Synthesis of Enantioenriched Propargylic Fluorides from Allenylsilanes

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SUPPORTING INFORMATION

General. Infrared spectra were recorded on a Paragon 1000 FT-IR spectrometer and only peaks of interest were reported. ^{1}H NMRs were reported on Bruker DPX 200, DPX 400, AV 400 and AV 500 spectrometers, at a frequency of 200, 400 and 500 MHz respectively. ^{13}C NMRs were recorded on Bruker AV 400 and AV 500 spectrometers at a frequency of 100 or 125 MHz respectively with $CDCl_3$ as the internal reference. Mass spectra (*m/z*) were recorded on Micromass GCT in Chemical Ionisation (NH_3, CI^+) or Field Ionisation (FI). Analytical thin layer chromatography (TLC) was performed on Merck Silica 60 F_{254} plates. All reactions were carried out under an argon atmosphere in dried glassware with magnetic stirring.

General Procedure for the Synthesis of Racemic Alkynols[1]

To a stirred solution of trimethylsilylacetylene (331 μL, 2 mmol) in dry THF (4 mL) at -78^{o}C, was added a solution of *n*-BuLi (2.5M) in hexane (0.96 mL, 2.4 mmol). The solution was stirred for 30 minutes prior to addition of the aldehyde (2 mmol). The reaction mixture was subsequently stirred for a further 5 minutes and then warmed to 0^{o}C for 2 h. The reaction was quenched with H_2O (10 mL), the aqueous layer extracted with Et_2O (3 x 15 mL). The combined organic layers were collected, dried over $MgSO_4$ and concentrated at reduced pressure. The crude product was purified by column chromatography.

All racemic alkynols used for the synthesis of their corresponding allenylsilanes have been previously described in the literature.

General Procedure for the Synthesis of Mesylates[2]

Triethylamine (558 μL, 4 mmol) was added to a stirred solution of an alkynol (2 mmol) in dry DCM (alcohol-free, 2 mL) at 0^{o}C. This was followed by the addition of methanesulfonyl chloride (232 μL, 3 mmol). The reaction was allowed to warm up to room temperature and stir for 3.5 h. It was quenched with H_2O (15 mL) and the aqueous layer was extracted with DCM (3 x 15 mL). The combined organic layers were dried over $MgSO_4$ and then filtered and concentrated at reduced pressure.

All mesylates have previously been reported in the literature except for the following two compounds.

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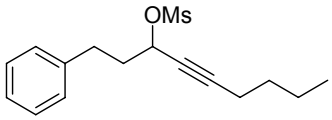
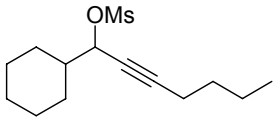
[1] A. Ajamian and J. L. Gleason, *Org. Lett.*, 2003, **5**, 2409.
[2] M. C. Pacheco and V. Gouverneur, *Org. Lett.*, 2005, **7**, 1267.



1-Phenylnon-4-yn-3-yl methanesulfonate: υ_{max}(film)/cm^{-1} 2181 and 1190; δ_H (400 MHz; $CDCl_3$) 0.93 (3H, t, J = 7.3 Hz, $CH_2CH_2CH_3$), 1.38-1.57 (4H, m, $(CH_2)_2$), 2.10-2.30 (4H, m, $(CH_2)_2$), 2.76-2.88 (2H, m, $PhCH_2CH_2$), 3.12 (3H, s, CH(O*Ms*)), 5.14-5.20 (1H, m, CH_2CH(OMs)), 7.20-7.33 (5H, m, *Ph*); δ_C (100 MHz; $CDCl_3$) 8.6, 13.5, 18.3, 21.9, 30.3, 31.0, 37.7, 39.1, 72.1, 75.7, 84.8, 126.3, 127.3, 128.5, 140.2; *m/z* (CI^+) $C_{16}H_{22}O_3S$ calc. 294.1290, found 294.1291.



1-Cyclohexylhept-2-ynyl methanesulfonate: υ_{max}(film)/cm^{-1} 2179 and 1177; δ_H (400 MHz; $CDCl_3$) 0.92 (3H, t, J = 7.2 Hz, CH_2CH_3), 1.07-1.40 (9H, m, $CH(CH_2)_4$), 1.64-1.93 (8H, m, $(CH_2)_4$), 3.16 (3H, s, CH(O*Ms*)), 4.98 (1H, d, J = 6.2 Hz, C*H*(OMs)); δ_C (100 MHz; $CDCl_3$) 13.5, 18.4, 21.9, 27.2, 29.6, 29.8, 29.9, 33.6, 40.2, 44.3, 67.6, 80.1, 86.0; *m/z* (CI^+) $C_{13}H_{20}$ (decomposed enyne product) calc. 176.1565, found 176.1569.

