Synthesis of Branched Polyether Ligands Designed for Selective Complexation of Small Cations

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Dale, J. and Fredriksen, S. B., 1992. Synthesis of Branched Polyether Ligands Designed for Selective Complexation of Small Cations. – Acta Chem. Scand. 46: 271–277.

Singly branched symmetrical tri- and hexa-ether ligands have been prepared, starting from 2-hydroxymethyl-2-methyl-1,3-propanediol (as alkoxide). Singly branched un-symmetrical tetra- and penta-ether ligands have also been made by a step-wise procedure, converting first the triol into 3-hydroxymethyl-3-methyloxetane. It proved advantageous also to prepare the symmetrical ligands by such a multi-step procedure.

Via the same oxetane intermediate, a doubly branched penta-ether ligand was also prepared.

The tricyclic cage molecule 1 (Fig. 1) would be expected to exist in a highly symmetrical diamond-lattice conformation, offering perfect octahedral hexacoordination to small cations such as Li^+ and Mg^{2+}, and has served as our guide in the design of novel ligands containing only 1,5-related ether oxygens as compared with the 1,4 ether oxygens as found in most other polyether ligands. Thus, macrocyclic ligands like 1,5,9,13-tetraoxacyclohexadecane and 1,5,9-trioxacyclododecane can be identified in structure 1, and we have already shown[1,2] that the latter (12-crown-3) is the stronger complexing agent since it can only realize its unique diamond-lattice conformation in the complexed state, while the former (16-crown-4) is the weaker com-plexing agent because of competition from an alternative and perfect diamond-lattice conformation adopted by the free ligand.

In addition to these macrocyclic ligands, a variety of branched ligands can obviously be derived from the same cage molecule 1 (Fig. 1). It was of interest to prepare such molecules for comparison of the 'branching effect' with the 'macrocyclic effect' in facilitating the organization of ether oxygens around a cation. We now report the synthesis of four such ligands (3, 4, 5, 6) each of which contains one branching point (which must be a quaternary carbon for reasons of chemical stability). We also describe the syn-theses of three related structurally 'mixed' ligands (7, 8, 9)
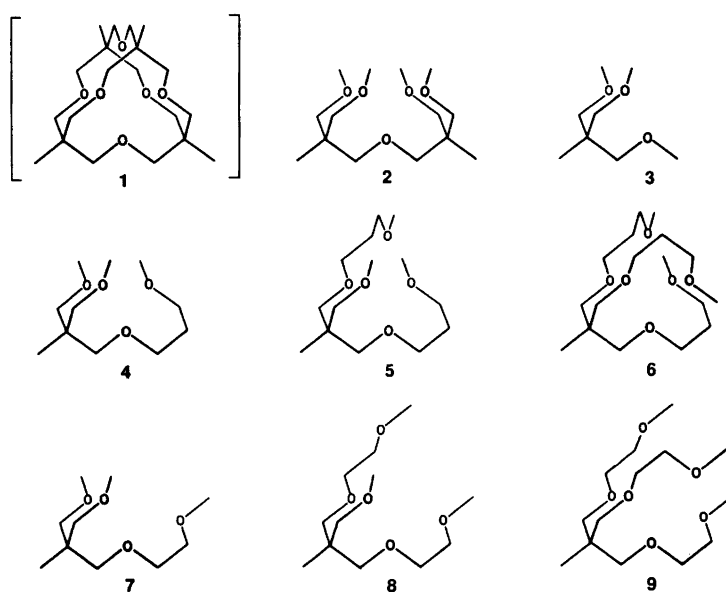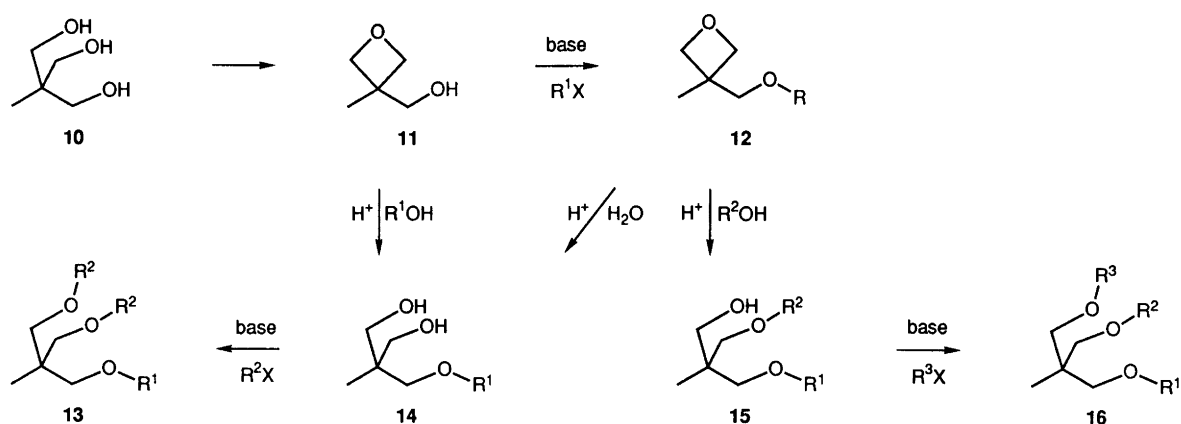

Fig. 1. Polyether ligands drawn in the diamond-lattice conformation with convergent ether oxygens as required for complexation.

Scheme 1.

in which a 1,4-dioxa system instead of a 1,5-dioxa system is present in each elongated branch. Finally, we report the synthesis of one ligand (2) containing two branching points.

