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Revisiting the Corey–Chaykovsky reaction: the solvent effect and the formation of β-hydroxy methylthioethers

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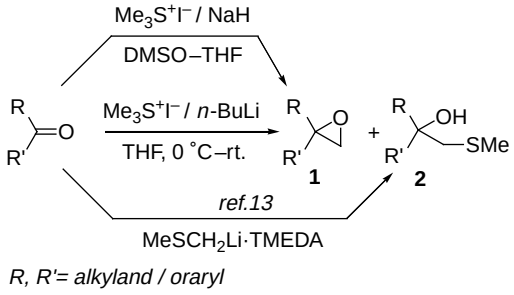
Abstract—The classical Corey–Chaykovsky (CC) reaction of ketones in ethereal solvents (i.e., THF or Et_2O) resulted in the production of a significant amount of β-hydroxy methylthioether **2** along with normal epoxide product **1**. Some interesting and synthetically useful transformations of the CC reaction product of cyclopropyl ketones were also described.

1. Introduction

The classical Corey–Chaykovsky (CC) reaction[1] is a practical and useful transformation (a formal *S*-ylide [1+2] cycloaddition)[2] for the synthesis of epoxides (or cyclopropane derivatives) from the corresponding carbonyl (or activated olefinic) compounds, which is thus widely used in the routine organic synthesis.[3] In connection with an ongoing synthetic program, we recently found that the chemical yields and the distribution of reaction products were quite dependent on the reaction conditions and the type of carbonyl substrates. The CC reactions performed in ethereal solvents (i.e., THF or Et_2O)[3a,4] rather than the traditional DMSO (or a solvent mixture with THF) resulted in the production of a significant amount of β-hydroxy methylthioether **2** along with the normal epoxide product **1** (Scheme 1) in many cases investigated (see examples in Scheme 2 on the next page).[5,6]

β-Hydroxy methylthioethers are useful intermediates or precursors in the preparation of α-hydroxy aldehyde,[7] vinyl[8] or allyl sulfide,[9] epoxide,[10] and olefin.[11] Some direct methods to their syntheses are available in the literatures.[12,13] For example, one such method for the preparation of methylthioethers is carbonyl addition by a TMEDA-complexed (methylthio)methyllithium reagent[13] as shown in Scheme 1. We record herein for the first time the significant solvent effect and the unusual formation of β-hydroxy methylthioether (sulfide) **2** in the classical CC reaction.



Scheme 1. Formation of β-hydroxy methylthioether **2**.

As shown in Table 1, we studied the effects of the solvent and the base of the CC reaction by employing cycloheptanone as a model substrate. Reactions performed in ethereal solvents (i.e., THF or diethyl ether, entries 1 and 2) generally afforded a significant amount of sulfide **2a** along with the normal epoxide product **1a**, while in the original solvent system (DMSO or a solvent mixture with THF (v/v 1:1)) produced solely epoxide **1a** in a good yield (entry 6). There was no observable reaction occurred (entry 3) in nonpolar solvent like toluene, as the sulfonium salt precursor used appeared hardly dissolved in the reaction medium. Interestingly, the base used for the generation of *S*-ylide had a remarkable effect as well. For example, although NaH in THF was incapable of effecting the desired *S*-ylide-transfer reaction at all (entry 5), the use of *tert*-BuOK in THF gave (entry 7) the epoxide product in good yield. Intriguingly, *tert*-BuOK seems more effective than NaH as base for the generation of *S*-ylide . Other organic lithium or sodium bases (entries 8 and 9) were practically equal effective in THF in regard to the product ratio (**1a/2a**). Apparently, the iodide salt of the sulfonium precursor is

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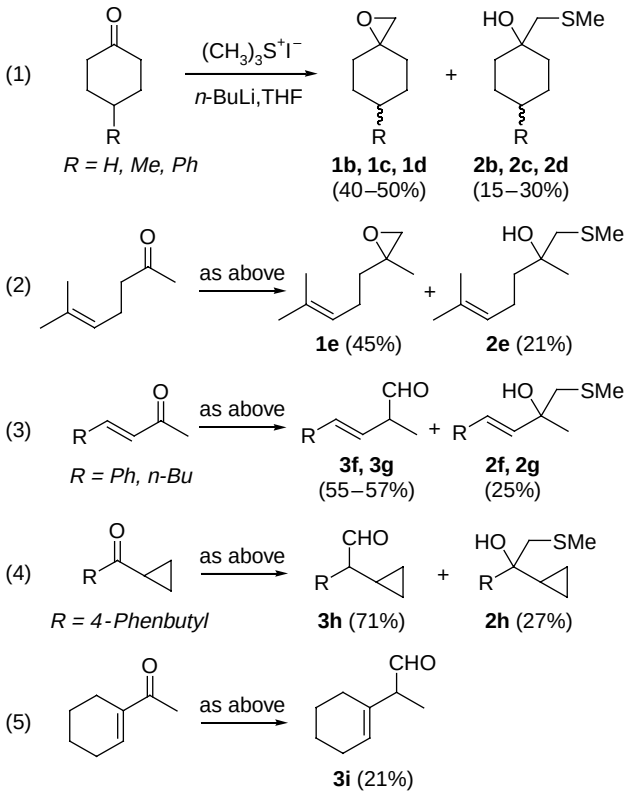


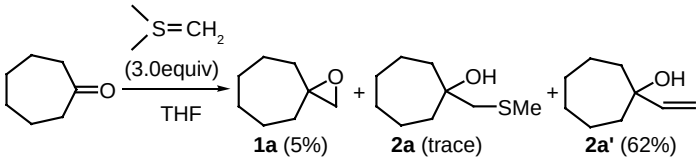
Scheme 2. Formation of sulfide **2** from carbonyl substrates.

