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[14] As depicted in Scheme 1, the combination of **5** and $(CuOTf)_2 \cdot C_6H_6$, provides slightly higher enantioselectivity, but is less efficient than **6** and CuCN (50% vs. >98% conversion). Further examination of the former system is in progress.
[15] Tripeptide **8** and its derived Me ester afford similar results.
[16] When D-Val is used as AA1, the sense of enantioselection is reversed, indicating that the stereochemical identity of AA1 is critical to the sense of stereochemical induction and that the D,L-ligand may deliver lower levels of enantioselectivity than the L,L isomer.
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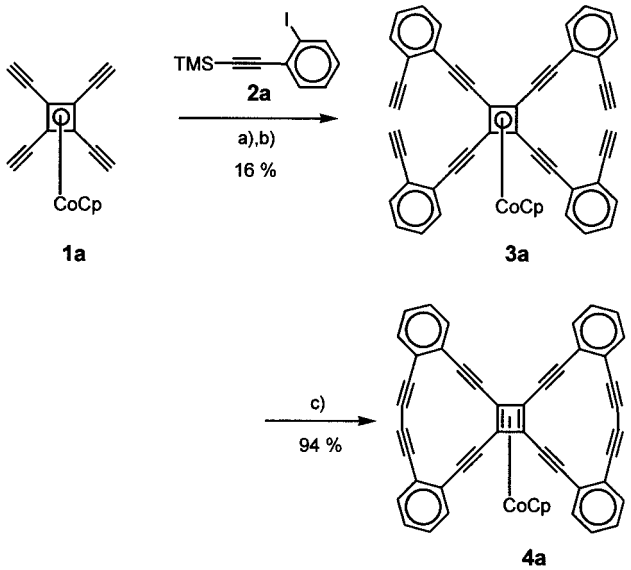
[22] Reaction of di-2-methylpentylzinc (cf. **24**, Scheme 2) with **20a** in the presence of **19** that has been pretreated with Et_2Zn affords alkylation products with *ee* levels similar to those shown in Scheme 2 (76 – 78% *ee*). These data indicate that reactions with Et_2Zn are not promoted by amine ligands that are reduced in situ by various metal hydrides (see ref. [5]).

Concave Butterfly-Shaped Organometallic Hydrocarbons?**

Matthew Laskoski, Gaby Roidl, Mark D. Smith, and Uwe H. F. Bunz*

Carbon-rich organometallic materials are of special interest because their structures display topologies, such as tetragonal or pentagonal, unattainable by their hydrocarbon counterparts.[1–3] In the realm of organic structures, Haley et al. made a series of large polycyclic hydrocarbons of hexagonal topology, in which benzene rings are separated by alkyne units.[4] We are interested in the chemistry and materials science of tetragonal cyclobutadiene complexes,[5] and herein we present the synthesis (**4a** – **c**, see Scheme 1 and 2) and single-



Scheme 1. Synthesis of the unsubstituted bow-tie complex **4a**. a) $[(PPh_3)_2PdCl_2]$, CuI, piperidine, 18 h, 25 °C; aqueous workup and chromatography. b) K_2CO_3, THF, methanol, 16 h, 25 °C. c) $Cu(OAc)_2$, CH_3CN (20 mL), 18 h, 80 °C; aqueous workup and chromatography.

