Synthesis and characterization of bis[1.1.1]orthocyclophano-18-crown-6 compounds

Hiroshi Hara,* Shin-ichi Watanabe, Makoto Yamada and Osamu Hoshino*

Faculty of Pharmaceutical Sciences, Science University of Tokyo, 12 Ichigaya Funagawara-machi, Shinjuku-ku, Tokyo 162, Japan

Two novel macrocyclic compounds 5S and 5A combining an 18-crown-6 and two cyclotriveratrylenes were synthesized by means of two methods from dibenzo-18-crown-6. The conformational isomers were separated using complexation with KSCN and their stereostructures were determined on the basis of ^{1}H NMR spectroscopic and thermal equilibration studies.

Introduction

For the last few decades, various types of host compounds have been synthesized for investigation of molecular recognition. In particular, macrocyclic compounds such as crown ethers [1] and cyclophanes [2,3] are frequently used as the basic skeleton of host compounds. Although cyclotriveratrylene (CTV) **1** [4] is one of the old-type cyclophanes, it is not very popular in the field of host–guest chemistry compared with calixarenes. The latter now seem to belong to the most useful category of cyclophanes because of their strong facility for complex formation with metal cations or organic molecules.[3] Recently, Atwood and co-workers [5] revealed a new ability of CTV as a host including a fullarene, C_{60}. The findings encouraged us to design a crown ether **5S** *syn*-conformationally armed with two CTV units, the shape† of which plausibly looks more capable of picking up C_{60} than does CTV itself. Moreover, the conformational change of the crown ether moiety by co-ordination with a metal cation is expected to change the size of the cavity. The present paper deals with the synthesis of the title compounds by two methods and their characterization.

The first method is as follows. Previously, we found that dibenzylveratroles **6** [7] and **7** are key compounds for the construction of 5-sila-CTV [8] and cyclopentaveratrylene.[9] Acid-catalysed condensation of veratrole and 2 mole equivalents of 6-bromoveratryl alcohol [8] produces the synthon **6**, which is easily reduced to give compound **7**. Then the procedure was applied to the synthesis of the title compounds.

Condensation of dibenzo-18-crown-6 **8** and 6-bromoveratryl alcohol was carried out in the following way. Although the reaction (150 mol equiv. of conc. H_2SO_4, room temperature, 1 h) of substrate **8** with 5 mol equiv. of 6-bromoveratryl alcohol in MeOH gave a complex mixture,‡ acid treatment (280 mol equiv. of conc. H_2SO_4, room temperature, 3 days) of crown ether **8** and 8 mol equiv. of the benzyl alcohol in MeOH–$CHCl_3$ (2:1) improved the reaction to give the expected tetrakis-(6-bromoveratryl)dibenzo-18-crown-6 **9** in 75% yield. The crown ether **9** was quite insoluble in MeOH or EtOH; however, its solubility in MeOH was improved remarkably by addition of KOH. Hydrogenolysis of tetrabromide **9** in 10% KOH–MeOH proceeded smoothly to give tetraveratryldibenzo-18-crown-6 **10** in high yield. The construction of two CTV skeletons was carried out by the reaction of compound **10** and paraformaldehyde. Although cyclization of 4,5-diveratrylveratrole **7** with $(HCHO)_n$ to CTV has already been accomplished by acid treatment (60% $HClO_4$) without an organic solvent,[7] employment of a solvent in the cyclization of substrate **10** was a necessary requirement for reaction to proceed. After attempts to optimize reaction conditions,[10] treatment of compound **10** with $(HCHO)_n$ in $CHCl_3$–MeOH (1:3 v/v) in the presence of conc. sulfuric acid was performed for biscyclization to give the target compound **5** in 76% yield, whose HPLC analysis [eluent; MeCN–water (4:1)] by use of a reversed-phase column (ODS) revealed a mixture of two conformational isomers **5S** and **5A** in the ratio 88:12 (retention time; **5S** > **5A**), while its TLC showed one spot. Separation and determination of the structure were successfully achieved as follows. Potassium thiocyanate (2 mol equiv.)§ was added to a mixture¶ of **5S** and **5A** in MeOH–$CHCl_3$ (7:2), and the whole was stirred at ambient temperature for 1 h to liberate a complex of *syn*-isomer **5S** with KSCN as a fine precipitate. Separation of the crystals and mother liquor followed by desalting with water furnished pure isomers **5S** and **5A**, respectively. Considering the easier complexation of isomer **5S** with KSCN, the conformation of isomer **5S** was presumed to be *syn*. Two types of AB patterns for benzylic protons in ^{1}H NMR spectra of both compounds confirm the completion of biscyclization. However, no information was obtained to enable us to distinguish stereostructures, because those spectra showed a remarkable resemblance to each other.‖ Interestingly, Collet and Gabard [10] have reported the racemization of an enantiomerically pure CTV analogue by the conformational interconversion of the CTV system on heating. Taking the findings into account, as the *anti* form **5A** is anticipated to be more stable than *syn* form **5S**, thermal equilibration of both isomers might occur. To confirm anticipation, three kinds of solvents were used for the thermal equilibration. The results are shown in Table 1. No change of stereostructure was observed in CH_2Cl_2 (entries 1 and 2), and refluxing in $CHCl_3$ caused considerable conformational interconversion (entries 3 and 4). In benzene, finally, each ratio of two isomers converged to quite similar values (entries 5 and 6) showing that equilibrium was reached. As equilibrium tends to give the *anti* form, conformation of isomer **5A** should be *anti* and that of **5S** *syn*. In order to confirm the stereostructures,** ^{1}H NMR spectra of compounds **5S**, **5A** and **9** were measured with potassium picrate as an additive for

