^{13}C NMR (22.5 MHz, $CDCl_3$) δ -4.5, -4.3, 18.1, 19.8, 21.4, 23.4, 26.0, 45.6, 51.7, 70.3, 80.0, 177.5; IR (neat) 3450, 1740, 1260 cm^{-1}; HPLC (vide supra).

General Procedure of the Eu-Complex Catalyzed Reaction with Enal: Preparation of Methyl 5-[(*tert*-Butyldimethylsilyl)oxy]-2-methyl-4-pentenoate. To a solution of acrolein (66 μL, 1.0 mmol) in CH_2Cl_2 (3 mL) was added a 30 w/v % $CF_2ClCFCl_2$ solution of (+)-Eu(dppm)$_3$ (172 μL, 0.025 mmol) at room temperature. After cooling to -70 °C, (*E*)-1-[(*tert*-butyldimethylsilyl)oxy]-1-methoxy-1-propene (304 mg, 1.5 mmol) was added to the solution. The reaction mixture was stirred for 1 h at that temperature and poured into saturated $NaHCO_3$. The resultant mixture was extracted with EtOAc, three times (totally 100 mL), and washed with brine. The extract was dried over $MgSO_4$ and evaporated under reduced pressure. The resultant crude product was purified by column chromatography to give methyl 5-[(*tert*-butyldimethylsilyl)oxy]-2-methyl-4-pentenoate in 85% yield (220 mg).

Methyl 5-[(*tert*-butyldimethylsilyl)oxy]-2-methyl-4-pentenoate: ^1H NMR (90 MHz, $CDCl_3$) δ 0.09 (s, 6 H), 0.95 (s, 9 H), 1.02 (d, *J* = 6.7 Hz, 3 H), 1.88 (m, 2 H), 3.27 (s, 3 H), 4.73 (m, 1 H), 6.15 (dt, *J* = 6.5, 2.0 Hz, 1 H); IR (neat) 1740, 1660, 1470, 1250, 1100, 840 cm^{-1}.

Methyl 5-[(*tert*-butyldimethylsilyl)oxy]-2,3-dimethyl-4-pentenoate (1:1 diastereomeric mixture): ^1H NMR (90 MHz, $CDCl_3$) δ 0.08 (s, 6 H), 0.09 (s, 6 H), 0.90 (s, 9 H) × 2, 1.05 (d, *J* = 6.7 Hz, 3 H), 1.13 (d, *J* = 6.7 Hz, 3 H), 1.26 (d, *J* = 6.7 Hz, 3 H), 1.38 (d, *J* = 6.7 Hz, 3 H), 2.3–2.7 (m, 1 H) × 2, 3.73 (s, 3 H) × 2, 5.00 (dd, *J* = 9.0, 11.5 Hz, 1 H), 5.30 (dd, *J* = 8.5, 11.5 Hz, 1 H), 6.40 (d, *J* = 11.5 Hz, 1 H), 6.41 (d, *J* = 11.5 Hz, 1 H); IR (neat) 1740, 1660, 1250, 1090 cm^{-1}.

(*E*)-Methyl 3-[(*tert*-butyldimethylsilyl)oxy]-2-methyl-4-hexenoate (1:1 diastereomeric mixture): ^1H NMR (90 MHz, $CDCl_3$) δ 0.08 (s, 6 H), 0.09 (s, 6 H), 0.83 (s, 9 H), 0.87 (s, 9 H), 1.00 (d, *J* = 6.7 Hz, 3 H), 1.13 (d, *J* = 6.7 Hz, 3 H), 1.65 (d, *J* = 6.0 Hz, 3 H), 1.67 (d, *J* = 6.0 Hz, 3 H), 2.5–2.8 (m, 1 H) × 2, 3.63 (s, 3 H), 3.67 (s, 3 H), 4.17 (dd, *J* = 6.0, 9.0 Hz, 1 H), 4.30 (dd, *J* = 6.0, 8.5 Hz, 1 H), 5.2–5.7 (m, 2 H) × 2; IR (neat), 1740, 1250, 840 cm^{-1}.

Ethyl 5-[(*tert*-butyldimethylsilyl)oxy]-3-methyl-4-pentenoate: ^1H NMR (90 MHz, $CDCl_3$) δ 0.09 (s, 6 H), 0.95 (s, 9 H), 1.02 (d, *J* = 6.7 Hz, 3 H), 1.25 (t, *J* = 6.7 Hz, 3 H), 1.96 (m, 1 H), 2.4 (m, 1 H), 4.15 (q, *J* = 6.7 Hz, 2 H), 4.92 (dd, *J* = 8.5, 11.5 Hz, 1 H), 6.30 (d, *J* = 11.5 Hz, 1 H); IR (neat) 1730, 1660, 1250, 1080 cm^{-1}.

