have the same sign (diatropic "antiaromatics") as opposed to the normal negative proportionality. In the case of **1**, the Trinajstić–Aihara RE is strongly negative and the "London" susceptibility contribution positive (paramagnetic), as expected for an "antiaromatic" species. However, bond alternation in **1** presumably enables the system to attain a positive RE, but does not change the sign of X_L. This is in contrast to bicyclo[6.2.0]-decapentaene, where stabilizing distortions increase the diatropicity but are probably insufficient to change the sign of the RE.[36]

Summary. The polycyclic hydrocarbon dicycloocta[*def:jkl*]-biphenylene (**1**) has been prepared and its physical properties examined. The ^{1}H NMR spectrum of **1** shows a marked ring current paratropism as predicted by McWeeny ring current theory; the UV-vis spectrum agrees well with a previous prediction by Vogler and Ege. Various resonance energy calculations for the related polycycles **3**, **2**, and **1** disagree considerably as to the sign and magnitude of RE in **1**, though all of the schemes predict the stability sequence (**3** > **2** > **1**) correctly. Of the current classification schemes for polycycles, the periphery model succeeds for **1** and **3**, but fails for **2**, while both the conjugated circuit theory and the algebraic structure count correctly describe the complete series.

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Registry No. 1, 64074-44-8; **2**, 36230-20-3; **3**, 259-79-0; **4**, 95-78-3; **5**, 15540-89-3; **6**, 15540-90-6; **7**, 15540-91-7; **8**, 68596-88-3; **9**, 63548-78-7; **10**, 87729-44-0; **11**, 87739-06-8; **13**, 87729-46-2; **14**, 92096-48-5; $HONH_2$·HCl, 5470-11-1; PPh_3, 603-35-0; HC(O)C(O)H, 107-22-2; HCHO, 50-00-0; chloral hydrate, 302-17-0; glyoxal trimer dihydrate, 40094-65-3.

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Synthetic Studies of the Furan–Carbonyl Photocycloaddition Reaction. A Total Synthesis of (±)-Avenaciolide

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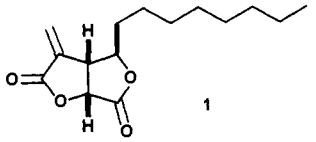
Abstract: The Paternò–Büchi photocycloaddition of furan and nonanal serves as an entry point for a new synthesis of the antifungal mold metabolite avenaciolide (**1**). The method of "ancillary stereocontrol" is employed to complete the stereospecific synthesis.

The furan–carbonyl photocycloaddition reaction provides a method for the addition of an enolate equivalent (furan) to an aldehyde which allows access to threo-aldol products.[2] Furthermore, the dihydrofuran photoadduct can be converted to a variety of functionalized systems with a high degree of stereochemical control.[2] Recently, we described the application of this method in a short synthesis of the highly congested mycotoxin asteltoxin.[3] Herein, we report on the efficient preparation of the antifungal metabolite (±)-avenaciolide[4,5] (**1**) which also employs



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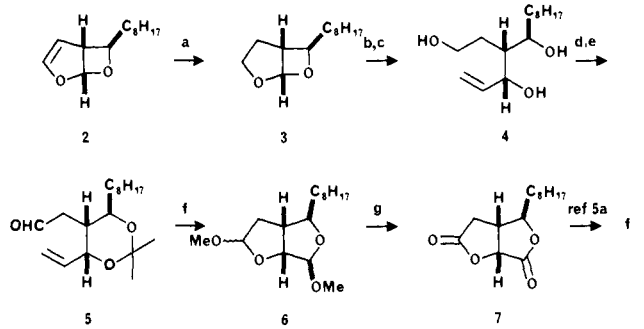
the furan–carbonyl photocycloaddition reaction as the springboard for the synthesis.[6] Our synthesis illustrates another key feature of the reaction: *multigram quantities of materials can be easily prepared in high yield and with complete stereochemical control so that its use as the first step in a synthesis design can be recommended.*