† Nolte and co-workers have reported synthesis of molecular clips which are novel host compounds with allosteric binding properties.[6]

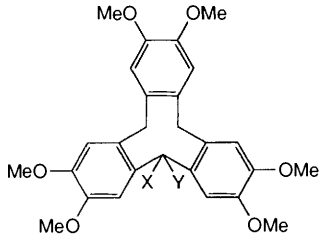
‡ Although reaction conditions [prolonged reaction time, elevated reaction temperature (up to 80 °C), acid (conc. H_2SO_4, CF_3CO_2H), solvent (MeOH, CH_2Cl_2 and $CHCl_3$) and molar equivalent of the alcohol] were explored, the reaction did not give satisfactory results.

§ KSCN is an effective guest to complex with 18-crown-6.[11]

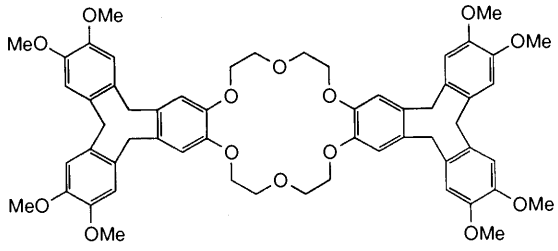
¶ 1:1 Mixture of isomers was prepared by thermal isomerization.

‖ Lee *et al.*[12] have synthesized a bisorthocyclophane **11**, but its stereochemistry has not been mentioned.

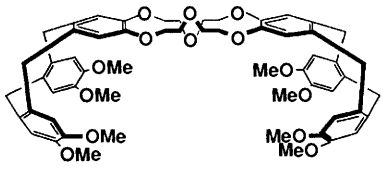
** Attempts under various conditions to prepare a single crystal for X-ray crystallographic analysis failed.



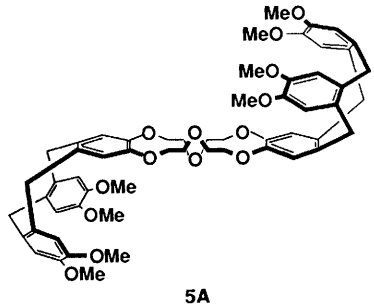
1 X = Y = H
2 XY = O
3 X = OH, Y = H
4 X = Br, Y = H



