mmol) in CH_2Cl_2 (5 mL), and the mixture was stirred for 1 h. The cooling bath was removed and stirring was continued for 12 h. The reaction mixture was washed successively with water and 5% aqueous $NaHCO_3$ solution. The organic layer was dried (Na_2SO_4) and concentrated to give 150 mg (94%) of hydrangenol (**10a**), mp 181–182 °C (PhH) [lit.[27] mp 181 °C], which was shown to be identical with an authentic sample by comparison of the spectral data (IR, NMR, MS) (Table II).[20]

3-(4-Methoxyphenyl)-8-hydroxy-3,4-dihydroisocoumarin (10b). A mixture of hydrangenol dimethyl ether (**9a**) (0.1 g, 0.35 mmol) and aluminum chloride (0.1 g, 0.75 mmol) in nitrobenzene (5 mL) was heated at 80 °C for 1 h. The mixture was subjected to steam distillation to remove nitrobenzene and the residue was chromatographed ($CHCl_3$ eluent) to give material, which upon crystallization (MeOH) furnished 10 mg (30%) of **10b**, mp 120–123 °C (MeOH) [lit.[27] mp 122–123 °C].

Phyllodulcin (10c). A stirred solution of phyllodulcin benzyl methyl ether (**9b**) (200 mg, 0.5 mmol) in CH_2Cl_2 (50 mL) at −78 °C was treated with a solution of BBr_3 (0.1 mL, 1 mmol) in CH_2Cl_2 (5 mL) by dropwise addition. The mixture was stirred for 1 h, and after removal of the cooling bath, stirring was continued for an additional 12 h. The mixture was processed as described for the preparation of **10a** to give 60 mg (45%) of phyllodulcin (**10c**), mp 128–130 °C (Et_2O–hexane) [lit.[14d] mp 130–132 °C] whose identity was established by spectral comparison (IR, NMR, MS) (Table II) with an authentic sample.[20]

2-(Diethylcarbamoyl)-4′-methoxystilbene (5). A solution of amide alcohol **3a** (1.06 g, 3.24 mmol) and *p*-toluenesulfonic acid (300 mg) in toluene (50 mL) was refluxed for 8 h. After washing with two portions of 5% aqueous $NaHCO_3$ solution, the organic layer was dried (Na_2SO_4) and evaporated to dryness to give 0.5 g (50%) of **5**: bp 206 °C (0.6 mm); IR (KBr) ν_{max} 1610 cm^{-1}; UV (EtOH) λ_{max} (log ϵ) 228 (3.97), 324 (3.84); NMR ($CDCl_3$) δ 0.90 (t, 3 H, J = 7 Hz), 1.27 (t, 3 H, J = 7 Hz), 3.00 (q, 2 H, J = 7 Hz), 3.43 (q, 2 H, J = 7 Hz), 3.67 (s, 3 H), 6.47–7.60 (m, 10 H); MS, m/e 309 (M^+).

2-(Diethylcarbamoyl)-3,4′-dimethoxystilbene. Following the procedure described for the preparation of **5**, **8a** was converted into the title compound in 82% yield: bp 145–150 °C (0.02 mm); IR (neat) ν_{max} 1625 cm^{-1}; NMR ($CDCl_3$) δ 0.99 (t, 3 H, J = 7.1), 1.30 (t, 3 H, J = 7.1), 3.10 (q, 2 H, J = 7.1), 3.50 (q, 2 H, J = 7.1), 3.81 (s, 6 H, 2 × CH_3), 6.72–7.48 (m, 9 H); MS, m/e 339 (M^+). Anal. ($C_{21}H_{25}NO_3$) C, H, N.

Acknowledgment. We are indebted to Professor M. Yamato for providing spectral data of (±)-hydrangenol and (±)-phyllodulcin. Financial support from NSERC of Canada to V.S. is gratefully acknowledged. We are indebted to the J. P. Bickell Foundation for a grant, which was crucial to the operation of our GC and HPLC equipment.

Registry No. **2a**, 2728-04-3; **3a**, 88430-92-6; **4a**, 37568-81-3; **4b**, 81428-86-6; **4c**, 85164-36-9; **4d**, 2674-44-4; **4e**, 88430-93-7; **4f**, 88430-94-8; **4g**, 88430-95-9; **5**, 88430-96-0; **6a**, 51674-10-3; **6b**, 3400-35-9; **6c**, 7291-34-1; **7a**, 88430-97-1; **7b**, 82780-48-1; **8a**, 88430-98-2; **9a**, 88430-99-3; **9b**, 88431-00-9; **10a**, 480-47-7; **10b**, 52213-49-7; **10c**, 480-46-6; 3-[phenyl(methyloxy)]-4-methoxybenzaldehyde, 6346-05-0; 2-(diethylcarbamoyl)-3-methoxybenzyl 4-methoxyphenyl ketone, 88431-01-0; 2-(diethylcarbamoyl)-3,4-dimethoxystilbene, 88431-02-1; furfural, 98-01-1; 3-formylthiophene, 498-62-4; methyl *p*-methoxybenzoate, 121-98-2; *p*-$MeOC_6H_4CHO$, 123-11-5; *m*-$MeOC_6H_4CHO$, 591-31-1; *o*-$MeOC_6H_4CHO$, 135-02-4; C_6H_5CHO, 100-52-7.

Supplementary Material Available: Table of combustion analyses for compounds **7a**, **7b**, **3a**, **4a–g**, **9a**, **9b**, and **3b** (1 page). Ordering information is given on any current masthead page.

(27) (a) Asahina, Y.; Asano, J. *Chem. Ber.* **1930**, *63*, 429. (b) Asahina, Y.; Asano, J. *Ibid.* **1930**, *63*, 2059.

Synthetic Studies on Cembranolides. Stereoselective Synthesis of Epoxy Ester Intermediates

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A stereorational synthesis of the epimeric epoxy esters **17** and **21** from methacrolein is described. The route employs two key stereodirected steps. The first, copper-catalyzed addition of vinylmagnesium bromide to conjugated lactone **7**, gives the trans product **8**. The second, iodolactonization of the derived diesters **11** or **12**, leads to the trans lactones **16b** or **16c**. Basic methanolysis then gives the epoxides **17b** or **17c**. The latter is converted to the epimeric epoxy ester **21** via selective saponification, treatment with acid, mesylation, and basic methanolysis. Additions of isopropenylcopper reagents to epoxy esters **17a–d** and a model epoxy ester **22** were examined with a view toward a proposed cembranolide synthetic plan.

We recently formulated a synthetic plan for cembranolide natural products that entails coupling of two complex synthons, a "diene piece" II and a "lactone piece" III (Scheme I).[1] The lactone piece was prepared with 4-cycloheptenone as the starting material.[1] However, all attempts to couple the monotosylate derivative IV with various organocopper reagents were unsuccessful.[2] Under forcing conditions with HMPA as cosolvent, an interesting rearrangement took place leading to epoxy lactone V, but still no coupling product could be detected.[2]

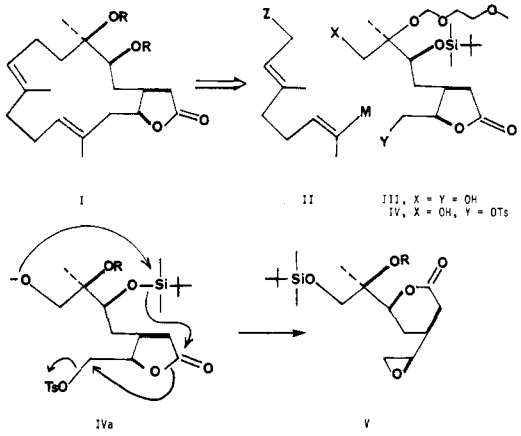
While we were unable to isolate any other products that might provide a clue for the apparent failure of such coupling experiments, we felt that at least part of the problem might be ascribed to the multiple oxygen sites present in tosylate IV and epoxide V that could coordinate with and deactivate the organocopper reagents. We also found it difficult to produce large quantities of lactone diol III, owing to the inefficient and capricious preparation of 4-cycloheptenone.[3] We therefore decided to modify our

(1) Marshall, J. A.; Royce, R. D., Jr. *J. Org. Chem.* **1982**, *47*, 693–8.
(2) Royce, R. D., Jr. "Synthetic Efforts Toward Crassin Acetate", Ph.D. Dissertation, Northwestern University, Evanston, IL, 1982, pp 93–103.

