



## Novel and versatile protocol for the preparation of functionalized benzocyclotrimers

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### ABSTRACT

2-Bromo-3-(trimethylstannyl)cyclopenta-1,3-diene is the key-intermediate for the synthesis of vic-bromo(trimethylstannyl)bicycloolefins via Diels–Alder reaction with dienophiles. The cycloadducts can be cyclotrimerized by copper(I) 2-thiophenecarboxylate (CuTC) to afford functionalized benzocyclotrimers.

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Highly functionalized benzocyclotrimers are valuable substrates for supramolecular chemistry.<sup>1,2</sup> Even though in recent years the preparation of such molecules has been greatly improved, the synthesis of precursors bearing the moieties able to impart supramolecular behavior is sometimes troublesome. Cyclotrimerization of vic-bromo(trimethyltin)olefins mediated by copper 2-thiophenecarboxylate (CuTC)<sup>3</sup> is the most general methodology to accomplish this reaction.<sup>4</sup> The alternative Heck-type methodology of bicyclic vinyl iodides or bromides fails to afford cyclotrimers in the presence of further unsaturations.<sup>5</sup> The key intermediate **1** for the synthesis of a general class of substituted cyclotrimers **2** can be ideally obtained from three approaches: (a) functionalization of the cycloadduct of cyclopentadiene with the dienophile of interest, and functionalization of the ethylidene moiety; (b) cycloaddition of a synthetic equivalent of 1-bromo-2-(trimethyltin)ethyne with a suitably substituted diene **5**; (c) Diels–Alder reaction between a suitable dienophile **6** and 2-bromo-3-(trimethylstannyl)cyclopenta-1,3-diene **7** (Fig. 1).

Strategy (a) provided a large number of cyclotrimers, but it requires poorly selective reagents, such as bromine or strong bases, consequently it is scarcely applicable to functionalized products.<sup>2c,4,6</sup> 1-Bromo-2-(trimethyltin)ethyne<sup>7</sup> **4**, which is critical in route (b), is a poor dienophile for Diels–Alder reactions, and the design of an effective synthetic equivalent of **4** is object of research

in our laboratories.<sup>8</sup> The last proposed retro-synthetic disconnection (c) is based on the availability of the key intermediate **7**.<sup>9</sup> In this Letter, we describe a practical synthesis of **7** and its general utility for the synthesis of variously substituted cyclotrimers.

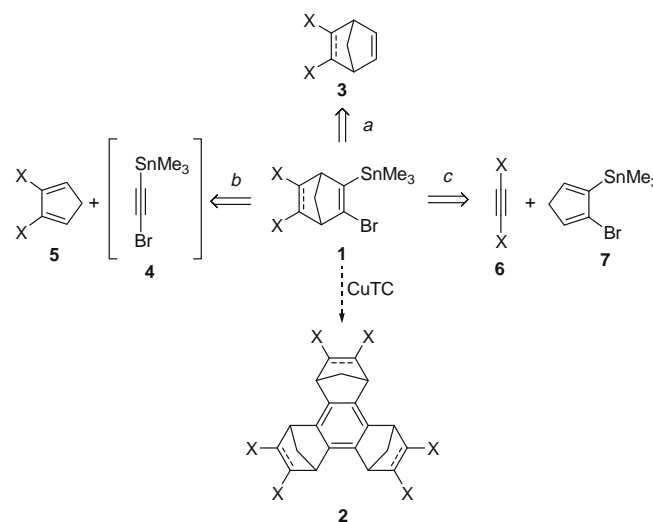
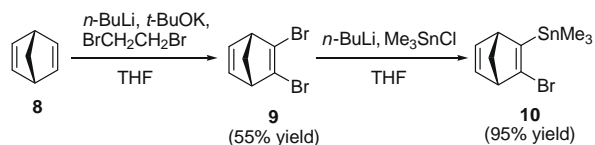
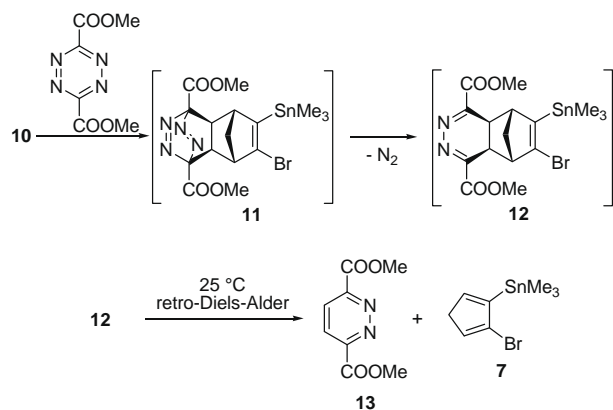


Figure 1. Possible strategies leading to precursors of cyclotrimers.

