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Cyclopropenyllithiums as a New Source of 1,1-Bismetallated Cyclopropyl Derivatives

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General

All reactions were carried out under argon using standard Schlenk techniques. ^1H and ^{13}C NMR spectra were recorded on a Bruker Avance 300 or Avance 500 instruments in CDCl_3 . Chemical shifts are given as ppm relative to the residual solvent peak (chloroform- d_1 : 7.26 ppm/77.0 ppm). Column chromatography purification was performed on Merck silica gel 60 (230-400 mesh ASTM). THF and Diethyl Ether were dried with sodium/benzophenone and distilled. Yields refer to isolated yields of compounds. Methyllithium (1.6M solution in diethyl ether), *t*-Butyllithium (1.7M solution in pentane), zinc bromide and copper (I) cyanide were purchased from Aldrich Chemicals Co Inc and used without further purification.

General Procedure for the allylmetalation of cyclopropenyllithium coming from tribromocyclopropane:

To a solution of the appropriate tribromocyclopropane (1 mmol) in dry diethyl ether (15 ml) at -78°C *t*BuLi was added dropwise (4 mmol, 2.35 ml, 1.7 M). The reaction mixture was warmed to -10°C for 1 h. Then, the reaction mixture was cooled to -30°C and allylmagnesium bromide (2 mmol, 1.3 M in diethyl ether) was added followed by a zinc bromide solution (2 mmol, 1 M in diethyl ether). The reaction solution was warmed to -10°C for 30 min. The reaction was quenched with 1M HCl. The aqueous layer was washed with diethyl ether (3 x 15 ml), the organic layers were combined and washed with saturated NaHCO_3 (1 x 20 ml), brine (20 ml) and dried over MgSO_4 .

1-allyl-1-butyl-cyclopropane 5: The reaction was performed with 1,1,2-tribromo-2-butylcyclopropane following the general allylmetalation procedure. Purification on silica gel (hexane as eluent) gave **5** in 81% yield as colorless oil. ^1H NMR (CDCl_3 , 300 MHz): 5.84-5.73 (m, 1H), 5.03-4.95 (m, 2H), 1.98-1.96 (d, $J = 6$, 2H), 1.31-1.19 (m, 6H), 0.85 (t, $J = 9$, 3H), 0.27-0.91 (m, 4H) ^{13}C NMR (CDCl_3 , 75 MHz): 136.8, 115.7, 40.35, 35.97, 29.75, 28.75, 22.96, 19.07, 14.07, 11.20.

1-allyl-cyclopropyl-benzene 6: The reaction was performed with 1,1,2-tribromo-2-phenylcyclopropane following the general allylmatalation procedure. Purification on silica gel (hexane as eluent) gave **6** in 75% yield as colorless oil. ^1H NMR (CDCl_3 , 300 MHz): 7.29-7.29 (m, 4H), 7.20-7.18 (m, 1H), 5.80-5.74 (m, 1H), 4.97-4.93 (m, 2H), 2.37 (d, $J = 3.6$, 2H), 0.92-0.83 (m, 2H), 0.77-0.71 (m, 2H). ^{13}C NMR (CDCl_3 , 75 MHz): 12.8, 14.2, 28.4, 43.9, 60.4, 116.2, 125.9, 128.0, 128.6, 136.1.

1-butyl-1-(1-methyl-allyl)-cyclopropane 7: To a mixture of 1,1,2-tribromo-2-butylcyclopropane (1 mmol) in diethyl ether (15 ml) at $-78\text{ }^\circ\text{C}$, $t\text{-BuLi}$ (4 mmol, 1.7 M) was added dropwise. The solution was heated to $-10\text{ }^\circ\text{C}$ for 1 h. The mixture was cooled to $-30\text{ }^\circ\text{C}$ and crotylmagnesium bromide (2.5 mmol, 1.3 M) was added followed by a zinc bromide solution (2.5 mmol, 1 M in diethyl ether). The mixture was warmed to $-10\text{ }^\circ\text{C}$ for 1 h. The reaction was quenched by 1M HCl. The aqueous layer was washed with diethyl ether (3 x 15 ml), saturated NaHCO_3 (1 x 20 ml), brine (20 ml) and dried over MgSO_4 . The organic layers were combined and evaporated. Purification on silica gel (hexane as eluent) gave **7** in 65% yield as colorless oil. ^1H NMR (CDCl_3 , 300 MHz): 5.81-5.74 (m, 1H), 4.98-4.94 (m, 2H), 1.92-1.89 (m, 1H), 1.30-1.22 (m, 6H), 0.99 (s, 3H), 0.89-0.86 (t, 3H), 0.31-0.23 (m, 4H). ^{13}C NMR (CDCl_3 , 75 MHz): 9.3, 9.8, 14.2, 16.2, 22.7, 29.3, 30.3, 42.3, 113.4, 142.5.

1-allyl-1-butyl-2,2-diiodo-cyclopropane 8: The reaction was performed with 1,1,2-tribromo-2-butylcyclopropane following the general allylmatalation procedure. Once the formation of the bismetalated cyclopropyl derivative was completed, a solution of iodine (4 mmol) in THF (4 ml) was added at $-10\text{ }^\circ\text{C}$ and the mixture was warmed to r.t. for 30 min. Purification on silica gel (hexane as eluent) gave **8** in 68% yield as colorless oil. ^1H NMR (CDCl_3 , 300 MHz): 5.90-5.78 (m, 1H), 5.18-5.10 (m, 2H), 2.45-2.40 (dd, $J = 7.2$, $J = 7.2$, 1H), 2.26-2.19 (dd, $J = 7.2$, $J = 7.2$, 1H), 1.61-1.56 (m, 2H), 1.54-1.50 (m, 2H), 1.34-1.1.30 (m, 4H), 0.92-0.87 (t, $J = 7.2$, 3H). ^{13}C NMR (CDCl_3 , 75 MHz) -43.3, 14.1, 22.7, 27.7, 29.2, 32.1, 36.5, 37.9, 42.5, 117.5, 134.4.

(2-allyl-2-butyl-cyclopropylidenemethyl)-benzene 9: The reaction was performed with 1,1,2-tribromo-2-butylcyclopropane following the general allylmatalation

procedure. Once the formation of the bismetalated cyclopropyl derivative was completed, $\text{BF}_3 \cdot \text{OEt}_2$ (1.5 mmol) was added followed by benzyldenemalonate (1.5 mmol) at -15°C and the reaction mixture was gradually warmed to room temperature over night. Purification on silica gel (hexane as eluent) gave **9** with a E:Z ratio of 15:85 in 60% yield as colorless oil. ^1H NMR (CDCl_3 , 300 MHz): 7.30-7.27 (m, 4H), 7.16-7.10 (m, 1H), 6.61-6.60 (t, $J = 1.8$, 1H), 5.66-5.53 (m, 1H), 4.99-4.88 (m, 2H), 2.46-2.32 (m, 1H), 2.31-2.29 (m, 1H), 1.26-1.2 (m, 6H), 0.99-0.98 (d, $J = 3$, 2H), 0.85-0.8 (t, 3H) ^{13}C NMR (CDCl_3 , 75 MHz): 11.20, 15.91, 21.03, 22.89, 27.77, 28.55, 34.63, 39.69, 115.4, 116.4, 126.0, 126.3, 128.8, 129.0, 135.1, 135.6.

1-(2-allyl-2-butyl-cyclopropylidenemethyl)-4-methyl-benzene 10: The reaction was performed with 1,1,2-tribromo-2-butylcyclopropane following the general allylmatalation procedure. Once the formation of the bismetalated cyclopropyl derivative was completed, tolualdehyde (4 mmol) was added at -15°C and the reaction mixture was gradually warmed to room temperature over night. Purification on silica gel (hexane as eluent) gave **10** with a E:Z ratio of 1:2 in 53% yield as colorless oil. ^1H NMR (CDCl_3 , 300 MHz): 7.42 (d, $J = 8.1$, 1H), 7.25-7.22 (d, $J = 6.3$, 2H), 7.19-7.10 (m, 0.5H), 6.71 (t, 1H), 6.66 (t, 1H), 5.92-5.60 (m, 1.5H), 5.08-4.93 (m, 3.5H), 2.50-2.43 (dd, $J = 8.1$, $J = 7.8$, 1H), 2.32 (s, 6H), 2.22-2.17 (m, 1H), 1.50-1.20 (m, 12H), 1.02 (d, $J = 1.8$, 2H), 0.90-0.87 (t, 6H) ^{13}C NMR (CDCl_3 , 75 MHz): 11.20, 15.91, 21.03, 22.89, 27.77, 28.55, 34.63, 39.69, 115.4, 116.4, 126.0, 126.3, 128.8, 129.0, 135.1, 135.6.

