Radical [n+1] Annulations with Sulfur Dioxide

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Supplemental Material

Table of Contents

General Experimental	3
Preparation of hex-5-enoic acid 2-thioxo-2H-pyridin-1-yl ester (17).	3
Preparation of 2-methylene-5-hexen-1-ol (36).	4
Preparation of 2-(phenylsulfanyl)-hexa-1,5-diene (30).	4
Preparation of 2-methylene-6-trimethylsilanyl-hex-5-yn-1-ol (37).	5
Preparation of 2-(phenylsulfanyl)-hex-1-en-5-yne (38)	6
Preparation of 5-methylene-2-phenylsulfanylmethylene-tetrahydro-thiopyran 1,1-dioxide (51).	7
Preparation of hepta-2,6-dienoic acid methyl ester (40).	7
Preparation of hepta-2,6-dien-1-ol (41).	8
Preparation of 7-(phenylsulfanyl)-hepta-1,5-diene (42).	8
Preparation of 2-phenylsulfanylmethyl-5-vinyl-tetrahydro-thiophene 1,1-dioxide (52).	9
Preparation of hept-2-en-6-ynoic acid methyl ester (44).	10
Preparation of hept-2-en-6-yn-1-ol (45).	11
Preparation of 7-(phenylsulfanyl)-hept-5-en-1-yne (46)	12
Preparation of 2-ethylidene-5-phenylsulfanylmethylene-tetrahydro-thiophene 1,1-dioxide (53).	12
Preparation of 2-methylene-hept-6-enoic acid methyl ester (48).	13

Preparation of 2-methylene-hept-6-en-1-ol (49).....	14
¹ H-NMR, Compound 18	17
¹³ C-NMR, Compound 18	18
HETCOR, Compound 18.....	19
COSY, Compound 18	20
¹ H-NMR, Compound 31	21
¹³ C-NMR, Compound 31	22
¹ H-NMR, Compound 51	23
¹³ C-NMR, Compound 51	24
¹ H-NMR, Compound 52	25
¹³ C-NMR, Compound 52	26
HETCOR, Compound 52.....	27
COSY, Compound 52	28
NOESY, Compound 52	29
¹ H-NMR, Compound 53	30
¹³ C-NMR, Compound 53	31
¹ H-NMR, Compound 54	32
¹³ C-NMR, Compound 54	33
References.....	34

General Experimental

Tetrahydrofuran and ether were distilled from sodium/benzophenone. Methanol was distilled over magnesium activated with iodine. DMSO was distilled over calcium hydride at reduced pressure. Dichloromethane was degassed prior to use by bubbling with nitrogen for 3 min. All other reagents were used as received. Photolyses were carried out in 15 ml or 48 ml heavy walled glass pressure vessels produced by ChemGlass (cat. # CG-1880-04) using a 450 W mercury lamp produced by ACE glass (cat. # 7825-34). Flash chromatography was performed using EM Science Silica Gel 60. FTIR spectra were recorded in deuteriochloroform solution. NMR spectra were recorded at 250-MHz or 500 MHz as specified with tetramethylsilane as the internal standard for proton and the CDCl_3 triplet as an internal standard for carbon. Mass spectra were obtained on an Electrospray Ionization Time of Flight (ESITOF) mass spectrometer.

Preparation of hex-5-enoic acid 2-thioxo-2H-pyridin-1-yl ester¹ (17).

Based on the procedure of Barton,¹ to a solution of 5-hexenoic acid (1.53 g, 13.4 mmol) in 45 ml of CH_2Cl_2 , oxalyl chloride (1.29 ml, 14.7 mmol) and a catalytic amount of DMF (0.052 ml, 0.67 mmol) were added dropwise. The solution was stirred at room temperature for 45 min until all the bubbling ceased. To this was added 2-mercaptopyridine-*N*-oxide sodium salt (2.20 g, 14.7 mmol) and the suspension was stirred at room temperature protected from light by covering the reaction flask with aluminum foil. After 30 min, the yellow suspension was quickly filtered and concentrated, and then dissolved in a minimal amount of 1:2 hexanes:ethyl acetate and filtered through a plug of silica gel. Volatiles were removed *in vacuo* to give 2.70 g (12.1 mmol, 90% yield) of the title compound as yellow oil.

TLC: 1:1 hexanes:ethyl acetate, UV, R_f =0.36.

¹H-NMR (500 MHz, CDCl_3): δ 7.70 (dd, J =1.5 Hz, 9.0 Hz, 1H), 7.56 (dd, J =1.0 Hz, 8.0 Hz, 1H), 7.22 (td, J =1.5 Hz, 8.5 Hz, 1H), 6.64 (td, J =2 Hz, 14 Hz, 1H) 5.82-5.69 (m, 1H), 5.10 (dd, J =17.5 Hz, 1.5 Hz, 2H), 2.74 (t, J =7.5 Hz, 2H), 2.25-2.21 (m, 2H), 1.96-1.93 (m, 2H) ppm.

¹³C- NMR (125 MHz, CDCl₃): δ 178.5, 175.9, 168.8, 137.7, 137.6, 133.56, 116.2, 112.6, 32.9, 30.9, 23.5 ppm.

Preparation of 2-methylene-5-hexen-1-ol² (36).

