Tetrahedron Letters, Vol. 35, No. 1, pp. 73-76, 1994
Printed in Great Britain

0040-4039/94 $6.00 + .00
Pergamon Press Ltd

Synthesis of Sterically Rigid Macrocycles by the Use of Pressure-Induced Repetitive Diels-Alder Reactions

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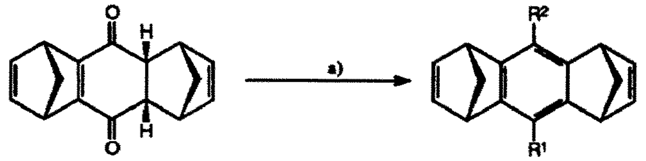
Keywords: Repetitive Diels-Alder reactions; bis-dienes; bis-dienophiles; *endo*-stereoselectivity

Abstract: Syntheses of the *syn*-dimethanotetrahydroanthracene and -tetracene derivatives **2a-d** and **6a,b** are described. Highly stereoselective, pressure-induced repetitive Diels-Alder reactions of these bis-dienophiles with bis-diene **7** lead to the sterically rigid macrocycles **10a**, **10d**, **13a** and **14a,b** having well defined cavities of different size.

Sterically rigid macrocycles having well defined cavities of different size should be able to form host-guest-complexes highly selectively. The investigations of non-covalent interactions in such model complexes and the comparison of the experimental data with force-field calculations can contribute to a better understanding of molecular recognition and enzyme activities. Here we report the synthesis of the macrocycles **10a**, **10d**, **13a**, **14a** and **14b** containing norbornane and benzene or naphthalene spacer-units. As already shown by Stoddart et al.[1a-c] for related oxygen-bridged systems, repetitive Diels-Alder additions of bis-dienophiles to bis-dienes should be useful as a "molecular LEGO set" to construct the desired macrocycles.

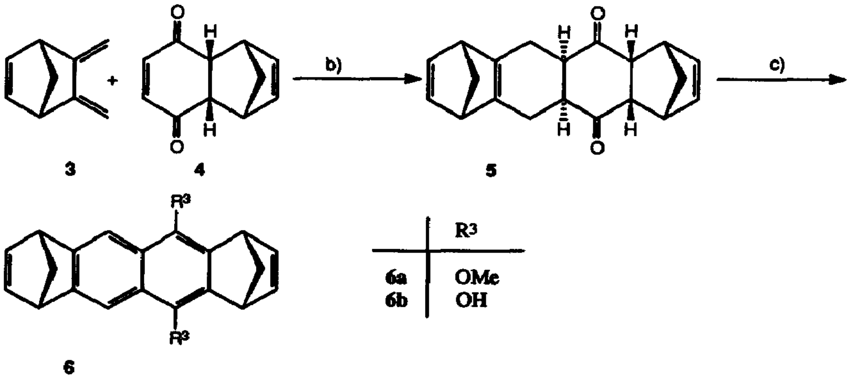
The synthesis of the suitable bis-dienophiles **2a-d** and **6a,b** having both methano-bridges *syn* to each other in all cases, starting from endione **1**[2] or bismethylenenorbornene **3**[3] and tetrahydromethanonaphthoquinone **4**[4] is outlined in Scheme 1 and Scheme 2.



1 **2**

	R1	R2
2a	OMe	OMe
2b	OH	OH
2c	OAc	OAc
2d	Me	OH

Scheme 1. Reaction conditions: a) **2a**: $(MeO_2)SO_2$, NaOH, H_2O, Ar, 2 d, 25°C; yield: 90%; **2b**: 1. NaOH, EtOH-H_2O, Ar; 5 min, 25°C; 2. HCl, H_2O; yield: 95%; **2c**: 1. pyridine, dimethylaminopyridine (DMAP), Ac_2O, Ar, 12 h, 40°C; 2. HCl, H_2O; yield: 96%; **2d**: 1. MeLi, Et_2O, Ar, 2 h, -78°C; 2. NH_4Cl, H_2O, 25°C; yield: 61%; 3. $LiN(iPr)_2$, Et_2O, Me_3SiCl, -18 to 25°C, 1 h; 4. H_2O, HCl, 25°C; yield: 73%; 5. MeOH, 40°C, 4 d; yield: 95%.



