the respective pairs of diastereomers (**9a** and **9b**) in 15–30% yield as amphorous white solids.

Diastereomeric pair **9a**: UV $\lambda_{max}$ 278 (log $\epsilon$ 4.77, MeOH); $^1$H NMR ($CDCl_3$) $\delta$ 3.68, 3.69, 3.78, and 3.85 (4 d, $J$ = 14 Hz, OMe's), 8.22, 8.24, 8.39, 8.43, 8.44, 8.46, 8.61 and 8.63 (8 s, Ad's), 8.68[16] (s, Ad's); $^{31}$P NMR ($CDCl_3$) $\delta$ 69.47, 69.80, 70.41, 70.53; FAB mass spectra, $m/e$ 2112 ($MH^+$), 2113 ($MH_2^+$), 2134 ($MNa^+$).

Anal. Calcd for $C_{98}H_{119}N_{15}O_{23}P_2S_2Si_4$: C, 55.69; H, 5.68; N, 9.94; S, 3.03. Found: C, 55.53; H, 5.72; N, 9.77; S, 3.05.

Diastereomeric pair **9b**: UV $\lambda_{max}$ 278 (log $\epsilon$ 4.76, MeOH); $^1$H NMR ($CDCl_3$) $\delta$ 3.38, 3.43, 3.81, and 3.88 (4 d, $J$ = 14 Hz, OMe's), 8.21, 8.22, 8.34, 8.38, 8.44, 8.45, 8.660, 8.663, 8.67, 8.68, 8.737, and 8.744 (12 s, Ad's); $^{31}$P NMR ($CDCl_3$) $\delta$ 70.20, 70.69, 70.98.[16]

Anal. Calcd for $C_{98}H_{119}N_{15}O_{23}P_2S_2Si_4 \cdot C_4H_8O_2$:[17] C, 55.65; H, 5.81; N, 9.54; S, 2.91. Found: C, 56.13; H, 5.89; N, 9.21; S, 2.77.

***P*-Thioadenylyl-(2′–5′)-*P*-thioadenylyl-(2′–5′)-adenosine (3).** The diastereomeric pairs **9a** and **9b** (100 mg) were separately deprotected by the same procedures used to prepare phosphorothioate dinucleotide **7** as described above to give corresponding diastereomeric pairs **3a** and **3b** in 80% and 73% yields, respectively.

Diastereomeric pair **3a**: UV $\lambda_{max}$ 258 ($H_2O$); $^1$H NMR ($D_2O$) $\delta$ 7.726, 7.730, 7.89, 7.94,[16] 8.05, 8.08, 8.12,[16] 8.18, 8.27, and 8.35 (10 s, Ad's); $^{31}$P NMR ($D_2O$) $\delta$ 55.1,[16] 56.3;[16] FAB mass spectrum, $m/e$ 1197 (M – $n$-$Bu_4N$). HPLC analysis:[15] $R_T$ 21.3, 21.7 min [A = 0.3 M ammonium phosphate (pH 7.0), B = methanol, 0–30% B, 20 min, hold 30% B].

Diastereomeric pair **3b**: UV $\lambda_{max}$ 258 ($H_2O$); $^1$H NMR ($D_2O$) $\delta$ 7.71, 7.81, 7.97, 8.00, 8.10,[16] 8.11, 8.14,[16] and 8.30 (8, s, Ad's); $^{31}$P NMR ($D_2O$) $\delta$ 54.58, 55.03, 55.93, 56.13; FAB mass spectrum, $m/e$ 1197 (M – $n$-$Bu_4N$). HPLC analysis:[15] $R_T$ 21.8, 22.2 min [A = 0.3 M ammonium phosphate (pH 7.0), B = methanol, 0–30% B, 20 min, hold 30% B].

**Snake Venom Phosphodiesterase Degradation.** The enzymatic hydrolysis of dimers Rp-A2′p(s)5′A (**7a**), Sp-A2′p(s)5′A (**7b**), and A2′p5′A were performed at 37 °C in a reaction vessel containing 200 mM Tris·HCl (pH 8.75), 2 mM $Mg(OAc)_2$, 200 $\mu$M dimer, and 2 units/mL PDEase. Samples (50 $\mu$L) were removed at the appropriate times and incubated at 95 °C for 5 min, cooled to 4 °C, and centrifuged for 5 min. The supernatants were analyzed by HPLC[15] with a 300 mM ammonium phosphate (pH 7.0) phase, eluted with a 1% per min gradient of methanol, and detected by absorbance at 260 nm.

**Acknowledgment.** We thank Dr. John G. Moffatt for his helpful suggestions. We thank Brian Schryver for his assistance in the enzymatic degradation experiments. We would also like to extend our appreciation to Drs. Laszlo G. Tokes and Michael L. Maddox for their help in the spectral characterization of the above compounds.

**Registry No.** **3a**, 90108-24-0; **3b**, 90191-59-6; **4**, 79154-57-7; **5**, 58463-04-0; **6a**, 90108-20-6; **6b**, 90191-55-2; **7a**, 90108-21-7; **7b**, 90191-56-3; **8a**, 90108-22-8; **8b**, 90191-57-4; **9a**, 90108-23-9; **9b**, 90191-58-5.

(16) Nuclear magnetic resonances were superimposed and the corresponding integration was consistent.

(17) This sample was analyzed as a monosolvate after lyophilization from dioxane.

# Studies on Terpenes. 8. Total Synthesis of (±)-Linderalactone, (±)-Isolinderalactone, and (±)-Neolinderalactone, Germacrane Furanosesquiterpenes

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The synthesis of linderalactone (**1**), isolinderalactone (**2**), and neolinderalactone (**3**) is described and exploits the unique ability of these fluxional systems to enter into Cope and abnormal Cope rearrangements. The symmetrical $\beta$-diketone **10** was converted into the vinyl furan **16** by standard reactions and subsequently alkylated with ethyl bromoacetate, followed by sodium borohydride reduction to give the lactones **18** and **18a**. Methylenation of **18** and **18a** gave isolinderalactone (**2**) and epiisolinderalactone (**5**), respectively. Heating **2** at 160 °C established an equilibrium (3:2) with linderalactone (**1**), and similar treatment of **5** gave neolinderalactone (**3**).

