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Preparation and Reactions of 2-Chloro-3,4-epoxy-1-butene: A Convenient Route to (*Z*)-3-Chloroallylic Alcohols

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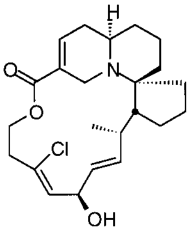
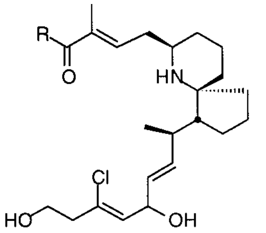
Epoxide **2** was prepared from 3,4-dichloro-1-butene (**1**) by epoxidation with *m*-CPBA and subsequent dehydrohalogenation of the intermediate dichloroepoxide with molten KOH, affording **2** in 64% overall yield (2 steps). Catalytic CuBr/SMe$_2$-mediated S_N2' addition of sp^2- or sp^3-hybridized Grignard reagents to 2-chloro-3,4-epoxy-1-butene (**2**) afforded (*Z*)-3-chloroallylic alcohols such as **3** in good yields and with high regio- and stereoselectivity.

Introduction

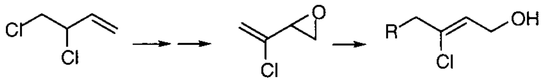
The marine natural products halichlorine (**1**) and the pinnaic acids (**2** and **3**) are of particular interest to organic synthesis chemists because of their interesting biological activities and unique structural frameworks.[1] One problem in the synthesis of this class of marine alkaloids is the preparation of the internal (*Z*)-chloroalkene moieties. The most general method for the preparation of (*Z*)-chloroalkenes has been the Pd(II)-mediated coupling of Grignard or organozinc nucleophiles with 1,1-dichloro-1-alkenes.[2] (*Z*)-Chloroalkenes have also been prepared by acid-catalyzed dehydration of ketones in the presence of acyl halides.[3] (*Z*)-3-Chloroallylic alcohols have been prepared via the electrophilic addition of $CH_2O\cdot Me_2AlCl$ to alkynes.[4] (*E*)-Chloroalkenes have been prepared by Ru(I)-mediated coupling of alkynes with enones.[5] We envisioned that copper-catalyzed S_N2' opening of the title compound (epoxide **5)** would provide a verstatile entry to (*Z*)-3-chloroallylic alcohols with high regio- and stereoselectivity. Herein, we report an improved preparation of epoxide **5**. Copper(I) bromide/dimethyl sulfide mediated S_N2' opening of epoxide **5** with Grignard reagents afforded the (*Z*)-3-chloroallylic alcohols **6** in good yields and with high regio- and stereoselectivity.



Halichlorine (**1**)



R = OH, Pinnaic acid (**2**)
R = NHCH$_2$CH$_2$SO$_3$H, Tauropinnaic acid (**3**)



4 **5** **6**

Preparation of 2-Chloro-3,4-epoxy-1-butene. Epoxide **5** was prepared (Scheme 1) by epoxidation of the commercially available dichloroalkene **4**. It had been reported that treatment of the dichloroepoxide (**7**) with different bases gave variable yields of the epoxide **5**, accompanied by unreacted starting material and the other regioisomer.[6] After some experimentation, we found that dropwise addition of **7** to molten potassium hydroxide (neat, 120 °C, bath temperature) under a nitrogen atmosphere gave clean conversion to epoxide **5** (64% overall yield from **4**).

Preparation of (*Z*)-3-Chloroallylic Alcohols. Treatment of the title compound (**5**) with a solution of 1.0 M phenylmagnesium bromide (**8**) in THF afforded (Table 1) a mixture of the 1,4-addition products (*Z*/*E*-**9**), the 1,2-addition product (**10**), and the 1,1-addition product (**11**) in a ratio of 2.5:1.0:3.5, respectively, in 70% total yield. To improve the regioselectivity of this reaction, copper(I) bromide/dimethyl sulfide catalysis was investigated. By careful optimization of the reaction conditions, the desired (*Z*)-3-chloroalkene **9** could be made the dominant product of the reaction. Changing the reaction solvent or using other additives in the reaction, including LiBr, HMPA, or TMSCl as a trapping agent, either had no effect or adversely affected the desired outcome.

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(1) For the structural determination and biological activity of halichlorine, see: (a) Kuramoto, M.; Tong, C.; Yamada, K.; Chiba, T.; Hayashi, Y.; Uemura, D. *Tetrahedron Lett.* **1996**, *37*, 3867. (b) Arimoto, H.; Hayakawa, I.; Kuramoto, M.; Uemura, D. *Tetrahedron Lett.* **1998**, *39*, 861. (c) Trauner, D.; Churchill, D. G.; Danishefsky, S. J. *Helv. Chim. Acta* **2000**, *83*, 2344. For the structural determination and biological activity of the pinnaic acids, see: (d) Chou, T.; Kuramoto, M.; Otani, Y.; Shikano, M.; Yazawa, K.; Uemura, D. *Tetrahedron Lett.* **1996**, *37*, 3871. For the synthesis of halichlorine, see: (e) Trauner, D.; Schwarz, J. B.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **1999**, *38*, 3542. (f) Trauner, D.; Danishefsky, S. J. *Tetrahedron Lett.* **1999**, *40*, 6513. For approaches to halichlorine and the pinnaic acids, see: (g) Keen, S. P.; Weinreb, S. M. *J. Org. Chem.* **1998**, *63*, 6739. (h) Arimoto, H.; Asano, S.; Uemura, D. *Tetrahedron Lett.* **1999**, *40*, 3583. (i) Lee, S.; Zhao, Z. *Org. Lett.* **1999**, *1*, 681. (j) Koviach, J. L.; Forsyth, C. J. *Tetrahedron Lett.* **1999**, *40*, 8529. (k) Wright, D. L.; Schulte, J. P., II.; Page, M. A. *Org. Lett.* **2000**, *2*, 1847. (l) Shindo, M.; Fukuda, Y.; Shishido, K. *Tetrahedron Lett.* **2000**, *41*, 929. (m) Yakota, W.; Shindo, M.; Shishido, K. *Heterocycles* **2001**, *54*, 871.