(*E*)-Ethyl 3-[(*tert*-butyldimethylsilyl)oxy]-4-hexenoate: ^1H NMR (90 MHz, $CDCl_3$) δ 0.09 (s, 6 H), 0.90 (s, 9 H), 1.25 (t *J* = 6.7 Hz, 3 H), 1.65 (d, *J* = 6.0 Hz, 3 H), 2.38 (dd, *J* = 6.7, 15.0 Hz, 1 H), 2.53 (dd, *J* = 7.5 Hz, 15.0 Hz, 1 H), 4.15 (q, *J* = 6.7 Hz, 2 H), 4.53 (m, 1 H), 5.53 (m, 2 H); IR (neat) 1740, 1250, 1060, 880, 840, 750 cm^{-1}.

3,1′-*syn*-3-[1′-(Carbomethoxy)ethyl]-1-[(trimethylsilyl)oxy]-1-cyclopentene:[14] ^1H NMR (90 MHz, $CDCl_3$) δ 0.08 (s, 9 H), 1.10 (d, *J* = 6.7 Hz, 3 H), 1.5–2.5 (m, 5 H), 2.90 (m, 1 H), 3.67 (s, 3 H), 4.48 (m, 1 H); IR (neat) 1730, 1680, 1250 cm^{-1}.

3,1′-*anti*-3-[1′-(Carbomethoxy)ethyl]-1-[(trimethylsilyl)oxy]-1-cyclopentene:[14] ^1H NMR (90 MHz, $CDCl_3$) δ 0.08 (s, 9 H), 1.10 (d, *J* = 6.7 Hz, 3 H), 1.5–2.5 (m, 5 H), 2.90 (m, 1 H), 3.67 (s, 3 H), 4.60 (m, 1 H); IR (neat) 1730, 1680, 1250 cm^{-1}.

3,1′-*syn*-3-[1′-(Carbomethoxy)ethyl]-1-cyclopentanone:[15] ^1H NMR (90 MHz, $CDCl_3$) δ 1.23 (d, *J* = 6.7 Hz, 3 H), 1.4–2.6 (m, 8 H), 3.67 (s, 3 H); IR (neat) 1750, 1730, 1470, 1080 cm^{-1}.

3,1′-*anti*-3-[1′-(Carbomethoxy)ethyl]-1-cyclopentanone:[15] ^1H NMR (90 MHz, $CDCl_3$) δ 1.20 (d, *J* = 6.7 Hz, 3 H), 1.4–2.6 (m, 5 H), 3.70 (s, 3 H); IR (neat) 1750, 1730, 1470, 1080 cm^{-1}.

3,1′-*syn*-3-[1′-(Carbomethoxy)ethyl]-1-[(trimethylsilyl)oxy]-1-cyclohexene:[14] ^1H NMR (90 MHz, $CDCl_3$) δ 0.08 (s, 9 H), 1.10 (d, *J* = 6.7 Hz, 3 H), 1.3–2.6 (m, 8 H), 3.67 (s, 3 H), 4.68 (m, 1 H); IR (neat) 1730, 1680, 1250, cm^{-1}.

3,1′-*anti*-3-[1′-(Carbomethoxy)ethyl]-1-[(trimethylsilyl)oxy]-1-cyclohexene:[14] ^1H NMR (90 MHz, $CDCl_3$) δ 0.08 (s, 9 H), 1.13 (d, *J* = 6.7 Hz, 3 H), 1.3–2.6 (m, 8 H), 3.67 (s, 3 H), 4.83 (m, 1 H); IR (neat) 1730, 1680, 1250 cm^{-1}.

3,1′-*syn*-3-[1′-(Carbomethoxy)ethyl]-1-cyclohexanone:[15] ^1H NMR (90 MHz, $CDCl_3$) δ 1.22 (d, *J* = 6.7 Hz, 3 H), 1.3–2.7 (m, 10 H), 3.67 (s, 3 H); IR (neat) 1730, 1460, 1080, cm^{-1}.

3,1′-*anti*-3-[1′-(Carbomethoxy)ethyl]-1cyclohexanone:[15] ^1H NMR (90 MHz, $CDCl_3$) δ 1.20 (d, *J* = 6.7 Hz, 3 H), 1.3–2.7 (m, 10 H), 3.70 (s, 3 H), 4.83 (m, 1 H); IR (neat) 1730, 1460, 1080 cm^{-1}.

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Synthesis of 2-Benzylidenebenzocyclobutenones via an Intramolecular Stille Coupling Reaction

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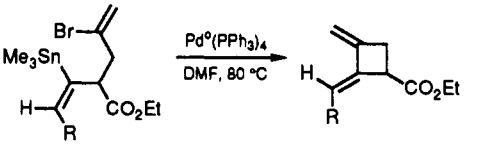
The coupling of vinylstannanes with vinyl or aryl bromides mediated by Pd^0 complexes was first by Stille[1] and has since found many applications. Particularly intriguing to us was the report by Piers and Lu who showed that an intramolecular version of this coupling reaction could be utilized to generate 2-alkylidene-3-methylenecyclobutanecarboxylates[2] (eq 1).



