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Preparation of 2-Iodo Allylic Alcohols from 2-Butyn-1,4-diol

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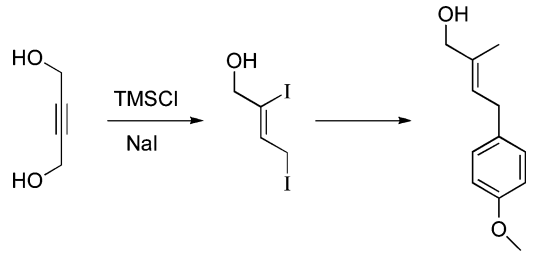
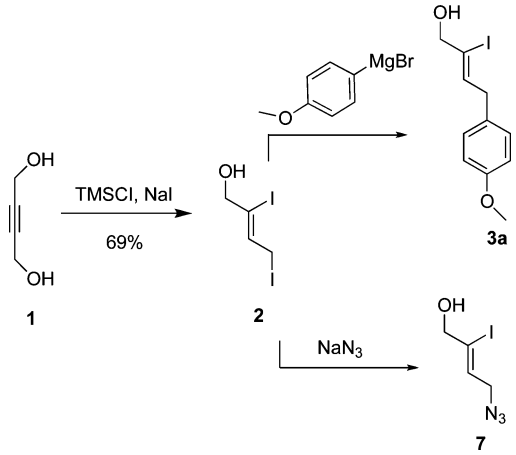


The conversion of 2-butyn-1,4-diol to (*Z*)-2,4-diiodobut-2-en-1-ol proceeded efficiently using in situ generated trimethylsilyl iodide. Coupling with Grignard reagents and other nucleophiles delivered (*2Z*)-2-iodo allylic alcohols. The geometry of the products was established by nOe.

The efficient stereocontrolled construction of disubstituted and trisubstituted alkenes is a continuing challenge in organic synthesis. In 1982, Gras reported that trimethylsilyl iodide (TMSI) converted the inexpensive 2-butyn-1,4-diol **1** to the *E* isomer of **2** with high regiocontrol.[1a] Curiously, no further exploration of **2** had been reported since that time.[1b]

SCHEME 1

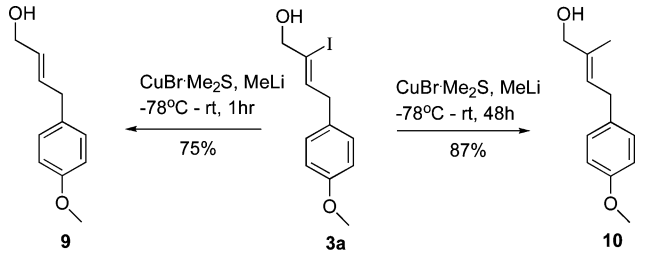


We have found (Scheme 1) that the conversion of **1** to **2** proceeded efficiently using in situ generated[2] TMSI; however, the product formed was actually the *Z* isomer. The diiodide **2** can be coupled with Grignard reagents to give the (*2Z*)-2-iodo allylic alcohols **3** (Table 1). Substitution of the allylic iodide of **2** with various other nucleophiles was also carried out (Table 2). The diiodide **2** is thus a useful synthon for the preparation of geometrically defined trisubstituted alkenes.

The handling of **2** did initially present some difficulty, as it was not stable to silica gel, nor to distillation. Eventually, we found that reductive workup, followed by filtration through a 20:1 mixture of silica gel/copper bronze powder delivered gram quantities of **2** as an off-white solid that could be stored cold for several weeks, and used as needed.

The coupled products could be taken through further transformations (Scheme 2). Brief exposure of **3a** to Me_2CuLi gave the reduced product **9** as a single geometric isomer.[6] Alternatively, prolonged exposure to Me_2CuLi led to the methylated product **10**, again as a single geometric isomer.[7]

SCHEME 2



The geometry of **2** was assigned by nOe studies (Figure 1). Irradiation of the alkenyl proton at δ 6.26 resulted in positive signals corresponding to both allylic postitions (δ 4.31, δ 3.96, Figure 1). If the alkene geometry had been *E*, no positive peak corresponding to the methylene protons of the allylic alcohol would be present in the nOe spectrum. Grignard substituted product **3a** was also found to have *Z* geometry based on the nOe. Irradiation of the alkenyl proton at δ 6.05 produced two

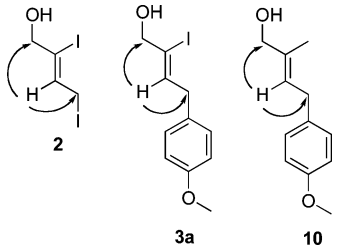


FIGURE 1. nOe Studies.

