

The Synthesis of 12-Crown-3 Ligands Carrying Ligating Side-arms

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Multi-step syntheses of 1,5,9-trioxacyclododecanes carrying methoxymethyl substituents in either one, two or all three of the ring positions 3, 7 and 11 are reported. The most successful route involves the elaboration of an appropriately substituted diol which is converted into a monotosylate and cyclized intramolecularly at moderate dilution. The side-arm may be present as such already in the diol chain, but more often as a precursor oxetane unit which is reductively opened after formation of the macrocycle. The less successful but simpler route involves the intermolecular reaction of a shorter diol chain with an appropriate di-iodide.

These novel ligands show enhanced complexation of Li^+ and Mg^{2+} with selectivity against Na^+ and Ca^{2+} . The conformation of the complexed ligand is of diamond-lattice type as predicted.

In earlier publications¹⁻⁵ we have shown that polyether ligands of 1,5-dioxa type, instead of the usual 1,4-dioxa type, give selective, although relatively weak, complex formation with Li^+ in preference to Na^+ . Among our reported ligand structures, open-chain polyethers with one or two branching points gave the least stable complexes.^{2,4} Macrocyclic ligands, especially those without substituents, gave the most stable Li^+ complexes, that of 12-crown-3 being more stable than that of 16-crown-4.^{1,2} However, the Li^+ selectivity shown by 16-crown-4 was completely lost in 12-crown-3, since, in this case, Na^+ formed a very stable 2:1 sandwich complex. It was possible to prevent Na^+ complexation by having geminal substituents in the 3-, 7- and 11-positions (3,3,7,7,11,11-hexamethyl-1,5,9-trioxacyclododecane), but the complexation strength for Li^+ then became very much reduced.^{1,2}

From this background it seemed possible that alkoxy-methyl substituents in one or more of the 3-, 7- and 11-positions might function both to prevent sandwich formation, hence Na^+ complexation, and to increase complex

stability by combining the macrocyclic effect with the branching effect in one and the same molecule.

The envisaged ligands in their expected complex conformations, with all ether oxygens converging towards a coordination centre of octahedral geometry, are shown in Fig. 1. For reasons of chemical stability during synthesis, the substituted ring carbons had to be quaternary. This was not considered a disadvantage, as an alkyl group on the branching point would render the back side of the ligand more lipophilic. Those units that carry no ligating side-arm could be left unsubstituted or be geminally dimethyl-substituted on the middle carbon atom. A major synthetic problem was foreseen when two or three side-arms are present; that of obtaining the desired *cis*-stereoisomer and suppressing the formation of the *trans*.

The hope was that the tetra- and penta-ethers **a** and **b** (Fig. 1) would be specific for Li^+ , excluding Na^+ because of size, Mg^{2+} because of insufficient coordination number, and Ca^{2+} for both reasons. A further hope was that the hexaether **c** (Fig. 1) would be specific for Mg^{2+} because of its higher charge and the possibility of obtaining full octahedral hexacoordination.

The general synthetic approach was to construct a symmetric open-chain diol and convert it into the monotosylate. This could then be cyclized with base in an intramolecular reaction, taking full advantage of the dilution conditions. The methoxymethyl side-arms were either present in the diol chain before cyclization (Schemes 1 and 3), or produced after cyclization by reductive cleavage of spiro-linked oxetane units present in the chain, followed by methylation (Schemes 2, 3 and 4). Intermolecular reactions between a shorter diol and a di-iodide (Schemes 4 and 5) to produce the macrocycle were less successful.

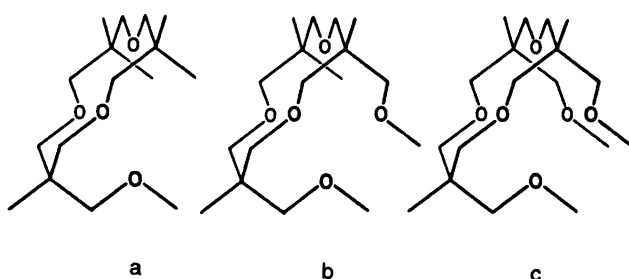
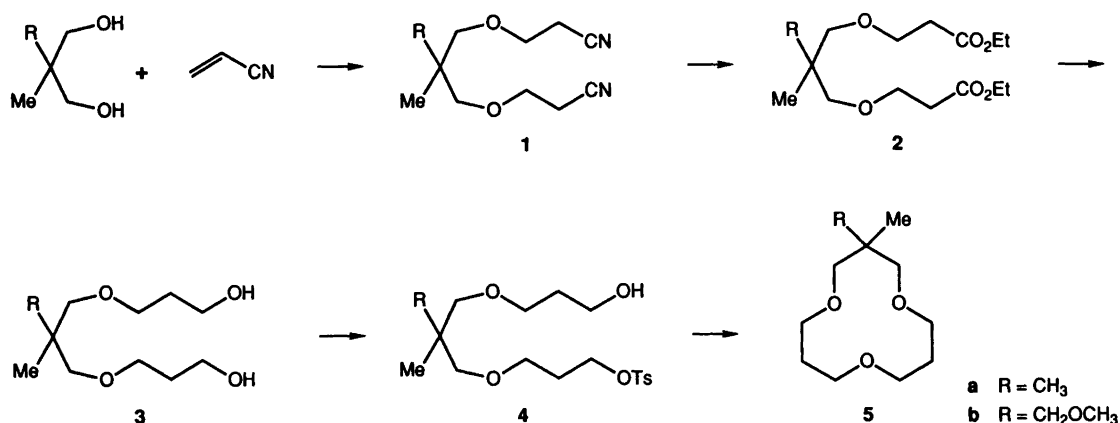


Fig. 1. Diamond-lattice conformations of 12-crown-3 ligands with one, two or three ligating side-arms. Methyl substituents are drawn in all vacant '3-positions'.



Scheme 1.

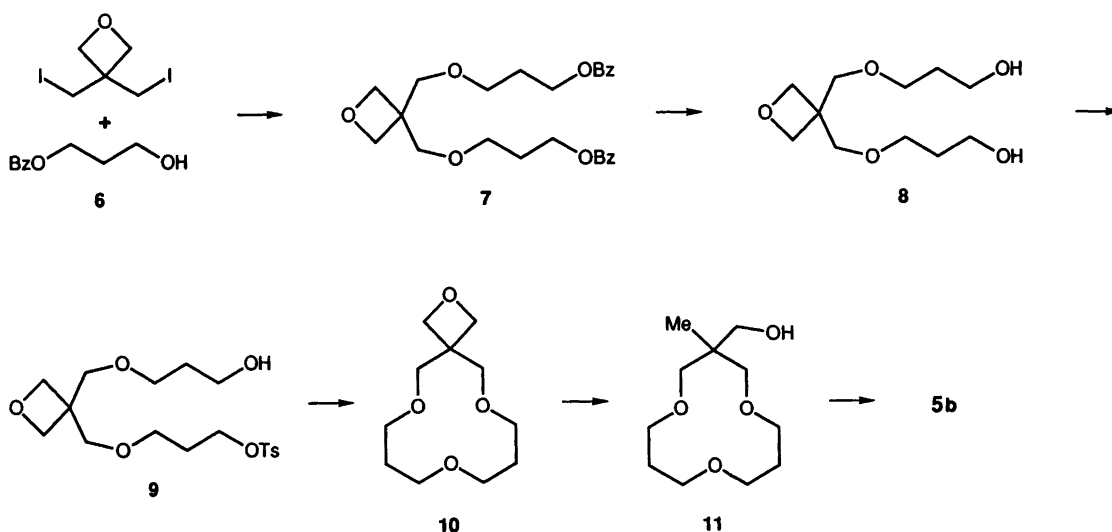
Preparation of diols. The diols **3a** and **3b** (Scheme 1) were made from the appropriately substituted 1,3-propanediol by double chain extension with acrylonitrile, followed by ester formation and LiAlH_4 reduction, each step in 60–90% yield. Attempts to prepare the diol **8** (Scheme 2) directly from 3,3-bis(iodomethyl)oxetane and a large excess of 1,3-propanediol gave a low yield (<30% by GLC) and serious separation problems. It became necessary to use a multi-step procedure via a mono-protected 1,3-propanediol (Scheme 2). Of the several protective groups tried out, the benzyl group was adopted in most cases, as it could be removed in the presence of the oxetane group by catalytic hydrogenation. Monobenzyl derivatives of 1,3-propanediol and 3,3-bis(hydroxymethyl)oxetane were prepared in yields of 48 and 41%, respectively.

The dibenzylated mono-oxetane **7** (Scheme 2) was obtained in 43% yield, and removal of the protection gave the diol **8** (78%). Similarly, the dibenzylated bis-oxetanes **13a**, **13b** and **13c** (Scheme 3) were obtained in 50–80% yield, and deprotection led to the diols **14a**, **14b** and **14c**, all

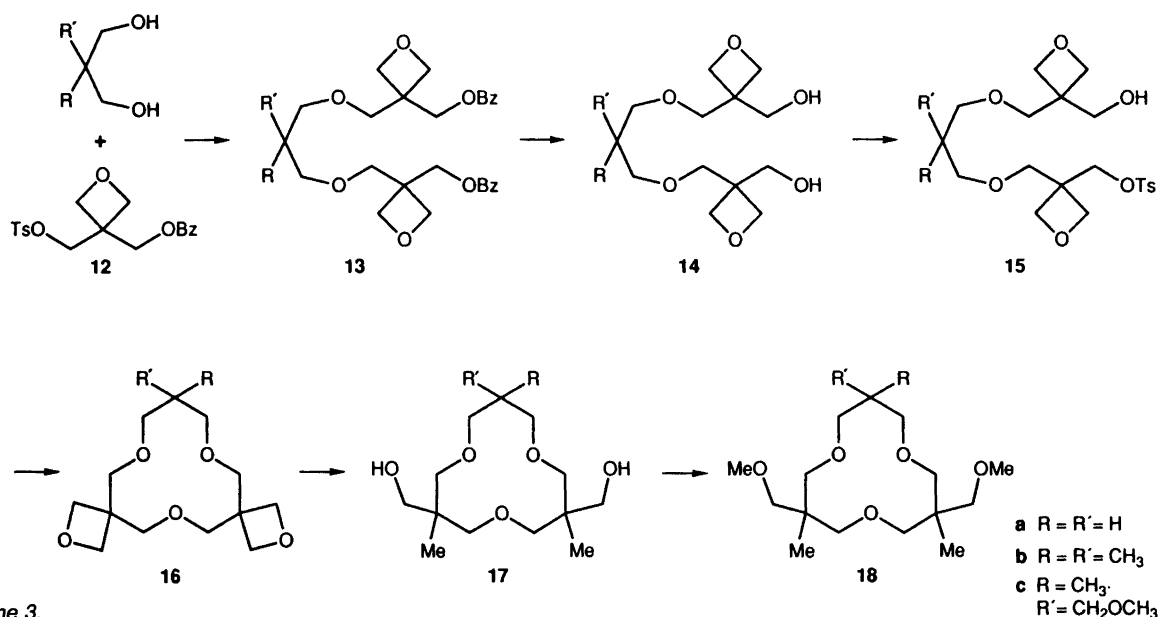
in 60–65% yield. The dibenzylated tris-oxetane **19** (Scheme 4) was prepared in 81% yield and deprotected to yield the diol **20** (99%). Finally, the diol **23** was obtained from its mono-tetrahydropyranyl ether in 96% yield.

Monotosylation of diols. The monotosylates **4a** and **4b** were obtained in yields of 33% by the standard method using tosyl chloride in CHCl_3 /pyridine. This reaction was slow, and it proved preferable to use NaH as a base in THF containing small amounts of DMSO. The reaction was then finished in less than 1 h at room temperature. A short reaction time was essential to avoid subsequent conversion into the chloride. The monotosylates **9**, **15a**, **15b**, **15c** and **21** were separated from the corresponding diols and ditosylates by repeated chromatography on silica in yields of 51, 33, 50, 49 and 22%, respectively.

Intermolecular cyclizations. Moderate dilution (ca. 0.03 M) was used, since the reaction rate becomes too slow under high-dilution conditions. The reaction between the tetra-



Scheme 2.

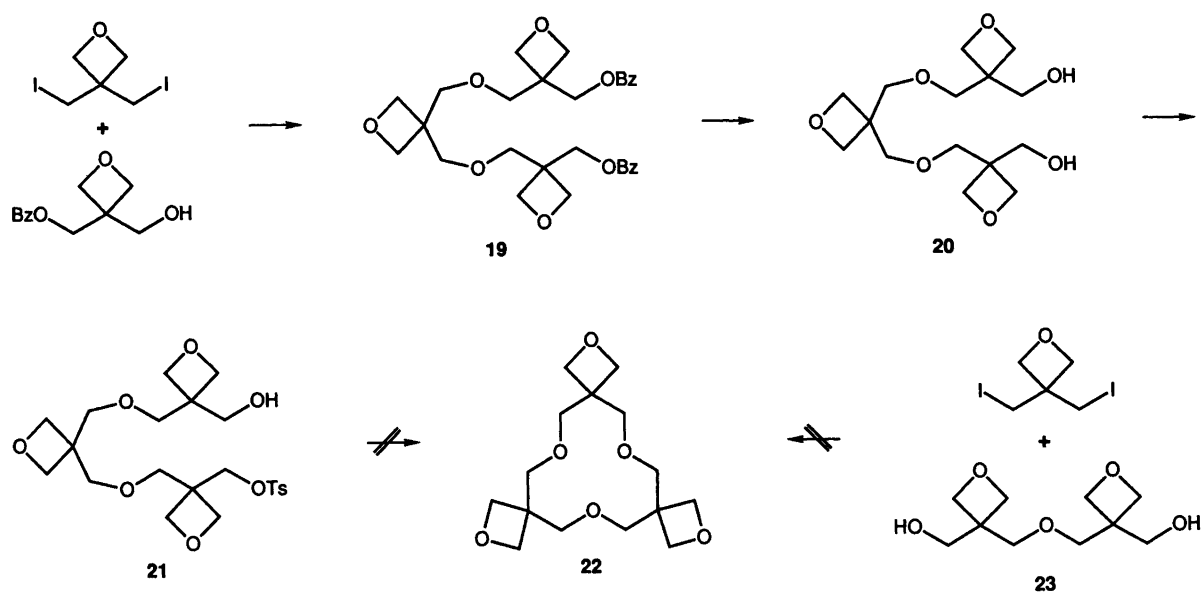


Scheme 3.