more likely to produce a significant amount of sulfide **2a** compared with other counteranion salts (i.e., entries 10[3e] and 11).[14] Although the use of an excess amount of the *S*-ylide in THF suppressed largely the formation of sulfide **2a**, major vinylation product **2a′** was generated along with a small yield of epoxide **1a** (Eq. 1).[15]

We further examined a variety of carbonyl substrates under the *n*-BuLi/THF conditions. As shown in Scheme 2, aliphatic or cyclic alkanones (Eqs. 1 and 2) generally gave a yield of 15–30% for the sulfide product **2**. While cyclopropyl or α,β-unsaturated ketones afforded a significant amount of **2** as well, the corresponding epoxide product **1** initially formed underwent a rapid pinacol-type rearrangement to give an aldehydic product **3** (Eqs. 3 and 4) as the major product during chromatographic purification on silica gel (mild acidic conditions) or by exposing to an activated silica gel (*SiO_2, dried in an oven at 200 °C for 2 h). The CC reaction of hindered α,β-unsaturated ketone (i.e., Eq. 5)[1d] under similar conditions gave a low yield of aldehyde product **3i**.

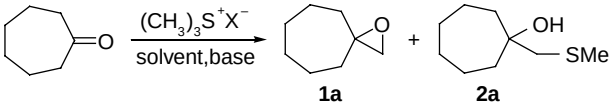
Interestingly, somewhat labile spiro-epoxidation product **5** derived from cyclopropyl ketone **4** was readily converted into the ring-opened product diol **9** or the pinacol-type rearrangement product aldehyde **6**[16] under mild 'aqueous' or 'dry' acidic conditions, respectively, in a good yield, as shown in Scheme 3. The formal regioselective dihydroxylation product **9** from triene **7** can be further transformed into the homoallylic iodo acetate **10** via a stereoselective Julia-type olefination protocol developed recently in our laboratory.[17] Alternatively, the aldehyde product **6** can be prepared from cyclopropyl triene **7** by a highly regioselective bromohydration with NBS in an aqueous THF (to bromohydrin **8**) and the subsequent saponification in methanol in good overall yield.[18] These functionalized acyclic prenylated intermediates (**6**, **9**, and **10**) may be of great value in organic synthesis.

The cyclopropyl sulfide **2h** prepared from the corresponding cyclopropyl ketone can be converted into the halogenated allylsulfide **11** under different mild acidic conditions as shown in Scheme 4. Highly stereoselective production of



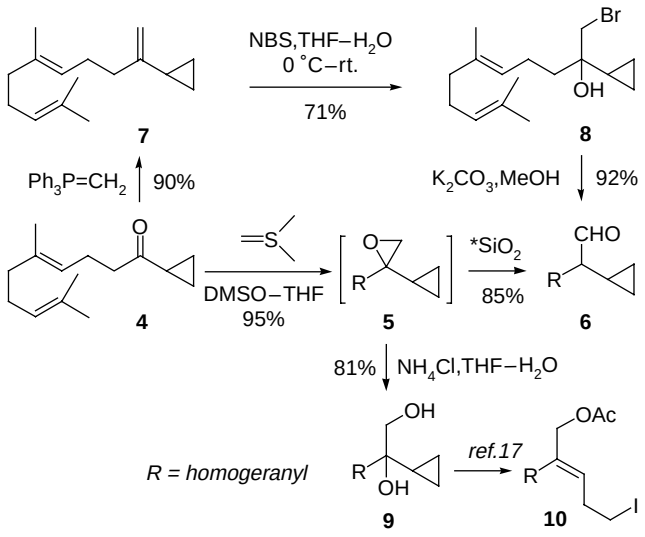
(1)

Table 1. Effects of solvent and base[a]

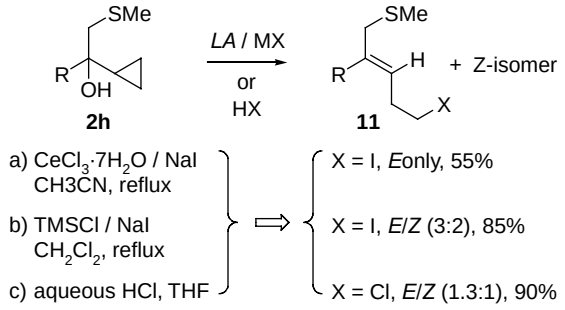


Entry	X	Solvent	Base[b]	**1a** (%)[c]	**2a** (%)[c]
1	I	THF	*n*-BuLi	41	27
2	I	Et_2O	*n*-BuLi	45	29
3	I	Toluene	*n*-BuLi	—	—
4	I	THF–toluene (1/1)	*n*-BuLi	47	25
5	I	THF	NaH	—	—
6	I	DMSO–THF (1/1)	NaH	85	—
7	I	THF	*t*-BuOK	81	—
8	I	THF	LDA	56	25
9	I	THF	$NaN(TMS)_2$	52	21
10	$MeOSO_3$	THF	*n*-BuLi	71	10
11	F_3CSO_3	THF	*n*-BuLi	83	6

[a] Reactions were performed in 1–2 mmol scale.
[b] 1.0 equiv of base was used.
[c] Isolated yield.



