(ca. 2.3:1 **14**/**15**; 87 mg, 0.32 mmol) in 1% H_2SO_4 (acetone–water, 7:1, 10 mL) was stirred at 50 °C for 2 days, and the reaction mixture was diluted with water. The aqueous layer was extracted with ether, and the combined ether extracts were successively washed with water and brine. Concentration of the dried solvent ($MgSO_4$) afforded an oily residue, which was purified by silica gel column chromatography to yield **22** (nearly colorless oil; 36 mg, 55% yield) together with the lactone **23** (nearly colorless oil; 14 mg, 24% yield). For **22**: IR (neat) 3400, 2950, 1720, 1460, 1370, 1315, 1290, 1100, 1070, 980, 870, 820, 770 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.32 (3 H, s), 1.00–3.00 (11 H, m), 3.70 (3 H, s), 4.00–4.35 (1 H, m); mass spectrum, *m/e* 198 (M^+), 180, 166, 148, 139, 121, 101, 95, 93, 80; mass spectrum, *m/e* calcd for **22** ($C_{11}H_{18}O_3$, M^+) 198.1256, found 198.1253. The spectral data of **23** were as follows: IR (neat) 2950, 1725, 1460, 1360, 1160, 1100, 980 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.30 (3 H, s), 1.20–3.00 (10 H, m), 4.70–4.88 (1 H, m); mass spectrum, *m/e* 166, 148, 139, 122, 107; mass spectrum, *m/e* calcd for **23** ($C_{10}H_{14}O_2$, M^+) 166.0994, found 166.0991.

Methyl (1*S,3*S**,5*R**)-3-Methyl-6-oxobicyclo[3.3.0]octane-3-carboxylate (2).** To a stirred suspension of the alcohol **22** (176 mg, 0.9 mmol) and Celite (381 mg) in methylene chloride (5 mL) was added PCC (381 mg, 1.9 mmol) at room temperature. The whole reaction mixture was stirred for 3 h under the same conditions, followed by filtration through a short pad of Florisil. Additional ether was used to rinse the Florisil. The filtrate was concentrated in vacuo to afford an oily residue, which was purified by silica gel column chromatography to yield 2 as a nearly colorless oil: 159 mg (90% yield); IR (neat) 2950, 1720, 1460, 1190, 1160 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.30 (3 H, s), 1.50–3.20 (10 H, m), 3.70 (3 H, s); mass spectrum, *m/e* 196, 168, 164, 151, 140, 137, 109, 96, 93, 81; mass spectrum, *m/e* calcd for **2** ($C_{11}H_{16}O_3$, M^+) 196.1099, found 196.1099.

Acknowledgment. We are grateful to Miwa Sawahata for her technical assistance. We also thank Kazuko Uchida for mass spectrometric measurements.

Registry No. (±)-**1**, 55123-33-6; (±)-**2**, 87419-62-3; (±)-**5a**, 87351-11-9; (±)-**5b**, 87351-12-0; **6**, 87351-13-1; (±)-**10**, 87351-14-2; (±)-**11**, 87351-15-3; (±)-**12**, 87351-16-4; (±)-**14**, 87351-17-5; (±)-**15**, 87351-18-6; (±)-**18**, 87351-19-7; **19**, 87351-20-0; (±)-**20**, 87351-21-1; (±)-**22**, 87351-22-2; (±)-**23**, 87419-63-4.

Synthesis of Two Macrolide Aggregation Pheromones from the Flat Grain Beetle, *Cryptolestes pusillus* (Schönherr)[1]

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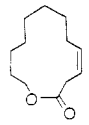
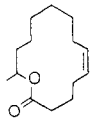
The flat grain beetle, *Cryptolestes pusillus* (Schönherr), is a major world-wide pest of stored grain.[2] We have recently isolated two macrolides (**1** and **2**) from the volatiles and frass of this insect.[3,4] The most abundant macrolide, **1**, is an aggregation pheromone for the flat grain beetle, while the other macrolide, **2**, appears to act as a synergist. We report the stereoselective syntheses of **1** and enantiomers of **2**.

