A Publication
of Reliable Methods
for the Preparation
of Organic Compounds

Working with Hazardous Chemicals

The procedures in *Organic Syntheses* are intended for use only by persons with proper training in experimental organic chemistry. All hazardous materials should be handled using the standard procedures for work with chemicals described in references such as "Prudent Practices in the Laboratory" (The National Academies Press, Washington, D.C., 2011; the full text can be accessed free of charge at http://www.nap.edu/catalog.php?record_id=12654). All chemical waste should be disposed of in accordance with local regulations. For general guidelines for the management of chemical waste, see Chapter 8 of Prudent Practices.

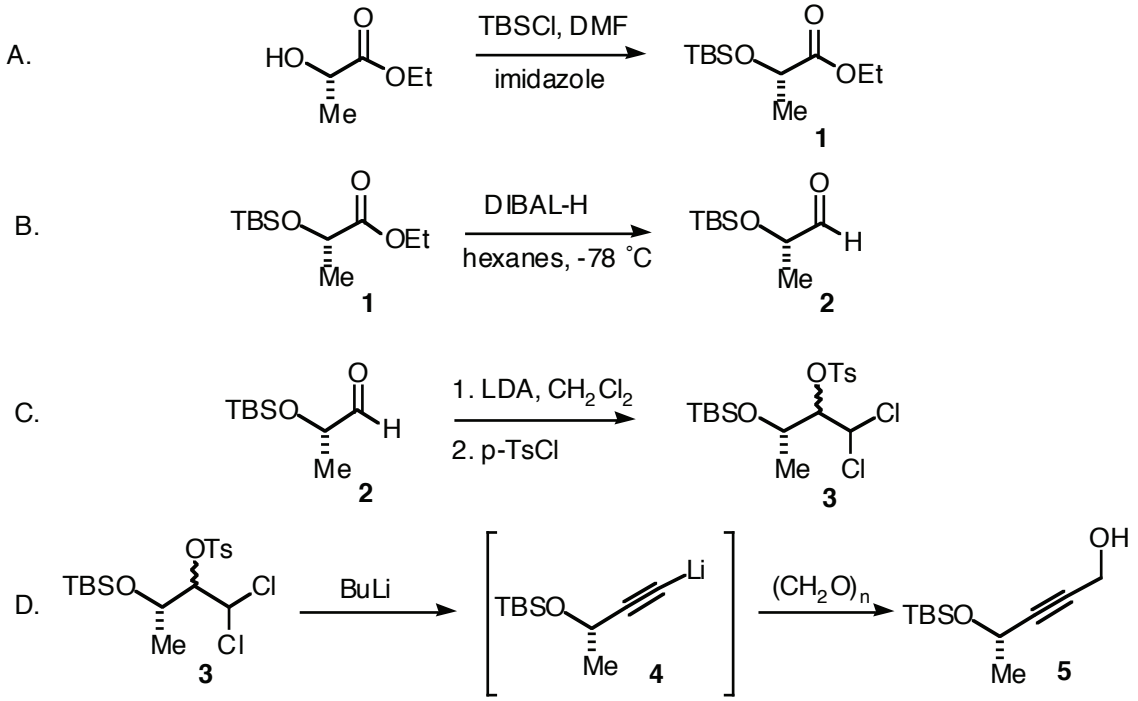
In some articles in *Organic Syntheses*, chemical-specific hazards are highlighted in red "Caution Notes" within a procedure. It is important to recognize that the absence of a caution note does not imply that no significant hazards are associated with the chemicals involved in that procedure. Prior to performing a reaction, a thorough risk assessment should be carried out that includes a review of the potential hazards associated with each chemical and experimental operation on the scale that is planned for the procedure. Guidelines for carrying out a risk assessment and for analyzing the hazards associated with chemicals can be found in Chapter 4 of Prudent Practices.

The procedures described in *Organic Syntheses* are provided as published and are conducted at one's own risk. *Organic Syntheses, Inc.*, its Editors, and its Board of Directors do not warrant or guarantee the safety of individuals using these procedures and hereby disclaim any liability for any injuries or damages claimed to have resulted from or related in any way to the procedures herein.

September 2014: The paragraphs above replace the section "Handling and Disposal of Hazardous Chemicals" in the originally published version of this article. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

DOI:10.15227/orgsyn.081.0157
Organic Syntheses, Vol. 81, p. 157-170 (2005); Coll. Vol. 11, p. 615-625 (2009).

GENERATION OF NONRACEMIC 2-(*t*-BUTYLDIMETHYLSILYLOXY)-3-BUTYNYLLITHIUM FROM (*S*)-ETHYL LACTATE: (*S*)-4-(*t*-BUTYLDIMETHYLSILYLOXY)-2-PENTYN-1-OL



Submitted by James A. Marshall, Mathew M. Yanik, Nicholas D. Adams, Keith C. Ellis, and Harry R. Chobanian.[1]
Checked by Venugopal Gudipati, Tiffany Turner, and Dennis P. Curran.

1. Procedure

A. (S)-Ethyl 2-(t-Butyldimethylsilyloxy)propanoate (**1**). A 2-L, two-necked, round-bottomed flask equipped with a mechanical stirrer and inert gas inlet (Note 1) is charged with (*S*)-ethyl lactate (118 g, 1.0 mol), 500 mL of dimethylformamide (DMF), and imidazole (102 g, 1.5 mol) (Note 2). The solution is cooled in an ice bath and *tert*-butyldimethylsilyl chloride

(TBDMSCl) (150 g, 1.0 mol) is added in three 50-g portions, at intervals of 30 min between each addition. After the addition of the third portion, a white precipitate forms. The ice bath is allowed to melt gradually overnight. After 18 h, the reaction mixture is diluted with 300 mL of water and 500 mL of hexanes. The aqueous phase is separated and extracted with 300 mL of hexanes, and the combined hexane extracts are washed with three 50-mL portions of saturated brine, dried over $MgSO_4$, filtered, and concentrated by rotary evaporation to afford 240 g (103%) of the TBDMS ether as a colorless liquid. The product is distilled under vacuum (bp 70-78 °C, 0.5 mmHg; bath temperature 95-105 °C) (Note 3) to afford 222 g (96%) of ester **1** as a colorless liquid (Notes 4, 5).

B. (S)-2-(t-Butyldimethylsilyloxy)propanal (**2**). A 2-L, single-necked, round-bottomed flask equipped with a large magnetic stirbar, rubber septum, and inert gas inlet (Note 1) is charged with (*S*)-ethyl 2-(*t*-butyldimethylsilyloxy)propanoate (**1**) (69.9 g, 300 mmol) and 600 mL of hexanes, and cooled in a dry ice-acetone bath at –78 °C. A 500-mL, round-bottomed flask equipped with a rubber septum and inert gas inlet is charged with 310 mL of DIBAL-H (1.0M in hexanes, 310 mmol) (Note 6) and cooled to –78 °C. The DIBAL-H solution is transferred by cannula into the well-stirred solution of ester over 20 to 25 min. After completion of the addition, the reaction mixture is stirred for 1 h at –78 °C and then quenched by addition of 30 mL of MeOH and stirred for 15 min at –78 °C. The cold solution is transferred to a 2-L flask equipped with a mechanical stirrer containing 600 mL of saturated Rochelle salt and the resulting mixture is vigorously stirred for 3.5 h (Note 7). The aqueous phase is separated and extracted with 200 mL of hexanes, and the combined organic extracts are washed with 100 mL of saturated brine, dried over $MgSO_4$, filtered, and concentrated by rotary evaporation (Note 8). After removal of the solvent, the residue is distilled (bp 45-52 °C, 0.5 mmHg, bath temperature 65-80 °C) to afford 50.3-50.9 g (91-92%) of aldehyde **2** as a colorless oil (Notes 9, 10).