1,1,2-triallyl-2-butylcyclopropane 11: The reaction was performed with 1,1,2-tribromo-2-butylcyclopropane following the general allylmatalation procedure. Once the formation of the bismetalated cyclopropyl derivative was completed, the mixture was cooled to -78°C and copper cyanide was added (4 mmol), the mixture was then warmed to -20°C for 30 min. Once the transmetalation was complete allyl bromide was added (4 mmol) and the mixture was stirred for additional 12 h at room temperature. The reaction was quenched by $\text{NH}_4\text{OH}:\text{NH}_4\text{Cl}$ 1:2. Purification on silica gel (hexane as eluent) gave **11** in 60% yield as colorless oil. ^1H NMR (CDCl_3 , 300 MHz): 5.78-5.70 (m, 3H), 5.05-4.98 (m, 6H), 2.33-2.10 (m, 6H), 1.34-1.24 (m, 6H), 0.89-0.85 (t, $J = 6$, 3H), 0.25-0.21 (q, $J = 6$, $J = 9$, 2H) ^{13}C NMR (CDCl_3 , 75 MHz): 137.3, 137.2, 137.1, 115.9, 115.6, 36.7, 36.5, 36.3, 31.8, 28.9, 28.2, 27.5, 23.3, 23.1

2-allyl-2-butyl-cyclopropanecarboxylic acid 15: to a solution of 1-butylcyclopropanecarboxylic acid (1 mmol) in diethyl ether (15 ml), MeLi (2.2 mmol, 1.6 M) was added dropwise at -78 °C. The solution was warmed to room temperature for 1 h. The mixture was cooled again to -50 °C and allylmagnesium bromide (2.2 mmol, 1.3 M) was added followed by a solution of zinc bromide (2.2 mmol, 1 M in diethyl ether). The reaction mixture was warmed to room temperature for 30 min. The reaction was quenched by 1M HCl. The aqueous layer was washed with diethyl ether (3 x 15 ml), the organic layers were combined and washed with saturated NaHCO₃ (1 x 20 ml), brine (20 ml) and dried over MgSO₄. Purification on silica gel (hexane:ethyl acetate 1:2 as eluent) gave **15** as a unique diastereoisomer in 50% yield. ¹H NMR (CDCl₃, 200 MHz): 5 0.87 (t, J = 5.3, 3H), 0.96 (dd, J = 7.9, 4.5, 1H), 1.13 – 1.37 (m, 11H), 1.52 (dd, J = 7.9, 5.5, 1H), 2.08-2.37 (m, 2H), 5.00 – 5.09 (m, 2H), 5.64 – 5.84 (m, 1H), 1.50-12.0 (bs, 1H); ¹³C NMR (CDCl₃, 50 MHz): 14.0, 21.3, 22.6, 25.5, 26.0, 29.3 (overlapped two peaks), 31.8, 33.5, 37.0, 16.5, 135.7, 179.4.

General Procedure for allylmetalation of 1-hexyl-3-hydroxymethylcyclopropene: MeLi (2.2 mmol, 1.6M) was added dropwise to a mixture of the alcohol (1 mmol) in diethyl ether (15 ml) at -78 °C. The solution was warmed to room temperature for 1 h. Then the reaction mixture was cooled again to -50 °C and allylmagnesium bromide (2.2 mmol, 1.7 ml, 1.3 M) was added followed by a solution of zinc bromide (2.2 mmol, 22 ml, 1 M in diethyl ether). The reaction mixture was stirred for 4 h at -50 °C. The reaction was quenched by 1M HCl. The aqueous layer was washed with diethyl ether (3 x 15 ml), the organic layers were combined and washed with saturated NaHCO₃ (1 x 20 ml), brine (20 ml) and dried over MgSO₄.

(2-allyl-2-butyl-cyclopropyl)-methanol 16: The general procedure followed. The organic layers were combined and evaporated. Purification on silica gel (hexane:ethyl acetate 1:25 as eluent) gave **16** in 72% yield as a colorless oil, as unique isomer. ¹H NMR (CDCl₃, 300 MHz): 5.91-5.69 (m, 1H), 5.05-4.97 (m, 2H), 3.72-3.53 (m, 2H), 2.10-2.01 (dd, J = 9, J = 12, 1H), 1.89-1.82 (dd, J = 6, J = 6, 1H), 1.4-1.35 (m, 6H), 0.87 (t, 3H), 0.55-0.51 (q, 1H), 0.16-0.13 (t, 1H) ¹³C NMR (CDCl₃, 75 MHz): 1.00, 14.11, 16.19, 23.02, 25.7, 29.02, 29.68, 30.44, 41.46, 63.40, 116.2, 136.2.

((1S,2R)-2-allyl-2-butyl-1-phenylcyclopropyl)methanol 17:

The general procedure followed. The organic layers were combined and evaporated. Purification on silica gel (hexane:ethyl acetate 1:25 as eluent) gave **17** in 60% yield as yellow oil, with d.r. 4:1. ¹H NMR (CDCl₃, 300 MHz): 7.34-7.13 (m, 7H), 5.71-5.58 (m, 1H), 4.90-4.80 (m, 2H), 3.94-3.90 (d, 1H), 3.6-3.53 (d, 1H), 2.08-1.97 (m, 2H), 1.77-1.69 (m, 2H), 1.47-1.07 (m, 8H), 0.93-0.83 (m, 6H), 0.69-0.67 (m, 3H). ¹³C NMR (CDCl₃, 75 MHz): 141.0, 137.0, 136.5, 130.4, 128.3, 128.2, 126.6, 126.4, 116.1, 115.9, 68.5, 68.4, 39.0, 38.3, 35.9, 33.7, 31.4, 29.7, 29.2, 28.6, 23.0, 22.8, 22.1, 14.1.

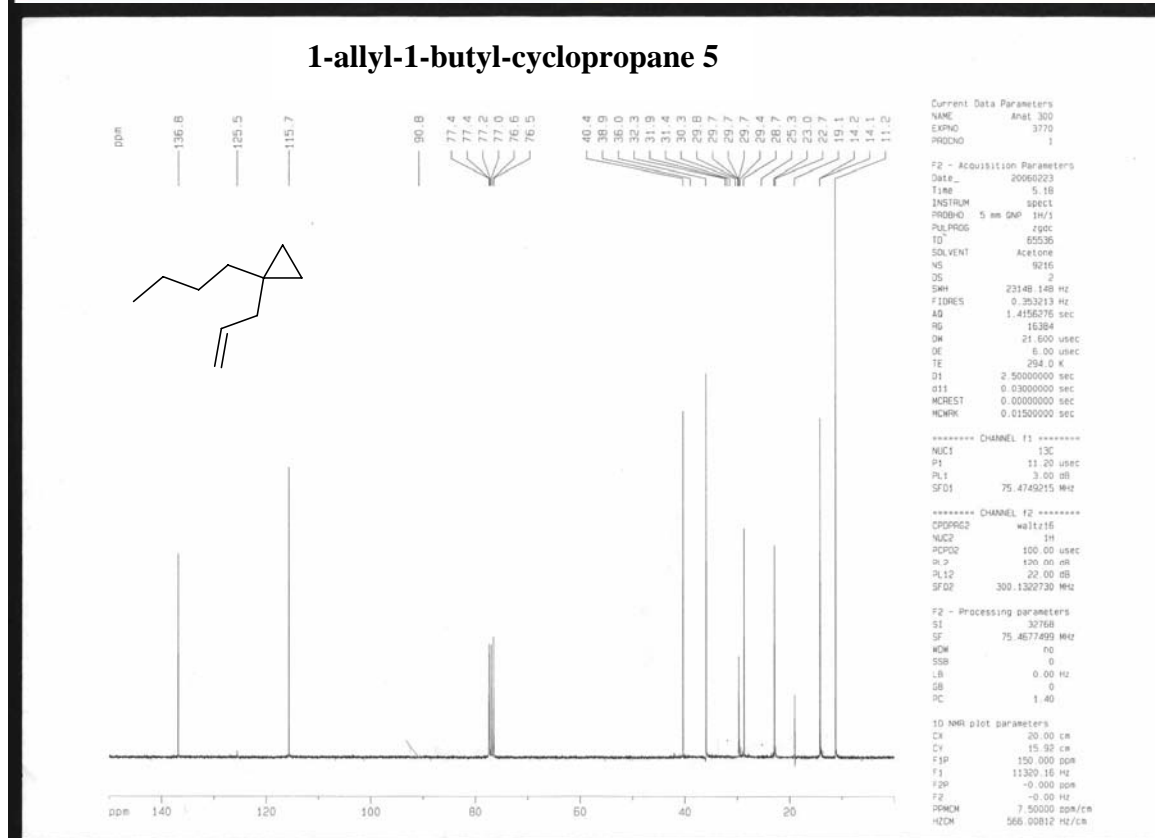
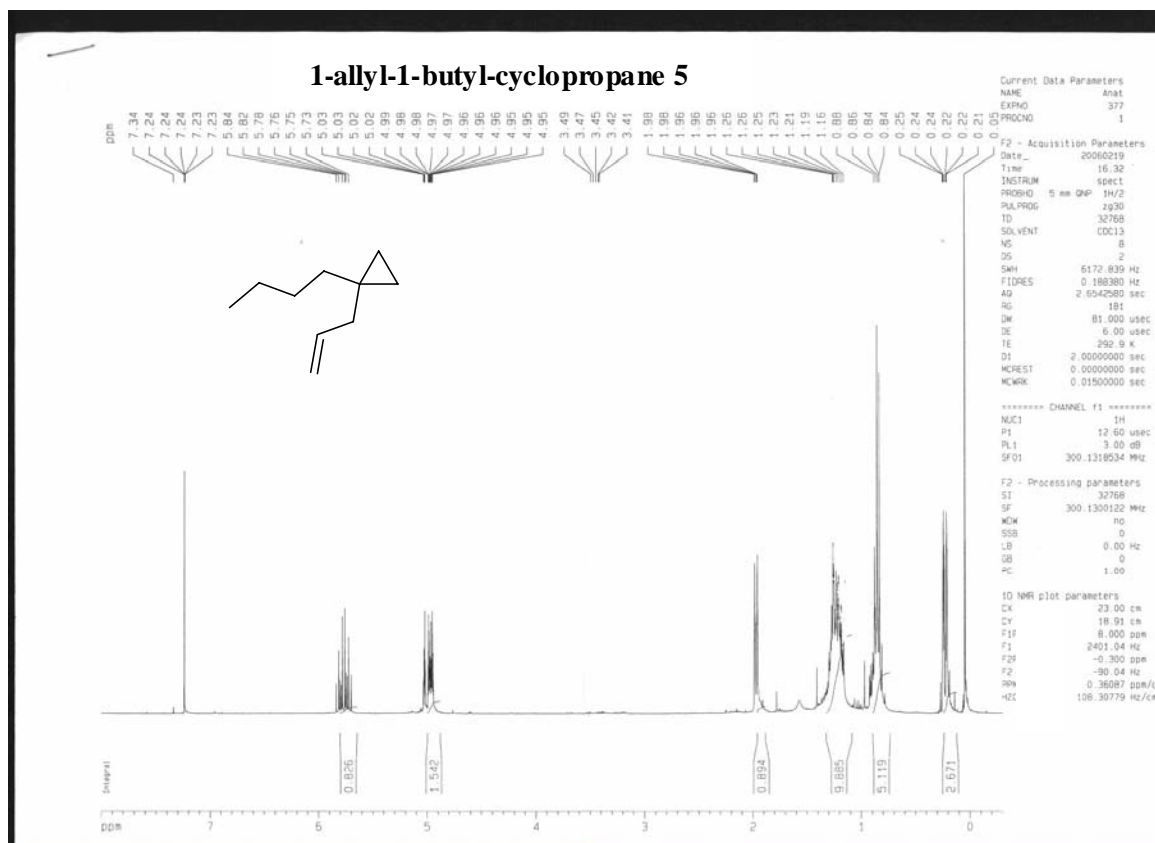
(2-allyl-2-butyl-3,3-diiodo-cyclopropyl)-methanol 18: The general procedure was followed. When the allylmatalation reaction was over, iodine (5 mmol) in THF (8 ml) was added at -20 °C and the mixture is stirred at this temperature for additional 45 min. Purification on silica gel (hexane:ethyl acetate 1:25 as eluent) gave **18** in 50% yield as a yellow oil. ¹H-NMR (CDCl₃, 300 MHz): 5.81-5.72 (m, 1H), 5.15-5.07 (m, 2H), 3.63-3.49 (m, 2H), 2.4 (dd, *J* = 12, 1H), 2.2 (dd, *J* = 6, *J* = 12, 1H), 1.5-1.1 (m, 7H), 0.85 (t, 3H).

