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Synthesis of a Pondaplin Dimer and Trimer. Aromatic Interactions in Novel Macrocycles

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Received October 30, 2003

Synthetic challenges in the use of an oxabicyclo[2.2.2]octenone moiety as a masked arene for the synthesis of pondaplin are disclosed. During the course of a study of the Heck reaction as a tool for macrocyclization to provide strained paracyclophanes, novel macrocycles displaying intra- and intermolecular aromatic interactions have been synthesized. The geometry of these interactions is compared to recent computational literature data.

Introduction

Pondaplin[1] (**1**) is a cyclic prenylated phenylpropanoid isolated from *Annona glabra*, which is commonly referred to as pond apple. Pond apple has been used in traditional medicine as an insecticide and parasiticide.[2,3] In 1999, McLaughlin and co-workers isolated the compound from the ethanol extracts of its leaves.[1] Pondaplin was found to have moderate and somewhat selective antitumor activity when screened across six human tumor cell lines in a seven-day MTT human solid tumor cytotoxicity test.[1] Pondaplin is a structurally unique molecule as it appears to be the only example of a [9]paracyclophane natural product. Closely related are some members of the cyclopeptide alkaloid family of natural products, notably the 14-membered [10]paracyclophane pandamine[4,5] and the 13-membered [10]metacyclophane zizyphine A.[6−10] In comparison with these compounds, pondaplin contains a shorter tether that bears five sp^2 centers, imparting a high degree of strain energy and a potentially significant deformation of the aromatic ring from planarity.[11,12]

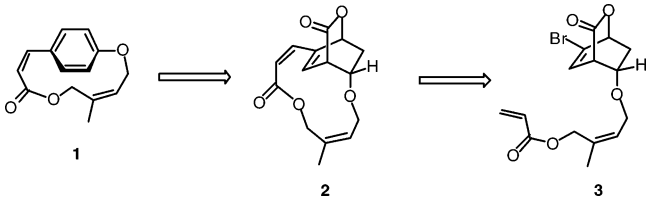

FIGURE 1. Retrosynthetic analysis of pondaplin (**1**).

Results and Discussion

Results from our laboratories,[13] as well as a recent communication by Bressy and Piva,[14] have shown that a ring-closing metathesis approach to the synthesis of pondaplin, while attractive based upon its simplicity, is unsuitable due to the highly strained structure and the greater stability of the undesired E geometry of the trisubstituted olefin. Because of these findings, we devised a strategy that would construct a macrocycle containing a core that would serve as a masked aromatic ring and would not impose the same degree of strain on the molecule during the cyclization events (Figure 1). To this end, we selected an oxabicyclo[2.2.2]octenone core structure. Following ring closure, extrusion of carbon dioxide and subsequent oxidation would provide the aromatic ring.

We believed the requisite bicyclooctenone could be obtained by a Diels−Alder reaction of 5-bromo-2-pyrone[15,16] (**4**) and the *tert*-butyldimethylsilyl enol ether[17,18] of acetaldehyde (**5**). The compounds were prepared according to literature precedent, and cycloaddition pro-

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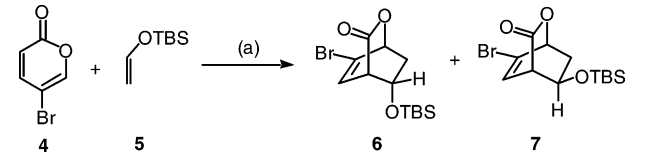
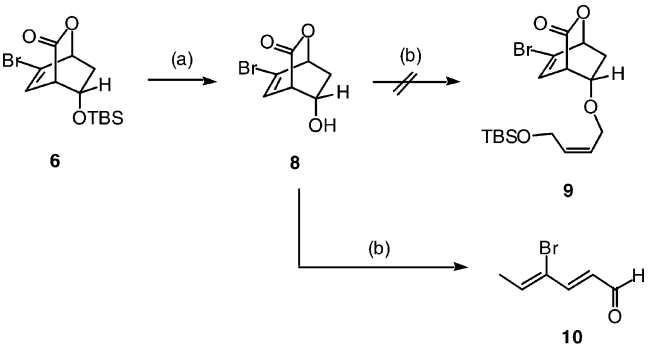
10.1021/jo0356006 CCC: $27.50
Published on Web 02/25/2004

SCHEME 1[a]



[a] Reagents: (a) sealed tube, 95 °C, 2d or microwave irradiation, 6 h (73%; *endo*/*exo* 5:1).

SCHEME 2[a]



[a] Reagents: (a) HF·pyridine, THF (77%); (b) MsO OTBS, TEA, CH_2Cl_2.

ceeded smoothly to give the endo adduct **6** as the predominant product (Scheme 1). This result is in agreement with the work of Afarinkia and Posner.[19] It is possible that this type of cycloaddition is not a concerted Diels−Alder reaction. Addition of the electron-rich olefin to the pyrone followed by closure to provide the bridged lactone has been suggested by some empirical findings.[20]

With the oxabicyclo[2.2.2]octenone core in hand, we sought to liberate the secondary alcohol and append the remainder of the tether (Scheme 2). The cleavage of the silyl ether proceeded optimally with HF·pyridine. This reagent proved superior to TBAF, TBAF/HOAc, KF/18-crown-6, LiBr/18-crown-6, and HOAc. The free alcohol **8** was treated with a model allylic mesylate (a cis-disubstituted olefin was used as a model for the Z-trisubstituted olefin present in the natural product) and mild base, but instead of forming the expected product, the alcohol fragmented to yield solely 4-bromohexa-2,4-(*E*,*Z*)-dienal (**10**). Although other conditions were investigated, these bicyclic lactones are known to be labile in acid and base, and ether formation could not be achieved in preference to fragmentation.

