Naturally Occurring Ten-Membered Lactones: Total Synthesis of (±)-Diplodialide A, (±)-Diplodialide C, and (±)-Decan-9-olide[1]

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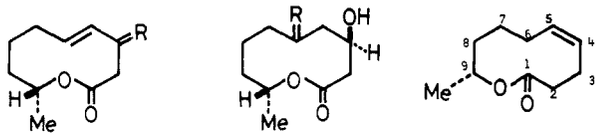
Diplodialide A (1) and diplodialide C (3), the culture filtrate of *Diplodia pinea*, and decan-9-olide (5), the metasternal secretion of *Phoracantha synonyma*, have been synthesized in racemic form from enediol bis(trimethylsilyl) enol ether 7.

Diplodialides A (1), B (2), C (3), and D (4), containing a ten-membered lactone moiety in their structures, are the first open-chain pentaketides isolated from *Diplodia pinea* (IFO 6472).



1 R = O 3 R = H_2 5 $\Delta^{4,5}$ = H_2

2 R = OH, H 4 R = O 6

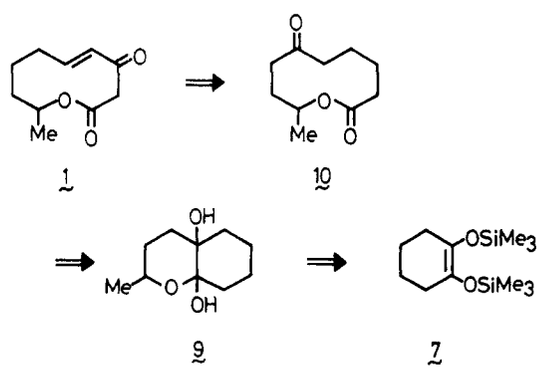
Wada and co-workers discovered that diplodialide A (1) showed a significant inhibitory activity against progesterone 11α-hydroxylase in vegetable cell cultures of *Rhizopus stolonifer* at 125 ppm.[2] Subsequently, decan-9-olide (5) and dec-4-en-9-olide (6) were isolated from the metasternal gland secretion of *Phoracantha synonyma* by Moore et al.[3]

Extensive studies have been recently reported on the total synthesis of these biologically important substances.[4] Herein, we wish to describe the details of our own work in this area, which provided a new method for the exclusive formation of the ten-membered lactone by oxidative cleavage of the bicyclic glycol 9.[5]

Retrosynthetic analysis of diplodialide A (1) suggests a need for formation of a bicyclic glycol 9 at an earlier stage of the synthesis. As is illustrated in Scheme I, the skeleton of the keto lactone 10 would be generated from the bicyclic glycol derivative 9 possessing an internal hemiketal ring system, in which the feasibility of a ring opening by oxidation could be assumed. Thus, one of the key steps in our synthesis is preparation of the bicyclic glycol 9, of which synthesis is shown in Scheme II.

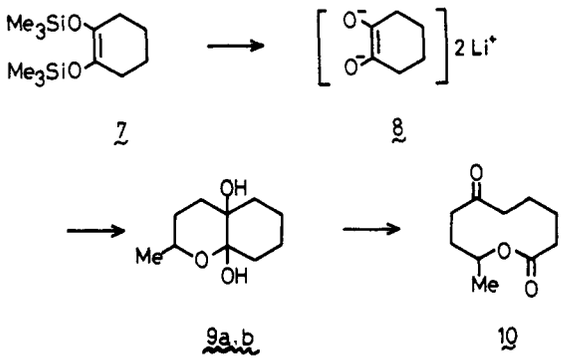
The enediol bis(trimethylsilyl) enol ether 7,[6] readily prepared in high yield by the modified acyloin condensation of

Scheme I



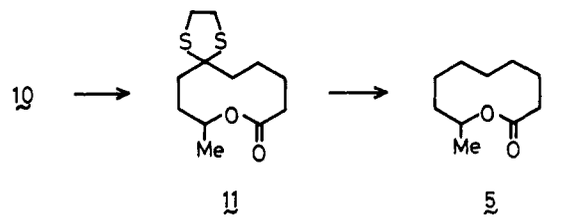
1 10 9 7

Scheme II



7 8 9a,b 10

Scheme III



10 11 5

diethyl adipate in the presence of chlorotrimethylsilane, was converted by addition of 2.0 equiv of methyllithium in monoglyme into its 1,2-enediolate 8, which was immediately subjected to alkylation with 3-hydroxy-1-iodobutane in tetrahydrofuran–hexamethylphosphoramide to give two diastereomeric bicyclic glycols, **9a** (mp 110–111 °C) and **9b** (mp 130–132 °C) in 87% isolated yield. The ring opening of **9a** and **9b** with lead tetraacetate in benzene was carried out to afford the desired keto lactone **10**, mp 44–44.5 °C (lit.[7] mp 37–37.5 °C), in nearly quantitative yield.