C. 1,1-Dichloro-(3S)-(t-butyldimethylsilyloxy)-2-butyl p-toluene-sulfonate (**3**). A 2-L, single-necked, round-bottomed flask equipped with a large magnetic stirbar and a 500-mL pressure equalizing addition funnel (Note 1) is charged with aldehyde **2** (44.3 g, 235 mmol), dichloromethane (45.0 mL, 705 mmol), and 500 mL of tetrahydrofuran (Note 11) and the mixture is cooled in a dry ice-acetone bath at –78 °C. A 500-mL, three-necked, round-bottomed flask equipped with a magnetic stirbar, a graduated 150-mL pressure-equalizing addition funnel, and two rubber septa is charged with 250 mL of THF and diisopropylamine (49.3 mL, 376 mmol) and then cooled with an ice bath. The addition funnel on the 500-mL flask is charged with 141 mL of BuLi solution (2.5M in hexanes, 352 mmol) which is added dropwise to the solution of amine over 30 min. The resulting solution of LDA is transferred by cannula to the addition funnel on the 2-L flask, and this solution is added dropwise over 1 h to the reaction mixture, resulting in a color change to light yellow. After 30 min, the mixture is warmed to 0 °C for 30 min with a change in color to dark brown. The addition funnel is replaced with a rubber septum, and *p*-toluenesulfonyl chloride (44.8 g, 235 mmol) is added in one portion through a funnel. After 10 min, the ice bath is removed and the mixture is stirred for 1.5 h. The reaction is quenched by addition of 10 mL of water, stirred for 30 min, and then transferred to a separatory funnel and extracted with 250 mL of 10% HCl and 150 mL of 1N NaOH solution. Each of these aqueous extracts is separately back-extracted with 500 mL of Et_2O, and the combined organic phases are washed with 100 mL of brine, dried over $MgSO_4$, and filtered into a 1-L, round-bottomed flask for use in the next step. The solvent is removed under reduced pressure whereupon 80-85 g of the dichloro tosylate **3** is obtained as a dark brown oil which is used in the next step without purification (Note 12).

D. (S)-4-(t-Butyldimethylsilyloxy)-2-pentynol (**5**). THF (500 mL) is added to tosylate **3** (76 g, *ca* 177 mmol) prepared as described above, and the 1-L flask is equipped with a large magnetic stirbar and a pressure-equalizing addition funnel fitted with a nitrogen inlet. The solution is cooled in a dry ice-acetone bath at –78 °C for 20 min and the addition funnel is charged with 219 mL of BuLi solution (2.5M in hexanes, 548 mmol) which is then added dropwise over ca. 1 h to the reaction mixture. When the addition is complete, the solution is stirred for 30 min at –78 °C and warmed over 1 h to 0 °C. The reaction mixture is then recooled to –78 °C. To the

resulting black solution of lithium acetylide **4** is then added paraformaldehyde (10.6 g, 354 mmol) (Note 13) in one portion. After 15 min, the mixture is allowed to warm to room temperature over 4 h during which time the suspension of paraformaldehyde gradually dissolves. The reaction is quenched by addition of 200 mL of aqueous ammonium chloride solution, and the aqueous layer is separated and extracted with three 200-mL portions of Et_2O. The combined organic extracts are washed with 100 mL of 1N NaOH and 50 mL of brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure to give the desired product contaminated with *tert*-butyldimethylsilanol. The product is purified by fractional distillation (Note 14) to give 21-24 g (44-53% overall from aldehyde **2**) of the alcohol **5** as a colorless oil (Notes 15, 16).

2. Notes

1. All glassware and needles were dried in an oven at 120 °C overnight and assembled under a nitrogen purge or flame-dried immediately prior to use. All reactions were performed under nitrogen (submitters) or argon (checkers).

2. (*S*)-Ethyl lactate (98%) and imidazole (99+%) were purchased from Aldrich Chemical Co. TBDMSCl was purchased from FMC Corporation (submitters) or Aldrich (checkers). A newly opened bottle of dimethylformamide (ACS Reagent grade, 0.02% water) was used as received.

3. The distillation was conducted in a 500-mL, round bottomed flask equipped with a magnetic stirring bar and a variable take-off distillation head.

4. The ester **1** displayed the following properties: $[\alpha]_D$ –25.9 (c 1.56, $CHCl_3$); IR (thin film): cm^{-1} 1753; ^1H NMR (300 MHz, $CDCl_3$) δ: 0.05 (s, 3H), 0.08 (s, 3H), 0.88 (s, 9H), 1.23 (t, J = 7.2 Hz, 3H), 1.36 (d, J = 6.6 Hz, 3H), 4.11 (m, 1H), 4.25 (q, J = 7.2 Hz, 2H); ^{13}C NMR (75 MHz,$CDCl_3$) δ: –5.3, –4.9, 14.2, 18.3, 21.3, 25.7, 60.7, 68.4, 174.1.

5. The submitters report that by the same procedures without modifications the (*R*)-enantiomer can be prepared from (*R*)-isobutyl lactate,

available from Sigma Chemical Co. The physical properties for (*R*)-isobutyl 2-(*t*-butyldimethylsilyloxy)-propanoate are: bp 85-88 °C, 0.1 mmHg; $[\alpha]_D$ +28.7 (c 1.61, $CHCl_3$); IR (thin film) 1763 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 0.06 (s, 3H), 0.09 (s, 3H), 0.89 (s, 9H), 0.91 (d, *J* = 6.6 Hz, 6H), 1.38 (d, *J* = 6.6 Hz, 3H), 1.94 (septet, 1H), 3.88 (dq, *J* = 10.5, 6.9 Hz, 2H), 4.28 (q, *J* = 6.6 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: –5.4, –5.0, 18.3, 19.0, 21.4, 25.7, 27.7, 68.4, 70.8, 174.1

6. DIBAL-H (1.0M in hexanes) was purchased from Aldrich Chemical Co. Hexanes from a freshly opened bottle (ACS Reagent Grade) was used as solvent.

7. Potassium sodium tartrate (Rochelle salt) was purchased from Fluka (purum p.a. grade). The quantity of salt solution specified was found to be optimal (2 mL/mmol of DIBAL-H). Use of less salt resulted in incomplete complexation. The submitters reported similar yields with stirring overnight.

8. Concentration is carried out without heating. Heating the rotary evaporator bath above 35 °C results in lower yields due to the volatility of the aldehyde.

9. The aldehyde contains small amounts of the starting ester and the overreduced alcohol along with other minor impurities. It can be stored for short periods of time (1-2 days) in a freezer at –20 °C without significant deterioration. However long term storage is not recommended.

10. The enantiomeric excess of aldehyde **2** was estimated to be >96% by derivatization as the Schiff bases with (*S* and *R*)-α-methylbenzylamine as described below. Spectral characteristics for aldehyde **2**: $[\alpha]_D$ –12.1 (c 1.96, $CHCl_3$); IR (thin film): cm^{-1} 1741; ^1H NMR (300 MHz, $CDCl_3$) δ: 0.07 (s, 3H), 0.08 (s, 3H), 0.9 (s, 9H), 1.26 (d, *J* = 6.9 Hz, 3H), 4.07 (dq, *J* = 6.9, 1.3 Hz, 1H), 9.59 (d, *J* = 1.3 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: –4.8, 18.1, 18.5, 25.6, 73.8, 204.2.

