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of Organic Compounds

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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.

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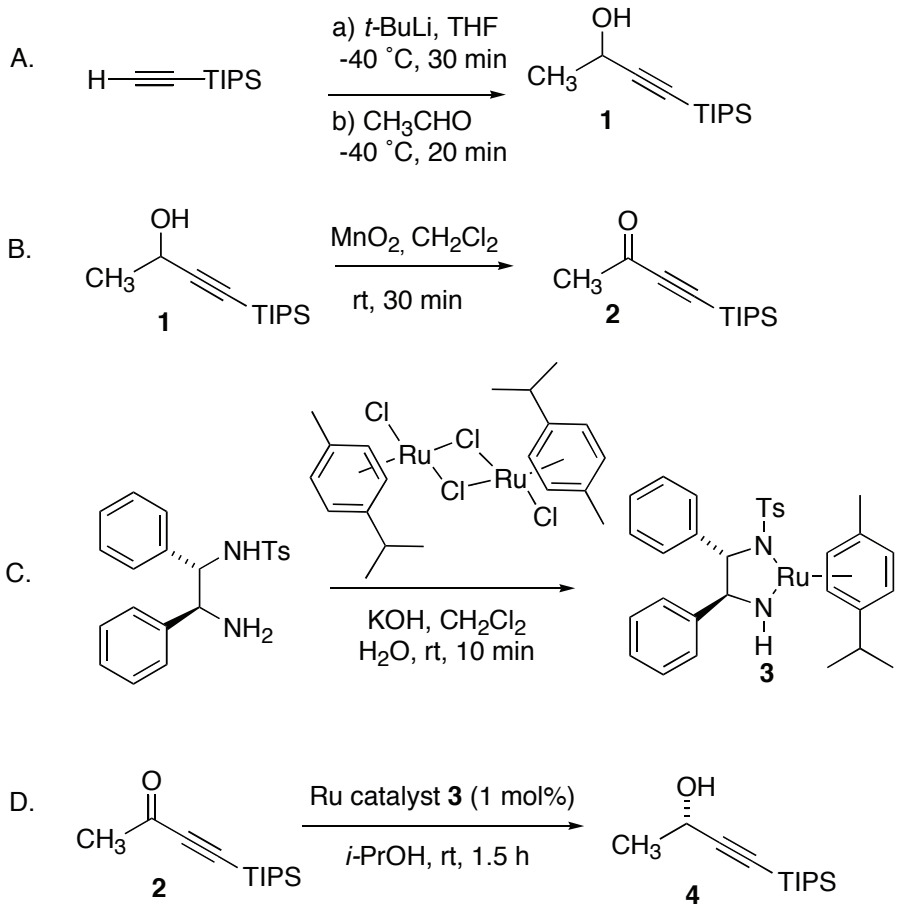
SYNTHESIS OF 4-TRIISOPROPYLSILYL-3-BUTYN-2-OL BY ASYMMETRIC TRANSFER HYDROGENATION



Submitted by James A. Marshall, Patrick Eidam, and Hilary Schenck Eidam.[1a]
Checked by Kai Zhang and Dennis P. Curran.[1b]

1. Procedure

A. *(rac)-4-Triisopropylsilyl-3-butyn-2-ol (1).* A single-necked, flame-dried, 250-mL round-bottomed flask equipped with a magnetic stir bar and a rubber septum fitted with an argon inlet needle is flushed with argon and charged with triisopropylsilyl acetylene (95%, 6.1 mL, 4.75 g, 26.0 mmol) (Note 1) and dry THF (54 mL) (Note 2) by syringe through the septum. The reaction mixture is cooled to –40 °C (bath temperature) by means of a dry ice-acetonitrile bath and *tert*-BuLi (1.7 M in pentane, 18 mL, 32.3 mmol) is added dropwise by means of a syringe (Note 3). The resulting bright yellow mixture is stirred at –40 °C for 30 min and then ACS reagent grade

acetaldehyde (>99.5%, 2.3 mL, 39.2 mmol) is added in one portion by means of a syringe. The reaction mixture is stirred for 20 min at –40 °C and then poured over a rapidly stirring solution of saturated aqueous NH_4Cl (75 mL) at room temperature. After 15 min, the phases are separated and the aqueous layer is extracted with diethyl ether (2 x 40 mL). The combined organic extracts are washed with brine, dried over $MgSO_4$, filtered, and the solvent is removed with a rotary evaporator (40 °C, water aspirator pressure). The residue is purified by bulb-to-bulb distillation (95 °C, 0.2 mmHg; Note 4) to yield the racemic alcohol (5.8 g, 98%) as a clear oil (Notes 5, 6, 7). This material is used in the next step without further purification.

