In Situ Manganese Dioxide Alcohol Oxidation−Wittig Reactions: Preparation of Bifunctional Dienyl Building Blocks

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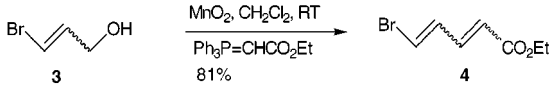
There is continuing interest in the preparation of functionalized building blocks for the stereocontrolled preparation of alkenes and dienes.[1,2] In principle, the 3-halopropenals **1** and **2** would seem to be ideal bifunctional precursors to alkenes and dienes via aldehyde elaboration/cross coupling. However, numerous reports[3] in the literature refer to the difficulties encountered in the isolation of 3-chloro- and 3-bromopropenal, their rapid decomposition at room temperature, their sensitivity to light, and the fact that they have a severe irritant effect on the mucous membranes of the eyes and nose. These problems have undoubtedly limited the applications of halopropenals in synthesis. It should be noted, however, that Meyer, Marek, and Normant have developed conditions for the preparation of 2*E*- and 2*Z*-iodopropenal and demonstrated that these compounds are more stable than the corresponding chlorides or bromides (they can be stored in solution in the refrigerator for several weeks), although they retain lachrymatory properties.[4]

1 **2**

We have recently described an in situ manganese dioxide alcohol oxidation−Wittig procedure[5] and demonstrated its utility for the elaboration of 3-bromopropen-1-ol **3** as shown in Scheme 1. This procedure avoids the need to isolate the intermediate bromopropenals **1** and **2** and produces the bromodienoate **4** directly. Bromodienoate **4**, prepared in this way, has been employed as a precursor to the lower side of the chain of the manumycin antibiotics.[6]

Scheme 1



3 **4**

The original investigation illustrated in Scheme 1 was carried out on an isomeric mixture of bromopropenols **3** (*E*: *Z* = 3:1).[7] Herein we describe the extension of this methodology to isomerically pure 3-bromopropenols **3*E*** and **3*Z***, illustrate that the bromopropenol geometry is retained, explore the range of Wittig reagents that can be utilized in this procedure, and apply the methodology in natural product synthesis. Scheme 2 illustrates the procedures used to prepare **3*E*** and **3*Z*** and their further elaboration.

Thus, ethyl propiolate **5a** was readily converted into the *Z*-bromoacrylate **6**,[8a] and propriolic acid **5b** into *E*-bromoacylate **7**,[8b] using published stereoselective procedures (Scheme 2). Reduction with lithium aluminum hydride[9] then gave the requisite 3-bromopropenols **3*Z*** and **3*E*** in good overall yield as pure stereoisomers. These compounds were then subjected to the in situ alcohol oxidation−Wittig conditions using (carboethoxymethylene)triphenylphosphorane. As shown in Scheme 2 and Table 1, in both cases the bromodienoates **4** were obtained in good yield and with complete retention of the preexisting alkene geometry.

A range of related stabilized Wittig reagents were also explored (Table 1). In all cases the products were obtained with faithful retention of the original alkenyl geometry but as isomers about the newly formed double bonds. These *E*: *Z* ratios were generally in the expected ranges with the *E*-isomers predominating. A notable exception involved the reaction of **3*Z*** with (cyanomethylene)triphenylphosphorane; in this reaction the *Z*,*Z*-product **13*Z*,*Z*** predominated (**13*Z*,*Z***:**13*E*,*Z*** was ca.5:2). Reaction of **3*E*** with (cyanomethylene)triphenylphosphorane, however, gave a mixture of **13*E*,*E*** and **13*Z*,*E*** in which the *E*,*E*-isomer predominated as expected. Further studies are proceeding to rationalize the former result and to apply the unexpected observation.

The utility of the products from the in situ alcohol oxidation−Wittig sequence has been illustrated by the synthesis of a simple natural product[10] and its stereoisomer (Scheme 3). Adduct **11*E*,*E*** was reduced with

(1) For recent references in this area, see: Castet-Caillabet, D.; Ramondenc, Y.; Plé, G.; Duhamel, L. *Tetrahedron* **1999**, *55*, 7583−7588. Crousse, B.; Mladenova, M.; Ducept, P.; Alami, M.; Linstrumelle, G. *Tetrahedron* **1999**, *55*, 4353−4368. Brasseur, D.; Rezaei, H.; Fuxa, A.; Alexakis, A.; Mangeney, P.; Marek, I.; Normant, J.-F. *Tetrahedron Lett.* **1998**, *39*, 4821−4824. Raeppel, S.; Toussaint, D.; Suffert, J. *Synlett* **1998**, 537−539. Takacs, J. M.; Jaber, M. R.; Clement, F.; Walters, C. *J. Org. Chem.* **1998**, *63*, 6757−6760. Wang, Z.; Lu, X.; Lei, A.; Zhang, Z. *J. Org. Chem.* **1998**, *63*, 3806−3807. Lipshutz, B. H.; Ullman, B.; Lindsley, C.; Pecchi, S.; Buzard, D. J.; Dickson, D. *J. Org. Chem.* **1998**, *63*, 6092−6093. Lipshutz, B. H.; Lindsley, C. *J. Am. Chem. Soc.* **1997**, *119*, 4555−4556.

(2) For recent reviews on two directional synthesis/bifunctional reagents, see: Ross, C. S.; Schreiber, S. L. *Acc. Chem. Res.* **1994**, *27*, 9−17. Magnusson, S. R. *Tetrahedron* **1995**, *51*, 2167−2213.

