Synthesis and structure of tetraols with convergent and divergent arrays of hydroxy groups

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As hydrogen-bonding hosts with a partially flexible framework, two types of tetrahydroxy compounds with respectively convergent and divergent arrays of hydroxy groups were prepared. The structures of the tetraol with a diethyleneoxy bridge (**1a**), and that with a *m*-phenylenedioxy bridge (*syn*-**13a** and *anti*-**13b**) were determined by X-ray crystallographic studies. *syn*-**13a** forms an inclusion crystal with 1,4-dioxane, one molecule of which is bound in the cleft of *syn*-**13a** and the other in the intermolecular cavity.

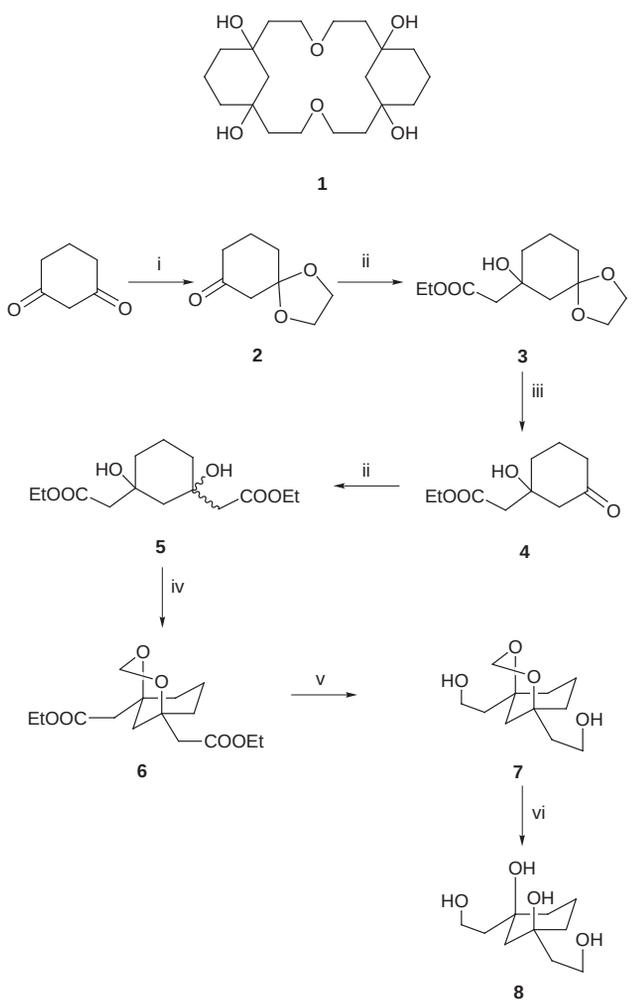
During the recent development of host–guest chemistry, it was recognized that the direction of recognition groups and their fluctuation are important factors to determine the selectivity of molecular recognition and the ability of self-assembly formation. Attaching interaction groups to a scaffold in a convergent fashion leads to a host that binds guest in solution, while attaching them in a divergent fashion leads to a tecton[1] that forms self-assembly either in solution or in the solid state. For such chemistry both in the liquid phase and in the crystalline phase, a number of host molecules with a rigid framework have been synthesized, such as crown ethers, cryptands, carcerands, cyclodextrins, cyclophanes, calixalenes, molecular cleft, and porphyrins.[2] In addition to the ability of a host to display expected intermolecular interactions to bind a guest, conformational changes triggered by intermolecular forces are another important feature of functions of host molecules as exemplified in induced-fit binding of substrates by enzymes.[3] For the design of these host molecules, partial flexibility should be given to the host structure.[4] However, controlling flexibility/rigidity of a molecule requires extensive knowledge of potential energies of all conformers, and we are still far away from our ultimate goal of fine tuning of the flexibility of the host framework structure.

As part of our programme aimed at developing a new host with controlled flexibility, we describe here the synthesis and the structural characterization of novel host molecules, tetrahydroxylic compounds, where the arrangement and dynamics of the hydroxy groups can be controlled by bridging groups with varying flexibility.

Results and discussion

Two types of tetraols were prepared, both of which have a *trans*-cyclohexane-1,3-diol unit in common. Tetraol **1** has ethyleneoxy bridging units while tetraol **13** has a *m*-phenylene unit in addition to the ethyleneoxy unit to provide flexibility to the dimeric structure. Scheme 1 shows the synthesis of the common precursor **7**.[5]

Nucleophilic addition of an enolate anion, generated from ethyl acetate and lithium diisopropylamide, to the carbonyl group of cyclohexane-1,3-dione gave the cyclohexane-1,3-diol **5** in four steps. An attempt to perform the addition reaction of two enolate anions to cyclohexane-1,3-dione in one step to directly obtain diester **5** was unsuccessful. Thus, the reaction between cyclohexane-1,3-dione and an excess of the ester enolate anion afforded only the corresponding stable enolate from the β-diketone, which was unreactive toward the nucleophile. The addition reactions were, therefore, carried out stepwise *via*



Scheme 1 *Reagents and conditions*: i, ethylene glycol, TsOH(cat.), benzene, reflux; ii, EtOAc, LDA, THF, −78 °C; then H_3O^+; iii, H^+ THF; iv, $(CH_2O)_n$, EtOH, TsOH(cat.), benzene; then *m*-xylene; v, $LiAlH_4$, THF; vi, H^+ MeOH.

