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D-Glucose-based azacrown ethers with a phosphonoalkyl side chain: application as enantioselective phase transfer catalysts

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Abstract

Five chiral α-D-glucose-based monoaza-15-crown-5 ethers with a phosphonoalkyl side chain **5a**–**e** have been synthesized. The substituent at the nitrogen atom has a major influence on the cation extraction ability of the azacrown. The new lariat ethers **5a**–**e** show significant asymmetric induction as phase transfer catalysts in the Michael addition of 2-nitropropane to chalcone.

1. Introduction

Chiral crown ethers have received considerable attention due to their ability to serve as models for the study of chiral recognition in enzymatic reactions.[1] It has also been observed that the optically active crown ethers could be used as catalysts in enantioselective reactions.[2] A variety of such macrocycles has been synthesized, and much attention focused on systems derived from carbohydrates.[3] Crown ethers anellated to different pyranosidic or furanosidic carbohydrates have also been described.[4]

In recent papers, we have reported the synthesis of a novel class of D-glucose-based crown ethers and their application in asymmetric reactions. These compounds are 15-membered monoazacrown ethers anellated to a methyl-[5] or to a phenyl-4,6-*O*-benzylideneglucopyranoside[6] unit and are useful catalysts in asymmetric reactions. It is known that armed azacrown ethers, especially lariat ethers (azacrowns with heteroatom-containing podand arms) have a unique guest specificity via the macro-ring-side arm cooperativity.[7] We found that the presence of a substituent on the nitrogen atom played an important role in the cation binding ability, and hence in the catalytic activity of the azacrown ethers.[6b] In sugar-based azacrowns, the impact of alkyl and arylalkyl groups, as well as that of substituents containing an oxygen

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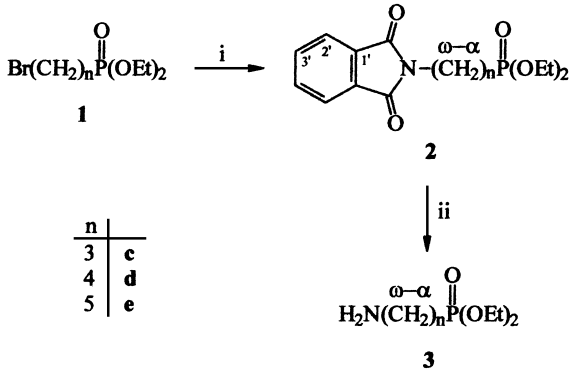
atom, have been evaluated.[5a] The effects of phosphorus-containing side arms on the complexing abilities have been studied only in simple azacrown ethers.[8] As the lariat ethers incorporating a phosphonoalkyl substituent showed interesting cation binding properties, it was a challenge for us to synthesize D-glucose-based azacrown ethers with a phosphonoalkyl group on the nitrogen atom and to study their complexing properties and applicability in enantioselective reactions.

2. Results and discussion

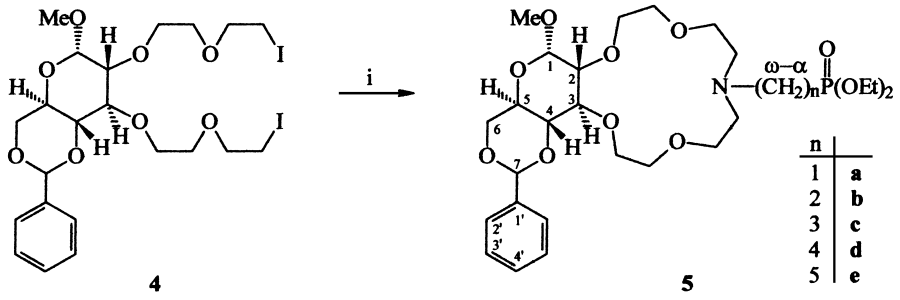
2.1. Synthesis of new azacrown ethers 5a–e

We used a method described previously[5a] for the synthesis of the new lariat ethers. The key intermediates, ω-aminoalkylphosphonates **3c**–**e** were prepared by the, in this case hitherto new, Gabriel synthesis (Scheme 1) in two steps. Intermediate **3a** (**3**, *n*=1) was also obtained through the corresponding phthalimido derivative **2a** (**2**, *n*=1) synthesized, in this case, by a different approach (see Experimental).



