A Novel Synthesis of Hemispherands

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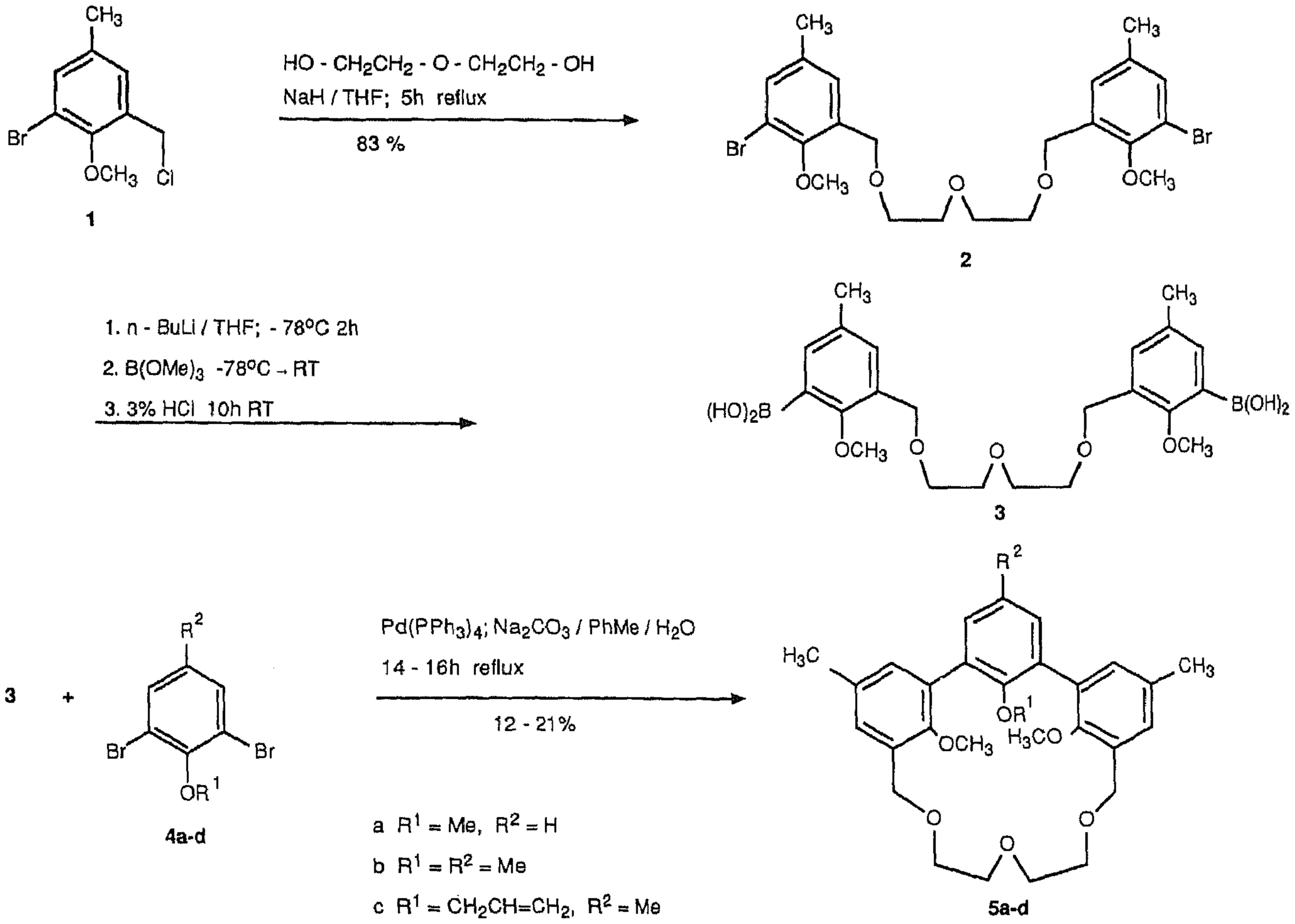
Abstract: A novel, flexible synthesis of hemispherands {2,5,8-trioxa[9](3,3″)*m*-terphenylophanes **5a–d**} with different central aromatic groups is described. The key step comprises the introduction of the central aromatic ring in the last step of the synthesis via a Suzuki cross-coupling reaction using palladium tetrakis(triphenylphosphine) as a catalyst and sodium or potassium cations serving as a template ion in the macrocyclization.