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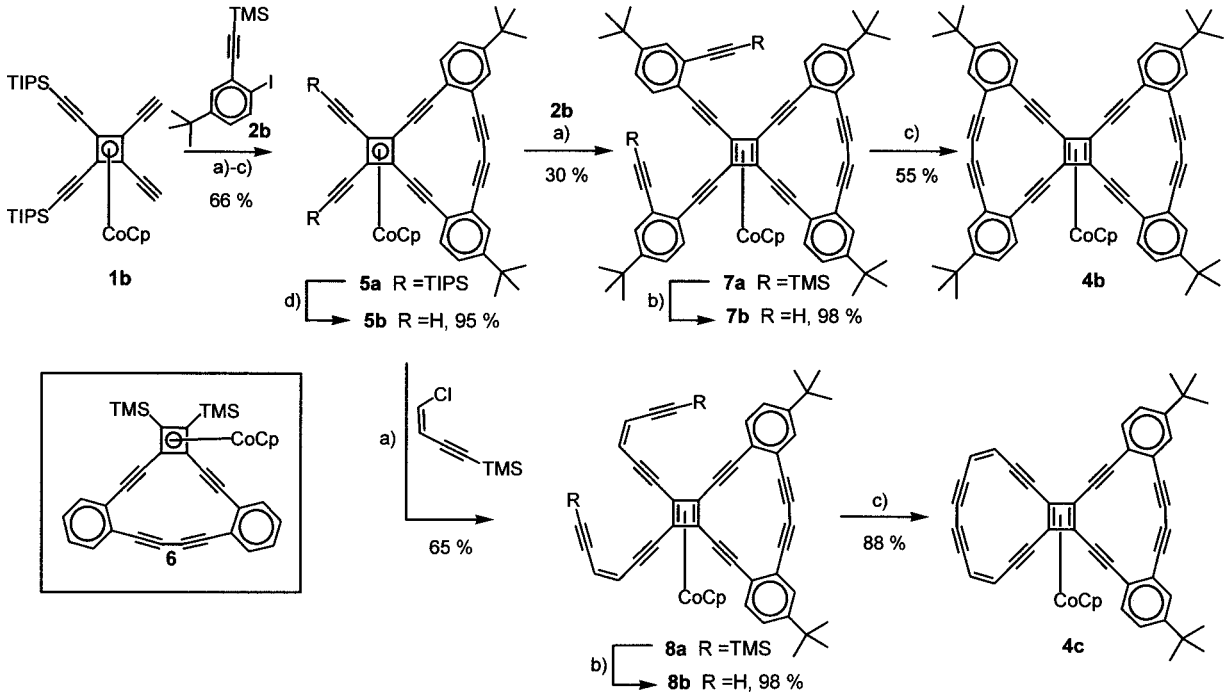

Scheme 2. Synthesis of the substituted bow-tie complexes **4b** and **4c**. a) $[(PPh_3)_2PdCl_2]$, CuI, piperidine, 18 h, 25 °C; aqueous workup and chromatography. b) K_2CO_3, THF, methanol, 16 h, 25 °C. c) $Cu(OAc)_2$, CH_3CN, 18 h, 80 °C; aqueous workup and chromatography. d) $Me_4N^+F^-$, DMSO, diethyl ether 2 h, 25 °C; aqueous workup and chromatography. TMS = trimethylsilyl.

crystal X-ray structure analysis (**4b**, see Figure 1) of novel, large, concave organometallic hydrocarbons (**4**) with a central tetraethynylcyclobutadiene(cyclopentadienylcobalt) core.

