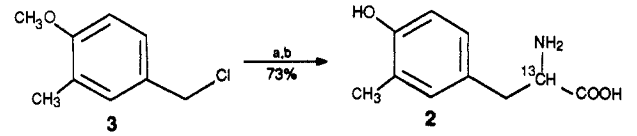
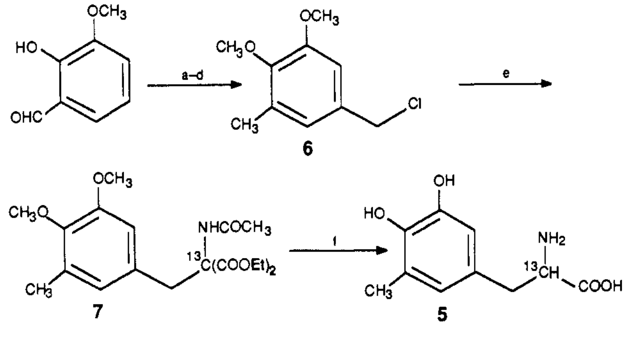
Scheme I[a]



[a](a) NaOEt, AcNH^{13}CH(COOEt)$_2$, EtOH; (b) 47% HI, HOAc, reflux.

Scheme II[a]



[a](a) 10% Pd/C, HOAc, H$_2$; (b) 37% HCHO, KOH, H$_2$O; (c) CH$_2$N$_2$, CH$_3$OH; (d) HCl, Et$_2$O; (e) NaOEt, AcNH^{13}CH(COOEt), EtOH; (f) 47% HI, HOAc, reflux.

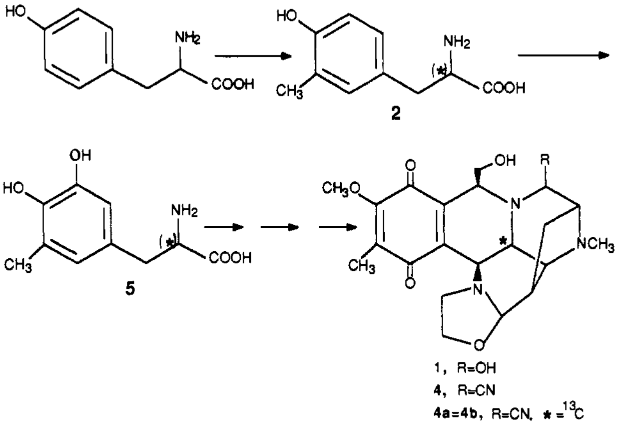
mg, 0.25 mmol) was dissolved in 10 mL of water and divided into two equal portions, and each was divided equally among the three broths at 60 and 72 h after inoculation. After an additional 24 h, the fermentation was worked up in the usual manner[3] to yield 3.1 mg of crystalline cyanonaphthyridinomycin (**4a**). This was diluted with 5.0 mg of unlabeled **4** and recrystallized again.

The 100.6-MHz ^{13}C NMR spectrum of **4a** in CDCl$_3$ revealed an intense resonance for C-13c (53.2 ppm). When normalized to the resonance for C-6 (62.3 ppm) and corrected for dilution with authentic **4**, a 16.8% enrichment in ^{13}C was determined. On the basis of the quantity of **2** fed and that of **4a** produced (determined by UV at 270 nm during the purification), a 1.7% incorporation of **2** had been obtained.

Since formation of the isoquinoline ring could be envisioned to occur by a biochemical Friedel–Crafts reaction, the presence of an hydroxyl ortho to the ring closure seemed likely. To test this, 5′-methyl-[2-^{13}C]DOPA (**5**) was synthesized. 5′-Methyl-DOPA has previously been synthesized in 3% overall yield and what would be a 14% yield for steps after a ^{13}C label could be reasonably introduced.[9] To circumvent this poor yield we adapted the procedure of Knabe et al.[10] using *o*-vanillin as starting material. This was converted in four steps to the benzyl chloride **6** (35% overall yield). Coupling of **6** with diethyl acetamido[2-^{13}C]-malonate[8] yielded 66% of adduct **7**, and hydrolysis with 47–51% HI and glacial acetic acid at reflux provided **5** in 93% yield (Scheme II). A portion of **5** (57 mg, 0.27 mmol) was fed to *S. lusitanus* (5 × 200 mL production broths) as described above and subsequent workup and purification afforded 10.1 mg of **4b**. This, too, was diluted with authentic **4** and recrystallized again. The ^{13}C NMR spectrum obtained from this sample was nearly identical with that obtained from **4a**. In this case a 12.4% enrichment at C-13c was determined, indicating a 2.1% incorporation of **5**.

These results provide strong evidence that **2** and **5**, previously unknown as natural products, are intermediates in the biosynthesis of **1**, and the early stages of the pathway may now reasonably be formulated as shown in Scheme III.

