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Synthesis of (*E*,*Z*)-5-Bromo-1,1-dimethoxy-5-trimethylsilyl-4-pentene, an Upper Chain Allenic Prostaglandin Building Block

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ABSTRACT

This work explores the synthetic route to allenic prostaglandins. In a search for more efficient and reliable methods for the introduction of the allene moiety into the side chains of prostaglandins, the synthons, the (*E*) and (*Z*) isomers of 1-bromo-5,5-dimethoxy-1-trimethylsilyl-1-pentene **(13a)** and (**13b**), have been prepared and converted to *R*,*S*-1,1-dimethoxy-6-phenyl-4,5-hexadiene (**16**), a prostaglandin analog.

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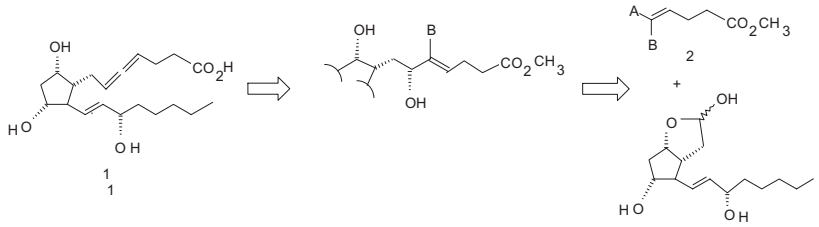
INTRODUCTION

The luteolytic activity of 4,5-dehydro $PGF_{2\alpha}$, **1**, has been shown to be greater than that of $PGF_{2\alpha}$[1] in several animal species. Allenic prostaglandins with the allenic moiety in both the superior[1,2] and inferior[1] chains have been prepared. Compound **1** has the greater luteolytic effect.[3] All previous syntheses of **1** have employed a cuprate induced conversion of a propargyllic acetate to an allene as the key step in the construction of the allene containing side chain.[1–3] Crabbe and Carpio,[2] for example, added the acetate of 4-pentyne-1-ol to Corey's lactol[2,4–8] and generated the propadiene unit from the resulting propargylic acetate using lithium dimethyl cuprate. Here we seek a simpler strategy for the synthesis of **1**, which would avoid the subsequent oxidation and reduction steps, which are problematic in the reported[1] synthesis of **1**.

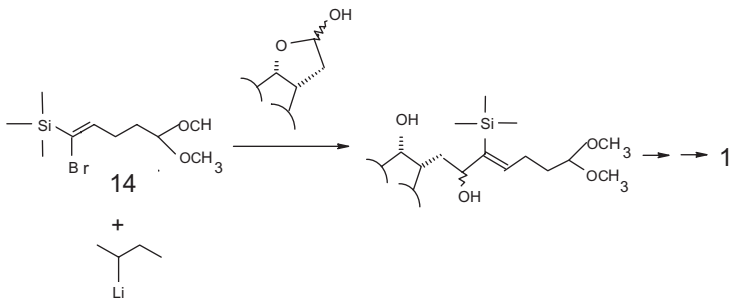
An attractive route for the introduction of the allene group is via difunctional olefin **2,** in which **A** serves as a nucleophyllic site for addition to Corey's lactol and **B** is a functional group capable of generating a double bond in the resulting allylic alcohol.[9–22]

The silyl bromo olefin (where **A** is a trimethyl silyl group and **B** is a bromine) appeared to be an ideal synthon for this purpose. Halogen metal exchange could generate the needed nucleophile and the Peterson reaction[15] could deliver the allenic group with the other portions of the molecule at the proper oxidation level. In this work we show that the protected derivatives of 5-trimethylsilyl-4-pentynoic acid do not survive the hydroalumination reaction. This makes it impossible to prepare **1** by this route.

Since acetals are more resistant to reduction than esters or ortho esters and are easily converted to the readily oxidizable aldehydes, the synthesis of the corresponding acetal was undertaken to provide an intermediate that can be used in the preparation of **1** (Sch. 2)



Scheme 1. A retrosynthetic analysis of the route to prostaglandin **1**.



Scheme 2. The use of an acetal in the preparation of **1**.