Based on the procedure of Trost,² a solution of *n*-butyllithium (17 ml of a 2.5 M solution in hexanes, 41.6 mmol) in anhydrous ether (31 ml) was cooled to 0 °C and *N,N,N,N*-tetramethylethylenediamine (6.28 ml, 41.63 mmol) was added. The mixture was stirred for 15 min, cooled to -78 °C, and methallyl alcohol **35** (1.75 ml, 20.81 mmol) was added. The mixture was stirred at room temperature for 24 h. The resulting yellow suspension was cooled to -78 °C and allyl bromide (1.89 ml, 15.62 mmol) in 2.6 ml of anhydrous ether was added dropwise. After stirring at -78 °C for 1 h, the cooling bath was removed, and the mixture was stirred for an additional 5 h. The reaction was quenched with saturated aqueous NH₄Cl solution (30 ml), and the aqueous layer extracted with ether (2 x 30 ml). The combined ether layers were washed with water (6 x 30 ml), saturated aqueous CuSO₄ solution (2 x 60 ml) and brine (50 ml), dried over MgSO₄, filtered and concentrated to give 929 mg (7.73 mmol, 50% crude yield) of the title compound as a yellow oil. This material was used in the next step without further purification.

¹H-NMR (500 MHz, CDCl₃): 5.82 (ddt, J=17.0 Hz, 10.5 Hz, 5.0 Hz, 1H), 5.04 (br s, 1H), 5.03 (dt, J=18.2 Hz, 2.5 Hz, 1H), 4.97 (dd, J=9.5 Hz, 2.5 Hz, 1H), 4.88 (d, J=2.0 Hz, 1H), 4.07 (s, 2H), 2.25-2.23 (m, 2H), 2.17-2.14 (m, 2H) ppm.

Preparation of 2-(phenylsulfanyl)-hexa-1,5-diene³ (30).

Based on the procedure of Castro,³ 2-methylene-5-hexen-1-ol **36** (840 mg, 6.88 mmol) and CCl₄ (1.86 ml, 19.3 mmol) was dissolved in 14 ml of anhydrous THF and the mixture was cooled to -78 °C for 1 h. Hexamethylphosphorous triamide (1.27 ml, 6.99 mmol) was added dropwise to the reaction mixture. In a separate flask, thiophenol (0.718 ml, 6.992 mmol) was combined with triethylamine (1.07 ml, 7.68 mmol) and 7 ml of dry THF, and added to the reaction mixture dropwise. After 20 min, the cooling bath was removed and

the mixture was stirred for 5 h. Ether (50 ml) was added and the resulting white precipitate was removed by filtration. The organic phase was washed sequentially with 10% NaOH (4 x 50 ml), water (50 ml) and brine (50 ml). The organic phase was dried over MgSO₄, filtered and concentrated *in vacuo*. Purification by flash chromatography using hexanes afforded 91 mg (0.45 mmol, 6.5% yield) of the title compound as a clear oil.

TLC: 5:1 hexanes:ethyl acetate, UV, I₂, R_f=0.36.

IR (CDCl₃): 3070, 1644, 729 cm⁻¹.

¹H-NMR (500 MHz, CDCl₃): δ 7.35-7.19 (m, 5H), 5.82 (ddt, J=16.3 Hz, 10.5 Hz, 6.5 Hz, 1H), 5.05 (td, J=16.3 Hz, 2.0 Hz, 1H), 4.98 (d, J=10.5 Hz, 1H), 4.92 (s, 1H), 4.86 (s, 1H), 3.57 (s, 2H), 2.31-2.83 (m, 2H), 2.26-2.21 (m, 2H) ppm.

¹³C-NMR (125 MHz, CDCl₃): δ 143.9, 138.1, 136.4, 129.9, 128.7, 126.2, 114.9, 113.5, 40.5, 33.7, 31.8 ppm.

HRMS calc'd. for C₁₃H₁₇S 205.1063, found 205.1046.

Preparation of 2-methylene-6-trimethylsilyl-hex-5-yn-1-ol (37).

Based on the procedure by Trost,² a solution of *n*-butyllithium (5.44 ml of a 2.5 M solution in hexanes, 13.63 mmol) in 9 ml of anhydrous ether was cooled to 0 °C and *N,N,N,N*-tetramethylethylenediamine (2.05 ml, 13.63 mmol) was added. The mixture was stirred for 15 minutes, cooled to -78 °C and methallyl alcohol **35** (490 mg, 6.80 mmol) was added. The mixture was stirred at room temperature for 24 h. The resulting yellow suspension was cooled to -78 °C and (3-bromo-prop-1-ynyl)-trimethylsilane (1.00 g, 5.23 mmol) was added dropwise. After the mixture was stirred at -78 °C for 1 h, the cooling bath was removed and the mixture was stirred for an additional 5 h. The reaction was quenched with saturated aqueous NH₄Cl solution (30 ml) and the aqueous layer was extracted with ether (2 x 30 ml). The combined ether layers were washed with water (6 x 30 ml), saturated aqueous CuSO₄ solution (2 x 60 ml) and brine (50 ml), dried over MgSO₄, filtered and concentrated. Purification by flash column chromatography using a gradient eluent of hexanes to 10:1 hexanes:ethyl acetate afforded 243 mg (1.33 mmol, 25% yield) of the title compound as a yellow oil, containing minor impurities. It was used in the next step without further purification.

TLC: 5:1=hexanes:ethyl acetate, UV, *p*-anisaldehyde stain, I₂ stain, R_f=0.29.

IR (CDCl₃): 3497, 3156, 2963, 2172, 1418, 1091, 844, 741, 650 cm⁻¹.

