Two-step Synthesis of D_3 and C_{3h} Cryptophanes

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Dihalides X–(Z)–X, [Z = $(CH_2)_n$; n = 1—7 or $CH_2CH{=}CHCH_2$] react with the phenol group of vanillyl alcohol to give the dialkylated derivatives $HOCH_2$–Ar–O–(Z)–O–Ar–CH_2OH (**2**), which in turn, in the presence of formic acid, afford the corresponding D_3 cryptophanes (**3**), with, in some cases, minor amounts of the C_{3h} isomers (**4**).

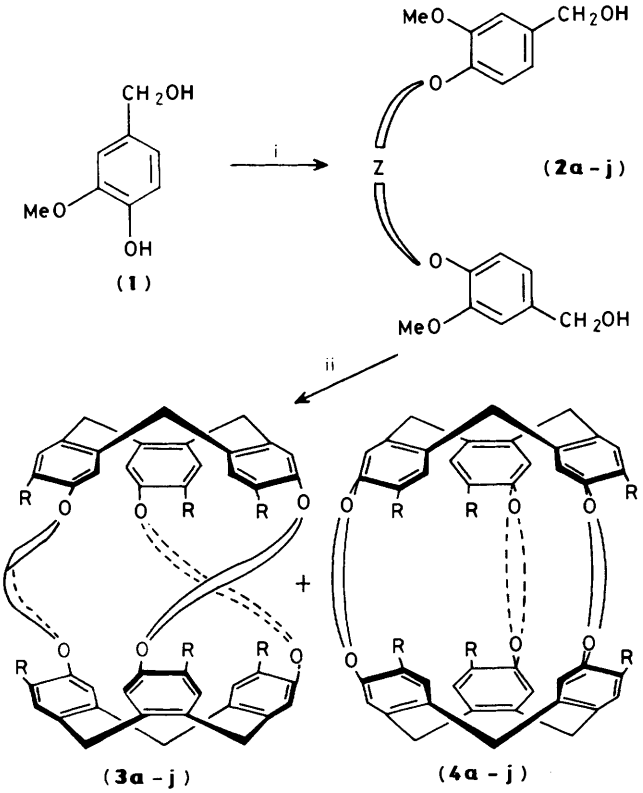
We report an exceptionally short and simple synthesis of D_3 and C_{3h} cryptophanes[1] (Scheme 1), in only two steps from vanillyl alcohol (**1**), instead of the six to eight steps of the previous 'template directed procedure'.[2—6] In addition to its simplicity and shortness, the new method has the advantage that it does not require high dilution conditions, and therefore lends itself to the preparation of much larger quantities of cryptophanes than does the template procedure. This circumstance clearly opens new perspectives in the chemistry and applications of these unusual molecules.[1—7]

Vanillyl alcohol (**1**) (20 mmol) in ethanol (10 ml) was treated with NaOH, (2 ml, 10 M) and refluxed for 3 h in the

Table 1. Two-step cryptophane synthesis.[a]

	Bridge structure Z	Diols[b] % (**2**)	Diols[b] M.p./°C	Cryptophanes % (**3**)	Cryptophanes % (**4**)	Eluant[c]	
a	$(CH_2)_2$	35	145	5	0	CH_2Cl_2–Et_2O	90:10
b	$(CH_2)_3$	65	153	17	0	CH_2Cl_2–Me_2CO	90:10
c	$(CH_2)_4$	70	146	8	2	CH_2Cl_2–Me_2CO	90:10
d	$(CH_2)_5$	70	115	(11.5	5.5)[d]	CH_2Cl_2–Et_2O	90:10
e	$(CH_2)_6$	70	134	7.5	2	C_6H_6–Me_2CO	85:15
f	$(CH_2)_7$	70	90	(4.5	0)[d]	$CHCl_3$–Et_2O	95:5[e]
g	$(CH_2)_8$	74	115	0	0	CH_2Cl_2–Et_2O	95:5[f]
h	*cis*-$CH_2CH{=}CHCH_2$	65	93	10	8	CH_2Cl_2–Et_2O	85:15
i	*trans*-$CH_2CH{=}CHCH_2$	28[g]	140	5	<1	CH_2Cl_2–Et_2O	80:20
j	$CH_2C{\equiv}CCH_2$	26	114	0	0	CH_2Cl_2–Et_2O	95:5[h]