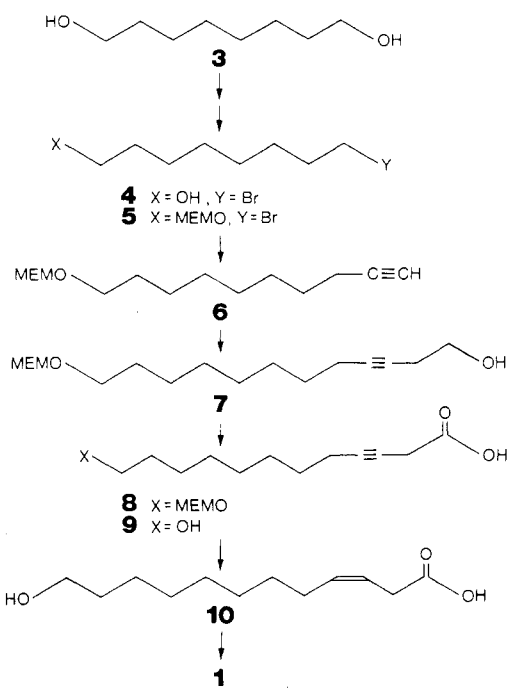


1



2

Scheme I



In the initial structural identification of **1**, there was some uncertainty as to whether the unsaturation was *E* or *Z*. Thus, the synthesis of **1** was designed so that either *E* or *Z* unsaturation could be introduced in one of the last steps, via stereoselective reduction of an alkyne. In the synthesis of **1**, the route as far as intermediate **7** was patterned after that of Maurer and Grieder,[5] who have reported the THP analogue of **7**. Thus, 1,8-octanediol (**3**) was converted to 8-bromo-1-octanol (**4**) with 48% aqueous HBr.[5] The hydroxyl of **4** was protected by reaction with (β-methoxyethoxy)methyl chloride, yielding the (β-methoxyethoxy)methyl ether **5** (Scheme I). Reaction of **5** with lithium acetylide in THF/HMPA[6] gave terminal alkyne **6**, which was converted to the homopropargylic alcohol **7** by sequential reaction with ethyl magnesium bromide and ethylene oxide.[7] Oxidation of **7** with pyridinium dichromate in DMF gave only low yields of the desired β,γ-unsaturated carboxylic acid. Inverse addition[8] of an acetone solution of **7** to Jones reagent at 0 °C gave the β,γ-unsaturated acid **8** in moderate yield, with no detectable hydrolysis of the MEM protecting group. Removal of the MEM protecting group was achieved with THF/H_2O/HCl, conditions which did not isomerize the unsaturation. The resulting hydroxy acid, **9**, was stereoselectively reduced with P-2 nickel[9] to the (*Z*)-β,γ-unsaturated hydroxy acid **10**. Cyclization of **10** to **1** was achieved

(1) This work was presented in part at the combined meeting of the Entomological Societies of America, Canada, and Ontario, November 29–December 3, 1982, in Toronto, and at the Chemical Institute of Canada annual meeting in Calgary, Alberta, June 5–8, 1983.

(2) Barak, A. V.; Harein, P. K. *J. Econ. Entomol.* **1981**, *74*, 197. Mueller, D. K. Insects Unlimited Inc., Indianapolis, IN, personal communication.

(3) The manuscript describing isolation, identification, and bioassay of **1** and **2** is in preparation and will be submitted to the *Journal of Chemical Ecology*.

(4) J.W.W. has also identified **2** in the frass and volatiles of *Cryptolestes ferrugineus* (Stephens).

(5) Maurer, B.; Grieder, A. *Helv. Chim. Acta* **1977**, *60*, 1155.

(6) Beckmann, W.; Doerjer, G.; Logemann, E.; Merkel, C.; Schill, G.; Zurcher, C. *Synthesis* **1975**, 423.

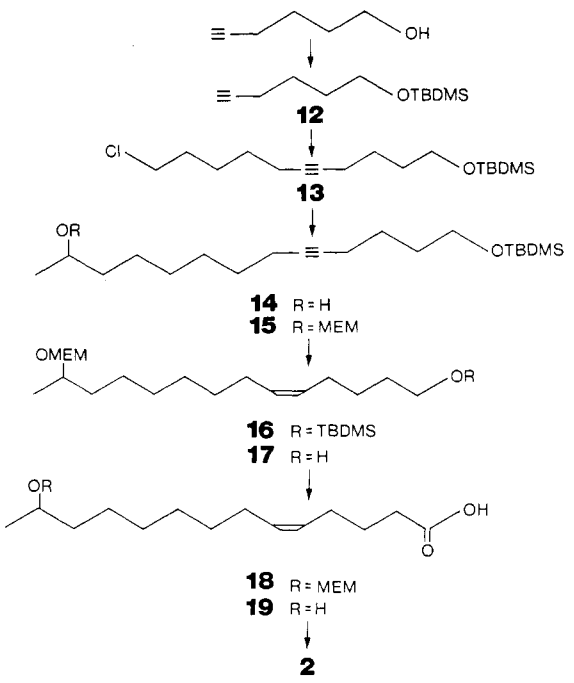
(7) Brandsma, . "Preparative Acetylenic Chemistry", 1st ed.; Elsvier: New York, 1971; p 32.

(8) Holland, B. C.; Gilman, N. W. *Synth. Commun.* **1974**, *4*, 203.

(9) Brown, C. A.; Ahuja, V. K. *J. Chem. Soc., Chem. Commun.* **1973**, 553.

0022-3263/83/1948-4404$01.50/0

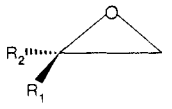
Scheme II



in moderate yield by using the double activation method of Corey.[10] Synthetic 1 was chromatographically and spectrally identical with natural 1, and was of equivalent biological activity.[3]

Attempts to improve the yield in the cyclization step, including changing solvents, rates of addition, and the dilution factor, all met with failure. The addition of catalytic amounts of silver salts, as recommended by Gerlach et al.,[11] also proved fruitless.