¹H-NMR (500 MHz, CDCl₃): δ 5.07 (s, 1H), 4.92 (s, 1H), 4.10 (s, 2H), 2.39 (t, J=7.5 Hz, 2H), 2.31 (t, J=7.5 Hz, 2H), 0.14 (s, 9H) ppm.

¹³C-NMR (125 MHz, CDCl₃): δ 147.4, 111.0, 85.3, 80.4, 65.9, 32.1, 19.1, 0.2 ppm.

HRMS (M+1) calc'd for C₁₀H₁₉OSi 183.1183, found 183.1200.

Preparation of 2-(phenylsulfanyl)-hex-1-en-5-yne (38)

Based on the procedure of Castro,³ 2-methylene-6-trimethylsilyl-hex-5-yn-1-ol **37** (243 mg, 1.33 mmol) and CCl₄ (0.35 ml, 3.67 mmol) were dissolved in 4 ml of anhydrous THF and the mixture was cooled to -78 °C. Hexamethylphosphorous triamide (0.36 ml, 2.00 mmol) was added dropwise to the reaction mixture. In a separate flask, thiophenol (0.27 ml, 2.66 mmol) was combined with triethylamine (0.37 ml, 2.66 mmol) and 2 ml of anhydrous THF, and added dropwise to the reaction mixture. After 20 min, the cooling bath was removed and the mixture was stirred for 5 h. Ether (50 ml) was added and the resulting white precipitate was removed by filtration. The organic phase was washed sequentially with 10% NaOH (4 x 50 ml), water (50 ml) and brine (50 ml). The organic phase was dried over MgSO₄, filtered and concentrated to afford 488 mg of the crude title compound. To remove the silyl group, 285 mg of this material was dissolved in 13 ml of THF and tetrabutylammonium fluoride (1.0 M in THF, 1.04 ml, 1.04 mmol) was added and stirred at room temperature for 1.5 h. Volatiles were removed *in vacuo*. The residue was dissolved in dichloromethane (30 ml) and washed sequentially with water (3 x 30 ml) and brine (30 ml). The organic phase was dried over MgSO₄, filtered and concentrated to afford 202 mg of the crude product. Purification by flash column chromatography using hexanes afforded 42 mg (0.21 mmol, 21% yield) of the title compound as a yellow oil.

TLC: 10:1 hexanes:ethyl acetate, UV, *p*-anisaldehyde stain, I₂ stain, R_f=0.3.

¹H-NMR (500 MHz, CDCl₃): δ 7.35-7.34 (m, 2H), 7.29-7.26 (m, 2H), 7.21-7.19 (m, 1H), 4.95 (s, 1H), 4.90 (s, 1H), 3.57 (s, 2H), 2.44 (t, J=7.5 Hz, 2H), 2.37(td, J=7.5 Hz, 2.5 Hz, 2H), 1.98 (t, J=2.5 Hz, 1H) ppm.

^{13}C NMR (500 MHz, CDCl_3): δ 142.7, 136.2, 130.3, 128.9, 126.5, 114.4, 83.8, 68.9, 40.5, 33.2, 17.3 ppm.

Preparation of 5-methylene-2-phenylsulfanylmethylene-tetrahydro-thiopyran 1,1-dioxide (51).

Cyclization substrate 2-(phenylsulfanylmethyl)-hex-1-en-5-yne **38** (42 mg, 0.21 mmol) and diphenyl disulfide (7.0 mg, 0.03 mmol) were dissolved in 3 ml of dichloromethane and were placed into a 15 ml heavy walled glass pressure vessel. The solution was cooled to $-78\text{ }^\circ\text{C}$ and 3 ml of SO_2 gas was condensed into the reaction mixture using a dry ice condenser. The mixture became yellow in color. The dry ice condenser was removed and the pressure vessel sealed and irradiated with a 450 W Hg lamp for 63 h. During that time the solution turned brown in color. The mixture was cooled to $-78\text{ }^\circ\text{C}$ and the pressure vessel was slowly opened to air and left standing in the hood at room temperature until all of the SO_2 gas escaped. Volatiles were removed *in vacuo* to afford a brown oil that contained the desired product, diphenyl disulfide and an additional impurity. Purification by preparative TLC using 2:1 hexanes:ethyl acetate afforded 10 mg (0.04 mmol, 18% yield) of the title compound.

TLC: 2:1 hexanes:ethyl acetate, UV, *p*-anisaldehyde stain, I_2 stain, $R_f=0.32$.

IR (CDCl_3): 2984, 2902, 1650, 1473, 1309, 1138, 910, 737 cm^{-1} .

^1H -NMR (500 MHz, CDCl_3): δ 7.52 (s, 1H), 7.48-7.46 (m, 2H), 7.39-7.37 (m, 3H), 5.19 (s, 1H), 5.13 (s, 1H), 3.73 (s, 2H), 2.78 (t, $J=6.5\text{ Hz}$, 2H), 2.45 (t, $J=6.5\text{ Hz}$, 2H) ppm.

^{13}C -NMR (125 MHz, CDCl_3): δ 138.2, 137.2, 132.7, 132.2, 131.6, 129.7, 128.8, 118.6, 62.3, 34.2, 27.8 ppm.

HRMS ($M+1$) calc'd for $\text{C}_{13}\text{H}_{14}\text{O}_2\text{S}_2$ 267.0496, found 267. 0508.