B. 4-Triisopropylsilyl-3-butyn-2-one (2). A one-necked, flame-dried, 250-mL round-bottomed flask equipped with a magnetic stir bar and a rubber septum fitted with an argon inlet needle is flushed with argon. The septum is temporarily removed and the flask is charged sequentially with CH_2Cl_2 (54 mL), 4-triisopropylsilyl-3-butyn-2-ol (**1**) (5.8 g, 25.6 mmol) and technical grade MnO_2 (85%, 34.4 g, 336.9 mmol) (Notes 8, 9), which is added in one portion. The reaction mixture is stirred at room temperature for 30 min and then filtered through a short pad of Celite. The Celite is washed with CH_2Cl_2 (2 x 30 mL) and the solvent is removed on a rotary evaporator (40 °C, water aspirator pressure). The resulting yellow oil is purified by bulb-to-bulb distillation (80 °C, 0.2 mmHg; Note 4) to yield ketone **2** (5.0–5.1 g, 87–89%) as a clear oil (Notes 10, 11). This material is used in the next step without further purification.

C. *RuCl[(S,S)-NTsCH(C_6H_5)CH(C_6H_5)NH_2(η^6-cymene) (3).* (Note 12)**.** A one-necked, flame-dried, 50-mL round-bottomed flask equipped with a magnetic stir bar and a rubber septum fitted with an argon inlet needle is flushed with argon. The septum is temporarily removed and the flask is charged with CH_2Cl_2 (6 mL), (1*S*,2*S*)-(+)-*N*-*p*-toluenesulfonyl-1,2-diphenylethylene-diamine (126 mg, 0.34 mmol), dichloro(*p*-cymene)ruthenium(II) dimer (107 mg, 0.17 mmol), and powdered KOH (141 mg, 2.5 mmol) (Note 1). The resulting orange mixture is stirred for 5 min at room temperature and then distilled H_2O (6 mL) is added in one portion by means of a syringe. The resulting biphasic mixture is stirred for 10 min during which time the organic phase turns dark purple. The mixture is transferred to a separatory funnel, diluted with 10 mL of H_2O and the layers are separated. The aqueous phase is extracted with CH_2Cl_2 (2 x 10 mL). The combined organic extracts are dried over CaH_2 (Note 1), filtered

and solvent is removed with a rotary evaporator (40 °C, water aspirator pressure) to furnish the catalyst **3** (180–182 mg, 86–87%) as a dark purple solid that is used in the subsequent reduction without additional purification.

D. *(S)-4-Triisopropylsilyl-3-butyn-2-ol (4)*. A one-necked, flame-dried, 500-mL round-bottomed flask equipped with a magnetic stir bar and a rubber septum fitted with an argon inlet needle is flushed with argon. Isopropyl alcohol (250 mL) and 4-triisopropylsilyl-3-butyn-2-one (**2**) (5.1 g, 22.7 mmol) are added to the flask through the septum by syringe. The ruthenium catalyst **3** (180 mg, 0.3 mmol) is taken up in a minimal amount of CH_2Cl_2 (~5 mL) and added to the reaction mixture in one portion by means of a syringe. The mixture is stirred for 1.5 h and then the solvent is removed with a rotary evaporator (40 °C, water aspirator pressure). The brown residue is purified by bulb-to-bulb distillation (95 °C, 0.2 mmHg; Note 4) to yield the alcohol **4** (5.0 g, 85% for three steps) as a clear oil (Notes 13, 14, 15).

2. Notes

1. All chemicals were purchased from Aldrich Chemical Co. and were used without further purification. The submitters purchased THF and CH_2Cl_2 as optidry Fischer Paks from Fischer Scientific. The checkers purchased dry CH_2Cl_2 from Aldrich and used THF from a sodium/benzophenone still.