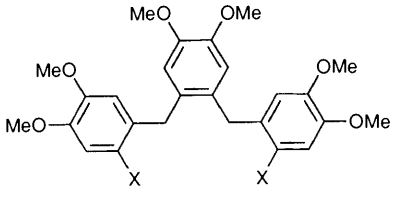
5S *syn*
5A *anti*



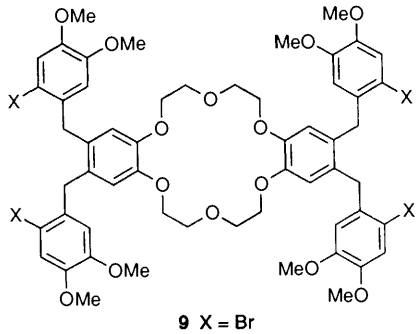
5S



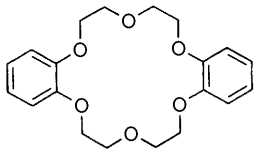
5A



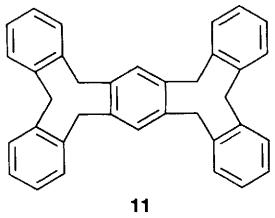
6 X = Br
7 X = H



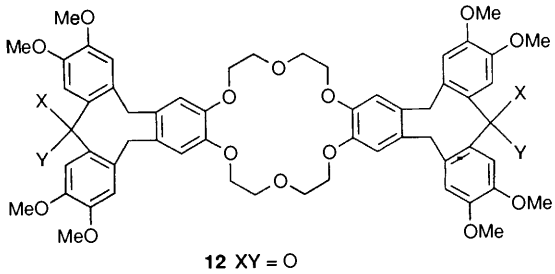
9 X = Br
10 X = H



8



11



12 XY = O
13 X = OH, Y = H
14 X = Br, Y = H

Table 1

Entry	Substrate	Solvent	Ratio of product (5S:5A)[a]
1	**5S**	CH_2Cl_2	100:0
2	**5A**	CH_2Cl_2	0:100
3	**5S**	$CHCl_3$	61:39
4	**5A**	$CHCl_3$	40:60
5	**5S**	Benzene	37:63
6	**5A**	Benzene	38:62

[a] Ratio **5S**:**5A** was estimated by HPLC measurement using a TOSOH TSXgel ODS-80Tm column [eluent: MeCN–water (4:1)].

complexation to the crown parts. The pattern of signals for methylene protons of crown ether moieties in **5S** and **9** was unchanged, while that in isomer **5A** became broad. This observation showed that the complex of compound **5S** with potassium picrate remains symmetrical, while that of compound **5A** with the salt unsymmetrical, confirming stereostructures of two conformational isomers.

In the present cyclization, the preference for isomer **5S** is probably due to a template effect of the solvent,[13] which assists in forming a bowl-shaped transition state in the second cyclization step leading to *syn*-isomer **5S**. In dimethylformamide (DMF) the *syn*-conformer was predominantly formed (**5S**:**5A** = 98:2; chemical yield 54%).

The second method is construction of isomers **5S and 5A** by reduction[9] of a cyclic diketone **12**. Treatment of tetrabromide **9** with BuLi followed by diethyl carbonate afforded the dione **12** in 49% yield. To settle the reaction conditions for the reduction of compound **12**, cyclotriveratrylenone **2** was used as a model

compound. After several attempts†† to obtain CTV **1** from compound **10**, the alcohol **3** was brominated by PBr_3 to afford compound **4** which was reduced with $NaBH_3CN$–$ZnCl_2$[18] to give CTV **1**. The sequence of reaction conditions was applied to the dione **12**. $LiAlH_4$ reduction of compound **12** gave a diol **13** (86% yield), the ^1H NMR spectrum of which showed a 1:1 mixture of two conformers (*syn* and *anti*). Bromination and subsequent reduction of compound **13** under conditions similar to those noted for compound **3** furnished a mixture of compounds **5S** and **5A** in 48% yield from compound **13**, in the ratio 47:53. This finding indicated that reduction of cyclotriveratrylenone units in compound **12** proceeded from both faces equivalently, because the conformation of the ketone **2** is not rigid at room temperature.[15] Hence, the present procedure is not useful for selective synthesis of *syn* isomer **5S**, though it should be valuable for the construction of macrocyclic compounds bearing substituents, such as a methylenedioxy group, labile to strong acid.

Finally, the function of isomer **5S** was investigated by the use of several organic compounds (C_{60}, *m*-dinitrobenzene, anthraquinone, β-naphthol, hydroquinone monomethyl ether) under various conditions. Contrary to our expectation, however, no inclusion was observed. This might be owing to steric hindrance caused by eight methoxyl groups in CTV units.

In conclusion, we accomplished a synthesis of bis[1.1.1]-orthocyclophano-18-crown-6 compounds by two methods, and separation and characterization of two conformational isomers **5S** and **5A** were carried out. This methodology is very useful for the construction of orthocyclophanes, the benzene rings of which are substituted by different patterns of electron-donating groups.

