



A Publication
of Reliable Methods
for the Preparation
of Organic Compounds

Working with Hazardous Chemicals

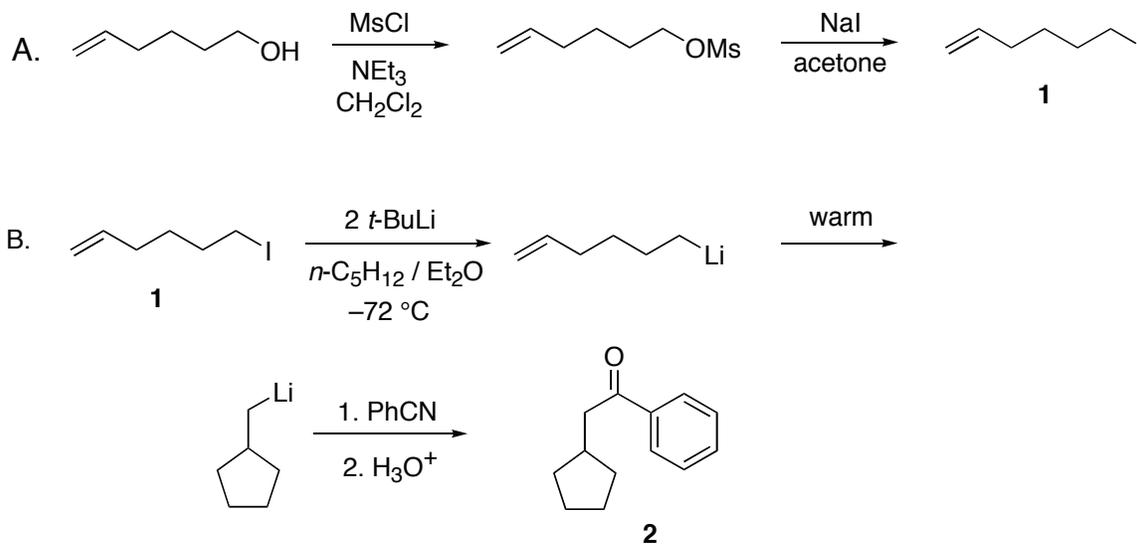
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September 2014: The paragraphs above replace the section "Handling and Disposal of Hazardous Chemicals" in the originally published version of this article. The statements above do not supersede any specific hazard caution notes and safety instructions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

**GENERATION AND CYCLIZATION OF 5-HEXENYLLITHIUM:
2-CYCLOPENTYLACETOPHENONE
(Ethanone, 2-cyclopentyl-1-phenyl-)**



Submitted by William F. Bailey, Matthew R. Luderer, Michael J. Mealy, and Eric R. Punzalan.¹

Checked by Scott E. Denmark and Stephen L. MacNeil.

1. Procedure

Caution! tert-Butyllithium is extremely pyrophoric and must not be allowed to come into contact with the atmosphere. This reagent should only be handled by individuals trained in its proper and safe use. It is recommended that transfers be carried out by using a 10-mL or smaller glass syringe filled to no more than 2/3 capacity, or by cannula. For a discussion of procedures for handling air-sensitive reagents, see Aldrich Technical Bulletin AL-134. [Note added August 2009.]

A. *6-Iodo-1-hexene (1)*. A flame-dried, 1-L, one-necked, round-bottomed flask equipped with a magnetic stirbar and a pressure-equalizing addition funnel fitted with a nitrogen inlet adapter is charged with 10.0 g

(0.100 mol) of 5-hexen-1-ol, 15.2 g (0.151 mol) of triethylamine, and 500 mL of dichloromethane (Note 1). The flask is cooled in an ice-salt bath (0 to -5 °C) for 30 min and then 9.3 mL (0.12 mol) of methanesulfonyl chloride (Note 2) is added dropwise via the addition funnel. The reaction mixture is stirred at -5 to -10 °C for an additional 1 h before being transferred to a cold 1-L separatory funnel and washed successively with 150 mL of cold water, 150 mL of cold 10% (ca. 3.3N) aqueous hydrochloric acid, 150 mL of cold, saturated, aqueous sodium bicarbonate solution, and 150 mL of cold brine (Note 3). The organic layer is dried over MgSO_4 and then divided into three portions (Note 4). One portion is filtered into a 300-mL, round-bottomed flask and concentrated by rotary evaporation at 8-10 mm in a 20-25 °C water bath, and this is repeated with the remaining two portions to give the desired mesylate as a clear, pale-yellow oil (Note 5).

