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Synthesis of the *syn* and *anti* isomer of 1,4,5,8,9,12-hexahydro-2,3,6,7,10,11-hexamethylidene-1,4:5,8:9,12-trimethanotriphenylene and Diels–Alder reactivity of the *syn* isomer

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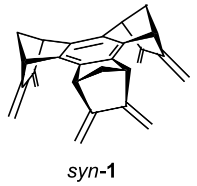
Abstract—The title compounds, new members in the class of tris-annelated benzenes with [2.2.1] bicyclic rings, were obtained in high yields by coupling of 2-bromo-3-trimethyltin-5,6-dimethylenenorborn-2-ene with copper(I) 2-thiophenecarboxylate (CuTC). The *syn* isomer was reacted with 3 equiv. of the dienophiles TCNE, DMAD, PTAD and norbornadiene to afford the corresponding cycloadducts. © 2002 Elsevier Science Ltd. All rights reserved.

Benzene rings annelated with three [2.2.1] bicyclic moieties present excellent characteristics as potential host molecules in the field of supramolecular chemistry. These compounds come into two configurations, *syn* (where the methano bridges are co-oriented) and *anti*. Quite evidently, the *syn* isomers offer better features as host structures.

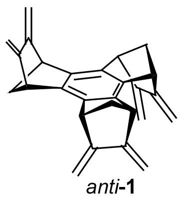
These molecules can be synthesized by coupling of three *vic*-bromotrimethylstannyl[2.2.1]bicyclo olefins, mediated by copper salts.[1] The statistical 1:3 *syn* to *anti* ratio is frequently even more in favour of the *anti* isomer because of the steric hindrance of the 'arms'. Therefore, *syn* trimers with long and functionalized 'arms', which appear as most interesting host molecules, may be generated in negligible quantity with respect to the *anti* isomers. One possible way out of this problem is the synthesis of *syn* trimers with short 'arms', however functionalized with groups which may allow their lengthening. The feasibility of this project was tested with the title compound **1** in the *syn* configuration, by the reaction of the heterocyclic dienic groups with selected dienophiles.

The synthesis of the tris-annelated benzenes **1** was accomplished by cyclotrimerization of the monomer **5**. In turn, the monomer was obtained with the synthetic path presented in Scheme 1.

The Diels–Alder addition of the *E*:*Z* mixture of 1,4-dichloro-2-butene to cyclopentadiene gave the two isomers of 5,6-di(chloromethyl)bicyclo[2.2.1]hept-2-ene **2**.[2] Bromination afforded the mixture of dibromides **3**,[3] that was subjected to exhaustive dehydrohalogenation with KOH in refluxing ethanol, yielding **4** as the sole species. Bromide **4** was lithiated by a twofold excess of lithium diisopropylamide in the presence of trimethyltin chloride to give the properly functionalized triene **5**.



syn-**1**



anti-**1**

The cyclotrimerization reaction was a crucial step. Early attempts with the $Cu(NO_3)_2 \cdot 3H_2O$ promoter failed to afford the desired cyclotrimers, leading to the formation of complex mixtures of products (the characterized products were the protodestannylated monomer **4** and the dibromodimers **6**, in the C_s and C_2 configuration).

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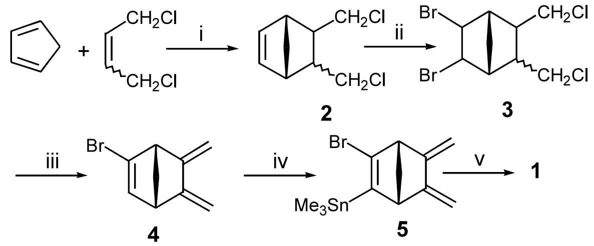
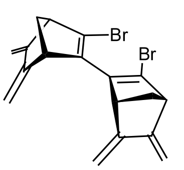
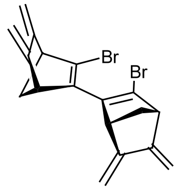


Scheme 1. *Reagents, conditions (yields):* i: benzene, 175°C (40%); ii: Br_2, CCl_4, 70°C (98%); iii: KOH, EtOH, reflux (70%); iv: LDA, Me_3SnCl, THF, rt (90%); v: CuTC, NMP, rt (98%).



