

## Stereocontrol in Nickel Mediated Syntheses of Cyclobutabenzenes. The Selective preparation of *Cis* and *Trans* Derivatives of 7,8-Dibromocyclobutabenzene.

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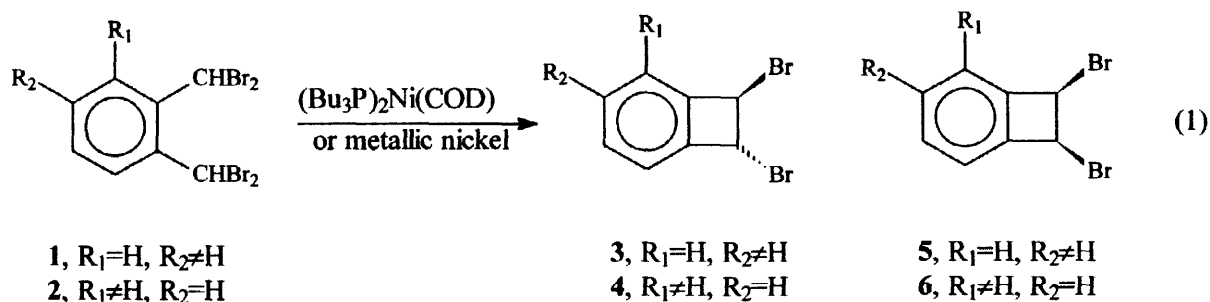
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**Abstract:** Most  $\alpha,\alpha,\alpha',\alpha'$ -tetrabromo-*o*-xylenes that are substituted at the *ortho* and *meta* positions yield, upon applying nickel mediated cyclization conditions, the respective *trans*-7,8-dibromocyclobutabenzenes derivatives as major products. However, when the *ortho* substituent is an ester or an amide, a good stereochemical control can be achieved by running the reactions with or without the presence of phosphines. The bromine atom at the 7 position can be substituted specifically with inversion by methoxy, yielding the 7-Br-8-OMe respective cyclobutabenzene, that can be reacted in a stereospecific Diels-Alder reaction to form the *cis*-bromo-methoxy-tetrahydronaphthalene derivative.

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### INTRODUCTION.

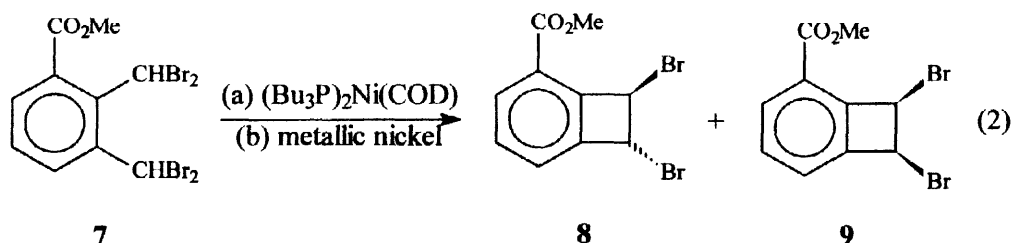
Cyclobutabenzenes are important compounds; they serve as synthons for *ortho*-xylylenes (*o*-quinodimethanes) in organic synthesis,<sup>1</sup> as building blocks in some natural compounds and drugs,<sup>2</sup> and as key compounds for the study of the Mills-Nixon effect.<sup>3</sup> The most common method for their preparation is based on iodide mediated ring closure of  $\alpha,\alpha,\alpha',\alpha'$ -tetrabromo-*o*-xylene, that yields a mixture of *cis* and *trans* dibromo-, diiodo- and iodo-bromocyclobutabenzenes.<sup>4</sup> Other methods are based on pyrolysis under relatively harsh conditions<sup>5</sup> or are system specific.<sup>6</sup> Recently, we have developed a new method that is based on nickel mediated ring closure of  $\alpha,\alpha,\alpha',\alpha'$ -tetrabromo-*o*-xylenes.<sup>7</sup> The main advantages of this method are the following: (i) The reaction does not path through *o*-quinodimethane as an intermediate, and thus it is suitable for the preparation of bicyclobutabenzene<sup>8</sup> and tricyclobutabenzene.<sup>9</sup> (ii) The reaction is stereospecific. (iii) The starting materials are commercially available or can be easily made in large quantities and good yields. (iv) The conditions for the preparation of the cyclobutabenzenes are relatively mild, i.e., a temperature range of 60–80 °C and DMF as a solvent or co-solvent. Most of the system studied (of the type 1 and 2)<sup>10</sup> yield, under nickel mediated cyclization conditions, the respective *trans* dibromocyclobutabenzenes (3 or 4) as the major product, and the *cis* isomer (5 or 6, respectively), as the minor product, with a selectivity  $\geq 9:1$  (equation 1). The *trans* isomers are usefull synthons for *ortho*-quinodimethanes, that can be trapped by dienophiles in stereo- and regiospecific Diels-Alder reactions to yield the respective tetrahydronaphthalene products, whereas the *cis*



isomer is stable under the Diels-Alder reactions conditions.<sup>7,8,10</sup> However, in some cases the opposite stereochemistry of the dibromocyclobutabenzene was observed, and most of the product was *cis*-dibromocyclobutabenzene. We report here the selective preparation of some systems of the type 4 and 6, where a simple control of the stereochemistry of the reaction was achieved. We also report the selective substitution of the bromine atom at the 8 position by methoxy, to give the respective *trans*-7-methoxy-8-bromocyclobutabenzene, and its reaction with tetracyanoethylene.