(1) (a) Gras, J. L.; Kong Win Chang, Y. Y.; Bertrand, M. *Tetrahedron Lett.* **1982**, *23*, 3571. (b) While this work was in progress, the reduction of **2** with In metal was reported: Hirashita, T.; Arai, S.; Mitsui, K.; Makino, H.; Araki, A. *Chem. Lett.* **2006**, *35*, 314.

(2) Olah, G. A.; Narang, S. C.; Gupta, B. G. B.; Malhotra, R. *J. Org. Chem.* **1979**, *44*, 1247.

(3) For the alternative (*E*)-isomer of **3b**, see: Shotwell, J. B.; Krygowski, E. S.; Hines, J.; Koh, B.; Huntsman, E. W. D.; Choi, H. W.; Scheenkloth, J. S., Jr.; Wood, J. L.; Crews, C. M. *Org. Lett.* **2002**, *4*, 3087.

(4) Klaps, E.; Schmid, W. *J. Org. Chem* **1999**, *64*, 7537.

(5) (a) Gamez, P.; Ariente, C.; Gore, J.; Cazes, B. *Tetrahedron* **1998**, *54*, 14825. (b) Ensley, H. E.; Buescher, R. R.; Lee, K. *J. Org. Chem.* **1982**, *47*, 404.

(6) For the alternative (*Z*)-isomer of **9**, see: Pregg, G. G.; George, M. V. *Aust. J. Chem.* **1990**, *43*, 1789.

(7) For the alternative (*Z*)-isomer of **10**, see: Chan, W. K.; Lee, T. D. Y.; Huang, F. C. U.S. Patent 4,758,586, 1986, 73.

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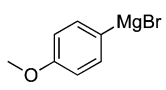
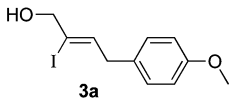
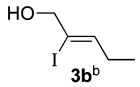
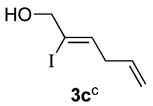
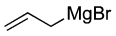
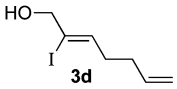
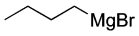
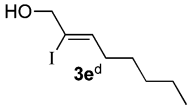
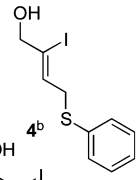
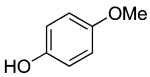
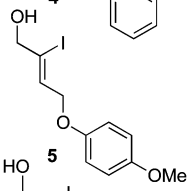
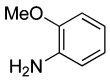
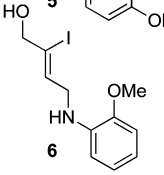
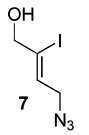
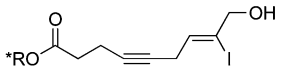
TABLE 1. Preparation of Iodoalkenes

Entry	Grignard	Product	Yield[a]
1		 **3a**	84%
2	MeMgBr	 **3b**[b]	53%
3		 **3c**[c]	30%
4		 **3d**	69%
5		 **3e**[d]	51%

[a] Isolated yield. [b] Reference 3. [c] Reference 4. [d] Reference 5.

TABLE 2. Preparation of Substituted Allylic Alcohols

Entry	Nucleophile	Product	Yield[a]
1		 **4**[b]	70
2		 **5**	60
3		 **6**	68
4	NaN_3	 **7**	88
5		 **8**	58

[a] Isolated yield, R* = L-menthyl ester. [b] Reference 8.

positive signals corresponding to the allylic methylene protons (δ 4.27, δ 3.47, Figure 1). Replacement of the alkenyl iodide with a methyl group resulted in the expected *E* product **10** which, upon irradiation of the alkenyl proton at δ 5.61, showed positive nOe signals present at δ 4.06 and δ 3.36, due to the two allylic methylene groups.

The facile preparation of (*2Z*)-2-iodo allylic alcohols reported here makes these derivatives readily available for further use in target-directed synthesis. We believe that the modular strategy outlined here will be a convenient, general way to prepare geometrically defined disubstituted and trisubstituted alkenes.

