identical with an authentic sample.

Reaction of 8 with Methanolic Silver Nitrate. A solution of 8 (130 mg, 0.5 mmol) and methanolic (150 mL) silver nitrate (300 mg, 1.8 mmol) was stirred vigorously. After 30 min the methanol was removed under reduced pressure and the organic product was dissolved in ethyl ether. Filtration and concentration of the solution yielded methyl 1-naphthoate (80 mg, 0.43 mmol, 86%) of proper spectral properties.

$\Delta^{1,1}$-Bi-1*H*-cyclobuta[*de*]naphthalene (3). Procedure A. Zinc (50 mg, 0.77 mmol) activated with silver was suspended in a solution of 8 (256 mg, 1.0 mmol) in tetrahydrofuran (15 mL). The mixture was refluxed for 10 h, cooled, filtered, and concentrated under reduced pressure. Column chromatography of the residue on silica gel using hexane as eluent led to (1) 1*H*-cyclobuta[*de*]naphthalene[3a,g] (20 mg, 0.14 mmol, 14%) and (2) 3 (40 mg, 0.145 mmol, 34% conversion): a white solid; mp 191-195 °C; IR (KBr, cm^{-1}) 1560, 1460, 1380, 1140, 1060, 1005, 910, 740; ^1H NMR ($CDCl_3$) δ 7.31 (dd, 4 H, J = 2 and 4 Hz, ortho), 7.55-7.7 (m, 8 H, *meta and para*); ^{13}C NMR ($CDCl_3$) δ 114.6 (2 C, $C_{2,7}$), 122.3 (2 C, $C_{4,5}$), 125.7 (1 C, C_9), 131.15 (2 C, $C_{3,6}$), 143.7 (1 C, C_8), 144.2 (2 C, $C_{1a,7a}$), 149.7 (1 C, C_1); exact mass for $C_{22}H_{12}$, m/e (calcd) 276.0939, m/e (obsd) 276.0943. Anal. Calcd for $C_{22}H_{12}$: C, 95.62; H, 4.38. Found: C, 95.07; H, 4.37.[4]

Procedure B. 1,1'-Bi-1*H*-cyclobuta[*de*]naphthalene[3h] (11; 278 mg, 1 mmol), *tert*-butyl hypochlorite (110 mg, 1 mmol), and azobis(isobutyronitrile) (10 mg, 0.6 mmol) in carbon tetrachloride (15 mL) were refluxed 6 h. Removal of the volatiles left crude 1-chloro-1,1'-bi-1*H*-cyclobuta[*de*]naphthalene [12; ^1H NMR ($CDCl_3$) δ 5.80 (s, 1 H, bridge H), 6.8-7.6 (m, 12 H, aromatic); mass calcd for $C_{22}H_{13}Cl$ 312.5, found 312-314] that was used for conversion to 3.

Lithium diisopropylamide [1.0 mmol, prepared from *n*-butyllithium (1.1 mmol, 1.1 equiv) and diisopropylamine (100 mg, 1.0 mmol) at -78 °C] was added to crude 12 (~310 mg, 1.0 mmol) in tetrahydrofuran (15 mL) at 0 °C. After the mixture had been stirred for 3 h at room temperature and the volatiles were removed under reduced pressure, chromatography of the residue on silica gel with hexane yielded 3 (65 mg, 24%) identical with previous 3.

Elimination of 12 (310 mg, 1.0 mmol) was also effected with 1,5-diazabicyclo[5.4.0]undec-5-ene (DBU, 150 mg, 1.0 mmol) in refluxing tetrahydrofuran (10 mL) for 8 h. Isolation and purification of the product as above gave 3 (57 mg, 21%).