A brief survey of these syntheses and the complexation properties of such ligands has already been presented.[2]

Synthesis of singly branched ligands by one-pot alkylation of a triol. The obvious starting material for the synthesis of the trigonally symmetrical ligands **3**, **6** and **9** is 2-hydroxy-methyl-2-methyl-1,3-propanediol **10** (Scheme 1). In view of the well-established difficulty in preparing ethers from neo-pentyl bromide,[3,4] and the fact that it is possible to alkylate neopentyl alcohol,[5] we chose to use the triol as the alkoxide partner in the Williamson synthesis (although it is known that the corresponding tribromide indeed reacts with nucleophiles[6–8] and hence shows no 'neopentyl effect'). As alkylating agents were used methyl iodide for **3**, 3-methoxypropyl iodide (or tosylate) for **6**, and 2-methoxy-ethyl iodide (or tosylate) for **9**. The most favourable base system was NaH in THF.[9] However, in agreement with reported observations,[10] the reaction was extremely slow even with methyl iodide. A mixture containing incompletely methylated products was obtained after two days at 35 °C using an excess of base and the alkylating reagent. The tris-methylated product **3** could be separated from the less volatile mono- and bis-methyl derivatives by distillation (max. yield 54 %). Even lower yields were obtained in DMSO or tetraglyme, or by using methyl tosylate.

Similarly, use of an excess of 2-methoxyethyl iodide as the alkylating agent, led only to a mixture of alkylated products after 14 days at reflux. Although the yield of the tris-alkylated compound **9** was 67 % by GLC analysis, the isolated yield after column chromatography was only 33 %. No improvement was obtained using DMF or DMSO at 100 °C.

With 3-methoxypropyl iodide under optimum conditions (NaH in refluxing THF), the yield of the tris-alkylated compound **6** was still lower (30 % by GLC analysis), and only 8 % could be isolated by column chromatography, the remainder being mono- and bis-alkylated intermediates.

It is thus possible to obtain in low yield, by a one-pot homo-alkylation of 2-hydroxymethyl-2-methyl-1,3-pro-panediol, the symmetrical ligands **3**, **6** and **9**. The steadily decreasing rate is probably not due to increasing steric hindrance (see below), but rather to the observed copious precipitation of sodium iodide (or tosylate) as the reaction proceeds, which may occlude the alkoxide reagents.

Synthesis of singly branched ligands via oxetane intermediates. Instead of direct tris-alkylation of 2-hydroxy-methyl-2-methyl-1,3-propanediol **10** to produce the symmetrical ligands **3**, **6** and **9**, the initial formation of the oxetane **11** (Scheme 1) would allow controlled monoalkyl-ation (**12**). Subsequent hydrolytic or alcoholytic ring opening followed by new alkylation would allow the synthesis of any such ligand **13** and **16** and hence provide a synthetic route also to the unsymmetrical ligands **4**, **5**, **7** and **8** (Fig. 1).

The preparation of the oxetane **11** from the triol **10** via the cyclic carbonate is particularly easy.[11] The subsequent preparation of the intermediate **12** proceeded in good yield (88 % for $R^1 = CH_3$; 73 % for $R^1 = CH_2CH_2OCH_3$; and 68 % for $R^1 = CH_2CH_2CH_2OCH_3$) as expected because of reduced steric hindrance when two branches are tied together to form the oxetane ring.[12–14]

The intermediates **14** and **15** were obtained by acid-catalysed solvolysis of the oxetanes **11** and **12** in water or the appropriate alcohol. Yields were in the range 50–75 %, and methanol was used in preference to higher alcohols whenever applicable, since the solvolysis was then faster and yields higher. In this way, the diol **14** ($R^1 = CH_3$) could be obtained by methanolysis of oxetane **11** in 60 % yield, and the diols **14** ($R^1 = CH_2CH_2OCH_3$) and **14** ($R^1 = CH_2CH_2CH_2OCH_3$) by hydrolysis of the oxetane **12** in 52 and 73 % yields, respectively. Similarly, the alcohols **15** ($R^1 = R^2 = CH_3$), **15** ($R^1 = R^2 = CH_2CH_2OCH_3$) and **15** ($R^1 = R^2 = CH_2CH_2CH_2OCH_3$) were obtained from a combination of the appropriately substituted oxetane **12** and the corresponding alcohol in yields of 76, 52 and 59 %, respectively. The mixed-structure alcohols **15** ($R^1 = CH_2CH_2OCH_3$,

$R^2 = CH_3$) and **15** ($R^1 = CH_2CH_2CH_2OCH_3$, $R^2 = CH_3$) were obtained by hydrolysis of the relevant oxetane **12** in yields of 75 and 74 %, respectively.

The final conversion of the alcohol **15** into the ligand **16**, and the diol **14** into ligand **13**, was effected by base and the appropriate alkylating agent, either as the iodide or as the tosylate, in THF. Thereby, the desired unsymmetrical ligands **4, 5, 7** and **8**, as well as the symmetrical ligands **6** and **9** already obtained, could be prepared. More than one combination could, of course, produced the same ligand, and it was found that the alcohols **15** ($R^1 = R^2 = CH_2CH_2OCH_3$) and **15** ($R^1 = R^2 = CH_2CH_2CH_2OCH_3$) were easily alkylated to give the symmetrical ligands **9** and **6** in high yield (81 and 73 %, respectively), while the corresponding diol **14** could not be completely alkylated with the same reagents. In reactions with methyl iodide, however, both alcohol **15** and diol **14** were easily methylated to give ligands **4, 5, 7** and **8** in yields of 86, 87, 96 and 75 %, respectively.