To circumvent this problematic rearrangement, the cycloaddition was performed with a more elaborate dienophile (**11**) prepared in two steps from acryloyl chloride. Subsequent cycloaddition with 5-bromo-2-pyrone did provide the desired linear precursor (**12**) with good endo-to-exo selectivity, albeit in diminished yield (Scheme 3). However, Heck macrocyclization proved unsuccessful under a variety of conditions, including the use of highly active ligands such as tri-2-furylphosphine.

An alternate strategy involved installation of a vinyl group via a Stille reaction followed by ring-closing metathesis (Scheme 4). Disappointingly, vinyl bromide **12** proved to be totally inert to the Stille vinylation conditions, despite the fact that a simple model (**6**) readily underwent the reaction (Scheme 5). Consequently, this approach to pondaplin was abandoned so that attention could be focused on other synthetic strategies, some of which are under investigation in our laboratory.

One of these alternate strategies, while unsuccessful in generating the target molecule, provided extremely interesting results. Heck macrocyclization of a simple linear precursor was considered a potentially attractive route to pondaplin. The linear precursor (**21**) was prepared quickly and efficiently, in six steps and 62% overall yield, from commercially available THP-protected propargyl alcohol (Scheme 6). The sequence began with methoxycarbonylation of THP-propargyl alcohol. Subsequent conjugate addition and DIBAL reduction provided allylic alcohol **18**.[21] Mitsunobu etherification, deprotection, and acylation afforded linear precursor **21**.

Extensive investigation of the Heck macrocyclization failed to develop conditions to provide pondaplin.[13b] However, a pondaplin dimer (**22**) was successfully generated under several sets of reaction conditions. The optimal yield of the dimer was 38% (Scheme 7). This dimer has also been prepared in our laboratories by a different method.[21] A 10-fold increase in concentration led to the formation of a trimeric structure (**23**) as well. The availability of these novel macrocycles led us to examine their X-ray structures and investigate the existing aromatic interactions.

One of the salient features of the X-ray crystal structure of the pondaplin dimer (Figure 2) is the parallel-displaced arrangement of the aromatic rings. This parallel-displaced geometry is one of three main paradigms of aromatic interaction.[22] Aromatic interactions are likely to influence crystal packing and supramolecular structure.[22−26] Recently, high level ab initio calculations have been used to assess the optimal parallel-displaced geometry.[27] This method using an estimated completed basis set of MP2 binding energies found optimal values for R_1, the interplane distance, and R_2, the center-to-center distance, to be 3.4 and 1.6 Å, respectively. These values were compared to the work of others in the field who have calculated optimal R_1/R_2 values of 3.5/1.6,[28] 3.6/1.8,[29] 3.6/1.8,[30] and 3.4/ 1.6[31] using MP2, CCSD(T), MP2, and

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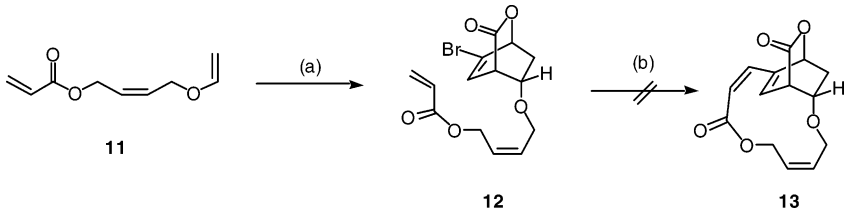
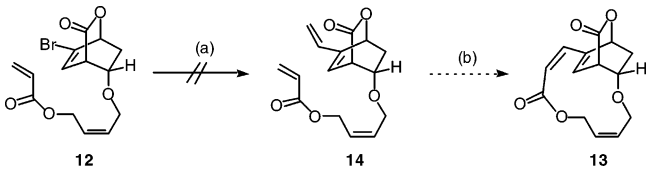
SCHEME 3[a]



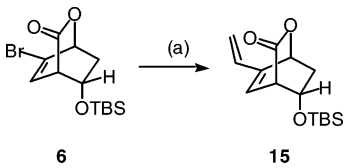
[a] Reagents: (a) 5-bromo-2-pyrone, CH_2Cl_2, sealed tube, 100 °C, 16 h or microwave irradiation, 150 °C, 2 h (25%; *endo*/*exo* 5:1); (b) Heck macrocyclization conditions.

SCHEME 4[a]



[a] Reagents: (a) vinyl tri-*n*-butyltin, $Pd(PPh_3)_4$, BHT, THF, reflux or vinyl tri-*n*-butyl tin, $PdCl_2(PPh_3)_2$, CH_3CN, reflux; (b) ring-closing metathesis (RCM).

SCHEME 5[a]



[a] Reagents: (a) vinyl tri-*n*-butyltin, $Pd(PPh_3)_4$, THF, reflux (52%).

experimental estimation, respectively. If the arrangement of the aromatic rings in the pondaplin dimer is described according to this method, the interplane distance, R_1, is 3.4 Å, and the offset, R_2, is 1.7 Å. These values were obtained using the CrystMol program to analyze the crystal structure and are in excellent agreement with the literature data for optimal orientation.

The X-ray structure of the pondaplin trimer shows it to be relatively flat in shape, with adjacent molecules in the lattice offset relative to one another. Closer inspection

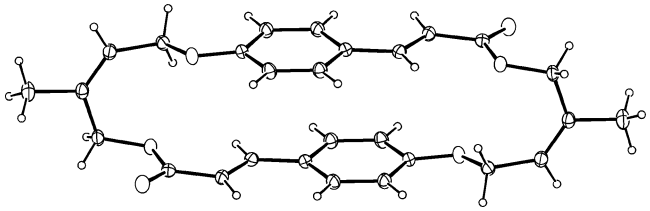


FIGURE 2. ORTEP drawing of **22**.