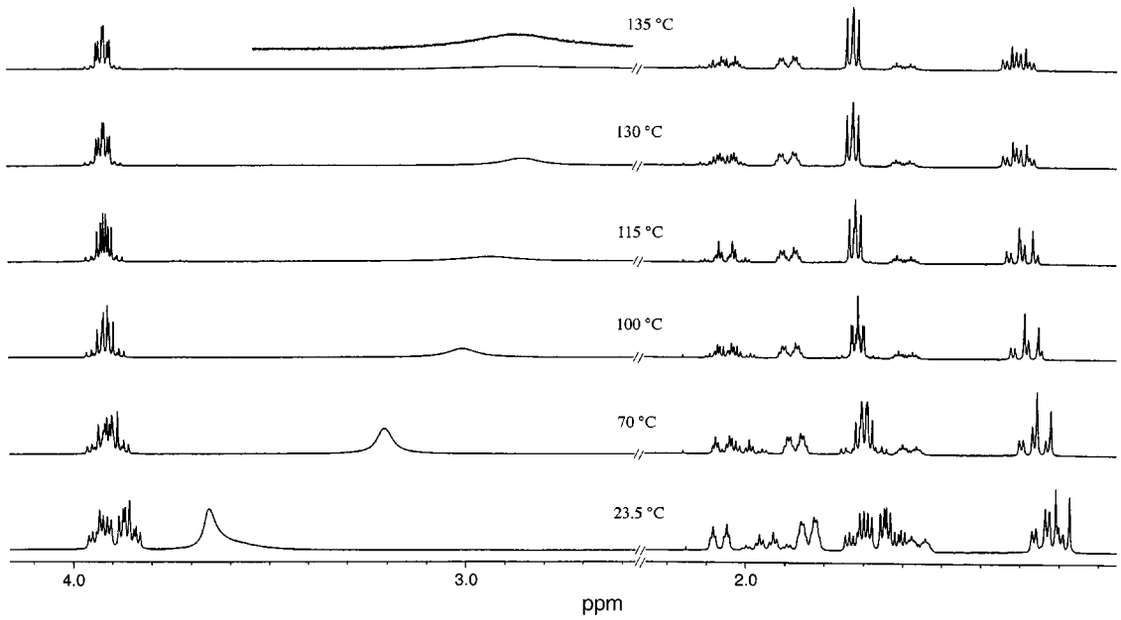


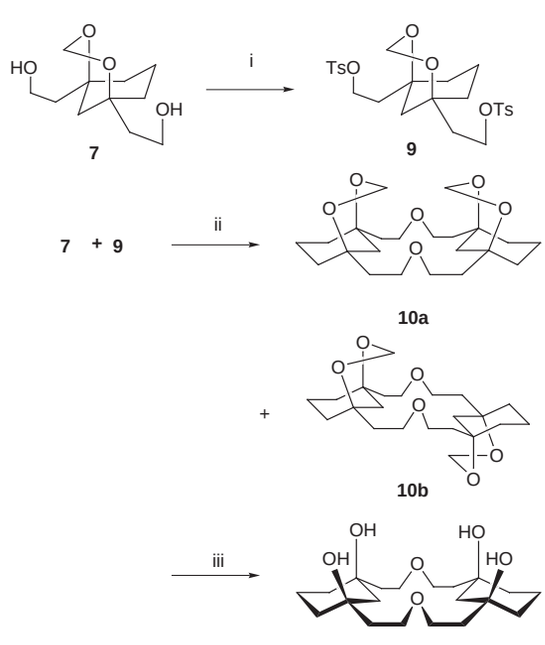
Fig. 1 ^{1}H NMR spectra of **8** in $CDCl_2CDCl_2$ in the temperature range of 23.5–135 °C.

cyclic ketal protection. The ^{1}H NMR spectrum of **5** indicated that this diester was a 1 : 1 mixture of *cis* and *trans* isomers: the two sets of α-methylene proton signals at δ 2.43, 2.42 and δ 2.70, 2.60 were ascribed to the *cis* and *trans* isomers, respectively. The R_f-values (TLC) of these isomers were so close that the separation of these isomers by silica gel column chromatography on a large scale was, in practice difficult. In order to protect the two hydroxy groups of diester **5**, direct ketalization was examined by using 2,2-dimethoxypropane, but failed possibly due to the strained 1,3-dioxacyclane products. The mixture of *cis*/*trans* isomers **5** was treated with paraformaldehyde under acidic conditions to give a mixed acetal as an intermediate. Subsequent thermal decomposition of the mixed acetal afforded cyclic acetal **6** selectively from the *cis* isomer of **5**, while the *trans* isomer of **5** was converted to a lactone during pyrolysis. Cyclic acetal **6** and the lactone were successfully separated by silica gel column chromatography. A mixture of *cis*- and *trans*-**5** was recovered from the lactone by treating it with dilute sulfuric acid. Reduction of acetal **6** with lithium aluminium hydride gave diol **7**, which adopts the chair-boat conformation as confirmed by observation of ^{1}H NMR nuclear Overhauser enhancement (NOE) between the acetal methylene protons and the cyclohexane ring protons. After hydrolysis of diol **7** with aq. HCl, white crystalline solids were obtained; recrystallization from $CHCl_3$ gave **8** in 84% yield.

Tetraol **8** was characterized by ^{1}H and ^{13}C NMR, mass spectroscopy, and elemental analysis. In the ^{1}H NMR spectrum, the two methylene protons at the α-positions to the primary hydroxy groups appear as magnetically inequivalent protons in $CDCl_3$, while they become equivalent in CD_3OD. Similar behaviour was observed for the β-methylene protons to the primary hydroxy groups. These observations indicate that intramolecular hydrogen bonding between the primary OH group and the tertiary OH group is formed in $CDCl_3$ and it breaks in CD_3OD. The variable-temperature ^{1}H NMR spectra of **8** in $CDCl_2CDCl_2$ (Fig. 1) indicated that the methylene protons α to the primary hydroxy group appear as multiplets centred at δ 3.9 at 23.5 °C and as a doublet of triplets at 135 °C. The intramolecular hydrogen bonding in an apolar solvent is thus cleaved at high temperature. In contrast, the axial and equatorial protons of the cyclohexane ring appeared separately, and this spectral pattern did not change upon heating, showing that the chair conformation with hydroxyethyl groups in the equatorial position is rather rigid. Conformational analysis by ^{1}H NMR of 1,3-disubstituted cyclohexanes has been reported.[6]

Vapour-pressure osmometry showed that the molecular weight of **8** was 235 in a 0–0.023 M solution in $CHCl_3$, suggesting that **8** is monomeric in $CHCl_3$.

The synthetic route to **1a** is illustrated in Scheme 2. For the



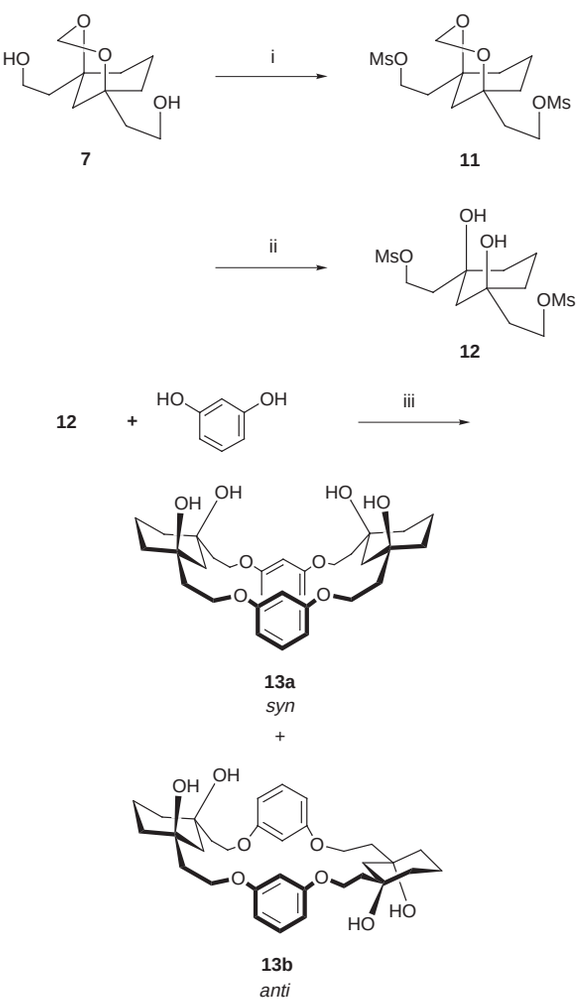
Scheme 2 *Reagents and conditions*: i, *p*-TsCl, DMAP, Et_3N, CH_2Cl_2; ii, KO^{t}Bu, DME–DMSO; iii, H^+, MeOH.

dimer preparation, the two hydroxy groups of **7** were converted to toluene-*p*-sulfonate, methanesulfonate, chloride, bromide, or iodide as leaving groups, and the coupling reactions with **7** were attempted. Various base–solvent combinations were tried to obtain dimers **10a** and **10b**. The combination of ditosyl compound **9** and potassium *tert*-butoxide in Me_2SO gave dimers **10a** and **10b** in low yield. When other leaving groups (halogens) were used, α,β-elimination took place in preference to the coupling reaction. Treatment of a mixture of **10a** and **10b** with HCl in methanol afforded the desired dimer **1a** having *cisoid* tetrahydroxy groups. *syn* Isomer **1a** was isolated and purified by medium-pressure liquid chromatography (MPLC), and charac-

terized by NMR, MS and IR spectra, whereas the *anti* isomer was not isolated because it formed only indistinct spots on TLC.