Dry acetone (200 mL) and then 18.5 g (0.12 mol) of anhydrous sodium iodide (Note 6) are added to the above 300-mL flask, which is then equipped with a magnetic stirbar and a Friedrichs condenser fitted with a nitrogen inlet adapter. The pale-yellow solution is stirred in the dark under a positive pressure of nitrogen at gentle reflux for 4 h (Note 7). The resulting mixture is allowed to cool to room temperature and the acetone is then removed by rotary evaporation at 8–10 mm in a 20-25 °C water bath. The residue is partitioned between 50 mL of pentane and 50 mL of 10% aqueous sodium thiosulfate solution by swirling the flask until all of the precipitate dissolves. The aqueous phase is discarded and the organic layer is washed with 50 mL of brine, dried over MgSO_4 , filtered, and concentrated by rotary evaporation at 8–10 mm in a 20-25 °C water bath. The residue is then passed through a 60-mL, medium porosity, sintered-glass funnel containing ca. 20 g of alumina (Note 8) using ca. 100 mL of pentane as eluent. The pentane is removed by rotary evaporation at 8–10 mm in a 20-25 °C water bath to give 17.44-17.97 g (83–86% overall from the alcohol) of **1** as a clear, colorless oil (Notes 9 and 10).

B. 2-Cyclopentylacetophenone (2). A 500-mL, two-necked, round-bottomed flask (Note 11) equipped with an egg-shaped magnetic stir bar (4 cm x 1.5 cm), argon inlet adapter, and a rubber septum is flame-dried and allowed to cool to room temperature under a positive pressure of argon. A thermometer is inserted through the septum (Note 12) and the flask is charged with 114 mL of dry, alkene-free pentane and 76 mL of anhydrous diethyl ether (Notes 13, 14). The solution is cooled to approximately $-72\text{ }^{\circ}\text{C}$ using a 2-propanol-dry ice bath and 52 mL of a 1.90M solution of *tert*-butyllithium (*t*-BuLi) in heptane (98.8 mmol) is added via teflon cannula at a rate of approximately 1.7 mL/min so as to maintain an internal temperature below ca. $-68\text{ }^{\circ}\text{C}$ (Notes 15, 16). A two-necked, 100-mL, round-bottomed flask equipped with a rubber septum and argon inlet adapter is flame-dried under an atmosphere of argon, allowed to cool to room temperature, and then charged with 10.0 g (47.6 mmol) of oxygen-free 6-iodo-1-hexene (**1**) (Note 17) and 50 mL of dry, alkene-free pentane (Note 14). The iodide solution is cooled to $-72\text{ }^{\circ}\text{C}$ using a 2-propanol-dry ice bath and then transferred via a teflon cannula under a positive pressure of argon to the stirred, $-72\text{ }^{\circ}\text{C}$ solution of *t*-BuLi at a rate of approximately 1.4 mL/min so as to maintain an internal temperature below $-65\text{ }^{\circ}\text{C}$ (Note 18). The last of the iodide solution is transferred through the cannula by addition of 5 mL of dry pentane to the flask. Upon completion of the addition, the mixture is stirred at $-72\text{ }^{\circ}\text{C}$ for 15 min and the cooling bath is then removed. After 3.5 h (Note 19), the opaque, pale-yellow solution is cooled to ca. $0\text{ }^{\circ}\text{C}$ in an ice-water bath, and 4.85 g (47.0 mmol) of benzonitrile (Note 20) is added dropwise via syringe (Note 21). The cooling bath is removed, and the bright-orange solution is allowed to stir for 1 h. The reaction mixture is then re-cooled in an ice-water bath and 35.0 mL of 10% (ca. 3.3N) aqueous hydrochloric acid is added rapidly via syringe (Note 22). Once the exotherm abates, the cooling bath is removed, and stirring is continued for 2 h. The contents of the flask are completely transferred to a 500-mL separatory funnel by repeated washings with pentane and ether, shaken vigorously, and the aqueous layer is discarded. The organic phase is washed with 50 mL of water and 50 mL of brine, dried over MgSO_4 , filtered, and concentrated by rotary evaporation at 8–10 mm. Kugelrohr distillation of the residue (bath temperature ca. $180\text{ }^{\circ}\text{C}$, 5 mm) affords 6.64-6.78 g (75-77 %) of pure **2** as a clear, colorless oil (Notes 10, 23, 24).