The germacrane furanosesquiterpenes, linderalactone (**1**),[2] isolinderalactone (**2**), and neolinderalactone (**3**)[3] were isolated by Takeda from the root of the shrub *Lindera strychnifolia* Vill. Their structures are based upon chemical degradation, and for linderalactone (**1**), an X-ray crystal structure is available.[4]

Linderalactone (**1**), on heating at 160 °C undergoes a reversible Cope rearrangement to isolinderalactone (**2**) (ratio 2:3).[5] It was determined that isolinderalactone (**2**) is antipodal to the elemane sesquiterpenes by chemical correlation with isofuranogermacrene(**4**), of known absolute configuration. Takeda has extensively examined the relationship between the conformation of cyclodeca-1,5-diene-type sesquiterpenes and the stereochemistry of their Cope rearrangement products (Scheme I). NOE studies have concluded that the stereochemical outcome of such rearrangements is dependent upon the confomation of the ten-membrered ring. with this technique neolinderalactone (**3**) was shown to exist as a 4:1 mixture of the conformers **3**/**3a**, at room temperature. Cope rearrangement of neolinderalactone (**3**) (300 °C for 1–2 min) gave isolin-

(1) Address correspondence to Department of Chemistry, Indiana University, Bloomington, IN 47405.

(2) Takeda, K.; Minato, H.; Ishikawa, M. *J. Chem. Soc.* **1964**, 4578. The same germacrolides have been isolated from *Neolitsea zeylanica*: Joshi, B. S.; Kamat, N.; Govindachari, T. R. *Tetrahedron* **1967**, 261. The root is used in Chinese medicine as an aromatic stomachic: Key, J. D. "Chinese Herbs, Their Botany, Chemistry and Pharmacodynamics"; C. E. Tuttle Co.: VT, 1976; p 112.

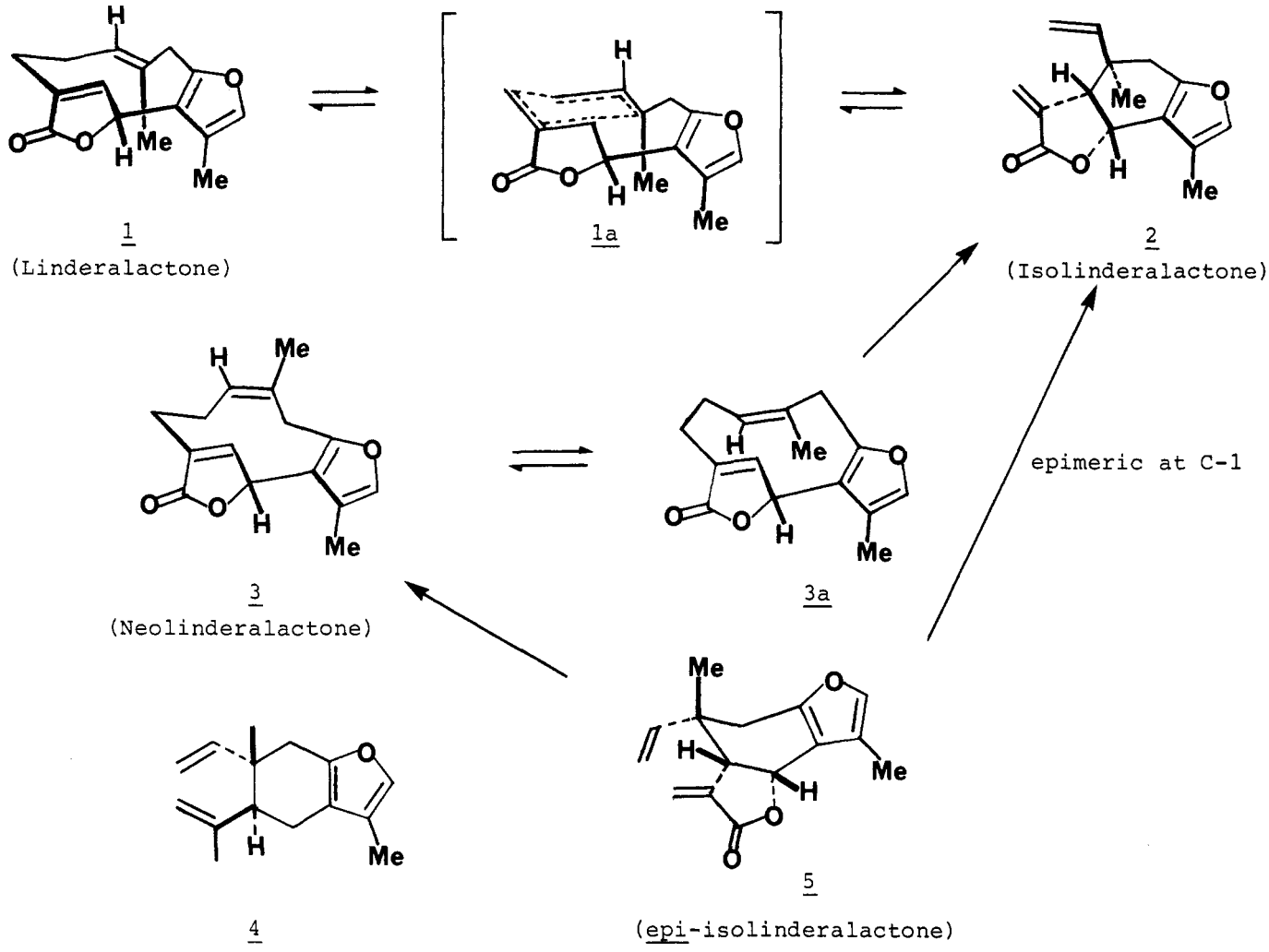
(3) Takeda, K.; Horibe, I.; Teroake, M. *J. Chem. Soc. C* **1969**, 2786. Tori, K.; Horibe, I.; Kuriyama, K.; Takeda, K. *J. Chem. Soc. D* **1970**, 957.