(3) Protopopova, T. V.; Skoldinov, A. P. *Zh. Obshch. Khim.* **1958**, *29*, 945−948. Patel, B. A.; Kim, J.-I.; Bender, D. D.; Kao, L.-C.; Heck, R. F. *J. Org. Chem.* **1981**, *46*, 1061−1067. Meyers, A. I.; Babiak, K. A.; Campbell, A. L.; Comins, D. L.; Fleming, M. P.; Henning, R.; Heuschmann, M.; Hudspeth, J. P.; Kane, J. M.; Reider, P. J.; Roland, D. M.; Shimizu, K.; Tomioka, K.; Walkup, R. D. *J. Am. Chem. Soc.* **1983**, *105*, 5015−5024. Grabowski, E. J. J.; Autrey, R. L. *Tetrahedron* **1969**, *25*, 4315−4330.

(4) Meyer, C.; Marek, I.; Normant, J.-F. *Synlett* **1993**, 386-388. See also: Raeppel, S.; Toussaint, D.; Suffert, J. *Synlett* **1998**, 537−539.

(5) Wei, X.; Taylor, R. J. K. *Tetrahedron Lett.* **1998**, *39*, 3815−3818. See also: Blackburn, L.; Wei, X.; Taylor, R. J. K. *Chem. Commun.* **1999**, 1337−1338.

(6) Alcaraz, L.; Macdonald, G.; Ragot, J.; Lewis, N. J.; Taylor, R. J. K. *Tetrahedron* **1999**, *55*, 3707−3716. See also: Macdonald, G.; Alcaraz, L.; Wei, X.; Lewis, N. J.; Taylor, R. J. K. *Tetrahedron* **1998**, *54*, 9823−9836.

(7) Jung, M. E.; Light, L. A. *Tetrahedron Lett.* **1982**, *23*, 3851−3854. Delorme, D.; Girard, Y.; Rokach, J. *J. Org. Chem.* **1989**, *54*, 3635−3640.

(8) (a) Ma, S.; Lu, X. *Chem. Commun.* **1990**, 1643−1644; *Org. Synth.* **1993**, *72*, 112−115. (b) Just, G.; Ouellet, R. *Can. J. Chem.* **1976**, *54*, 2925−2934.

(9) MacInnes, I.; Schorstein, D. E.; Suckling; C. J.; Wrigglesworth, R. *J. Chem. Soc., Perkin Trans. 1* **1981**, 1103−1108.

(10) Bohlmann, F.; Kleine, K.-M.; Arndt, C. *Chem. Ber.* **1966**, *99*, 1642−1647.

(11) For a recent review, see: Sonogashira, K. In *Metal-catalyzed Cross-coupling Reactions*; Diederich, F., Stang, P. J., Eds.; Wiley-VCH: Berlin, 1998; pp 203−229.

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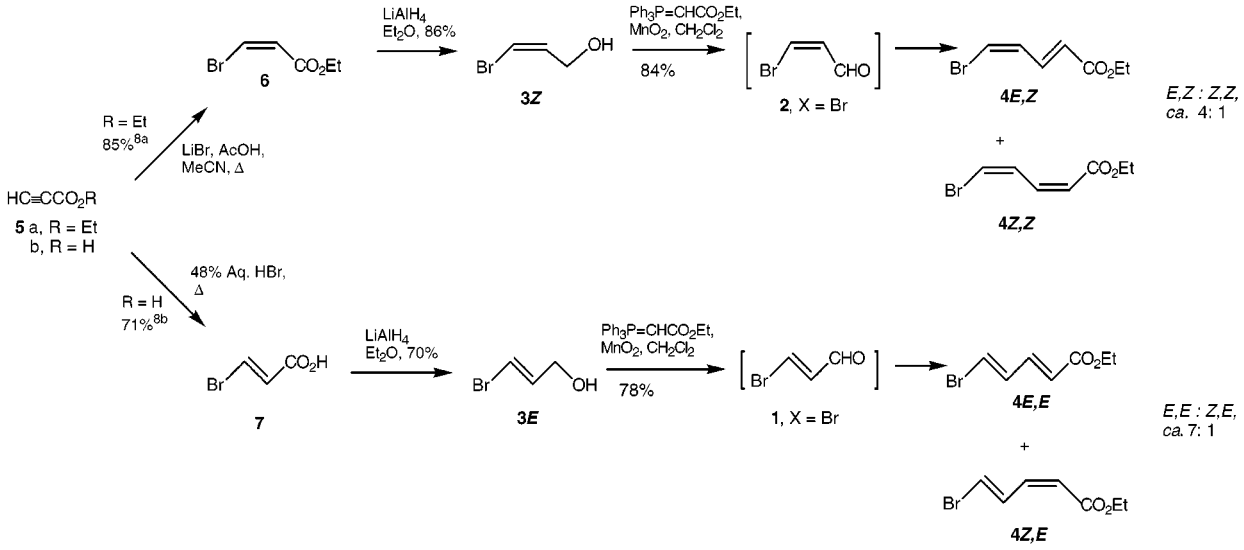
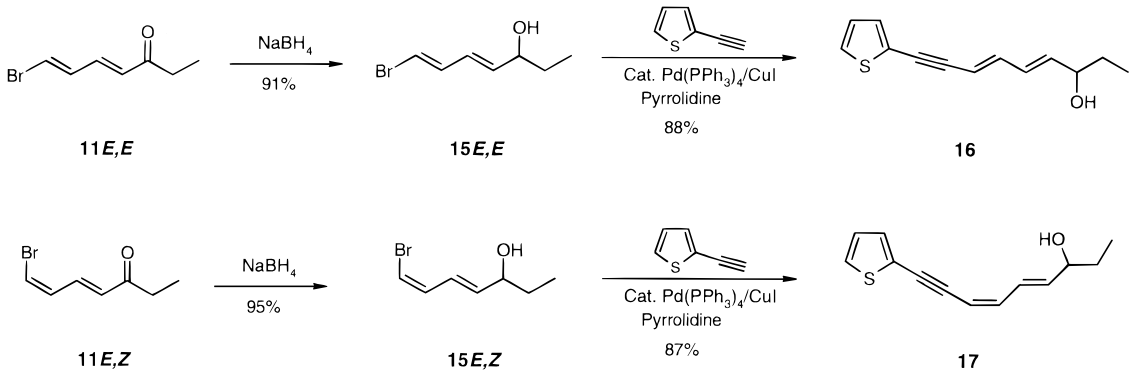
Scheme 2



Scheme 3



sodium borohydride to give bromodienol **15*E,E***, which underwent efficient Sonogashira coupling[11] with 2-ethynylthiophene[12] to complete the first reported synthesis of 9-(2-thienyl)-nona-4*E*,6*E*-dien-8-yn-3-ol (**16**), isolated from the roots of *Anthemis saguramica* Sosn. The same sequence was followed using the isomeric dienone **11*E,Z*** to give the natural product isomer **17** in high yield.