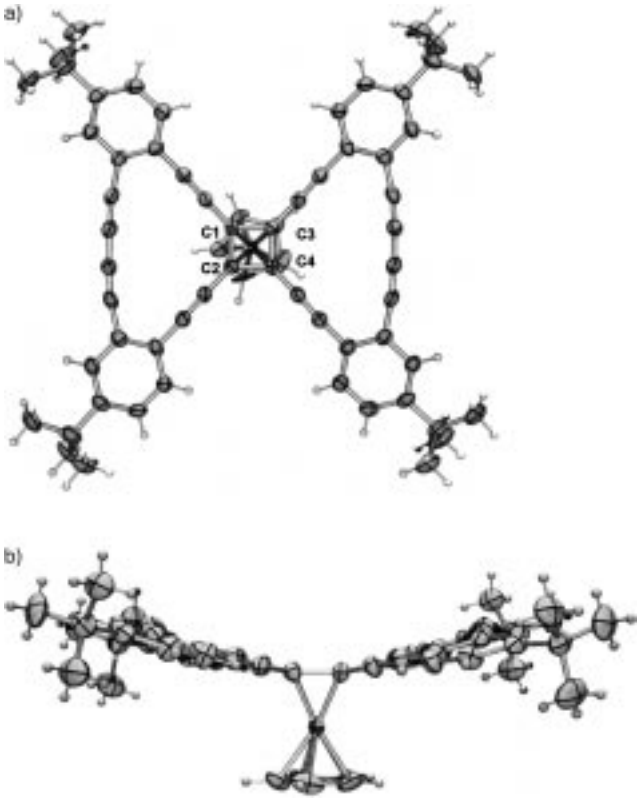

Figure 1. Structure of the butterfly compound **4b**. a) Top view. Selected bond lengths [Å]: C1-C2, C3-C4 1.448(5), C1-C3, C2-C4 1.472(5). b) Side view.

Topologies of type **4** are attractive because related species featuring the tetraethynylcylobutadiene motif have been suggested by Jarrold et al.[6] to play an important role in the formation of fullerenes such as C_{60}.

Vollhardt, Youngs et al.[7] have developed a powerful method to assemble dehydrobenzo[14]annulenes,[8–10] which is suitable for preparing the butterfly complexes **4**. Starting from **1a**,[11] fourfold Pd-catalyzed coupling with **2a** furnishes **3a** after chromatography and removal of the trimethylsilyl groups by K_2CO_3 in methanol in an overall yield of 16% (64% per coupling step; Scheme 1). Treatment of **3a** with $Cu(OAc)_2$ in acetonitrile/THF under conditions described by Vögtle and Berscheid[9] and recently utilized by us[10] leads to **4a** as sole product in 94% yield (Table 1). The almost quantitative yield was surprising and is probably due to the preorganization of the alkyne groups in **3a** with respect to each other. While **3a** is well soluble in dichloromethane and pentane, **4a** is only slightly soluble in THF, but practically insoluble in pentane or halogenated solvents, which hampered attempts to obtain single crystals. Interest in expanding this concept and obtaining more soluble derivatives led us to explore a step-by-step route to **4b** and **4c**. Starting from **1b**, Pd-catalyzed reaction with **2b** followed by deprotection, Cu-catalyzed coupling, and removal of the triisopropylsilyl (TIPS) groups furnishes **5b** as a valuable intermediate. Repetition of the sequence (Scheme 2) leads, via **7**, to the tetrakis-*tert*-butyl-substituted compound **4b** (Table 1), which is very soluble in THF, dichloromethane, and pentane.

Coupling of the intermediate **5a** (Table 1) to 1-chloro-4-trimethylsilylbuten-3-yne followed by deprotection and ring closure of **8b** furnishes the unsymmetrical **4c** (Table 1), in which one dehydroannulene and one dehydrobenzoannulene

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Table 1. Spectroscopic data for selected compounds.

4a: Yield: 94%; dark red crystalline solid; m.p. >200°C (decomp); IR (neat): $\tilde{\nu}$ = 2924, 2361, 2342, 1458 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.73 (dd, $^3J_{H,H}$ = 7.32 Hz, $^4J_{H,H}$ = 1.7 Hz, 4H), 7.52 (dd, $^3J_{H,H}$ = 7.32 Hz, $^4J_{H,H}$ = 1.7 Hz, 4H), 7.42 (quint. d, $^3J_{H,H}$ = 7.32 Hz, $^4J_{H,H}$ = 1.7 Hz, 8H), 5.01 (s, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 131.81, 131.17, 129.99, 129.90, 128.57, 124.33 (12C), 84.61 (5C), 93.48, 90.21, 80.00, 68.21 (12C), 62.83 (4C)