With the compound **10** as a substrate, we attempted the synthesis of racemic decan-9-olide (5), diplodialide C (3), and diplodialide A (1). Thioketalization of **10** with ethanedithiol in the presence of boron trifluoride afforded the corresponding dithio lactone 11 (mp 71–72 °C) in 90% yield, which upon desulfurization with Raney nickel in refluxing methanol provided (±)-decan-9-olide (5) in 90% yield (Scheme III). The synthetic material was identical with the natural olide by comparison with gas chromatography and mass spectrometry.[8]

Treatment[9] of **5** with phenylselenenyl bromide in the presence of lithium diisopropylamide in tetrahydrofuran at −78 °C followed by oxidation with 30% hydrogen peroxide at 0 °C for 1 h gave the cis-α,β-unsaturated lactone **12** in 82% yield (Scheme IV). Attempted epoxidation of **12** with basic hydrogen peroxide led to none of the desired epoxides. However, reaction of **12** with *m*-chloroperbenzoic acid using a catalytic amount of 4,4′-thiobis(6-*tert*-butyl-3-methylphenol)

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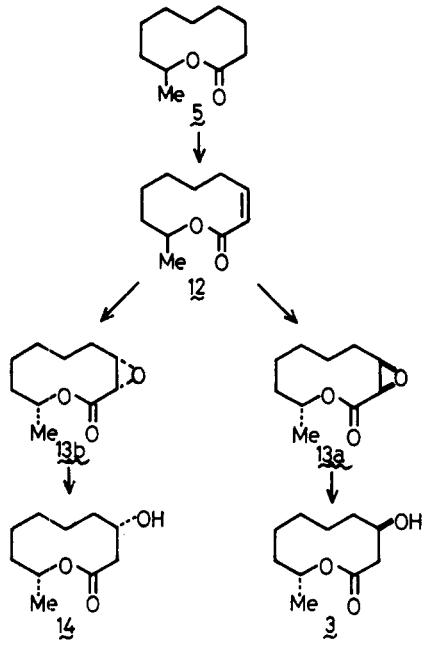
Scheme IV

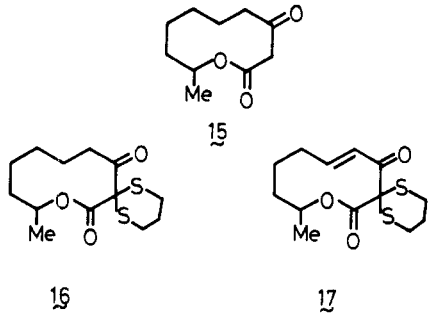


in refluxing ethylene dichloride[10] followed by preparative thin-layer chromatography on silica gel gave a 68% yield of the epoxy lactones **13a** and **13b** in a ratio of 1:2, respectively.

Since the stereochemical assignment of the epoxy lactones obtained in this way could not be fully confirmed by spectral data, we proceeded by the following chemical transformations to get a natural specimen. Reduction of **13a** with lithium metal in liquid ammonia containing *tert*-butyl alcohol at −45 °C afforded (±)-diplodialide C (**3**) in 45% yield, whose spectral properties were identical with those of the natural diplodialide C in all respects. By a similar reduction, **13b** gave epidiplodialide C (**14**) in 40% yield.

At first, a direct transformation of the trans-α,β-unsaturated dithioketo lactone **17** to diplodialide A (**1**) was attempted.

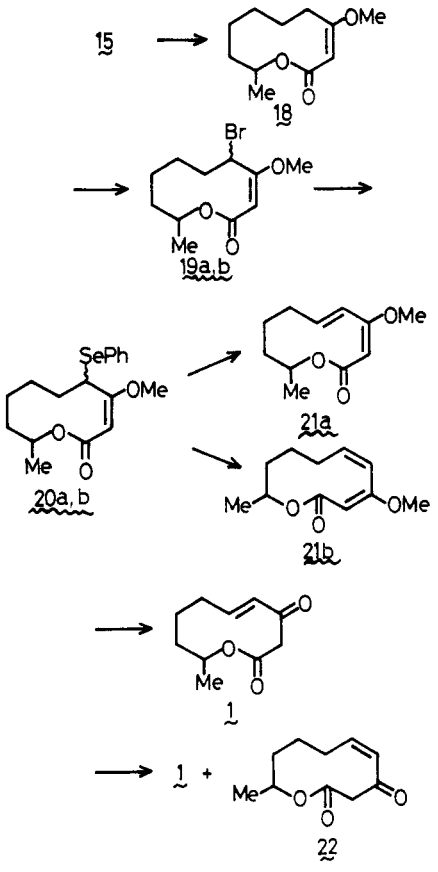
Oxidation of diplodialide C (**3**) and epidiplodialide C (**14**) with chromic anhydride in pyridine gave the same β-keto lactone **15.** The compound **15** was also obtained in 63% overall



yield from **12** through a similar sequence (epoxidation and reduction followed by oxidation) without isolation of the intermediates (**13a,b, 3,** and **14**). Treatment[11] of the β-keto lactone **15** with propane-1,3-dithiol di-*p*-toluenesulfonate gave the dithioketo lactone **16** in 97% yield. Selenenylation[9] of **16** with phenylselenenyl bromide in tetrahydrofuran at −78 °C followed by selective oxidation with 30% hydrogen peroxide at 0 °C provided the desired trans-α,β-unsaturated dithioketo lactone **17** in 50% yield. However, many attempts for desulfurization of **17** resulted in failure, and only the overreduced β-keto lactone **15** was obtained.

Subsequently, attention was turned to the enol ether lactone **18** as a potential precursor to introduce the double bond at the C-4 and C-5 positions. The β-keto lactone **15** was

Scheme V



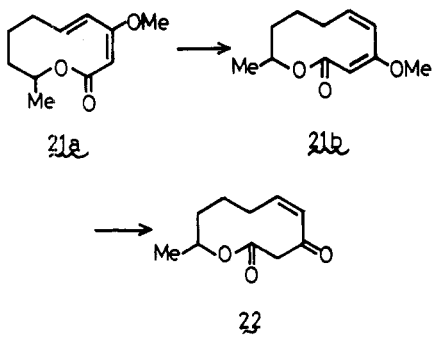
treated with dimethyl sulfate in refluxing methyl ethyl ketone to afford the enol ether lactone **18** in 90% yield (Scheme V). Bromination of **18** with *N*-bromosuccinimide in carbon tetrachloride gave a mixture of **19a** and **19b** in 32 and 58% yields, respectively.