It should also be noted that the bromodienoates **4*E,E*** and **4*E,Z*** have been employed as key intermediates in the total syntheses of AF- and AK-toxins by Crombie et al.,[13] with Stille coupling being employed to elaborate the vinyl bromide unit.

In summary, we have utilized bromopropenols **3*E*** and **3*Z*** in the in situ oxidation−stabilized Wittig sequence and demonstrated that the reactions proceed easily and efficiently, obviating the need to isolate the intermediate aldehydes. We have also shown that the preexisting alkene geometry is retained and that this procedure therefore produces a range of bifunctional diene building blocks that have potential in natural product synthesis.

Experimental Section

General Directions. Elemental analyses were carried out at the University of Newcastle. Chromatography is medium-pressure flash column chromatography and was performed using ICN silica gel (32−63) or Matrex silica gel 60 (70−200) using the eluant specified. Petroleum ether is the fraction with bp 40−60 °C and was redistilled before use. Diethyl ether was distilled from sodium−benzophenone ketyl immediately before use. Water is distilled water. Except where specified, all reagents were purchased from commercial sources and were used without further purification.

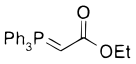
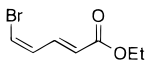
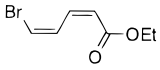
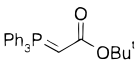
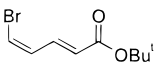
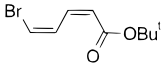
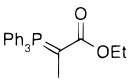
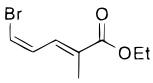
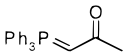
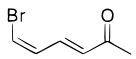
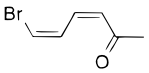
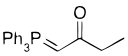
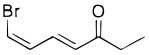
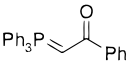
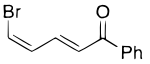
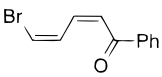
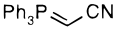
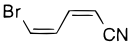
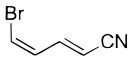
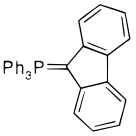
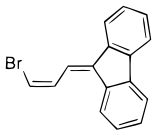
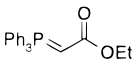
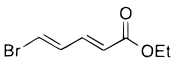
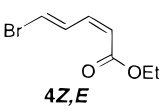
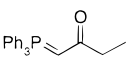
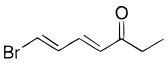
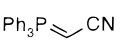
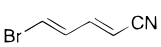
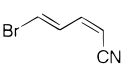
3-Bromo-2*Z*-propenol (3*Z*). A solution of ethyl 3-bromo-2*Z*-propenoate **6**[8a] (2.69 g, 15 mmol) in dry diethyl ether (8 mL) was added dropwise to a stirred mixture of $LiAlH_4$ (380 mg, 10 mmol) in dry diethyl ether (30 mL) under a N_2 atmosphere at 0 °C. The mixture was stirred at 0 °C for 1 h and then quenched at 0 °C by addition of water (0.4 mL), 15% NaOH (0.4 mL), and more water (1.2 mL), followed by filtration. The mixture was diluted with diethyl ether (50 mL), washed with saturated $NaHCO_3$ (15 mL), and dried over Na_2SO_4. Evaporation of the solvent in vacuo gave the title compound **3*Z*** (1.76 g, 86%), which was used directly in the next step without any further purification: colorless oil, R_f 0.31 (1:1 petroleum ether−diethyl ether); ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.70 (s, 1H), 4.32 (dd, J = 5.8, 1.4, 2H), 6.28 (dt, J = 7.3, 1.4, 1H), 6.37 (dt, J = 7.3, 5.8, 1H); ^{13}C NMR (67.9 MHz, $CDCl_3$) δ 60.8, 108.8, 133.9; IR (film) ν_{max} 3340 cm^{-1}; MS (EI) m/z 137, 135 ($M^+ - 1$); HRMS (EI) m/z 134.9448 (calcd for $C_3H_4{}^{79}BrO$ 134.9446, 1.9 ppm error).

3-Bromo-2*E*-propenol (3*E*). A solution of 3-bromo-2*E*-propenoic acid **7**[8b] (1.51 g, 10 mmol) in dry diethyl ether (8 mL) was added dropwise to a stirred mixture of $LiAlH_4$ (380 mg, 10 mmol) in dry diethyl ether (30 mL) under a N_2 atmosphere at 0 °C. The mixture was stirred at 0 °C for 2 h and then quenched at 0 °C by addition of water (0.4 mL), 15% NaOH (0.4 mL), and more water (1.2 mL), followed by filtration. Workup as above gave the title compound **3*E*** (952 mg, 70%), which was used directly in the next step without any further purification: colorless oil, R_f 0.31 (1:1 petroleum ether−diethyl ether); ^{1}H

(12) Beny, J.-P.; Dhawan, S. N.; Kagan, J.; Sundlass, S. *J. Org. Chem.* **1982**, *47*, 2201−2204.