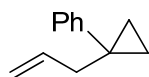
(2-allyl-2-butyl-3-iodo-cyclopropyl)-methanol 20: The general procedure was followed. When the allylmatalation reaction was over, iodine (2.2 mmol) in THF (5 ml) was added at -20 °C and the mixture was stirred at this temperature for additional 30 min. Purification on silica gel (hexane:ethyl acetate 1:25 as eluent) gave **20** in 55% yield as a yellow oil. ¹H NMR (CDCl₃, 300 MHz): 6.00-5.72 (m, 1H), 5.14-5.04 (m, 2H), 3.72-3.66 (dd, *J* = 6, *J* = 12, 1H), 3.58-3.52 (dd, *J* = 6, *J* = 12, 1H), 2.37 (d, *J* = 6, 1H), 2.31-2.24 (m, 1H), 2.06-1.99 (m, 1H), 1.55-1.47 (m, 2H), 1.36-1.15 (m, 6H), 0.81 (t, 3H).

(1R,2S)-1-allyl-1-butyl-2-((2-methoxypropan-2-yloxy)methyl)cyclopropane 21: *n*-BuLi (1.2 mmol, 1.6M) was added dropwise to a mixture of (1 mmol) in diethyl ether (15 ml) at -78 °C. The solution was warmed to -60 °C for 20 min. Then the mixture was warmed to -50 °C, and allylmagnesium bromide (1.2 mmol, 0.93 ml, 1.3 M) was added followed by a solution of zinc bromide (1.2 mmol, 1 M in diethyl ether). The reaction mixture was warmed to -30 °C for 3.5 hours. The reaction was quenched by 1 M NaHCO₃. The aqueous layer was washed with diethyl ether (3 x 15 ml), the

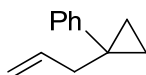
organic layers were combined and washed with saturated NaHCO_3 (1 x 20 ml), brine (20 ml) and dried over K_2CO_3 . Purification on alumina (pentane:ether 100:1 as eluent) gave **21** in 90% yield as a yellow oil. ^1H NMR (CDCl_3 , 300 MHz): 5.78-5.64 (m, 1H), 5.01-4.90 (m, 2H), 3.42-3.40 (dd, $J=6$ $J=9$, 1H), 3.26-3.23 (dd, $J=6$ $J=9$, 1H), 0.07-0.04 (t, $J=6$, 1H). ^{13}C NMR (CDCl_3 , 75 MHz): 141.0, 137.0, 136.5, 130.4, 128.3, 128.2, 126.6, 126.4, 116.1, 115.9, 68.5, 68.4, 39.0, 38.3, 35.9, 33.7, 31.4, 29.7, 29.2, 28.6, 23.0, 22.8, 22.1, 14.1.

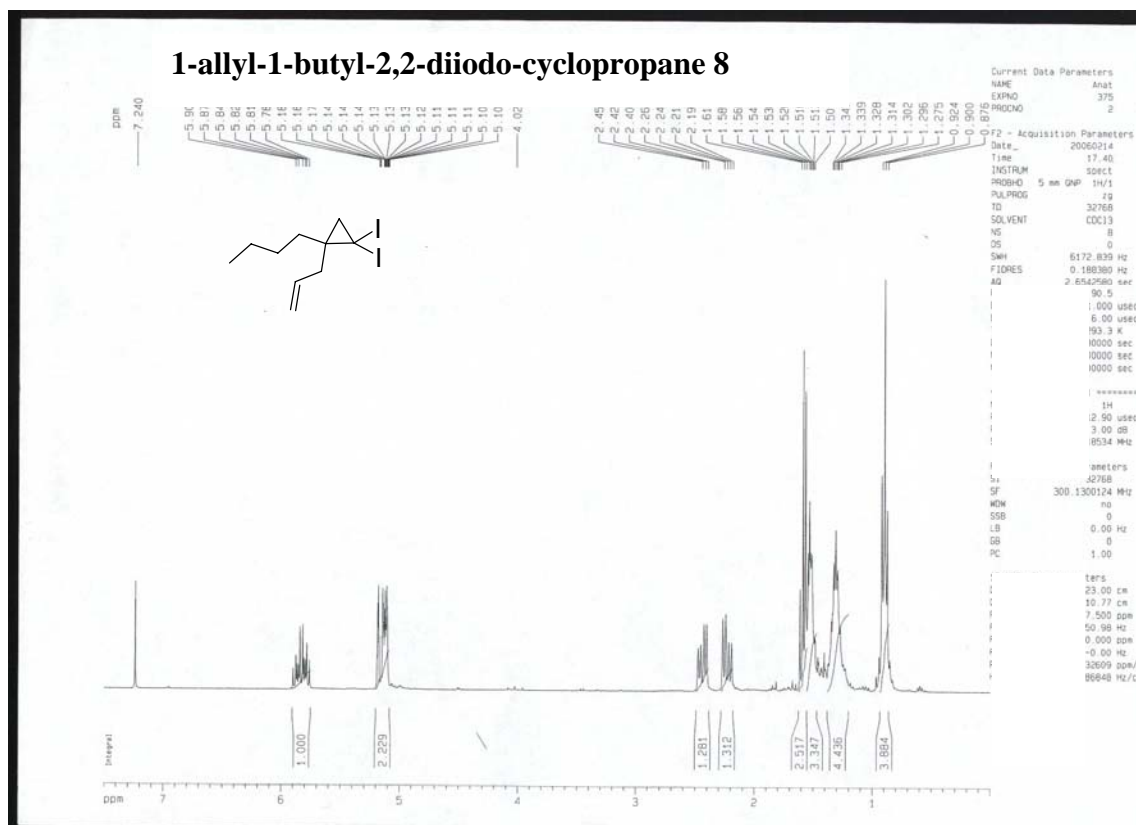
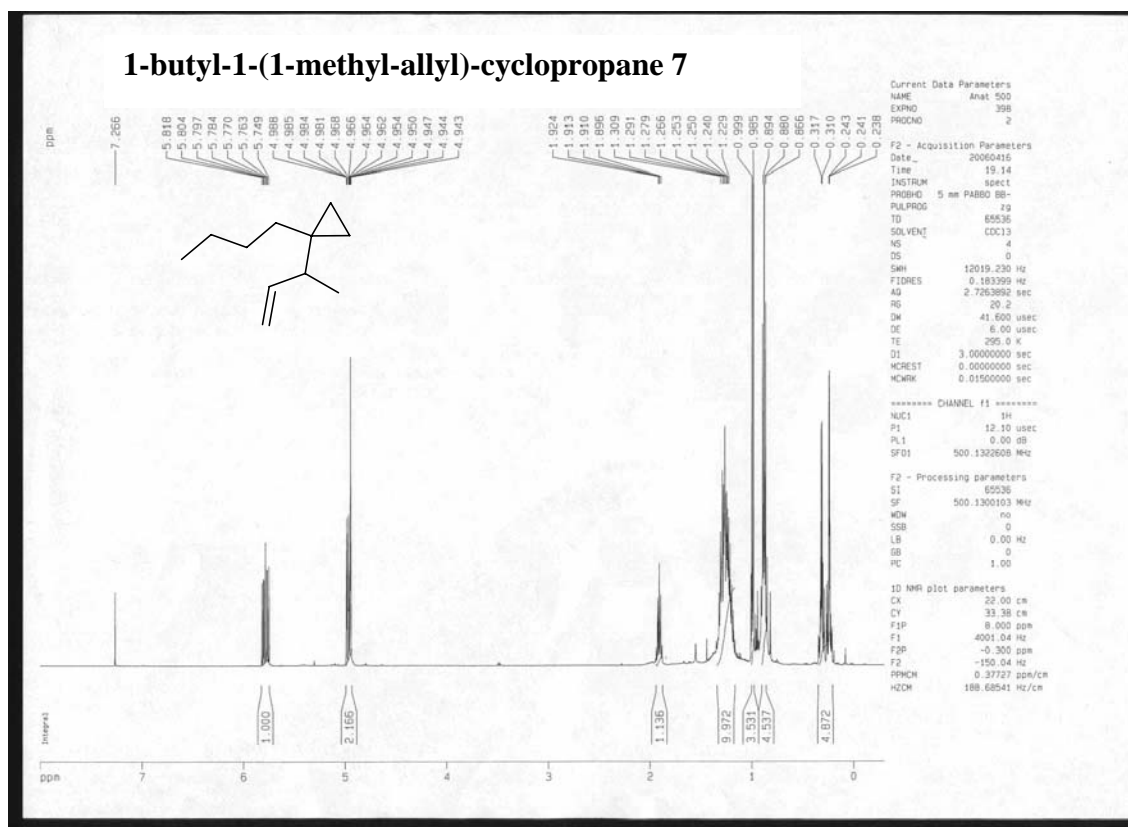
NMRs