Scheme 1. Reagents and conditions: (i) potassium phthalimide, DMF, 100°C, 8 h; (ii) $(H_2N)_2 \cdot H_2O$, EtOH, 78°C, 1 h then HCl, 78°C, 30 min

Aminoethylphosphonate **3b** (**3**, *n*=2) was prepared by the Michael addition of ammonia to diethyl vinylphosphonate. The α-D-glucose-based bis-iodo podand[5a] **4** was cyclized with the aminoalkylphosphonates **3a**–**e** in boiling acetonitrile in the presence of sodium carbonate (Scheme 2). In dilute solutions, the polycondensation side reactions were suppressed and the desired intramolecular cyclization took place in high conversion to give the *N*-phosphonoalkyl azacrown ethers **5a**–**e** in fairly good yields (51–70%) after purification by chromatography. The products **5a**–**e** were characterized by ^{31}P, ^{1}H and ^{13}C NMR, as well as mass spectroscopic data. The ^{1}H and ^{13}C NMR spectral parameters were similar to those of azacrown derivatives described earlier.[6b] The molecular weights of **5a**–**e** were supported by CIMS and FABMS. The elemental composition was confirmed in all cases by HR-FAB. In the EI mass spectra of products **5a**–**e** we observed two different fragmentation patterns depending on the length of the hydrocarbon chain binding the P=O moiety to the azacrown ether. With compounds **5a** and **5b**, the fragments were formed mainly by bond fission in the 'sugar' part of the molecules, while in the case of azacrowns **5c**–**e**, the fragmentation occurred preferentially at the 'crown' part. The fragments at 452 and 156 *m/z* were of significant intensity in all cases (see Experimental) that are due to the (sugar-based azacrown)-CH_2^+ and the $C_7H_8O_4^+$ fragments, respectively. The latter one is the sugar residue from product **5a**–**e**. The $(CH_2)_nP(O)(OEt)_2^+$, the $CH_2N(CH_2)_nP(O)(OEt)_2^+$, as well as the $(CH_2)_2N(CH_2)_nP(O)(OEt)_2^+$ fragments could also be found in the mass spectra of products **5a**–**e**. The $M-H^+$, $M-Me^+$, $M-MeO^+$, $M-EtO^+$ and $M-P(O)(OEt)_2^+$ fragments were of low intensity.

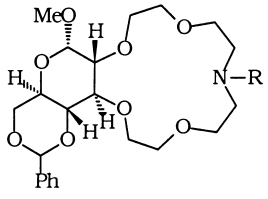


Scheme 2. Reagents and conditions: (i) $H_2N(CH_2)_nP(O)(OEt)_2$ (**3a–e**), CH_3CN, 82°C, 48 h

2.2. *Extracting properties of the new azacrown ethers **5a–e***

The phase transfer properties (in a liquid–liquid system) of the newly synthesized crown ethers **5a–e** were characterized by the extraction of picrate salts (lithium, sodium, potassium and ammonium picrates) from water into dichloromethane following the procedure described by Kimura et al.[9] The data collected in Table 1 show the amount of the transferred salt as the percentage of the initial salt concentration (extractability %). The concentration of the picrates in water was measured by UV spectroscopy. The unsubstituted azacrown ether **6** used as the reference compound[5c] has a surprisingly high extracting ability (EA) towards the cations investigated but does not show a notable selectivity to any of the alkali- or ammonium cations (EA: 87–98%).

Table 1
Extraction of alkali metal and ammonium picrates with different azacrown ethers



Compound	R	Extractability (%)[a]			
		Li^+	Na^+	K^+	NH_4^+
5a	$(CH_2)P(O)(OEt)_2$	8	29	16	5
5b	$(CH_2)_2P(O)(OEt)_2$	35	30	17	29
5c	$(CH_2)_3P(O)(OEt)_2$	4	15	24	43
5d	$(CH_2)_4P(O)(OEt)_2$	46	47	54	63
5e	$(CH_2)_5P(O)(OEt)_2$	38	59	59	63
6	H	87	87	96	98

[a] Room temperature; aqueous phase (5 ml); [picrate] = $5 \cdot 10^{-3}$ M; organic phase (CH_2Cl_2, 5 ml); [crown ether] = $1 \cdot 10^{-2}$ M. Defined as % picrate extracted into the organic phase, determined by UV spectroscopy. Error = ±1%.