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**Scheme 1.** Synthesis of the stannylated precursor of cyclopentadiene 7.



**Scheme 2.** Tetrazine route leading to cyclopentadiene 7.

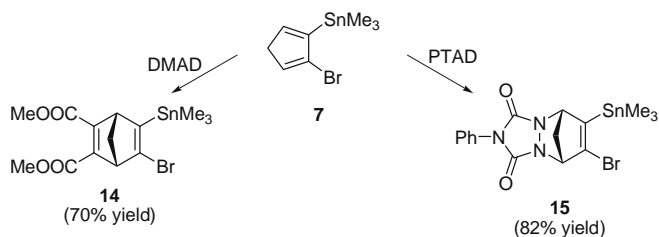
The protocol starts with the synthesis of the 2,3-dibromobicyclo[2.2.1]hepta-2,5-diene **9** from commercially available norbornadiene **8**, according to reported procedures based on the use of potassium *tert*-butanolate/*n*-butyllithium super-base.<sup>10</sup> The trimethyltin moiety is introduced at this stage, via a metal-halogen exchange operated with *n*-butyllithium at  $-78\text{ }^{\circ}\text{C}$  (Scheme 1).<sup>6b</sup>

The resulting *vic*-bromo(trimethyltin)norbornadiene **10** is submitted to cycloaddition with dimethyl 1,2,4,5-tetrazine-3,6-dicarboxylate,<sup>11</sup> to afford cycloadduct **11** that undergoes facile retro-Diels-Alder with loss of nitrogen to furnish intermediate **12** (Scheme 2).<sup>12</sup> A second retro-Diels-Alder reaction spontaneously occurs affording pyridazine **13** and substituted cyclopentadiene **7** which can be easily isolated.<sup>13</sup>

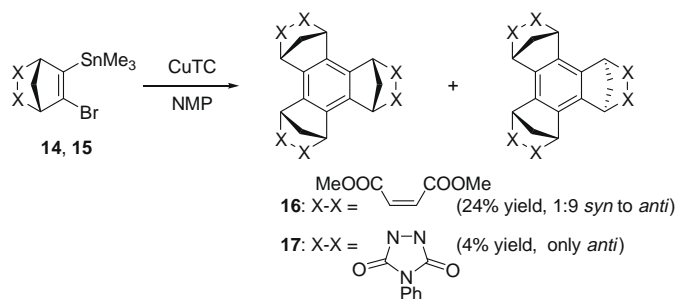
Cyclopentadiene **7** cannot be stored for a prolonged time; therefore, after rapid isolation it is reacted with electron-poor olefins at room temperature. The cycloaddition is generally smooth and exothermic, furnishing the expected cycloadducts in a few hours (Scheme 3).<sup>14</sup>

The PTAD cycloadduct **15** is crystalline and it is readily purified by fractional crystallization, alternatively product **14** is isolated after a fast filtration on a short silica-gel pad.<sup>15</sup>

Cyclotrimers **16** and **17** were obtained after reaction with CuTC in dry NMP at  $-20\text{ }^{\circ}\text{C}$  (Scheme 4).<sup>16</sup> The *syn* to *anti* diastereoselectivity and the yields of the products strictly reflect the steric hindrance of the substituents. In detail, **14** furnished a 1:9 *syn* to *anti* mixture of **16**: this unfavorable diastereomeric ratio is imputable to the steric repulsion between the carboxymethyl moieties



**Scheme 3.** Diels-Alder reactions leading to cyclotrimerization precursors.



**Scheme 4.** Copper-mediated reactions leading to benzocyclotrimers.

acting on the plane of the ethylidene fragment of the bicycle.<sup>17</sup> More striking is the effect of the *endo*-cycloadduct of PTAD **15**: in this case, the sole *anti*-cyclotrimer **17** was obtained.

In conclusion, we proposed an original and versatile protocol for the preparation of highly functionalized precursors of benzocyclotrimers. These compounds were submitted to standard procedure for the cyclotrimerization, affording two original functionalized benzocyclotrimers, which will be further investigated as supramolecular scaffolds.