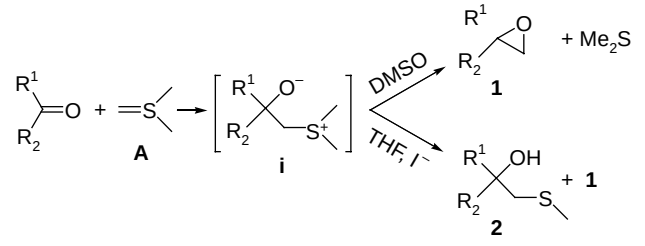
Scheme 3. Homologation of cyclopropyl ketone **4**.



Scheme 4. Synthesis of halogenated allylsulfide.

trisubstituted bifunctional iodo olefin **11** was achieved under the mediation of a mild Lewis acidic reagent system $CeCl_3 \cdot 7H_2O$/NaI as shown.[17]

The distinct solvent effect of THF observed in the classical CC reaction was probably attributed to its strong chelating character for lithium cation (solvation effect) and thus rendered the corresponding iodo anion more nucleophilic to attack effectively the zwitterionic intermediate **i** intermolecularly in a competing pathway leading to the methylthioether **2** in a significant amount (Scheme 5).



Scheme 5.

In short, the methylthioether **2** was identified as a general major side-product in the classical CC reaction when ethereal solvent (i.e., THF or Et_2O) and an organolithium base (i.e., *n*-BuLi) were employed. The presence of DMSO in the reaction medium favored the epoxide formation pathway greatly. Although we were unable to tune the reaction selectively to the formation of the methylthioether **2** favorably over epoxide **1**,[19] this interesting reaction pathway reflected the significant medium effect in nucleophilic reactions in general and the *S*-ylide **A** may be regarded as a synthon of (methylthio)methyl anion equivalent.

2. Experimental

For product purification by flash column chromatography, silica gel (200–300 mesh) and light petroleum ether (bp 30–60 °C) were used. All solvents were purified and dried by standard techniques, and distilled prior to use. All organic extracts were dried over Na_2SO_4, unless otherwise noted. IR spectra were recorded on a Nicolet FT-170SX spectrometer as liquid film. ^1H and ^{13}C NMR spectra were taken on a Varian mercury 300 MHz spectrometer with TMS as an internal standard and $CDCl_3$ as solvent unless otherwise noted. EI-MS spectrum were obtained on HP-5988A GC/MS instrument. HRMS were determined on a Bruker Daltonics APEXII 47e FT-ICR spectrometer. All air and moisture-sensitive reactions were performed in a flame-dried glassware under stream of nitrogen. Other commercially available chemical reagents and solvents were used as received without further purification unless indicated otherwise.

2.1. Typical procedure for ketone homologation under conditions of *n*-BuLi/$(CH_3)_3S^+I^-$/THF

To a stirred slurry of trimethylsulfonium iodide (400 mg, 1.95 mmol) in THF (4.5 mL) was added *n*-BuLi (1.60 M, 1.08 mL) dropwise at 0 °C under Ar. The resulting mixture was stirred for 10 min at 0 °C, to which cycloheptanone (168 mg, 1.5 mmol) in THF (1.5 mL) was added dropwise. The stirring was continued for 0.5 h at 0 °C and then warmed gradually to room temperature over 1 h. The reaction was quenched with water (5 mL) and extracted with Et_2O (2×30 mL). The organic layer was washed with water, brine, and dried over $MgSO_4$. After the solvent was evaporated in vacuo, the crude residue was purified by flash column chromatography on silica gel (PET/AcOEt= 50:1→30:1) to afford 77 mg (41%) of epoxide **1a** and 70 mg (27%) of methylthioether **2a**. *1-Oxa-spiro[2.6]-nonane* (**1a**). R_f=0.68 (PET/AcOEt=8:1); IR (film) ν_{max} 2956, 2924, 2855, 1597, 1456, 1377, 1260, 1072, 1022, 802 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 2.62 (s, 2H), 1.71–1.45 (m, 12H) ppm; EIMS (*m/z*, %): 126 (M^+, 4.1), 125 (16), 112 (7), 98 (6), 79 (45), 67 (94), 55 (100); HRMS (ESI) *m/z* obsd 127.1120 ($[M+H]^+$, calcd 127.1118 for $C_8H_{15}O$). *1-Methylsulfanylmethyl-cycloheptanol* (**2a**). R_f= 0.22 (PET/AcOEt=7:1); IR (film) ν_{max} 3443, 2922, 2865, 1458, 1435, 1346, 1200, 1116, 1035, 960, 797 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 2.67 (s, 2H), 2.23 (s, 1H, OH), 2.18 (s, 3H), 1.80–1.28 (m, 12H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$) δ 75.2, 49.1, 40.5 (2C), 29.6 (2C), 22.4 (2C), 18.2 ppm; EIMS (*m/z*, %): 174 (M^+, 2), 113 (26), 95 (33), 62 (100); HRMS (ESI) *m/z* obsd 175.1161 ($[M+H]^+$, calcd 175.1157 for $C_9H_{19}OS$).

2.1.1. 1-Vinyl-cycloheptanol (2a′). R_f=0.21 (PET/AcOEt=7:1); IR (film) ν_{max} 3374, 3085, 2925, 2856, 1640, 1460, 1342, 1272, 1200, 1088, 1031, 995, 917, 846 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.03 (dd, 1H, J=17.4, 10.8 Hz), 5.21 (d, 1H, J=17.4 Hz), 4.99 (d, 1H, J=10.8 Hz), 1.80–1.37 (m, 12H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$) δ 146.6, 110.1, 75.5, 41.1 (2C), 29.4 (2C), 22.1 (2C) ppm; HRMS (ESI) *m/z* obsd 141.1276 ($[M+H]^+$, calcd 141.1274 for $C_9H_{17}O$).