(S) and (*R*)-α-*Methylbenzylimines of (S)-4-(t-Butyldimethylsilyloxy) propanal.* To a solution of (*S*)-aldehyde **2** (0.150 g, 0.74 mmol), 4Å molecular sieves (0.100 g), in 1 mL of CH_2Cl_2 was added (*S*)-α-methylbenzylamine (100 μL, 0.77 mmol, Aldrich, 98% ee by GLC analysis). After 2 h, the mixture was filtered through Celite, rinsed with CH_2Cl_2, and concentrated affording the (*S*,*S*)-imine as a colorless oil (0.215 g, 95%). The imine from (*R*)-α-methylbenzylamine (96% ee by GLC analysis) was prepared in identical fashion. The ratio of diastereoisomers determined through integration of the ^{1}H NMR spectra was 98:2 for the (*S*,*S*) derivative and 96.5:3.5 for the (*S*,*R*) derivative. **(*S*,*S*) Imine**: $[\alpha]_D$ –55.2 (c 1.20, $CHCl_3$); IR (thin film) 2968, 2951, 2864, 1675 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 0.11 (s, 6H), 0.93 (s, 9H), 1.26, (d, *J* = 6.3 Hz, 3H), 1.50 (d, *J* = 6.6 Hz, 3H), 4.29 (q, *J* = 6.6 Hz, 1H), 4.38 (q, *J* = 6.3 Hz, 1H), 7.24-7.34 (m, 5H), 7.62 (d, *J* = 5.4 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: –4.7, –4.6, 18.2, 21.8, 24.3, 25.8, 68.9, 70.7, 126.5, 126.8, 128.4, 144.6, 166.4. **(*S*,*R*) Imine**: $[\alpha]_D$ +46.2 (c 1.20 $CHCl_3$); ^{1}H NMR δ: –0.03 (s, 3H), 0.03 (s, 3H), 0.85 (s, 9H), 1.29 (d, *J* = 6.6 Hz, 3H), 1.48 (d, *J* = 6.6 Hz, 3H), 4.27 (q, *J* = 6.6 Hz, 1H), 4.32 (qd, *J* = 6.6 Hz, 5.4 Hz, 1H), 7.23-7.40 (m, 5H), 7.59 (d, *J* = 5.4 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: –4.8, –4.7, 18.1, 21.7, 24.2, 25.8, 68.9, 70.7, 126.5, 126.8, 128.3, 144.4, 166.2.

11. THF (99.9% anhydrous, inhibitor free) and CH_2Cl_2 (99.8% anhydrous) were obtained from Aldrich Chemical Co. and used as received. The submitters distilled diisopropylamine and stored it over KOH. The checkers used 99.5% diisopropylamine as received from Aldrich. *p*-Toluenesulfonyl chloride (99%) was obtained from Acros Chemical Co. (submitters) or Avocado (checkers).

12. This material consisted of a 45:55 mixture of diastereomers based on ^{1}H NMR analysis. R_f = 0.53 (10% EtOAc/hexanes, phosphomolybdic acid stain). Spectral characteristics for tosylate **3**: ^{1}H NMR (300 MHz, $CDCl_3$) δ: 0.08 (s, 6H), 0.09 (s, 6H), 0.88 (s, 18H), 1.24 (d, *J* = 6.3 Hz, 3H), 1.29 (d, *J* = 6.0 Hz, 3H), 2.44 (s, 6H), 4.04 (dq, *J* = 6.0, 7.5 Hz, 1H), 4.34 (dq, *J* = 3.3, 6.3 Hz, 1H), 4.70 (dd, *J* = 3.3, 6.0 Hz, 1H), 4.74 (dd, *J* = 2.1, 7.2 Hz, 1H), 5.81 (d, *J* = 6.3 Hz, 1H), 6.00 (d, *J* = 2.1 Hz, 1H),7.31 (d, *J* = 8.4 Hz, 4H), 7.82 (dd, *J* = 5.4, 8.4 Hz, 4H).

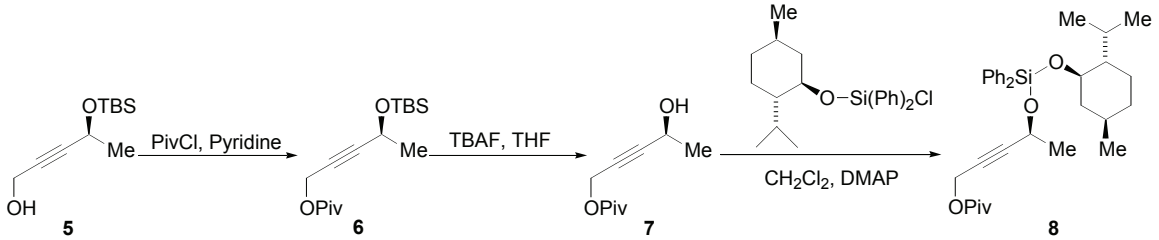
13. Paraformaldehyde (95%) was obtained from Aldrich Chemical Co. (submitters) or Baker (checkers) and was dried azeotropically with

benzene by concentrating a benzene solution (100 mL per gram of paraformaldehyde) at 45 °C by rotary evaporation, repeating this process, and then drying the residue under high vacuum overnight. Dry paraformaldehyde was stored in a sealed container under argon. Butyllithium was obtained from Acros Chemical Co (submitters) or Aldrich (checkers).

14. The submitters reported that an immediate preliminary distillation is advisable to minimize contact time with the dark polymeric byproducts which results in decomposition and lowered yields. This is achieved by means of a Kugelrohr distillation apparatus preheated to 80 °C. Care should be exercised to prevent bumping in the early stage of this distillation. However, the checkers had problems with bumping and preferred direct fractional distillation according to the following procedure. After concentration, the flask containing the crude product was equipped with a 30 x 1.5 cm distillation column and evacuated at 0.1 mm. After an initial period of distillation at room temperature to remove residual solvent, a first fraction of bp up to 45 °C was collected; this is believed to be TBSOH. The main product fraction (21-24 g) was collected at bp 79-82 °C.

15. The ee of alcohol **5** was determined to be >97% by derivatization with a chiral silylating reagent (Note 16). Physical characteristics for alcohol **5**: R_f = 0.42 (25% EtOAc/hexanes, phosphomolybdic acid); $[\alpha]_D$ –53.0 (c 1.42, $CHCl_3$); IR (thin film): cm^{-1} 3370; ^1H NMR (300 MHz, $CDCl_3$): δ 0.09 (s, 3H), 0.11 (s, 3H), 0.89 (s, 9H), 1.39 (d, *J* = 6.5 Hz, 3H), 2.44 (t, *J* = 6.2 Hz, 1H), 4.27 (dd, *J* = 6.2, 1.7 Hz, 2H), 4.54 (tq, *J*= 6.5, 1.7 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: –5.0, –4.7, 18.2, 25.2, 25.7, 50.8, 59.0, 81.4, 88.0.

16. The enantiomeric purity of alcohol 5 was determined by conversion to the silyl ether 8 via the following sequence:



5 **6** **7** **8**

To a solution of (*S*)-pentynol **5** (0.107 g, 0.50 mmol) in pyridine (2.4 mL) is added trimethylacetyl chloride (PivCl, 0.1 mL, 0.8 mmol) (Note 17). After 3 h, ice (*ca* 3 g) is added and the mixture is stirred vigorously. After 1 h, 10% aqueous HCl (5 mL) is added and the resulting mixture is extracted with three 10-mL portions of ethyl acetate. The combined organic extracts are washed with 20 mL of brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue is purified by chromatography on silica gel (elution with 1% EtOAc/hexanes) to afford 0.129 g (87%) of ester **6** (Note 18).

To a solution of (*S*)-ester **6** (0.566 g, 1.90 mmol) in 20 mL of THF at 0 °C is added tetrabutylammonium fluoride (3.0 mL, 3.0 mmol) (Note 19). After 15 min, the reaction mixture is warmed to room temperature. After 3 h, 20 mL of aqueous saturated NH_4Cl is added and the mixture is extracted with three 10-mL portions of Et_2O. The combined organic extracts are washed with 20 mL of brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue is purified by chromatography on silica gel (elution with 20% EtOAc/hexanes) to afford 0.271 g (78%) of alcohol **7** (Note 20).

To a solution of (*S*)-alcohol **7** (0.052 g, 0.28 mmol) in 2.8 mL of CH_2Cl_2 is added (–)-chloromenthyloxydiphenylsilane (0.105 g, 0.28 mmol) (Note 21) followed by DMAP (0.035 g, 0.29 mmol). After 2 h, the mixture is concentrated and the residue is purified by chromatography on silica gel (elution with 1% EtOAc/hexanes) to afford 0.112 g (76%) of silylmenthol derivative **8**. The identical procedures are employed with the (*R*)-pentynol (Note 22).