Hemispherands represent an interesting class of host molecules in supramolecular chemistry. The synthesis and the complexation with alkali and alkylammonium salts were reported first by Cram *et al.*[2] In the parent molecule (e.g. **5b**) the molecular cavity is composed of a rigid *m*-teranisyl moiety in which three oxygen binding sites are conformationally organized prior to complexation, and a flexible polyether chain. Cram *et al.* also published hemispherands composed of three[3,4] or four[5] anisyl units or anisyl and cyclic urea units.[6,7] In our laboratories we developed strategies for the synthesis of hemispherands with a modified central aromatic ring. This aromatic ring could be introduced either by using pyrylium salt chemistry[8] or condensation of an incorporated dibenzyl ketone moiety with nitromalonodialdehyde.[9] In this paper we present our preliminary results on a novel, flexible synthesis of this type of compound in which the central aromatic ring is introduced in the last step of the synthesis via a Suzuki coupling[10] using a Pd(0) catalyst.

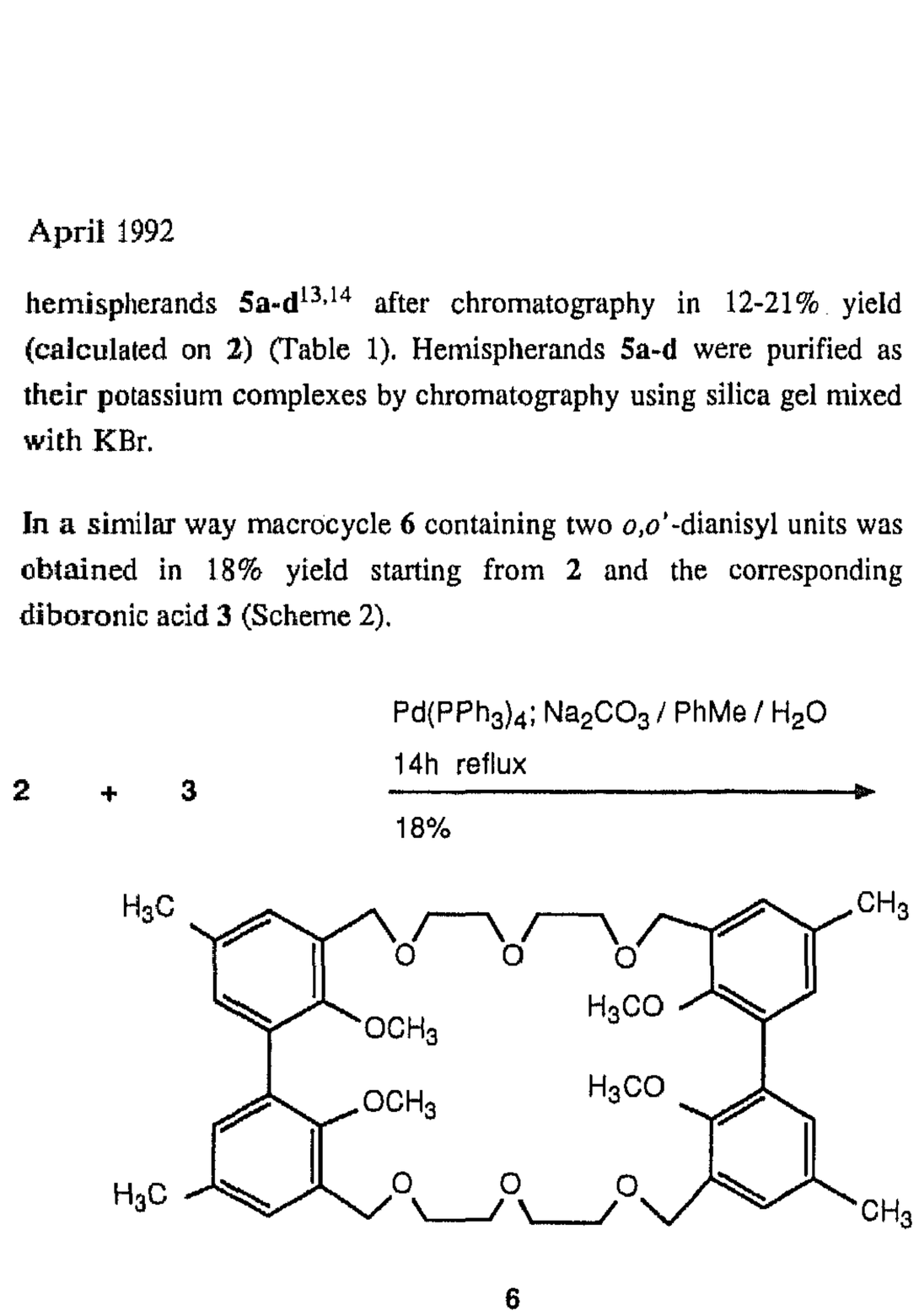
The reaction sequence is summarized in Scheme 1. Reaction of the easily accessible 2-bromo-6-(chloromethyl)-4-methylanisole[11] **1** (prepared in two steps from 4-methylanisole) with diethylene glycol in THF in the presence of NaH as a base afforded compound **2**[12] as a colorless oil in 83% yield after bulb to bulb distillation (bp 160-170 °C, 5 x 10^{-2} mm Hg). Compound **2** was transformed in the diboronic acid **3** upon treatment with *n*-BuLi in THF followed by reaction of the resulting dilithio compound with trimethyl borate and subsequent treatment with 3% HCl. Diboronic acid **3** could not be purified on account of slow decomposition and was therefore used as such in the macrocyclization step. Aryl dibromides **4a-d** were obtained in high yields from commercially available phenols by alkylation with methyl iodide or allyl bromide. Crude diboronic acid **3** was subjected to modified Suzuki cross-coupling conditions (toluene/aq Na_2CO_3/-2% $Pd(PPh_3)_4$/reflux) with aryl dibromides **4a-d** to give the