As can be seen, the phosphonoalkyl side arms have significant influence on the EA of the azacrown ring. Introduction of the phosphonoalkyl substituents decreased the EA of the parent azacrown ether **6** in all cases. The impact of the long chains was smaller than that of the substituents with shorter chains (e.g. the EA values for compound **5d** (n=4) and **5a** (n=1) are 46–63% and 5–29%, respectively). For the potassium cation, the relative order of the EA values is the following: 96% for **6** (n=0), 59% for

5e (*n*=5), 54% for **5d** (*n*=4), 24% for **5c** (*n*=3), 17% for **5b** (*n*=2) and 16% for **5a** (*n*=1). On the other hand, the selectivity of derivatives **5a–e** was improved significantly relative to that of unsubstituted **6**. In this respect, compound **5c** (*n*=3) seems to be the best, which transports 10 times more ammonium picrate (EA=43%) into the organic phase than lithium picrate (EA=4%). Azacrown **5b** extracts twice as much lithium ion as potassium ion. With the exception of **5a** and **5b**, the azacrown ethers **5c–e** form the most stable complex with ammonium picrate among the picrates investigated. Regarding the stability of the complex with different cations, a similar trend can be observed for azacrowns **5c–e** as follows: $NH_4^+ > K^+ > Na^+ > Li^+$. Compounds **5a** and **5b** revealed the $Li^+ > Na^+ > NH_4^+ > K^+$ order. The complex effect of the *N*-substituents is presumably due to steric and electronic effects. The presence of the phosphonoalkyl side chain obviously means some kind of steric hindrance in the complexation. On the other hand, the phosphonoalkyl moiety affects the electron density on the nitrogen atom. While the phosphonomethyl substituent can be regarded as an electron-withdrawing group, the phosphonoalkyl substituents with longer carbon atom chains may increase the electron density on the nitrogen atom. The third effect may be the side arm cooperativity due to the oxygen atom of the phosphoryl moiety (Fig. 1). The length of the side arm is decisive.

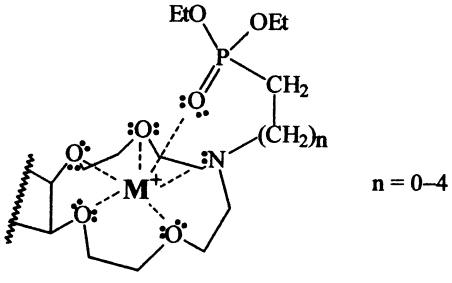
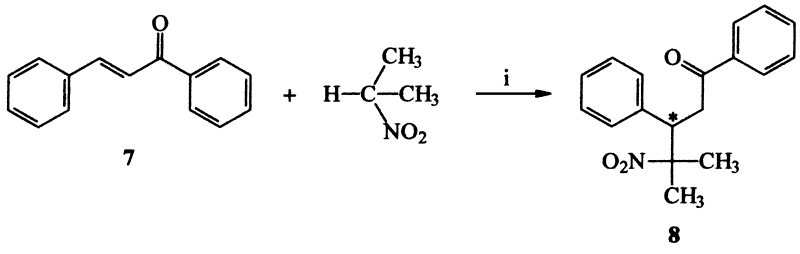


Figure 1.

2.3. Chiral induction by the new azacrown ethers *5a–e* in an asymmetric Michael addition

The compounds **5a–e** proved to be effective as chiral phase transfer catalysts in the Michael addition of 2-nitropropane to chalcone **7** (Scheme 3). The Michael addition was carried out in toluene with solid sodium *tert*-butoxide as the base (35 mol%) in the presence of chiral catalyst **5a–e** (7 mol%) at room temperature. After the usual work-up procedure, the adduct **8** was isolated by preparative TLC. The asymmetric induction, expressed in terms of the enantiomeric excess (ee), was monitored by determining the specific rotation of product **8** and comparing it with the literature data for the pure enantiomer and by ^{1}H NMR spectroscopy using (+)-Eu(hfc)$_3$ as chiral shift reagent. The results given in Table 2 show that the (*S*)-(+)-adduct **8** was always in excess and, what is more important, that the substituent on the nitrogen atom of the catalyst has a significant influence on both the yield and the asymmetric induction.