RESULTS AND DISCUSSION

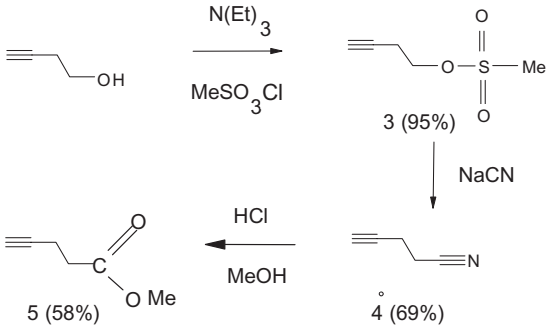
In order to conserve the oxidation state of the carboxylic acid group, protection by converting it to an orthoester was investigated. Following the route of Whiting et al.[23] who have prepared a homolog of **9** with lower yield, 4-butyne-1-ol was mesylated to **3** and treated with sodium cyanide to give 4-cyanobutyne, **4 (**85%, overall yield). The cyano group of **4** was converted to the ester group of **5** by treatment with methanol, HCl, and water (Sch. 3).

Since the ester could be subject to reduction in the subsequent reactions an attempt was made to protect it by preparing the bicyclic ortho ester,[26] **6.** The 4-cyanobutyne, **4**, was treated with dry HCl in methanol followed by triethylamine and 1,1,1-*tris*(hydroxymethyl)ethane to give the bicyclic orthoester, 1-(3-butynyl)-4-methyl-2[2,2,2]octane, **6** (Sch. 4). Despite several attempts to silylate this compound by treatment with DBU followed by TMSCl and AgCl no silylated orthoester was obtained. This approach was therefore abandoned.

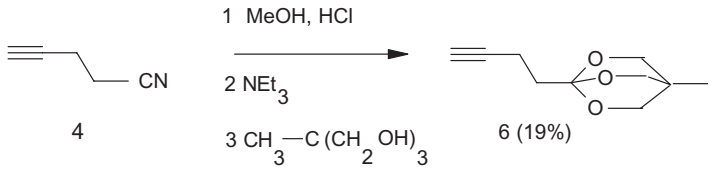
Treatment of 4-cyanobutyne, **4,** with gaseous HCl in anhydrous methanol gave iminoester, **7**, which on treatment with methanol in hexane gave trimethyl ortho-4-pentynoate, **8** (Sch. 5).

The ease of hydrolysis of orthoesters was confirmed by the observation that percolation of compound **8** through silica gel converted it to the corresponding ester, **5**.

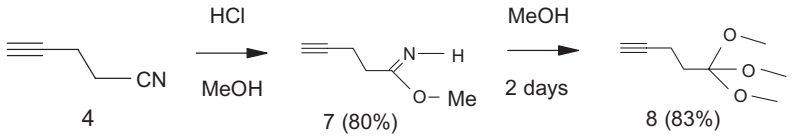
Silylation of orthoester, **8**, with DBU, silver chloride, and TMSCl, gave the silyl orthoester **9**. Alternatively **4** could be silylated and then converted to silyl orthoester **10** by a similar procedure but the overall yield was lower.[24,25] Treatment of the silylated orthoester, **9**, with silica gel gave methyl 5-trimethylsilyl-4-pentynoate, **10**, in quantitative yield (Sch. 6).



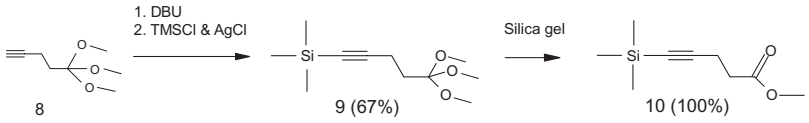
Scheme 3. The conversion of 4-butyne-1-ol to ester (**5**).



Scheme 4. Preparation of the bicyclic orthoester **(6)**.



Scheme 5. Preparation of trimethyl ortho-4-pentynoate (**8**).



Scheme 6. Preparation of methyl 5-trimethylsilyl-4-pentynoate (**10**).

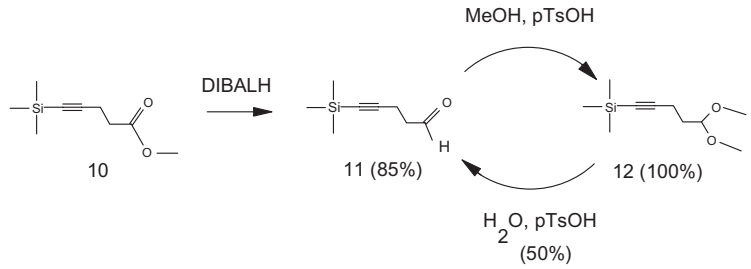
Reduction of **10** with one equivalent of DIBALH converted it to the corresponding aldehyde, **11**. Aldehyde, **11**, was protected by conversion to acetal **12** in quantitative yield by treatment with absolute methanol and tosic acid. Acetal **12** was readily hydrolyzed to aldehyde **11** (Sch. 7).