2.1.2. 1-Oxa-spiro[2.5]octane. (Compound **1b**, yield 50%), R_f=0.69 (PET/AcOEt=8:1); IR (film) ν_{max} 2955, 2924, 2855, 1596, 1456, 1377, 1257, 1072, 1022, 802 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 2.61 (s, 2H), 1.68–1.45 (m, 10H) ppm; HRMS (ESI) *m/z* obsd 113.0958 ($[M+H]^+$, calcd 113.0961 for $C_7H_{13}O$).

2.1.3. 1-Methylsulfanylmethyl-cyclohexanol. (Compound **2b**, yield 30%), R_f=0.20 (PET/AcOEt=7:1); IR (film) ν_{max} 3446, 2930, 2856, 1446, 1349, 1242, 1171, 1147, 1058, 969 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 2.65 (s, 2H), 2.18 (s, 3H), 1.73–1.17 (m, 10H) ppm; EIMS (*m/z*, %): 160 (M^+, 11), 142 (3), 99 (53), 81 (88), 62 (100); HRMS (ESI) *m/z* obsd 161.0998 ($[M+H]^+$, calcd 161.0995 for $C_8H_{17}OS$).

2.1.4. 6-Methyl-1-oxa-spiro[2.5]octane. (Compound **1c**, yield 40%), R_f=0.60 (PET/AcOEt=8:1); IR (film) ν_{max} 2922, 2852, 1597, 1447, 1261, 1024, 799 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 2.61 (d, J=1.4 Hz, *trans*-OCH_2), 2.56 (s, *cis*-OCH_2), 1.90–1.66 (m, 4H), 1.55–0.80 (m, 5H), 0.94 (d, J=6.2 Hz, *cis*-CH_3), 0.92 (d, J=6.6 Hz, *trans*-CH_3) ppm; ^{13}C NMR (50 MHz, $CDCl_3$) δ 59.5, 54.8, 53.8, 33.9, 33.2, 32.6, 32.3, 31.4, 31.3, 22.0, 21.5 ppm; HRMS (ESI) *m/z* obsd 127.1120 ($[M+H]^+$, calcd 127.1118 for $C_8H_{15}O$).

2.1.5. *cis*-4-Methyl-1-methylsulfanylmethyl-cyclohexanol. (Compound **2c**, *cis*/*trans* 10:1, total yield 15%), R_f=0.1 (PET/AcOEt=8:1); IR (film) ν_{max} 3449, 2921, 2857, 1449, 1372, 1234, 998 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 2.75 (s, 2H), 2.41 (s, 1H, OH), 2.18 (s, 3H), 1.80–1.44 (m, 7H), 1.11–0.85 (m, 2H), 0.90 (d, 3H, J=6.4 Hz) ppm; ^{13}C NMR (50 MHz, $CDCl_3$) δ 71.1, 44.3, 36.6, 31.4, 31.3, 21.1, 17.9 ppm; EIMS (*m/z*, %): 174 (M^+, 9.3), 113 (49), 95 (89), 62 (100); HRMS (ESI) *m/z* obsd 175.1156 ($[M+H]^+$, calcd 175.1152 for $C_9H_{19}OS$). *trans-4-Methyl-1-methylsulfanylmethyl-cyclohexanol* (**2c**). R_f=0.12 (PET/AcOEt=8:1); IR (film) ν_{max} 3445, 2923, 2859, 1453, 1089, 1049, 1009 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 2.59 (s, 2H), 2.16 (s, 3H), 2.05 (s, 1H, OH), 1.71–1.29 (m, 9H), 0.91 (br s, 3H) ppm; EIMS (*m/z*, %): 174 (M^+, 8.4), 113 (35), 95 (64), 62 (100); HRMS (ESI) *m/z* obsd 175.1154 ($[M+H]^+$, calcd 175.1152 for $C_9H_{19}OS$).

2.1.6. 6-Phenyl-1-oxa-spiro[2.5]octane. (Compound **1d**, yield 48%), R_f=0.23 (PET/AcOEt=8:1); IR (film) ν_{max} 3025, 2998, 2935, 2856, 1601, 1491, 1446, 1181, 1097, 979, 911, 753, 699 cm^{-1}; ^1H NMR (80 MHz, $CDCl_3$) δ 7.35–7.25 (m, 5H), 2.70 (s, 2H), 2.60–2.53 (m, 1H), 2.13–1.38 (m, 8H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$) δ 146.1, 128.4, 126.8, 126.7, 126.2, 126.1, 59.1, 54.9, 53.9, 43.3, 33.8, 33.2, 31.5 ppm; EIMS (*m/z*, %): 188 (M^+, 13), 174 (4), 168 (4.8), 143 (12), 129 (19), 115 (30), 104 (100), 91 (59); HRMS (ESI) *m/z* obsd 189.1276 ($[M+H]^+$, calcd 189.1274 for $C_{13}H_{17}O$).