Initial attempts for elimination of the bromo atom of **19a** and **19b** with various basic reagents were discouraging owing to the epimerization at C-4[12] with no formation of the diene lactone **21.** However, a difficult introduction of the double bond was finally achieved by utilizing the phenylselenenyl derivative in place of the bromo function. Selenenylation[13] of **19a** with sodium selenophenolate in ethanol at 50 °C for 6 h provided a 67% yield of the phenylseleno lactone **20a,** which was subjected to oxidation with 30% hydrogen peroxide at room temperature to give the diene lactone **21a** in nearly quantitative yield. In the same way, **19b** gave a 65% yield of **20b,** which in turn afforded a quantitative yield of the diene lactone isomer **21b.** We assumed that **21a** and **21b** are the cis and trans double-bond isomers introduced in this way, respectively. However, the correctness of this assignment could not be proven until the completion of the following chemical transformations. Hydrolysis of the diene lactone **21a** with trifluoroacetic acid in tetrahydrofuran at −20 °C for 2 h occurred to yield (±)-diplodialide A (**1**) as the sole product in 72% isolated yield, whose spectral properties were identical with those of the natural diplodialide A in all respects.

On the other hand, a similar treatment of the diene lactone isomer **21b** afforded a mixture of (±)-diplodialide A (**1**) and *cis*-diplodialide A (**22**) in a ratio of 7:5 (44%) together with unchanged **21b** (56%). *cis*-Diplodialide A (**22**) could be assumed to isomerize to diplodialide A (**1**) in a solution of trifluoroacetic acid.

It is noteworthy that during measurement of the NMR spectrum of the diene lactone **21a,** it was gradually changed with acid in the solvent to the diene lactone isomer **21b** and a prolonged exposure of the sample to the solvent finally

Scheme VI



furnished *cis*-diplodialide A (**22**)[14] (Scheme VI). On the basis of this observation, **21a** was treated with 10% hydrochloric acid in chloroform at room temperature overnight to give *cis*-diplodialide A (**22**) in 73% yield.

Experimental Section

Melting points were measured with a Yanaco MP-J2 hot stage microscope and with a Yamato MP-1 melting point apparatus. All melting points are uncorrected. Infrared (IR) spectra were obtained using a JASCO IRA-2 diffraction grating infrared spectrophotometer. Nuclear magnetic resonance (NMR) spectra were determined with a Hitachi R-24A (60 MHz) or a R-20B (60 MHz) spectrometer; high-field (100 MHz) FT NMR spectra were recorded on a JEOL FX-100 spectrometer. Chemical shifts are reported in parts per million on the δ scale, relative to tetramethylsilane as an internal standard. Data are presented as follows: chemical shift (multiplicity, integrated intensity, coupling constants). Mass spectra (MS) were recorded on a Hitachi RMU-7M or a JEOL D-300 mass spectrometer. Microanalyses were determined with a Yanagimoto CHN recorder MT-2. Thin-layer chromatography was carried out using Merck GF_{254} silica gel plates. Tetrahydrofuran (THF) and dimethoxyethane (DME) were distilled from lithium aluminum hydride; hexamethylphosphoramide (HMPA) was distilled from calcium hydride. Diethyl ether and benzene were dried over sodium metal. Enediolbis(trimethylsilyl) enol ether **7** was prepared from diethyl adipate by the acyloin condensation using chlorotrimethylsilane according to the modified procedure.[6]

1,6-Dihydroxy-3-methyl-2-oxabicyclo[4.4.0]decanes 9a and 9b. To a solution of 25.8 g (100 mmol) of enediol bis(trimethylsilyl) enol ether **7** in 200 mL of dry dimethoxyethane cooled to −20 °C was added dropwise over 30 min 125 mL (200 mmol) of a 1.60 M solution of methyllithium in ether. The heterogeneous mixture was stirred at −20 °C for 1 h. After removal of the solvent under vacuum, a mixed solvent of tetrahydrofuran–hexamethylphosphoramide (200 mL, 1:1) was added to the residue followed by the addition of 22.0 g (100 mmol) of 3-hydroxy-1-iodobutane via syringe over a 1-h period at −20 °C. The whole mixture was allowed to stir at room temperature for 17 h. The reaction mixture was diluted with brine, extracted with ether, dried over anhydrous magnesium sulfate, and concentrated to give the crude material, which was chromatographed on silica gel to give 16.18 g (87%) of a crystalline mixture of **9a** and **9b**. Fractional recrystallization from ether gave pure **9a** and **9b**, respectively. **9a:** mp 110–111 °C; IR (Nujol) ν_{max} 3558, 3293 cm^{-1}; NMR (Me_2SO-d_6) δ 1.03 (d, 3 H, J = 7 Hz), 3.57 (s, 1 H), 4.00 (m, 1 H), 5.32 (s, 1 H).

Anal. Calcd for $C_{10}H_{18}O_3$: C, 64.48; H, 9.74. Found: C, 64.45; H, 9.72.

9b: mp 130–132 °C; IR (Nujol) ν_{max} 3450, 3350 cm^{-1}; NMR (Me_2SO-d_6) δ 1.02 (d, 3 H, J = 7 Hz), 3.63 (s, 1 H), 4.00 (m, 1 H), 5.20 (s, 1 H).