(13) Crombie, L.; Horsham, M. A.; Jarrett, S. R. M. *J. Chem. Soc., Perkin Trans. 1* **1991**, 1511−1524.

Table 1. In Situ Oxidation−Wittig Reaction of 3-Bromo-2*E*- and -2*Z*-propenol (3*E* and 3*Z*)

Entry	Alcohol	Ylide	Products (Yield)			
i	**3*Z***		 **4*E*,*Z***	68%	 **4*Z*,*Z***	16%
ii	**3*Z***		 **8*E*,*Z***	75%	 **8*Z*,*Z***	15%
iii	**3*Z***		 **9*E*,*Z***	60%[a]		
iv	**3*Z***		 **10*E*,*Z***	65%	 **10*Z*,*Z***	8%
v	**3*Z***		 **11*E*,*Z***	63%[b]		
vi	**3*Z***		 **12*E*,*Z***	60%	 **12*Z*,*Z***	6%
vii	**3*Z***		 **13*Z*,*Z***	50%	 **13*E*,*Z***	18%
viii	**3*Z***		 **14**	35%		
ix	**3*E***		 **4*E*,*E***	68%	 **4*Z*,*E***	10%
x	**3*E***		 **11*E*,*E***	56%[b]		
xi	**3*E***		 **13*E*,*E***	45%	 **13*Z*,*E***	15%

[a] A mixture of byproducts, which probably contained **9*Z*,*Z***, was isolated. [b] TLC analysis indicated the presence of trace amounts of what is believed to be the isomeric compounds **11*Z*,*Z*** and **11*E*,*E***, but they were too volatile to be isolated.

NMR (270 MHz, $CDCl_3$) δ 1.80 (s, 1H), 4.11−4.14 (m, 2H), 6.35−6.39 (m, 2H); ^{13}C NMR (67.9 MHz, $CDCl_3$) δ 62.9, 107.8, 136.5; IR (film) ν_{max} 3352 cm^{-1}; MS (EI) *m/z* 137, 135 ($M^+ - 1$); HRMS (EI) *m/z* 134.9449 (calcd for $C_3H_4{}^{79}BrO$ 134.9446, 2.4 ppm error).

Synthesis of Bromodienes by in Situ Oxidation−Wittig Reactions. General Procedure. A mixture of 3-bromo-2-propenol ***3E*** or ***3Z*** (41 mg, 0.3 mmol), Wittig reagent (0.36 mmol, 1.2 equiv) and manganese dioxide (261 mg, 10 equiv) in dry dichloromethane (9 mL) was stirred for 1−2 days and monitored by TLC (1:1 diethyl ether−petroleum ether) until the starting material was no longer detectable. The manganese dioxide was removed by suction through a pad of Celite, which was then washed with additional dichloromethane (10 mL). The solution was concentrated to about 1 mL and loaded to a silica gel column. Elution with diethyl ether−petroleum ether gave the pure product. The reactions of ***3E*** and ***3Z*** with (carboethoxymethylene)triphenylphosphorane have also been carried out on a 300 mg scale in comparable yield.

(a) From 3-Bromo-2*Z*-propenol. Ethyl 5-bromopenta-2*E*,4*Z*-dienoate (4*E*,*Z*): colorless oil (68%), R_f 0.60 (2:1 petroleum ether−diethyl ether); ^1H NMR (270 MHz, $CDCl_3$) δ 1.32 (t, J = 7.0, 3H, CH_3), 4.24 (q, J = 7.0, 2H, CH_2), 6.08 (dt, J = 15.5, 0.7, 1H, H-2), 6.59 (dt, J = 7.3, 0.7, 1H, H-5), 6.78 (ddd, J = 10.6, 7.3, 0.7, 1H, H-4), 7.59 (ddd, J = 15.5, 10.6, 0.7, 1H, H-3); ^{13}C NMR (67.9 MHz, $CDCl_3$) δ 14.2, 60.6, 116.5, 125.2, 130.6, 138.8, 166.4; IR (film) ν_{max} 1713 cm^{-1}; MS (EI) *m/z* 206, 204 (M^+); HRMS (EI) *m/z* 203.9790 (calcd for $C_7H_9{}^{79}BrO_2$ 203.9786, 2.2 ppm error). The NMR data were consistent with those published.[13]

Ethyl 5-bromopenta-2*Z*,4*Z*-dienoate (4*Z*,*Z*): colorless oil (16%), R_f 0.64 (2:1 petroleum ether−diethyl ether); ^1H NMR (270 MHz, $CDCl_3$) δ 1.30 (t, J = 7.0, 3H, CH_3), 4.20 (q, J = 7.0, 2H, CH_2), 5.89 (d, J = 11.4, 1H, H-2), 6.61 (d, J = 7.3, 1H, H-5), 6.95 (dd, J = 11.4, 10.9, 1H, H-3), 7.99 (dd, J = 10.9, 7.3, 1H, H-4); ^{13}C NMR (67.9 MHz, $CDCl_3$) δ 14.2, 60.3, 117.3, 121.3, 128.5, 138.2, 165.9 ppm; IR (film) ν_{max} 1710, cm^{-1}; MS (EI) *m/z* 206, 204 (M^+); HRMS (EI) *m/z* 203.9786 (calcd for $C_7H_9{}^{79}BrO_2$ 203.9786, 0.1 ppm error). Anal. Calcd for $C_7H_9BrO_2$: C, 41.00; H, 4.42. Found: C, 40.63; H, 4.49.