Scheme I[a]



2 **3** **4** **5** **6** **7**

[a] (a) H_2, Rh/Al_2O_3, EtOAc, 97%; (b) 0.1 N HCl, THF (1:4), 96%; (c) CH_2=CHMgBr, THF, room temperature, 80%, (5:1); (d) acetone, $CuSO_4$, *p*-TSOH, 85%; (e) PCC, NaOAc, CH_2Cl_2, 91%; (f) O_3, MeOH, −78 °C, then Me_2S, room temperature, then K_2CO_3, then HCl, 31%; (g) MCPBA, BF_3·OEt_2, CH_2Cl_2, 80%.

Photocycloaddition of nonanal (32.7 g) in furan (350 mL) with a Hanovia 450-W lamp equipped with a Vycor filter for 20 h

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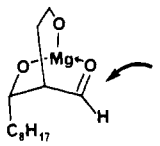
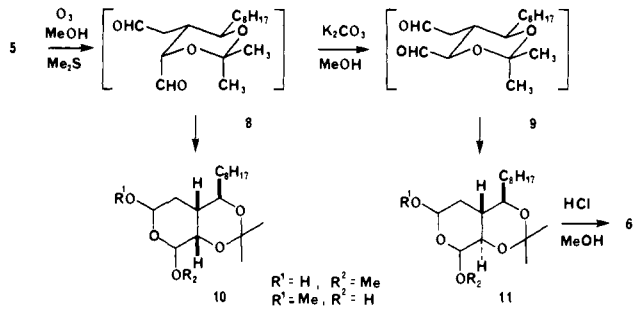


Figure 1.

Scheme II



provided the single exo-substituted Paternò–Büchi oxetane **2** (48.7 g) in near quantitative yield. In this manner, two readily available starting materials are joined and two of the three stereocenters in the target system are created. The high degree of stereocontrol and the efficiency and simplicity of the experimental operation of these photocycloaddition reactions speak well for their continued use in stereoselective synthesis.

In the present application, we required a method for the insertion of carbon monoxide into the acetal bond of the oxetane. A stereospecific procedure was developed as follows. Hydrogenation of the photoaldol adduct[2] and hydrolysis provided the lactol without complications arising from epimerization. Treatment of the lactol with excess vinylmagnesium bromide provided the triol **4** and the corresponding epimer in a 5:1 ratio (Scheme I). Although the stereochemistry at the allylic carbinol site of the major diastereomer is opposite to that required for avenaciolide synthesis, we recognized that this could be corrected at a later stage (vide infra). The diastereofacial selectivity, albeit modest, is of interest in that it does not correspond to simple chelation-controlled addition of the Grignard reagent to a β-hydroxy-α-alkyl aldehyde.[7] Bischelation of the magnesium counterion with the diol to provide the bicyclic activated complex shown in Figure 1 would provide an explanation for the observed facial selectivity as exo addition should be favored. In such a complex, the β-alkyl substituent blocks the endo mode of addition and becomes the stereocontrolling element.

Triol differentiation was effectively achieved via the formation of the acetonide. Oxidation of the remaining primary alcohol with PCC[8] to the aldehyde **5** set the stage for final skeletal construction and correction of the offending stereocenter. In a one-pot operation consisting of ozonolysis in methanol, reduction with dimethyl sulfide, base-catalyzed epimerization with potassium carbonate, and acidification with hydrochloric acid, the acetonide **5** was converted to the bis(methoxy lactols) **6** as a 2:1 mixture of methoxy anomers. Intermediates in this sequence could be isolated without difficulty and illustrate the sequence of events that transpires in this key transformation. Ozonolytic cleavage and reduction of **5** provided the bis(aldehyde) derivatives **10**, presumably by way of the axial aldehyde **8** (Scheme II). Base-catalyzed equilibration gave rise to the desired stereoisomeric system **11**, by way of the equatorial aldehyde **9**. This 1,3-stereochemical control device was introduced by Stork in his erythronolide A studies and was termed "ancillary stereocontrol".[9] Having performed two critical functions, the acetonide was removed by acidification, and the bis(methoxy lactols) were obtained after acetalization. A feature of the ancillary stereocontrol procedure is that the stereochemical outcome of the Grignard addition is inconsequential to the avenaciolide synthesis. Accordingly, the 5:1 mixture of stereoisomers produced in this step was employed in subsequent transformations.