Experimental

Reactions for formation and separation of compounds **5S** and **5A** and subsequent work-up involving recrystallization were carried out at or below room temperature for the prevention of isomerization.[10] All mps were measured on Yanagimoto melting point apparatus (MP-S3) and are uncorrected. ^1H NMR spectra were recorded on a JEOL model GSX-500, JNM-EX-270 or FX-100 spectrometer for samples in $CDCl_3$ solution with Me_4Si as internal standard. *J* Values are in Hz. Mass spectra were measured on a JEOL model JMS-SX102A or Hitachi model M-80 spectrometer. Preparative TLC (PLC) was performed on precoated silica gel plates (Merck Kieselgel 60 F_{254}).

4,4′,5,5′-Tetrakis-(6-bromoveratryl)dibenzo-18-crown-6 9

To an ice-cooled, stirred solution of dibenzo-18-crown-6 **8** (0.18 g, 0.5 mmol) and 6-bromoveratryl alcohol (0.99 g, 4 mmol) in $CHCl_3$ (5 cm^3)–MeOH (5 cm^3) was added dropwise a cooled solution of conc. H_2SO_4 (7.65 cm^3, 290 mmol) in MeOH (5 cm^3) during 30 min, and the whole was stirred at room temperature for 3 days. The reaction mixture was made alkaline with saturated aq. $NaHCO_3$ and the product was extracted with $CHCl_3$. The organic phase was washed with brine and dried over $MgSO_4$. Evaporation of the solution under reduced pressure gave a brown solid (1.1 g), which was purified by column chromatography on silica gel with $CHCl_3$ as eluent to furnish crystals (0.48 g, 75% yield based on substrate **8**). Recrystallization from $CHCl_3$–MeOH afforded fine *prisms*, mp 191–192 °C; δ_H 3.67 (12 H, s, OMe × 4), 3.85 (12 H, s, OMe × 4), 3.86 (8 H, s, $ArCH_2Ar$ × 4), 3.95 (8 H, m, $ArOCH_2CH_2O$ × 4), 4.05 (8 H, m, $ArOCH_2CH_2O$ × 4) and 6.39, 6.54 and 7.01 (each 4 H, s, together ArH × 12); *m/z* 1276 (M^+) (Found: C, 52.7; H, 4.6. $C_{56}H_{60}Br_4O_{14}$ requires C, 52.68; H, 4.74%).

4,4′,5,5′-Tetraveratryldibenzo-18-crown-6 10

10% Pd–C (750 mg) was added to a solution of tetrakis-(6-bromoveratryl)dibenzo-18-crown-6 **9** (3.1 g, 2.5 mmol) in 10% KOH–MeOH (400 cm^3), and the mixture was subjected to hydrogenolysis under hydrogen for 4 h. The catalyst was filtered off and the filtrate was concentrated under reduced pressure. To the residue was added saturated aq. NH_4Cl and the product was extracted with CH_2Cl_2. The organic phase was washed with brine and dried over $MgSO_4$. Evaporation of the solution under reduced pressure gave crystals (3.0 g), which were recrystallized from $CHCl_3$–MeOH to afford *compound* **10** (1.9 g, 81%) as fine prisms, mp 160–161 °C; δ_H 3.76 (12 H, s, OMe × 4), 3.80 (8 H, s, $ArCH_2Ar$ × 4), 3.84 (12 H, s, OMe × 4), 3.97 (8 H, m, $ArOCH_2CH_2O$ × 4), 4.09 (8 H, m, $ArOCH_2CH_2O$ × 4), 6.53 (4 H, d, *J* 2.2, ArH × 4), 6.57 (4 H, dd, *J* 8.1 and 2.2, ArH × 4), 6.64 (4 H, s, ArH × 4) and 6.75 (4 H, d, *J* 8.1, ArH × 4); *m/z* 960 (M^+) (Found: C, 69.7; H, 6.6. $C_{56}H_{64}O_{14}$ requires C, 69.98; H, 6.71%).