***tert*-Butyl 5-bromopenta-2*E*,4*Z*-dienoate (8*E*,*Z*):** colorless oil (75%), R_f 0.63 (1:1 petroleum ether−diethyl ether); ^1H NMR (270 MHz, $CDCl_3$) δ 1.51 (s, 9H, ^{t}Bu), 6.01 (dt, J = 15.4, 0.7, 1H, H-2), 6.54 (dt, J = 7.2, 0.7, 1H, H-5), 6.75 (ddd, J = 10.8, 7.2, 0.7, 1H, H-4), 7.51 (ddd, J = 15.4, 10.8, 0.7, 1H, H-3); ^{13}C NMR (67.9 MHz, $CDCl_3$) δ 28.1, 80.8, 115.8, 127.1, 130.7, 137.9, 165.7; IR (film) ν_{max} 1710 cm^{-1}; MS (CI) *m/z* 252, 250 (MNH_4^+); HRMS (CI) *m/z* 250.0444 (calcd for $C_9H_{17}{}^{79}BrNO_2$ 250.0443, 0.6 ppm error).

***tert*-Butyl 5-bromopenta-2*Z*,4*Z*-dienoate (8*Z*,*Z*):** colorless oil (15%), R_f 0.67 (1:1 petroleum ether−diethyl ether); ^1H NMR (270 MHz, $CDCl_3$) δ 1.49 (s, 9H, ^{t}Bu), 5.81 (dt, J = 11.6, 1.0, 1H, H-2), 6.56 (dt, J = 7.3, 1.0, 1H, H-5), 6.87 (ddd, J = 11.6, 10.8, 1.0, 1H, H-3), 7.97 (ddd, J = 10.8, 7.3, 1.0, 1H, H-4); ^{13}C NMR (67.9 MHz, $CDCl_3$) δ 28.2, 80.9, 116.6, 123.3, 128.5, 137.2, 165.4; IR (film) ν_{max} 1710 cm^{-1}; MS (CI) *m/z* 252, 250 (MNH_4^+); HRMS (CI) *m/z* 250.0443 (calcd for $C_9H_{17}{}^{79}BrNO_2$ 250.0443, 0 ppm error).

Ethyl 2-methyl-5-bromopenta-2*E*,4*Z*-dienoate (9*E*,*Z*): colorless oil (60%), R_f 0.45 (4:1 petroleum ether−diethyl ether); ^1H NMR (270 MHz, $CDCl_3$) δ 1.33 (t, J = 7.0, 3H, CH_3), 1.97 (br s, 3H, 2-Me), 4.25 (q, J = 7.0, 2H, CH_2), 6.57 (d, J = 7.3, 1H, H-5), 6.94 (dd, J = 10.9, 7.3, 1H, H-4), 7.48 (d, J = 10.9, 1H, H-3); ^{13}C NMR (67.9 MHz, $CDCl_3$) δ 13.5, 14.2, 60.8, 115.5, 128.1, 131.5, 132.4, 167.9; IR (film) ν_{max} 1709 cm^{-1}; MS (EI) *m/z* 220, 218 (M^+); HRMS (CI) *m/z* 236.0293 (calcd for $C_8H_{15}{}^{79}BrNO_2$ 236.0286, 2.9 ppm error).

6-Bromohexa-3*E*,5*Z*-dien-2-one (10*E*,*Z*): colorless oil (65%), R_f 0.41 (1:1 petroleum ether−diethyl ether); ^1H NMR (270 MHz, $CDCl_3$) δ 2.35 (s, 3H, CH_3), 6.30 (d, J = 15.8, 1H, H-3), 6.65 (d, J = 7.3, 1H, H-6), 6.80 (dd, J = 10.5, 7.3, 1H, H-4), 7.43 (dd, J = 15.8, 10.5, 1H, H-5); ^{13}C NMR (67.9 MHz, $CDCl_3$) δ 27.2, 117.3, 131.1, 133.7, 137.5, 198.5; IR (film) ν_{max} 1689 cm^{-1}; MS (EI) *m/z* 176, 174 (M^+); HRMS (EI) *m/z* 173.9684 (calcd for $C_6H_7{}^{79}BrO$ 173.9680, 2.1 ppm error). This compound readily isomerizes to **7*E*,*E*** in $CDCl_3$.

6-Bromohexa-3*Z*,5*Z*-dien-2-one (10*Z*,*Z*): colorless oil (8%), R_f 0.49 (1:1 petroleum ether−diethyl ether); ^1H NMR (270 MHz, $CDCl_3$) δ 2.27 (s, 3H, CH_3), 6.23 (dt, J = 11.5, 1.0, 1H, H-3), 6.62 (dt, J = 7.3, 1.0, 1H, H-6), 6.78 (ddd, J = 11.5, 10.8, 1.0, 1H, H-4), 7.97 (ddd, J = 10.8, 7.3, 1.0, 1H, H-5); ^{13}C NMR (67.9 MHz, $CDCl_3$) δ 32.2, 118.8, 127.9, 129.5, 136.3, 199.4; IR (film) ν_{max} 1685 cm^{-1}; MS (EI) *m/z* 176, 174 (M^+); HRMS (EI) *m/z* 173.9688 (calcd for $C_6H_7{}^{79}BrO$ 173.9680, 4.5 ppm error).

7-Bromohepta-4*E*,6*Z*-dien-3-one (11*E*,*Z*): colorless oil (63%), R_f 0.42 (1:1 petroleum ether−diethyl ether); ^1H NMR (270 MHz, $CDCl_3$) δ 1.14 (t, J = 7.3, 3H, CH_3), 2.66 (q, J = 7.3, 2H, CH_2), 6.33 (dt, J = 15.8, 0.7, 1H, H-4), 6.62 (dt, J = 7.3, 0.7, 1H, H-7), 6.78 (ddd, J = 10.5, 7.3, 0.7, 1H, H-6), 7.46 (ddd, J = 15.8, 10.5, 0.7, 1H, H-5); ^{13}C NMR (67.9 MHz, $CDCl_3$) δ 8.1, 33.6, 117.1, 131.2, 132.8, 136.4, 201.0; IR (film) ν_{max} 1691 cm^{-1}; MS (EI) *m/z* 190, 188 (M^+); HRMS (EI) *m/z* 187.9841 (calcd for $C_7H_9{}^{79}BrO$ 187.9837, 2.3 ppm error).