Conversion of the bis(methoxy lactols) **6** to the known bis(lactone)[5a] **7** could be achieved directly by the Grieco oxidation with MCPBA and $BF_3{\cdot}OEt_2$,[10] a method which proved to be superior to two-step hydrolysis/oxidation procedures. Methylenation of the bis(lactone) **7** to provide (±)-avenaciolide[11] was performed by the published procedure of Johnson[5a,b] which was employed in the first synthesis of this substance.

In summary, the synthesis of (±)-avenaciolide has been achieved in 10 steps in a manner that is amenable to the multigram preparation of this substance. Further studies of the furan–carbonyl photocycloaddition reaction are in progress and will be reported in due course.

Experimental Section

Infrared spectra were recorded on a Nicolet 5 SX FT-IR spectrometer, ν_{max} in cm^{-1}. Bands are characterized as strong (s), medium (m), and weak (w). ^1H magnetic resonance spectra were recorded on a Bruker WM-250 (250 MHz) and are reported in parts per million using $CDCl_3$ as standard on a δ scale. Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad), integration, and coupling constant (Hz). ^{13}C magnetic resonance spectra were recorded on a Bruker WM-250 (62.9 MHz) and are reported in parts per million using $CDCl_3$ as standard on a δ scale. A Hewlett-Packard 5985-GC/MS system equipped with a 2% OV-101 column (3 ft × 1/4 in. × 2 mm) on Chromosorb WHP 100/120 was used to obtain mass spectra. Microanalyses were performed by Atlantic Microlaboratories, Inc., Atlanta, GA. Melting points were recorded on a MEL-TEMP apparatus and are uncorrected.

All reactions were carried out under nitrogen atmosphere and were monitored by analytical thin-layer chromatographic methods (TLC) using E. Merck silica gel 60F-24 glass plates (0.25 mm). Flash chromatography was carried out by using E. Merck silica gel 60 (230–400 mesh). Ozone was produced by a Welsbach Corporation Ozonator, style T-709, with the voltage set at 100 V and oxygen pressure at 7 psi to give approximately 2% ozone concentration.

Ether and tetrahydrofuran were distilled from sodium benzophenone ketyl. Nonyl aldehyde was distilled and stored at 0 °C. $BF_3{\cdot}Et_2O$ and triethylamine were distilled over CaH_2. $BF_3{\cdot}Et_2O$ was stored at 0 °C. Hexanes were purified by distillation. All other reagents were used as received.

Large-Scale Preparation of 2-[(*R*,*S*)(*S*,*R*)]-Hydroxy-3(*R*,*S*)-(1-(*R*,*S*)-hydroxy-1-nonyl)tetrahydrofuran. Nonyl aldehyde (32.66 g, 0.23 mol) and furan (200 mL, 187.2 g, 2.75 mol) were mixed in a 250-mL photolysis flask equipped with a quartz immersion well containing a Vycor filter and a 450-W Hanovia lamp. The system was kept at −20 °C with an isopropyl alcohol bath cooled by a Cryocool Immersion Cooler (CC100). Nitrogen was bubbled throughout the duration of the reaction, and the solution was stirred vigorously. Additional furan (150 mL, 140.4 g, 2.06 mol) was added during the course of the reaction. TLC analysis indicated completion of the reaction after 20 h. After evaporation of excess furan, ^{13}C and ^1H NMR analysis of the resultant oil (48.70 g, ca. 100%) indicated the desired photoadduct had been formed, without contamination from unreacted nonyl aldehyde.