## RESULTS AND DISCUSSION.

When 7 was subjected to  $(Bu_3P)_2Ni(COD)$  cyclization conditions the major products was 8, with



8:9 ratio of 3:1 (equation 2a). However, when the mediator was nickel powder, the main product was 9 when the solvent was hexane,<sup>11</sup> and the only product when THF was used as a solvent<sup>11</sup> (equation 2b). In

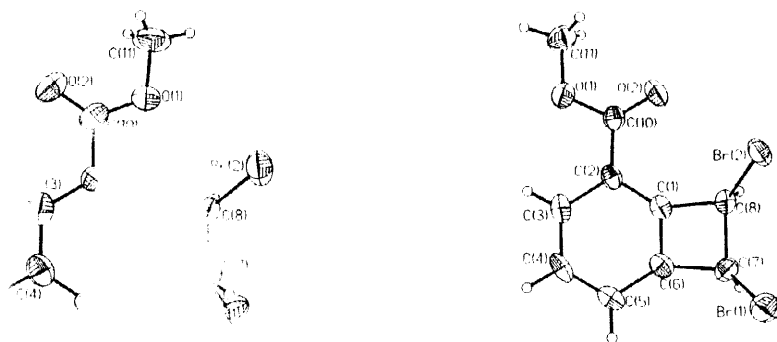
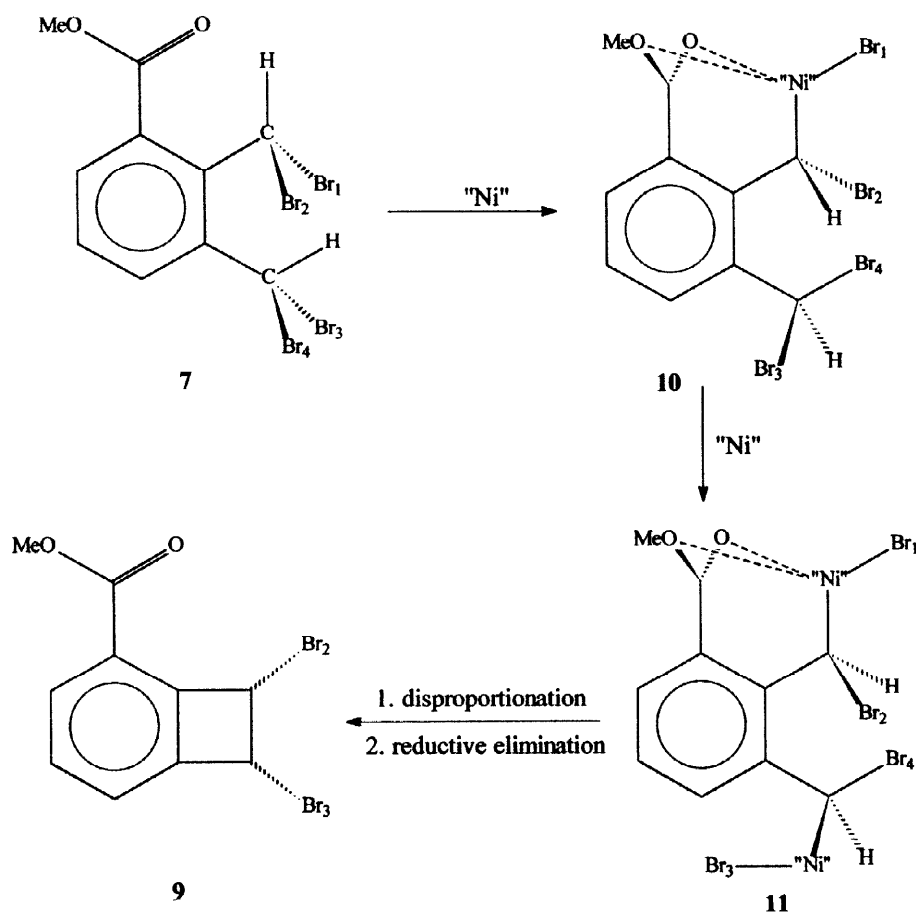


Figure 1: Ellipsoid plots of 8 and 9 (right).

order to be sure that the NMR based assignments are correct, each of the major products of the reactions was crystallized, and the structure determined (figure 1). The X-ray structure confirmed the NMR based assignment of the product. Such a sharp dependence of the *trans* to *cis* products ratio on the mediator (i.e.,  $(\text{Bu}_3\text{P})_2\text{Ni}(\text{COD})$  or metallic nickel) has not been observed for other substrates that were cyclized, and this observation needed an explanation.

A mechanistic analysis of the reaction of metallic nickel with 7 is described in scheme 1. Insertion

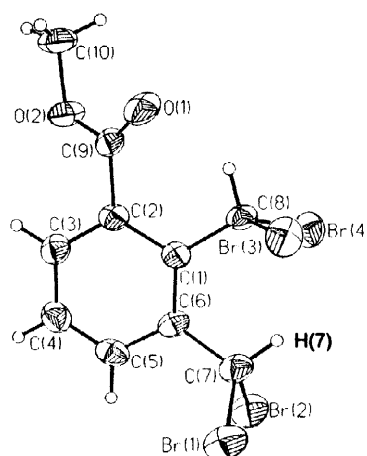


**Scheme 1.** Proposed mechanism for the metallic nickel mediated ring closure of 5. "Ni" = solvated Ni(0) atom

of a nickel species into one of the C-Br bonds is thought to be the first step in nickel mediated coupling.<sup>12</sup> In the case of 7, insertion of the Ni to the C-Br<sub>1</sub> bond leads to 10, where the nickel is stabilized by internal complexation to ester group. This requires a rotation around the C<sub>(arom)</sub>-C<sub>(NiBr)</sub>. Since the size of Br is similar the that of methyl (van-der-Wals radii are 1.95 and 2.0 Å, respectively), and therefore CHBr<sub>2</sub> is similar to *i*-propyl, it is assumed that the two CHBr<sub>2</sub> are "geared".<sup>13</sup> The second CHBr<sub>2</sub> group has therefore to rotate, resulting in hindering Br<sub>4</sub> while Br<sub>3</sub> is exposed. Steric congestion around Br<sub>4</sub> forces the second nickel<sup>12</sup> to insert into the exposed C-Br<sub>3</sub> bond (to form 11), yielding after disproportionation and reductive elimination the *cis* product 9. The internal complexation of the nickel (in 10) must be important only if the nickel atom is not ligated (or bound to weak ligands such as DMF) since that in the case of the