1-Phenyl-5-bromopenta-2*E*,4*Z*-dien-2-one (12*E*,*Z*): white solid, mp 69−70 °C (60%), R_f 0.38 (1:1 petroleum ether−diethyl ether); ^1H NMR (270 MHz, $CDCl_3$) δ 6.69 (dt, J = 7.3, 0.8, 1H, H-5), 6.92 (ddd, J = 10.8, 7.3, 0.8, 1H, H-4), 7.15 (dt, J = 15.4, 0.8, 1H, H-2), 7.45−7.63 (m, 3H, ArH), 7.72 (ddd, J = 15.4, 10.8, 0.8, 1H, H-3), 7.92−8.00 (m, 2H, ArH); ^{13}C NMR (67.9 MHz, $CDCl_3$) δ 117.9, 128.5, 128.7, 128.8, 131.3, 133.0, 137.7, 138.8, 190.8; IR (solid film) ν_{max} 1656 cm^{-1}; MS (EI) *m/z* 238, 236 (M^+); HRMS (CI) *m/z* (MNH_4^+) 254.0184 (calcd for $C_{11}H_{13}{}^{79}BrNO$ 254.0181, 1.2 ppm error). Anal. calcd for $C_{11}H_9BrO$: C, 55.72; H, 3.83. Found: C, 55.49; H, 3.89. The NMR data were consistent with those published.[14]

1-Phenyl-5-bromopenta-2*Z*,4*Z*-dien-2-one (12*Z*,*Z*): white solid, mp 74−75 °C (6%), R_f 0.46 (1:1 petroleum ether−diethyl ether); ^1H NMR (270 MHz, $CDCl_3$) δ 6.66 (dt, J = 7.5, 1.1, 1H, H-5), 6.96 (dt, J = 11.5, 1.1, 1H, H-2), 7.07 (ddd, J = 11.5, 10.5, 1.1, 1H, H-3), 7.45−7.62 (m, 3H, ArH), 7.92−7.99 (m, 3H, ArH, H-4). This compound readily isomerized to **9*E*,*Z*** and further characterization was not possible.

5-Bromopenta-2*Z*,4*Z*-dienonitrile (13*Z*,*Z*): white solid, mp 33−34 °C (50%), R_f 0.48 (1:1 petroleum ether−diethyl ether); ^1H NMR (270 MHz, $CDCl_3$) δ 5.49 (dd, J = 11.4, 1.5, 1H, H-2), 6.75 (dd, J = 7.0, 1.5, H-5), 7.13−7.28 (m, 2H, H-3, H-4); ^{13}C NMR (67.9 MHz, $CDCl_3$) δ 101.1, 115.8, 118.8, 128.7, 143.9; IR (solid film) ν_{max} 2216 cm^{-1}; MS (EI) *m/z* 159, 157 (M^+); HRMS (EI) *m/z* 156.9533 (calcd for $C_5H_4{}^{79}BrN$ 156.9527, 3.9 ppm error).

5-Bromopenta-2*E*,4*Z*-dienonitrile (13*E*,*Z*): white solid, mp 31−32 °C (18%), R_f 0.30 (1:1 petroleum ether−diethyl ether); ^1H NMR (270 MHz, $CDCl_3$) δ 5.58 (d, J = 15.9, 1H, H-2), 6.67 (d, J = 7.3, 1H, H-5), 6.77 (dd, J = 10.3, 7.3, 1H, H-4), 7.37 (dd, J = 15.9, 10.3, 1H, H-3); ^{13}C NMR (67.9 MHz, $CDCl_3$) δ 102.7, 117.5, 118.1, 130.0, 145.1; IR (solid film) ν_{max} 2216 cm^{-1}; MS (EI) *m/z* 159, 157 (M^+); HRMS (EI) *m/z* 156.9527 (calcd for $C_5H_4{}^{79}BrN$ 156.9527, 0 ppm error).

4-Bromo-1,1-biphenylenebuta-3*Z*-diene (14): yellow solid, mp 84−86 °C (35%), R_f 0.45 (1:1 petroleum ether−diethyl ether); ^1H NMR (270 MHz, $CDCl_3$) δ 6.67 (dd, J = 7.3, 1.4, 1H, H-4), 7.25−7.46 (m, 5H, Ar−H, H-3), 7.65−7.86 (m, 5H, ArH, H-2); ^{13}C NMR (67.9 MHz, $CDCl_3$) δ 115.0, 119.7, 120.1, 120.7, 120.9, 125.2, 127.1, 127.2, 128.5, 128.6, 128.7, 136.8, 138.2, 139.2, 139.3, 141.4; MS (EI) *m/z* 284, 282 (M^+); HRMS (EI) *m/z* 282.0032 (calcd for $C_{16}H_{11}{}^{79}Br$ 282.0044, 4.2 ppm error). Anal. calcd for $C_{16}H_{11}$-Br: C, 67.87; H, 3.92. Found: C, 67.70; H, 3.99.