	R3
6a	OMe
6b	OH

Scheme 2. Reaction conditions: b) Toluene, 90°C, 4 d; yield: 75%; c) 1. Me_3SiCl, diazabicycloundecene (DBU), MeCN, 4 h, -10 to 25°C; 2. H_2O, HCl; yield: 95%; 3. Dichlorodicyano-p-benzoquinone (DDQ,) toluene, 2,4,6-trimethylpyridine, 25°C, 15 h; yield: 49%; **6a**: MeI, DBU, MeCN, 20 h, 25°C, then H_2O, HCl; yield: 86%; **6b**: DBU, MeCN, 1 h, 25°C, then H_2O, HCl; yield: 95%.

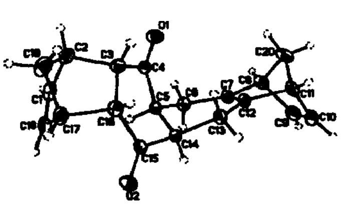
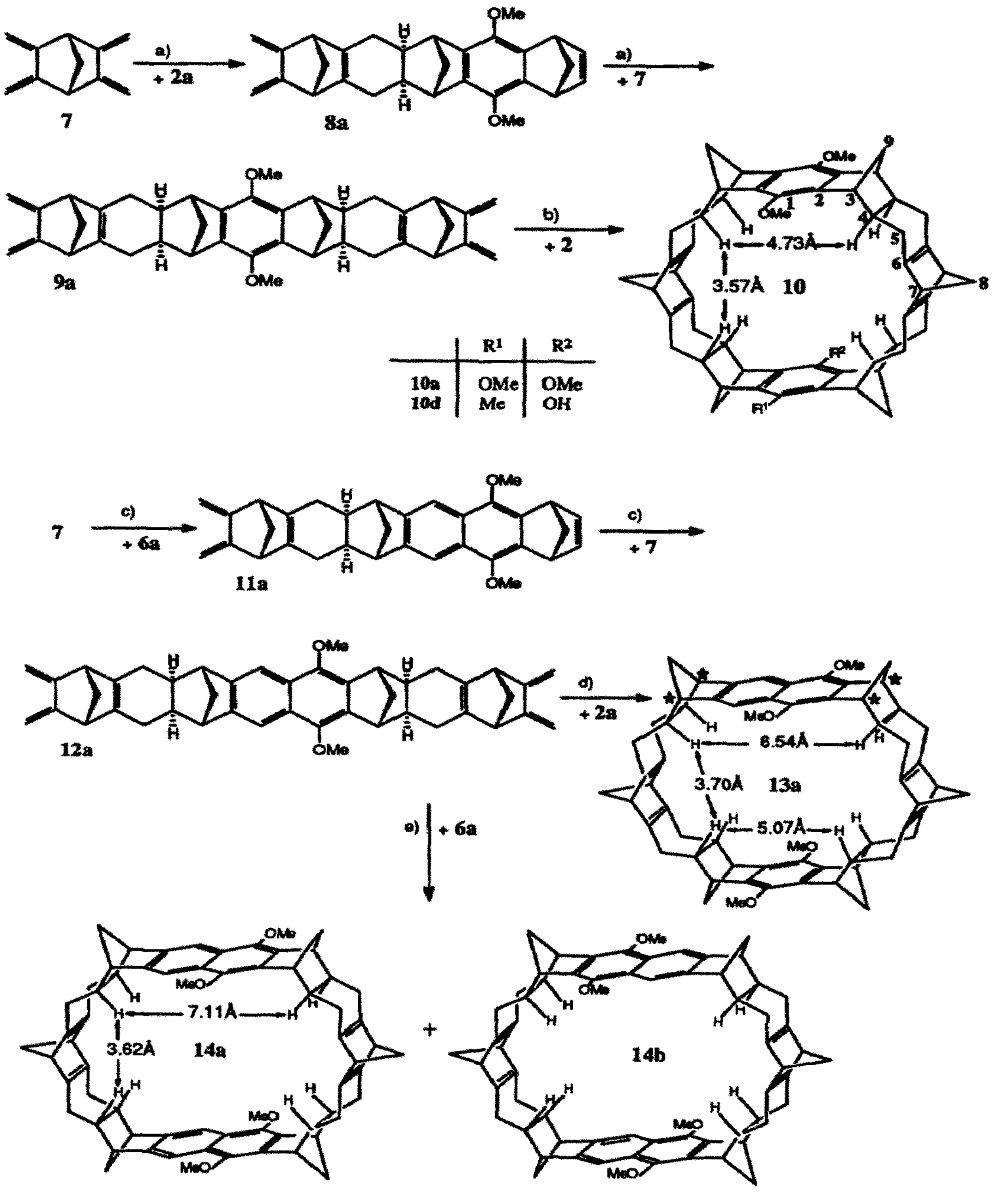


Fig. 1. X-ray analysis of 5.