Anal. Calcd for $C_{10}H_{18}O_3$: C, 64.48; H, 9.74. Found: C, 64.55; H, 9.74.

6-Oxodecan-9-olide (10). To a suspension of a mixture of **9a** and **9b** (15.98 g, 85.9 mmol) in 300 mL of dry benzene was added 57.15 g (129 mmol) of lead tetraacetate. After 2 h at room temperature, ethylene glycol (5 mL) was added to the reaction mixture and this solution was stirred for an additional 30 min. The organic layer was washed with aqueous sodium bicarbonate and dried over anhydrous magnesium sulfate. The solvent was evaporated in vacuo to leave the crude keto lactone. Purification on silica gel (elution with 3:1 *n*-hexane–ethyl acetate) gave 15.80 g (100%) of an oily product. Recrystallization from petroleum ether afforded pure crystalline keto lactone **10:** mp 44–44.5 °C (lit.[7] 37–37.5 °C); IR (Nujol) ν_{max} 1716, 1700, 1280 cm^{-1}; NMR (CCl_4) δ 1.21 (d, 3 H, J = 6 Hz), 4.95 (m, 1 H).

Anal. Calcd for $C_{10}H_{16}O_3$: C, 65.19; H, 8.75. Found: C, 64.96; H, 8.73.

6,6-(Ethylenedithio)decan-9-olide (11). To a solution of 25.76 g (140 mmol) of the keto lactone **10** in 200 mL of acetic acid cooled to 0 °C was added dropwise 21.0 g (150 mmol) of boron trifluoride. To this solution was added dropwise 14.1 g (150 mmol) of ethanedithiol over a 30-min period, and the resulting mixture was stirred at room temperature overnight. After concentration of the solvent under reduced pressure, the reaction mixture was diluted with water and extracted with ether. The organic layer was washed with aqueous sodium bicarbonate, dried over anhydrous magnesium sulfate, and evaporated to give the crude material, which was chromatographed on silica gel. Elution with *n*-hexane–ethyl acetate (10:1) gave 32.76 g (90%) of the ethylenedithio lactone **11**. Recrystallization from petroleum ether gave pure crystalline lactone **11:** mp 71–72 °C; IR (Nujol) ν_{max} 1720, 1220 cm^{-1}; NMR (CCl_4) δ 1.22 (d, 3 H, J = 6 Hz), 3.20 (s, 4 H), 4.90 (m, 1 H).

Anal. Calcd for $C_{12}H_{20}O_2S_2$: C, 55.34; H, 7.74; S, 24.62. Found: C, 55.41; H, 7.79; S, 24.62.

(±)-Decan-9-olide (5). To a solution of 30.0 g (115 mmol) of dithio lactone **11** in 500 mL of methanol was added Raney nickel (freshly prepared from 400 g of Raney nickel alloy), and the mixture was refluxed with stirring overnight. After filtration of the Raney nickel, the filtrate was evaporated in vacuo to give the crude material, which was chromatographed on silica gel. Elution with *n*-hexane–ethyl acetate (10:1) yielded 16.51 g (85%) of (±)-decan-9-olide (**5**) as a colorless oil: IR (film) ν_{max} 1720, 1240 cm^{-1}; NMR (CCl_4) δ 1.22 (d, 3 H, J = 7 Hz), 4.95 (m, 1 H); MS *m/e* 170 (M^+), 155 ($M^+ - CH_3$), 152 ($M^+ - H_2O$), 98; GLC[8] [(a) 12 ft of 5% Carbowax 20M on Gas Chrom Z] synthetic 10.28 min and natural 10.23 min, [(b) 6 ft of 5% OV-101 on Gas Chrom Q] synthetic 3.42 min and natural 3.43 min (both columns were maintained at 130 °C). Gas chromatography and mass spectrometry results were in accord with those of natural decan-9-olide.

(*Z*)-Dec-2-en-9-olide (12). To a solution of 6.0 g (60 mmol) of diisopropylamine in 100 mL of dry tetrahydrofuran at −78 °C was added dropwise 30 mL (60 mmol) of a 2.0 M solution of *n*-butyllithium in hexane. After 30 min at −78 °C, a solution of 8.5 g (50 mmol) of lactone **11** in 20 mL of dry tetrahydrofuran was added dropwise and the mixture was stirred at −78 °C for 1 h under an atmosphere of nitrogen. To this solution was added at once a solution of phenylselenenyl bromide prepared by the addition of bromine (1.62 mL, 30 mmol) to diphenyl diselenide (9.39 g, 30 mmol) in 30 mL of dry tetrahydrofuran. After the reaction mixture was brought to 0 °C, 30 mL of water and 6 mL of acetic acid were added to the mixture followed by the addition of 30% hydrogen peroxide (28 g). After additional stirring for 1 h at 0 °C, the product was isolated by addition of aqueous sodium bicarbonate followed by extraction with ether. Evaporation of the solvent, dried over anhydrous magnesium sulfate, gave an oily residue, which was chromatographed on silica gel. Elution with *n*-hexane–ether (10:1) gave 6.89 g (82%) of pure unsaturated lactone **12:** IR (film) ν_{max} 3036, 1710, 1621, 814 cm^{-1}; NMR (CCl_4) δ 1.33 (d, 3 H, J = 7 Hz), 5.10 (m, 1 H), 5.72 (dd, 1 H, J = 1 and 11.5 Hz), 6.25 (m, 1 H); UV (EtOH) λ_{max} 212 nm; MS *m/e* 168 (M^+), 124, 98.