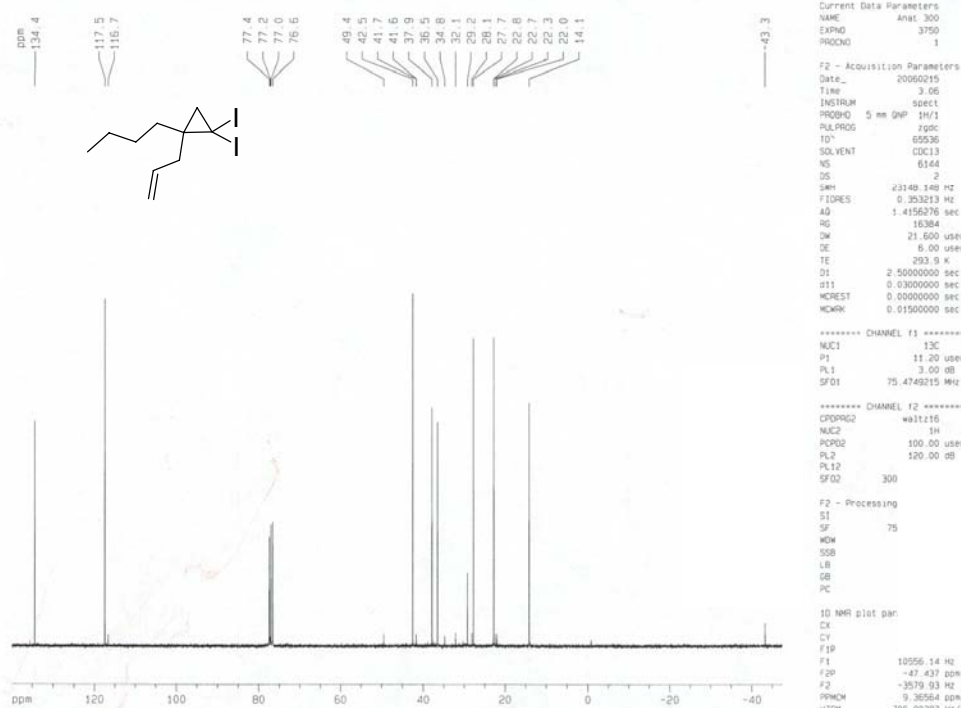


1-allyl-cyclopropyl-benzene 6

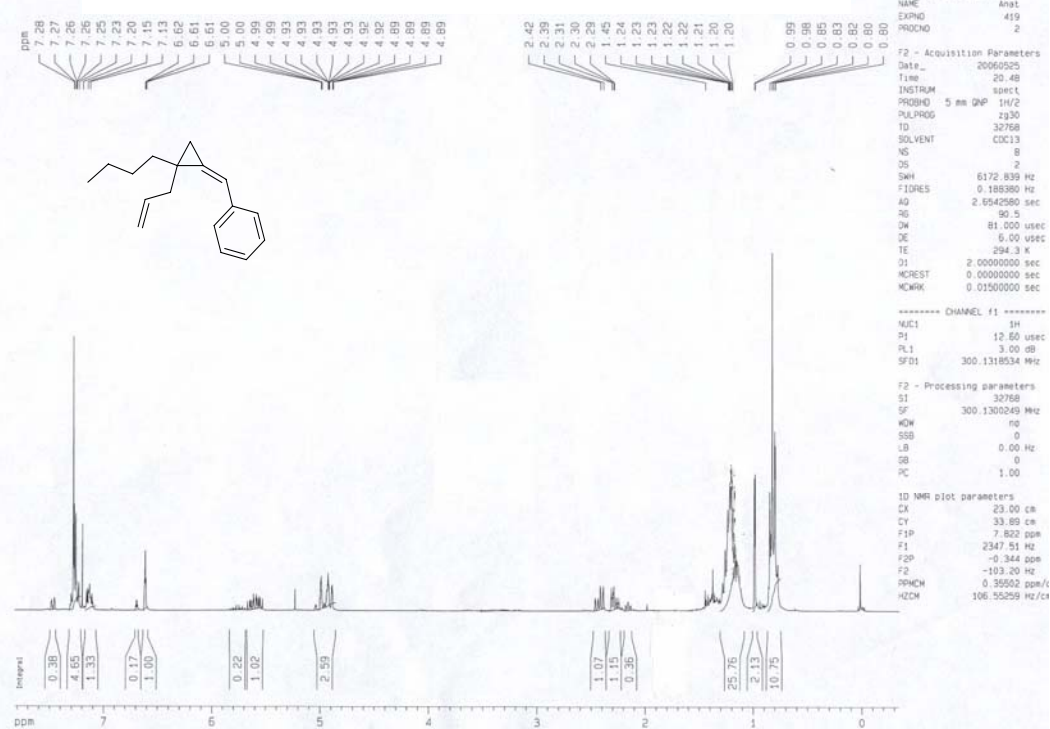




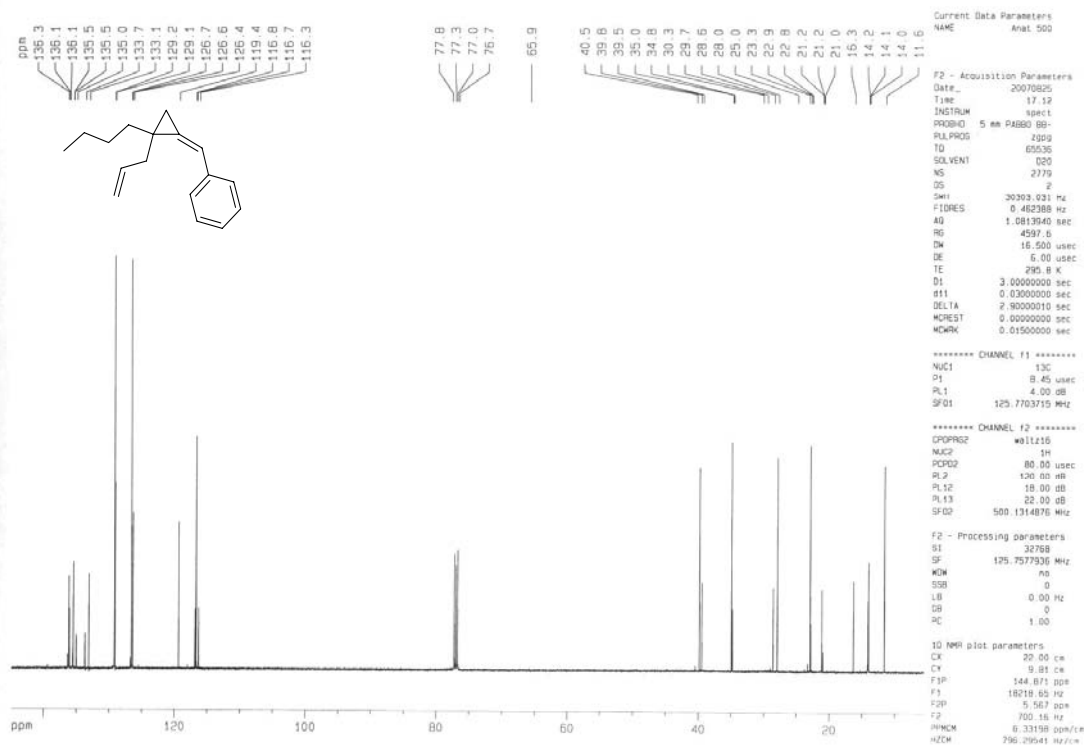
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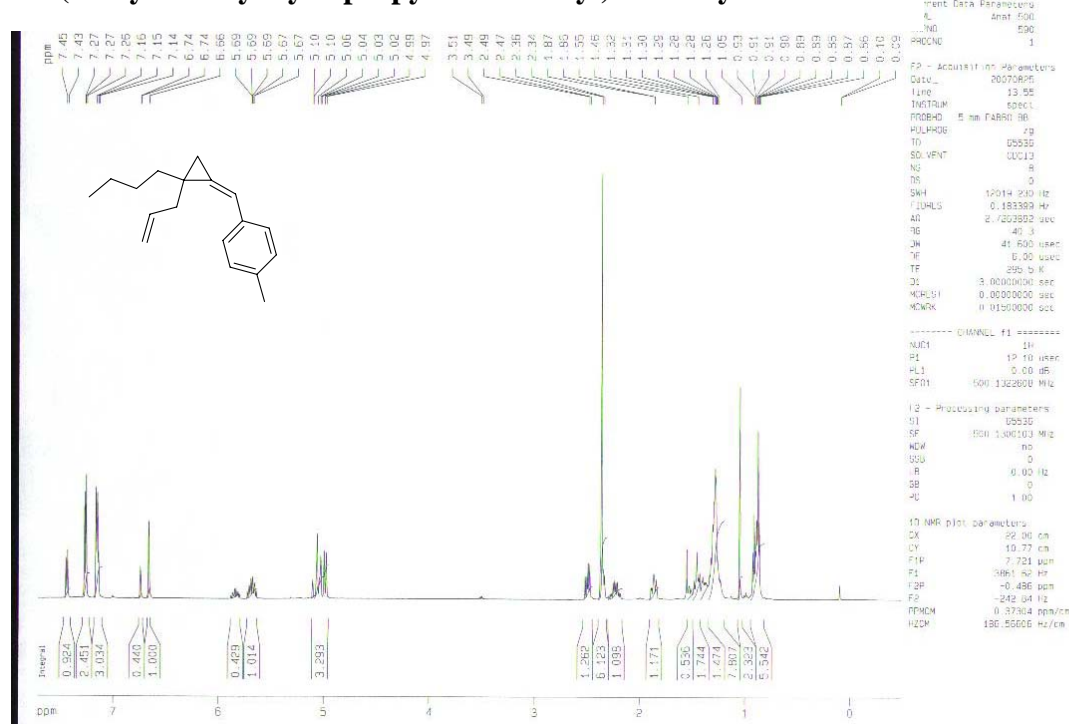
