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Graphical Abstract

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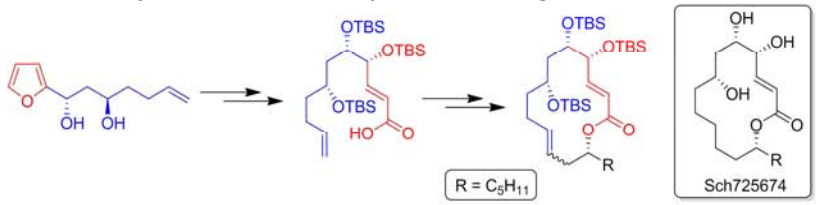

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Enantioselective Synthesis of Macrolactone Core of the Natural Product Sch725674[⊥]

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ABSTRACT

An enantioselective synthesis of the macrolactone core of natural product Sch725674 was accomplished from furfural. Key reactions in assembly of the macrolactone are the use of furan as a but-2-ene-dione equivalent and ring closing metathesis.

1. Introduction

During the investigations on isolation of bio-active natural products, the group at Schering-Plough Company isolated a 14-membered macrolactone natural product Sch725674 (**1**) (fig. 1) from the culture of *Aspergillus* sp.[1] The natural product **1** consists of an α, β unsaturated lactone and three free chiral secondary hydroxy groups in which two are contiguous. While the structure of Sch725674 was assigned based on extensive NMR experiments, absolute stereochemistry of the chiral centers was not assigned. We undertook the total synthesis and assignment of the stereochemistry of the natural product keeping in mind the requirement for a general procedure to access all stereoisomers of the natural product. During the course of our investigations, The Curran's group at the University of Pittsburg disclosed the total synthesis of Sch725674.[2] They assigned the stereochemistry of the natural product as 4*R*,5*S*,7*R*,13*R* by synthesizing all the possible diastereomers using an elegant ingenious flourous tagging technology developed in their group and comparison of the data with that reported for the natural product. We have been involved in the total synthesis of macrolides[3] and in this article we disclose our efforts in detail towards the total synthesis of Sch725674 which culminated in the successful assembly of the macrolactone core; an analogue of a key intermediate in Curran's synthesis.

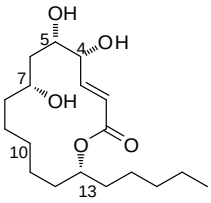
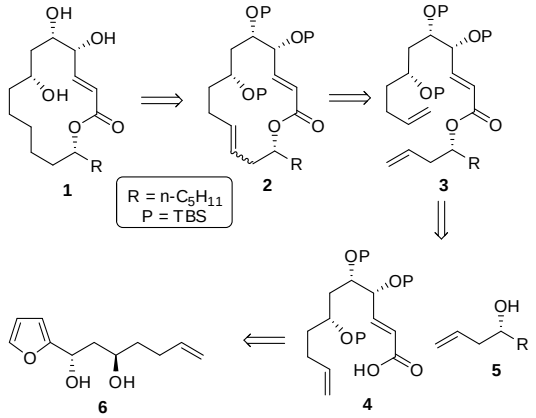


Fig 1: Sch 725674 **(1)**

As depicted in Scheme-1, our approach for the synthesis of Sch725674 relied on the selective hydrogenation of the C10-C11 olefin in macrolactone **2** and subsequent deprotection of the silyl groups. Synthesis of the macrolactone **2** is planned by RCM of the ester **3**. Formation of the C1-C11 fragment **4**, which is the acid unit of the ester was envisaged by elaboration of the 1,3-diol **6**. Oxidative opening of the furan[4] in **6** and further oxidation to the acid with required *E*-geometry is planned to assemble the C1-C11 acid fragment, while asymmetric allylation of *n*-hexanal is envisaged for the synthesis of the homoallylic alcohol fragment **5**.

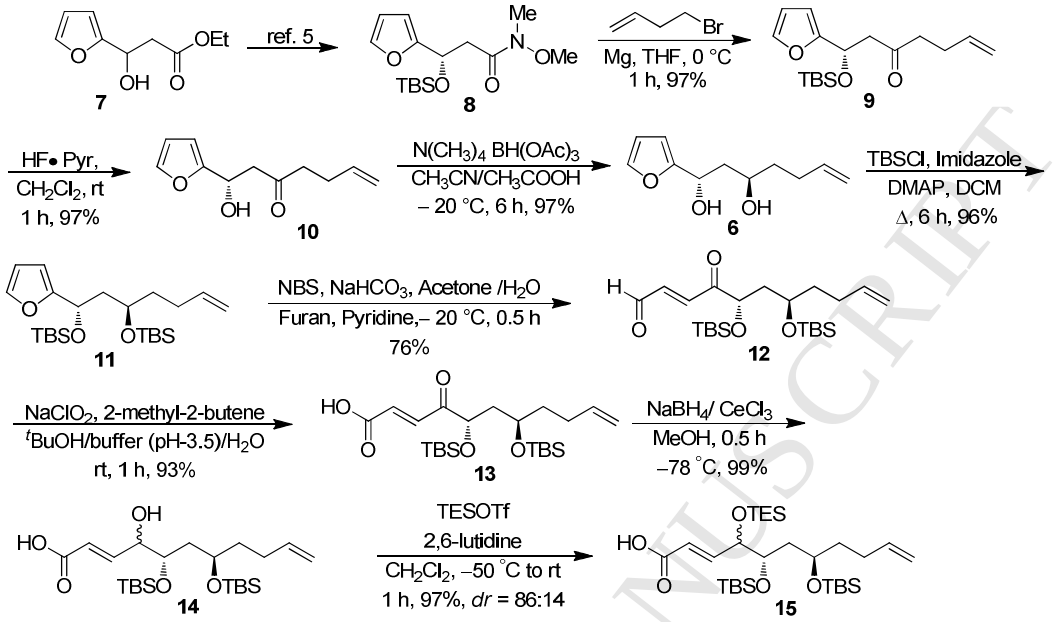


Scheme-1. Retrosynthesis for Sch725674

2. Results and Discussion

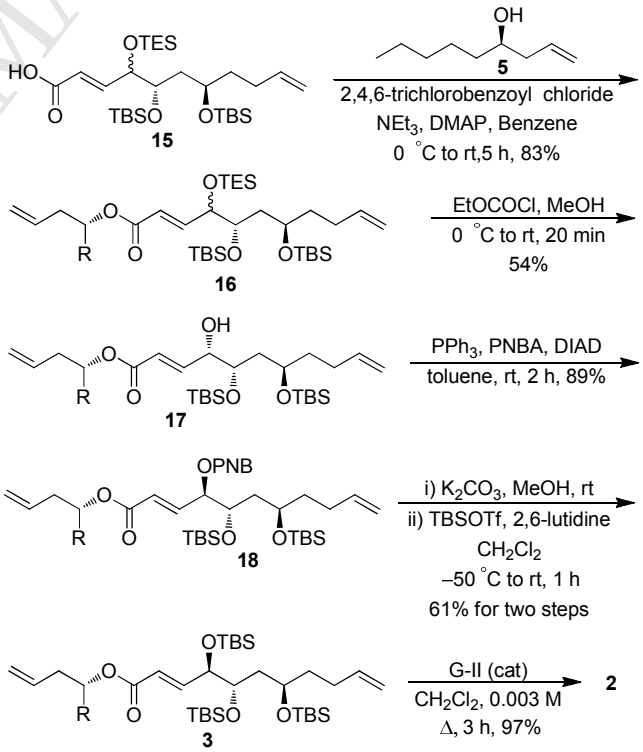
Accordingly, synthesis of the C1-C11fragment **4** began with the addition of 1-butenylmagnesium bromide to the Weinreb amide **8**[5] to furnish the silyloxy ketone **9** in 97% yield. Exposure of **9** to HF·pyridine afforded the hydroxy ketone **10** in 97% yield. Stereoselective reduction of the keto group in **10** with tetramethylammoniumtriacetoxy borohydride[6]gave the 1,3-diol **6** in 97% yield. Protection of both hydroxy groups in **6** as the *bis*-silylether **11** was accomplished using standard reaction conditions in 96% yield. Pivotal oxidation of the furan in **11** with

NBS proceeded smoothly to afford the keto aldehyde **12** in 76% yield, which on further oxidation with $NaClO_2$ furnished the acid **13** in 93% yield. Stereoselective reduction of the ketone in **13** under Luche reduction conditions rendered the alcohol **14**[7] in 99% yield which was protected as the TES ether **15** in 97% yield using TESOTf in presence of 2,6-lutidine (scheme-2).



Scheme-2: Synthesis of the C1-C11 acid fragment of Sch725674

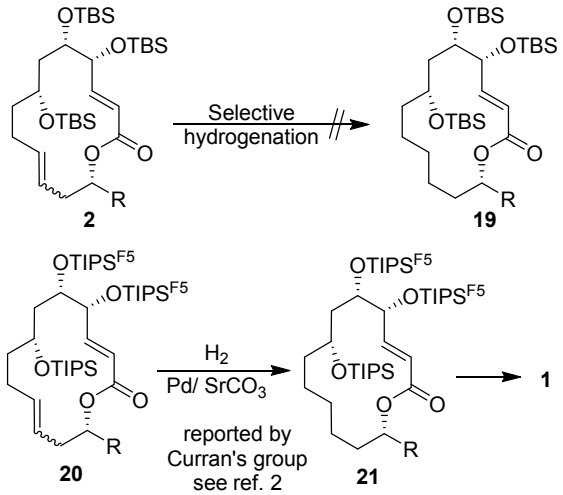
After successfully synthesizing the acid fragment, the required known homoallylic alcohol **5** was synthesized from *n*-hexanal using a procedure described earlier.[8] Yamaguchi esterification of the acid unit **15** with the alcohol **5** produced the ester **16** in 83% yield. At this stage, selective deprotection of the TES ether in **16** in presence of the TBS ether was effected by using EtOCOCl in MeOH to afford the allylic alcohol **17** in 54% yield. Mitsunobu inversion of the alcohol furnished the corresponding p-nitrobenzoate **18** in 89% yield. Reaction of **18** with K_2CO_3/ MeOH produced a 1:1 mixture of the required inverted alcohol and methyl 4-nitrobenzoate as an inseparable mixture. However, protection of the free alcohol as the TBS ether cleanly furnished **3** (61% yield for two steps), which on reaction with Grubbs' second generation afforded the macrolactone **2**[9] in excellent yield (Scheme-3).



Scheme-3: Synthesis of the macrolactone **2**

After the eventful assembly of the macrolactone core of **1**, we faced an unexpected difficulty in selective hydrogenation of the active olefin at C10-C11 position in macrolactone **2** in presence of the unsaturated C2-C3 olefin. Standard hydrogenation with Pd/C, $Pd/BaCO_3$ and with $Pd/CaCO_3$ produced a mixture of compounds. In a solitary instance, we could see the formation of

product **19** arising from the reduction of the required olefin, however the reaction was non-reproducible. Similar tendencies were observed in the hydrogenation of a structurally similar macrolactone **20** by the Curran's group.[10] The Curran's group circumvented the problem arose in the partial hydrogenation of the olefin in a structurally similar lactone **20** containing florous tagged silicon by using $Pd/SrCO_3$ for the hydrogenation (Scheme-4). They have elaborated the resultant lactone **21** to the natural product **1**. We believe such a hydrogenation should provide the required macrolactone which can be elaborated to Sch725674 **(1)** using the procedure reported by Curran's group.



Scheme -4: Synthesis of **1** reported by Curran's group

3. Conclusions

In conclusion, enantioselective synthesis of the macrolactone core of Sch725674 is accomplished from furfural. Pivotal steps in the synthetic sequence include the assembly of the required acid unit by elaboration of a chiral furyl carbinol and ring closing metathesis (RCM) to construct the macrolactone. The macrolactone is structurally similar to that reported by the Curran's group which was elaborated to the natural product.

4. Experimental section

General Procedures: Unless stated otherwise, all reagents were purchased from commercial sources and were used without additional purification. All reactions were performed under an inert atmosphere unless noted otherwise. THF was freshly distilled over Na-benzophenone ketyl. Petroleum ether (PE) refers to the fraction boiling in the 60–80 °C range. Column chromatography was performed on silica gel (Acme grade, 100–200 mesh). TLC plates (Merck pre-coated silica gel 60 F254 plates) were made visual with UV light, in an iodine chamber, or with phosphomolybdic acid spray. Melting points were recorded using a Buchi M-560 melting point apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer spectrophotometer. ^{1}H (400 MHz) and ^{13}C (100 MHz) NMR spectra were recorded on a Bruker 400 MHz spectrometer using $CDCl_3$ or CD_3OD as the solvent. High-resolution mass spectrometry (HRMS) was performed using a Waters Micromass Q-TOF operating in the ESI mode. Optical rotations were measured on a Rudolph Autopol IV polarimeter at 25 °C. β-Silyloxy amide **8** was synthesized according to the procedure described earlier[5] by us.

(*S*)-1-((tert-butyldimethylsilyl)oxy)-1-(furan-2-yl)hept-6-en-3-one (9): To an ice-cold solution of **8** (10.0 g, 31.8 mmol) in dry THF (30 mL) was added 4-butenylmagnesiumbromide (64 mL of 1 M solution in THF, 64 mmol) [freshly prepared from 4-bromobut-1-ene (6.7 mL, 64 mmol) and Mg turnings (2.3 g, 95.4 mmol)] dropwise over a period of 1 h, maintaining the temperature at 0 °C. After the reaction was complete (TLC), it was quenched by careful addition of sat. NH_4Cl solution (20 mL) at 0 °C. The aqueous layer was extracted with EtOAc (3 ×30 mL) and the combined organic layer was washed with brine solution (30 mL). The pale yellow residue obtained after evaporation of the solvent was purified by silica gel column chromatography (PE–EtOAc, 98:2) to obtain **9** (9.52 g, 30.9 mmol, 97%) as a colorless oil. $[\alpha]_D^{25}$ –69.3 (*c* 1.0, $CHCl_3$) IR (neat): ν_{max} 2956, 2932, 1720, 1216cm^{-1}. ^{1}H NMR ($CDCl_3$): δ (ppm) = 7.33 (d, *J* = 1.6 Hz, 1H), 6.29 (dd, *J* = 3.2, 1.8 Hz, 1H), 6.17 (d, *J* = 3.2 Hz, 1H), 5.79 (ddt, *J* = 16.8, 10.2, 6.4 Hz, 1H), 5.21 (dd, *J* = 8.4, 4.4 Hz, 1H), 5.01 (d, *J* = 17.2 Hz, 1H), 4.96 (d, *J* = 10.2 Hz, 1H), 3.05 (dd, *J* = 15.2, 8.6 Hz, 1H), 2.68 (dd, *J* = 15.2, 4.4 Hz, 1H), 2.51– 2.55 (m, 2H), 2.29–2.33 (m, 2H), 0.81 (s, 9H), 0.03 (s, 3H), –0.10 (s, 3H). ^{13}C NMR ($CDCl_3$): δ (ppm) = 207.6, 155.8, 141.6, 137.0, 115.2, 110.1, 106.1, 65.0, 49.4, 43.4, 27.3, 25.7 (3 × C), 18.0, –5.1, –5.3. HRMS (ESI): *m/z* $[M + Na]^+$ calcd for $C_{17}H_{28}O_3SiNa$: 331.1705; found: 331.1705.