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13. Dimethyl 1,2,4,5-tetrazine-3,6-dicarboxylate (770 mg, 3.89 mmol) was added to a solution of **10** (1.30 g, 3.89 mmol) in DCM (20 mL), and the mixture was stirred for 15 min at room temperature. The solvent was removed in vacuum at 0 °C, *n*-hexane (50 mL) was added, and the resulting slurry was filtered, washing the solid residue with *n*-hexane (2 × 50 mL). The resulting solution was concentrated at 0 °C to afford **7** (1.20 g, 100%): colorless oil. <sup>1</sup>H NMR (200 MHz, CDCl<sub>3</sub>): δ 6.55 (m, 1 H), 6.45 (m, 1 H), 3.02 (m, 2 H), 0.30 (s, 9 H). <sup>13</sup>C NMR (50 MHz, CDCl<sub>3</sub>): δ 151.8, 146.8, 132.7, 129.0, 46.1, –7.0. GC-MS (70 eV) *m/z* = 308 (M<sup>+</sup>, 5), 263 (6), 199 (20), 165 (100%). The intensity of <sup>1</sup>H NMR signals halved after 24 h at rt. This decrease was accompanied to the appearance of a complex set of other signals that can be attributed to the tautomers resulting from the [1,5]sigmatropic shift of the 1,3-cyclopentadienic skeleton. No Diels–Alder dimeric products were detected by GC-MS in the mixtures.
14. *General procedure for the cycloaddition of 7 to dienophiles.* Freshly prepared **7** (500 mg, 1.62 mmol) was dissolved in DCM (15 mL), and the dienophile (1.62 mmol) was added. The mixture was stirred at room temperature for 1–4 h. Volatile materials were removed and the residue was purified by filtration on florisil or silica-gel.
15. Compound **14**: colorless oil. <sup>1</sup>H NMR (200 MHz, CDCl<sub>3</sub>): δ 4.00 (m, 1 H), 3.95 (m, 1 H), 3.79 (s, 3 H), 3.78 (s, 3 H), 2.25 (m, 2 H), 0.25 (s, 9 H). <sup>13</sup>C NMR (50 MHz, CDCl<sub>3</sub>): δ 167.2, 166.3, 154.5, 152.6, 151.3, 148.8, 72.6, 65.0, 62.3, 54.0, 53.9, –7.3. Compound **15**: mp = 157–159 °C (DCM/*n*-hexane). <sup>1</sup>H NMR (200 MHz, CDCl<sub>3</sub>): δ 7.49–7.32 (m, 5 H), 5.10 (bs, 2 H), 2.22 (d, *J* = 9.1 Hz, 1 H), 2.17 (d, *J* = 9.1 Hz, 1 H), 0.26 (s, 9 H). <sup>13</sup>C NMR (50 MHz, CDCl<sub>3</sub>): δ 160.6, 159.5, 147.6, 133.5, 133.4, 131.0, 130.3, 127.4, 73.8, 72.1, 50.5, –7.5.
16. *anti-16*: mp = 250–252 °C (EtOAc/cyclohexane). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ (ppm): 4.35 (q, *J* = 1.7 Hz, 2 H), 4.34 (t, *J* = 1.5 Hz, 2 H), 4.29 (q, *J* = 1.7 Hz, 2 H), 3.78 (s, 6 H), 3.765 (s, 6 H), 3.760 (s, 6 H), 2.50 (dt, *J* = 8.0, 1.7 Hz, 2 H), 2.47 (dt, *J* = 8.1, 1.7 Hz, 1 H), 2.13 (dt, *J* = 8.0, 1.7 Hz, 2 H), 2.12 (dt, *J* = 8.1, 1.7 Hz, 1 H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ (ppm): 165.0, 164.9, 164.5, 150.3, 150.2, 149.6, 137.8, 137.7, 137.5, 64.9, 64.0, 52.1, 52.01, 52.00, 51.0, 50.9, 50.7. *syn-16*: mp = 289–290 °C (DCM/cyclohexane), 7.2 mg (2% yield). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ (ppm): 4.34 (t, *J* = 1.5 Hz, 6 H), 3.75 (s, 18 H), 2.57 (dt, *J* = 7.9, 1.5 Hz, 3 H), 2.17 (dt, *J* = 7.9, 1.5 Hz, 3 H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ (ppm): 164.5, 149.7, 137.4, 66.7, 51.9, 50.9. *anti-17*: mp = >300 °C dec. (DCM/*n*-hexane). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ (ppm): 7.38–7.30 (m, 3 H), 7.25–7.17 (m, 6 H), 7.07–7.02 (m, 4 H), 6.86–6.80 (m, 2 H), 5.81 (br s, 2 H), 5.76 (br s, 2 H), 5.73 (br s, 2 H), 2.81 (dt, *J* = 10.5, 1.4 Hz, 1 H), 2.70 (dt, *J* = 10.2, 1.7 Hz, 2 H), 2.23 (dt, *J* = 10.5, 1.4 Hz, 1 H), 2.13 (dt, *J* = 10.2, 1.7 Hz, 2 H); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ (ppm): 158.5, 157.9, 156.3, 133.6, 133.4, 131.4, 130.9, 129.33, 129.31, 128.8, 128.4, 125.1, 124.7, 62.6, 62.6, 62.3, 50.6, 48.4.
17. Favorable diastereoisomeric ratio was observed when a coordinating group is present in the apical position, presumably because of a template effect on the cyclotrimerization reaction: Ref. 9.