(1)

As part of our continuing interest in developing new routes to precursors of a variety of *o*-quinodimethanes,[3] we would like to report that the $Pd(PPh_3)_4$-catalyzed intramolecular coupling of compounds bearing both vinylstannane and aryl bromide moieties serves as a facile route to 2-benzylidenebenzocyclobutenones.

Very few examples of this arrangement of functional groups have been reported.[4] For example, 2-methylenebenzocyclobutene has been prepared in low yield by Trahanovsky[4a] via flash vacuum pyrolysis of 3-[(benzoyloxy)methyl]benzofuran and 2-(carbethoxyethylidene)-benzocyclobutenone was obtained by Cava[4b] from the dione and (carbethoxymethylene)triphenylphosphorane; the Wittig reaction did not yield the simple alkylidene analogues. The method described in this paper promises to be synthetically useful for the preparation of a variety of members of this class of compounds.

Reaction of the acetylenic ketone **1a**, prepared by coupling of 6-bromo-3,4-(methylenedioxy)benzoyl chloride with phenylacetylene in the presence of catalytic amounts of $PdCl_2(PPh_3)_2/CuI$,[5] 1.2 equiv of Bu_3SnH in toluene containing 2–3 mol % $PdCl_2(PPh_3)_2$, and PPh_3 (5.8 mol %) at room temperature for 5 min followed by a 2-h reflux, resulted in the formation of the isomeric 2-benzylidenebenzocyclobutenones **2a** and **3a** in a 1.1:1 ratio in 58% combined yield (70% based on recovered starting material). The initial exposure of **1** to these reaction conditions presumably afforded a mixture of stereoisomeric vinylstannanes **4a**,[6] which upon heating coupled with retention of configuration to give **2a** and **3a** (Scheme I).

†Holder of NSERC PGS Scholarship, 1989–91.

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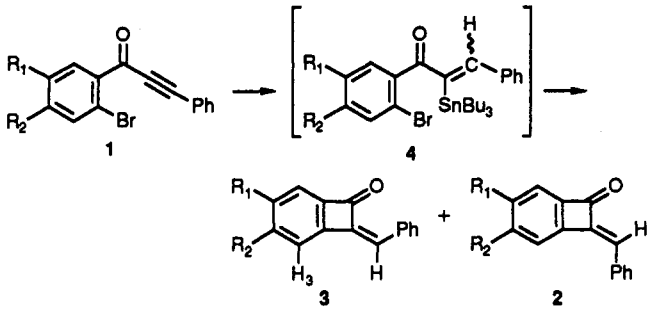
Scheme I[a]

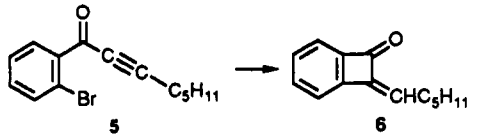


[a] Series: (a) $R_1 = R_2 = OCH_2O$; (b) $R_1 = R_2 = H$; (c) $R_1 = OCH_3$, $R_2 = H$.

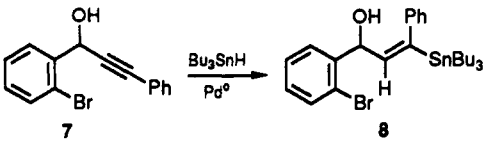
Compounds **2a** and **3a** were obtained as orange and bright yellow solids, respectively. Each showed strong absorption at 1766 cm^{-1} and a single vinylic hydrogen at δ 6.62 and 6.29, respectively. The specific stereochemical assignment is based on NOE studies. Thus, irradiation of the vinylic peak of **2** (δ 6.62) gave an NOE response only in the ortho hydrogens of the phenyl group. In contrast, irradiation of the δ 6.29 peak in **3** gave an enhancement both in the ortho phenyl hydrogens and H_3 [δ 6.96 (d, J = 0.8 Hz)].

Similar treatment of the enones **1b** and **1c** afforded mixtures of the benzocyclobutenones **2b,c** and **3b,c** in 50–70% yield in ratios of about 1.5:1.