(2) Minato, A.; Suzuki, K. *J. Am. Chem. Soc.* **1987**, *109*, 1257.

(3) Moughamir, K.; Mezgueldi, B.; Atmani, A.; Mestdagh, H.; Rolando, C. *Tetrahedron Lett.* **1998**, *39*, 59.

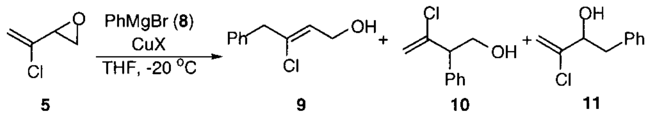
(4) Rodini, D. J.; Snider, B. B. *Tetrahedron Lett.* **1980**, *21*, 3857.

(5) Trost, B. M.; Pinkerton, A. B. *J. Am. Chem. Soc.* **1999**, *121*, 1988.

(6) Hawkins, E. C. E. *J. Chem. Soc.* **1958**, 248.

10.1021/jo020079l CCC: $22.00

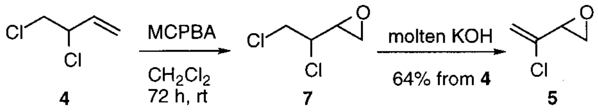
Table 1. Effect of CuX and Equivalents on Regiochemistry and Stereochemistry of S_N2' Addition Product



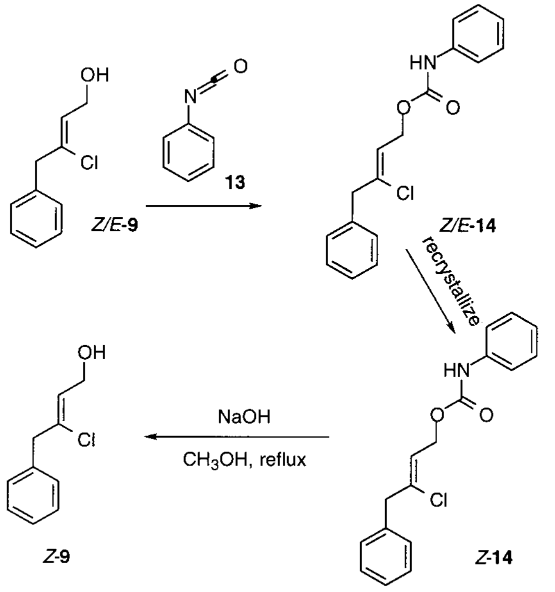
entry	CuX	equiv of CuX	temp (°C)	product distributn[a]			yield[b]	Z:E ratio[a] (**9**)
				9	**10**	**11**		
1	Br/SMe$_2$[c]	0.000	−40	2.5	1.0	3.5	70%	36:1
2	Br/SMe$_2$[c]	0.025	−40	4.5	1.0	trace	69%	12:1
3	Br/SMe$_2$[c]	0.050	−40	6.5	1.0	trace	67%	26:1
4	Br/SMe$_2$[c]	0.100	−40	10.9	1.0	trace	61%	22:1
5	Br/SMe$_2$[c]	0.100	−20	12.1	1.0	trace	71%	16:1
6	Br/SMe$_2$[c]	0.200	−20	14.2	1.0	trace	69%	17:1
7	Br/SMe$_2$[d]	0.200	−20	16.6	1.0	trace	81%	15:1
8	Br/SMe$_2$[d]	1.000	−20	54.1	1.0	trace	64%	14:1
9	Cl[d]	0.200	−20	22.8	1.0	trace	72%	12:1
10	Cl[d]	1.000	−20	37.1	1.0	trace	66%	14:1
11	Br[d]	0.200	−20	25.2	1.0	trace	67%	16:1
12	Br[d]	1.000	−20	18.7	1.0	trace	84%	15:1
13	Br[d,e]	0.200	−20	22.6	1.0	trace	66%	14:1
14	Br/PPh$_3$	0.200	−20	18.4	1.0	trace	70%	16:1
15	I[d]	0.200	−20	8.0	1.0	trace	64%	13:1
16	I[d]	1.000	−20	3.8	1.0	trace	50%	10:1
17	CN[d]	0.200	−20	21.9	1.0	trace	75%	16:1
18	CN[d]	1.000	−20	6.4	1.0	trace	79%	11:1

[a] From ^1H NMR. [b] Isolated. [c] Saturated aqueous NH_4Cl workup. [d] Aqueous 5% HCl workup. [e] Dried.

Scheme 1



Scheme 2



Other Grignard reagents also participated efficiently in this reaction (Table 2). With these additions, the products corresponding to **10** and **11** were observed at most as minor product (<3%, combined).

The alcohols as prepared were sufficiently pure for most purposes. We found that, for **9**, the purity could be improved by recrystallization of the derived phenyl urethane **14** (Scheme 2).