The *syn* geometry of **1a** was confirmed by X-ray crystallographic analysis. The two cyclohexane rings assumed a chair conformation and the hydrogen-bonding network among the four hydroxy groups stabilized the rigid conformation with a collapsed cleft between the two cyclohexane rings.[7] The ^{1}H NMR spectrum of **1a** in $CDCl_3$ was similar to that in CD_3OD, indicating that **1a** has a rigid framework as compared to **8**. The methylene protons β to the ether oxygen were shifted downfield as the solvent changes from $CDCl_3$ to CD_3OD, indicating some conformational changes. In the variable-temperature ^{1}H NMR spectra in $CDCl_2CDCl_2$ from 24 to 130 °C, almost no changes in coupling constants were observed. The methylene protons β to the ether oxygen were shifted downfield upon heating, which can be attributed to changes in conformation or solvation.

For the synthesis of dimers **13a** and **13b**, dimesyl compound **11** was employed as a precursor (Scheme 3). The reaction of



Scheme 3 *Reagents and conditions*: i, MsCl, Et_3N, CH_2Cl_2; ii, $Ph_3C^+BF_4^-$, CH_2Cl_2; then aq. $NaHCO_3$; iii, Cs_2CO_3, DMF.

cyclic acetal **11** with resorcinol in the presence of caesium carbonate in the DME–DMF mixed solvent system also gave corresponding cyclic acetal dimers in 10% yield, but various attempts to deprotect the methylenedioxy group were unsuccessful. This is presumably due to a side reaction in which the generated formyl cation reacts with the resorcinol group under acidic conditions. Therefore, the cyclic acetal had to be removed prior to the coupling of the dimesyl unit with resorcinol to prevent the foregoing reaction. The cyclic acetal protecting group of **11** was removed by trityl tetrafluoroborate–

Table 1 Crystal data for **13a**·1.5$C_4H_8O_2$

Formula	$C_{38}H_{56}O_{11}$
Formula weight	688.85
Space group	*C*2/*c*
a/Å	21.458(2)
b/Å	16.518(1)
c/Å	21.437(2)
β/°	95.581(6)
Vol./Å^3	7562.5(8)
Z	8
ρ (calc.)/g cm^{-3}	1.21
Temp. *T*/°C	23
Crystal dimensions/mm	0.25 × 0.25 × 0.25
Radiation	graphite-monochromated Cu-K_α radiation and a 12 kW rotating anode generator
Linear absorption coeff./cm^{-1}	7.21
Detector aperture	9.0 mm horizontal 13.0 mm vertical
Scan type	ω–2θ
Scan rate	16.0° min^{-1} in ω
2θ limits	2.0° < 2θ < 120.1°
Reflections measured	5477 total, 5321 unique
Reflections used	3894
No. of variables	494
R	0.062
R_w	0.071

CH_2Cl_2 to afford **12** in 65% yield. The combination of diol **12**, resorcinol and caesium carbonate in DMF gave dimers **13a** and **13b** in 6% yield. Each isomer was separated successfully by MPLC, and characterized by NMR and MS spectra. The purity of the dimers was higher than 95% as checked by ^{1}H NMR and ^{13}C NMR spectroscopy. The aromatic carbons of **13a** and **13b** in the ^{13}C NMR spectra in $CDCl_3$ and CD_3OD are diagnostic: *syn*-**13a** displayed signals at δ_C 159.6 (C-1, -3) and at δ_C 107.5 (C-4, -6), while *anti*-**13b** displayed signals at δ_C 159.71 (C-1), 157.87 (C-3), 108.26 (C-4 or 6), 106.25 (C-6 or 4), whose assignments were made by ^{1}H–^{13}C proton-detected single-quantum coherence (HSQC) experiments. The number of magnetically inequivalent aromatic carbons observed in **13b** was consistent with its *anti* structure. From the ^{1}H NMR spectra, it was difficult to distinguish between the two isomers owing to their similar coupling patterns. In the variable-temperature ^{1}H NMR spectra of **13a** in $CDCl_2CDCl_2$, the aromatic 5-H (δ 7.11) was shifted upfield by 0.04 ppm and the aromatic 4-H and 6-H upfield by 0.02 ppm as the temperature was varied from 25 to 100 °C, suggesting that conformational changes of the bridge occurred with increasing temperature.

By X-ray diffraction crystallographic study, the crystal structures of **1a**, **13a**, and **13b** were determined. **13a** crystallizes in the monoclinic space group *C*2/*c* with eight molecules per unit cell. **13b** crystallizes in the monoclinic space group $P2_1/c$ with two molecules per unit cell. Crystal data are listed in Tables 1 and 2. As shown in Fig. 2, both **13a** and **13b** have a cavity consisting of two benzene rings and two cyclohexane rings. The size of the cavity is 5.9 Å (the H···H distance between the closest hydrogens of the cyclohexane rings) × 6.3 Å (the H···H distance between the closest hydrogens of the benzene rings) for **13a** and 5.8 × 6.4 Å for **13b**, as clearly seen in the top views. As the side views show, the benzene rings are almost parallel to the cyclohexane rings for **13a**, while they are nearly perpendicular to them for **13b**. It is noteworthy that the *syn* isomer, **13a**, forms an inclusion crystal with 1,4-dioxane, while other tetraols, **1a** and **13b**, do not. Two crystallographically different 1,4-dioxane molecules are included in the crystal. One is bound with the shallow cleft of **13a** as shown in Fig. 3. The other is bound in an intermolecular cavity (not shown). In the crystal, **13a** assumes a conformation where the cyclohexane ring is nearly coplanar to the neighboring molecule, and the hydroxy groups form hydrogen bonds with those in the next molecule to form a linear array of molecules. This arrangement of **13a** makes intermolecular

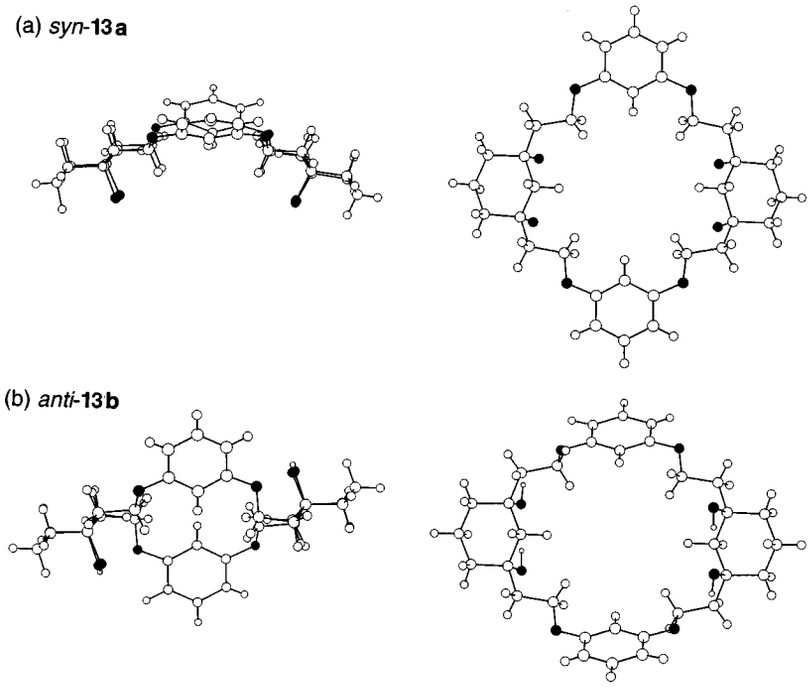


Fig. 2 Structures of (a) **13a** and (b) **13b** obtained from X-ray crystallographic studies.