2. The submitters reported that the use of diethyl ether in place of THF resulted in diminished yields and the formation of impurities not separable by distillation.

3. The submitters reported that the use of *n*-BuLi (20.2 mL of 1.6 M *n*-BuLi in hexanes) afforded the adduct **1** in quantitative yield. The spectra of the sample prepared in this way were identical to those of the sample from the *tert*-BuLi experiment.

4. Bulb-to-bulb distillations were performed with an Aldrich Kugelrohr apparatus.

5. Physical characteristics for 4-triisopropylsilyl-3-butyn-2-ol **(1)**: R_f = 0.41 (15% EtOAc-hexane) on Merck silica gel 60 F 254 precoated 250 μm plates; IR (film): 3325, 2943, 2866, 2173, 1464 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ: 1.08 (m, 21 H), 1.48 (d, J = 6.6 Hz, 3 H), 1.78 (s, 1 H), 4.55 (q, J = 6.6 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 11.1, 18.5, 24.5, 58.7, 84.3, 109.8.

6. The submitters reported that the product was contaminated by up to

3% triisopropylacetylene in some runs. This was analyzed by integration of the alkynyl H signal at 2.35 ppm in the ^{1}H NMR spectrum.

7. An analytical sample was prepared by chromatography on silica gel. A 1.5 cm x 20 cm glass column packed with 9 g of EMD silica gel 60 was used to purify 20 mg of alcohol by elution with 10% diethyl ether in hexanes. Anal. Calcd for $C_{13}H_{26}OSi$: C, 68.96; H, 11.57. Found: C, 68.96; H, 11.66.

8. MnO_2 was purchased from Aldrich Chemicals and dried in an oven at 110 °C overnight prior to use.

9. The submitters reported that exposure to less than 13 equiv of MnO_2 resulted in incomplete conversion and formation of byproducts upon prolonged reaction times.

10. Physical characteristics for 4-triisopropylsilyl-3-butyn-2-one **(2)**: R_f = 0.76 (15% EtOAc-hexane) on Merck silica gel 60 F 254 precoated 250 μm plates; IR (film): 2946, 2868, 2147, 1684, 1464, 1196 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.10 (m, 21 H), 2.37 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 11.3, 18.4, 32.8, 95.2, 104.6, 184.4.

11. An analytical sample was prepared by chromatography on silica gel. (A 1.5 cm x 20 cm glass column packed with 9 g of of EMD silica gel 60 was used to purify 20 mg of ketone by elution with 5% diethyl ether in hexanes. Anal. Calcd for $C_{13}H_{24}OSi$: C, 69.58; H, 10.78. Found: C, 69.56; H. 10.89.

12. The procedure described for the preparation of RuCl[(*S*,*S*)-NTsCH(C_6H_5)CH(C_6H_5)NH_2(η^6-cymene) was taken from reference 9.

13. Physical characteristics for *(S)*-4-triisopropylsilyl-3-butyn-2-ol (**4**): Same as for racemic 4-triisopropylsilyl-3-butyn-2-ol; $[\alpha]_D^{20}$ –21.3 (c = 1.58, $CHCl_3$). The er of this material was found to be >95:5 by ^{19}F NMR analysis [δ–73.68 ppm (major) and –73.02 ppm (minor), in $CDCl_3$ versus benzotrifluoride as an internal standard at –63.72 ppm] of the *(R)*-Mosher ester. To prepare the Mosher ester, 4-triisopropylsilyl-3-butyn-2-ol (4 mg), (*S*)-(+)-methoxy-α-trifluoromethylphenylacetyl chloride (5 μL) and dry pyridine (0.15 mL) were added to a one-necked, flame-dried, 5-mL round-bottomed flask. The flask was equipped with a magnetic stir bar and a rubber septum and was flushed with argon. The reaction mixture was stirred at room temperature for 2 h, then the volatiles were evaporated to yield the crude (*R*)-Mosher ester, which was directly analyzed by ^{19}F NMR spectroscopy without purification.