The crucial step in the synthesis of **6a,b** is the stereoselective Diels-Alder reaction of **3** with **4** leading exclusively to the *syn*-adduct **5**. The structure of **5** could be assigned by a X-ray analysis[5] (Figure 1). The highly stereoselective *endo*-attack of the diene **3** found here is in accord with molecular orbital considerations and has also been observed in related Diels-Alder reactions[6a,b]. The addition of dienophile **4** occurs from its sterically less hindered side. If 5,8-dihydro-5,8-methano-1,4-naphtho-quinone[7] - the product of dehydrogenation of **4** - is used as a dienophile, the Diels-Alder reaction with **3** is stereounselective leading to a (62:38) mixture of the corresponding *syn*- and *anti*-adducts.

The bis-diene **7**[8] reacts with the bis-dienophile **2a** or **6a** at 125°C and ambient pressure leading to the monoadduct **8a** or **11a** and with an excess of **7** to the bisadduct **9a** or **12a** (Scheme 3). Due to the *endo*-selectivity of the bis-diene and the *exo*-selectivity of the bis-dienophile all methano-bridges in the Diels-Alder adducts are *syn* to one another. The new bis-dienes **9a** and **12a** show the same *endo*-stereoselectivity as **3** or **7** and react with the bis-dienophiles **2a**, **2d**, and **6a** in these cases, however, only at high pressure (8kbar, 125°C), leading to the desired macrocycles **10a**, **10d**, **13a**, **14a** and **14b**. The reaction of **12a** with **6a** gives a (1:1) mixture of **14a** and**14b** which, hitherto, could not be separated by means of chromatographic methods.

The pressure-induced Diels-Alder reaction of the bis-diene **12a** having a naphthalene spacer with the bis-dienophile **6a** having only a benzene spacer is remarkable. According to the consideration of simple molecular models these two reactants **12a** and **6a** should not fit into a cyclic array. Semiempirical quantummechanical AM1[9a] and PM3[9b] calculations show, however, that the central atoms of the naphthalene unit in **13a** can be bent out of the plane through the bridge-head carbon atoms labeled by asterisks. An outward deviation by 0.4 Å from that plane is sufficient for **13a** to be formed without building up too much strain, whereas the second spacer unit - the benzene ring - is almost planar (an inward deviation of the central atoms from planarity is calculated to be only 0.05 Å). In the symmetrical macrocycles **10** and **14** having each both spacer units of the same type no significant deviation of the arene units from planarity is predicted. To proof these predictions we are now trying to grow single-crystals of these macrocycles suitable for X-ray structure analyses.



	R1	R2
10a	OMe	OMe
10d	Me	OH

Scheme 3. The H-H distances of the macrocycles were derived from semiempirical quantum mechanical PM3 calculations of their corresponding hydrocarbons (the AM1 values do not differ significantly from the PM3 data). Reaction conditions: a) **9a**: toluene, NEt_3 , Ar, 125°C, 2.5 d; yield: 60%; b) **10a,d**: toluene / CH_3CN (8:2), Ar, 125°C, 8-10kbar, 4 d; yield: 50-60%; c) **12a**: toluene, NEt_3 , Ar, 125°C, 2.5 d; yield: 75%; d) **13a**: toluene, Ar, 125°C, 8-10kbar, 4 d; yield: 60%; e) **14a,b**: toluene, Ar, 125°C, 8-10kbar, 4 d; yield: 52%.

All new macrocycles were characterized by their spectral data. In the ^{1}H and ^{13}C NMR spectrum of **10a** (Table 1) the number and multiplicity of signals correspond to its high symmetry. The other macrocycles are less symmetric showing more complex spectra but their structures could be assigned unambiguously from the comparison of their spectra with those of **10a**.