Scheme 1

hemispherands **5a-d**[13,14] after chromatography in 12-21% yield (calculated on **2**) (Table 1). Hemispherands **5a-d** were purified as their potassium complexes by chromatography using silica gel mixed with KBr.

In a similar way macrocycle **6** containing two *o,o'*-dianisyl units was obtained in 18% yield starting from **2** and the corresponding diboronic acid **3** (Scheme 2).



Scheme 2

Table 1. Hemispherands **5a-d** and macrocycle **6**.

compd	yield[a](%)	mp (°C)	lit mp (°C)
5a	14	191-193	192-193[9]
5b	15	208-210	208-209[2]
5c	21	133-135	
5d	12	151-152.5	150-152[9]
6	18	117-119	116-119[9]

[a] calculated on **2**.

Table 2. Formation of **5c** using different catalysts and conditions.

entry	catalyst	conditions[a]	yield[b](%)
1	$Pd(PPh_3)_4$	Li_2CO_3/PhMe/H_2O	0
2	$Pd(PPh_3)_4$	Na_2CO_3/PhMe/H_2O	21
3	$Pd(PPh_3)_4$	K_2CO_3/PhMe/H_2O	21
4	$Pd(PPh_3)_4$	Cs_2CO_3/PhMe/H_2O	8
5	$Pd(PPh_3)_4$	K_3PO_4/dioxane	32
6	$Ni(PPh_3)_2Cl_2$	K_2CO_3/PhMe/H_2O	12
7	$Ni(Acac)_2$	K_2CO_3/PhMe/H_2O	8

[a] reflux for 14-16 h.
[b] isolated yields after chromatography.