17. Pyridine was freshly distilled from calcium hydride and stored under nitrogen over potassium hydroxide. Trimethylacetyl chloride (99%) was obtained from Aldrich Chemical Company and used as received.

18. Physical characteristics of (*S*)-ester **6**: R_f = 0.83 (25% EtOAc/hexanes, cerium molybdate); $[\alpha]_D$ –36.0 (*c* 0.79, $CHCl_3$); IR (thin film): cm^{-1} 2968, 1745; ^1H NMR (500 MHz, $CDCl_3$) δ: 0.11 (s, 3H), 0.13 (s, 3H), 0.90 (s, 9H), 1.21 (s, 9H), 1.40 (d, J = 6.5 Hz, 3H), 4.55 (qt, J = 6.0, 2.0 Hz, 1H), 4.68 (d, J = 2.0 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: –5.0, –4.6, 18.2, 25.1, 25.8, 27.1, 38.7, 52.3, 58.9, 77.5, 88.9, 177.7.

19. Tetrabutylammonium fluoride (1.0M in THF) was obtained from Aldrich Chemical Company and used as received.

20. Physical characteristics of (*S*)-alcohol **7**: R_f = 0.30 (25% EtOAc/hexanes, cerium molybdate); IR (thin film): cm^{-1} 3440, 2986, 1745; $[\alpha]_D$ –18.1 (*c* 1.2, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ: 1.22 (s, 9H), 1.46 (d, *J* = 7.0 Hz, 3H), 4.57 (dq, *J* = 1.5 Hz, 6.5 Hz, 1H), 4.69 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 24.0, 27.0, 38.7, 52.2, 58.3, 78.3, 88.2, 177.9.

21. The (–)-chloromenthyloxydiphenylsilane was prepared from (–)-menthol (Aldrich, >99% ee) according to the published procedure: Weibel, D. B.; Walker, T. R.; Schroeder, F. C.; Meinwald, J. *Org. Lett.* **2000**, *2*, 2381.

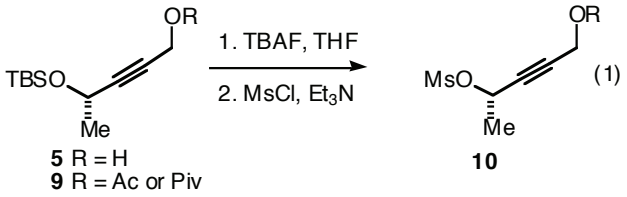
22. Diagnostic ^1H NMR peaks (singlets) are located at δ 4.62 (*S*) and δ 4.57 (*R*) ppm, respectively, in the ^1H NMR spectra of the crude products prior to chromatography. Physical characteristics of the (*S*)-silylmenthyl derivative **8**: R_f = 0.67 (25% EtOAc/hexanes, cerium molybdate); $[\alpha]_D$ –73.5 (*c* 0.63, $CHCl_3$); IR (thin film): cm^{-1} 2960, 1745; ^1H NMR (500 MHz, $CDCl_3$) δ: 0.56 (d, *J* = 6.9 Hz, 3H), 0.87 (d, *J* = 6.3 Hz, 3H), 0.90 (d, *J* = 7.2 Hz, 3H), 0.80-0.94 (m, 2H), 1.22 (s, 9H), 1.12-1.33 (m, 3H), 1.42 (d, *J* = 6.6 Hz, 3H), 1.56-1.62 (m, 2H), 2.09 (m, 1H), 2.33 (m, 1H), 3.63 (dt, *J* = 10.2, 4.2 Hz, 1H), 4.62 (d, *J* = 1.5 Hz, 2H), 4.72 (dq, *J* = 6.6, 1.5 Hz, 1H), 7.33-7.46 (m, 6H), 7.65-7.70 (m, 4H); ^{13}C NMR (125 MHz $CDCl_3$) δ: 15.6, 21.3, 22.3, 22.6, 24.9, 25.3, 27.1, 31.5, 34.4, 38.7, 45.2, 50.0, 52.3, 59.2, 73.5, 77.8, 88.4, 127.6, 130.1, 133.1, 133.5, 135.1, 177.8. (*R*)-silylmenthyl derivative: $[\alpha]_D$ +1.1 (*c* 0.94, $CHCl_3$); IR (thin film): cm^{-1} 2957, 1739; ^1H NMR (300 MHz, $CDCl_3$) δ: 0.59 (d, *J* = 7.2 Hz, 3H), 0.85 (d, *J* = 6.3 Hz, 3H), 0.91 (d, *J* = 7.2 Hz, 3H), 0.79-0.92 (m, 2H), 1.12 (apparent q, *J* = 12.0 Hz, 1H) 1.21 (s, 9H), 1.24-1.34 (m, 2H), 1.46 (d, *J* = 6.3 Hz, 3H), 1.56-1.62 (m, 2H), 2.02 (m, 1H), 2.38 (m, 1H), 3.64 (dt, *J* = 10.2, 4.2 Hz, 1H), 4.57 (d, *J* = 1.5 Hz, 2H), 4.73 (qt, *J* = 6.6, 1.5 Hz, 1H), 7.33-7.45 (m, 6H), 7.64-7.72 (m, 4H); ^{13}C NMR (125 MHz $CDCl_3$) δ: 15.6, 21.3, 22.2, 22.6, 24.9, 25.3, 27.1, 31.5, 34.4, 38.7, 45.2, 50.0, 52.3, 59.2, 73.6, 77.8, 88.3, 127.6, 130.1, 133.3, 135.1, 177.7.

Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

3. Discussion

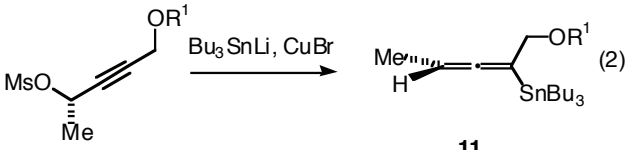
The present route to (*S*)-4-(*t*-butyldimethylsilyloxy)-2-pentyn-1-ol is based on a procedure for the preparation of terminal alkynes reported by a group from the Chemical Process Department at the DuPont Pharmaceutical Company.[2] This alcohol serves as a convenient starting material for the preparation of 1-acyloxy 4-mesylates **10** (eq 1).



5 R = H
9 R = Ac or Piv

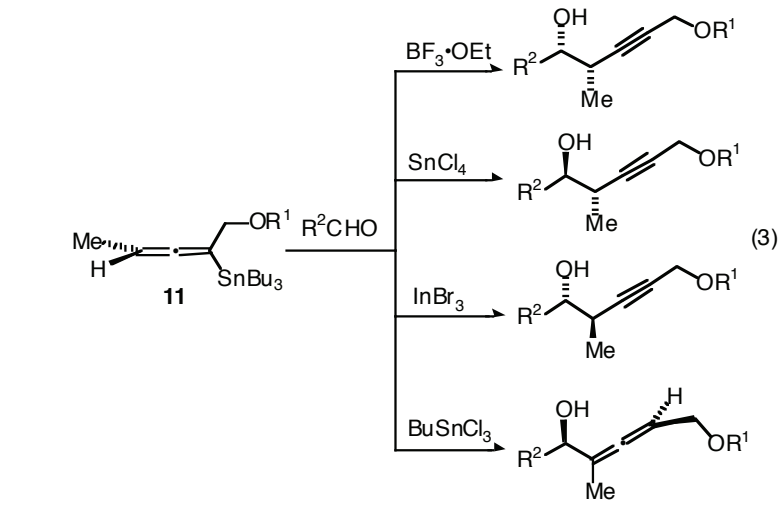
10

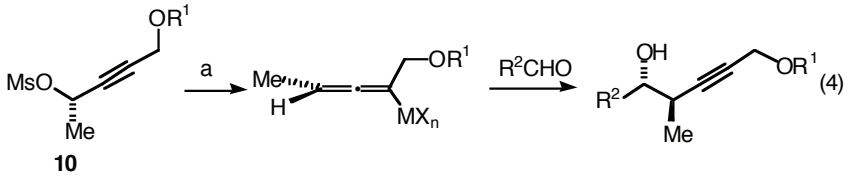
These mesylates, in turn, can be converted to enantioenriched allenyltin, zinc, and indium reagents which add to aldehydes with excellent diastereo-and enantioselectivity to afford either syn- or anti-homopropargylic alcohols or allenylcarbinols (eq 2, 3, and 4). [3,4] Adducts of this type serve as useful intermediates for the synthesis of polyketide and hydrofuran natural products.[5]



