Cyclotrimerization of 'Oxabenzonorbornadiene': Synthesis of *syn*- and *anti*-5,6,11,12,17,18-Hexahydro-5,18:6,11:12,17-triepoxytrinaphthylene

by **Ottorino De Lucchi**[a]), **Arif Daştan**[a])[b]), **Aliye Altundaş**[c]), **Fabrizio Fabris***[a]), and **Metin Balci***[d])

[a]) Department of Chemistry, Università Cà Foscari di Venezia, I-30123 Venezia (e-mail: fabrisfa@unive.it)
[b]) Department of Chemistry, Atatürk University, TR-25240 Erzurum
[c]) Department of Chemistry, Gazi University, TR-06100, Ankara
[d]) Department of Chemistry, Middle East Technical University, TR-06531 Ankara
(e-mail: mbalci@metu.edu.tr)

An efficient synthetic route to the concave-shaped, potentially ionophoric *syn*- and *anti*-isomers of 5,6,11,12,17,18-hexahydro-5,18:6,11:12,17-triepoxytrinaphthylene (**4**) was elaborated. Starting from 'oxabenzonorbornadiene' (**5**), the stannylated precursor **9** was prepared in three steps, followed by cyclotrimerization catalyzed by copper(I) thiophene-2-carboxylate (CuTC) , which afforded **4** in a *syn*/*anti* ratio of 5 :4.

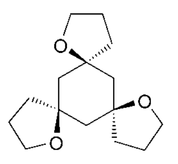
Introduction. – New frontiers in supramolecular chemistry and, specifically, in metal-ion binding can be opened only by putting forth new molecules with unprecedented geometries. Noteworthy efforts in this field have been made, *e.g.*, by the groups of *Paquette* [1] and *Lee* [2], who prepared the ionophores **1**–**3**, in which the ether O-atoms are included in rigid structures to improve binding affinity and/or selectivity for different ions.

Here we present the preparation and characterization of benzocyclotrimers of type **4** (=5,6,11,12,17,18-hexahydro-5,18:6,11:12,17-triepoxytrinaphthylene) from 'oxabenzonorbornadiene' (=1,4-dihydro-1,4-epoxy-naphthalene; **5**). Compounds of type **4** – closely related, *e.g.*, to the known cyclotrimer *syn*-**6** [3] – are potentially interesting due to their highly concave structures, with the O-atoms being in a viable arrangement for ion binding.

Results and Discussion. – The synthesis of racemic **4** started from **5**, which was treated with Br_2 and *t*-BuOK to afford the mono-brominated derivative **7** (*Scheme*). The latter was then brominated/dehydrobrominated again, which gave rise to the corresponding dibromo compound **8** by means of a procedure established previously [4].

The typical stannylation [5] of **7** by means of $(i\text{-}Pr)_2NLi$ (LDA) at low temperature (0° or $-78°$), followed by quenching with Me_3SnCl, failed to produce the desired bromostannyl derivative, most probably because of ring-opening of the substrate. However, metallation of **8** with BuLi under optimized conditions (reaction time and temperature), followed by quenching with Me_3SnCl, enabled us to isolate the desired stannyl derivative **9** in 90% yield after chromatographic purification.

When compound **9** was subjected to copper(I) thiophene-2-carboxylate (CuTC) in *N*-methylpyrolidin-2-one (NMP) at $-20°$, cyclotrimerization to *syn*- and *anti*-**4** was



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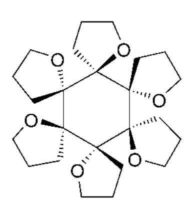

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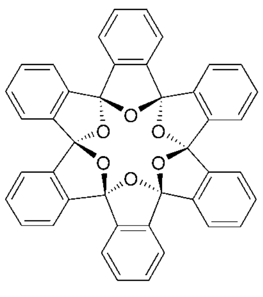

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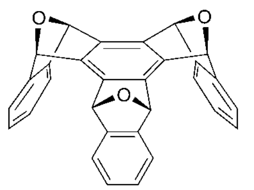
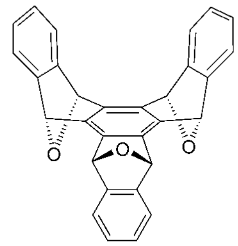
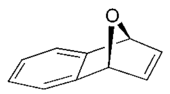