Scheme III



Acknowledgment. Dr. Milton Zmijewski, Jr., now at the Eli Lilly Co., originally provided the culture of *S. lusitanus* and authentic samples of cyanonaphthyridinomycin. This work was supported by Public Health Service Grants GM 31715 and GM 32110 to S.J.G. The NMR spectra were obtained on a Bruker AM 400 spectrometer purchased in part with grants from the National Science Foundation (CHE-8216190) and from the M. J. Murdock Charitable Trust to Oregon State University.

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[11] Characterized by IR and ^{1}H and ^{13}C NMR spectra and comparison with natural abundance **6**. Elemental analysis for **6** at natural abundance. Anal. Calcd for C$_{19}$H$_{27}$NO$_7$: C, 59.83; H, 7.13; N, 3.67. Found: C, 59.61; H, 7.20; N, 3.68.

9,18-Diphenyltetrabenz[*a*,*c*,*h*,*j*]anthracene: A Remarkably Twisted Polycyclic Aromatic Hydrocarbon

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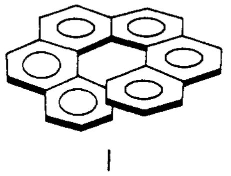
Helical organic molecules have long attracted the attention of synthetic chemists, and their efforts have been rewarded with the successful preparation and characterization of a variety of twisted compounds.[1] Among the most pleasing constructions are the helicenes (e.g., **1**), spiral polycyclic aromatic hydrocarbons in which the axis of the molecular helix is roughly perpendicular to the mean planes of the constituent rings. However, one also can imagine a twisted hydrocarbon ribbon (**2**) in which the helix propagates in a direction parallel to the aromatic ring planes. Since simple



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2

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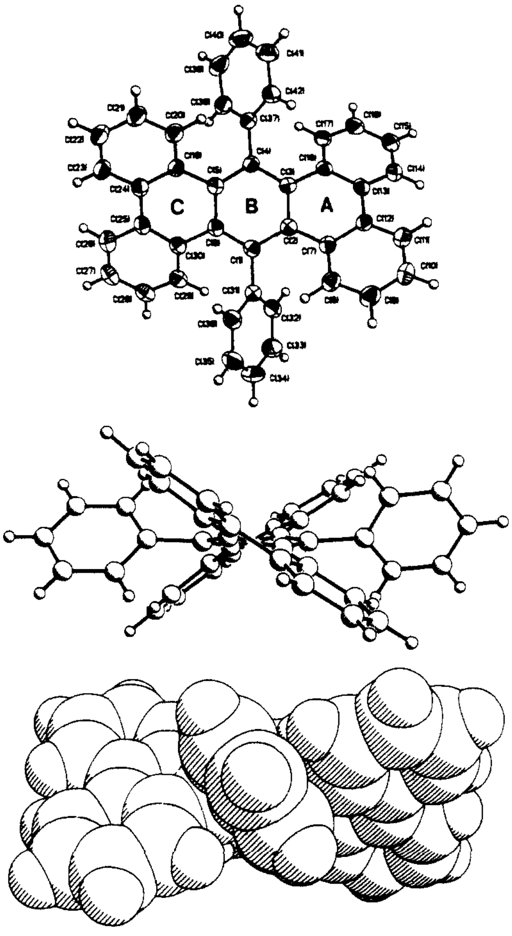
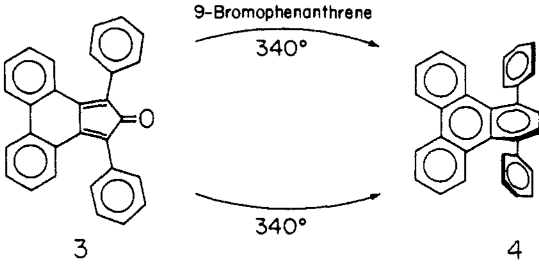


Figure 1. Three views of compound **4**.

linear acenes are planar, such a helical geometry must be enforced with properly chosen substituents.

Preliminary molecular mechanics calculations (MMPI[2]) suggested that 9,18-diphenyltetrabenz[*a,c,h,j*]anthracene (**4**) would be twisted by greater than 60° along the long axis of the anthracene. In principle, **4** could be formed by addition of 9,10-phenanthryne to phencyclone (**3**) followed by loss of carbon monoxide. Compounds which serve as precursors of phenanthryne under mild conditions are, unfortunately, difficult to prepare,[3] but 9-bromophenanthrene has been employed as a phenanthryne equivalent in cycloadditions conducted at over 300 °C.[4] On the assumption that **4** would survive such drastic conditions, we pyrolyzed a 1:1 mixture of phencyclone[5] and 9-bromophenanthrene[6] at 340 °C for 4 h to yield a black solid. This was crushed and continuously extracted with hexane, and the extract was chromatographed on silica gel (solvent, 97:3 hexane–benzene) to give pure **4**[7] as yellow crystals in 4% yield. Curiously, we later discovered that **4** was formed (~2%) upon pyrolysis of **3** alone, suggesting that **3** decomposes at high temperature to give phenanthryne and other, as yet uncharacterized, products.