(4) Takeda, K.; Horibe, I.; Minato, H. *Chem. Commun.* **1968**, 378. Takeda, K.; Tori, K.; Horibe, I.; Ohtsura, M.; Minato, H. *J. Chem. Soc. C* **1970**, 2697. Takeda, K.; Horibe, I.; Teraoka, M.; Minato, H. *Chem. Commun.* **1968**, 637. Koyama, H.; Tsukuda, Y. M. *J. Chem. Soc., Perkin Trans. 2* **1977**, 646.

(5) Takeda, K.; Horibe, I.; Minato, H. *J. Chem. Soc. C* **1970**, 1142. Takeda, K.; Horibe, I.; Toraoka, M.; Minato, H. *Ibid.* **1969**, 1493. Takeda, K.; Horibe, I.; Minato, H. *J. Chem. Soc., Perkin Trans 1* **1973**, 2212.

0022-3263/84/1949-2317$01.50/0 

Scheme I




deralactone (2) (ca. 5%), which is itself in equilibrium with linderalactone (1).[6] Therefore, this conversion must proceed from the conformer **3a** rather than **3**. A missing natural product in this rearrangement sequence is epi-isolinderalactone (**5**). If **5** were made in the course of the syntheseis of isolinderalactone (epimeric at C-1), it should undergo Cope rearrangement to give neolinderalactone (**3**), which allows entry into the linderalactone (1)/isolinderalactone (2) manifold. While there has been considerable synthetic activity reported in the area of germacrene sesquiterpenes,[7] the germacrene furanosesquiterpenes have received no published attention. It should be noted that the Cope–retro-Cope rearrangement has formed the basis of a number of sesquiterpene syntheses.[8]

## Results

3,5-Dimethoxybenzoic acid (**6**) was reduced with $Li/NH_3$ by using the procedure of Bosch[9] and the resulting dianion **6a**, quenched with methyl iodide to the dihydrobenzoic acid **7** (87%). Reduction of **7** with $LiAlH_4$ gave the alcohol **8** (Scheme II). Attempts to oxidize the alcohol **8** to the aldehyde **8a** lead to fragmentation, resulting in aromatization to give, among other products, dimethylorcinol **8b**. Using the reagent $CrO_3(py)_2/CH_2Cl_2$, we could isolate a low yield of the aldehyde **8a** (characterized as a semicarbazone), but this would be quite impractical as a synthetic step.[10] Consequently, it was decided to postpone this oxidation step until later in the sequence. Furthermore, as part of this study, we found that it was necessary to protect the neopentyl hydroxyl group of **8** prior to acid hydrolysis in order to give respectable yields in subsequent steps and preclude water-soluble products.[11]

It was decided to protect **8** as its methyl ether **9**, since we could prepare **9** in some 95% yield, whereas the benzyl ether proved less convenient. Treatment of **8** with NaH/MeI/THF/72 h gave **9** (95%), which was directly hydrolyzed by using 4 N HCl/THF/20 °C to give the crystalline β-diketone **10** (88%).

With the use of conditions developed by Stetter,[12] a solution of the symmetrical β-diketone **10** in aqueous methanolic potassium hydroxide was treated with ethyl

(6) Even at room temperature linderalactone is partially isomerized to isolinderalactone. For an authorative description of the stereochemical consequences of the Cope rearrangement, see: Doering, W. v. E.; Roth, W. R. *Tetrahedron* **1962**, 67. For a review describing Cope rearrangements of the germacrene sesquiterpenes, see: Takeda, K. *Ibid.* **1974**, 1525.

(7) "The Total Synthesis of Natural Products"; Ap Simon, J., Ed.; Wiley-Interscience: New York, 1983; Vol. 5.

(8) Corey, E. J.; Hortmann, A. G. *J. Am. Chem. Soc.* **1963**, *87*, 5736. Grieco, P.; Nishizawa, M. *J. Org. Chem.* **1977**, *42*, 1717. Fujimoto, Y.; Shimizu, T.; Tatsuno, T. *Tetrahydron Lett.* **1976**, 2041. Still, W. C. *J. Chem. Soc.* **1977**, *99*, 4186.