syn-**4**



anti-**4**



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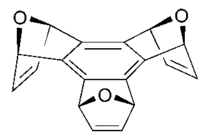
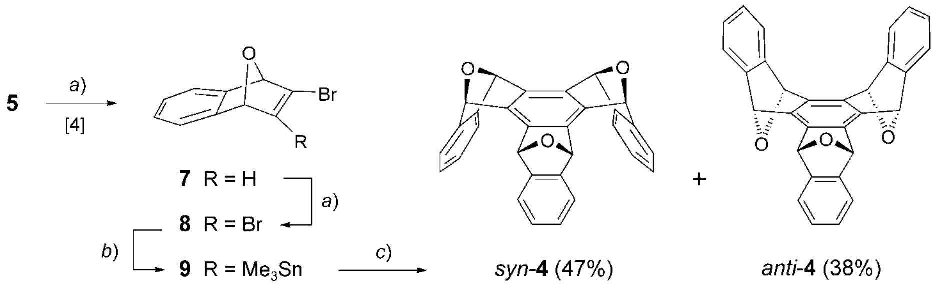


syn-**6**

observed (*Scheme*). Under these optimized conditions for the synthesis of cyclotrimers [6], the *syn*- and *anti*-isomers were isolated in 47 and 38% yield, respectively.

Scheme



a) 1. Br_2, CCl_4, Δ; 2. *t*-BuOK, THF; 90% (**5** → **7**), 88% (**7** → **8**). *b*) 1. BuLi, THF, −78°; 2. Me_3SnCl, −78°; 90%. *c*) Copper(I) thiophene-2-carboxylate (CuTC), *N*-methylpyrrolidin-2-one (NMP), −20°; 47% *syn*-**4**, 38% *anti*-**4**.

The structural assignment of the two diastereoisomeric trimers **4** was achieved by NMR spectroscopy. The ^{1}H-NMR spectrum of *syn*-**4** showed only two resonances: an *AA'BB'* system arising from the three peripheral aromatic rings, and a *singlet* at δ(H) 6.15 due to the six magnetically equivalent H-atoms in benzylic (bridgehead) positions. The C_3 symmetry of *syn*-**4** was further confirmed by five ^{13}C-NMR resonances.

The C_S-symmetric *anti*-isomer of **4** displayed a more-complex ^{1}H-NMR pattern of aromatic signals, and a set of three (instead of one) benzylic *singlets*. The structure of the compound was in accordance with 15 observed ^{13}C-NMR resonances (mirror plane).

As a side product (*ca.* 1%) of the above cyclotrimerization, the protodestannylated compound **7** was also observed, probably due to the presence of residual H_2O in the solvent. Interestingly, no other products were observed in the crude reaction mixture, even though the presence of dimers was carefully checked.

The observed 5:4 ratio of *syn*-**4**/*anti*-**4** is in contrast to the unfavorable statistic distribution of products expected for the nearly iso-energetic structures1). In fact, cyclotrimerizations carried out with CuTC have shown higher *syn*/*anti* ratios only when enantiomerically pure, hindered, and when ether-bearing substrates were used [6c]. On the contrary, *syn*/*anti* ratios ranging from 1:3 to 1:8 have been reported for racemic, unfunctionalized, or hindered substrates with ether functions [6a, b, d, e]. Our finding, thus, seems to indicate a positive effect of the three O-atoms in coordinating to Cu^{I} during the reaction.

In conclusion, we have achieved the first highly effective synthesis of the *syn*- and *anti*-isomers of 5,6,11,12,17,18-hexahydro-5,18:6,11:12,17-triepoxytrinaphthylene (**4**). These compounds are interesting as potential ionophores, and as O-containing precursors of fullerene-type compounds.

Experimental Part

General. All substances reported in this paper were used or prepared in *racemic* forms. The synthesis of compound **8** has been described in detail previously [4]. All solvents were dried and distilled prior to use. All reactions were carried out under Ar gas and monitored by thin-layer chromatography (TLC) or ^{1}H-NMR spectroscopy. Flash chromatography (FC) was performed on silica gel (60-mesh, *Merck*). TLC was carried out on silica gel *60* F_{254} (0.2 mm, on aluminum plates; *Merck*). Melting points (m.p.) are uncorrected. IR Spectra: in cm^{-1}. ^{1}H- and ^{13}C-NMR spectra were recorded on *Varian* (400/100 MHz) or *Brucker* (300/75 MHz) spectrometers; δ in ppm, J in Hz. GC/MS Spectra (70 eV): in *m*/*z* (rel. %).