To sum up, it is remarkable that this multi-step procedure (oxetane formation, alkylation, oxetane ring opening and final alkylation) should be more efficient than direct one-pot tris-alkylation using an excess of the alkylating reagent. Clearly, increasing steric hindrance as substituents are introduced is not the explanation, and occlusion of the alkoxide reagent with the precipitated salts in the one-pot reaction seems likely.

Synthesis of a doubly branched ligand. The conversion of the oxetane alcohol **11** into its ether **18** (Scheme 2) should provide a route to the simplest doubly branched ligand **2**. An attempt, for this purpose, to convert the alcohol **11** into the chloride using thionyl chloride resulted in a cyclic sulfite as the main product. The preparation of the tosylate **17** was, on the other hand, straightforward and the ether **18** could be obtained in a yield of 74 %. Acid-catalysed ring opening in water or methanol provided the tetraol **19** or the diol **20** (isomer mixture) in yields of 68 and 80 % respectively. Both could be methylated with CH_3I–NaH–THF to furnish the same tetramethoxy ligand **2**, the yield from **19** being 68 %.

All of the ligands **2–9** are stable distillable liquids. As already communicated,[2] the most promising complexing agent for Li, considering both complexation strength and selectivity *vis-à-vis* Na, is the doubly branched penta-ether **2**, even though ligands **6** and **9** are both hexa-ethers. Our detailed complexation studies will be the subject of a separate paper.

Experimental

2-Methoxyethyl tosylate, 3-methoxypropyl tosylate, 2-methoxyethyl iodide and 3-methoxypropyl iodide were prepared by standard procedures.[15]

Synthesis of ligands **3, 6** *and* **9** *by one-pot reactions.*

4-Methoxymethyl-4-methyl-2,6-dioxaheptane[16] (**3**). The procedure was similar to that described for **6** below, using the triol **10** (10.5 g, 87 mmol), methyl iodide (74.1 g, 522 mmol), sodium hydride (80 % suspension in oil, 10.3 g, 340 mmol) and dry THF (150 ml). The total reaction time was 2 days at 35 °C. The product mixture was distilled to give pure **3**, yield 7.6 g (54 %), b.p. 152–154 °C, and a fraction (b.p. 160–194 °C) containing the mono- and bis-methylated derivatives. ^1H NMR (200 MHz, CD_3CN): δ 0.89 (3 H, s, CH_3), 3.12 (6 H, s, CH_2O), 3.27 (9 H, s, CH_3O).

8-(2,6-Dioxaheptyl)-8-methyl-2,6,10,14-tetraoxapentadecane (**6**). The reaction was run under nitrogen. The triol **10** (4.0 g, 33 mmol) was dissolved in dry THF (100 ml). Sodium hydride (80 % dispersion in oil, 1.10 g, 37 mmol) was added, and the mixture was refluxed for 2 days. 3-Methoxypropyl iodide (8.60 g, 43 mmol) dissolved in THF (20 ml) was added to the suspension, and the reaction mixture was refluxed for 2 days. This addition procedure was repeated three times. The reaction mixture was analysed at regular intervals by GLC–MS. The total reaction time was 14 days. After cooling, most of the solvent was evaporated off, ether was added to the residue, and precipitated sodium iodide was filtered off. The ether solution was washed consecutively with dilute sodium thiosulfate
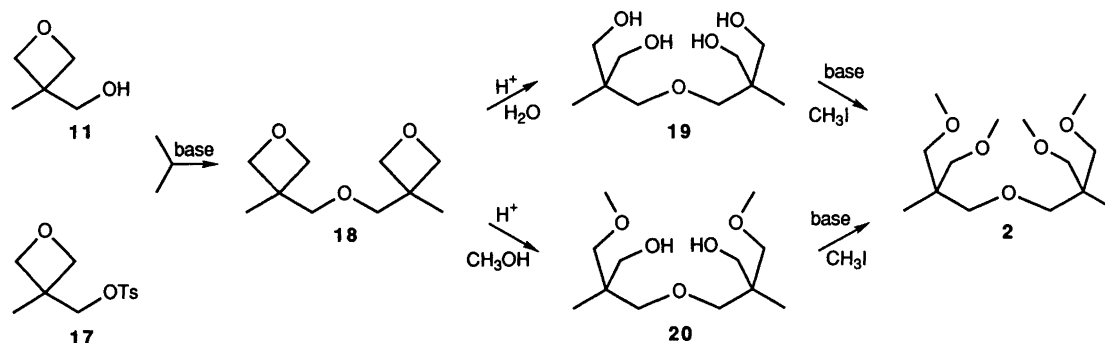
Scheme 2.