[a] All yields correspond to isolated pure products. [b] Satisfactory elemental analyses (C, H) and ^1H n.m.r. spectra (200.13 MHz) were obtained for all diols (**2**). [c] The faster-running isomer was (**3**), with one exception [(**3e**) slower than (**4e**)]. [d] Provisional assignment of the D_3 and C_{3h} isomers (see text). [e] 4.5% of cyclotetraveratrylene (**5f**) was also isolated. [f] 10% of (**5g**) was the only isolated product. [g] Low yield due to the use of a 1:1 ratio of vanillyl alcohol to dihalide. [h] The cryptophanes (**3j**) and (**4j**), obtained by template method, display R_f 0.54 and 0.50, respectively, with this eluant.

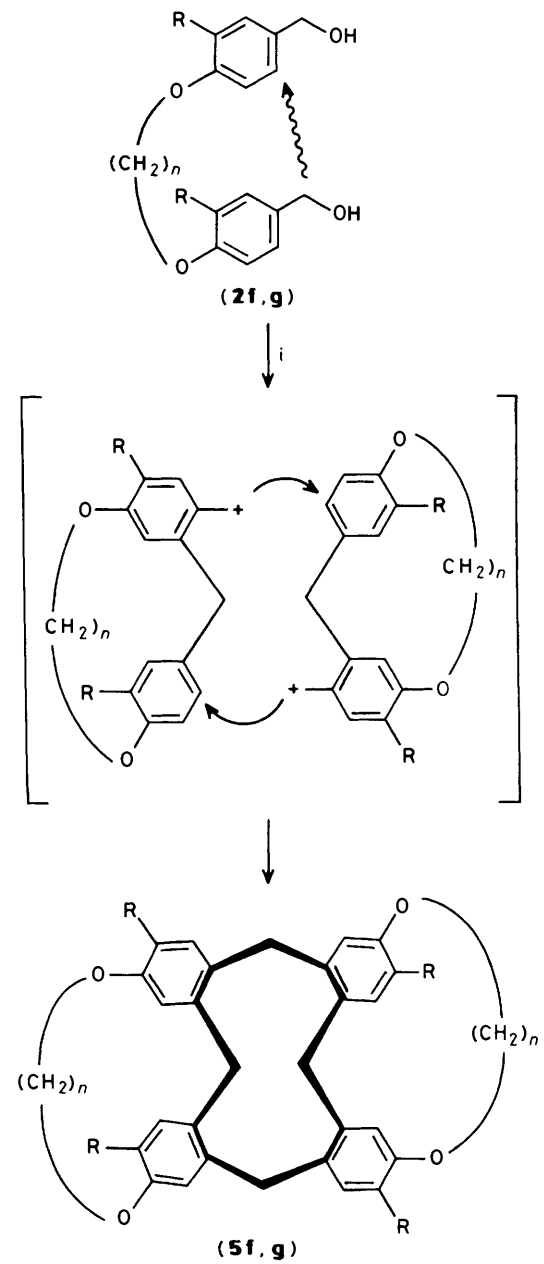


Scheme 1. R = OMe. *Reagents and conditions*: i, NaOH (10 M), Br-$(CH_2)_n$-Br (n = 1—8, **a—g**), *cis*- or *trans*-1,4-dichlorobut-2-ene (**h,i**), 1,4-dichlorobut-2-yne (**j**), 3 h ethanol reflux; ii, HCO_2H, 2—3 h, 55 °C (**a—g**), or 15 h room temperature (**h—j**).

presence of a dihalide X-(Z)-X [Br-$(CH_2)_n$-Br, *cis*- or *trans*-Cl-CH_2CH=$CHCH_2$-Cl, or Cl-$CH_2C{\equiv}CCH_2$-Cl] (10 mmol). The crystalline diols (**2a—j**) were collected by filtration after addition of water and further amounts could be obtained by extraction of the filtrates with dichloromethane, followed by column chromatography on silica gel (dichloromethane–acetone, 70:30 as the eluant). Recrystallization from propan-2-ol eventually gave the pure diols, Table 1.