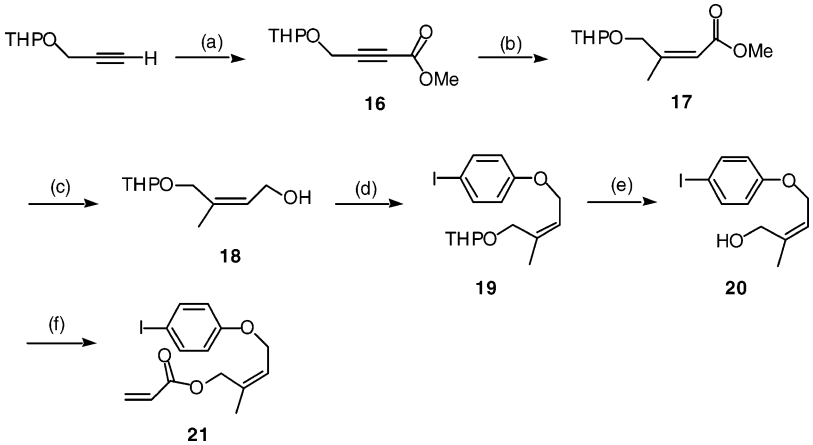
reveals an association between the aromatic rings of adjacent molecules (Figure 3). The average R_1 value is 3.6 Å, and the average R_2 value is only 1.5 Å.

The aromatic interaction in this case appears to be of the parallel-displaced variety as well. The implication of intermolecular π stacking in this example is all the more intriguing due to the lattice structure. The series of offset trimer molecules form a helix in the crystal lattice (Figure 4). Six molecules of the trimer serve to carry the helix through one turn, which is approximately 19.9 Å in length. Observation of the lattice in a broader scope reveals that individual helices interlock in the crystal.

Conclusion

While the methods presented herein have not yet found utility in the total synthesis of the highly unusual natural product pondaplin, large macrocycles with interesting properties have resulted from this work. The dimeric structure appears to display intramolecular parallel-displaced π stacking. While pondaplin itself is exceed-

SCHEME 6[a]



[a] Reagents: (a) *n*-BuLi, THF, −78 °C, 1 h then MeOC(O)Cl, −78 oC → 10 °C, 2 h (quant.); (b) Me_2CuLi, THF, −78 °C, 4 h (90%); (c) DIBAL, $PhCH_3$, 0 °C, 1 h (84%); (d) *p*-iodophenol, DEAD, PPh_3, PhMe (90%); (e) 50% aq. HOAc, 40 °C, 5 h (quant.); (f) acryloyl chloride, TEA, CH_2Cl_2, 12 h (91%).

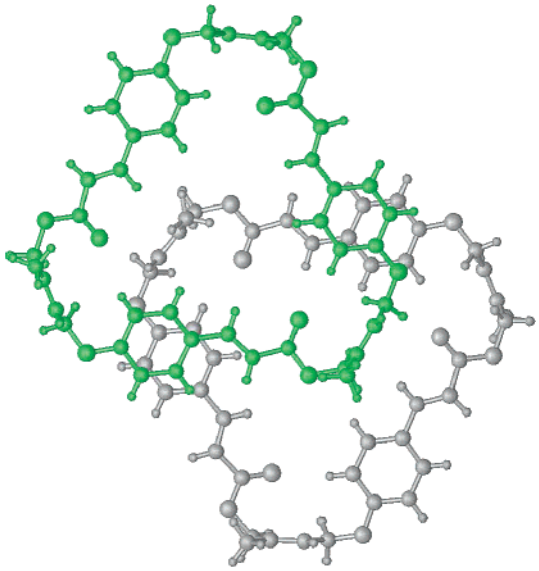


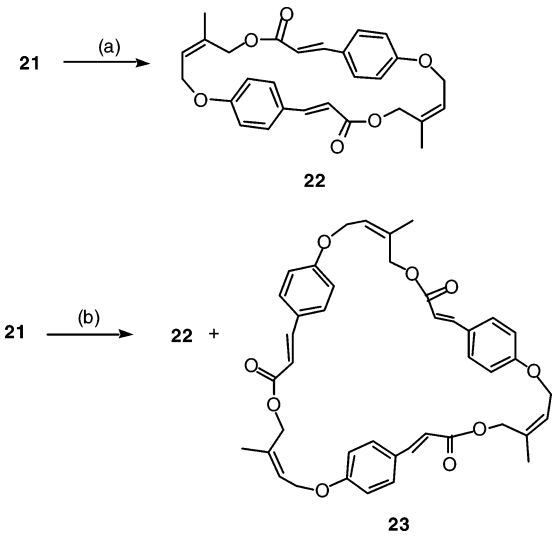
FIGURE 3. View of X-ray structure of **23** indicating adjacent trimer molecules.

ingly rigid, the dimer possesses a larger number of degrees of freedom. Consequently, it appears that the solid-state conformation is not, in fact, imposed by rigidity but is the result of the energetic benefit of this interaction. Furthermore, the geometry of the π array is in good agreement with the computational predictions that have appeared in the literature. The intermolecular π stacking observed in the crystal structure of the trimer is also in close agreement with the computational predictions. This association appears to be responsible for the helical supramolecular structure displayed in the unit cell.

