Synthesis of Malyngolide, an Antibiotic from the Marine Blue-Green Alga *Lyngbya majuscula* Gomont

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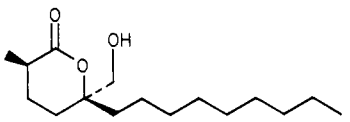
Malyngolide (1) was synthetized, starting from the condensation of dianion 2, obtained by metalation with lithium diisopropylamide of the sodium salt of tiglic acid, and decanal. Successive esterification of **3a** and oxidation with Jones reagent of **4a** afforded **5** in very good yield. Olefination of **5** with methylenemagnesium iodide gave **6**, which was converted to the corresponding iodolactone **7**. Hydrolysis of **7** to **1** was accomplished by $Hg(ClO_4)_2$ in dimethoxyethane/water (path A). Malyngolide (1) was also obtained by condensation of **2** with 2-[(2-oxoundec-1-yl)oxy]tetrahydropyran (**9b**). Removal of the THP protecting group in **10** by 6 N HCl affords **1** (path B).

Recently the isolation and structure determination of malyngolide (**1**), the major antibiotic in the lipid extract



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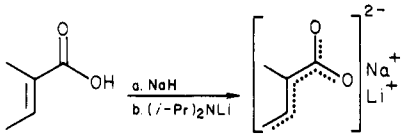
of the shallow water variety of the blue-green alga *Lyngbya majuscula* Gomont from Kahala Beach, Oahu, has been reported.[1]

In connection with our interest in total synthesis of head to tail terpenoids starting from dienolates derived from a C_5 unit with a prenyl structure,[2] we report the synthesis of racemic **1** starting from the dianion **2** of tiglic acid.[3] We



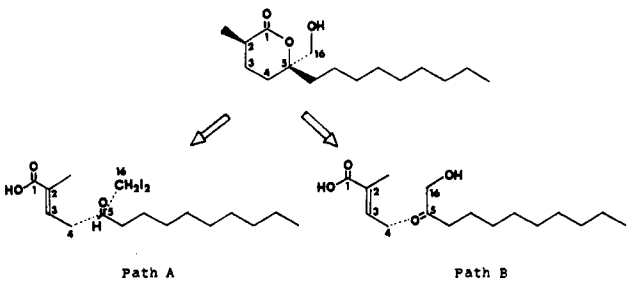
2

envisioned a strategy in which the segment C_1–C_4 of the lactone ring is provided by tiglic acid, while the tetrasubstituted C_5 atom and the side chains are supplied in path A by decanal and methylene iodide and in path B by 2-oxoundecan-1-ol (Scheme I).

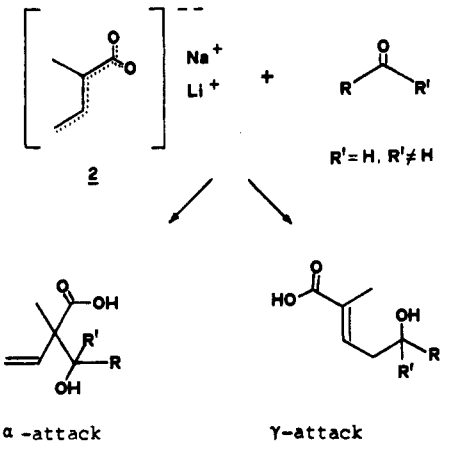
The dianion **2** was readily prepared by adding 1 equiv of lithium diisopropylamide at 0 °C to a suspension of the sodium salt of tiglic acid, obtained from the acid and sodium hydride in dry THF. The dianion **2** in THF is a homogeneous, quite stable solution that can be handled at room temperature without self-condensation.

It is known that the ambidentate nature of an allylic nucleophilic center may lead to attack from both the α and γ positions. The reaction of a dienolate with a carbonyl compound at low temperature under kinetically controlled conditions leads to α attack; at higher temperatures electrophilic attack at the α position becomes reversible, consequently leading to the exclusive formation of the thermodynamically more stable δ-hydroxy acid.[4]

Scheme I



Scheme II



The behavior of **2** toward carbonyl compounds is the same as previously observed for the dianion obtained by metalation with lithium diisopropylamide of the sodium salt of 3-methyl-2-butenoic acid.[2] In fact only attack at the α position was observed when a carbonyl compound was added to **2** at −78 °C in dry THF. On the other hand γ condensation occurred exclusively on adding a carbonyl compound to a solution of **2** in THF/HMPA (9:1) at room temperature or at reflux (Scheme II).