Table 1. ^{1}H NMR (300 MHz, $CDCl_3$) and ^{13}C NMR (75 MHz, $CDCl_3$) Data of **10a**, **10d**, **13a** and **14a,b.**

10a: ^{1}H NMR: δ = 1.47 (m, 8 H, 4-H), 1.69 (dm, 4 H, 9-H), 1.91 (dm, 4 H, 9-H), 1.83-2.05 (m, 8 H, 5-H), 1.99 (m, 4 H, 8-H), 2.50 (dm, 8 H, 5-H), 3.04 (m, 4 H, 7-H), 3.07 (m, 8 H, 3-H), 3.82 (s, 12 H, $OC\underline{H}_3$); ^{13}C NMR: δ = 30.45 (CH_2, C-5), 43.04 (CH, C-4), 43.65 (CH_2, C-9), 47.22 (CH, C-3), 56.11 (CH, C-7), 61.35 ($O\underline{C}H_3$), 70.34 (CH_2, C-8), 137.97 (C, C-2), 142.59 (C, C-1), 149.16 (C, C-6); *the multiplicity of the ^{13}C signals were determined by using the DEPT procedure; the assignment is supported by 2D-NMR measurements (H-H- and C-H-COSY).*

10d: ^{1}H NMR: δ = 1.25 (s, 3 H), 1.35-1.5 (m, 8 H), 1.6-1.7 (m, 4 H), 1.85-1.95 (m, 16 H), 2.4-2.55 (m, 8 H), 2.90 (s, 2 H), 2.93 (s, 2 H), 3.04 (s, 6 H), 3.06 (s, 2 H), 3.82 (s, 3 H), 3.84 (s, 3 H), 4.22 (s, 1 H); ^{13}C NMR: δ = 14.71, 26.90, 29.37, 29.70, 30.44, 30.53, 30.65, 31.93, 42.41, 42.75, 42.77, 42.99, 43.83, 43.90, 45.95, 47.13, 47.41, 48.29, 56.16, 61.21, 61.85, 69.94, 115.59, 130.39, 137.92, 138.21, 139.39, 142.35, 142.97, 146.42, 149.43, 149.36, 149.44.

13a: ^{1}H NMR: δ = 1.25-1.67 (m, 10 H), 1.7-2.18 (m, 18 H), 2.4-2.65 (m, 8 H), 3.0-3.1 (m, 10 H), 3.32 (s, 2 H), 3.65 (s, 6 H), 3.9 (s, 6 H), 7.65 (s, 2 H); ^{13}C NMR: δ = 30.13, 30.44, 41.07, 41.42, 41.68, 42.35, 44.59, 44.69, 44.78, 46.54, 47.72, 47.88, 49.82, 56.12, 61.03, 61.83, 70.80, 112.70, 127.41, 135.37, 137.88, 143.15, 144.45, 146.78, 146.98, 147.67, 147.97, 149.78, 149.90.

14a,b: ^{1}H NMR: δ = 1.38-1.5 (m, 2•12 H), 1.62-1.78 (m, 2•4 H), 1.90-2.10 (m, 2•8 H), 2.98 (m, 2•4 H), 3.13 (m, 2•4 H), 3.25 (m, 4 H), 3.80 (s, 12 H), 3.82 (s, 12 H), 7.57 (s, 4 H), 7.58 (s, 4 H).

Acknowledgement: We are grateful to the Deutsche Forschungsgemeinschaft and Fonds der Chemischen Industrie for financial support. We thank Mr. Heinz Bandmann for performing the NMR measurements.

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5. *X-ray structure determination of 5: crystal dimensions:* 0.65×0.58×0.41 mm^3, *colorless, Nicolet* R3m/V *diffractometer,* Mo-K_α*-radiation,* T = 293 K, *monoclinic,* a = 20.800(2), b = 6.170(1), c = 14.524(2) Å, β = 127.95(1), V = 1469.8(3) Å^3; Z = 4, d_{cal} =1.321 gcm^{-3}, μ = 0.08 mm^{-1}, SG: Cc, 4300 *unique intensities* ($2\theta_{max}$ = 50°), 4126 *observed* ($F_0 \geq 4\sigma(F)$), *extinction correction,* 201 *parameters refined, riding groups for all hydrogen atoms; common isotropic U-values for each group* R = 0.0349, R_w = 0.0366, $w^{-1} = \sigma^2(F_0) + 0.001 \bullet F_0^2$, *maximum residual electron density* 0.46 e/Å^3. *Further details of the crystal structure investigation are available on request from the Fachinformationszentrum Energie Physik Mathematik,* D-76344 *Eggenstein-Leopoldshafen, on quoting the depository number* CSD 400374, *the authors names, and the full citation of the journal.*
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(*Received in Germany* 14 *October* 1993; *accepted* 2 *November* 1993)