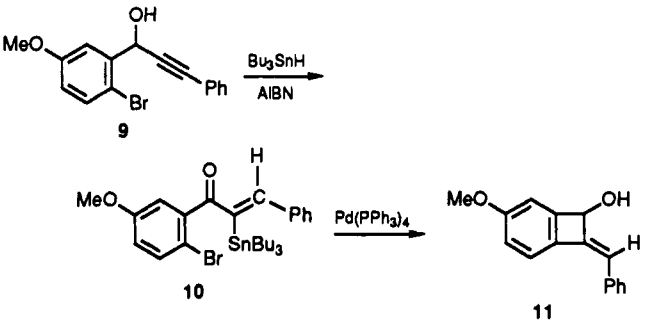
Thus far the phenyl group appears to be the substituent of choice on the terminus of the acetylene. For example, when the pentyl-substituted acetylenic ketone **5** was subjected to the usual cyclization conditions, the desired benzocyclobutenone **6** seemed to have been formed as judged by the appearance of a strong absorption at 1766 cm^{-1} in the infrared spectrum of the crude reaction product. Attempts at purification of this material by silica gel chromatography (Chromatotron) yielded a variety of products having carbonyl frequencies at 1774, 1760, 1752, 1750, 1746, and 1727 cm^{-1}. Rechromatography of the fraction having the highest C=O frequency again afforded a mixture of compounds having a similar set of multiple carbonyl frequencies. None of the components of this mixture have been identified.



In our experience, the acetylenic ketones are preferred for benzocyclobutene formation over the corresponding alcohols or acetates since the regiochemistry of the Bu_3SnH addition is clearly in the desired manner. For example, Pd^0-catalyzed addition of Bu_3SnH to the alcohol **7** afforded the stannane **8**[6] in up to 90% yield; no further reaction was observed even on prolonged heating. The acetate of **7** gave lower yields of the analogous regiochemical addition product.



We have also investigated the stepwise transformation of both the acetylenic ketones and the corresponding alcohols to benzocyclobutene derivatives. In these experiments the addition of Bu_3SnH was carried out under free-radical conditions (benzene, AIBN, reflux) and the resultant vinylstannane then cyclized with $Pd(Ph_3)_4$. This sequence was considerably more capricious, and the results varied both with respect to the aromatic substituents and the ynone or acetylenic alcohol moiety. In the best case, the alcohol **9** was converted into **10** in 55% yield; cyclization of the latter afforded 45% of 2-benzylidenebenzocyclobutenol **11**, identified by PDC oxidation to **2c**, upon cyclization with $Pd(PPh_3)_4$ in toluene. In contrast, the analogous conversions of the acetate of **9** took place in 3 and 50% yield, respectively.



Moore[7] and Liebeskind[8] have shown that benzocyclobutene-1,2-diones are valuable intermediates in the synthesis of naphtha- and anthraquinones. The 2-benzylidenebenzocyclobutenones **2** and **3**, which can be prepared with predictable aromatic substitution patterns, offer a versatile addition to this methodology since the benzylidene group can be considered at latent carbonyl function. The conversion of derivatives such as **2c** and **3c** into regiospecifically substituted anthraquinones and other chemistry of these unique compounds is being investigated.

Experimental Section

General. Solvents for the extractions and chromatographic purifications were routinely distilled prior to use. Reagent-grade toluene kept over 4A molecular sieves was used without prior distillation. Triethylamine was distilled from $LiAlH_4$ and kept under N_2 over 4A molecular sieves.

Preparation of Ynones. 1c. 5-Methoxy-2-bromobenzoic acid (4.04 g, 17.5 mmol), and $SOCl_2$ (20 mL) were refluxed under a stream of N_2. The reaction was judged to be complete (no broad band >3000 cm^{-1}, COCl at 1787 cm^{-1}) after 1 h, and the clear yellowish solution was evaporated under reduced pressure. The residue was diluted twice with 25 mL of CCl_4 and evaporated under reduced pressure, finally at 1 Torr for 1 h.

Phenylacetylene (1.78 g, 17.5 mmol), CuI (10 mg), PPh_3 (20 mg), and $PdCl_2(PPh_3)_2$[9] (20 mg) were added to the above product.

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The flask was flushed with N_2 for a few minutes. Dry triethylamine (30 mL) was introduced via a cannula, and the mixture was stirred at room temperature for 20 h. The reaction was complete at this point as evidenced by IR spectroscopy (loss of the COCl band at 1787 cm^{-1}, appearance of an acetylenic ketone CO and C≡C bands at 1650 cm^{-1} and at 2100 cm^{-1}, respectively). Methanol (5 mL) was then added to the brown suspension, and the solvents were removed under reduced pressure to leave a black paste. The residue was triturated with ether (50 mL), and the white precipitate that formed with filtered off and washed with ether (2 × 50 mL). Flash silica gel chromatography (ether/ethyl acetate, with an increasing proportion of ethyl acetate) gave a red-orange solid, which was crystallized from hexanes/ether to yield **1c**, mp 51 °C, as tan crystals (2.66 g, 48% yield from the acid): ^1H NMR δ 3.83 (s, 3 H), 6.92 (dd, 1 H, J = 8.8, 3.1 Hz; IR (CH_2Cl_2) 1652 (CO), 2210 (C≡C) cm^{-1}; MS (m/z) 316 and 314 (34, M^+), 288 and 286 (20), 235 (23), 129 (100); HRMS $C_{16}H_{11}{}^{81}BrO_2$ 315.9923 (calcd), 315.9926 (found); $C_{16}H_{11}{}^{79}BrO_2$ 313.9942 (calcd), 313.9950 (found).