Diols (**2**) were converted into the corresponding D_3 and C_{3h} cryptophanes (**3**) and (**4**), respectively, by dissolving them in formic acid. Concentrations of (**2**) of *ca.* 1 g per 500 ml of HCO_2H gave the best yields. For larger scale preparations, the quantity of solvent could be reduced by a factor of ~two (*e.g.*, 10 g of (**2**) in 2 l of formic acid], with only a moderate effect on the yields [*e.g.*, 15% yield in a 10 g scale preparation of (**3b**), instead of 17% in optimum conditions]; higher concentrations were detrimental, however. Typically, the solution was warmed for 2—3 h at 55 °C [aliphatic bridges, (**2a—g**)], or allowed to stand at room temperature overnight [unsaturated bridges, (**2h—j**)]. The solvent was removed *in vacuo* (rotatory evaporator), and the cryptophanes were separated from the by-products (mostly polymeric materials) by chromatography over silica gel followed by recrystallization from acetone or acetone–methanol. The yields of pure products are indicated in Table 1.

Most of the cryptophanes obtained by the above two-step procedure were identified by comparison with specimens prepared by the template route and described earlier[2—6] [namely, the D_3 isomers (**3a,b,h,i,j**), and the C_{3h} isomers (**4b,h,i,j**)]. The structures of the new cryptophanes (**3—4c,d,e,f,g**) were established by mass and ^{1}H n.m.r. spectroscopy (200 MHz). These methods, however, did not allow us



Scheme 2. R = OMe, n = 7,8. *Reagents and conditions*: i, HCO_2H, 2—3 h, 55 °C.

to determine, for each diastereoisomeric pair, which was the D_3, and which was the C_{3h} isomer. The C_{3h} structure (**4c**) was assigned to the minor isomer of the pair (**3c/4c**), since the latter was identical with a sample obtained by catalytic hydrogenation (H_2, 5% Pd on C) of the acetylenic bridges of the known[3] C_{3h} cryptophane (**4j**). We have provisionally assigned the D_3 structure to the major isomer of the pairs (**3d,e,f/4d,e,f**), because the other results described in Table 1 indicate that the two-step procedure preferentially affords D_3 cryptophanes in all cases, even when the template method gives the C_{3h} isomer. For instance, diol (**2b**) exclusively yields (**3b**), whereas the template route[5] preferentially gives (**4b**), with a 1.85:1 C_{3h}/D_3 ratio. In the same way, (**2h**) shows a slight preference for forming the D_3 isomer (**3h**) (1:0.8), while again the template method gives an inverse result (0.5:1).[6]

The two-step method is especially convenient for the preparation of gram quantities of the medium-sized D_3 cryptophanes having aliphatic bridges, Z = $(CH_2)_{3-6}$ [*i.e.*, (**3b—e**)]. As the length of the bridges increases, the yields drop, and the reaction takes a different course beyond Z = $(CH_2)_6$. Beside the cryptophane (**3f**), the reaction of diol (**2f**) furnished 4.5% of a new product, which we assigned the unusual doubly-bridged cyclotetraveratrylene structure (**5f**). In the case of (**2g**), only the analogous compound (**5g**) was isolated (10%). The structure of (**5g**) was established by mass spectroscopy (M^+ *m/z* 764), ^1H and ^{13}C n.m.r. spectroscopy, and by chemical correlation with cyclotetraveratrylene.[8] The treatment of (**5g**) with an excess of BBr_3 in dichloromethane (3 h, room temp.) gave the octaphenol cyclotetracatechylene, identical with a sample prepared by demethylation of cyclotetraveratrylene. The formation of (**5f,g**) presumably occurs because the length of the bridge allows the intramolecular cyclization of diols (**2f,g**), followed by a head-to-tail dimerization, Scheme 2. Compounds (**5f**) and (**5g**) exhibit a highly strained and rigid 'roof like' conformation, as shown by variable temperature n.m.r. experiments (details will be given elsewhere).

We have no explanation for the failure of the acetylenic diol (**2j**) to give a cryptophane on reaction with formic acid. More generally, we cannot yet provide any consistent mechanistic pathway that would explain how six C–C bonds can be created in a stereoselective fashion between three molecules of (**2**), to give a cryptophane molecule.

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