General Procedures for the Synthesis of Allenylsilanes

Synthesis of Dimethylphenylsilyl Lithium[3]

Lithium wires (0.10 g, 94 mmol) suspended in mineral oil were washed for 15 minutes in dry hexane (27 mL) under an argon atmosphere. The hexane was removed and the lithium suspended in dry THF (27 mL). The mixture was stirred with chlorodimethyl(phenyl)silane (6.71 mL, 40 mmol) at 0^{o}C for 6 hours, to form a red-purple solution, which was used crude in the next stage of the procedure.

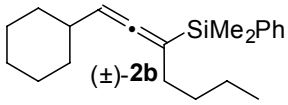
Protocol A:[4] To a stirred solution of CuCN.2LiCl [prepared by dissolving copper(I) cyanide (537 mg, 6 mmol) and lithium chloride (509 mg, 12 mmol) in dry THF (12 mL)], a solution of *n*-BuLi in hexane (6 mmol) was added dropwise at -78^{o}C under an argon atmosphere. After 15 minutes, a solution of 1-cyclohexyl-3-(trimethylsilyl)prop-2-ynylmethanesulfonate (2 mmol) in dry THF (5 mL) was added. It was left for 2 h and allowed to warm up to room temperature overnight. The reaction mixture was quenched with $NH_4Cl_{(aq)}$ (25 mL) and the aqueous layer extracted with Et_2O (3 x 20 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure, affording 487 mg of (1-cyclohexylhepta-1,2-dien-3-yl)trimethylsilane (yellow oil, 97% yield).

Protocol B: To a stirred solution of CuCN.LiCl [prepared by dissolving copper (I) cyanide (1.08 g, 12 mmol) and lithium chloride (1.02 g, 24 mmol) in dry THF (24 mL)], a solution on $LiSiMe_2Ph$ (8 mL) was added dropwise at -78^{o}C under argon atmosphere. After 15 minutes, a solution of 1-phenylnon-4-yn-3-yl methane sulfonate (1.18 g, 4 mmol) in dry THF (4 mL) was added. After 2 hours, the reaction mixture was allowed to warm to room temperature overnight. The reaction mixture was quenched with $NH_4Cl_{(aq)}$ (15 mL) and the aqueous layer extracted with ether (3 x 10 mL). The combined organic layers were dried over $MgSO_4$ and then filtered and concentrated under reduced pressure. The crude reaction mixture was purified by column chromatography (silica, hexane) affording 720 mg of (±)-**2a** (colourless oil,

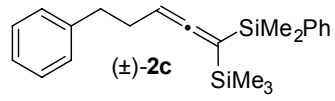
[3] I. Fleming, R. S. Roberts and S. C. Smith, *J. Chem. Soc., Perkin Trans. 1,* 1998, 1209.
[4] T. Nishiyama, T. Esumi, Y. Iwabuchi, H. Irie and S. Hatakeyama, *Tetrahedron Lett.*, 1998, **39**, 43.

54% yield).

Allenylsilane (±)-**2a**[5] has previously been reported.



(1-Cyclohexylhepta-1,2-dien-3-yl)dimethyl(phenyl)silane ((±)-2b): Protocol B was used. υ_{max}(film)/cm^{-1} 1920, 1427 and 833; δ_H (400 MHz; $CDCl_3$) 0.37 (6H, s, Si*Me*$_2$Ph), 0.86 (3H, t, *J* = 7.3 Hz, CH_2CH_3), 1.02-1.46 (10H, m, $(CH_2)_5$), 1.61-1.78 (5H, m, $(CH_2)_{3/2}$), 1.91 (2H, td, *J* = 7.3, 3.0 Hz, CCH_2CH_2), 4.88 (1H, quin., *J* = 3.0 Hz, *CH*C), 7.35-7.40 (3H, m, *Ph*), 7.53-7.57 (2H, m, *Ph*); δ_C (100 MHz; $CDCl_3$) -2.7, 13.9, 22.5, 26.3, 29.3, 31.3, 33.6, 33.8, 37.2, 92.5, 96.0, 127.7, 128.9, 133.9, 137.2, 205.4; *m/z* (CI$^+$) $C_{21}H_{32}Si$ (M$^+$) calc. 312.2273, found 312.2273.