4b: Yield: 55%; dark red crystalline solid; m.p. >220°C (decomp); IR (neat): $\tilde{\nu}$ = 2943, 2855, 2333, 2144, 1667, 1461, 1244 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.65 (d, $^3J_{H,H}$ = 8.3 Hz, 4H), 7.53 (s, 4H), 7.43 (d, $^3J_{H,H}$ = 8.3 Hz, 4H), 4.97 (s, 5H), 1.34 (s, 36H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 151.18, 130.96, 127.45, 126.83, 126.52, 123.68 (24C), 92.98, 89.25, 84.52, 79.23 (16C), 83.91 (5C), 62.31 (4C), 35.17, 31.26 (16C); UV/Vis ($CHCl_3$): λ_{max} (ε) = 296 (27530), 323 nm (22787)

4c: Yield: 88%; orange-red crystalline solid; m.p. >190°C (decomp); IR (neat): $\tilde{\nu}$ = 2956, 2333, 2167, 1644, 1584, 1450, 1400, 1100, 1017 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.65 (d, $^3J_{H,H}$ = 8.2 Hz, 2H), 7.52 (d, $^4J_{H,H}$ = 1.9 Hz, 2H), 7.42 (dd, $^3J_{H,H}$ = 8.2 Hz, $^4J_{H,H}$ = 1.9 Hz, 2H), 6.72 (d, $^3J_{H,H}$ = 9.9 Hz, 2H), 6.34 (d, $^3J_{H,H}$ = 9.9 Hz, 2H), 4.95 (s, 5H), 1.33 (s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 151.39, 130.98, 127.47, 126.56 (12C), 123.79, 116.87 (4C), 96.46, 94.01, 93.31, 88.68, 88.19, 84.44, 84.08, 79.20 (16C), 83.68 (5C), 63.33, 62.99 (4C), 35.19, 31.80 (8C); UV/Vis ($CHCl_3$): λ_{max} (ε) = 333 nm (313)

5a: Yield: 82%; dark red oil; IR (neat): $\tilde{\nu}$ = 3106, 2943, 2852, 2338, 2143, 1462, 1246 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.49 (d, $^3J_{H,H}$ = 8.2 Hz, 2H), 7.44 (s, 2H), 7.38 (d, $^3J_{H,H}$ = 8.2 Hz, 2H), 4.93 (s, 5H), 1.31 (s, 18H), 1.14 (s, 42H), 0.05 (s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 150.80, 130.48, 127.13, 126.64, 126.32, 123.40 (12C), 100.78, 96.97, 92.21, 88.91 (8C), 83.60 (5C), 61.96, 61.38 (4C), 34.90, 30.99 (8C), 18.70, 11.11 (18C), 1.01 (6C); HRMS (EI): *m/z*: calcd for [M^+] ($C_{59}H_{71}CoSi_2$) 894.4426; found 894.4401

are fused to the tetraethynylcyclobutadiene core. The latter demonstrates the versatility of the double annulation process. All of the polycycles **4** are surprisingly stable and can be stored under ambient conditions for extended periods of time without polymerization or decomposition. If the cycles are heated to temperatures above 190°C shiny-black, insoluble, but amorphous materials form.

Attempts to obtain mass spectra of **4a–c** under electron impact conditions failed due to their immedaite decomposition, but gratifyingly, the *tert*-butyl substituents increase the propensity of **4b** to develop high-quality single crystals. The X-ray crystal structure of **4b** is shown in Figure 1.[12] The bond lengths and bond angles are in excellent agreement with earlier values published for **6** (see Scheme 2),[10] but an interesting aspect of the structure of **4b** is its considerable deviation from planarity in the solid state (Figure 1b). Two planes, which are each defined by the central cyclobutadiene ring and two of the four alkyne groups, are tilted by 13°, leading to a (net) kink of 26° of the two dehydroannulenes with respect to each other. This tilt is considerably larger than that in alkynylated and butadiynylated cyclobutadiene(tricarbonyl)iron complexes.[13] To establish whether the bending of the large hydrocarbon ligand is a crystal packing effect or "real", we performed a semiempirical (PM3-tm, SPARTAN PRO) calculation of **4a**. In the computationally optimized structure the tilting is even stronger, and the plane of the cyclobutadiene complex is kinked away by 16° from the dehydroannulene. Increasing the steric bulk of the cyclopentadienyl ring through pentamethyl substitution leads to an additional increase in the kink angle from 16° to 20° (PM3-tm), qualitatively indicating that steric effects play a role. These results are in interesting contrast to Vollhardt's [N]phenylenes, in which bending of the aromatic core is likewise observed, but which is attributed solely to crystal packing effects.[14b]