Conclusion

Chloroalkenes are useful intermediates for target-directed synthesis. Pd- and Ni-mediated coupling of chloroalkenes with organometallic reagents yield di- and trisubstituted alkenes[7] and nitriles.[8] The chloroalkene moiety can also be converted to a ketone,[9] an α-haloketone,[10,11] a vinyl silane,[12] an alkene,[13] or an alkyne.[14] The approach delineated here will make (*Z*)-3-chloroallylic alcohols more readily available for use in organic synthesis.

Experimental Section

General Methods. All air- and moisture-sensitive reactions were performed under an atmosphere of dry nitrogen. Tetrahydrofuran (THF) was distilled from sodium metal/benzophenone ketyl, and methylene chloride (CH_2Cl_2) was distilled from calcium hydride immediately prior to use. ^1H NMR and ^{13}C NMR spectra were recorded at 400 or 100 MHz, respectively using deuteriochloroform ($CDCl_3$) as solvent with 1% v/v TMS (tetramethylsilane) = 0.00 as an internal standard, unless otherwise specified. ^{13}C multiplicities were determined with the aid of an APT (attached proton test) pulse sequence, differentiating the signals for methyl and methine carbons as down, "d", from methylene and quaternary carbons as up, "u". The infrared (IR) spectra were determined as neat oils on 4 mm sodium chloride plates, unless otherwise indicated. Mass spectra (MS) were obtained by chemical ionization (CI) in NH_3 or CH_4 or by electronic ionization (EI) with an ionizing potential of 70 eV, unless otherwise indicated. Elemental analyses were performed by Galbraith Laboratories, Knoxville,

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(7) (a) Ratovelomanana, V.; Linstrumelle, G. *Synth. Commun.* **1984**, *14*, 179. (b) Ramiandrasoa, P.; Brehon, B.; Thivet, A.; Alami, M.; Cahiez, G. *Tetrahedron Lett.* **1997**, *38*, 2447. (c) Littke, A. F.; Dai, C. Y.; Fu, G. C. *J. Am. Chem. Soc.* **2000**, *122*, 4020. (d) Dai, C. Y.; Fu, G. C. *J. Am. Chem. Soc.* **2001**, *123*, 2719.

(8) Yamamura, K.; Murahashi, S. I. *Tetrahedron Lett.* **1977**, 4429.

(9) (a) Mukaiyama, T.; Imamoto, T.; Kobayashi, S. *Chem. Lett.* **1973**, 261. (b) Mukaiyama, T.; Imamoto, T.; Kobayashi, S. *Chem. Lett.* **1973**, 715. (c) Yoshioka, H.; Takasaki, K.; Kobayashi, M.; Matsumoto, T. **1979**, *37*, 3489.

(10) Morton, H. E.; Leanna, M. R. *Tetrahedron Lett.* **1993**, *34*, 4481.

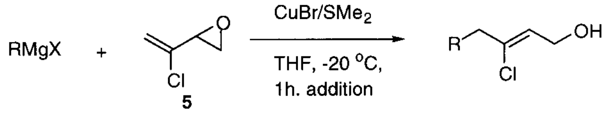
(11) Griesbaum, K.; Lie, G. O.; Raupp, E. *Chem. Ber.* **1981**, *114*, 3273.

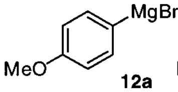
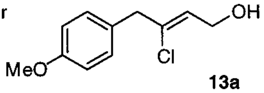
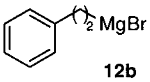
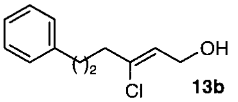
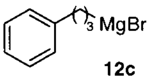
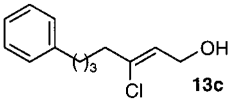
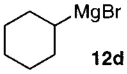
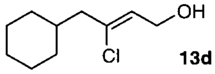
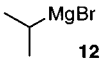
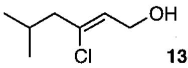
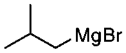
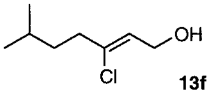
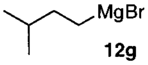
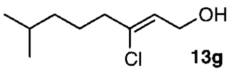
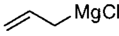
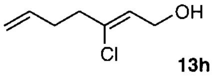
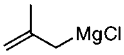
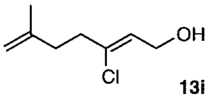
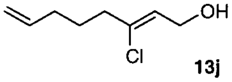
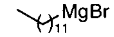
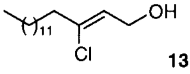
(12) Hurdlik, P. F.; Kulkarni, A. K.; Jain, S.; Hurdlik, A. F. *Tetrahedron* **1983**, *39*, 877.

(13) Vanderesse, R.; Brunet, J. J.; Caubere, P. *J. Org. Chem.* **1981**, *46*, 1270.

(14) Hatch, L. F.; Chiola, V. *J. Am. Chem. Soc.* **1951**, *73*, 360.

Table 2. Examples of Grignard Addition to 2-Chloro-3,4-epoxy-1-butene



Entry	Grignard Reagent		Product		Yield	Z/E Ratio
1		12a		13a	89%	11.1 : 1.0
2		12b		13b	82%	16.3 : 1.0
3		12c		13c	77%	20.1 : 1.0
4		12d		13d	74%	23.5 : 1.0
5		12e		13e	76%	22.1 : 1.0
6		12f		13f	78%	18.0 : 1.0
7		12g		13g	80%	15.2 : 1.0
8		12h		13h	72%	7.0 : 1.0
9		12i		13i	74%	6.5 : 1.0
10		12j		13j	87%	13.9 : 1.0
11		12k		13k	77%	14.5 : 1.0

TN. Substances for which C, H, N analyses are not reported were purified as specified and gave spectroscopic data consistent with being ≥95% the assigned structure. For column chromatography, 230−400 mesh 60 Å silica gel was used following to the procedure of Taber.[15] R_f values indicated refer to thin-layer chromatography (TLC) on 2.5 × 10 cm, 250 μm analytical plates coated with silica gel GF developed in 20% MTBE/PE solvent system, unless otherwise indicated. Solvents are reported as volume/volume mixtures. All glassware was oven dried and cooled under a dry nitrogen stream immediately prior to use. MTBE is methyl *tert*-butyl ether; PE is petroleum ether.