15,16,22,23,43,44,50,51-Octamethoxy-2,5,8,30,33,36-hexaoxanonacyclo[35.19.0.$0^{9,29}$.$0^{11,27}$.$0^{13,18}$.$0^{20,25}$.$0^{39,55}$.$0^{41,46}$.$0^{48,53}$]hexapentacontane-1(37),9(29),10,13(18),14,16,20(25),21,23,27,38,41(46),42,44,48(53),49,51,55-octadecaene-19,47-dione 12

To a solution of tetrakis-(6-bromoveratryl)dibenzo-18-crown-6 **9** (51 mg, 0.04 mmol) in tetrahydrofuran (THF) (4 cm^3) was added BuLi (0.11 cm^3, 0.18 mmol; 1.6 mol dm^{-3} in hexane) at 0 °C (bath temperature) under Ar and the whole was stirred at the same temperature for 10 min. Then $(EtO)_2CO$ (14 mm^3, 0.12 mmol) was added, and the mixture was stirred for 1 h and warmed up to ambient temperature. After quenching with saturated aq. NH_4Cl, the product was extracted with CH_2Cl_2. The organic phase was washed with brine and dried over $MgSO_4$. Evaporation of the solution under reduced pressure gave a pale yellow solid (51 mg), which was purified by PLC [developed with $CHCl_3$–MeOH (70:1)] to furnish the *dione* **12** (20 mg, 49%) as crystals, mp 243–245 °C (from AcOEt–hexane); δ_H 3.72 (8 H, s, $ArCH_2Ar$ × 4), 3.79 (12 H, s, OMe × 4), 3.94 (12 H, s, OMe × 4), 4.10 (16 H, m, OCH_2CH_2O × 4) and 6.42, 6.72 and 7.39 (each 4 H, s, together ArH × 12); *m/z* 1012 (M^+) (Found: M^+, 1012.3902. $C_{58}H_{60}O_{16}$ requires *M*, 1012.3882).

Cyclotriveratrylen-5-ol 3

To an ice-cooled, stirred solution of ketone **2**[9] (232 mg, 0.5 mmol) in THF (14 cm^3) was added $LiAlH_4$ (26 mg, 0.66 mmol) under Ar and the whole was stirred at 35 °C for 1.5 h. Saturated aq. Na_2SO_4 was added to the reaction mixture, and the deposit was filtered off. The filtrate was concentrated under reduced pressure and the product was extracted with CH_2Cl_2. The organic phase was washed with brine and dried over $MgSO_4$. Evaporation of the solution under reduced pressure gave crystals (254 mg), which were recrystallized from benzene to furnish compound **3** (149 mg, 64%) as crystals, mp 234–235 °C (lit.,[15] 236–237 °C); δ_H 3.56 [2 H, d, *J* 14, $ArCH(H)Ar$ × 2], 3.83 (6 H, s, OMe × 2), 3.84 (6 H, s, OMe × 2), 3.86 (6 H, s, OMe × 2), 4.76 [2 H, d, *J* 14, $ArCH(H)Ar$ × 2], 6.77, 6.80 and 7.28 (each 2 H, s, together ArH × 6) and 6.98 [1 H, s, $ArCH(OH)Ar$].

Cyclotriveratrylene 1

To an ice-cooled, stirred solution of compound **3** (47 mg, 0.01 mmol) in abs. CH_2Cl_2 (4 cm^3) was added dropwise PBr_3 (0.015 cm^3, 0.15 mmol) under Ar and the whole was stirred at the same temperature for 1.5 h and then at ambient temperature for 1 h. Ice-cooled water was added to the reaction mixture and the product was extracted with CH_2Cl_2. The organic phase was washed successively with saturated aq. $NaHCO_3$ and brine, and

†† To avoid thermal conformational interconversion[10] of CTV **1**, the reaction was carried out at room temperature. However, attempted reduction of ketone **2** to CTV **1** [H_2 (60 psi)/10% Pd–C[12] or BH_3/THF[14]] and of bromide **3**[15] to CTV **1** [Me_3SiCl–NaI–MeCN in benzene[16] or $LiAlH_4$–$AlCl_3$ in THF[17]] was unsuccessful.

dried over $MgSO_4$. Evaporation of the solution under reduced pressure gave bromide **4** as a brown solid (53 mg), which was immediately subjected to the following reaction.