solution and water, and dried (MgSO$_4$), and the solvent was evaporated. The residue was distilled through a Vigreux column to give a fraction (1.3 g, b.p. 30–100 °C/0.05 mmHg) containing the by-product 1,6-dimethoxyhexane (due to a Wurtz-reaction) in addition to **14** (R^1 = CH$_2$CH$_2$CH$_2$OCH$_3$) and **15** (R^1 = R^2 = CH$_2$CH$_2$OCH$_3$), and a fraction (1.2 g, b.p. 100–130 °C/0.01 mmHg) containing **15** (R^1 = R^2 = CH$_2$CH$_2$CH$_2$OCH$_3$) and **6**. The mono- and bis-alkylated intermediates were identified by GLC–MS. Only the symmetrical ligand **6** was isolated by column chromatography on neutral alumina (Fluka Type 507 C) with ethyl acetate–hexane (1:1) as the eluant. Yield 0.89 g (8 %), colourless oil. ^{1}H NMR (200 MHz, CD$_3$CN): δ 0.87 (3 H, s, CH$_3$), 1.74 (6 H, quint., J 6.4 Hz, CH$_2$), 3.21 (6 H, s, CH$_2$O), 3.25 (9 H, s, CH$_3$O), 3.39 (6 H, t, J 6.4 Hz, CH$_2$O), 3.41 (6 H, t, J 6.4 Hz, CH$_2$O). ^{13}C NMR (75 MHz, CD$_3$CN): δ 17.9, 30.7, 41.7, 58.7, 68.9, 70.2, 74.0. MS (CI, isobutane, m/z >100, rel. int. >10 %): 337 (100), 247 (13), 191 (22), 157 (14), 143 (54), 103 (26).

A small quantity of 1,6-dimethoxyhexane was isolated by preparative GLC. ^{1}H NMR (60 MHz, CDCl$_3$): δ 1.4 (4 H, m, CH$_2$), 1.8 (4 H, m, CH$_2$), 3.3 (6 H, s, CH$_3$O), 3.4 (4 H, m, CH$_2$O). MS (CI, isobutane, m/z >100, rel. int. >10 %): 147 (67), 115 (100).

7-(2,5-Dioxahexyl)-7-methyl-2,5,9,12-tetraoxatridecane (**9**). The procedure was similar to that described above, using the triol **10** (6.5 g, 54 mmol), 2-methoxyethyl iodide (37.2 g, 200 mmol), sodium hydride (80 % suspension in oil, 7.0 g, 233 mmol) and dry THF (100 ml). The total reaction time was 14 days. Distillation of the crude product after work-up gave a fraction (2.2 g, b.p. 80–94 °C/0.01 mmHg) containing the mono- and di-alkylated compounds **14** (R^1 = CH$_2$CH$_2$OCH$_3$) and **15** (R^1 = R^2 = CH$_2$CH$_2$OCH$_3$), and a fraction (6.3 g, b.p. 94–100 °C/0.01 mmHg) containing the di- and tri-alkylated compounds **15** (R^1 = R^2 = CH$_2$CH$_2$OCH$_3$) and **9**. The symmetrical ligand **9** was isolated by column chromatography on neutral alumina (Fluka Type 507 C) with ethyl acetate–hexane (1:1) as the eluant. Yield 5.3 g (33 %), colourless oil. ^{1}H NMR (200 MHz, CD$_3$CN): δ 0.87 (3 H, s, CH$_3$), 3.26 (6 H, s, CH$_2$O), 3.29 (9 H, s, CH$_3$O), 3.43–3.51 (12 H, m, OCH$_2$CH$_2$O). ^{13}C NMR (75 MHz, CD$_3$CN): δ 17.8, 41.7, 59.0, 71.7, 72.5, 74.4. MS (CI, isobutane, m/z >100, rel. int. >5 %): 295 (43), 219 (13), 163 (24), 143 (100), 129 (25).

3-(2,5-Dioxahexyl)-3-methyloxetane (**12**, R^1 = CH$_2$CH$_2$OCH$_3$). Method A. The reaction was run under nitrogen. 3-Hydroxymethyl-3-methyloxetane[11] (**11**) (8.00 g, 780 mmol) was dissolved in dry THF (100 ml). Sodium hydride (80 % dispersion in oil, 2.38 g, 790 mmol) was added, and the mixture was refluxed for 1 day. 2-Methoxyethyl tosylate (18 g, 790 mmol) dissolved in dry THF (30 ml) was added, and the reaction mixture was refluxed for 2 days. After cooling, the THF was evaporated off, ether was added to the residue, and precipitated sodium tosylate was filtered off. The ether solution was washed with water and dried

(MgSO$_4$). The solvent was evaporated, and the residue was distilled through a Vigreux column. Yield 9.2 g (73 %), b.p. 93–98 °C/15 mmHg.

Method B. The procedure was similar, but using 2-methoxyethyl iodide as the alkylating reagent **12** (R^1 = CH$_2$CH$_2$OCH$_3$) was obtained in a yield of 70 %. ^{1}H NMR (60 MHz, CDCl$_3$): δ 1.30 (3 H, s, CH$_3$), 3.40 (3 H, s, CH$_3$O), 3.6–3.8 (6 H, m, CH$_2$O), 4.40 (4 H, q, J 6 Hz, CH$_2$ ring). MS (CI, isobutane, m/z > 100 rel. int. > 5 %): 161 (29), 131 (51).

3-(2,6-Dioxaheptyl)-3-methyloxetane (**12**, R^1 = CH$_2$CH$_2$CH$_2$OCH$_3$). The procedure was as described above, using 3-hydroxymethyl-3-methyloxetane[11] (**11**) (15.3 g, 150 mmol), 3-methoxypropyl iodide (30 g, 150 mmol), sodium hydride (80 % dispersion in oil, 4.8 g, 160 mmol) and dry THF (350 ml). The crude product was distilled through a Vigreux column. Yield 17.4 g (68 %), b.p. 120–122 °C/18 mmHg. ^{1}H NMR (60 MHz, CDCl$_3$): δ 1.30 (3 H, s, CH$_3$), 1.85 (2 H, quint., J 6 Hz, CH$_2$), 3.35 (3 H, s, CH$_3$O), 3.48 (2 H, s, CH$_2$O), 3.5–3.6 (4 H, m, CH$_2$O), 4.43 (4 H, q, J 6 Hz, CH$_2$ ring). MS (CI, isobutane): 175 (MH)$^+$.