Experimental Section

7-Bromo-5-*endo*-(*tert*-butyldimethylsilanyloxy)-2-oxabicyclo[2.2.2]oct-7-en-3-one (6) and 7-Bromo-5-*exo*-(*tert*-butyldimethylsilanyloxy)-2-oxabicyclo[2.2.2]oct-7-en-3-one (*7*). A mixture of *tert*-butyldimethylsilyl vinyl ether 5 (691.8 mg, 4.38 mmol) and 5-bromo-2-pyrone (**4**, 766.2 mg, 4.38 mmol) in CH_2Cl_2 (0.5 mL) was heated in a sealed tube at 95 °C for 2 days or was irradiated in a monomode microwave reactor at 300 W (temperature controlled cycle: 100 °C) for 6 h. The crude reaction mixture was subjected to column chromatography (5% ethyl acetate/petroleum ether) to afford **6** as a white solid (908 mg, 62%). The *exo* product **7** was obtained as a white solid (78.6 mg, 6%). Endo: R_f 0.79 (25% ethyl acetate/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.04 (s, 3 H), 0.05 (s, 3 H), 0.83 (s, 9 H), 1.65 (d, J = 14.0 Hz, 1 H), 2.52 (ddd, J^1 = 14.0 Hz, J^2 = 7.5 Hz, J^3 = 3.9 Hz, 1 H), 3.63 (dd, J^1 = 6.5 Hz, J^2 = 3.5 Hz, 1 H), 4.29−4.31 (m, 1 H), 5.05 (dd, J^1 = 3.8 Hz, J^2 = 1.7 Hz, 1 H), 6.43 (dd, J^1 = 6.4 Hz, J^2 = 2.3 Hz, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ −4.8, −4.8, 17.8, 25.5, 37.8, 52.0, 64.2, 80.6, 119.7, 128.0, 170.3; IR (KBr plate) 2954, 2929, 2887, 2856, 1769, 1617, 1104 cm^{-1}; HRMS (ESI) m/z 355.0342 (M^+ calcd. for $C_{13}H_{21}BrO_3Si$ + Na, 355.0341). Exo: R_f 0.70 (25% ethyl acetate/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.05 (s, 3 H), 0.07 (s, 3 H), 0.83 (s, 9 H), 1.90 (dt, J^1 = 13.7 Hz, J^2 = 3.5 Hz, 1 H), 2.27 (ddd, J^1 = 13.8 Hz, J^2 = 8.5 Hz, J^3 = 1.5 Hz, 1 H), 3.48 (dd, J^1 = 6.9 Hz, J^2 = 3.3 Hz, 1 H), 4.15 (dt, J^1 = 8.6 Hz, J^2 = 3.1 Hz, 1 H), 5.01 (m, 1 H), 6.43

SCHEME 7[a]



[a] Reagents: (a) $Pd(OAc)_2$, PPh_3, CF_3CO_2Ag, DMF (1 mM), 100 °C, 20 h (38%); (b) $Pd(OAc)_2$, P(2-furyl)$_3$, CF_3CO_2Ag, DMF (10 mM), 90 °C, 21 h (**22**, 7%; **23**, 7%).

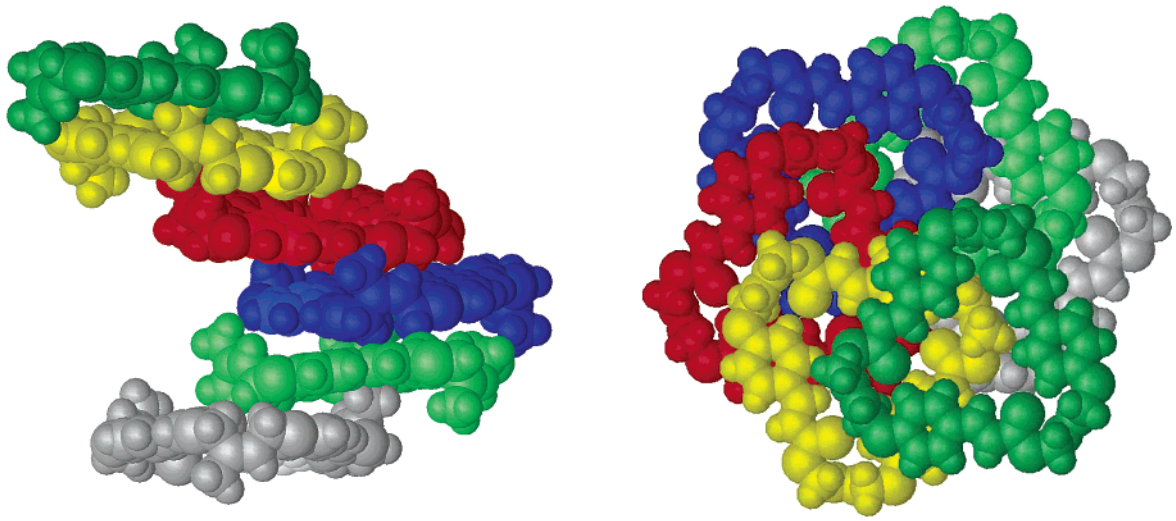


FIGURE 4. Side and top views of the X-ray structure of **23** indicating the helix formed by six trimer molecules.

(dd, $J^1 = 6.9$ Hz, $J^2 = 2.5$ Hz, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ −4.4, −4.5, 18.3, 26.0, 36.4, 52.6, 66.4, 81.0, 123.6, 128.3, 169.5.