2. Notes

1. 5-Hexen-1-ol and triethylamine were purchased from Acros Organics and used without further purification. Alternatively, 5-hexen-1-ol may be prepared from 2-(chloromethyl)tetrahydropyran according to the literature procedure for the preparation of 4-penten-1-ol (Brooks, L. A.; Snyder, H. R. *Org. Synth. Coll. Vol. III* **1955**, 698). Dichloromethane (certified ACS) was purchased from Fisher Scientific and was used as received.

2. Methanesulfonyl chloride was purchased from Aldrich Chemical Co. and used as received. This reagent, when taken from a previously opened container, is distilled from phosphorus pentoxide prior to use.

3. The separatory funnel, water, 10% hydrochloric acid, saturated sodium bicarbonate solution, and brine are cooled to ca. 0 °C in a freezer prior to use.

4. The dried organic layer is filtered and concentrated in ca. 150-mL portions.

5. The mesylate is used in the next step without further purification and is essentially pure; a small quantity of residual dichloromethane has no effect on the yield of the Finkelstein reaction. The mesylate has the following spectroscopic properties: ^1H NMR (CDCl_3): δ 1.46 - 1.52 (m, 2H), 1.71 - 1.77 (m, 2H), 2.06 - 2.10 (q, $J = 7.1$ Hz, 2H), 2.98 (s, 3H), 4.21 (t, $J = 6.6$ Hz, 2H), 4.95 - 5.02 (m, 2H), 5.72 - 5.80 (m, 1H); ^{13}C NMR (CDCl_3): δ 24.5, 28.4, 32.9, 37.2, 69.9, 115.1, 137.8.

6. Acetone (certified ACS) was purchased from Fisher Scientific and was dried over calcium sulfate and filtered prior to use. Anhydrous sodium iodide was purchased from Acros Organics and used as received.

7. Aluminum foil is wrapped around the flask and lower part of the condenser during the reaction.

8. Alumina, adsorption, ca. 150 mesh, was purchased from Aldrich Chemical Co. and used as received.

9. The known iodide **1**² is isolated in high purity (> 99 % by GC analysis) and may be used without further purification. The material displays the following properties: $n_{\text{D}}^{20} = 1.5121$ (lit.³ $n_{\text{D}}^{20} = 1.5106$); ^1H

NMR (CDCl₃: δ 1.46 - 1.55 (m, 2H), 1.80 - 1.87 (m, 2H), 2.05 - 2.11 (m, 2H), 3.19 (t, *J* = 7.0, 2H), 4.95 - 5.04 (m, 2H), 5.74–5.84 (m, 1H); ¹H NMR (CDCl₃: δ 6.9, 29.6, 32.6, 32.9, 115.0, 138.1; IR (neat) 3076, 2931, 2856, 1641, 1441, 1215, 1176, 991, 912 cm⁻¹. The iodide may be stored indefinitely in a freezer if first saturated with dry argon.

10. The purity of **1** and **2** is assessed by analytical gas-liquid chromatography (GC) on a Hewlett-Packard 5890 gas chromatograph equipped with a flame-ionization detector and fitted with a 50 m x 0.2 mm HP-5 fused silica glass capillary column using linear temperature programming from an initial temperature of 150 °C for 5 min to a final temperature of 200 °C for 10 min at a rate of 5 °C/min.

11. A one-necked Ace Glass 6935 flask with style-C side well (ordering code 6935-72) was used by the submitters, but the checkers found the use of a two-neck flask to be equally satisfactory.

12. An Omega model HH22 type J-K digital thermometer, connected to a type K thermocouple probe inserted directly into the flask, was used to measure the temperature.