2.1.7. *cis*-1-Methylsulfanylmethyl-4-phenyl-cyclohexanol. (Compound **2d**, *cis*/*trans* 3.9:1, total yield 26%), R_f=0.04 (PET/AcOEt=8:1); IR (film) ν_{max} 3444, 3059, 3026, 2928, 2859, 1695, 1600, 1494, 1450, 1347, 1198, 1054, 972, 757, 699 cm^{-1}; ^1H NMR (80 MHz, $CDCl_3$) δ 7.33–7.18 (m, 5H), 2.92 (s, 2H), 2.63 (s, OH), 2.65–2.45 (m, 1H), 2.24 (s, 3H), 2.03–1.29 (m, 8H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$) δ 146.0, 128.3, 126.7, 126.1, 71.4, 60.3, 43.7, 43.2, 37.5, 30.8, 21.0, 17.9, 14.1 ppm; EIMS (*m/z*, %): 236 (M^+, 0.7), 218 (0.11), 174 (13), 157 (10), 129 (7), 91 (39), 77 (9), 62 (100); HRMS (ESI) *m/z* obsd 237.1311 ($[M+H]^+$, calcd 237.1308 for $C_{14}H_{21}OS$). *trans-1-Methylsulfanylmethyl-4-phenyl cyclohexanol* (**2d**). R_f=0.043 (PET/AcOEt=8:1); IR (film) ν_{max} 3530, 3468, 3026, 2928, 2857, 1601, 1493, 1442, 1312, 1211, 1143, 1060, 979, 756, 699 cm^{-1}; ^1H NMR (80 MHz, $CDCl_3$) δ 7.33–7.21 (m, 5H), 2.69 (s, 2H), 2.52–2.40 (m, 1H), 2.23 (s, 3H), 2.06–1.45 (m, 8H) ppm; EIMS (*m/z*, %): 236 (M^+, 8.3), 218 (1.8), 174 (81), 157 (6.1), 91 (100); HRMS (ESI) *m/z* obsd 237.1310 ($[M+H]^+$, calcd 237.1308 for $C_{14}H_{21}OS$).

2.1.8. 2-Methyl-2-(4-methyl-pent-3-enyl)-oxirane. (Compound **1e**, yield 45%), R_f=0.91 (PET/AcOEt=8:1); IR (film) ν_{max} 3035, 2966, 2923, 2857, 1449, 1384, 1265, 1108, 1072, 901, 796 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 5.09 (t, 1H, J=7.1 Hz), 2.59 (q, 2H, J=6.4 Hz), 2.07 (q, 2H, J=7.6 Hz), 1.68 (s, 3H), 1.60 (s, 3H), 1.24–1.11 (m, 2H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 131.9, 123.6, 56.8, 53.9, 36.8, 25.6, 23.8, 20.9, 17.6 ppm; EIMS (*m/z*, %): 140 (M^+, 0.04), 125 (0.2), 109 (6.5), 82 (7), 67 (32), 55 (19), 41 (100); HRMS (ESI) *m/z* obsd 141.1277 ($[M+H]^+$, calcd 141.1274 for $C_9H_{17}O$). *2,6-Dimethyl-1-methylsulfanyl-hept-5-en-2-ol* (**2e**, yield 21%). R_f=0.90 (PET/AcOEt=8:1); IR (film) ν_{max} 3446, 2969, 2919, 2858, 1700, 1665, 1442, 1376, 1241, 1150, 1114, 1021, 917, 835 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 5.11 (t, 1H, J=6.8 Hz), 2.65 (d, 2H, J=4.0 Hz), 2.26 (s, 1H, OH), 2.16 (s, 3H), 2.10–1.99 (m, 2H), 1.68 (s, 3H), 1.61 (s, 3H), 1.58–1.49 (m, 2H), 1.23 (s, 3H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$) δ 131.8, 124.1, 72.6, 47.7, 41.1, 26.1, 25.7, 22.7, 18.1, 17.6 ppm; EIMS (*m/z*, %): 188 (M^+, 0.8), 173 (0.2), 170 (3.2), 155 (1), 26 (18), 109 (67), 69 (100); HRMS (ESI) *m/z* obsd 189.1310 ($[M+H]^+$, calcd 189.1308 for $C_{10}H_{21}OS$).

2.1.9. 2-Methyl-4-phenyl-but-3-enal. (Compound **3f**, yield 57%), R_f=0.51 (PET/AcOEt=6:1); IR (film) ν_{max} 3427, 2974, 2716, 1724, 1639, 1598, 1450, 968, 747, 694 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 9.66 (d, 1H, J=1.4 Hz), 7.41–7.25 (m, 5H), 6.55 (d, 1H, J=16.0 Hz), 6.16 (dd, 1H, J=16.0, 7.6 Hz), 3.26 (t, 1H, J=7.0 Hz), 1.33 (d, 3H, J=7.0 Hz) ppm; EIMS (*m/z*, %): 160 (M^+, 11), 141 (0.3), 131 (100), 91 (43), 77 (9.3); HRMS (ESI) *m/z* obsd 161.0963 ($[M+H]^+$, calcd 161.0961 for $C_{11}H_{13}O$). *2-Methyl-1-methylsulfanyl-4-phenyl-but-3-en-2-ol* (**2f**, yield 25%). R_f=0.30 (PET/AcOEt=6:1); IR (film) ν_{max} 3443, 3026, 2974, 2918, 1598, 1578, 1494, 1369, 1269, 1067, 970, 749, 694 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.42–7.20 (m, 5H), 6.69 (d, 1H, J=16.0 Hz), 6.25 (d, 1H, J=16.0 Hz), 2.81 (q, 2H, J=13.6 Hz) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 136.7, 135.1, 128.5, 128.0, 127.5, 126.4, 72.7, 48.2, 27.6, 18.0 ppm; EIMS (*m/z*, %): 208 (M^+, 2), 147

(100), 129 (34), 91 (7), 77 (11); HRMS (ESI) *m/z* obsd 191.0888 ($[M-H_2O+H]^+$, calcd 191.0889 for $C_{12}H_{15}S$).