C_S-**6**



C_2-**6**

At variance, the reaction of the monomer **5** with a stoichiometric amount of copper(I) 2-thiophenecarboxylate (CuTC)[4,5] in NMP afforded a 1:4 mixture of *syn* and *anti* cyclotrimers **1** in almost quantitative yield.[6] Because of the small steric hindrance exerted by the exocyclic dienic system, the isomer ratio is not too far from the statistical 1:3 ratio. The isomers were separated by chromatography (silica gel, eluant dichloromethane–hexanes 3:7) and recrystallized from methanol.

The characterization of the two isomers rests on NMR.[6] Particularly informative are the patterns and the number of signals in ^1H and ^{13}C spectra which reflect the C_{3v} and C_s symmetries of *syn*-**1** and *anti*-**1**.

The Diels–Alder reactivity of *syn*-**1** was tested toward strong dienophiles, as TCNE, dimethylacetylene dicarboxylate (DMAD), PTAD and $^1O_2$, and also toward the weaker norbornadiene. Conditions and results are reported in Table 1. The tris-adducts *syn*-**7**, *syn*-**8**, *syn*-**9** and *syn*-**10** have been fully characterized by the usual NMR techniques.[6]

syn-**1** Proved to be less reactive than the monomeric subunits 5,6-dimethylidenebicyclo[2.2.1]hept-2-ene or 2,3-dimethylidene-1:4-methanonaphthalene,[7] requiring drastic conditions. The reaction with $^1O_2$, by irradiation of *syn*-**1** in $CDCl_3$ for 2 h with visible light (100 W) under O_2 bubbling and in the presence of catalytic amounts of TPP, led to the formation of non-symmetrical intermediates that decomposed upon further irradiation.

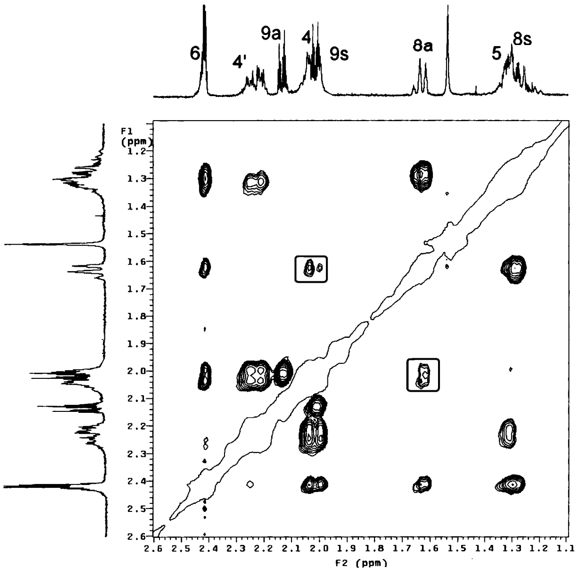
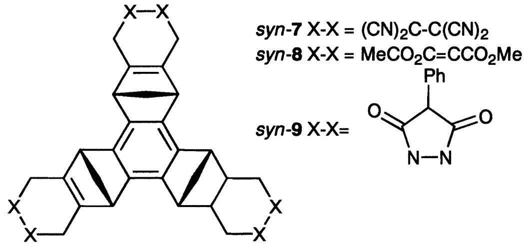
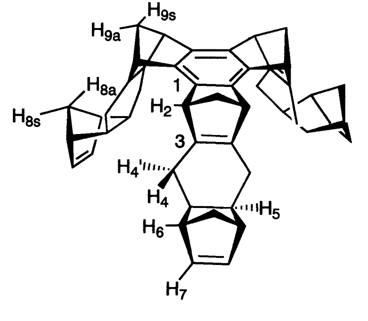


Figure 1. Part of the NOESY spectrum of *syn*-**10**. The dipolar interactions between proton H_{8a} and protons H_4 are highlighted.