14. GC analysis on a β-Dex column temperature programmed from 130 to 180 °C gave a single peak at 22.35 min (submitters). GC analysis on an Agilent MP-1 column (1909/Z-413E, 30 m x 0.32 mm), temperature ramp 10 °C per min from 50 °C to 315 °C, gave a single peak at 10.61 min (checkers). Anal. Calcd for $C_{13}H_{26}OSi$: C, 68.96; H, 11.57. Found: C, 69.03; H, 11.74.

15. The submitters measured $[\alpha]_D^{20}$ –19.5 (c = 1.55, $CHCl_3$) for a run on the same scale and concentration. When they performed the reduction at a ten-fold higher concentration of ketone, the derived alcohol **4** exhibited $[\alpha]_D^{20}$ –16.5 (c = 1.81, $CHCl_3$).

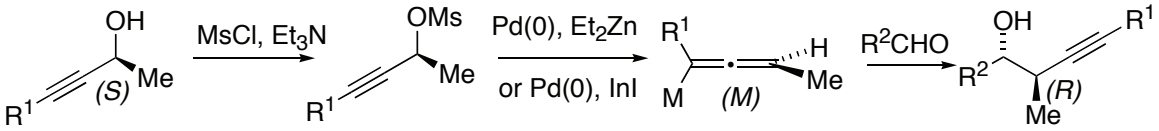
Safety and Waste Disposal Information

All hazardous materials should be handled and disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

3. Discussion

The palladium-catalyzed conversion of enantioenriched propargylic mesylates such as **2** to enantioenriched allenylzinc (**3**) or indium (**4**) reagents and in situ additions to aldehydes provides a convenient route to homopropargylic alcohol intermediates related to polyketide natural products (Scheme 1).[2,3,4]

Scheme 1. Synthesis of Enantioenriched Homopropargylic Alcohols from Propargylic Mesylates



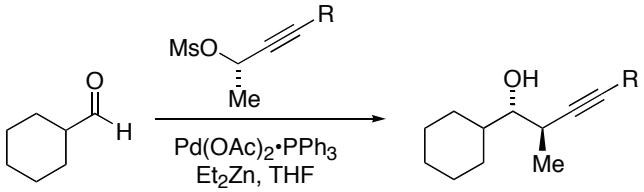
Although the alcohol precursor of mesylate (*S*)-**2a** and its enantiomer are commercially available,[5] their high cost discourages widespread use of the methodology. Accordingly, we have explored simple and economical preparations through use of chiral pool starting materials[6] or lipase

resolution of racemic propargylic alcohols for a more cost effective synthesis.[7,8] The TMS reagents **2b**, prepared through lipase resolution of racemic **1b**, show significantly higher diastereoselectivity than the parent alkyne **2a**. While this alternative represents an improvement, the intrinsic inefficiency of optical resolution coupled with the volatility of the resolved alcohols represent significant drawbacks to the methodology. The present procedure employs Noyori asymmetric hydrogenation of alkynyl ketones to prepare the alkynyl TIPS derivative **1c** of 3-butyn-2-ol.[9] This route offers several major advantages compared with the previous approaches to the parent **1a** and the TMS alcohol **1b**:

(1) Unlike alcohol **1a** and its alkynyl TMS analog **1b**, the TIPS compound **1c** is nonvolatile and completely insoluble in water, thereby allowing facile isolation by simple extraction;
(2) all intermediates can be vacuum-dried and purified by short path distillation;
(3) both enantiomers of the chiral catalyst are readily available;
(4) the catalyst precursor can be stored without loss of activity; and,
(5) addition reactions of the derived TIPS allenylzinc reagent to aliphatic aldehydes proceeds readily and with comparable diastereoselectivity to additions of the parent reagent or the TMS derivative.

The outcome of addition reactions of the three allenylzinc reagents generated in situ from mesylates **2a**, **2b**, and **2c** to cyclohexane-carboxaldehyde is summarized in Table 1.