The synthetic route to 2 was designed so that a chiral center could be incorporated by using the chiral synthons (*R*)-(+)- and (*S*)-(−)-methyloxirane (11). These synthons



11a $R_1 = CH_3$, $R_2 = H$
11b $R_1 = H$, $R_2 = CH_3$

are available in high enantiomeric purity from ethyl (*S*)-(+)-lactate.[12-14] The synthetic route (Scheme II) was initially developed with racemic methyloxirane and then repeated with the chiral synthons. Thus, the synthesis of 2 commenced with the *tert*-butyldimethylsilyl ether (12) of 5-hexyn-1-ol. The lithium salt of 12 was alkylated with 1-chloro-5-iodopentane[15] to give chloride 13. Stereo- and regiospecific reaction of the Grignard of 13[16] with the appropriate methyloxirane, utilizing cuprous iodide catalysis,[17] gave alcohol 14. Alcohol 14 was protected as the (β-methoxyethoxy)methyl ether 15 and stereoselectively reduced to 16 with P-2 nickel. Selective deprotection of the primary hydroxyl with acetic acid/THF/H_2O (3:1:1), followed by oxidation of the resulting alcohol 17 with pyridinium dichromate in DMF, produced the carboxylic acid 18 in high yield. Removal of the MEM protecting group resulted in hydroxy acid 19. Lactonization of 19 with 2-chloro-*N*-methylpyridinium iodide[19] in acetonitrile gave 2, spectrally and chromatographically identical with natural 2.

The optical purity of the enantiomers of 19, the immediate precursor of 2, was checked by reaction of the methyl ester (CH_2N_2) of each enantiomer with (+)-methoxy(trifluoromethyl)phenylacetyl chloride.[20] The resulting diastereomers gave 400-MHz ^1H NMR spectra in which the 13-methyl groups had chemical shifts differing by 0.05 ppm. In each case, there was only one diastereomer detectable. We estimate the enantiomeric excess of each enantiomer at >90%.[21]

Experimental Section

^1H NMR spectra were recorded on a Varian XL-100 or a Bruker WM400 spectrometer. Mass spectra were obtained by using a Hewlett-Packard 5985B GC/MS/DS system at 70 eV. High-resolution mass spectra were run on an MS-50 at the University of British Columbia. Elemental analyses were performed at Simon Fraser University. GLC analyses were performed on 0.21-mm-i.d. SP2100 or SE-30 capillary columns on a Hewlett-Packard 5880 gas chromatograph. Optical rotations were measured on a Perkin-Elmer P-22 spectropolarimeter (0.5 dm cell) and a Rudolph polarimeter, Model 70 (1.0 dm cell). IR spectra were recorded with a Perkin-Elmer 599B infrared spectrometer.

Tetrahydrofuran was dried by distillation from lithium tetrahydridoaluminate. Hexamethylphosphoric triamide was distilled from calcium hydride. Acetylene was purified by passage through a cold trap (−78 °C) and through traps loaded with NaOH pellets and alumina (activity I).

Flash chromatography was performed by the method of Still[22] with 40–63-μm silica gel (E. Merck No. 9385).

Synthesis of Macrolide 1. Preparation of 1-[(2-Methoxyethoxy)methoxy]-8-bromooctane (5). 8-Bromo-1-octanol (4) was prepared from 1,8-octanediol (Aldrich Chemical Co., Inc.) via the method of Maurer and Grieder.[5]

Diisopropylethylamine (48.9 g, 380 mmol) and freshly distilled (β-methoxyethoxy)methyl chloride (47.0 g, 380 mmol) were stirred in 500 mL of dry methylene chloride at 0 °C. 8-Bromo-1-octanol (51.5 g, 246 mmol) was added dropwise over 30 min. The solution was stirred overnight at room temperature and extracted with water (2 × 300 mL). The organic layer was dried over anhydrous $MgSO_4$, concentrated, and vacuum distilled to give 5: 55.7 g (76%); bp 118–125 (0.35 mmHg); ^1H NMR ($CDCl_3$) δ 1.25–1.65 (m, 10 H), 1.75–1.95 (m, 2 H), 3.39 (t, J = 6.5 Hz, 2 H), 3.39 (s, 3 H), 3.45–3.74 (m, 6 H), 4.69 (s, 2 H); mass spectrum, *m/e* (relative intensity) 297 (2), 295 (2), 223 (9), 221 (10), 137 (9), 89 (80).

Preparation of 1-[(2-Methoxyethoxy)methoxy]-9-decyne (6). Alkyne 6 was prepared in 88% yield [bp 105–111 °C (0.3 mmHg)] via the standard procedure of Beckmann et al.:[6] IR (film)

(10) Corey, E. J.; Nicolau, K. C. *J. Am. Chem. Soc.* **1974**, *96*, 5614. Corey, E. J. Nicolau, K. C.; Melvin, L. S. *Ibid.* **1975**, *97*, 653. Corey, E. J.; Nicolau, K. C.; Tora, T. *Ibid.* **1975**, *97*, 2287. Corey, E. J. Ulrich, P.; Fitzpatrick, J. M. *Ibid.* **1976**, *98*, 222.