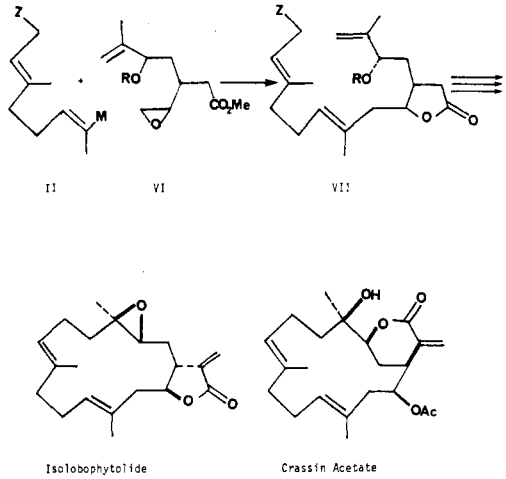
(3) Wilson, S. R.; Wiesler, D. P. *Synth. Commun.* **1980**, *10*, 339–44. We are indebted to Professor Wilson for helpful advice on the preparation of enone **5**.

0022-3263/84/1949-0747$01.50/0

Scheme I



Scheme II



Isolobophytolide Crassin Acetate

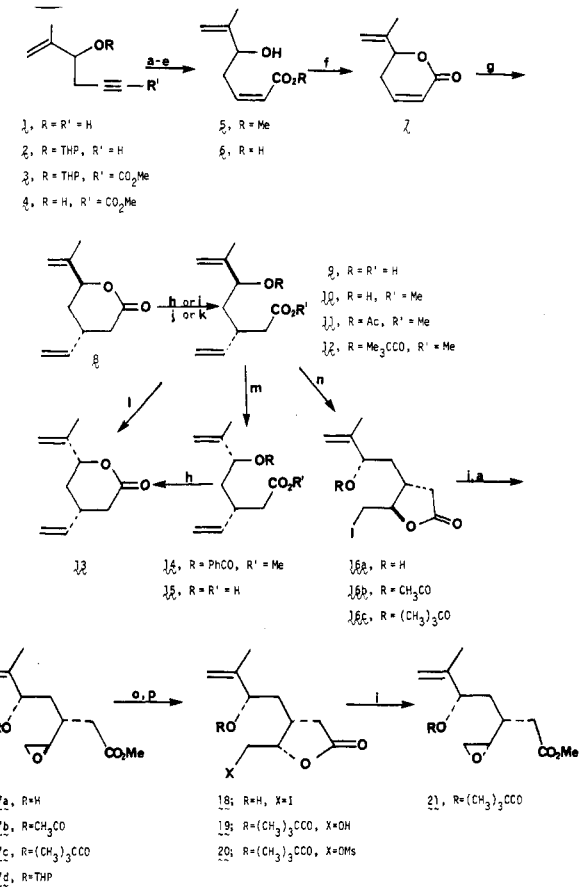
synthetic plan utilizing a leaner version (VI) of the "lactone piece" (Scheme II). In this report we describe (1) a stereoselective route to various epoxy esters related to VI and (2) the addition of isopropenylcopper reagents to such epoxy esters.

Our starting material for these studies, lactone **7**, was prepared from methacrolein by a route (Scheme III) recently described by Pirkle for the methyl, pentyl, and tridecyl analogues.[4] Addition of propargylmagnesium bromide followed by protection of the alcohol adduct led to the tetrahydropyranyl ether **2**. Carbomethoxylation of **2**, via the lithio derivative, and methanolysis of the tetrahydropyranyl ether afforded the hydroxy ester **4**. This was partially hydrogenated and saponified to give the hydroxy acid **6**. Lactonization was readily effected with aqueous acid to afford lactone **7** in greater than 70% overall yield from alcohol **1**.

Copper-catalyzed addition of vinylmagnesium bromide to lactone **7** proceeded smoothly to give the adduct **8** in 85% yield as a single stereoisomer. Pirkle found that the addition of methyl- and benzylcopper reagents to the analogous lactones also led to the trans products, most likely via axial attack on the conjugated lactone double bond.[4]

The isomeric cis lactone **13** could be prepared via inversion of the carbinyl center of trans lactone **8**. Two routes were developed. The first entailed saponification to hydroxy acid **9** followed by treatment with triphenylphosphine and diethyl azodicarboxylate (DEAD).[5] While

Scheme III[a]



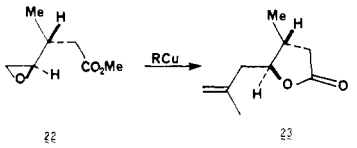
[a] (a) DHP, PPTS, CH_2Cl_2, 4 h. (b) *n*-BuLi, −78 °C; $ClCO_2Me$. (c) MeOH, PPTS, 3 h. (d) H_2/Pd-$BaSO_4$, pyridine, 3 h. (e) NaOH, H_2O, 3 h. (f) H_2O, HCl, 1.5 h. (g) CH_2=$CHMgBr$, 0.2 equiv of CuI, THF, −40 °C, 1.5 h. (h) NaOH, H_2O, 25 °C, 90 min. (i) K_2CO_3, MeOH, 25 °C, 1 h. (j) Ac_2O, pyridine, 25 °C, 12 h. (k) $(CH_3)_3CCOCl$, pyridine, 25 °C, 12 h. (l) DEAD, Ph_3P, THF, −40 °C, 3 h. (m) DEAD, Ph_3P, $PhCO_2H$, THF, 25 °C, 3 h. (n) 4 equiv of I_2, CH_2Cl_2, 0 °C, 48-96 h. (o) 1 equiv of NaOH, 2:1:1 THF-MeOH-H_2O, 25 °C, 14 h; 10% HCl, 25 °C, 1 h. (p) CH_3SO_2Cl, Et_3N, CH_2Cl_2, 0 °C, 30 min.

this route was direct, a small amount of the trans lactone **8** was invariably produced as a byproduct. Cleaner material was obtained via methanolysis of lactone **8** followed by inversion with benzoic acid, using triphenylphosphine and DEAD. The benzoate **14**, thus produced, afforded solely the cis lactone **13** upon saponification followed by acidification. Lactonization of the cis hydroxy acid **15** was virtually instantaneous, whereas the trans isomer **9** required prolonged standing, in keeping with the assigned structures.[6]

We now wished to selectively epoxidize the vinyl grouping of acid **9** or the related ester derivatives **10–12**. The proximity of the carboxylic function in these intermediates made halolactonization followed by base treatment the protocol of choice.[7] The approach promised not only olefin chemoselectivity but also high stereoselectivity as well. Since both epoxide stereoisomers **17** and **21** were desired, kinetic and thermodynamic iodolactonizations were examined. Our initial investigations with acid **9** in buffered aqueous medium were unpromising. The reaction

(4) Pirkle, W. H.; Adams, P. E. *J. Org. Chem.* **1980**, *45*, 4117–21.
(5) Mitsunobu, O. *Synthesis*, **1981**, 1–28.
(6) The cis lactone **13** is diequatorially substituted, whereas the trans lactone **9** possesses one axial substituent.
(7) Cf. Bartlett, P. A.; Myerson, J. *J. Am. Chem. Soc.* **1978**, *100*, 3950–2.

Table I



22 23

entry	cuprate[a]	conditions[b]	yield, %
1	$R_2CuCNLi_2$	−78 °C, 1 h; −40 °C, 1 h	trace[c]
2	$R_2CuCNLi_2$ (2×)	−40 to 0 °C, 5 h	81
3	RCuCNLi (2×)	−78 to 25 °C, 1h	84
4	R_2CuLi (2×)	−60 to −40 °C, 2 h	70
5	RMgBr/CuI (9:1)	−23 °C, 3 h	64

[a] R = isopropenyl. [b] All reactions conducted in diethyl ether. [c] The epoxy ester **22** was recovered.

was slow, and multiple products were produced. Better results were obtained with the benzyltrimethylammonium salt of **9** (R = H, R′ = $PhCH_2NMe_3$) in tetrahydrofuran or benzene. Addition of iodine led to an exothermic reaction in which only the cis and trans iodo lactones **16a** and **18** were produced. Unfortunately, the ratio of these two lactones was essentially 1:1 in both solvents. Much higher stereoselectivity was realized in thermodynamic iodolactonization experiments using esters **11** and **12**. Methylene chloride proved to be the solvent of choice. In both cases the reactions proceeded with greater than 95% trans selectivity as judged by TLC behavior as well as ^1H and ^{13}C NMR analysis. The acetate **11** afforded the γ-lactone **16b** in 83% yield, and the pivalate **12** gave the related γ-lactone **16c** in 87% yield upon prolonged exposure to iodine. Basic methanolysis of lactone acetate **16b** yielded the epoxy esters **17a** (acetate cleavage) and **17b**. The pivalate **16c** was cleanly converted to epoxy ester **17c** under similar conditions.