1,2-Dichloro-3,4-epoxybutane (7). To a stirring slurry of 123.6 g (500 mmol) of 70% *m*-CPBA in 200 mL of CH_2Cl_2 at ambient temperature was added 21.7 mL (200 mmol) of 3,4-dichloro-1-butene (**4**) over 5 min. Stirring was continued until TLC showed the dichloroalkene to be consumed (72 h). The reaction mixture was then cooled to 0 °C and filtered to remove solids, which were rinsed with an additional 50 mL of chilled (−78 °C) CH_2Cl_2. The filtrate was concentrated in vacuo and filtered again to remove solids, which were rinsed again with chilled (−78 °C) CH_2Cl_2. The filtrate was then cooled to 0 °C and neutralized with 125 mL of saturated aqueous $NaHCO_3$ with vigorous stirring to remove residual acid. The organic layer was then partitioned between Et_2O and brine. The combined organic extract was dried (Na_2SO_4) and then concentrated to a pale yellow oil. The oil was bulb-to-bulb distilled, $bp_{0.1mm}$(pot) = 85 °C, to afford 23.7 g (85% yield) of 1,2-dichloro-3,4-epoxybutane (**7**) as a clear colorless liquid (1.3:1 mixture of diastereomers): ^{1}H NMR ($CDCl_3$) *major isomer* δ 2.78 (dd, 1H, J = 2.50 and 4.76 Hz), 2.94 (dd, 1H, J = 4.08 and 4.75 Hz), 3.28 (ddd, 1H, J = 2.50 and 4.08 Hz and 7.26 Hz), 3.73 (dt, 1H, 5.3 and 7.26 Hz), 3.89 (d, 2H, J = 5.3 Hz), *minor isomer* δ 2.89 (dd, 1H, J = 2.50 and 4.75 Hz), 3.00 (dd, 1H, J = 4.08 and 4.75 Hz), 3.18 (tt, 1H, J = 2.50 and 4.08 Hz), 3.76 (m, 3H); ^{13}C NMR (u) δ 46.3, 47.8, (d) δ 52.3, 60.1, *minor isomer* (u) δ 44.6, 46.8, (d) δ 53.3, 60.7; IR (neat) 3065, 3001, 2956, 1430, 1256 cm^{-1}; MS (CI) *m/z* 105 ([M − Cl]$^+$, 100), 107 (31); HRMS calcd for C_4H_6ClO ([M − Cl]$^+$) 105.0107, found 105.0112.

2-Chloro-3,4-epoxy-1-butene (5). In a two-neck 100 mL round-bottom flask equipped with an addition funnel and a short-path distillation head was placed 10.5 g of KOH (187.3 mmol), which was melted at 120 °C (bath). Then, 15.0 g of epoxide **7** (106.4 mmol) was added over 15 min to the molten KOH with rapid stirring. The desired epoxide (**5**) flash distilled into the receiving flask. After complete addition of **7**, the bath temperature was raised to 200 °C. The distillate was then dried (Na_2SO_4) and filtered. This afforded 8.34 g (75% yield) of 2-chloro-3,4-epoxy-1-butene (**5**) as a clear colorless liquid: ^{1}H NMR ($CDCl_3$) δ 2.89−2.95 (m, 2H), 3.53−3.54 (m, 1H), 5.46 (d, 1H, J = 1.7 Hz), 5.62 (dd, 1H, J = 1.2 and 1.7 Hz); ^{13}C NMR (u) δ 7.4, 115.2, 137.9, (d) δ 52.6; IR (neat) 1730, 1632, 1458, 1394, 1261, 1112, 899 cm^{-1}; MS (CI) *m/z* 104 (M$^+$, 100), 106 (M$^+$, 40); HRMS calcd for C_4H_5ClO (M$^+$) 104.0029, found 104.0026.

General Procedure. (*Z*)-3-Chloro-4-phenyl-2-buten-1-ol (9). Epoxide **5** (205 mg, 1.95 mmol) and CuBr/SMe_2 (82 mg, 0.40 mmol) were suspended in THF (1.9 mL) and cooled to −20 °C. Then, dropwise addition of 4.6 mL of 0.5 M phenylmagnesium bromide (2.3 mmol in THF) was effected over 1.25 h. The mixture was stirred at −20 °C for an 1 h and then warmed to room temperature. The reaction mixture was quenched with 10 mL of 5% aqueous HCl and then partitioned between Et_2O and brine. The combined organic extract was dried (Na_2SO_4) and concentrated in vacuo. The residue was chromatographed to give **9** (298 mg, 86% yield) as a mixture (*Z*/*E*, 16.4:1) as a pale yellow oil: ^{1}H NMR ($CDCl_3$) *major isomer* δ 1.84 (bs, exch, 1H), 3.63 (s, 2H), 4.29 (d, 2H, J = 6.1 Hz), 5.74 (tt, 1H, J = 1.2 and 6.1 Hz), 7.21−7.34 (m, 5H), *minor isomer* δ 1.25 (bs, exch, 1H), 3.74 (s, 2H), 6.00 (t, 1H, J = 7.4 Hz); ^{13}C NMR (u) δ 45.8, 60.0, 136.0, 136.9, (d) δ 126.3, 127.2, 128.7, 129.3; IR (neat) ν 3334, 3029, 2916, 1660, 1495, 1454, 1071, 1011 cm^{-1}; MS (CI) *m/z* 200 (M + NH_4^+, 100), 202 (36); HRMS calcd for (M$^+$) $C_{10}H_{15}NClO$ 200.0842, found 200.0832; TLC R_f = 0.16.