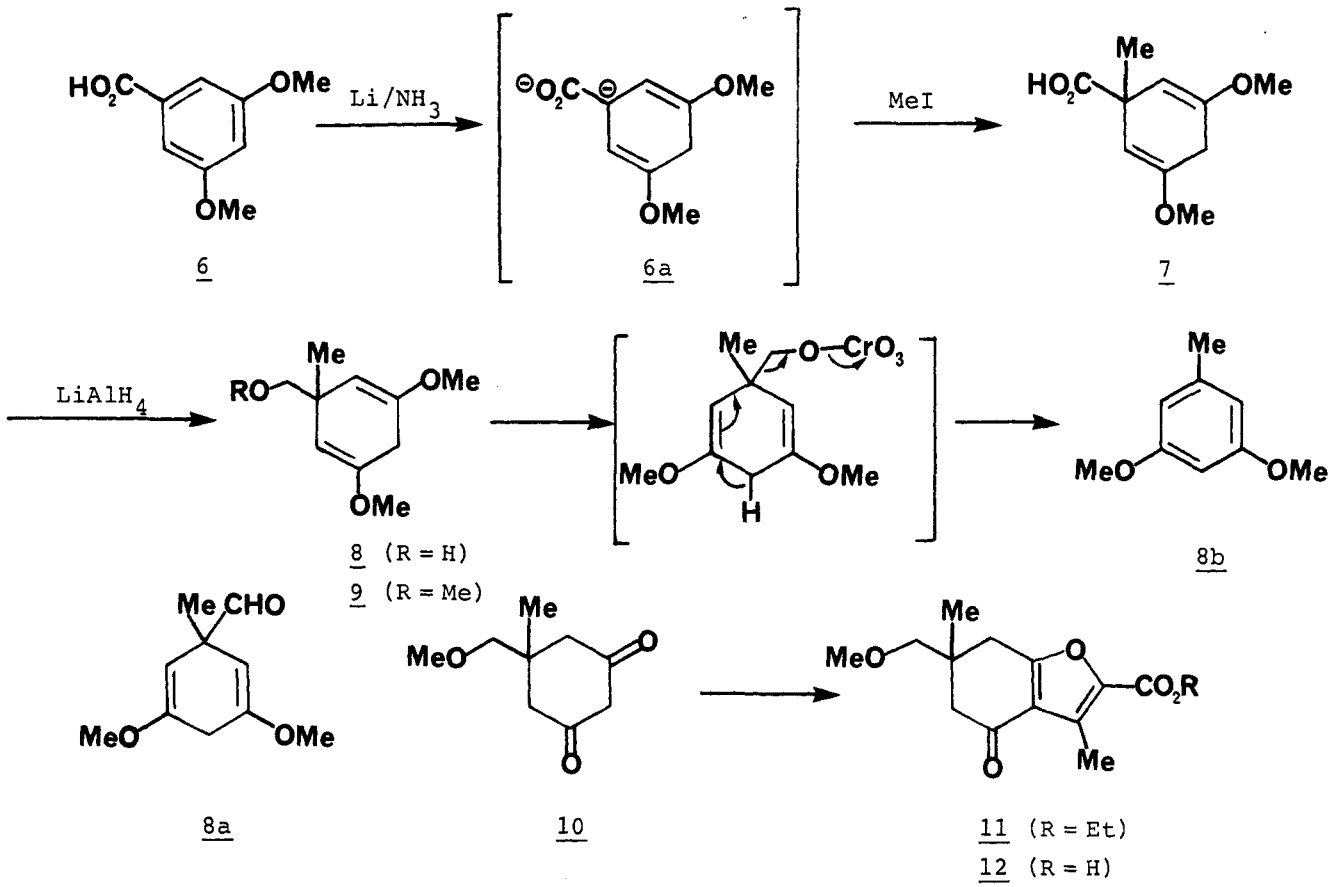
(9) Bekkum, v. H.; Bosch, v. C. B.; Minnenpathuis, v. G.; Demos, J. C.; Wijk, v. A. M. *Recl. Trav. Chim. Pays-Bas* **1971**, *90*, 137. Chapman, O. L.; Fitton, P. *J. Am. Chem. Soc.* **1963**, *85*, 41.

(10) Ehlinger, E. E. Ph.D. Dissertation, The Ohio State University, 1979.

(11) The deprotected 1,3-dione related to **10** was made by mild acid hydrolysis of **8**. It was difficult to extract it from the aqueous media, and it also gave problems in the furan annulation step.

(12) Stetter, H.; Lauterbach, R. *Angew. Chem.* **1957**, *71*, 673; *Chem. Ber.* **1969**, *93*, 603.

Scheme II




6 6a 7

8 (R = H)
9 (R = Me)

8b

8a 10 11 (R = Et)
12 (R = H)

2-chloroacetoacetate to give the 3-methyltetrahydrobenzofuran **11** (57%). While in recent years a number of methods have been developed for the annulation of a furan ring onto a cyclohexyl ring,[13] the relatively unknown Stetter mtehod was very simple, using a commercially available reagent and readily conducted on a 10-g scale. The furan ester **11** was readily hydrolyzed to the acid **12** (85%) by treatment with KOH in aqueous methanol at reflux. The furan acid **12** is a minor (ca. 5%) contaminant in the preparation of **11**. Despite more recent and so-called improved methods for decarboxylating 2-carboxyfurans,[14] we found that treatment of **12** with Cu powder in diethylene glycol containing pyridine heated at 160–165 °C for 10 h gave the benzofuran **13** (85%).[12]

At this stage we decided to deprotect the neopentyl alcohol since, if this were delayed, it could prove problematic when the γ-lactone was intact. Treatment of **13** with $BBr_3/CH_2Cl_2/-70$ °C,[15] and then warming to 20 °C, gave the required neopentyl alcohol **14** (96%). Oxidation of **14**, using pyridinium chlorochromate gave the aldehyde **15** in 74% yield. The subsequent treatment of **15** with triphenyl phosphonium methylide, in THF at 0 °C, was completly chemospecific to give the vinyl derivative **16** (68%, after bulb-to-bulb distillation).

It was anticipated that alkylation of **16** would produce a mixture of epimers at C-6. This provides access to both **3** and **5** and **1** and **2** (Scheme III). Consequently, we should be able to test the abnormal Cope rearrangement of **5** into **3** and subsequently into **1** ⇄ **2**, thereby providing a unique pathway for epimerizaiton at C-1.

When the procedure of Heathcock[15,16] was followed, the kinetic enolate of **16** was generated with lithium diisopropylamide in THF at −70 °C, warmed to −20 °C, and quenched with ethyl bromoacetate to give **17** (90%) as a 1:1 mixture of epimers at C-6. The epimeric mixture could not be separated by chromatography. Reduction of the mixture (**17**), with $NaBH_4$/3 N NaOH/mEOH/72 h gave the lactones **18** and **18a** (47% from **16**). The mixture of **18** and **18a** was separated by trituration with diethyl ether. The epimer **18a** separated as a crystalline solid, and the other epimer remained as an oil. These assignments are based upon the subsequent Cope rearrangement results. Treatment of crystalline **18a** with LDA/THF/$CH_2{=}N^+Me_2I^-$ followed by MeI/MeOH/$NaHCO_3$[17] gave epiisolinderalactone (**5**). When **5** was heated to 160–165 °C for 30 min it underwent Cope rearrangement to give neolinderalactone (**3**): $^1$H NMR δ 1.59 (3 H, s), 2.05 (3 H, d, $J$ = 1.3 Hz), 5.16 (1 H), 6.80 (1 H), 7.04 (1 H, q, $J$ = 1.3 Hz) (compared with authentic **3**, kindly supplied by Professor Takeda).