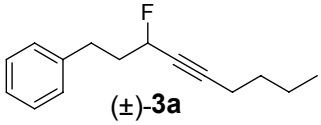


(1-(Dimethylphenyl)silyl)-5-phenylpenta-1,2-dienyl)trimethylsilane ((±)-2c): Protocol B was used. υ_{max}(film)/cm^{-1} 1920, 1427, 894 and 838; δ_H (400 MHz; $CDCl_3$) 0.00 (9H, s, Si*Me*$_3$), 0.39 (6H, s, Si*Me*$_2$Ph), 2.24-2.29 (2H, m, CH_2CH), 2.61-2.69 (2H, m, CH_2CH_2), 4.48-4.52 (1H, m, C*H*C), 7.18-7.55 (10H, m, *Ph* and SiMe$_2$*Ph*); δ_C (100 MHz; $CDCl_3$) -1.4, 0.0, 29.5, 36.7, 75.6, 89.6, 125.8, 127.6, 127.7, 128.3, 128.4, 128.9, 133.8, 140.6, 141.4, 212.6; *m/z* (CI$^+$) $C_{22}H_{30}Si_2$ (M$^+$) calc. 350.1886, found 350.1887.

General Procedure for Electrophilic Fluorodesilylation

Protocol A: To a stirred solution of (1-cyclohexylhepta-1,2-dien-3-yl)trimethylsilane (210 mg, 0.84 mmol) in acetonitrile (7 mL) was added Selectfluor^{TM} (297 mg, 0.84 mmol). The mixture was kept under argon atmosphere at room temperature for 6 h, then quenched with $NaHCO_{3(aq)}$ (10 mL). The aqueous layer was extracted with Et_2O (3 x 10 mL) and the combined organic layers dried over $MgSO_4$. This solution was concentrated and purification by column chromatography (silica, hexane) afforded 115 mg of (±)-**3b** (yellow oil, 70% yield).

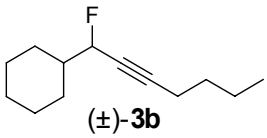
Protocol B: To a stirred solution of 1-cyclohexylhepta-1,2-dien-3-yl)dimethyl(phenyl)silane (187 mg, 0.60 mmol) in acetonitrile (3 mL) was added Selectfluor^{TM} (212 mg, 0.60 mmol). The mixture was kept under argon atmosphere at room temperature for 24 h, at which point it was quenched with $NaHCO_{3(sat)}$ (5 mL). The aqueous layer was extracted with Et_2O (3 x 5 mL) and the combined organic layers dried over $MgSO_4$. This solution was concentrated and purification by column chromatography (silica, pet 40-60/Et_2O; 95/5) afforded 55 mg of (±)-**3b** (colourless oil, 47% yield).



(3-Fluoronon-4-ynyl)benzene ((±)-3a):[6] Protocol B was used. υ_{max}(film)/cm^{-1} 2241, 1604, 1497, 1455 and 1348; δ_H (400 MHz; Acetone-d_6) 0.94 (3H, t, *J* = 7.2 Hz, CH_2CH_3), 1.40-1.58 (4H, m, $CH_2(CH_2)_2CH_3$), 2.03-2.24 (2H, m, CH_2CHF), 2.29 (2H, tdd, *J* = 13.8, 6.8, 1.9 Hz, CH_2CH_2C), 2.76-2.89 (2H, m, $PhCH_2CH_2$), 5.10 (1H, dm, *J* = 48.8 Hz, CH_2CFHC), 7.20-7.25

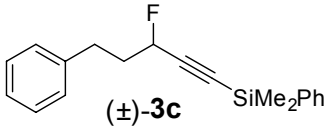
[5] T. Katsuhira, T. Harada, K. Maejima, A. Osada and A. Oku, *J. Org. Chem.*, 1993, **23**, 6166.
[6] L. Carroll, M. C. Pacheco, L. Garcia and V. Gouverneur, *Chem. Commun.*, 2006, **39**, 4113.