Determination of the Crystal Structure of 1-(Diphenylmethylene)-1*H*-cyclobuta[*de*]naphthalene (2d). A plate-like prismatic, colorless crystal of 2d of approximate dimensions 0.20 × 0.45 × 0.50 mm was mounted on the tip of a thin glass fiber. The crystal 2d was examined by X-ray methods at room temperature, and data were collected on an Enraf-Nonius CAD4 diffractometer with graphite monochromated Mo K_α radiation (λ = 0.710 73 Å). The cell parameters and standard deviations were determined by least-squares fitting from 24 reflections well distributed in reciprocal space and lying in the 2θ range between >25° and 30°: Intensity data were collected by the ω-2θ scan mode [scan angle (ω) = 0.75 + 0.35 tan θ, scan speed (deg/min) = 0.65-5° (in ω)] with a 2θ range between 4° and 50°. A total of 3070 reflections was measured with 1768 unique data having $I > 3.0\sigma(I)$. The data were corrected for Lorentz and polarization effects and for decay but not for absorption. The crystal parameters of 2d at room temperature are space group $p2_{1/c}$, a = 12.085 (2) Å, b = 16.993 (1) Å, c = 8.134 (2) Å, β = 103.58 (1)°, V = 1623.66 Å^3, Z = 4.0, formula weight = 304.39, D_{calcd} = 1.2459 g cm^{-3}, and u = 0.655.

Solution and Refinement of Structure of 2d. Analytical forms of the scattering factors for neutral atoms were used throughout the analysis and Δf and $i\Delta f''$ terms were included for all atoms. All crystallographic computations were carried out on a PDP 11/44 computer using the structure determination package (SDP).

The space group, $p2_{1/c}$, for 2d was determined unambiguously from the systematic absences. The statistical distributions of the reflection intensities also suggest that the space group is likely centrosymmetric. The unit cell contains four molecules and thus there is one molecule per each crystallographic asymmetric unit. The structure of 2d was solved via a combination of MULTAN, difference Fourier, and least-squares refinements of the heavy atoms. All of the hydrogens appeared on the difference electron density map. The function minimized during the least-squares refinement process was $\Sigma w(|F_o| - |F_c|)^2$, where the assigned weighted are given as $w = [\sigma(I)^2 + (pI)^2]^{1/2}$ and p = 0.02 was chosen to make $\Sigma w \Delta F$ uniformly distributed in $|F_o|$. The final full-matrix least-squares refinement cycle with anisotropic thermal parameters for all non-hydrogen atoms, isotropic for hydrogens, gave R_f = 0.033 and R_{wf} = 0.040, where $R_f = \Sigma||F_o| - |F_c||/\Sigma|F_o|$ and $R_{wf} = \Sigma w^{1/2}||F_o| - |F_c||/\Sigma_w{}^{1/2}|F_o|$, for the 1768 reflections having $I > 3.0\sigma(I)$ with 282 variables. The final difference Fourier map showed no significant features, with a maximum peak height of 0.115 e/Å^3. The bond angles and bond distances in 2d are summarized in Tables 1 and 2 (supplementary material).

Acknowledgment. We thank the National Science Foundation for support of this research.

Supplementary Material Available: X-ray data for 1-(diphenylmethylene)-1*H*-cyclobuta[*de*]naphthalene and ^1H NMR spectra for $\Delta^{1,1}$-bi-1*H*-cyclobuta[*de*]naphthalene (15 pages). Ordering information is given on any current masthead page.

A Strategy for the Convergent Synthesis of Gilvocarcins via Chromium Carbene Benzannulation. 1-*O*-Methyldefucogilvocarcin V in Seven Steps†

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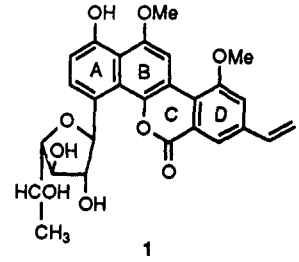
Of the *C*-aryl glycosides[1] which have been shown to have promising antitumor activity, members of the gilvocarcin group[2] (e.g. gilvocarcin V, 1) are particularly interesting because of their potency. Several approaches to the synthesis of the tetracyclic gilvocarcin "aglycons" have proven successful,[3] but there has been no report of the synthesis of a fully functionalized glycosylated natural product.[4]



1

Our approach to the preparation of gilvocarcins is based on the elaboration of simple *C*-phenyl glycosides **5b** to the complex *C*-aryl glycoside structures **2b**. We imagined that this might be effected directly by a Dötz chromium carbene benzannulation[5] of the appropriately substituted phenyl acetylene 4 (Scheme I). The highly regioselective Dötz reaction tolerates numerous functional groups including the ester and olefin required for gilvocarcins.