reaction mediated by  $(\text{Bu}_3\text{P})_2\text{Ni}(\text{COD})$  the reaction yields the thermodynamically more stable *trans* product (**8**) which can be achieved only if free rotation around the  $\text{C}(\text{HBr}_2)\text{-C}(\text{aromatic})$  bond (i.e. the internal complexation is unimportant) exists.

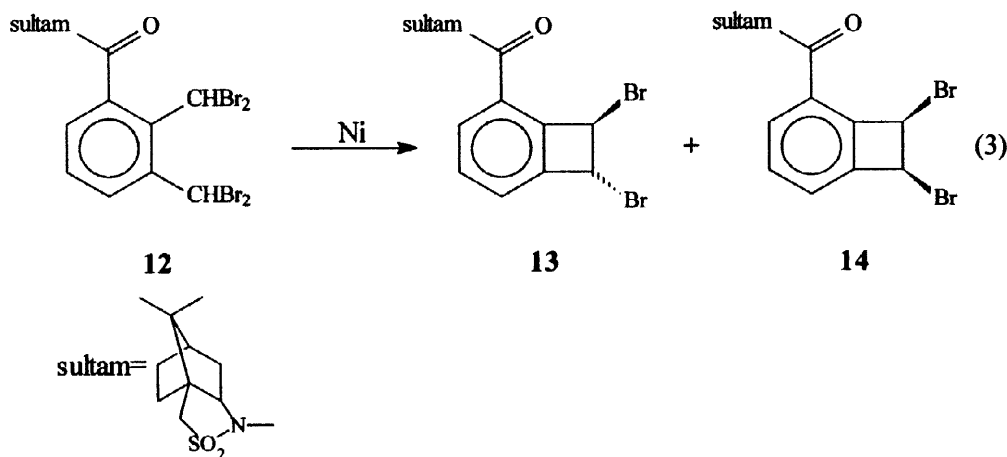
The explanation above depends on the existence of the "gear effect" in **7**. Thus, **7** was crystallized and structurally studied (figure 2). Indeed, the two  $\text{CHBr}_2$  groups are "geared". The distances between  $\text{H}_7$



**Figure 2:** Ellipsoid plot of **7**.

and  $\text{Br}_3$  and  $\text{Br}_4$  are 2.802 and 2.615 Å, respectively, well below the sum of vdW radii of H and Br (3.05 Å).

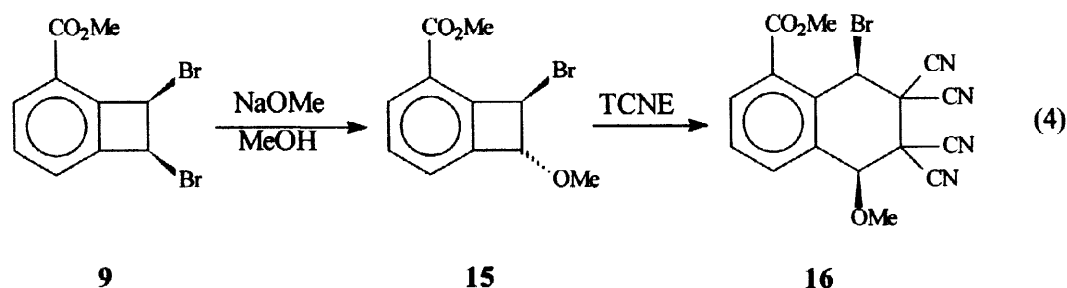
The mechanistic discussion presented above with the support of the structural information of **7** suggests two immediate conclusions. (a) If the cyclization reaction that is mediated by metallic nickel would be carried out in the presence of a strong ligand, the major product should be the *trans* isomer (i.e., **8**). (b) Other substituents that are capable of complexing the nickel (e.g., an amide) should exhibit similar



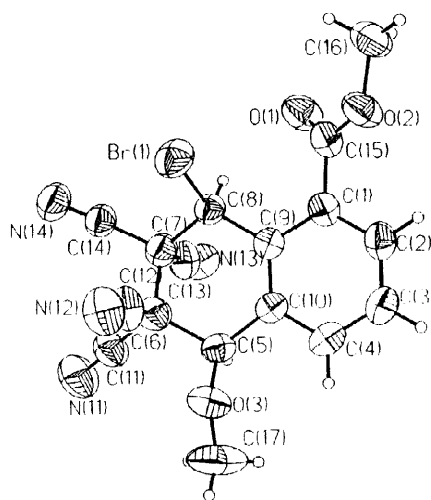
behavior to **7**. In order to verify point (a), the cyclization reaction described in equation 2b was carried out in the presence of two equivalents of tributylphosphine. The ratio between **8** and **9** was reversed; whereas without phosphine the product ratio **8:9** is 1:4, with two equivalents of phosphine it is 4.3:1. To study point (b) the cyclization reaction of **12** was carried out without and with phosphine (equation 3); in the first case, the product ratio **13:14** was 1:1, whereas in the presence of phosphine it was 5:1. Thus, it is concluded that (a) the mechanistic suggestion presented in scheme 1 is a well working hypothesis that is supported by experimental evidences, and (b) the stereochemistry of the cyclization product of systems like **7** and **12** can be easily controlled by simply adding or not adding phosphine, whereas all other reaction conditions are identical.