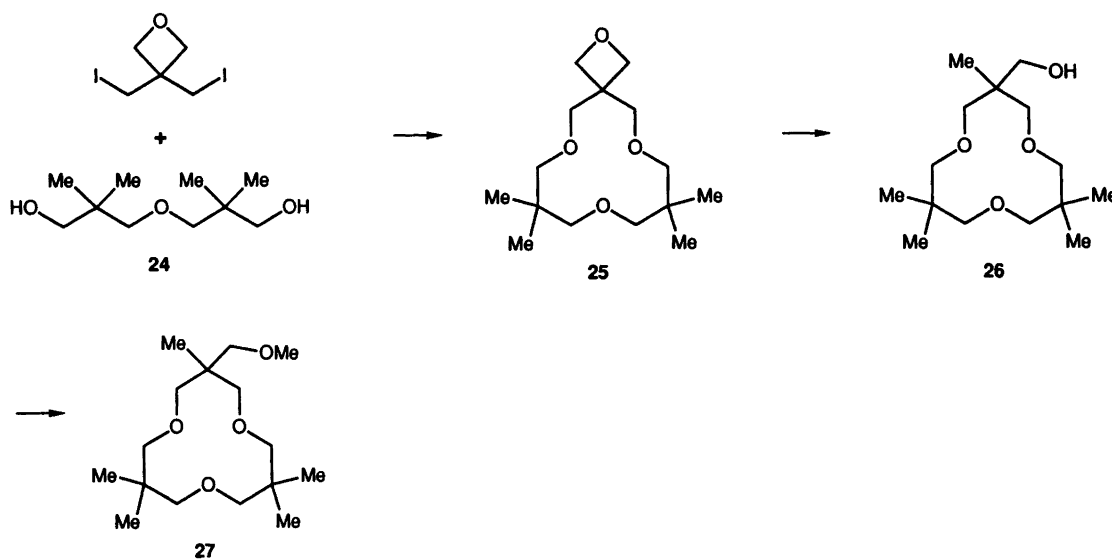
methylsubstituted diol **24** and 3,3-bis(iodomethyl)oxetane (Scheme 5) in DMSO, with NaH as the base, gave the macrocycle **25** in 19% yield. Attempts to make macrocycle **10** by this shorter route, using the same di-iodide and 4-oxa-1,7-heptanediol, resulted in less than 2–5% (GLC–MS) of the cyclic product.

The diol **23**, carrying two spiro-linked oxetane rings, gave, under the same conditions, no cyclic product **22** (Scheme 4). Also unsuccessful was the attempt to prepare a monospiro precursor for the hexaether **c** (Fig. 1) with two side-arms already present, from the reaction between 2,6-dimethyl-2,6-bis(methoxymethyl)-4-oxa-1,7-heptanediol and 3,3-bis(iodomethyl)oxetane.

Intramolecular cyclizations. Optimum cyclization reaction conditions were first worked out using the more easily accessible monotosylates **4a** and **4b**. Various combinations of bases (NaH, LiH, LDA) and solvents (THF, dioxane, DMF, DMA, DMSO) were tried at moderate dilution (0.03–0.07 M). The best result was obtained using LDA (lithium di-isopropylamide)/DMA at room temperature for 15 h, when GLC–MS analysis of the volatiles showed the presence of 90% cyclic product. The isolated yields of **5a** and **5b** were 55 and 48%, respectively. This system was first also adopted when the chain contained oxetane units to avoid the risk of ring cleavage, which is known to occur with BuLi.⁶ Later, it was found that such cleavage did not



Scheme 4.



Scheme 5.

actually take place when DMSO alone was the solvent. On addition of BuLi directly to the solution of the monotosylates **9**, **15a**, **15b** and **15c** in DMSO, the cyclized products **10**, **16a**, **16b** and **16c** (Schemes 2 and 3) were obtained in yields of 27, 48, 69 and 67%, respectively. No cyclized product **22** could, however, be obtained from the monotosylate **21** (Scheme 4). Thus, of the several possible intermediates for the synthesis of the hexaether **c** (Fig. 1), only the dispiro compound **16c** was obtained.

The optimized yield in the cyclization step shows an intriguing dependence on the substitution pattern along the chain (Table 1). Thus, when substituents are present only in the 6-position of the tosylate, the yield is high when these are methyl or methoxymethyl groups, but drops when these are tied together to form an oxetane unit. On the other hand, no reduction in yield is observed when oxetane units

occupy both the 2- and the 10-positions, provided the 6-carbon is unsubstituted or carries methyl or methoxymethyl substituents. When the 6-carbon also carries an oxetane unit, the yield drops to zero.

Similar trends are observed (Table 1) in the two-step intermolecular reactions, considering the structure of the intermediate that undergoes the last and decisive cyclization step. The yields however are much lower here.

We believe that these observations can be explained on the basis of the conformational situation of the chain before cyclization. Since all CO-bonds are strongly *anti*-preferred,⁷ the necessary chain folding that will allow the reactive end groups to meet can only take place at positions 2, 6 and 10. Such bending, obtained by forming a *gauche*⁺ *gauche*⁺ 'corner', is known to be the normal situation in this type of polyether.^{2,7} Furthermore, it is evident

Table 1. Yields in the cyclization of 11-tosyloxy-4,8-dioxa-1-undecanols^a and 11-iodo-4,8-dioxa-1-undecanols^b substituted in the 2-, 6-, or 10-position.

Reaction	2-Substituents	6-Substituents	10-Substituents	Isolated yields (%)
Intramolecular from monotosylate				
4a → 5a	None	Dimethyl	None	55
4b → 5b	None	Methyl, methoxymethyl	None	48
9 → 10	None	'Spiro-oxetane'	None	27
15a → 16a	'Spiro-oxetane'	None	'Spiro-oxetane'	48
15b → 16b	'Spiro-oxetane'	Dimethyl	'Spiro-oxetane'	69
15c → 16c	'Spiro-oxetane'	Methyl, methoxymethyl	'Spiro-oxetane'	67
21 → 22	'Spiro-oxetane'	'Spiro-oxetane'	'Spiro-oxetane'	0
Intermolecular from diol + di-iodide				
(23) ^c → 22	'Spiro-oxetane'	'Spiro-oxetane'	'Spiro-oxetane'	<2 ^d
(24) ^c → 25	Dimethyl	Dimethyl	'Spiro-oxetane'	19
(oxaheptanediol) ^c → 10	None	None	'Spiro-oxetane'	<5 ^d

^aOne step intramolecular reaction. ^bLast and decisive step in the intermolecular reaction of 4-oxa-1,7-heptanediols with 3,3-bis-(iodomethyl)oxetane. ^cParentheses indicate an intermediate formed in the first step. ^dDetermined by GLC.

that if corner formation becomes impossible, the adverse effect on cyclization rate will be particularly pronounced when the central 6-position is involved. Our conclusion is that the preferred conformation at those carbon atoms that are part of an oxetane unit is not, as normally observed, *gauche*⁺, *gauche*⁺ with respect to the main chain, but *anti*, *anti*.

Reductive oxetane ring cleavage. The reductive oxetane ring opening of spiro-compounds **10**, **16a**, **16b**, **16c** and **25** was carried out with LiAlH₄ in monoglyme or THF. Among these, the monospiro macrocycles **10** and **25** gave the simple alcohols **11** and **26** in quantitative yields.

The dispiro macrocycle **16a** gave a mixture of the *cis*- and *trans*-diols **17a** (GLC-ratio 7:3), which could be separated by column chromatography. The assignment of configuration was impossible by NMR spectroscopy, but was achieved by X-ray structure determination⁸ of the main isomer (isolated in 48% yield), which fortunately turned out to be the desired *cis*-isomer. Since, statistically, the two isomers should be formed in equal amounts, this outcome required an explanation. In the last and decisive step, one side of the molecule already carries one side-arm undoubtedly engaged in Li⁺ complex formation together with the ring oxygens. Hydride attack on the last oxetane unit should then occur more easily from the opposite and unobstructed side to produce the *cis*-isomer. This augured well for the remaining ring-opening reactions.

However, in the case of the *gem*-dimethyl-substituted analogue **16b**, no stereoselectivity was observed. The *cis*- and *trans*-diols **17b** were formed in the GLC ratio 1:1, and they could be isolated by column chromatography.

The result for the methoxymethyl-substituted dispiro macrocycle **16c** was even more disappointing. The very unfavourable statistical situation for the all-*cis*-isomer (1:3) demanded high stereo-selectivity in both ring-opening steps: *cis* with respect to the methoxymethyl substituent. Three isomeric diols **17c** were now produced in the GLC ratio 6:2:1. The main component was isolated by chromatography, and assigned the *trans*-diol configuration. The two *cis*-diols, of which only one had the correct stereochemistry, could not be separated.

Methylation. The final methylation of the hydroxymethyl groups to produce the ligands **5b**, **18a**, **18b**, **18c** and **27** was carried out by standard procedures in high yields. The *cis*- and *trans*-isomers of **18a** and **18b** were obtained from the respective *cis*- and *trans*-diols. From the mixture of the two *cis*-diols **17c**, an inseparable mixture of *cis*- and *trans*-hexaethers **18c** was obtained. Pure *trans*-**18c** was, however, obtained from the *trans*-diol **17c**.

The complexation studies of these ligands will be reported in a separate paper. They have indeed confirmed that the effect of one and two ligating side-arms is to enhance the complexation strength for Li⁺ and to prevent complexation of Na⁺ and Ca²⁺. On the other hand, Mg²⁺

also becomes complexed, although less strongly than Li⁺, when ligating side-arms are present.

Even more gratifying is the result from an X-ray structure determination⁹ of the LiClO₄ complex of ligand **5b**, since its conformation is, in every detail, exactly that (**a**) derived in Fig. 1 from the diamond lattice.

Experimental

3,3-Dimethyl-1,5,9-trioxacyclododecane (**5a**, Scheme 1).

6,6-Dimethyl-4,8-dioxaundecanedinitrile (1a). Acrylonitrile (36.7 g, 0.69 mol) was slowly added to 2,2-dimethyl-1,3-propanediol (30.0 g, 0.29 mol) and aqueous KOH (20%, 8 ml) at room temperature. The reaction mixture was then stirred overnight at 40°C. After it had cooled, water and CHCl₃ was added, the phases were separated, and the organic phase was washed with dilute H₂SO₄. The solution was dried (K₂CO₃) and concentrated. The crude product was distilled in a Claisen flask. Yield 55.2 g (91%), b.p. 125–130°C/0.2 mmHg. ¹H NMR (300 MHz, CDCl₃): δ 0.90 (6 H, s, CH₃), 2.55 (4 H, t, *J* 3.5 Hz, CH₂CN), 3.10 (4 H, s, CCH₂O), 3.55 (4 H, t, *J* 3.5 Hz, OCH₂CH₂CN). ¹³C NMR (50 MHz, CDCl₃): δ 19.0, 22.2, 36.5, 66.0, 76.7, 118.7. MS (CI, isobutane): *m/z* 211 (78, MH), 140 (100).

6,6-Dimethyl-4,8-dioxaundecanedioic acid diethyl ester (2a). The dinitrile **1a** (15.6 g, 74.2 mmol) was dissolved in abs. ethanol (60 ml), and conc. H₂SO₄ (20 ml) was slowly added at room temperature. The reaction mixture was refluxed for 24 h. After being cooled, the mixture was poured on ice (100 g) and stirred for 10 min. The phases were separated, and the water phase was extracted with ether/ethyl acetate (2:1). The combined organic solutions were dried (MgSO₄), and the solvents were evaporated. The residue was distilled through a Vigreux column. Yield 15.4 g (68%), b.p. 125–130°C/0.1 mmHg. ¹H NMR (300 MHz, CDCl₃): δ 0.85 (6 H, s, CH₃), 1.26 (6 H, t, *J* 7.2 Hz, OCH₂CH₃), 2.55 (4 H, t, *J* 6.4 Hz, CH₂CO₂Et), 3.16 (4 H, s, CH₂O), 3.68 (4 H, t, *J* 6.5 Hz, OCH₂CH₂CO₂Et), 4.15 (4 H, q, *J* 7.1 Hz, CO₂CH₂CH₃). ¹³C NMR (50 MHz, CDCl₃): δ 14.4, 22.2, 35.5, 36.5, 60.6, 67.1, 77.2, 172.4. MS (CI, isobutane): *m/z* 305 (100, MH), 259 (7), 187 (13), 141 (7), 131 (11), 119 (31), 101 (16).

6,6-Dimethyl-4,8-dioxa-1,11-undecanediol (3a). The reaction was run under nitrogen. To a stirred and cooled suspension of LiAlH₄ (8.83 g, 0.23 mol) in dry THF (100 ml) was added a solution of the diethyl ester **2a** (35.4 g, 0.116 mol) in THF (200 ml). The reaction mixture was refluxed for 4 h. After being cooled, the mixture was poured on ice (100 g) and H₂SO₄, and stirred vigorously for 5 min. The solution was extracted several times with ether, the ether solution was dried (MgSO₄), and the solvent was evaporated. The residue was distilled through a Vigreux column. Yield 21.3 g (83%), b.p. 140–142°C/0.3 mmHg. ¹H

NMR (300 MHz, CDCl_3): δ 0.89 (6 H, s, CH_3), 1.81 (4 H, quint, J 5.7 Hz, CH_2), 3.19 (4 H, s, CH_2O [C5, C7]), 3.47 (2 H, br s, OH), 3.59 (4 H, t, J 5.7 Hz, CH_2O [C3, C9]), 3.75 (4 H, t, J 5.6 Hz, CH_2OH). ^{13}C NMR (50 MHz, CDCl_3): δ 22.6, 32.0, 36.1, 62.1, 70.9, 76.7. MS (CI, isobutane): m/z 221 (49, MH), 145 (17).