Scheme 3. Reagents and conditions: (i) catalyst (**5a–e**), NaO*t*Bu, PhMe, 20°C, 48 h

Table 2
Addition of 2-nitropropane to chalcone (**7**) catalyzed by azacrown ethers **5a–e**[a]

Entry	Catalyst	Yield (%)[b]	ee (%)[c]
1	5a	31	63
2	5b	42	61
3	5c	38	60
4	5d	39	82 (83)[d]
5	5e	40	79
6[5c]	6	53	61

[a] Base *t*-BuONa; reaction time 48 h; temperature 20 °C.
[b] Based on substance isolated by preparative TLC.
[c] Determined by specific rotation comparison.
[d] Determined by ^{1}H NMR spectroscopy.

Apparently, azacrown ethers **5a–e** are not very efficient phase transfer catalysts in the solid–liquid phase Michael addition mentioned above: after a 48 h period of stirring, adduct **8** was formed in only 31–42% chemical yield. The new products **5a–e** showed, however, significant asymmetric induction: an enantiomeric excess of 60–83% was detected (Table 2). As a comparison, use of the unsubstituted azacrown **6** reported earlier resulted in an enantiomeric excess of 61%.[5c] As can be seen, the length of the chain connecting the nitrogen atom and the P=O moiety has a major influence on the enantioselectivity. The catalysts having shorter side arms **5a** (*n*=1), **5b** (*n*=2) and **5c** (*n*=3) were as efficient as reference compound **6** (ee: 60–63%). The use of azacrowns with longer arms **5d** (*n*=4) and **5e** (*n*=5) resulted in a significant increase in the enantioselectivity (ee: 79–82%). Among the catalysts tested, lariat ether **5d**, connecting the phosphoryl group by a four carbon atom chain to the nitrogen, proved to be the best: an enantiomeric excess of 82% was observed for the (*S*)-(+)-**8** adduct. This compound (**5d**) seems to have the optimum length for the hydrocarbon spacer connecting the P=O moiety to the nitrogen atom of the azacrown. The phosphonobutyl side arm is flexible and can bend over to assist the complexation responsible for the asymmetric induction.

3. Experimental

The ^{31}P, ^{13}C and ^{1}H NMR spectra were taken on a Bruker DRX-500 spectrometer operating at 202.4, 125.7 and 500 MHz, respectively. Chemical shifts are downfield relative to 85% H_3PO_4 or TMS. The coupling constants are given in hertz. EI-mass spectra were obtained on a Finnigan Automass 120 spectrometer at 70 eV. FAB measurements were conducted on a reverse geometry VG ZAB-2SEQ instrument using a 30 kV Cs^+ ion gun and 8 kV accelerating voltage.

The sugar-based bis-iodo podand **4** was synthesized as described earlier.[5a]

*3.1. The preparation of ω-aminoalkylphosphonates **3a–e***

*3.1.1. Diethyl 1-aminomethylphosphonate **3a***

Compound **3a** was synthesized from diethyl phthalimidomethylphosphonate **2a** obtained in the Arbuzov reaction of *N*-bromomethylphthalimide and triethyl phosphite[13] by reaction with hydrazine hydrate[14] as shown above for the preparation of aminopropylphosphonate **3c**. ^{31}P NMR ($CDCl_3$) δ 28.0; ^{13}C NMR ($CDCl_3$) δ 16.1 (*J*=5.4, CH_3), 37.4 (*J*=149.6, C_α), 61.6 (*J*=7.0, CH_2CH_3); MS, *m/z* 167 (M^+).

*3.1.2. Diethyl 2-aminoethylphosphonate **3b***

Compound **3b** was prepared by the Michael-type addition of ammonia to diethyl vinylphosphonate;[10] bp 96–100°C (0.4 mmHg) [lit.[11] 93–95°C (4.0 mmHg)]; ^{31}P NMR ($CDCl_3$) δ 30.8; ^{1}H NMR ($CDCl_3$) δ 1.29 (t, *J*=7.2, 6H, Me), 1.85–1.93 (m, 2H, CH_2P), 2.92–3.01 (m, 2H, CH_2N), 4.01–4.13 (m, 4H, CH_2O); MS, *m/z* 181 (M^+).