7-Bromo-5-*endo*-hydroxy-2-oxabicyclo[2.2.2]oct-7-en-3-one (8). Silyl ether **6** (50 mg, 0.15 mmol) was dissolved in dry THF (3 mL) and cooled to 0 °C. HF·pyridine (0.18 mL, 0.15 mmol) was added, and the reaction mixture was stirred at room temperature for 30 min. Additional aliquots of HF·pyridine were added every 30 min until the reaction had gone to completion. The mixture was then diluted with Et_2O and neutralized with saturated aqueous $NaHCO_3$. The organic layer was separated, washed with brine, dried ($MgSO_4$), filtered, and concentrated. The crude product was purified by silica gel chromatography (gradient 20−30% acetone/hexanes) to give **8** as a white solid (25 mg, 77%). R_f 0.22 (30% acetone/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.72 (dt, $J^1 = 14.4$ Hz, $J^2 = 1.6$ Hz, 1 H), 2.67 (ddd, $J^1 = 14.4$ Hz, $J^2 = 7.8$ Hz, $J^3 = 3.8$ Hz, 1 H), 3.80 (dd, $J^1 = 6.4$ Hz, $J^2 = 3.3$ Hz, 1 H), 4.42 (m, 1 H), 5.12 (dd, $J^1 = 3.8$ Hz, $J^2 = 2.1$ Hz, 1 H), 6.43 (dd, $J^1 = 6.4$ Hz, $J^2 = 2.4$ Hz, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 35.6, 52.4, 66.0, 81.2, 120.7, 128.0, 170.6; IR (KBr plate) 3404, 2923, 2849, 1756 cm^{-1}; HRMS (ESI) *m*/*z* 217.9583 (M^+ calcd. for $C_7H_7BrO_3$, 217.9579).

4-Bromohexa-2,4-(*E*,*Z*)-dienal (10). To a solution of mono-TBS-protected *cis*-2-buten-1,4-diol (175.5 mg, 0.87 mmol) in CH_2Cl_2 at 0 °C was added TEA (275.3 μL, 1.98 mmol). Methanesulfonyl chloride (67.3 μL, 0.87 mmol) was then added. Once the starting material had been quantitatively converted to the mesylate (as monitored by TLC), the bicyclic alcohol **8** (172.7 mg, 0.79 mmol) in CH_2Cl_2 (2 mL) was added. The mixture was stirred at ambient temperature overnight. The crude reaction mixture was diluted with CH_2Cl_2 and washed with 10% HCl, saturated aqueous $NaHCO_3$, and brine. The organic layer was dried ($MgSO_4$), filtered, and concentrated. Silica gel chromatography (10% acetone/hexanes) afforded none of the expected product; however, 4-bromosorbaldehyde, **10**, was isolated. This compound was also isolated when using preformed mesylate and when attempting to remove the TBS ether from **6** using TBAF/HOAc (average yield 50%). R_f 0.50 (30% acetone/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.99 (d, $J = 6.9$ Hz, 3 H), 6.44 (dd, $J^1 = 14.8$ Hz, $J^2 = 7.7$ Hz, 1 H), 6.56 (q, $J = 6.8$ Hz, 1 H), 7.07 (d, $J = 14.8$ Hz, 1 H), 9.64 (d, $J = 7.7$ Hz, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 18.2, 124.3, 131.4, 140.2, 150.5, 192.5.

4-Vinyloxybut-2-(*Z*)-enyl Acrylate (11). A mixture of the allylic alcohol (1.00 g, 7.04 mmol) [prepared from *cis*-2-buten-1,4-diol and acryloyl chloride] and $Hg(OAc)_2$ (673 mg, 2.11 mmol) in ethyl vinyl ether (6.75 mL) was heated at reflux for 14 h. The mixture was then diluted with CH_2Cl_2 and washed with 5% aqueous KOH. The aqueous layers were back extracted with CH_2Cl_2, and the combined organic layers were dried (Na_2SO_4). The organic layer was filtered and concentrated. The crude product was passed through a silica gel plug (20% acetone/ hexanes) to afford **11** as a clear, colorless oil (438 mg, 37%). R_f 0.69 (30% acetone/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.06 (dd, $J^1 = 6.8$ Hz, $J^2 = 2.3$ Hz, 1 H), 4.22 (dd, $J^1 = 14.3$ Hz, $J^2 = 2.2$ Hz, 1 H), 4.38 (d, $J = 5.9$ Hz, 2 H), 4.75 (d, $J = 6.4$ Hz, 2 H), 5.72−5.89 (m, 3 H), 6.13 (dd, $J^1 = 17.3$ Hz, $J^2 = 10.5$ Hz, 1 H), 6.39−6.60 (m, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 60.2, 63.7, 87.2, 126.7, 128.1, 129.4, 131.0, 151.1; IR (KBr plate) 2934, 1726, 1636, 1617, 1186 cm^{-1}; HRMS (ESI) *m*/*z* 169.0868 (M^+ calcd. for $C_9H_{12}O_3$ + H, 169.0865).