3 4

Single crystals of **4** were obtained by the slow evaporation of hexane–benzene solutions, and an X-ray crystallographic analysis[8] yielded the structure illustrated in Figure 1. Compound **4** occupies a general position in the crystal lattice and adopts a highly twisted conformation in order to relieve severe hydrogen–carbon nonbonded interactions. As shown in the space-filling drawing in Figure 1, a pair of hydrogens "clamps" each of the proximal carbons of the phenyl substituents. These H–C distances range from 2.33 to 2.43 Å, although the actual internuclear nonbonded H–C distances are probably slightly shorter, since X-ray crystallography tends to underestimate the length of C–H bonds.[9] The anthracene nucleus of **4** is twisted by 65.7° end to end. The deformation is spread rather evenly among the three rings of the anthracene, with rings A, B, and C (see Figure 1) contributing 22.5°, 23.6°, and 19.6° to the overall twist.[10] Significant bond alternation is observed only in rings A and C, where the long bonds average 1.475 Å and the short bonds 1.411 Å. As might be expected from the twist, the four external angles of the type C(1)–C(2)–C(7) are significantly greater than the usual 120° (average 124.6°) while the internal angles of the types C(3)–C(2)–C(7) (average 117.1°) and C(1)–C(2)–C(3) (average 118.3°) are slightly contracted.

Although highly strained and distorted, compound **4** is remarkably stable. The crystals do not melt or discolor when heated in air to over 350 °C, and their solutions are stable to air, light, and ordinary acids and bases. One apparent electronic effect of the nonplanar deformation is a 15–30-nm red shift in the major features of the UV absorption spectrum of **4** when compared with that of the presumably planar tetrabenz[*a,c,h,j*]anthracene.[11] We are encouraged by the stability and high helical pitch of these compounds that polycyclic aromatic ribbons with twists of 90° or even 180° may soon by synthesized.

Supplementary Material Available: X-ray data for **4**, including description of data collection and tables of crystal parameters, data measurements, atomic coordinates, anisotropic and isotropic thermal parameters, bond lengths and angles, and H atom coordinates (8 pages). Ordering information is given on any current masthead page.

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(7) For **4**: mp >350 °C, ^{1}H NMR (250 MHz, $CDCl_3$) δ 6.96 (ddd, 4 H, J = 8, 7, 1 Hz), 7.18 (dd, 4 H, J = 8, 1 Hz), 7.39 (m, 14 H), 8.35 (dd, 4 H, J = 8, 1 Hz); MS, m/z 530 (M^+, 100%), 451 ($M - H - C_6H_6$, 18%); exact mass 530.2036, calcd for $C_{42}H_{26}$ 530.2034.

(8) Two similar crystals of compound **4**, measuring 0.22 × 0.25 × 0.50 mm and 0.20 × 0.25 × 0.46 mm, were used for X-ray measurements. Crystal data: $C_{42}H_{26}$, M_r = 530.63; monoclinic, space group $P2_1/n$ (standard: $P2_1/c$); a = 14.851 (3) Å, b = 10.136 (3) Å, c = 18.425 (4) Å, β = 96.55 (2)°, V = 2755 (1) Å^3, Z = 4, d_{calcd} = 1.28 g/cm^3. Intensity measurements were made with $3° < 2\theta < 110°$ by using graphite monochromated Cu Kα radiation (λ = 1.541 78 Å) at 175 K on a Nicolet R3m diffractometer. A total of 3470 unique reflections were measured, and after applying Lorentz, polarization, and background corrections, 3016 were considered to be observed [$|F_o| > 3\sigma(F_o)$]. The structure was solved by direct methods using the SHELXTL software. In the final cycles of blocked-cascade least-squares refinement, all non-hydrogen atoms were refined anisotropically. H(8), H(17), H(20), and H(29) were refined with isotropic temperature factors, and a riding model with idealized geometry [C–H = 0.96 Å, $B(H) = 1.2B(C)$] was used for all other hydrogens. Refinement with 395 parameters converged at R = 0.041 and R_w = 0.047 with goodness of fit = 1.57. Full details are provided in the Supplementary Material.

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(10) Crystal packing forces are probably responsible for the unequal twists of rings A and C and other deviations of **4** from an ideal C_2 (or possibly D_2) symmetry.

(11) UV absorption spectra (λ_{max} (nm) with log ε in parentheses): tetrabenz[*a,c,h,j*]anthracene,[12] 295 (5.0), 336 (4.54), 363.5 (3.36), 382.5 (3.24); compound **4**, 324 (5.1), 350 (shoulder, 4.6), 390 (shoulder, 3.2), 413 (3.0).

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