The cyclobutadiene ring in **4b** is not square but rectangular, according to X-ray diffraction data, suggesting some degree of bond fixation induced by the annulation of the aromatic [14]dehydroannulenes;[14, 15] the C1–C2 and C3–C4 (1.448(5) Å) bonds are shorter than the C1–C3 and C2–C4 (1.472(5) Å) bonds. While the bond fixation is not dramatic, it supports the annulation of two Hückel-aromatic dehydroannulenes onto the metal-complexed cyclobutadiene ring. Aromaticity effects thus induce subtle changes in the geometry of the normally square CpCo-stabilized cyclobutadiene. This trend is clearly supported by the comparison of the ^1H NMR data of **4c** and its open precursor **8b**. While in **8b** the signals of the vinyl protons appear at δ = 5.92 and 6.06, the same protons resonate at δ = 6.34 and 6.72 in **4c**, suggesting that the newly formed dehydro[14]annulene is aromatic and thus reduces the delocalization of the cyclobutadiene complex.

In conclusion we have synthesized the organometallic butterfly complexes **4a–c** by a combination of Pd- and Cu-catalyzed coupling reactions and determined the molecular structure of **4b** as the first example of a structurally characterized molecular topology that resembles that in Jarrold's perethynylated cyclobutadienes, which are fascinating intermediates en route to C_{60}.[16] The extension of this concept towards larger systems of higher unsaturation may lead to the formation of fullerenes from cyclobutadiene-containing precursors under appropriate matrix-assisted laser desorption ionization time-of-flight (MALDI-TOF) conditions, similar to the coalescence of suitable cyclophynes elegantly demonstrated independently by Rubin et al.[16] and Tobe et al.[17]

Experimental Section

4b: A round-bottom flask was charged[11] with **5a** (0.098 g, 0.11 mmol), tetramethylammonium fluoride (0.300 g, 10.9 mmol), DMSO (5 mL), and diethyl ether (10 mL). The resulting mixture was stirred at 25°C for 2 h. Aqueous workup (diethyl ether) followed by removal of the solvent in vacuo yielded **5b** as a dark red oil. This was coupled immediately to 4-iodo-3-(trimethylsilylethynyl)-1-*tert*-butylbenzene[18] (**2b**) (90 mg, 0.250 mmol) under addition of [$(PPh_3)_2PdCl_2$] (1.5 mg, 0.002 mmol), CuI (1.0 mg, 0.007 mmol), and piperidine (10 mL). The reaction mixture was purged with N_2 and stirred for 18 h at ambient temperature. Aqueous workup and subsequent chromatography on silica gel with CH_2Cl_2/hexanes (1:1) yielded pure **7a** (R = $SiMe_3$; 34 mg, 30%) as a red oil. A round-bottom flask was charged with **7a** (34 mg, 0.033 mmol), K_2CO_3 (0.100 g, 0.72 mmol), THF (3 mL), and methanol (10 mL). The resulting mixture was stirred at 25°C for 4 h. Aqueous workup with diethyl ether followed by removal of the solvent in vacuo yielded **7b** as a dark red oil (29 mg, 98%). $Cu(OAc)_2$ (0.200 g, 1.10 mmol) and CH_3CN (20 mL) were added to the oil **7b** and the reaction mixture was heated to 80°C for 18 h. Aqueous workup and chromatography on silica gel with CH_2Cl_2/hexanes (1:1) yielded pure **4b** (16 mg, 55%) as a dark red crystalline solid.