The use of acetal **12** as a synthon for the introduction of an allyl group into prostaglandins was tested by treating it with DIBALH and quenching with bromine to give a mixture of the two bromoalkenyl derivatives **13a** and **13b** (Sch. 8). The work of Zweifel et al.[9,18,24] shows that the treatment of silylated acetylenes by the use of DIBALH and bromine gives the *E* isomer as the major product and the *Z* isomer as the minor product. These products were separable by chromatography.

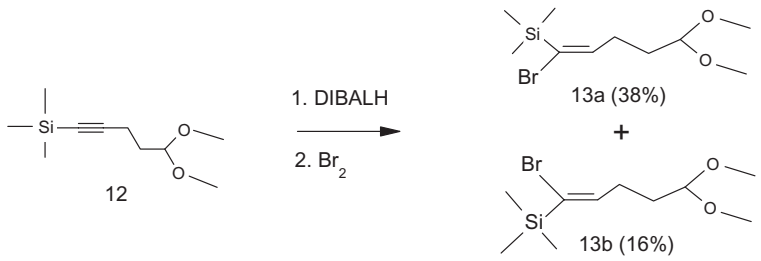
Reductive removal of bromine from the mixture of bromo-alkylated intermediate **13b** was effected by treatment of the compound with one equivalent of tBuLi. Quenching the lithiated intermediate with methanol gave silylated acetals **14a** and **14b** (Sch. 9). No attempt was made to separate these two isomers and it was not possible to establish the ratio.

Quenching the lithiated intermediate with benzaldehyde gave isomeric oily alcohols, **15a** and **15b** (Sch. 10), which were separable by preparative thin layer chromatography.

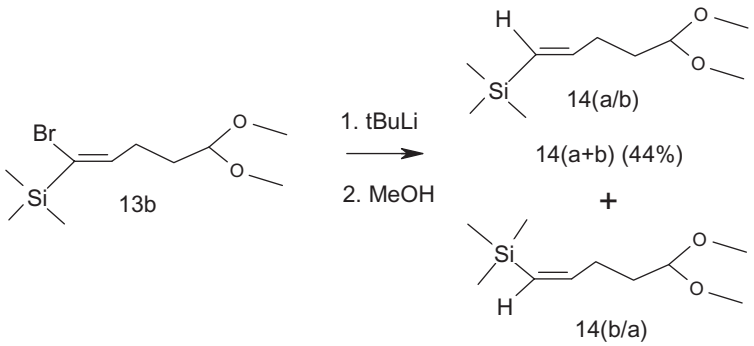
Treatment of **15a** with KH in THF as suggested by Peterson[15] gave a mixture of racemic allene **16** (30%) and alkyne **17** (24%) (Sch. 11).



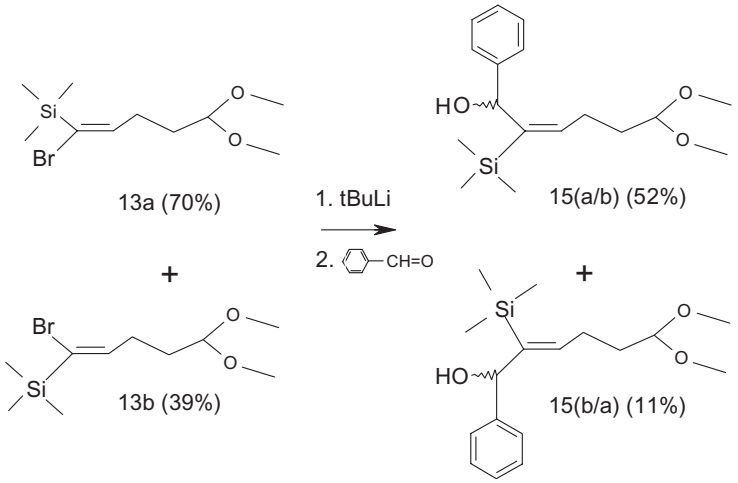
Scheme 7. Preparation and reversible hydrolysis of the silylated acetal (**10**).



Scheme 8. The reductive bromination of the acetal (**12**).

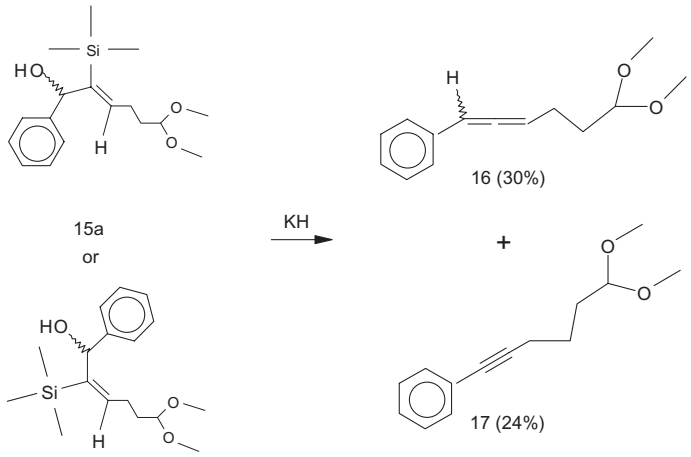


Scheme 9. Preparation of the mixed *E* and *Z* isomers of 1,1-dimethoxy-4-pentene, **14(a/b)**.