(11) Gerlach, H.; Oertle, K.; Thalmann, A. *Helv. Chim. Acta* **1976**, *59*, 755.

(12) (*S*)-(−)-Methyloxirane: Seuring, B.; Seebach, D. *Helv. Chim. Acta* **1977**, *60*, 113.

(13) Johnston, B. D.; Slessor, K. N. *Can. J. Chem.* **1979**, *57*, 233.

(14) The method of Johnston and Slessor for production of (*R*)-(+)-methyloxirane[13] gave low yields of impure product. Thus, the improved procedure of Hillis and Ronald was used in later work. Hillis, L. R.; Ronald, R. C. *J. Org. Chem.* **1981**, *46*, 3348.

(15) Ahmad, K.; Bumpus, F. M.; Strong, F. M. *J. Am. Chem. Soc.* **1948**, *70*, 1699.

(16) It was essential to pass distilled 13 through a short column of silica gel, eluting with petroleum ether (bp 30–60 °C), before attempting to form the Grignard. This procedure removed traces of moisture and silyl alcohols.

(17) Huynh, C.; Derguini-Boumechal, F.; Linstrumelle, G. *Tetrahedron Lett.* **1979**, *17*, 1503.

(18) Corey, E. J.; Gras, J.-L.; Ulrich, P. *Tetrahedron Lett.* **1976**, *11*, 809.

(19) Mukaiyama, T.; Vsui, M.; Saigo, K., *Chem. Lett.* **1976**, 49.

(20) Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543.

(21) Experiments to determine chiral purity of the enantiomers of 2 with chiral NMR shift reagents resulted in minimal resolution of the 13-methyl groups (~2 Hz), with considerable line broadening.

(22) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

3305, 2130 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.25–1.65 (m, 12 H), 1.92 (t, 1 H, J = 1.5 Hz), 2.16 (td, 2 H, J = 6, 2.5 Hz), 3.37 (s, 3 H), 3.45–3.74 (m, 6 H), 4.68 (s, 2 H); mass spectrum, m/e (relative intensity) 241 (2), 105 (89), 89 (100), 81 (98), 59 (95). Anal. Calcd for $C_{14}H_{26}O_3$: C, 69.39; H, 10.81. Found: C, 69.44; H, 10.98.

Preparation of 12-[(2-Methoxyethoxy)methoxy]-3-dodecyn-1-ol (7). Alkynol 7 was prepared via the reaction sequence used by Maurer and Grieder[5] to make the THP analogue of 7. However, since high-vacuum distillation of a small sample resulted in extensive decomposition, crude 7 was used in the subsequent reaction. An analytical sample of 7 was purified by TLC (hexane/EtOAc, 1:1): IR (film) 3450, 2268, 1055 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.25–1.65 (m, 12 H), 2.05–2.28 (m, 3 H), 2.42 (tt, 2 H, J = 6.3, 2.5 Hz), 3.38 (s, 3 H), 3.45–3.74 (m, 8 H), 4.69 (s, 2 H); mass spectrum, m/e (relative intensity) 227 (100), 211 (34), 197 (45), 105 (47), 89 (77). Anal. Calcd for $C_{16}H_{30}O_4$: C, 67.10; H, 10.56. Found: C, 67.29; H, 10.40.

Preparation of 12-[(2-Methoxyethoxy)methoxy]-3-dodecynoic Acid (8). A solution of chromium trioxide (6.25 g, 62.5 mmol) in 1.5 M H_2SO_4 (100 mL, 150 mmol) was maintained between 5 and 10 °C while 4.76 g (~16.6 mmol) of 7 in acetone (200 mL) was added over 6 h. The mixture was stirred another 2 h at room temperature. Ether (150 mL) was added, and the mixture was extracted with brine (3 × 150 mL). The organic phase was concentrated under reduced pressure without heating and then taken up in ether (100 mL). The ethereal solution was extracted with 1 M NaOH (2 × 75 mL). The combined basic extracts were acidified with 6 M H_2SO_4 and back-extracted with ether (3 × 75 mL). The combined ether extracts were washed with water and brine, dried over anhydrous $MgSO_4$, and concentrated. Final purification was accomplished by flash chromatography on silica gel (20 cm × 5 cm i.d.) eluted with hexane/EtOAc/AcOH (60:40:1), yielding 3.34 g (67%) of 8, which solidified upon refrigeration: IR (film) 3500–2800, 2258, 1718 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.2–1.8 (m, 12 H), 2.06–2.50 (m, 2 H), 3.26 (t, 2 H, J = 2 Hz), 3.40 (s, 3 H), 3.44–3.78 (m, 6 H), 4.71 (s, 2 H), 5.41 (br s, 1 H); mass spectrum of the methyl ester (CH_2N_2), m/e (relative intensity) 255 (1), 89 (45), 59 (100).