6,6-Dimethyl-11-tosyloxy-4,8-dioxo-1-undecanol (4a). The diol **3a** (8.00 g, 36.3 mmol) and pyridine (4.00 g, 50 mmol) were dissolved in dry, ethanol-free CHCl_3 . Tosyl chloride (6.92 g, 36.3 mmol), dissolved in CHCl_3 (75 ml), was added over 15 h with stirring and ice cooling. The reaction mixture was stirred at room temperature for 2 days, then poured onto ice, and the phases were separated. The organic phase was washed with water, dried (MgSO_4), and concentrated. Flash chromatography (silica, ethyl acetate/hexane 2:1) afforded the pure monotosylate. Yield 4.50 g (33%), pale yellow oil. ^1H NMR (300 MHz, CDCl_3): δ 0.82 (6 H, s, CH_3), 1.81 (2 H, quint, J 5.6 Hz, CH_2 [C2]), 1.88 (2 H, quint, J 6.1 Hz, CH_2 [C10]), 2.45 (3 H, s, Ar- CH_3), 2.53 (1 H, br s, OH), 3.08 (2 H, s, CH_2O [C5 or C7]), 3.14 (2 H, s, CH_2O [C5 or C7]), 3.41 (2 H, t, J 5.9 Hz, CH_2O [C3]), 3.58 (2 H, t, J 5.6 Hz, CH_2O [C9]), 3.75 (2 H, t, J 5.6 Hz, CH_2OH), 4.13 (2 H, t, J 6.3 Hz, CH_2OTs), 7.35 (2 H, d, J 8.5 Hz, Ar-H), 7.80 (2 H, d, J 8.4 Hz, Ar-H).

The corresponding ditosylate, obtained as a by-product, was eluted first (3.00 g, pale yellow oil). ^1H NMR (200 MHz, CDCl_3): δ 0.80 (6 H, s, CH_3), 1.86 (4 H, quint, J 6.0 Hz, CH_2 [C2, C10]), 2.44 (6 H, s, Ar- CH_3), 3.11 (4 H, s, CH_2O [C5, C7]), 3.46 (4 H, t, J 5.6 Hz, CH_2O [C3, C9]), 4.19 (4 H, t, J 6.2 Hz, CH_2OTs), 7.34 (2 H, d, J 8.5 Hz, Ar-H), 7.78 (2 H, d, J 8.4 Hz, Ar-H).

Cyclization experiments. Test reactions with various combinations of base and solvent were carried out to find the best cyclization conditions for the monotosylate **4a**. The volatile reaction products were analysed by GLC-MS. With NaH/dioxane, the 12-membered ring was formed in 60% after 24 h at reflux, while NaH/THF/DMF gave only 25% cyclic product after 2 days at room temperature. With NaH/DMSO at 60°C, 80% cyclic product was formed after 24 h at 60°C, while lithium diisopropylamide/dimethylacetamide (LDA/DMA) gave 90% cyclic product after 15 h at room temperature. No cyclic product was formed with LDA/dioxane, or with pyridine/DMF. In some of the reactions, diol **3a** was formed (the monotosylate starting material contained no diol). No increased cyclization tendency due to a template effect was observed when LiClO_4 was added.

3,3-Dimethyl-1,5,9-trioxacyclododecane (5a). The reaction was run under nitrogen. BuLi (1.6 M solution in hexane, 4 ml, 6.4 mmol) was slowly added to a stirred and ice-cooled solution of diisopropylamine (2 ml) in dry diethyl ether (5 ml). Solvent and excess diisopropylamine were removed with a stream of nitrogen gas. The resulting dry lithium diisopropylamide was dissolved in dry DMA (50 ml), and

the monotosylate **4a** (1.98 g, 5.29 mmol) dissolved in DMA (30 ml) was slowly added with stirring and cooling. The reaction mixture was then stirred overnight at room temperature. Ether was added, and the solution was washed several times with water. After drying (MgSO_4) and evaporation of the solvent, the cyclic product was isolated by column chromatography (silica, ethyl acetate/hexane 4:3). Yield 0.59 g (55%), colourless oil. (The product could also be isolated by distillation in a Kugelrohr apparatus, oven temp. 130–145°C/12 mmHg.) ^1H NMR (300 MHz, $\text{CD}_3\text{CN}/\text{CD}_3\text{OD}$ 95:5): δ 0.88 (6 H, s, CH_3), 1.77 (4 H, quint, J 5.4 Hz, CH_2O [C7, C11]), 3.24 (4 H, s, CH_2O), 3.59 and 3.62 (8 H, AB system, J 4.8 Hz, CH_2O [C6, C12 and C8, C10]). ^{13}C NMR (75 MHz, $\text{CD}_3\text{CN}/\text{CD}_3\text{OD}$ 95:5): δ 23.2, 29.4, 36.7, 68.3, 70.0, 77.0. MS (CI, isobutane): m/z 203 (100, MH), 201 (7.8), 145 (2.5), 135 (1.6), 133 (2.3), 128 (1.5), 117 (5.0), 115 (5.5), 101 (2.3).

3-Methoxymethyl-3-methyl-1,5,9-trioxacyclododecane (5b).

Reaction Path A, Scheme 1.

6-Methoxymethyl-6-methyl-4,8-dioxoundecanedinitrile (1b). Following the procedure described for the preparation of the dinitrile **1a**, the reaction of acrylonitrile (12.3 g, 232 mmol), 2-methoxymethyl-2-methyl-1,3-propanediol⁴ (13.0 g, 97 mmol) and KOH (4 ml, 20%) gave 17.4 g (75%) of dinitrile **1b**, b.p. 140–145°C/0.05 mmHg. ^1H NMR (200 MHz, CDCl_3): δ 0.96 (3 H, s, CH_3), 2.63 (4 H, t, J 6.1 Hz, $\text{OCH}_2\text{CH}_2\text{CN}$), 3.24 (2 H, s, CH_2OCH_3), 3.32 (3 H, s, CH_2OCH_3), 3.36 (4 H, s, CCH_2O), 3.65 (4 H, t, J 6.1 Hz, $\text{OCH}_2\text{CH}_2\text{CN}$). ^{13}C NMR (50 MHz, CDCl_3): δ 17.5, 19.0, 41.1, 59.6, 66.1, 73.5, 75.7, 118.6.

A small amount of the corresponding mononitrile was isolated by distillation. ^1H NMR (200 MHz, CDCl_3): δ 0.80 (3 H, s, CH_3), 2.55 (2 H, t, J 6.2 Hz, $\text{OCH}_2\text{CH}_2\text{CN}$), 2.63 (1 H, br s, OH), 3.28 (4 H, s, CH_2O), 3.40 (3 H, s, CH_2OCH_3), 3.47 (2 H, s, CH_2OH), 3.60 (2 H, t, J 6.2 Hz, $\text{OCH}_2\text{CH}_2\text{CN}$). ^{13}C NMR (50 MHz, CDCl_3): δ 17.4, 18.9, 40.9, 59.7, 66.2, 68.6, 74.6, 77.8, 118.4.

6-Methoxymethyl-6-methyl-4,8-dioxoundecanedioic acid diethyl ester (2b). Using dinitrile **1b** (14.0 g, 58 mmol), abs. ethanol (50 ml) and conc. H_2SO_4 (15 ml), and following the procedure described for the preparation of **2a**, 11.5 g (59%) of **2b** was obtained, b.p. 140–150°C/0.01 mmHg. ^1H NMR (200 MHz, CDCl_3): δ 0.85 (3 H, s, CH_3), 1.22 (6 H, t, J 7.4 Hz, OCH_2CH_3), 2.50 (4 H, t, J 6.4 Hz, $\text{CH}_2\text{CO}_2\text{Et}$), 3.15 (2 H, s, CH_2OCH_3), 3.22 (4 H, s, CH_2O), 3.25 (3 H, s, CH_3O), 3.63 (4 H, t, J 6.4, $\text{OCH}_2\text{CH}_2\text{CO}_2\text{Et}$), 4.11 (4 H, q, J 7.4 Hz, $\text{CO}_2\text{CH}_2\text{CH}_3$). ^{13}C NMR (50 MHz, CDCl_3): δ 15.7, 18.7, 36.5, 42.0, 60.3, 61.3, 67.8, 74.4, 76.4, 171.4.

6-Methoxymethyl-6-methyl-4,8-dioxo-1,11-undecanediol (3b). The experimental procedure was similar to that described

for the preparation of **3a**, using the diethyl ester **2b** (11.5 g, 34.4 mmol), LiAlH_4 (2.61 g, 68.8 mmol) and dry THF (125 ml). Yield 7.53 g (87%), b.p. 125–138°C/0.05 mmHg, colourless oil. $^1\text{H NMR}$ (200 MHz, CDCl_3): δ 0.91 (3 H, s, CH_3), 1.81 (4 H, quint, J 5.5 Hz, CH_2), 2.83 (2 H, br s, OH), 3.24 (2 H, s, CH_2OCH_3), 3.30 (3 H, s, OCH_3), 3.31 (4 H, s, CH_2O), 3.59 (4 H, t, J 5.5 Hz, CH_2O [C3, C9]), 3.76 (4 H, t, J 5.5 Hz, CH_2OH) $^{13}\text{C NMR}$ (50 MHz, CDCl_3): δ 18.0, 32.0, 40.6, 60.0, 62.2, 71.0, 74.7, 76.6.

6-Methoxymethyl-6-methyl-11-tosyloxy-4,8-dioxo-1-undecanol (4b). The standard procedure described for the preparation of **4a** was followed, using the diol **3b** (3.85 g, 15.4 mmol), tosyl chloride (2.93 g, 15.4 mmol), pyridine (3 ml) and ethanol-free CHCl_3 (75 ml). Yield 2.1 g (33%), oil. $^1\text{H NMR}$ (200 MHz, CDCl_3): δ 0.81 (3 H, s, CH_3), 1.80 (2 H, quint, J 5.5 Hz, CH_2 [C2]), 1.88 (2 H, quint, J 5.5 Hz, CH_2 [C10]), 2.36 (3 H, s, Ar- CH_3), 2.90 (1 H, br s, OH), 3.10 (2 H, s, CH_2O [C5 or C7]), 3.15 (2 H, s, CH_2O [C5 or C7]), 3.19 (3 H, s, CH_3O), 3.22 (2 H, s, CH_2OCH_3), 3.32 (2 H, t, J 6.0 Hz, CH_2O [C3]), 3.48 (2 H, t, J 5.6 Hz, CH_2O [C9]), 3.64 (2 H, t, J 5.7 Hz, CH_2OH), 4.03 (2 H, t, J 5.7 Hz, CH_2OTs), 7.27 (2 H, d, J 8.4 Hz, Ar-H), 7.70 (2 H, d, J 8.3 Hz, Ar-H). $^{13}\text{C NMR}$ (50 MHz, CDCl_3): δ 17.6, 21.7, 29.3, 32.0, 40.8, 59.6, 62.1, 66.8, 70.9, 73.68, 73.73, 73.9, 74.4, 128.3, 130.3, 133.8, 145.8. The corresponding ditosylate was isolated as a by-product in the reaction.

3-Methoxymethyl-3-methyl-1,5,9-trioxacyclododecane (5b). The same procedure as for the cyclization of **4a** was followed, using monotosylate **4b** (1.24 g, 3.08 mmol), diisopropylamine (0.65 g, 6.42 mmol), BuLi (1.6 M sol. in hexane, 2.50 ml, 4.0 mmol), dry ether (5 ml) and dry DMA (80 ml). GLC-MS analysis of the reaction mixture after 1 day at room temperature showed that the 12-membered ring was the exclusive volatile product (97%). After work-up (as for **5a**), the cyclic product was isolated by column chromatography (silica, ether/hexane 2:1, then neutral aluminium oxide, ether/hexane 2:1). Yield 0.34 g (48%), colourless oil. $^1\text{H NMR}$ (300 MHz, CDCl_3): δ 0.87 (3 H, s, CH_3), 1.77 (4 H, m, CH_2 [C7, C11]), 3.24 (2 H, s, CH_2OCH_3), 3.24 and 3.37 (4 H, AB system, J 9.0 Hz, CH_2O [C2, C4]), 3.30 (3 H, s, CH_2OCH_3), 3.56–3.62 (8 H, m, CH_2O [C6, C12 and C8, C10]). $^{13}\text{C NMR}$ (75 MHz, CDCl_3): δ 17.9, 28.6, 40.6, 59.4, 67.5, 69.2, 73.7, 77.0.

Reaction Path B, Scheme 2.

3-Benzoyloxy-1-propanol (6). 1,3-Propanediol (20.0 g, 0.263 mol) dissolved in dry THF (50 ml) was added to a stirred and ice-cooled suspension of NaH (80% suspension in oil, 7.88 g, 0.263 mol) in THF (100 ml), and the mixture was refluxed for 5 h. Benzyl bromide (45.0 g, 0.263 mol) dissolved in THF (300 ml) was added over 12 h, and the reaction mixture was then refluxed for 3 days. After cooling, filtration and concentration, ether was added, and the solution was washed with water and dried (MgSO_4). The

solvent was evaporated, and the residue was distilled in a Claisen flask. Yield 21.1 g (48%), b.p. 80–82°C/0.05 mmHg. $^1\text{H NMR}$ (200 MHz, CDCl_3): δ 1.86 (2 H, m, CH_2), 3.0 (1 H, br s, OH), 3.65 (2 H, t, J 5.9 Hz, CH_2OH), 3.76 (2 H, t, J 5.8 Hz, CH_2OBz), 4.51 (2 H, s, OCH_2Ph), 7.32 (5 H, s, Ar-H).