Preparation of hepta-2,6-dienoic acid methyl ester⁴ (40).

Based on the procedure of Crandall,⁴ sodium metal (1.09 g, 47.6 mmol) was dissolved in 60 ml of anhydrous methanol while cooling in an ice bath to $0\text{ }^\circ\text{C}$. A vigorous reaction ensued and the temperature rose to $40\text{ }^\circ\text{C}$. When reaction mixture returned to $0\text{ }^\circ\text{C}$, methyl diethylphosphonoacetate (10.00 g, 47.64 mmol) was added. The reaction mixture was stirred for 15 min at room temperature, and was again cooled to $0\text{ }^\circ\text{C}$; 4-pentenal **39**

(3.36 ml, 34.0 mmol) was added via syringe. The mixture was stirred at room temperature for 1.5 h, after which 60 ml of water was added and the mixture was extracted with ether (3 x 60 ml). The organic phase was washed with brine (60 ml), dried over MgSO₄, filtered and concentrated giving 3.35 g (23.9 mmol, 70% yield) of the title compound as a light yellow oil.

TLC: 1:1 hexanes:ethyl acetate, UV, *p*-anisaldehyde stain, I₂ stain, R_f=0.7.

¹H-NMR (500 MHz, CDCl₃): δ 6.98 (dt, J=16.0 Hz, 6.5 Hz, 1H), 5.84 (d, J=16.0 Hz, 1H), 5.79 (ddt, J=16.5 Hz, 10.0 Hz, 6.5 Hz, 1H), 5.05 (dd, J=16.5 Hz, 2.0 Hz, 1H), 5.00 (dd, J=10.0 Hz, 2.0 Hz, 1H), 3.72 (s, 3H), 2.31-2.29 (m, 2H), 2.24-2.21 (m, 2H) ppm.

¹³C-NMR (125 MHz, CDCl₃): δ 167.1, 148.7, 137.1, 121.4, 115.7, 51.5, 32.1, 31.6 ppm.

Preparation of hepta-2,6-dien-1-ol⁵ (41).

A solution of hepta-2,6-dienoic acid methyl ester **40** (400 mg, 2.85 mmol) in 9.5 ml of anhydrous THF was cooled to 0 °C and DIBAL-H (1.0 M solution in toluene, 7.13 ml, 7.13 mmol) was added. The cooling bath was removed and the solution was stirred at room temperature for 2 h. The mixture was chilled in an ice bath, and then quenched by the sequential addition of 0.3 ml of 15% NaOH, 0.3 ml of ether and 0.7 ml of water. The mixture was stirred at room temperature for 15 min and then dried over MgSO₄ and filtered through Celite. The solvent was removed *in vacuo* affording 319 mg of the crude product, which contained toluene as an impurity as determined by ¹H-NMR. The spectrum was identical to that in the literature.^{Error! Bookmark not defined.} This material was used in the next step without further purification.

TLC: 5:1 hexanes:ethyl acetate, I₂ stain, *p*-anisaldehyde stain, R_f=0.31.

¹H-NMR (250 MHz, CDCl₃): 5.81-5.65 (m, 3H), 5.01 (d, J=16.5 Hz, 1H), 4.96 (d, J=9.3 Hz, 1H), 4.08(d, J=4.0 Hz, 2H), 2.15 (m, 4H).

Preparation of 7-(phenylsulfanyl)-hepta-1,5-diene (42).

Based on the procedure of Castro,³ hepta-2,6-dien-1-ol **41** (300 mg, 2.66 mmol) and CCl₄ (0.66 ml, 6.86

mmol) were dissolved in 8 ml of anhydrous THF and the mixture was cooled to -78 °C for 1h. Hexamethylphosphorous triamide (0.45 ml, 2.50 mmol) was added dropwise to the reaction mixture. In a separate flask, thiophenol (0.308 ml, 3.001 mmol) was combined with triethylamine (0.419 ml, 3.006 mmol) and 7 ml of anhydrous THF, and added to the reaction mixture dropwise. After 20 min, the cooling bath was removed and the mixture was stirred for 5 h. Ether (50 ml) was added and the resulting white precipitate was removed by filtration. The organic phase was washed sequentially with 10% NaOH (4 x 50 ml), water (50 ml) and brine (50 ml). The organic phase was dried over MgSO₄, filtered and concentrated. Purification by flash column chromatography using hexanes afforded 105 mg (0.514 mmol, 21% yield) of the title compound as a yellow oil containing 12% of diphenyl disulfide as an impurity.

TLC: 5:1 hexanes:ethyl acetate, UV, *p*-anisaldehyde stain, I₂ stain, R_f=0.65.

IR (CDCl₃): 3006, 2963, 1640, 1438, 1417, 908, 746 cm⁻¹.

¹H-NMR (500 MHz, CDCl₃): δ 7.35-7.17 (m, 5H), 5.74 (ddt, J=17.0 Hz, 10.5 Hz, 6.2 Hz, 1H), 5.55-5.52 (m, 2H), 4.98 (d, J=17.0 Hz, 1H), 4.95 (d, J=10.5 Hz, 1H), 3.52 (d, J=5.5 Hz, 2H), 2.09-2.05 (m, 4H) ppm.

¹³C-NMR(125 MHz, CDCl₃): δ 138.1, 130.0, 129.2, 128.8, 127.3, 126.2, 125.6, 114.9, 36.6, 33.4, 31.8 ppm.