Preparation of 12-Hydroxy-3-dodecynoic Acid (9). The MEM-protected hydroxy acid 8 (3.4 g, 12.2 mmol) was stirred at room temperature for 48 h in a mixture of THF/H_2O/concentrated HCl (12:2:1). Ether (200 mL) was added and the mixture was washed with brine (2 × 150 mL), dried over anhydrous $MgSO_4$, and concentrated in vacuo to yield 2.23 g (93%) of 9 as a waxy solid, which was used without further purification. An analytical sample was purified by flash chromatography, eluting with hexane/EtOAc/AcOH (60:40:1): IR (film) 3700–2400, 2260, 1727 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.20–1.90 (m, 12 H), 2.06–2.3 (m, 2 H), 3.28 (dt, 2 H, J = 7, 2.5 Hz), 4.13 (t, 2 H, J = 6.5 Hz), 5–6 (br s, 2 H); mass spectrum of the methyl ester (CH_2N_2), m/e (relative intensity) 226 (1), 194 (3), 93 (88), 81 (90), 79 (100), 67 (86); high-resolution mass spectrum calcd for $C_{12}H_{20}O_3$ m/e 212.1412, obsd 212.1420.

Preparation of 12-Hydroxy-(*Z*)-3-dodecenoic Acid (10). P-2 nickel (6 mmol) was prepared as described by Brown and Ahuja[9] and used to reduce alkyne 9 (2.9 g, 13.7 mmol) to the *Z* olefin 10. However, the workup was modified as follows. Charcoal was added to the reaction mixture, and the suspension was filtered through glass-fiber filter paper. The filtrate was concentrated under reduced pressure, and the residue was partioned between water (50 mL) and ether (100 mL). The mixture was acidified with 6 M H_2SO_4, the ether was decanted, and the aqueous portion was extracted with ether (2 × 50 mL). The combined ether extracts were washed with brine, dried over anhydrous $MgSO_4$, and concentrated. The concentrate was purified by flash chromatography on silica gel (20 cm × 5 cm i.d.), eluting with hexane/EtOAc/AcOH (100:50:1) to give 2.55 g (87%) of hydroxy acid 10, which solidified upon refrigeration: IR (film) 3700–2300, 1716 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.15–1.75 (m, 12 H), 1.9–2.1 (m, 2 H), 3.09 (d, 2 H, J = 5.5 Hz), 3.64 (t, 2 H, 6.5 Hz), 5.2–5.5 (br s, 2 H), 5.58 (m, 2 H); mass spectrum, m/e (relative intensity) 196 (19), 178 (10), 81 (86), 67 (100), 55 (86). Anal. Calcd for $C_{12}H_{22}O_3$: C, 67.26; H, 10.35. Found: C, 67.14; H, 10.43.

Preparation of (*Z*)-3-Dodecenolide (1). The intermediate pyridyl thioester of 10 was formed by adding hydroxy acid 10 (100.5 mg, 0.47 mmol) to a stirred solution of 2,2′-dipyridyl disulfide (220 mg, 1 mmol) and triphenylphosphine (262 mg, 1 mmol) in dry, deoxygenated xylene (10 mL) under argon. The mixture was stirred for 1 hr at room temperature and then transferred to a dropping funnel and diluted with xylene (200 mL). This solution was added dropwise over 8 h to refluxing xylene (150 mL). Refluxing was continued for 1 h after the addition was complete, and the xylene was removed at reduced pressure. The remaining oil was flash chromatographed on silica gel (12 cm × 2.5 cm i.d.), eluting with hexane/EtOAc (40:1) to yield 30.8 mg (33%) of an oil (98% pure by capillary GLC). This material was identical spectrally and chromatographically with 1, isolated from *C. pusillus*: IR (film) 1735 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.21–1.32 (m, 6 H), 1.32–1.46 (m, 4 H), 1.57–1.66 (m, 2 H), 2.05–2.12 (m, 2 H), 2.99–3.06 (m, 2 H), 4.03–4.08 (t, 2 H, J = 5 Hz), 5.45–5.56 (m, 2 H); mass spectrum, m/e (relative intensity) 196 (6), 178 (5), 81 (76), 67 (100), 54 (91). Anal. Calcd for $C_{12}H_{20}O_2$: C, 73.43; H, 10.27. Found: C, 73.80; H, 10.18.

Synthesis of Macrolide 2. (*R*)-(+)-Methyloxirane was made in 48% yield from (*S*)-(+)-ethyl lactate via the method of Hillis and Ronald;[13] $[\alpha]^{21}_D$ +12.1° (neat).[12] (*S*)-(−)-Methyloxirane was prepared in 36% yield by the procedure of Seuring and Seebach;[12] $[\alpha]^{23}_D$ −14.1° (neat). In the following synthetic procedure, the appropriate chiral or racemic methyloxirane was used at the appropriate step. Yields and procedures reported are for the synthesis of the (*S*)-(+)-2 and were similar for the parallel procedures leading to (*R*)-(−)-2 and racemic 2.