*3.1.3. Diethyl 3-aminopropylphosphonate **3c***

A 75 mL DMF solution of 8.60 g (33.2 mmol) of bromopropylphosphonate **1c** and 9.21 g (49.8 mmol) of potassium phthalimide was stirred at 100°C for 8 h. The mixture was cooled to 25°C and the precipitated material filtered off. The filtrate was concentrated in vacuo and the residue so obtained taken up in 100 mL of chloroform. After extraction with 3×30 mL of water, the organic phase was dried ($MgSO_4$). Evaporation of the solvent afforded 10.6 g (93%) of **2c** in a purity of 95% (GC–MS). ^{31}P NMR ($CDCl_3$) δ 31.3; ^{1}H NMR ($CDCl_3$) δ 1.29 (t, *J*=7.3, 6H, Me), 1.74–2.03 (m, 4H, $(CH_2)_2P$), 3.74 (t, *J*=7.1, 2H, CH_2N), 4.03–4.16 (m, 4H, CH_2O), 7.68–7.86 (m, 4H, Ar) [lit.[12] δ 1.32 (t, *J*=7, 6H, Me), 1.51–2.25 (m, 4H, $(CH_2)_2P$), 3.68 (m, 2H, CH_2N), 4.15 (m, 4H, CH_2O), 7.75 (m, 4H, Ar)]; ^{13}C NMR ($CDCl_3$) δ 16.3 (*J*=5.7, Me), 21.9 (*J*=4.4, C_β), 23.3 (*J*=143.1, C_α), 38.1 (*J*=19.7, C_γ), 61.6 (*J*=6.5, CH_2O), 123.1 ($C_{3'}$), 131.9 ($C_{1'}$), 133.9 ($C_{2'}$), 168.1 (C=O); MS, *m/z* (rel. int.) 325 (M^+, 2), 280 (6), 252 (5), 188 (6), 165 (21), 160 (54), 152 (100).

To 10.5 g (30.7 mmol) of **2c** in 130 mL of abs. ethyl alcohol was added 2.1 mL (42.4 mmol) of 98% hydrazine hydrate and the contents of the flask were stirred at reflux for 1 h. The volatile components were removed in vacuo and the oil so obtained distilled to give 2.10 g (51%) of **3c**. Bp 85–90°C (0.2 mmHg) [lit.[10] 114–116°C (1.5 mmHg)]; ^{31}P NMR ($CDCl_3$) δ 32.8; ^{13}C NMR ($CDCl_3$) δ 16.6 (*J*=5.7, Me), 23.2 (*J*=142.0, C_α), 26.6 (*J*=5.0, C_β), 42.7 (*J*=17.4, C_γ), 61.7 (*J*=6.6, CH_2O); MS, *m/z* 195 (M^+).

*3.1.4. Diethyl ω-aminoalkylphosphonates **3d** and **3e***

Intermediates **3d** and **3e** were prepared in a similar way from bromoalkylphosphonates **1d** and **1e** via intermediates **2d** and **2e**, respectively.

2d: Yield 66%; ^{31}P NMR ($CDCl_3$) δ 32.1; ^{1}H NMR ($CDCl_3$) δ 1.31 (t, *J*=7.0, 6H, Me), 1.65–1.89 (m, 6H, $(CH_2)_3P$), 3.70 (t, *J*=7.1, 2H, CH_2N), 4.03–4.16 (m, 4H, CH_2O), 7.68–7.88 (m, 4H, Ar) [lit.[12] δ 1.30 (t, *J*=7, 6H, Me), 1.47–2.10 (m, 6H, $(CH_2)_3P$), 3.63 (m, 2H, CH_2N), 4.05 (m, 4H, CH_2O), 7.75 (m, 4H, Ar)]; ^{13}C NMR ($CDCl_3$) δ 16.4 (*J*=5.5, Me), 19.8 (*J*=4.9, C_β), 25.1 (*J*=141.3, C_α), 29.3 (*J*=16.2, C_γ), 37.2 (C_δ), 61.6 (*J*=6.3, CH_2O), 123.2 ($C_{3'}$), 132.1 ($C_{1'}$), 134.0 ($C_{2'}$), 168.4 (C=O); MS, *m/z* (rel. int.) 339 (M^+, 7), 294 (10), 266 (4), 202 (2), 179 (47), 165 (62), 160 (100), 152 (75).