(*S*)-1-(furan-2-yl)-1-hydroxyhept-6-en-3-one (10): To a solution of **9** (0.84g, 2.72 mmol) in THF (3 mL), pyridine (0.5 mL, 6.2 mmol) and HF·Pyridine complex (70% w/v, 0.5 mL) was added dropwise at 0 °C, and was stirred at rt for 1 h. After the reaction was complete (TLC), solid $NaHCO_3$ (0.5 g) was introduced into the reaction mixture portionwise until the effervescences ceased. The contents were filtered through a short pad of celite and the solvent was evaporated to obtain a pale yellow oil which was purified by silica gel column chromatography (PE–EtOAc, 9:1) to obtain **10** (0.51 g, 97%) as a colorless oil. $[\alpha]_D^{25}$ –32.1 (*c* 1.0, $CHCl_3$). IR (neat): ν_{max} 3447, 1715, 1406, 1011, 740 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ (ppm) = 7.35 (d, *J* = 2.4 Hz, 1H), 6.32 (dd, *J* = 3.2, 2.0 Hz, 1H), 6.25 (d, *J* = 3.2 Hz, 1H), 5.79 (ddt, *J* = 16.8, 10.2, 6.4 Hz, 1H), 5.17–5.23 (m, 1H), 5.03 (d, *J* = 18.4 Hz, 1H), 4.99 (d, *J* = 11.2 Hz, 1H), 3.34 (s, 1H), 3.03 (dd, *J* = 17.2, 8.8 Hz, 1H), 2.88 (dd, *J* = 17.2, 3.2 Hz, 1H), 2.56 (t, *J* = 7.2 Hz, 2H), 2.34 (dd, *J* = 13.8, 6.8 Hz, 2H). ^{13}C NMR ($CDCl_3$): δ (ppm) = 209.8, 154.8, 142.1, 136.6, 115.5, 110.2, 106.2, 63.7, 47.2, 42.5, 27.3. HRMS (ESI): *m/z* $[M + Na]^+$ calcd for $C_{11}H_{14}O_3Na$: 217.0841; found: 217.0841.

(1*S*,3*R*)-1-(furan-2-yl)hept-6-ene-1,3-diol (6): Tetramethylammonium triacetoxyborohydride (2.7 g, 10.3 mmol) was added to a mixture of acetonitrile/acetic acid (2:1, 15 mL) at 0 °C and stirred at rt for 0.5 h. The mixture was cooled to –30 °C and a solution of **10** (1.0 g, 5.15 mmol) in acetonitrile/acetic acid (2:1, 15 mL) was added dropwise to the reaction mixture. The reaction mixture was allowed to warm upto –20 °C and was stirred for additional 6 h. After the reaction was complete (TLC), it was quenched by addition of sat. sodium potassium tartrate solution (5 mL) and with sat. $NaHCO_3$ solution (15 mL). The aqueous layer was extracted with EtOAc (10 mL × 3), the combined organic layer was washed with brine (10 mL), dried over Na_2SO_4. Evaporation of the solvent gave a pale yellow oil which on purification by silica gel column chromatography (PE–EtOAc, 2:1) afforded **6** (0.99 g, 97%) as a colorless oil. $[\alpha]_D^{25}$ –34.0 (*c* 1.1, $CHCl_3$). IR (neat): ν_{max} 3378, 2924, 1642, 1445, 914, 738 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ (ppm) = 7.37 (d, *J* = 2.0 Hz, 1H), 6.33 (dd, *J* = 3.2, 2.0 Hz, 1H), 6.25 (d, *J* = 3.2 Hz, 1H), 5.81 (ddt, *J* = 16.8, 10.0, 6.8 Hz, 1H), 5.02–5.07 (m, 2H), 4.97 (d, *J* = 10.2 Hz, 1H), 3.92–3.98 (m, 1H), 3.52 (bs, 1H), 2.80 (bs, 1H), 2.11–2.31 (m, 2H), 1.99–2.02 (m, 1H), 1.87–1.90 (m, 1H), 1.56–1.61 (m, 2H). ^{13}C NMR ($CDCl_3$): δ (ppm) = 156.6, 141.8, 138.2, 114.9, 110.1, 105.6, 68.6, 65.3, 41.0, 36.3, 29.9. HRMS (ESI): *m/z* $[M + Na]^+$ calcd for $C_{11}H_{16}O_3Na$: 219.0997; found: 217.0999.

(1*S*,3*R*)-1,3-bis((tert-butyldimethylsilyl)oxy)-1-(furan-2-yl)hept-6-en (11): To a solution of the diol **6** (0.24 g, 1.22 mmol) in CH_2Cl_2 (5 mL) was added TBDMSCl (0.9 g, 6.0 mmol), imidazole (0.49 g, 7.2 mmol) and 4-(dimethylamino)pyridine (0.73 g, 6.0 mmol). The reaction mixture was refluxed for 6 h, and after the reaction was complete (TLC), it was poured into water (10 mL). The aqueous layer was extracted with Et_2O (10 mL × 3). The combined organic layer was washed with brine (10 mL), dried over Na_2SO_4 and the solvent was evaporated to obtain a yellow oil which on purification by silica gel column chromatography (PE–EtOAc, 99:1) to yield **11** (0.5 g, 96%) as a colorless oil. $[\alpha]_D^{25}$ –31.6 (*c* 1.0, $CHCl_3$). IR (neat): ν_{max} 2956, 2930, 1255, 1078, 836, 774 cm^{-1}. ^1H NMR ($CDCl_3$): δ (ppm) = 7.36 (d, *J* = 1.6 Hz, 1H), 6.300 (dd, *J* = 3.2, 2.8 Hz, 1H), 6.16 (d, *J* = 2.8 Hz, 1H), 5.81 (ddt, *J* = 16.8, 10.0, 6.6 Hz, 1H), 5.00 (d, *J* = 16.8 Hz, 1H), 4.94 (d, *J* = 10.2 Hz, 1H), 4.80 (dd, *J* = 8.0, 5.2 Hz, 1H), 3.83 (t, *J* = 6.0 Hz, 1H), 2.04–2.11 (m, 3H), 1.86–1.87 (m, 1H), 1.50–1.55 (m, 2H), 0.89 (s, 9H), 0.85 (s, 9H), 0.07 (s, 3H), 0.04 (s, 3H), 0.02 (s, 3H), –0.20 (s, 3H). ^{13}C NMR ($CDCl_3$): δ (ppm) = 156.9, 141.3, 138.7, 114.3, 110.0, 106.2, 68.8, 65.2, 44.4, 36.8, 29.2, 25.9 (3 × C), 25.8 (3 × C), 18.1 (2 × C), –4.1, –4.3, –4.8, –5.0. HRMS (ESI): *m/z* $[M + Na]^+$ calcd for $C_{23}H_{44}O_3Si_2Na$: 447.2727; found: 447.2729.

(5*S*,7*R*,*E*)-5,7-bis((tert-butyldimethylsilyl)oxy)-4-oxoundeca-2,10-dienal (12): To a stirred suspension of **11** (0.19 g, 0.45 mmol) and $NaHCO_3$ (0.075 g, 0.89 mmol) in acetone/H_2O (9:1, 4 mL) at –20 °C was added N-bromosuccinimide (0.095 g, 0.54 mmol) portion wise and was stirred at the same temperature for 0.5 h. Furan (0.16 mL, 2.23 mmol) was introduced into the reaction mixture at –20 °C to quench the excess NBS and was stirred for additional 0.5 h. Pyridine (0.04 mL) was added to the mixture and was stirred at rt for additional 2 h. The reaction mixture was then poured into pH-7.5 buffer (5 mL) and the aqueous layer was washed with EtOAc (5 mL × 3). The combined organic layer was washed with brine, dried over Na_2SO_4 and the solvent was evaporated to obtain a yellow color oil which on purification by silica gel column chromatography (PE–EtOAc, 99:1) furnished **12** (0.15 g, 76%) as a colorless oil. $[\alpha]_D^{25}$ –4.2 (*c* 0.5, $CHCl_3$). IR (neat): ν_{max} 2956, 2932, 1703, 1698, 1446, 1256, 1110, 837 cm^{-1}. ^1H NMR ($CDCl_3$): δ (ppm) = 9.77 (d, *J* = 7.6 Hz, 1H), 7.28 (d, *J* = 16.2 Hz, 1H), 6.93 (dd, *J* = 16.1, 7.6 Hz, 1H), 5.79 (ddt, *J* = 16.6, 10.2, 6.4 Hz, 1H), 5.01 (d, *J* = 17.2 Hz, 1H), 4.96 (d, *J* = 10.2 Hz, 1H), 4.39 (t, *J* = 6.8 Hz, 1H), 3.83 (quin, *J* = 6.0 Hz, 1H), 2.04–2.08 (m, 2H), 1.78–1.82 (m, 2H), 1.59–1.63 (m, 2H), 0.91 (s, 9H), 0.88 (s, 9H), 0.08 (s, 3H), 0.06 (s, 3H), 0.04 (s, 3H), 0.03 (s, 3H). ^{13}C NMR ($CDCl_3$): δ (ppm) = 200.2, 192.9, 140.7, 138.3, 138.1, 114.8, 76.0, 68.8, 42.2, 36.6, 29.2, 25.8 (3 × C), 25.7 (3 × C), 18.2, 18.1, –3.9, –4.3, –4.5, –4.6. HRMS (ESI): *m/z* $[M + Na]^+$ calcd for $C_{23}H_{44}O_4Si_2$ + CH_3OH + Na: 495.2938; found: 495.2939.

(5*S*,7*R*,*E*)-5,7-bis((tert-butyldimethylsilyl)oxy)-4-oxoundeca-2,10-dienoic acid (13): A solution of $NaClO_2$ (0.075 g, 0.85 mmol) in H_2O (1 mL) was added to a solution of **12** (0.25 g, 0.57 mmol) 2-methylbut-2-ene (0.26 mL, 2.26 mmol) in ^{t}BuOH/phosphate buffer pH 3.5 (2:1, 3 mL) at 10 °C. After stirring at rt for 1 h, the reaction mixture was diluted with H_2O (5 mL) and was acidified with 1 N aq. HCl solution (2 mL). The aqueous layer was extracted with EtOAc (3 × 5 mL) and the combined organic layer was washed with brine (10 mL) and dried over Na_2SO_4. The solvent was evaporated off to afford a pale yellow oil, which on purification by silica gel column chromatography (PE–EtOAc, 9:1), gave acid **13** (0.24 g, 0.52 mmol, 93%) as a pale yellow oil. $[\alpha]_D^{25}$ –5.5 (*c* 1.0, $CHCl_3$). IR (neat): ν_{max} 3419, 2955, 2931, 1709, 1257, 837 cm^{-1}. ^1H NMR ($CDCl_3$): δ (ppm) = 7.51 (d, *J* = 15.6 Hz, 1H), 6.80 (d, *J* = 15.6 Hz, 1H), 5.79 (ddt, *J* = 17.0, 10.2, 6.4 Hz, 1H), 5.01 (d, *J* = 17.2 Hz, 1H), 4.96 (d, *J* = 10.2 Hz, 1H), 4.36 (t, *J* = 6.0 Hz, 1H), 3.83 (quin, *J* = 5.6 Hz, 1H), 2.07 (AB_q, *J* = 14.4, 6.8 Hz, 2H), 1.76–1.82 (m, 2H), 1.57–1.64 (m, 2H), 0.91 (s, 9H), 0.88 (s, 9H), 0.07 (s, 3H), 0.06 (s, 3H), 0.05 (s, 3H), 0.03 (s, 3H). ^{13}C NMR ($CDCl_3$): δ (ppm) = 200.1, 169.8, 138.2, 137.2, 130.6, 114.7, 76.0, 68.8, 42.0, 36.7, 29.2, 25.8 (3 × C), 25.7 (3 × C), 18.0 (2 × C), –3.9, –4.2, –4.5, –4.8. HRMS (ESI): *m/z* $[M + Na]^+$ calcd for $C_{23}H_{44}O_5Si_2Na$: 479.2625; found: 479.2628.

(4*S*,5*S*,7*R*,*E*)-5,7-bis((tert-butyldimethylsilyl)oxy)-4-hydroxyundeca-2,10-dienoic acid (14): $CeCl_3 \cdot 7H_2O$ (0.25g, 0.68 mmol) was added to a solution of **13** (0.2 g, 0.45 mmol) in MeOH (5 mL) at rt and the reaction mixture was stirred for 0.5 h at room temperature. The reaction mixture was cooled to –78 °C and $NaBH_4$ (0.03 g, 0.81 mmol) was added slowly portion wise. The mixture was stirred for an additional 0.5 h at the same temperature and then quenched by careful addition of water (2 mL). Most of the solvent was evaporated off and water (10 mL) was added to the white solid thus obtained. The aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic layer was washed with brine (10 mL), dried over anhydrous Na_2SO_4 and the solvent was evaporated off to give a colorless oil. This crude oil was subjected to silica gel column chromatography (PE–EtOAc, 4:1) to afford secoacid **14** (0.2 g, 99%) as a colorless oil. $[\alpha]_D^{25}$ –10.0 (*c* 1.5, $CHCl_3$). IR (neat): ν_{max} 3420, 2957, 2928, 1715, 1260, 835 cm^{-1}. ^1H NMR ($CDCl_3$): δ (ppm) = 7.07 (dd, *J* = 15.6, 3.6 Hz, 1H), 6.14 (dd, *J* = 15.6, 1.6 Hz, 1H), 5.79 (ddt, *J* = 17.2, 10.2, 6.4 Hz, 1H), 5.01 (d, *J* = 17.2 Hz, 1H), 4.96 (d, *J* = 10.2 Hz, 1H), 4.26 (s, 1H), 3.78–3.86 (m, 2H), 2.05–2.10 (m, 2H), 1.86–1.93 (m, 1H), 1.55–1.60 (m, 3H), 0.89 (s, 9H), 0.87 (s, 9H), 0.08 (s, 3H), 0.07 (s, 3H), 0.04 (s, 3H), 0.03 (s, 3H). ^{13}C NMR ($CDCl_3$): δ (ppm) = 171.2, 151.5, 138.1, 120.9, 114.8, 73.1, 72.2, 69.9, 41.2, 36.9, 29.2, 25.8 (3 × C), 25.7 (3 × C), 18.0, 17.9, –4.0, –4.1, –4.3, –4.5. HRMS (ESI): *m/z* $[M + Na]^+$ calcd for $C_{23}H_{46}O_5Si_2Na$: 481.2781; found: 481.2784.