2.1.10. 2-Methyl-oct-3-enal. (Compound **3g**, yield 55%), R_f=0.34 (PET/AcOEt=20:1); IR (film) ν_{max} 3440, 3030, 2958, 2927, 2857, 2710, 1728, 1694, 1460, 1301, 1064, 971 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 9.52 (d, 1H, J=2.7 Hz), 5.80–5.54 (m, 1H), 5.35 (dd, 1H, J=15.4, 8.0 Hz), 2.99 (m, 1H), 2.06–1.95 (m, 2H), 1.35–1.10 (m, 4H), 1.17 (d, 3H, J=6.0 Hz), 0.87 (t, 3H, J=7.0 Hz) ppm; EIMS (*m/z*, %): 140 (M^+, 3.2), 127 (4), 111 (23), 83 (90), 69 (100); HRMS (ESI) *m/z* obsd 141.1276 ($[M+H]^+$, calcd 141.1274 for $C_9H_{17}O$). *2-Methyl-1-methylsulfanyl-oct-3-en-2-ol* (**2g**, yield 25%). R_f=0.25 (PET/AcOEt=7:1); IR (film) ν_{max} 3448, 3022, 2959, 2924, 2858, 1666, 1459, 1372, 1242, 1161, 1110, 1064, 973, 931, 808 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 5.66 (dt, 1H, J=15.4, 6.5 Hz), 5.45 (d, 1H, J=15.6 Hz), 2.65 (q, 2H, J=13.4 Hz), 2.11 (s, 3H), 2.08–1.95 (m, 2H), 1.40–1.16 (m, 4H), 1.29 (s, 3H), 0.85 (t, 3H, J=7.0 Hz) ppm; ^{13}C NMR (50 MHz, $CDCl_3$) δ 135.2, 129.1, 72.2, 48.2, 31.3, 31.2, 27.4, 22.1, 17.9, 13.9 ppm; EIMS (*m/z*, %): 173 ($[M-15]^+$, 0.14), 170 ($[M-18]^+$, 0.06), 127 (24), 71 (100); HRMS (ESI) *m/z* obsd 189.1319 ($[M+H]^+$, calcd 189.1314 for $C_{10}H_{21}OS$).

2.1.11. 2-Cyclopropyl-6-phenyl-hexanal. (Compound **3h**, yield 71%), R_f=0.36 (PET/AcOEt=8:1); IR (film) ν_{max} 3429, 3025, 2932, 2714, 1723, 1602, 1456, 1023, 909, 734, 699 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 9.69 (d, 1H, J=2.6 Hz), 7.28–7.16 (m, 5H), 2.62 (t, 2H, J=7.6 Hz), 1.77–1.44 (m, 7H), 0.89–0.72 (m, 1H), 0.61–0.57 (m, 2H), 0.27–0.21 (m, 2H) ppm; EIMS (*m/z*, %): 216 (M^+, 1.2), 183 (0.6), 169 (1.8), 157 (3.5), 91 (100), 77 (9.1); HRMS (ESI) *m/z* obsd 217.1590 ($[M+H]^+$, calcd 217.1587 for $C_{15}H_{21}O$). *2-Cyclopropyl-1-methylsulfanyl-6-phenyl-hexan-2-ol* (**2h**, yield 27%). R_f=0.20 (PET/AcOEt=8:1); IR (film) ν_{max} 3477, 3004, 2934, 2856, 1602, 1495, 1454, 1022, 911, 824, 746, 699 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.32–7.18 (m, 5H), 2.73 (s, 2H), 2.64 (t, 2H, J=7.6 Hz), 2.17 (d, 3H, J=1.4 Hz), 1.73–1.46 (m, 6H), 0.86–0.77 (m, 1H), 0.49–0.31 (m, 4H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$) δ 142.6, 128.4, 128.2, 125.6, 71.3, 47.0, 40.7, 35.9, 32.0, 23.5, 18.8, 17.9, 0.47, 0.24 ppm; EIMS (*m/z*, %): 264 (M^+, 0.27), 249 (0.34), 246 (0.09), 203 (40), 117 (57), 91 (100), 77 (8.6); HRMS (ESI) *m/z* obsd 282.1891 ($[M+NH_4]^+$, calcd 282.1887 for $C_{16}H_{28}ONS$).

2.1.12. 2-Cyclohex-1-enyl-propionaldehyde. (Compound **3i**, yield 21%), R_f=0.29 (PET/AcOEt=20:1); IR (film) ν_{max} 3419, 3037, 2932, 2839, 2714, 1723, 1659, 1610, 1453, 1385, 1140, 1019 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 9.50 (d, 1H, J=1.8 Hz), 5.60 (m, 1H), 2.92 (q, 1H, J=7.0 Hz), 2.06–1.82 (m, 4H), 1.65–1.45 (m, 4H), 1.17 (d, 3H, J=6.8 Hz) ppm; HRMS (ESI) *m/z* obsd 139.1120 ($[M+H]^+$, calcd 139.1118 for $C_9H_{15}O$).