Experimental Section

Preparation of (2*Z*)-2,4-Diiodo-2-buten-1-ol (2). Sodium iodide (8.11 g, 0.054 mol) and dry CH_3CN (15.0 mL) were combined under nitrogen in a round-bottom flask. TMSCl was added, and the mixture was stirred at room temperature for 10 min. 2-Butyne-1,4-diol (2.00 g, 0.023 mol) in dry CH_3CN (12.0 mL) was added at once, and stirring was continued for 30 min. The mixture was partitioned between diethyl ether and, sequentially, 10% aqueous $Na_2S_2O_3$ and saturated aqueous $NaHCO_3$. A small piece of clean Cu wire was added to the organic layer to stabilize the diiodide. The combined organic layer was dried (Na_2SO_4) and concentrated. The residue was filtered through 100 g of 20:1 flash silica gel/Cu powder with 15% MTBE/pet ether (each collecting tube contained a piece of clean Cu wire) to yield **2** as an off-white solid (5.22 g, 69% yield). TLC $R_f = 0.29$ (MTBE/PE, 23:77); mp 56−59 °C; ^{1}H NMR δ 6.26 (tt, 1H, $J = 8.2$ Hz, $J = 1.4$ Hz), 4.31 (bd, 2H, $J = 6.8$ Hz), 3.96 (d, 2H, $J = 8.2$ Hz), 1.97 (bs, 1H); ^{13}C NMR[9] δ *u* 112.8, 71.0, 7.2; δ 131.6; IR (film): 3248, 3020, 1630, 1144 cm^{-1}; MS: 323(11), 306(58), 214(60), 196(67), 169(100); HRMS Calcd for $C_4H_6OI_2$ (M^+): 323.8508, Obsd: 323.8520.

(2*Z*)-2-Iodo-4-(4-methoxyphenyl)-2-buten-1-ol (3a) (Method A). (*Z*)-2,4-Diiodo-2-buten-1-ol (0.350 g, 1.08 mmol) and CuBr−Me_2S (0.450 g, 2.18 mmol) were taken up in dry THF and cooled to −40 °C. 4-Methoxyphenyl magnesium bromide (1.75 M, 3.8 mL, 6.6 mmol) was added, and the mixture was stirred for 30 min at −40 °C and then allowed to warm up to room temperature (2 h). The mixture was partitioned between brine and diethyl ether. The combined organic layer was dried (Na_2SO_4) and concentrated. The residue was chromatographed to yield **3a** as a yellow oil (0.278 g, 85% yield). TLC $R_f = 0.31$ (MTBE/PE, 30:70); ^{1}H NMR δ 7.14 (d, 2H, $J = 8.8$ Hz), 6.84 (d, 2H, $J = 8.8$ Hz), 6.05 (t, 1H, $J = 6.8$ Hz), 4.27 (bs, 2H), 3.78 (s, 3H), 3.47 (d, 2H, $J = 6.8$ Hz), 2.09 (bs, 1H); ^{13}C NMR δ *u* 158.2, 130.5, 108.6, 71.5, 41.0; δ 135.2, 129.4, 114.0, 55.2; IR (film): 3378, 2907, 2833, 1610, 1510 cm^{-1}; MS: 304(100), 205(11), 177(39), 159(82), 147(72), 144(47), 121-(79); HRMS Calcd for $C_{11}H_{13}O_2I$ (M^+): 303.9949, Obsd: 303.9960.

(2*Z*)-2-Iodohepta-2,6-dien-1-ol (3d) (Method B). (*Z*)-2,4-Diiodo-2-buten-1-ol (0.300 g, 0.926 mmol) and CuCN (0.097 g, 1.08 mmol) were taken up in dry THF and cooled to −40 °C. Allyl magnesium bromide (2.0 M, 2.50 mL, 5.0 mmol) was added, and the mixture was stirred for 30 min at −40 °C and then allowed to warm to room temperature (2 h). The mixture was partitioned between saturated aqueous NH_4Cl and diethyl ether. The combined organic layer was dried (Na_2SO_4) and concentrated. The residue was chromatographed to yield **3d** as a yellow oil (0.152 g, 69% yield). TLC $R_f = 0.43$ (MTBE/PE, 30:70); ^{1}H NMR δ 5.92 (t, 1H, $J = 6.4$ Hz), 5.84 (m, 1H, $J = 6.8$ Hz), 5.05 (dq, 1H, $J = 18.0$ Hz, $J = 1.2$ Hz), 5.01 (dq, 1H, $J = 8.0$ Hz, $J = 1.2$ Hz), 4.24 (d, 2H, $J = 6.8$ Hz), 2.27 (td, 2H, $J = 6.8$ Hz), 2.19 (td, 2H, $J = 6.4$ Hz), 1.95 (t, 1H, $J = 6.8$ Hz); ^{13}C NMR δ *u* 115.4, 108.5, 71.6, 34.8, 32.1; δ 137.3, 135.5; IR (film): 3329, 1629, 1441, 1083, 993, 912 cm^{-1}; MS: 240(89), 238(2), 196(11), 169(33), 93(100); HRMS Calcd for $C_7H_{11}OI$ (M^+): 237.9855, Obsd: 237.9850.