The cis lactone **19** was easily prepared from epoxy diester **17c** via selective saponification and acid treatment. The mesylate derivative **20** was smoothyl transformed to epoxy ester **21** by basic methanol. This product was uncontaminated by the isomeric epoxy ester **17c**. While no studies have yet been carried out with cis lactone **13**, it should be noted that application of the foregoing methodology could be used to prepare the remaining two stereoisomers of epoxy ester VI. Thus, a route is in hand for the production of intermediates that could lead to both crassin- and isolobophytolide-type cembranolides[8] (Scheme II).

Additions of organocopper reagents to epoxides are fairly commonplace in contemporary synthetic chemistry.[9] However, only a few cases of vinyl transfer have been reported, and examples of isopropenyl transfer are rare. We therefore deemed it worthwhile to examine additions of isopropenyl to epoxy ester **17** and a model epoxy ester **22**[7] with several types of copper reagents. Recent reports indicated that Gilman-type[10] and higher order mixed cyanocuprates might be especially effective.

Our findings are summarized in Tables I and II. The reactions were strikingly temperature dependent. No addition was observed from −78 to −40 °C, and at −40 to −30 °C, the organocopper species rapidly decomposed. In the case of epoxy ester **22** (Table I) the mixed Gilman reagent RCuCNLi[10] gave the best results followed closely by the recently reported higher order mixed cuprate $R_2CuCNLi_2$.[11] The Gilman reagent R_2CuLi[9] and a CuI–isopropenylmagnesium bromide reagent were also effective.[12] In all cases, careful control of temperature and the use of excess reagent were essential to success.

The epoxy ester acetate **17b** showed more complex behavior (Table II). At −78 °C no reaction was observed with the Gilman cuprate (entry 1), whereas at −40 °C a 4:1 mixture of desired lactone **24b** and lactone **26**, the product of S_N2' displacement, was produced (entry 2).[13] The S_N2' displacement was totally predominant with the mixed Gilman reagent giving rise to esters **25** and **26** along with recovered epoxy ester **17b** (entry 3). In a subsequent repetition of this experiment, the dienyl epoxy ester **25** was the predominant product and none of the trienyl lactone **26** could be found. In both cases, the dienyl lactone **24b** was not produced. Thus, S_N2' displacement is strongly favored over epoxide cleavage in these cases. The pivalate **17c** also showed a tendency for S_N2' displacement with the Gilman cuprates. In an effort to minimize this reaction, we prepared the tetrahydropyranyl ether **17d** from hydroxy ester **17a**. This epoxide proved unreactive with the Gilman reagent (entry 4) and the Grignard reagent (entry 5). However, the mixed Gilman reagent was found to give the desired lactone **24d** in 61% yield along with recovered epoxide (entry 7).

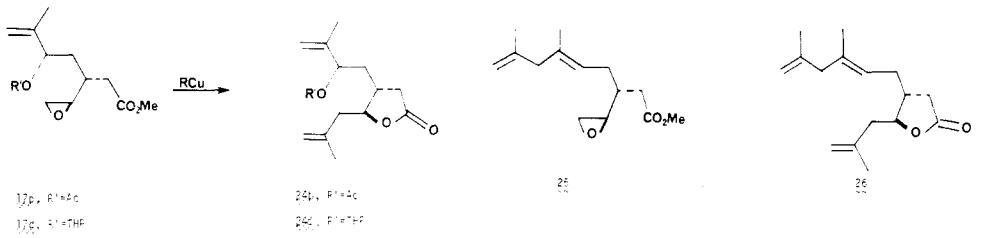
While these results are encouraging, additional modifications of epoxy ester **17** or the organocopper reagent would be desireable for effective implementation of Scheme II.

Experimental Section[14]

2-Methylhex-1-en-5-yn-3-ol (1). A slurry of 20 g (0.823 mol) of oven-dried magnesium powder, 100 mg (0.37 mmol) of mercuric chloride, and 200 mL of anhydrous ether was stirred vigorously as 1 g of 80% propargyl bromide in toluene was added via syringe. After 15 min, the reaction initiated, whereupon the slurry was cooled to −20 °C and a solution of 80 g (0.537 mol) of 80% propargyl bromide in toluene and 32 mL (0.388 mol) of methacrolein in 200 mL of ether was added via syringe pump over 16 h. After an additional 24 h of vigorous stirring at −20 °C, the creamy solution was poured into 250 mL of saturated aqueous NH_4Cl and the separated aqueous layer was back-extracted with three 100-mL portions of ether. The combined organic layers were

(8) Cf. Weinheimer, A. J.; Chang, C. W. J.; Matson, J. A. *Fortchr. Chem. Org. Naturst.* **1979**, *36*, 286–387.
(9) Posner, G. H. *Org. React.* **1975**, *22*, 253–400.
(10) Acker, R. D. *Tetrahedron Lett.* **1977**, 3407–10; **1978**, 2399–402.
(11) Lipschutz, B.; Kozlowski, J.; Wilhelm, R. S. *J. Am. Chem. Soc.* **1982**, *104*, 2305–7.
(12) Cf. Huynh, C.; Berguini-Boumechal, F.; Linstrumelle, G. *Tetrahedron Lett.* **1979**, 1503–6.
(13) Cf. Magid, R. M. *Tetrahedron*, **1980**, *36*, 1901–30.
(14) (a) The apparatus and methods described by G. W. Kramer, M. M. Midland and A. B. Levy [Brown, H. C. "Organic Syntheses via Boranes"; Wiley: New York, 1975; pp 191–202] were used to maintain an argon or nitrogen atmosphere in the reaction flask. (b) Anhydrous solvents were obtained by distillation from sodium benzophenone ketyl (diethyl ether, tetrahydrofuran, 1,2-dimethoxyethane, and dioxane), calcium hydride (dichloromethane and hexamethylphosphoramide), or sodium (benzene and toluene). (c) Infrared absorption maxima are reported in wavenumbers (cm^{-1}) and are standardized by reference to the 1601-cm^{-1} peak of polystyrene. (d) Proton magnetic resonance spectra were recorded on IBM NR-80 and Varian EM-390 spectrometers. Carbon-13 spectra were recorded at 20 MHz on an IBM NR-80 Fourier transform spectrometer. All samples were prepared as dilute solutions in deuteriochloroform ($CDCl_3$). Chemical shifts (δ) are reported downfield from tetramethylsilane (Me_4Si), in parts per million (ppm) of the applied field. Peak multiplicities are abbreviated: singlet s, doublet d, triplet t, quartet q, and multiplet m. Coupling constants (*J*) are reported in hertz (Hz). (e) Gas chromatography–mass spectral analysis (GC/MS) was performed on a Finnigan 4021 instrument. High-resolution mass spectra (HRMS) were determined at the Center for Mass Spectrometry, University of Pennsylvania. (f) Combustion microanalyses were performed by Micro-Tech Laboratories, Inc. Skokie, IL. (g) Analytical thin-layer chromatography (TLC) was routinely used to monitor reactions. Plates precoated with E. Merck silica gel 60 F254 of 0.25 mm thickness, supplied by Brinkmann Instruments, were used. (h) Column chromatography was performed with E. Merck silica gel 60 (230–400 ASTM mesh) according to the procedure of Still et al. (Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923–5).