3,3-Bis(tosyloxymethyl)oxetane. The standard procedure described for the preparation of **4a** was followed, using 3,3-bis(hydroxymethyl)oxetane¹⁰ (3.60 g, 30.5 mmol), tosyl chloride (11.6 g, 61.0 mmol) and pyridine (5 ml) in ethanol-free CHCl_3 (40 ml). After flash chromatography (silica, ethyl acetate/hexane 4:3) of the oily crude product, 8.4 g (65%) of the ditosylate was obtained, m.p. 102–105°C, white needles. The compound could also be crystallized from ethanol, CHCl_3 /hexane, or THF/hexane (m.p. 107–112°C). (A previously reported procedure,¹¹ using 3,3-bis(iodomethyl)oxetane, silver *p*-toluenesulfonate and acetonitrile, produced the ditosylate in 93% yield). $^1\text{H NMR}$ (300 MHz, CDCl_3): δ 2.47 (6 H, s, Ar- CH_3), 4.21 (4 H, s, CH_2OTs), 4.32 (4 H, s, oxet- CH_2), 7.57 (8 H, q, J 8.6 Hz, Ar-H). $^{13}\text{C NMR}$ (50 MHz, CDCl_3): δ 21.9, 43.0, 69.5, 74.8, 128.5, 130.6, 130.7, 146.1.

3-Chloromethyl-3-tosyloxymethyl oxetane was isolated as a by-product. $^1\text{H NMR}$ (300 MHz, CDCl_3): δ 2.47 (3 H, s, Ar- CH_3), 3.82 (2 H, s, CH_2Cl), 4.32 (s, 2 H, CH_2OTs), 4.40 (4 H, q, J 3.2 Hz, oxet- CH_2), 7.60 (4 H, q, J 8.3 Hz, Ar-H).

3,3-Bis(iodomethyl)oxetane was prepared according to a standard procedure, using 3,3-bis(tosyloxymethyl)oxetane (1.63 g, 3.82 mmol), NaI (3.00 g, 20.0 mmol) and acetone (40 ml). The crude product was distilled in a 'Kugelrohr' apparatus (70–90°C/0.1 mmHg). Yield 1.16 g (90%), yellow oil which crystallized in the refrigerator, m.p. 50–52°C. (A previously reported procedure,¹¹ using 3,3-bis(chloromethyl)oxetane, NaI and acetonitrile, produced the diiodide in 89% yield). $^1\text{H NMR}$ (60 MHz, CDCl_3): δ 3.73 (4 H, s, CH_2I), 4.40 (4 H, s, oxet- CH_2).

1,11-Di(benzyloxy)-6,6-(2-oxapropane-1,3-diyl)-4,8-dioxo-undecane (7). The alcohol **6** (7.40 g, 44.5 mmol) was dissolved in dry DMSO (40 ml), NaH (80% dispersion in oil, 1.60 g, 53.3 mmol) was added, and the mixture was stirred at 60°C for 4 h. 3,3-Bis(iodomethyl)oxetane (7.50 g, 22.2 mmol) dissolved in DMSO (25 ml) was added, and the reaction mixture was stirred overnight at 60°C. The solution was cooled, ether was added, and the solution was washed several times with water. After drying (MgSO_4) and evaporation of the solvent, the crude product was purified by flash chromatography (silica, ethyl acetate/hexane 3:4). Yield 4.0 g (43%), oil. $^1\text{H NMR}$ (300 MHz, CDCl_3): δ 1.88 (4 H, quint, J 6.3 Hz, CH_2), 3.54 (4 H, t, J 6.3 Hz, CH_2O [C3, C9 or C5, C7]), 3.55 (4 H, t, J 6.3 Hz, CH_2O [C3, C9 or C5, C7]), 3.57 (4 H, s, CH_2OBz), 4.42 (4 H, s, oxet- CH_2), 4.49 (4 H, s, OCH_2Ph), 7.30 (10 H, s,

ArH). ^{13}C NMR (75 MHz, CDCl_3): δ 29.8, 43.0, 70.0, 72.8, 74.6, 74.7, 76.1, 128.3, 128.4, 129.2, 138.0.

6,6-(2-Oxapropane-1,3-diyl)-4,8-dioxo-1,11-undecanediol (8). The reaction was run under nitrogen. To a stirred and ice-cooled suspension of palladium-on-charcoal (10%, 5.40 g) in abs. ethanol (85 ml) were added the dibenzyl compound **7** (2.70 g, 6.51 mmol) and 1,4-cyclohexadiene (12.2 ml, 130.2 mmol). The reaction mixture was stirred at room temperature until TLC analysis showed that the reaction was complete. The catalyst was filtered off and the solution was concentrated to give an oil which was subjected to column chromatography (silica, chloroform/ethanol 10:1). Yield 1.2 g (78%), colourless oil. ^1H NMR (300 MHz, acetone- d_6): δ 1.81 (4 H, quint, J 6.3 Hz, CH_2), 3.1 (2 H, br s, OH), 3.65 (4 H, t, J 6.3 Hz, CH_2O [C3, C9]), 3.65 (4 H, t, J 6.3 Hz, CH_2OH), 3.67 (4 H, s, CH_2O), 4.15 (4 H, s, oxet- CH_2). ^{13}C NMR (75 MHz, acetone- d_6): δ 33.0, 44.0, 59.0, 68.6, 72.2, 75.6.

11-Tosyloxy-6,6-(2-oxapropane-1,3-diyl)-4,8-dioxo-1-undecanol (9). The reaction was run under nitrogen. The diol **8** (0.82 g, 3.50 mmol) and dry DMSO (1 ml) were dissolved in dry THF (15 ml). NaH (80% dispersion in oil, 0.12 g, 4.00 mmol) was added and the mixture was stirred at 60 °C for 3 h whereupon it was cooled to 0 °C and tosyl chloride (0.67 g, 3.50 mmol) dissolved in THF (10 ml) was added over 10 min. The reaction mixture was stirred at room temperature for 45 min, then diluted with ether/ethyl acetate (1:1), and the organic solution was washed with water. After drying (MgSO_4) and concentration, the monotosylate **9** was isolated by column chromatography (silica, ethyl acetate/hexane 2:1). Yield 0.70 g (51%), pale yellow oil. ^1H NMR (300 MHz, CDCl_3): δ 1.80 (4 H, m, $\text{CH}_2\text{CH}_2\text{CH}_2\text{O}$), 3.10 (1 H, br s, OH), 2.95 (3 H, s, Ar- CH_3), 3.30–3.80 (8 H, m, CH_2O [C3 and C9], CH_2OH , CH_2OTs), 4.10 (4 H, br s, CH_2O), 4.45 (4 H, d, oxet- CH_2), 7.45 (2 H, d, J 8.3 Hz, Ar-H), 7.80 (2 H, d, J 8.3 Hz, Ar-H). ^{13}C NMR (75 MHz, CDCl_3): δ 21.5, 29.0, 31.7, 45.1, 61.2, 67.0, 69.8, 70.4, 71.6, 72.1, 76.2, 127.7, 129.7, 133.0, 145.0.

2,6,10,14-Tetraoxaspiro[3.11]pentadecane (10). The reaction was run under nitrogen. The monotosylate **9** (0.47 g, 1.21 mmol) was dissolved in dry DMSO (25 ml), and BuLi (1.6 M solution in hexane, 0.80 ml, 1.28 mmol) was slowly added while keeping the temperature at 5–10 °C. The reaction mixture was stirred at 60 °C overnight. GLC–MS analysis then showed that the 12-membered ring was the only volatile reaction product. Ether/ethyl acetate (1:1) was added to the cooled reaction mixture and the organic solution was washed several times with water and then dried (MgSO_4), and the solvents were evaporated. Column chromatography (silica, ether/ethanol/hexane 10:1:2) afforded pure **10** as an oil, yield 71 mg (27%). ^1H NMR (300 MHz, CDCl_3): δ 1.79 (4 H, quint, J 5.1 Hz, CH_2 [C8, C12]), 3.57 (4 H, t, J 5.3 Hz, CH_2O [C7, C13 or C9, C11]), 3.65 (4 H, t,

J 5.3 Hz, CH_2O [C7, C13 or C9, C11]), 3.80 (4 H, s, CH_2O [C5, C15]), 4.42 (4 H, s, CH_2O [C1, C3]). ^{13}C NMR (75 MHz, CDCl_3): δ 28.5, 43.5, 68.2, 69.6, 72.2, 77.6. MS (CI, CH_4): m/z 217 (42, MH), 215 (11), 187 (4), 129 (8), 127 (5), 117 (31), 115 (26), 113 (6), 112 (4), 111 (6), 110 (8), 103 (5), 101 (5).

With LDA/DMA, less than 2% (GLC–MS) cyclic product was formed. With NaH/DMA, the 12-membered ring constituted 23% of the volatile reaction products after 1 day. Attempts to make **10** by an intermolecular cyclization similar to that described for the preparation of **25** (Scheme 5) were not successful. Using 4-oxa-1,7-heptadecanediol (made by reduction of the corresponding diester, which in turn was obtained from 4-oxa-1,7-heptadecanedinitrile¹²) and 3,3-bis(iodomethyl)oxetane, and trying various combinations of bases and solvents, less than 5% of cyclic product (GLC–MS) was formed.

3-Hydroxymethyl-3-methyl-1,5,9-trioxacyclododecane (11). The reaction was run under nitrogen. The spiro-compound **10** (40 mg, 0.18 mmol) dissolved in dry monoglyme (1 ml) was added to a stirred and ice-cooled suspension of LiAlH_4 (30 mg, 0.79 mmol) in monoglyme (2 ml). The reaction mixture was refluxed overnight. After cooling, ether and water were added and the phases were separated. The ether solution was dried (MgSO_4) and concentrated. The oily crude product was pure by GLC and NMR. Yield 40 mg (99%). ^1H NMR (300 MHz, CDCl_3): δ 0.72 (3 H, s, CH_3), 1.76–1.79 (4 H, m, CH_2O [C7, C11]), 3.1 (1 H, br s, OH), 3.38 and 3.62 (4 H, AB system, J 9.7 Hz, CH_2O [C2, C4]), 3.45 (2 H, br s, CH_2OH), 3.55 (4 H, q, CH_2O), 3.61 (4 H, m, CH_2O). ^{13}C NMR (75 MHz, CDCl_3): δ 18.2, 28.6, 40.7, 68.4, 70.1, 70.6, 70.8, 74.7. MS (CI, CH_4): m/z 219 (100, MH), 217 (14), 187 (5), 145 (12), 143 (5), 135 (19), 129 (9), 117 (49), 115 (27), 113 (9), 111 (6), 103 (7), 100 (10).

3-Methoxymethyl-3-methyl-1,5,9-trioxacyclododecane (5b). The compound was obtained from **11** in 90% yield (GLC) following a standard method with NaH and MeI in dry THF. For the spectral data, see above.

3,7-Di(methoxymethyl)-3,7-dimethyl-1,5,9-trioxacyclododecane (18a, Scheme 3).

3-Benzoyloxymethyl-3-hydroxymethyloxetane. The compound was made from 3,3-bis(hydroxymethyl)oxetane¹⁰ (9.0 g, 76.2 mmol), NaH (80% dispersion in oil, 2.63 g, 87.7 mmol) and benzyl bromide (13.0 g, 76.2 mmol) in dry DMSO (20 ml)/dry THF (150 ml), following the procedure described for the preparation of **6**. After distillation through a Vigreux column, 6.50 g (41%) of the monobenzyl compound was obtained, b.p. 140–145 °C/0.01 mmHg, colourless oil. The product could also be isolated by flash chromatography (silica, ethyl acetate/hexane 2:1). ^1H NMR (300 MHz, CDCl_3): δ 2.69 (1 H, br s, OH), 3.76 (2 H, s, CH_2OH), 3.90 (2 H, s, CH_2OBz), 4.45 (4 H, AB

system, J 6.1 Hz, oxet-CH₂), 4.55 (2 H, s, OCH₂Ph), 7.25–7.39 (5 H, m, Ar-H). ¹³C NMR (75 MHz, CDCl₃): δ 44.1, 66.0, 73.4, 73.6, 76.4, 127.7, 127.9, 128.5, 137.6.

The dibenzyl-compound was isolated as a by-product. ¹H NMR (300 MHz, CDCl₃): δ 3.67 (4 H, s, CH₂OBz), 4.46 (4 H, s, oxet-CH₂), 4.50 (4 H, s, OCH₂Ph), 7.26–7.33 (10 H, m, Ar-H). ¹³C NMR (75 MHz, CDCl₃): δ 43.6, 71.1, 73.1, 76.2, 126.6, 127.3, 128.1, 137.9.

3-Benzyloxymethyl-3-tosyloxymethyloxetane (12). *Method A.* The standard procedure described for the preparation of **4a** was followed, using 3-benzyloxymethyl-3-hydroxymethyloxetane (5.00 g, 24.0 mmol), pyridine (4 ml), tosyl chloride (5.49 g, 28.8 mmol) and ethanol-free CHCl₃ (20 ml). Flash chromatography (silica, ethyl acetate/hexane 3:4) of the crude product afforded **12** as an oil. Yield 7.15 g (82 %).

Method B. The procedure was similar to that described for the preparation of **9**, using 3-benzyloxymethyl-3-hydroxymethyloxetane (11.0 g, 52.8 mmol), NaH (80 % dispersion in oil, 1.82 g, 60.7 mmol), tosyl chloride (10.1 g, 53.0 mmol), dry DMSO (5 ml) and dry THF (75 ml). The crude product was purified by flash chromatography (silica, ethyl acetate/hexane 3:4). Yield 15.5 g (81 %), pale yellow oil. ¹H NMR (300 MHz, CDCl₃): δ 2.43 (3 H, s, Ar-CH₃), 3.66 (2 H, s, CH₂OTs), 4.29 (2 H, s, CH₂OBz), 4.38 (4 H, q, J 6.5 Hz, oxet-CH₂), 4.44 (2 H, s, OCH₂Ph), 7.21–7.34 (5 H, m, Ar[Bz]-H), 7.35 (2 H, d, J Hz, Ar[Ts]-H), 7.80 (2 H, d, J 8.4 Hz, Ar[Ts]-H). ¹³C NMR (75 MHz, CDCl₃): δ 21.6, 43.0, 70.39, 70.44, 73.4, 75.5, 127.5, 127.6, 127.8, 128.0, 128.4, 130.0, 132.5, 137.7, 145.1.

