was worked up as usual. The residue was a 1.5:1 mixture of ketones **4a** and **4b**, as shown by GLC analysis.

The catalyzed Diels–Alder reaction of dienone **6** with diene **2** and its workup followed the procedure of the **2–3** reaction. A 1.5:1 mixture of the ketones **4a** and **4b** was obtained, as shown by GLC analysis.

Bicyclo[4.4.0]-8,10-dien-2-one (6). A solution of 0.18 g (1 mmol) of octalone **3** in 2 mL of dry toluene was added to a solution of 0.265 g (0.25 mmol) of $Yb(fod)_3$ in 5 mL of dry toluene in a glass ampule. Then enough solvent to form 10 mL of the final solution was added. The ampule was degassed, sealed in vacuo, and heated at 100 °C for 7 h in a heating bath. After the usual workup, the resulting oil was purified by column chromatography on 12 g of silica gel (elution with pentane) to yield 130 mg (88%) of colorless, oily ketone **6**: IR 3040 (m, olefinic CH), 1680 (s, C=O), 1620 (s, C=C) cm^{-1}; ^1H NMR δ 1.0–3.4 (m, 9, methylenes, CH), 6.28 (m, 2, H-8, H-9), 7.67 (m, 1, H-10); ^{13}C NMR δ 21.4 (C-4), 30.1 (C-5), 30.9 (C-7), 34.0 (C-6), 40.0 (C-3), 124.7 (C-9), 130.9 (C-10), 134.6 (C-8), 135.3 (C-1), 200.3 (C-2). Anal. Calcd for $C_{10}H_{12}O$: C, 81.08; H, 8.11. Found: C, 81.20; H, 8.05.

Diels–Alder Adduct 7. A mixture of 1.5 g (13.6 mmol) of ketone **1b**, 6.90 g (82 mmol) of diene **2**, and 20 mg of hydroquinone was heated in a degassed, sealed tube at 160 °C for 72 h. The volatile materials were removed under vacuum and the crude residue was chromatographed on 110 g of silica gel. Elution with 9:1 pentane–ether afforded 0.85 g (32%) of octalone **7**: IR 3030 (m, olefinic CH), 1702 (s, C=O), 1655 (w, C=C), 1085 (s, C—O—C) cm^{-1}; ^1H NMR δ 1.12 (Me), 1.51 (H-7B), 1.78 (H-4A), 1.82 (H-4B), 1.87 (H-6), 2.07 (H-5B), 2.12 (H-7A), 2.29 (H-5A), 2.53 (H-3A, H-3B), 3.24 (H-10), 3.26 (OMe), 5.80 (H-8A, H-8B), 5.87 (H-9A, H-9B); ^{13}C NMR δ 21.0 (Me), 23.8 (C-4), 27.4 (C-7), 28.9 (C-5), 39.0 (C-6), 41.1 (C-3), 50.9 (C-1), 57.7 (OMe), 79.4 (C-10), 123.1 (C-9), 127.5 (C-8), 214.4 (C-2). Anal. Calcd for $C_{12}H_{18}O_2$: C, 74.22; H, 9.28. Found: C, 74.53; H, 9.40.

Catalytic Hydrogenations. The reductions of olefinic ketones **4** and **7** were carried out according to the following procedure. Platinum oxide (30 mg) in 8 mL of dry ethanol was stirred under a hydrogen atmosphere until cessation of hydrogen absorption. A solution of 0.77 mmol of the ketone in 5 mL of dry ethanol was added and the reaction carried out at room temperature and atmospheric pressure. It was terminated at the stage of consumption of the required amount of hydrogen. The workup followed the normal procedure.

(6β,10α)-14β-Methoxytricyclo[8.4.0.0^{1,10}]tetradecan-2-one (5a): mp 71–72 °C (pentane); IR 1700 (s, C=O), 1093, 1082 (s, C—O—C) cm^{-1}; ^1H NMR δ 1.26 (H-9B), 1.29 (H-11B), 1.34 (H-7A, H-7B or H-8A, H-8B), 1.37 (H-5B), 1.44 (H-13B), 1.46 (H-12B), 1.47 (H-8A, H-8B or H-7A, H-7B), 1.54 (H-12A), 1.58 (H-11A), 1.88 (H-9A), 1.89 (H-4B), 1.96 (H-4A), 2.00 (H-13A), 2.11 (H-5A), 2.23 (H-3B), 2.27 (H-6), 2.36 (H-10), 2.54 (H-3A), 3.24 (OMe), 4.03 (H-14); ^{13}C NMR δ 19.2 (C-12), 20.8 (C-8), 22.0 (C-4), 22.7 (C-13), 26.1 (C-5), 26.7 (C-11), 28.6 (C-9), 29.4 (C-7), 30.1 (C-10), 35.9 (C-6), 37.9 (C-3), 56.2 (OMe), 57.0 (C-1), 79.0 (C-14), 213.0 (C-2). Anal. Calcd for $C_{15}H_{24}O_2$: C, 76.27; H, 10.17. Found: C, 76.28; H, 10.35.