Table 2 Crystal data for **13b**

Formula	$C_{32}H_{44}O_8$
Formula weight	556.69
Space group	$P2_1/c$
a/Å	11.727(4)
b/Å	10.915(4)
c/Å	12.109(4)
β/°	112.25(2)
Vol./Å^3	1434.6(8)
Z	2
ρ (Calc.)/g cm^{-3}	1.289
Temp. T/°C	23
Crystal dimensions/mm	0.40 × 0.30 × 0.20
Radiation	graphite-monochromated Mo-K_α radiation and a 12 kW rotating anode generator
Linear absorption coeff./cm^{-1}	0.91
Detector aperture	6.0 mm horizontal 6.0 mm vertical
Scan type	ω–2θ
Scan rate	16.0° min^{-1} in ω
2θ limits	$2.0° < 2\theta < 60.0°$
Reflections measured	4584 total, 4395 unique
Reflections used	2939
No. of variables	270
R	0.036
R_w	0.052

cavities in the crystal, in which the second 1,4-dioxane is included (Fig. 4).

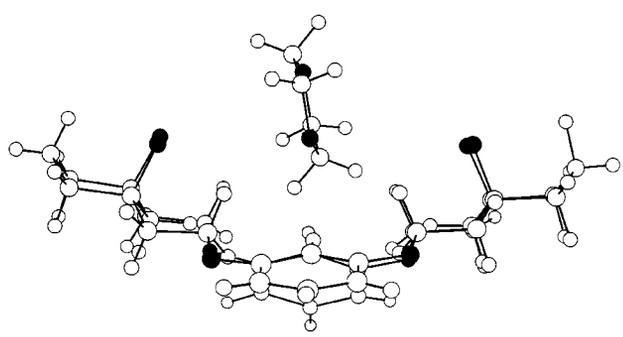


Fig. 3 Structures of a complex between **13a** and 1,4-dioxane obtained from X-ray crystallographic studies.

Experimental

General remarks

^{1}H NMR spectra were recorded on a JEOL A-500 (500 MHz), a JEOL GX-400 (400 MHz), and a JEOL JNM FX 90Q (90 MHz) FT NMR spectrometer. Chemical shifts are reported in parts per million and referenced to internal $CHCl_3$ (^{1}H δ 7.25) or $CDCl_3$ (^{13}C δ 77.0). Coupling constants are reported in hertz (Hz) and splitting patterns are designated as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), AB q (AB quartet), br (broad). IR spectra were recorded on a BIO-RAD FTS-7 FT-IR spectrometer. Mass spectra were obtained with a JEOL JMS DX-300 mass spectrometer. Elemental analyses were performed at the Microanalysis Center of the Department of Pharmaceutical Sciences, Kyoto University. Analytical TLC was performed on plates coated with a 0.25 mm thickness of silica gel 60-F254 (Merck). Column chromatography was performed using Merck Kieselgel 60 (70–230 mesh) or Pharma basic aluminium oxide activity grade I. Gas–liquid chromatography was conducted on a Shimadzu GC-4B gas chromatograph, equipped with a 3 m and a 1 m glass column packed with 30% silicone DC550 on Celite 545 and silicone SE30. MPLC was performed with a silica gel pre-packed column [Lobar Größe A(240-10) LiChroprep Si 60 (40–63 μm, Merck)]. Single-crystal X-ray diffraction was performed on a Rigaku AFC7R diffractometer.

Materials

Unless otherwise noted, materials were obtained from commercial sources and used after distillation under nitrogen. THF, diethyl ether, *n*-hexane, triethylamine, DME and diisopropylamine were distilled over sodium benzophenone ketyl and stored under nitrogen. Ethyl acetate, DMSO, DMF and 1,2-dichloroethane were distilled from CaH_2, and 1,4-dioxane from $LiAlH_4$.

1,4-Dioxaspiro[4.5]decan-7-one 2

This compound was prepared according to the reported method.[8] A mixture of cyclohexane-1,3-dione (75.0 g, 0.669

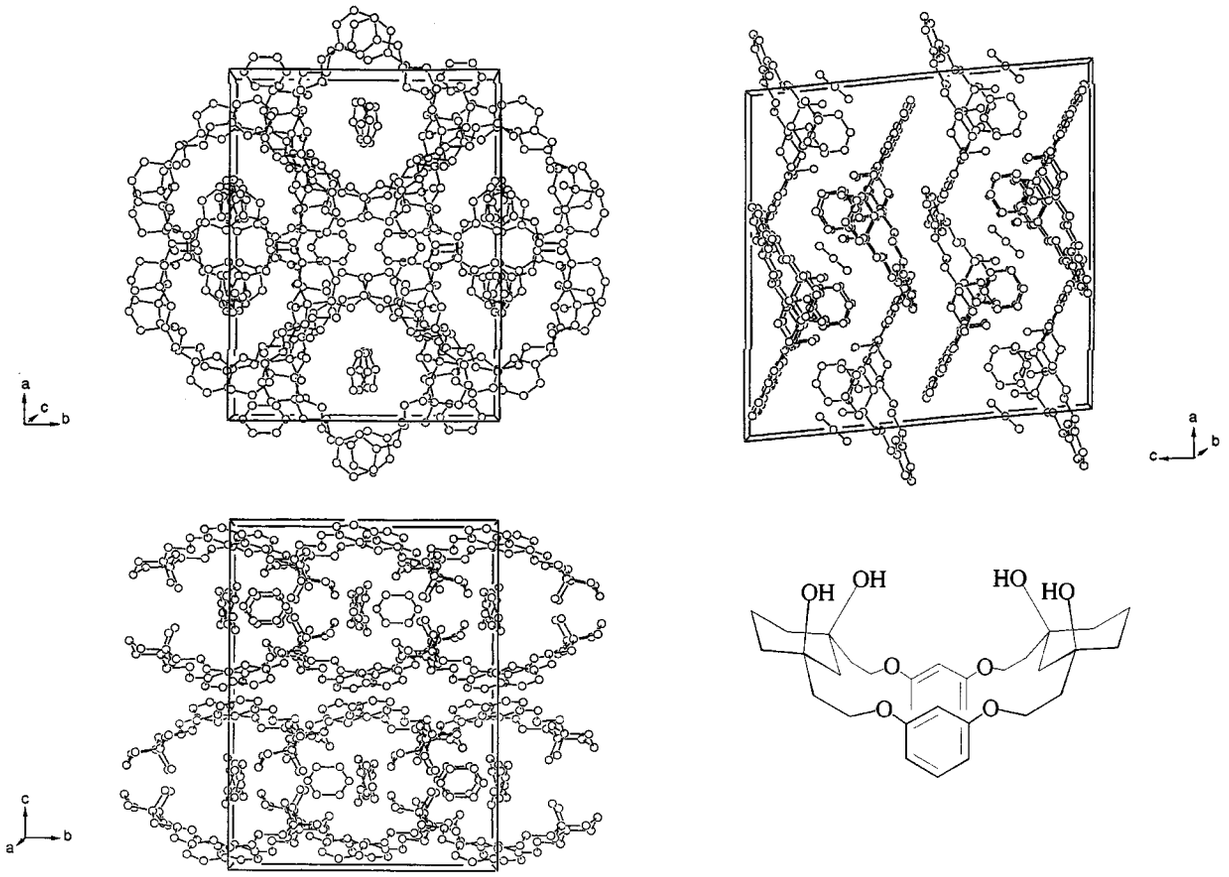


Fig. 4 Perspective view of the crystal structure of **13a**·1.5 1,4-dioxane.

mol), ethylene glycol (41.5 g, 0.669 mol) and toluene-*p*-sulfonic acid monohydrate (TsOH) (1.27 g, 6.69 mmol) in 1.8 l of benzene was efficiently stirred and refluxed for 4.5 h. Slightly more than the theoretical amount of water was collected in a Dean–Stark trap. The benzene solution was washed successively with saturated aq. $NaHCO_3$ (60 ml) and saturated aq. NaCl (50 ml × 2). After drying of the solution over anhydrous $MgSO_4$ the solvent was distilled off and the product **2** was purified by vacuum distillation at 62–75 °C/0.15 mmHg (71.5 g, 60%); ^{1}H NMR (90 MHz, $CDCl_3$) δ 1.75–2.46 (m, 6H), 2.58 (s, 2H), 3.95 (s, 4H, OCH_2CH_2O).