The diastereomeric lactone **18**, on similar methylenation, gave isolinderalactone (**2**). When synthetic isolinderalactone (**2**) was heated at 160–165 °C for 20 min, it underwent Cope rearrangement to a mixture of linderalactones **1** and **2** (2:3).

In summary, this first synthesis of the lineralactones **1–3** provides a unique opportunity to epimerize at a quaternary carbon atom (C-1) by using two Cope rearrangements. The so-called abnormal Cope rearrangement enabled epiisolinderalactone (**5**) (an unnatural member of this series) to be converted into neolinderalactone (**3**), and by further

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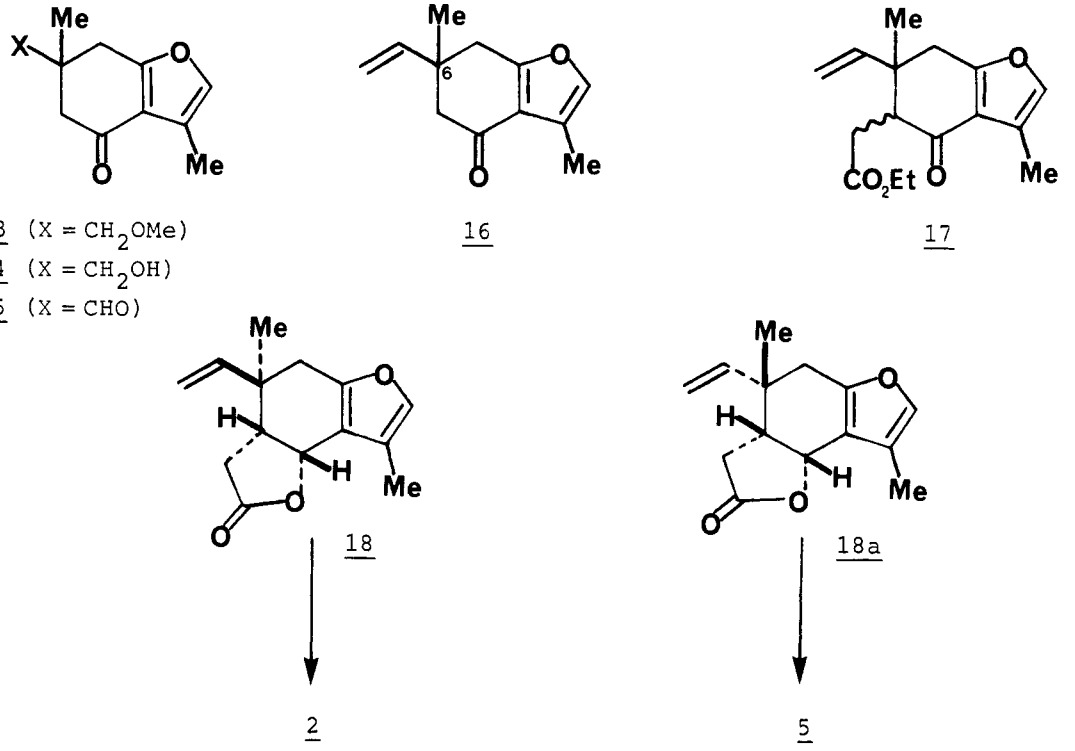
(15) Grieco, P.; Nishizawa, M.; Oguri, T.; Burke, S.; Marinovic, N.; *J. Am. Chem. Soc.* **1977**, *99*, 5773. Wege, P.; Clark, R. D.; Heathcock, C. H. *J. Org. Chem.* **1976**, *41*, 3144.
(16) Danheiser, R. L.; Stork, G. *J. Org. Chem.* **1973**, *38*, 1775.
(17) Danishefsky, S.; Kitahara, T.; McKee, R.; Schuda, P. F. *J. Am. Chem. Soc.* **1976**, *98*, 6715.

Scheme III




rearrangement, into linderalactone (1) and isolinderalactone (2).

While this work was in progress,[18] Schlessinger reported the total synthesis of vernolepin, using a similar strategy involving symmetrical β-diketones such as **10**,[19] thus demonstrating the general applicability of this plan to complex sesquiterpenes.

## Experimental Section

**1-Methyl-3,5-dimethoxy-1,4-dihydrobenzoic Acid (7).**[9] Birch reduction of 3,5-dimethoxybenzoic acid (**6**, 48 g), followed by quenching with methyl iodide, gave **7** (45.4 g 87%): mp 28–30 °C; IR ($CHCl_3$) 3500–2500, 1700, 1610 $cm^{-1}$; $^1H$ NMR δ 1.40 (3 H, s), 2.78 (2 H, br s), 3.60 (6 H, s), 4.73 (2 H, br s); MS, $C_{10}H_{14}O_4$ requires 198.0892, found 198.0895.