(6β,10α)-14α-Methoxytricyclo[8.4.0.0^{1,10}]tetradecan-2-one (5b): mp 151–153 °C (pentane); IR 1718 (s, C=O), 1100, 1088 (s, C—O—C) cm^{-1}; ^1H NMR δ 1.26 (H-9B), 1.29 (H-11B), 1.34 (H-7A, H-7B or H-8A, H-8B), 1.37 (H-5B), 1.44 (H-13B), 1.46 (H-12B), 1.47 (H-8A, H-8B or H-7A, H-7B), 1.54 (H-12A), 1.58 (H-11A), 1.88 (H-9A), 1.89 (H-4B), 1.96 (H-4A), 2.00 (H-13A), 2.11 (H-5A), 2.23 (H-3B), 2.27 (H-6), 2.36 (H-10), 2.54 (H-3A), 3.24 (OMe), 4.03 (H-14); ^{13}C NMR δ 19.2 (C-12), 20.8 (C-8), 22.0 (C-4), 22.7 (C-13), 26.1 (C-5), 26.7 (C-11), 28.6 (C-9), 29.4 (C-7), 30.1 (C-10), 35.9 (C-6), 37.9 (C-3), 56.2 (OMe), 57.0 (C-1), 79.0 (C-14), 213.0 (C-2). Anal. Calcd for $C_{15}H_{24}O_2$: C, 76.27; H, 10.17. Found: C, 76.50; H, 10.15.

10α-Methoxy-1β-methyl-6β-bicyclo[4.4.0]decan-2-one (8): IR 1700 (s, C=O), 1100, 1072 (s, C—O—C) cm^{-1}; ^1H NMR δ 1.22 (s, 3, Me), 3.22 (s, 3, OMe); ^{13}C NMR δ 21.8 (Me), 23.3 (C-8), 24.1 (C-4), 27.1 (C-7), 27.7 (C-9), 29.5 (C-5), 40.7 (C-3), 42.7 (C-6), 52.0 (C-1), 57.1 (OMe), 85.0 (C-10), 215.4 (C-2). Anal. Calcd for $C_{12}H_{20}O_2$: C, 73.47; H, 10.20. Found: C, 73.20; H, 10.25.

Acknowledgment. F.F., L.M., and A.T. thank the Consiglio Nazionale delle Ricerche and the Ministero della Pubblica Istruzione for financial support of the work in Perugia. A.T. and E.W. are indebted to NATO for its grant (No. 257.81) support. L.R. is grateful to Drs. Maria Kajtar-Peredy and Esther Gacs-Baitz for their skillful assistance in compiling the NMR data.

Absolute Configuration of CC-1065 by X-ray Crystallography on a Derivatized Chiral Fragment (CPI) from the Natural Antibiotic

David G. Martin,* Robert C. Kelly, William Watt, Nancy Wicnienski, Stephen A. Mizsak, James W. Nielsen, and Mark D. Prairie

Research Laboratories, The Upjohn Company, Kalamazoo, Michigan 49001

Received April 28, 1988

CC-1065, **1**, a novel, potent antitumor antibiotic isolated from *Streptomyces zelensis*, displayed remarkable cytotoxic and in vivo antitumor activity.[1] Spectral and crystallographic analyses yielded the structure of **1** but did not establish the absolute configuration of its two asymmetric centers.[2] The chirality of the antibiotic has been inferred from modeling studies of CC-1065–DNA interactions and the CC-1065–(*N*-3-adenine)–DNA adduct.[3] These studies indicated that the adduct could only be accommodated if the spirocyclopropyl group extends below the plane of the page as drawn (**1**). Recent developments have allowed us to rigorously confirm the indicated stereochemistry by single-crystal analysis of a heavy atom derivative of the chiral fragment, CPI (**3**), prepared from natural CC-1065.