Preparation of 2-(*tert*-Butyldimethylsiloxy)-11-chloro-5-undecyne (13). Alkyne 12 was prepared quantitatively from 5-hexyn-1-ol (Farchan Laboratories, Albany International) by treatment with *tert*-butyldimethylsilyl chloride, following the standard procedure. To a solution of alkyne 12 (26.5 g, 125 mmol) and a few crystals of triphenylmethane in 250 mL of dry THF, cooled to −40 °C, was added 62 mL (130 mmol) of 2.1 M *n*-BuLi in hexane. The solution was allowed to warm to 0 °C over 20 min and then cooled again to −40 °C. Dry HMPA (100 mL) was added, followed by dropwise addition of 1-chloro-5-iodopentane (29.3 g, 126 mmol). The solution was warmed to room temperature over 6 h, stirred overnight, and then poured into water (500 mL). The product was extracted with ether (3 × 150 mL). The combined ether extracts were back-washed with 5% aqueous sodium thiosulfate, water, and brine, dried over anhydrous $MgSO_4$, concentrated, and vacuum distilled to give 13: 29.9 g (76%); bp 115–125 (0.05 mmHg); IR (film) 2160, 1100 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.05 (s, 6 H), 0.90 (s, 9 H), 1.37–1.93 (m, 10 H), 2.03–2.41 (m, 4 H), 3.55 (t, 2 H, J = 6.5 Hz), 3.63 (t, 2 H, J = 5.5 Hz); mass spectrum, m/e (relative intensity) 261 (3), 259 (11), 149 (21), 107 (45), 93 (100). Anal. Calcd. for $C_{17}H_{33}OSiCl$: C, 64.41; H, 10.49. Found: C. 64.09; H, 10.61.

Preparation of (13*S*)-1-(*tert*-Butyldimethylsiloxy)-5-tetradecyn-13-ol ((13*S*)-14). Chloride 13 was washed through a short column of silica gel with petroleum ether immediately before use to remove traces of moisture and silyl alcohol. The resulting oil was coverted to the Grignard reagent as follows. Dry THF (50 mL) and magnesium turnings (6.1 g, 250 mmol) were stirred under argon. 1,2-Dibromoethane (~1 mL) was added, and after the exothermic reaction subsided, additional dry THF (50 mL) was added. Chloride 13 (37.5 g, 118 mmol) was added, first as a 5-mL aliquot and then dropwise over 4 h under reflux. Six further 1-g portions of Mg turnings were added at intervals during this time. Reflux was continued for 1 h after the addition was complete. The mixture was cooled to room temperature and the liquid portion transferred under argon to a dry flask. The remaining solids were washed with dry THF (25 mL), and the washings were transferred. The resulting solution was cooled to −30 °C, purified CuI[23] (1.7 g, 9 mmol) was added, and the solution was stirred for 15 min. A solution of (*S*)-(−)-methyloxirane ((*S*)-11; 7.54 g, 130 mmol) in dry THF (20 mL) was added dropwise over 30 min. The reaction mixture was slowly warmed to room temperature over 6 h, stirred overnight, and poured into cold saturated NH_4Cl solution (400 mL). The mixture was extracted with ether (3 × 200 mL), and the combined ether extracts were washed with brine, dried over anhydrous $MgSO_4$, and concentrated to yield (13*S*)-14 (30.3, 76% crude yield), which was used without further

(23) Linstrumelle, G.; Krieger, J. K.; Whitesides, G. M. *Org. Synth.* **1976**, *55*, 103.

purification. An analytical sample was purified by flash chromatography on silica gel (15 cm × 2.5 cm i.d.) eluted with hexane/EtOAc (9:2): IR (film) 3340, 1100 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.05 (s, 6 H), 0.90 (s, 9 H), 1.18 (d, 3 H, J = 5.5 Hz), 1.23–1.65 (m, 14 H), 1.95 (br s, 1 H), 2.10–2.20 (m, 4 H), 3.62 (t, 2 H, J = 6.5 Hz), 3.75–3.85 (m, 1 H); mass spectrum, m/e (relative intensity) 283 (17), 189 (10), 95 (78), 75 (100), 45 (52); high-resolution mass spectrum calcd for $C_{20}H_{40}O_2Si$ m/e 340.2797, obsd 340.2785; $[\alpha]^{31}_D$ + 3.6° (c 1.82, $CHCl_3$).

Preparation of (13*S*)-13-[(2-Methoxyethoxy)methoxy]-(*Z*)-5-tetradecen-1-ol ((13*S*)-17). The hydroxyl function of (13*S*)-**14** was protected as the MEM ether, via standard procedures.[18] The crude product was flash chromatographed in three batches on silica gel (20 cm × 5 cm i.d.) eluted with hexane/EtOAc (9:1), giving (13*S*)-**15**: 14.8 g (78%); IR (film) 1100, 1039 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.05 (s, 6 H), 0.90 (s, 9 H), 1.16 (d, 3 H, J = 5.5 Hz), 1.23–1.65 (m, 14 H), 2.10–2.20 (m, 4 H), 3.40 (s, 3 H), 3.53–3.60 (m, 2 H), 3.63 (t, 2 H, J = 6.5 Hz), 3.68–3.75 (m, 3 H), 4.73 (d, 1 H, J = 7.5 Hz), 4.79 (d, 1 H, J = 7.5 Hz); $[\alpha]^{31}_D$ +4.8° (c 4.94, $CHCl_3$). Anal. Calcd for $C_{24}H_{48}O_4Si$: C, 67.24; H, 11.29. Found: C, 67.29; H, 11.48.