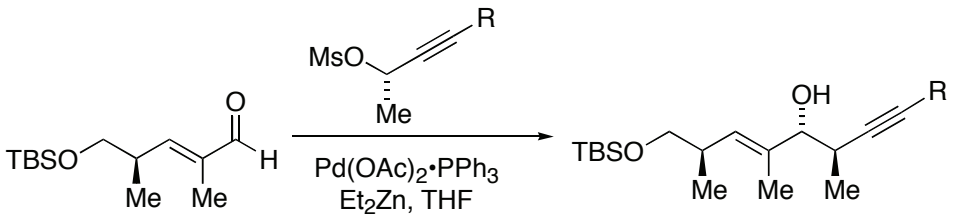
Table 1. Comparison of Addition Reactions of Allenylzinc Reagents Derived in situ from the Mesylate of *(S)*-3-Butyn-2-ol (**2a**) and the Silylated Analogs **2b** and **2c** to Cyclohexanecarboxaldehyde.



R	yield	dr	er
H (**2a**)	86	19:1	99:1
TMS (**2b**)	84	24:1	97:3
TIPS (**2c**)	89	19:1	98:2

An even larger difference in diastereoselectivity for the three reagents was observed with an α-methylated enal (Table 2). Removal of the TIPS group from the adducts is easily effected in minutes with tetrabutylammonium fluoride in THF.

Table 2. Comparison of Addition Reactions of Allenylzinc Reagents Derived in situ from the Mesylate of *(S)*-3-Butyn-2-ol (**2a**) and the Silylated Analogs **2b** and **2c** to a Conjugated Aldehyde.



R	yield	dr
H (**2a**)	71	85:15
TMS (**2b**)	56	88:12
TIPS (**2c**)	80	92:8

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Appendix
Chemical Abstracts Nomenclature; (Registry Number)

(*rac*)-4-Triisopropylsilyl-3-butyn-2-ol: 3-Butyn-2-ol, 4-[tris(1-methylethyl)silyl]-: (726202-65-9)

Triisopropylsilyl acetylene: Silane, ethynyltris(1-methylethyl)-;(89343-06-6)

tert-BuLi: Lithium, (1,1-dimethylethyl)-; (594-19-4)

Acetaldehyde; (75-07-0)

4-Triisopropylsilyl-3-butyn-2-one: 3-Butyn-2-one, 4-[tris(1-methylethyl)silyl]-: (183852-48-4)

Manganese Dioxide; (1313-13-9)

RuCl[(*S*,*S*)-NTsCH(C_6H_5)CH(C_6H_5)NH_2(η^6-cymene): Ruthenium, [*N*-[(1*S*,2*S*)-2-(amino-κN)-1,2-diphenylethyl]-4-methyl-benzenesulfonamidato-κN]chloro[(1,2,3,4,5,6-η)-1-methyl-4-(1-methylethyl)benzene]-; (192139-90-5)

(1*S*,2*S*)-(+)-*N*-*p*-toluenesulfonyl-1,2-diphenylethylenediamine: Benzenesulfonamide, *N*,*N*'-(1,2-diphenyl-1,2-ethanediyl)bis[4-methyl-, [*S*-(*R**,*R**)]-; (170709-41-8)

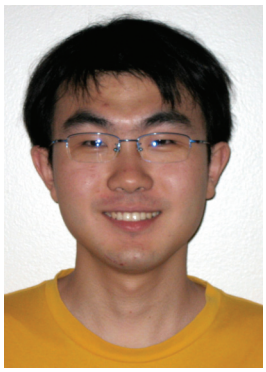
Dichloro(*p*-cymene)ruthenium(II) dimer; (52462-29-0)

(*S*)-4-Triisopropylsilyl-3-butyn-2-ol: (*S*)-3-Butyn-2-ol, 4-[tris(1-methylethyl)silyl]-;

James Marshall received a BS degree in Chemistry from the University of Wisconsin PhD degree in 1960 from the University of Michigan with Professor Robert E. Ireland. After two years as an NIH postdoctoral Fellow in the laboratory of William. S. Johnson at Stanford University, he joined the faculty of Northwestern University in 1962 and advanced to the rank of full Professor in 1968. The following year he moved to the University of South Carolina and was subsequently appointed the inaugural Guy Lipscomb Professor of Chemistry. In 1995 he was appointed Thomas Jefferson Professor of Chemistry at the University of Virginia. A central theme in Professor Marshall's research has been the development and application of stereoselective reactions to natural product synthesis.