1b. In the case of 2-bromobenzoic acid, the intermediate 2-bromobenzoyl chloride[10] was purified by distillation (150–160 °C (1 Torr)) in 94% yield (CO at 1787 cm^{-1}). **1b**, obtained in 73% yield from the acid chloride, was purified by distillation and obtained as a slightly yellowish oil: ^1H NMR δ 7.4 (m, 5 H), 7.66 (m, 3 H), 8.06 (m, 1 H); IR ($CHCl_2$) 2197 (C≡C), 1650 (C=O) cm^{-1}; MS (m/z) 286 and 284 (20, M^+), 258 and 256 (37), 202 (57), 129 (100); HRMS $C_{15}H_9{}^{81}BrO$ 285.9576 (calcd), 285.9797 (found); $C_{15}H_9{}^{79}BrO$ 283.9837 (calcd), 283.9837 (found).

1a. 6-Bromo-3,4-(methylenedioxy)benzoyl chloride was obtained in 64% yield after crystallization from hexanes/ethyl acetate (CO 1785 cm^{-1}). The ynone **1a** was prepared as above for **1c** and purified by precipitating out the salts with ethyl acetate, evaporating the filtrate, and recrystallizing the residue from hexanes/ethyl acetate: yield 60%, golden crystals; mp 101 °C; ^1H NMR 6.07 (s, 2 H), 7.10 (s, 1 H), 7.40 (m, 4 H), 7.61 (m, 2 H); IR (CH_2Cl_2) 1641 (CO), 2188 (C≡C) cm^{-1}; MS 330 and 328 (40, M^+), 302 and 300 (41, –CO), 163 (46), 129 (100); HRMS $C_{16}H_9{}^{81}BrO_3$ 329.9716 (calcd), 329.9714 (found); $C_{16}H_9{}^{79}BrO_3$ 327.9735 (calcd), 327.9732, (found).

Preparation of Benzylidenebenzocyclobutenones 2c/3c. Tributyltin hydride (0.04 mL, 2.8 mmol) was added via syringe over 5 min to a solution of ynone **1c** (0.82 g, 2.6 mmol), $PdCl_2(PPh_3)_2$ (0.06 g), and PPh_3 (0.06 g) in 20 mL of toluene. The turbid orange solution was stirred for 3 h at room temperature and then refluxed for 2 h under N_2. The reaction was judged to be complete by IR spectroscopy (loss of C≡C at 2200 cm^{-1}, appearance of a strong band at 1766 cm^{-1}). The resultant black solution was evaporated under reduced pressure, and the residue was stirred with 30 mL of hot hexanes and then chilled in a freezer. Flash silica gel chromatography of the precipitate (2:1 hexanes/ethyl acetate) afforded a 1.3:1 mixture of **2c/3c** (49% yield) as a yellow solid. An NMR spectrum of the mother liquor indicated an additional 10% of the cyclization products. To obtain analytical data for each pure isomer, a small quantity of the mixture (150 mg) was separated on a Chromatron plate (4 mm) using 10:1:1 hexanes/CH_2Cl_2/ether. The nonoverlapping fractions were further purified by crystallization from ether/hexanes to give each isomer in pure form.

2c (*E* isomer): mp 127 °C, ^1H NMR δ 3.86 (s, 3 H), 6.69 (s, 1 H), 7.03 (dd, J = 2.1, 0.8 Hz, 1 H), 7.11 (dd, J = 8.0, 2.2 Hz, 1 H), 7.32 (m, 1 H), 7.43 (m, 2 H), 7.56 (m, 2 H), 7.78 (d, 1 H, J = 8.2 Hz); ^{13}C NMR δ 186.5, 161.5, 158.5, 152.1, 147.2, 135.2, 128.7, 128.3, 128.1, 123.2, 122.8, 115.6, 104.0, 55.8; IR 1765 cm^{-1}; MS (m/z) 236 (95, M^+), 221 (15), 208 (40), 165 (100); HRMS $C_{16}H_{12}O_2$ 236.0837 (calcd), 236.0837 (found).