2,3-Epoxydecan-9-olides 13a and 13b. To a solution of 126 mg (0.75 mmol) of the unsaturated lactone **12** in 20 mL of ethylene dichloride in the presence of 4,4′-thiobis(6-*tert*-butyl-3-methylphenol) was added 170 mg (0.85 mmol) of *m*-chloroperbenzoic acid. After the reaction mixture was refluxed with stirring for 17 h, the solvent was removed in vacuo and the residue was taken up in methylene chloride and washed with a 5% sodium hydroxide solution. The solvent, dried over anhydrous magnesium sulfate, was evaporated to give 126 mg of crude product, which was separated by preparative thin-layer chromatography on silica gel using *n*-hexane–ether (10:1). There was obtained 27 mg (19%) of **13a** and 50 mg (36%) of **13b** as an oil, respectively. **13a:** IR (film) ν_{max} 1746, 1200, 1175 cm^{-1}; NMR (CCl_4) δ 1.30 (d, 3 H, J = 7 Hz), 2.80–3.05 (m, 1 H), 3.50 (d, 1 H, J = 5 Hz), 5.40 (m, 1 H); MS *m/e* 128 (M^+), 127, 109. **13b:** IR (film) ν_{max} 1723, 1290, 1035 cm^{-1}; NMR (CCl_4) δ 1.28 (d, 3 H, J = 7 Hz), 3.00–3.36 (m, 2 H), 5.10 (m, 1 H); MS *m/e* 128 (M^+), 127, 109.

(±)-Diplodialide C (3) and Epidiplodialide C (14). To a solution of 10 mL of liquid ammonia containing 4 mg (0.57 mmol) of lithium metal cooled to −45 °C was added a solution of 50 mg (0.27 mmol) of the epoxy lactone **13a** and *tert*-butyl alcohol (1 drop) in 4 mL of dry ether–tetrahydrofuran (1:1). After the addition was complete, the reaction mixture was stirred for 15 min at −45 °C. The reaction was quenched by the addition of solid ammonium chloride. The product was purified by preparative thin-layer chromatography on silica gel using *n*-hexane–ethyl acetate (3:2) to give 23 mg (45%) of (±)-diplodialide C (**3**) as a colorless oil: IR (CCl_4) ν_{max} 3600, 3400, 1725, 1250,

1030 cm^{-1}; NMR (CCl_4) δ 1.22 (d, 3 H, J = 7 Hz), 2.20 (dd, 1 H, J = 9 and 15 Hz), 2.70 (dd, 1 H, J = 4 and 15 Hz), 4.20 (m, 1 H), 4.90 (m, 1 H). The NMR and IR spectra were in complete accord with those of natural diplodialide C provided by Dr. K. Wada.

Following a procedure similar to that described above, 27 mg (0.146 mmol) of **13b** gave 11 mg (40%) of epidiplodialide C (**14**) as an oil: IR (CCl_4) ν_{max} 3616, 3439, 1723, 1180, 1040 cm^{-1}; NMR (CCl_4) δ 1.22 (d, 3 H, J = 7 Hz), 2.10–2.70 (m, 2 H), 3.90 (m, 1 H), 4.85 (m, 1 H); MS m/e 168 ($M^+ - H_2O$), 150, 109, 98.

3-Oxodecan-9-olide (15). (a) Oxidation of a Mixture of (±)-Diplodialide C (3) and Epidiplodialide C (14). To a solution of 15.8 g (200 mmol) of pyridine in 200 mL of methylene chloride was added with vigorous stirring 10.0 g (100 mmol) of chromic anhydride, and the mixture was stirred at room temperature for 30 min. To this solution was added a solution of 4.59 g (24.6 mmol) of a mixture of **3** and **14** in 5 mL of methylene chloride. The whole mixture was stirred at room temperature for 5 h. After removal of the solvent under reduced pressure, the residue was taken up in ether and washed with aqueous sodium bicarbonate. The organic layer was dried over anhydrous magnesium sulfate and evaporated to afford the crude product **15.** Purification on silica gel using n-hexane–ethyl acetate (10:1) gave 3.746 g (82%) of pure β-keto lactone **15** as an oil: IR (film) ν_{max} 1740, 1710, 1270 cm^{-1}; NMR (CCl_4) δ 1.23 (d, 3 H, J = 6 Hz), 3.22 (s, 2 H), 5.00 (m, 1 H); UV (5% KOH–MeOH) λ_{max} 276 nm; MS m/e 184 (M^+), 166, 151, 143, 125.

(b) Respective Oxidation of 3 and 14. By a similar oxidation to that described above, 3 mg (16 μmol) of **3** and 5 mg (26 μmol) of **14** gave 1 and 2 mg of the same β-keto lactone **15,** respectively.

2,2-(Propanedithio)-3-oxodecan-9-olide (16). To a solution of 184 mg (1 mmol) of β-keto lactone **15** in 5 mL of anhydrous ethanol was added 457 mg (1.1 mmol) of propane-1,3-dithiol di-p-toluenesulfonate and 686 mg (7 mmol) of potassium acetate. The reaction mixture was refluxed overnight. After removal of the solvent in vacuo, the residue was extracted with ether and dried over anhydrous magnesium sulfate. Evaporation of the solvent and purification by chromatography on silica gel using n-hexane–ethyl acetate (5:1) gave 280 mg (97%) of pure lactone **16** as a colorless oil: IR (film) ν_{max} 1730, 1710, 1230 cm^{-1}; NMR (CCl_4) δ 1.28 (d, 3 H, J = 7 Hz), 2.30–3.40 (m, 6 H), 5.00 (m, 1 H); MS m/e 290, 289, 288 (M^+), 192, 163, 146.