In order to investigate the possible role of the cation and the catalyst, the reaction of **3** with **4c** to give **5c** was carried out under different conditions (Table 2). Variation of the cation (Li^+, Na^+, K^+, Cs^+; entries 1-4) indicates that Na^+ and K^+ probably serve as a template ion in the macrocyclization reaction. A Pd(0) catalyst appears to be superior to a Ni^{2+} one (entries 3,6,7).

Although the yields of the hemispherands **5a-d** are still moderate, we feel that the described approach can compete with other methods because of its limited number of reaction steps and its flexibility.

Representative macrocyclization procedure

A solution of aryl dibromide **4c** (0.31 g, 1.0 mmol) and crude diboronic acid **3** (0.46 g, 1.0 mmol) in 95% EtOH (5 mL) was added to a vigorously stirred, hot mixture of tetrakis(triphenylphosphine)-palladium(0) (23 mg, 0.02 mmol) and Na_2CO_3 (50 mL, 2M aq solution) in toluene (50 mL). The mixture was refluxed for 14 h and subsequently cooled to room temperature. After separation of the layers the aqueous layer was extracted with CH_2Cl_2 (3 x 20 mL). The combined organic layers were washed with 1N HCl (3 x 10 mL) and water (20 mL). After evaporation of the solvents, the residue was dissolved in MeOH (15 mL) and stirred for 1 h with a saturated methanolic KBr solution (15 mL). After removal of the MeOH the residue was flash chromatographed (wet SiO_2:KBr, 10:1). The non-ionic impurities were eluted with CH_2Cl_2; changing the eluent to CH_2Cl_2:MeOH, 93:7 v/v gave **5c**.KBr. The fractions containing **5c**.KBr were combined, washed with 3% HCl (3 x 10 mL), water (10 mL), and dried with $MgSO_4$. After evaporation of the solvent the residue was recrystallized from 95% EtOH to give pure hemispherand **5c** as a white solid.

References and Notes

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(12) **2**: ^{1}H NMR ($CDCl_3$) δ 7.50 (d, 2 H, J = 1.6 Hz, ArH), 7.29 (d, 2 H, J = 1.6 Hz, ArH), 4.58 (s, 4 H, $ArCH_2O$), 3.81 (s, 6 H, OCH_3), 3.69 (s, 8 H, OCH_2CH_2O), 2.27 (s, 6 H, CH_3); mass spectrum (EI), *m/e* 530.024 (M^+, calcd for $C_{20}H_{28}Br_2O_5$ 530.030).

(13) **5c**: ^{1}H NMR ($CDCl_3$) δ 7.24 (s, 2 H, ArH, inner), 7.06 (s, 4 H, ArH, outer), 5.0-4.8 (m, 1 H, -C*H*=CH_2), 4.72 and 4.41 (ABq, 4 H, J = 11.6 Hz, $ArCH_2O$), 4.63-4.56 and 4.47-4.40 (m, 2 H, =CH_2), 3.75-3.5 (m, 8 H, OCH_2CH_2O), 3.38 (s, 6 H, OCH_3), 3.25 (d, 2 H, J = 6.3 Hz, OCH_2-CH=), 2.45 (s, 3 H, CH_3, inner), 2.32 (s, 6 H, CH_3, outer); mass spectrum (FAB, 3-nitrobenzyl alcohol as a matrix), *m/e* 541 (100%; [M + Na]$^+$). Anal. Calcd for $C_{32}H_{38}O_6$: C, 74.10; H, 7.38. Found: C, 73.88; H, 7.32.

(14) Using KBr/Et_3N/DMF and 2% $Pd(PPh_3)_4$ gave hemispherand **5c** in a yield of 38%. Unfortunately this yield could not always be reproduced.