**1-Methyl-3,5-dimethoxy-1,4-dihydrobenzyl Alcohol (8).** Lithium aluminum hydride reduction of **7** (45 g, 0.227 mol) as described gave **8** (used directly in the next stage), mp 48–52 °C.[9]

**5-Methyl-5-(methoxymethyl)-1,3-cyclohexanedione (10).** To a suspension of sodium hydride (9.3 g, 0.388 mol) in dry THF (100 mL) at 0 °C was added **8** (34 g, 0.185 mol) in THF (125 mL). The mixture was warmed to 20 °C and mechanically stirred for 3 h. Methyl iodide (182 g, 1.28 mol) was slowly added (1 h), the above mixture was heated at reflux for 72 h, and methyl iodide (portions of 46 g) was added after 24 and 48 h. The mixture was cooled to 20 °C, diluted with water (250 mL), and extracted with ether (3 × 250 mL). The extracts were washed with water (200 mL) and brine (100 mL) and dried ($MgSO_4$), and the solvent was removed in vacuo to give the crude methyl ether **9** (34.8 g, 95%) as a colorless oil: IR (film) 1695, 1664, 1205, 950, 905, 825 $cm^{-1}$; $^1H$ NMR δ 1.13 (3 H, s), 2.73 (2 H, br s), 3.10 (2 H, s), 3.33 (3 H, s), 3.55 (6 H, s), 4.50 (2 H, br s). The crude enol ether **9** (37 g, 0.187 mol) in THF (600 mL) at 20 °C was treated with 4 N HCl (370 mL). After 6 h the mixture was extracted with ethyl acetate (3 × 300 mL) and the extract washed with water (200 mL) and saturated aqueous sodium chloride (150 mL), dried ($MgSO_4$), and evaporated in vacuo to give the β-diketone **10** (27.9 g, 88%). The crude product was washed with ether, filtered, and dried to give pure **10** (23.8 g, 75%): mp 92–93 °C (from $CH_2Cl_2$/petroleum ether); IR ($CHCl_3$) 1705, 1610, 1450, 1110 $cm^{-1}$; $^1H$ NMR δ 1.02 (3 H, s), 2.34 (2 H, m), 2.54 (4 H, br s), 3.20 (5 H, s); MS, $C_9H_{14}O_3$ requires 170.0942, found 170.0946. Anal. Found: C, 63.78; H, 8.12. $C_9H_{14}O_3$ requires C, 63.50; H, 8.29.

**Ethyl 3,6-Dimethyl-4-oxo-6-(methoxymethyl)-4,5,6,7-tetrahydrobenzofuran-2-carboxylate (11).** The β-diketone **10** (10 g, 0.059 mol) was added to a solution of potassium hydroxide (3.3 g, 0.059 mol) in water (120 mL). After 5 min, ethyl 2-chloroacetoacetate (9.8 g, 0.059 mol) in methanol (30 mL) was added, and the mixture was stirred at 20 °C for 72 h. The reaction was acidified with 4 N HCl (150 mL) and extracted with ethyl acetate (3 × 150 mL). The combined extracts were washed with saturated aqueous $NaHCO_3$ solution (3 × 100 mL) and brine (100 mL) and dried ($MgSO_4$), and the solvent was removed in vacuo to give the furan ester **11** (9.33 g, 57%) as a viscous yellow oil; IR (film) 2910, 1705, 1680, 1600, 1235, 1120, 1100 $cm^{-1}$; $^1H$ NMR δ 0.94 (3 H, s), 1.23 (3 H, t, $J$ = 7 Hz), 2.00–3.10 (4 H, m), 2.40 (3 H, s), 3.08 (2 H, s), 3.20 (3 H, s), 4.22 (2 H, q, $J$ = 7 Hz); MS, $C_{15}H_{20}O_5$ requires 280.1310, found 280.1317.

**3,6-Dimethyl-4-oxo-6-(methoxymethyl)-4,5,6,7-tetrahydrobenzofuran-2-carboxylic Acid (12).** To a soluton of the furan ester **11** (10.4 g, 0.037 mol) in methanol (42 mL) and water (16 mL) was added potassium hydroxide (14.5 g), and the solution was heated at reflux for 2 h. The mixture was cooled to 20 °C, diluted with water (80 mL), acidified with concentrated HCl, and extracted with ethyl acetate (3 × 125 mL). The extract was washed with water (50 mL), and brine (50 mL), dried ($MgSO_4$), and evaporated in vacuo to give the **furan acid 12** (7.98 g, 85%): mp 140–142 °C (from EtOAc/petroleum ether, 1:2): IR ($CHCl_3$) 3200–2700, 1675, 1455, 1110 $cm^{-1}$; $^1H$ NMR δ 1.10 (3 H, s), 2.10–3.10 (4 H, m), 2.59 (3 H, s), 3.20 (2 H, s), 3.36 (3 H, s), 9.88 (1 H, br s); MS, $C_{13}H_{16}O_5$ requires 252.0997, found 252.1004. Anal. Found: C, 61.95; H, 6.38. $C_{13}H_{16}O_5$ requires C, 61.90; H, 6.39.

**3,6-Dimethyl-4-oxo-6-(methoxymethyl)-4,5,6,7-tetrahydrobenzofuran (13).** The furan acid **12** (2.6 g, 10.3 mmol) in diethylene glycol (12.5 mL) was treated with copper powder (0.42 g) and dry pyridine and heated at 160–165 °C for 10 h. The ice-cooled mixture was diluted with water (15 mL), acidified (4 N HCl, 25 mL), and extracted with ether (3 × 30 mL). The combined ether extracts were washed with water (2 × 10 mL) and saturated aqueous $NaHCO_3$ solution (15 mL), dried ($MgSO_4$), and evaporated to give a brown oil. Bulb-to-bulb distillation (110 °C

(18) Preliminary communication: Gopalan, A.; Magnus, P. *J. Am. Chem. Soc.* **1980**, *102* 1756. For part 7 in this series, see: Exon, C.; Nobbs, M.; Magnus, P. *Tetrahedron* **1981**, *37*, 4515.