Scheme 10. The preparation of a racemic *E* and *Z* mixture of 6-hydroxy-1,1-dimethoxy-6-phenyl-5-trimethylsilyl-4-hexene, (**15a/b**).

The NMR spectra of the silylated acetylenic compounds and the allenic compound clearly show that there is restricted rotation about the C2 to C3 bond. This makes extracting the NMR parameters difficult. The J^4 and J^5 values reported for the allenic system are typical. The overall yield of *E* and *Z* isomers of 5-bromo-1,1-dimethoxy-5-trimethylsilyl-4-pentene (**13a**) and (**13b**) based on 3-butynol was 13%.



Scheme 11. The dehydrosilylation of compound (**15a/b**).

EXPERIMENTAL

Reagents were used as purchased from Aldrich or they were dried appropriately before use. HCl (g) was dried by sparging through conc. H_2SO_4 and was then passed through a Dryerite trap. TLC was performed on Silica Gel 60 F_{254} plates from Merck and visualized by UV and/or iodine vapor. Column chromatography was carried out on 70–230 mesh silica gel from Merck and Flash chromatography was also done on 70–230 mesh silica gel from Merck. The solvents used as eluants were concentrated using a cold trap equipped rotary evaporator to facilitate proper disposal of used solvents. Infrared spectra were recorded on a Perkin Elmer 1600 series FTIR spectrometer.

NMR spectra were recorded on a Bruker Aspect 3000 200 MHz instrument in either $CDCl_3$ or in C_6D_6 or on a Varian EM390 90 MHz instrument. Shifts are relative to internal Me_4Si. The use of the verb "concentrated" refers to evaporation under reduced pressure (water aspirator) using a rotary evaporator. Mass spectra and elemental analyses were determined by Galbraith Laboratories, Knoxville, TN.

Methyl 3-butyne-1-sulfonate (3). A solution of 3-butyne-1-ol (225 g, 0.357 mol) in CH_2Cl_2 was placed in a round-bottomed flask and the stirred mixture was cooled to $-10^{\circ}C$. Triethylamine (70 mL, 51 g, 0.50 mol) was added and then mesyl chloride (49 g, 0.427 mol) was added dropwise with stirring. After 3 h at $-10^{\circ}C$ the solution was allowed to warm to room temperature, extracted with saturated $NaHCO_3$, dried

(Na_2SO_4) and concentrated to give a reddish-black oil. This oil was purified by chromatography over silica gel (benzene, an attempt to use toluene was unsuccessful). Concentration gave **3**, a reddish viscous oil (50 g, 0.34 mol, 95%). Spectral data for **3**. IR (neat) 3310, 3020, 1980, 1365, 1345, 1180, 995, 965, 907, 820, 710, 655 cm^{-1}. ^1H NMR (200 MHz, C_6D_6): δ 4.15 (t, 2H, $J = 6.4$ Hz), 2.8 (s, 3 H), 2.52 (td, 2H, $J = 6.4$, 2.7 Hz), 2.13 (t, 1H, $J = 2.7$). ^{13}C NMR (200 MHz, C_6D_6): δ 79.9 (d, $J = 14.6$ Hz), 71.5 (d, $J = 73.1$ Hz), 68.1 (t, $J = 22.2$ Hz), 37.0 (q, $J + 33$ Hz), 19.4 (t, $J = 34.6$ Hz). Anal. calcd. for $C_5H_8O_3S$: C, 40.53; H, 5.44. Found: C, 40.54; H, 5.34.

4-Cyano-1-butyne (4). A solution of **3** (110 g, 0.7 mol) and sodium cyanide (175 g, 3.57 mol) in DMF (300 mL) was stirred at room temperature for 2 h. A deep brown oil (48 g) was obtained after purification by Flash column chromatography (CH_2Cl_2). Distillation (80°C/35 Torr) gave **4**, a colorless oil (40 g, 0.506 mol, 69%). Spectral data for **4.** IR (CH_2Cl_2) 3306, 2918, 2238, 2114, 1340, 1323. cm^{-1}. ^1H NMR (200 MHz, C_6D_6): δ 2.2 (m, 4H), 2.09 (s, 1H). ^{13}C NMR (200 MHz, C_6D_6): δ 118.9 (s,), 80.8 (d, $J = 8$ Hz), 71.3 (d, $J = 51$ Hz), 17.2 (t, $J = 30$ Hz), 15.5 (t, $J = 29$ Hz). Anal. calcd. for C_5H_5N: C, 75.92; H, 6.37. Found: C, 75.76; H, 6.58.