7-Ethoxycarbonylmethyl-7-hydroxy-1,4-dioxaspiro[4.5]decane 3

To a solution of lithium diisopropylamide (LDA) (0.521 mol) in dry THF (320 ml) was added dropwise ethyl acetate (45.9 g, 0.521 mol) at −78 °C under nitrogen with stirring. Stirring was continued for an additional hour. A solution of ketal **2** (71.5 g, 0.401 mol) in dry THF (100 ml) was added dropwise to the reaction mixture. After being stirred for 30 min, the reaction mixture was hydrolyzed by adding 4 M hydrochloric acid (200 ml) in one portion. The organic layer was separated. The aqueous layer was neutralized and extracted several times with diethyl ether. The combined organic extracts were washed with saturated aq. NaCl and dried over anhydrous $MgSO_4$. The solvent was evaporated under reduced pressure to give 109.4 g of a pale yellow oil, consisting mainly of the desired product as determined by GLC. This material was used directly in the next step without further purification. For analysis, a small portion of **3** was purified by column chromatography (SiO_2, hexane–EtOAc = 2 : 1); TLC (silica gel) R_f 0.24 (hexane–EtOAc = 2 : 1); ^{1}H NMR (90 MHz, $CDCl_3$) δ 1.26 (t, J = 7.2 Hz, 3H, $CO_2CH_2CH_3$), 1.37–2.07 (m, 8H), 2.53 (s, 2H, CH_2CO_2Et), 3.97 (s, 4H, OCH_2CH_2O), 4.18 (q, J = 7.2 Hz, 2H, $CO_2CH_2CH_3$); IR (liquid film, cm^{-1}) 3512m, 2945w, 2882w, 1731s (C=O).

Ethyl (1-hydroxy-3-oxocyclohexyl)acetate 4

To the crude product **3** (109.4 g) obtained above were added THF (80 ml) and 10.5 M hydrochloric acid (80 ml) and the mixture was stirred at ambient temperature for 9 h. To this reaction mixture was added aq. $NaHCO_3$ until the aqueous layer was neutralized. The aqueous layer was extracted several times with diethyl ether, and the combined extracts were washed with saturated aq. NaCl and dried over Na_2SO_4. The solvent was removed and the residue was distilled under reduced pressure to yield a liquid (69.1 g, 68% based on monoketal **2**), bp 100–136 °C/0.25–0.3 mmHg; ^{1}H NMR (90 MHz, $CDCl_3$) δ 1.27 (t, J = 7.3 Hz, 3H, $CO_2CH_2CH_3$), 1.45–2.54 (m, 8H), 2.54 (s, 2H, CH_2CO_2Et), 4.21 (q, J = 7.3 Hz, 2H, $CO_2CH_2CH_3$); IR (liquid film, cm^{-1}) 3488m, 2959w, 1714s (C=O).

Diethyl 1,3-dihydroxycyclohexane-1,3-diacetate 5

To a solution of LDA (0.346 mol) in dry THF (250 ml) was added dropwise dry ethyl acetate (30.5 g, 0.346 mol) at −78 °C under nitrogen with stirring. Stirring was continued for 1 h. A solution of the hydroxycyclohexanone **4** (23.1 g, 0.115 mol) in dry THF (150 ml) was added dropwise to the reaction mixture. After being stirred for 1 h, the reaction mixture was hydrolyzed by adding 4 M hydrochloric acid (170 ml) in one portion, and the stirred solution was warmed to room temperature. The organic layer was separated, the aqueous layer was neutralized, and extracted several times with diethyl ether, and the combined extracts were washed with saturated aq. NaCl and dried over anhydrous Na_2SO_4. The solvent was removed and the residue was distilled under reduced pressure to yield (31.3 g, 94%) of a pale yellow liquid (mixture of *cis* and *trans* isomers); bp 138–151 °C/0.25 mmHg. The ^{1}H NMR spectrum of the product revealed that the ratio of the two isomers was *ca.* 1 : 1. For analysis, the two isomers were separated by column chromatography (SiO_2, hexane–EtOAc = 3 : 1): *cis* isomer; TLC (silica

gel) R_f 0.26 (hexane–EtOAc = 2:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.26 (t, J = 7.1 Hz, 6H, $CO_2CH_2CH_3$), 1.32 (ddd, ^2J = 13.7 Hz, ^3J = 4.3, 13.7 Hz, 2H), 1.57 (d, J = 14.0 Hz, 1H), 1.52–1.60 (m, 1H), 1.85–1.79 (m, 2H), 1.95 (dt, ^2J = 14.0 Hz, ^4J = 2.6 Hz, 1H), 2.01 (dtt, ^2J = 13.8 Hz, ^3J = 3.7, 13.8 Hz, 1H), 2.42 ($\frac{1}{2}$AB q, J = 15.0 Hz, 2H, CH_2CO_2Et), 2.43 ($\frac{1}{2}$AB q, J = 15.0 Hz, 2H, CH_2CO_2Et), 4.15 (q, J = 7.1 Hz, 4H, $CO_2CH_2CH_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.15, 16.67, 36.31, 44.32, 46.87, 60.58, 71.47, 171.80; IR (liquid film, cm^{-1}) 3454 (br), 2981m, 2939m, 2875m, 1732s (C=O), 1196m: *trans* isomer; TLC (silica gel) R_f 0.29 (hexane–EtOAc = 2:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.27 (t, J = 7.1 Hz, 6H, $CO_2CH_2CH_3$), 1.49–1.68 (m, 6H), 2.60 ($\frac{1}{2}$AB q, J = 16.0 Hz, 2H, CH_2CO_2Et), 2.70 ($\frac{1}{2}$AB q, J = 16.0 Hz, 2H, CH_2CO_2Et), 4.17 (q, J = 7.1 Hz, 4H, $CO_2CH_2CH_3$); IR (liquid film, cm^{-1}) 3501br, 2982m, 2940m, 2874m, 1727s, 1712s (C=O), 1192m.