(19) Kieczykowski, G. R.; Quesada, M. L.; Schlessinger, R. H. *J. Am. Chem. Soc.* **1980**, *102*, 782.

at 0.1 mmHg) gave the furan **13** (1.83 g, 85%): IR (film) 2910, 1674, 1620, 1555, 1420, and 1100 $cm^{-1}$; $^1H$ NMR $\delta$ 1.13 (3 H, s), 2.23 (3 H, d, $J$ = 1.5 Hz), 2.42 (2 H, q, $J$ = 16 Hz), 2.81 (2 H, q, $J$ = 18 Hz), 3.24 (2 H, s), 3.36 (3 H, s), 7.11 (1 H br s); MS, $C_{12}H_{16}O_3$ requires 208.1099, found 208.1104. Anal. Found: C, 69.47; H, 7.90. $C_{12}H_{16}O_3$ requires C, 69.21; H, 7.74.

**3,6-Dimethyl-4-oxo-6-(hydroxymethyl)-4,5,6,7-tetrahydrobenzofuran (14).** To a solution of boron tribromide (2 mL) in dichloromethane (20 mL) at −70 °C, under argon, was added a solution of the furan methyl ether **13** (2.0 g, 9.6 mmol) in dichloromethane (15 mL). The solution was stirred at −70 °C for 45 min and then slowly warmed to 0 °C over 45 min. Continued stirring at 20 °C for 3 h completed the reaction (TLC). The mixture was poured into water (25 mL) and extracted with dichloromethane (3 × 25 mL), and the extract was washed with saturated aqueous $NaHCO_3$ solution (25 mL) and brine (25 mL), dried ($MgSO_4$), and evaporated in vacuo to give the demethylated furan **14** (1.8 g (96%) purified by chromatography over silica gel): IR (film) 3430, 2930, 1670, 1565, 1435, 1050 $cm^{-1}$; $^1H$ NMR $\delta$ 1.08 (3 H, s), 2.17 (3 H, d, $J$ = 1.5 Hz), 2.38 (1 H, br s, OH), 2.40 (2 H, q, $J$ = 16 Hz), 2.79 (2 H, q, $J$ = 17 Hz), 3.47 (2 H, s), 7.09 (1 H, br s); MS, calcd for $C_{11}H_{14}O_3$ 194.0942, found 194.0946.

**3,6-Dimethyl-4-oxo-6-formyl-4,5,6,7-tetrahydrobenzofuran (15).** To a suspension of pyridinium chlorochromate (2.2 g, 10.2 mmol) in dichloromethane (5 mL) at 20 °C was added the furan alcohol **14** (0.9 g, 5.84 mmol) in dichloromethane (4 mL). The mixture was stirred for 3 h and diluted with ether (40 mL), and the ether was decanted. The sticky black solid residue was further washed thoroughly with ether (2 × 20 mL), and the combined ether washings were filtered through a short column of silica gel and washed with additional ether (150 mL). The ether extract was dried ($MgSO_4$), and the solvent was removed in vacuo to give the aldehyde **15** (0.66 g, 74%): mp 70–74 °C (from petroleum ether); IR ($CHCl_3$) 2720, 1738, 1680, 1565, 14408 1075 $cm^{-1}$; $^1H$ NMR $\delta$ 1.25 (3 H, s), 2.12 (3 H, d, $J$ = 1.5 Hz), 2.58 (2 H, q, $J$ = 17 Hz), 2.95 (2 H, q, $J$ = 17 Hz), 7.03 (1 H, br s), 9.45 (1 H, s); MS calcd for $C_{11}H_{12}O_3$ 192.0786, found 192.0791.

**3,6-Dimethyl-4-oxo-6-vinyl-4,5,6,7-tetrahydrobenzofuran (16).** To a suspension of triphenylmethylphosphonium iodide (2.74 g, 6.77 mmol) in dry THF (10 mL) at 0 °C under $N_2$ was added dropwise a 1.6 M solution of $n$-BuLi in hexane (4.2 mL, 6.72 mmol). To this orange-red solution was added the aldehyde **15** (1.3 g, 6.77 mmol) in THF (6 mL). The mixture was warmed to 20 °C and after 30 min diluted with water (30 mL) and extracted with ether (3 × 50 mL). The ether extract was filtered through a column of silica gel and washed with additional ether (200 mL). The ether solution was dried ($MgSO_4$) and evaporated by in vacuo to give a pale yellow oil, which was purified by bulb-to-bulb distillation (110 °C at 0.5 mmHg) to give the vinyl furan **16** as a colorless oil (0.88 g, 68%): IR (film) 3090, 2960, 1675, 1436, 1070, 920 $cm^{-1}$; $^1H$ NMR $\delta$ 1.15 (3 H, s), 2.12 (3 H, d, $J$ = 1.5 Hz), 2.41 (2 H, d, $J$ = 16 Hz), 2.78 (2 H, d, $J$ = 18 Hz), 4.90 (1 H, d, $J$ = 18 Hz), 4.70–6.0 (3 H, ABX, $J$'s = 18 Hz and 10 Hz). Anal. Found: C, 75.55; H, 7.63. $C_{12}H_{14}O_2$ requires C, 75.76; H, 7.42.

**3,6-Dimethyl-4-oxo-5-[(ethoxycarbonyl)methyl]-6-vinyl-4,5,6,7-tetrahydrobenzofuran (17).** To a solution of diisopropylamine (0.6 g, 5.9 mmol) in dry THF (3 mL) under argon at 0 °C was added $n$-BuLi (1.6 M, 3.8 mL in hexane). After 10 min the mixture was cooled to −70 °C and the vinylfuran **16** (0.88 g, 4.63 mmol) in THF (4 mL) was added over 5 min. The solution was warmed to −20 °C and ethyl bromoacetate (2.26 g, 13.5 mmol) added. After 2 h at 20 °C, water (20 mL) was added and the mixture extracted with ether (3 × 25 mL). The combined extracts were washed with brine (25 mL), dried ($MgSO_4$), and evaported in vacuo to give the furan **17** (1.15 g (90%) as a mixture of epimers, 1:1): IR (film) 3080, 2960, 1730, 1675, 1560, 1425, 920 $cm^{-1}$; $^1H$ NMR $\delta$ 0.95 (3 H, s), 1.13 (3 H, s), 1.20 (3 H, t, $J$ = 7 Hz), 2.08 (3 H, d, $J$ = 1.5 Hz), 2.18–3.18 (5 H, m), 4.08 (2 H, q, $J$ = 7 Hz), 4.75–6.10 (3 H, m), 7.0 (1 H, br s); MS calcd for $C_{15}H_{20}O_4$ 276.1361, found 276.1368. The product was used directly in the next stage.

