz, 1H, anomeric H), 5.50 (s, 1H, PhCH), 7.19–7.52 (m, 5H, Ph); CIMS *m/z* 498 (M+H, 9), 452 (100). Anal. calcd for $C_{25}H_{39}O_9N$: C, 60.36; H, 7.85; N, 2.82%. Found: C, 60.29; H, 7.80; N, 2.85%.

3.3. General procedure for the Michael addition of 2-nitropropane to chalcone in the presence of azacrown

The corresponding azacrown (0.1 mmol) and sodium *tert*-butoxide (0.05 g, 0.5 mmol) were added to the solution of chalcone (0.3 g, 1.44 mmol) and 2-nitropropane (0.3 mL, 3.36 mmol) in dry toluene (3 mL). The mixture was stirred under argon atmosphere at room temperature. After a reaction time of 48 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 (7 mL) 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 adduct. Mp 146–148°C; $[\alpha]_D^{20}$ +80.8 (c 1.5, CH_2Cl_2) for the pure (+)-(*S*)-enantiomer.[4b] ^1H NMR ($CDCl_3$) δ 1.54 (s, 3H, CH_3), 1.63 (s, 3H, CH_3), 3.27 (dd, 1H, J_1=17.2, J_2=3.2, COCH), 3.67 (dd, 1H, J_1=17.2, J_2=10.4, COCH), 4.15 (dd, 1H, J_1=10.4, J_2=3.2, CH_2CH), 7.18–7.32 (m, 5H, CHPh), 7.42–7.85 (m, 5H, C(O)Ph).

3.4. General procedure for Darzens condensation

A toluene solution (3 mL) of 1.3 mmol of phenyl 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 argon atmosphere. After completing the reaction 7 mL of toluene were added, the organic phase washed with water, dried over $MgSO_4$ and solvent evaporated. The product was isolated by preparative TLC using CH_2Cl_2 as eluent. Results are collected in Table 2. $[\alpha]_{578}^{20}$ −214 (c 1, CH_2Cl_2) for pure 2*R*,3*S* enantiomer.[13] ^1H NMR ($CDCl_3$) δ 4.08 (d, 1H, *J*=1.9 Hz, CH), 4.29 (d, 1H, *J*=1.9 Hz, CH), 7.35–7.45 (m, 5H, CHPhH), 7.49 (t, 2H, COPhH-*m*), 7.62 (t, 1H, COPhH-*p*), 8.01 (d, 2H, COPhH-*o*). The ^1H NMR spectra of substituted (−)-(2*R*,3*S*)-epoxy-1,3-diphenyl-1-propanone **11** and **12** were essentially identical with those reported in the literature.[13]

3.4.1. trans-*(−)-2,3-Epoxy-3-(2-nitrophenyl)-1-phenyl-1-propanone* ***10***

Yield: 72% (colorless crystals); mp 69–70°C; $[\alpha]_D^{20}$ −48.7 (c 1, CH_2Cl_2); 29% ee. ^1H NMR $CDCl_3$ δ 4.23 (d, *J*=1.75 Hz, 1H), 4.63 (d, *J*=1.65 Hz, 1H), 7.27–8.22 (m, 9H, 2Ph); ^{13}C NMR ($CDCl_3$) δ 57.7 (C-O), 59.6 (C-O), 124.9 (Ph, CH), 127.4 (Ph, CH), 128.5 (Ph, CH), 128.9 (Ph, CH), 129.5 (Ph, CH),

132.6 (Ph, CH), 134.1 (Ph, CH), 134.7 (Ph, CH), 135.4 (Ph, CH), 192.6 (C=O); FABMS *m/z* 270 (M+H). Anal. calcd for $C_{15}H_{11}NO_4$: C, 66.91; H, 4.08; N, 5.20%. Found: C, 66.90; H, 4.05; N, 5.18%.

3.4.2. trans-*(−)-2,3-Epoxy-3-(4-nitrophenyl)-1-phenyl-1-propanone* ***11***

Yield: 63%; $[\alpha]_D^{20}$ −161 (c 1, CH_2Cl_2); 61% ee. Two crystallizations from ethanol and hexane gave the pure enantiomer, $[\alpha]_D^{20}$ −272 (c 1, CH_2Cl_2); (lit.[12] $[\alpha]_{557}^{20}$ −274, c 2, CH_2Cl_2); mp 138–140°C (lit.[12] 140–142°C).

*3.4.3. (−)-(2*R,3S*)-Epoxy-3-(4-Chlorophenyl)-1-phenyl-1-propanone* ***12***

Yield: 54%; $[\alpha]_D^{20}$ −127 (c 0.33, CH_2Cl_2); 59% ee. Three crystallizations from ethanol and hexane gave the pure enantiomer, $[\alpha]_D^{20}$ −224 (c 1, CH_2Cl_2); (lit.[12] $[\alpha]_{577}^{20}$ −253, c 2.0, CH_2Cl_2); mp 64–66°C (lit.[13] 68°C).