1,11-Di(benzyloxy)-2,2;10,10-bis(2-oxapropane-1,3-diyl)-4,8-dioxaundecane (13a). 1,3-Propanediol (0.88 g, 11.6 mmol) was dissolved in dry DMSO (20 ml), NaH (80 % dispersion in oil, 0.40 g, 13.3 mmol) was added, and the mixture was stirred at 60 °C for 2 h. After cooling to room temperature, the tosylate **12** (4.19 g, 11.6 mmol) dissolved in DMSO (15 ml) was added, and the reaction mixture (clear, yellow-brown) was stirred until TLC analysis (silica, ethyl acetate/hexane 2:1) showed that no unchanged tosylate was present. The addition procedure was repeated with the second equivalent of NaH and tosylate. The reaction mixture was thereafter stirred at room temperature until TLC analysis (silica, ethyl acetate/hexane 2:1) showed that no unchanged tosylate was present. Ether/ethyl acetate (5:1) was added, and the solution was washed several times with water. After drying (MgSO₄) and evaporation of the solvent, the crude product was purified by flash chromatography (silica, ethyl acetate/hexane 2:1). Yield 3.85 g (73 %), pale yellow oil. ¹H NMR (300 MHz, CDCl₃): δ 1.82 (2 H, quint, J 6.4 Hz, CH₂), 3.51 (4 H, t, J 6.4 Hz, CH₂O [C5, C7]), 3.63 (4 H, s, CH₂O [C3, C9]), 3.66 (4 H, s, CH₂OBz), 4.47 (8 H, s, oxet-CH₂), 4.55 (4 H, s, OCH₂Ph), 7.28–7.37 (10 H, m, Ar-H). ¹³C NMR (75 MHz, CDCl₃): δ 29.7, 43.8, 68.2, 71.3, 71.9, 73.3, 76.2, 127.4, 127.5, 128.3, 138.1.

With 3-benzyloxymethyl-3-iodomethyloxetane, made from the corresponding tosylate following a standard procedure, the disubstituted product was obtained in the same yield. In an attempt to make **13a** from 3-benzyloxymethyl-3-hydroxymethyloxetane and 1,3-di-iodopropane, following a procedure similar to the one above, the only reaction product was 3-benzyloxymethyl-3-allyloxymethyloxetane. A small amount of the crude product was purified by preparative TLC (silica, ether/hexane 2:1). ¹H NMR (300 MHz, CDCl₃): δ 3.67 (2 H, s, CH₂O), 3.69 (2 H, s, CH₂O), 3.99–4.02 (2 H, m, CH₂=), 4.49 (4 H, s, oxet-CH₂), 4.56 (2 H, s, OCH₂Ph), 5.15–5.30 (2 H, m, OCH₂), 5.80–5.95 (1 H, m, -CH=), 7.34 (5 H, m, Ar-H). ¹³C NMR (75 MHz, CDCl₃): δ 43.8, 71.3, 72.2, 73.3, 76.3, 116.8, 127.4, 127.5, 128.2, 134.6, 138.1. MS (CI, isobutane): m/z 249 (MH), 207, 191, 177, 151, 137, 125, 107. The same product was obtained when 1,3-dibromo- or 1,3-di(tosyloxy)-propane was used, and when the solvent was changed to THF.

2,2;10,10-Bis(2-oxapropane-1,3-diyl)-4,8-dioxo-1,11-undecanediol (14a). The experimental procedure was as described for the deprotection of **7**, using the dibenzyl compound **13a** (2.52 g, 5.52 mmol), 1,4-cyclohexadiene (2.4 g, 30.0 mmol) hydrogenation catalyst (10 % palladium-on-charcoal, 5.00 g) and abs. ethanol (75 ml). Fresh catalyst and more 1,4-cyclohexadiene were added during the reaction time of 5 days. The catalyst was filtered off, and the solution was concentrated to give an oil which was subjected to column chromatography (silica, chloroform/ethanol 5:1). Yield 0.91 g (60 %), colourless oil. ¹H NMR (300 MHz, acetone): δ 1.83 (2 H, quint, J 6.2 Hz, CH₂), 3.0 (2 H, br s, OH), 3.56 (4 H, t, J 6.3 Hz, CH₂O [C5, C7]), 3.64 (4 H, s, CH₂O), 3.76 (4 H, s, CH₂OH), 4.37 (8 H, q, J 5.3 Hz, oxet-CH₂). ¹³C NMR (75 MHz, acetone-*d*₆): δ 30.0, 44.9, 63.8, 68.2, 72.5, 75.3.

11-Tosyloxy-2,2;10,10-bis(2-oxapropane-1,3-diyl)-4,8-dioxo-1-undecanol (15a). The same procedure as for the preparation of **9** was followed, using the diol **14a** (1.79 g, 6.48 mmol), NaH (80 % dispersion in oil, 0.22 g, 7.33 mmol), dry DMSO (1 ml), tosyl chloride (1.24 g, 6.48 mmol) and dry THF (50 ml). The monotosylate was isolated by column chromatography (silica, CHCl₃/ethanol 10:1). Yield 0.93 g (33 %), colourless oil. ¹H NMR (300 MHz, CDCl₃): δ 1.77 (2 H, quint, J 6.2 Hz, CH₂), 2.46 (3 H, s, Ar-CH₃), 2.74 (1 H, t, OH), 3.46 (2 H, t, J 6.2 Hz, CH₂O [C5 or C7]), 3.51 (2 H, t, J 6.2 Hz, CH₂O [C5 or C7]), 3.61 (2 H, s, OCH₂), 3.72 (2 H, s, OCH₂), 3.88 (2 H, d, CH₂OH), 4.25 (2 H, s, CH₂OTs), 4.37 (4 H, q, J 6.5 Hz, oxet-CH₂), 4.45 (4 H, q, J 6.1 Hz, oxet-CH₂), 7.13 (2 H, d, J 8.0 Hz, Ar-H), 7.80 (2 H, d, J 8.3 Hz, Ar-H). ¹³C NMR (75 MHz, CDCl₃): δ 21.6, 29.7, 43.1, 44.2, 66.0, 68.3, 68.5, 70.5, 71.1, 74.4, 75.5, 76.4, 128.0, 130.0, 132.4, 145.1.

The first fraction collected contained the corresponding ditosylate. A small amount was purified by crystallization from THF/hexane, m.p. 94–96 °C, white powder. ¹H NMR (300 MHz, CDCl₃): δ 1.70 (2 H, quint, J 6.2 Hz, CH₂), 2.46

(6 H, s, Ar-CH₃), 3.42 (4 H, t, *J* 6.2 Hz, CH₂O [C5, C7]), 3.60 (4 H, s, CH₂O), 4.25 (4 H, s, CH₂OTs), 4.37 (8 H, q, *J* 6.5 Hz, oxet-CH₂), 7.37 (4 H, d, *J* 8.0 Hz, Ar-H), 7.81 (4 H, d, *J* 8.3 Hz, Ar-H). ¹³C NMR (75 MHz, CDCl₃): δ 21.5, 29.4, 42.9, 68.0, 70.3, 70.9, 75.3, 127.8, 129.8, 132.5, 145.0.

2,6,10,13,17-Pentaoxadispiro[3.3.3.7]octadecane (16a). The cyclization was carried out as described above for the preparation of **10**, using the monotosylate **15a** (820 mg, 1.90 mmol), BuLi (1.6 M solution in hexane, 1.3 ml, 2.10 mmol) and dry DMSO (35 ml). The dispiro compound **16a** was isolated by column chromatography (silica, ether/ethanol/hexane 10:1:1) as white crystals, yield 238 mg (48%), m.p. 94–95 °C. ¹H NMR (300 MHz, CDCl₃): δ 1.79 (2 H, quint, *J* 5.1 Hz, CH₂), 3.65 (4 H, t, *J* 5.1 Hz, CH₂O [C14, C16]), 3.76 (4 H, s, CH₂O [C5, C7 or C12, C18]), 3.80 (4 H, s, CH₂O [C5, C7 or C12, C18]), 4.41 (8 H, s, CH₂O [C1, C3, C9, C11]). ¹³C NMR (75 MHz, CDCl₃): δ 27.7, 43.5, 70.3, 72.4, 74.3, 77.6. MS (CI, isobutane): *m/z* 259 (100, MH), 257 (3), 228 (3), 159 (3), 141 (3), 129 (3), 127 (4), 110 (3), 101 (3).

Traces of the cyclic dimer (24-membered ring) were detected. GC–MS (CI, isobutane): *m/z* 517 (1, MH), 367 (100), 259 (23), 101 (16).

cis- and trans-3,7-bis(hydroxymethyl)-3,7-dimethyl-1,5,9-trioxacyclododecane (17a). The standard reduction procedure described above for the preparation of **11** was followed, using the dispiro compound **16a** (200 mg, 0.77 mmol), LiAlH₄ (200 mg, 5.27 mmol) and dry monoglyme (10 ml). GLC–MS analysis (cap. GLC) after 1 day showed that no spiro compound was present. The reaction mixture was poured onto ice, neutralized with H₂SO₄ and extracted several times with ether. The ether solution was dried (4 Å molecular sieves) and concentrated. The two isomeric diols, formed in the ratio 27:73 (GLC), were separated by column chromatography (silica, CHCl₃/methanol 95:5).

The *trans*-diol was eluted first, yield 22 mg (11%), m.p. 110–111 °C. ¹H NMR (300 MHz, CDCl₃): δ 0.75 (6 H, s, CH₃), 1.82 (2 H, quint, *J* 5.3 Hz, CH₂), 2.97 (2 H, t, OH), 3.43 and 3.67 (4 H, AB system, *J* 9.0 Hz, CH₂O [C2, C8 or C4, C6]), 3.44 and 3.57 (4 H, AB system, *J* 8.8 Hz, CH₂O [C2, C8 or C4, C6]), 3.53 (4 H, d, CH₂OH), 3.69 (4 H, m, CH₂O [C10, C12]). ¹³C NMR (75 MHz, CDCl₃): δ 18.1, 26.7, 40.5, 70.37, 70.43, 73.9, 76.4. MS (EI): *m/z* 262 (0.8, M), 189 (2), 179 (5), 161 (3), 159 (3), 131 (3), 129 (6), 119 (3), 117 (5), 115 (5), 113 (5), 103 (8), 101 (7).

The *cis*-diol was further purified by column chromatography (silica, ether/ethanol/hexane 10:1:1). Yield 96 mg (48%), m.p. 102–103 °C. ¹H NMR (300 MHz, CDCl₃): δ 0.78 (6 H, s, CH₃), 1.82 (2 H, quint, *J* 5.1 Hz, CH₂), 2.75 (2 H, br s, OH), 3.39 and 3.62 (4 H, AB system, *J* 9.0 Hz, CH₂O [C2, C8 or C4, C6]), 3.41 and 3.56 (4 H, AB system, *J* 8.8 Hz, CH₂O [C2, C8 or C4, C6]), 3.54 (4 H, br s, CH₂OH), 3.68 (4 H, m, CH₂O [C10, C12]). ¹³C NMR (75 MHz, CDCl₃): δ 18.0, 27.2, 40.8, 69.6, 70.1, 74.0, 76.1. MS (EI): *m/z* 262 (0.7, M), 189 (11), 179 (9), 161 (3), 159 (5),

131 (4), 129 (7), 117 (6), 115 (7), 113 (5), 103 (9), 101 (7). The structure of the *cis*-diol was confirmed by X-ray crystallography (C. Rømme, University of Oslo, Norway. *Unpublished results.*)

cis-3,7-Bis(methoxymethyl)-3,7-dimethyl-1,5,9-trioxacyclododecane (18a). The *cis*-diol **17a** (60 mg, 0.23 mmol) was dissolved in dry DMSO (2 ml). BuLi (1.6 M solution in hexane, 0.40 ml, 0.64 mmol) was added, and the mixture was stirred for 1 h at 60 °C, after which it was cooled to room temperature. Methyl iodide (131 mg, 0.92 mmol) dissolved in DMSO (0.5 ml) was added, and the reaction mixture was stirred at room temperature for 2 h. Ether/ethyl acetate (5:1) was added, and the solution was washed with water. After drying (MgSO₄) and evaporation of the solvents, the crude product was purified by chromatography (silica, ether/ethanol/hexane 10:1:1, then CHCl₃/THF 20:1). Yield 64 mg (96%), colourless oil. ¹H NMR (300 MHz, CD₃CN/CD₃OD 95:5): δ 0.83 (6 H, s, CH₃), 1.95 (2 H, quint, *J* 5.2, CH₂), 3.17 and 3.38 (4 H, AB system, *J* 8.7 Hz, CH₂O [C2, C8 or C4, C6]), 3.18 and 3.26 (4 H, AB system, *J* 8.7 Hz, CH₂O [C2, C8 or C4, C6]), 3.19 (4 H, s, CH₂OCH₃), 3.26 (6 H, s, CH₂OCH₃), 3.51–3.62 (4 H, m, CH₂O [C10, C12]). ¹³C NMR (75 MHz, CD₃CN/CD₃OD 95:5): δ 18.4, 28.5, 41.6, 56.7, 70.4, 73.8, 75.5, 77.7. MS (CI, isobutane): *m/z* 291 (100, MH), 272 (6), 260 (9), 178 (7), 175 (6), 145 (5), 142 (9), 129 (7), 118 (6), 113 (6), 100 (7).

trans-3,7-Bis(methoxymethyl)-3,7-dimethyl-1,5,9-trioxacyclododecane (18a). The procedure was as described above, using the *trans*-diol **17a** (20 mg, 0.076 mmol), BuLi (1.6 M solution in hexane, 0.15 ml, 0.24 mmol), methyl iodide (43.3 mg, 0.31 mmol) and dry DMSO (1 ml). The crude product was purified by column chromatography (silica, ether/hexane/ethanol 10:1:0.25). Yield 20 mg (91%), colourless oil. ¹H NMR (300 MHz, CDCl₃): δ 0.88 (6 H, s, CH₃), 1.80 (2 H, quint, *J* 5.1 Hz, CH₂), 3.21 and 3.38 (4 H, AB system, *J* 8.7 Hz, CH₂O [C2, C8 or C4, C6]), 3.23 and 3.29 (4 H, AB system, *J* 8.9 Hz, CH₂O [C2, C8 or C4, C6]), 3.32 (10 H, s, CH₃O, CH₂O), 3.62 (4 H, m, CH₂O [C10, C12]). ¹³C NMR (75 MHz, CDCl₃): δ 18.0, 27.7, 40.8, 59.5, 69.4, 73.1, 74.8, 77.1. MS (CI, CH₄): *m/z* 291 (100, MH), 289 (4), 203 (4), 175 (6), 173 (3), 143 (7), 129 (4), 117 (9), 115 (5), 111 (3), 103 (8), 101 (10).