The crude photoadduct (48.70 g, 0.23 mol) was dissolved in 500 mL of EtOAc, and 4 g (ca. 10% w/w) of 5% Rh/Al_2O_3 catalyst was added to the mixture. Hydrogenation after 9 h at 1 atm yielded the desired oxetane as the sole product. The catalyst was carefully filtered off, EtOAc was removed by rotary evaporation, and the crude hydrogenation adduct was dissolved in a 4:1 THF/0.1 N HCl solution (250 mL) to yield the desired lactol after stirring for 2–3 min. The reaction mixture was quenched by addition of saturated solution of sodium bicarbonate. After evaporation of ca. 50% of the THF, the solution was extracted with ether (4 × 150 mL). The combined ether extracts were washed with brine and dried with $MgSO_4$. Rotary evaporation of the solvent afforded the desired lactol (44.9 g, 0.19 mol, 85% from nonanal). The yellow oil crys-

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(11) (±)-Avenaciolide prepared in this manner exhibited identical spectroscopic properties (^1H NMR, ^{13}C NMR, IR, MS) with those previously reported.[5]

tallized upon standing at room temperature.

TLC R_f 0.11 (50% E/H); IR (CH_2Cl_2) 3599 (m), 3422 (m) cm^{-1}; ^1H NMR (both isomers) ($CDCl_3$) δ 5.50 (m, 2), 4.15 (m, 1), 3.90 (m, 4), 3.50 (m, 1), 2.15 (m, 4), 1.90 (m, 4), 1.26 (brs, 24), 0.88 (t, 6); ^{13}C NMR ($CDCl_3$) δ 100.9, 98.3, 72.9, 71.4, 62.3, 66.8, 53.0, 49.8, 36.4, 35.9, 31.8, 29.6, 29.2, 28.4, 25.8, 25.7, 25.3, 22.6, 14.0; MS (70 eV), *m/e* (relative intensity) 230 (37.5) (M^+); mp 43-44 °C. Anal. Calcd for $C_{13}H_{26}O_2$: C, 67.85; H, 11.30. Found: C, 67.63; H, 11.48.

[1(*R*,*S*),5(*R*,*S*)]-6(*R*,*S*)-*n*-Octyl-1-2,7-dioxabicyclo[3.2.0]hept-3-ene (2). Nonyl aldehyde (2.0 g, 14 mmol) and furan (2.5 equiv) were mixed in a quartz tube and photolyzed as described above. After $9^1/_2$ h, excess furan was evaporated to give 2.9 g (13.8 mmol, 98.6%) of crude photoadduct without any remaining starting material. Flash chromatography (20% ether/hexanes, 1% Et_3N) afforded 2.63 g (12.5 mmol, 90%) of the photoadduct as a pale yellow oil.

TLC R_f 0.84 (50% E/H); IR (CH_2Cl_2) 1604 (m), 1466 (m), 1457 (m) cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.60 (m, 1), 6.26 (brd, 1, J = 5.06 Hz), 5.29 (t, 1, 2.90 Hz), 4.51 (m, 1), 3.4 (m, 1), 1.76 (m, 2), 1.26 (bs, 12), 0.88 (t, 3, J = 6.5 Hz); ^{13}C NMR ($CDCl_3$) δ 147.9, 107.8, 104.0, 92.3, 48.8, 37.0, 31.7, 29.3, 29.2, 29.0, 24.3, 22.5, 13.9; MS (70 eV), *m/e* (relative intensity) 210 (35) (M^+), 114 (30), 97 (100).