10

11

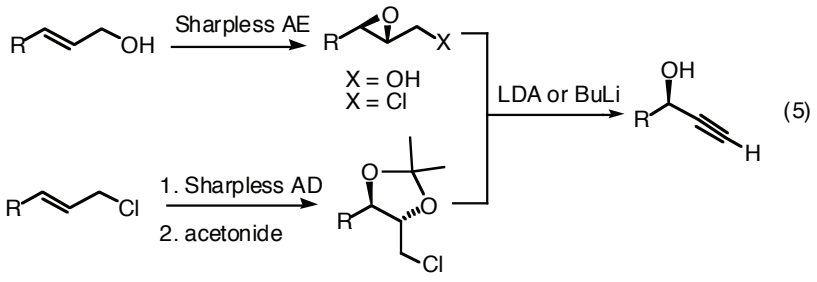




10

a. $Pd(OAc)_2$, Ph_3P, Et_2Zn (MX_n = ZnOMs); $Pd(dppf)_2$, InI (MX_n = In(OMs)I

Previous syntheses of terminal alkynes from aldehydes employed Wittig methodology with phosphonium ylides and phosphonates.[6,7] The DuPont procedure circumvents the use of phosphorus compounds by using lithiated dichloromethane as the source of the terminal carbon. The intermediate lithioalkyne **4** can be quenched with water to provide the terminal alkyne or with various electrophiles, as in the present case, to yield propargylic alcohols, alkynylsilanes, or internal alkynes. Enantioenriched terminal alkynylcarbinols can also be prepared from allylic alcohols by Sharpless epoxidation and subsequent basic elimination of the derived chloro- or bromomethyl epoxide (eq 5). A related method entails Sharpless asymmetric dihydroxylation of an allylic chloride and base treatment of the acetonide derivative.[8] In these approaches the product and starting material contain the same number of carbons.


R
OH
Sharpless AE
R
O
X
X = OH
X = Cl
LDA or BuLi
OH
R
H
(5)
R
Cl
1. Sharpless AD
2. acetonide
O
O
R
Cl

1. Department of Chemistry, McCormick Road, P.O. Box 400319, University of Virginia, Charlottesville, VA 2290, E-mail: jam5x@virginia.edu.

2. Wang, Z.; Yin, J.; Campagna, S.; Pesti, J. A.; Fotunak, J. M. *J. Org. Chem.* **1999**, *64*, 6918.

3. a) Marshall, J. A. *Chem. Rev.* **1996**, *96*, 31. (b) Marshall, J. A. in "Lewis Acids in Organic Synthesis," H. Yamamoto Ed., Vol. 1, Wiley-VCH, Weinheim, (**2000**). Chapter 10, pp. 453-520.

4. Marshall, J. A. *Chem. Rev.* **2000**, *100*, 3163.

5. a) Marshall, J. A.; Lu, S.-H.; Johns, B. A. *J. Org. Chem.* **1998**, *63*, 817. b) Marshall, J. A.; Palovich, M. R. *J. Org. Chem.* **1998**, *63*, 3701. c) Marshall, J. A.; Johns, B. A. *J. Org. Chem.* **1998**, *63*, 7885. d) Marshall, J. A.; Fitzgerald, R. A. *J. Org. Chem.* **1999**, *64*, 4477. e) Marshall, J. A.; Johns, B. A. *J. Org. Chem.* **2000**, *65*, 1501. f) Marshall, J. A.; Yanik, M. M. *J. Org. Chem.* **2001**, *66*, 1373.

6. a) Horner, L.; Hoffmann, H.; Wippel, H. G.; Klaher, G. *Chem. Ber.* **1959**, 2499. b) Wadsworth, W. S. Jr.; Emmons, W. D. *J. Am. Chem. Soc.* **1961**, *83*, 1733. c) Corey, E. J.; Achiwa,K.; Katzenellenbogen, J. A. *J. Am. Chem. Soc.* **1969**, *91*, 4318. d) Corey, E. J.; Fuchs, P. L. *Tetrahedron Lett.* **1972**, 3769. e) Gilbert, J. C.; Weerasooriya, U. *J. Org. Chem.* **1982**, *47*, 1837. f) Muller, S.; Liepold, B.; Roth, G. J.; Bestmann, H. J. *Syn Lett* **1996**, 521.

7. a) For a previous synthesis of the pivalic ester related to mesylate **10** from *(R)*-methyl lactate and $Ph_3P{=}CBr_2$, see Marshall, J. A.; Xie, S. *J. Org. Chem.* **1995**, *60*, 7230. b) An analogous synthesis of *(S)*-3-butyn-2-ol derivatives has also been reported; Ku, Y.-Y.; Patel, R. R.; Elisseou, E. M.; Sawick, D. P. *Tetrahedron Lett.* **1995**, 36*, 2738*.

8. a) Yadav, J. S.; Chander, M. C.; Rao, C. S. *Tetrahedron Lett.* **1989**, *30*, 5455. b) Yadav, J. S.; Chander, M. C.; Joshi, R. V. *Tetrahedron Lett.* **1988**, *29*, 2737.

Appendix
Chemical Abstracts Nomenclature (Registry Number)

(*S*)-Ethyl lactate: Propanoic acid, 2-hydroxy-, ethyl ester, (2*S*)-; (687-47-8)

Imidazole: 1*H*-Imidazole; (288-32-4)

tert-Butyldimethylsilyl chloride; Silane, chloro(1,1-dimethylethyl)dimethyl-; (18162-48-6)

(*S*)-Ethyl 2-(*tert*-butyldimethylsilyloxy)propanoate: Propanoic acid, 2-[[(1,1-dimethylethyl) dimethylsilyl]oxy], ethyl ester; (106513-42-2)

DIBAL-H: Diisobutylaluminum hydride; Aluminum, hydrobis(2-methylpropyl)-; (1191-15-7)

Rochelle salt: Butanedioic acid, 2,3-dihydroxy-(2R,3R)-, monopotassium monosodium salt ; (304-59-6)

(*S*)-2-(*tert*-Butyldimethylsilyloxy)propanal: Propanal, 2-[[(1,1-dimethylethyl)dimethyl silyl]oxy]-, (2S)-; (87727-28-4)