Before successful crystallization and X-ray crystallography on CC-1065 allowed assignment of its structure, efforts to prepare a crystalline heavy-atom derivative were precluded by an apparent degradation of the antibiotic under acidic and basic conditions.[4] Further studies revealed a fragmentation under alkaline conditions and the addition of acid across the spirocyclopropylcyclohexadienyl system under acidic conditions.[5] The availability of the chiral cyclopropapyrroloindole CPI (**3**) from alkaline fragmentation of natural CC-1065 allowed the attempted preparation of crystalline heavy-atom derivatives having the potential to rigorously establish the absolute configuration by X-ray crystallography. Efforts on derivatizing CPI were part of the extensive synthetic studies prompted by the structural novelty and antitumor potency of CC-1065.[6] The toxicity[7] of CC-1065 precluded its development as an antitumor drug, but synthetic analogues that are *N*-acyl derivatives of the vinylogous amide of CPI displayed improved antitumor potency and efficacy without the unusual toxicity of the antibiotic itself.[8] The obser-

(1) (a) Hanka, L. J.; Dietz, A.; Gerpheide, S. A.; Kuentzel, S. L.; Martin, D. G. *J. Antibiot.* **1978**, *31*, 1211. (b) Martin, D. G.; Biles, C.; Gerpheide, S. A.; Hanka, L. J.; Krueger, W. C.; McGovren, P. J.; Mizsak, S. A.; Neil, G. L.; Stewart, J. C.; Visser, J. *J. Antibiot.* **1981**, *34*, 1119.

(2) Chidester, C. G.; Krueger, W. C.; Mizsak, S. A.; Duchamp, D. J.; Martin, D. G. *J. Am. Chem. Soc.* **1981**, *103*, 7629.

(3) Hurley, L. H.; Reynolds, V. L.; Swenson, D. H.; Petzold, G. L.; Scahill, T. A. *Science (Washington, D.C.)* **1984**, *226*, 843.

(4) Martin, D. G.; Chidester, C. G.; Duchamp, D. J.; Mizsak, S. A. *J. Antibiot.* **1980**, *33*, 902.

(5) Martin, D. G.; Mizsak, S. A.; Krueger, W. C. *J. Antibiot.* **1985**, *38*, 746.

(6) Kelly, R. C.; Gebhard, I.; Wicnienski, N.; Aristoff, P. A.; Johnson, P. D.; Martin, D. G. *J. Am. Chem. Soc.* **1987**, *109*, 6837 and references cited.

(7) McGovren, J. P.; Clarke, G. L.; Pratt, E. A.; DeKoning, T. F. *J. Antibiot.* **1984**, *37*, 63.

0022-3263/88/1953-4610$01.50/0

vation that the most biologically active analogues had the same chirality as the natural product[8] added to the urgency of rigorously establishing its absolute configuration. Analogue synthesis requiring many steps and suffering from problems in removing blocking groups prompted exploration of direct acylation of CPI.

The coexistence of vinologous amide, spirocyclopropylcyclohexadienone, and indolone systems in CPI complicated predictions on the outcome of direct acylation. Experimentally, monoacylation of CPI by treatment with an acid chloride in the presence of mild base was not observed. Treating CPI with only 1 equiv of acid chloride afforded a 50% yield of bis(acyl) derivative **4** along with a 50% recovery of CPI, indicating that an initial acylation was followed by a second, more rapid acylation. With 2 equiv of acid chloride an essentially quantitative yield of **4** was obtained. Selective hydrolysis of **4** proved equally interesting and useful. Exactly 1 equiv of sodium hydroxide cleaved the *O*-acylate and recyclized the phenolic chloride to the spirocyclopropyl system[9] in **5**, but any excess base resulted in hydrolysis of **5** to CPI. Milder base (methanolic ammonia) afforded delightful results; the desired **5** was formed in 80% overall yield from CPI.

The complex systems present in CPI obscure rationalizing whether the initial event involves O-acylation or N-acylation. The possibility that the vinylogous amide system in **3** could acylate initially on oxygen to an intermediate such as **6** is precedented in the literature.[10] In an intermediate like **6**, strain energy of the cyclopropyl system coupled with the energy gain on aromatization would make this initial product vulnerable to attack by chloride-producing **7**. Intermediate **7**, carrying an ordinary aromatic amine in place of the vinologous amide, should rapidly react with a second acid chloride affording the O,N-diacylated product **4**. Alternatively, the possibility that N-acylation is the initial event affording **5**, the same product obtained by selective hydrolysis of **4**, cannot be excluded on theoretical grounds. Strain and aromatization energies could make **5** equally vulnerable to chloride attack producing **8** or susceptible to direct acylation to **4**. A third possibility for the initial event, opening the spirocyclopropyl system prior to acylation, is unlikely for at least two reasons. In the first place, the spirocyclopropyl system in CPI is stable in the presence of HCl.[11] Secondly, addition of HCl across the spirocyclohexadienone system of CPI, if it did occur, would produce the same chloromethyl phenolic analogue previously found amenable to clean monoacylation on nitrogen in high yield.[6]

Experimental observations lead us to favor the first possibility (O-acylation) as the initial event. In contrast to CPI, **5** was easily opened by chloride affording **8**; **8** was readily recyclized to **5** with dilute base[6] and acylated to **4**. However, a competitive acylation with 4-chlorobenzoyl chloride established that **3** is much more rapidly acylated than **8** and that **8** in turn is more rapidly acylated than **5**.

