Synthesis and application in asymmetric synthesis of azacrown ethers derived from D-glucose

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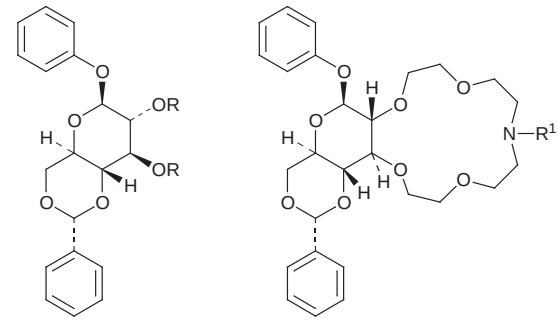
New chiral monoaza-15-crown-5 derivatives and lariat ethers anellated to phenyl β-D-glucoside have been synthesized which show significant asymmetric induction as phase transfer catalysts in the Michael addition of 2-nitropropane to chalcone (84% ee) and in the Darzens condensation of phenacyl chloride with benzaldehyde (74% ee).

One of the most attractive types of asymmetric synthesis is that in which chiral products are generated under the influence of chiral crown ether catalysts. Although many optically active crown ethers have been prepared, only a few have been used successfully as catalysts in asymmetric reactions.[1] Previously, we reported the asymmetric Michael addition of phenyl acetate to acrylate catalyzed by chiral crown ethers composed of two glucose units (85% ee).[1,2] The substituents on the sugar unit of the macrocycle[1,2] and the side arms at the nitrogen atom in the crown ring[3] play an important role in the catalytic activity of the crown ethers. The latter compounds with heteroatoms in the side arm, named lariat ethers or armed crown ethers, are known to display special complexation, high lipophilic character and unique guest specificity *via* macroring–side arm cooperativity.[4] It is therefore reasonable to study the effect of using different pendant arms on the chiral crown ether catalyst in asymmetric reactions.

We now report on the synthesis and application of new monoaza-15-crown-5 compounds **4**–**12**.



1 R = H
2 R = $(CH_2)_2O(CH_2)_2Cl$
3 R = $(CH_2)_2O(CH_2)_2I$

4 R^1 = Bu
5 R^1 = $Pr^i{}_2CH$
6 R^1 = C_6H_{11}
7 R^1 = $C_6H_{11}CH_2$
8 R^1 = Bn
9 R^1 = $Ph(CH_2)_2$
10 R^1 = $HO(CH_2)_2$
11 R^1 = $MeO(CH_2)_2$
12 R^1 = $HO(CH_2)_3$

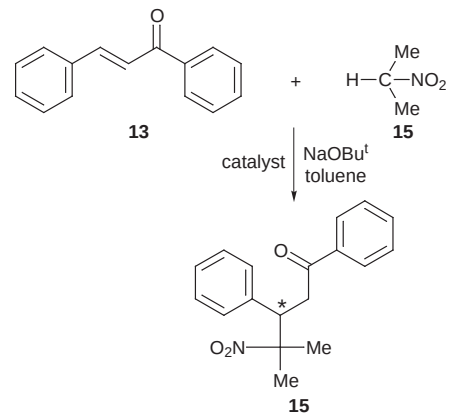
Their synthesis starts from phenyl 4,6-*O*-benzylidene-β-D-glucopyranoside **1**. The vicinal free hydroxy groups in compound **1** were alkylated using the method of Di Cesare and Gross,[5] with bis(2-chloroethyl) ether acting as solvent and reagent, under liquid–liquid (LL) two-phase reaction conditions, in the presence of tetrabutylammonium hydrogen sulfate (as a phase transfer catalyst) and 50% aq. NaOH to give compound **2** (room temperature, 8 h, column chromatography). The exchange of chlorine for iodine in **2** was carried out using NaI in acetone (reflux, 24 h), resulting in the bis(iodide) derivative **3**. Compound **3** was cyclized with various primary amines: *n*-butylamine, 2,4-dimethylpentan-3-ylamine, cyclohexylamine, cyclohexylmethylamine, benzylamine, 2-phenylethylamine, ethanolamine, 2-methoxyethylamine and propanolamine, respectively, according to the method described previously,[6] which requires dry Na_2CO_3 in MeCN as solvent (reflux, 32–40 h, column chromatography). We thus obtained the corresponding 15-membered macrocycles **4**–**12**, the yields of the ring closure steps after chromatography being in the range 32–54% (Table 1). All structures were ascertained by ^{1}H NMR, ^{13}C NMR, COSY, mass and elemental analysis.‡