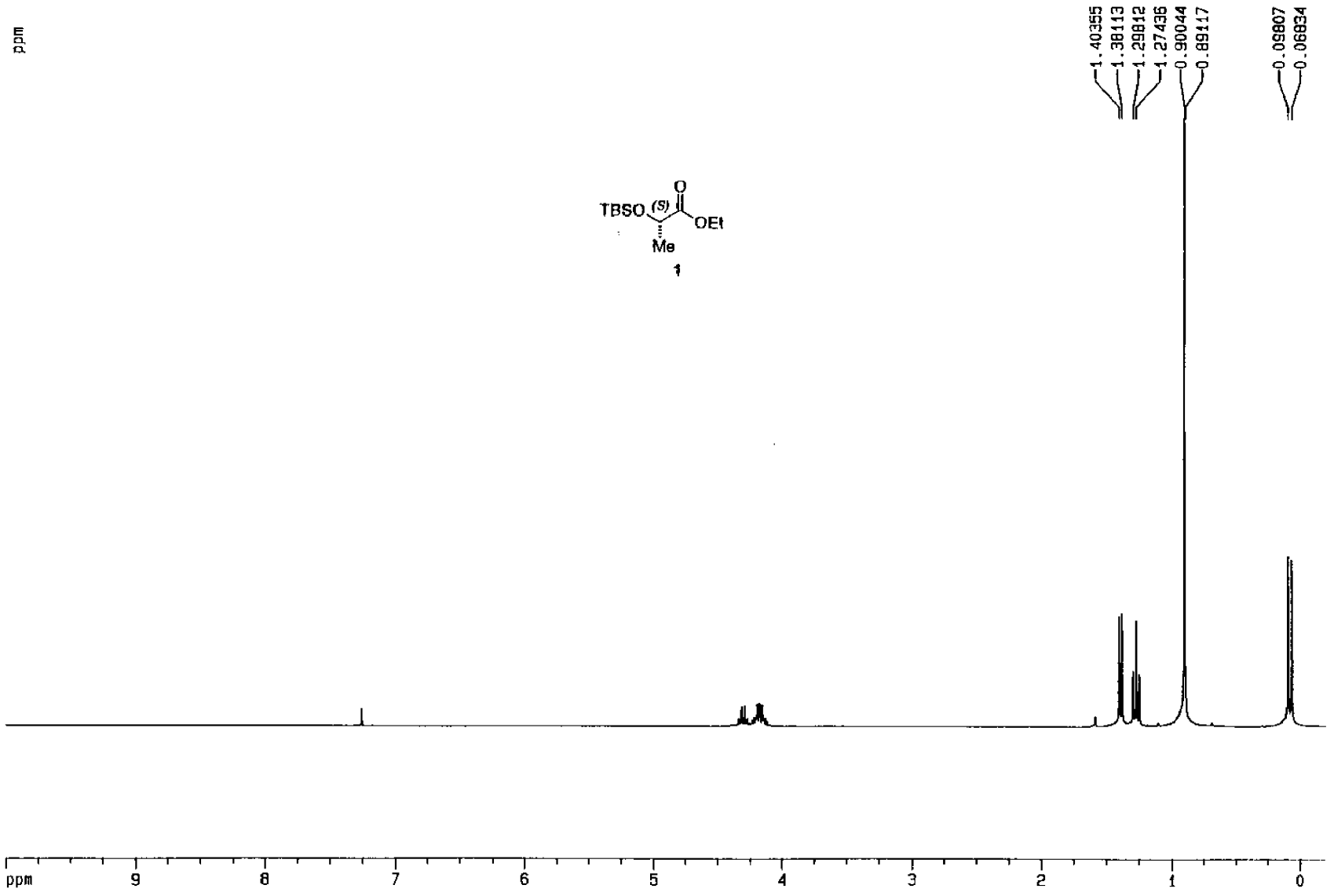
1,1-Dichloro-(3*S*)- (*tert*-butyldimethylsilyloxy)-2-butyl p-toluenesulfonate: 2-Butanol, 1,1-dichloro-3-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-, 4-methylbenzene sulfonate, (3*S*)-; (329914-17-2)

Diisopropylamine: 2-Propanamine, *N*-(1-methylethyl)-; (109-72-8)

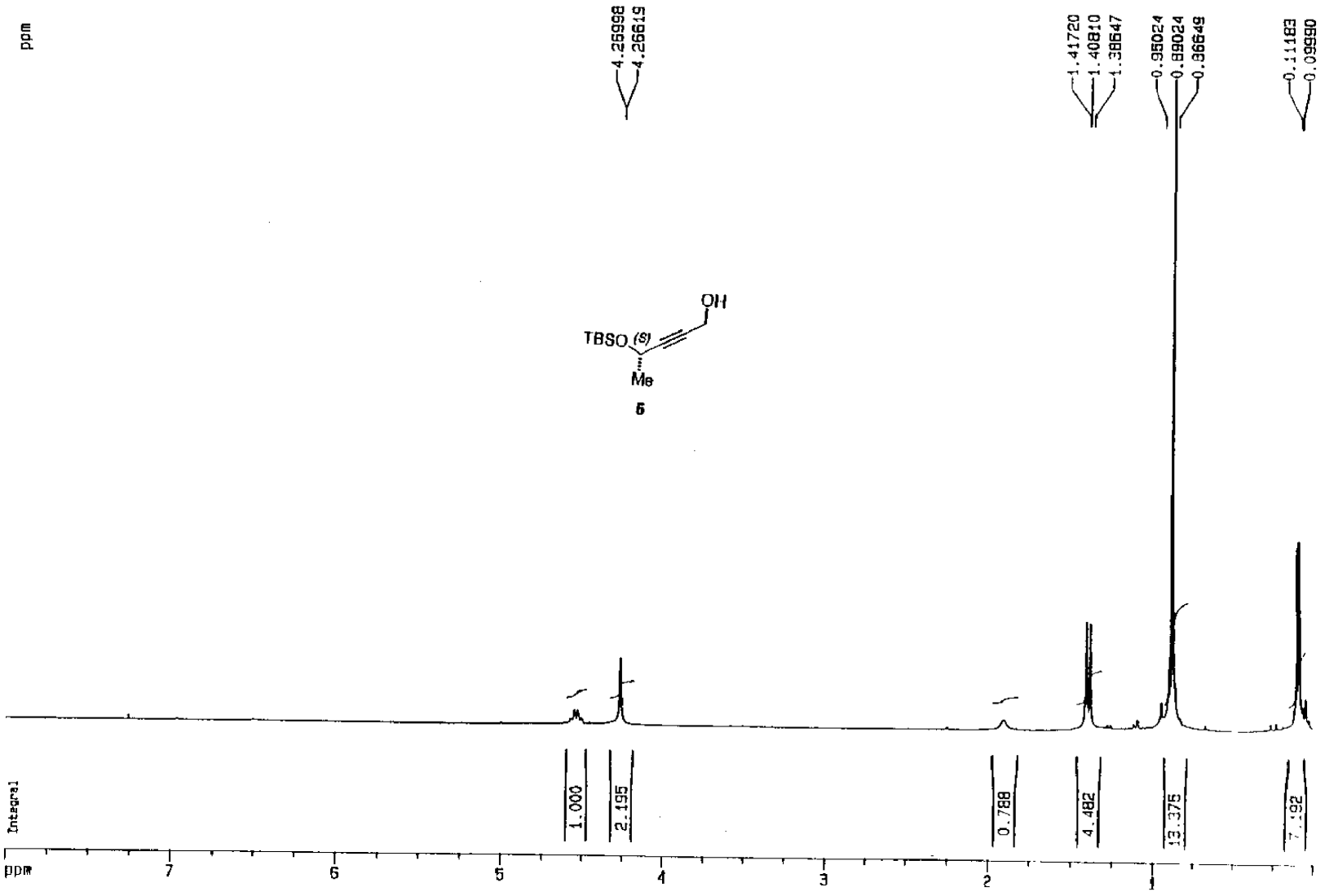
Butyllithium; Lithium, butyl-; (109-72-8)

Lithium diisopropylamide: 2-Propanamine, *N*-(1-methylethyl)-, lithium salt; (4111-54-0)