Table II



entry	cuprate[a]	epoxide	conditions[b]	results
1	R_2CuLi	17b	−78 °C, 3 h	recovered 17b[c]
2	R_2CuLi	17b	−40 °C, 1 h	44% 24b, 13% 26
3	RCuCNLi (8×)	17b	−40 to −20 °C, 3 h	65% recovered 17b, 24% 25, 10% 26
4	R_2CuLi (3×)	17d	−60 to −20 °C, 3 h	recovered 17d[c]
5	RMgBr/CuI (3:1)	17d	−23 to 20 °C, 3 h	recovered 17d[c]
6	RCuCNLi (2.5×)	17d	−60 °C, 45 min	recovered 17d[c]
7	RCuCNLi (8×)	17d	−60 to −40 °C, 1.5 h	61% 24d
8	$R_2CuCNLi_2$ (3×)	17d	−20 °C, 5 h	multiple products

[a] R = isopropenyl. [b] All reactions were conducted in diethyl ether. [c] A trace of γ-lactone was detected.

washed with 50 mL of water and brine and dried ($MgSO_4$). The solvent was removed under reduced pressure. Distillation of the residue [Kugelrohr, 45 °C (0.25 mmHg)] afforded 40.0 g (94%) of alcohol 1: IR (film) 3350, 3260, 3055, 2310, 1650, 1015, 900 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.08, 4.96 (2 br s, 2 H, CH_2=C), 4.29 (br q, J = 6 Hz, CH_2CHOH), 2.50 (q, J = 3 Hz, CH_2CHOH), 2.11 (t, 1 H, HC≡C), 1.81 (br s, 3 H, CH_3C=C). Anal. Calcd for $C_7H_{10}O$: C, 76.32; H, 9.15. Found: C, 76.32; H, 9.40.

2-Methylhex-1-en-5-yn-3-ol Tetrahydropyranyl Ether (2). The procedure of Grieco was employed.[15] A solution of 30 g (0.273 mol) of alcohol 1, 50.7 g (0.603 mol) of dihydropyran, 6.0 g (0.024 mol) of pyridinium *p*-toluenesulfonate, and 1 L of anhydrous methylene chloride was stirred at 25 °C under an inert atmosphere for 4 h. The reaction was then diluted with 1.5 L of ether and washed with 300 mL of 1:1 water/brine solution. The separated organic layer was dried and the solvent was removed under reduced pressure to afford 50 g of crude product. Distillation [Kugelrohr, 90 °C (0.5 mmHg)] afforded 45.1 g (85%) of the tetrahydropyranyl ether 2: IR (film) 3280, 3160, 2950, 2250, 1650, 1445, 1140, 1120, 820 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.99, 4.80 (2 br s, 2 H, CH_2=C), 2.48 (m, 2 H, CH_2C≡CH), 2.00 (t, 1 H, J = 3.0 Hz, HC≡C), 1.76 (br s, 3 H, CH_3C=C), 1.80–1.20 (aliphatic CH_2's); MS, m/e 192 (M^+). Anal. Calcd for $C_{12}H_{18}O_2$: C, 74.18; H, 9.34. Found: C, 74.01; H, 9.31.

Methyl 5-Hydroxyhept-6-en-2-ynoate Tetrahydropyranyl Ether (3). The procedure of Trost was followed.[16] A solution of 45.1 g (0.232 mol) of ether 2 in 500 mL of THF was cooled to −78 °C and 165 mL of 1.7 M *n*-butyllithium (0.281 mol) was added dropwise with vigorous stirring over 20 min. After an additional 30 min at −78 °C, the resulting yellow-orange solution was slowly added via cannula to a precooled (−78 °C) solution of 36 mL (0.467 mol) of methyl chloroformate in 300 mL of THF. The resulting off-white solution was allowed to warm to 25 °C over 1 h. The mixture was poured into 500 mL of 5% aqueous sodium dihydrogen phosphate and the separated aqueous layer was extracted with three 100-mL volumes of ether. The combined organic extracts were washed with 100 mL of water and brine and dried (Na_2SO_4). The solvent was removed under reduced pressure. Distillation [Kugelrohr, 90–100 °C (0.25 mmHg)] of the residue gave 57.7 g (98%) of ester 3: IR (film) 2905, 2240, 1700, 1440, 1250, 1035, 1005 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.95 (br m, CH_2=C), 4.40–3.50 (carbinyl), 3.70 (s, CH_3O), 2.60 (m, CH_2C≡C), 1.90–1.30 (aliphatic CH_2's). Anal. Calcd for $C_{14}H_{20}O_4$: C, 66.64; H, 7.99. Found: C, 66.52; H, 7.96.

Methyl 5-Hydroxy-6-methylhept-6-en-2-ynoate (4). The procedure of Grieco was employed.[15] A solution of 57.7 g (0.229 mol) of tetrahydropyranyl ether 3, 7.0 g (0.028 mol) of pyridinium *p*-toluenesulfonate, and 1 L of absolute ethanol was stirred at 60 °C for 4 h. The solution was cooled and most of the ethanol was removed under reduced pressure. The residue was diluted with 250 mL of ether and water. The separated aqueous layer was back-extracted with two 100-mL volumes of ether, and the combined organic layers were washed with 50 mL of water and brine. The solution was dried ($MgSO_4$) and the solvent was removed under reduced pressure. Distillation [Kugelrohr, 123 °C (1.5 mmHg)] afforded 38.0 g (99%) of the ester 4: IR (film) 3400, 2950, 2230, 1720, 1440, 1260, 1040 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.12, 4.92 (2 br s, CH_2=C), 4.30 (br q, J = 4.0 Hz, CHOH), 3.73 (s, 3 H, CH_3O), 2.62 (d, J = 6 Hz, CH_2C≡C), 1.80 (br s, 3 H, CH_3C=C). Anal. Calcd for $C_9H_{12}O_3$: C, 64.27; H, 7.19. Found: C, 64.16; H, 7.21.

Methyl (*Z*)-5-Hydroxy-6-methyl-2,6-heptadienoate (5). The method of Fieser was modified.[17] A 500-mL one-neck Morton flask equipped with a septum inlet and a magnetic stir bar was rinsed with 10% aqueous NH_4OH and acetone, and oven-dried. A slurry of 1 g of 5% Pd on $BaSO_4$ and 150 mL of pyridine was added to this conditioned flask, which was then affixed to a glass hydrogenation apparatus. After thorough evacuation and purging with hydrogen gas, the catalyst/pyridine slurry was stirred vigorously until the catalyst had fully equilibrated (ca. 45 min). To this black mixture was added a solution of 25.82 g (0.153 mol) of acetylenic ester 4 in 100 mL of pyridine via syringe. After 4 h of vigorous stirring at 25 °C, the alkyne had taken up 1 equiv of hydrogen. The reaction mixture was then filtered through a short pad of Celite with ether. The filtrate was diluted with 500 mL of ether and was washed twice with 100 mL of water, three times with 150 mL of saturated aqueous $CuSO_4$, once again with 100 mL of water, and once with 100 mL of brine. The solution was dried ($MgSO_4$) and the solvent was removed under reduced pressure. Distillation [Kugelrohr, 90 °C (0.3 mmHg)] afforded 24.0 g (92%) of hydroxy ester 5: IR (film) 3015, 2950, 1725, 1710, 1375, 1225, 1010, 790 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.40 (dt, J = 8.0, 12.0 Hz, CH_2CH=CH), 5.87 (dt, J = 12.0, 1.5 Hz, CH_2CH=$CHCO_2R$), 4.99, 4.80 (2 br s, 2 H, CH_2=C), 4.20 (t, J = 6.0 Hz, $RCHOH$), 3.67 (s, 3 H, CH_3O), 2.90 (br m, 2 H, RCH_2CH=C), 1.78 (br s, 3 H, CH_3C=C). Anal. Calcd for $C_9H_{14}O_3$: C, 63.51; H, 8.29. Found: C, 63.61; H, 8.46.

(*Z*)-5-Hydroxy-6-methyl-2,6-heptadienoic Acid Lactone (7). A solution of 9.5 g (55.8 mmol) of hydroxy ester 5, 12 g (300 mmol) of NaOH, and 200 mL of water was stirred at 25 °C for 1 h. The resulting homogeneous solution was poured into 700 mL of 10% aqueous HCl and this acidic solution was stirred at 25 °C for 90 min. The aqueous solution was then thoroughly extracted with five 100-mL volumes of methylene chloride and the combined organic extracts were washed once with 50 mL of saturated aqueous $NaHCO_3$ and brine. The solution was dried ($MgSO_4$) and the solvent was removed under reduced pressure.

