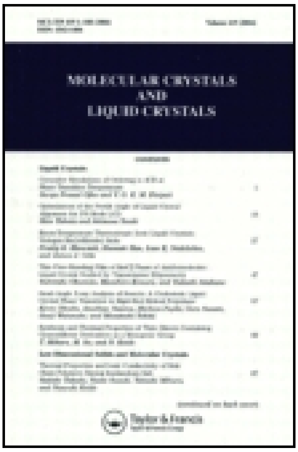

Molecular Crystals and Liquid Crystals Science and Technology. Section A. Molecular Crystals and Liquid Crystals
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/gmcl19

Separation of Racemic and Meso-1,2-Bis(2-[(2-Bromo-4,5-Dimethoxyphenyl)Hydroxymethyl]-4,5-Dimethoxybenzyl]-4,5-Dimethoxybenzenes by Host-Guest Inclusion

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To cite this article: Hiroshi Hara , Hiroshi Nakamura , Shi-Ichi Watanabe , Tomomi Murata & Osamu Hoshino (1996): Separation of Racemic and Meso-1,2-Bis(2-[(2-Bromo-4,5-Dimethoxyphenyl)Hydroxymethyl]-4,5-Dimethoxybenzyl]-4,5-Dimethoxybenzenes by Host-Guest Inclusion, Molecular Crystals and Liquid Crystals Science and Technology. Section A. Molecular Crystals and Liquid Crystals, 276:1-2, 47-50

To link to this article: http://dx.doi.org/10.1080/10587259608039359

Mol. Cryst. Liq. Cryst., 1996, Vol. 276, pp. 47–50
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SEPARATION OF RACEMIC AND MESO-1,2-BIS{2-[(2-BROMO-4,5-DIMETHOXYPHENYL)HYDROXYMETHYL]-4,5-DIMETHOXYBENZYL}-4,5-DIMETHOXYBENZENES BY HOST-GUEST INCLUSION

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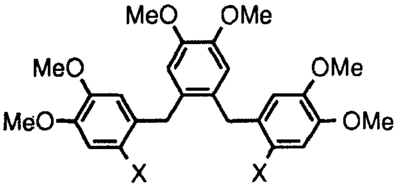
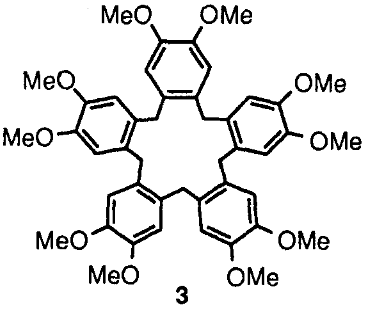
Abstract Diastereoisomers of title compounds were separated by inclusion of solvent and their stereostructures were determined by ^{1}H-NMR measurement using a chiral shift reagent, Eu(tfc)$_3$.

In the course of synthetic study on orthocyclophanes, we have adopted a divergent method in which reaction of veratrol with 6-bromoveratryl alcohol in the presence of acid gives a core compound (**1**),[1, 2] and then 6-bromoveratraldehyde (**2**)[2] serves as a key building block for extention of benzyl unit.

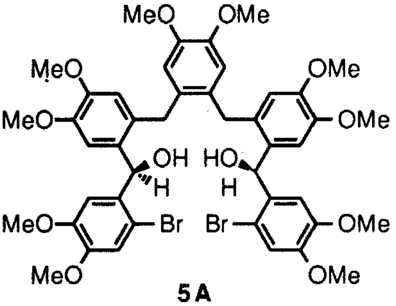


1 : X = Br
2 : X = H
4 : X = Li

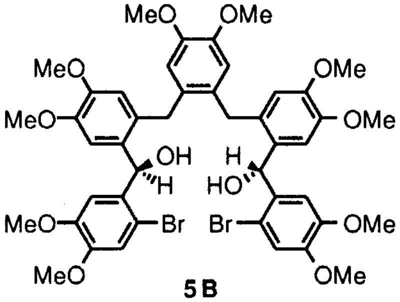


3

In one step for synthesis of cyclopentaveratrylene (**3**),[2] a dilithiolide (**4**), derived from **1** and n-BuLi, was reacted with 2.1 eq. of **2** at -50 °C for 2 h to give 1,2-bis{2-[(2-bromo-4,5-dimethoxyphenyl)hydroxymethyl]-4,5-dimethoxybenzyl}-4,5-dimethoxybenzene (**5**), mp 107-113 °C, in 73 % yield Plain structure of the product was confirmed on the basis of IR spectrum [3585 cm^{-1} (OH)] and mass spectrum [*m/z* 926 (M$^+$), 928 (M$^+$+2), 930 (M$^+$+4); 1 : 2 : 1 ratio]. Although the product showed one spot on thin layer chromatography under several conditions, its ^{1}H-NMR spectrum revealed it was a mixture of diastereoisomers (1 : 1 ratio) (Chart 1). Synthesis of the target compound (**3**) was accomplished in three steps from **5** without separation.



5A



5B

When purification of **5** was carried out, a novel character of the dibromodiol structure was observed. Recrystallization of the mixture from AcOEt-hexane furnished one isomer (**5 A**)[3] as 1 : 1 adduct with AcOEt. On the other hand, the residue was recrystallized from Et_2O-acetone to afford another isomer (**5 B**)[3] as 1 : 1 complex with Et_2O. Host-guest ratios of the complexes were estimated by integral ratio of aromatic protons of the hosts and methyl protons of the solvents on those ^{1}H-NMR spectra (Charts 2 and 3), respectively. Attempts to determine stereostructures of **5 A** and **5 B** by HPLC analysis using various types of chiral columns were unsuccessful. After all, we could clarify their stereostructures by 270 MHz ^{1}H-NMR measurement using a chiral shift reagent, Eu(tfc)$_3$ (Charts 4 and 5). Methine protons of benzhydrol moieties in **5 B** were splitted by formation of diastereomers and those in **5 A** not. Therefore, stereostructure of **5 A** was decided to be *meso* and **5 B** *racemic*, respectively.