(4*S*,5*S*,7*R*,*E*)-5,7-bis((tert-butyldimethylsilyl)oxy)-4-((triethylsilyl)oxy)undeca-2,10-dienoic acid (15): To a solution of **14** (0.19 g, 0.414 mmol) and 2,6-lutidine (0.28 mL, 2.5 mmol) in CH_2Cl_2 (5 mL) was added TESOTf (0.28 mL, 1.24 mmol) at –50 °C. The mixture was allowed to warm up to room temperature and was stirred at this temperature. After the reaction was complete (TLC), it was quenched by addition of sat. aq $NaHCO_3$ solution (5 mL). The reaction mixture is acidified with 1N HCl till is slightly acidic, and was extracted with EtOAc (3 × 10 mL). The combined organic layer was washed with brine (5 mL), dried over Na_2SO_4 and the solvent was evaporated off to give a colorless oil. Purification by silica gel column chromatography (PE–EtOAc, 4:1) afforded acid **15** (0.23 g, 0.4 mmol, 97%) as a colorless oil. The ^1H NMR spectrum of the compound showed a diastereomeric mixture of 86:14. $[\alpha]_D^{25}$ –31.5 (*c* 1.35, $CHCl_3$). IR (neat): ν_{max} 3493, 2956, 2884, 1703, 1255, 835, 774 cm^{-1}. ^1H NMR ($CDCl_3$): δ (ppm) = 7.24 (dd, *J* = 15.6, 3.2 Hz, $1H_{maj}$), 7.06 (dd, *J* = 15.6, 5.6 Hz, $0.16H_{min}$), 6.08 (dd, *J* = 15.6, 1.6 Hz, $1H_{maj}$), 5.98 (d, *J* = 15.6 Hz, $0.16H_{min}$), 5.79 (ddt, *J* = 17.2, 13.2, 6.4 Hz, $1.16H_{maj+min}$), 4.99 (d, *J* = 17.2 Hz, $1.16H_{maj+min}$), 4.36 (s, $1H_{maj}$), 4.14 (d, *J* = 6.8 Hz, $0.16H_{min}$), 3.80–3.87 (m, $2.32H_{maj+min}$), 1.99–2.11 (m, $2.32H_{maj+min}$), 1.68–1.73 (m, $1.16H_{maj+min}$), 1.48–1.58 (m, $1.16H_{maj+min}$), 1.26–1.30 (m, $2.32H_{maj+min}$), 0.96 (t, *J* = 7.9 Hz, $10.4H_{maj+min}$), 0.90 (s, $10.4H_{maj+min}$), 0.87 (s, $10.4H_{maj+min}$), 0.61 (q, *J* = 7.8 Hz, $7H_{maj+min}$), 0.04–0.10 (m, $13.9H_{maj+min}$). ^{13}C NMR ($CDCl_3$): δ (ppm) = 171.5, 150.6, 138.7, 120.6, 114.2, 74.5, 72.6, 69.4, 40.1, 37.2, 26.0(3 × C), 25.8 (3 × C), 22.6, 18.1, 17.9, 6.8 (3 × C), 4.8 (3 × C), –3.9, –4.0, –4.1, –4.4 (Minor isomer was not observed in ^{13}C NMR spectrum). HRMS (ESI): *m/z* $[M + Na]^+$ calcd for $C_{29}H_{60}O_5Si_3Na$: 595.3646; found: 595.3647.

Preparation of (*R*)-non-1-en-4-ol (5): $Ti(O^iPr)_4$ (0.45 mL) was added to a stirring solution of $TiCl_4$ (0.05 mL) in CH_2Cl_2 (10 mL) at 0 °C. The solution was allowed to warm up to room temperature and was stirred at rt for 1 h. Ag_2O (0.23 g, 1.0 mmol) was added to the reaction mixture and the stirring was continued for further 5 h under exclusion of light. The mixture was then diluted with CH_2Cl_2 (20 mL) and (*S*)-BINOL (0.57 g, 1.99 mmol) was added and the stirring was continued for additional 2 h. The catalyst thus prepared was cooled to –10 °C, hexanal (1.0 g, 9.98 mmol) and allyltributyltin (3.4 mL, 10.98 mmol) were added sequentially. The temperature was raised to 0 °C and the reaction was stirred for 24 h at the same temperature. After the reaction was complete (TLC), sat. $NaHCO_3$ solution (100 mL) was added to the reaction mixture and was stirred vigorously. The aqueous layer was extracted with Et_2O (3 × 30 mL) and the combined organic layer was washed with brine, dried over Na_2SO_4 and the solvent was evaporated in vacuo to obtain orange red oil which was purified by silica gel column chromatography (PE–EtOAc, 99:1) to afford homoallylic alcohol **5** (1.35 g, 9.14 mmol, 92%) as a colorless oil. The enantiomeric purity of the alcohol **5** was determined by HPLC analysis of its 4-nitrobenzoate ester as described by Feng *et al.* $[\alpha]_D^{25}$ +9.0 (*c* 1.0, $CHCl_3$), Lit.[8] $[\alpha]_D^{25}$ +9.0 (*c* 1.0, $CHCl_3$). IR (neat): ν_{max} 3493, 2956, 1475, 1150 cm^{-1}. ^1H NMR ($CDCl_3$): δ (ppm) = 5.83 (ddd, *J* = 17.2, 9.6, 7.6 Hz, 1H), 5.13 (d, *J* = 17.2 Hz, 1H), 5.13 (d, *J* = 11.6 Hz, 1H), 3.64 (dt, *J* = 7.2, 4.4 Hz, 1H), 2.27–2.33 (m, 1H), 2.10–2.17 (m, 1H), 1.70 (bs, 1H), 1.45 (bs, 1H), 1.30 (bs, 5H), 0.89 (t, *J* = 6.8 Hz, 3H). ^{13}C NMR ($CDCl_3$): δ (ppm) = 135.2, 118.3, 70.9, 42.2, 36.7, 31.8, 25.6, 22.8, 14.3. HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_9H_{18}ONa$: 165.1255; found: 165.1253.

(4*S*,5*S*,7*R*,*E*)-(*R*)-non-1-en-4-yl 5,7-bis((tert-butyldimethylsilyl)oxy)-4-((triethylsilyl)oxy)undeca-2,10-dienoate (**16**): To a solution of **15** (0.475 g, 0.83 mmol) in benzene (5 mL) was added NEt_3 (0.58 mL) and 2,4,6-trichlorobenzoyl chloride (0.15 mL, 0.96 mmol) at 0 ° C and was stirred at rt for 0.5 h. After the formation of mixed anhydride (TLC), the solution was cooled to 0 °C and a solution of 4-(dimethylamino)pyridine (0.5 g, 4.1 mmol) and alcohol **5** (0.14 g, 1.0 mmol) was introduced dropwise in to the reaction mixture. The reaction mixture was warmed to room temperature and was stirred for additional 5 h. After the completion of the reaction (TLC), it was quenched by addition of sat. $NaHCO_3$ solution (10 mL) and the aqueous layer was washed with EtOAc (3 × 10 mL). The combined organic layer was washed with brine (5 mL), dried over Na_2SO_4 and the solvent was evaporated off to give a pale yellow oil. Purification of the residue by silica gel column chromatography (PE–EtOAc, 99:1) afforded ester **16** (0.47 g, 0.674 mmol, 83%) as a colorless oil. $[\alpha]_D^{25}$ –21.0 (*c* 0.8, $CHCl_3$). IR (neat): ν_{max} 2957, 2932, 1741, 1571, 1273, 1119, 917, 857 cm^{-1}. ^1H NMR ($CDCl_3$): δ (ppm) = 7.10 (dd, *J* = 15.6, 3.2 Hz, $1H_{maj}$), 6.91(dd, *J* = 15.6, 6.0 Hz, $0.16H_{min}$), 6.05 (d, *J* = 1.6 Hz, $1H_{maj}$), 6.01 (d, *J* = 1.6 Hz, $0.16H_{min}$), 5.70–5.94 (m, $2.32H_{maj+min}$), 4.91–5.08 (m, $5.8H_{maj+min}$), 4.33 (s, $1H_{maj}$), 4.08 (d, *J* = 4.8 Hz, $0.16H_{min}$), 3.75–3.85 (m, $2.32H_{maj+min}$), 2.31–3.36 (m, $2.32H_{maj+min}$), 1.67–1.73 (m, $1.16H_{maj+min}$), 1.45–1.60 (m, $3.48H_{maj+min}$), 1.28 (s, $9.28H_{maj+min}$), 0.63–0.98 (m, $34.8H_{maj+min}$), 0.57–0.62 (m, $6.9H_{maj+min}$), 0.03–0.09 (m, $13.9H_{maj+min}$). ^{13}C NMR ($CDCl_3$): δ (ppm) = 166.1, 147.5, 138.8, 133.8, 121.6, 117.5, 114.2, 74.5, 73.2, 72.6, 69.4, 40.1, 38.6, 37.1, 33.6, 31.6, 29.4, 26.0 (2 × C), 25.9 (2 × C), 25.8 (2 × C), 24.9, 22.5, 18.0, 17.9, 13.9, 6.8 (3 × C), 4.8 (3 × C), –3.9 (2 × C), –4.0 (2 × C) (Minor isomer was not observed in ^{13}C NMR spectrum). HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{38}H_{76}O_5Si_3Na$: 719.4898; found: 719.4899.

(4*S*,5*S*,7*R*,*E*)-(*R*)-non-1-en-4-yl 5,7-bis((tert-butyldimethylsilyl)oxy)-4-hydroxyundeca-2,10-dienoate (17): Ethyl chloroformate (26 µL, 0.28 mmol) was added to an ice-cold solution of **16** (0.05 g, 0.071 mmol) in MeOH (4 mL) and was stirred at room temperature. After ~20 min, TLC indicated the completion of the reaction. Solid $NaHCO_3$ (20 mg) was introduced into the reaction mixture, stirred for 5 mins, and was filtered through a short pad of celite. The solvent was evaporated off and the crude residue thus obtained was purified by silica gel column chromatography (PE–EtOAc, 97:3) to afford the alcohol **17** (0.016 g, 0.038 mmol, 54%) as a colorless oil. $[\alpha]_D^{25}$ –8.0 (*c* 0.35, $CHCl_3$). IR (neat): ν_{max} 3492, 2932, 1718, 1462, 1255, 774 cm^{-1}. ^1H NMR ($CDCl_3$): δ (ppm) = 6.93 (dd, *J* = 15.6, 3.6 Hz, 1H), 6.11 (d, *J* = 1.6 Hz, 1H), 6.07 (d, *J* = 1.6 Hz, 1H), 5.70–5.84 (m, 2H), 4.95–5.08 (m, 5H), 4.22 (t, *J* = 2.4 Hz, 1H), 3.78–3.82 (m, 2H), 2.57 (d, *J* = 8.8 Hz, 1H), 2.33 (t, *J* = 6.4 Hz, 2H), 2.05–2.11(m, 2H), 1.88–1.95 (m, 1H), 1.58 (bs, 2H), 1.26 (bs, 8H), 0.89 (s, 12H), 0.86 (s, 9H), 0.10 (s, 3H), 0.09 (s, 3H), 0.08 (s, 3H), 0.07 (s, 3H). ^{13}C NMR ($CDCl_3$): δ (ppm) = 165.9, 148.7, 138.2, 133.7, 121.8, 117.5, 114.7, 73.2, 73.0, 72.2, 69.7, 41.3, 38.6, 36.8, 33.5, 31.6, 29.2, 25.8 (3 × C), 25.7 (3 × C), 24.9, 22.5, 18.0, 17.9, 13.9, –4.0, –4.1, –4.2, –4.5. HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{32}H_{62}O_5Si_2Na$: 605.4033; found: 605.4038.

(4*R*,5*S*,7*R*,*E*)-5,7-bis((tert-butyldimethylsilyl)oxy)-1-((*R*)-non-1-en-4-yloxy)-1-oxoundeca-2,10-dien-4-yl 4-nitrobenzoate (18): Diisopropylazodicarboxylate (72 µL, 0.37 mmol) was added to a solution of alcohol **17** (0.072 g, 0.123 mmol), PPh_3 (0.097 g, 0.37 mmol) and 4-nitrobenzoic acid (0.062 g, 0.37 mmol) in toluene (0.6 mL) at 0 °C and was allowed to stir at room temperature for 2 h. The solvent was evaporated off and the crude residue thus obtained was purified by silica gel column chromatography (PE–EtOAc, 99:1) afforded the ester **18** (0.08 g, 0.11 mmol, 89%) as a pale yellow oil. $[\alpha]_D^{25}$ +20.1(*c* 0.75, $CHCl_3$). IR (neat): ν_{max} 2955, 2930, 1728, 1266, 1116, 837 cm^{-1}. ^1H NMR ($CDCl_3$): δ (ppm) = 8.32 (d, *J* = 8.8 Hz, 2H), 8.23 (d, *J* = 8.8 Hz, 2H), 6.98 (dd, *J* = 15.6, 5.6 Hz, 1H), 6.03 (d, *J* = 15.6 Hz, 1H), 5.70–5.86 (m, 2H), 5.66 (t, *J* = 1.6 Hz, 1H), 4.96–5.08 (m, 5H), 4.13 (bs, 1H), 3.84 (t, *J* = 5.6 Hz, 1H), 2.29–2.37 (m, 2H), 2.10 (ABq, *J* = 14.4, 6.8 Hz, 2H), 1.70 (t, *J* = 6.0 Hz, 2H), 1.53–1.64 (m, 2H), 1.26 (bs, 8H), 0.88 (s, 12H), 0.85 (s, 9H), 0.13 (s, 3H), 0.07 (s, 3H), 0.05 (s, 3H), –0.01 (s, 3H). ^{13}C NMR ($CDCl_3$): δ (ppm) = 165.1, 163.7, 150.6 (2 × C), 140.8, 138.2, 135.2 (2 × C), 133.5, 130.8, 124.4, 123.6, 117.7, 114.7, 77.7, 73.9, 71.2, 69.3, 41.6, 38.5, 36.9, 33.5, 31.6, 29.2, 25.8 (3 × C), 25.7 (3 × C), 24.9, 22.5, 18.0, 17.9, 13.9, –3.6, –4.0, –4.2, –4.3. HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{39}H_{65}NO_8Si_2Na$: 754.4146; found: 754.4146.