(15) Grieco, P. A.; Miyashita, M.; Yoshikoshi, A. *J. Org. Chem.* **1977**, *42*, 3772–4.
(16) Trost, B.; Runge, T. *J. Am. Chem. Soc.* **1981**, *103*, 7559–72.
(17) Fieser, L.; Fieser, M. "Reagents for Organic Synthesis"; Wiley: New York, 1967; Vol. 1, 566.

Distillation [Kugelrohr, 100 °C (0.25 mm Hg)] gave 7.0 g (91%) of unsaturated lactone **7**: IR (film) 3015, 2950, 1725, 1710, 1375, 1225, 1010, 790 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.05 (dt, 1 H, J = 4.0, 9.0 Hz, C*H*=CHCO$_2$R), 6.06 (dt, J = 9.0, 1.5 Hz, CH=C*H*CO$_2$R), 5.15, 5.00 (2 br s, 2 H, CH_2=C), 4.88 (t, 1 H, J = 7 Hz, CHOR), 2.50 (m, 2 H, C*H*$_2$CHOR), 1.88 (br s, 3 H, CH_3C=C); ^{13}C NMR ($CDCl_3$) δ 164.0, 145.2, 141.2, 120.6, 113.4, 80.2, 27.8, 17.8; MS, m/e 138 (M^+). Anal. Calcd for $C_8H_{10}O_2$: C, 69.53; H, 7.30. Found: C, 69.13; H, 7.44.

***rel*-(3*S*,5*R*)-6-Methyl-5-hydroxy-3-vinyl-6-heptenoic Acid Lactone (8).** A slurry of 1.378 g (7.25 mmol) of cuprous iodide in 80 mL of THF was cooled to −40 °C and 25 mL of 1.3 M vinylmagnesium bromide was added dropwise with stirring. After 45 min, a solution of 2.914 g (21.1 mmol) of unsaturated lactone **7** in 20 mL of THF was added dropwise to the cooled yellow-brown reaction mixture. After 90 min at −40 °C the reaction was quenched with 10 mL of 10% aqueous NH_4Cl, allowed to warm to 25 °C, and extracted with three 20-mL portions of ether. The combined organic extracts were washed twice with 10 mL of 10% aqueous NH_4Cl and once with 10 mL of brine and dried ($MgSO_4$), and the solvent was removed under reduced pressure to afford 3.2 g of crude product. Distillation [Kugelrohr, 110 °C (0.25 mmHg)] afforded 2.71 g (75%) of lactone **8**: IR (film) 2900, 1735, 1640, 1450, 1240, 910 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.82 (m, 1 H, CH_2=C*H*), 5.11 (m, 2 H, C*H*$_2$=CH), 4.82 (dd, 1 H, R_2CHOR), 2.90–2.50 (m, allylics), 1.79 (br s, 3 H, CH_3C=C); ^{13}C NMR ($CDCl_3$) δ 170.7, 142.4, 139.4, 115.3, 112.9, 79.7, 34.6, 32.1, 31.6, 18.4; MS, m/e 166 (M^+). Anal. Calcd for $C_{10}H_{14}O_2$: C, 72.26; H, 8.49. Found: C, 72.12; H, 8.57.

***rel*-(3*S*,5*R*)-Methyl 5-Hydroxy-6-methyl-3-vinyl-6-heptenoate (10).** A solution of 11.4 g (68.7 mmol) of lactone **8** and 20.0 g (189 mmol) of anhydrous Na_2CO_3 in 350 mL of dry methanol was stirred at 25 °C for 1 h. The solvent was removed under reduced pressure and the residue was diluted with 300 mL of water and extracted with three 200-mL portions of ether. The combined organic extracts were washed with 50 mL of water and brine and dried ($MgSO_4$), and the solvent was removed under reduced pressure to afford 12.92 g (95%) of hydroxy ester **10**: IR (film) 3425, 2925, 1740, 1660, 1450, 910 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.79 (m, 1 H, CH_2=C*H*), 5.20–4.75 (m, 4 H, CH_2=C), 4.08 (t, 1 H, J = 6.0 Hz, R_2CHOH), 3.60 (s, 3 H, CH_3O), 2.80–2.30 (m, allylics), 1.74 (br s, 3 H, CH_3C=C). A satisfactory elemental analysis could not be obtained due to slow relactonization to lactone **8**.

***rel*-(3*S*,5*R*)-Methyl 5-Acetoxy-6-methyl-3-vinyl-6-heptenoate (11).** A solution of 175 mL of pyridine and 13.6 g (68.7 mmol) of hydroxy ester **10** was stirred at 0 °C as a solution containing 15 mL of acetic anhydride in 20 mL of pyridine was slowly added dropwise. The reaction mixture was then allowed to warm to 25 °C with stirring for 16 h. The solution was cooled to 0 °C and 60 mL of methanol was added. After stirring for 30 min at 25 °C the solution was diluted with 200 mL of water and extracted with four 100-mL volumes of ether. The combined organic extracts were washed with 100 mL of water, three 100-mL portions of saturated aqueous $CuSO_4$, and one 100-mL portion of brine and dried ($MgSO_4$), and the solvent was removed under reduced pressure. Distillation [Kugelrohr, 110 °C (0.25 mmHg)] of the residue afforded 15.5 g (99%) of acetate **11**: IR (film) 3070, 2940, 1740, 1640, 1440, 1380, 1250, 1010, 910 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.97–4.90 (m, 5 H, vinyl CH's), 3.67 (s, 3 H, CH_3O), 2.05 (s, 3 H, CH_3CO), 1.72 (br s, 3 H, CH_3C=C). Anal. Calcd for $C_{13}H_{20}O_4$: C, 64.98; H, 8.39. Found: C, 65.42; H, 8.30.

***rel*-(3*S*,5*R*)-Methyl 5-(2,2,2-Trimethylacetoxy)-6-methyl-3-vinyl-6-heptenoate (12).** A solution of 451 mg (2.28 mmol) of hydroxy ester **10** and 1.31 mL of trimethylacetyl chloride in 10 mL of pyridine was stirred at room temperature for 24 h. The solution was treated with 1 mL of water, and after 3 h, ether was added and the mixture was washed with water, aqueous $CuSO_4$, water, aqueous K_2CO_3, and brine. The solution was dried ($MgSO_4$), the solvent was removed under reduced pressure, and the residue was chromatographed on silica gel (2% ethyl acetate–hexane) to afford 518 mg (78%) of the diester **12**: ^1H NMR ($CDCl_3$) δ 5.9–4.9 (m, 5 H, vinyl), 3.62 (s, 3 H, CH_3O), 2.5–2.2 (m, 2 H, CH_2CO), 1.70 (br s, 3 H, vinyl CH_3), 1.19 [s, 9 H, $(CH_3)_3C$]. Anal. Calcd for $C_{16}H_{24}O_4$: C, 68.05; H, 9.28. Found: C, 68.38; H, 9.48.

***rel*-(3*S*,5*S*)-3-Vinyl-5-hydroxy-6-methyl-6-heptenoic Acid Lactone (13). A. From Benzoate 14.** A solution of 179 mg (0.593 mmol) of benzoate **14** and 575 mg (10.2 mmol) of potassium hydroxide in 5.0 mL of water was stirred at reflux for 4 h. The reaction was then cooled to 25 °C and the alkaline solution was washed with 10 mL of ether followed by acidification with 10% aqueous HCl. The acidified solution was extracted with five 15-mL volumes of methylene chloride, the combined organic extracts were washed with brine and dried (Na_2SO_4), and the solvent was removed under reduced pressure. The residue was diluted with 25 mL of benzene and the resulting solution was refluxed for 1 h with azeotropic removal of water (Dean–Stark trap). The benzene solution was cooled to 25 °C, washed with two 15-mL volumes of saturated aqueous sodium bicarbonate and brine, and dried (Na_2SO_4), and the solvent was removed under reduced pressure to afford 97 mg of crude lactone. Distillation [Kugelrohr, 100 °C (0.5 mmHg)] afforded 70 mg (71%) of lactone **13**: IR (film) 3060, 2900, 1730, 1240, 1080, 920 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.80, 5.07 (2 m, 5 H, vinyls), 4.78 (dd, 1 H, J = 3.6, 11.4 Hz, R_2CHO), 1.81 (br s, 3 H, vinyl CH_3); ^{13}C NMR ($CDCl_3$) δ 170.1, 142.4, 139.4, 114.7, 112.9, 82.8, 35.3, 35.2, 33.5, 17.5. Anal. Calcd for $C_{10}H_{14}O_2$: C, 72.26; H, 8.49. Found: C, 72.35; H, 8.53.