The *cis* dibromocyclobutabenzene is unreactive under Diels-Alder conditions.<sup>8,10</sup> However, as the reactivity of the bromine atoms at the 7 and 8 positions in **8** are expected to be different, it is principally possible to react only one of them with inversion, yielding the respective *trans*-7,8-differently disubstituted cyclobutabenzenes. A further request for a synthetically useful process is that the stereochemistry of the Diels-Alder reaction (i.e., conrotatory ring opening and *endo* addition) of this less symmetric cyclobutabenzene derivative will be retained.

Reacting **9** with one equivalent of sodium methoxide in methanol yielded **15** that was reacted with tetracyanoethylene to give the Diels-Alder product **16** (equation 4). The structure of **16** was assigned by



NMR, and was confirmed by the X-ray structure determination (figure 3). As evident from the structure,



**Figure 3:** Ellipsoid plot of **16**.

the stereospecificity of the Diels-Alder process is retained, and the addition of a dienophile to the less symmetric system **15** is stereospecific.

## CONCLUSIONS

In this paper we have shown that the nickel mediated cyclobutabenzene synthesis can be used to form *cis* and *trans* 7,8-dibromocyclobutabenzene derivatives, providing that the starting material (i.e., the  $\alpha,\alpha,\alpha',\alpha'$ -tetrabromo-*o*-xylene) is substituted at the *ortho* position by a group that is capable of complexing the C-Ni-Br intermediate. In such cases, this complexation and the “gear effect” between the two CHBr<sub>2</sub> groups cause the formation of the *cis* product. The presence of a strong ligand (i.e., tributylphosphine) in the reaction causes the formation of mainly the *trans* isomer. Thus, in these systems the stereochemical control is simple and facile. When the *cis* product is desirable, the reaction is carried out in THF or hexane, with nickel powder and 50 equivalents of DMF. When the *trans* isomer is desired, the reaction is carried out under identical conditions, but with added phosphine.

It was further shown that one bromine can be selectively replaced to yield the *trans* differently substituted systems, that reacts stereospecifically with dienophiles.

## EXPERIMENTAL SECTION

**General.** All solid starting materials were recrystallized prior to use. The solvents were freshly distilled prior to use from potassium-benzophenone ketyl (THF) and CaH<sub>2</sub> (DMF and Hexane). Metallic nickel was Nickel sponge gd.IIb2152 (Johnson, Matthey and Co. Ltd) used without any treatment. Florisil used for chromatography was Riedel-de Hean Florisil. <sup>1</sup>H NMR spectra were recorded on a 200 MHz spectrometer (50.4 MHz for <sup>13</sup>C) in CDCl<sub>3</sub> unless otherwise noted. Reported melting points are uncorrected.

**Methyl 2,3-Dimethylbenzoate:** A solution of 2,3-dimethylbenzoic acid (3 g, 19 mmol), methanol (80 ml), and H<sub>2</sub>SO<sub>4</sub> (2 ml) was refluxed for 24 h. The reaction mixture was cooled to rt, water (100 ml) were added and the product extracted with CHCl<sub>3</sub> (3×50 ml), washed with NaOH 2M (100 ml), brine, water, dried over MgSO<sub>4</sub> and the solvents were removed under reduced pressure. The product was distilled (140 °C, 0.1mmHg) to give 3.2 g (97% yield) of the product. <sup>1</sup>H NMR (CDCl<sub>3</sub>) : 7.51 (d, 1H, *J* 8.0 Hz), 7.26 (d, 1H, *J* 8.0 Hz), 7.10 (t, 1H, *J* 8.0 Hz), 3.67 (s, 3H), 2.44 (s, 3H), 2.30 (s, 3H); <sup>13</sup>C NMR (CDCl<sub>3</sub>): 169.0, 137.8, 137.4, 133.0, 131.0, 127.6, 125.1, 51.7, 20.4, 16.5.

**Methyl 2,3-Bis(dibromomethyl)benzoate (7):** A solution of methyl 2,3-dimethylbenzoate (0.37 g, 2.25 mmol), NBS (2g, 11.2 mmol) and CCl<sub>4</sub> (70 ml) was refluxed and irradiated (using a 375W sun-light lamp as the light and heat sources) until completion of the reaction (monitored by <sup>1</sup>H NMR). The reaction mixture was cooled to rt, filtered, and the solvents removed under reduced pressure. The product was purified over a Florisil column (hexane/CH<sub>2</sub>Cl<sub>2</sub> 3/1) to give 0.6g (55% yield) of the product; m.p. 158°C; <sup>1</sup>H NMR (CDCl<sub>3</sub>) : 8.29 (d, 1H, *J* 8.0 Hz), 8.15 (s, 1H), 7.84 (s, 1H), 7.79 (d, 1H, *J* 8.0 Hz), 7.49 (t, 1H, *J* 8.0 Hz), 3.94 (s, 3H); <sup>13</sup>C NMR (CDCl<sub>3</sub>): 166.7, 144.9, 137.9, 135.3, 131.1, 130.3, 125.7, 53.0, 37.0, 31.9.