General procedure for the synthesis of diols **14** and alcohols **15**. The oxetane (**11**, **12**) was dissolved in water or the appropriate alcohol (methanol, 2-methoxyethanol or 3-methoxypropanol), conc. H$_2$SO$_4$ (5–15 drops) was added, and the reaction mixture was stirred until GLC analysis showed that all the oxetane had reacted. The reaction mixture was neutralized with solid sodium hydrogen carbonate, the solvent was evaporated (water, methanol, 2-methoxyethanol) or recovered by distillation (3-methoxypropanol). The residue was dissolved in ether or dichloromethane, and the solution was washed with water. After drying (MgSO$_4$), the solvent was evaporated off, and the crude product was distilled through a Vigreux column or in a columnless distillation flask.

2-Methoxymethyl-2-methyl-1,3-propanediol (**14**, R^1 = Me). 3-Hydroxymethyl-3-methyloxetane[11] (**11**) (2.70 g, 26.4 mmol), conc. H$_2$SO$_4$ (10 drops), methanol (25 ml). The reaction time was 9 h at reflux. Yield 2.1 g (60 %), b.p. 60–62 °C/0.04 mmHg. ^{1}H NMR (60 MHz, CDCl$_3$): δ 0.85 (3 H, s, CH$_3$), 3.23 (2 H, br s, OH), 3.35 (5 H, br s, CH$_2$O, CH$_3$O), 3.60 (4 H, br s, CH$_2$OH).

2-(2,5-Dioxahexyl)-2-methyl-1,3-propanediol (**14**, R^1 = CH$_2$CH$_2$OCH$_3$). Oxetane **12** (R^1 = CH$_2$CH$_2$OCH$_3$) (1.61 g, 10.0 mmol), conc. H$_2$SO$_4$ (5 drops), water (10 ml). The reaction time was 20 h at 80 °C. Yield 0.93 g (52 %), b.p. 86–88 °C/0.04 mmHg. MS (CI, isobutane): 179 (MH)$^+$.

2-(2,6-Dioxaheptyl)-2-methyl-1,3-propanediol (**14**, R^1 = CH$_2$CH$_2$CH$_2$OCH$_3$). Oxetane **12** (R^1 = CH$_2$CH$_2$CH$_2$OCH$_3$) (1.50 g, 8.61 mmol), conc. H$_2$SO$_4$ (5 drops), water (10 ml). The reaction time was 24 h at 80 °C. Yield 1.2 g (73 %), b.p. 95–96 °C/0.001 mmHg. ^{1}H NMR (60 MHz, CDCl$_3$):

δ 0.85 (3 H, s, CH$_3$), 1.82 (2 H, quint., CH$_2$), 3.05 (2 H, br s, OH), 3.40–3.60 (15 H, m, CH$_2$O, CH$_3$O, CH_2OH).

2-Methoxymethyl-2-methyl-4-oxa-1-pentanol[16] *(15, R^1 = R^2 = CH$_3$).* 3-Methoxymethyl-3-methyloxetane[17] *(12, R^1 = CH$_3$) (21.4 g, 184 mmol), conc. H$_2$SO$_4$ (20 drops), methanol (100 ml). The reaction time was 10 h at reflux. Yield 20.7 g (76%), b.p. 99–100 °C/12 mmHg. ^{1}H NMR (60 MHz, CDCl$_3$): δ 0.87 (3 H, s, CH$_3$), 2.87 (1 H, t, OH), 3.33 (10 H, br s, CH$_2$O, CH$_3$O), 3.53 (2 H, d, CH_2OH).

2-(2,5-Dioxahexyl)-2-methyl-4,7-dioxa-1-octanol (15, R^1 = R^2 = CH$_2$CH$_2$OCH$_3$). Oxetane 12 (R^1 = CH$_2$CH$_2$OCH$_3$) (6.20 g, 38.7 mmol), conc. H$_2$SO$_4$ (15 drops), 2-methoxyethanol (25 ml). The reaction time was 12 h at 40 °C and then 1 h at reflux. Yield 4.8 g (52%), b.p. 93–95 °C/0.01 mmHg. ^{1}H NMR (60 MHz, CDCl$_3$): δ 0.88 (3 H, s, CH$_3$), 3.10 (1 H, br s, OH), 3.40–3.60 (20 H, m, CH$_2$O, CH$_3$O, CH_2OH). MS (CI, isobutane): 237 (MH)$^+$.

2-(2,6-Dioxaheptyl)-2-methyl-4,8-dioxa-1-nonanol (15, R^1 = R^2 = CH$_2$CH$_2$CH$_2$OCH$_3$). Oxetane 12 (R^1 = CH$_2$CH$_2$CH$_2$OCH$_3$) (2.00 g, 11.5 mmol), conc. H$_2$SO$_4$ (5 drops), 3-methoxypropanol (9.0 g). The reaction time was 24 h at 60 °C. Yield 1.8 g (59%), b.p. 108–110 °C/0.001 mmHg. ^{1}H NMR (60 MHz, CDCl$_3$): δ 0.87 (3 H, s, CH$_3$), 1.87 (4 H, quint., CH$_2$), 3.10 (1 H, br s, OH), 3.40–3.60 (24 H, m, CH$_2$O, CH$_3$O, CH_2OH).