3d: Yield 73%; ^{31}P NMR ($CDCl_3$) δ 32.1; ^{13}C NMR ($CDCl_3$) δ 16.3 (*J*=5.8, Me), 25.1 (*J*=140.9, C_α), 26.0 (*J*=7.1, C_β), 32.0 (*J*=18.5, C_γ), 40.4 (C_δ), 61.3 (*J*=6.3, CH_2O); MS, *m/z* 209 (M^+).

2e: Yield 80%; ^{31}P NMR ($CDCl_3$) δ 32.6; ^{13}C NMR ($CDCl_3$) δ 16.4 (*J*=5.8, Me), 22.0 (*J*=5.1, C_β), 25.3 (*J*=140.6, C_α), 27.6 (*J*=17.0, C_γ), 28.0 (C_δ), 37.6 (C_ε), 61.5 (*J*=6.3, CH_2O), 123.1 ($C_{3'}$), 132.0 ($C_{1'}$), 133.9 ($C_{2'}$), 168.3 (C=O); MS, *m/z* (rel. int.) 353 (M^+, 3), 308 (6), 280 (1), 216 (4), 193 (32), 179 (16), 165 (67), 160 (100), 152 (46).

3e: Yield 89%; ^{31}P NMR ($CDCl_3$) δ 32.7; ^{13}C NMR ($CDCl_3$) δ 16.6 (*J*=5.7, Me), 22.4 (*J*=4.1, C_β), 25.7 (*J*=141.4, C_α), 27.9 (*J*=16.4, C_γ), 29.1 (C_δ), 40.0 (C_ε), 61.6 (*J*=5.8, CH_2O); MS, *m/z* 223 (M^+).

*3.2. General procedure for the preparation of methyl-4,6-O-benzylidene-2,3-dideoxy-α-D-glucopyranosido[2,3-h]-N-(O,O-diethyl phosphonoalkyl)-1,4,7,10-tetraoxa-13-azacyclopentadecanes **5a–e***

Dry Na_2CO_3 (8.0 g, 75.5 mmol) was suspended in a solution of the corresponding ω-aminoalkylphosphonates **3a–e** (10.5 mmol) and bis-iodo compound **4** (6.60 g, 9.73 mmol) in dry acetonitrile

(200 mL) under argon. The contents of the flask were stirred at boiling point for 48 h until the disappearance of the bis-iodo compound. After cooling, the mixture was filtered and washed with acetonitrile. The combined acetonitrile solution was concentrated in vacuo. The oil so obtained was dissolved in 60 mL of chloroform, washed with 10 mL of water and dried (Na_2SO_4). The crude product obtained after evaporating the solvent was purified by column chromatography (silica gel, 7% methanol in dichloromethane) to give lariat ethers **5a**–**e**.

5a: Yield 40%; $[\alpha]_D^{20}$ +39.6 (*c* 1, $CHCl_3$); mp 88–90°C; ^{31}P NMR ($CDCl_3$) δ 28.5; ^{1}H NMR ($CDCl_3$) δ 1.28 (t, *J*=7.0, 6H, CH_2CH_3), 3.61 (s, 3H, MeO), 3.96–4.06 (m, 4H, OCH_2CH_3), 4.23 (d, *J*=5.8, 1H, C_6-H), 5.10 (d, *J*∼3, 1H, C_1-H), 5.75 (s, 1H, C_7-H), 7.30–7.52 (m, 5H, Ar); ^{13}C NMR ($CDCl_3$) δ 16.9 (*J*=6.2, CH_2CH_3), 51.2 (*J*=153.8, C_α), 54.5 (bd, *J*∼16.0, CH_2NCH_2), 55.0 (CH_3O), 60.6 (*J*=6.5, CH_3CH_2), 96.9 (C_1), 100.7 (C_7), 125.9 ($C_{2'}$), 128.0 ($C_{3'}$), 128.7 ($C_{4'}$), 137.1 ($C_{1'}$); MS, *m/z* (rel. int.) 589 (M^+, 1), 588 (M−H, 1), 558 (M−31, 6), 544 (M−45, 3), 452 (100), 208 (12), 194 (17), 180 (7), 156 (29), 151 (8). CIMS, *m/z* (rel. int.) 590 (M+H, 10), 452 (100); FAB, 590 (M+H); HRFAB, (M+H) found: 590.2691, $C_{27}H_{45}NO_{11}P$ requires 590.2730.