$ZnCl_2$ (10 mg, 0.075 mmol) and $NaBH_3CN$ (10 mg, 0.15 mmol) were added to THF (1 cm^3) under Ar and the mixture was stirred at room temperature for 20 min. To the mixture was added a solution of compound **4** (53 mg) in THF (1.5 cm^3) and the whole was stirred at the same temperature for 5 h. Saturated aq. $NaHCO_3$ was added to the reaction mixture and the product was extracted with $CHCl_3$. The organic phase was washed with brine and dried over $MgSO_4$. Evaporation of the solution under reduced pressure gave pale yellow crystals (41 mg), which were purified by PLC [developed with benzene–AcOEt (1:1)] to furnish compound **1** (30 mg, 66% yield based on alcohol **3**) as crystals. All physical data of compound **1** were coincident with those of an authentic sample.[19]

15,16,22,23,43,44,50,51-Octamethoxy-2,5,8,30,33,36-hexaoxanonacyclo[35.19.0.0$^{9.29}$.0$^{11.27}$.0$^{13.18}$.0$^{20.25}$.0$^{39.55}$.0$^{41.46}$.0$^{48.53}$]hexapentacontane-1(37),9(29),10,13(18),14,16,20(25),21,23,27,38,41(46),42,44,48(53),49,51,55-octadecaene-19,47-diol 13

To an ice-cooled, stirred solution of dione **12** (20 mg, 0.02 mmol) in THF (5 cm^3) was added $LiAlH_4$ (2 mg, 0.05 mmol) under Ar, and the whole was stirred at the same temperature for 1 h. Saturated aq. Na_2SO_4 was added to the reaction mixture, and the product was extracted with CH_2Cl_2. The organic phase was washed with brine and dried over $MgSO_4$. Evaporation of the solution under reduced pressure gave crystals (19 mg), which were purified by PLC [developed with $CHCl_3$–MeOH (20:1)] to furnish the *diol* **13** (17.3 mg, 86%) as crystals, mp 173–175 °C (AcOEt–hexane); δ_H 3.49 and 3.50 [each 2 H, d, *J* 14, ArC*H*(H)Ar], 3.81, 3.83, 3.85 and 3.86 (each 6 H, s, OMe), 3.90 (8 H, br s, $ArOCH_2CH_2O$ × 4), 4.10 (8 H, m, $ArOCH_2CH_2O$ × 4), 4.68 and 4.70 [each 2 H, d, *J* 14, ArCH(*H*)Ar], 6.73, 6.79 and 7.27 (each 4 H, s, together ArH × 12) and 6.95 [2 H, s, ArC*H*(OH)Ar × 2]; *m/z* 1016 (M^+) (Found: M^+, 1016.4203. $C_{58}H_{64}O_{16}$ requires *M*, 1016.4194).

***syn*-15,16,22,23,43,44,50,51-Octamethoxy-2,5,8,30,33,36-hexaoxanonacyclo[35.19.0.0$^{9.29}$.0$^{11.27}$.0$^{13.18}$.0$^{20.25}$.0$^{39.55}$.0$^{41.46}$.0$^{48.53}$]-hexapentacontane-1(37),9(29),10,13(18),14,16,20(25),21,23,27,38,41(46),42,44,48(53),49,51,55-octadecaene 5S and *anti*-15,16,22,23,43,44,50,51-octamethoxy-2,5,8,30,33,36-hexaoxanonacyclo[35.19.0.0$^{9.29}$.0$^{11.27}$.0$^{13.18}$.0$^{20.25}$0$^{39.55}$.0$^{41.46}$.0$^{48.53}$]hexapentacontane-1(37),9(29),10,13(18),14,16,20(25),21,23,27,38,41(46),42,44,48(53),49,51,55-octadecaene 5A**

(a) From compound 10. To an ice-cooled, stirred solution of compound **10** (48 mg, 0.05 mmol) and paraformaldehyde (113 mg, 3.8 mmol) in $CHCl_3$ (5 cm^3)–MeOH (10 cm^3) was added dropwise a cooled solution of conc. H_2SO_4 (11.6 cm^3, 207 mmol) in MeOH (5 cm^3) during 15 min and the whole was stirred at room temperature for 4 h. The reaction mixture was made alkaline with saturated aq. $NaHCO_3$ and the product was extracted with $CHCl_3$. The organic phase was washed with brine and dried over $MgSO_4$. Evaporation of the solution under reduced pressure gave a pale yellow solid (50 mg), which was purified by column chromatography on silica gel with $CHCl_3$–MeOH (5:1) as eluent to furnish a mixture of isomers **5S** and **5A** (38 mg, 76% yield based on compound **10**) as crystals. Ratio (**5S**:**5A** = 88:12) of the isomers was estimated by HPLC measurement using a TOSOH TSX gel ODS-80Tm column [eluent: MeCN–water (4:1), flow: 0.5 cm^3 min^{-1}, retention time: 18.5 min for **5S**, 15 min for **5A**].