(3H, m, *Ph*CH_2), 7.29-7.35 (2H, m, *Ph*CH_2); δ_C (100 MHz; Acetone-d_6) 13.6, 18.4 (d, *J* = 3.2 Hz), 21.9, 30.4 (d, *J* = 2.4 Hz), 30.7 (d, *J* = 2.4 Hz), 37.9 (d, *J* = 22.7 Hz), 78.8 (d, *J* = 26.1 Hz), 82.3 (d, *J* = 165.4 Hz), 91.1 (d, *J* = 10.3 Hz), 126.1, 127.7, 128.5, 133.8, 140.8; δ_F (376.56 MHz; Acetone-d_6) -171.9; *m/z* (FI) $C_{15}H_{20}F$ (MH^+) calc. 219.1471, found 219.1470.



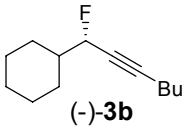
(±)-**3b**

(1-Fluorohept-2-ynyl)cyclohexane ((±)-3b):[6] Protocol A and B were used. υ_{max}(film)/cm^{-1} 2236 and 1338; δ_H (400 MHz; Acetone-d_6) 0.90-0.95 (3H, t, *J* = 7.2 Hz, $(CH_2)_3CH_3$), 1.05-1.30 (6H, m, $(CH_2)_3$), 1.38-1.58 (4H, m, $(CH_2)_2$), 1.65-1.72 (2H, m, CH_2), 1.73-1.90 (3H, m, CH_2CH), 2.24-2.30 (2H, ddd, *J* = 13.9, 7.1, 2.0 Hz, CCH_2), 4.90 (1H, ddt, *J* = 48.8, 6.1, 1.8 Hz, CHCHF); δ_C (100 MHz; Acetone-d_6) 13.5, 18.4 (d, *J* = 3.2 Hz), 21.9, 25.7, 26.9 (d, *J* = 2.9 Hz), 28.2 (d, *J* = 4.6 Hz), 30.8 (d, *J* = 2.6 Hz), 43.2 (d, *J* = 20.8 Hz), 78.0 (d, *J* = 26.3 Hz), 87.2 (d, *J* = 167.0 Hz), 91.0 (d, *J* = 10.2 Hz); δ_F (376.56 MHz; Acetone-d_6) -176.1; *m/z* (FI) $C_{13}H_{21}F$ (M^+) calc. 196.1627, found 196.1631.



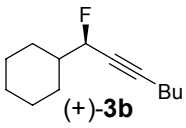
(±)-**3c**

(3-Fluoro-5-phenylpent-1-ynyl)dimethyl(phenyl)silane ((±)-3c): Protocol B was used. υ_{max}(film)/cm^{-1} 2241, 1248 and 845; δ_H (400 MHz; $CDCl_3$) 0.57 (6H, s, $SiMe_2Ph$), 2.17-2.40 (2H, m, CH_2CHF), 2.85-3.01 (2H, m, $PhCH_2CH2$), 5.21 (1H, ddd, *J* = 48.3, 7.1, 5.6 Hz, CH_2CHF), 7.28-7.33 (3H, m, *Ph*), 7.38-7.43 (2H, m, *Ph*), 7.46-7.51 (3H, m, *Ph*), 7.71-7.78, 2H, m, *Ph*); δ_C (100 MHz; $CDCl_3$) -1.2, 30.7 (d, *J* = 4.8 Hz), 37.5 (d, *J* = 27,6 Hz), 82.0 (d, *J* = 167.8 Hz), 91.8 (d, *J* = 8.8 Hz), 103.2 (d, *J* = 28.9 Hz), 126.2, 128.0, 128.5 (d, *J* = 4.8 Hz), 129.6, 133.6, 133.9, 136.1, 140.5; δ_F (376.56 MHz; $CDCl_3$) – 175.0; *m/z* (FI) $C_{19}H_{21}FSi$ (M^+) calc. 296.1397, found 296.1400.



(-)-**3b**

(*S*)-(1-Fluorohept-2-ynyl)cyclohexane ((-)-3b): Protocol A was used. Protocol A: $[\alpha]_D^{25}$ -0.88 (c = 1.00, $CHCl_3$).



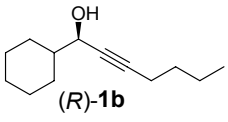
(+)-**3b**

(*R*)-(1-Fluorohept-2-ynyl)cyclohexane ((+)-3b): Protocol B was used. $[\alpha]_D^{17.3}$ +0.53 (c = 0.95, $CHCl_3$).