Results and Discussion

Path A. As indicated in Scheme III, of the 16 carbon atoms in the malyngolide backbone, a hydroxy acid (**3a**) was synthesized in 70% yield by reaction of **2** with decanal at −78 °C (overnight) and room temperature (36 h) and converted to methyl ester **3b** by treatment with diazo-

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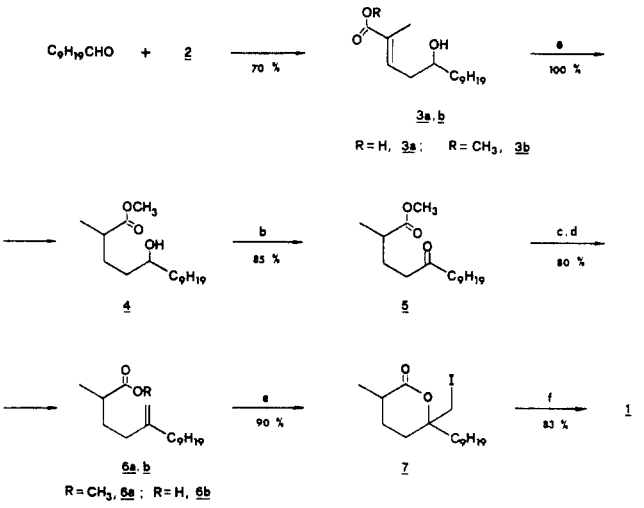
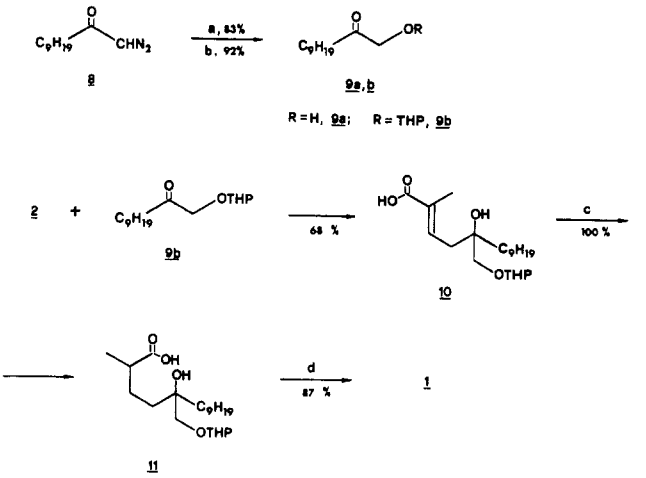
Scheme III[a]



[a] (a) H_2/Pd-C; (b) Jones reagent; (c) $CH_2(MgI)_2$; (d) KOH; (e) I_2/CH_3CN; (f) $Hg(ClO_4)_2$.

Scheme IV[a]



[a] (a) 2 N H_2SO_4; (b) DHP, Amberlyst H15; (c) H_2/Pd-C; (d) 6 N HCl.

methane. The reaction is highly regio- and stereoselective, giving only the (*E*)-hydroxy ester **3b** derived from α attack, as shown by the ^1H NMR spectrum, which contains a triplet for the vinylic hydrogen at δ 6.85.[5]

Reduction of **3b** with H_2 on Pd/C to the saturated ester **4** proceeded in quantitative yield, whereas the reduction of **3a** under the same conditions afforded the corresponding saturated lactone.

Oxidation of **4** was accomplished with Jones reagent in acetone at 0 °C, to give the ester **5** in 85% yield.[6]

The C_{16} carbon atom of the malyngolide backbone was introduced by using methylenemagnesium iodide, a very useful methylenation reagent.[7] This reagent, prepared from methylene iodide and Mg/Hg amalgam in dry ether–benzene (1:1), rapidly olefinates carbonyl compounds in a few minutes at room temperature. Ester **6a**, obtained in 80% yield, showed the typical IR absorption for the terminal double bond at 905 cm^{-1} and an ^1H NMR signal characteristic of two vinylic hydrogens at δ 4.7 and was hydrolyzed to the acid (**6b**) in quantitative yield.

Ring closure to a δ-lactone was accomplished by the iodolactonization reaction. This reaction has been used to regioselectively functionalize the double bond and proceeds smoothly in high yield both with *N*-iodosuccinimide (NIS) in $CHCl_3$[8] or with I_2 in acetonitrile.[9] Little stereoselectivity was observed in the cyclization,[10] since a 60:40 mixture of diastereoisomeric iodolactones was isolated under both sets of conditions, as determined by ^1H NMR analysis.