HRMS (M+1) calc'd. For C₁₃H₁₇S 205.1066, found 205.1046.

Preparation of 2-phenylsulfanylmethyl-5-vinyl-tetrahydro-thiophene 1,1-dioxide (52).

Cyclization substrate 7-(phenylsulfanyl)-hepta-1,5-diene **42** (200 mg, 0.84 mmol, containing 13.5 % of diphenyl disulfide) was dissolved in 14 ml of dichloromethane and placed into a 48 ml heavy walled glass pressure vessel. The solution was cooled to -78 °C and 14 ml of SO₂ gas was condensed into the reaction mixture using a dry ice condenser. The mixture became yellow in color. The dry ice condenser was removed and the pressure vessel sealed and irradiated with a 450 W Hg lamp for 17 h. During the photolysis, the solution turned brown in color. The mixture was cooled to -78 °C and the pressure vessel was slowly opened to air and left standing in the hood at room temperature until all of the SO₂ gas evaporated. Volatiles were removed *in vacuo* to give 237 mg (0.78 mmol, 92%) of the title compound as a brown oil. The two inseparable

products were a 4:1 mixture of diastereomers as determined by ^1H -NMR. The peaks were assigned following extensive HETCOR and COSY analysis. The major diastereomer is tentatively assigned as the *cis* isomer based on a NOESY peak between the two methine hydrogens at δ 3.58 and δ 3.12 ppm.

TLC: 5:1 hexanes:ethyl acetate, UV, I_2 , $R_f=0.65$.

IR (CDCl_3): 3006, 1750, 1708, 1418, 914, 726 cm^{-1} .

Major diastereomer:

^1H -NMR (500 MHz, CDCl_3): δ 7.41-7.24 (m, 5H), 5.80-5.73 (m, 1H), 5.44 (d, $J=10.0$ Hz, 1H), 5.40 (d, $J=17.0$ Hz, 1H), 3.58 (ddd, $J=11.5$ Hz, 7.8 Hz, 7.8 Hz, 1H), 3.53 (d, $J=13.8$ Hz, 1H), 3.15-3.09 (m, 1H), 2.95 (dd, $J=13.8$ Hz, 10.0 Hz, 1H), 2.52-2.46 (m, 1H), 2.37-2.22 (m, 1H), 1.94-1.85 (m, 1H), 1.81-1.72 (m, 1H) ppm.

^{13}C -NMR (125 MHz, CDCl_3): δ 134.1, 130.8, 129.4, 128.7, 127.5, 122.8, 66.3, 60.3, 33.4, 27.4, 27.1 ppm.

Minor diastereomer:

^1H -NMR (500 MHz, CDCl_3): δ 7.41-7.24 (m, 5H), 5.80-5.73 (m, 1H), 5.44 (d, $J=10.0$ Hz, 1H), 5.40 (d, $J=17.0$ Hz, 1H), 3.67 (ddd, $J=8.0$ Hz, 8.0 Hz, 8.0 Hz, 1H), 3.52 (d, $J=14.0$ Hz, 11.0 Hz, 1H), 2.37-2.22 (m, 2H), 2.13-1.99 (m, 2H) ppm.

^{13}C -NMR (125 MHz, CDCl_3): δ 133.9, 131.0, 129.6, 128.5, 127.6, 122.6, 65.6, 59.0, 32.6, 26.1, 25.7 ppm.

HRMS ($M+1$) calc'd. for $\text{C}_{13}\text{H}_{16}\text{O}_2\text{S}_2$ 269.0662, found 269.0665.

Preparation of hept-2-en-6-ynoic acid methyl ester⁶ (44).

Based on the procedure of Liu,⁶ a solution of freshly distilled oxalyl chloride (6.65 g, 51.6 mmol) in 230 ml of anhydrous THF was cooled to -78 °C. A solution of anhydrous DMSO (4.10 ml, 57.8 mmol) in 20 ml of anhydrous THF was added over a period of 10 min using an addition funnel, and then stirred for 1 h. Next, 4-pentyn-1-ol **43** (3.65 g, 43.4 mmol) was added dropwise over a period of 20 min. The formation of a white precipitate was observed. The reaction mixture was stirred for 1 h. Triethylamine (18.04 ml, 129.5 mmol) was added slowly using an addition funnel and stirred for 1.5 h. The cooling bath was removed and the reaction mixture was stirred at room temperature for 1 h. Solids were removed by filtration and the filter cake

was washed with 30 ml of THF. The filtrate was cooled to 0 °C. In a separate flask, a solution of NaH (60% suspension in mineral oil, 2.17 g, 54.2 mmol) in 20 ml of anhydrous THF was cooled to 0 °C. Methyl diethylphosphonoacetate (10.2 ml, 55.4 mmol) was added slowly while maintaining the temperature below 25 °C. When addition was complete, the Wadsworth-Horner-Emmons reagent was cooled to 0 °C and stirred for 30 min. It was then added via cannula to the reaction flask containing the aldehyde and stirred overnight.

The next morning, 200 ml of ether was added, and the mixture was washed sequentially with aqueous saturated NH₄Cl solution (200 ml), 1N HCl (200 ml), and brine (200 ml), dried over MgSO₄, filtered and the volatiles removed *in vacuo* to afford 6.62 g of the crude product. Purification by flash column chromatography using 6:1 hexanes:ethyl acetate afforded 2.46 g (17.6 mmol, 41% yield) of the title compound as a yellow oil.