4-(7-Bromo-2-oxabicyclo[2.2.2]oct-7-en-5-yloxy)-but-2-(*Z*)-enyl Acrylate (12). A mixture of 5-bromo-2-pyrone (**4**, 52.5 mg, 0.30 mmol) and vinyl ether **11** (50.0 mg, 0.30 mmol) in CH_2Cl_2 (0.6 mL) was heated at 100 °C in a sealed tube for 30 h. The crude reaction mixture was loaded directly onto a silica gel column. Chromatography (gradient 20−30% ethyl acetate/petroleum ether) provided **12** in 25% yield (25.5 mg) as a white solid. R_f 0.61 (gradient 20−30% ethyl acetate/petroleum ether); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.78 (d, $J =$ 14.0 Hz, 1 H), 2.58 (ddd, $J^1 = 14.2$ Hz, $J^2 = 7.7$ Hz, $J^3 = 3.9$ Hz, 1 H), 3.93 (dd, $J^1 = 6.4$ Hz, $J^2 = 3.2$ Hz, 1 H), 4.04 (dt, $J^1 = 7.7$ Hz, $J^2 = 2.5$ Hz, 1 H), 4.08−4.20 (m, 2 H), 4.66−4.74 (m, 2 H), 5.10 (m, 1 H), 5.69−5.78 (m, 2 H), 5.85 (dd, $J^1 = 10.5$ Hz, $J^2 = 1.2$ Hz, 1 H), 6.13 (dd, $J^1 = 17.3$ Hz, $J^2 = 10.4$ Hz, 1 H), 6.42 (dd, $J^1 = 17.3$ Hz, $J^2 = 1.3$ Hz, 1 H), 6.48 (dd, $J^1 = 6.4$ Hz, $J^2 = 2.4$ Hz, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 35.4, 48.9, 60.3, 65.2, 71.0, 80.8, 120.7, 127.6, 128.0, 128.4, 130.4, 131.7, 166.2, 170.3; IR (KBr plate) 2916, 2852, 1764, 1723, 1618, 1181 cm^{-1}; HRMS (ESI) *m*/*z* 365.0023 (M^+ calcd. for $C_{14}H_{15}BrO_5$ + Na, 365.0001).

5-*endo*-(*tert*-Butyldimethylsilanyloxy)-7-vinyl-2-oxabicyclo[2.2.2]oct-7-en-3 -one (15). To a solution of bicyclic vinyl bromide **6** (100 mg, 0.30 mmol), $Pd(PPh_3)_4$ (17.3 mg, 0.02 mmol), and di-*tert*-butylphenol (3.1 mg, 0.02 mmol) in THF (3.2 mL) was added vinyltri-*n*-butyltin (105.2 μL, 0.36 mmol). The reaction mixture was stirred at ambient temperature for 2 days. The crude reaction mixture was concentrated in vacuo and was loaded directly onto a silica gel column. Chromatography (gradient 5−20% ether/hexanes) afforded **15** as a yellow oil (40.6 mg, 48%). R_f 0.50 (30% acetone/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.04 (s, 3 H), 0.07 (s, 3 H), 0.82 (s, 9 H), 1.57−1.65 (m, 1 H), 1.93−2.06 (m, 1 H), 3.47 (dd, $J^1 = 6.5$ Hz, $J^2 = 3.4$ Hz, 1 H), 4.11 (dt, $J^1 = 8.5$ Hz, $J^2 = 3.1$ Hz, 1 H), 5.19 (d, $J = 10.9$ Hz, 1 H), 5.31 (d, $J = 17.7$ Hz, 1 H), 5.37 (m, 1 H), 6.11 (dd, $J^1 = 6.5$ Hz, $J^2 = 2.1$ Hz, 1 H), 6.30 (dd, $J^1 = 17.6$ Hz, $J^2 = 10.9$ Hz, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ −4.9, −4.8, 17.5, 25.6, 36.2, 50.5, 67.2, 72.7, 115.2, 124.2, 130.9, 144.0, 171.1; IR (KBr plate) 2955, 2929, 2856, 1765, 1640, 1103 cm^{-1}; HRMS (ESI) *m*/*z* 281.1634 (M^+ calcd. for $C_{15}H_{24}O_3Si$ + H, 281.1573).

Methyl-4-(tetrahydropyran-2-yloxy)but-2-ynoate (16). A solution of THP-protected propargyl alcohol (10 mL, 71.12 mmol) in THF (175 mL) was cooled to −78 °C. *n*-Butyllithium (50 mL, 1.6 M in hexanes, 78.23 mmol) was added dropwise, and the resultant mixture was stirred at −78 °C for 1 h. Methyl chloroformate (6.1 mL, 78.23 mmol) was then added dropwise, and the solution was allowed to warm to −10 °C over a period of 2 h. The reaction was then quenched with saturated aqueous NH_4Cl and warmed to room temperature. The mixture was concentrated, and the residue was redissolved in Et_2O. The organic layer was washed with 10% aq. HCl, sat. $NaHCO_3$, and brine. Drying ($MgSO_4$) was followed by filtration and concentration to give a quantitative yield of the product as an orange oil. Purification was accomplished with silica gel chromatography (5−20% acetone/hexanes) to give **16** as a colorless oil. R_f 0.52 (30% acetone/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ, 1.49−1.81 (m, 6 H), 3.51−3.54 (m, 1 H), 3.75 (s, 3 H), 3.77−3.82 (m, 1 H), 4.35 (s, 2 H), 4.78 (apparent t, $J = 3.3$ Hz, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 18.7, 25.2, 30.0, 52.7, 53.5, 61.9, 83.9, 97.1, 153.5; IR (KBr plate) 2949, 2872, 1719, 1256 cm^{-1}; HRMS (ESI) *m*/*z* 197.0823 (M^+ calcd. for $C_{10}H_{14}O_4$ + H, 197.0814).