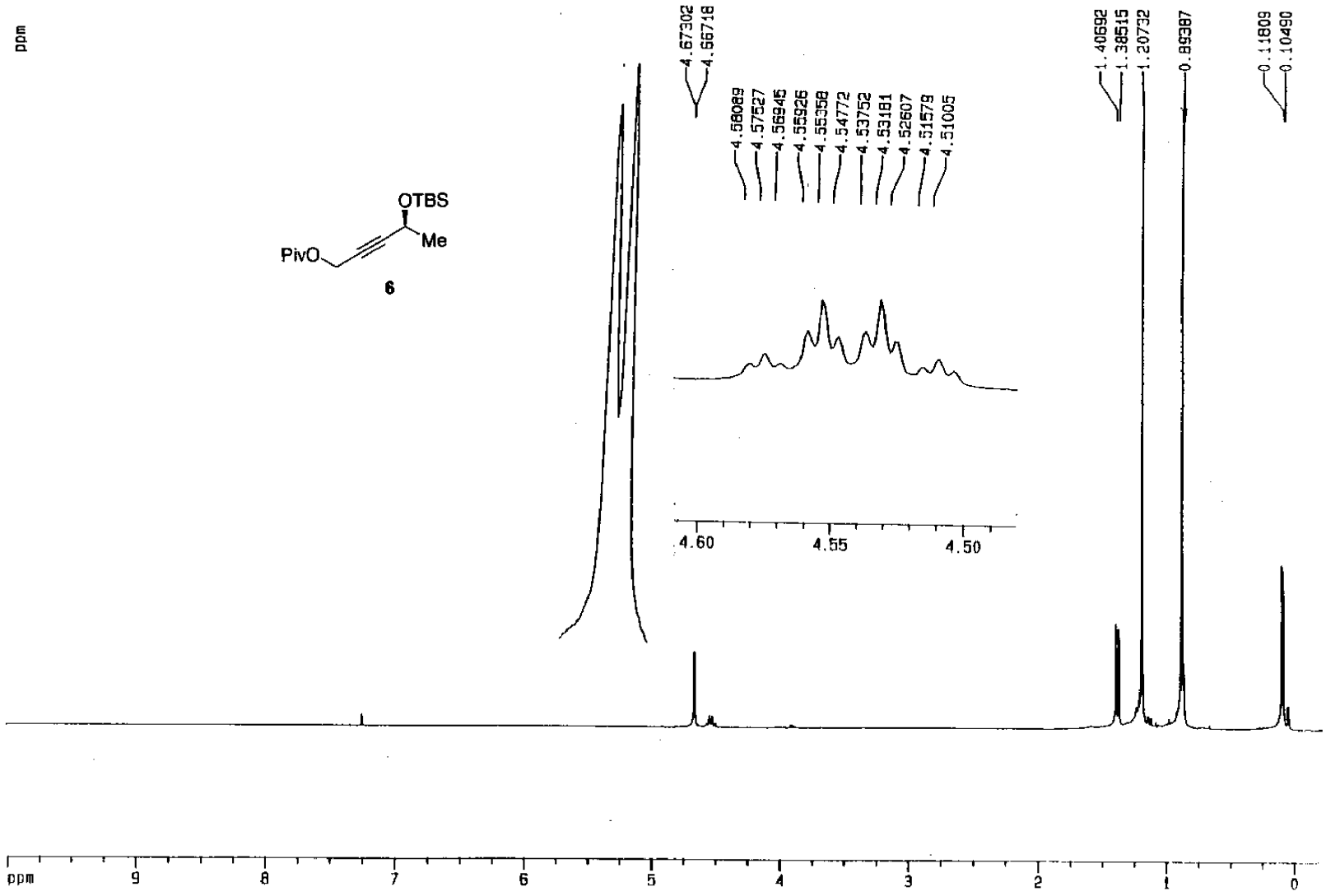
p-Toluenesulfonyl chloride: Benzenesulfonyl chloride, 4-methyl-; (98-59-9)

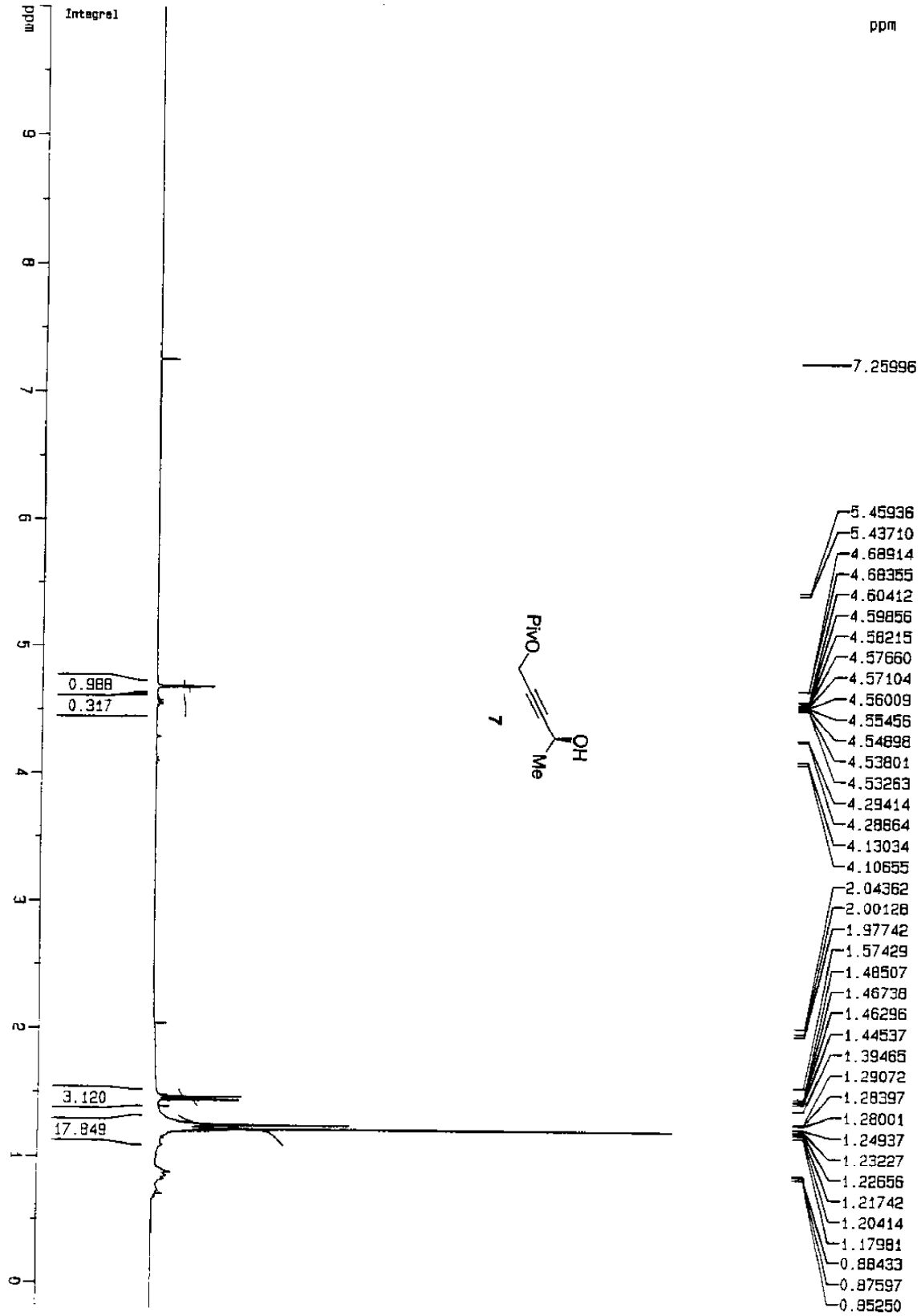

ppm
1.40355
1.38113
1.29812
1.27436
0.90044
0.89117
0.09807
0.06834
TBSO
(S)
OEt
Me
1
ppm
9
8
7
6
5
4
3
2
1
0

