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Synthesis of D-Glucose-based Azacrown Ethers with Phosphinoxidoalkyl Side Chains and Their Application to an Enantioselective Reaction

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Abstract

Five chiral α-D-glucose-based monoaza-15-crown-5 ethers with phosphinoxidoalkyl side chains of one to five carbon atoms (**5a–e**) have been synthesised. The cation binding ability of the new lariat ethers was evaluated by the picrate extraction method. The substituents at the nitrogen atom were not a major influence on the cation extraction ability of the azacrown ether; the compounds showed, however, a significant asymmetric induction as phase transfer catalysts in the Michael addition of 2-nitropropane to chalcone (95% ee).

Introduction

Optically active crown ethers, and within these, the carbohydrate-based macrocycles are able to produce asymmetric induction in certain reactions. Although numerous crown ethers incorporating one or more monosaccharide units have been synthesised [1], only a few proved to be effective phase transfer catalysts in enantioselective reactions [2]. A representative group of these compounds is the chiral lariat ethers containing methyl-α-D-glucopyranose moieties [3]. It is known that armed azacrown ethers, especially lariat ethers (azacrown ethers with heteroatom-containing podand arms) have a unique guest specificity via the macroring-side arm cooperativity [4].

We have shown that in the chiral lariat ethers derived from monosaccharides, the substituents on the nitrogen atom have a significant effect not only on the coordinating ability of the macrocycles, but also on their catalytic activity in enantioselective reactions [5]. The effect of phosphorus-containing side arms on the complexing abilities of macrocycles has been studied in simple achiral azacrown ethers [6]. It was also observed that using D-glucose-based monoaza-15-crown-5 ethers with phosphonoalkyl side chains as phase transfer catalyst in a Michael addition, the asymmetric induction was dependent on the length of the side arm [7]. It was a challenge for us to synthesise D-glucose-based azacrown ethers with phosphinoxidoalkyl side chains of different length on the nitrogen atom to study their complexing properties and applicability to enantioselective reactions.

Experimental

The ^{31}P-, ^{13}C- and ^{1}H NMR spectra were taken on a Bruker DRX-500 spectrometer recorded at 202.4, 125.7 and 500 MHz, respectively. Chemical shifts are downfield relative to 85% H_3PO_4 or TMS. The couplings are given in Hz. 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 synthesised as described earlier [3]. The ω-bromoalkylphthalimides (**1b–e**) were prepared as described earlier [8], except for 1-bromomethylphthalimide (**1a**) which was synthesised according to [9].

General procedure for the preparation of ω-aminoalkylphosphine oxides **3a–e**

A solution of 15.2 mmol of ω-bromoalkylphthalimide (**1a–e**) and 3.5 g (15.2 mmol) of ethyldiphenylphosphonite in 10 mL of dry toluene was stirred at room temperature for 10 minutes, then the solvent was removed. The residue was kept

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at 150 °C for 12 h. After cooling to 25 °C, the mixture was taken up in 25 mL chloroform. The solvent was filtered off and the filtrate was concentrated *in vacuo*. The product was purified by column chromatography (silica gel, 2% methanol in chloroform) to give **2a–e**.

To 9 mmol of **2** in 60 mL of abs. ethyl alcohol was added 0.6 mL (12.7 mmol) of 98% hydrazine hydrate and the contents of the flask were stirred at reflux for 1 h. The mixture was cooled to 25 °C and 37% HCl was added to ensure pH = 1. Then the mixture was stirred at the boiling point for 0.5 h. After filtering off the insoluble material the volatile components were removed *in vacuo* and then the residue was taken up in 25 mL chloroform. Then the insoluble material was filtered off to afford **3a–e** after evaporation.

*Diphenyl 1-aminomethylphosphine oxide (***3a***)*

2a: Yield 60%; m.p. 205–206 °C, [lit. [10] 206–207 °C]; ^{31}P NMR ($CDCl_3$) δ 27.2; ^{1}H NMR ($CDCl_3$) δ 4.61 (d, J = 5.35, 2H, C(α)H$_2$), 7.37–7.90 (m, 14H, Ar); ^{13}C NMR ($CDCl_3$) δ 38.9 (C_a), 123.5 (C_4), 128.7 (J = 12.1, $C_{3'}$), 131.5 (J = 9.7, $C_{2'}$), 131.9 (C_2), 132.5 (J = 2.3, $C_{4'}$), 133.2 (J = 98.5, $C_{1'}$), 134.2 (C_3), 167.2 (C_1); MS, *m/z* 361 (M^+, 23), 201 (P(O)Ph$_2$, 100), 160 (M^+-P(O)Ph$_2$, 24). Microanalysis: calcd. for $C_{21}H_{16}NO_3P$ m.w. 361, C 69.80, H 4.46, N 3.88%; found C 69.75, H 4.49, N 3.86%.