3c (*Z* isomer): mp 143 °C; ^1H NMR δ 3.84 (s, 3 H), 6.37 (s, 1 H), 6.98 (dd, J = 2.0, 0.8 Hz, 1 H), 7.09 (dd, J = 7.9, 2.2 Hz, 1 H), 7.25 (m, 1 H), 7.37 (m, 2 H), 7.46 (dd, J = 8.1, 0.8 Hz, 1 H), 7.89 (m, 2 H); ^{13}C NMR δ 184.5, 161.2, 156.0, 154.0, 148.0, 135.3, 129.1, 128.5, 127.9, 124.9, 124.1, 120.0, 119,9, 103.9, 55.8; IR (CH_2Cl_2) 1766 cm^{-1}; MS (m/z) 236 (100, M^+), 221 (16), 208 (42, –CO), 193 (100), 165 (98); HRMS $C_{16}H_{12}O_2$ 236.0837 (calcd), 236.0836 (found).

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Preparation of Benzylidenebenzocyclobutenes 2b/3b. The procedure for the unsubstituted analogue was the same as above except that after evaporation of the solvent the residue was separated by Chromatotron with 6:1 hexanes/CH_2Cl_2 to yield the separated isomers in 70% combined yield (E/Z ratio of 1.5:1). Samples of each were crystallized from ether/hexanes.

2b (*E* isomer): mp 91 °C; ^1H NMR δ 6.86 (s, 1 H), 7.36 (m, 1 H), 7.45 (m, 3 H), 7.55 (m, 2 H), 7.62 (m, 2 H), 7.86 (m, 1 H); ^{13}C NMR δ 187.0, 158.3, 156.7, 148.3, 134.8, 134.7, 130.1, 128.8, 128.7, 128.5, 121.6, 121.1, 119.1; IR (CH_2Cl_2) 1768 cm^{-1}; MS (m/z) 206 (65, M^+), 178 (100); HRMS $C_{15}H_{10}O$ 206.0732 (calcd), 206.0752 (found).

3b (*Z* isomer): mp 120 °C; ^1H NMR δ 6.55 (s, 1 H), 7.3 (m, 2 H), 7.4 (m, 2 H), 7.5 (m, 3 H), 7.94 (m, 2 H); ^{13}C NMR δ 184.8, 160.1, 154.4, 149.1, 135.2, 135.0, 129.6, 129.4,2x, 128.6, 123.1, 121.2, 118.7; IR (CH_2Cl_2) 1757 cm^{-1}: MS (m/z) 206 (67, M^+), 178 (100); HRMS $C_{15}H_{10}O$ 206.0732 (calcd), 206.0737 (found).

2a/3a. The procedure was the same as for **2c/3c** but in this case the ynone **1a** was stirred with Bu_3SnH at room temperature for only 5 min. After evaporation of the solvent, the residue was separated on a Chromatotron plate was eluent of increasing polarity starting from pure hexanes to hexanes/CH_2Cl_2 mixtures. The E isomer **2a** was separated but the Z isomer **3a** was contaminated with unreacted ynone. In all, the cyclized products were obtained in 58% yield (1.1:1 E/Z ratio), together with 18% recovered starting material.

2a (*E* isomer): mp 131 °C (ethyl acetate/hexanes); ^1H NMR δ 6.62 (s, 2 H), 6.95 (d, J = 0.8 Hz, 1 H), 7.26 (s, 1 H), 7.31 (m, 1 H), 7.41 (m, 2 H), 7.50 (m, 2 H, J = 7 Hz); ^{13}C NMR δ 184.3, 156.4, 151.2, 150.4, 146.3, 135.3, 128.7, 128.1, 120.0, 114.7, 102.7, 102.6, 101.5; IR (CH_2Cl_2) 1761 cm^{-1}; MS (m/z) 250 (100, M^+), 222 (44, –CO), 163 (63); HRMS $C_{16}H_{10}O/_3$ 250.0630 (calcd) 250.0649 (found).

3a (*Z* isomer): mp 130 °C (CH_2Cl/hexanes); ^1H NMR δ 6.09 (s, 2 H), 6.29 (s, 1 H), 6.91 (s, 1 H), 6.96 (s, 1 H), 7.24 (m, 1 H), 7.36 (m, 2 H), 7.88 (m, 2 H); ^{13}C NMR δ 182.3, 158.5, 154.7, 150.1, 148.6, 147.1, 135.3, 129.2, 128.5, 127.8, 118.9, 102.3, 101.6, 99.61; IR (CH_2Cl_2) 1750 cm^{-1}; MS (m/z) 250 (100, M^+), 222 (39), 163 (67); HRMS $C_{16}H_{10}O_3$ 250.0630 (calcd), 250.0622 (found).