Methyl 4-pentynoate (5). A solution of nitrile **4** (32.52 g, 0.412 mol) in absolute MeOH (27.7 mL, 0.648 mol) was cooled to −10°C and saturated with dry HCl (g, H_2SO_4, Dryerite). After concentration water (7.42 mL, 0.412 mol) was added and the ester, **5** (26.8 g, 0.24 mol, 58%), was extracted into ether. An insoluble residue of 4-pentynoic acid (6.68 g, 0.068 mol, 10%) remained. Spectral data for **5.** IR (neat) 3299, 2960, 2131, 1738, 1439, 1367 cm^{-1}. ^1H NMR (200 MHz, C_6D_6): δ 3.27 (s, 3H), 2.14 (m, 4H), 1.79 (m, 1H). ^{13}C NMR (200 MHz, C_6D_6): 171.5 (s), 82.7 (d, $J = 2.7$ Hz), 69.4 (d, $J = 84.4$ Hz), 51.2 (q, $J = 159.0$ Hz), 33.1 (t, $J = 40.0$ Hz), 14.5 (t, $J = 40.5$ Hz).

1-(3-Butynyl)-4-methyl-2,6,7-trioxobicyclo[2.2.2]octane (6). A solution of nitrile **4** (9.0 g, 0.114 mol) in dry methanol (5.2 mL) was cooled to −10°C and the solution was saturated with dry HCl. After 10 min addition of dry THF (50 mL) caused the intermediate to precipitate. The pH was raised to 5.0 by the addition of anhydrous triethylamine and 1,1,1-*tris*(hydroxymethyl)ethane (11 g, 0.092 mol) was added. Stirring was continued for 16 h at room temperature. Concentration gave a residue which was extracted with CH_2Cl_2.. After drying (Na_2SO_4) concentration gave a white crystalline solid (5 g) which was purified by sublimation (3 mmHg, bath temperature 71°C) to afford **6** (5.0 g, 0.022 mol, 19%) as a white crystalline solid. Spectral data for **6.** IR (neat) 3302, 2121, 1060 cm^{-1}. ^1H NMR (200 MHz, C_6D_6): δ 3.61

(s, 6H), 2.7 (m, 2H), 2.4 (m, 2H), 1.87 (t, 1H, J=2.7 Hz), 0.16 (s, 3H). ^{13}C NMR (200 MHz, C_6D_6): δ 108.5 (s), 84.3 (d, J = 39 Hz), 72.4 (t, J = 54 Hz), 36.8 (t, J = 88 Hz), 30.0 (s), 13.8 (q, J = 110 Hz), 13.4 (t, J = 90).

Methyl 4-pentynoateiminoester (7). A solution of nitrile **4** (2.0 g, 0.025 mol) and dry methanol (1.125 mL, 3.9 g, 0.0278 mol) in ether (6.8 mL) was prepared, stirred for 5 min and then cooled to −10°C. The solution was saturated with dry HCl gas which caused the temperature to rise to 40°C. It was again cooled to −10°C, hexane was added and the solution was concentrated. On cooling to Dry Ice temperature white crystals of **7** (3.0 g. 0.020 mol, 80%) formed. These crystals were washed with dry ether until the pH of the ether was 7.0. The white crystalline solid was held 24 h in an evacuated dessicator over KOH, NaOH, and P_2O_5 before it was used in subsequent reactions. Spectral data for **7.** IR ($CDCl_3$) 3310, 2227, 1663, 1472, 1412 cm^{-1}. ^{1}H NMR (200 MHz, $CHCl_3$): δ 4.33 (s, 3H), 4.19 (s, 1H), 2.99 (t, 2H, J = 7.0 Hz), 2.67 (t, 2H J = 7.0 Hz), 2.07 (s, 1H). ^{13}C NMR (200 MHz, $CHCl_3$): δ 178 (s), 79 (s), 71 (d, J = 75 Hz), 60.8 (q, J = 19 Hz), 32 (t, J = 30 Hz), 15 (t, J = 3 Hz).