In order to demonstrate the viability of this approach, we prepared phenyl acetylene 4 and employed this readily available intermediate in the conversion of *o*-bromoanisole to the known methyl ether **2a**[3c] of defucogilvocarcin V.[6] The intermediate required for this transformation is the

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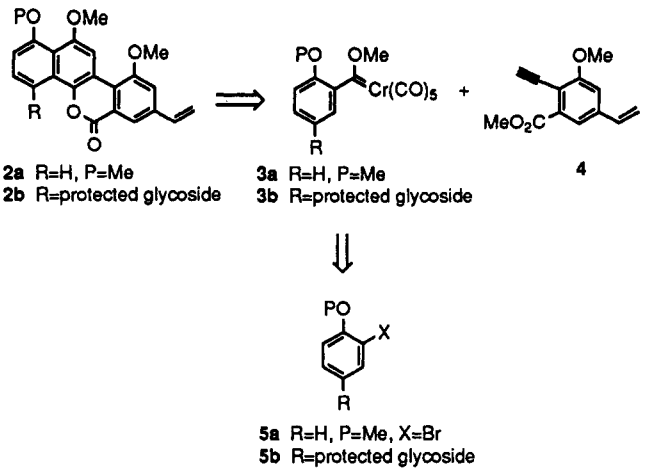
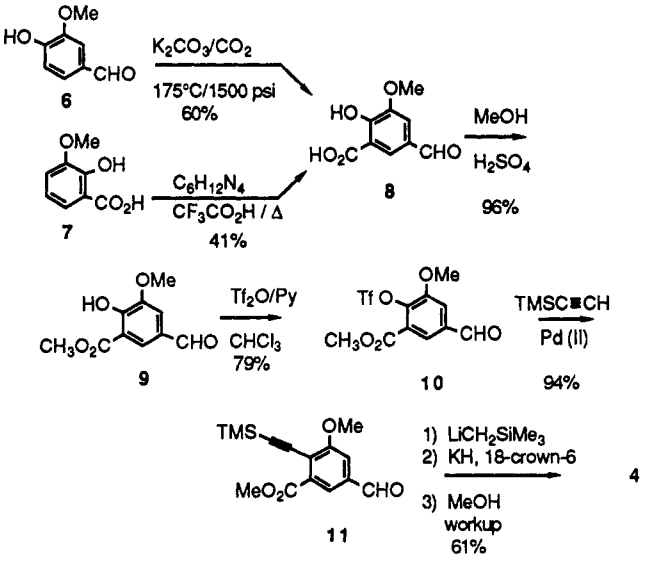
Scheme I



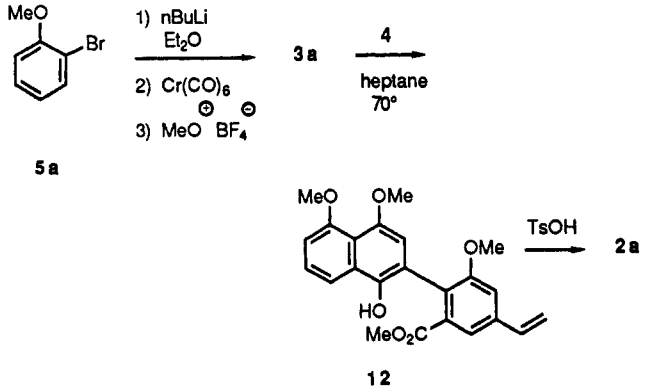
Scheme II



known, easily obtained methoxyphenyl chromium carbene complex **3a**.[7]

The preparation of acetylene **4** began with the Kolbe–Schmidt carboxylation of vanillin **6**.[8] Alternatively, the desired acid **8** could be synthesized by heating 3-methoxysalicyclic acid **7** with hexamethylenetetramine in CF_3CO_2H followed by hydrolysis of the resulting imine.[9] While this method proceeds in slightly lower yields, it proved to be more practical for our purposes.

Scheme III



The known acid **8** was esterified in refluxing methanol containing H_2SO_4. The phenolic hydroxyl group of ester **9** was then activated for coupling by treatment with triflic anhydride and pyridine.[10] The resulting triflate **10** reacted with (trimethylsilyl)acetylene in the presence of $(Ph_3P)_2PdCl_2$ as the catalyst[11] to give the phenylacetylene **11**.