3a: Yield 82%; m.p. 100 °C, [lit. [11] 101–102 °C]; ^{31}P NMR ($CDCl_3$) δ 29.5; ^{1}H NMR ($CDCl_3$) δ 4.06 (s, 2H, C(α)H$_2$), 7.05–7.85 (m, 10H, Ar), 8.91(s, 2H, NH$_2$); ^{13}C NMR ($CDCl_3$) δ 37.7 (J = 71.3, C_a), 129.0 (J = 12.4, $C_{3'}$), 131.4 (J = 10.3, $C_{2'}$), 132.9 (J = 2.2, $C_{4'}$), 133.5 (J = 98.1, $C_{1'}$); MS, *m/z* 231 (M^+, 3), 202 (P(O)Ph$_2$ + H^+,100). Microanalysis: calcd. for $C_{13}H_{14}NOP$ m.w. 231, C 67.52, H 6.10, N 6.06%; found C 67.48, H 6.14, N 6.00%.

*Diphenyl 2-aminoethylphosphine oxide (***3b***)*

2b: Yield 63%; m.p. 155–158 °C, [lit. [12] 164–167 °C]; ^{31}P NMR ($CDCl_3$) δ 29.3; ^{1}H NMR ($CDCl_3$) δ 2.72–2.81 (m, 2H, C(α)H$_2$), 4.04–4.12 (m, 2H, C(b)H$_2$), 7.40–7.82 (m, 14H, Ar); ^{13}C NMR ($CDCl_3$) δ 28.8 (J = 69.4, Ca), 32.1 (C_b), 123.4 (C_4), 128.9 (J = 11.9, $C_{3'}$), 131.0 (J = 9.6, $C_{2'}$), 132.2 (C_2), 132.1 (J = 2.0, $C_{4'}$), 132.4 (J = 99.1, $C_{1'}$), 134.1 (C_3), 167.9 (C_1); MS, *m/z* 375 (M^+, 5), 202 (P(O)Ph$_2$ + H^+, 100), 173 (M^+-(P(O)Ph$_2$ + H), 27). Microanalysis: calcd. for $C_{22}H_{18}NO_3P$ m.w. 375, C 70.39, H 4.83, N 3.73%; found C 70.34, H 4.84, N 3.70%.

3b: Yield 89%; m.p. 68–70 °C, [lit. [13] 70–74 °C]; ^{31}P NMR ($CDCl_3$) δ 35.1; ^{1}H NMR ($CDCl_3$) δ 2.85–3.10 (m, 2H, C(α)H$_2$), 3.10–3.42 (m, 2H, C(b)H$_2$), 7.20–7.97 (m, 10H, Ar), 8.67 (s, 2H, NH2); ^{13}C NMR ($CDCl_3$) δ 27.3 (J = 70.5, C_a), 34.8 (C_b), 129.2 (J = 12.0, $C_{3'}$), 131.0 (J = 9.2, $C_{3'}$), 131.9 (J = 2.3, $C_{4'}$), 132.8 (J = 98.1, $C_{1'}$); MS, *m/z* 245 (M^+, 5), 215 (CH$_2$P(O)Ph$_2$, 97), 202 (P(O)Ph$_2$ + H^+, 91), 201 (P(O)Ph$_2$, 100). Microanalysis: calcd. for $C_{14}H_{16}NOP$ m.w. 245, C 68.55, H 6.58, N 5.71%; found C 68.58, H 6.54, N 5.68%.

*Diphenyl 3-aminopropylphosphine oxide (***3c***)*

2c: Yield 65%; m.p. 111–113 °C; ^{31}P NMR ($CDCl_3$) δ 32.6; ^{1}H NMR ($CDCl_3$) δ 1.95–2.04 (m, 2H, C(b)H$_2$), 2.30–2.36 (m, 2H, C(α)H$_2$), 3.76 (t, J = 6.73, 2H, C(g)H$_2$), 7.40–7.85 (m, 14H, Ar); ^{13}C NMR ($CDCl_3$) δ 21.3 (J = 3.0, C_b), 27.5 (J = 72.4, C_a), 38.6 (J = 17.0, C_g), 123.4 (C_4), 128.8 (J = 11.6, $C_{3'}$), 130.9 (J = 9.7, $C_{2'}$), 132.2 (C_2), 132.0 (J = 2.4, $C_{4'}$), 132.5 (J = 99.3, $C_{1'}$), 134.1 (C_3), 168.4 (C_1); MS, *m/z* 389 (M^+, 3), 216 (CH$_2$P(O)Ph$_2$ + H^+, 78), 215 (CH$_2$P(O)Ph$_2$, 100), 201 (P(O)Ph$_2$, 56). Microanalysis: calcd. for $C_{23}H_{20}NO_3P$ m.w. 389, C 70.94, H 5.18, N 3.60%; found C 70.98, H 5.22, N 3.58%.