2,2-(Propanedithio)diplodialide A (17). To a solution of 160 mg (1.6 mmol) of diisopropylamine in 10 mL of dry tetrahydrofuran at −78 °C was added dropwise 0.8 mL (1.5 mmol) of a 1.9 M solution of n-butyllithium in hexane. After the mixture was stirred for 30 min, a solution of 257 mg (0.89 mmol) of lactone **16** in 5 mL of dry tetrahydrofuran was added dropwise and the mixture was stirred at −78 °C for an additional 1 h under an atmosphere of nitrogen. To this solution was added at once a solution of phenylselenenyl bromide prepared by the addition of bromine (0.03 mL, 1.2 mmol) to diphenyl diselenide (300 mg, 2 mmol) in 5 mL of dry tetrahydrofuran. After the reaction mixture was warmed to 0 °C, 0.6 mL of water and 0.12 mL of acetic acid were added to the mixture followed by the addition of 30% hydrogen peroxide (0.65 g). Stirring was continued at 0 °C for 1 h, and the product was isolated by the addition of aqueous sodium bicarbonate followed by extraction with ether. Evaporation of the solvent gave 274 mg of crude material, which was purified by preparative thin-layer chromatography on silica gel using n-hexane–ethyl acetate (5:1) to provide 128 mg (50%) of **17.** Recrystallization from ether–n-hexane afforded pure **17:** mp 105–106 °C; IR (Nujol) ν_{max} 1720, 1690, 1630 cm^{-1}; NMR ($CDCl_3$) δ 1.22 (d, 3 H, J = 6 Hz), 2.60–3.60 (m, 6 H), 5.18 (m, 1 H), 6.14 (d, 1 H, J = 16 Hz), 6.60 (m, 1 H); UV (EtOH) λ_{max} 235 nm; MS m/e 288, 287, 286 (M^+), 258, 163, 146.

(*E*)-3-Methoxydec-2-en-9-olide (18). To a solution of 368 mg (2 mmol) of β-keto lactone **15** in 30 mL of dry methyl ethyl ketone was added with stirring 227 mg (2.2 mmol) of diethyl sulfate in the presence of excess potassium carbonate (6.0 g). After the reaction mixture was refluxed overnight, the solvent was removed under reduced pressure. The residue was extracted with ether, and the combined organic layer was dried over anhydrous magnesium sulfate. Evaporation of the solvent gave the crude product **18,** which was chromatographed on silica gel using n-hexane–ether (5:1) to afford 356 mg (90%) of pure enol ether lactone **18:** IR (film) ν_{max} 1690, 1600, 1210, 1040, 840, 810 cm^{-1}; NMR (CCl_4) δ 1.28 (d, 3 H, J = 7 Hz), 3.60 (s, 3 H), 4.80 (s, 1 H), 5.04 (m, 1 H); UV (EtOH) λ_{max} 238 nm; MS m/e 198 (M^+), 183, 170, 154, 111.

(*E*)-4-Bromo-3-methoxydec-2-en-9-olides 19a and 19b. To a solution of 198 mg (1 mmol) of the enol ether lactone **18** in 15 mL of carbon tetrachloride in the presence of 1 mg of benzoyl peroxide was added 178 mg (1 mmol) of N-bromosuccinimide. The reaction mixture was refluxed for 3 h. After removal of the solvent under reduced pressure, the resulting residue was extracted with ether. The organic layer was washed with water, dried over anhydrous magnesium sulfate, and concentrated in vacuo to give the crude material. The crude product was purified by preparative thin-layer chromatography on silica gel using n-hexane–ethyl acetate (10:1) to give 89 mg (32%) of **19a** and 160 mg (58%) of **19b** as an oil, respectively. **19a:** IR (film) ν_{max} 1705, 1600, 1210, 1050, 800 cm^{-1}; NMR ($CDCl_3$) δ 1.34 (d, 3 H, J = 6 Hz), 3.69 (s, 3 H), 4.98 (s, 1 H), 4.98 (t, 1 H, J = 5.8 Hz); UV (EtOH) λ_{max} 241 nm; MS m/e 278, 276 (M^+), 263, 261, 250, 248, 236, 234. **19b:** IR (film) ν_{max} 1690, 1590, 1230, 1050, 815, 740 cm^{-1}; NMR ($CDCl_3$) δ 1.31 (d, 3 H, J = 6.4 Hz), 3.71 (s, 3 H), 5.02 (s, 1 H), 5.97 (t, 1 H, J = 6.6 Hz); UV (EtOH) λ_{max} 242 nm; MS m/e 278, 276 (M^+), 263, 261, 250, 248, 236, 234.

(*E*)-3-Methoxy-4-(phenylseleno)dec-2-en-9-olides 20a and 20b. To a solution of 86 mg (0.31 mmol) of bromo lactone **19a** in 10 mL of anhydrous ethanol was added 107 mg (0.34 mmol) of diphenyl diselenide. To this suspension cooled to 0 °C was added 13 mg (0.34 mmol) of sodium borohydride. After the addition was complete, the mixture was heated to 50 °C for 6 h under an atmosphere of nitrogen. Evaporation of the solvent followed by extraction with methylene chloride gave the crude oily product. Purification of the crude material by preparative thin-layer chromatography on silica gel using n-hexane–ethyl acetate (5:1) gave 75 mg (67%) of pure lactone **20a** as a colorless oil: IR (film) ν_{max} 3050, 1690, 1600, 1580, 740, 690 cm^{-1}; NMR ($CDCl_3$) δ 1.25 (d, 3 H, J = 6.6 Hz), 3.67 (s, 3 H), 5.09 (s, 1 H), 5.24 (m, 1 H), 5.48 (dd, 1 H, J = 5 and 11 Hz), 7.20–7.80 (m, 5 H); UV (EtOH) λ_{max} 223, 240 nm; MS m/e 356, 354, 352, 351, 350, 348 (M^+).