(b) From compound 13. To an ice-cooled, stirred solution of diol **13** (17 mg, 0.017 mmol) in abs. CH_2Cl_2 (5 cm^3) was added dropwise PBr_3 (2.6 mm^3, 0.026 mmol) under Ar, and the whole was stirred at the same temperature for 2 h. Ice-cooled water was added to the reaction mixture and the product was extracted with $CHCl_3$. The organic phase was washed successively with saturated aq. $NaHCO_3$ and brine, and dried over $MgSO_4$. Evaporation of the solution under reduced pressure gave dibromide **14** as a brown solid (25 mg), which without purification was subjected to the following reduction.

$ZnCl_2$ (2 mg, 0.013 mmol) and $NaBH_3CN$ (2 mg, 0.026 mmol) were added to THF (1 cm^3) under Ar and the mixture was stirred at room temperature for 20 min. To the mixture was added a solution of dibromide **14** (25 mg, 0.02 mmol) in THF (2 cm^3) and the whole was stirred at the same temperature for 2 h. Saturated aq. $NaHCO_3$ was added to the reaction mixture and the product was extracted with $CHCl_3$. The organic phase was washed with brine and dried over $MgSO_4$. Evaporation of the solution under reduced pressure gave a mixture of isomers **5S** and **5A** (8 mg, 48% yield based on diol **13**) as pale yellow crystals. Ratio (**5S**:**5A** = 47:53) of the isomers was estimated by HPLC measurement under the same conditions as above.

Separation of isomers 5S and 5A

To a solution of a mixture (825 mg, 0.84 mmol; **5S**:**5A** = 1:1) in $CHCl_3$ (35 cm^3) and MeOH (10 cm^3) was added KSCN (163 mg, 1.68 mmol), and the whole was stirred at room temperature for 1 h to generate a precipitate, which was collected on a Celite filter. To the residue obtained by evaporation of the filtrate under reduced pressure was added $CHCl_3$ and water, and the whole was stirred. After filtration of the mixture, the organic phase of the filtrate was washed with brine and dried over $MgSO_4$. Evaporation of the solution under reduced pressure gave pale yellow crystals (460 mg). Ratio of the isomers (**5S**:**5A**) was estimated to be 8:92 by HPLC measurement under the same conditions as above. Recrystallization twice from aq. MeCN at room temperature furnished pure anti-*isomer* **5A** (70 mg, 17%) as needles, mp 271–273 °C; δ_H 3.51 [4 H, d, *J* 13.5, ArC*H*(H)Ar × 4], 3.54 [2 H, d, *J* 13, ArC*H*(H)Ar × 2], 3.83 (12 H, s, OMe × 4), 3.84 (12 H, s, OMe × 4), 3.94 (8 H, m, $ArOCH_2CH_2O$ × 4), 4.06 [4 H, m, ArOC*H*(H)CH_2O × 4], 4.13 [4 H, m, ArOCH(*H*)CH_2O × 4], 4.73 [4 H, d, *J* 14, ArCH(*H*)Ar × 4], 4.76 [2 H, d, *J* 15, ArCH(*H*)Ar × 2] and 6.79, 6.82 and 6.83 (each 4 H, s, ArH × 12); *m/z* 984 (M^+) (Found: M^+, 984.4294. $C_{58}H_{64}O_{14}$ requires *M*, 984.4296).