Patrick M. Eidam was born in 1978 in New Castle, PA. Following his graduation with a BS degree in Chemistry from Lafayette College, he entered graduate school at the University of Virginia and joined the research group of Professor James Marshall. He received his PhD degree in 2006 and subsequently obtained a position with the Medicinal Chemistry division at Glaxo Smith Kline in King of Prussia, PA.

Hilary Schenck Eidam was born in 1978 in York, PA. She received a B.S. degree in chemistry from Gettysburg College in 2000 followed by a PhD degree in chemistry from the University of Virginia in the laboratory of Milton Brown. After postdoctoral research with Professor James Marshall at Virginia she joined the Medicinal Chemistry group at Glaxo Smith Kline in King of Prussia, PA.



Kai Zhang was born in China and got his B.S. degree in Chemistry from University of Science and Technology of China in 2005. He came to United States in August 2005 as a graduate student and joined Professor Dennis P. Curran's group at the University of Pittsburgh.

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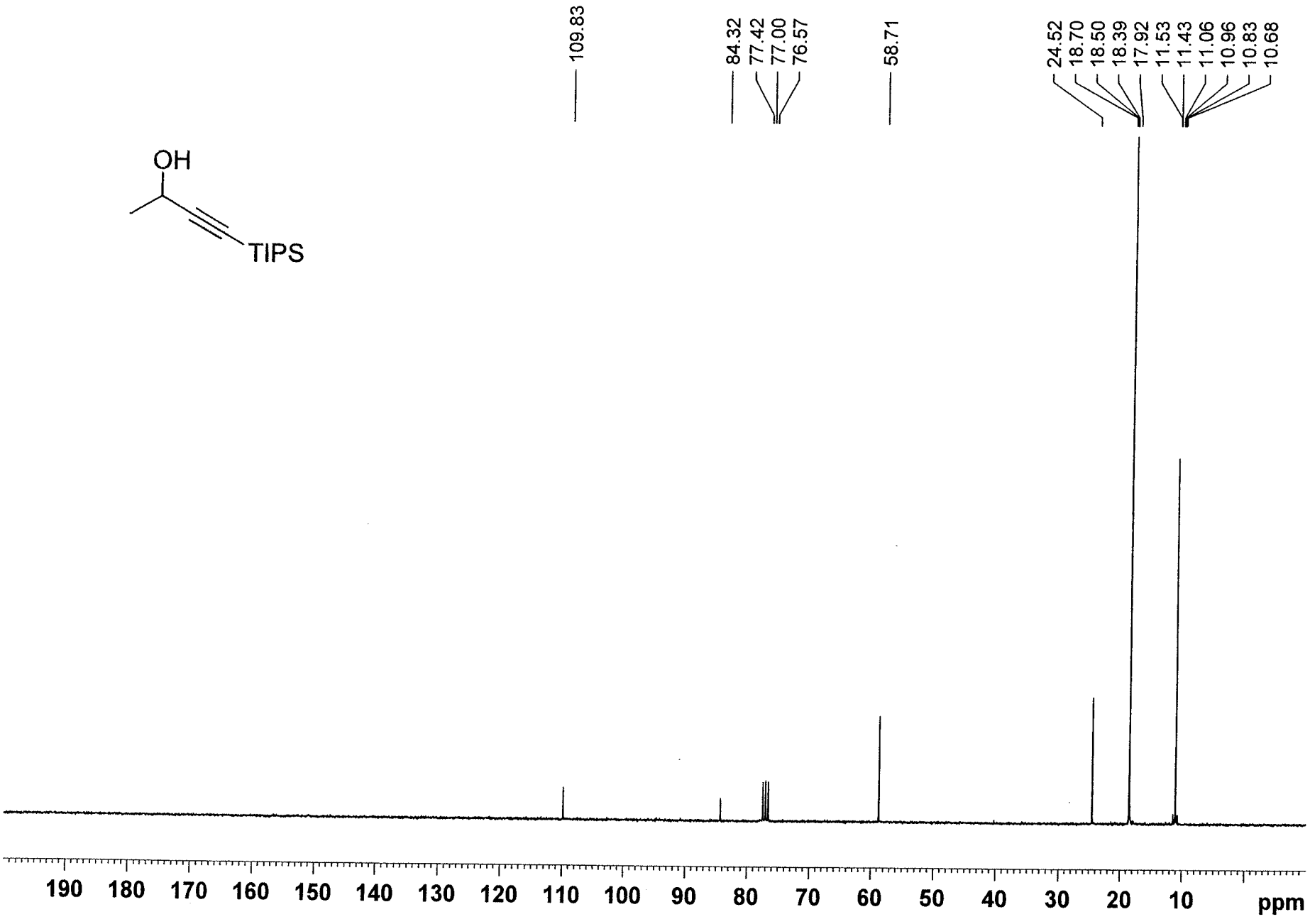