2-Methoxymethyl-2-methyl-4,7-dioxa-1-octanol (15, R^1 = CH$_2$CH$_2$OCH$_3$, R^2 = Me). Oxetane 12 (R^1 = CH$_2$CH$_2$-OCH$_3$) (7.50 g, 46.8 mmol), conc. H$_2$SO$_4$ (5 drops), methanol (60 ml). The reaction time was 3 h (reflux). Yield 6.7 g (75%), b.p. 133–138 °C/25 mmHg. ^{1}H NMR (60 MHz, CDCl$_3$): δ 0.90 (3 H, s, CH$_3$), 3.10 (1 H, br s, OH), 3.35–3.60 (16 H, m, CH$_2$O, CH$_3$O, CH_2OH).

2-Methoxymethyl-2-methyl-4,8-dioxa-1-nonanol (15, R^1 = CH$_2$CH$_2$CH$_2$OCH$_3$, R^2 = Me). Oxetane 12 (R^1 = CH$_2$CH$_2$CH$_2$OCH$_3$) (5.7 g, 28.7 mmol), conc. H$_2$SO$_4$ (15 drops), methanol (30 ml). The reaction time was 3 h (reflux). Yield 4.4 g (74%), b.p. 151–154 °C/25 mmHg. MS (CI, isobutane): 207 (MH)$^+$.

Synthesis of ligands 13 from diols 14.

4-Methoxymethyl-4-methyl-2,6,10-trioxaundecane (4). The diol 14 (R^1 = CH$_2$CH$_2$CH$_2$OCH$_3$) (0.79 g, 4.1 mmol) was dissolved in dry THF (15 ml), sodium hydride (80% dispersion in oil, 0.36 g, 12 mmol) was added, and the mixture was refluxed for 24 h. After cooling to 35 °C, methyl iodide (2.31 g, 16.3 mmol) was added, and the reaction mixture was stirred overnight. The solvent was evaporated off, ether was added to the residue, and precipitated sodium iodide was filtered off. The ether solution was washed consecutively with sodium thiosulfate solution and water, dried (MgSO$_4$), and the solvent was evaporated. The crude

product was pure by GLC and NMR. Yield 0.78 g (86%). ^{1}H NMR (200 MHz, CDCl$_3$): δ 0.93 (3 H, s, CH$_3$), 1.82 (2 H, quint., J 6.4 Hz, CH$_2$), 3.23 (4 H, s, CH$_2$O), 3.26 (2 H, s, CH$_2$O), 3.32 (6 H, s, CH$_3$O), 3.33 (3 H, s, CH$_3$O), 3.45 (2 H, t, J 6.4 Hz, CH$_2$O), 3.47 (2 H, t, J 6.4 Hz, CH$_2$O). ^{13}C NMR (50 MHz, CDCl$_3$): δ 17.9, 30.7, 41.5, 58.7, 59.5, 68.9, 70.2, 74.0, 76.2. MS (CI, isobutane, m/z ≥ 99, rel. int. > 4%): 221 (100), 189 (7), 157 (4), 133 (12), 131 (60), 103 (16), 99 (40).

7-Methoxymethyl-7-methyl-2,5,9-trioxadecane (7). The procedure was as described for 4, using the diol 14 (R^1 = CH$_2$CH$_2$OCH$_3$) (0.90 g, 5.0 mmol), sodium hydride (80% dispersion in oil, 0.36 g, 12 mmol) and methyl iodide (2.83 g, 19.9 mmol). The crude product was pure by GLC and NMR spectroscopy. Yield 1.0 g (96%). ^{1}H NMR (300 MHz, CDCl$_3$): δ 0.94 (3 H, s, CH$_3$), 3.24 (4 H, s, CH$_2$O), 3.31 (6 H, s, CH$_3$O), 3.32 (2 H, s, CH$_2$O), 3.38 (3 H, s, CH$_3$O), 3.50–3.58 (4 H, m, CH$_2$O). ^{13}C NMR (75 MHz, CD$_3$CN): δ 17.4, 40.8, 59.0, 59.3, 71.0, 71.9, 74.0, 75.8. MS (CI, isobutane, m/z > 98, rel. int. > 2%): 207 (9), 175 (3), 143 (11), 131 (37), 129 (11), 119 (24), 99 (100).

General procedure for the synthesis of ligands 16 from alcohols 15. The reaction was run under nitrogen. The alcohol was dissolved in dry THF and the solution was cooled, the base was added, and the mixture was refluxed overnight. Then the alkylating agent, dissolved in THF, was added, and the reaction mixture was refluxed until GLC analysis showed that all the alcohol had reacted. A slight excess was used both of the base and of the alkylating agent. The reaction mixture was cooled, and the solvent was evaporated off. Ether was added to the residue, precipitated salts were filtered off, and the ether solution was washed with water (also with sodium thiosulfate solution if an alkyl iodide had been used). After drying (MgSO$_4$), ether was evaporated, and the residue was distilled through a Vigreux column or in a columnless distillation flask.

4-Methoxymethyl-4-methyl-2,6,10-trioxaundecane (4). Compound 15 (R^1 = R^2 = Me) (4.00 g, 27.0 mmol), 3-methoxypropyl tosylate (8.21 g, 33.6 mmol), potassium (1.17 g, 30.0 mmol), THF (40 ml). The reaction mixture was refluxed for 3 days. Yield 4.5 g (76%), b.p. 98–100 °C/10 mmHg. For the spectral data, see above.