On the other hand, the deposit collected on the Celite filter was stirred in $CHCl_3$ and water, and the Celite was filtered off. The organic phase of the filtrate was washed with brine and dried over $MgSO_4$. Evaporation of the solution below room temperature under reduced pressure gave syn-*isomer* **5S** (254 mg, 62%) as crystals. The ratio of the isomers (**5S**:**5A**) was estimated to be 100:0 by HPLC measurement under the same conditions as above. Recrystallization from CH_2Cl_2–MeOH at room temperature afforded needles, mp 272–273 °C; δ_H 3.51 [4 H, d, *J* 13.5, ArC*H*(H)Ar × 4], 3.54 [2 H, d, *J* 13, ArC*H*(H)Ar × 2], 3.82 (12 H, s, OMe × 4), 3.83 (12 H, s, OMe × 4), 3.94 (8 H, br t, $ArOCH_2CH_2O$ × 4), 4.05 [4 H, m, ArOC*H*(H)CH_2O × 4], 4.15 [4 H, m, ArOCH(*H*)CH_2O × 4], 4.73 [4 H, d, *J* 13.5, ArCH(*H*)Ar × 4], 4.76 [2 H, d, *J* 13, ArCH(*H*)Ar × 2] and 6.78, 6.81 and 6.84 (each 4 H, s, ArH × 12); *m/z* 984 (M^+) (Found: M^+, 984.4291).

Acknowledgements

The authors are indebted to Miss N. Sawabe, Mrs F. Hasegawa and Mr H. Igarashi, this Faculty, for ^1H NMR and mass spectral measurements, and elemental analyses.

References

1 G. W. Gokel, *Crown Ethers and Cryptands*, 1991, The Royal Society of Chemistry, Cambridge; *Host–Guest Complex Chemistry I*, ed. F. Vögtle, 1981, Springer-Verlag, Berlin, Heidelberg, New York; *Host–Guest Complex Chemistry II*, ed. F. Vögtle, 1982, Springer-Verlag, Berlin, Heidelberg, New York; *Host–Guest Complex Chemistry III*, ed. F. Vögtle, and E. Weber, 1984, Springer-Verlag, Berlin, Heidelberg, New York, Tokyo.

2 F. Diederich, *Cyclophanes*, 1991, The Royal Society of Chemistry, Cambridge.
3 C. D. Gutsche, *Calixarenes*, 1989, The Royal Society of Chemistry, Cambridge.
4 A. Collet, *Tetrahedron*, 1987, **43**, 5725.
5 J. W. Steed, P. C. Junk and J. L. Atwood, *J. Am. Chem. Soc.*, 1994, **116**, 10 346.
6 R. P. Sijbesma and R. J. M. Nolte, *J. Am. Chem. Soc.*, 1991, **113**, 6695; 1992, **114**, 9807; J. N. H. Reek, R. P. Sijbesma and R. J. M. Nolte, *Tetrahedron Lett.*, 1994, **35**, 2801.
7 B. Umezawa, O. Hoshino, H. Hara and S. Mitsubayashi, *J. Chem. Soc. C*, 1970, 465.
8 H. Hara, H. Satoh and O. Hoshino, *Heterocycles*, 1992, **33**, 43.
9 H. Hara, H. Nakamura, S. Watanabe and O. Hoshino, *Tetrahedron Lett.*, 1994, **35**, 5261.
10 A. Collet and J. Gabard, *J. Org. Chem.*, 1980, **45**, 5400.
11 J. D. Dunitz, M. Dobler, P. Seiler and R. P. Phizackerley, *Acta Crystallogr., Sect. B*, 1974, **30**, 2733. Other references are cited in ref. 1.
12 W. Y. Lee, W. Sim and D. K. Choi, *J. Chem. Soc., Perkin Trans. 2*, 1992, 881.
13 D. J. Cram, M. E. Tanner and C. B. Knobler, *J. Am. Chem. Soc.*, 1991, **113**, 7717.
14 G. P. Thakar and B. C. Subba Rao, *J. Sci. Ind. Res., Sect. B*, 1962, **21**, 583.
15 R. C. Cookson, B. Halton and I. D. R. Stevens, *J. Chem. Soc. B*, 1968, 767.
16 T. Sakai, K. Miyata, M. Utaka and A. Takeda, *Tetrahedron Lett.*, 1987, **28**, 3817.
17 J. Blackwell and W. J. Hickinbottom, *J. Chem. Soc.*, 1961, 1405.
18 S. Kim, Y. J. Kim and K. H. Ahn, *Tetrahedron Lett.*, 1983, **24**, 3369.
19 B. Umezawa, O. Hoshino, H. Hara, K. Ohyama, S. Mitsubayashi and J. Sakakibara, *Chem. Pharm. Bull.*, 1969, **17**, 2240.

Paper 5/04529K
Received 10*th July* 1995
Accepted 25*th September* 1995