(4*R*,5*S*,7*R*,E)-(*R*)-non-1-en-4-yl 4,5,7-tris((tert-butyldimethylsilyl)oxy)undeca-2,10-dienoate (3): To a stirred solution of **18** (0.08 g, 0.11 mmol) in MeOH (3 mL), was added K_2CO_3 (0.03 g, 0.22 mmol) and stirred at room temperature for 0.5 h. After completion of the reaction (TLC), it was filtered through a short pad of celite and the solvent was evaporated off. The crude residue thus obtained was purified by silica gel column chromatography (PE–EtOAc, 99:1) to afford a 1:1 inseparable mixture of the inverted alcohol and methyl 4-nitrobenzoate as judged by the ^1H NMR spectrum.

To a stirred solution of the mixture obtained above (0.054 g) was added 2,6-lutidine (32 µL, 0.28 mmol) and TBSOTf (26 µL, 0.14 mmol) at –50 °C. The mixture was allowed to warm to room temperature and was stirred at room temperature for 1 h. The reaction mixture was poured into sat. aqueous $NaHCO_3$ solution (5 mL) and the aqueous layer was extracted with Et_2O (3 × 5 mL). The combined organic layer was washed with brine (5 mL), dried over Na_2SO_4. The residue obtained after evaporation of solvent was purified by silica gel column chromatography (PE–EtOAc, 99:1) to afford the ester **3** (0.047 g, 61% for two steps) as

a colorless oil. $[\alpha]_D^{25}$ –2.9 (*c* 1.0, $CHCl_3$). IR (neat): ν_{max} 2956, 2931, 1716, 1256 cm^{-1}. ^1H NMR ($CDCl_3$): δ (ppm) = 6.90 (dd, *J* = 15.6, 5.6 Hz, 1H), 5.93 (d, *J* = 15.6 Hz, 1H), 5.70–5.84 (m, 2H), 4.90–5.08 (m, 5H), 4.14 (t, *J* = 1.6 Hz, 1H), 3.84–3.87 (m, 1H), 3.78–3.81 (m, 1H), 2.33 (bs, 2H), 2.03–2.08 (m, 2H), 1.54–1.58 (m, 4H), 1.27 (bs, 8H), 0.86–0.92 (m, 30H), 0.09 (s, 3H), 0.08 (s, 3H), 0.07 (s, 3H), 0.06 (s, 3H), 0.05 (s, 3H), 0.03 (s, 3H). ^{13}C NMR ($CDCl_3$): δ (ppm) = 165.9, 147.4, 138.5, 133.7, 122.3, 117.5, 114.5, 77.0, 74.1, 73.3, 69.4, 42.1, 38.6, 37.3, 33.5, 31.6, 29.2, 26.0 (3 × C), 25.9 (2 × C), 25.8 (2 × C), 25.7 (2 × C), 24.9, 22.5, 18.3, 18.2, 18.0, 13.9, –3.5, –3.6, –3.9, –4.0, –4.4, –4.6. HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{38}H_{76}O_5Si_3Na$: 719.4898; found: 719.4896.

(3*E*,5*R*,6*S*,8*R*,14*R*)-5,6,8-tris((tert-butyldimethylsilyl)oxy)-14-pentyloxacyclotetradeca-3,11-dien-2-one (2): To a stirred solution of **3** (0.016 g, 0.023 mmol) in CH_2Cl_2 (7.5 mL) was added Grubbs' second generation catalyst (2 mg, 0.0023 mmol) and was heated to reflux for 3 h. After the reaction was complete (TLC), the solvent was evaporated off and the crude residue thus obtained was purified by silica gel column chromatography (PE–EtOAc, 99:1) to afford the macrolactone **2** (0.015 g, 97%) as a colorless oil. $[\alpha]_D^{25}$ +36.2 (*c* 0.8, $CHCl_3$). IR (neat): ν_{max} 2958, 2942, 1715, 1262, 832 cm^{-1}. ^1H NMR ($CDCl_3$): δ (ppm) = 6.79 (dd, *J* = 15.6, 4.4 Hz, 1H), 5.96 (dd, *J* = 15.6, 1.6 Hz, 1H), 5.30–5.34 (m, 2H), 4.98 (tdd, *J* = 8.0, 4.8, 2.8 Hz, 1H), 4.46 (d, *J* = 2.4 Hz, 1H), 3.72–3.77 (m, 1H), 2.31–2.38 (m, 2H), 2.21–2.25 (m, 1H), 1.95–2.08 (m, 1H), 1.87–1.91(m, 1H), 1.63–1.72 (m, 1H), 1.50–1.56 (m, 1H), 1.25–1.55 (m, 9H), 0.86–0.94 (m, 30H), 0.13 (s, 3H), 0.12 (s, 3H), 0.11 (s, 3H), 0.08 (s, 3H), 0.07 (s, 3H), 0.06 (s, 3H). ^{13}C NMR ($CDCl_3$): δ (ppm) = 166.8, 148.4, 133.3, 126.1, 120.8, 77.7, 73.2, 73.0, 65.5, 42.9, 38.8, 35.3, 34.2, 31.6, 27.4, 26.0 (3 × C), 25.9 (3 × C), 25.8 (3 × C), 25.3, 22.5, 18.4, 18.2, 18.1, 13.9, –3.3, –4.4, –4.6, –4.7, –4.8, –5.0. HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{36}H_{72}O_5Si_3Na$: 691.4585; found: 691.4588.

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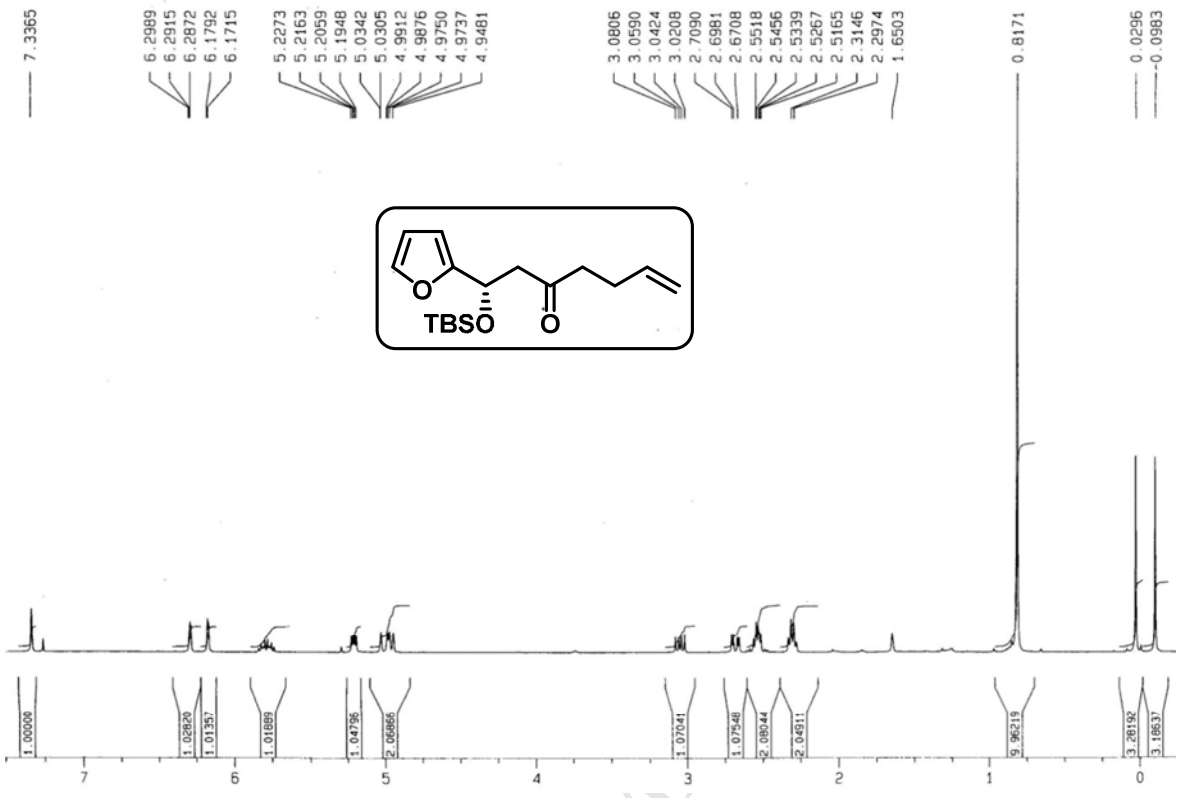
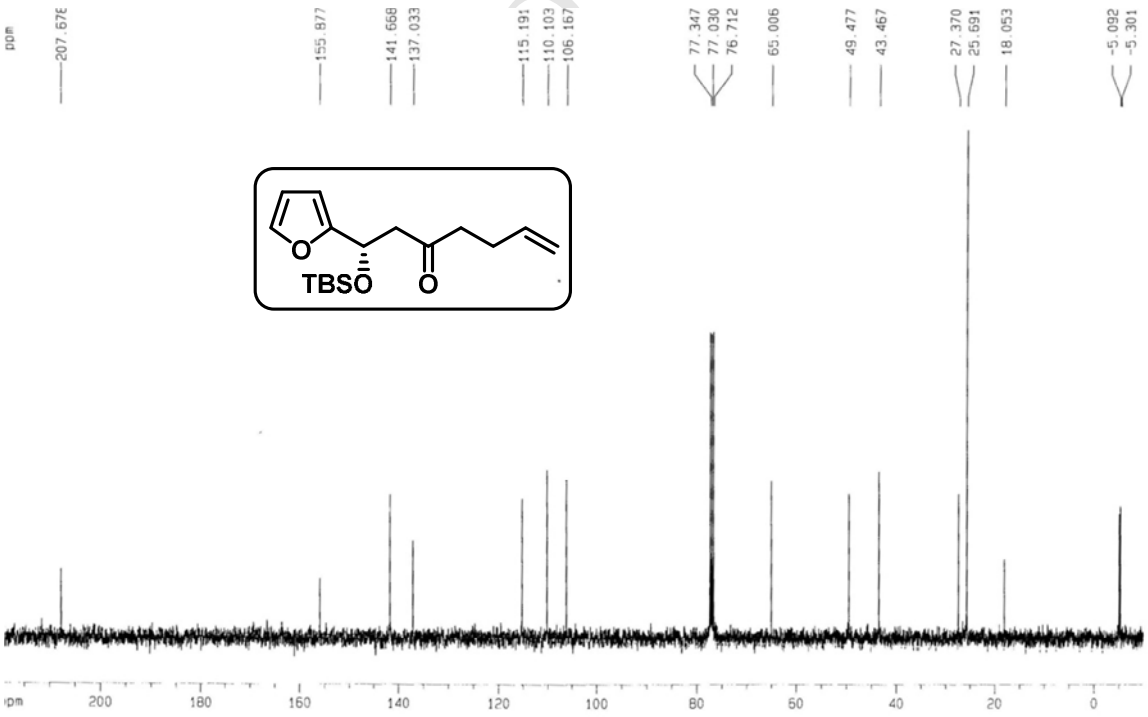
7. Luche, J. L. *J. Am. Chem. Soc*. **1978**, *100*, 2226. The diastereomeric ratio of the product alcohol is inconclusive from NMR at this stage. However, a diastereomeric ratio of 84:16 was observed in ^1H NMR spectrum when **14** was converted to **15** which was also a non-separable mixture. This diastereomeric mixture was used as such in the next step. Separation of the major diasteromer **17** was accomplished in the TES deprotection of **16** in 54% yield.
8. a) Das, B.; Laxminarayana, K.; Krishnaiah, M.; Kumar, D. N. *Helv. Chic. Acta* **2009**, *92*, 1840. b) Feng, J. P.; Shi, Z, F.; Zhang, J, T.; Qi, X, L.; Cao, X. P. *J. Org. Chem.* **2008**, 73, 6873.
9. Although, ^1H NMR spectrum of **2** exhibited a single isomer, we were unable to ascertain the configuration at the newly formed C10-C11 olefin in the metathesis reaction. However *E*/Z ratio of the C10-C11 olefin is of no consequence as hydrogenation of the olefin is the next step in the synthetic sequence.
10. Moretti, J. D. PhD thesis, University of Pittsburg, **2010**. Wang, X. PhD thesis, University of Pittsburg, **2009**.

Supplementary Material

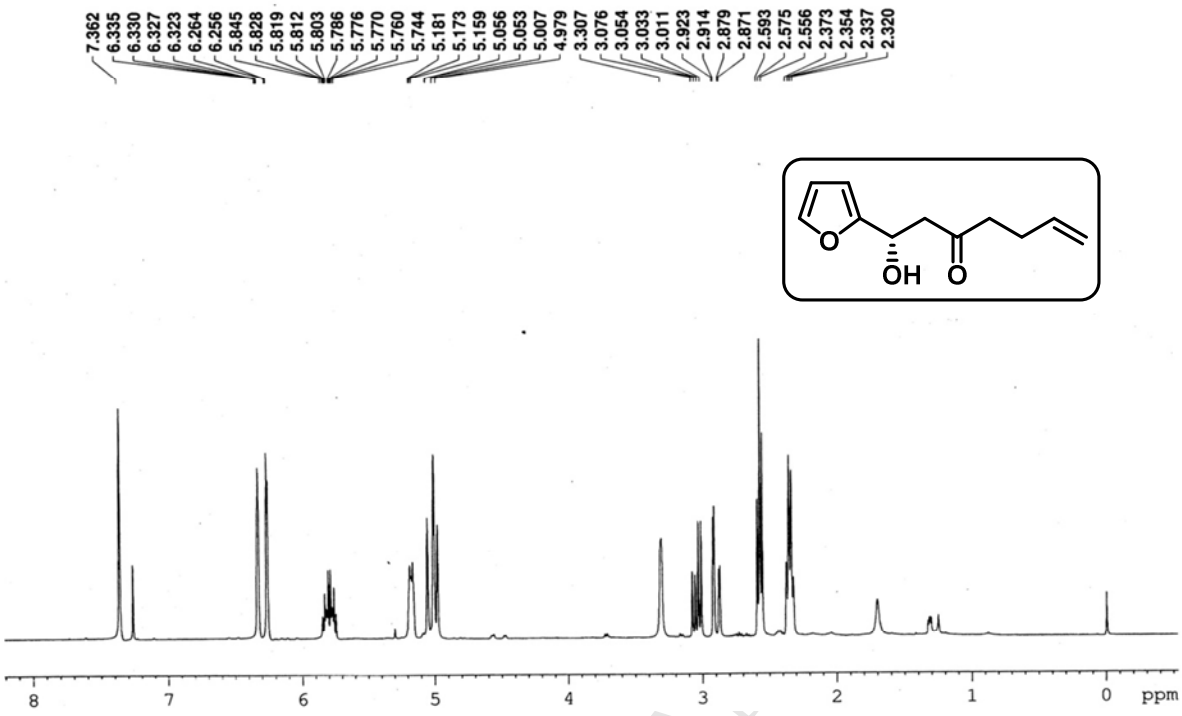
Copies of ^1H NMR and ^{13}C NMR spectra for all the new compounds synthesized are provided.