(*Z*)-3-Chloro-4-phenyl-2-buten-1-ol Phenylurethane (14). The mixture of **9** (190 mg, 1.04 mmol) was dissolved in CH_2Cl_2 (10 mL) to which was added pyridine (125 μL, 122.3 mmol) and phenyl isocyanate (130 μL, 1.2 mmol). The resulting mixture was stirred vigorously at room temperature. After 4 h, the reaction was complete (TLC). The mixture was quenched with 10 mL of 5% aqueous HCl and partitioned between Et_2O and brine. The combined organic extract was dried (Na_2SO_4) and concentrated in vacuo. The residue was chromatographed to afford **14** (254 mg, 84% yield) as a white crystalline residue (mp 63−65 °C). This was recrystallized from PE to afford 239 mg of bright white needles (*Z*/*E*, ≥99:1): ^{1}H NMR ($CDCl_3$) δ 3.66 (s, 2H), 4.83 (d, 2H, J = 6.2 Hz), 5.75 (t, 1H, J = 6.2 Hz), 6.64 (bs, exch, 1H), 7.07 (t, 1H, J = 6.7 Hz), 7.23−7.38 (m, 9H); ^{13}C NMR (u) δ 45.6, 62.0, 136.4, 137.6, 138.0, d: δ 121.7, 123.5, 127.1, 128.6, 129.1; IR (thin film) 3323, 3029, 1708, 1601, 1539, 1445 cm^{-1}; MS (CI) *m/z* 301 (M$^+$, 95), 302 (M + H$^+$, 81), 303 (44), 304 (29); HRMS calcd for $C_{17}H_{16}NClO_2$ (M$^+$) 301.0869, found 301.0859. Anal. Calcd for $C_{17}H_{16}NClO_2$: C,

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67.66; H, 5.34; N, 4.64. Found: C, 67.37; H, 5.37; N, 4.64. TLC: $R_f = 0.51$; R_f (10% MTBE/PE) = 0.25. Mp: 74−75 °C.

(*Z*)-3-Chloro-4-(4-methoxyphenyl)-2-buten-1-ol (13a). By a procedure similar to that for **9**, epoxide **5** (200 mg, 1.9 mmol) and $CuBr/SMe_2$ (81 mg, 0.39 mmol) were suspended in THF (1.9 mL) and cooled to −20 °C. Then, dropwise addition of 4.6 mL of 0.5 M (4-methoxyphenyl)magnesium bromide (2.3 mmol in THF) was effected over 1.25 h. The mixture was stirred at −20 °C for 1 h and then warmed to room temperature. The reaction mixture was quenched with 10 mL of 5% aqueous HCl and then partitioned between Et_2O and brine. The combined organic extract was dried (Na_2SO_4) and concentrated in vacuo. The residue was chromatographed to give **13a** (360 mg, 89% yield) as a mixture (*Z*/*E*, 11.1:1) as a pale green oil: ^1H NMR ($CDCl_3$) *major isomer* δ 1.87 (bs, exch, 1H), 3.57 (s, 2H), 3.79 (s, 3H), 4.29 (d, 2H, $J = 6.2$ Hz), 5.72 (tt, 1H, $J = 1.0$ and 6.2 Hz), 6.86 (dq, 2H, 2.1 and 8.6 Hz), 7.14 (dq, 2H, 2.1 and 8.6 Hz), *minor isomer* δ 1.21 (bs, exch, 1H), 3.68 (s, 3H), 5.98 (t, 1H, $J = 7.4$ Hz); ^{13}C NMR (u) δ 44.7, 59.8, 128.7, 136.1, 158.5, (d) δ 55.2, 113.8, 125.7, 130.0; IR (neat) 3354, 2908, 1611, 1513, 1248, 1035 cm^{-1}; MS (CI) 212 (M$^+$, 100), 214 (31); HRMS calcd for $C_{11}H_{13}ClO_2$ 212.0604, found 212.0598; TLC $R_f = 0.16$.

(*Z*)-3-Chloro-6-phenyl-2-hexen-1-ol (13b). By a procedure similar to that for **9**, epoxide **5** (203 mg, 1.9 mmol) and $CuBr/SMe_2$ (82 mg, 0.40 mmol) were suspended in THF (1.9 mL) and cooled to −20 °C. Then, dropwise addition of 4.6 mL of 0.5 M (phenylethyl)magnesium bromide (2.3 mmol in THF) was effected over 1.5 h to give **13b** (329 mg, 82% yield) as a mixture (*Z*/*E*, 16.3:1) as a pale yellow oil: ^1H NMR ($CDCl_3$) *major isomer* δ 1.58 (bs, exch, 1H), 1.87−1.95 (m, 2H), 2.37 (t, 2H, $J = 7.3$ Hz), 2.62 (t, 2H, $J = 7.7$ Hz), 4.29 (d, 2H, $J = 6.1$ Hz), 5.72 (tt, 1H, 0.9 and 6.1 Hz), 7.17−7.34 (m, 5H), *minor isomer* δ 1.25 (bs, exch, 1H), 2.46 (t, 2H, $J = 7.4$ Hz), 4.04 (d, 2H, $J = 7.4$ Hz), 5.86 (t, 1H, $J = 7.4$ Hz); ^{13}C NMR (u) δ 28.7, 34.6, 38.7, 59.7, 136.7, 141.6, (d) δ 124.8, 125.9, 126.4, 128.4, 128.5, 129.0; IR (neat) 3342, 3027, 2942, 1661, 1454, 1028 cm^{-1}; MS (CI) *m*/*z* 228 (M + NH$_4^+$, 100), 230 (32); HRMS calcd for $C_{12}H_{19}NClO$ (M + NH$_4^+$) 228.1155, found 228.1153; TLC $R_f =$ 0.23.