Methyl (*Z*)-3-Methyl-4-(tetrahydropyran-2-yloxy)but-2-enoate (17). A solution of methyllithium (35.6 mL, 1.4 M in Et_2O, 49.81 mmol) was added dropwise to a suspension of cuprous iodide (4.83 g, 25.36 mmol) in THF (80 mL) at 0 °C. A distinct color change occurred during the course of the addition from brown to yellow to green to black. This mixture was stirred at 0 °C for an additional 0.5 h, after which the temperature was lowered to −78 °C. A solution of alkyne **16** (4.48 g, 22.64 mmol) in THF (45 mL) was then added dropwise to the dialkyl cuprate via a cannula. The mixture was maintained at −78 °C with stirring for 4 h and was subsequently quenched with one reaction volume of sat. NH_4Cl. The mixture was then allowed to warm to room temperature, and the precipitate was removed. The organic layer was then separated from the blue aqueous layer, and the aqueous layer was extracted with Et_2O. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated. The crude reaction mixture was immediately loaded onto a silica gel column, and the product eluted with 30%

acetone/hexanes. The product, **17**, was obtained as a yellow oil (3.80 g, 17.76 mmol) in 79% yield. R_f 0.40 (10% ethyl acetate/petroleum ether); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.46−1.55 (m, 4 H), 1.55−1.60 (m, 1 H), 1.60−1.80 (m, 1 H), 1.95 (s, 3H), 3.46−3.50 (m, 1 H), 3.63 (s, 3 H), 3.80−3.85 (m, 1 H), 4.58 (apparent t, J = 3.6 Hz, 1 H), 4.67 (AB, J = 13.7 Hz, 2 H), 5.69 (apparent t, J = 1.5 Hz, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 19.4, 21.8, 25.3, 30.5, 50.9, 62.2, 66.4, 98.6, 116.4, 157.1, 166.2; IR (KBr plate) 2947, 2870, 1718, 1648, 1154 cm^{-1}; HRMS (ESI) m/z 215.1285 (M^+ calcd. for $C_{11}H_{18}O_4$ + H, 215.1283).

(*Z*)-3-Methyl-4-(tetrahydropyran-2-yloxy)but-2-en-1-ol (18). A solution of α,β-unsaturated ester **17** (3.80 g, 17.75 mmol) in $PhCH_3$ (40 mL) was cooled to 0 °C. DIBAL (39 mL, 1 M in hexanes, 39.05 mmol) was added dropwise via cannula. After the addition was completed, the reaction was allowed to warm to room temperature. After 1 h, the reaction was quenched at 0 °C by the addition of one-half reaction volume of water. The white precipitate was removed by filtration, and the biphasic solution was diluted with Et_2O. The layers were separated, and the organic layer was washed with 10% aq. HCl, sat. $NaHCO_3$, and brine. The organic layer was then dried over $MgSO_4$, filtered, and concentrated to yield a clear, colorless oil (2.77 g, 84% yield) that was suitable for use without purification. R_f 0.40 (30% acetone/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.47−1.58 (m, 4 H), 1.63−1.69 (m, 2 H), 1.76 (s, 3 H), 2.36 (br s, 1 H), 3.47−3.52 (m, 1 H), 3.78−3.82 (m, 1 H), 4.01−4.14 (m, 4 H), 4.59 (apparent t, J = 3.4 Hz, 1 H), 5.63 (t, J = 6.9 Hz, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 19.0, 21.7, 25.3, 30.3, 58.1, 61.8, 65.1, 96.8, 128.5, 135.7; IR (KBr plate) 3406, 2942, 2871, 1671, 1020 cm^{-1}; HRMS (ESI) m/z 209.1144 (M^+ calcd. for $C_{10}H_{18}O_3$ + Na, 209.1154).

2-[4-(4-Iodophenoxy)-2-methylbut-2-enyloxy]tetrahydropyran (19). To a solution of allylic alcohol **18** (2.72 g, 13.30 mmol), *p*-iodophenol (2.92 g, 13.30 mmol), and PPh_3 (3.66 g, 13.97 mmol) in THF (130 mL) at 0 °C, DEAD (2.20 mL, 13.97 mmol) was added dropwise. The mixture was warmed to room temperature and stirred for 12 h. The solvent was then removed in vacuo, and the residue was purified by silica gel column chromatography (20% acetone/hexanes). The product was obtained as a yellow oil (4.65 g, 90%). R_f 0.69 (30% acetone/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.48−1.60 (m, 4 H), 1.67−1.73 (m, 2H), 1.83 (s, 3H), 3.47−3.51 (m, 1 H), 3.81−3.86 (m, 1 H), 4.08 (AB, J = 12.1 Hz, 1 H), 4.19 (AB, J = 12.1 Hz, 1 H), 4.52−4.59 (m, 3 H), 5.60−5.63 (t, J = 6.9 Hz, 1 H), 6.66 (d, J = 9.1 Hz, 2 H), 7.51 (d, J = 9.1 Hz, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 19.3, 21.7, 25.4, 30.5, 62.2, 64.2, 65.5, 82.7, 97.7, 117.1, 123.5, 137.6, 138.3, 158.5; IR (KBr plate) 2940, 2868, 1484, 1236, 1019 cm^{-1}; HRMS (ESI) m/z 411.0442 (M^+ calcd. for $C_{16}H_{21}O_3I$ + Na, 411.0433).

4-(4-Iodophenoxy)-2-methylbut-2-en-1-ol (20). A solution of THP-protected allylic alcohol **19** (4.39 g, 11.32 mmol) in 50% aq. HOAc (75 mL) was heated at 40 °C for 5 h. The reaction mixture was then concentrated and extracted with CH_2Cl_2. The organic layer was then dried over $MgSO_4$, filtered, and concentrated to give the free allylic alcohol as an orange oil. The crude product was purified by silica gel chromatography (30% acetone/hexane) to give a nearly quantitative yield of a white solid. R_f 0.49 (30% acetone/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.86 (s, 3 H), 4.18 (s, 2 H), 4.53 (d, J = 6.6 Hz, 2 H), 5.60 (t, J = 6.6 Hz, 1 H), 6.66 (d, J = 8.7 Hz, 2 H), 7.53 (d, J = 8.7 Hz, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.4, 61.9, 64.0, 117.1, 122.2, 138.2; IR (KBr pellet) 3334, 2935, 1486, 1241, 1004 cm^{-1}; HRMS (ESI) m/z 326.9869 (M^+ calcd. for $C_{11}H_{13}O_2I$ + Na, 326.9858).