3c: Yield 83%; m.p. 49–51 °C; ^{31}P NMR ($CDCl_3$) δ 36.0; ^{1}H NMR ($CDCl_3$) δ 1.93–2.08 (m, 2H, C(b)H$_2$), 2.55–2.68 (m, 2H, C(α)H$_2$), 3.03–3.17 (m, 2H, C(g)H$_2$), 7.21–7.86 (m, 10H, Ar), 8.59 (s, 2H, NH$_2$); ^{13}C NMR ($CDCl_3$) δ 19.9 (J = 3.0, C_b), 26.7 (J = 71.4, C_a), 40.4 (J = 13.5, C_g), 129.0 (J = 11.9, $_{3'}$), 131.0 (J = 9.4, $C_{2'}$), 132.1 (J = 2.4, $C_{4'}$), 132.4 (J = 98.5, $C_{1'}$); MS, *m/z* 259 (M^+, 4), 201 (P(O)Ph$_2$, 100). Microanalysis: calcd. for $C_{15}H_{18}NOP$ m.w. 259, C 69.48, H 7.00, N 5.40%; found C 69.53, H 7.02, N 5.38%.

*Diphenyl 3-aminobutylphosphine oxide (***3d***)*

2d: Yield 61%; m.p. 98–100 °C; ^{31}P NMR ($CDCl_3$) δ 33.0; ^{1}H NMR ($CDCl_3$) δ 1.56–1.65 (m, 2H, C(b)H$_2$), 1.72–1.80 (m, 2H, C(g)H$_2$), 2.26–2.36 (m, 2H, C(α)H$_2$), 3.61 (t, J = 7.05, 2H, C(d)H2), 7.36–7.77 (m, 14H, Ar); ^{13}C NMR ($CDCl_3$) δ 18.6 (J = 3.3, C_b), 29.1 (J = 72.4, C_a), 29.4 (J = 15.0, C_g), 37.0 (C_d), 123.2 (C_4), 128.7 (J = 11.6, $C_{3'}$), 130.8 (J = 9.3, $C_{2'}$), 132.0 (C_2), 131.7 (J = 1.9, $C_{4'}$), 132.7 (J = 98.6, $C_{1'}$), 134.0 (C_3), 168.3 (C1); MS, *m/z* 403 (M^+, 4), 201 (P(O)Ph$_2$, 100). Microanalysis: calcd. for $C_{24}H_{22}NO_3P$ m.w. 403, C 71.45, H 5.50, N 3.47%; found C 71.53, H 5.52, N 3.48%.

3d: Yield 75%; m.p. 35–37 °C; ^{31}P NMR ($CDCl_3$) δ 36.4; ^{1}H NMR ($CDCl_3$) δ 1.51–1.65 (m, 2H, C(b)H$_2$), 1.80–1.93 (m, 2H, C(g)H$_2$), 2.23–2.36 (m, 2H, C(α)H$_2$), 3.83–3.96 (m, 2H, C(d)H$_2$), 7.27–7.77 (m, 10H, Ar), 8.39 (s, 2H, NH$_2$); ^{13}C NMR ($CDCl_3$) δ 18.9 (J = 3.0, C_b), 28.2 (C_g), 28.6 (J = 69.8, C_a), 39.3 (C_d), 128.9 (J = 11.8, $C_{3'}$), 130.8 (J = 9.5, $C_{2'}$), 131.8 (J = 2.1, $C_{4'}$), 132.4 (J = 98.1, $C_{1'}$); MS, *m/z* 273 (M^+, 4), 257 ((CH$_2$)$_4$P(O)Ph$_2$, 16), 244 ((CH$_2$)$_3$P(O)Ph$_2$, 29), 229 ((CH$_2$)$_2$P(O)Ph$_2$, 28), 216 (CH$_2$P(O)Ph$_2$ + H^+, 53), 215 (CH$_2$P(O)Ph$_2$, 86), 202 (P(O)Ph$_2$ + H^+,100), 201 (P(O)Ph$_2$, 55). Microanalysis: calcd. for $C_{16}H_{20}NOP$ m.w. 273, C 70.31, H 7.38, N 5.12%; found C 70.35, H 7.41, N 5.08%.