(*Z*)-3-Chloro-7-phenyl-2-hepten-1-ol (13c). By a procedure similar to that for **9**, epoxide **5** (205 mg, 2.0 mmol) and $CuBr/SMe_2$ (81 mg, 0.39 mmol) were suspended in THF (1.9 mL) and cooled to −20 °C. Then, dropwise addition of 4.6 mL of 0.5 M (phenylpropyl)magnesium bromide (2.3 mmol in THF) was effected over 1.25 h to give **13c** (327 mg, 77% yield) as a mixture (*Z*/*E*, 20.1:1) as a pale yellow oil: ^1H NMR ($CDCl_3$) *major isomer* δ 1.58−1.65 (m, 4H), 1.88 (bs, exch, 1H), 2.33−2.37 (m, 2H), 2.60−2.64 (m, 2H), 4.26 (d, 2H, $J = 6.2$ Hz), 5.69 (tt, 1H, $J = 0.9$ and 6.2 Hz), 7.16−7.30 (m, 5H), *minor isomer* δ 4.10 (d, 2H, $J = 7.3$ Hz), 5.83 (t, 1H, $J = 7.3$ Hz); ^{13}C NMR (u) δ 26.7, 30.3, 35.6, 39.1, 59.7, 136.9, 142.2, (d) δ 124.5, 125.7, 128.3; IR (neat) 3334, 1661, 1503, 1496 cm^{-1}; MS (CI) *m*/*z* 242 (M + NH$_4^+$, 100), 244 (31); HRMS calcd for $C_{13}H_{21}NClO$ (M + NH$_4^+$) 242.1311, found 242.1300; TLC $R_f = 0.24$.

(*Z*)-3-Chloro-4-cyclohexyl-2-buten-1-ol (13d). By a procedure similar to that for **9**, epoxide **5** (203 mg, 1.9 mmol) and $CuBr/SMe_2$ (83 mg, 0.40 mmol) were suspended in THF (1.9 mL) and cooled to −20 °C. Then, dropwise addition of 4.6 mL of 0.5 M phenylmagnesium bromide (2.3 mmol in THF) was effected over 1.5 h to give **13d** (264 mg, 74% yield) as a mixture (*Z*/*E*, 23.5:1) as a pale yellow oil: ^1H NMR ($CDCl_3$) *major isomer* δ 0.79−0.87 (m, 2H), 1.04−1.26 (m, 3H), 1.57−1.68 (m, 6H), 2.01 (bs, exch, 1H), 2.16 (d, 2H, $J = 6.5$ Hz), 4.25 (d, 2H, $J = 6.2$ Hz), 5.64 (t, 1H, $J = 6.2$ Hz), *minor isomer* δ 4.08 (d, 2H, $J = 7.4$ Hz), 5.84 (t, 1H, $J = 7.4$ Hz); ^{13}C NMR (u) δ 26.0, 26.3, 32.5, 47.1, 59.7, 135.7, (d) δ 34.9, 125.5; IR (neat) 3327, 1660, 1089, 1061, 1013 cm^{-1}; MS (CI) *m*/*z* 206 (M + NH$_4^+$, 100), 208 (33); HRMS calcd for $C_{10}H_{21}NClO$ (M + NH$_4^+$) 206.1312, found 206.1301; MS (EI) *m*/*z* 188 (M$^+$, 100), 190 (32); HRMS calcd for $C_{10}H_{17}ClO$ (M$^+$) 188.0968, found 188.0962; TLC $R_f = 0.30$.

(*Z*)-3-Chloro-5-methyl-2-hexen-1-ol (13e). By a procedure similar to that for **9**, epoxide **5** (203 mg, 1.9 mmol) and $CuBr/SMe_2$ (83 mg, 0.40 mmol) were suspended in THF (1.9 mL) and cooled to −20 °C. Then, dropwise addition of 4.6 mL of 0.5 M isopropylmagnesium bromide (2.3 mmol in THF) was effected over 1.25 h to give **13e** (214 mg, 76% yield) as a mixture (*Z*/*E*, 22.1:1) as a pale yellow oil: ^1H NMR ($CDCl_3$) *major isomer* δ 0.91 (d, 6H, $J = 6.5$ Hz), 1.57 (bs, exch, 1H), 2.01 (h, 1H, $J = 6.5$ Hz), 2.19 (d, 2H, $J = 7.1$ Hz), 4.31 (d, 2H, $J = 6.2$ Hz), 5.71 (t, 1H, $J = 6.2$ Hz), *minor isomer* δ 2.26 (d, 2H, $J = 7.2$ Hz), 5.92 (t, 3H, $J = 7.2$ Hz); ^{13}C NMR (u) δ 48.7, 60.0, 136.7, (d) δ 22.0, 26.0, 125.7; IR (neat) 3318, 2957, 1661 cm^{-1}; MS (EI) *m*/*z* 148 (M$^+$, 100), 150 (32); HRMS Calcd for $C_7H_{13}ClO$ (M$^+$) 148.0655, found 148.0653; TLC $R_f = 0.19$.