Application of the Peterson olefination procedure[12] with $TMSCH_2MgCl$ was followed by elimination with KH in the presence of 18-crown-6. Quenching with methanol and sodium carbonate gave the target acetylene **4** in 28% yield overall from vanillin **6**.

The key step in the construction of the tetracycle was effected by heating 1.5 equiv of phenylacetylene **4** with carbene **3a** in heptane to afford the annulated product **12** in 43% yield. Lactonization of **12** with *p*-TsOH in benzene gave 1-*O*-methyldefucogilvocarcin V **2a** in 95% yield.

This short and efficient synthesis demonstrates our ability to prepare the aromatic gilvocarcin V aglycon in two steps from an appropriately substituted benzene derivative (A-ring precursor) and the readily available phenylacetylene **4**. This methodology may be useful for the synthesis of the glycosylated gilvocarcins.

Experimental Section[13]

Methyl 5-Formyl-2-hydroxy-3-methoxybenzoate (9). To a solution of 4.47 g (22.8 mmol) of acid **8**[9] in 350 mL of anhydrous methanol at 0 °C was added 30 mL of concentrated H_2SO_4. The ice bath was removed, and the mixture was stirred and heated at reflux for 70 min. After cooling, the solution was concentrated. The precipitate was filtered and recrystallized (acetone/MeOH), leaving 4.60 g (96%) of a white solid: mp 132.5–133.5 °C; ^1H NMR ($CDCl_3$) δ 3.98 (s, 3 H), 4.03 (s, 3 H), 7.56 (d, J = 2 Hz, 1 H), 7.98 (d, J = 2 Hz, 1 H), 9.85 (s, 1 H), 11.68 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 52.9, 56.3, 112.3, 112.8, 127.2, 128.1, 149.6, 157.5, 170.2, 190.0; IR (CCl_4) 3150, 2850, 2750, 1699, 1683 cm^{-1}. Anal. Calcd for $C_{10}H_{10}O_5$: C, 57.13; H, 4.80. Found: C, 56.86; H, 4.78.

Methyl 5-Formyl-3-methoxy-2-[[(trifluoromethyl)-sulfonyl]oxy]benzoate (10). A solution of the phenol **9** (2.47 g, 11.8 mmol) was dissolved in 20 mL of dry pyridine and 4 mL of dry $CHCl_3$ under argon. Then 2.4 mL (4.0 g, 14.3 mmol) of freshly distilled triflic anhydride was added. After 2 h, the solution

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(13) Solvents were purified and dried by standard methods before use. Ether refers to diethyl ether. Flash chromatography was performed using E. Merck silica gel 60 (70–230 mesh). ^1H and ^{13}C NMR spectra were recorded at 400.1 and 100.6 MHz, repectively. Mass spectra were obtained at 70 eV under electron impact conditions.

was poured into ether (50 mL) and washed with water. The organic extracts were washed with 5% HCl (5 × 25 mL), H_2O (2 × 20 mL), saturated $CuSO_4$ (2 × 20 mL), and then brine (2 × 30 mL). Drying (Na_2SO_4) and removal of the solvent gave 3.22 g (79%) of **10** as a yellow oil, which solidified after 2 days at −20 °C. Recrystallization ($MeOH/H_2O$) afforded **10** as a yellow solid: mp 58–60 °C; ^1H NMR ($CDCl_3$) δ 3.99 (s, 3 H), 4.02 (s, 3 H), 7.72 (d, J = 2 Hz, 1 H), 8.08 (d, J = 2 Hz, 1 H), 10.0 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 52.9, 56.7, 114.2, 118.5 (center of triflate quartet), 126.2, 126.3, 135.6, 141.4, 152.6, 163.4, 189.5; IR (neat) 2850, 2750, 1733, 1708 cm^{-1}. Anal. Calcd for $C_{11}H_9F_3SO_7$: C, 38.60; H, 2.63. Found: C, 38.82; H, 2.63.