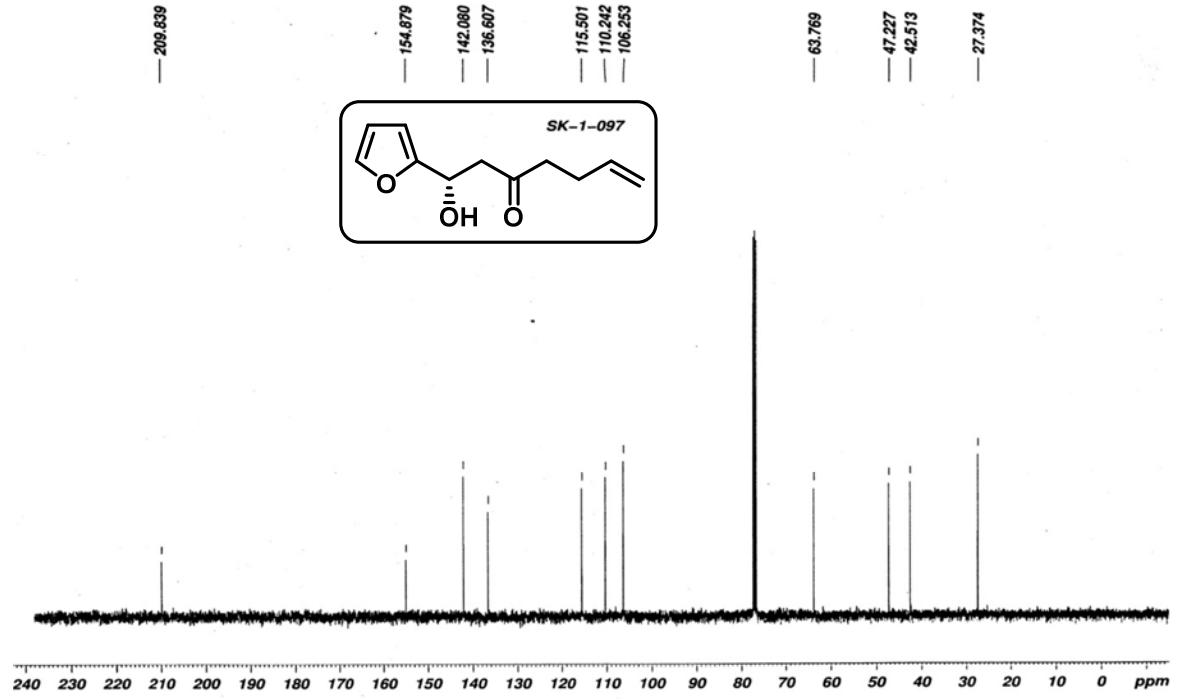
^{1}H NMR spectrum of compound **9**



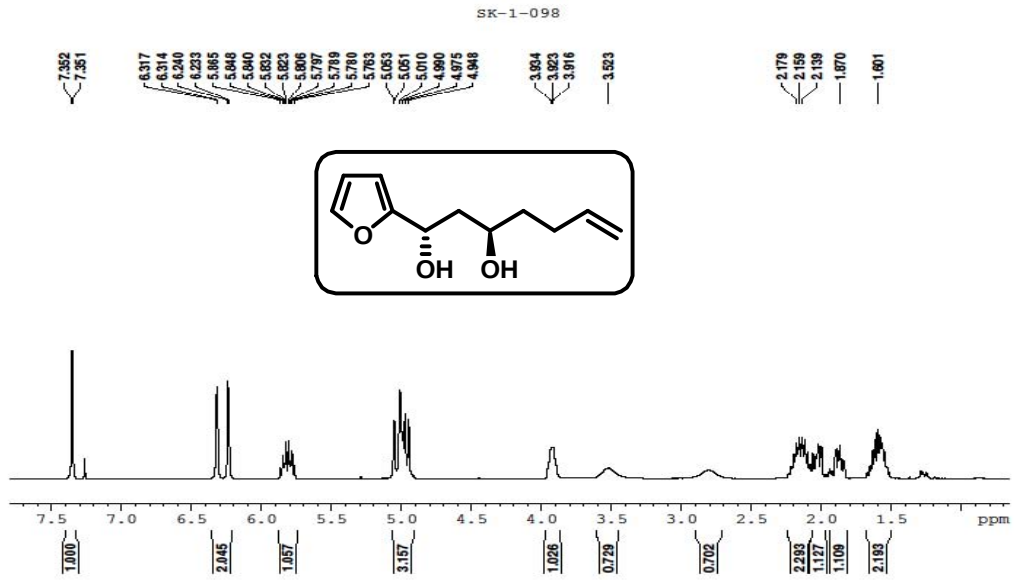
^{13}C NMR spectrum of compound **9**



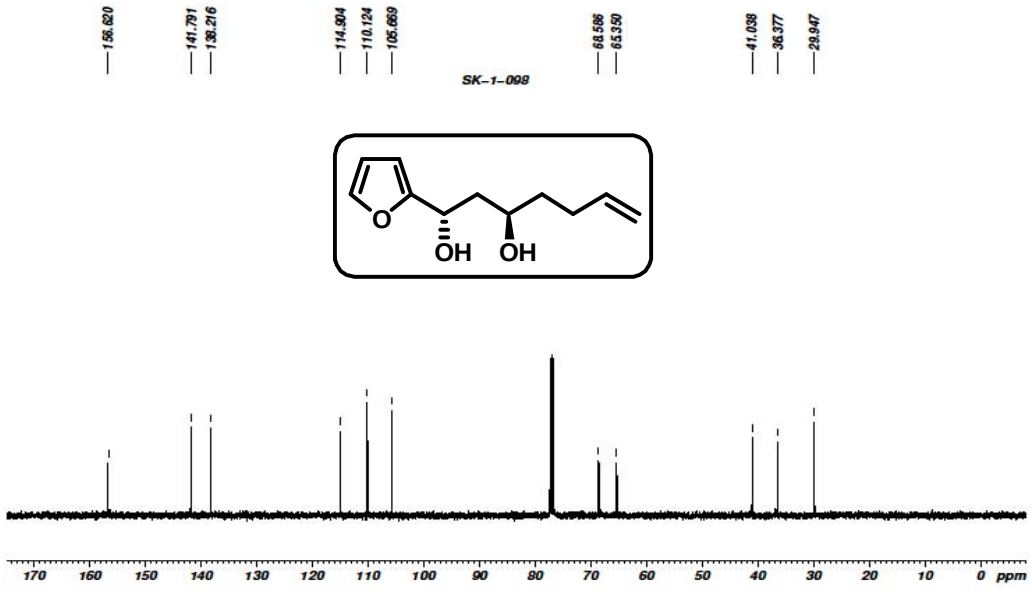
^{1}H NMR spectrum of compound **10**



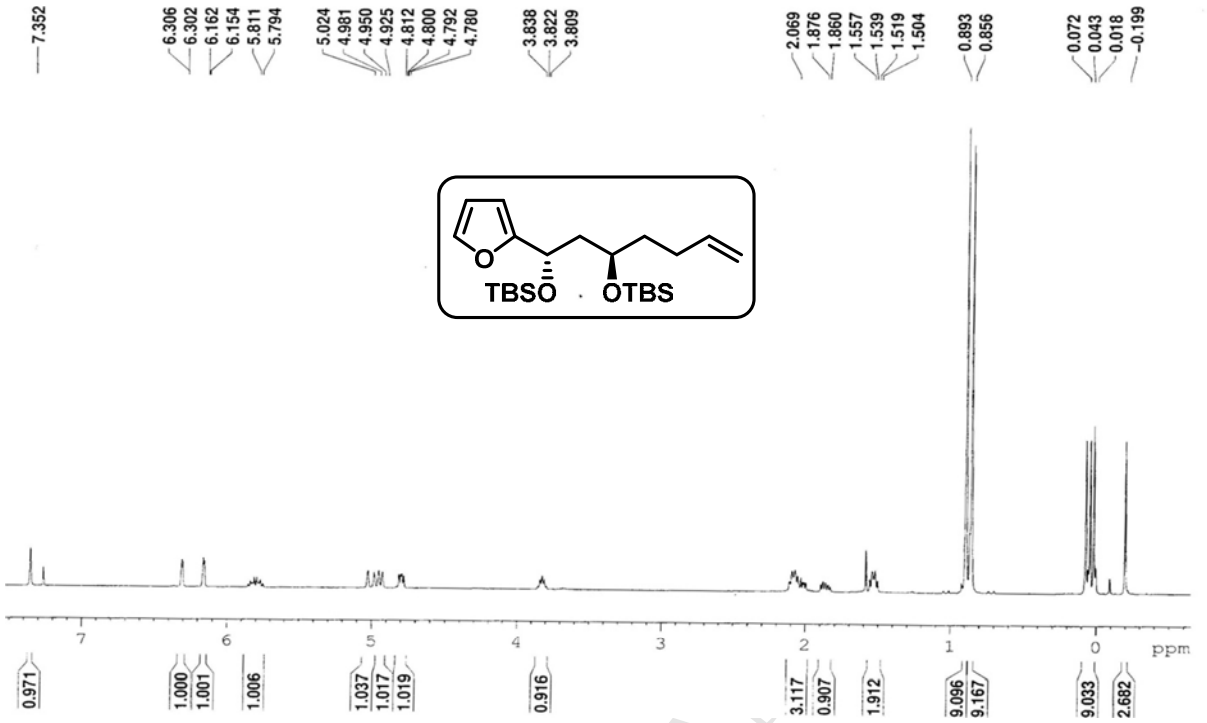
^{13}C NMR spectrum of compound **10**



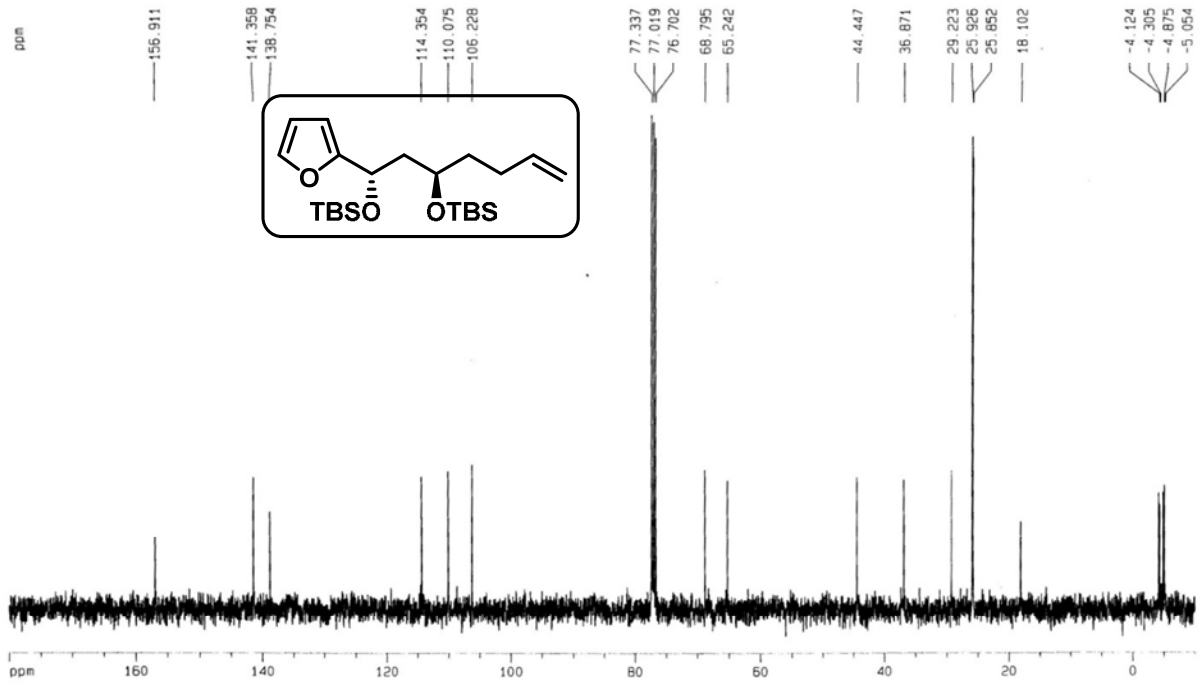
^{1}H NMR spectrum of compound **6**



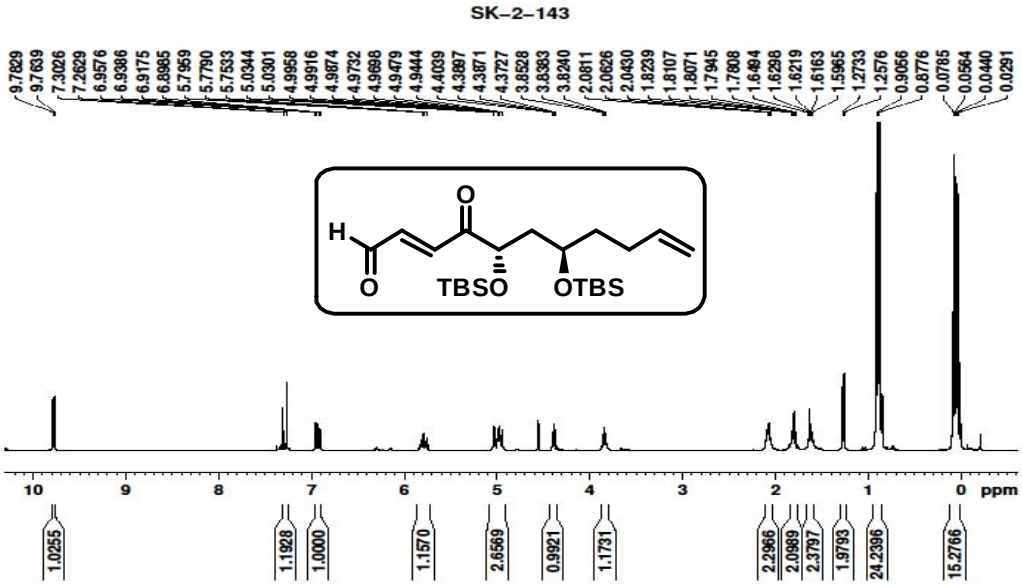
^{13}C NMR spectrum of compound **6**



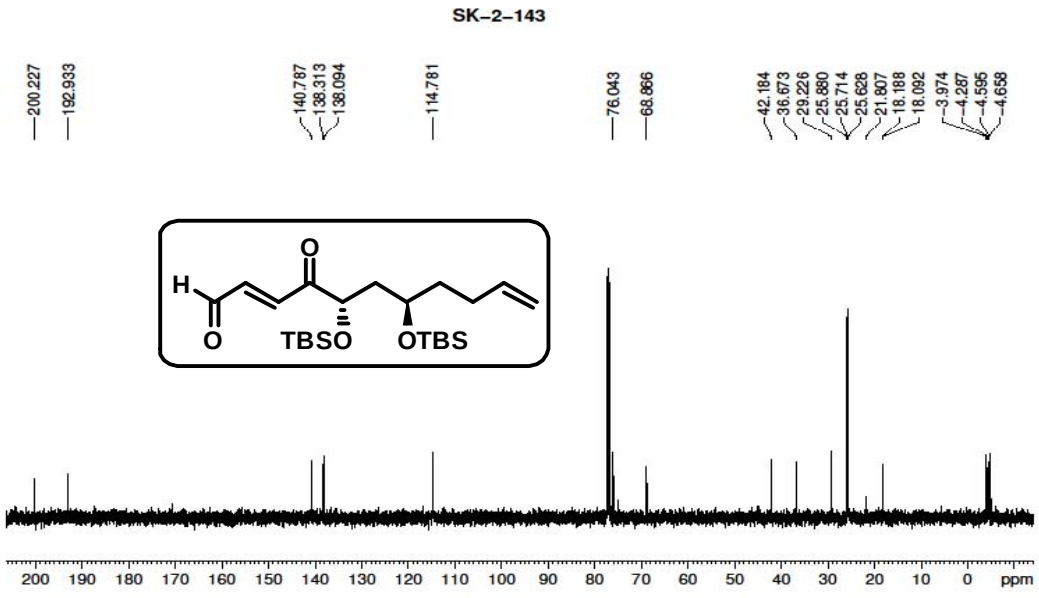
^{1}H NMR spectrum of compound **11**



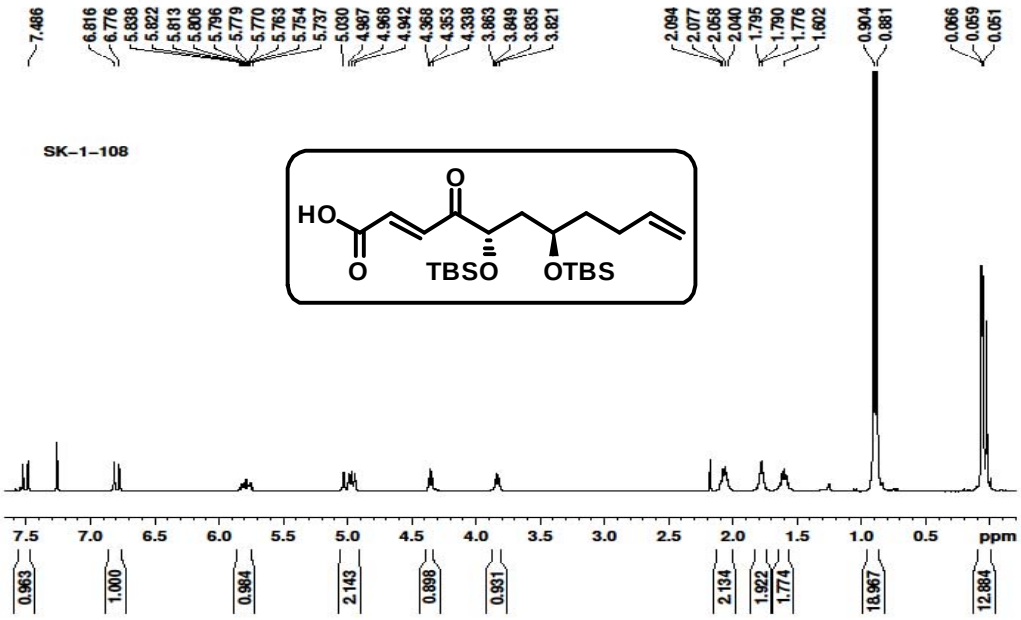