Analogous compounds (**6**[2] and **7**[4]) have no ability of solvent inclusion. Therefore,

Chart 1
5 (mixture)
[100 MHz]

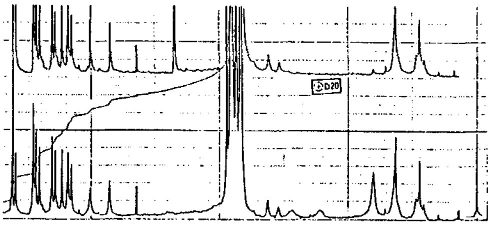


Chart 2
5A • AcOEt
[100 MHz]

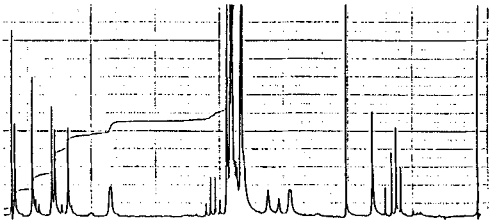


Chart 3
5B • Et $_2$O
[100 MHz]

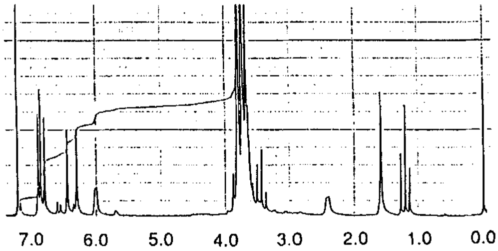


Chart 4
5A • AcOEt
+ Eu(tfc)$_3$
[270 MHz]

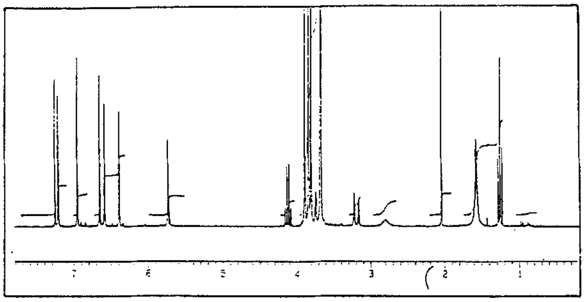
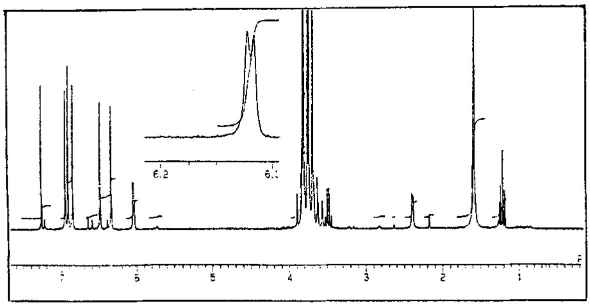
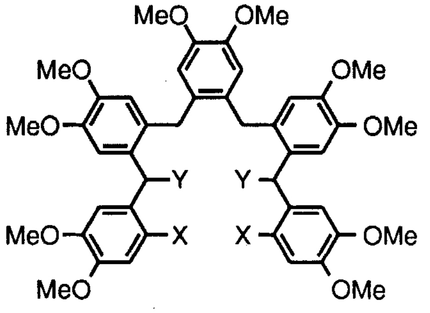


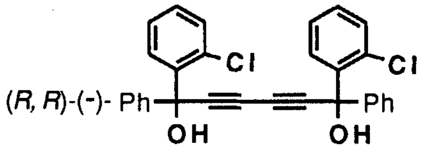
Chart 5
5B • Et $_2$O
+ Eu(tfc)$_3$
[270 MHz]



existence of both substituents (hydroxyl and bromo groups) are requisite in the inclusion of AcOEt or Et_2O. Other solvents (MeOH, benzene, hexane) employed for recrystallization of **5** were not included.



6 : X = Br, Y = H
7 : X = H, Y = OH



8

Toda and his group have energetically investigated on host-guest chemistry in the solid state.[5] They have reported that a chiral host compound (**8**) has quite strong ability of solvent inclusion. Considering the facts, it is noticeable that **5** and **8** have bis(*o*-halogenobenzhydrol) moiety as a common structure. In contrast with flexible structure of **5**, rigid diacetylene skeleton and two hydroxyl groups existing apart from each other in **8** may generate excellent effect for guest trapping.[6]

REFERENCES AND NOTES

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2. H. Hara, H. Nakamura, S. Watanabe, and O. Hoshino, Tetrahedron Lett., 35, 526, (1994).
3. **5A**·AcOEt, mp 121-122 °C; **5B**·Et_2O, mp 197-200 °C.
4. **7** (diastereomixture) was prepared from **4** and veratraldehyde in a manner similar to that noted for **5**. **7**: an amorphous mass (82 %); ^{1}H-NMR δ 2.32, 2.92, (each brs, OH), 5.51, 5.69 (each s, C*H*OH); IR ($CHCl_3$) 3575 cm^{-1} (OH); MS (m/z) 770 (M^+).
5. F. Toda, Top. Curr. Chem., 140, 43 (1987); *Idem*, *ibid.*, 149, 211, (1988), and references cited therein.
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