Although bisacylation and selective hydrolysis was a remarkably clean route to the heavy atom derivative **5**, this approach was not clean enough with other acid chlorides to provide a general route for efficient analogue synthesis. Further studies indicated that the anion of the vinologous amide of CPI could be generated without deprotonating the pyrrole nitrogen and directly acylated.[6] A general method suitable for analogue synthesis or recoupling the fragments of CC-1065 is based on an efficient selective direct acylation of the aromatic secondary amine of the chloromethyl phenolic analogue of CPI.[6]

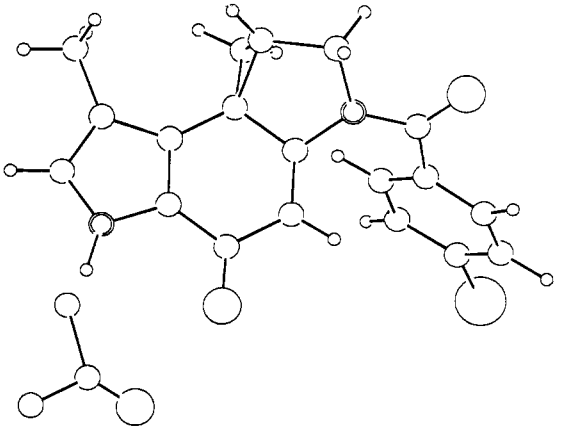


Figure 1. Computer-generated drawing illustrating that the quaternary carbon of **5** has the *R* configuration and the methine carbon the *S* configuration. The absolute configuration was determined by anomalous dispersion.

The heavy atom derivative **5** was moderately labile to hydrolysis. Attempted reverse phase (C18) chromatography of **5** with aqueous methanol resulted in extensive hydrolysis to CPI. A fresh sample of **5** was efficiently purified by counter-current chromatography (CCC),[12] and homogeneous **5** readily crystallized, providing suitable crystals for X-ray crystallography. The enantiomer determination, using the method of Bijvoet,[13] was carried out by calculating structure factors for both enantiomers and performing a computer search to find the reflections most significantly affected by anomalous dispersion. The enantiomer with the quaternary carbon in the *R* configuration and the methine carbon in the *S* configuration (Figure 1) was strongly favored over its mirror image; thus, rigorously establishing that **5** and hence CC-1065 itself has the absolute configuration previously inferred.[3]

Experimental Section[14]

Bisacylation of CPI with 4-Chlorobenzoyl Chloride 4. To 11.2 mg (0.056 mmol) of natural CPI[5] was added 19.2 mL of 7.2 mM triethylamine in methylene chloride (0.138 mmol) and 17 mL of 7.9 mM chlorobenzoyl chloride in methylene chloride (0.134 mmol). After 1.5 h of stirring at room temperature in subdued light, TLCD indicated the absence of CPI and the presence of a clean, more lipophilic component. After evaporation under reduced pressure, trituration of the residue with 3 mL of aqueous 85% MeOH afforded a white suspension, which was briefly chilled.

(8) (a) Warpehoski, M. A. *Tetrahedron Lett.* **1986**, *27*, 4103. (b) Warpehoski, M. A.; Kelly, R. C.; McGovren, J. P.; Wierenga, W. *Proc. Am. Assoc. Cancer Res.* **1985**, *26*, 870. (c) Warpehoski, M. A.; Gebhard, I.; Kelly, R. C.; Krueger, W. C.; Li, L. H.; McGovren, J. P.; Prairie, M. D.; Wicnienski, N. A.; Wierenga, W. *J. Med. Chem.* **1988**, *31*, 590.

(9) Baird, R.; Winstein, S. *J. Am. Chem. Soc.* **1963**, *85*, 567.

(10) (a) Speziale, A. J.; Smith, L. R. *J. Org. Chem.* **1962**, *27*, 4361. (b) Leonard, N. J.; Adamcik, J. A. *J. Am. Chem. Soc.* **1959**, *81*, 595.