Trimethyl ortho-4-pentynoate (8). A solution of iminoester **7** (2.00 g, 0.025 mol) and methanol (1.95 g, 2.4 mL, 0.61 mol) in dry hexane was stirred for three days at room temperature under nitrogen. Concentration gave **8** (2.67 g, 0.0169 mol, 83%) as a colorless oil. Spectral data for **8.** IR (neat) 3280, 2950, 2840, 2120, 1419, 1328, 1219, 1149, 1040 cm^{-1}. ^{1}H NMR (90 MHz, $CHCl_3$): δ 3.27 (s, 9H), 2.2 (m, 3H), 2.12 (s, 1H), 1.92 (m, 2H).

Methyl 4-pentynoate (5) from 8. A solution of orthoester **8** (100 mg, 0.633 mmol) in CH_2Cl_2, C_6H_{14} (4:1) was percolated through a silica gel column (2.15 g, 70–230 mesh). The major fraction on concentration gave **5** (71 mg, 100%). Spectral data for **5.** As reported above.

Trimethyl ortho-5-trimethylsilyl-4-pentynoate (9). A mixture of orthoester **8** (4.7 g, 0.030 mol), DBU (5.5 g, 0.036 mol), and AgCl (0.86 g, 0.006 mol) in CH_2Cl_2 (124 mL) was heated to reflux and TMSCl (3.9 g, 0.036 mol) was added. After 25 h at reflux the solution was concentrated and the residue was extracted with hexane. The hexane solution was filtered through Celite and concentrated to give a colorless oil (7.0 g). Distillation (82°C/1 mmHg) gave **9 (**4.6 g, 67%). Spectral data for **9.** IR (neat) 2950, 2830, 2170, 1740, 1670, 1438, 1245, 1100, 1045, 965, 919, 842 cm^{-1}. ^{1}H NMR (90 MHz, $CHCl_3$): δ 3.15 (s, 9H), 2.2 (m, 2H), 2.0 (m, 2H), 0.15 (s, 9H).

Methyl 5-trimethylsilyl-4-pentynoate (10). A solution of orthoester **9** (17.48 g, 0.076 mol) in CH_2Cl_2, C_6H_{14} (4:1) was percolated through a silica gel column (450 g, 70–230 mesh). This solution on concentration

gave **10** (13.0 g, 0.076 mol, 100%). Spectral data for **10.** IR (neat) 2962, 2183, 1740, 1440, 1368, 1205, 1175 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 3.55 (s, 3H), 2.44 (m, 4H), 0.15 (s, 9H). ^{13}C NMR (200 MHz, C_6D_6): δ 171.5 (s), 105.7 (s), 85.0 (s), 51.2 (q, $J = 88$ Hz), 33.1 (t, $J = 100$ Hz), 15.9 (t, $J = 99$ Hz), 0.12 (q, $J = 105$ Hz). Anal. calcd. for $C_9H_{16}O_2Si$: C, 58.65; H, 8.75. Found: C, 58.68; H, 8.79.

Methyl 5-trimethylsilyl-4-pentynoate (10) from 5. A mixture of ester **5** (26.8 g, 0.24 mol), AgCl (6.9 g, 0.048 mol), and DBU (51.0 g, 0.336 mol) in anhydrous CH_2Cl_2 (500 mL) was brought to reflux then TMSCl (31.2 g, 0.288 mol) was added and refluxing was continued for 25 h. Concentration gave a colorless oil which was extracted into hexane, filtered through Celite and concentrated to **10** (30.1 g, 0.16 mol, 69%). Spectral data for **10**. See above.

5-Trimethylsilyl-4-pentynal (11). A stirred solution of **10** (23.5 g, 0.13 mol) in toluene was maintained at -65 to -70°C during the addition of a solution of DIBALH (20.3 g, 0.143 mol) in toluene (25 mL) with stirring. After 23 min MeOH (50 mL) was added and the reaction was allowed to warm to room temperature. After filtration through a sintered glass funnel, concentration gave a yellowish oil (18 g) which was purified by flash column chromatography (50 g, hexane). Concentration gave a colorless oil, **11** (17.0 g, 0.111 mol, 85.4%). Spectral data for **11.** IR (neat) 2950, 2170, 1745, 1230 cm^{-1}. ^1H NMR (200 MHz, C_6D_6): δ 9.8 (s, 1H), 2.6 (m, 4H) 0.2 (s, 9H); ^{13}C NMR (200 MHz, C_6D_6): δ 199.7 (d, $J = 129$ Hz), 175.4 (s), 85.3 (s), 105.7 (s), 85.3 (s), 42.6 (t, $J = 93$ Hz), 14.1 (t, $J = 98.4$ Hz), 0.2 (s, 9H, $J = 104$). ^{29}Si NMR (200 MHz, C_6D_6): δ -19.7 (s). MS m/z 139 (M^+), 109, 85, 83, 73, 61, 59, 53. Anal. calcd. for $C_8H_{14}OSi$: C, 62.28; H, 9.15. Found: C, 58.68; H, 9.70.