By a similar sequence to that described above for the preparation of **20a,** 30 mg (0.10 mmol) of **19b** yielded 23 mg (65%) of **20b** after purification by preparative thin-layer chromatography on silica gel: IR (film) ν_{max} 3050, 1710, 1600, 1580, 740, 700 cm^{-1}; NMR ($CDCl_3$) δ 1.32 (d, 3 H, J = 6 Hz), 3.62 (s, 3 H), 4.28 (dd, 1 H, J = 6 and 8 Hz), 4.66 (m, 1 H), 4.99 (s, 1 H), 7.10–7.70 (m, 5 H); UV (EtOH) λ_{max} 220, 240 nm; MS m/e 356, 354, 352, 351, 350, 348 (M^+).

(*E,E*)-3-Methoxydeca-2,4-dien-9-olide (21a) and (*E,Z*)-3-Methoxydeca-2,4-dien-9-olide (21b). A solution of 79 mg (0.22 mmol) of the seleno lactone **20a** in 5 mL of tetrahydrofuran was treated with a 30% hydrogen peroxide solution at room temperature for 3 h. The reaction mixture was taken up in methylene chloride. The organic layer was washed with aqueous sodium bicarbonate and dried over anhydrous magnesium sulfate, and the solvent was evaporated in vacuo to give the crude diene lactone. Purification of the diene lactone by preparative thin-layer chromatography on silica gel using n-hexane–ethyl acetate (5:1) gave 42 mg (95%) of pure diene lactone **21a** as a colorless oil: IR (film) ν_{max} 1690, 1590, 1220, 800 cm^{-1}; NMR (CCl_4–Me_2SO-d_6, 1:1) δ 1.14 (d, 3 H, J = 6.4 Hz), 3.60 (s, 3 H), 4.59 (m, 1 H), 4.89 (s, 1 H), 5.80 (d, 1 H, J = 2 Hz), 5.84 (d, 1 H, J = 2 Hz); UV (EtOH) λ_{max} 256 nm; MS m/e 196 (M^+), 181, 127, 98.

By analogy to the reaction described above, 38 mg (0.10 mmol) of **20b** gave 22 mg (100%) of the diene lactone isomer **21b** as a colorless oil: IR (film) ν_{max} 1690, 1600, 1210, 810, 740 cm^{-1}; NMR (CCl_4–Me_2SO-d_6, 1:1) δ 1.45 (d, 3 H, J = 6.4 Hz), 3.63 (s, 3 H), 4.97 (m, 1 H), 5.08 (s, 1 H), 5.76–5.90 (m, 2 H); UV (EtOH) λ_{max} 261 nm; MS m/e 196 (M^+), 181, 127, 125, 98.

(±)-Diplodialide A (1) and *cis*-Diplodialide A (22). (a) Hydrolysis of (*E,E*)-3-Methoxydeca-2,4-dien-9-olide (21a). A solution of 18 mg (0.09 mmol) of the diene lactone **21a** in 2 mL of tetrahydrofuran was treated with trifluoroacetic acid (2 mL) at −20 °C for 2 h. The reaction mixture was neutralized with aqueous sodium bicarbonate and extracted with methylene chloride. After removal of the solvent, the crude product was purified by preparative thin-layer chromatography on silica gel using n-hexane–ethyl acetate (5:1) to afford 12 mg (72%) of (±)-diplodialide A (**1**) as a colorless oil: IR (CCl_4) ν_{max} 1735, 1705, 1645, 1260, 965 cm^{-1}; NMR ($CDCl_3$) δ 1.26 (d, 3 H, J = 7 Hz), 3.34 (d, 1 H, J = 14.5 Hz), 3.79 (d, 1 H, J = 14.5 Hz), 5.14 (m, 1 H), 5.80 (d, 1 H, J = 16 Hz), 6.52–6.90 (m, 1 H); UV (EtOH) λ_{max} 232 nm; MS m/e 182 (M^+), 164, 154, 122, 68. The NMR, IR, UV, and mass spectra were identical with those of natural diplodialide A kindly provided by Dr. K. Wada.

(b) Hydrolysis of (*E,Z*)-3-Methoxydeca-2,4-dien-9-olide (21b). A solution of 40 mg (0.20 mmol) of the diene lactone isomer **21b** in 2 mL of tetrahydrofuran was treated with trifluoroacetic acid (2 mL) at −20 °C for 2 h. After a similar workup, the crude product was purified by preparative thin-layer chromatography on silica gel using n-hexane–ethyl acetate (5:1). There was obtained a mixture of 16 mg (44%) of diplodialide A (**1**) and *cis*-diplodialide A (**22**) together with 22 mg (56%) of the unchanged diene lactone **21b.** The mixture of these products (16 mg) was purified again by preparative thin-layer chromatography on silica gel impregnated with silver nitrate using the same solvent system to give 7 mg of (±)-diplodialide A (**1**) and 5 mg

of *cis*-diplodialide A (**22**), respectively. Recrystallization of *cis*-diplodialide A (5 mg) from *n*-hexane–ether gave pure **22**: mp 58 °C; IR (film) ν_{max} 1740, 1700, 1640, 1260 cm^{-1}; NMR (acetone-d_6) δ 1.23 (d, 3 H, J = 6.8 Hz), 3.32 (d, 1 H, J = 14.7 Hz), 3.50 (d, 1 H, J = 14.7 Hz), 5.07 (m, 1 H), 5.71 (ddd, 1 H, J = 4.5, 10, and 12 Hz), 6.18 (dd, 1 H, J = 1.9 and 12 Hz); UV (EtOH) λ_{max} 225 nm; MS *m/e* 182 (M$^+$), 164, 154, 122, 95.