(3-Bromo-1,4-epoxy-1,4-dihydronaphthalen-2-yl)(trimethyl)stannane (**9**). To a stirred soln. of **8** (2.00 g, 6.6 mmol) [4] in anh. THF (20 ml) at −78°, a 2.5 M soln. of BuLi in hexanes (2.8 ml, 7.0 mmol) was added dropwise within 2 min, and stirred at this temp. for another 2 min. Then, Me_3SnCl (1.31 g, 6.6 mmol) was added in one portion. The resulting soln. was maintained at −78° for 2 h, and was then allowed to warm to r.t. overnight. Then, H_2O (50 ml) was added, the mixture was extracted with Et_2O (3 × 40 ml), and the combined org. extracts were dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by FC (CH_2Cl_2/hexane 3:7): 2.30 g (90%). Colorless crystals (Et_2O/hexane 1:2). M.p. 56°. IR (KBr): 3068*w*, 2987*m*, 2910*w*, 1566*m*, 1447*m*, 1035*m*, 977*m*, 842*s*, 765*s*. ^{1}H-NMR (300 MHz, $CDCl_3$): 7.40–7.34 (*m*, 1 arom. H); 7.21–7.15 (*m*, 1 arom. H); 7.06–6.79 (*m*, 2 arom. H); 5.81 (br. *s*, H−C(4)); 5.44 (br. *s*, H−C(1)); 0.27 (*s*, Me_3Sn). ^{13}C-NMR (75 MHz, $CDCl_3$): 151.7; 147.9; 147.1 (two overlapping C); 125.7; 125.0; 120.6; 119.6; 89.2; 87.4; −9.4. GC/MS: 386 (12, M^+), 371 (14), 341 (7), 307 (52), 165 (92), 157 (90), 118 (100). Anal. calc. for $C_{13}H_{15}BrOSn$: C 40.46, H 3.92; found: C 40.44, H 3.95.

5,6,11,12,17,18-Hexahydro-5,18:6,11:12,17-triepoxytrinaphthylene (**4**). To a stirred soln. of **9** (1.93 g, 5.0 mmol) in anh. *N*-methylpyrrolidin-2-one (NMP; 25 ml) at −20°, copper(I) thiophene-2-carboxylate (CuTC; 1.43 g, 7.5 mmol) was added portionwise. The resulting slurry was maintained at this temp. for 30 min. Then, a 10% aq. soln. of NH_3 (20 ml) was added, and the mixture was stirred until the brown solid disappeared. The crude was extracted with Et_2O (3 × 20 ml), and the combined org. extracts were dried ($MgSO_4$) and concentrated *in vacuo*. The product was purified by FC (hexane/Et_2O 95:5): the first fraction contained the side product **7** (11 mg, 1%), and the the second and third fractions afforded *anti*-**4** (270 mg, 38% yield) and *syn*-**4** (334 mg, 47%), respectively.

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1) The calculated enthalpy of formation at the PM3 semi-empirical level [7] for *syn*- and *anti*-**4** was 106.442 and 106.472 kcal/mol, resp.

Data of syn-**4**. Colorless crystals. M.p. 274° (CH_2Cl_2/hexane 1 : 1). IR (KBr): 3056*w*, 3006*m*, 2929*w*, 1458*m*, 1266*m*, 985*s*, 842*s*, 758*s*. ^{1}H-NMR (300 MHz, $CDCl_3$): 7.18 – 7.14 (*AA'* part of *AA'BB'* system, 6 arom. H); 6.97 – 6.89 (*BB'* part of *AA'BB'* system, 6 arom. H); 6.15 (*s*, 6 H, H–C(5), H–C(6), H–C(11), H–C(12), H–C(17), H–C(18)). ^{13}C-NMR (50 MHz, $CDCl_3$): 146.9; 135.9; 126.8; 120.4; 80.9. Anal. calc. for $C_{30}H_{18}O_3$: C 84.49, H 4.25; found: C 84.51, H 4.29.

Data of anti-**4**. Colorless crystals. M.p. 255° (CH_2Cl_2/hexane 1 : 2). IR (KBr): 3068*w*, 2998*m*, 2928*w*, 1458*m*, 1354*w*, 1274*m*, 985*m*, 842*s*, 765*s*, 656*s*. ^{1}H-NMR (200 MHz, $CDCl_3$): 7.42 – 7.29 (*m*, 4 arom. H); 7.26 – 7.18 (*m*, 2 arom. H); 7.14 – 7.06 (*m*, 2 arom. H); 7.05 – 6.96 (*m*, 4 arom. H); 6.13, 6.09, 6.06 (3*s*, H–C(5), H–C(6), H–C(11), H–C(12), H–C(17), H–C(18)). ^{13}C-NMR (50 MHz, $CDCl_3$): 146.4 (two overlapping C); 146.4; 136.1; 135.7; 135.6; 126.43; 126.39; 126.3; 120.4; 120.3; 119.8; 80.6; 80.5; 80.4. Anal. calc. for $C_{30}H_{18}O_3$: C 84.49, H 4.25; found: C 84.46; H 4.26.

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