(8) Denis, R. C.; Gravel, D. *Tetrahedron Lett.* **1994**, *35*, 4531.

(9) ^{13}C multiplicities were determined with the aid of a JVERT pulse sequence, differentiating the signals for methyl and methine carbons as "d" from methylene and quaternary carbons as "u".

(2*Z*)-2-Iodo-4-(phenylthio)-2-buten-1-ol (4). Thiophenol (0.112 g, 1.01 mmol) and KOH (0.080 g, 1.42 mmol) were dissolved in 1 mL of 1:1 acetone/H_2O. One hundred milligrams of Cu powder was added to the solution, which was then stirred at room temperature for 5 min. A solution of **2** (0.195 g, 0.601 mmol) in 0.5 mL of 1:1 acetone/H_2O was added dropwise via syringe over 5 min. The mixture was stirred for 3 h at room temperature and then partitioned between CH_2Cl_2 and H_2O. The organic layer was dried (Na_2SO_4) and concentrated. The residue was chromatographed to yield **4** as a colorless oil (0.129 g, 70% yield). TLC $R_f = 0.44$ (MTBE/PE, 15:85); ^{1}H NMR δ 7.37 (dt, 2H, $J = 8$ Hz, $J = 1.6$ Hz), 7.29 (m, 2H, $J = 7.6$ Hz), 7.22 (tt, 1H, $J = 7.2$ Hz, $J = 1.2$ Hz), 6.05 (tt, 1H, $J = 7.2$ Hz, $J = 1.2$ Hz), 4.22 (d, 2H, $J = 1.2$ Hz), 3.67 (d, 2H, $J = 6.8$ Hz), 1.97 (t, 1H, $J = 7.2$ Hz); ^{13}C NMR δ υ 135.1, 110.9, 71.2, 39.0; δ 131.4, 130.2, 129.0, 126.6; IR (film): 3351, 1637, 1581, 1070, 740 cm^{-1}; MS: 306(54), 289-(59), 196(14), 179(50), 161(76), 147(57) 110(100), 109(48); HRMS Calcd for $C_{10}H_{11}OSI$ (M^+): 305.9575, Obsd: 305.9581.

(*Z*)-((1*R*,2*S*,5*R*)-2-Isopropyl-5-methylcyclohexyl)-9-hydroxy-8-iodo-7-nonen-4-ynoate (8). (1*R*,2*S*,5*R*)-2-Isopropyl-5-methylcyclohexyl-4-pentynoate (0.100 g, 0.423 mmol) was dissolved in 0.5 mL of DMF and stirred for 5 min. K_2CO_3 (0.128 g, 0.930 mmol) and CuI (0.081 g, 0.426 mmol) were added at once, and the mixture was stirred for 30 min. Compound **2** (0.205 g, 0.632 mmol) was added at once, and the mixture was stirred at room temperature for 72 h. The mixture was partitioned between Et_2O and, sequentially, saturated aqueous NH_4Cl and H_2O. The organic layer was dried (Na_2SO_4) and concentrated. Chromatography of the residue afforded **8** (0.106 g, 58% yield) as a light-yellow oil. TLC $R_f = 0.10$ (MTBE/PE, 15:85); ^{1}H NMR δ 5.91 (tt, 1H, $J = 6.4$ Hz, $J = 1.2$ Hz), 4.62 (td, 1H, $J = 4.4$ Hz), 4.18 (d, 2H, $J = 1.2$ Hz), 2.95 (d, 2H, $J = 6.4$ Hz), 2.61 (s, 1H), 2.40 (m, 4H), 1.91 (d, 1H, $J = 11.2$ Hz), 1.80 (m, 1H, $J = 2.4$ Hz), 1.60 (m, 2H), 1.41 (m, 1H, $J = 3.6$ Hz), 1.30 (m, 1H), 0.98 (qd, 1H, $J = 3.2$ Hz), 0.90 (d, 1H, $J = 11.2$ Hz), 0.84 (d, 3H, $J = 6.4$ Hz), 0.83 (m, 1H), 0.82 (d, 3H, $J = 6.8$ Hz), 0.69 (d, 3H, $J = 7.2$ Hz); ^{13}C NMR δ υ 171.7, 109.1, 79.4, 76.9, 71.1, 40.9, 34.2, 34.2, 26.2, 23.4, 14.9; δ 131.1, 74.5, 46.9, 31.3, 26.2, 22.0, 20.8, 16.3; IR (film): 3441, 1727, 1453, 1259, 1175 cm^{-1}; MS: 450(M + NH_4, 14), 312(100), 186(30), 151(40), 138(27), 123(15); HRMS Calcd for $C_{19}H_{33}O_3NI$ (M + NH_4): 450.1505, Obsd: 450.1489.