P-2 nickel (1 mmol) was used to reduce alkyne (13*S*)-**15** (9.85 g, 23 mmol) via the published method.[9] The product (13*S*)-**16** (9.9 g, 100%, >98% pure by GLC) was used without further purification: IR (film) 1100, 1039 cm^{-1}; ^1H NMR (C_6D_6) δ 0.13 (s, 6 H), 1.05 (s, 9 H), 1.19 (d, 2 H, J = 5.5 Hz), 1.26–1.70 (m, 14 H), 2.09–2.19 (m, 4 H), 3.2 (s, 3 H), 3.34 (t, 2 H, J = 5.5 Hz), 3.61 (t, 2 H, J = 6.5 Hz), 3.70–3.80 (m, 3 H), 4.74 (d, 1 H, J = 7.5 Hz), 4.79 (d, 1 H, J = 7.5 Hz), 5.5–5.55 (m, 2 H); mass spectrum (CI, isobutane), m/e 431 (P + 1); high-resolution mass spectrum calcd for $C_{24}H_{50}O_4Si$ m/e 430.3478, obsd 430.3460; $[\alpha]^{33}_D$ +4.7° (c 4.17, $CHCl_3$).

Crude (13*S*)-**16** (9.4 g, 22 mmol) was stirred at room temperature for 24 h in 100 mL of AcOH/THF/H_2O (3:1:1). The solution was concentrated under reduced pressure, and the silanol removed by pumping under high vacuum (0.1 mmHg) for 12 h at 40 °C. The resulting (13*S*)-**17** (6.9 g, 100%, >95% pure by GLC) was used without further purification: IR (film) 3420, 1100, 1038 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.15 (d, 3 H, J = 5.5 Hz), 1.25–1.48 (m, 10 H), 1.49–1.64 (m, 4 H), 1.98–2.10 (m, 5 H), 3.40 (s, 3 H), 3.57 (t, 2 H, J = 5.5 Hz), 3.65 (t, 2 H, J = 6.5 Hz), 3.68–3.75 (m, 3 H), 4.72 (d, 1 H, J = 7.5 Hz), 4.78 (d, 1 H, J = 7.5 Hz), 5.30–5.40 (m, 2 H); $[\alpha]^{34}_D$ +6.5° (c 2.31, $CHCl_3$). Anal. Calcd for $C_{18}H_{36}O_4$: C, 68.31; H, 11.47. Found: C, 68.19; H, 11.29.

Preparation of (13*S*)-13-[(2-Methoxyethoxy)methoxy]-(*Z*)-5-tetradecenoic Acid ((13*S*)-18). Alcohol (13*S*)-**17** was oxidized to (13*S*)-**18** (95%, >90% pure by GLC of the methyl ester (CH_2N_2)) with pyridinium dichromate in DMF, following the normal procedure.[18] An analytical sample was further purified by flash chromatography on silica gel (15 cm × 2.5 cm i.d.), eluting with hexane/EtOAc/AcOH (100:20:1): IR (film) 3550–2200, 1729 cm^{-1}; ^1H NMR (C_6H_6) δ 1.18 (d, 3 H, J = 5.5 Hz), 1.32–1.52 (m, 10 H), 1.58–1.72 (m, 4 H), 2.00–2.15 (m, 4 H), 2.19 (t, 2 H, J = 7.0 Hz), 3.20 (s, 3 H), 3.43 (t, 2 H, J = 4.5 Hz), 3.65–3.82 (m, 3 H), 4.77 (d, 1 H, J = 7.5 Hz), 4.81 (d, 1 H, J = 7.5 Hz), (br s, 1 H); high-resolution mass spectrum, calcd for $C_{18}H_{33}O_5$ (P − 1) 329.2328, obsd 329.2335; $[\alpha]^{33}_D$ +7.2° (c 3.33, $CHCl_3$).

Preparation of (13*S*)-13-Hydroxy-(*Z*)-5-tetradecenoic Acid ((13*S*)-19). Deprotection of (13*S*)-**18** (6.37 g, 19 mmol) was carried out as described for **9**. Purification by flash chromatography on silica gel (20 cm × 5 cm i.d.) with hexane/EtOAc/AcOH (75:25:1) yielded (13*S*)-**19** (3.34 g, 72%) as a colorless oil: IR (film) 3600–2300, 1711 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.22 (d, 2 H, J = 5.5 Hz), 1.25–1.57 (m, 10 H), 1.73 (quintet, 2 H, J = 6 Hz), 1.98–2.10 (m, 2 H), 2.10–2.18 (m, 2 H), 2.38 (t, 2 H, J = 7.0 Hz), 3.82–3.90 (m, 1 H), 5.30–5.38 (m, 1 H), 5.42–5.50 (m, 1 H), 7.0–7.5 (br s, 2 H); mass spectrum of the methyl ester (CH_2N_2), m/e (relative intensity) 238 (3.5), 81 (100), 67 (94), 55 (83), 45 (72); high-resolution mass spectrum, calcd for $C_{14}H_{26}O_3$ m/e 242.1882, obsd 242.1880; $[\alpha]^{32}_D$ +4.9° (c 4.06, $CHCl_3$).