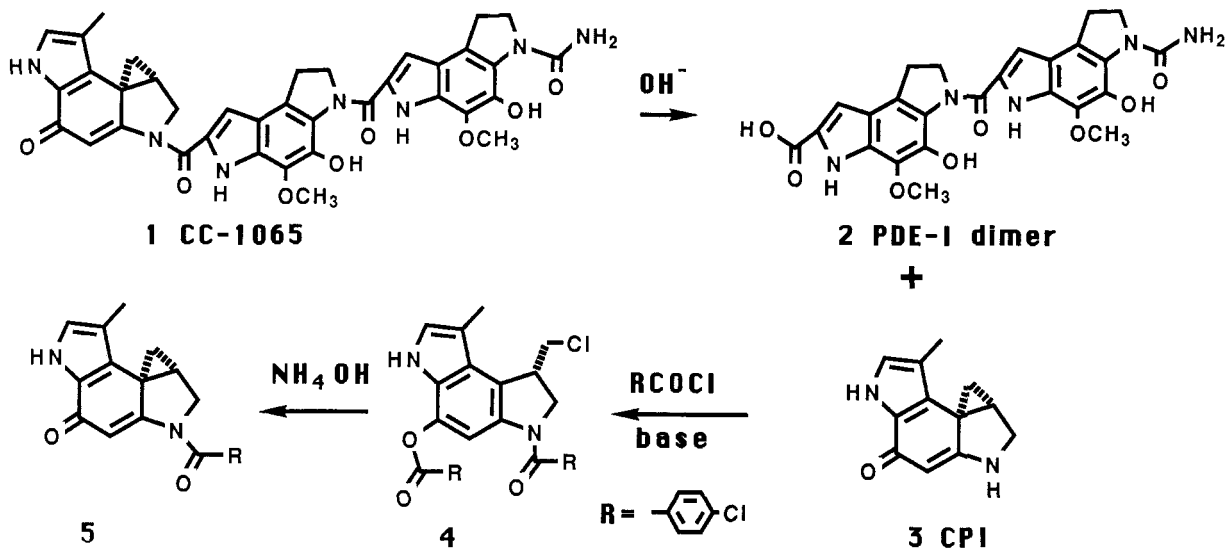
(11) No new TLCD peaks were observed in a solution of CPI treated with HCl. After 15 min the R_f and 340-nm response were the same as control CPI. After 17 h at ambient temperature, the peak was broadened with approximately 50% of the initial 340-nm response.

(12) (a) Ito, Y.; Conway, W. D. *Anal. Chem.* **1984**, *56*, 534A. (b) Martin, D. G.; Biles, C.; Peltonen, R. E. *Am. Lab.* **1986**, *18*(10), 21 and references cited.

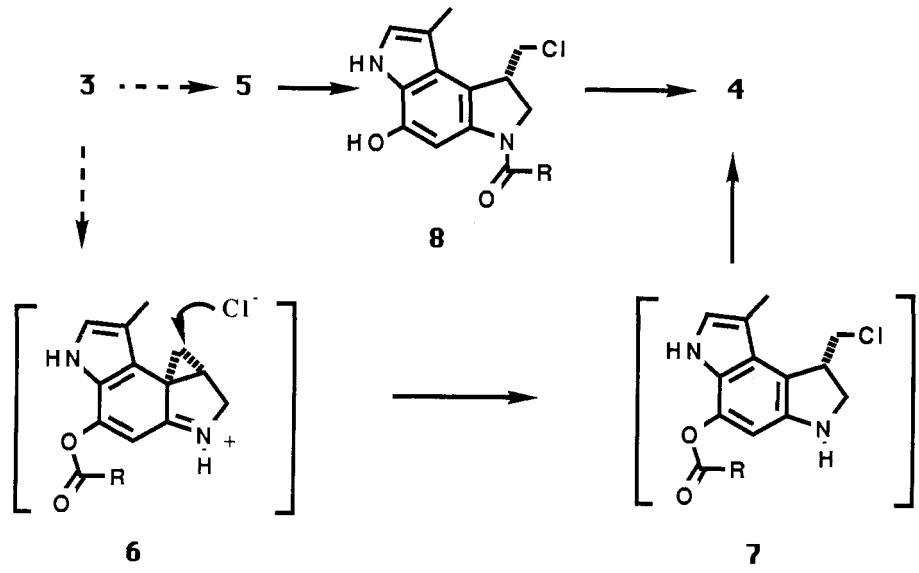
(13) Bijvoet, J. M. *Endeavor* **1955**, *14*, 71.