TLC: 3:1 hexanes:ethyl acetate, UV, *p*-anisaldehyde stain, I₂ stain, R_f=0.33.

¹H NMR (500 MHz, CDCl₃): δ 6.97 (dt, J=16.0 Hz, 6.5 Hz, 1H), 5.89 (d, J=16.0 Hz, 1H), 3.72 (s, 3H), 2.43-2.42 (m, 2H), 2.36-2.33 (m, 2H), 1.99 (t, J=4.5 Hz, 1H) ppm.

¹³C-NMR (500 MHz, CDCl₃): δ 166.8, 146.7, 122.2, 82.7, 69.5, 51.6, 31.1, 17.5 ppm.

Preparation of hept-2-en-6-yn-1-ol⁶ (45).

Based on the procedure of Liu,⁶ a solution of hept-2-en-6-ynoic acid methyl ester **44** (1.65 g, 11.9 mmol) in 60 ml of anhydrous THF was cooled to 0 °C, and DIBAL-H (1.0 M solution in toluene, 19.7 ml, 23.8 mmol) was added. The cooling bath was removed and the solution was stirred at room temperature for 2 h. After cooling the mixture on ice, the reaction was quenched by sequential addition of 1.0 ml of 15% NaOH, 1.0 ml of ether and 2.4 ml of water. The mixture was stirred at room temperature for 15 min, then dried over MgSO₄ and filtered through Celite. The solvent was removed *in vacuo* affording 1.16 g (9.75 mmol, 82% yield) of the title compound as a pale yellow oil.

¹H-NMR (500 MHz, CDCl₃): δ 5.80-5.71 (m, 2H), 4.13 (d, J=4.5 Hz, 2H), 2.28-2.27 (m, 4H), 1.96 (t, J=2.5 Hz, 1H) ppm.

¹³C-NMR (125 MHz, CDCl₃): δ 130.7, 130.6, 83.8, 68.9, 63.6, 31.2, 18.5 ppm.

Preparation of 7-(phenylsulfanyl)-hept-5-en-1-yne (46)

Based on the procedure of Castro,³ hept-2-en-6-yn-1-ol **45** (1.95 g, 17.7 mmol) and CCl₄ (4.70 ml, 48.7 mmol) were dissolved in 25 ml of anhydrous THF and the mixture was cooled to -78 °C for 1 h. Hexamethylphosphorous triamide (4.83 ml, 26.55 mmol) was added dropwise to the reaction mixture. In a separate flask, thiophenol (3.63 ml, 35.40 mmol) was combined with triethylamine (4.93 ml, 35.40 mmol) and 10 ml of anhydrous THF, and added dropwise to the reaction mixture. After 20 min, the cooling bath was removed and the mixture was stirred for 5 h. Ether (50 ml) was added and the white precipitate was removed by filtration. The organic phase was washed sequentially with 10% NaOH (4 x 50 ml), water (50 ml) and brine (50 ml). The organic phase was dried over MgSO₄, filtered and concentrated. Purification by flash column chromatography using a gradient of hexanes to 49:1 hexanes:ethyl acetate afforded 570 mg (2.82 mmol, 16% yield) of the title compound as a yellow oil, which contained a small amount of diphenyl disulfide as an impurity.

TLC: 10:1 hexanes:ethyl acetate, UV, I₂, R_f=0.30.

IR (CDCl₃): 3309, 3006, 2145, 1708, 1418, 920, 736, 648 cm⁻¹.

¹H-NMR (500 MHz, CDCl₃): δ 7.35-7.17 (m, 5H), 5.59-5.57 (m, 2H), 3.52 (d, J=5.5 Hz, 2H), 2.22-2.15 (m, 4H), 1.94 (t, J=2.5 Hz, 1H) ppm.

¹³C-NMR (125 MHz, CDCl₃): δ 135.3, 132.0, 130.2, 128.8, 126.7, 126.3, 83.8, 68.8, 36.5, 31.3, 18.6 ppm.

HRMS (M+1) calc'd. for C₁₃H₁₅S 203.0871, found 203.0889.

Preparation of 2-ethylidene-5-phenylsulfanylmethylene-tetrahydro-thiophene 1,1-dioxide (53).

Allylic sulfide 7-(phenylsulfanyl)-hept-5-en-1-yne **46** (113 mg, 0.56 mmol) and diphenyl disulfide (24 mg, 0.11 mmol) were dissolved in 8 ml of dichloromethane and placed into a 48 ml heavy walled glass pressure vessel. The solution was cooled to -78 °C and 8 ml of SO₂ gas was condensed into the reaction mixture using a dry ice condenser. The mixture became yellow in color. The dry ice condenser was removed, the

pressure vessel sealed and irradiated with a 450 W Hg lamp for 63 h. During photolysis the solution turned brown in color. The mixture was cooled to -78 °C and the pressure vessel was slowly opened to air and left standing in the hood at room temperature until all of the SO₂ gas had evaporated. Volatiles were removed *in vacuo* to give a brown oil that contained the desired product, unreacted starting material, diphenyl disulfide and an unknown impurity. Purification by flash column chromatography using a gradient of hexanes to 10:1 hexanes:ethyl acetate afforded 32 mg (0.12 mmol, 21% yield) of title compound as a yellow oil.

TLC: 5:1 hexanes:ethyl acetate, UV, I₂, R_f=0.11.