Diethyl 2,4-dioxabicyclo[3.3.1]nonane-1,5-diacetate 6

The cyclohexane-1,3-diol **5** (5.03 g, 0.017 mol, a mixture of *cis* and *trans*) was mixed with paraformaldehyde (3.14 g, 0.105 mol) in a mixture of ethanol (10.1 ml) and benzene (30 ml). After addition of TsOH (0.066 g), the mixture was heated at 50 °C (bath temp.) for 1 h and refluxed for 3 h with a Dean–Stark trap. Evaporation of the solvent afforded the mixed acetal. To this residue was added *m*-xylene (20 ml) and the reaction mixture was heated at 150 °C for 2 h. The solvent was removed under reduced pressure, and the residue was purified by column chromatography (SiO_2, hexane–EtOAc = 4:1) to give 2.18 g (42%) of a colorless oil **6**; TLC (silica gel) R_f 0.31 (hexane–EtOAc = 4:1); MS *m*/*z* 300 (M^+), 299 ($M^+ - H$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.26 (t, J = 7.1 Hz, 6H, $CO_2CH_2CH_3$), 1.31 (ddd, ^2J = 13.5 Hz, ^3J = 4.9, 13.5 Hz, 2H), 1.50 (d, J = 14.3 Hz, 1H), 1.50–1.56 (m, 1H), 1.70–1.76 (m, 2H), 2.14 (dtt, ^2J = 13.4 Hz, ^3J = 4.8, 13.4 Hz, 1H), 2.44 ($\frac{1}{2}$AB q, J = 14.6 Hz, 2H, CH_2CO_2Et), 2.54 ($\frac{1}{2}$AB q, J = 14.6 Hz, 2H, CH_2CO_2Et), 2.916 (dt, ^2J = 14.4 Hz, ^4J = 2.7 Hz, 1H), 4.12 ($\frac{1}{2}$AB q, J = 7.2, 10.8 Hz, 2H, CH_2CO_2Et), 4.14 ($\frac{1}{2}$AB q, ^2J = 10.8 Hz, ^3J = 7.2 Hz, 2H, CH_2CO_2Et), 4.70 (d, J = 5.7 Hz, 1H, OCH_2O), 5.12 (d, J = 5.7 Hz, 1H, OCH_2O).

2,4-Dioxabicyclo[3.3.1]nonane-1,5-diethanol 7

To a suspension of lithium aluminium hydride (1.913 g, 0.050 mol) in dry THF (45 ml) was added dropwise a solution of diester **6** in dry THF (15 ml) at 0 °C under nitrogen, and the mixture was stirred at ambient temperature for 1 h. To the mixture were added water (1.9 ml), 15% aq. sodium hydroxide (1.9 ml), and water (5.7 ml) in this order with vigorous stirring. The precipitate was filtered off. After concentration of the filtrate, the residue was purified by column chromatography on silica gel (EtOAc–ethanol = 10:1) to afford a white solid **7**. (4.19 g, 92%); TLC (silica gel) R_f 0.33 (hexane–EtOAc = 10:1); MS *m*/*z* 216 (M^+), 215 ($M^+ - H$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.16 (ddd, ^2J = 13.5 Hz, ^3J = 5.0, 13.5 Hz, 2H), 1.23 (d, J = 14.4 Hz, 1H), 1.53–1.61 (m, 1H), 1.66 ($\frac{1}{2}$AB q dd, ^2J = 14.6 Hz, ^3J = 4.3, 6.0 Hz, 2H, CH_2CH_2OH), 1.81 ($\frac{1}{2}$AB q dd, ^2J = 14.6 Hz, ^3J = 4.9, 8.2 Hz, 2H, CH_2CH_2OH), 1.85–1.90 (m, 2H), 2.09 (dtt, ^2J = 13.3 Hz, ^3J = 4.8, 13.3 Hz, 1H), 2.43 (dt, ^2J = 14.3 Hz, ^3J = 2.7 Hz, 1H), 3.76 ($\frac{1}{2}$AB q dd, ^2J = 11.2 Hz, ^3J = 4.9, 6.1 Hz, 2H, CH_2CH_2OH), 3.89 ($\frac{1}{2}$AB q dd, ^2J = 11.2 Hz, ^3J = 4.3, 8.2 Hz, 2H, CH_2CH_2OH), 4.73 (d, J = 5.7 Hz, 1H, OCH_2O), 5.11 (d, J = 5.7 Hz, 1H, OCH_2O); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.75, 35.88, 37.64, 43.09, 58.64, 75.22, 84.14; IR (liquid film, cm^{-1}) 3385br, 2934m, 2772w, 1155m, 1087m, 1014m.

1,3-Dihydroxycyclohexane-1,3-diethanol 8

Acetal **7** (0.088 g, 0.407 mmol) was dissolved in methanol (2 ml) and 2.0 M HCl–methanol (2 ml) was added. The mixture was stirred at ambient temperature for 3 days. The solvent was evaporated under reduced pressure. The residue was chromatographed on a silica gel column with EtOAc–ethanol (10:1) to give 0.070 g (84%) of **8**. An analytical sample was prepared by recrystallization from EtOAc–ethanol to give white crystals; mp 101–104 °C; TLC (silica gel) R_f 0.32 (EtOAc–ethanol = 10:1); MS *m*/*z* 186 ($M^+ - H_2O$), 168 ($M^+ - 2H_2O$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.20 (d, J = 13.8 Hz, 1H), 1.23 (ddd, ^2J = 13.7 Hz, ^3J = 4.4, 13.7 Hz, 2H), 1.52–1.59 (m, 1H), 1.63 ($\frac{1}{2}$AB q dd, ^2J = 14.8 Hz, ^3J = 3.8, 6.3 Hz, 2H, CH_2CH_2OH), 1.73 ($\frac{1}{2}$AB q dd, ^2J = 14.8 Hz, ^3J = 4.0, 8.1 Hz, 2H, CH_2CH_2OH), 1.89–1.83 (m, 2H), 1.99 (dtt, ^2J = 13.8 Hz, ^3J = 3.7, 13.8 Hz, 1H), 2.12 (dt, ^2J = 13.9 Hz, ^4J = 2.6 Hz, 1H), 3.09 (t, J = 3.8 Hz, 2H, primary OH), 3.85–4.00 (m, 4H, CH_2CH_2OH), 4.781 (s, 2H, tertiary OH); ^{13}C NMR (22.5 MHz, $CDCl_3$) δ 16.71, 37.64, 43.58, 44.58, 59.16, 74.08; IR (liquid film, cm^{-1}) 3338br, 2939m, 1449w, 1422m, 1150m, 1029m, 852m (Calc. for $C_{10}H_{20}O_4$: C, 58.80; H, 9.87. Found: C, 58.59; H, 9.82%).

Ditosyl unit 9

The procedure of Marshall[9] was modified. To a stirred, cooled (0 °C) solution of diol **7** (4.501 g, 0.021 mol), 4-(dimethylamino)pyridine (DMAP) (130 mg), and triethylamine (8.7 ml, 0.062 mol) in CH_2Cl_2 (60 ml) was added toluene-*p*-sulfonyl chloride (*p*-TsCl) (11.11 g, 0.058 mol). The reaction mixture was stirred for 8.5 h at ambient temperature. The mixture was treated with diethyl ether (50 ml) and filtered, and the filter cake was washed with diethyl ether. The filtrate was evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (hexane–EtOAc = 2:1) to afford 9.997 g (92%) of ditosyl compound **9** as a viscous pale yellow oil; ^{1}H NMR (90 MHz, $CDCl_3$) δ 1.79 (t, J = 7.4 Hz, 4H, CH_2CH_2O), 0.97–2.20 (m, 8H), 2.44 (s, 6H, aryl CH_3), 4.17 (t, J = 6.8 Hz, 4H, CH_2CH_2O), 4.56 ($\frac{1}{2}$AB q, J = 5.9 Hz, 1H, OCH_2O), 4.75 ($\frac{1}{2}$AB q, J = 5.9 Hz, 1H, OCH_2O), 7.39 ($\frac{1}{2}$AB q, J = 8.7 Hz, 4H, ArH), 7.82 ($\frac{1}{2}$AB q, J = 8.7 Hz, 4H, ArH); IR (liquid film, cm^{-1}) 2950m, 2769w 1358s, 1190s, 1176s; MS *m*/*z* 524 (M^+), 481 ($M^+ - 43$).