1,1-Dimethoxy-5-trimethylsilyl-4-pentyne (12). Anhydrous pTsOH (300 mg) was added to a solution of **11** (6.0 g, 0.039 mol) in absolute methanol. The reaction mixture was stirred for 1 h at room temperature. The solution was concentrated and the residue was dissolved in CH_2Cl_2 and washed with aqueous $NaHCO_3$. After drying (Na_2SO_4) concentration gave **12** (7.8 g, 0.039 mol, 100%). Spectral data for **12.** IR (neat) 2950, 2836, 2176, 1250, 1110, 1060, 840 cm^{-1}. ^1H NMR (200 MHz, C_6D_6): δ 4.29 (t, 1H, $J = 5.8$ Hz), 3.08 (s, 6H), 2.11 (t, 2H, $J = 6.4$ Hz), 1.65 (q, 2H, $J = 6.0$ Hz), 0.04 (s, 9H). ^{13}C NMR (200 MHz, C_6D_6): δ 106.9 (s), 103.4 (d, $J = 65.4$ Hz), 84.4 (s), 52.4 (q, $J = 88.8$ Hz), 31.8 (t, $J = 103.0$ Hz), 15.5 (t, $J = 96.0$ Hz), 0.18 (q, $J = 103.5$ Hz). ^{29}Si NMR (200 MHz, C_6D_6) δ -19.7. MS m/z; ms 199, 169, 127, 111, 97, 89, 75, 73). Anal. calcd. for $C_{10}H_{20}O_2Si$: C, 59.95; H, 10.06. Found: C, 59.68; H, 10.27.

5-Trimethylsilyl-4-pentynal (11) from 12. A solution of **12** (155 mg, 0.775 mmol) in 95% THF and a trace of pTsOH was refluxed for 12 h. The solution was cooled and extracted with hexane. Concentration gave **11** (60 mg, 0.389 mmol, 50%), a colorless oil. Spectral data for **11.** As reported above.

***E* and *Z* Isomers ocf 5-Bromo-1,1-dimethoxy-5-trimethylsilyl-4-pentene (13a) and (13b).** A stirred solution of **12** (5.0 g, 0.025 mol) in anhydrous hexane (10 mL) was cooled to -50°C. A solution of DIBALH (7.1 g, 0.050 mol) in anhydrous hexane (5 mL) was added dropwise at -50°C. After stirring for 45 min at -50°C the reaction mixture was allowed to warm to room temperature. Concentration gave an oil which was dissolved in anhydrous THF (12 mL). This solution was cooled to -70°C and bromine (12 g, 0.075 mol) in anhydrous CH_2Cl_2 was added with stirring at that temperature. After this solution had warmed to room temperature it was contacted with a solution of NaOH (24 g, 0.6 mol) in water (100 mL) with vigorous stirring. After drying (Na_2SO_4), concentration gave a colorless oil (8.2 g) that was dissolved in ether and purified by column chromatography over silica gel (500g, elution with CH_2Cl_2). The major fraction was isomer , **13a** (2.6 g, 9.4 mmol, 38%), and the minor fraction was isomer, **13b** (1.1 g, 0.4 mmol, 16%). Spectral data for **13a.** IR (neat) 1600, 840 cm^{-1}. ^{1}H NMR (90 MHz, $CDCl_3$): δ 6.7 (t, 1H, $J = 8$ Hz), 4.3 (t, 1H, $J = 6$ Hz), 3.3 (s, 6H), 2.2 (m, 2H), 1.7 (m, 2H), 0.3 (s, 3H), 0.2 (m, 6H). MS *m/e* 248, 207, 201, 169. Spectral data for **13b.** IR (neat) 1600, 840 cm^{-1}. ^{1}H NMR (90 MHz, $CDCl_3$): δ 6.3 (t, 1H, $J = 7$ Hz), 4.4 (t, 1H, $J = 6$ Hz), 3.3 (s, 6H), 2.2 (m, 2H), 1.8 (m, 2H), 0.3 (s, 3H), 0.2 (s, 6H). MS *m/e* 248, 209, 207, 201, 169. Anal. calcd. for $C_{10}H_{21}O_2BrSi$: Br, 28.47. Found: Br, 24.0.