3,7-Bis(methoxymethyl)-3,7,11,11-tetramethyl-1,5,9-trioxacyclododecane (18b, Scheme 3).

1,11-Di(benzyloxy)-6,6-dimethyl-2,2;10,10-bis(2-oxapropane-1,3-diyl)-4,8-dioxaundecane (13b). Method A. The same procedure as described for the preparation of **13a** was followed, using 2,2-dimethyl-1,3-propanediol (2.16 g, 20.7 mmol), NaH (80% dispersion in oil, 1.50 g, 50 mmol), the tosylate **12** (15.0 g, 41.4 mmol) and dry DMSO (150 ml). The crude product was purified by flash chromatography (silica, CHCl₃/ethyl acetate 10:1, then ethyl acetate/hex-

ane 1:2). Yield 4.75 g (47%), pale yellow oil. ^1H NMR (200 MHz, CDCl_3): δ 0.85 (6 H, s, CH_3), 3.17 (4 H, s, CH_2O), 3.56 (4 H, s, CH_2O), 3.64 (4 H, s, CH_2O), 4.50 (8 H, q, J 6.0 Hz, oxet- CH_2), 4.53 (4 H, s, OCH_2Ph), 7.31 (10 H, s, Ar-H). ^{13}C NMR (50 MHz, CDCl_3): δ 22.3, 37.0, 44.4, 72.0, 72.7, 73.9, 76.7, 128.1, 128.2, 128.9, 139.5.

A small amount of the mono-substituted intermediate was also isolated. ^1H NMR (200 MHz, CDCl_3): δ 0.88 (6 H, s, CH_3), 2.45 (1 H, br s, OH), 3.29 (2 H, s, CH_2O), 3.40 (2 H, br s, CH_2OH), 3.62 (4 H, s, CH_2O), 4.44 (4 H, s, oxet- CH_2), 4.53 (2 H, s, OCH_2Ph), 7.31 (5 H, s, Ar-H). ^{13}C NMR (50 MHz, CDCl_3): δ 22.0, 36.7, 44.2, 71.8, 71.9, 73.2, 73.8, 76.8, 80.9, 128.2, 128.3, 129.0, 139.6.

Method B. 3-Benzyloxymethyl-3-hydroxymethylloxetane (103 mg, 0.50 mmol) was dissolved in dry DMSO (2 ml). NaH (80% dispersion in oil, 30 mg, 1.0 mmol) was added, and the mixture was stirred at 60°C for 5 h. 2,2-Dimethyl-1,3-dibromopropane (56.9 mg, 0.25 mmol) dissolved in DMSO (1 ml) was added, and the reaction mixture was stirred for 6 h at 115°C and then cooled. Ether was added, and the organic phase was washed several times with water. The crude product (95 mg) after drying (MgSO_4) and evaporation of the solvent was not further purified. The disubstituted product constituted 79% (analysed by GLC-MS) of the volatile reaction products, but TCL (silica, CHCl_3/THF 5:1) revealed that several other products were also formed.

6,6-Dimethyl-2,2;10,10-bis(2-oxapropane-1,3-diyl)-4,8-dioxa-1,11-undecanediol (14b). Deprotection of the dibenzyl compound **13b** was carried out by the same procedure as for **13a**, using **13b** (4.65 g, 9.60 mmol), hydrogenation catalyst (10% palladium-on-charcoal, 9.0 g), 1,4-cyclohexadiene (15.4 g, 19.2 mmol) and abs. ethanol (90 ml). Regular supplies of fresh catalyst and more 1,4-cyclohexadiene were necessary during the reaction time of 10 days. The catalyst was filtered off and the solution was concentrated to give an oil which was subjected to column chromatography (silica, $\text{CHCl}_3/\text{ethanol}$ 5:1). Yield 1.87 g (64%), oil. ^1H NMR (200 MHz, CDCl_3): δ 0.85 (6 H, s, CH_3), 3.18 (4 H, s, CH_2O), 3.36 (2 H, br s, OH), 3.72 (4 H, s, CH_2O), 3.88 (4 H, s, CH_2OH), 4.41 (8 H, q, J 6.3 Hz, oxet- CH_2). ^{13}C NMR (50 MHz, CDCl_3): δ 22.5, 36.3, 44.3, 66.6, 75.3, 78.0.

6,6-Dimethyl-11-tosyloxy-2,2;10,10-bis(2-oxapropane-1,3-diyl)-4,8-dioxa-1-undecanol (15b). The procedure was as described for the preparation of monosylate **15a**, using the diol **14b** (150 mg, 0.49 mmol), NaH (80% dispersion in oil, 17.7 mg, 0.59 mmol), tosyl chloride (93.9 mg, 0.49 mmol), dry DMSO (0.5 ml) and dry THF (15 ml). The crude product after work-up was chromatographed (silica, $\text{CHCl}_3/\text{methanol}$ 5:1). The second fraction contained the monotosylate, yield 113 mg (50%), oil. ^1H NMR (200 MHz, CDCl_3): δ 0.80 (6 H, s, CH_3), 2.44 (3 H, s, Ar- CH_3), 3.13 (2 H, s, CH_2O), 3.17 (2 H, s, CH_2O), 3.57 (2 H, s, CH_2O), 3.7 (1 H, br s, OH), 3.72 (2 H, s, CH_2O), 3.90 (2

H, br s, CH_2OH), 4.22 (2 H, s, CH_2OTs), 4.34 (4 H, q, J 6.4 Hz, oxet- CH_2), 4.43 (4 H, q, J 6.2 Hz, oxet- CH_2), 7.35 (2 H, d, J 8.4 Hz, Ar-H), 7.78 (2 H, d, J 8.4 Hz, Ar-H). ^{13}C NMR (50 MHz, CDCl_3): δ 22.2, 43.4, 67.1, 70.9, 71.9, 75.8, 75.9, 76.7, 76.9, 77.6, 77.9, 78.0, 128.5, 130.5.

The first fraction contained the corresponding ditosylate (67 mg, oil). ^1H NMR (200 MHz, CDCl_3): δ 0.74 (6 H, s, CH_3), 2.43 (6 H, s, Ar- CH_3), 3.08 (4 H, s, CH_2O), 3.55 (4 H, s, CH_2O), 4.21 (4 H, s, CH_2OTs), 4.34 (8 H, q, J 6.4 Hz, oxet- CH_2), 7.34 (4 H, d, J 8.4 Hz, Ar-H), 7.78 (4 H, d, J 8.4 Hz, Ar-H). ^{13}C NMR (50 MHz, CDCl_3): δ 22.1, 36.7, 43.5, 70.9, 71.7, 75.7, 77.5, 126.5, 130.6, 134.2, 145.7.

15,15-Dimethyl-2,6,10,13,17-pentaoxadispiro[3.3.3.7]octadecane (16b). The procedure was as described for the dispiro compound **16a**, using the monotosylate **15b** (90 mg, 0.20 mmol), BuLi (1.6 M solution in hexane, 0.15 ml, 0.24 mmol) and dry DMSO (7 ml). The crude product was purified by chromatography (silica, ether/ethanol/hexane 10:1:1). Yield 39 mg (69%), m.p. 83–84°C, white needles. ^1H NMR (200 MHz, CDCl_3): δ 0.80 (6 H, s, CH_3), 3.19 (4 H, s, CH_2O), 3.70 (4 H, s, CH_2O), 3.77 (4 H, s, CH_2O), 4.38 (8 H, s, CH_2O [C1, C3, C9, C11]). ^{13}C NMR (50 MHz, CDCl_3): δ 22.6, 36.5, 44.0, 74.9, 78.1, 79.8. MS (CI, isobutane): m/z 287 (84, MH), 179 (11), 169 (20), 167 (20), 155 (11), 151 (11), 149 (21), 127 (11), 119 (11), 115 (14), 113 (18), 101 (20).

cis- and trans-3,7-bis(hydroxymethyl)-3,7,11,11-tetramethyl-1,5,9-trioxacyclododecane (17b). The same procedure as described for the reductive ring opening of **16a** was followed, using the dispiro compound **16b** (22 mg, 0.077 mmol), LiAlH_4 (20 mg, 0.53 mmol) and dry monoglyme (1.5 ml). The reaction time was 2 days. The *cis*- and *trans*-diols were formed in the ratio 1:1 (GLC-MS), and were separated by column chromatography (silica, ether/hexane/ethanol 10:1:0.25). Total yield 16.2 mg (72%). The *trans*-diol was eluted first, yield 7 mg, m.p. 114–115°C. ^1H NMR (300 MHz, CDCl_3): δ 0.72 (6 H, s, CH_3), 0.85 (6 H, s, CH_3), 3.22 and 3.29 (4 H, AB system, J 9.2 Hz, CH_2O [C10, C12]), 3.36 and 3.74 (4 H, AB system, J 9.3 Hz, CH_2O [C2, C8 or C4, C6]), 3.37 and 3.60 (4 H, AB system, J 9.0 Hz, CH_2O [C2, C8 or C4, C6]), 3.5 (2 H, br s, OH), 3.58 (4 H, s, CH_2OH). ^{13}C NMR (75 MHz, CDCl_3): δ 18.1, 22.5, 36.2, 40.7, 70.0, 76.6, 76.8, 79.3. MS (CI, isobutane): m/z 291 (100, MH), 287 (29), 219 (27).

The yield of *cis*-diol was 8 mg, m.p. 117–119°C. ^1H NMR (300 MHz, CDCl_3): δ 0.75 (6 H, s, CH_3 [C3, C7]), 0.83 (6 H, s, CH_3), 3.23 and 3.28 (4 H, AB system, J 9.2 Hz, CH_2O [C10, C12]), 3.42 and 3.60 (4 H, AB system, J 9.3 Hz, CH_2O [C2, C8 or C4, C6]), 3.47–3.55 (8 H, CH_2OH and CH_2O [C2, C8 or C4, C6]), 3.5 (2 H, br s, OH). ^{13}C NMR (75 MHz, CDCl_3): δ 18.0, 22.7, 36.2, 40.9, 69.7, 76.3, 76.6, 79.1. MS (CI, isobutane): m/z 291 (100, MH), 289 (7), 287 (16).

In another experiment (with an even greater excess of LiAlH_4), the *cis:trans* ratio was 1:9.

cis-3,7-Bis(methoxymethyl)-3,7,11,11-tetramethyl-1,5,9-trioxacyclododecane (**18b**). The *cis*-diol **17b** was methylated following the procedure described for the preparation of **18a** above, using *cis*-diol **17b** (8 mg, 0.028 mmol), BuLi (1.6 M sol. in hexane, 0.1 ml, 0.16 mmol), methyl iodide (16 mg, 0.11 mmol) and dry DMSO (1.5 ml). Yield 5 mg (57 %, crude product), oil. ¹H NMR (300 MHz, CDCl₃): δ 0.81 (6 H, s, CH₃), 0.86 (6 H, s, CH₃), 3.14 and 3.35 (4 H, AB system, *J* 8.5 Hz, CH₂O [C2, C8 or C4, C6]), 3.21 and 3.24 (4 H, AB system, *J* 8.5 Hz, [C2, C8 or C4, C6]), 3.31 (4 H, s, CH₂OCH₃), 3.32 (6 H, s, CH₂OCH₃), 3.53 (4 H, br s, CH₂O [C10, C12]). ¹³C NMR (75 MHz, CDCl₃): δ 17.9, 22.7, 36.3, 41.1, 59.5, 75.4, 75.5, 77.2, 78.3. MS (CI, CH₄): *m/z* 319 (3 MH), 304 (21), 303 (100), 301 (4), 273 (4), 215 (5), 203 (8), 201 (6), 187 (7), 185 (4), 183 (3), 178 (3), 171 (9), 169 (5), 159 (3), 157 (3), 147 (11), 145 (6), 139 (7), 131 (11), 123 (5), 117 (21), 115 (16), 111 (6), 109 (5), 101 (16), 59 (100).

trans-3,7-Bis(methoxymethyl)-3,7,11,11-tetramethyl-1,5,9-trioxacyclododecane (**18b**). The procedure described above was followed, using the *trans*-diol **17b** (18.2 mg, 0.063 mmol), BuLi (1.6 M solution in hexane, 0.15 ml, 0.24 mmol), methyl iodide (39 mg, 0.27 mmol) and dry DMSO (2 ml). Column chromatography (silica, ether/hexane/ethanol 10:1:0.25) of the crude product afforded 20 mg (100 %) of **18b** as an oil. ¹H NMR (300 MHz, CDCl₃): δ 0.75 (6 H, s, CH₃), 0.77 (6 H, s, CH₃), 3.06 and 3.35 (4 H, AB system, *J* 8.8 Hz, CH₂O [C2, C8 or C4, C6]), 3.12 and 3.33 (4 H, AB system, *J* 9.1 Hz, [C2, C8 or C4, C6]), 3.14 and 3.19 (4 H, CH₂O [C10, C12]), 3.19 (4 H, s, CH₂OCH₃), 3.26 (6 H, s, CH₂OCH₃). ¹³C NMR (75 MHz, CDCl₃): δ 16.9, 21.6, 35.2, 39.9, 58.5, 74.4, 74.5, 76.0, 77.2. MS (CI, CH₄): *m/z* 319 (57, MH), 316 (5), 219 (5), 147 (5), 145 (5), 131 (4), 117 (13), 115 (9), 109 (4), 101 (7), 59 (100).