Table 1 Yield and characterisation data of compounds **2**–**12**

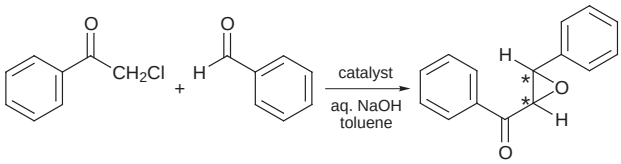
Compound	Yield (%)[a]	$[\alpha]^{20}$ (c 1, $CHCl_3$)	Mp/°C
2	29	−35.5	74–75
3	95	−28.6	58–59
4	44	−43.0	105–106
5	32	−35.4	58–60
6	39	−39.2	oil
7	32	−41.1	107–108
8	42	−34.9	oil
9	48	−44.3	153–55
10	48	−35.2	oil
11	54	−40.1	oil
12	45	−44.9	oil

[a] After column chromatography.

Compounds **4**–**12** were then used as phase transfer catalysts in different reactions in which enantiomeric mixtures can be formed. These catalysts proved to be effective in two reactions: the Michael addition of 2-nitropropane to chalcone (Scheme 1),



Scheme 1



16 17 18

Scheme 2

and the Darzens condensation of phenacyl chloride with benzaldehyde (Scheme 2).

The Michael addition was carried out in a solid–liquid (SL) system; in toluene, employing solid NaOBu^t as base (35 mol%) and chiral catalyst (7 mol%) at room temperature.§ After the usual work-up procedure the adduct was isolated by preparative TLC, and the asymmetric induction, expressed in terms of the enantiomeric excess (ee), was monitored by measuring the optical rotation of the product **15** and comparing it with literature values[3] and by ^{1}H NMR analysis using (+)-Eu(hfc)$_3$ as a chiral shift reagent. The results are shown in Table 2.

As can be seen, the substituents at the N-atom of the catalyst have a significant influence on both the chemical yield and the enentioselectivity. In all cases the (*S*)-(+)-adducts **15** were found to be in excess. The catalyst having the bulky 2,4-dimethylpentan-3-yl group at the N-atom gave the lowest chemical yield and chiral induction (entry 2), and the crown ether having a phenylethyl group (**9**) proved to be the best (entry 6). The methyl ether **11** showed a higher ee value than its free hydroxy analogue **10** (entry 8 and 7). The length of the side arm is decisive: catalyst **8** having a benzyl group shows poor chiral induction (6% ee), while compound **9** containing a phenylethyl group gives high enantioselectivity (84% ee).

The Darzens condensation (Scheme 2) was performed in a binary LL system, using a toluene–30% aq. NaOH (5 : 1) mixture.¶ The work-up procedure and determination of ee was carried out in a similar manner to that mentioned for the Michael addition. In all cases the epoxy ketone product **18** with a negative optical rotation was found to be in excess, which on the basis of the optical rotation of the pure enantiomer, corresponds to an absolute configuration of (2*R*,3*S*).[7] Low enantioselectivities were obtained using catalysts **4**–**8** (entries 1–5). The macrocycle **10** [R = $(CH_2)_2$OH] having the hydrophilic hydroxyethyl group at the N-atom gave 52% ee (entry 7) but this value was dramatically reduced (13% ee) for its methyl ether **11** (entry 8). It is interesting to note that the effect of the compound containing a free hydroxy group on the magnitude of the enantioselectivity for the Darzens condensation is the reverse of that for the Michael reactions (entries 7 and 8). The importance of the chain-length at the N-atom in the catalytic activity is reflected particularly in the experiment shown in entry 9: catalyst **12** [R = $(CH_2)_3$OH] proved to be the most effective, resulting in 74% ee at room temperature. With regard to the effectiveness of the crown ether structure for enantiomeric induction, we suppose that the substituent at the nitrogen atom of the catalyst takes part in the complexation of the salt of the anion by complexation of the cation in the third dimension, working as a pseudo-lariat ether, and as a consequence increases the effectiveness of the phase transfer process. Reactions running in the absence of chiral catalyst give only racemic products.