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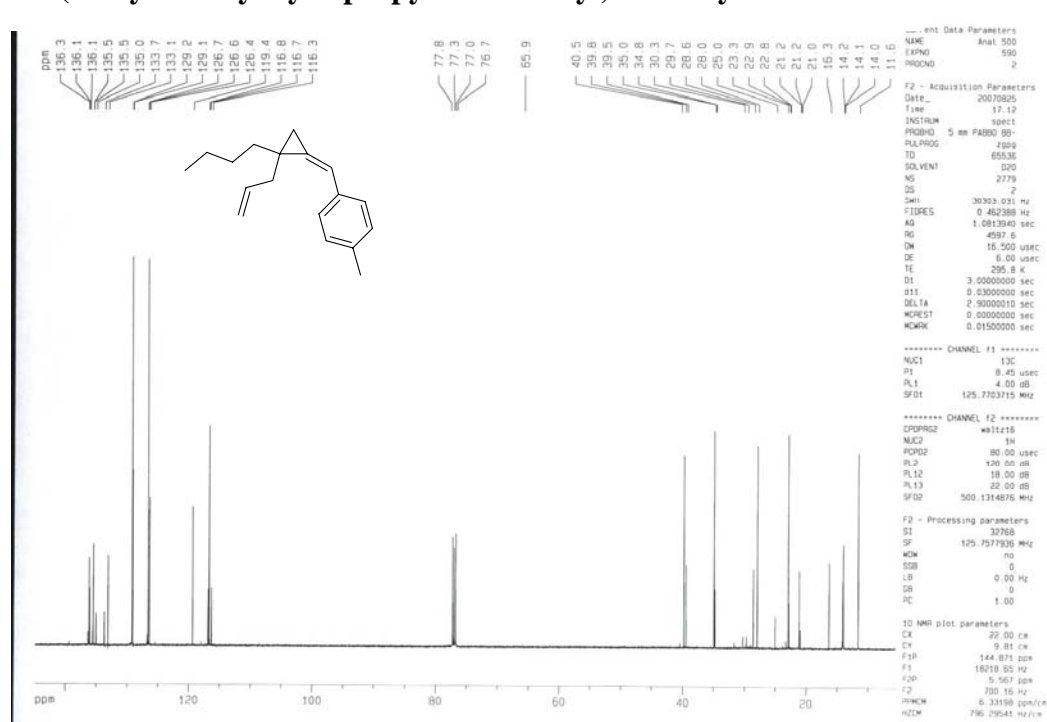
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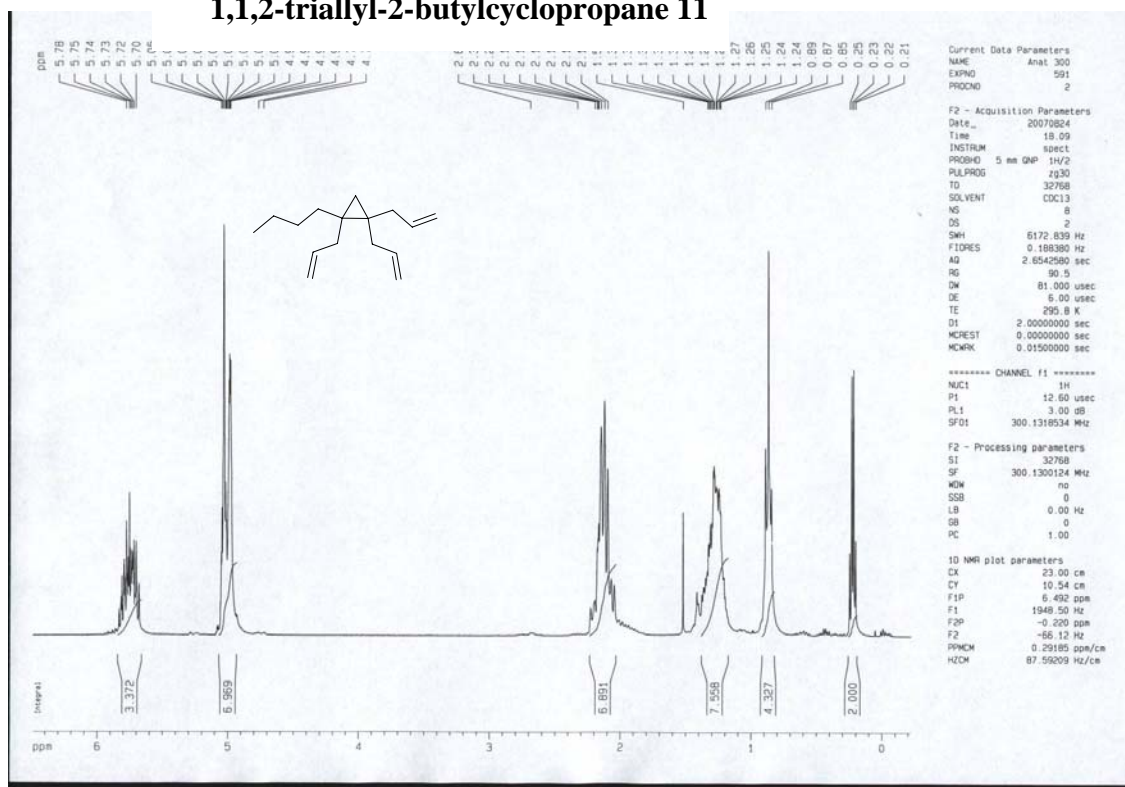
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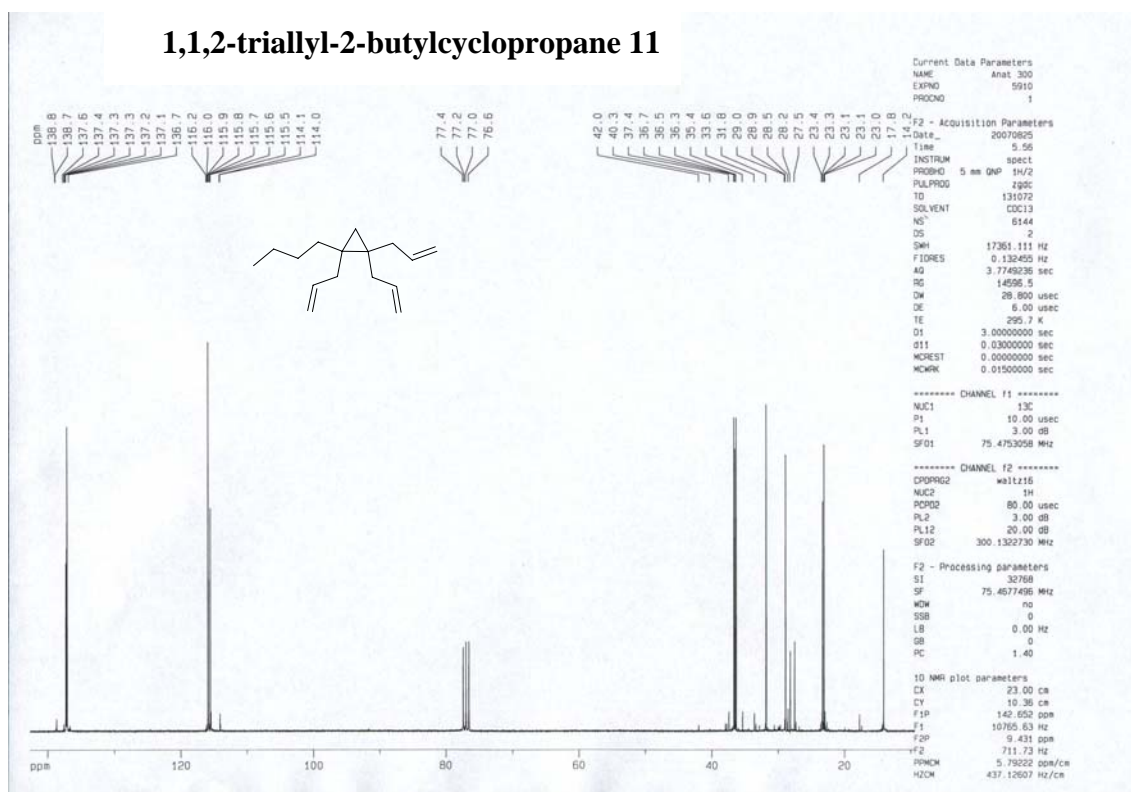