Preparation of 7. To a solution of 67.3 mL of *n*-BuLi (1.2 M in hexanes, 81 mmol) in 50 mL of THF at –78 °C was added dropwise over 40 min phenylacetylene (8.90 mL, 81 mmol). The solution was stirred for 20 min, and then 2-bromobenzaldehyde (15 g, 81 mmol) was introduced dropwise over 20 min. The resulting green-black solution was stirred for a further 25 min then quenched at –78 °C with dropwise addition of aqueous saturation NH_4Cl (20 mL over 30 min). The mixture was allowed to warm to room temperature and worked up in the usual way by extraction with 50 mL of ether. The crude brown oil was distilled (<1 Torr) to yield **7** (8.18 g, 35%) as a slightly yellowish oil: ^1H NMR δ 2.7 (br s, 1 H), 5.99 (s, 1 H), 7.1–7.6 (m, 8 H), 7.83 (dd, J = 5.6, 1.8 Hz, 1 H); IR (CH_2Cl_2) 3600, 1030 cm^{-1}; MS (m/z) 288 and 286 (5, M^+), 287 and 285 (5), 207 (100), 185 (54), 77 (60).

Preparation of 8. To a solution of **7** (140 mg, 0.488 mmol, 1 equiv) and $PdCl_2(PPh_3)_2$ (28 mg) in benzene (15 mL) was added Bu_3SnH (130 μL, 0.488 mmol). The solution was stirred for 1 h and evaporated under reduced pressure, and the residual red oil was purified on a Chromatotron plate (1 mm; 9:1 hexanes/ethyl acetate). The yield of **8** was 90%: ^1H NMR δ 0.6–1.5 (m, 27 H), 2.03 (d, J = 3.8 Hz, 1 H), 5.46 (dd, J, 8.1, 3,3 Hz, 1 H), 5.95 (d, 8.1, J[Sn–H] = 60 Hz, 1 H), 6.95 (m, 5 H), 7.45 (dd, J = 9, 1.2 Hz, 1 H), 7.54 (dd, J = 8, 1.8 Hz, 1 H); MS (m/z) 523 (30), 522 (20), 521 (24), 520 (34), 519 (17), 518 (10), 517 (12), 56 (100).

Preparation of 9. The same procedure as for **7** was used but purification was accomplished by flash chromatography (3:1 hexanes/ethyl acetate) to yield **9** as a brownish oil (50%): ^1H NMR δ 2.58 (d, J = 5.3 Hz, 1 H), 5.93 (d, J = 5.3 Hz, 1 H), 6.75 (dd, J = 8.8, 3.1 Hz, 1 H), 7.3 (m, 3 H), 7.4 (m, 4 H).

Preparation of Adduct 10. Alcohol **5** (1.48 g, 4.68 mmol, 1 equiv), Bu_3SnH (1.75 mL, 1.5 equiv), and azobis(isobutyronitrile) (59 mg, 0.1 equiv) were refluxed in 50 mL of benzene under N_2 for 2.5 h. The solvent was removed under reduced pressure, and the residue was chromatographed on a 4-mm Chromatotron plate with 6:1 hexanes/ethyl acetate as eluent. The adduct **10** was obtained in 55% yield: ^1H NMR δ 0.5–1.6 (m, 27 H), 2.09 (d, J = 5.2 Hz, 1 H), 3.78 (s, 3 H), 5.72 (dd, J = 5.3, 1.7 Hz, 1 H), 6.70

(dd, J = 8.3, 3.1 Hz, 1 H), 7.07 (d, J = 3.1 Hz, 1 H), 7.22 (m, 6 H), 7.43 (d, J = 8.7 Hz, 1 H).

Preparation of 11. Adduct **10** (290 mg, 0.48 mmol), 2,6-di-*tert*-butylphenol (a few crystals), and $Pd(PPh_3)_4$ (28 mg) were refluxed in 25 mL of toluene for 4.5 h, and the solvent was removed under reduced pressure. The residue was chromatographed on a 2-mm Chromatotron plate with 3:1 hexanes/ethyl acetate as eluent to afford 45% of **11**. Oxidation of **9** with PDC gave the ketone **2c**. ^1H NMR of **11**: δ 2.50 (m, 1 H), 3.79 (s, 3 H), 3.79 (s, 3 H), 5.42 (m, 1 H), 6.36 (s, 1 H), 6.89 (m, 2 H), 7.2-7.6 (m, 6 H); ^{13}C NMR δ 55.4, 75.3, 107.0, 117.3, 117.6, 123.1, 127.0, 127.5, 128.6, 135.7, 137.2, 143.1, 152.6, 161.2.

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Registry No. **1a**, 134419-76-4; **1b**, 134419-77-5; **1c**, 134419-78-6; **2a**, 134419-79-7; **2b**, 134419-81-1; **2c**, 134419-83-3; **3a**, 134419-80-0; **3b**, 134419-82-2; **3c**, 134419-84-4; **6**, 134419-90-2; **7**, 134419-85-5; **8**, 134419-86-6; **9**, 134419-87-7; **10**, 134419-88-8; **11**, 134419-89-9; phenylacetylene, 536-74-3; 2-bromo-5-methoxybenzaldehyde, 7507-86-0; 5-methoxy-2-bromobenzoic acid, 22921-68-2; 2-bromobenzoic acid, 88-65-3; 2-bromobenzoyl chloride, 7154-66-7; 6-bromo-3,4-(methylenedioxy)benzoyl chloride, 55171-62-5; 2-bromobenzaldehyde, 6630-33-7.