*Diphenyl 3-aminopentylphosphine oxide (***3e***)*

2e: Yield 71%; oil; ^{31}P NMR ($CDCl_3$) δ 32.7; ^{1}H NMR ($CDCl_3$) δ 1.39–1.47 (m, 2H, C(g)H$_2$), 1.60–1.70 (m, 4H, C(b)H$_2$, C(d)H$_2$), 2.20–2.30 (m, 2H, C(α)H$_2$), 3.61 (t, J = 7.10, 2H, C(e)H$_2$), 7.38–7.85 (m, 14H, Ar); ^{13}C NMR ($CDCl_3$) δ 21.1 (J = 3.4, C_b), 28.2 (C_d), 28.3 (J = 16.4, C_g), 29.7 (J = 71.8, Ca), 37.8 (C_e), 123.3 (C_4), 128.6 (J

= 11.4, $C_{3'}$), 130.9 (J = 9.5, $C_{2'}$), 132.2 (C_2), 131.8 (J = 1.9, $C_{4'}$), 133.0 (J = 98.1, $C_{1'}$), 134.0 (C_3), 168.5 (C_1); MS, *m/z* 417 (M^+, 6), 257 ($(CH_2)_4P(O)Ph_2$, 97), 216 ($CH_2P(O)Ph_2 + H^+$, 100), 215 ($CH_2P(O)Ph_2$, 96) 202 ($P(O)Ph_2 + H^+$, 92) 201 ($P(O)Ph_2$, 93). Microanalysis: calcd. for $C_{25}H_{24}NO_3P$ m.w. 417, C 71.93, H 5.79, N 3.36%; found C 71.95, H 5.81, N 3.38%.

3e: Yield 85%; oil; ^{31}P NMR ($CDCl_3$) δ 37.4; ^1H NMR ($CDCl_3$) δ 1.40–1.62 (m, 4H, C(b)H_2, C(g)H_2), 1.69–1.83 (m, 2H, C(d)H_2), 2.28–2.43 (m, 2H, C(α)H_2), 2.86–3.02 (m, 2H, C(e)H_2), 7.34–7.78 (m, 10H, Ar), 8.38 (s, 2H, NH_2); ^{13}C NMR ($CDCl_3$) δ 20.4 (J = 3.0, C_b), 26.2 (C_d), 27.0 (J = 14.4, C_g), 28.2 (J = 70.8, C_a), 39.1 (C_e), 128.5 (J = 11.7, $C_{3'}$), 130.5 (J = 9.1, $C_{2'}$), 131.8 (J = 2.5, $C_{4'}$), 132.8 (J = 98.3, $C_{1'}$); MS, *m/z* 287 (M^+, 3), 201 ($P(O)Ph_2$, 100). Microanalysis: calcd. for $C_{17}H_{22}NOP$ m.w. 287, C 71.05, H 7.72, N 4.87%; found C 71.01, H 7.75, N 4.82%.

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

4.2 g (40 mmol) of dry Na_2CO_3 was suspended in the solution of 5.5 mmol of the corresponding ω-aminoalkylphosphosphine oxide (**3a–e**) and 3.73 g (5.5 mmol) of bis-iodo compound **4** in 200 mL of dry acetonitrile under argon. The contents of the flask were stirred at the boiling point for 48 h until the disappearance of the bis-iodo compound (TLC). After cooling to 20 °C, the mixture was filtered and the filtrate washed with acetonitrile. The combined acetonitrile solution was concentrated *in vacuo*. The crude product obtained after evaporation was purified by column chromatography (silica gel, 5% methanol in chloroform) to give lariat ethers **5a–e**.

*Methyl-4, 6-O-benzylidene-2, 3-dideoxy-α-D-glucopyranosido[2, 3-h]-N-(diphenyl phosphinoxido-methyl-)-1,4,7,10-tetraoxa-13-azacyclopentadecane (**5a**)*