3,7,11-Tri(methoxymethyl)-3,7,11-trimethyl-1,5,9-trioxacyclododecane (**18c**, Scheme 3).

1,11-Di(benzyloxy)-6-methoxymethyl-6-methyl-2,2;10,10-bis(2-oxapropane-1,3-diyl)-4,8-dioxadecane (**13c**). The procedure was as described for the preparation of **13a**, using 2-methoxymethyl-2-methyl-1,3-propanediol⁴ (2.85 g, 21.2 mmol), NaH (60 % dispersion in oil, 2.40 g, 60 mmol), the tosylate **12** (15.4 g, 42.5 mmol) and dry DMSO (100 ml). Flash chromatography (silica, ethyl acetate/hexane 1:1) afforded the dibenzyl compound **13c** as a pale yellow oil. Yield 8.93 g (82 %). ¹H NMR (200 MHz, CDCl₃): δ 0.92 (3 H, s, CH₃), 3.21 (2 H, s, CH₂OCH₃), 3.29 (4 H, s, CH₂O), 3.31 (4 H, s, CH₂O), 3.59 (3 H, s, CH₂OCH₃), 3.67 (4 H, s, CH₂O), 4.48 (8 H, AB system, *J* 6 Hz, oxet-CH₂), 4.56 (4 H, s, OCH₂Ph), 7.34 (10 H, s, Ar-H). ¹³C NMR (50 MHz, CDCl₃): δ 18.2, 44.8, 60.0, 72.3, 73.1, 74.1, 74.6, 76.1, 77.6, 78.2, 128.0, 128.1, 128.8, 138.6.

6-Methoxymethyl-6-methyl-2,2;10,10-bis(2-oxapropane-

1,3-diyl)-4,8-dioxadecane (**14c**). To a cooled suspension of hydrogenation catalyst (10 % palladium-on-charcoal, 16 g) in abs. ethanol (20 ml) were added the dibenzyl compound **13c** (8.0 g, 15.5 mmol) and 1,4-cyclohexadiene (20 ml) dissolved in abs. ethanol (100 ml). The reaction mixture was refluxed for 1 h and then cooled. The catalyst was filtered off and the solution was concentrated to give an oil which was subjected to flash chromatography (silica, ether/ethanol/hexane 10:1:1). Yield 3.21 g (62 %). ¹H NMR (200 MHz, acetone-*d*₆): δ 0.92 (3 H, s, CH₃), 3.24 (2 H, s, CH₂OCH₃), 3.27 (4 H, s, CH₂O), 3.36 (3 H, CH₂OCH₃), 3.62 (4 H, s, CH₂O), 3.78 (4 H, d, CH₂OH), 4.0 (2 H, t, OH), 4.40 (8 H, s, oxet-CH₂). ¹³C NMR (50 MHz, acetone-*d*₆): δ 18.2, 42.3, 46.1, 59.8, 65.0, 74.1, 75.1, 76.3, 76.7.

6-Methoxymethyl-6-methyl-11-tosyloxy-2,2;10,10-bis(2-oxapropane-1,3-diyl)-4,8-dioxadecane (**15c**). The procedure was as described for the preparation of the monotosylate **15b**, using the diol **14c** (300 mg, 0.90 mmol), NaH (60 % dispersion in oil, 50 mg, 1.25 mmol), tosyl chloride (171 mg, 0.90 mmol), dry DMSO (0.5 ml) and dry THF (25 ml). The crude product after work-up was chromatographed (silica, CHCl₃/THF 5:1). Yield 214 mg (49 %). ¹H NMR (200 MHz, CDCl₃): δ 0.85 (3 H, s, CH₃), 2.46 (3 H, s, Ar-CH₃), 3.16 (2 H, s, CH₂OCH₃), 3.27 (2 H, s, CH₂O), 3.28 (5 H, s, CH₂OH and CH₂OCH₃), 3.30 (2 H, s, CH₂O), 3.59 (2 H, s, CH₂O), 3.73 (2 H, s, CH₂O), 3.90 (1 H, br s, OH), 4.24 (2 H, s, CH₂OTs), 4.33–4.46 (8 H, m, oxet-CH₂), 7.32 (2 H, d, *J* 8.4 Hz, Ar-H), 7.80 (2 H, d, *J* 8.4 Hz, Ar-H). ¹³C NMR (50 MHz, CDCl₃): δ 17.9, 41.4, 43.7, 44.7, 59.8, 67.2, 70.9, 72.1, 74.6, 75.0, 75.8, 75.9, 76.2, 76.9, 77.0, 128.4, 130.5, 145.6.

15-Methoxymethyl-15-methyl-2,6,10,13,17-pentaoxadispiro[3.3.3.7]octadecane (**16c**). The procedure was as described for the preparation of dispiro compound **16a**, using the monotosylate **15c** (800 mg, 1.64 mmol), BuLi (1.6 M solution in hexane, 1.28 ml, 2.05 mmol) and dry DMSO (40 ml). The crude product was purified by chromatography (silica, ether/ethanol/hexane 10:1:1). Yield 349 mg (67 %), colourless oil. ¹H NMR (200 MHz, CDCl₃): δ 0.80 (3 H, s, CH₃), 3.22 (2 H, s, CH₂OCH₃), 3.23 and 3.45 (4 H, AB system, *J* 9.5 Hz, CH₂O [C14, C16]), 3.30 (3 H, s, CH₂OCH₃), 3.70 and 3.72 (4 H, CH₂O [C12, C18]), 3.78 (4 H, s, CH₂O [C5, C7]), 4.36–4.45 (8 H, m, CH₂O [C1, C3, C9, C11]). ¹³C NMR (50 MHz, CDCl₃): δ 18.3, 41.3, 44.3, 59.9, 74.9, 75.0, 77.0, 77.1, 78.0, 78.2. MS (CI, CH₄): 317 (60, MH), 229 (6), 205 (8), 201 (8), 185 (6), 177 (9), 169 (8), 159 (10), 133 (10), 131 (12), 124 (8), 122 (7), 117 (14), 115 (23), 113 (12), 101 (38).

3,7-Bis(hydroxymethyl)-11-methoxymethyl-3,7,11-trimethyl-1,5,9-trioxacyclododecane (**17c**). The same procedure as described for the reductive ring opening of **16a** was followed, using the dispiro compound **16c** (349 mg, 1.10 mmol), LiAlH₄ (200 mg, 5.27 mmol) and dry THF (15 ml).

The reaction time was 1 day. The three isomeric diols were formed in the ratio 6:2:1 (GLC–MS). One of the isomers was isolated by column chromatography (silica, ether/ethanol/hexane 10:0.5:1). Yield 153 mg, colourless oil. ^1H NMR (200 MHz, CDCl_3): δ 0.72 (6 H, s, CH_3 [C3, C7]), 0.82 (3 H, s, CH_3 [C11]), 3.21–3.72 (21 H, m, CH_3O , all CH_2). ^{13}C NMR (75 MHz, CD_2Cl_2): δ 18.1, 18.2, 41.0, 41.05, 41.1, 59.47, 59.51, 69.8, 69.9, 76.38, 76.44, 76.6, 76.8, 77.0, 77.1, 77.2. Complex formation of this isomer with excess LiClO_4 (in $\text{CD}_3\text{CN}/\text{CD}_3\text{OD}$, 95:5) caused a shift of the ^1H and ^{13}C NMR signals, and revealed three different methyl groups as well as three different quaternary carbons. Thus, this compound, which was eluted first, was the *trans*-diol.

The two *cis*-diols (ratio 4:3, determined by GLC–MS) were the main components in the second fraction. Addition of excess LiClO_4 now confirmed that four different methyl groups and four different quaternary carbons were present. ^1H NMR (200 MHz, CDCl_3) of the mixture of *cis*-diols) δ 0.74 (s, CH_3 , [C3, C7]), 0.80 (s, CH_3 [C11]), 0.88 (s, CH_3 [C11]), 2.4 (br s, OH), 3.22–3.65 (21 H, m, CH_3O , all CH_2) ^{13}C NMR (75 MHz, CD_2Cl_2): δ 18.0, 18.3, 40.9, 41.2, 59.4, 59.5, 69.4, 69.8, 76.38, 76.43, 76.5, 76.6, 76.7, 76.8, 76.9, 77.0, 77.5. The total yield of diols was 276 mg (78%). In both THF and monoglyme, the ratio between the three isomers varied from one reaction to another.

trans-3,7,11-Tris(methoxymethyl)-3,7,11-trimethyl-1,5,9-trioxacyclododecane (**18c**). The *trans*-isomer was obtained by methylation of the *trans*-diol **17c**. Using the *trans*-diol **17c** (142 mg, 0.44 mmol), NaH (60% dispersion in oil, 60 mg, 1.5 mmol), methyl iodide (250 mg, 1.76 mmol) and dry THF (7 ml), and following the procedure described below, 105 mg (68%) of the *trans*-ether **18c** was obtained as a colourless oil. NMR (200 MHz, CDCl_3): δ 0.83 (3 H, s, CH_3), 0.85 (6 H, s, CH_3), 3.23 (6 H, s, CH_2OCH_3), 3.32 (9 H, s, CH_2OCH_3), 3.16–3.43 (12 H, m, CH_2O). ^{13}C NMR (50 MHz, $\text{CD}_3\text{CN}/\text{CD}_3\text{OD}$, 95:5): δ 18.4, 41.7, 59.6, 75.9, 76.1, 77.3, 77.4. MS (CI, CH_4): 349 (75, MH), 332 (4), 282 (4), 268 (4), 263 (9), 251 (6), 240 (5), 225 (5), 198 (7), 168 (11), 166 (11), 156 (13), 141 (13), 139 (14), 127 (15), 113 (11), 111 (31), 101 (18).

cis- and *trans*-3,7,11-tris(methoxymethyl)-3,7,11-trimethyl-1,5,9-trioxacyclododecane (**18c**). The mixture of the two *cis*-diols **17c** (114 mg, 0.36 mmol) was dissolved in dry THF (5 ml), NaH (60% dispersion in oil, 40 mg, 1.0 mmol) was added, and the mixture was refluxed overnight and then cooled. Methyl iodide (200 mg, 1.41 mmol) was added, and the reaction mixture was stirred at 35 °C for 1 day. The solvent was evaporated off, the residue was taken up in ether, and the solution was washed with water and dried (CaCl_2). Column chromatography (silica, ether/hexane 1:3) of the crude product gave a mixture of the *cis*- and *trans*-compounds (ratio 5:6, determined from the NMR spectrum) which could not be separated. Yield 90 mg (72%), colourless oil. The spectral data for the *cis*-isomer

were obtained from the mixture. NMR (200 MHz, CDCl_3): δ 0.86 (9 H, s, CH_3), 3.21 (6 H, s, CH_2OCH_3), 3.32 (9 H, s, CH_2OCH_3), 3.16–3.43 (12 H, m, CH_2O). ^{13}C NMR (50 MHz, $\text{CD}_3\text{CN}/\text{CD}_3\text{OD}$, 95:5): δ 18.4, 41.8, 59.7, 76.1, 77.6.

Attempts to make 2,6,10,13,17,20-hexaoxatrispiro[3.3.3.3.3.3]-icosane (22, Scheme 4).

Path A, by intramolecular cyclization.

1,11-Di(benzyloxy)-2,2;6,6;10,10-tris(2-oxapropane-1,3-diyl)-4,8-dioxaundecane (**19**). 3-Benzyloxymethyl-3-hydroxymethyloxetane (6.35 g, 30.5 mmol) was dissolved in dry DMSO (40 ml). NaH (80% dispersion in oil, 1.20 g, 36.6 mmol) was added, and the mixture was stirred at 60 °C for 5 h. 3,3-Bis(iodomethyl)oxetane (5.15 g, 15.2 mmol) dissolved in DMSO (15 ml) was added, and the reaction mixture was stirred overnight and cooled. Ether was added, and the solution was washed with water and dried (MgSO_4). The solvent was evaporated off, and the crude product was purified by flash chromatography (silica, CHCl_3/THF 5:1). Yield 6.15 g (81%), pale yellow oil. ^1H NMR (300 MHz, CDCl_3): δ 3.69 (4 H, s, CH_2O), 3.70 (4 H, s, CH_2O), 3.75 (4 H, s, CH_2O), 4.48 (8 H, AB system, J 5.9 Hz, oxet- CH_2), 4.50 (4 H, s, oxet- CH_2), 4.85 (4 H, s, OCH_2Ph), 7.28–7.35 (10 H, m, Ar-H). ^{13}C NMR (75 MHz, CDCl_3): δ 44.0, 44.2, 71.4, 72.5, 72.6, 73.4, 76.1, 76.3, 127.6, 127.7, 128.4, 138.1.

2,2;6,6;10,10-Tris(2-oxapropane-1,3-diyl)-4,8-dioxa-1,11-undecanediol (**20**). To a stirred and cooled suspension of hydrogenation catalyst (10% palladium-on-charcoal, 5.40 g) were added the dibenzyl compound **19** (2.70 g, 5.41 mmol), dissolved in abs. ethanol (100 ml), and 1,4-cyclohexadiene (8.70 g, 109 mmol) dissolved in ethanol (20 ml). The reaction mixture was stirred at room temperature until the reaction was complete (4 days). Fresh supplies of catalyst and cyclohexadiene were necessary. The catalyst was filtered off, and the solvent was evaporated. The crude product was pure by GLC and NMR spectroscopy. Yield 1.70 g (99%), colourless oil. ^1H NMR (300 MHz, acetone- d_6): δ 3.70 (4 H, s, CH_2O), 3.72 (4 H, s, CH_2O), 3.73 (4 H, s, CH_2O), 3.78 (2 H, s, CH_2OH), 4.38 (8 H, s, oxet- CH_2), 4.39 (4 H, s, oxet- CH_2). ^{13}C NMR (75 MHz, acetone- d_6): δ 44.3, 45.1, 63.7, 72.8, 73.0, 75.3, 75.6.