Dimesyl unit 11

To a stirred, cooled (0 °C) solution of diol **7** (0.956 g, 4.42 mmol) and triethylamine (1.54 ml, 11.05 mmol) in CH_2Cl_2 (15 ml) was added methanesulfonyl chloride (MsCl) (1.114 g, 9.73 mmol). The reaction mixture was stirred for 4 h at ambient temperature. A small amount of white solid was precipitated. The mixture was filtered, and the mother liquor was evaporated under reduced pressure. The residue was purified by column chromatography on silica gel ($CHCl_3$–EtOAc = 6:1) to afford dimesyl compound **11**, as a colorless oil, which slowly solidified upon storage at room temperature *in vacuo* to give a white solid (1.390 g, 84%); ^{1}H NMR (90 MHz, $CDCl_3$) δ 1.02–2.28 (m, 7H), 1.94 (t, J = 6.6 Hz, 4H, CH_2CH_2O), 2.33–2.61 (m, 1H), 3.04 (s, 6H, CH_3), 4.29–4.57 (m, 4H), 4.80 ($\frac{1}{2}$AB q, J = 5.9 Hz, 1H, OCH_2O), 5.09 ($\frac{1}{2}$AB q, J = 5.9 Hz, 1H, OCH_2O).

cis-1,3-Bis(2-mesylethyl)cyclohexane-1,3-diol 12

Acetal **7** (5.358 g, 14.39 mmol) and trityl tetrafluoroborate (5.894 g, 17.85 mmol) were stirred in dichloromethane (125 ml) for 7 h at ambient temperature. To the reaction mixture was added saturated aq. $NaHCO_3$ (50 ml) and the two-phase mixture was stirred for 15 min. The organic phase was washed with water, dried over anhydrous Na_2SO_4, and evaporated *in vacuo*. The residue was chromatographed over silica gel ($CHCl_3$–EtOAc = 1:1) to afford 3.394 g (65%) of **12** as an oil; ^{1}H NMR (90 MHz, $CDCl_3$) δ 1.13–2.11 (m, 8H), 1.91 (t, J = 6.4 Hz, 4H, CH_2CH_2O), 3.05 (s, 6H, CH_3), 3.58 (br s, 2H, tertiary OH), 4.45 (t, J = 6.4 Hz, 4H, CH_2CH_2O); IR (liquid film, cm^{-1}) 3485br, 2941m, 1350s, 1173s.

Acetal dimers 10a and 10b

A mixture of diol **7** (0.433 g, 2.0 mmol) and potassium *tert*-butoxide (0.494 g, 4.4 mmol) in dry DME (15 ml) was efficiently stirred and heated at 80 °C (bath temp.) for 1 h. A solution of ditosyl compound **9** (1.049 g, 2.0 mmol) in Me_2SO (5 ml) was added, and the reaction mixture was heated to reflux and stirred for 13 h. The suspension was cooled to 25 °C, filtered, and washed with diethyl ether. The solvent was removed under reduced pressure. The residue was partitioned between 20 ml of CH_2Cl_2 and 10 ml of water, the two layers were separated, and the aqueous layer was extracted again with two 20 ml portions of CH_2Cl_2. The combined organic phases were dried over Na_2SO_4. The solvent was evaporated, leaving an oil, which was chromatographed on silica gel (hexane–EtOAc = 4:1) to give 16 mg (2.1%) of a mixture of *syn* and *anti* isomers as a white solid. Analytical samples of each isomer were purified by MPLC (hexane–EtOAc = 10:1). First fraction: TLC (silica gel) R_f 0.40 (hexane–EtOAc = 2:1); MS *m*/*z* 395 ($M^+ - H$), 393 ($M^+ - 3H$), 368 ($M^+ - C_2H_4$), 320; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.32 (ddd, ^2J = 13.3 Hz, ^3J = 4.8, 13.3 Hz, 4H), 1.51 (d, J = 15.1 Hz, 2H), 1.40–1.53 (m, 6H), 1.65 ($\frac{1}{2}$AB q dd, ^2J = 15.0 Hz, ^3J = 2.1, 7.2 Hz, 4H, CH_2CH$_2$O), 1.79 ($\frac{1}{2}$AB q dd, ^2J = 15.0 Hz, ^3J = 2.6, 8.5 Hz, 4H, CH_2CH$_2$O), 2.14 (dtt, ^2J = 13.1 Hz, ^3J = 4.8, 13.1 Hz, 2H), 2.65 (dt, ^2J = 15.1 Hz, ^4J = 2.5 Hz, 2H), 3.36 (ddd, ^2J = 10.2 Hz, ^3J = 2.1, 8.5 Hz, 4H, CH$_2$CH_2O), 3.59 (ddd, ^2J = 10.2 Hz, ^3J = 2.6, 7.2 Hz, 4H, CH$_2$CH_2O), 4.74 (d, J = 5.6 Hz, 2H, OCH$_2$O), 5.16 (d, J = 5.6 Hz, 2H, OCH$_2$O); ^{13}C NMR (22.5 MHz, $CDCl_3$) δ 18.10, 36.13, 36.60, 42.37, 67.59, 74.23, 85.22. Second fraction: TLC (silica gel) R_f 0.40 (hexane–EtOAc = 2:1); MS *m*/*z* 395 ($M^+ - H$), 393 ($M^+ - 3H$), 368 ($M^+ - C_2H_4$), 320; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.29 (ddd, ^2J = 13.4 Hz, ^3J = 4.8, 13.4 Hz, 4H), 1.43 (d, J = 15.1 Hz, 2H), 1.40–1.52 (m, 6H), 1.64 ($\frac{1}{2}$AB q dd, ^2J = 14.9 Hz, ^3J = 2.3, 7.9 Hz, 4H, CH_2CH$_2$O), 1.77 ($\frac{1}{2}$AB q dd, ^2J = 14.9 Hz, ^3J = 2.4, 7.5 Hz, 4H, CH_2CH$_2$O), 2.14 (dtt, ^2J = 13.2 Hz, ^3J = 4.6, 13.2 Hz, 2H), 2.76 (dt, ^2J = 15.1 Hz, ^4J = 2.5 Hz, 2H), 3.38 (ddd, ^2J = 10.2 Hz, ^3J = 2.4, 7.5 Hz, 4H, CH$_2$CH_2O), 3.59 (ddd, ^2J = 10.2 Hz, ^3J = 2.3, 7.9 Hz, 4H, CH$_2$CH_2O), 4.77 (d, J = 5.6 Hz, 2H, OCH$_2$O), 5.18 (d, J = 5.6, 2H, OCH$_2$O).