IR (CDCl₃): 2983, 2949, 1639, 1605, 1441, 1306, 1133, 988, 908, 737 cm⁻¹.

¹H-NMR (500 MHz, C₆D₆): δ 7.35 (dd, J=2.7 Hz, 2.7 Hz, 1H), 7.24 –7.11 (m, 5H), 5.75 (ddd, J=17.0 Hz, 10.5 Hz, 7.5 Hz, 1H), 5.13 (dd, J=10.5 Hz, 1.0 Hz, 1H), 5.12 (dd, J=17.0 Hz, 1.0 Hz, 1H), 3.09 (ddd, J=10.5 Hz, 7.5 Hz, 7.5 Hz, 1H), 2.22 (dddd, J=17.3 Hz, 8.3 Hz, 2.8 Hz, 2.8 Hz, 1H), 2.01 (dddd, J=17.3 Hz, 8.7 Hz, 8.7 Hz, 2.8 Hz, 1H), 1.70-1.62 (m, 1H), 1.53 (dddd, J=15.8 Hz, 6.5 Hz, 6.0 Hz, 3.0 Hz, 1H).

¹³C NMR (125 MHz, CDCl₃): δ 134.2, 133.5, 132.5, 131.4, 129.7, 128.8, 127.5, 123.4, 64.2, 24.7, 23.4 ppm.

HRMS (M+1) calc'd for C₁₃H₁₅O₂S₂ 267.0504, found 267. 0508.

Preparation of 2-methylene-hept-6-enoic acid methyl ester⁷ (48).

Based on the procedure of Borhan,⁷ a suspension of NaH (60% dispersion in mineral oil, 1.40 g, 34.9 mmol) in 20 ml of anhydrous THF was cooled to 0 °C. A solution of methyl diethylphosphonoacetate (5.86 ml, 31.8 mmol) in 20 ml of anhydrous THF was added dropwise via an addition funnel. The resulting mixture was stirred at room temperature for 1 h, then cooled to 0 °C and 5-bromo-pentene **47** (1.88 ml, 15.9 mmol) dissolved in 20 ml of anhydrous THF was added dropwise via an addition funnel. The cooling bath was removed and the resulting reaction mixture was refluxed for 20 h. The mixture was cooled to 0 °C and 50 ml of water was added, followed by extraction with Et₂O (3 x 50 ml). The organic phase was washed with 50 ml of brine, dried over MgSO₄ and filtered. The volatiles were removed *in vacuo* affording 4.15 g (94% crude yield) of a yellow oil containing some impurities. This was used in the next step without further purification. Thus, a solution of

crude 2-(diethoxyphosphoryl)-hept-6-enoic acid methyl ester (4.15 g, 14.9 mmol) in 50 ml of water was combined with K_2CO_3 (4.12 g, 29.8 mmol) and formaldehyde (37% w/w solution in water, 5.23 ml, 59.6 mmol). This mixture was heated to 80 °C for 3 h, and then cooled to room temperature and extracted with Et_2O (4 x 30 ml). The organic phase was washed with brine (50 ml), dried over $MgSO_4$ and filtered. The solvent was removed *in vacuo* to afford 1.95 g (12.6 mmol, 85% crude yield) of the title compound as a yellow oil containing some impurities. The material was used in the next step without further purification.

TLC: 2:1 hexanes:ethyl acetate, I_2 stain, R_f =0.58.

1H -NMR (250 MHz, $CDCl_3$): δ 6.14 (s, 1H), 5.82-5.75 (m, 1H), 5.52 (s, 1H), 5.01 (d, J =17.3 Hz, 1H), 4.96 (d, J =10.3 Hz, 1H), 3.75 (s, 3H), 2.31 (t, J =7.6 Hz, 2H), 2.09-2.04 (m, 2H), 1.59-1.34 (m, 2H) ppm.

Preparation of 2-methylene-hept-6-en-1-ol⁷ (49).

Based on the procedure of Borhan,⁷ a solution of 2-methylene-hept-6-enoic acid methyl ester **48** (1.95 g, 11.6 mmol) in 23 ml of anhydrous THF was cooled to 0 °C, and DIBAL-H (20% w/w solution in toluene, 21.0 ml, 25.5 mmol) was added. The cooling bath was removed, and the reaction mixture was stirred at room temperature overnight. The mixture was again cooled on ice and quenched by sequential addition of 1.0 ml of 15% NaOH, 1.0 ml of ether and 2.6 ml of water. The mixture was stirred at room temperature for 15 min, then dried over $MgSO_4$ and filtered through Celite. The solvent was removed *in vacuo* affording 3.36 g of the crude product (100% yield), which contained toluene as an impurity as determined by 1H -NMR. This was used in the next step without further purification.

TLC: 1:1 hexanes:ethyl acetate, I_2 stain, R_f =0.46.

1H -NMR (250MHz, $CDCl_3$): δ 5.86-5.79 (m, 1H), 5.08-4.90 (m, 4H), 4.10 (s, 2H), 2.10-2.07 (m, 4H), 1.62-1.56(m, 2H) ppm.