4-(4-Iodophenoxy)-2-methylbut-2-enyl Acrylate (21). To a solution of the free alcohol **20** (3.70 g, 12.18 mmol) in CH_2Cl_2 (40 mL) at 0 °C was added TEA (2.55 mL, 18.27 mmol). Acryloyl chloride (1.1 mL, 13.40 mmol) was then added dropwise, and the reaction was allowed to warm to room temperature overnight. The reaction mixture was then diluted with EtOAc (40 mL), and the organic layer was washed with 10% HCl, sat. $NaHCO_3$, and brine. The organic phase was dried ($MgSO_4$), filtered, and concentrated to give the crude product as a brown oil. Purification by silica gel chromatography (10−30% acetone/hexanes) gave the product, a mild lachrymator, as a yellow oil (3.38 g, 9.44 mmol) in 78% yield. R_f 0.66 (30% acetone/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.89 (s, 3 H), 4.62 (d, J = 6.5 Hz, 2 H), 4.76 (s, 2 H), 5.72 (t, J = 6.5 Hz, 1 H), 5.88 (dd, J^1 = 10.4 Hz, J^2 = 1.4 Hz, 1 H), 6.16 (dd, J^1 = 17.3 Hz, J^2 = 10.4 Hz, 1H), 6.45 (dd, J^1 = 17.3 Hz, J^2 = 1.4 Hz, 1 H), 6.71 (d, J = 8.9 Hz, 2 H), 7.57 (d, J = 8.9 Hz, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.3, 62.8, 64.0, 82.9, 117.0, 124.8, 128.0, 131.0, 135.4, 138.1, 158.3, 165.8; IR (KBr plate) 2940, 1724, 1484, 1237, 1176 cm^{-1}; HRMS (ESI) m/z 358.0057 (M^+ calcd. for $C_{14}H_{15}O_3I$, 358.0066).

3-[4-(4-Hydroxy-3-methylbut-(*Z*)-2-enyloxy)phenyl]-(*E*)-acrylate Dimer (22). A mixture of **21** (100 mg, 0.28 mmol), $Pd(OAc)_2$ (6.3 mg, 0.028 mmol), triphenylphosphine (7.3 mg, 0.028 mmol), and silver trifluoroacetate (68 mg, 0.31 mmol) in DMF (280 mL) was heated at 100 °C for 20 h. The reaction mixture was then concentrated to dryness and immediately loaded onto a silica column (20% acetone/hexanes). The dimer **22** was isolated as a white solid (24.5 mg, 38%). R_f 0.37 (30% acetone/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.87 (s, 3H), 4.68 (d, J = 7.3 Hz, 2 H), 4.74 (s, 2 H), 5.68 (t, J = 7.1 Hz, 1 H), 5.95 (d, J = 16 Hz, 1 H), 6.84 (d, J = 9.0 Hz, 2 H), 7.21 (d, J = 9.0 Hz, 2 H), 7.40 (d, J = 16 Hz, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 22.8, 63.3, 64.3, 115.0, 115.6, 124.0, 126.8, 129.6, 136.8, 144.6, 160.3, 166.6; IR (KBr plate) 2923, 1707, 1628, 1601 cm^{-1}; HRMS (ESI) m/z 461.1944 (M^+ calcd. for $C_{28}H_{28}O_6$ + H, 461.1964); X-ray crystallography confirmed this structure.

3-[4-(4-Hydroxy-3-methylbut-(*Z*)-2-enyloxy)phenyl]-(*E*)-acrylate Trimer (23). A mixture of **21** (536 mg, 1.50 mmol), $Pd(OAc)_2$ (33.6 mg, 0.15 mmol), tri-2-furylphosphine (34.8 mg, 0.15 mmol), and silver trifluoroacetate (363.7 mg, 1.65 mmol) in DMF (150 mL) was heated at 90 °C for 21 h. The reaction mixture was then concentrated and loaded directly onto a silica gel column. Chromatography (20% acetone/hexanes) afforded the trimer **23** as a white solid (23 mg, 7%), as well as dimer **22** (23 mg, 7%). R_f 0.61 (30% acetone/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.88 (s, 3H), 4.74 (s, 2 H), 4.78 (d, J = 5.9 Hz, 2 H), 5.64 (t, J = 5.7 Hz, 1 H), 6.33 (d, J = 15.9 Hz, 1 H), 6.96 (d, J = 8.7 Hz, 2 H), 7.48 (d, J = 8.7 Hz, 2 H), 7.68 (d, J = 15.9 Hz, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 22.0, 63.0, 64.6, 114.8, 115.3, 125.8, 127.0, 129.9, 135.0, 145.3, 160.6, 167.1; IR (KBr plate) 2930, 1708, 1631, 1602 cm^{-1}; HRMS (ESI) m/z 713.2695 (M^+ calcd. for $C_{42}H_{42}O_9$ + Na, 713.2727); X-ray crystallography confirmed this structure.

Acknowledgment. The authors would like to thank Prof. Edward R. Thornton for helpful discussions. This work was supported by grants from the National Science Foundation (CHE 99-01449) and the National Institutes of Health (CA-40081).

Supporting Information Available: ^{1}H and ^{13}C NMR spectra for all new compounds and X-ray data for compounds **22** and **23**. This material is available free of charge via the Internet at http:// pubs.acs.org.

JO0356006