B. From Hydroxy Acid 9. A modification of Mellilo's method was used.[18] A solution of 362 mg (1.98 mmol) of freshly prepared hydroxy acid **9** and 670 mg (2.56 mmol) of triphenylphosphine in 20 mL of THF was cooled to −40 °C, whereupon 0.42 mL (2.70 mmol) of diethyl azodicarboxylate was added via syringe. After stirring at −40 °C for 3 h the resulting yellow solution was warmed to 25 °C and the solvent was removed under reduced pressure. The residue was chromatographed on silica gel with 25% ethyl acetate–hexane to afford 251 mg (75%) of lactone **13** contaminated with 8% of the trans-fused δ-lactone **8** on the basis of ^{13}C NMR analysis.

***rel*-(3*R*,5*R*)-Methyl 3-Vinyl-5-(benzoyloxy)-6-methyl-6-heptenoate (14).** The method of Grynkiewicz was used.[19] A solution consisting of 855 mg (4.32 mmol) of hydroxy ester **10**, 1.05 g (8.60 mmol) of benzoic acid, and 2.26 g (8.62 mmol) of triphenylphosphine in 30 mL of THF was stirred at 25 °C as a solution of 1.30 mL (8.25 mmol) of diethyl azodicarboxylate in 10 mL of THF was slowly added dropwise. This mixture was stirred at 25 °C for 3 h whereupon the solvent was removed under reduced pressure and the residue was diluted with 40 mL of CH_2Cl_2. The organic layer was then washed with 20 mL of saturated aqueous sodium bicarbonate and brine and dried (Na_2SO_4), and the solvent was removed at reduced pressure. Chromatography on silica gel using 10% ethyl acetate–hexane afforded 1.2 g of crude benzoate which was distilled [Kugelrohr, 170 °C (0.5 mmHg)] to afford 800 mg (61%) of benzoate **14**: IR (film) 3075, 2950, 1740, 1720, 1660, 1605, 1460, 1280, 720 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.02, 7.40 (2 m, 5 H, aromatics), 5.90–4.70 (m, 5 H, vinyls), 3.66 (s, 3 H, CH_3O), 1.72 (br s, 3 H, CH_3C=C). Anal. Calcd for $C_{18}H_{22}O_4$: C, 71.50; H, 7.33. Found: C, 71.75; H, 7.47.

***rel*-(3*R*,4*R*)-5-Iodo-4-hydroxy-3-[*rel*-(2*S*)-2-acetoxy-3-methyl-3-butenyl)]pentanoic Acid Lactone (16b).** The method of Bartlett was modified.[7] A solution of 6.59 g (27.4 mmol) of acetoxy ester **11** in 20 mL of methylene chloride was added dropwise to a precooled (0 °C) solution of 24.8 g (98.0 mmol) of iodine in 400 mL of methylene chloride with vigorous stirring. The resulting brown solution was stirred at 0 °C for 60 h in the dark and then it was warmed to 25 °C and poured into 300 mL of 10% aqueous sodium thiosulfate. The separated organic layer was dried ($MgSO_4$) and the solvent was removed under reduced pressure.

Chromatography of the residue on silica gel with 25% ethyl acetate–hexane afforded 8.05 g (83%) of iodo lactone **16b**. Analysis by ^{13}C NMR and analytical HPLC showed this product to be one diasteroisomer: IR (film) 2900, 1780, 1730, 1650, 1375, 1240, 1170 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.25 (dd, 1 H, J = 4.0, 9.0 Hz, CHOAc), 5.06 (br s, 2 H, CH_2=C), 4.10 (m, 1 H, lactone carbinyl), 3.42 (dd, 2 H, J = 3.0, 5.0 Hz, CH_2I), 2.12 (s, 3 H, CH_3CO), 1.81 (br s, CH_3C=C); ^{13}C NMR ($CDCl_3$) δ 174.5, 169.8, 142.1, 113.1, 82.6, 74.6, 37.8, 36.3, 35.1, 21.0, 18.4, 6.1. A satisfactory

(18) Mellilo, D. G.; Liu, T.; Ryan, K.; Sletzinger, M.; Shinkai, I. *Tetrahedron Lett.* **1981**, *22*, 913–6.
(19) Grynkiewicz, G.; Burzynska, H. *Tetrahedron* **1976**, *32*, 2109–11.

elemental analysis of this compound could not be obtained due to rapid decomposition.

***rel*-(3*R*,4*R*)-5-Iodo-4-hydroxy-3-[*rel*-(2*S*)-2-(2,2,2-trimethylacetoxy)-3-methyl-3-butenyl)]pentanoic Acid Lactone (16c).** A solution of 20.6 g (73.0 mmol) of ester **12** and 73 g (287 mmol) of I_2 in 1 L of methylene chloride was stirred for 5 days at 0 °C in the dark. The solution was washed with 10% aqueous sodium sulfite and water. After drying over $MgSO_4$, the solvent was removed under reduced pressure and the residue was chromatographed on silica gel (15% ethyl acetate–hexane) to give 22.5 g (87%) of iodo lactone **16c**: IR (film) 2950, 1785, 1735, 1660, 1250, 1140, 1050 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.18 [dd, 1 H, J = 4.0, 9.0 Hz, $(CH_3)_3CO_2CH$], 4.98, 4.92 (CH_2=C), 4.2–3.8 (m, 1 H, H-4), 3.38 (dd, 2 H, J = 2.0, 6.0, CH_2I), 3.0–2.2 (m, 2 H, H-2), 1.77 (s, vinyl CH_3), 1.26 [s, 9 H, $(CH_3)_3C$]. This material was somewhat unstable and was therefore used directly in the next step.

***rel*-(3*R*,5*S*)-Methyl 3-[*rel*-(1*R*)-1,2-Epoxyethyl]-5-hydroxy-6-methyl-6-heptenoate (17a) and *rel*-(3*R*,5*S*)-Methyl 3-[*rel*-(1*R*)-1,2-Epoxyethyl]-5-acetoxy-6-methyl-6-heptenoate (17b).** The method of Bartlett was used.[7] A solution of 7.0 g (66.0 mmol) of anhydrous Na_2CO_3 in 80 mL of anhydrous methanol was vigorously stirred at 25 °C as a solution containing 3.09 g (9.10 mmol) of iodo lactone **16b** in 20 mL of methanol was added dropwise. After 2 h of vigorous stirring the methanol was removed under reduced pressure and the residue was diluted with 100 mL of ether. The organic layer was washed with 50 mL of water and brine and dried ($MgSO_4$), and the solvent was removed under reduced pressure to afford 1.4 g of crude product mixture. Chromatography on silica gel using 25% ethyl acetate–hexane afforded 832 mg (36%) of epoxy acetate **17b**: IR (film) 2920, 1740, 1650, 1440, 1375, 1240, 1010 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.36 (t, 1 H, J = 6.0 Hz, CHOAc), 5.05, 4.95 (2 br s, 2 H, CH_2=C), 3.70 (s, 3 H, CH_3O), 3.00–2.45 (m, 3 H, epoxide), 2.02 (s, 3 H, CH_3CO), 1.77 (br s, 3 H, CH_3C=C); ^{13}C NMR ($CDCl_3$) δ 172.0, 169.6, 142.5, 113.4, 74.8, 54.1, 51.2, 47.0, 35.8, 35.1, 33.6, 20.7, 17.4; mass spectrum, calcd for $C_{11}H_{16}O_3$ (M^+ – CH_3CO_2H) m/e 196.1100, found (M^+ – CH_3CO_2H) m/e 196.1100.

There was subsequently eluted 600 mg (31%) of epoxy alcohol **17a**: IR (film) 3400, 2900, 1730, 1660, 1440, 1255, 1205, 1165, 905 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.10, 4.82 (2 br s, 2 H, CH_2=C), 4.40 (dd, J = 6.0, 9.0 Hz, CHOH), 3.77 (s, 3 H, CH_3O), 2.65–2.05 (m, 3 H, epoxide), 1.71 (br s, 3 H, CH_3C=C); ^{13}C NMR ($CDCl_3$) δ 172.6, 145.0, 110.2, 84.2, 81.6, 63.3, 51.6, 38.3, 37.2, 36.9, 17.7. Anal. Calcd for $C_{11}H_{18}O_4$: C, 61.66; H, 8.47. Found: C, 61.26; H, 8.34.