3.4.4. trans-*(−)-2,3-Epoxy-3-(4-methoxyphenyl)-1-phenyl-1-propanone* ***13***

Yield: 31%; mp 58–60°C (lit.[12] 60–63°C); $[\alpha]_D^{20}$ −16 (c 1, CH_2Cl_2); 12% ee (lit.[12] $[\alpha]_{577}^{20}$ −305, c 2.0, CH_2Cl_2, 90% ee); ^{1}H NMR ($CDCl_3$) δ 3.83 (s, 3H, OCH_3), 4.08 (d, 1H, *J*=1.9 Hz, CH), 4.63 (d, 1H, *J*=1.9 Hz, CH), 7.38–8.01 (m, 9H, Ph). Anal. calcd for $C_{16}H_{14}O_3$: C, 75.58; H, 5.55%. Found: C, 75.61; H, 5.54%.

3.5. Self-condensation of phenacylchloride

A 6 mL toluene solution of 0.8 g (5.2 mmol) of phenacyl chloride and 0.1 g (0.2 mmol) of catalyst **2g** was treated with 2.0 mL of 30% NaOH solution. The mixture was stirred at room temperature for 1 h. After completing the reaction 14 mL of toluene were added, the organic phase washed with water, dried over $MgSO_4$ and solvent evaporated. The product was purified by column chromatography (silica gel, CH_2Cl_2) to give 0.6 g (85%) of **14**. Mp 123–130°C; $[\alpha]_D^{20}$ −60.6 (c 1, CH_2Cl_2). Diastereomeric ratio *cis:trans*=23:77 (by ^{1}H NMR); separation by preparative TLC (silica gel, CH_2Cl_2) to give the pure *trans*-form of **14** (0.4 g); mp 122–124°C; $[\alpha]_D^{20}$ −74 (c 1, CH_2Cl_2); 64% ee. Two crystallizations from hexane afforded the pure enantiomer, (−)-(2*R*,3*S*)-epoxy-1,3-diphenyl-4-chlorobutan-1-one. Mp 124–126°C; $[\alpha]_D^{20}$ −116 (c 1, CH_2Cl_2); ^{1}H NMR δ 3.88 (d, *J*=12 Hz, 1H), 4.02 (d, *J*=15 Hz, 1H), 4.38 (s, 1H), 7.22–8.02 (m, 10H, Ph). ^{13}C NMR δ 44.1 (C-Cl), 65.4 (C-O), 66.1 (C-O), 126.3 (Ph, CH), 128.4 (Ph, CH), 128.6 (Ph, CH), 128.8 (Ph, CH), 129 (Ph, CH), 129.1 (Ph, CH), 134.4 (Ph, CH), 136.0 (Ph, CH), 193.6 (C=O). Anal. calcd for $C_{16}H_{13}ClO_2$: C, 70.40; H, 4.77; Cl, 13.0%. Found: C, 70.42; H, 4.76; Cl, 12.96%.

3.6. X-Ray crystal structure determinations[16–19]

Diffraction data were collected for both **12** and **14** at room temperature using Mo-Kα radiation. Initial structure models, obtained routinely by direct methods (SHELXS93), were smoothly refined to the final scattering model by using full-matrix least-squares and anisotropic displacement variables for non-H atoms. All hydrogen atoms both in **12** and **14** were positioned using geometric constrains and included within the final refinement cycles with so-derived contributions using SHELXL97. Pertinent crystallographic data for **12**: monoclinic $P2_1$ (no. 4), *a*=4.379(1), *b*=10.740(2), *c*=13.465(2) [Å], β=92.53(1) [°], *V*=632.6(2) [Å^3], *Z*=2, $D_{(calc)}$=1.358 [g/cm^3], data: N_{Tot}=2433, N_{Uniq}=1952, $R_{(int)}$=0.039, N_{Obs} [$I>2.0\sigma(I)$]=988, refinement: N_{ref}=1952, N_{par}=163, *R*=0.0550, R_w=0.1478, *S*=0.82; for **14**: monoclinic $P2_1$ (no. 4), *a*=6.990(1), *b*=5.053(1), *c*=18.544(2) [Å], β=91.74(1) [°], *V*=654.7(2) [Å^3], *Z*=2,

$D_{(calc)}$=1.383 [g/cm^3], data: N_{Tot}=4632, N_{Uniq}=3793, $R_{(int)}$=0.021, N_{Obs} [$I>2.0\sigma(I)$]=2215, refinement: N_{ref}=3793, N_{par}=172, R=0.0476, R_w=0.1178, S=0.91. Absolute configurations for both **12** and **14** were assigned on the basis of the refined Flack parameters (x=−0.02(14) for **12** and x=−0.03(8) for **14**).

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