General Procedure for the Synthesis of Enantioenriched Alkynols[7]

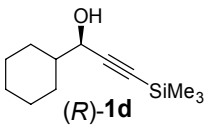
To a solution of $Zn(OTf)_2$ (0.558 g, 1.47 mmol) and (+)-*N*-methylephedrine (0.328 g, 1.82 mmol) in toluene (7 mL), was added triethylamine (0.511 mL, 3.64 mmol). After 1h 45 min, trimethylsilylacetylene (1.722 mL, 12.21 mmol) was added. After 15 minutes, a solution of cyclohexane carboxyaldehyde (0.144 µL, 1.19 mmol) in toluene (7 mL), was added *via* cannula. The reaction was then sealed with a screw cap and heated to 60°C. After 20 h, purification by column chromatography (silica, hexane/Et_2O; 85/15) afforded 249 mg of (*R*)-**1d** (yellow oil, 99% yield, 97% ee).

[7] D. Strand, P-O. Norby and T. Rein, *J. Org. Chem.*, 2006, **71**, 1879.



(*R*)-**1b**

(*R*)-1-Cyclohexylhept-2-yn-1-ol ((*R*)-1b):[8] $[\alpha]^{19.1}$ -4.1 (c = 0.68, $CHCl_3$)$[\alpha]_{D(lit)}^{25}$ -6.6 (c = 1.04, $CHCl_3$); 94% *ee* determined using the 3,5 dinitrobenzoate ester (Chirapak AD, 5% *i*-PrOH in hexane, 254 nm) t_r 27.8 (major) t_r 36.2 (minor).

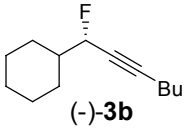


(*R*)-**1d**

(*R*)-1-Cyclohexyl-3-(trimethylsilyl)prop-2-yn-1-ol ((*R*)-1d):[9] $[\alpha]_D^{24.9}$ -5.8 (c = 1.00, $CHCl_3$), $[\alpha]_{D(lit)}^{25}$ -6.7 (c = 1.20, $CHCl_3$); 97% *ee* determined using the benzoate ester (Chirapak AD, hexane, 254 nm) t_r 6.2 (minor) t_r 7.1 (major).

Procedure for the Synthesis of Propargylic Fluoride (-)-3b with DAST[10]

To a stirred solution of (diethyl amino)sulphur trifluoride (DAST) (0.083 mL, 0.624 mmol) in anhydrous DCM (alcohol-free, 2 mL), was added (R)-1-cyclohexylhept-2-yn-1-ol (100 mg, 0.52 mmol) in DCM (1 mL) at -78°C. After 1 h at -78°C, the solution was quenched with $K_2CO_{3(sat)}$ (5 mL). The aqueous layer was extracted with Et_2O (3 x 5 mL) and the combined organic layers dried with $MgSO_4$. Concentration and purification by column chromatography (silica, hexane) afforded 71 mg of (-)-**3b** (colourless oil, 70% yield).



(-)-**3b**

(*S*)-(1-Fluorohept-2-ynyl)cyclohexane ((-)-3b): $[\alpha]_D^{25}$ -0.74 (c = 0.68, $CHCl_3$).

General Procedure for ^{13}C NMR in chiral liquid crystal solutions

Preparation of samples for ^{13}C NMR analysis in chiral liquid crystals followed the procedures described by Courtieu et al[11,12] and employed commercial poly(g-benzyl L-glutamate) (PBLG; Sigma) with a degree of polymerisation (DP) of 400-450 using $CDCl_3$ as co-solvent. Typically 100-120 mg PBLG was placed in a 5 mm NMR tube and a solution of 80-100 mg of solute in $CDCl_3$ added. Following dissolution the samples were mixed automatically by repeated inversion for many hours, usually overnight, and the homogeneity of the anisotropic phase assessed by observing the ^2H lock resonance. A pure doublet peak is expected for the $CDCl_3$ deuterium resonance owing to the appearance of quadrupolar coupling in the liquid crystalline phase; if a residual peak corresponding to any isotropic phase was apparent an additional 10 mg of PBLG was added to the tube and the process repeated until only the doublet resonance was observed. Prior to data acquisition it was found advantageous to optimise field homogeneity ("shim") on a standard (isotropic) $CDCl_3$ solution so as to minimise field optimisation of the liquid crystalline sample. ^{13}C data were collected on a Bruker AV 500 spectrometer operating at 125 MHz and equipped with a ^{13}C-optimised cryogenic probe. Sample temperatures were regulated at 298K and typically 256-512 transients collected with broadband proton decoupling. Spectra were processed with modest Gaussian apodization to enhance peak resolution.