(*Z*)-3-Chloro-6-methyl-2-hepten-1-ol (13f). By a procedure similar to that for **9**, epoxide **5** (204 mg, 1.9 mmol) and $CuBr/SMe_2$ (83 mg, 0.40 mmol) were suspended in THF (1.9 mL) and cooled to −20 °C. Then, dropwise addition of 4.6 mL of 0.5 M isobutylmagnesium bromide (2.3 mmol in THF) was effected over 1.25 h. The mixture was stirred at −20 °C for 1 h and then warmed to room temperature. The reaction mixture was quenched with 10 mL of 5% aqueous HCl and then partitioned between Et_2O and brine. The combined organic extract was dried (Na_2SO_4) and concentrated in vacuo. The residue was chromatographed to give **13f** (240 mg, 78% yield) as a mixture (*Z*/*E*, 18.0:1) as a pale yellow oil: ^1H NMR ($CDCl_3$) *major isomer* δ 0.91 (d, 6H, $J = 6.6$ Hz), 1.45 (q, 2H, $J = 6.8$ Hz), 1.55 (h, 1H, $J = 6.6$ Hz), 1.78 (bs, exch, 1H), 2.34 (t, 2H, $J = 0.6$ and 6.8 Hz), 4.29 (d, 2H, $J = 6.2$ Hz), 5.72 (tt, 1H, $J = 1.0$ and 6.2 Hz), *minor isomer* δ 2.39 (t, 2H, $J = 7.5$ Hz), 4.15 (d, 2H, $J = 7.5$ Hz), 5.98 (t, 1H, $J = 7.5$ Hz); ^{13}C NMR (u) δ 36.3, 37.3, 59.8, 137.7, (d) δ 22.4, 27.1, 124.0; IR (neat) 3323, 1662, 1468, 1007 cm^{-1}; MS (EI) *m*/*z* 161 ([M − H]$^+$, 100), 163 (33); HRMS calcd for $C_8H_{14}ClO$ ([M − H]$^+$) 161.0733, found 161.0726; TLC $R_f = 0.30$.

(*Z*)-3-Chloro-7-methyl-2-octen-1-ol (13g). By a procedure similar to that for **9**, epoxide **5** (204 mg, 1.9 mmol) and $CuBr/SMe_2$ (82 mg, 0.40 mmol) were suspended in THF (1.9 mL) and cooled to −20 °C. Then, dropwise addition of 4.6 mL of 0.5 M phenylmagnesium bromide (2.3 mmol in THF) was effected over 1.5 h to give **13g** (269 mg, 80% yield) as a mixture (*Z*/*E*, 15.2:1) as a pale yellow oil: ^1H NMR ($CDCl_3$) *major isomer* δ 0.88 (d, 6H, $J = 6.7$ Hz), 1.17 (q, 2H, $J = 7.3$ Hz), 1.52−1.60 (m, 3H), 2.32 (t, 2H, 7.3 Hz), 4.30 (d, 2H, $J = 6.2$ Hz), 5.72 (tt, 1H, $J = 0.9$ and 6.2 Hz), *minor isomer* δ 1.03 (d, 6H, $J = 6.7$ Hz), 2.37 (t, 2H, $J = 7.4$ Hz), 4.15 (t, 2H, $J = 7.4$ Hz), 5.86 (t, 1H, $J = 7.4$ Hz); ^{13}C NMR (u) δ 25.0, 37.8, 39.6, 59.8, 137.4, (d) δ 22.5, 27.7, 124.2; IR (neat) 3322, 2955, 1662, 1468, 1016 cm^{-1}; MS (EI) *m*/*z* 176 (M$^+$, 100), 178 (32); HRMS calcd for $C_9H_{17}ClO$ (M$^+$) 176.0968, found 176.0972; TLC $R_f =$ 0.27.

(*Z*)-3-Chloro-2,6-heptadien-1-ol (13h). By a procedure similar to that for **9**, epoxide **5** (200 mg, 1.9 mmol) and $CuBr/SMe_2$ (78 mg, 0.38 mmol) were suspended in THF (1.9 mL) and cooled to −20 °C. Then, dropwise addition of 4.6 mL of 0.5 M phenylmagnesium bromide (2.3 mmol in THF) was effected over 1.25 h to give **13h** (201 mg, 72% yield) as a mixture (*Z*/*E*, 7.0:1) as a pale yellow oil: ^1H NMR ($CDCl_3$) *major isomer* δ 1.49 (bs, exch, 1H), 2.32−2.36 (m, 2H), 2.42−2.46 (m, 2H), 4.30 (d, 2H, $J = 6.2$ Hz), 5.00−5.03 (m, 1H), 5.07 (ddt, 1H, $J = 1.6$, 1.7, and 17.1 Hz), 5.75 (tt, 1H, $J = 1.0$ and 6.2 Hz), 5.79 (ddt, 1H, $J = 6.7$, 10.3, and 17.1 Hz), *minor isomer* δ 1.23 (bs, exch, 1H), 4.09 (d, 2H, $J = 7.4$ Hz), 5.86 (t, 1H, $J = 7.4$ Hz); ^{13}C NMR (u) δ 31.3, 38.7, 59.8, 115.7, 136.4, (d) δ 124.9, 136.6; IR (neat) 3332,1661, 1642 cm^{-1}; MS (CI) *m*/*z* 145 ([M − H]$^+$), 147 (34); HRMS calcd for $C_7H_{10}ClO$ ([M − H]$^+$) 145.0420, found 145.0415; TLC $R_f = 0.25$.