Preparation of (13*S*)-13-Methyl-(*Z*)-5-tridecenolide ((13*S*)-2). A solution of 2-chloro-*N*-methylpyridinium iodide (4.2 g, 17 mmol) in dry acetonitrile (250 mL) was heated to reflux under argon. A solution of (13*S*)-**19** (1.0 g, 4.1 mmol) and triethylamine (3.4 g, 34 mmol) in dry acetonitrile (250 mL) was added dropwise over 6 h. The resulting solution was refluxed a further 2 h, cooled, and concentrated. The concentrate was poured into water (100 mL) and extracted with pentane (3 × 50 mL). The combined pentane extracts were washed with water, dried over anhydrous $MgSO_4$, and concentrated. The resulting product was flash chromatographed on silica gel (18 cm × 2.5 cm i.d.), eluting with hexane/EtOAc (40:1) to give (13*S*)-**2** (494 mg, 49%). This (13*S*)-**2** was spectrally and chromatographically identical with **2** isolated from *C. pusillus*: IR (film) 1725, 1248, 1216 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.23 (d, 2 H, 5.5 Hz), 1.25–1.68 (m, 13 H), 1.70–1.78 (m, 1 H), 1.78–1.98 (m, 2 H, 2.17–2.37 (m, 2 H), 2.23 (ddd, 1 H), J = 2.5, 9, 15 Hz), 2.44 (ddd, 1 H, J = 2.5, 9, 15 Hz), 4.94–5.03 (m, 1 H), 5.33 (td, 1 H, J = 4.5, 10.5 Hz), 5.40 (td, 1 H, J = 4.5, 10.5 Hz); mass spectrum, m/e (relative intensity) 224 (9.1), 81 (94.5), 67 (91.5), 55 (77.1), 41 (100); high-resolution mass spectrum, calcd for $C_{14}H_{24}O_2$ m/e 224.1776, obsd 224.1776; (13*S*)-(+)-**2**, $[\alpha]^{32}_D$ +49.6° (c 4.62, $CHCl_3$); (13*R*)-(−)-**2**, $[\alpha]^{35}_D$ −46.4° (c 2.19, $CHCl_3$).

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Registry No. **1**, 87371-99-1; (*S*)-(+)-**2**, 87420-69-7; (*R*)-(−)-**2**, 87420-70-0; (±)-**2**, 77761-59-2; **3**, 629-41-4; **4**, 50816-19-8; **5**, 87372-00-7; **6**, 87372-01-8; **7**, 87372-02-9; **8**, 87372-03-0; **9**, 87372-04-1; **10**, 87372-05-2; **10** pyridylthio ester, 87372-06-3; **11b**, 16088-62-3; **12**, 73448-13-2; **13**, 87372-07-4; (*S*)-**14**, 87372-08-5; (*S*)-**15**, 87372-09-6; (*S*)-**16**, 87372-10-9; (*S*)-**17**, 87372-11-0; (*S*)-**18**, 87372-12-1; (*S*)-**19**, 87420-71-1; lithium acetylide, 1111-64-4; ethylene oxide, 75-21-8; 5-hexyn-1-ol, 928-90-5; 1-chloro-5-iodopentane, 60274-60-4.

Lithium Bromide Catalyzed Homologation of Aldehydes with Aryldiazomethanes

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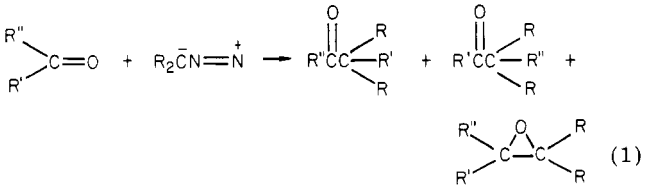
In the course of an investigation of the reaction of organolithium compounds with *N*-nitrosoformamides,[1] the beneficial effect of lithium bromide on stereoselective dimerization of aryldiazomethanes to *cis*-stilbenes and on the homologation of aromatic aldehydes with phenyldiazomethane was observed.[2,3] The present paper describes a more detailed study of the latter reaction.[4]

Although the homologation of carbonyl compounds with diazoalkanes can be useful for the elaboration of carbon–carbon bonds, epoxide formation as well as the possible generation of the isomeric homologated product may detract from its usefulness (eq 1).[4] Lewis acids and aliphatic



(1)

alcohols have been shown to be valuable in promoting homologation though the various factors that may affect

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