(14) Carbon NMR spectra were recorded on a Varian XL 200 spectrometer at 50 MHz. Chemical shifts were reported in ppm from tetramethylsilane. Fast atom bombardment mass spectra (FABMS) were recorded on a Varian MAT CH5-DF spectrometer. Circular dichroism spectra (CD) were recorded on a JASCO 500-C CD spectropolarimeter. X-ray intensity measurements were carried out on a Syntex $P2_1$ diffractometer controlled by a Harris computer. TLC densitometry (TLCD) was carried out on Whatmann LKC18D plates monitored with a Shimadzu CS-930 dual-wavelength TLC scanner. CCC was carried out with an Ito multilayer coil separator–extractor (P. C. Inc.). Mallinckrodt AR ethyl ether from a freshly opened can was used; B & J high-purity solvents were used for all other solvents.

Scheme I



Scheme II



The solid was collected, washed with aqueous MeOH, and dried, affording 30.7 mg of homogeneous **4**: TLCD (3:1 acetone–water, 250 nm) R_f 0.31; FABMS $(M + H)^+$ 513; UV (dioxane) 243 nm (ϵ 51 550), 271 (sh) (21 750), 307 (sh) (11 750); CD (dioxane, nm) (molar ellipticity) 300 (−9000), 250 (+18 000), 228 (−43 000); ^{13}C NMR (deuterioacetone) δ (multiplicity) 11.3 (q), 42.9 (d), 48.2 (t), 56.1 (t), 106.2 (d), 110.7 (s), 120.6 (s), 126.1 (d), 126.3 (s), 126.5 (s), 129.2 (s), 129.4 (2 d), 129.7 (2 d), 129.8 (2 d), 132.6 (2 d), 136.1 (s), 136.6 (s), 136.6 (s), 137.1 (s), 140.2 (s), 164.4 (s), 167.4 (s). Recrystallization attempts on **4** afforded only needles unsuitable for X-ray analysis.

***N*2-(4-Chlorobenzoyl)-CPI (5).** A solution of **4** (30 mg) in 5.5 mL of DMF was diluted with 22 mL of 5 mM methanolic NH_4OH.[15] After 43 h in the dark at room temperature, the solution was evaporated to dryness under reduced pressure, leaving a viscous oil. TLC densitometry indicated that the major component had regained UV absorbtion above 340 nm and displayed an intermediate polarity[16] between CPI and **4**, consistent with expected properties for **5**. An efficient purification of **5** was obtained by CCC. The biphasic solvent system obtained from equal parts of hexane, ethyl acetate, MeOH, and water evenly partitioned an aliquot of crude **5** between its phases and was used for CCC. The column (2.6 mm i.d.) had an approximate capacity of 330 mL. The upper phase was used as mobile phase at a flow rate of 3 mL/min while the coil was rotated at 800 rpm; approximately 309 mL or 94% of the stationary phase was retained. Collected fractions of the mobile phase were monitored by TLC densitometry. After 335 mL of mobile phase, homogeneous **5** was present in the next 152 mL of eluate. Evaporation left 13 mg of essentially pure **5**: HRMS $(M + H)^+$ 339.0882 ($C_{19}H_{16}ClN_2O_2$ requires 339.0900); UV (MeOH) 235 (sh) (14 600), 291 (12 200), 353 (12 300); CD (MeOH) 355 (−15 700), 290 (+114 000), 268 (sh) (+61 500), 240 (−65 500); ^{13}C NMR ($CDCl_3$) 9.8 (q), 21.0 (d), 21.6 (t), 32.3 (s), 53.9 (t), 112.3 (d), 113.8 (s), 123.8 (d), 129.0 (2 d), 129.5 (2 d), 132.7 (s), 132.7 (s), 138.2 (s), 60.0 (s), 168.4 (s), 176.3 (s). After spectral analyses, slow crystallization of recovered **5** from acetone–cyclohexane afforded clear, thin plates of an acetone solvate suitable for X-ray diffraction studies. Crystalline **5** did not have a well-defined melting point; crystals gradually darkened and softened above 200 °C.

Single-Crystal X-ray Diffraction Analysis of 5. Crystal data are: monoclinic; $C_{19}H_{15}N_2O_2Cl$* 0.35 (C_3H_6O); M_r = 359.21; space group C2; a = 20.670 (2) Å, b = 7.468 (1) Å, c = 11.695 (1) Å, β = 96.53 (1)°; Z = 4; D_{calcd} = 1.36 g/cm^3; μ(Cu Kα) = 19.4 cm^{-1}; T = 123 K; R = 0.105 for 1518 unique reflections (R = 0.066 for 721 reflections > 3σ). A clear, thin plate of dimensions 0.13

(15) Prepared by diluting 1 part of aqueous 1 N NH_4OH with 200 parts of MeOH.