5b: Yield 46%; $[\alpha]_D^{20}$ +51.1 (*c* 1, $CHCl_3$); mp 83–84°C; ^{31}P NMR ($CDCl_3$) δ 31.7; ^{1}H NMR ($CDCl_3$) δ 1.36 (t, *J*=7.0, 6H, CH_2CH_3), 3.45 (s, 3H, MeO), 4.09–4.17 (m, 4H, OCH_2CH_3), 4.27 (d, *J*=5.7, 1H, C_6-H), 5.02 (d, *J*=2.9, 1H, C_1-H), 5.56 (s, 1H, C_7-H), 7.36–7.50 (m, 5H, Ar); ^{13}C NMR ($CDCl_3$) δ 16.4 (*J*=4.8, CH_2CH_3), 22.8 (*J*=140.5, C_α), 48.4 (C_β), 53.6 (CH_2NCH_2), 55.2 (MeO), 62.1 (*J*=6.5, OCH_2), 62.3 (C_5), 68.7 (C_6), 81.8 (C_2), 96.8 (C_1), 101.2 (C_7), 125.9 ($C_{2'}$), 128.2 ($C_{3'}$), 129.0 ($C_{4'}$), 136.9 ($C_{1'}$); MS, *m/z* (rel. int.) 602 (M−1, 3), 588 (M−15, 3), 572 (M−31, 6), 558 (M−45, 14), 466 (M−137, 3), 452 (14), 222 (26), 208 (75), 194 (30), 166 (25), 156 (100). CIMS, *m/z* (rel. int.) 604 (M+H, 28), 558 (37), 452 (100); FAB, 604 (M+H); HRFAB, (M+H) found: 604.2832, $C_{28}H_{47}NO_{11}P$ requires 604.2887.

5c: Yield 62%; $[\alpha]_D^{20}$ +43.0 (*c* 1, $CHCl_3$); mp 69–72°C; ^{31}P NMR ($CDCl_3$) δ 32.5; ^{1}H NMR ($CDCl_3$) δ 1.31 (t, *J*=7.0, 6H, CH_2CH_3), 3.42 (s, 3H, MeO), 4.04–4.14 (m, 4H, OCH_2CH_3), 4.24 (d, *J*=5.3, 1H, C_6-H), 4.94 (d, *J*∼2, 1H, C_1-H), 5.54 (s, 1H, C_7-H), 7.29–7.50 (m, 5H, Ar); ^{13}C NMR ($CDCl_3$) δ 16.3 (*J*=6.0, CH_2CH_3), 19.5 (C_β), 22.9 (*J*=140.7, C_α), 53.5 (CH_2NCH_2), 54.2 (*J*=15.7, C_γ), 55.0 (MeO), 61.7 (*J*=5.9, OCH_2), 62.2 (C_5), 68.6 (C_6), 81.7 (C_2), 96.9 (C_1), 101.0 (C_7), 125.8 ($C_{2'}$), 128.0 ($C_{3'}$), 128.8 ($C_{4'}$), 137.0 ($C_{1'}$); MS, *m/z* (rel. int.) 616 (M−H, 3), 602 (M−15, 3), 586 (M−31, 8), 572 (M−45, 12), 480 (M−137, 2), 452 (75), 236 (30), 222 (58), 208 (58), 180 (48), 156 (100). CIMS, *m/z* (rel. int.) 618 (M+H, 13), 572 (20), 452 (100); FAB, 618 (M+H); HRFAB, (M+H) found: 618.2957, $C_{29}H_{49}NO_{11}P$ requires 618.3043.