**trans- and cis- Methyl-7,8-dibromocyclobuta[2,3]benzoate (8 and 9).** (a) **Mediated by (Bu<sub>3</sub>P)<sub>2</sub>Ni(COD).** A solution of **7** (0.154 g, 0.32 mmole) in dry and degassed DMF (3 ml) was cannulated under argon into a Schlenk flask containing (Bu<sub>3</sub>P)<sub>2</sub>Ni(COD) (0.184 g, 0.32 mmol). The reaction was stirred at 75 °C for 1 h, and the solvents removed under reduced pressure. The product was purified over a Florisil column (hexane/CH<sub>2</sub>Cl<sub>2</sub> 4/1) to give a mixture of **8** and **9**, 17mg (17% yield) in a ratio of 3:1; **8**: m.p. 87 °C; <sup>1</sup>H NMR (CDCl<sub>3</sub>) : 7.99 (d, 1H, *J* 8.0 Hz), 7.53 (t, 1H, *J* 8.0 Hz), 7.38 (d, 1H, *J* 8.0 Hz), 5.55 (s, 1H), 5.44 (s, 1H), 3.91 (s, 3H); <sup>13</sup>C NMR (CDCl<sub>3</sub>): 164.5, 143.4, 143.4, 132.3, 131.8, 127.4, 126.1, 52.1, 49.9, 49.6; HRMS: calcd for C<sub>10</sub>H<sub>8</sub>Br<sub>2</sub>O<sub>2</sub> 317.8891/319.8887/321.885 found: 317.8946/319.8864/321.8893. **9**: m.p. 108–109 °C; <sup>1</sup>H NMR (CDCl<sub>3</sub>): 7.96 (d, 1H, *J* 8.0 Hz), 7.45 (t, 1H, *J* 8.0 Hz), 7.37 (d, 1H *J* 8.0 Hz), 5.93 (d, 1H, *J* 4.0 Hz), 5.80 (d, 1H *J* 4.0 Hz) 3.92 (s, 3H). <sup>13</sup>C NMR (CDCl<sub>3</sub>): 164.5, 144.1, 143.7, 131.9, 131.4, 127.2, 125.8, 52.1, 51.6, 50.50; HRMS: calcd for C<sub>10</sub>H<sub>8</sub>Br<sub>2</sub>O<sub>2</sub> 317.8891/319.8887/321.885 found: 317.8937/319.8865/321.8834. (b) **Mediated by metallic nickel powder in hexane:** A stirred suspension of **7** (0.25 g, 0.52 mmol), nickel powder (0.155 g, 2.64 mmol), DMF (2.0 ml, 25.83 mmol), and hexane (18 ml) was refluxed for 63 h. The reaction was cooled to rt, filtered and the solvents removed under reduced pressure. The product was purified over a Florisil column (hexane/CH<sub>2</sub>Cl<sub>2</sub> 3/1) to give **8** and **9**, 183 mg (71% isolated yield, 95% yield based on recovered sm.) in a ratio of 1:4.3. (c) **Mediated by metallic nickel powder in THF:** A stirred suspension of **7** (0.25 g, 0.52 mmol), nickel powder (0.155 g, 2.64 mmol), DMF (2.0 ml, 25.83 mmol) and THF (8 ml) was refluxed for 18 h. The reaction was cooled to rt, filtered and the solvents removed under reduced pressure. The product was purified over a Florisil column (Hexane/CH<sub>2</sub>Cl<sub>2</sub> 3/1) to give **9** as the only 50 mg of the product, (30% isolated yield, 80% yield based on recovered s.m.). (d) **Mediated by metallic nickel powder in THF in the presence of Bu<sub>3</sub>P:** A stirred suspension of **7** (0.25 g, 0.52 mmol), nickel powder (0.155 g, 2.64 mmol), Bu<sub>3</sub>P (0.26 ml, 1.04 mmol), DMF (2.0 ml, 25.83 mmol) and hexane (18 ml) was refluxed for 7.5 h. The reaction was cooled to rt, filtered and the solvents removed under reduced

pressure. The product was purified over a Florisil column (hexane/ $\text{CH}_2\text{Cl}_2$  3/1) to give 40 mg of **8** and **9** (24% yield) in a ratio of 4:1.

The separation between **8** and **9** was achieved by careful chromatography on a Florisil column (hexane/ $\text{CH}_2\text{Cl}_2$  3/1). First to be eluted is **8**, and then **7** and **9**.

**2,3-Bis(dibromomethyl)benzoic acid** A solution of  $\text{Br}_2$  (11 ml, 0.21 mol) in  $\text{CCl}_4$  (45 ml) was added dropwise into an irradiated refluxing solution (using a 375W sun-light lamp as the light and heat sources) of 2,3-dimethylbenzoic acid (8.0 gr, 53 mmol) until completion of the reaction. (monitored by  $^1\text{H}$  NMR). The reaction mixture was cooled to rt and the solvents removed under reduced pressure. The product was purified by crystallization (ethyl acetate) to give 20g (82% yield) of the product;  $^1\text{H}$  NMR ( $\text{DMF-D}_7$ ) : 8.39 (s, 1H), 8.34 (d, 1H,  $J$  7.2 Hz), 7.94 (d, 1H,  $J$  7.8 Hz), 7.86 (s, 1H), 7.75 (t, 1H,  $J$  7.7 Hz);  $^{13}\text{C}$  NMR ( $\text{DMF-D}_7$ ): 168.6, 144.8, 137.7, 135.2, 132.1, 131.9, 128.4, 37.6, 33.4.

**2,3-Bis(dibromomethyl)benzoyl chloride:** A solution of 2,3-bis(dibromomethyl)benzoic acid (2.0 g, 4.29 mmole) in  $\text{SOCl}_2$  (15 ml) was refluxed for 1h. Excess of  $\text{SOCl}_2$  was removed under reduced pressure and the product was used without any further purification for the next amidation step.