5a: Yield 65%; $[\alpha]_D^{20}$ + 30.33 (c 1, $CHCl_3$); m.p. 89–92 °C; ^{31}P NMR ($CDCl_3$) δ 28.70; ^1H NMR ($CDCl_3$) δ 2.58–2.95 (m, 4H, CH_2–N–CH_2), 3.34 (s, 3H, OMe), 3.39 (symm, 2H, C(a)H_2), 3.97 (symm, 1H, C_6–H), 4.17 (d, J = 5.80, ^1H, C_6–H), 4.89 (symm, 1H, C_1–H), 5.45 (s, ^1H, C_7–H), 7.18–7.72 (m, ^{15}H, Ar); ^{13}C NMR ($CDCl_3$) d 54.4 (C_α), 55.3 (MeO), 55.8 (CH_2–N–CH_2), 62.5 (C_5), 68.8 (C_6), 81.7 (C_2), 97.2 (C_1), 101.3 (C_7), 126.0 ($C_{2'}$), 128.3 ($C_{3'}$), 128.9 ($C_{4'}$), 129.0 (J = 12.6, $C_{3''}$), 129.1 (J = 12.6, $C_{(3''')'}$), 130.7 (J = 8.8, $C_{2''}$), 130.8 (J = 8.8, $C_{(2''')'}$), 131.6 (J = 97.5, $C_{1''}$), 131.8 (J = 97.6, $C_{(1'')}$), 132.4 ($C_{4''}$), 137.1 ($C_{1'}$). MS-FAB *m/z*, 654 (M + H); HRFAB $(M + H)_{found}$ = 654.2841, $C_{35}H_{45}NO_9P$ requires 654.2832.

*Methyl-4, 6-O-benzylidene-2, 3-dideoxy-α-D-glucopyranosido[2, 3-h]-N-(diphenyl phosphinoxido-ethyl-)-1,4,7,10-tetraoxa-13-azacyclopentadecane (**5b**)*

5b: Yield 61%; $[\alpha]_D^{20}$ + 39.50 (c 1, $CHCl_3$); m.p. 97–100 °C; ^{31}P NMR ($CDCl_3$) δ 37.19; ^1H NMR ($CDCl_3$) δ 2.26–2.45 (m, 2H, C(a)H_2), 2.63–2.79 (m, 2H, C(b)H2), 2.79–2.95 (m, 4H, CH_2–N–CH_2), 3.47 (s, 3H, OMe), 4.24 (d, J = 10.55, ^1H, C_6–H), 4.29 (d, J = 6.19, ^1H, C_6–H), 5.03 (symm, ^1H, C_1–H), 5.60 (s, ^1H, C_7–H), 7.30–7.85 (m, 15H, Ar); ^{13}C NMR ($CDCl_3$) d 26.2 (J = 68.6, C_α), 47.9 (C_b), 52.9 (CH_2–N–CH_2), 54.6 (MeO), 61.6 (C_5), 68.0 (C_6), 81.2 (C_2), 97.3 (C_1), 100.4 (C_7), 125.3 ($C_{2'}$), 127.6 ($C_{3'}$), 128.3 ($C_{4'}$), 128.2 (J = 12.1, $C_{3''}$), 129.9 (J = 9.6, $C_{2''}$), 131.4 (J = 2.0, $C_{4''}$), 131.5 (J = 101.0, $C_{1''}$), 136.4 ($C_{1'}$). MS-FAB *m/z*, 668 (M + H); HRFAB, $(M + H)_{found}$ = 668.2971, $C_{36}H_{47}NO_9P$ requires 668.2988.

*Methyl-4, 6-O-benzylidene-2, 3-dideoxy-α-D-glucopyranosido[2, 3-h]-N-diphenyl phosphinoxido-propyl-)-1,4,7,10-tetraoxa-13-azacyclopentadecane (**5c**)*

5c: Yield 52%; $[\alpha]_D^{20}$ + 29,67 (c 1, $CHCl_3$); m.p. 99–101 °C; ^{31}P NMR ($CDCl_3$) δ 33.99; ^1H NMR ($CDCl_3$) δ 1.69–2.89 (m, 2H, C(b)H_2), 2.25–2.40 (m, 2H, C(a)H_2), 2.41–3.02 (m, 6H, CH_2–N–CH_2, C(g)H_2), 3.42 (s, 3H, OMe), 4.09 (symm, 1H, C_6–H), 4.24 (d, J = 5.80, ^1H, C_6–H), 4.94 (symm, 1H, C_1–H), 5.53 (s, 1H, C_7–H), 7.30–7.82 (m, 15H, Ar); ^{13}C NMR ($CDCl_3$) d 21.0 (C_b), 27.4 (J = 71.4, C_α), 51.7 (C_g), 53.9 (CH_2–N–CH_2), 55.2 (MeO), 62.6 (C_5), 68.8 (C_6), 81.9 (C_2), 97.2 (C_1), 101.3 (C_7), 125.4 ($C_{2'}$), 128.3 ($C_{3'}$), 129.1 ($C_{4'}$), 128.5 (J = 12.5, $C_{3''}$), 130.8 (J = 8.8, $C_{2''}$), 131.9 ($C_{4''}$), 132.6 (J = 101.0, $C_{1''}$), 137.2 ($C_{1'}$). MS-FAB *m/z*, 682 (M + H); HRFAB, $(M + H)_{found}$ = 682.3152, $C_{37}H_{49}NO_9P$ requires 682.3145.