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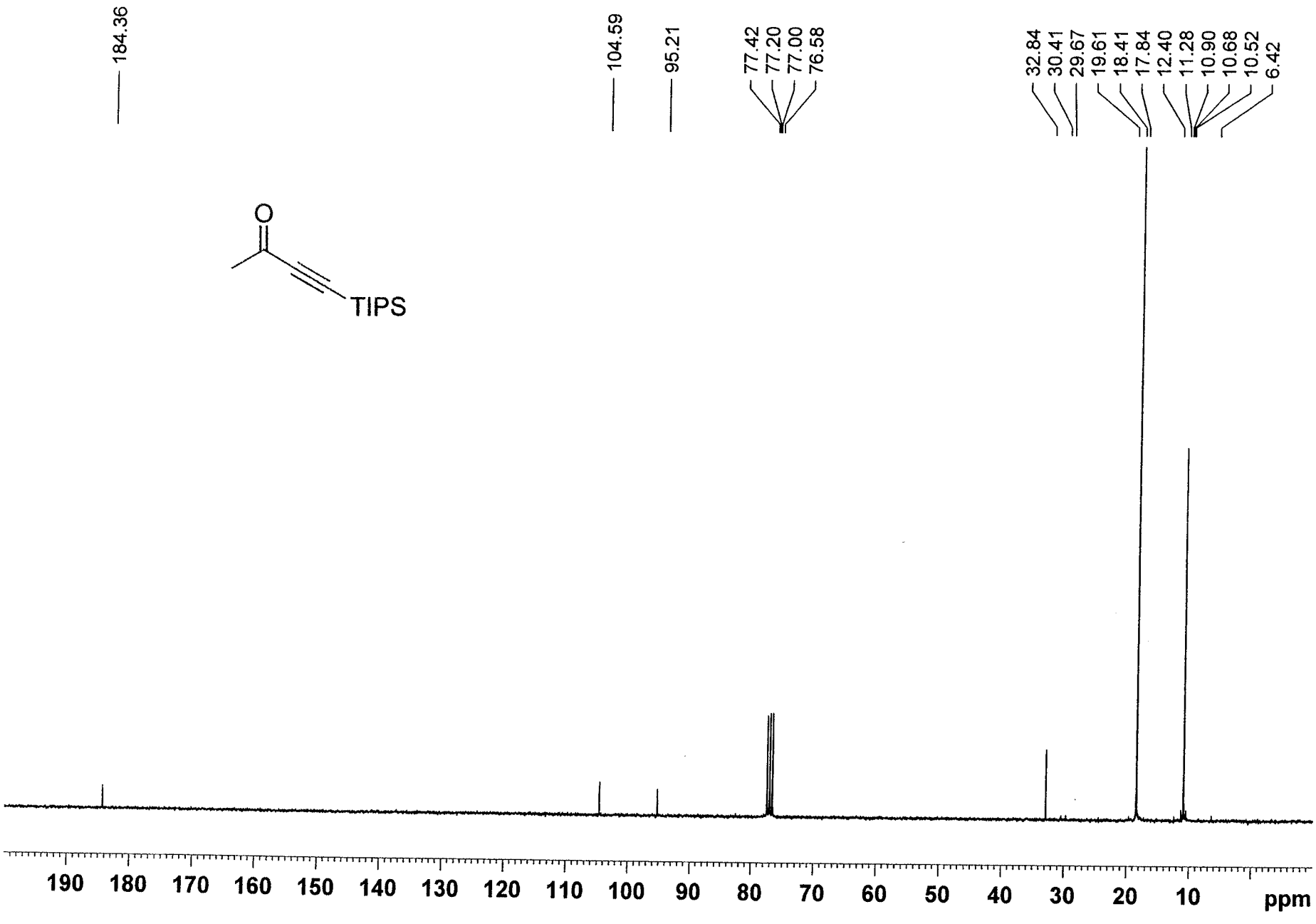