Supplementary Material Available: ^1H NMR spectra for compounds **2a-c**, **3a-c**, and **11** (12 pages). Ordering information is given on any current masthead page.

Studies on the Reactivity of Bicyclomycin 3′-*O*-Methanesulfonate. A Novel Ring-Expansion Transformation

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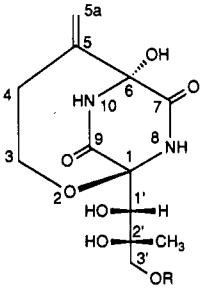
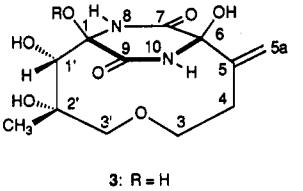
A series of fascinating transformations and rearrangements has been described for the clinically useful antibiotic[1] bicyclomycin (**1**) and derivatives under a variety of



1: R = H
2: R = SO_2CH_3
4: R = $C(O)NHCH_2CH_3$



3: R = H
10: R = CH_3

conditions.[2-4] In this paper, we report that bicyclomycin

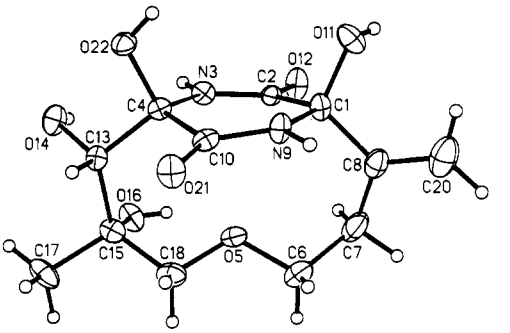
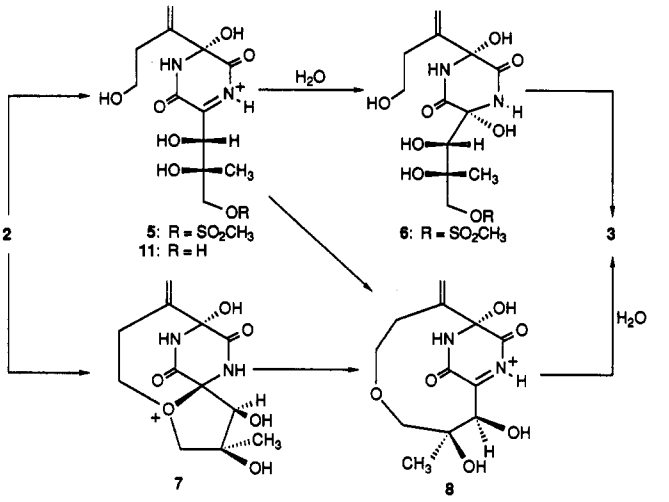


Figure 1. View of compound **3** with atom-labeling scheme. The non-hydrogen atoms are shown as 40% equiprobability envelopes and hydrogens as spheres of arbitrary diameter.

Scheme I. Proposed Pathways for the Conversion of Compound 2 to Compound 3



3′-*O*-methanesulfonate[5] (**2**) is stereospecifically converted in H_2O to the ring-expanded adduct **3**, a compound that is isomeric with the natural product.

Bicyclomycin 3′-*O*-methanesulfonate (**2**) was prepared according to the procedure of Muller and co-workers.[5] Addition of **2** to an unbuffered aqueous solution led to the gradual reduction of the pH of the solution from 6.5 to 2.0 and the formation of **3** (24 h). Identification of **3** was accomplished with the aid of ^1H and ^{13}C NMR and FAB mass spectroscopy and was verified by X-ray crystallographic analysis. Distinctive signals noted for **3** in the ^1H NMR spectrum include the two doublets (J = 9.0 Hz) at δ 3.03 and 3.13 for the diastereotopic C(3′) methylene protons and in the ^{13}C NMR spectrum the resonances at δ 80.57 and 80.91 for the C(1) and C(6) carbons. In the solid state, the expanded ring in **3** adopts a staggered conformation in which the ether oxygen atom is directed toward the center of the 2,5-piperazinedione ring system (Figure 1). The six-membered ring in **3** is noticeably flatter than that determined for either **1**[6] or the corresponding 3′-*O*-ethyl carbamate derivative **4**[7] (i.e., the sum of endocyclic torsion angle moduli for the six-membered ring in **4** is 150.3°, while it is 63.4° in **3**). This perturbation is attributed to the expanded ring system present in **3**. The X-ray structure for **3** also reveals that the relative configuration at C(6) in this adduct is the same as in **1** and

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