*Methyl-4, 6-O-benzylidene-2,3-dideoxy-α-D-glucopyranosido[2, 3-h]-N-(diphenyl phosphinoxido-butyl-)-1,4,7,10-tetraoxa-13-azacyclopentadecane (**5d**)*

5d: Yield 58%; $[\alpha]_D^{20}$ + 28.89 (c 1, $CHCl_3$); m.p. 90–92 °C; ^{31}P NMR ($CDCl_3$) δ 35.03; ^1H NMR ($CDCl_3$) δ 1.45–1.60 (m, 2H, C(b)H_2), 1.60–1.75 (m, 2H, C(g)H_2), 2.20–2.42 (m, 2H, C(a)H_2), 2.42–2.59 (m, 2H, C(d)H_2), 2.64–2.85 (m, 4H, CH_2–N–CH_2), 3.34 (s, 3H, OMe), 4.07 (symm, 1H, C_6–H), 4.16 (d, J = 5.65, 1H, C_6–H), 4.90 (symm, 1H, C_1–H), 5.42 (s, 1H, C_7–H), 7.17–7.82 (m, 15H, Ar).; ^{13}C NMR ($CDCl_3$) d 19.3 (J = 2.5, C_b), 26.1 (J = 12.0, C_g), 27.6 (J = 71.0, C_a), 52.9 (C_d), 53.4 (CH_2–N–CH_2), 54.8 (MeO), 61.9 (C5), 68.3 (C_6), 81.5 (C_2), 96.5 (C_1), 100.7 (C_7), 125.5 ($C_{2'}$), 127.8 ($C_{3'}$), 128.4 (J = 12.0, $C_{3''}$), 128.5 ($C_{4'}$), 130.2 (J = 9.0, $C_{2''}$), 131.5 ($C_{4''}$), 132.3 (J = 99.0, $C_{1''}$), 136.6 ($C_{1'}$). MS-FAB *m/z*, 696 (M + H); HRFAB, $(M + H)_{found}$ = 696.3294, $C_{38}H_{51}NO_9P$ requires 696.3301.

*Methyl-4, 6-O-benzylidene-2,3-dideoxy-α-D-glucopyranosido[2, 3-h]-N-(diphenyl phosphinoxido-pentyl-)-1,4,7,10-tetraoxa-13-azacyclopentadecane (**5e**)*

5e: Yield 59%; $[\alpha]_D^{20}$ + 28.05 (c 1, $CHCl_3$); m.p. 89–92 °C; ^{31}P NMR (CDCl3) δ 36.00; ^1H NMR ($CDCl_3$) δ 1.38–1.75 (m, 6H, C(b)H_2, C(g)H_2, C(d)H_2), 2.04–2.23 (m, 2H, C(a)H_2), 2.64–2.85 (m, 4H, CH_2–N–CH_2), 3.39 (s, 3H, OMe), 4.16 (symm, 1H, C_6–H), 4.22 (d, J = 5.90, 1H, C_6–H), 4.92 (symm, 1H, C_1–H), 5.47 (s, 1H, C_7–H), 7.28–7.85 (m, 15H, Ar); MS-FAB *m/z*, 710 (M + H); HRFAB (M + H)$_{found}$ = 710.3471, $C_{39}H_{53}NO_9P$ requires 710.3458.

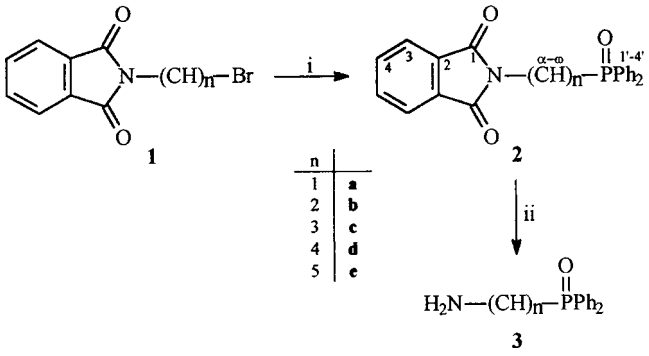
General procedure for the Michael addition of 2-nitropropane to chalcone in the presence of azacrown **5a–e**