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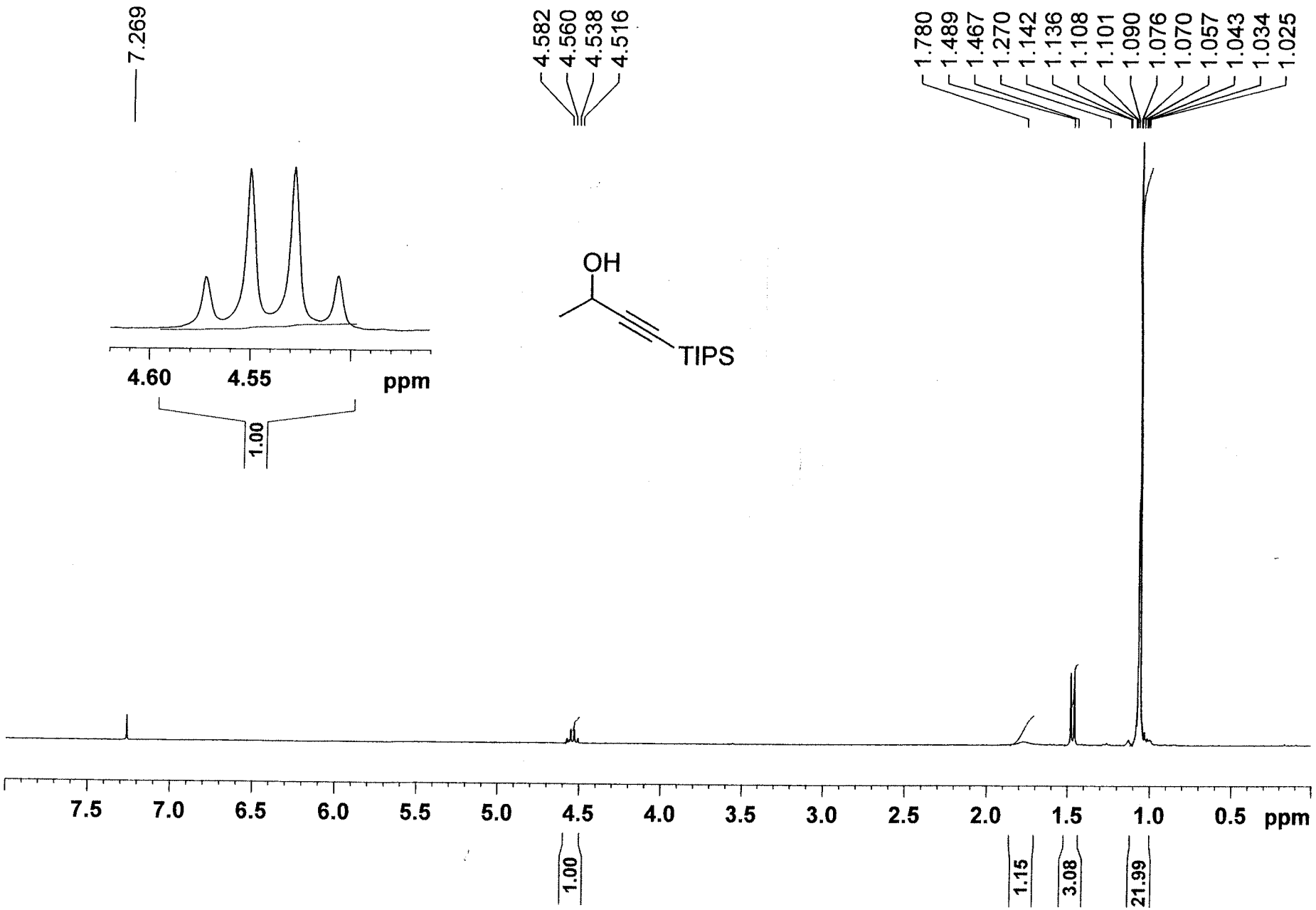

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