2.2. Preparation of epoxide 5, aldehyde 6, and diol 9

NaH (600 mg, 15.0 mmol, 60% dispersion in mineral oil, washed three times with *n*-hexane distilled from CaH_2) was placed in round-bottomed flask (50 mL) and DMSO (10 mL, distilled from CaH_2) was introduced under Ar. The resulting mixture was heated with stirring to 70–75 °C. After 20 min, the reaction mixture was diluted with THF (10 mL) and then cooled to 0 °C. A solution of trimethylsulfonium iodide (3.06 g, 15.0 mmol) in DMSO (10 mL) was added over a period of about 5 min. After the addition of the THF (5 mL) solution of ketone **4** (2.2 g, 10.0 mmol) at 0 °C, stirring was continued for 30 min at 0 °C then warmed gradually to room temperature over 1 h. The reaction was quenched by water (10 mL) and extracted with Et_2O (200 mL). The organic layer was washed with water (4×10 mL) brine and dried over $MgSO_4$ and concentrated to give 2.2 g (95%) of the epoxide **5** as pale yellow oil. *2-Cyclopropyl-2-(4,8-dimethyl-nona-3,7-dienyl)-oxirane* (**5**). R_f=0.69 (PET/AcOEt=10:1); IR (film) ν_{max} 3084, 2967, 2921, 2856, 1669, 1447, 1379, 1229, 1149, 1104, 1023, 943, 826 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.15–5.05 (m, 2H), 2.54 (d, 1H, J=5.4 Hz), 2.47 (d, 1H, J=3.9 Hz), 2.20–2.13 (m, 2H), 2.10–1.95 (m, 4H), 1.83–1.73 (m, 2H), 1.67 (s, 3H), 1.62 (s, 3H), 1.59 (s, 3H), 1.18–1.09 (m, 1H), 0.48–0.41 (m, 1H), 0.39–0.27 (m, 2H), 0.21–0.14 (m, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 135.4, 131.3, 124.2, 123.8, 58.6, 51.6, 39.6, 36.2, 26.6, 25.6, 23.6, 17.6, 15.9, 13.2, 1.8, 0.5 ppm; EIMS (*m/z*, %): 234 (M^+, 0.11), 203 (0.75), 165 (0.76), 123 (4.7), 95 (9.7), 81 (31.7), 69 (100); HRMS (ESI) *m/z* obsd 252.2322 ($[M+NH_4]^+$, calcd 252.2322 for $C_{16}H_{30}ON$).

The crude epoxide **5** was loaded on a short pad of silica gel (activated in an oven at 200 °C for 2 h) eluting with PET–AcOEt (100/1) to give 1.9 g (90%) of the aldehyde **6**. *2-Cyclopropyl-6,10-dimethyl-undeca-5,9-dienal* (**6**). R_f=0.72 (PET/AcOEt=10:1); IR (film) ν_{max} 3080, 2968, 2921, 2856, 2711, 1725, 1448, 1379, 1106, 1022, 822, 668 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.70 (d, 1H, J=2.7 Hz), 5.10–5.06 (m, 2H), 2.11–1.98 (m, 6H), 1.84–1.77 (m, 1H), 1.64 (s, 3H), 1.63–1.49 (m, 2H), 1.60 (s, 3H), 1.59 (s, 3H), 0.76–0.71 (m, 1H), 0.61–0.56 (m, 2H), 0.31–0.18 (m, 2H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 204.5, 136.1, 131.4, 124.2, 123.6, 56.2, 39.7, 29.5, 26.7, 25.7, 25.3, 17.7, 16.0, 10.7, 3.8, 3.0 ppm; EIMS (*m/z*, %): 234 (M^+, 0.1), 205 (0.1), 191 (1), 123 (6), 95 (12), 81 (45), 69 (100); HRMS (ESI) *m/z* obsd 252.2324 ($[M+NH_4]^+$, calcd 252.2322 for $C_{16}H_{30}ON$).

The crude epoxide **5** (1.1 g, 4.7 mmol) was taken up in a mixture of THF (5 mL) and saturated aqueous NH_4Cl (5 mL). After stirring for 8 h at ambient temperature, the reaction mixture was extracted with AcOEt (100 mL). The organic phase was washed with water and brine, dried over $MgSO_4$ and concentrated. The crude product was purified by flash chromatography on silica gel (PET/AcOEt=4:1) to give 960 mg (81%) of diol **9** as a white solid. *2-Cyclopropyl-6,10-dimethyl-undeca-5,9-diene-1,2-diol* (**9**). R_f=0.17 (PET/AcOEt=4:1). mp 54–56 °C (recrystallized from EtOH); IR (film) ν_{max} 3407, 3083, 3005, 2966, 2924, 2857, 1667, 1643, 1448, 1379, 1265, 1153, 1105, 1075, 1040, 1022, 914, 875, 823 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 5.16–5.06 (m, 2H), 3.48 (d, 2H, J=8.7 Hz), 2.55 (t, 1H, OH, J=9.0 Hz), 2.31–1.99 (m, 6H), 1.65 (s, 3H), 1.64–1.53 (m, 2H), 1.60 (s, 3H), 1.58 (s, 3H), 0.82–0.68 (m, 1H), 0.39–0.32 (m, 4H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$) δ 135.5, 131.3, 124.3, 124.2, 72.2, 69.0, 39.6, 37.9, 26.6, 25.6, 22.2, 17.6, 16.2, 15.9, −0.5, −0.9 ppm; EIMS (*m/z*, %): 234 ($[M-H_2O]^+$, 0.4), 221 (0.55), 203 (2.6), 191 (1.2), 165

(1.6), 136 (7.2), 121 (6.6), 95 (14.7), 81 (40), 69 (100); HRMS (ESI) *m/z* obsd 270.2432 ($[M+NH_4]^+$, calcd 270.2428 for $C_{16}H_{32}O_2N$).