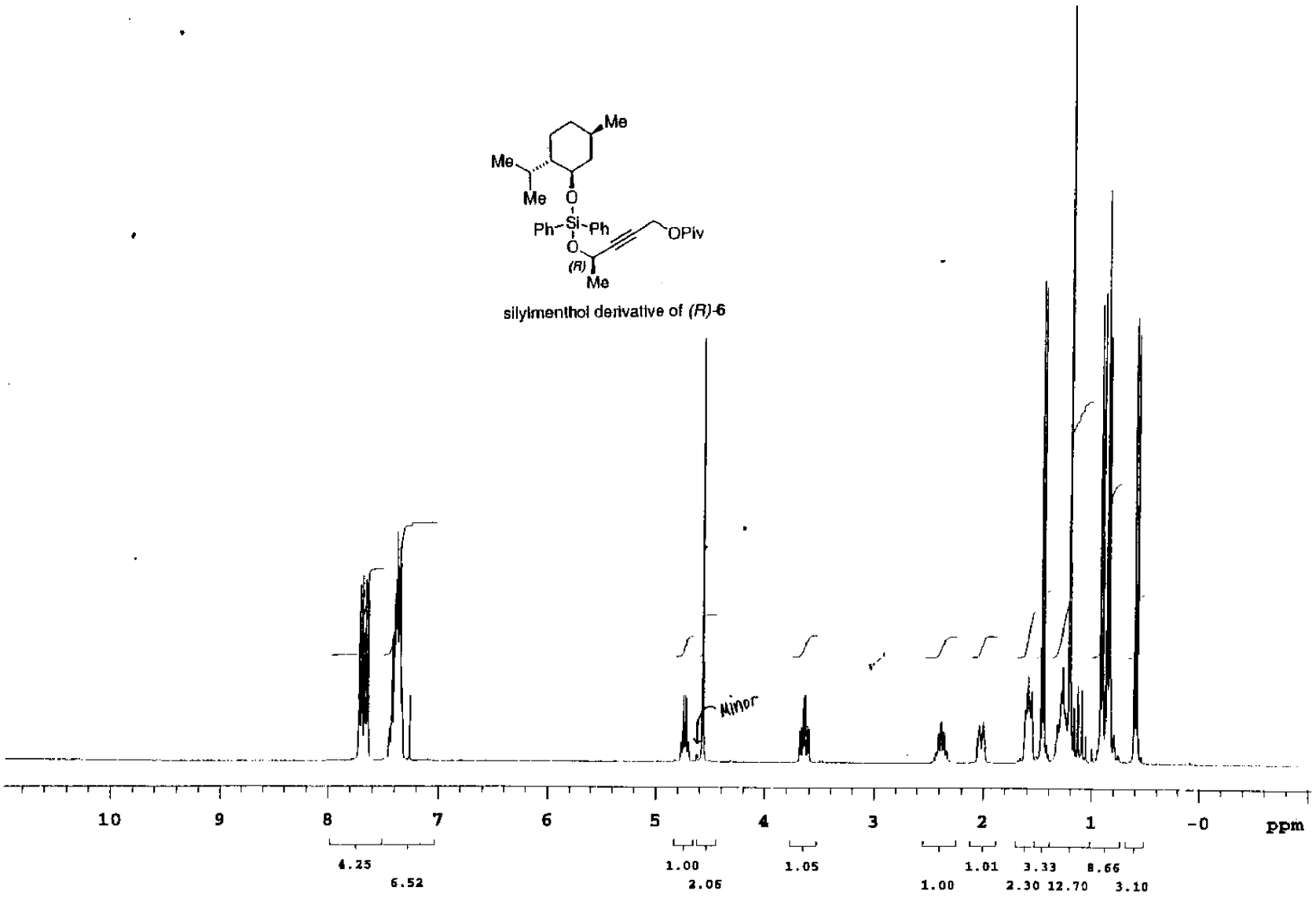
vg0303.154

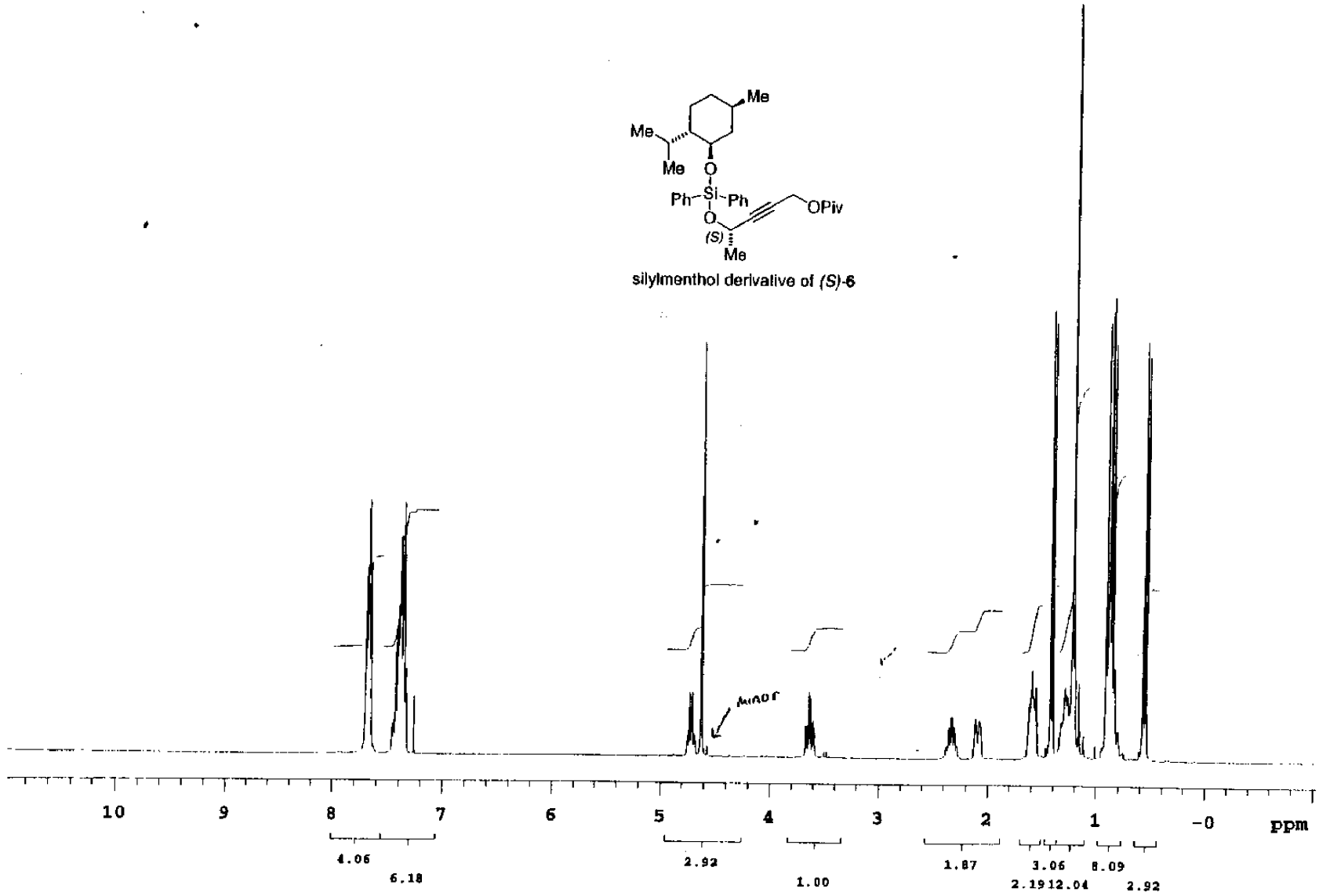

ppm
4.25998
4.26619
1.41720
1.40810
1.38647
0.95024
0.89024
0.86649
0.11183
0.09990
OH
TBSO (S)
Me
6
Integral
1.000
2.195
0.788
4.482
13.375
7.192
ppm
7
6
5
4
3
2
1

vgdp1202.151




Integral
ppm
0.988
0.317
3.120
17.849
PivO
OH
Me
7
7.25996
5.45936
5.43710
4.68914
4.68355
4.60412
4.59856
4.58215
4.57660
4.57104
4.56009
4.55456
4.54898
4.53801
4.53263
4.29414
4.28864
4.13034
4.10655
2.04362
2.00128
1.97742
1.57429
1.48507
1.46738
1.46296
1.44537
1.39465
1.29072
1.28397
1.28001
1.24937
1.23227
1.22656
1.21742
1.20414
1.17981
0.88433
0.87597
0.85250


Me
Me
Me
O
Ph
Si
Ph
OPiv
O
(R)
Me
silylmenthol derivative of (R)-6
Minor
10
9
8
7
6
5
4
3
2
1
-0
ppm
4.25
6.52
1.00
2.06
1.05
1.00
1.01
2.30
3.33
12.70
8.66
3.10


Me
Me
Me
O
Ph
Si
Ph
OPiv
O
(S)
Me
silylmenthol derivative of (S)-6
minor
10
9
8
7
6
5
4
3
2
1
-0
ppm
4.06
6.18
2.92
1.00
1.87
3.06
2.19
12.04
8.09
2.92