Table 2 Effect of chiral crown catalysts **4**–**12** on the asymmetric Michael addition and Darzens condensation

		Michael addition		Darzens condensation	
Entry	Catalyst	Yield (%)[a]	Ee (%)[b]	Yield (%)	Ee (%)[b]
1	**4**	61	27	92	4
2	**5**	15	4	33	3
3	**6**	50	23	94	4
4	**7**	53	24	70	8
5	**8**	56	6	88	4
6	**9**	78	82 (84)[c]	72	30
7	**10**	71	45	86	52 (53)[c]
8	**11**	65	60	72	13
9	**12**	42	6	68	74

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

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Notes and References

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‡ *Selected data* for **2**: δ_H(250 MHz, $CDCl_3$, $SiMe_4$) 7.50–7.06 (m, 10 H, ArH), 5.56 (s, 1 H, Benzylidene-CH), 5.06 (d, *J* 7.6, 1 H, anomer-H), 4.36 (dd, *J* 10.5, 4.3, 1 H, H-6), 4.09–3.53 (m, 21 H, 8 CH_2O, 5 CH). For **3**: 7.50–7.05 (m, 10 H, ArH), 5.56 (s, 1 H, benzylidene-CH), 5.06 (d, *J* 7.6, 1 H, anomer-H), 4.38–4.36 (dd, *J* 10.5, 4.3, 1 H, H-6), 4.02–3.52 (m, 18 H, 8 CH_2O, 2 CH), 3.21–3.18 (m, 3 H, H-2, H-3, H-5). For **9**: 7.37–7.02 (m, 15 H, ArH), 5.54 (s, 1 H, benzylidene-CH), 5.06 (d, *J* 7.6, 1 H, anomer-H), 4.36 (dd, *J* 10.5, 4.3, 1 H, H-6), 4.10–3.57 (m, 15 H, 6 CH_2O and 3 CH), 3.54–3.47 (m, 2 H, H-2, H-5), 2.89–2.76 (m, 8 H, 3 NCH_2, CH_2Ph).

§ The Michael addition was performed as follows: 1.44 mmol of chalcone and 3.36 mmol of 2-nitropropane were dissolved in 3 ml of anhydrous toluene, and then 0.1 mmol of crown ether and 0.5 mmol of base were added. The mixture was stirred under an Ar atmosphere. After completing the reaction (8–40 h) a mixture of 7 ml of toluene and 10 ml of water was added. The organic phase was processed in the usual manner. The product was purified on silica gel by preparative TLC with hexane–ethyl acetate (10 : 1) as eluent; mp 146–148 °C, $[\alpha]_D^{20}$ + 68 (*c* 1, CH_2Cl_2) (84% ee) (lit.,[3] +80.8, for pure enantiomer), δ_H 7.85 (m, 2 H, Ph), 7.52 (m, 3 H, Ph), 7.25 (m, 5 H, Ph), 4.18–3.25 (m, 3 H, CH_2, CH), 1.62 (s, 3 H, CH_3), 1.54 (s, 3 H, CH_3).

¶ Typical experimental procedure for the asymmetric Darzens condensation: a toluene solution of 1.3 mmol of phenacyl chloride (3 ml) was treated with 1.9 mmol of benzaldehyde and 0.1 mmol of catalyst in 0.6 ml of 30% NaOH solution. The mixture was stirred under Ar atmosphere. After completing the reaction 7 ml of toluene were added, the organic phase washed with water, dried over $MgSO_4$ and the solvent evaporated. The residue was chromatographed on preparative silica gel of 2 mm thickness (Kieselgel 60 GF_{254}), using CH_2Cl_2 as eluent; $(\alpha)_{578}^{20}$ −111 (*c* 1, CH_2Cl_2) (52% ee) (lit.,[7] −214, for pure enantiomer); δ_H 8.01 (m, 2 H, Ph), 7.60 (t, 1 H, Ph), 7.48 (t, 2 H, Ph), 7.40–7.30 (m, 5 H, Ph), 4.29 (d, *J* 2, 1 H), 4.08 (d, *J*, 1 H).

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