13. Pentane (HPLC grade) was purchased from Fisher Scientific and used as received. Anhydrous diethyl ether was purchased from Mallinckrodt Inc. and distilled under nitrogen from a dark blue solution of sodium and benzophenone.

14. The appropriate volume of solvent is most conveniently transferred under argon from flame-dried graduated cylinders fitted with rubber septa using stainless steel double-tipped cannulas. Although the proportions of pentane and diethyl ether used as solvent are not crucial to the success of the lithium-iodine exchange, it is necessary to run the reaction in a solvent system that contains enough diethyl ether to render the *t*-BuLi dimeric.⁴ The submitters have found that a solvent mixture composed of 3:2 (by volume) of pentane and ether gives reproducible results.

15. The concentration of solutions of *t*-BuLi in heptane, purchased from FMC, Lithium Division, were determined immediately prior to use by titration with 2-butanol in xylene using 1,10-phenanthroline as the indicator following the procedure described by Watson and Eastham.⁵ A typical procedure is as follows: a flame-dried, 25-mL, round-bottomed flask, equipped with a magnetic stirbar, is charged under a blanket of argon with 3 mL of a 0.10 % (w/v) solution of 1,10-phenanthroline in dry benzene and

0.40-0.50 mL of *t*-BuLi in heptane; the violet solution is titrated with a ca. 1.0M solution of 2-butanol in xylenes until the pale yellow end point is reached. It should be noted that the nominal concentration recorded on commercial samples of an organolithium is often in error, particularly once the original seal is breached, or if the material has been stored for an extended period, and it is essential that the actual concentration be determined immediately prior to use. At least two molar equivalents of *t*-BuLi must be used in the exchange reaction: a full equivalent of *t*-BuLi is consumed in reaction with the *tert*-butyl iodide, generated as a by-product of the exchange, to give lithium iodide, isobutylene, and isobutane.⁴ A slight surplus of *t*-BuLi in excess of 2 molar equiv is not deleterious, since residual *t*-BuLi is rapidly consumed by proton abstraction from diethyl ether when the reaction mixture is warmed to room temperature,⁴ but a large excess should be avoided.

16. A commercial solution of *t*-BuLi in pentane may be substituted for *t*-BuLi in heptane. However, the lower volatility and higher flash-point of the heptane solvent makes *t*-BuLi in heptane *much* easier and safer to handle than this alternative.

17. The 6-iodo-1-hexene is rendered free of oxygen by bubbling argon through the neat iodide for at least 5 min prior to use.

18. The exchange reaction is exothermic and too rapid an addition of the iodide will cause a temperature rise that may lead to the formation of unwanted side-products. A white precipitate of LiI is observed when approximately two-thirds of the iodide solution has been added.

19. The solution warms slowly to room temperature; after 1.5 h the internal temperature is approximately 15-20 °C.

20. Benzonitrile, purchased from Aldrich Chemical Co., was distilled from calcium hydride and saturated with dry argon for at least 5 min prior to use.

21. An approximately 5 °C exotherm was noted during the addition.

22. The addition of the hydrochloric acid solution results in an exotherm of approximately 20 °C, accompanied by the appearance of a white precipitate and a viscous, orange oil.

23. The known ketone **2**,⁶ which is isolated in high purity (>99% by GC analysis), exhibits the following physical and spectroscopic properties: $n_D^{20} = 1.5362$; $^1\text{H NMR}$ (CDCl_3): δ 1.13 - 1.22 (m, 2H), 1.50 - 1.68 (m, 4H), 1.84 - 1.91 (m, 2H), 2.38 (7-line pattern, $J = 7.7$ Hz, 1H), 2.98 (d, $J = 7.1$ Hz, 2H), 7.43 - 7.46 (m, 2H), 7.52 - 7.56 (m, 1H), 7.94 - 7.97 (m, 2H); $^{13}\text{C NMR}$ (CDCl_3): δ 24.9, 32.7, 36.0, 44.7, 128.0, 128.5, 132.8, 137.2, 200.31; IR (neat) 3062, 2951, 2868, 1685, 1448, 1209, 752, 690 cm^{-1} ; Anal. calcd for $\text{C}_{13}\text{H}_{16}\text{O}$: C, 82.94; H, 8.57, Found: C, 82.71; H, 8.50

24. Purification by short-path distillation (138-139 °C/4.5 mm) resulted in a slightly diminished yield (6.25 g, 71%).

Waste Disposal Information

All toxic materials were disposed of in accordance with “Prudent Practices for Disposal of Chemicals from Laboratories”; National Academy Press; Washington, DC, 1995.