(16) TLC (7:3 MeOH–H_2O): **4**, R_f 0.02; **5**, R_f 0.31; **3**, R_f 0.54. By reconstituting the oil in a defined volume of acetone and comparing the response with that from a known quantity of homogeneous **5**, TLCD indicated that approximately 15 mg (80% overall from **3**) of **5** was present.

× 0.06 × 0.16 mm was used for intensity measurements with Cu Kα radiation and a graphite monochromator. The step-scan technique was used with a scan speed of 2°/min, a scan width of 3.4°, and a $2\theta_{max}$ of 138°. Of the 1518 unique reflections measured, 721 had intensities greater than 3σ. A partial trial solution, 27 atoms, was obtained by direct methods by using MULTAN80.[17] The remaining atoms were found by successive Fourier syntheses. The structure was refined by least squares; parameters varied were coordinates of all non-hydrogen atoms, anisotropic thermal parameters for non-hydrogen atoms, isotropic thermal parameters for solvent atoms, and a site occupancy factor for the solvent. The enantiomer determination, using the method Bijvoet,[18] was carried out by calculating structure factors for both enantiomers and computer searching for the reflections most significantly affected by anomalous dispersion. Found were 34 reflections, which were scanned very accurately over each of their four positions with 23 showing an enantiomeric preference. Of these 23 reflections, 22 favored the enantiomer with its quaternary carbon in the *R* configuration and its methine carbon in the *S* configuration (Figure 1). Further details of the X-ray determination including fractional coordinates and bond lengths and angles are readily available.[18]

Conversion of 5 to 8. Repeating the mild methanolic NH_4OH hydrolysis of **4** under slightly modified conditions proved interesting. Slightly less water was present since the 5 mM NH_4OH was prepared by diluting concentrated NH_4OH with MeOH instead of diluting aqueous 1 N NH_4OH with MeOH as before. Unlike the previous hydrolysis, TLCD after 22, 42, and 72 h indicated the presence of a minor component of intermediate mobility between **4** and **5**, subsequently found to be **8**.[19] After 6 days, only **5** and a small amount of **3** were evident, and the solution was evaporated to dryness, reconstituted in acetone, and stored in the freezer for 16 days. After storage, TLCD indicated that **8** was the major component with **5** as a minor component along with a small amount of **3**. A sample of homogeneous **8** was isolated by CCC with the solvent phases from hexane–ethyl ether–MeOH–Water (1:2:2:1). **8**: HRMS $(M + H)^+$ 375.0639 ($C_{19}H_{17}Cl_2N_2O_2$ requires 375.0667). Treating **8** with dilute methanolic NH_4OH afforded **5**. Acylating **8** with 4-chlorobenzoyl chloride and triethylamine afforded **4**. TLCD indicated that an acetone solution of pure **5** was rapidly converted into homogeneous **8** by HCl or pyridine hydrochloride.

Competitive Acylation of a Mixture of 3, 5, and 8. The previously described mixture of **3**, **5**, and **8** was treated with the same conditions used to acylate **3**, and the acylation to **4** was monitored at intervals by TLCD. Under these conditions, **3** was essentially all reacted in the first 2 min, half of **8** remained after 20 min, and one-third after 2 h, and 78% of **5** remained after 20 h.

(17) Main, P.; Fiske, S. J.; Hull, S. E.; Lessinger, L.; Germain, G.; Declercq, J. P.; Woolfson, M. MULTAN80. A system of computer programs for the automatic solution of crystal structures from X-ray diffraction data; Universities of York, England, and Louvain, Belgium, 1980.

(18) Watt, W.; Martin, D. G.; Duchamp, D. J.; Mizsak, S. A.; Nielsen, J. W.; Prairie, M. D. *Acta Crystallogr.*, in press.

(19) TLCD (3:1 MeOH–H_2O, 280 nm): **4**, R_f 0.05; **8**, R_f 0.24; **5**, R_f 0.44; **3**, R_f 0.63.