(*Z*)-3-Chloro-6-methyl-2,6-heptadien-1-ol (13i). By a procedure similar to that for **9**, epoxide **5** (202 mg, 1.9 mmol) and $CuBr/SMe_2$ (83 mg, 0.40 mmol) were suspended in THF (1.9 mL) and cooled to −20 °C. Then, dropwise addition of 4.6 mL of 0.5 M phenylmagnesium bromide (2.3 mmol in THF) was effected over 1.25 h to give **13i** (226 mg, 74% yield) as a mixture (*Z*/*E*, 6.5:1) as a pale yellow oil: ^1H NMR ($CDCl_3$) *major isomer* δ 1.50 (bs, exch, 1H), 1.73 (s, 3H), 2.27 (t, 2H, $J = 7.6$ Hz), 2.48 (t, 2H, $J = 7.6$ Hz), 4.30 (d, 2H, $J = 6.1$ Hz), 4.70 (t, 1H, $J = 0.9$ Hz), 4.79 (t, 1H, $J = 0.9$ Hz), 5.74 (tt, 1H, $J = 1.0$ and 6.1 Hz), *minor isomer* δ 1.26 (bs, exch, 1H), 1.76

(s, 3H), 4.11 (d, 2H, *J* = 7.5 Hz), 5.89 (t, 1H, *J* = 7.5 Hz); ^{13}C NMR (u) δ 35.8, 38.1, 60.2, 111.3, 137.2, 144.4, (d) δ 22.8, 125.1; IR (neat) ν 3331, 2936, 1651, 1445, 1375, 1105, 1016, 891, 646 cm^{-1}; MS (EI) *m/z* 160 (M$^+$, 100), 162 (31); HRMS calcd for $C_8H_{13}ClO$ (M$^+$) 160.0655, found 160.0663; TLC R_f = 0.25.

(*Z*)-3-Chloro-2,7-octadien-1-ol (13j). By a procedure similar to that for **9**, epoxide **5** (200 mg, 1.9 mmol) and CuBr/SMe$_2$ (78 mg, 0.38 mmol) were suspended in THF (1.9 mL) and cooled to −20 °C. Then, dropwise addition of 4.6 mL of 0.5 M phenylmagnesium bromide (2.3 mmol in THF) was effected over 1.25 h to give **13j** (266 mg, 87% yield) as a mixture (*Z*/*E*, 13.8:1) as a pale yellow oil: ^{1}H NMR (CDCl$_3$) *major isomer* δ 1.56 (bs, exch, 1H), 1.64 (p, 2H, *J* = 7.4 Hz), 2.03 (dtt, 2H, *J* = 1.3, 6.7, and 7.4 Hz), 2.33 (t, 2H, *J* = 7.4 Hz), 4.28 (d, 2H, *J* = 6.2 Hz), 4.97−5.00 (m, 1H), 5.04 (ddt, 1H, *J* = 1.7, 1.7, and 17.2 Hz), 5.71 (tt, 1H, *J* = 0.9 and 6.2 Hz), 5.77 (ddt, 1H, 6.7, 10.2, and 17.2 Hz), *minor isomer* δ 1.25 (bs, exch, 1H), 2.41 (t, 2H, *J* = 7.4 Hz), 4.14 (d, 2H, *J* = 7.4 Hz); ^{13}C NMR (u) δ 26.2, 32.5, 38.6, 59.7, 115.1, 136.9; (d) δ 124.6, 137.9; IR (neat) 3316, 2935, 1661, 1642, 1433 cm^{-1}; MS (EI) *m/z* 160 (M$^+$, 100), 162 (31); HRMS calcd for $C_8H_{13}ClO$ (M$^+$) 160.0655, found 160.0654; TLC R_f = 0.26.

(*Z*)-3-Chloro-2-hexadecen-1-ol (13k). By a procedure similar to that for **9**, epoxide **5** (200 mg, 1.9 mmol) and CuBr/SMe$_2$ (78 mg, 0.38 mmol) were suspended in THF (1.9 mL) and cooled to −20 °C. Then, dropwise addition of 4.6 mL of 0.5 M phenylmagnesium bromide (2.3 mmol in THF) was effected over 1.25 h to give **13k** (402 mg, 76% yield) as a mixture (*Z*/*E*, 14.5:1) as a pale yellow oil: ^{1}H NMR (CDCl$_3$) *major isomer* δ 0.88 (t, 3H, *J* = 6.8 Hz), 1.26 (s, 22H), 1.55 (bs, exch, 1H), 2.32 (t, 2H, *J* = 7.4 Hz), 4.29 (d, 2H, *J* = 6.2 Hz), 5.72 (t, 1H, *J* = 6.2 Hz), *minor isomer* δ 2.36 (t, 2H, *J* = 7.4 Hz), 4.13 (d, 2H, *J* = 7.4 Hz), t, 1H, *J* = 7.4 Hz); ^{13}C NMR (u) δ 22.92, 27.38, 28.80, 29.56, 29.58, 29.74, 29.85, 29.87, 29.90, 32.14, 39.59, 60.04, 137.77, (d) δ 14.37, 124.41; IR (neat) 3320, 1661, 1466 cm^{-1}; MS (EI) *m/z* 274 (M$^+$, 100), 276 (31); HRMS calcd for $C_{16}H_{31}ClO$ (M$^+$) 274.2063, found 274.2072; TLC R_f = 0.22.

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Supporting Information Available: ^{1}H and ^{13}C spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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