Preparation of 8-(phenylsulfanyl)-octa-1,6-diene (50). Based on the procedure of Castro,³ 2-methylene-hept-6-en-1-ol **49** (1.16 g, 9.75 mmol) and CCl_4 (3.08 ml, 31.92 mmol) were dissolved in 30 ml of anhydrous THF and the mixture was cooled to -78 °C for 1 h. Hexamethylphosphorous triamide (3.16 ml, 17.40

mmol) was added dropwise to the reaction mixture. In a separate flask, thiophenol (23.86 ml, 23.23 mmol) was combined with triethylamine (3.24 ml, 23.22 mmol) and 10 ml of anhydrous THF, and added dropwise to the reaction mixture. After 20 min. the cooling bath was removed and the mixture was stirred for 5 h. Ether (50 ml) was added and the resulting white precipitate was removed by filtration. The organic phase was washed sequentially with 10% NaOH (4 x 50 ml), water (50 ml) and brine (50 ml). The organic phase was dried over MgSO₄, filtered and concentrated. Purification by flash column chromatography using 99:1 hexanes:ethyl acetate afforded 1.00 g (4.58 mmol, 40% yield) of title compound as a yellow oil. It contained 50% of phenyl disulfide as an impurity as estimated by ¹H-NMR. This was used in the next step without further purification.

TLC: 6:1 hexanes:ethyl acetate, UV, *p*-anisaldehyde stain, I₂ stain, R_f=0.5.

IR (CDCl₃): 2932, 1477, 1439, 912, 749, 700 cm⁻¹.

¹H-NMR (500 MHz, CDCl₃): δ 7.37-7.20 (m, 5H), 5.83 (ddt, J=17.0 Hz, 10.2 Hz, 4.8 Hz, 1H), 5.04 (d, J=17.0 Hz, 1H), 4.99 (d, J=10.2 Hz, 1H), 4.97 (s, 1H), 4.86 (s, 1H), 3.56 (s, 2H), 2.21 (t, J=8.0 Hz, 2H), 2.09 (dt, J=7.6 Hz, 7.6 Hz, 2H), 1.58 (tt, J=7.6 Hz, 7.6 Hz, 2H), 1.61-1.46 (m, 2H) ppm.

¹³C-NMR (500 MHz, CDCl₃): δ 144.5, 138.7, 137.1, 129.2, 127.6, 126.3, 114.8, 113.3, 40.5, 34.0, 33.5, 27.0 ppm.

HRMS (M+1) calc'd. for C₁₄H₁₉S 219.1201, found 219.1202.

Preparation of 6-methylene-2-phenylsulfanylmethyl-thiepane 1,1-dioxide (54). Cyclization substrate 8-(phenylsulfanyl)-octa-1,6-diene **50** (154 mg, 0.353 mmol) was dissolved in 5 ml of dichloromethane and placed into a 15 ml heavy walled glass pressure vessel. The solution was cooled to -78 °C and 5 ml of SO₂ gas were condensed into the reaction mixture using a dry ice condenser. The mixture became yellow in color. The dry ice condenser was removed, the pressure vessel sealed and irradiated with a 450 W Hg lamp for 17 h. During the photolysis, the solution turned brown in color. The mixture was cooled to -78 °C and the pressure vessel was slowly opened to air and left standing in the hood at room temperature until all of the SO₂ gas had evaporated. Volatiles were removed *in vacuo* to give 114 mg of brown oil that contained the desired product and diphenyl

disulfide by ^1H -NMR. Purification by preparative TLC using 2:1 hexanes:ethyl acetate afforded 46 mg (0.20 mmol, 50% yield) of the title compound.

TLC: 2:1 hexanes:ethyl acetate, UV, *p*-anisaldehyde stain, I_2 stain, $R_f=0.32$.

IR (CDCl_3): 3006, 1440, 1315, 991, 681 cm^{-1} .

^1H -NMR (500 MHz, CDCl_3): 7.40-7.23 (m, 5H), 5.23 (s, 1H), 5.21 (s, 1H), 3.89 (AB, $J=14.5$ Hz, 1H), 3.84 (AB, $J=14.5$ Hz, 1H), 3.77 (dd, $J=14.0$ Hz, 2.0 Hz, 1H) 3.08 (tt, $J=2.0$ Hz, 11.2 Hz, 1H), 2.84 (dd, $J=14.0$ Hz, 11.2 Hz, 1H), 2.51 (dt, $J=15.2$ Hz, 5.1 Hz, 1H), 2.44-2.32 (m, 2H), 2.08-2.02 (m, 1H), 1.83 (dddd, $J=16.0$ Hz, 10.0 Hz, 10.0 Hz, 2.0 Hz, 1H), 1.59-1.54 (m, 1H) ppm.

^{13}C -NMR (125 MHz, CDCl_3): 136.0, 134.3, 129.7, 129.5, 127.0, 121.7, 64.2, 62.6, 35.3, 31.1, 26.5, 26.2 ppm.

HRMS ($M+1$) calc'd for $\text{C}_{14}\text{H}_{19}\text{O}_2\text{S}_2$ 283.0831, found 283.0821.

¹³C-NMR, Compound 18

HETCOR, Compound 18

c1ccc(cc1)S2CCCC(S(=O)(=O)2)C2

COST

¹H-NMR, Compound 31

¹³C-NMR, Compound 31

¹H-NMR, Compound 51

¹³C-NMR, Compound 51

¹H-NMR, Compound 52

¹³C-NMR, Compound 52

HETCOR

52

C=CC1(CCS(=O)(=O)C1)CC2=CC=CC=C2

cos x

[illegible]

NOESY, Compound 52

NOESY

¹H-NMR, Compound 53

¹³C-NMR, Compound 53

¹H-NMR, Compound 54

¹³C-NMR, Compound 54

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