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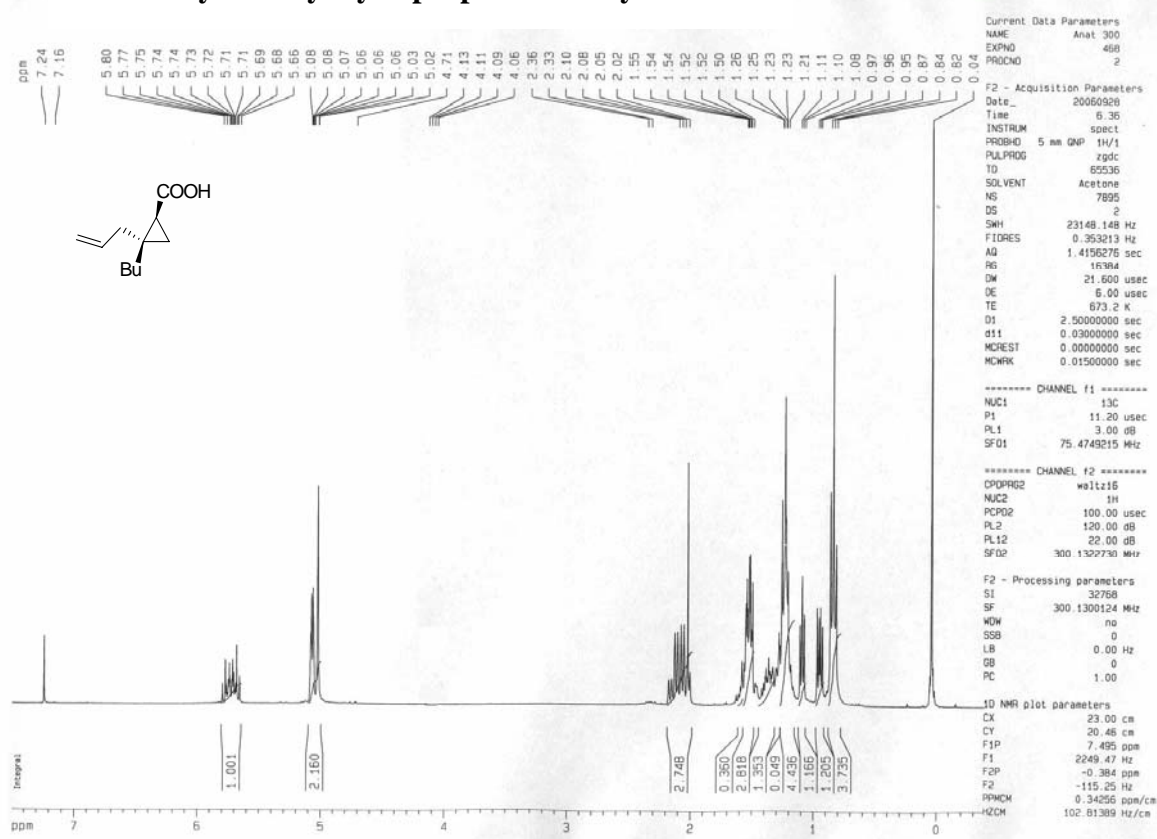
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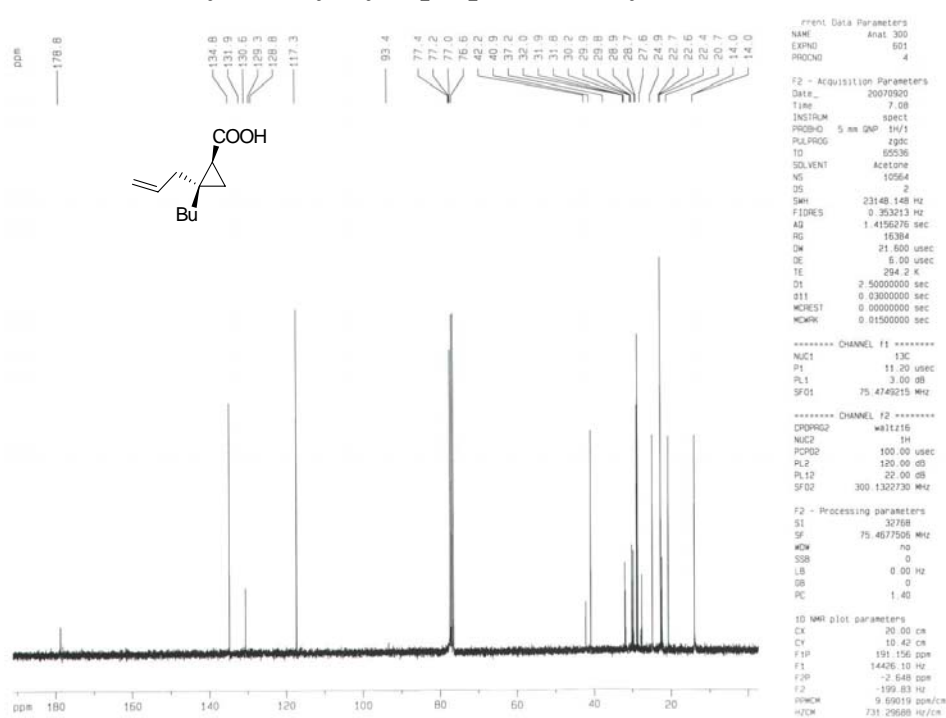
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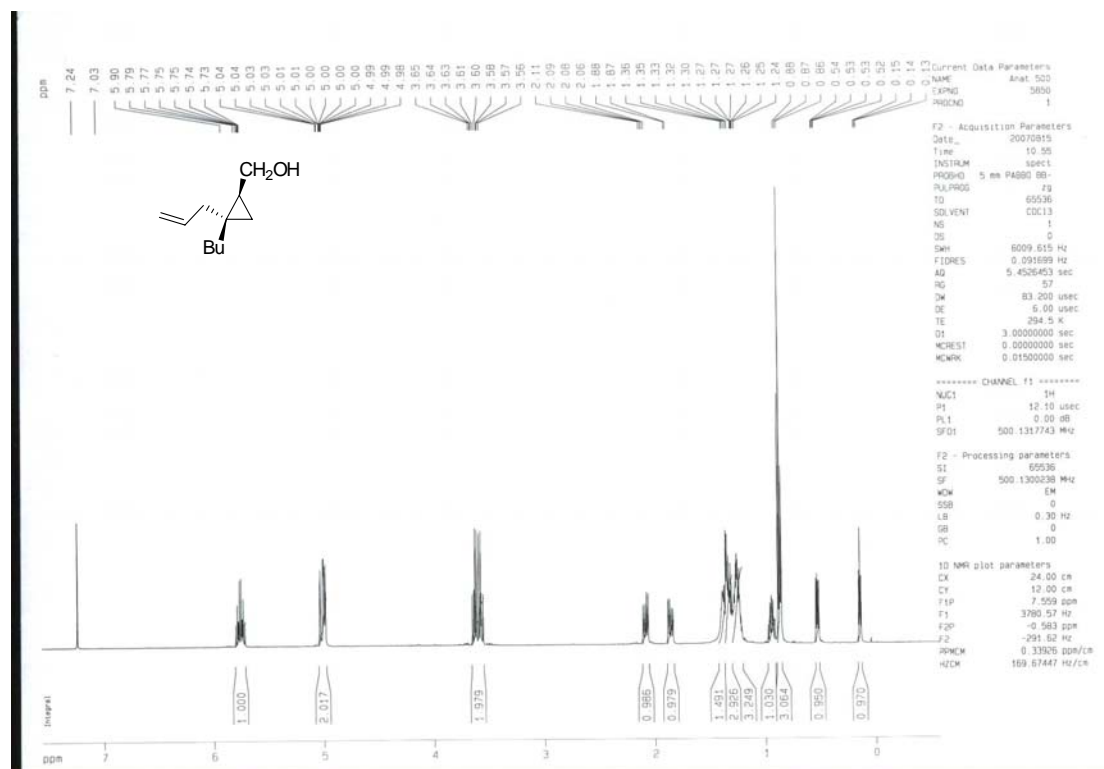
2-allyl-2-butyl-cyclopropanecarboxylic acid 15