0.1 mmol of the appropriate azacrown (**5a–e**) and 0.05 g (0.5 mmol) of sodium *tert*-butoxide were added to the solution of 0.3 g (1.44 mmol) of chalcone (**7**) and 0.3 mL (3.36 mmol) of 2-nitropropane in 3 mL of dry toluene. The mixture was stirred under an argon atmosphere at room temperature. After a reaction time of 48 h, 7 mL of toluene was added and the mixture was extracted with 10 mL of water. The organic phase was washed with 7 mL of water, and dried (Na_2SO_4). The crude product obtained after evaporation was purified by preparative TLC (silica gel, hexane–ethyl acetate (10 : 1) eluant) to give **8** in a pure form; m.p. 146–148 °C; $[\alpha]_D^{20}$ + 80.8 (c 1.5, dichloromethane) for the pure (+)-(*S*) enantiomer.[5b] ^1H NMR ($CDCl_3$) 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).

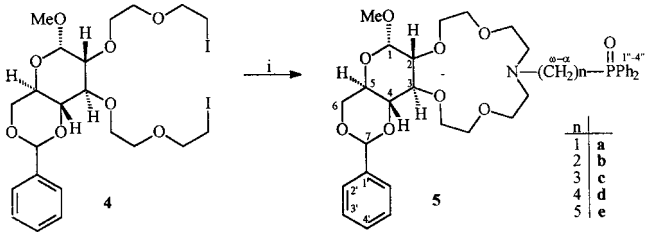
Results and discussion

*Synthesis of new azacrown ethers (**5a–e**)*

We used a method described previously [3, 7] for the synthesis of the new lariat ethers. The key intermediates, ω-aminoalkylphosphine oxides **3a–e** were prepared by a modified Gabriel synthesis (Scheme 1) in two steps. Intermediates **2a–e** were prepared by the Arbuzov reaction of bromoalkylphthalimides and ethyl-diphenylphosphinite. The α-D-glucose-based bis-iodo podand **4** [3] was cyclized with the aminoalkylphosphine oxides **3a–e** in boiling acetonitrile in the presence of sodium carbonate (Scheme 2). To avoid the intermolecular condensation, the reaction was performed in a diluted solution. The crude product obtained after 48 hours of reflux was purified by column chromatography. The yields were 52–65%. The products **5a–e** were characterized by ^{31}P, ^1H and ^{13}C NMR, as well as mass spectroscopic data. The ^1H and ^{13}C NMR spectral parameters were similar to those of azacrown derivatives described earlier [6b, 7]. In the ^{13}C NMR spectra of products **5a**, we observed that the signals of the two phenyl groups were duplicated due to the diastereotopy. This phenomenon was not observed in other cases for homologues. The elemental composition of **5a–e** was supported by HR-FABMS.



Scheme 1. Reagents and conditions: (i) PPh_2OEt, PhMe, 150 °C, 12 h, (ii) $(H_2N).H_2O$, EtOH, 78 °C, 1 h then HCl, 78 °C, 30 min.

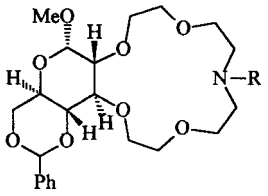


Scheme 2. Reagents and conditions: (i) $H_2N(CH_2)_nP(O)(OEt)_2$ (**3a–e**), CH_3CN, 82 °C, 48 h.

*Extracting properties of the new azacrown ethers (**5a–e**)*

The phase transfer catalytic properties (in a liquid-liquid system) of the newly synthesised crown ethers **5a–e** were characterised by the extraction of picrate salts (lithium, sodium, potassium and ammonium picrates) from water to dichloromethane following the procedure described by Kimura *et al.* [14]. 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 reference compound [5a] has a surprisingly high extracting ability (EA) towards the cation investigated but does not show a notable selectivity to any of the alkali- or ammonium cations (EA: 87–96%). (Selectivity indicates the difference between the alkali metal picrate extraction capabilities of host molecules.) The introduction of a phosphinoxidoalkyl side arm onto the nitrogen atom of the crown ether ring resulted in either similar or lower EA values than the corresponding values of **6**. As can be seen, the extracting properties (complex forming ability) of the compounds depend on the length of the chain connecting the nitrogen atom and the P=O moiety. Among the phosphinoxidoalkyl-azacrown ethers (**5a–e**), compound **5c** with a three carbon atom connecting chain forms the most stable complexes with all of the cations examined (72–91%) and compound **5a** having one methylene group between the N and the P atoms shows the lowest EA values (36–61%). The selectivity of the macrocycles is also dependent on their structure; the former compound (**5c**) possesses the best discrimination ability between the cations: it