(c) Hydrolysis of 21a with 10% Hydrochloric Acid. A solution of 22 mg (0.11 mmol) of **21a** in 5 mL of chloroform containing 1 drop of 10% hydrochloric acid was stirred at room temperature overnight. After removal of the solvent under reduced pressure, the crude product was purified by preparative thin-layer chromatography on silica gel impregnated with silver nitrate using *n*-hexane–ethyl acetate (5:1) to afford 15 mg (73%) of *cis*-diplodialide A (**22**) as colorless needles.

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Registry No.—**1**, 68296-70-8; **3**, 65450-86-4; **5**, 67400-99-1; **7**, 6838-67-1; **9**, 13030-90-5; **10**, 65371-25-7; **11**, 65371-26-8; **12**, 65371-27-9; **13a**, 65371-28-0; **13b**, 65391-45-9; **14**, 65450-87-5; **15**, 64681-03-4; **16**, 69653-43-6; **17**, 69653-44-7; **18**, 69653-45-8; **19a**, 69653-46-9; **19b**, 69744-58-7; **20a**, 69653-47-0; **20b**, 69685-69-4; **21a**, 69653-48-1; **21b**, 69653-49-2; **22**, 69685-70-7; 3-hydroxy-1-iodobutane, 6089-15-2.

References and Notes

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(12) Treatment of either **19a** or **19b** with *s*-collidine afforded the same proportional mixture of **19a** and **19b** in a ratio of 3:4.
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(14) An NMR spectrum of **21a** in deuteriochloroform after 30 min at room temperature exhibited in addition to a singlet at δ 4.89 (C-2 H) originating from **21a** a singlet at δ 5.08 (C-2 H) resulting from **21b**. After the sample had stood overnight, an NMR spectrum revealed none of **21a** and **21b** and showed signals owing to *cis*-diplodialide A (**22**).

East Indian Sandalwood Oil. 1. Stereoselective Synthesis of (±)-β-Santalene and (±)-β-Santalol†,[1]

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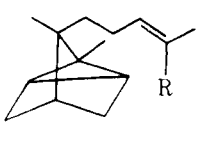
Sulfuric acid catalyzed rearrangement of γ-lactone **10** provides δ-lactone **11** as the major product. Reduction of **11** to lactols **12** with diisobutylaluminum hydride, followed by a Wittig reaction with isopropyltriphenylphosphorane, gives alcohol **13**, which is readily dehydrated to (±)-β-santalene (**5**). Acid-catalyzed alcoholysis of **11** provides ester **34**, whereas ammonolysis of **11** and dehydration of the intermediate hydroxyamide **32** with *p*-toluenesulfonyl chloride in pyridine provides nitrile **33**. Reduction of **33** or **34** with diisobutylaluminum hydride yields aldehyde **31**, which has been converted to (±)-β-santalol (**2**), (±)-*trans*-β-santalol (**7**), and dihydro-β-santalol (**3**). Compounds of the related iso series (**38**, **43**, and **46**) have been prepared from γ-lactone **10** using a similar sequence of reactions.

East Indian sandalwood oil, highly prized by perfumers for its sweet, woody fragrance, contains the sesquiterpene alcohols α-santalol (**1**) and β-santalol (**2**).[2] Other related sesquiterpenes in the oil include dihydro-β-santalol (**3**),[3] α-santalene (**4**), and β-santalene (**5**).[2] Many minor components have been identified,[4] several of which contribute to the overall odor character, but the santalols, which account for about 90% of the oil, are generally considered to be responsible for the main odor character.

The use of large quantities of East Indian sandalwood oil by the fragrance industry, together with the relatively high price and a sometimes sporadic supply of the oil, has encouraged research chemists to search for syntheses of the odor significant components. This report describes a new stereoselective synthesis of (±)-β-santalene (**5**) and (±)-β-santalol (**2**) from racemic camphene (**6**). In addition, (±)-*trans*-β-santalol (**7**), dihydro-β-santalol (**3**), tetrahydro-β-santalol (**8**), and compounds of the related iso series have been prepared. Previous syntheses were recently reviewed.[5]



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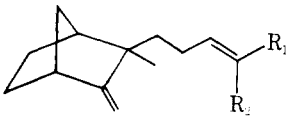
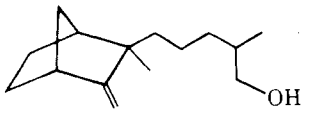


2, R_1 = CH_3; R_2 = CH_2OH
5, R_1 = R_2 = CH_3
7, R_1 = CH_2OH; R_2 = CH_3



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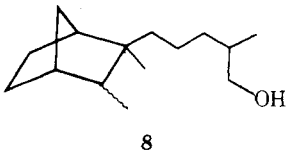

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† Dedicated to Professor Sir Derek Barton on the occasion of his 60th birthday.

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