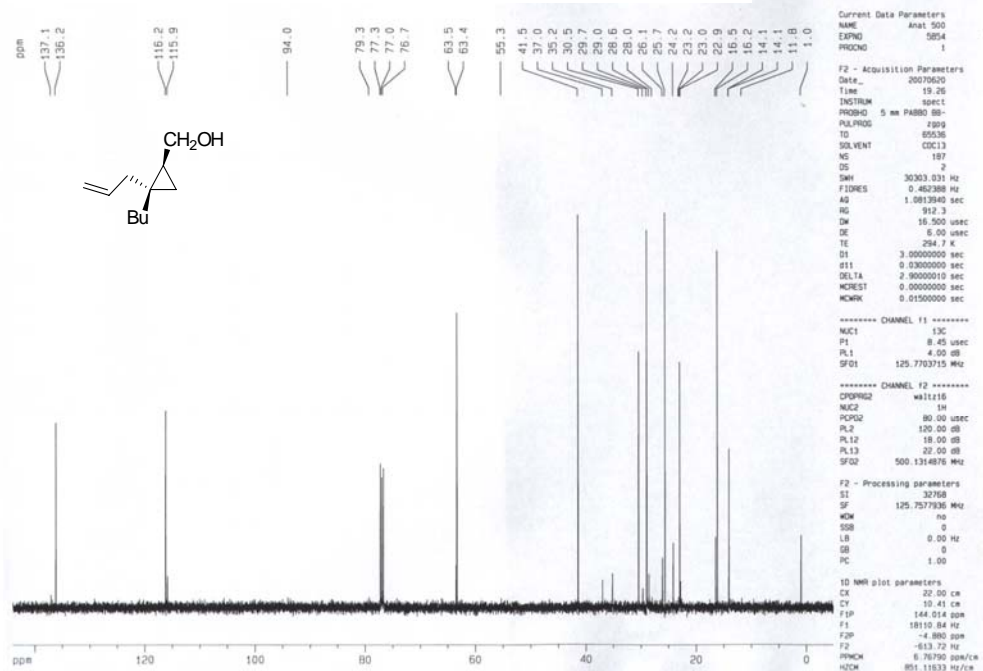
2-allyl-2-butyl-cyclopropanecarboxylic acid 15



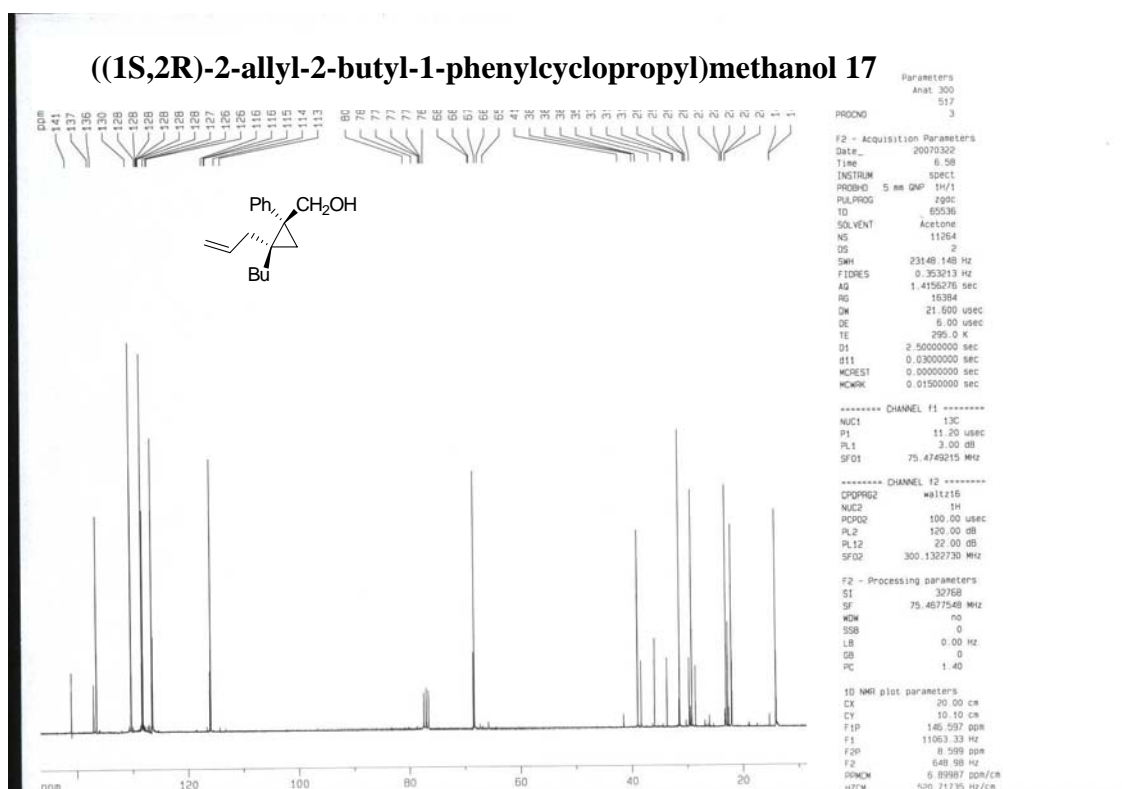
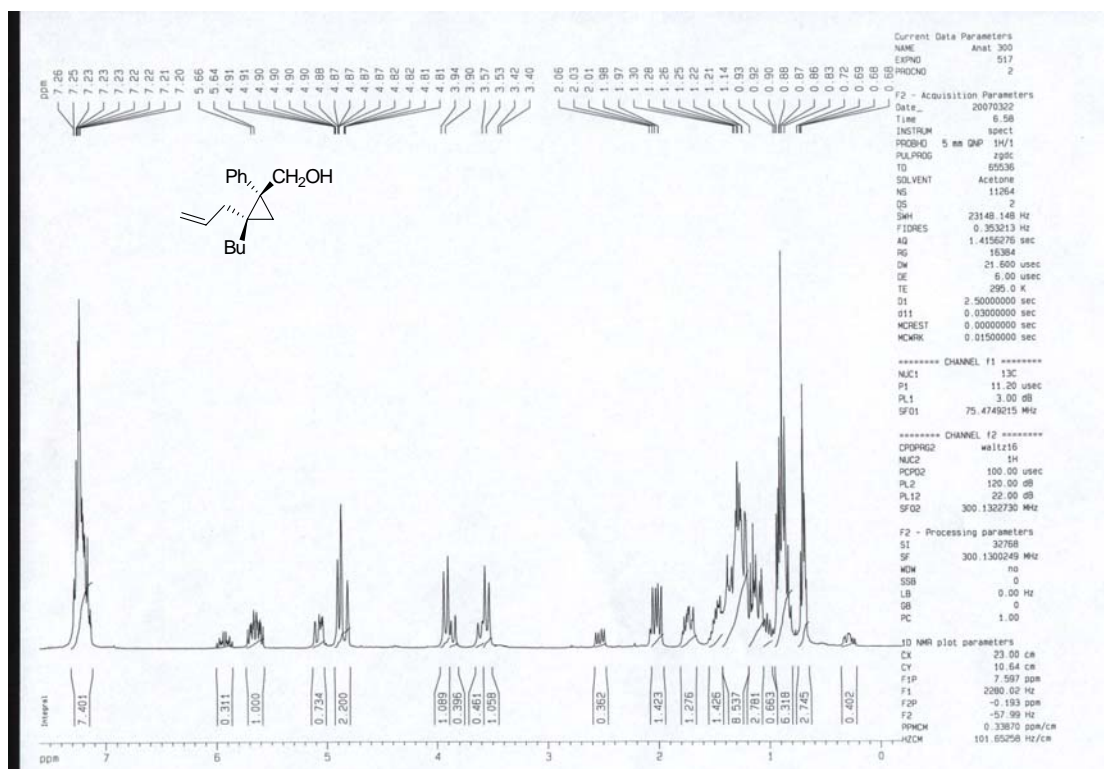
(2-allyl-2-butyl-cyclopropyl)-methanol 16