syn-**10**

Table 1. Results of the Diels–Alder additions to *syn*-**1**

Dienophile	Solvent	Dienophile:*syn*-**1** ratio	Adduct	Temp. (°C), time (h)	Yield (%)
TCNE	$CHCl_3$	3:1	*syn*-**7**	25, 0.3	100
DMAD	$CHCl_3$	3:1	*syn*-**8**	25, 0.3	100
PTAD	$CHCl_3$	3:1	*syn*-**9**	100, 48	50
$^1O_2$	$CDCl_3$	Excess	[a]	25, 2	–
Norbornadiene	Neat	Excess	*syn*-**10**	100, 7	70

[a] Unrecognized decomposition products.

Although a weak dienophile, norbornadiene added to *syn*-**1** with satisfactory yield. Remarkably, the reaction is highly stereoselective: the tris-adduct *syn*-**10** could be recovered as major product, where the methano bridge belonging to former *syn*-**1** and the methano bridge belonging to former norbornadiene are co-oriented. The orientation is demonstrated by the detection (by NOESY, see Fig. 1) of dipolar interactions between the 'inner' proton of the methano bridge in the norbornene moiety (H_{8a} in structure *syn*-**10**) and two methylene protons of the cyclohexene ring (H_4). For steric reasons, norbornadiene can only approach the *exo* face of the dienic systems of *syn*-**1**. Stabilizing secondary orbital interactions (phase concordance) are possible between the LUMO of the dienic system of *syn*-**1** and the HOMO of norbornadiene, either with the contribution to this orbital of the outer π(CH=CH) system (*endo* approach of norbornadiene), or with the $\pi(CH_2)$ contribution (*exo* approach).[8] The *exo* approach appears to be sterically less demanding, leading to the tris-adduct *syn*-**10**.

Acknowledgements

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6. *syn*-**1**: mp 250°C (dec.); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.05 (6H, s), 4.91 (6H, s), 3.84 (6H, t, $J=1.6$ Hz), 2.05 (3H, dt, $J=8.6$, 1.6 Hz), 1.91 (3H, dt, $J=8.6$, 1.6 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 148.10, 135.65, 101.87, 51.27, 50.25. *anti*-**1**: mp 230°C (dec.); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.18 (2H, s), 5.113 (2H, s), 5.107 (2H, s), 5.05 (2H, s), 5.01 (2H, s), 4.96 (2H, s), 3.86 (2H, m), 3.837 (2H, m), 3.833 (2H, m), 2.01 (2H, dt, $J=8.6$, 1.5 Hz), 1.95 (1H, dt, $J=8.6$, 1.5 Hz) 1.89 (2H, dt, $J=8.6$, 1.6 Hz), 1.86 (1H, dt, $J=8.6$, 1.7 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 149.25, 149.08, 148.15, 136.56, 135.82, 135.80, 101.89, 101.72, 101.57, 50.98, 50.74, 50.33, 50.27, 50.17. *syn*-**10**: mp 215°C (dec.); ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 5.99 (6H, m, H_7), 3.51 (6H, t, H_2, $J=1.6$ Hz), 2.42 (6H, t, H6, $J=1.8$ Hz), 2.23 (6H, m, $H_{4'}$), 2.14 (3H, dt, H_{9a}, $J=6.9$, 1.6 Hz), 2.02 (6H, m, H_4), 2.01 (3H, dt, H_{9s}, $J=6.9$, 1.6 Hz), 1.63 (3H, dt, H_{8a}, $J=8.3$, 1.7 Hz), 1.30 (6H, m, H_5), 1.29 (3H, dt, H_{8s}, $J=8.3$, 1.7); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 146.23 (6C, C_3), 137.27 (6C, C_7), 137.10 (6C, C_1), 62.44 (3C, C_9), 50.86 (6C, C_6), 50.56 (6C, C_2), 44.29 (3C, C_8), 37.83 (6C, C_5), 29.73 (6C, C_4). The assignments refer to the non-IUPAC numbering reported with the structure.
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