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[12] For **4b**: A red plate of **4b** ($0.25 \times 0.2 \times 0.08$ mm) was grown from dichloromethane. Data were obtained on a Bruker SMART APEX CCD diffractometer at 211 K. The structure was solved and refined by the programs SAINT+ and SHELXTX by using heavy atom (Patterson) methods. Hydrogen atoms were localized and refined in the riding mode. The crystal was fixed in a capillary. $CoC_{65}H_{53} \cdot CH_2Cl_2$ ($M_r = 977.93$); $Mo_{K\alpha}$ radiation $\lambda = 0.71073$ Å, graphite monochromator; $2\Theta_{max} = 22.50^\circ$, tetragonal, space group $I4_1$; $a = 19.156(5)$, $b = 19.156(5)$, $c = 15.842(7)$ Å, $V = 5814(3)$ Å^3, $Z = 48$, $\rho_{calcd} = 1.117$ g cm^{-3}, $\mu = 0.424$ mm^{-1}, 12129 reflections were measured and 4807 reflections with $I > 2\sigma(I)$ observed, $R = 0.0491$, $R_w = 0.1031$. Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-154093. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

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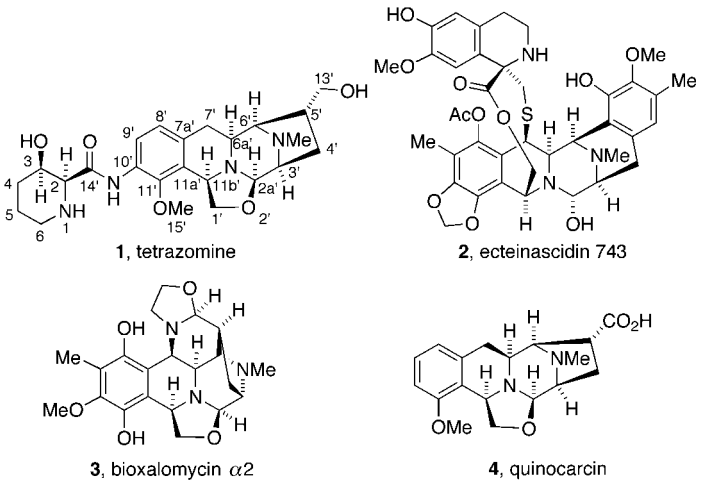
Total Synthesis of (−)-Tetrazomine and Determination of Its Stereochemistry**

Jack D. Scott and Robert M. Williams*

Dedicated to Professor K. Barry Sharpless on the occasion of his 60th birthday

The antitumor antibiotic tetrazomine **1** was isolated from *Saccharothrix mutabilis* at the Yamonouchi Pharmaceutical company by Suzuki et al.[1] Tetrazomine is a member of the tetrahydroisoquinoline family of antitumor antibiotics that



includes ecteinascidin 743 (**2**),[2] bioxalomycin $\alpha 2$ (**3**),[3] and quinocarcin (**4**).[4] Tetrazomine most closely resembles quinocarcin, except for the amino functionality at C10′, the unusual β-hydroxy pipecolic acid moiety, and the oxidation state of C13′. Neither the relative nor the absolute stereochemistry of tetrazomine were determined when the structure was initially reported.[1b] We have since determined that the absolute stereochemistry of the pipecolic acid moiety is 2*S*,3*R*.[5]

Preliminary antitumor/antimicrobial assays of tetrazomine revealed that this substance possesses activity against P388 leukemia in vivo and good antimicrobial activity against both Gram-negative and Gram-positive bacteria.[1a] Tetrazomine exerts its cytotoxic activity through oxidative damage to DNA by the superoxides formed in the auto-redox disproportionation of the fused oxazolidine, and possibly through DNA alkylation.[6]

The total synthesis of tetrazomine has not been reported in the literature,[7] although the synthesis of the AB-ring system of tetrazomine has been discussed by Ponzo and Kaufman.[8] Herein, we describe the first total synthesis of (−)-tetrazo-

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