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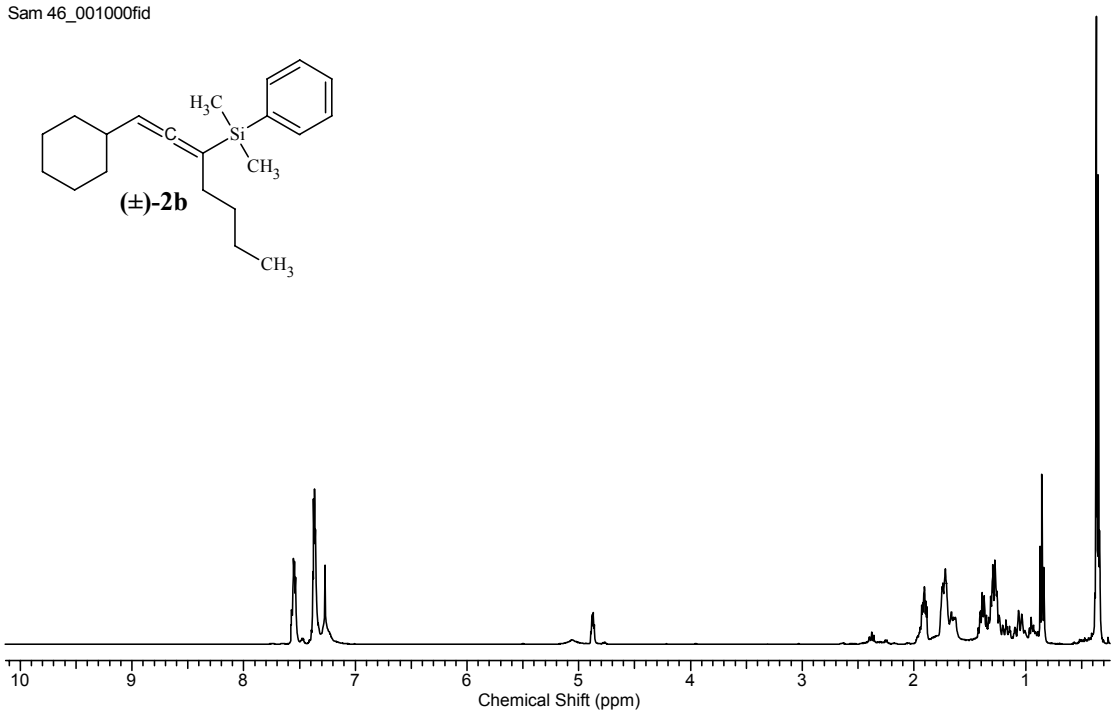
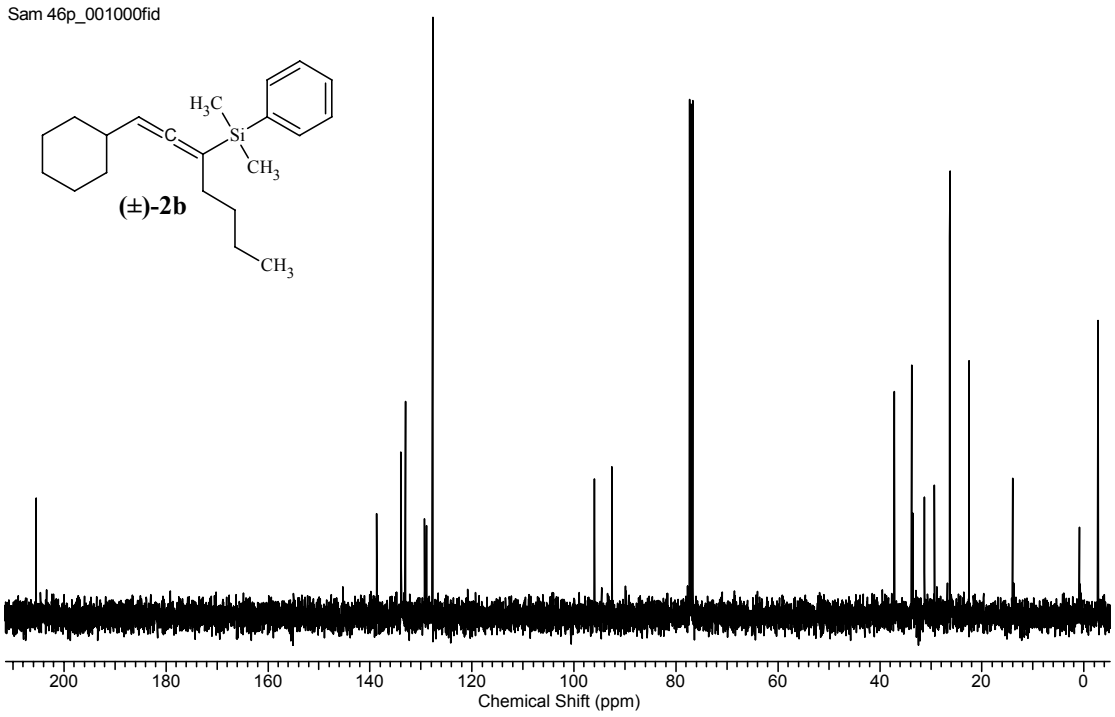
[8] N. K. Anand and E. M. Carreira, *J. Am. Chem. Soc.,* 2001, **123***,* 9687.
[9] D. E. Frantz, R. Fassler and E. M. Carreira, *J. Am. Chem. Soc.*, 2000, **122**, 1806.
[10] M. Prakesh, D. Grée and R. Grée, *Acc. Chem. Res.*, 2002, **35**, 175.
[11] A. Meddour, P. Berdague, A. Hedli, J. Courtieu and P. Lesot, *J. Am. Chem. Soc.*, 1997, **119**, 4502.
[12] M. Surfati, P. Lesot, D. Merlet and J. Courtieu, *Chem. Commun.*, 2000, 2069.