(b) From 3-Bromo-2*E*-propenol. Ethyl 5-bromopenta-2*E*,4*E*-dienoate (4*E*,*E*): colorless oil (68%), R_f 0.60 (1:1 petroleum ether−diethyl ether); ^1H NMR (270 MHz, $CDCl_3$) δ 1.30 (t, J = 7.2, 3H, CH_3), 4.21 (q, J = 7.2, 2H, CH_2), 5.92 (d, J = 15.4, 1H, H-2), 6.72−6.90 (m, 2H, H-4, H-5), 7.17 (ddd, J = 15.4, 9.7, 1.0, 1H, H-3); ^{13}C NMR (67.9 MHz, $CDCl_3$) δ 14.2, 60.6, 117.7, 122.2, 135.4, 140.9, 166.4; IR (film) ν_{max} 1713 cm^{-1}; MS (EI) *m/z* 206, 204 (M^+); HRMS (EI) *m/z* 203.9789 (calcd for $C_7H_9{}^{79}BrO_2$ 203.9786, 1.4 ppm error). The NMR data were consistent with those published.[13]

Ethyl 5-bromopenta-2*Z*,4*E*-dienoate (4*Z*,*E*): colorless oil (10%), R_f 0.66 (1:1 petroleum ether−diethyl ether); ^1H NMR (270 MHz, $CDCl_3$) δ 1.31 (t, J = 7.2, 3H, CH_3), 4.20 (q, J = 7.2, 2H, CH_2), 5.71 (ddd, J = 11.3, 1.1, 0.7, 1H, H-2), 6.46 (td, J = 11.3, 0.7, 1H, H-3), 6.80 (dt, J = 13.5, 0.7, 1H, H-5), 8.08 (ddd, J =

(14) Babudri, F.; Cicciomessere, A. R.; Farinola, G. M.; Fiandanese, V.; Marchese, G. *J. Org. Chem.* **1997**, 32911−3298.

13.5, 11.3, 1.1, 1H, H-4); ^{13}C NMR (67.9 MHz, $CDCl_3$) δ 14.2, 60.3, 118.4, 119.0, 133.8, 140.6, 165.8; IR (film) ν_{max} 1712, cm^{-1}; MS (CI) *m*/*z* 224, 222 (MNH_4^+); HRMS (CI) *m*/*z* 222.0124 (calcd for $C_7H_{13}{}^{79}BrNO_2$ 222.0130, 2.5 ppm error). Anal. calcd for $C_7H_9BrO_2$: C, 41.00; H, 4.42. Found: C, 40.68; H, 4.61.

7-Bromohepta-4*E*,6*E*-dien-3-one (11*E*,*E*): colorless oil (56%), R_f 0.43 (1:1 petroleum ether−diethyl ether); ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.12 (t, J = 7.3, 3H, CH_3), 2.59 (q, J = 7.3, 2H, CH_2), 6.22 (d, J = 15.4, 1H, H-4), 6.81−6.90 (m, 2H, H-6, H-7), 7.06 (ddd, J = 15.4, 7.0, 3.0, 1H, H-5); ^{13}C NMR (67.9 MHz, $CDCl_3$) δ 8.0, 34.3, 118.1, 129.5, 135.8, 138.4, 200.6; IR (film) ν_{max} 1682 cm^{-1}; MS (EI) *m*/*z* 190, 188 (M^+); HRMS (EI) *m*/*z* 187.9829 (calcd for $C_7H_9{}^{79}BrO$ 187.9837, 3.9 ppm error).

5-Bromopenta-2*E*,4*E*-dienonitrile (13*E*,*E*): white solid, mp 72−73 °C (45%), R_f 0.45 (1:1 petroleum ether−diethyl ether); ^{1}H NMR (270 MHz, $CDCl_3$) δ 5.43 (br d, J = 15.9, 1H, H-2), 6.75−6.97 (m, 3H, H-3, H-4, H-5); ^{13}C NMR (67.9 MHz, $CDCl_3$) δ 99.9, 117.4, 119.6, 134.7, 146.9; IR (film) ν_{max} 2215 cm^{-1}; MS (EI) *m*/*z* 159, 157 (M^+); HRMS (EI) *m*/*z* 156.9534 (calcd for $C_5H_4{}^{79}BrN$ 156.9527, 4.5 ppm error).

5-Bromopenta-2*Z*,4*E*-dienonitrile (13*Z*,*E*): colorless oil (15%), R_f 0.35 (1:1 petroleum ether−diethyl ether); ^{1}H NMR (270 MHz, $CDCl_3$) δ 5.29 (dt, J = 10.8, 0.7, 1H, H-2), 6.74 (ddd, J = 11.3, 10.8, 0.7, 1H, H-3), 6.92 (dt, J = 13.5, 0.7, 1H, H-5), 7.24 (ddd, J = 13.5, 11.3, 0.8, 1H, H-4); ^{13}C NMR (67.9 MHz, $CDCl_3$) δ 98.1, 116.5, 120.5, 133.5, 145.8; IR (film) ν_{max} 2217 cm^{-1}; MS (EI) *m*/*z* 159, 157 (M^+); HRMS (EI) *m*/*z* 156.9532 (calcd for $C_5H_4{}^{79}BrN$ 156.9527, 3.2 ppm error).

Reduction with $NaBH_4$. General Procedure. Freshly prepared 7-bromohepta-4,6-dien-3-one **11*E*,*E*** or **11*E*,*Z*** (18.9 mg, 0.1 mmol) was dissolved in methanol (2 mL). $NaBH_4$ (7.6 mg, 0.2 mmol) was added at 0 °C, and the solution was stirred at this temperature for 1 h. Aqueous ammonium chloride (5 mL) was added, and the resulting mixture was extracted with diethyl ether (3 × 40 mL). The organic layers were combined and dried with sodium sulfate. Evaporation of solvent in vacuo and flash chromatography (4:1 petroleum ether−diethyl ether) gave the corresponding alcohols **15*E*,*E*** and **15*E*,*Z*.**

7-Bromohepta-4*E*,6*E*-dien-3-ol (15*E*,*E*): colorless oil (91%), R_f 0.32 (1:1 petroleum ether−diethyl ether); ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.92 (t, J = 7.0, 3H, CH_3), 1.50−1.65 (m, 2H, CH_2), 1.62 (br s, 1H, OH), 4.07 (dq, J = 1.0, 6.5, 1H, C*H*OH), 5.74 (dd, J = 15.3, 6.5, 1H, H-4), 6.16 (ddd, J = 15.3, 10.6, 1.0, 1H, H-5), 6.32 (d, J = 13.3, 1H, H-7), 6.72 (dd, J = 13.3, 10.6, 1H, H-6); ^{13}C NMR (67.9 MHz, $CDCl_3$) δ 9.6, 30.0, 73.5, 108.9, 127.6, 136.8, 137.1; IR (film) ν_{max} 3350 cm^{-1}; MS (EI) *m*/*z* 191, 189 (M^+-1); HRMS (EI) *m*/*z* 188.9921 (calcd for $C_7H_{10}{}^{79}BrO$ 188.9915, 3.2 ppm error).