Methyl 5-Formyl-3-methoxy-2-[(trimethylsilyl)ethynyl]-benzoate (11). A solution of 557 mg (1.62 mmol) of triflate **10** in 5 mL of dry DMF was treated with 0.32 mL (2.3 mmol, 1.5 equiv) of (trimethylsilyl)acetylene, 1.0 mL of dry Et_3N, and 32.4 mg (0.046 mmol) of $(Ph_3P)_2PdCl_2$ and heated at 90 °C for 5 h under N_2. The resulting brown solution was cooled, diluted with 15 mL of H_2O, and extracted with 1:1 ether/petroleum ether (8 × 10 mL). The combined organic extracts were washed with water until neutral, filtered through Florisil, and dried over Na_2SO_4. Evaporation and recrystallization ($CHCl_3$/hexane) left 444 mg (94%) of **11** as a brown solid: ^1H NMR ($CDCl_3$) δ 0.29 (s, 9 H), 3.93 (s, 3 H), 4.00 (s, 3 H), 7.49 (d, J = 1.4 Hz, 1 H), 7.92 (d, J = 1.4 Hz, 1 H), 9.97 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ −0.2, 52.3, 56.5, 97.7, 110.2, 110.8, 118.6, 125.2, 135.5, 135.9, 161.8, 165.9, 190.6; IR (CCl_4) 3311, 2850, 2750, 2153, 1726, 1702 cm^{-1}; HRMS calcd 290.2065, found 290.2098.

Methyl 5-Ethenyl-2-ethynyl-3-methoxybenzoate (4). To a solution of 40.5 mg (0.140 mmol) of aldehyde **11** in 3 mL of dry ether at 0 °C was added 0.15 mL (0.15 mmol) of $(CH_3)_3SiCH_2MgCl$ (1.0 M in ether). The resulting solution was stirred at 0 °C for 1 h and then at 22 °C for 2 h before it was quenched with 5% HCl (1 mL) and extracted with ether (3 × 7 mL). The combined organic solution was washed with H_2O (2 × 5 mL) and then brine, dried (Na_2SO_4), and concentrated to give 47.4 mg (90%) of the (β-hydroxyalkyl)trimethylsilane: ^1H NMR ($CDCl_3$) δ 0.02 (s, 9 H), 0.26 (s, 9 H), 1.19 (t, J = 7 Hz, 2 H), 3.89 ("s", 6 H), 4.83 (t, J = 7 Hz, 1 H), 7.04 (d, J = 1.0 Hz, 1 H), 7.34 (d, J = 1.0, 1 H). The intermediate was dissolved in 1.0 mL of dry THF and added to 2 mL of THF containing 5.0 mg (0.12 mmol) of oil-free KH and 32 mg (0.12 mmol) of 18-crown-6. The reaction mixture was stirred under argon for 1 h, quenched with 3 mL of saturated Na_2CO_3 and 3 mL of MeOH, and diluted with 10 mL of ether. The organic phase was extracted with 3 × 5 mL of saturated Na_2CO_3, 3 × 5 mL of H_2O, and 2 × 5 mL of brine and dried over $MgSO_4$. Flash chromatography (10%, 40% then 75% EtOAc/Hex) left 17.3 mg (67%) of **4**: mp 255 °C; ^1H NMR ($CDCl_3$) δ 3.65 (s, 1 H), 3.93 (s, 3 H), 3.96 (s, 3 H), 5.39 (d, J = 10.9 Hz, 1 H), 5.85 (d, J = 17.6 Hz, 1 H), 6.70 (dd, J = 10.9, 17.6 Hz, 1 H), 7.08 (d, J = 1.4 Hz, 1 H), 7.54 (d, J = 1.4 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 52.2, 56.3, 77.6, 87.1, 111.1, 116.4, 120.2, 135.0, 135.6, 138.8, 161.8, 166.5; IR (neat) 3310, 1739 cm^{-1}; HRMS calcd 216.0786, found 216.0755.