In the course of the work it was noted that there was considerable variation between commercial batches of PBLG despite being nominally the same material, these being distinguished by the physical appearance and their efficacy in enantiomeric resolution. This made defining a reproducible protocol problematic and a "trial and error" approach was invariably needed to provide satisfactory results.

NMR Spectra of Allenylsilane and Propargylic Fluorides





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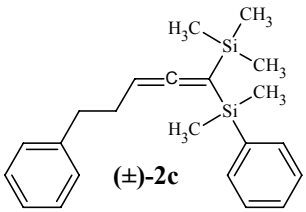
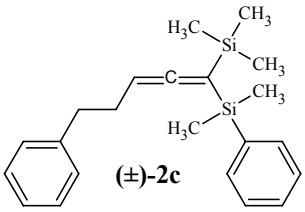


(±)-2c

Sam 46 C_000000fid



(±)-2c

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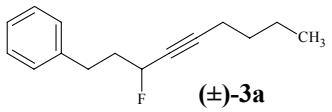

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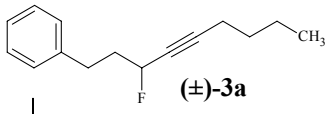

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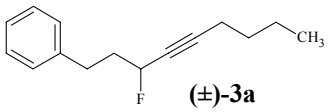

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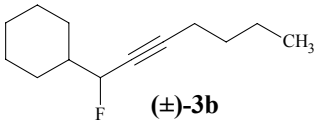

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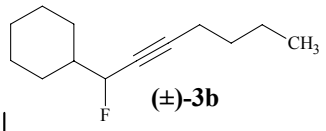

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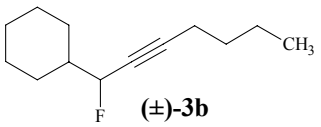

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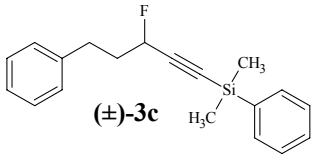

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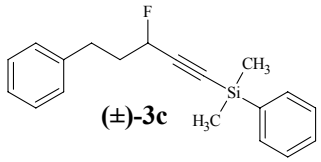

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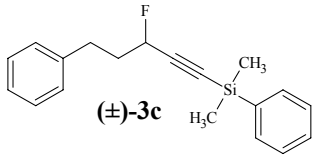

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