7-Bromohepta-4*E*,6*Z*-dien-3-ol (15*E*,*Z*): colorless oil (95%), R_f 0.30 (1:1 petroleum ether−diethyl ether); ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.95 (t, J = 7.5, 3H, CH_3), 1.55−1.66 (m, 2H, CH_2), 1.67 (br s, 1H, OH), 4.15 (q, J = 6.5, 1H, C*H*OH), 5.93 (dd, J = 14.6, 6.5, 1H, H-4), 6.18 (d, J = 6.5, 1H, H-7), 6.51−6.68 (m, 2H, H-5, H-6); ^{13}C NMR (67.9 MHz, $CDCl_3$) δ 9.6, 29.9, 73.8, 108.4, 125.9, 131.9, 140.2; IR (film) ν_{max} 3353 cm^{-1}; MS (EI) *m*/*z* 191, 189 (M^+-1); HRMS (EI) *m*/*z* 189.9986 (calcd for $C_7H_{11}{}^{79}BrO$ 189.9993, 3.7 ppm error).

Sonogashira Coupling. General Procedure. In a 5 mL round-bottom flask under nitrogen atmosphere was placed 7-bromohepta-4,6-dien-3-ol **15** (21 mg, 0.11 mmol) in degassed benzene (1 mL). To this solution was added pyrrolidine (0.013 mL, 11 mg, 0.154 mmol) and $(Ph_3P)_4Pd$ (5.1 mg, 0.0044 mmol). The resulting solution was protected from light and stirred for 0.75 h. 2-Ethynylthiophene[12] (13 mg, 0.12 mmol) and CuI (3.4 mg, 0.018 mmol) were added, and the reaction was stirred overnight. Upon completion, the solution was diluted with diethyl ether (70 mL) and washed with aqueous NH_4Cl (10 mL), water (2 × 10 mL), and brine (10 mL). Drying with Na_2SO_4, removal of solvent in vacuo, and column chromatography (5:1 petroleum ether−diethyl ether) gave the final product.

9-(2-Thienyl)-nona-4*E*,6*E*-dien-8-yn-3-ol (16): colorless oil (88%), R_f 0.26 (1:1 petroleum ether−diethyl ether); ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.94 (t, J = 7.4, 3H, CH_3), 1.60 (dq, J = 6.0, 7.4, 2H, CH_2), 1.62 (br s, 1H, OH), 4.13 (q, J = 6.0, 1H, C*H*OH), 5.81 (d, J = 14.8, 1H, H-7), 5.82 (dd, J = 15.0, 6.0, 1H, H-4), 6.32 (dd, J = 14.8, 10.7, 1H, H-6), 6.67 (dd, J = 15.0, 10.7, 1H, H-5), 6.98 (dd, J = 5.1, 3.6, 1H, H-4′), 7.19 (dd, J = 3.6, 1.2, 1H, H-3′), 7.24 (dd, J = 5.1, 1.2, 1H, H-5′); ^{13}C NMR (67.9 MHz, $CDCl_3$) δ 9.6, 30.1, 73.6, 85.3, 92.6, 111.0, 123.4, 127.1, 127.2, 129.5, 131.7, 138.8, 140.9; IR (film) ν_{max} 3355 cm^{-1}; MS (EI) *m*/*z* 218 (M^+); HRMS (EI) *m*/*z* 218.0774 (calcd for $C_{13}H_{14}OS$ 218.0765, 4.1 ppm error); UV (diethyl ether) 338 (21,000), 317 (27,000) nm [lit.[10] 338.5 (21,700), 317 (26,700) nm)]. The NMR data were consistent with those published.[10]

9-(2-Thienyl)-nona-4*E*,6*Z*-dien-8-yn-3-ol (17): colorless oil (87%), R_f 0.25 (1:1 petroleum ether−diethyl ether); ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.96 (t, J = 7.5, 3H, CH_3), 1.61 (dq, J = 6.3, 7.5, 2H, CH_2), 1.62 (br s, 1H, OH), 4.19 (q, J = 6.3, 1H, C*H*OH), 5.67 (d, J = 10.8, 1H, H-7), 5.91 (dd, J = 15.0, 6.3, 1H, H-4), 6.43 (t, J = 10.8, 1H, H-6), 6.80 (dd, J = 15.0, 10.8, 1H, H-5), 7.00 (dd, J = 5.1, 3.6, 1H, H-4′), 7.22 (dd, J = 3.6, 1.2, 1H, H-3′), 7.28 (dd, J = 5.1, 1.2, 1H, H-5′); ^{13}C NMR (67.9 MHz, $CDCl_3$) δ 9.7, 30.0, 73.8, 88.9, 90.4, 109.0, 123.3, 127.1, 127.4, 127.6, 131.8, 139.1, 139.8; IR (film) ν_{max} 3360 cm^{-1}; MS (EI) *m*/*z* 218 (M^+); HRMS (EI) *m*/*z* 218.0762 (calcd for $C_{13}H_{14}OS$ 218.0765, 1.6 ppm error); UV (diethyl ether) 338 (21,000), 317 (27,000) cm^{-1}.

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Supporting Information Available: Copies of ^{1}H NMR spectra of compounds **3**, **4**, and **8**−**17**. This material is available free of charge via the Internet at http://pubs.acs.org.

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