[1(*R*,*S*),5(*R*,*S*)]-6(*R*,*S*)-*n*-Octyl-2,7-dioxabicyclo[3.2.0]heptane (3). The photoadduct **2** (2.25 g, 10.71 mmol) was dissolved in 50 mL of EtOAc (0.2 M solution), and 200 mg (ca. 20% w/w) of 5% Rh/Al_2O_3 was added to the mixture. After 1 h of hydrogenation at 1 atm, the catalyst was filtered, and the solvent was removed to afford after flash chromatography (15% ether/hexanes, 1% Et_3N) 2.21 g (10.42 mmol, 97%) of the desired oxetane as a colorless oil.

TLC R_f 0.73 (50% E/H); IR ($CHCl_3$) 1100 (s) cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.85 (d, 1 , J = 3.88 Hz), 4.25 (m, 2), 4.05 (m, 1), 3.01 (m, 1), 1.83 (m, 4), 1.30 (brs, 12), 0.88 (t, 3, J = 6.5 Hz); ^{13}C NMR ($CDCl_3$) δ 105.7, 81.6, 67.3, 46.0, 36.8, 31.6, 29.3, 29.2, 29.0, 28.6, 24.3, 22.4, 13.8; MS (70 eV), *m/e* (relative intensity) 212 (24) (M^+), 99 (40).

[1(*R*,*S*),5(*R*,*S*)]-3[(*R*,*S*)(*S*,*R*)],8(*R*,*S*)-Dimethoxy-6(*R*,*S*)-*n*-octyl-2,7-dioxabicyclo[3.3.0]octane (6). The aldehyde **5** (14.40 g, 48 mmol) was dissolved in 250 mL (0.2 M) of methanol. The mixture turned blue after 50 min of ozonolysis at -78 °C, after which nitrogen gas was bubbled into the solution to remove excess ozone. Dimethyl sulfide (20 mL, excess) was added at -50 °C and solution was warmed to room temperature after 5 min. After 3 h of stirring anhydrous K_2CO_3 (5 g) was added to the mixture until the solution became milky white. TLC analysis indicated complete epimerization after 36 h (66% ether/hexane, R_f(starting material) = 0.47, R_f(product) = 0.26). The reaction mixture was cooled to 0 °C and dropwise addition of a saturated solution of hydrogen chloride in methanol continued until evolution of CO_2 gas ceased, and the solution became acidic (pH 1). After 30 min of stirring at room temperature, the reaction mixture was quenched by slow addition of saturated sodium bicarbonate solution. Insoluble salts were filtered and methanol was removed under vacuum. After extraction with ether the organic layers were dried over $MgSO_4$, and the solvent was removed by rotary evaporation. Flash chromatography of the red oil (10% ether/hexanes) gave 4.23 g (15 mmol) of the bis(methoxy lactols) **6** in 31% yield.

TLC R_f 0.73 (33% H/E); IR (CH_2Cl_2); ^1H NMR (major isomer only) ($CDCl_3$) δ 5.08 (dd, 1, J = 4.9 Hz, 1.6 Hz), 4.91 (s, 1), 4.49 (d, 1, J = 6.6 Hz), 3.81 (m, 1), 3.33 (s, 3), 3.31 (s, 3), 2.72 (m, 1), 2.1 (ddd, 1, J = 10.3, 8.7, 1.6 Hz), 1.9 (m, 1), 1.3 (brs, 12), 0.88 (t, 3, J = 6.5 Hz); ^{13}C NMR ($CDCl_3$) δ 108.9, 106.7, 88.7, 87.9, 87.8, 54.7, 46.3, 46.2, 39.3, 38.4, 38.2, 37.7, 31.8, 29.5, 29.2, 26.3, 22.6, 14.0; MS (70 eV), *m/e* (relative intensity) 173 (100), 113 (44). Anal. Calcd for $C_{16}H_{30}O_4$: C, 67.16; H, 10.48. Found: C, 66.98; H, 10.56.