**N-(sultam)-2,3-Bis(dibromomethyl)benzoyl amide (12):** NaH suspension in mineral oil (0.52 g, 21.6 mmol) was washed with hexane (3×3ml) under nitrogen. Toluene (40 ml) was added and the suspension was cooled to 0–5 °C. 2-Amino-d-camphane-10-sulfonic acid (1.00 g, 4.46 mmol) was added in small portions and the mixture was stirred for 30 min. at rt. The mixture was cooled to 0–5 °C and a solution of 2,3-bis(dibromomethyl)benzoyl chloride (2.08 gr, 4.3 mmol, obtained as described above) in toluene (10 ml) was added dropwise. The mixture was stirred at rt for 2 h, and the reaction was monitored by TLC (hexane/acetone 3/1). The mixture was cooled with ice bath, and water (50 ml) were carefully added. The product was extracted by hot ethyl acetate (3×40ml), washed with brine, dried over  $\text{MgSO}_4$ , and the solvents removed under reduced pressure. The product was purified by crystallization from ethyl acetate to give 2.27g of the product (80% yield);  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ) : 8.22 (d, 1H,  $J$  7.6 Hz), 7.78 (s, 1H), 7.48 (t, 1H,  $J$  7.6 Hz), 7.34 (d, 1H,  $J$  7.6 Hz), 6.90 (s, 1H), 4.16–1.00 (sultam signals);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ ): 167.9, 144.0, 137.0, 133.1, 130.3, 129.7, 129.4, 65.5, 53.4, 48.5, 47.94, 45.0, 38.3, 36.6, 33.1, 32.5, 26.5, 21.2, 19.9.

**Cyclization of 12 mediated by metallic nickel powder. (a) Without phosphine:** A stirred suspension of **12** (0.50 g, 0.75 mmol), nickel powder (0.50 g, 8.52 mmol), DMF (2.5 ml, 25.8 mmol) and THF (10 ml) was refluxed for 44 h and monitored by TLC (hexane/acetone 3/1). After completion the reaction mixture was cooled to rt, filtered and the solvents removed under reduced pressure. The products were purified over a silica column (63–200 mesh) ( $\text{CH}_2\text{Cl}_2$ ) to give **13** and **14** (50 mg, 13% yield) in a



ratio of 1:1;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ) : 7.69 (d, 1H,  $J$  8.0 Hz), 7.50 (t, 1H,  $J$  8.0 Hz), 7.35 (d, 1H,  $J$  8.0 Hz), 6.06 (d, 1H,  $J$  4.0 Hz, **13**), 5.82 (d, 1H,  $J$  4.0 Hz, (**14**)), 5.67 (s, 1H, (**13**)), 5.38(s, 1H, (**13**)), 4.30–0.94 (sultam signals); HRMS: calcd for  $\text{C}_{19}\text{H}_{21}\text{Br}_2\text{N}_1\text{O}_3\text{S}_1$  500.9609/502.9589/504.9568 found: 500.9650/502.9592.

**(b) With tributylphosphine:** A stirred suspension of **10** (0.50 g, 0.75 mmol), nickel powder (0.50 g, 8.52 mmol),  $\text{Bu}_3\text{P}$  (0.38 ml, 1.52 mmol), DMF (2.5 ml, 25.8 mmol) and THF (10 ml) was refluxed for 22 h and monitored by T.L.C (hexane/acetone 3/1). After completion, the reaction was cooled to rt, filtered and the solvents removed under reduced pressure. The product was purified over a silica column (63–200 mesh) ( $\text{CH}_2\text{Cl}_2$ ) to give **13** and **14** (45.5 mg, 12% yield) in a ratio of 5:1, respectively.

**Methyl-7-bromo-8-metoxycyclobuta[2,3]benzoate (15):** Na (10mg, 0.43 mmol) was added to methanol (12 ml) that was stirred until all the Na was dissolved. **9** (100 mg, 0.3 mmol) was added and the reaction was refluxed for 7 h until no s.m. detected on T.L.C. (hexane/acetone 3/1). The reaction was cooled to rt, water (30 ml) were added and the product was extracted with  $\text{CHCl}_3$  (5×20ml), dried over  $\text{MgSO}_4$ , and the solvents removed under reduced pressure. The product was purified over a Florisil column ( $\text{CH}_2\text{Cl}_2$ ), and then crystallized from hexane to give 35 mg (41% yield) of **15**;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ): 7.98 (d, 1H,  $J$  7.2 Hz), 7.46 (m, 2H), 5.33 (s, 1H), 5.01 (s, 1H), 3.92 (s, 3H), 3.57 (s, 3H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ ): 165.0, 143.4, 142.8, 131.8, 130.7, 127.5, 126.2, 88.5, 57.3, 51.9, 47.0; HRMS: molecular peak ( $\text{C}_{11}\text{H}_{11}\text{Br}_1\text{O}_3$ ) was not found, calcd for M-H  $\text{C}_{11}\text{H}_{10}\text{Br}_1\text{O}_3$  268.9813/270.9792. found: 268.9690/270.9775.

**Methyl-(8-bromo-6,6,7,7-tetracyano-5-methoxy)-5,6,7,8-tetrahydro-1-naphthoate (16):** A solution of **15** (20.0 mg, 0.037 mmol) and tetracyanoethylene (10.0 mg, 0.078 mmol) in benzene- $\text{D}_6$  (0.4 ml) was fire sealed in an NMR tube under vacuum ( $10^{-2}$  mbar). The tube was allowed to stand at  $145^\circ\text{C}$  for 11 h while the reaction was monitored by  $^1\text{H}$ -NMR spectroscopy. When no s.m. was detected the tube was cracked open and the solvent was removed under reduced pressure. The product was purified over a Florisil column ( $\text{CH}_2\text{Cl}_2$ ) and crystallized from hexane/ $\text{CH}_2\text{Cl}_2$  to give 22 mg (75% yield) of **16**; m.p.  $169^\circ\text{C}$ ;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ) : 8.06 (d, 1H,  $J$  7.6 Hz), 7.73 (d, 1H,  $J$  7.6 Hz), 7.61 (t, 1H,  $J$  7.6 Hz), 7.09 (s, 1H), 5.14 (s, 1H), 4.05 (s, 3H), 3.98 (s, 3H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ ): 166.0, 133.6, 131.4, 131.0, 130.9, 130.0, 129.9, 111.3, 109.2, 109.1, 107.5, 80.1, 63.0, 53.2, 44.0, 41.4, 38.6; HRMS: calcd for  $\text{C}_{17}\text{H}_{11}\text{Br}_1\text{N}_4\text{O}_3$  398.0015/399.9994. found: 397.9984/400.0004.