8-Methoxymethyl-8-methyl-2,6,10,14-tetraoxapentadecane (5). *Method A.* Compound 15 (R^1 = R^2 = CH$_2$CH$_2$CH$_2$OCH$_3$) (0.90 g, 3.4 mmol), sodium hydride (80% dispersion in oil, 0.14 g, 4.6 mmol), methyl iodide (1.3 g, 9.2 mmol), THF (10 ml). The reaction time was 1 day at 35 °C. The crude product was pure by GLC and NMR spectroscopy. Yield 0.82 g (87%).

Method B. Compound 15 (R^1 = CH$_2$CH$_2$CH$_2$OCH$_3$, R^2 = Me) (3.40 g, 16.5 mmol), sodium hydride (80% dispersion in oil, 0.60 g, 20.0 mmol), 3-methoxypropyl tosylate (4.89 g, 20.0 mmol), THF (30 ml). The reaction

mixture was refluxed for 3 days. Yield 2.8 g (61 %), b.p. 95–96 °C/0.001 mmHg. ^{1}H NMR (300 MHz, CDCl$_3$): δ 0.92 (3 H, s, CH$_3$), 1.82 (4 H, quint., J 6.4 Hz, CH$_2$), 3.23 (2 H, s, CH$_2$O), 3.26 (4 H, s, CH$_2$O), 3.31 (3 H, s, CH$_3$O), 3.33 (6 H, s, CH$_3$O), 3.45 (4 H, t, J 6.4 Hz, CH$_2$O), 3.46 (4 H, t, J 6.4 Hz, CH$_2$O). ^{13}C NMR (75 MHz, CDCl$_3$): δ 17.4, 30.0, 40.9, 58.6, 59.3, 68.2, 69.8, 73.5, 75.8. MS (CI, isobutane, m/z ≥99, rel. int. ≥7 %): 279 (100), 189 (30), 157 (23), 133 (23), 125 (77), 103 (29), 101 (11), 99 (38).

8-(2,6-Dioxaheptyl)-8-methyl-2,6,10,14-tetraoxapentadecane (6). Compound 15 (R^1 = R^2 = CH$_2$CH$_2$CH$_2$OCH$_3$) (1.40 g, 5.30 mmol), 3-methoxypropyl tosylate (1.90 g, 7.78 mmol), sodium hydride (80 % dispersion in oil, 0.18 g, 5.80 mmol), THF (15 ml). The reaction mixture was refluxed for 3 days. Yield 1.3 g (73 %), b.p. 109–112 °C/0.003 mmHg. For the spectral data, see above.

7-Methoxymethyl-7-methyl-2,5,9-trioxadecane (7). Compound 15 (R^1 = R^2 = Me) (5.00 g, 33.7 mmol), 2-methoxyethyl tosylate (8.20 g, 35.8 mmol), sodium hydride (80 % dispersion in oil, 1.0 g, 33 mmol), THF (50 ml). The reaction mixture was refluxed for 2 days. Yield 5.2 g (75 %), b.p. 86–87 °C/10 mmHg. For the spectral data, see above.

7-Methoxymethyl-7-methyl-2,5,9,12-tetraoxatridecane (8). *Method A.* Compound 15 (R^1 = R^2 = CH$_2$CH$_2$OCH$_3$) (0.90 g, 3.8 mmol), sodium (0.09 g, 3.9 mmol), methyl iodide (1.1 g, 7.8 mmol), THF (10 ml). The reaction mixture was stirred overnight at 35 °C. Yield 0.75 g (75 %), b.p. 60–61 °C/0.001 mmHg.

Method B. Compound 15 (R^1 = CH$_2$CH$_2$OCH$_3$, R^2 = Me) (4.00 g, 20.8 mmol), sodium hydride (80 % dispersion in oil, 0.69 g, 23 mmol), 2-methoxyethyl tosylate (6.30 g, 27.4 mmol), THF (50 ml). Yield 3.8 g (69 %), b.p. 106–108 °C/0.5 mmHg. ^{1}H NMR (300 MHz, CD$_3$CN): δ 0.87 (3 H, s, CH$_3$), 3.18 (2 H, s, CH$_2$O), 3.25 (3 H, s, CH$_3$O), 3.26 (4 H, s, CH$_2$O), 3.29 (6 H, s, CH$_3$O), 3.43–3.51 (8 H, m, CH$_2$O). ^{13}C NMR (75 MHz, CD$_3$CN): δ 17.8, 41.6, 59.0, 59.5, 71.7, 72.5, 74.4, 76.2. MS (CI, isobutane, m/z >98, rel. int. >10 %): 251 (38), 175 (25), 143 (38), 131 (11), 129 (55), 119 (22), 99 (51).

7-(2,5-Dioxahexyl)-7-methyl-2,5,9,12-tetraoxatridecane (9). *Method A.* Compound 15 (R^1 = R^2 = CH$_2$CH$_2$OCH$_3$) (0.50 g, 2.1 mmol), sodium hydride (80 % dispersion in oil, 0.06 g, 2.2 mmol), 2-methoxyethyl tosylate (0.51 g, 2.2 mmol), THF (10 ml). The reaction mixture was refluxed for 1 day. The crude product was pure by GLC and NMR spectroscopy. Yield 0.50 g (81 %).

Method B. Compound 15 (R^1 = R^2 = CH$_2$CH$_2$OCH$_3$) (2.00 g, 8.46 mmol), sodium hydride (80 % dispersion in oil, 0.31 g, 10.4 mmol), 2-methoxyethyl iodide (1.90 g, 10.2 mmol), THF (25 ml). The reaction mixture was refluxed

for 2 days. Yield 1.8 g (72 %), b.p. 95–99 °C/0.001 mmHg. For the spectral data, see above.