Mixed *E* and *Z* Isomers of 1,1-Dimethoxy-5-trimethylsilyl-4-pentene (14a and b). A stirred solution of **13b** (0.32 g, 1.4 mmol) in anhydrous THF (5 mL) was cooled to -78°C and the temperature was kept below -65°C during the addition of a 1.5 M solution of tBuLi (1.6 mL, 2.4 mmol). After 5 min at -65°C the temperature was allowed to rise to -20°C and was held at that temperature for 1 h 18 min. Methanol (10 mL) was added. Concentration gave a mixture of **14a** and **b** (0.10 g, 0.5 mmol, 44%). The ratio of isomers in this oily liquid could not be established by chromatography or from the spectra. Spectral data for **14a** and **b**. IR (neat) 2950, 1605, 1240, 1120, 860, 833 cm^{-1}. ^{1}H NMR (90 MHz, $CDCl_3$): δ 6.3 (m, 2H), 4.4 (t, 1H, $J = 5$Hz), 3.3 (m, 6H), 2.2 (m, 2H), 1.7 (m, 2H), 0.1 (s, 3H), 0.04 (s, 6H).

***E* and *Z* isomers of *R,S*-6-Hydroxy-1,1-dimethoxy-6-phenyl-5-trimethylsilyl-4-hexene (15a) and (15b).** A solution of the mixed isomers **13a** and **13b** (1.3 g, 4.6 mmol) in anhydrous THF (25 mL) was cooled

to −78°C under nitrogen and 1.5 M tBuLi (6.7 mL, 9.7 mmol) was added with stirring. After 1 h at −78°C benzaldehyde (0.5 g, 0.5 mL 4.6 mmol) was added. Extraction with CH_2Cl_2 and concentration gave a colorless oil. This material was purified by preparative TLC (hexane 95%, EtOAc 5%). The major fraction was the isomer, **15a** (0.74 g, 2.4 mmol, 52%) and the minor fraction was the isomer, **15b** (0.15 g, 0.5 mmol, 11%). Spectral data for **15a.** IR (neat) 3450, 1600, 1100 cm^{-1}. ^1H NMR (90 MHz, $CDCl_3$): δ 7.3 (m, 5H), 5.9 (t, 1H, $J = 7.5$ Hz), 5.8 (s, 1H), 4.4 (t, 1H, $J = 6$ Hz), 3.3 (s, 6H), 3.2 (s, 1H), 2.2 (m, 2H), 1.8 (m, 2H), 0.1 (s, 9H). MS *m/z* 307, 218.

Spectral data for **15b.** IR (neat) 3400, 1600, 1240, 1120, 833 cm^{-1}. ^1H NMR (90 MHz, $CDCl_3$) δ 7.35 (m, 5H), 5.6 (m, 1H), 4.9 (m, 2H), 3.3 (s, 6H), 1.8 (m, 4H), 0.1 (s, 9H). MS *m/e* 307, 218.

***R,S*-1,1-Dimethoxy-6-phenyl-4,5-hexadiene (16) and 1,1-dimethoxy-6-phenyl-5-hexyne (17).** Potassium hydride (0.48 g, 12 mmol) was rinsed with anhydrous hexane and suspended in anhydrous THF. To this solution was added **15a** (1.08 g, 3.5 mmol) in anhydrous THF (5 mL). The reaction mixture was stirred for 2.5 h. TLC indicated that the reaction was complete at this time. Excess of MeOH (5 mL) was added and the mixture was concentrated to give 1.48 g of a colorless oil. This material was extracted into CH_2Cl_2 and purified by preparative TLC (95% hexane, 5% EtOAc). The less polar fraction was **16** (0.22 g, 1.0 mmol, 30%) and the more polar fraction was **17** (0.17 g, 0.8 mmol, 24%).

Spectral data for **16.** IR (neat) 1940, 1600, 1100 cm^{-1}. ^1H NMR (90 MHz, $CDCl_3$): δ 7.3 (m, 5H), 6.2 (quintet, 1H, $J^4 = 6.4$, $J^5 = 3.2$), 5.6 (q, 1H, $J = 6$ Hz), 4.4 (t, 1H, $J = 5$ Hz), 3.3 (s, 6H), 2.2 (m, 2H), 1.8 (m, 2H). MS *m/e* 218, 186, 143. Spectral data for **17.** IR (neat) 2804, 1600, 1490, 1125, 1065, 760, 695 cm^{-1}. ^1H NMR (90 MHz, $CDCl_3$): δ 7.29 (m, 5H), 4.4 (t, 1H, $J = 5$ Hz), 3.3 (s, 6H), 2.5 (t, 2H, $J = 6$H), 1.7 (m, 4H).

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