***rel*-(3*R*,5*S*)-Methyl 3-[*rel*-(1*R*)-1,2-Epoxyethyl]-5-(2,2,2-trimethylacetoxy)-6-methyl-6-heptenoate (17c).** To a solution of 22.5 g (57 mmol) of iodo lactone **16c** in 50 mL of methanol was added 20 g of anhydrous K_2CO_3. The suspension was stirred vigorously for 1 h and then diluted with ether and washed with brine. After drying over anhydrous $MgSO_4$, the solvent was removed under reduced pressure and the residue was chromatographed on silica gel to afford 12.7 g (75%) of epoxide **17c**: IR (film) 2940, 1735, 1655, 1290, 1160 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.20 [t, 1 H, J = 6.0, $(CH_3)_3CO_2CH$], 5.10 (br s, 2 H, CH_2=C), 3.75 (s, 3 H, CH_3O), 2.9–2.7 (m, 2 H, H-2), 2.6–2.3 (m, 3 H, oxirane), 1.70 (br s, 3 H, vinyl CH_3), 1.18 [s, 9 H, $(CH_3)_3C$]. Anal. Calcd for $C_{16}H_{26}O_5$: C, 64.41; H, 8.78. Found: C, 64.12; H, 8.86.

***rel*-(3*R*,5*S*)-Methyl 3-[*rel*-(1*R*)-1,2-Epoxyethyl]-5-hydroxy-6-methyl-6-heptenoate Tetrahydropyranyl Ether (17d).** A solution of 200 mg (0.934 mmol) of alcohol **17a**, 2.0 mL (22.0 mmol) of dihydropyran, and 25 mg (0.1 mmol) of pyridinium *p*-toluenesulfonate in 10 mL of methylene chloride was stirred at 25 °C for 2 h. The solution was diluted with 50 mL of ether and the organic layer was washed twice with 20-mL volumes of 1:1 water/brine and dried ($MgSO_4$). Removal of the solvent under reduced pressure and chromatography on silica gel using 10% ethyl acetate–hexane afforded 228 mg (82%) of ether **17d**: IR (film) 2925, 1740, 1440, 1140, 1090, 1050, 920 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.06, 4.78 (2 br s, 2 H, CH_2=C), 4.00–3.20 (m, 4 H, carbinyls), 3.78 (s, 3 H, CH_3O), 2.80–2.20 (m, 3 H, epoxide), 1.72 (br s, 3 H, CH_3C=C). Anal. Calcd for $C_{16}H_{26}O_5$: C, 64.41; H, 8.78. Found: C, 64.56; H, 8.99.

***rel*-(3*R*,5*S*)-Methyl 3-[rel-(1*S*)-1,2-Epoxyethyl]-5-hydroxy-6-methyl-6-heptenoate (21).** A solution of 3.54 g (11.9 mmol) of epoxy ester **17c** in 12 mL of 1 N NaOH and 25 mL of 2:1 THF–methanol was stirred overnight at room temperature. Aqueous 10% HCl was added to pH 3 and the mixture was stirred for 1 h and extracted with ethyl acetate. The extracts were washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was chromatographed on silica gel (25% ethyl acetate–hexane) to afford 2.5 g (74%) of hydroxy lactone **19**: IR (film) 3400, 2950, 1780, 1720, 1160, 920 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.12 [t, 1 H, J = 6.0, $(CH_3)_3CO_2CH$], 4.89 (m, 2 H, CH_2=C), 4.57 (m, 1 H, lactone carbinyl), 3.82 (br s, 2 H, CH_2OH), 2.60 (m, 2 H, H-2), 1.70 (br s, vinyl CH_3), 1.19 [s, 9 H, $(CH_3)_3C$]. Anal. Calcd for $C_{15}H_{24}O_5$: C, 63.36; H, 8.51. Found: C, 63.12; H, 8.23.

To a stirred solution of 140 mg (0.5 mmol) of hydroxy lactone **19** in 140 μL of triethylamine and 3 mL of methylene chloride at 0 °C was added 78 μL (0.6 mmol) of methanesulfonyl chloride. After 30 min, aqueous $NaHCO_3$ was added and the mixture was extracted with ether. The extracts were washed with water and brine and dried over $MgSO_4$. The solvent was removed under reduced pressure to give 180 mg (100%) of mesylate lactone **20**: IR (film) 2940, 1780, 1720, 1370, 1180, 920, 740 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.15 [t, 1 H, J = 6.0, $(CH_3)_3CO_2CH$], 4.95 (br s, 2 H, CH_2=C), 4.70 (dt, J = 3.0, 7.0, lactone carbinyl), 4.45 (d, 2 H, J = 3.0, CH_2OMs), 3.06 (s, 3 H, CH_3SO_3), 2.58 (m, 2 H, H-2), 1.74 (s, 3 H, vinyl CH_3), 1.19 [s, 9 H, $(CH_3)_3C$].

A mixture of 154 mg (0.425 mmol) of the above mesylate lactone **20** and 0.50 g of K_2CO_3 in 10 mL of methanol was stirred at room temperature for 15 min. Ether was added and the solution was washed with water and brine and dried over $MgSO_4$. The solvent was removed under reduced pressure and the residue was chromatographed on silica gel (25% ethyl acetate–hexane) to afford 110 mg (87%) of epoxy ester **21**: IR (film) 2950, 1285, 1165 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.32 [t, 1 H, J = 6.0 Hz, $(CH_3)_3CO_2CH$], 4.98, 4.90 (2 H, CH_2=C), 3.68 (s, 3 H, CH_3O), 2.96–2.30 (m, 3 H, epoxide), 2.0–1.6 (m, 2 H, H-2), 1.75 (br s, 3 H, vinyl CH_3), 1.20 [s, 9 H, $(CH_3)_3C$]; ^{13}C NMR ($CDCl_3$) δ 177.1, 171.9, 142.9, 112.6, 73.9, 54.2, 51.2, 45.8, 38.5, 34.9, 34.6, 26.8, 17.7; mass spectrum calcd for $C_{11}H_{16}O_3$ (M^+ – $(CH_3)_3CCO_2H$), m/e 196.1100; found (M^+ – $(CH_3)_3CCO_2H$), m/e 196.1100.

***rel*-(3*S*,4*R*)-4-Hydroxy-3,6-dimethyl-6-heptenoic Acid Lactone (23).** A stirred solution of 0.35 mL (3.94 mmol) of isopropenyl bromide in 5 mL of ether was cooled to –78 °C and 3.2 mL of 2.5 M *tert*-butyllithium in hexane was added dropwise via syringe. After 1 h of stirring at –78 °C the solution was transferred via cannula to a precooled (–78 °C) slurry of 380 mg (1.99 mmol) of copper(I) iodide in 3 mL of ether. The resulting solution was allowed to warm to –60 °C with vigorous stirring over 30 min. A solution of 147 mg (1.02 mmol) of epoxy ester **22** in 2 mL of ether was then added and the resulting reaction mixture was stirred at –60 to –40 °C for 2 h, whereupon 10 mL of saturated aqueous ammonium chloride was added and the reaction was warmed to 25 °C. The separated aqueous layer was extracted with two 10-mL portions of ether, and the combined organic extracts were washed with two 20-mL portions of 10% aqueous ammonium hydroxide and one 20-mL portion of brine and dried ($MgSO_4$), and the solvent was removed under reduced pressure. Chromatography of the residue on silica gel using 10% ethyl acetate–hexane afforded 110 mg (70%) of lactone **23**: IR (film) 2900, 1780, 1650, 1460, 1220, 1160, 1000, 900 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.84 (m, CH_2=C), 4.18 (q, 1 H, J = 5 Hz, CHO), 3.00–2.00 (m, allylics), 1.80 (br s, 3 H, CH_3C=C), 1.20 (d, 3 H, J = 5.0 Hz, CH_3CH); ^{13}C NMR ($CDCl_3$) δ 176.0, 140.8, 113.5, 85.3, 42.0, 36.7, 35.7, 22.6, 17.4. Anal. Calcd for $C_9H_{14}O_2$: C, 70.09; H, 9.15. Found: C, 69.94; H, 9.17.