^{13}C NMR spectrum of compound **11**



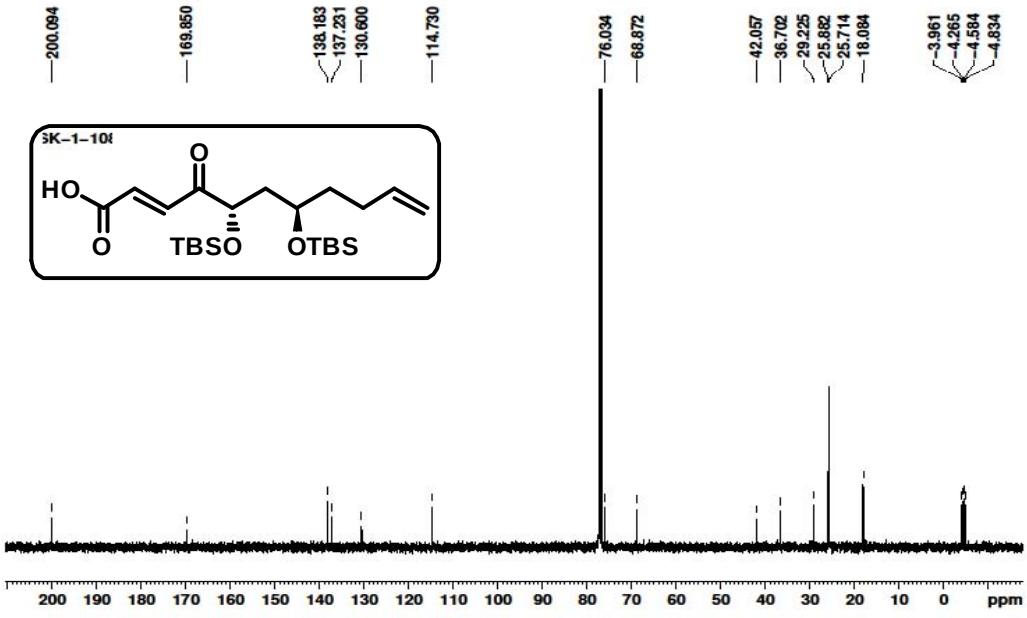
^{1}H NMR spectrum of compound **12**



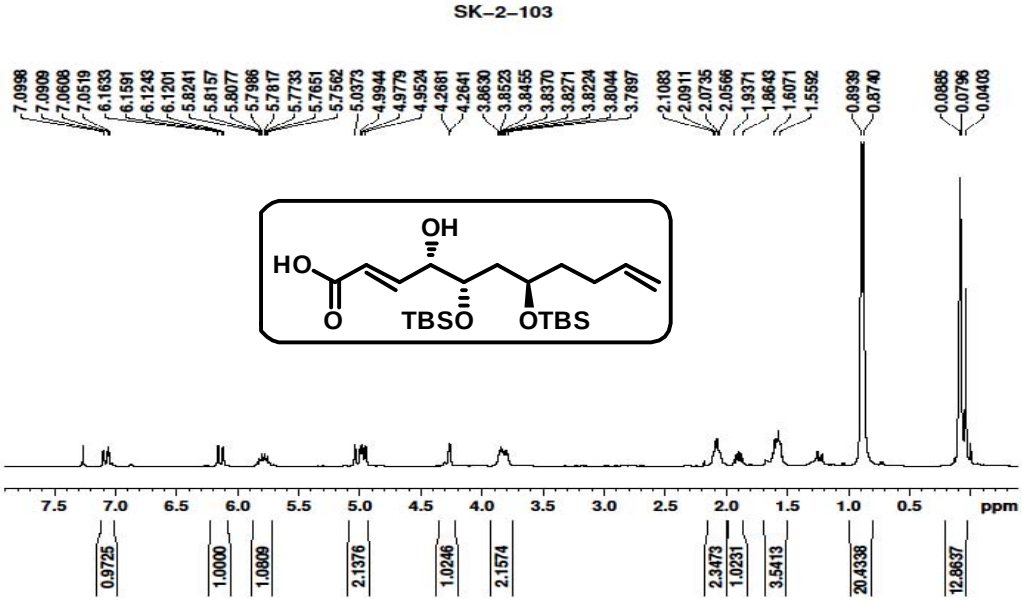
^{13}C NMR spectrum of compound **12**



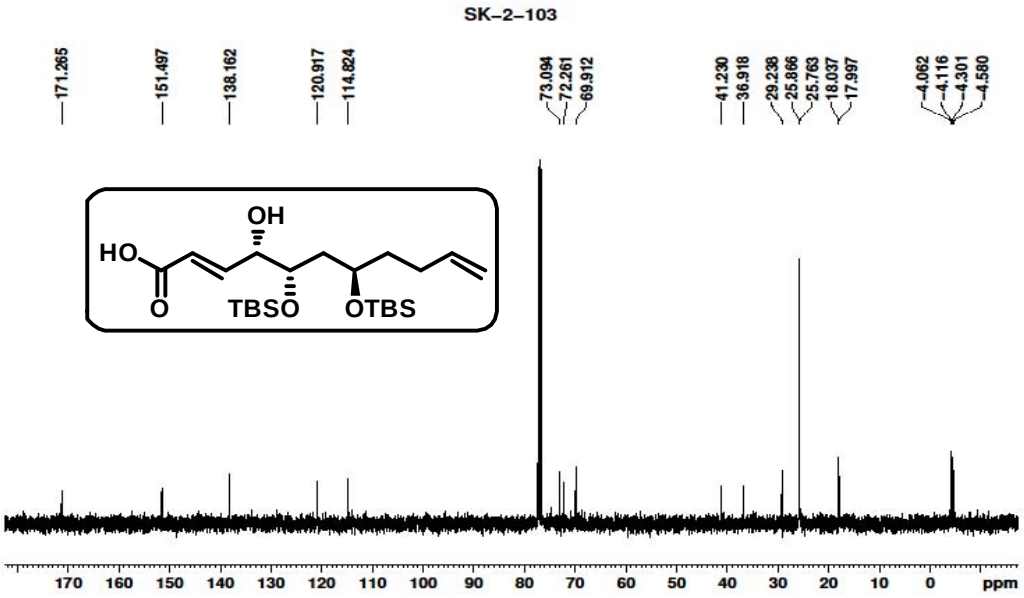
^{1}H NMR spectrum of compound **13**



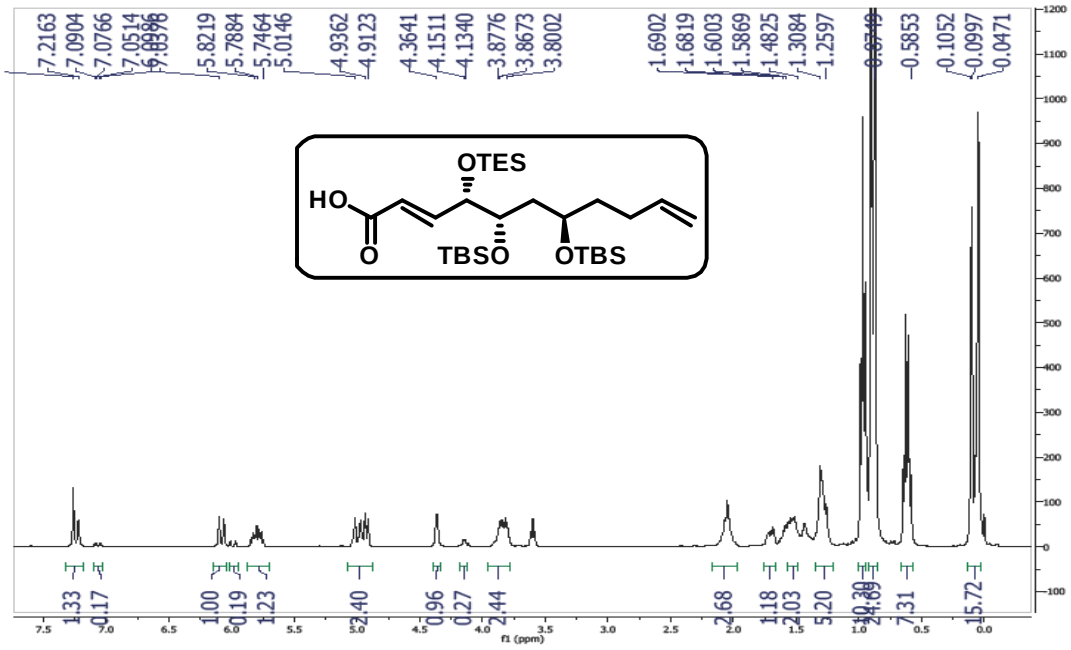
^{13}C NMR spectrum of compound **13**



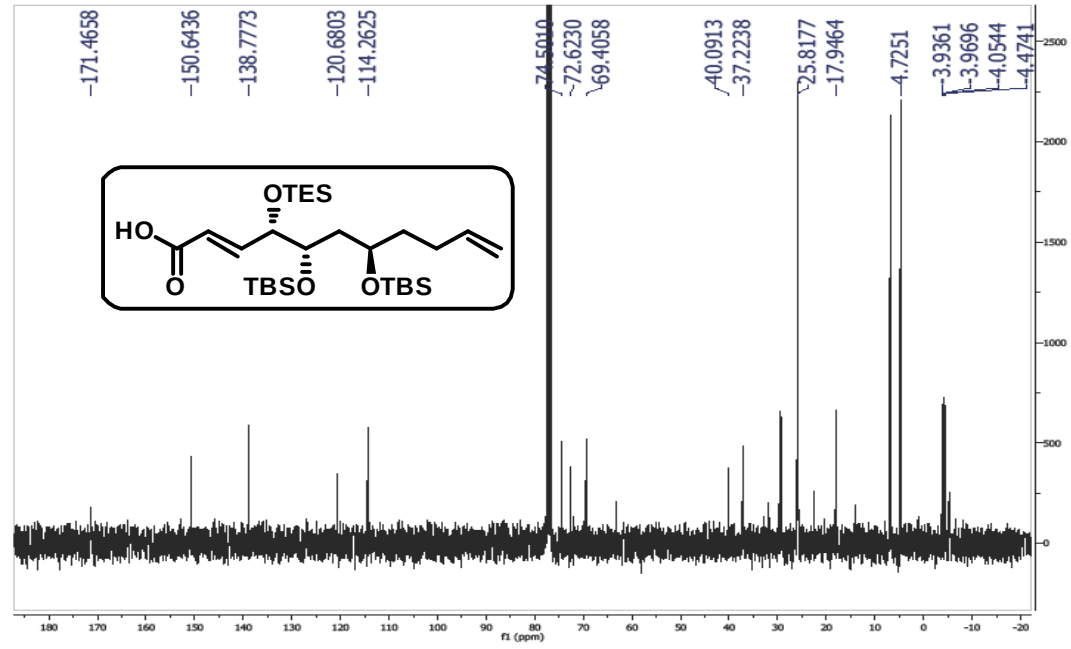
^{1}H NMR spectrum of compound **14**



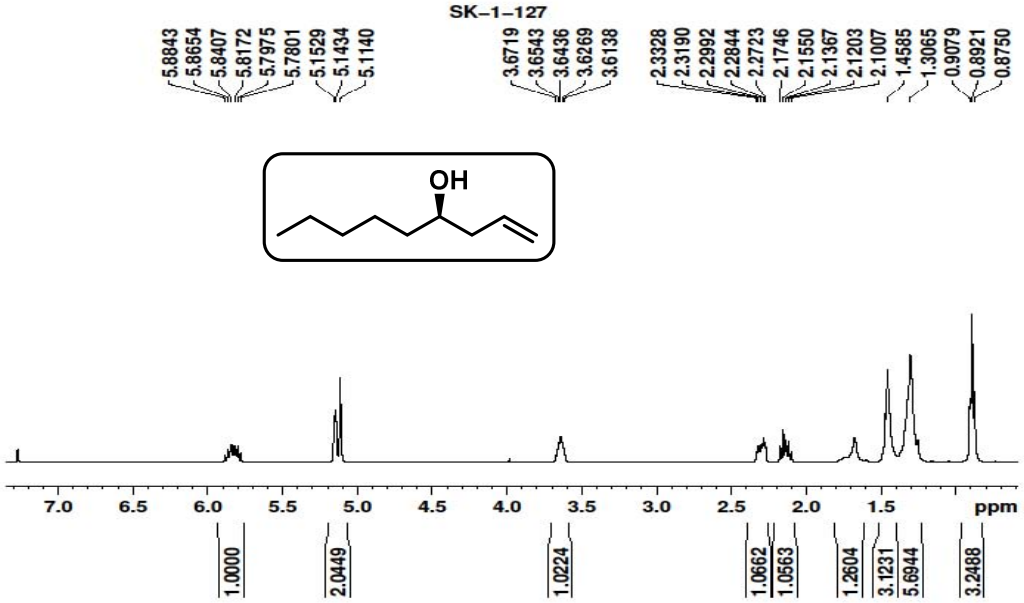
^{13}C NMR spectrum of compound **14**



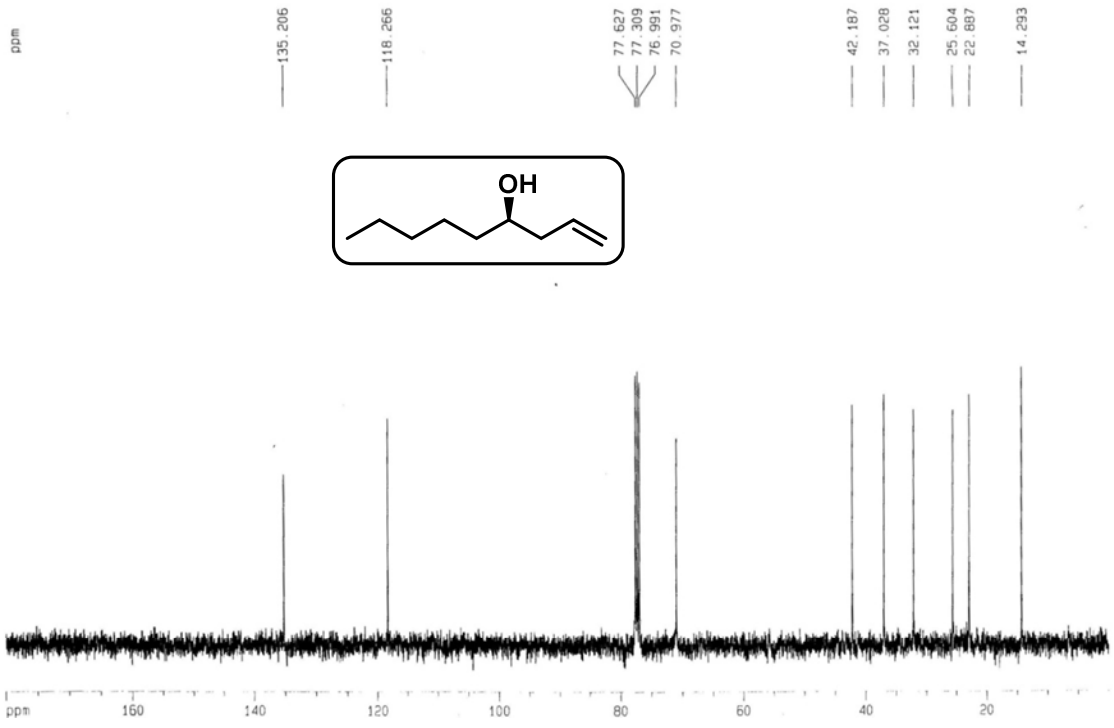