3-Methyl-3-toxyloxymethyloxetane (17). To a stirred and cooled solution of 3-hydroxymethyl-3-methyloxetane[11] (11) (15.0 g, 147 mmol) and pyridine (23.3 g, 292 mmol) in ethanol-free chloroform (15 ml) was slowly added tosyl chloride (28.0 g, 147 mmol) dissolved in chloroform (30 ml). The reaction mixture was then stirred at room temperature, and the reaction was followed by TLC (silica; ethyl acetate–hexane 1:1). The solution was poured on ice, the phases were separated and the organic phase was washed with dilute sodium hydrogen carbonate solution and water. The solution was dried (MgSO$_4$) and the solvent was evaporated off. The residue was crystallized from THF–hexane. Yield 30.1 g (80 %), m.på. 61–62 °C, white needles. ^{1}H NMR (60 MHz, CDCl$_3$): δ 1.33 (3 H, s, CH$_3$), 2.50 (3 H, s, ArCH$_3$), 4.17 (2 H, s, CH$_2$O), 4.40 (4 H, s, CH$_2$ ring), 7.65 (4 H, q, Ar-H).

Bis-(3-methyloxetan-3-ylmethyl) ether (18). The reaction was run under nitrogen. 3-Hydroxymethyl-3-methyloxetane[11] (11) (19.6 g, 192 mmol) was dissolved in dry THF (300 ml) and the solution was cooled to 0 °C. Sodium (4.41 g, 192 mmol) was added, and the mixture was refluxed until all of the sodium had reacted. 3-Methyl-3-tosyloxymethyloxetane (17) (49.2 g, 192 mmol) dissolved in dry THF (100 ml) was added, and the reaction mixture was refluxed for 48 h. After cooling, the solvent was evaporated off, ether was added to the residue, and precipitated sodium tosylate was filtered off. The ether phase was washed with water, dried (MgSO$_4$), and the solvent was evaporated off. The crude product was distilled through a Vigreux column. Yield 26.5 g (74 %), b.p. 110–111 °C/10 mmHg. ^{1}H NMR (60 MHz, CDCl$_3$): δ 1.33 (6 H, s, CH$_3$), 3.57 (4 H, s, CH$_2$O), 4.40 (4 H, q, J 6 Hz, CH$_2$ ring). MS (CI, isobutane): 187 (MH)$^+$.

2,6-Bis(hydroxymethyl)-2,6-dimethyl-4-oxa-1,7-heptanediol (19). A solution of the ether 18 (6.00 g, 32.2 mmol) and conc. H$_2$SO$_4$ (15 drops) in water (30 ml) was stirred at 60 °C for 20 h. After cooling, the mixture was neutralized with solid sodium hydrogen carbonate. Water was evaporated off, and final traces of water were azeotropically distilled off with ethanol. The crude product was dissolved in hot methanol, the solution was filtered, and the solvent was evaporated. The crude product was not further purified. Yield 4.9 g (68 %), m.p. 109–112 °C, white powder. ^{1}H NMR (60 MHz, CD$_3$OD): δ 0.88 (6 H, s, CH$_3$), 3.33 (4 H, s, CH$_2$O), 3.48 (8 H, s, CH_2OH).

2,6-Bis(methoxymethyl)-2,6-dimethyl-4-oxa-1,7-heptanediol (20). A solution of the ether 18 (1.00 g, 5.37 mmol) and conc. H$_2$SO$_4$ (5 drops) dissolved in methanol (10 ml) was refluxed for 10 h. After cooling, the reaction mixture was neutralized with solid sodium hydrogen carbonate, the

solution was filtered, and the solvent was evaporated off. The crude product was not further purified. Yield 1.1 g (80 %). ^{1}H NMR (200 MHz, CDCl$_3$): δ 0.82, 0.83 (6 H, s, CH$_3$), 3.31 (14 H, s, CH$_2$O, CH$_3$O), 3.34, 3.35 (2 H, t, OH), 3.5 (4 H, br s, CH$_2$OH). ^{13}C NMR (50 MHz, CDCl$_3$): δ 18.5, 41.6, 60.2, 69.3, 76.2, 78.2. MS (CI, isobutane): 251 $(MH)^+$.

4,8-Bis(methoxymethyl)-4,8-dimethyl-2,6,10-trioxaundecane (2). The tetraol 19 was methylated following the standard procedure described for 3, using the diol 19 (5.00 g, 22.5 mmol), sodium hydride (80 % dispersion in oil, 3.00 g, 100 mmol), methyl iodide (25.6 g, 180 mmol) and dry THF (60 ml). The reaction mixture was stirred for 2 days at 35 °C. The crude product was distilled through a Vigreux column. Yield 4.3 g (68 %), b.p. 72–74 °C/0.001 mmHg, colourless oil. ^{1}H NMR (200 MHz, CDCl$_3$): δ 0.93 (6 H, s, CH$_3$), 3.22 (4 H, s, CH$_2$O), 3.23 (8 H, s, CH$_2$O), 3.31 (12 H, s, CH$_3$O). ^{13}C NMR (50 MHz, CD$_3$CN): δ 17.9, 41.7, 59.4, 74.5, 76.2. MS (CI, isobutane, m/z > 100, rel. int. > 10 %): 279 (92), 161 (12), 131 (100).

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