***rel*-(3*R*,5*S*)-6-Methyl-5-hydroxy-3-[*rel*-(1*S*)-1-hydroxy-3-methyl-3-butenyl]-5-heptenoic Acid γ-Lactone (24a).** A solution of 60 mg (0.194 mmol) of THP ether **24d** and 5 mg (0.02 mmol) of pyridinium *p*-toluenesulfonate in 5.0 mL of dry methanol was stirred at reflux for 4 h. The solvent was removed under reduced pressure and the residue was diluted with ether and washed with two 10-mL portions of brine. Drying ($MgSO_4$) and removal of the solvent under reduced pressure gave 36 mg (83%) of hydroxy lactone **24a**: IR (film) 3400, 2900, 1780, 1650, 1460, 1380, 1180, 900 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.00–4.40 (m, 5 H, vinyl CH's and CHOH), 4.11 (m, 1 H, lactone carbinyl), 2.80–2.10 (m, allylics), 1.74, 1.70 (2 br s, vinyl CH_3's).

***rel*-(3*R*,5*S*)-6-Methyl-5-acetoxy-3-[*rel*-(1*S*)-1-hydroxy-3-methyl-3-butenyl]-6-heptenoic Acid γ-Lactone (24b).** A so-

lution of 0.20 mL (2.33 mmol) of isopropenyl bromide in 5 mL of ether was cooled to −78 °C, whereupon 2.25 mL of 2.0 M *tert*-butyllithium was added via syringe. After 1 h at −78 °C the solution of isopropenyllithium was transferred via cannula into a precooled (−78 °C) slurry of 218 mg (1.15 mmol) of copper(I) iodide in 5 mL of ether. The solution was warmed to −40 °C and 250 mg (1.03 mmol) of epoxy acetate **17b** in 5 mL of ether was slowly added. After stirring at −40 °C for 1 h the reaction mixture was quenched with 2 mL of saturated aqueous NH_4Cl. The separated organic layer was washed with three 10-mL portions of 10% aqueous NH_4OH followed by 10 mL of water and brine. Drying ($MgSO_4$) and removal of the solvent under reduced pressure gave 270 mg of a crude oil, which was purified via column chromatography on silica gel with 10% ethyl acetate–hexane to afford 35 mg (13%) of **26** and 120 mg (44%) of acetate **24b** contaminated with a small amount of epoxy acetate **17b**. **24b**: IR (film) 2900, 1780, 1740, 1380, 1250, 1020, cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.20 (dd, 1 H, J = 4.5, 7.8 Hz, CHOAc), 5.00–4.70 (m, 4 H, CH_2=C), 4.26 (q, 1 H, J = 6.0 Hz, lactone carbinyl), 3.00–2.20 (m, allylics), 2.08 (s, 3 H, CH_3CO_2), 1.79, 1.73 (2 br s, vinyl CH_3's); MS, calculated for $C_{15}H_{22}O_4$ m/e 266.1519, found m/e 266.1507.

***rel*-(3*R*,5*S*)-6-Methyl-5-hydroxy-3-[*rel*-(1*S*)-1-hydroxy-3-methyl-3-butenyl]-5-heptenoic Acid γ-Lactone Tetrahydropyranyl Ether (24d).** A solution of 5.0 mL of 0.5 M isopropenyllithium in ether was slowly added to a precooled (−78 °C) slurry of 225 mg (2.50 mmol) of copper(I) cyanide in 25 mL of ether. The reaction was warmed to −60 °C whereupon a solution of 95 mg (0.317 mmol) of epoxy ester **17d** in 5 mL of ether was added. The reaction mixture was stirred at −60 °C for 90 min, a solution of 5 mL of saturated aqueous NH_4Cl was added, and the reaction was allowed to reach room temperature. The separated organic layer was washed with three 10-mL volumes of 10% aqueous NH_4OH followed by 10 mL of water and brine. Drying ($MgSO_4$) and removal of the solvent under reduced pressure afforded 110 mg of crude product, which was chromatographed on silica gel with 15% ethyl acetate–hexane to furnish 60 mg (61%) of lactone **24d**: IR (film) 3050, 2900, 1780, 1630, 1460, 1380, 1030, 900 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.89 (m, vinyl CH's), 4.30–3.20 (br m, carbinyl protons), 2.80–2.00 (m, allylics), 1.82, 1.78 (2 br s, vinyl CH·s), 1.80–1.00 (m, aliphatics).

Methyl *rel*-(3*R*)-(5*E*)-3-[*rel*-(1*S*)-1,2-Epoxyethyl]-6,8-dimethyl-5,8-nonadienoate (25) and *rel*-(3*R*)-(5*E*)-3-[*rel*-(1*S*)-1-Hydroxy-3-methyl-3-butenyl]-6,8-dimethyl-5,8-nonadienoic Acid γ-Lactone (26). A solution of 0.55 mL (6.19 mmol) of isopropenyl bromide in 10 mL of ether was cooled to −78 °C, whereupon a solution of 5.0 mL of 2.5 M *tert*-butyllithium was added via syringe. After 1 h at −78 °C this yellow solution was transferred via cannula into a precooled (−78 °C) slurry of 556 mg (6.25 mmol) of copper(I) cyanide in 30 mL of ether and the reaction mixture was warmed to −40 °C. A solution of 200 mg (0.781 mmol) of acetate **17b** in 10 mL of ether was added and the reaction was stirred between −40 and −20 °C for 3 h. The solution was then warmed to 25 °C and quenched with 5 mL of saturated aqueous ammonium chloride. The separated organic layer was washed with three 10-mL portions of 10% aqueous NH_4OH followed by 10 mL of water and brine. Drying ($MgSO_4$) and removal of the solvent under reduced pressure afforded ca. 210 mg of crude product which was chromatographed on silica gel with 10% ethyl acetate–hexane to afford 130 mg (65%) of recovered **17b**, 47 mg (24%) of S_N2' product **25**, and 18.4 mg (10%) of bis adduct **26**. **25**: IR (film) 2900, 1740, 1640, 1440, 1380, 1260, 1200, 900 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.20 (br t, 1 H, CH=C), 4.77 (m, 2 H, CH_2=C), 3.68 (s, 3 H, CH_3O), 3.00–2.00 (m, allylics and epoxide), 1.65, 1.60 (2 br s, vinyl CH_3's); *MS*, calculated for $C_{14}H_{22}O_3$ m/e 238.1570, found m/e 238.1558. **26**: IR (film) 2900, 1780, 1640, 1440, 1210, 1070, 900 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.22 (m, 1 H, CH=C), 4.91–4.60 (m, 4 H, CH_2=C), 4.18 (br q, 1 H, lactone carbinyl), 2.80–2.00 (m, allylics), 1.81, 1.69, 1.60 (3 br s, vinyl CH_3's); MS, calculated for $C_{16}H_{24}O_2$ m/e 248.1777, found m/e 248.1760.

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Synthesis of Lipophilic 18-Crown-6 Diacids for the Membrane Transport of Alkaline-Earth Cations

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The synthesis of three different types of lipophilic 18-crown-6 diacids is described. A didecyl crown ether 2,3-diacid (**1**) was prepared as a minor product from a diiodide precursor (**12**) and *threo*-11,12-docosanediol by thallous ethoxide cyclization. The major nonpolymeric products resulted from elimination followed by cyclization to give 15-crown-5 derivatives. A crown ether 11,12-diamide 2,3-diacid (**4**) was prepared by a similar route involving cyclization of a benzyl protected precursor (**26**) and *N,N,N′,N′*-tetramethyltartaramide (**9**). Isomeric syn and anti 2,11(12)-diamide 3,12(11)-diacid derivatives **6** and **7** were prepared from the known crown ether bisanhydride **8** and alkylamines. The product mixture was separated by chromatography, and the isomers were identified by comparison of acidity and stability constants for complexation with those of closely related syn/anti crown ether acids.

The transport of ionic species through membranes is of central importance in biological systems and has an increasing role in the development of practical separation schemes. Several transport mechanisms have been proposed and demonstrated in natural and artificial systems. Of these, coupled transport mediated by mobile carriers (ionophores) presents one of the simplest mechanisms for the selective removal of a specific ion from a dilute solu-

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