[1(*R*,*S*)]-6(*R*,*S*)-*n*-Octyl-2,7-dioxabicyclo[3.3.0]oct-3,8-dione) (7). The bis(methoxy lactols) **6** (3.95 g, 13.8 mmol) were dissolved in 100 mL of CH_2Cl_2. MCPBA (55.2 mmol, 12.4 g, 4 equiv) and $BF_3{\cdot}Et_2O$ (1.38 mmol, 170 μL, 0.1 equiv) were added, and stirring was continued for 6 h. NMR analysis of an aliquot indicated oxidation of only the methoxy lactol of the less substituted ring had occurred. The bis(butyrolactone) was formed after an additional equivalent of MCPBA (3.1 g) and 2.5 equiv (4.4 mL) of $BF_3{\cdot}Et_2O$ were added. After stirring for 10 h, the white precipitate was filtered, and the filtrate was treated with saturated sodium bicarbonate solution. The solution was extracted with ether (3 × 100 mL), and the combined ether extracts were washed with brine and dried ($MgSO_4$). Removal of solvent and flash chromatography (10% ether/hexanes) of the residue afforded 2.79 g (11.0 mmol, 80%) of the desired bis(butyrolactone), which exhibited spectroscopic data[5b,d] identical with that previously reported for this compound.

TLC R_f 0.23 (33% H/E); IR (CH_2Cl_2) 1797 (s), 1788 (s), 1733 (m), 1729 (m), 1725 (m) cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.98 (d, 1, J = 7.6 Hz), 4.32 (m, 1), 3.05 (m, 1), 2.98 (dd, 1, J = 17.3, 9.3 Hz), 2.52 (dd, 1, J = 17.5, 3.30 Hz), 1.75 (m, 2), 1.25 (brs, 12), 0.88 (t, 3, J = 6.5 Hz); ^{13}C NMR ($CDCl_3$) δ 174.1, 170.2, 85.0, 77.0, 39.7, 35.1, 32.5, 31.5, 29.0, 28.9, 28.8, 24.6, 22.3, 13.7; MS (70 eV), *m/e* (relative intensity) 254 (0.4) (M^+), 141 (11.6). Anal. Calcd for $C_{14}H_{22}O_4$: C, 66.17; H, 8.66. Found: C, 65.95; H, 8.77.

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The Effect of Hydrophobic-Lipophilic Interactions on Chemical Reactivity. 4. A Case of 17-Membered-Ring "Neighboring-Group" Participation: Compelling Evidence for Self-Coiling

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Contribution from the Shanghai Institute of Organic Chemistry, Academia Sinica, Shanghai, China. *Received September 29, 1983*

Abstract: Hydrolytic rate constants of ω-substituted *p*-nitrophenyl esters of hexadecanoic acids (**16-Y**, Y = Br, SCH_3, OH, and SH) were measured in 50:50 (v/v) Me_2SO-H_2O. The relative rate constants k_{rel} with **16-H** as the reference are 2, 8, 16, and 124 s^{-1}, respectively. For **16-SH** at the initial substrate concentration of about 2×10^{-5} M, a rate-enhancing factor of at least 6 was brought about by a 17-membered-ring "neighboring-group" participation involving the ω-sulfhydryl end group. The above evaluation was based on, and alternative explanations were excluded by, additional experiments on effects of adding four thiols of increasing chain lengths as nucleophiles, rate dependence on the initial substrate concentrations, comparison of hydrolytic rates of **16-Y** with the short-chain reference **8-H**, and the effects of adding amylose. Thus the present study rigorously demonstrates that long-chain molecules can be forced to fold and then interact intramolecularly by hydrophobic forces. It also serves as compelling evidence for the phenomenon of self-coiling.

If enzymes can fold and coil in a myriad of ways to do their jobs, long-chain molecules might be made to duplicate part of such a feat in test tubes. Knowing that these long-chain molecules will aggregate and coil-up in some hydrophilic or lipophobic, thus

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