(2*E*)-4-(4-Methoxyphenyl)-2-buten-1-ol (9). To a slurry of CuBr−Me_2S (2.54 g, 12.3 mmol) in dry THF at −78 °C was added 1.4 M MeLi (19.3 mL, 27.0 mmol). The solution was stirred 30 min at −78 °C, and then a solution of **3a** (1.83 g, 6.02 mmol) in dry THF (12.0 mL) was added. The solution was stirred at −78 °C for 30 min and then allowed to reach room temperature and stirred for 1 h. The solution was quenched with water (2 mL) and filtered through Celite. The organic layer was dried (Na_2SO_4) and concentrated. The residue was chromatographed to yield **9** as a yellow oil (0.866 g, 75% yield). TLC $R_f = 0.21$ (MTBE/PE, 30:70); ^{1}H NMR δ 7.10 (d, 2H, $J = 8.4$ Hz), 6.84 (d, 2H, $J = 8.4$ Hz), 5.84 (m, 1H, $J = 15.2$ Hz, $J = 5.2$ Hz), 5.68 (m, 1H, $J = 15.2$ Hz, $J = 6.4$ Hz), 4.12 (bd, 2H, $J = 5.2$ Hz), 3.79 (s, 3H), 3.32 (d, 2H, $J = 6.4$ Hz), 1.53 (bs, 1H); ^{13}C NMR δ υ 158.0, 132.0, 63.5, 37.7; δ 132.0, 129.9, 129.5, 113.8, 55.2; IR (film): 3365, 1732, 1610, 1511, 1245 cm^{-1}; MS: 178(69), 159(48), 147(100), 129(23), 121(50); HRMS Calcd for $C_{11}H_{14}O_2$ (M^+): 178.0994, Obsd: 178.1001.

(2*E*)-4-(4-Methoxyphenyl)-2-methyl-2-buten-1-ol (10). To a slurry of CuBr−Me_2S (0.439 g, 2.13 mmol) in dry THF at −78 °C was added 1.5 M MeLi (2.85 mL, 4.28 mmol). The solution was stirred for 30 min at −78 °C, and then a solution of **3a** (0.323 g, 1.06 mmol) in dry THF (2.2 mL) was added. The solution was stirred at −78 °C for 30 min and then allowed to come to room temperature and was stirred at room temperature for 48 h. The mixture was quenched with water (1 mL) and filtered through Celite. The organic layer was dried (Na_2SO_4) and concentrated. The residue was chromatographed to yield **10** as clear colorless oil (0.177 g, 87% yield). TLC $R_f = 0.30$ (MTBE/PE, 30:70); ^{1}H NMR δ 7.12 (d, 2H, $J = 8.4$ Hz), 6.86 (d, 2H, $J = 8.4$ Hz), 5.61 (t, 1H, $J = 7.2$ Hz), 4.06 (s, 2H), 3.81 (s, 3H), 3.36 (d, 2H, $J = 7.2$ Hz), 1.80 (s, 3H), 1.60 (bs, 1H); ^{13}C NMR δ υ 157.8, 135.3, 133.0, 68.9, 32.9; δ 129.2, 125.5, 113.9, 55.3, 13.7; IR (film): 3356, 1610, 1511, 1245, 1033 cm^{-1}; MS: 192(23), 173(6), 161(100), 146(11), 121(30); HRMS Calcd for $C_{12}H_{16}O_2$ (M^+): 192.1150, Obsd: 192.1158.

Acknowledgment. We thank John Dykins for high-resolution mass spectra and the National Institutes of Health (GM060287) for financial support of this research.

Supporting Information Available: General experimental procedures and ^{1}H NMR and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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