^{1}H NMR spectrum of compound **15**



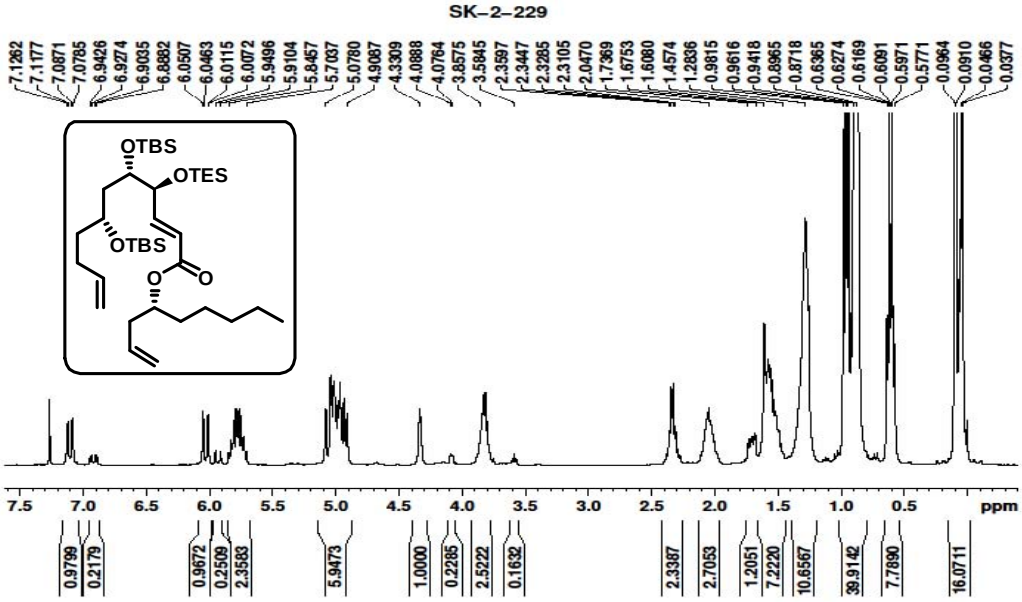
^{13}C NMR spectrum of compound **15**



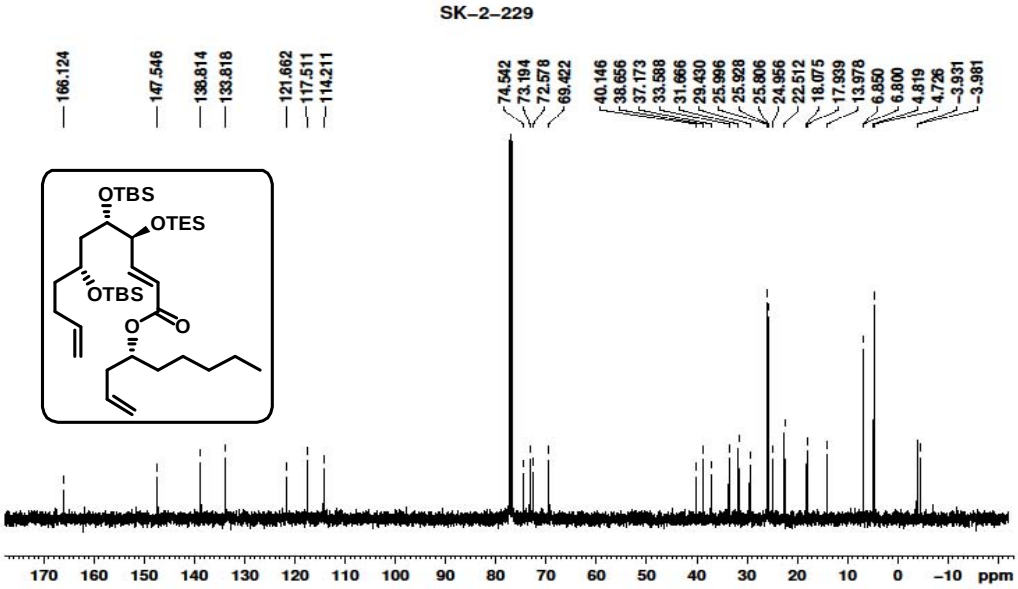
^{1}H NMR spectrum of compound **5**



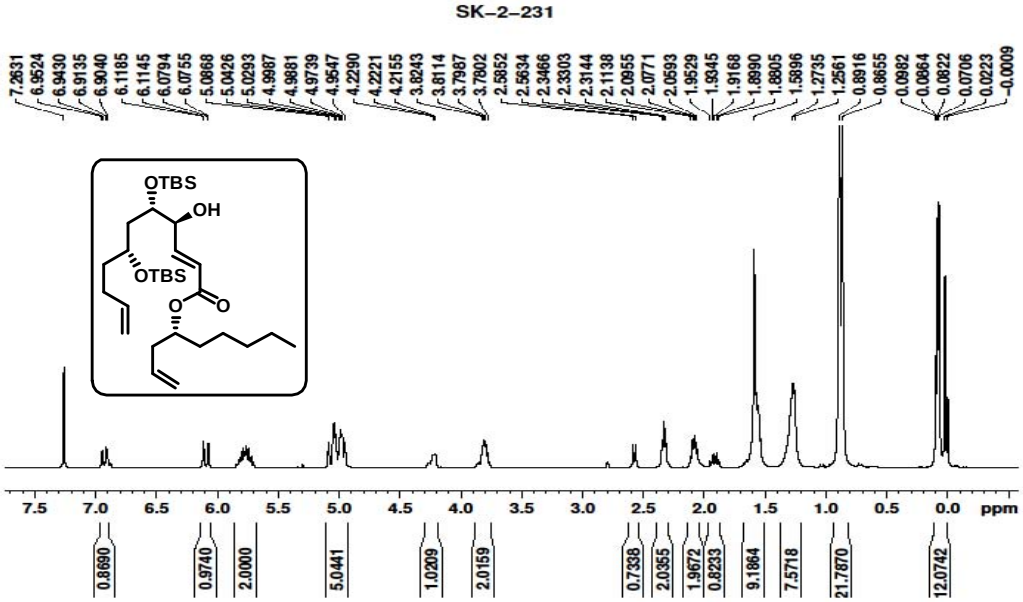
^{13}C NMR spectrum of compound **5**



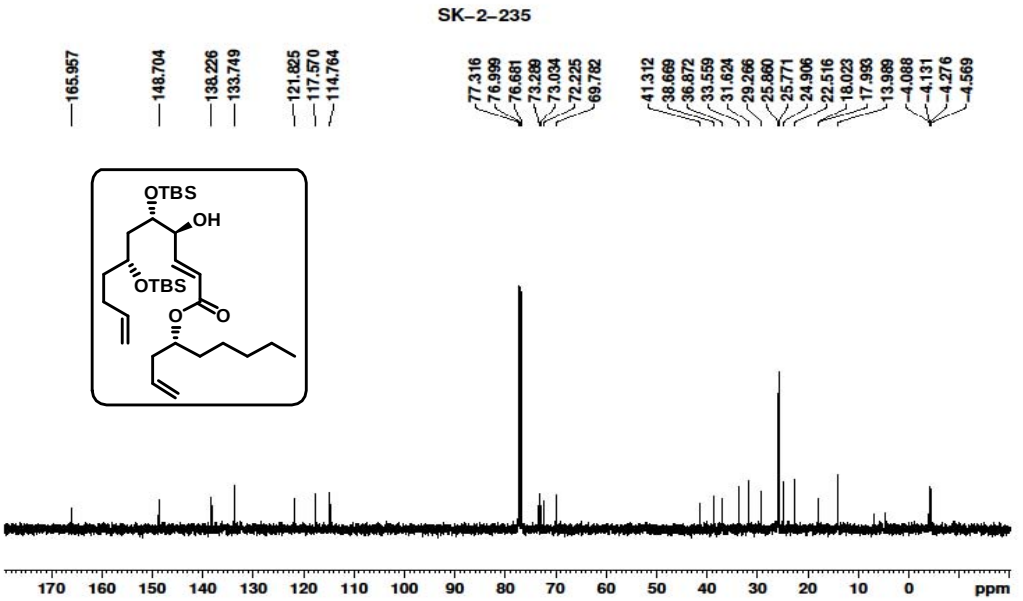
^{1}H NMR spectrum of compound **16**



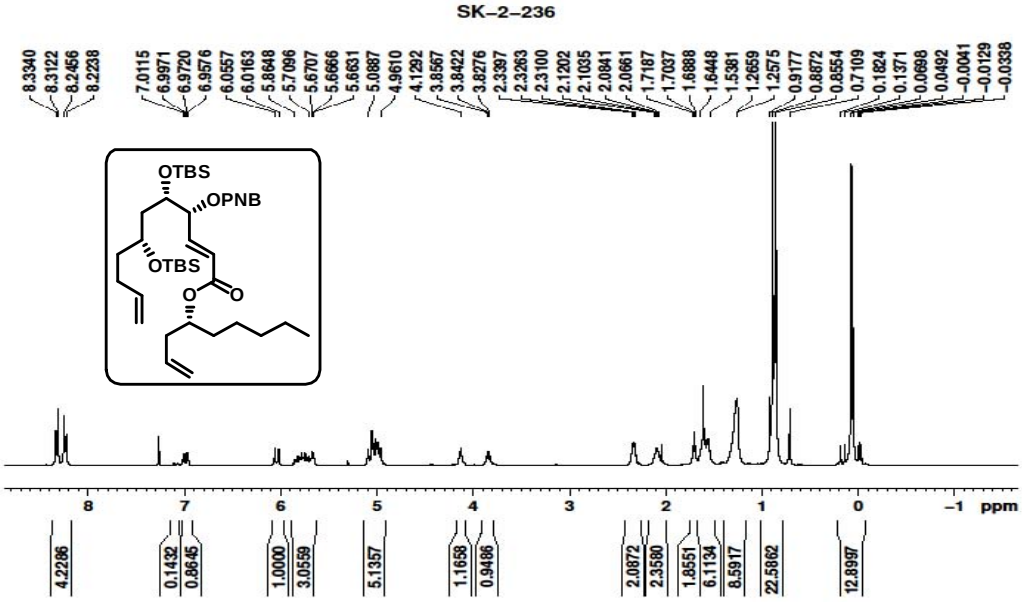
^{13}C NMR spectrum of compound **16**



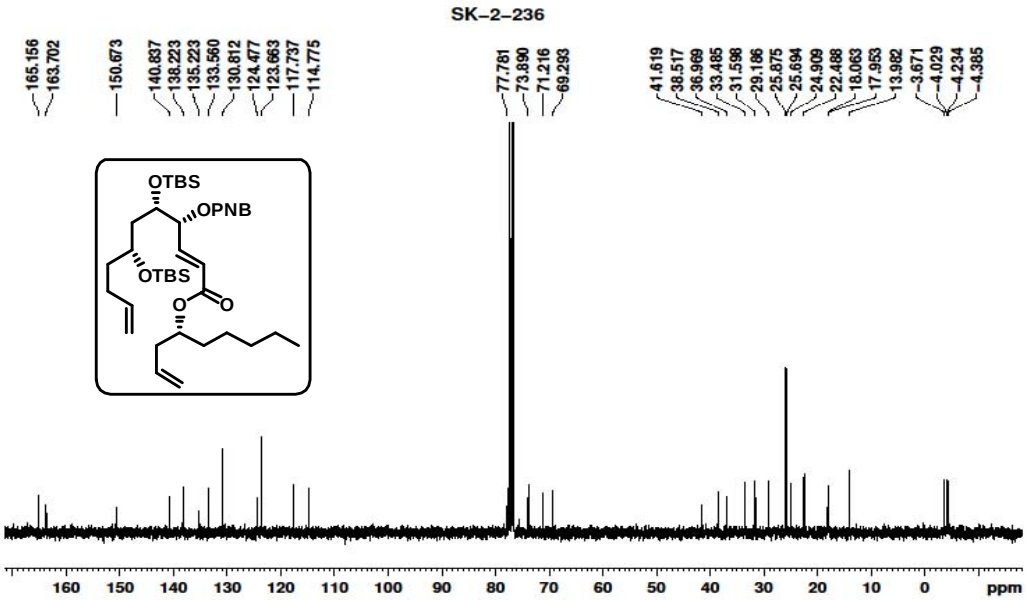
^{1}H NMR spectrum of compound **17**



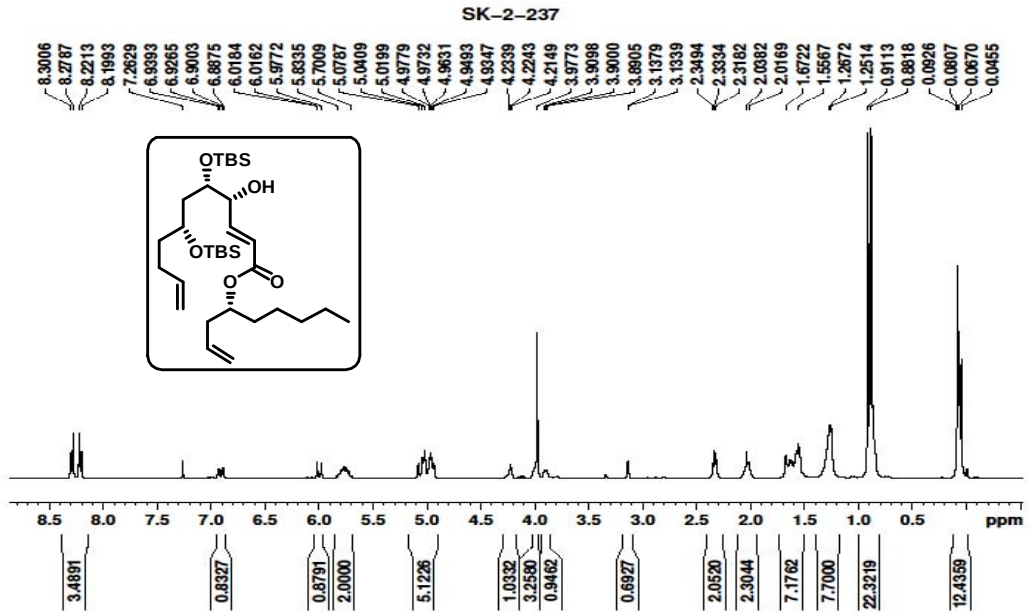
^{13}C NMR spectrum of compound **17**