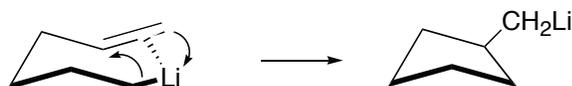
3. Discussion

The procedure described above may be used for the generation and 5-*exo* cyclization of a variety of substituted 5-hexenyllithiums and, with appropriate modification, provides a general route to a variety of other olefinic⁷ and acetylenic⁸ organolithiums that cyclize upon warming.⁹

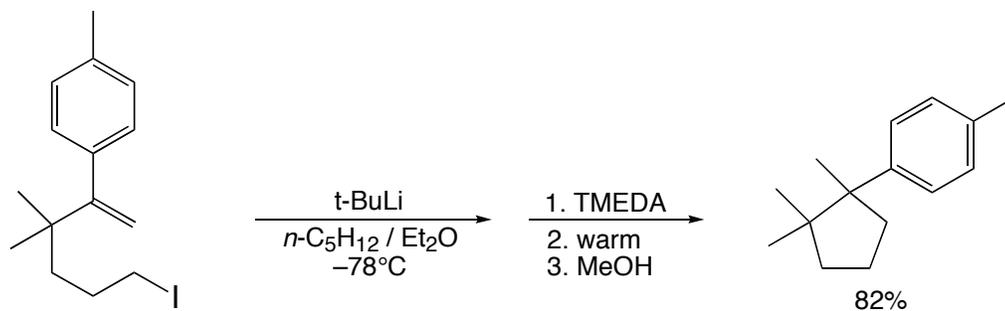
Primary alkyllithiums may be prepared rapidly and in virtually quantitative yield by treatment of a primary alkyl iodide with slightly more than two molar equiv of *t*-BuLi in a hydrocarbon–ether solvent system at low temperature.⁴ The exchange protocol outlined above for the preparation of 5-hexenyllithium (**1**) is a general one but its success often depends crucially on the appropriate choice of both halide and solvent. Primary alkyl iodides, rather than bromides, must be used to ensure that the reaction proceeds cleanly, most likely via a 10-I-2 ate-complex:¹⁰ addition of *t*-BuLi to a primary alkyl bromide often initiates radical-mediated processes. The

lithium-iodine exchange appears to involve a dimeric *t*-BuLi solvate and, for this reason, the best medium for the preparation of primary alkylolithiums by lithium-iodine exchange is a predominantly hydrocarbon solvent system that contains a quantity of a simple alkyl ether, such as Et₂O, MTBE, dibutyl ether, or the like, in which the *t*-BuLi is predominantly dimeric. Solvent systems containing THF, TMEDA, or other Lewis bases that render the *t*-BuLi monomeric should be avoided since elimination and coupling reactions often compete with exchange under these conditions.

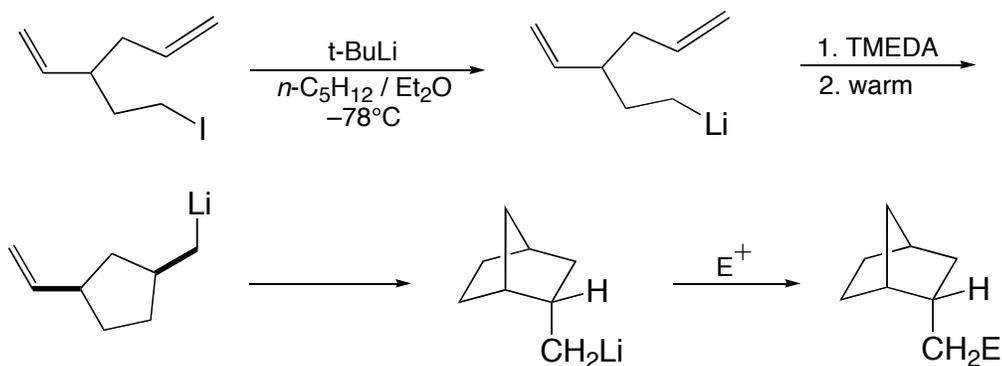
Cyclization of an organolithium tethered to a suitably positioned carbon-carbon π -bond is a thermodynamically favorable process that proceeds in a totally regioselective *exo*-fashion with a high degree of stereocontrol via a transition state in which the lithium atom is intramolecularly coordinated with the remote π -bond.⁹ The stereochemical outcome of the cyclization of a substituted 5-hexenyllithium follows from the preference of the substituent to occupy a pseudoequatorial position in the chair-like transition state depicted below.⁷