8-Ethenyl-1,10,12-trimethoxy-6*H*-benzo[*d*]naphtho[1,2-*b*]pyran-6-one (1-*O*-Methyldefucogilvocarcin V, 2a). A 5-mL round-bottom flask was charged with 19.2 mg (88.8 μmol) of acetylene **4**, 20.0 mg (59.2 μmol, 0.67 equiv) of chromium carbene **3a**,[7] and 1.0 mL of heptane and subjected to the freeze–thaw method (3 cycles) back-filling with argon each time. The orange solution was heated to 70 °C for 10 h under argon. Then CH_3CN (4.0 mL) and H_2O (2.0 mL) were added, and the mixture was stirred for 1 h under air and then extracted with ether (3 × 10 mL). The organic phases were combined, washed with H_2O (3 × 5 mL) and brine, and dried over $MgSO_4$. Flash chromatography (10% benzene/ether) gave 10.0 mg (43%) of ester **12** as a yellow oil: ^1H NMR ($CDCl_3$) δ 3.60 (s, 3 H), 3.66 (s, 3 H), 3.81 (s, 3 H), 3.85 (s, 3 H), 5.43 (d, J = 10.9 Hz, 1 H), 5.88 (d, J = 17.6 Hz, 1 H), 6.05 (s, 1 H), 6.42 (d, J = 8.2 Hz, 1 H), 6.57 (d, J = 8.2 Hz, 1 H), 6.66 (t, J = 8.2 Hz, 1 H), 6.80 (dd, J = 10.9, 17.6 Hz, 1 H), 7.00 (m, 2 H), 7.33 (dd, J = 8.2, 0.9 Hz, 1 H); IR (neat) 3400, 1729 cm^{-1}.

To ester **12**, 10.0 mg (0.025 mmol), in 5 mL of dry benzene was added 0.5 mg (2.7 mmol) of *p*-TsOH. The solution was stirred at reflux for 1.5 h. The solvent was removed in vacuo, and the residue was dissolved in CH_2Cl_2, extracted with H_2O (3 × 5 mL), and dried (Na_2SO_4). Flash chromatography (10% benzene/ether) gave 8.6 mg (95%) of **2a** as a yellow solid, mp 243–245 °C dec (lit.[3c] mp 244–247 °C dec), with NMR and IR spectra in agreement with the literature data.[3c]

Acknowledgment. This work was supported by the National Science Foundation (Grant No. 8705647) the National Institutes of Health (CA50720), and Brown University. NMR spectra were acquired with a Bruker AM400WB spectrometer, purchased with funds from the National Science Foundation. The Kratos MS-80 mass spectrometer was purchased with funds from the Division of Research Resources of the National Institutes of Health.

Registry No. **1**, 77879-90-4; **2a**, 112374-33-1; **3a**, 27436-99-3; **4**, 131066-92-7; **8**, 3507-08-2; **9**, 3507-09-3; **10**, 131066-90-5; **11**, 131066-91-6; **12**, 131066-93-8.

Supplementary Material Available: ^1H and ^{13}C NMR and infrared spectra for new compounds (structures **9**, **10**, **11**, and **4**) (13 pages). Ordering information is given on any current masthead page.

Quantitative Relationship between Optical Rotation and Conformation

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It has long been known[1] that the magnitude of optical rotation of a chiral aracemic compound depends on temperature, solvent, and concentration. These changes have often been ascribed, qualitatively, to changes in intermolecular association (solute–solute interaction) and in solvation (solute–solvent interaction), especially changes in solute–solute and solute–solvent hydrogen bonding.[1,2] On the other hand, J. H. Brewster recognized, some 30 years ago,[3] that specific (or molar) rotation is crucially dependent on conformation. A salient example is lactic acid, $CH_3CHOHCO_2H$: according to the polarizability of the four substituents at the chiral center (CO_2H, CH_3, OH, H) the *R* acid should be dextrorotatory[3] (as, in fact, are its esters and salts), whereas, actually, it is levorotatory in water. This finding is best interpreted in terms of a cyclic, internally hydrogen-bonded structure.[3]. It is not clear, however, whether hydrogen bonding affects specific rotation (in magnitude and, occasionally, in sign) directly or whether it does so indirectly (by affecting conformation), or both.

Recently[4] we reported large concentration effects on the conformational equilibrium in *cis*-3-hydroxythiane *S*-oxide (**1**, Scheme I[5]). In concentrated solution, this substance is either strongly self-associated through intermolecular

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0022-3263/91/1956-1668$02.50/0