2.3. Regioselective bromohydration of triene 7 and alternative preparation of aldehyde 6

To a stirred mixture of triene **7** (1.09 g, 5.0 mmol) in 10 mL of 50% aqueous THF was added NBS (890 mg, 5.0 mmol) portionwise. After stirring for 15 min at ambient temperature, the reaction was quenched with 2 mL of aqueous $NaHCO_3$ (5%) and extracted with Et_2O (2×50 mL). The organic phases were washed with water and brine, dried over $MgSO_4$ and concentrated. The crude residue was purified by flash chromatography on silica gel (PET/AcOEt=6:1) to give 1.05 g (71%) of bromohydrin **8** as a colorless oil. *Bromo-2-cyclopropyl-6,10-dimethyl-undeca-5,9-dien-2-ol* (**8**). R_f=0.70 (PET/AcOEt=10:1); IR (film) ν_{max} 3526, 3085, 3007, 2966, 2920, 2855, 1668, 1442, 1380, 1223, 1107, 1024, 826, 651 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.16 (t, 1H, J=7.2 Hz), 5.09 (t, 1H, J=7.2 Hz), 3.53 (s, 2H), 2.17–1.99 (m, 6H), 1.81–1.63 (m, 2H), 1.67 (s, 3H), 1.63 (s, 3H), 1.60 (s, 3H), 0.97–0.88 (m, 1H), 0.53–0.35 (m, 4H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 135.9, 131.5, 124.2, 123.7, 70.7, 44.2, 39.6, 39.3, 26.6, 25.7, 22.4, 17.7, 17.1, 16.0, −0.7, −0.02 ppm; EIMS (*m/z*, %): 298 ($[M-18]^+$, 0.05), 296 ($[M-18]^+$, 0.05), 283 (0.03), 273 (0.07), 253 (0.5), 217 (4.2), 123 (26), 105 (13), 93 (22), 81 (31), 69 (100); HRMS (ESI) *m/z* obsd 315.1322 ($[M+H]^+$, calcd 315.1319 for $C_{16}H_{28}OBr$).

A stirred mixture of bromohydrin **8** (445 mg, 1.5 mmol) in methanol (5 mL) at 0 °C was treated with powdered anhydrous K_2CO_3 (280 mg, 2.0 mmol) in one portion. The resulting mixture was stirred for 0.5 h while gradually warmed to room temperature. The reaction mixture was diluted with ether (40 mL) and washed successively with water, brine, and dried. After evaporation of the solvent, the residue was purified by flash chromatography on silica gel eluting with PET–AcOEt (100/1) to give 320 mg (92%) of aldehyde **6**, identical with the sample prepared above.

2.3.1. Acetic acid 2-(3-iodo-propylidene)-6,10-dimethyl-undeca-5,9-dienyl ester (10). The title compound was prepared according to Ref. 17, R_f=0.49 (PET/AcOEt=10:1); IR (film) ν_{max} 2961, 2930, 2863, 1742, 1668, 1447, 1375, 1229, 1024, 963 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.43 (t, 1H, J=6.6 Hz), 5.11–5.09 (m, 2H), 4.51 (s, 2H), 3.13 (t, 2H, J=7.2 Hz), 2.71–2.63 (m, 2H), 2.11–1.95 (m, 8H), 2.08 (s, 3H), 1.71 (s, 3H), 1.61 (s, 6H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.7, 136.2, 136.0, 131.2, 128.0, 124.2, 123.2, 67.8, 39.6, 32.7, 32.6, 28.9, 27.3, 26.6, 25.7, 21.0, 17.7, 4.5 ppm; EIMS (*m/z*, %): 404 (M^+, 2), 344 (2.4), 329 (3.1), 301 (4.5), 217 (6), 137 (28), 95 (30), 81 (66), 69 (100); HRMS (ESI) *m/z* obsd 422.1561 ($[M+NH_4]^+$, calcd 422.1550 for $C_{18}H_{33}O_2IN$).

2.3.2. (8-Iodo-5-methylsulfanylmethyl-oct-5-enyl)-benzene (11). The title compound was prepared according to a typical procedure described in Ref. 17, R_f=0.31 (PET/AcOEt=20:1); IR (film) ν_{max} 3082, 3025, 2929, 2855, 1602, 1453, 1423, 1245, 1167, 1028, 802, 745, 699 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.29–7.20 (m, 5H), 5.20 (t, 1H, J=7.0 Hz), 3.13 (t, 2H, J=7.1 Hz), 3.06 (s, 2H), 2.69–2.60 (m, 4H), 2.27–2.14 (m, 2H), 1.98 (s, 3H), 1.65–1.30 (m, 4H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$) δ 142.4, 137.6, 128.4, 128.3, 127.0, 125.7, 40.7, 35.7, 32.0, 31.3, 28.4, 27.8, 24.8, 5.5 ppm; EIMS (*m/z*, %): 374 (M^+, 0.4), 326 (4.8), 311 (0.2), 247 (25), 157 (15), 117 (45), 91 (100); HRMS (ESI) *m/z* obsd 375.0641 ($[M+H]^+$, calcd 375.0638 for $C_{16}H_{24}SI$).

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18. In contrast with this remarkable regioslectivity, diol **9** was prepared from triene **7** by Sharpless dihydroxylation with an AD-mix reagent system in a rather low yield (ca. 10%, poor regioselectivity). Similarly, electrophilic epoxidation of triene **7** with *m*-CPBA also lacks regioselectivity for the production of labile epoxide **5**.
19. This is apparently due to the inherent preference for the oxy-3-*exo*-tet ring closure process. It is evident that the addition of metal (Li, Na, or K) iodide in the reaction mixture (i.e., reaction in Table 1) could not increase the yield of the sulfide formation.