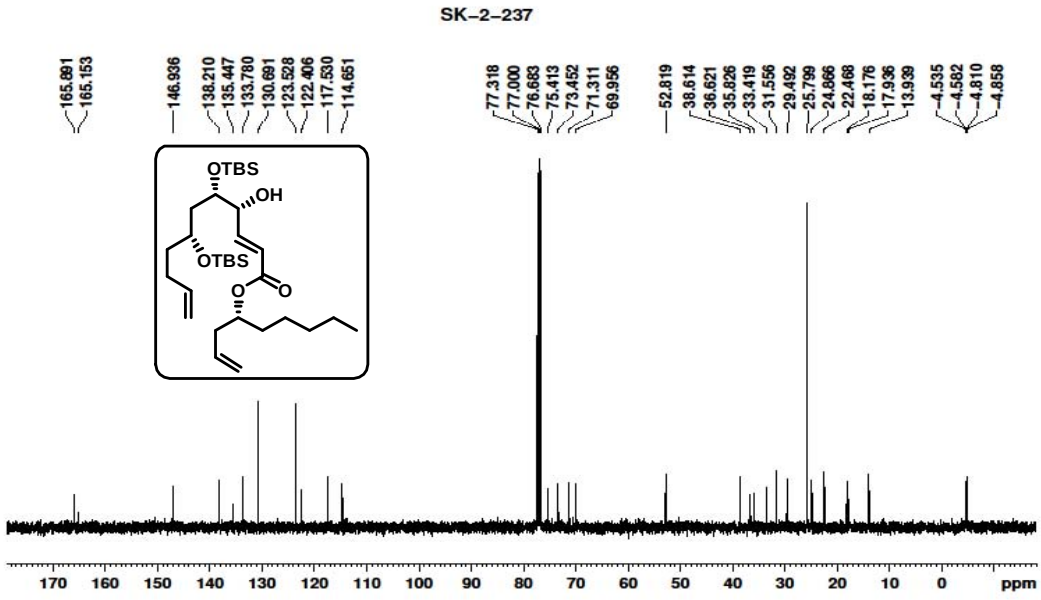
^{1}H NMR spectrum of compound **18**



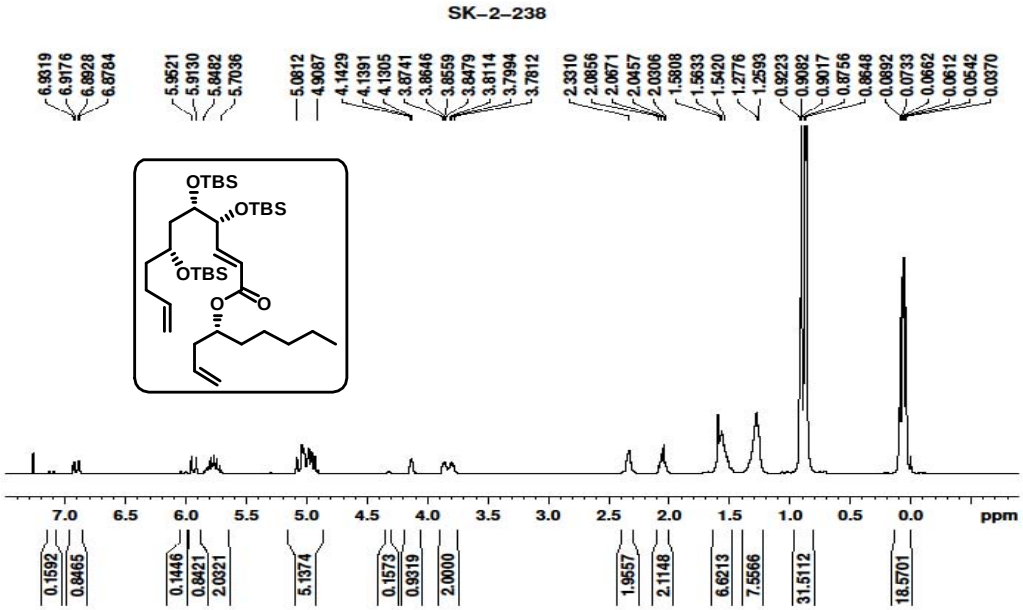
^{13}C NMR spectrum of compound **18**



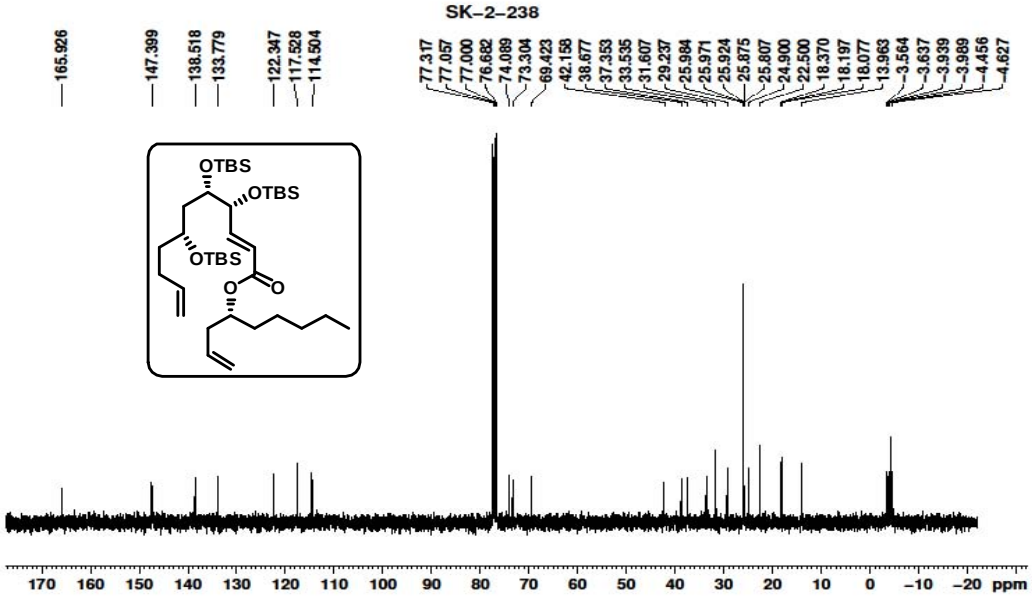
^{1}H NMR spectrum of compound obtained by reaction of **18** with K_2CO_3/MeOH



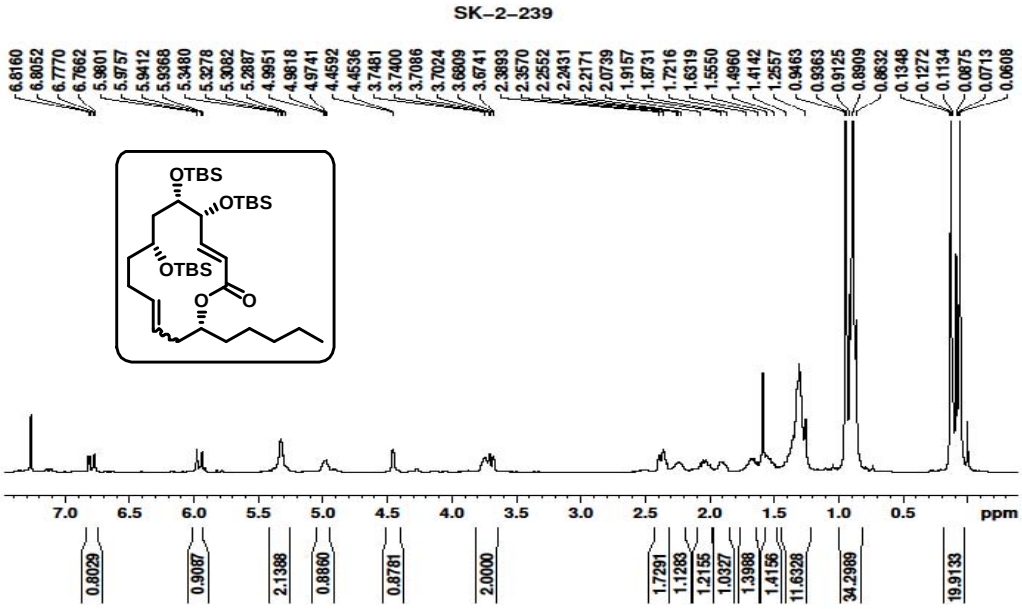
^{13}C NMR spectrum of compound obtained by reaction of **18** with K_2CO_3/MeOH



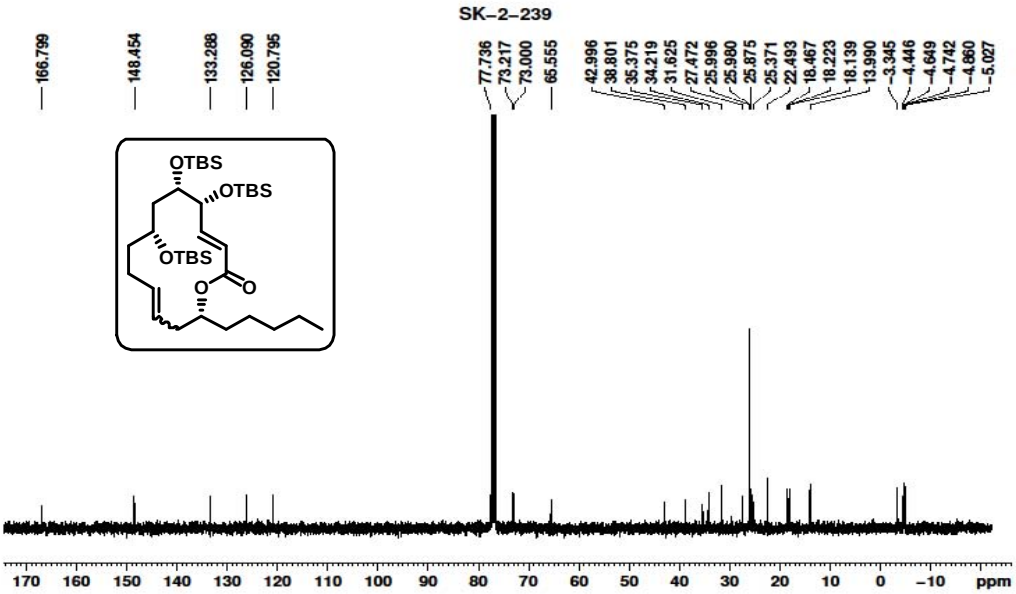
^{1}H NMR spectrum of compound **3**



^{13}C NMR spectrum of compound **3**



^{1}H NMR spectrum of compound **2**



^{13}C NMR spectrum of compound **2**