5d: Yield 50%; $[\alpha]_D^{20}$ +38.3 (*c* 1, $CHCl_3$); mp 58–60°C; ^{31}P NMR ($CDCl_3$) δ 33.3; ^{1}H NMR ($CDCl_3$) δ 1.34 (t, *J*=6.8, 6H, CH_2CH_3), 3.45 (s, 3H, MeO), 4.07–4.18 (m, 4H, OCH_2CH_3), 4.27 (d, *J*=5.3, 1H, C_6-H), 4.98 (d, *J*=2.5, 1H, C_1-H), 5.57 (s, 1H, C_7-H), 7.31–7.50 (m, 5H, Ar); ^{13}C NMR ($CDCl_3$) δ 16.6 (*J*=5.4, CH_2CH_3), 20.8 (C_β), 24.6 (*J*=139.4, C_α), 26.4 (*J*=13.3, C_γ), 54.0 (CH_2N), 55.3 (MeO), 61.9 (*J*=7.2, OCH_2), 62.6 (C_5), 68.9 (C_6), 82.0 (C_2), 97.1 (C_1), 101.3 (C_7), 126.1 ($C_{2'}$), 128.3 ($C_{3'}$), 129.1 ($C_{4'}$), 137.2 ($C_{1'}$); MS, *m/z* (rel. int.) 630 (M−1, 4), 616 (M−15, 3), 600 (M−31, 13), 586 (M−45, 8), 494 (M−137, 3), 452 (88), 250 (18), 236 (43), 222 (88), 193 (46), 156 (100). CIMS, *m/z* (rel. int.) 632 (M+H, 12), 586 (5), 452 (100); FAB, 632 (M+H); HRFAB, (M+H) found: 632.3141, $C_{30}H_{51}NO_{11}P$ requires 632.3200.

5e: Yield 42%; $[\alpha]_D^{20}$ +21.2 (*c* 1, $CHCl_3$); syrup; ^{31}P NMR ($CDCl_3$) δ 32.5; ^{1}H NMR ($CDCl_3$) δ 1.31 (t, *J*=7.1, 6H, CH_2CH_3), 3.43 (s, 3H, MeO), 4.02–4.12 (m, 4H, OCH_2CH_3), 4.26 (d, *J*=5.3, 1H, C_6-H), 4.97 (b s, 1H, C_1-H), 5.54 (s, 1H, C_7-H), 7.32–7.48 (m, 5H, Ar); ^{13}C NMR ($CDCl_3$) δ 16.3 (*J*=5.4, CH_2CH_3), 22.0 (*J*=4.9, C_β), 25.2 (*J*=140.5, C_α), 27.7 (*J*=16.8, C_γ), 28.6 (C_δ), 53.7 (CH_2N), 55.0 (MeO), 61.2 (*J*=6.4, OCH_2), 62.1 (C_5), 68.7 (C_6), 81.9 (C_2), 97.4 (C_1), 101.0 (C_7), 125.8 ($C_{2'}$), 128.0 ($C_{3'}$), 128.8 ($C_{4'}$), 137.0 ($C_{1'}$); MS, *m/z* (rel. int.) 644 (M−H, 7), 630 (M−15, 4), 614 (M−31, 13), 600 (M−45, 7), 508 (M−137, 6), 452 (86), 264 (21), 250 (38), 236 (100), 207 (36), 156 (77). CIMS,

m/z (rel. int.) 646 (M+H, 22), 600 (5), 452 (100); FAB, 646 (M+H); HRFAB, (M+H) found: 646.3335, $C_{31}H_{53}NO_{11}P$ requires 646.3356.

*3.3. General procedure for the Michael addition of 2-nitropropane to chalcone in the presence of azacrown **5a–e***

The corresponding azacrown **5a**–**e** (0.1 mmol) and sodium *tert*-butoxide (0.05 g, 0.5 mmol) were added to the solution of chalcone **7** (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 an 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 **8**; mp 146–148°C; $[\alpha]_D^{20}$ +80.8 (*c* 1.5, dichloromethane) for the pure (+)-(*S*)-enantiomer.[5b] ^{1}H 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).

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