***X-Ray structural determination of compounds 7,8,9 and 16.***

Crystals suitable for structure determination have been grown from (a) dichloromethane solution at -15 °C for **7**, (b) hexane/dichloromethane 8/1 solution at rt for **8** and **16** and (c) ethanol at rt for **9**. The structures were measured on Siemens SMART CCD area detector system three axis platform diffractometer, with a graphite monochromator at a wavelength of 0.71073 Å. The diffractometer measurement method was hemisphere data collection in  $\omega$  at 0.3° scan width four runs with 636, 465, 636, 465 frames,  $\varphi = 0, 88, 180, 270^\circ$ , with a detector distance of 4.891 cm. Intensity integration and data correction with Siemens SAINT V4.050, decay corrections were based on repeated 50 frames from the first run after the data collection, and absorption corrections were computed with Siemens SADABS program, empirically based on equivalent reflection. The structure solutions and the structure refinements (on  $F^2$ , full matrix) were computed with Siemens SHELXTL V.5.03, SGI-Version. Hydrogen atoms were treated as riding groups. Details of the crystal structure solutions are reported in table 1.

**Table 1.** Crystal data and structure refinement of **7**, **8**, **9** and **16**.

Compound	<b>8</b>	<b>9</b>	<b>7</b>	<b>16</b>
Empirical formula	C <sub>10</sub> H <sub>8</sub> Br <sub>2</sub> O <sub>2</sub>	C <sub>10</sub> H <sub>8</sub> Br <sub>2</sub> O <sub>2</sub>	C <sub>10</sub> H <sub>8</sub> Br <sub>4</sub> O <sub>2</sub>	C <sub>17</sub> H <sub>11</sub> BrN <sub>4</sub> O <sub>3</sub>
Formula weight	319.98	319.98	479.80	399.21
F(000)	616	616	896	800
Temperature (K)	298(2)	298(2)	298(2)	301
Crystal size - (mm)	0.31*0.24*0.14	0.31*0.24*0.17	0.34*0.22*0.07	0.56*0.44*0.27
Crystal color	colorless	colorless	colorless	colorless
Density (calculated)	1.955 Mg/m <sup>3</sup>	2.035 Mg/m <sup>3</sup>	2.406 Mg/m <sup>3</sup>	1.541 Mg/m <sup>3</sup>
Crystal system	monoclinic	monoclinic	monoclinic	monoclinic

Space group	P2 <sub>1</sub> /c	P2 <sub>1</sub> /n	P2 <sub>1</sub> /n	P2 <sub>1</sub> /n
Unit cell dimensions	$a = 16.6638(2)$ $b = 8.5551(2)$ $c = 7.7590(2)$ . $\alpha = 90^\circ$ $\beta =$ $100.5950(10)^\circ$ $\gamma = 90^\circ$	$a = 9.4773(6)$ $b = 7.7364(5)$ $c = 14.5282(8)$ . $\alpha = 90^\circ$ $\beta =$ $101.3770(10)^\circ$ $\gamma = 90^\circ$	$a = 9.6413(5)$ $b = 7.8414(4)$ $c = 17.5295(9)$ . $\alpha = 90^\circ$ $\beta = 91.7580(10)^\circ$ $\gamma = 90^\circ$	$a = 9.60630(10)$ $b = 17.7813(2)$ $c = 10.07160(10)$ . $\alpha = 90^\circ$ $\beta = 90.5237(8)^\circ$ $\gamma = 90^\circ$
Volume Z	1087.27(4) <sup>3</sup> 4	1044.28(11) <sup>3</sup> 4	1324.63(12) <sup>3</sup> 4	1720.28(3) <sup>3</sup> 4
Cell determination reflections used	35185	33265	35752	38168
$\Theta$ range for data collection	1.24 to 28.66°	2.37 to 28.32°	2.32 to 28.25°	2.29 to 28.31°
Limiting indices	-22 < h < 22, -11 < k < 11, -9 < l < 10	-11 < h < 12, -10 < k < 8, -13 < l < 18	-12 < h < 12, -10 < k < 10, -23 < l < 23	-12 < h < 12, -23 < k < 23, -13 < l < 13
$\Theta$ range for data collection	1.24 to 28.66°	2.37 to 28.32°	2.32 to 28.25°	2.29 to 28.31°
Computing data reduction	Siemens SAINT program V.4.050	Siemens SAINT program V.4.050	Siemens SAINT program V.4.050	Siemens SAINT program V.4.050
Data covered	>97%	>97%	>99%	>99%
R <sub>merg</sub> before/after correction	0.1672 / 0.0648	0.1746 / 0.0631	0.2592 / 0.0905	0.0858 / 0.0400