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



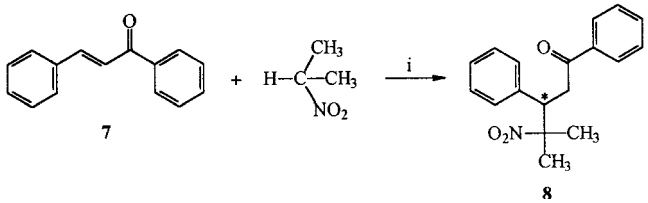
Compound	R	Extractability (%)[a]			
		Li^+	Na^+	K^+	NH_4^+
5a	$(CH_2)P(O)Ph_2$	36	61	50	48
5b	$(CH_2)_2P(O)Ph_2$	73	73	65	65
5c	$(CH_2)_3P(O)Ph_2$	72	91	90	89
5d	$(CH_2)_4P(O)Ph_2$	73	89	86	86
5e	$(CH_2)_5P(O)Ph_2$	72	85	82	82
6	H	87	87	96	98

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

transports close to two times more sodium picrate (EA: 61%) into the organic phase than lithium picrate (EA: 36%). The other compounds show a very modest improvement in the selectivity as compared to unsubstituted crown ether **6**. All of the new macrocycles form the weakest complexes with the lithium ion and the strongest complexes with the sodium ion under our conditions. The sequence for the cation binding ability was generally $Na^+ > K^+ \sim NH_4^+ > Li^+$ in our experiments. The complex impact of the N-substituents is presumably due to steric and electronic effects. The presence of the phosphinoxidoalkyl side chains obviously gives rise to some steric hindrance in the complexation. On the other hand, the phosphinoxidoalkyl moiety affects the electron density on the nitrogen atom. In the case of a longer bridge between the P and the N atoms (**5b–5e**) it can be regarded as an electron-releasing group; consequently it 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 P=O moiety.

*Chiral induction by the new azacrown ethers (**5a–e**)*

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 the 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 optical rotation ($[\alpha]_D$) of product **8** and comparing this value with the literature data of the pure enantiomer and by ^1H NMR spectroscopy using (+)-Eu(hfc)$_3$ as a 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 had a



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

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

Entry	Catalyst	Yield (%)[b]	ee (%)[c]
1	**5a**	39	60
2	**5b**	41	74
3	**5c**	32	77
4	**5d**	43	95 (94)[d]
5	**5e**	37	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 optical rotation.
[d] Determined by ^1H NMR spectroscopy.

significant influence on both the yield and the asymmetric induction.

Apparently, azacrown ethers **5a–e** are not too efficient phase transfer catalysts in the solid-liquid phase Michael addition mentioned above: after a 48 hour period of stirring, adducts **8** were formed only in 39–53% chemical yield. The new catalysts **5a–e** showed, however, significant asymmetric induction: an enantiomeric excess of 60–95% was detected (Table 2). As a comparison, the use of the unsubstituted azacrown ether **6** reported earlier resulted in an enantiomeric excess of 61% [5a]. As can be seen, the length of the chain connecting the nitrogen atom to the P=O moiety has a major influence on the enantioselectivity. The catalyst having the shortest side arm **5a** was as efficient as the reference compound **6** (ee: 60–61%). The use of azacrown ethers with longer arms (**5b** and **5c**) resulted in a significant increase in the enantioselectivity (ee: 74–77%). Among the catalysts tested lariat ether **5d**, connecting the P=O group by a four carbon atom chain to the nitrogen, proved to be the best: a record enantiomer excess of 95% was observed for the (*S*)-(+)-**8** adduct (until now, the highest value in this reaction was 87% [7]). Compound **5e** possessing a five carbon atom chain induced a smaller ee value (79%).

As can be seen, the length of the side arm plays an important role in the asymmetric induction. Four CH_2 units seem to be the optimum length for the carbon chain of the catalyst for this Michael reaction. Similarly to the complexing ability, the enantioselectivity induced by the chiral lariat ethers is also influenced by the length of the N-substituent. This is in accord with the expectation, as the phase transfer catalyzed Michael reaction also involves a complex between the macrocycle and the sodium cation. During the interaction of the chiral complex formed from 2-nitropropane, NaOtBu

and the lariat ether, and the activated double bond of the chalcone (**7**), the discrimination is affected by the length of the side arm. The exceptionally high enantiomeric excess of the reaction catalysed by compound **5d** is of interest and remains to be explained by a thorough molecular mechanics calculation.

Acknowledgements

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