Tetraphenylbutadienes via (1,1-Diphenylallyl)lithium

Barbara E. Simes[1] and Bruce Rickborn*

Department of Chemistry, University of California, Santa Barbara, California 93106

John M. Flournoy and Isadore B. Berlman[2]

E G & G Energy Measurements Inc., 130 Robin Hill Road, Goleta, California 93117

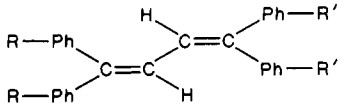
Received April 8, 1988

Tetraphenylbutadienes[3] (TPBs) exhibit interesting fluorescence features. The spectral and physical properties of TPBs can be controlled to some extent by the introduction of substituents on the aromatic rings, and methods to synthesize substituted TPBs are therefore of interest. The parent TPB has been prepared by the addition of excess PhMgBr to diethyl succinate, followed by dehydration of the resulting diol. This method, introduced many years ago by Wittig and von Lupin,[4] is suitable for the preparation of TPBs such as **1** in which R = R′ but would be inappropriate for the synthesis of unsymmetrical derivatives. Similar symmetry considerations are inherent in most other TPB preparative methods,[5] and examination of these procedures failed to provide an attractive solution to the problem of preparing unsymmetrical TPBs of the general structure **1** (R ≠ R′). This substitution pattern is of particular interest since it avoids the complications of *E,Z* isomerism.

Table I. Substituted Tetraphenylbutadienes (1)[a]

R =	R′	mp, °C
H	*p*-*n*-Pr	100–101
H	*m*-Br	136–138
H	*p*-Br	172–173
H	*p*-Ph	200–201
H	*o*-(bond)[b]	189–190
H	*o*-(–O–)[c]	167–169
H	*o*-(–S–)[d]	214–216
p-*n*-Pr	*p*-Br[e]	179–181
p-*n*-Br	*p*-Ph[f]	200–202

[a] These products were formed by the stiochiometric ratio procedure described in the Experimental Section, in yields (after recrystallization from HOAc or ethanol) that ranged from 15 to 35%; they were characterized by MS and ^1H NMR spectra. All products where R = H were prepared from 3,3-diphenylpropene and the appropriate substituted benzophenone. Other starting materials were [b] fluorenone; [c] xanthone; [d] thioxanthone; [e] 3,3-bis(4-propylphenyl)propene and 4,4′-dibromobenzophenone; [f] 4,4′-diphenylbenzophenone.



1

Indirect acid-enhancing methods such as Wittig ylide chemistry are widely employed to prepare olefins, and the parent TPB has been made by coupling of the 3,3-diphenyl-2-propenyl ylide to benzophenone.[5g] However, a more direct approach, which capitalizes on the inherent acidity[6] of 1,1-diphenylpropene (**2**), appeared to be feasible and is the subject of the present study. The sequence is illustrated in eq 1–3 for TPB itself (**1**, R = R′ = H).

(1) Recipient of President's Undergraduate, Faculty Women's, and College of Creative Studies Fellowships.

(2) On leave from The Hebrew University, Jerusalem.

(3) The *Chemical Abstracts* name for tetraphenylbutadiene is 1,1′,1″,1‴-(1,3-butadiene-1,4-diylidene)tetrakisbenzene.

(4) Wittig, G.; von Lupin, F. *Chem. Ber.* **1928**, *61*, 1627.

(5) (a) Brand, K.; Krucke-Amelung, D. *Chem. Ber.* **1939**, *72*, 1029. (b) Kuhn, R.; Plotzer, B. *Ibid.* **1940**, *73*, 1410. (c) Tadros, W.; Sakla, A. B.; Akhookh, Y. *J. Chem. Soc.* **1956**, 2701. (d) Wirth, H. O.; Koenigstein, O.; Kern, W. *Justus Liebigs Ann. Chem.* **1960**, *634*, 84. (e) Huttel, R.; Kratzer, J.; Bechter, M. *Chem. Ber.* **1961**, *94*, 766. (f) Sket, B.; Zupan, M. *Synth. Commun.* **1976**, *6*, 309. (g) Schweizer, E. E.; Kim, C. S. *J. Org. Chem.* **1971**, *36*, 4033.

(6) 1,1-Diphenylpropene was examined very early in work aimed at establishing acidity scales for hydrocarbons, where "pK_a" values of 30[7] and 36[8] were found (different scales). It appears not to have been reexamined in this context subsequently.[9]

(7) Conant, J. B.; Wheland, G. W. *J. Am. Chem. Soc.* **1932**, *54*, 1212.

(8) McEwen, W. K. *J. Am. Chem. Soc.* **1936**, *58*, 1124.

(9) Streitwieser, A., Jr.; Juaristi, E.; Nebenzahl, L. L. In *Comprehensive Carbanion Chemistry*; Buncel, E., Durst, T., Eds.; Elsevier: New York, 1980; Part A, Chapter 10.

0022-3263/88/1953-4613$01.50/0