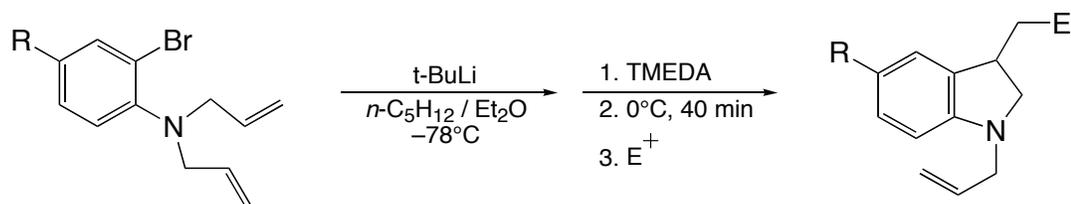
Despite the favorable thermodynamics associated with the cyclization of unsaturated organolithiums, the isomerization is often sluggish when the ring closure involves generation of a quaternary center or formation of a strained framework. In such cases it has been found that addition of lithiophilic Lewis bases such as THF or TMEDA facilitate the reaction.^{7,9} The preparation of cuparene, a sterically congested sesquiterpene possessing two adjacent quaternary centers, illustrates the methodology.¹¹



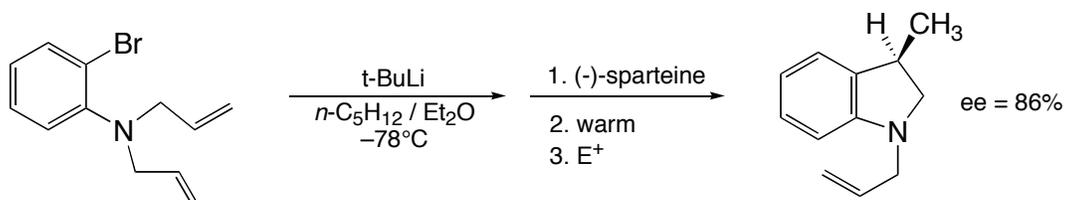
The predictable stereochemistry of the ring closure of substituted 5-hexenyllithiums, coupled with the ease with which the product organolithium may be functionalized, permits rational design of synthetic routes to polycyclic systems by sequential anionic cyclizations of polyolefinic alkyllithiums.¹² The preparation of stereoisomerically pure *endo*-2-substituted bicyclo[2.2.1]heptanes is illustrative of this approach to polycyclic systems.¹²



Heterocyclic systems, such as the substituted indoline illustrated below,¹³ may also be constructed via cyclization of unsaturated organolithiums and a recent review of the preparation of nitrogen- and oxygen-containing heterocycles via this approach is available.¹⁴



It should also be noted that the 5-exo-trig cyclization of achiral olefinic organolithiums has been found to proceed enantioselectively when conducted in the presence of a chiral ligand that serves to render the lithium atom stereogenic. Thus, for example, (*R*)-1-allyl-3-methylindoline has been prepared in 86 % ee by cyclization of an achiral aryllithium in the presence of an equivalent of (–)-sparteine.¹⁵