Tetraol dimer I 1a

Acetal **10** (mixture of *syn* and *anti* isomers) (38.8 mg, 0.098 mmol) was dissolved in 2.0 M HCl in methanol (2 ml), and the mixture was stirred at room temperature for 20 h. After evaporation of the solvent under reduced pressure, the residue was chromatographed on a silica gel column with EtOAc–$CHCl_3$ (4:1). The fractions containing product were combined and rechromatographed at medium pressure (EtOAc–$CHCl_3$ = 1:6) to give 8.4 mg (46%) of **1a** (*syn* isomer) as a white solid. An analytical sample was prepared by recrystallization from ethyl acetate to give white crystals, mp 210–215 °C; TLC (silica gel) R_f 0.41 (EtOAc–$CHCl_3$ = 4:1); MS *m*/*z* 372 (M^+), 354 ($M^+ - H_2O$), 336 ($M^+ - 2H_2O$), 329, 318 ($M^+ - 3H_2O$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.13 (ddd, ^2J = 13.5 Hz, ^3J = 4.3, 13.5 Hz, 4H), 1.20 (d, J = 13.2 Hz, 2H), 1.34 (dt, ^2J = 14.8 Hz, ^3J = 2.2 Hz, 4H, CH_2CH$_2$O), 1.36–1.44 (m, 2H), 1.69–1.76 (m, 4H), 1.97 (dtt, ^2J = 13.8 Hz, ^3J = 3.7, 13.8 Hz, 2H), 2.07 (ddd, ^2J = 14.8 Hz, ^3J = 4.6, 12.9 Hz, 4H, CH_2CH$_2$O), 2.17 (dt, ^2J = 13.2 Hz, ^4J = 2.4 Hz, 2H, CH$_2$CH_2O), 3.55 ($\frac{1}{2}$AB q dd, ^2J = 9.3 Hz, ^3J = 2.3, 4.5 Hz, 4H, CH$_2$CH_2O), 3.71 ($\frac{1}{2}$AB q dd, ^2J = 9.3 Hz, ^3J = 2.3, 12.8 Hz, 4H, CH$_2$CH_2O), 5.35 (s, 4H, tertiary OH); ^{13}C NMR (22.5 MHz, $CDCl_3$) δ 16.67, 39.64, 39.88, 41.55, 67.31, 71.75; IR (KBr, cm^{-1}) 3397s, 2935m, 2866m, 1175w, 1128w (Calc. for $C_{20}H_{36}O_6$·1/4H_2O: C, 63.72; H, 9.76. Found: C, 63.72; H, 9.92%).

Dimer II 13a and 13b

A suspension of Cs_2CO_3 (0.733 g, 2.250 mmol) in DMF (70 ml) was stirred at room temperature under N_2. A solution containing dimesyl compound **12** (0.676 g, 1.875 mmol) and resorcinol (0.206 g, 1.875 mmol) in DMF (10 ml) was added, and the mixture was stirred vigorously at 50 °C for 2 days. The solvent was removed *in vacuo*. The residue was taken up in THF–ethanol (10:1), and applied to an alumina column, which was eluted with THF–ethanol (10:1). After evaporation of the solvent, the residual mixture was chromatographed on a silica gel column with THF–$CHCl_3$ (1:5). The fractions containing products were combined and rechromatographed at medium pressure (EtOAc–$CHCl_3$ = 1:6) to give dimers **13a** and **13b** as a white solid, total yield 30 mg (6%) (*anti* isomer 16 mg, 3%; *syn* isomer 14 mg, 3%). **13a** (*syn* isomer): TLC (silica gel) R_f 0.60 (EtOAc–$CHCl_3$ = 4:1); MS *m*/*z* 556 (M^+), 538 ($M^+ - H_2O$), 520 ($M^+ - 2H_2O$), 502 ($M^+ - 3H_2O$), 484 ($M^+ - 4H_2O$); ^{1}H NMR (500 MHz, $CDCl_3$ + CD_3OD) δ 1.34 (ddd, ^2J = 13.6 Hz, ^3J = 4.1, 13.6 Hz, 4H), 1.37 (d, J = 14.3 Hz, 2H), 1.47–1.53 (m, 2H), 1.59–1.65 (m, 4H), 1.76 ($\frac{1}{2}$AB q t, ^2J = 14.6 Hz, ^3J = 6.0 Hz, 4H, CH_2CH$_2$O), 1.88 (m, 4H, CH_2CH$_2$O), 1.90–1.95 (m, 4H), 3.98 ($\frac{1}{2}$AB q dd, ^2J = 9.6 Hz, ^3J = 5.5, 6.8 Hz, 4H, CH$_2$CH_2O), 4.07 ($\frac{1}{2}$AB q dd, ^2J = 9.6 Hz, ^3J = 6.3, 6.3 Hz, 4H, CH$_2$CH_2O), 6.31 (t, J = 2.2 Hz, 2H, ArH), 6.37 (dd, J = 2.2, 8.3, 4H, ArH), 7.01 (t, J = 8.3 Hz, 2H, ArH); ^{13}C NMR (125 MHz, $CDCl_3$ + CD_3OD) δ 16,63, 37.85, 41.88, 42.00, 63.87, 72.13, 100.11, 107.45, 129.78, 159.63; **13b** (*anti* isomer): TLC (silica gel) R_f 0.60 (EtOAc–$CHCl_3$ = 4:1); MS *m*/*z* 556 (M^+), 538 ($M^+ - H_2O$), 520 ($M^+ - 2H_2O$), 502 ($M^+ - 3H_2O$), 484 ($M^+ - 4H_2O$); ^{1}H NMR (500 MHz, $CDCl_3$ + CD_3OD) δ 1.34 (ddd, ^2J = 13.5 Hz, ^3J = 3.9, 13.5 Hz, 4H), 1.38 (d, J = 14.5 Hz, 2H), 1.49–1.55 (m, 2H), 1.70–1.76 (m, 4H), 1.84 (t, J = 7.0 Hz, 8H, CH_2CH$_2$O), 1.85–1.96 (m, 4H), 4.03–4.11 (m, 8H, CH$_2$CH_2O), 6.32–6.40 (m, 6H), 7.00–7.04 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$ + CD_3OD) δ 16.85, 37.11, 41.93, 44.55, 63.91, 72.51, 101.98, 106.25, 108.26, 129.90, 157.87, 159.71.

X-Ray crystal structure determinations

Diffraction data were collected at 295 K with a Rigaku AFC-7R four-circle diffractometer having a rotating anode and using graphite-monochromated Cu-$K\alpha$ (λ = 1.541 78 Å) and Mo-$K\alpha$ (λ = 0.710 69 Å) radiations for **13a**·1.5$C_4H_8O_2$ and **13b**, respectively. The crystal data and details of the parameters associated with data collection for the two crystals are given in Tables 1 and 2. The unit-cell parameters were derived from least-squares refinement of 25 well centred reflections. The reflection intensities were monitored by three standard reflections for every 150 reflections, and the decay of intensities was within 2% for the two crystals. Reflection data were corrected for Lorentz and polarization effects. An empirical absorption correction, based on ψ scans, was applied.[10]

The structures for the compounds were solved by the direct method[11] and successive Fourier techniques[12] and refined anisotropically for non-hydrogen atoms by full-matrix least-squares calculations. Refinements were continued until all shifts were smaller than one-third of the standard deviations of the parameters involved. Atomic scattering factors and anomalous dispersion terms were taken from the literature.[13] All the hydrogen atoms were located from the difference Fourier maps, and their parameters were isotropically refined. The R- and R_w-values were 0.062 and 0.071 for **13a**·1.5$C_4H_8O_2$ and 0.036 and 0.052 for **13b**, respectively. The weighting scheme $w^{-1} = \sigma^2(F_o)$ was employed for both crystals. The final difference Fourier maps did not show any significant features in both cases. The calculations were performed on an IRIS Indigo XS-24 computer by using the program system teXsan.[14]

CCDC reference number for **13a**·1.5$C_4H_8O_2$ and **13b** 207/329. See http://www.rsc.org/suppdata/p1/1999/1885 for crystallographic files in .cif format.

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