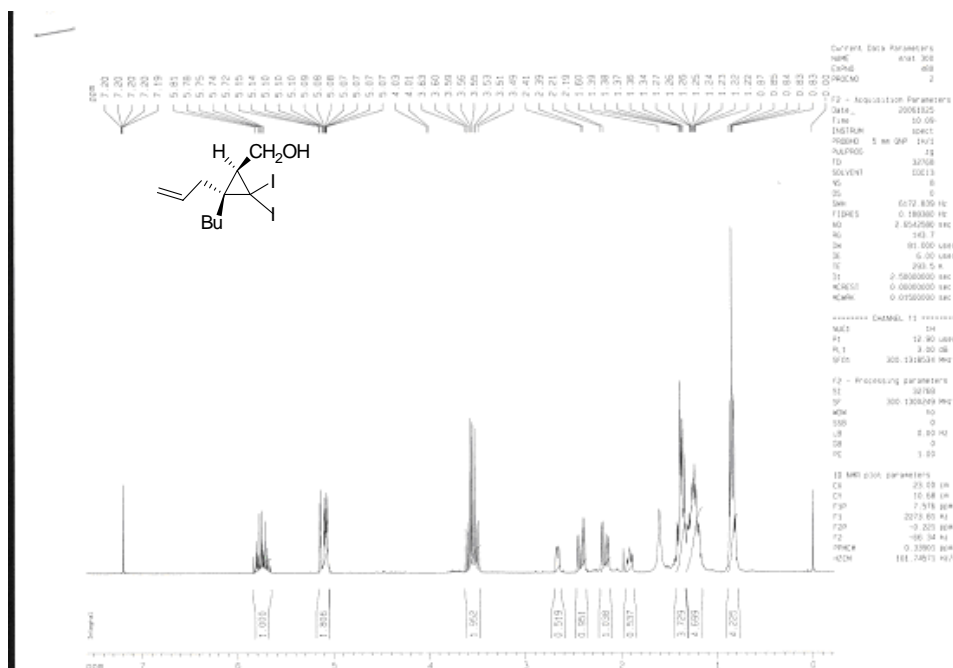
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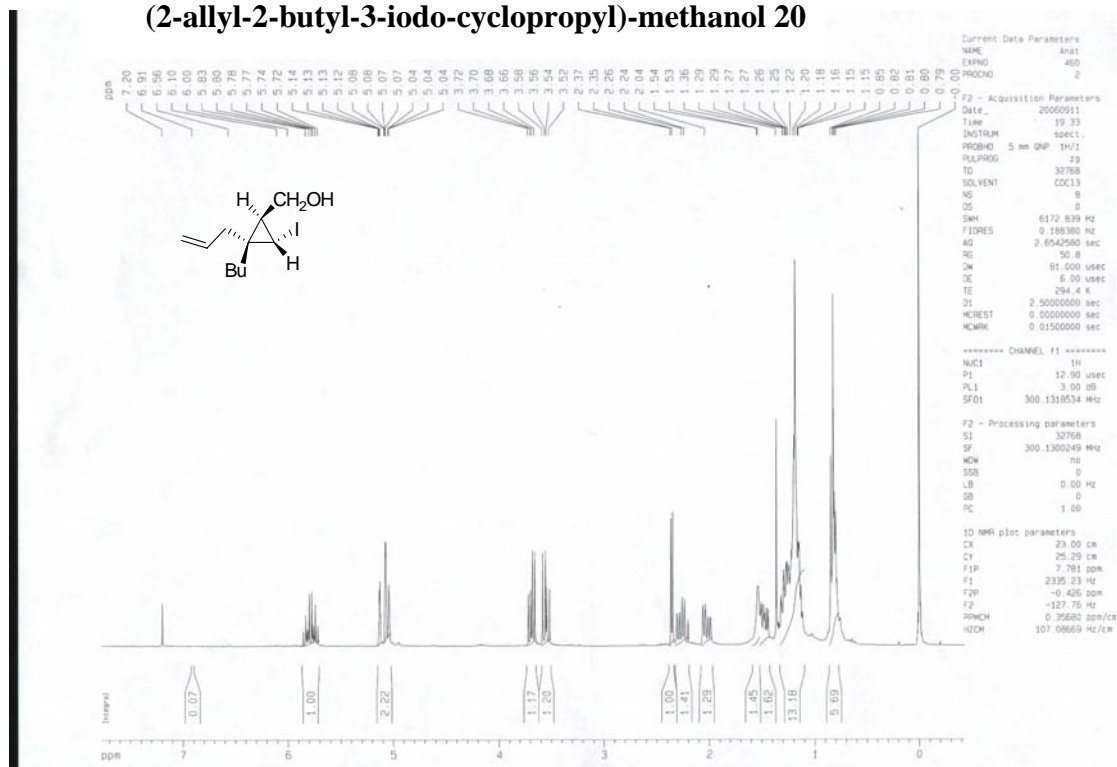
((1S,2R)-2-allyl-2-butyl-1-phenylcyclopropyl)methanol 17



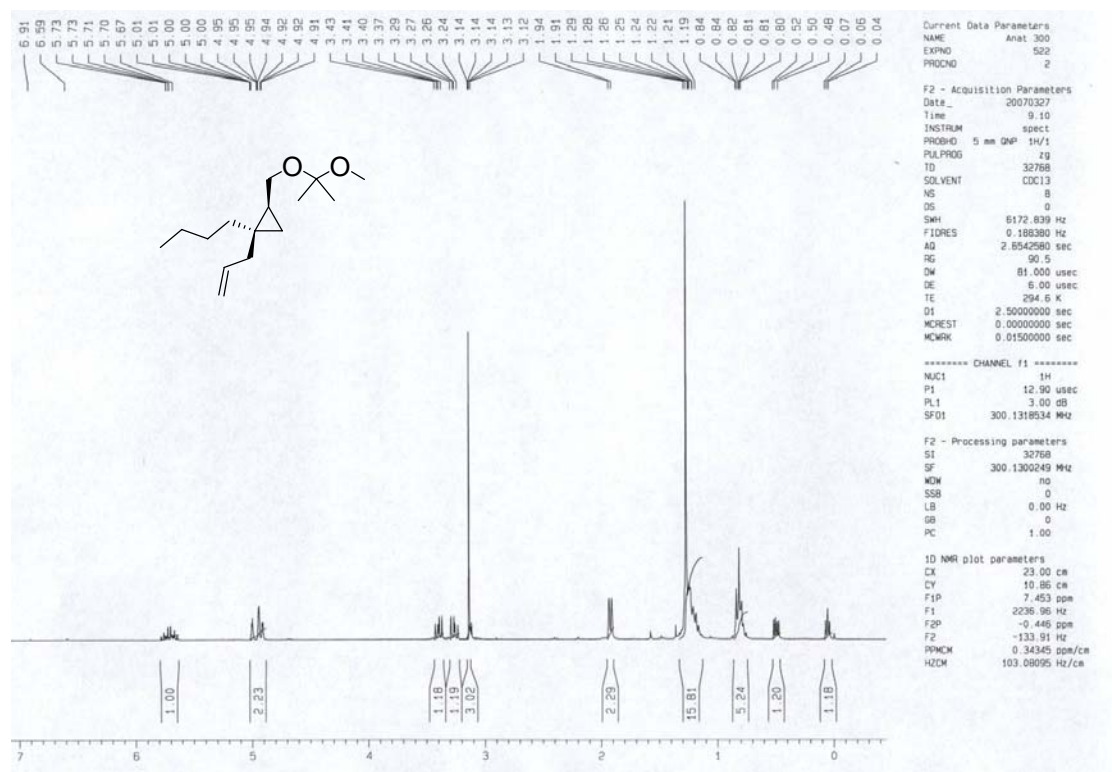
(2-allyl-2-butyl-3,3-diiodo-cyclopropyl)-methanol 18



(2-allyl-2-butyl-3-iodo-cyclopropyl)-methanol 20



(1R,2S)-1-allyl-1-butyl-2-((2-methoxypropan-2-yloxy)methyl)cyclopropane 21



(1R,2S)-1-allyl-1-butyl-2-((2-methoxypropan-2-yloxy)methyl)cyclopropane 21