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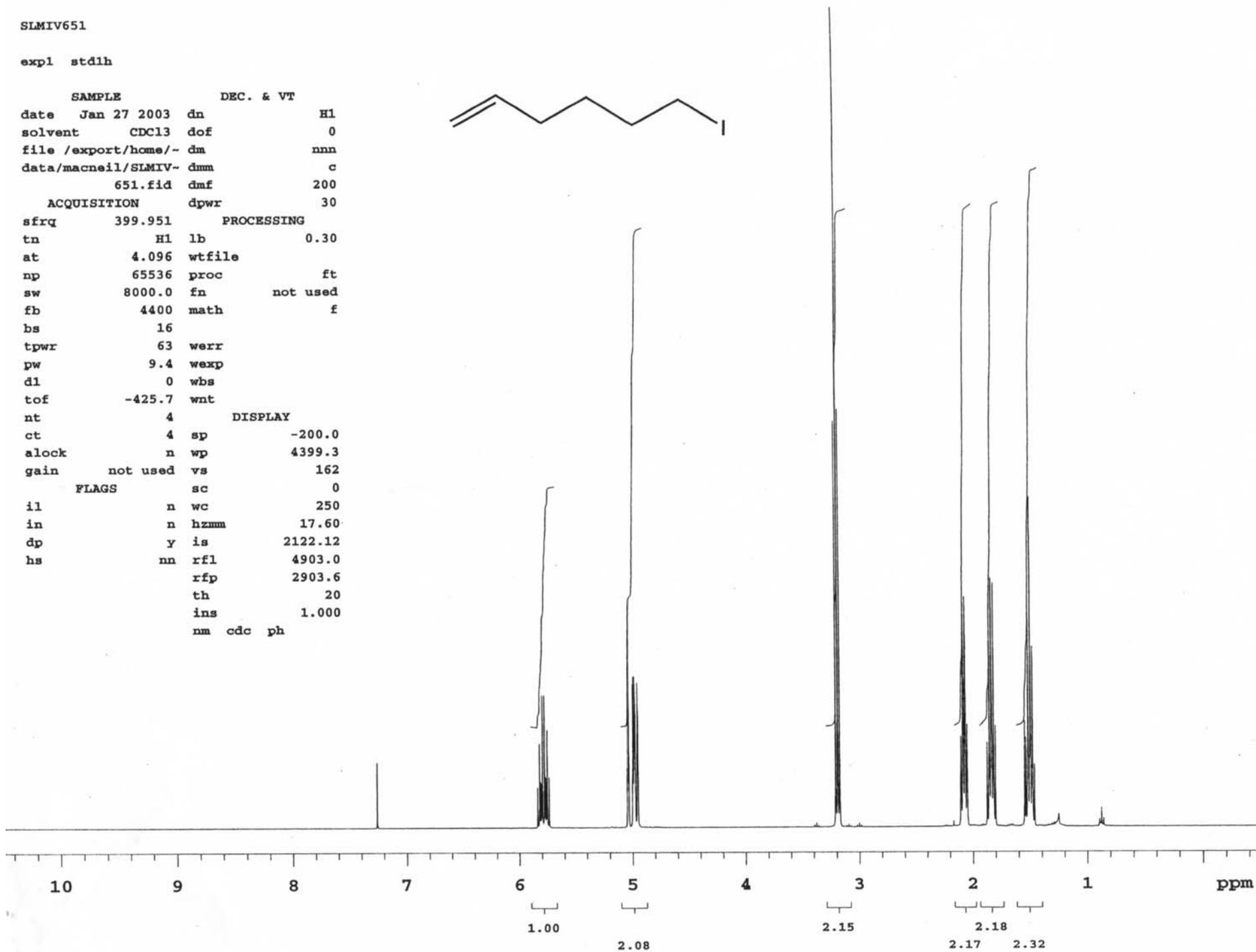
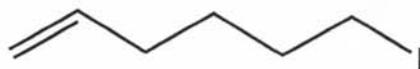
Appendix
Chemical Abstracts Nomenclature (Registry Number)

6-Iodo-1-hexene: 1-Hexene, 6-iodo-; (18922-04-8)
5-Hexen-1-ol; (821-41-0)
Triethylamine; Ethanamine, N,N-diethyl-; (121-44-8)
Methanesulfonyl chloride; (124-63-0)
5-Hexen-1-ol, methanesulfonate; (64818-36-6)
Sodium iodide; (7681-82-5)
2-Cyclopentylacetophenone: Ethanone, 2-cyclopentyl-1-phenyl-; (23033-65-0)
tert-Butyllithium; Lithium, (1,1-dimethylethyl)-; (594-19-4)
Benzonitrile; (100-47-0)

SLMIV651

exp1 std1h

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