11-Tosyloxy-2,2;6,6;10,10-tris(2-oxapropane-1,3-diyl)-4,8-dioxa-1-undecanol (**21**). Monotosylation was carried out following the procedure described for the preparation of **9**, using the diol **20** (310 mg, 0.97 mmol), NaH (80% dispersion in oil, 35 mg, 1.17 mmol), tosyl chloride (185 mg, 0.97 mmol), DMSO (0.5 ml) and dry THF (6 ml). The crude product was chromatographed (silica, CHCl_3/THF 5:1). Yield 99 mg (22%), colourless oil. ^1H NMR (300 MHz, CDCl_3): δ 2.43 (3 H, s, Ar- CH_3), 3.55 (2 H, s, CH_2O), 3.58 (2 H, s, CH_2O), 3.637 (2 H, s, CH_2O), 3.644

(2 H, s, CH₂O), 3.66 (2 H, s, CH₂OH), 4.22 (2 H, s, CH₂OTs), 4.331 (4 H, AB system, *J* 3.5 Hz, oxet-CH₂), 4.337 (4 H, AB system, *J* 6.6 Hz, oxet-CH₂), 4.44 (4 H, s, oxet-CH₂), 4.53 (1 H, s, OH), 7.34 (2 H, d, *J* 8.2 Hz, Ar-H), 7.77 (2 H, d, *J* 8.4 Hz, Ar-H). ¹³C NMR (75 MHz, CDCl₃): δ 21.8, 43.4, 44.2, 44.3, 70.7, 71.76, 71.82, 72.8, 75.7, 76.2, 76.3, 76.7, 128.5, 130.5, 145.8.

Attempts to cyclize the monotosylate **21** were performed in a way similar to that for **15a** and **15b**. No cyclic product was formed in this case.

Path B, by intermolecular cyclization.

3-Hydroxymethyl-3-tosyloxymethyloxetane. The procedure described for the preparation of **4** was followed, using 3,3-bis(hydroxymethyl)oxetane¹⁰ (4.00 g, 33.9 mmol), tosyl chloride (6.46 g, 33.9 mmol), pyridine (5 ml) and ethanol-free CHCl₃ (45 ml). The reaction time was 2 days. Column chromatography (silica, ethyl acetate/hexane 2:1) afforded the monotosylate as an oil, yield 4.8 g (52%). A small amount was crystallised from CHCl₃/hexane, m.p. 99–102 °C. ¹H NMR (300 MHz, CDCl₃): δ 2.27 (3 H, s, Ar-CH₃), 3.89 (2 H, s, CH₂OH), 4.31 (2 H, s, CH₂OTs), 4.35 and 4.44 (4 H, AB system, *J* 6.3 Hz, oxet-CH₂), 7.38 and 7.81 (4 H, q, *J* 8.3 Hz, Ar-H). ¹³C NMR (50 MHz, CDCl₃): δ 21.8, 44.2, 63.4, 70.7, 75.6, 128.4, 130.6, 145.9.

Tetrahydropyranlation of 3-hydroxymethyl-3-tosyloxymethyloxetane was carried out following a standard procedure,¹³ using 3-hydroxymethyl-3-tosyloxymethyloxetane (1.37 g, 5.0 mmol), dihydropyran (0.84 g, 10.0 mmol), pyridinium *p*-toluenesulfonate (50 mg) and dry CH₂Cl₂ (20 ml). Yield 1.79 g (100%, crude product), m.p. 64–66 °C. ¹H NMR (300 MHz, CDCl₃): δ 1.46–1.85 (6 H, m, CH₂), 2.46 (3 H, s, Ar-CH₃), 3.74 (2 H, m), 4.29 (2 H, s, CH₂OTs), 4.36 and 4.49 (4 H, q, oxet-CH₂), 4.41 (2 H, d), 4.51 (1 H, m), 7.36 and 7.81 (4 H, q, Ar-H).

Monotetrahydropyranyl ether of 2,2;6,6-bis(2-oxapropane-1,3-diyl)-4-oxa-1,7-heptanediol (23). 3,3-Bis(hydroxymethyl)oxetane¹⁰ (3.06 g, 25.9 mmol) was dissolved in dry DMSO, NaH (60% suspension in oil, 0.68 g, 17.0 mmol) was added, and the mixture was stirred at 60 °C for 1 h. The above tetrahydropyranyl ether (4.60 g, 12.9 mmol), dissolved in DMSO (35 ml), was added over 5 h, and the reaction mixture was stirred at room temperature for 2 days. DMSO was distilled at reduced pressure, ether/ethyl acetate was added to the residue, and the organic solution was washed with water. After drying (MgSO₄) and evaporation of the solvents, the product was isolated by flash chromatography (CHCl₃/methanol 9:1). Yield 2.22 g (57%), oil. ¹H NMR (300 MHz, CDCl₃): δ 1.52–1.79 (6 H, m), 3.50–4.0 (12 H, m), 4.44–4.59 (8 H, m). ¹³C NMR (50 MHz, CDCl₃): δ 19.7, 25.3, 30.5, 43.6, 44.3, 62.6, 65.4, 68.7, 72.5, 72.6, 72.8, 74.3, 76.1, 77.3, 99.3.

2,2;6,6-Bis(2-oxapropane-1,3-diyl)-4-oxa-1,7-heptanediol (23). The above monotetrahydropyranyl ether (0.52 g, 1.72

mmol) was dissolved in 2-propanol (30 ml), pyridinium *p*-toluenesulfonate (50 mg) was added, and the reaction mixture was stirred at room temperature until TLC-analysis showed that no starting material was left. The solvent was evaporated, and the product was isolated by chromatography (silica, ether/ethanol). Yield 0.36 g (96%), m.p. 105–107 °C, white needles. ¹H NMR (300 MHz, CDCl₃): δ 3.69 (4 H, s, CH₂OH), 3.76 (4 H, s, CH₂O), 4.47 and 4.50 (8 H, AB system, *J* 6.0 Hz, oxet-CH₂), 4.90 (2 H, br s, OH). ¹³C NMR (50 MHz, CDCl₃): δ 46.0, 64.3, 73.4, 77.1.

The intermolecular reaction between the diol **23** and 3,3-bis(tosyloxymethyl)oxetane was performed in a way similar to that for the preparation of **25**. Less than 2% (GLC-MS) of the cyclic product **22** was formed in this case.

The intermolecular reaction between the same bis-tosylate and 2,6-bis(methoxymethyl)-2,6-dimethyl-4-oxa-1,7-heptanediol,⁴ to obtain a mono-spiro compound analogous to **25**, failed to give the cyclic product.

3-Methoxymethyl-3,7,7,11,11-pentamethyl-1,5,9-trioxacyclododecane (27, Scheme 5).

2,2,6,6-Tetramethyl-4-oxa-1,7-heptanediol (24). The standard reduction procedure described for the preparation of **11** was followed, using bis-(3-methyloxetan-3-yl) methyl ether⁴ (3.00 g, 16.1 mmol), LiAlH₄ (1.2 g, 32.2 mmol) and dry monoglyme (75 ml). The solid crude product was recrystallized from ether/hexane to give white crystals, yield 2.9 g (95%), m.p. 87–88 °C. ¹H NMR (200 MHz, CDCl₃): δ 0.91 (12 H, s, CH₃), 2.7 (2 H, br s, OH), 3.26 (4 H, s, CH₂O), 3.43 (4 H, br s, CH₂OH). ¹³C NMR (75 MHz, CDCl₃): δ 21.8, 36.4, 70.8, 79.7. MS (CI, isobutane): *m/z* 191 (85), 189 (2), 173 (3), 117 (10), 87 (100).

Intermolecular cyclization experiments. Several combinations of base and solvent were tried to find the best cyclization conditions with 3,3-bis(tosyloxymethyl) and 3,3-bis(iodomethyl)oxetane. The volatile reaction products were analysed by GLC-MS. No cyclic product was obtained in DMF or in DMSO when K was the base, even at high temperature and with reaction times of several days (the alkoxide was generated in THF, the solvent was then changed). With BuLi in DMF or DMA, 10–30% of the cyclic product was obtained after 1–4 days at 50–60 °C (the alkoxide was generated in ether, the solvent was then changed). The best result was obtained with the bis-iodide using NaH/DMSO, in which case 30% cyclic product was formed after 1 day at 60 °C using LiH instead of NaH or adding LiClO₄ had no effect with respect to reaction time or amount of cyclic product.

8,8,12,12-Tetramethyl-2,6,10,14-tetraoxaspiro[3.11]penta-decane (25). The reaction was run under nitrogen. The diol **24** (2.45 g, 12.9 mmol) and LiClO₄ (2.74 g, 25.8 mmol) were dissolved in dry DMSO (50 ml). NaH (80% dispersion in oil, 1.16 g, 38.7 mmol) was added and the mixture was stirred at 70 °C for 3 h and then cooled to room

temperature. 3,3-Bis(iodomethyl)oxetane (4.35 g, 12.9 mmol) was added and the reaction mixture was stirred at 60°C overnight. GLC-MS analysis showed that the 12-membered ring constituted only 31% of the volatiles, and that unchanged starting materials were still present. However, prolonged reaction time led only to formation of more by-products. The reaction mixture was cooled, ether/ethyl acetate (2:1) was added, and the solution was washed several times with water. After drying (MgSO₄) and evaporation of the solvents, the oily crude product was flash chromatographed (silica, ether/ethyl acetate 4:1). The 12-membered ring was further purified by distillation in a Kugelrohr apparatus (100–115°C/0.01 mmHg). The product was an oil which crystallized in the refrigerator and was recrystallized from acetone. Yield 0.66 g (19%), m.p. 132–133°C, white needles. ¹H NMR (300 MHz, CDCl₃): δ 0.83 (12 H, s, CH₃), 3.16 (4 H, s, CH₂O), 3.24 (4 H, s, CH₂O), 3.78 (4 H, s, CH₂O), 4.42 (4 H, s, CH₂ [C1, C3]). ¹³C NMR (75 MHz, CDCl₃): δ 22.5, 36.2, 43.9, 74.5, 77.8, 78.2, 78.9. MS (CI, isobutane): *m/z* 273 (100, MH), 271 (3), 115 (5), 111 (4), 101 (7).

The dimeric 24-membered ring (8,8,12,12,23,23,27,27-octamethyl-2,6,10,14,18,21,25,29-octaoxadispiro[3.11.3.11]-triacontane) was isolated by chromatography as an oil which was crystallized from hexane. Yield 0.11 g, m.p. 128–130°C, white needles. ¹H NMR (300 MHz, CDCl₃): δ 0.89 (24 H, s, CH₃), 3.11 (8 H, s, CH₂O), 3.20 (8 H, s, CH₂O), 3.54 (8 H, s, CH₂O), 4.47 (8 H, s, CH₂ [C1, C3 and C17, C19]). ¹³C NMR (75 MHz, CDCl₃): δ 22.1, 36.6, 44.3, 72.7, 76.2, 77.1, 77.5. MS (CI, isobutane): *m/z* 545 (100, MH), 173 (13), 171 (18), 155 (37), 141 (11), 139 (27), 115 (45), 103 (19), 101 (14).

3-Hydroxymethyl-3,7,7,11,11-pentamethyl-1,5,9-trioxacyclododecane (**26**). The standard reduction procedure described for the preparation of **11** was followed, using the spiro compound **25** (350 mg, 1.28 mmol), LiAlH₄ (97.2 mg, 2.56 mmol) and dry monoglyme (20 ml). The crude product was pure by NMR spectroscopy and GLC. Yield 351 mg (100%), m.p. 77–79°C. ¹H NMR (300 MHz, CDCl₃): δ 0.72 (3 H, s, CH₃ [C3]), 0.83 (s, 6 H, CH₃ [C7, C11]), 0.85 (6 H, s, CH₃ [C7, C11]), 3.10 (1 H, br s, OH), 3.20 (4 H, s, CH₂O [C8, C10]), 3.22 and 3.31 (4 H, AB system, *J* 9.7 Hz, CH₂O [C6, C12]), 3.39 and 3.63 (4 H, AB system, *J* 9.0 Hz, CH₂O [C2, C4]), 3.52 (2 H, br s, CH₂OH). ¹³C NMR (75 MHz, CDCl₃): δ 17.9, 22.4, 22.5, 36.1, 40.6, 70.3, 76.2, 78.4, 79.1. MS (EI): *m/z* 274 (15, M), 205 (8), 191 (9),

189 (7), 187 (9), 175 (5), 154 (7), 157 (11), 139 (6), 133 (12), 121 (6), 117 (22), 115 (16), 105 (23), 103 (23), 101 (12).

3-Methoxymethyl-3,7,7,11,11-pentamethyl-1,5,9-trioxacyclododecane (**27**). The alcohol **26** was methylated following a standard procedure, using **26** (340 mg, 1.24 mmol), NaH (80% suspension in oil, 37.2 mg, 1.24 mmol), methyl iodide (324 mg, 2.28 mmol) and dry THF (8 ml). The product was purified by chromatography (silica, hexane/ethyl acetate 10:1). Yield 311 mg (87%), colourless oil. ¹H NMR (300 MHz, CD₃CN/CD₃OD 95:5): δ 0.79 (6 H, s, CH₃ [C7, C11]), 0.80 (6 H, s, CH₃ [C7, C11]), 0.83 (3 H, s, CH₃ [C3]), 3.12 and 3.37 (4 H, AB system, *J* 8.9 Hz, CH₂O [C2, C4]), 3.19 and 3.22 (4 H, AB system, *J* 1.8 Hz, CH₂O [C6, C12]), 3.21 (2 H, s, CH₂OCH₃), 3.25 (3 H, s, CH₂OCH₃), 3.26 (4 H, br s, CH₂O [C8, C10]). ¹³C NMR (75 MHz, CD₃CN/CD₃OD 95:5): δ 18.5, 23.1, 37.1, 41.9, 59.8, 76.5, 77.7, 79.3. MS (CI, isobutane): *m/z* 289 (100, MH), 219 (3), 203 (4), 201 (2), 189 (3), 173 (2), 147 (2), 139 (29), 117 (5), 115 (6), 101 (4).

Traces of dimer (24-membered ring) were detected by GLC-MS. MS (CI, isobutane): *m/z* 577 (17, MH), 491 (15), 289 (100), 101 (3).

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