**(4α,5α)-3,6-Dimethyl-4-hydroxy-6-vinyl-4,5,6,7-tetrahydro-5-benzofuran-5-acetic Acid Lactone (18 and 18a).** To a solution of sodium borohydride (0.78 g, 20.5 mmol) in methanol at 20 °C was added aqueous 3 N NaOH (5 mL) and the ester **17** (1.15 g, 4.16 mmol) in methanol (7 mL). After 24 h at 20 °C, further sodium borohydride (0.8 g) was added, and the mixture was left at 20 °C for 48 h. Addition of water (20 mL) and extraction with ether (20 mL) removed all neutral impurities. The aqueous layer was acidified with 2 $NH_2SO_4$ and extracted with ethyl acetate (3 × 20 mL). The combined extracts were washed with saturated aqueous $NaHCO_3$ (2 × 20 mL) and brine (20 mL), dried ($MgSO_4$), and evaporated in vacuo to give the epimer lactones **18** and **18a** (1:1) (0.5 g (47%) from **16**): $^1H$ NMR $\delta$ 1.09 (3 H, br s), 1.97 (3 H, d, $J$ = 1.2 Hz), 2.10–3.00 (5 H, m), 4.80–5.20 (2 H, m), 5.32 (1 H, br d), 5.68–6.02 (1 H, m), 7.00 (1 H, br s); MS, calcd for $C_{14}H_{16}O_3$ 232.1099, found 232.1105. The above mixture of epimeric lactones was triturated with ether to give a crystalline residue of **18a** (220 mg); mp 137–141 °C. Anal. Found: C, 72.21; H, 6.78. $C_{14}H_{16}O_3$ requires C, 72.41; H, 6.90. The ether was evaporated to give **18** (27 mg) as a gum.

**Epiisolinderalactone (5) and Its Cope Rearrangement to Neolinderalactone (3).** To a solution of diisopropylamine (0.45 mL, 3.21 mmol) in THF (2 mL) at 0 °C was added a 1.5 M solution of $n$-BuLi in hexane (2.15 mL, 3.2 mmol). After 10 min at 0 °C the solution was cooled to −76 °C, and the lactone **18a** (105 mg, 0.45 mmol) in THF (2 mL) was added. The resulting solution was warmed to −40 °C over 25 min and cooled to −76 °C, and Eschenmoser's salt (0.53 g, 2.85 mmol) was added. The mixture was warmed to 20 °C water (15 mL) added, and the solution was extracted with ethyl acetate (3 × 20 mL). The combined extracts were filtered through a short column of silica gel, dried ($MgSO_4$), and evaporated in vacuo to give the Mannich adduct, which was used directly in the next step.

The Mannich adduct was dissolved in methanol (3 mL), methyl iodide (6 mL) was added, and the mixture was stirred for 18 h. Evaporation, in vacuo, gave a residue which was partitioned between saturated aqueous $NaHCO_3$ solution (15 mL) and ethyl acetate (20 mL). The organic layer was separated, and ethyl acetate (20 mL) was added to the aqueous solution. The combined extracts were dried ($MgSO_4$) and evaporated in vacuo to give epiisolinderalactone (**5**, 15 mg, 14%): $^1H$ NMR $\delta$ 1.20 (3 H, s), 2.06 (3 H, d, $J$ = 1.2 Hz), 2.44–3.24 (3 H, m), 4.84–5.40 (3 H, m), 5.66–6.14 (1 H, m), 5.67 (1 H, d, $J$ = 1.5 Hz), 6.24 (1 H, d, $J$ = 1.5 Hz), 7.06 (1 H, br s). Epiisolinderalactone (**5**, 12 mg) was heated (sealed tube in toluene) at 160–165 °C for 30 min. TLC analysis (benzene:ethyl acetate, 9:1) showed the complete disappearance of **5** and the formation of a more polar product **3**, isolated by TLC: IR ($CHCl_3$) 1755, 1660 $cm^{-1}$; $^1H$ NMR $\delta$ 1.59 (3 H, s), 2.05 (3 H, d, $J$ = 1.3 Hz), 5.16 (1 H), 5.73 (1 H), 6.80 (1 H), 7.04 (1 H, q, $J$ = 1.3 Hz).

**Isolinderalactone (2) and Its Cope Rearrangement to Linderalactone (1).** Treatment of **18** (107 mg) as for **18a** gave isolinderalactone (**2**, 38 mg, 34%): $^1H$ NMR $\delta$ 0.98 (3 H, s), 2.09 (3 H, d, $J$ = 1.2 Hz), 2.50–2.71 (2 H, m), 2.92–3.12 (1 H, b), 4.95–5.30 (3 H, m), 5.65 (1 H, d, $J$ = 1.5 Hz), 5.68–6.00 (1 H m), 6.32 (1 H, d, $J$ = 1.5 Hz), 7.12 (1 H, br s); MS calcd for $C_{15}H_{16}O_3$ 244.1099, found 244.1105.

A small sample of **2** (2 mg) (sealed tube in toluene) was heated at 160–165 °C for 20 min. TLC (benzene:ethyl acetate, 9:1) indicated the presence of two products **1** and **2**, by comparison with authentic samples of linderalactone (**1**) and isolinderalactone (**2**), respectively.[4,5]

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