max/min transmission	1.00 / 0.32	1.00 / 0.32	1.00 / 0.22	1.00 / 0.56
Absorption coefficient $\mu$	7.426 mm <sup>-1</sup>	7.732 mm <sup>-1</sup>	12.135 mm <sup>-1</sup>	2.413 mm <sup>-1</sup>
Reflections integrated	12016	5755	14198	18951
Independent reflections	2732 ( $R_{\text{int}} = 0.0715$ )	2395 ( $R_{\text{int}} = 0.0900$ )	3201 ( $R_{\text{int}} = 0.1001$ )	4230 ( $R_{\text{int}} = 0.0443$ )
Refinement method	Full-matrix least-squares on $F^2$	Full-matrix least-squares on $F^2$	Full-matrix least-squares on $F^2$	Full-matrix least-squares on $F^2$
Data / restraints/ parameters	1673 / 0 / 135	1445 / 0 / 127	1778 / 0 / 145	2777 / 0 / 227
Goodness-of-fit on $F^2$	0.902	0.865	0.847	0.941
Weighting scheme	$w^{-1} = \sigma^2(F_0^2) + (0.0535 * P)^2 + 0 * P$ where $P = [(\max F_0^2) + (2F_c^2)]/3$			
Final R indices [ $I > 2\sigma(I)$ ]	R1 = 0.0385 wR2 = 0.0848	R1 = 0.0524 wR2 = 0.1047	R1 = 0.0525 wR2 = 0.1204	R1 = 0.0492 wR2 = 0.1239
R indices (all data)	R1 = 0.0688 wR2 = 0.1040	R1 = 0.0785 wR2 = 0.1094	R1 = 0.0845 wR2 = 0.1277	R1 = 0.0726 wR2 = 0.1387
Largest diff. peak and hole	1.107 and -0.423 e <sup>-3</sup>	1.150 and -1.692 e <sup>-3</sup>	1.503 and -0.844 e <sup>-3</sup>	1.072 and -0.326 e <sup>-3</sup>

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## References and notes.

1. Winters, M.P.; Stranberg, M.; Moore, H.W. *J. Org. Chem.*, **1994**, *59*, 7572-7574; Kametani, T.; Suzuki, Y.; Honda, T. *Heterocycles*, **1985**, *23*(2), 305-308; Bush, E.J.; Jones, D.W.; Thornton-Pett, M. *Tett. Lett.* **1994**, *35*(52), 9755-9758; Wheeler, D.M.S.; Wheeler, M.M. *Studies in Natural. Chem.* **1994**, *14*, 3-46; Nemoto, H.; Satoh, A.; Fukumoto, K.; Kabuto, C. *J. Org. Chem.* **1995**, *60*, 594-600; Hahn, S.F.; Martin, S.J.; McKelvy, M.L.; Patrick, D.W. *Macromolecules*, **1993**, *26*, 3870-3877; Fishback, T.L.; Farona, M.F. *J. Poly. Sci.* **1993**, *31A*, 2747-2750; Kirchhoff, R.A.; Carriere, C.J.; Bruza, K.J.; Rondan, N.G.; Sammler, R.L. *J. Macromol. Sci. Chem.* **1991**, *A28*(11&12), 1079-1113; Endo, T.; Koizumi, T.; Takata, T.; Chino, K. *J. Poly. Sci.* **1995**, *33A*, 707-715.
2. Duval, D.; Hennig, P.; Bouchet, J.P.; Vian, J.; Peglion, J.L.; Volland, J.P.; Platzer, N.; Guilhem, J. *Magn. Reson. Chem.* **1997**, *35*, 175-183.
3. Siegel, J. S. *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 1721-1723; Frank, N. L.; Siegel, J. S. in "Advances in Theoretically Interesting Molecules" **1995**, Vol. 3, JAI Press Inc., pp. 209-260.
4. Cava, N. P.; Napier, D. R. *J. Am. Chem. Soc.* **1956**, *78*, 500; Cava, N. P.; Napier, D. R. *J. Am. Chem. Soc.* **1957**, *79*, 1701-1705.
5. Schiess, P.; Rutschmann, S.; Toan, V.V.; *Tett. Lett.*, **1982**, *23*, 3669-3672.
6. Kobayashi, K.; Kawakita, M.; Mannami, T.; Konishi, H. *Tett. Lett.*, **1995**, *36*, 733-736.
7. Stanger, A.; Ashkenazi, N.; Shachter, A.; Bläser, D.; Stellberg, P.; Boese, R. *J. Org. Chem.*, **1996**, *61*, 2549-2552.
8. Stanger, A.; Schachter, A.; Ashkenazi, N.; Boese, R.; Stellberg, P. in "Organic Synthesis via Organometallics, OSM 5.", Helmchen, G.; Dibo, J.; Flubacher, D.; Wiese, B. Eds, Friedr. Vieweg & Sohn Verlagsgesellschaft mbH, Braunschweig/Wiesbaden, 1997, pp. 59-66.
9. Stanger, A.; Ashkenazi, N.; Boese, R.; Bläser, D.; Stellberg P. *Chem. Eur. J.* **1997**, *3*, 208-211.
10. Stanger, A.; Schachter, A.; Boese, R. manuscript in preparation.
11. Including 50 equivalents of DMF.
12. The mechanism postulated for nickel mediated coupling reactions involves two species of the type C-Ni-Br that disproportionate to give the coupling product (C-C), Ni(II) and Ni(0). See Yamamoto, T.; Wakabayashi, S.; Osakada, K. *J. J. Organomet. Chem.* **1992**, *428*, 223-237.

13. (a) As shown by the extensive studies of Mislow et. al. for isopropyl substituted benzene systems (see: Singh, M.D.; Siegel, J.; Biali, S.E.; Mislow, K. *J. Am. Chem. Soc.* **1987**, *109*, 3397-3402.). Since the hydrogen atom in  $\text{CHBr}_2$  is partially positive and the bromine atoms are partially negative, the “gear effect” in 1,2-bis(dibromomethyl) should be stronger than in 1,2-bis(*i*-propyl)benzene. (b) See also Berg, U.; Liljefors, T.; Roussel, C.; Sandström, J. *Acc. Chem. Res.* **1985**, *18*, 80-86.