The hydrolysis of iodolactone **7** to the corresponding alcohol was tested under several conditions, but good results were observed only with mercury(II) perchlorate in dimethoxyethane/water (9:1).[11] Under these conditions, malyngolide (**1**) was obtained in 91% yield after 30 min at 50 °C.

Path B. An alternative approach to **1** consists in the reaction between **2** and 2-[(oxoundec-1-yl)oxy]tetrahydropyran (**9b**) (Scheme IV).

Treatment of decanoyl chloride with an excess of diazomethane in dry ether afforded the corresponding diazo ketone **8**, isolated in quantitative yield as a crystalline solid.[12,13] On addition of 2 N H_2SO_4 to a solution of diazo ketone **8** in dioxane and then warming to 50 °C, the ketol **9a** was obtained as an oil which, after silica gel chromatography, was isolated in crystalline form. The reaction of the THP derivative (**9b**) with the dianion **2** at −78 °C, then at room temperature, and subsequently at 50 °C, followed by the usual workup, gave acid **10** in 68% yield. The mass spectrum of **10** showed *m/e* 370 (M^+) and 255 ($M^+ - CH_2OTHP$) and the ^1H NMR spectrum showed a triplet at δ 6.9 (J = 6 Hz), thus confirming the *E* configuration of the double bond.

Reduction of **10** with H_2 on Pd/C gave in quantitative yield the saturated acid **11**. Hydrolysis and lactonization of the latter were performed by 6 N HCl in methanolic solution and warming at 45 °C for 30 min. Malyngolide (**1**) was thus obtained pure in 87% yield after silica gel chromatography.

Experimental Section

General Procedures. Infrared spectra (IR) were recorded on a Perkin-Elmer 710B spectrophotometer and the frequencies are given in reciprocal centimeters. ^1H NMR spectra were determined in $CDCl_3$ on a Perkin-Elmer R12B spectrophotometer and the chemical shifts are expressed in parts per million from internal tetramethylsilane. Mass spectra were taken on a Varian MAT 111 instrument (70 eV). Thin-layer chromatography (TLC) was performed on silica gel sheets (IB2-F, Baker) and column chromatography on silica gel 60 (70–230 mesh, Merck).

Tetrahydrofuran (THF) was obtained anhydrous and oxygen-free by distillation over sodium benzophenone ketyl under argon. Diisopropylamine was distilled from calcium hydride and stored over molecular sieves under argon. Hexamethylphosphoric triamide (HMPA) was distilled over molecular sieves and stored under argon. *n*-Butyllithium was purchased from Fluka as a 1.5 M solution in *n*-hexane.

Methyl (*E*)-2-Methyl-5-hydroxytetradec-2-enoate (3b). To a suspension of NaH (1.44 g of 50% dispersion in oil, 30 mmol) in dry THF (50 mL) at 0 °C under argon was added tiglic acid (3 g, 30 mmol) in dry THF (30 mL) and the mixture was stirred

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at 40 °C for 3 h. The solution was cooled to 0 °C and then lithium diisopropylamide (prepared from 4.2 mL of diisopropylamine (4.23 g, 30 mmol) and 19.8 mL of a 1.5 M solution of *n*-BuLi (30 mmol) in *n*-hexane) in THF (30 mL) was slowly added. The mixture was stirred for 0.5 h and then heated for 1.5 h at 40 °C. After the mixture was cooled to −78 °C, dry HMPA (10 mL) was added and decanal (4.68 g, 30 mmol) in dry THF (30 mL) was slowly dropped in over a 1-h period; the reaction mixture was stirred at −78 °C overnight, then allowed to warm to room temperature, and stirred for 36 h. Ice–water and 2 N HCl were added and the mixture was extracted with ether. The ether extracts were washed with water and dried ($MgSO_4$). Removal of the solvent, esterification of the residues using an excess of diazomethane in ether, and successive chromatography on silica gel with hexane–ethyl acetate (7:3) as eluant afforded **3b** (5.67 g, 70% yield) as a clear oil: IR (neat) 3400 (OH), 1700 (C=O), 1640 (C=C) cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.9 (t, 3 H, CH_3), 1.1–1.8 (m, 16 H, CH_2), 1.85 (s, 3 H, CH_3C=C), 2.35 (t, 2 H, CH_2C=C, J = 7 Hz), 2.65 (s, 1 H, OH), 3.75 (s, 3 H, OCH_3), 3.55–3.9 (m, 1 H, CHOH), 6.9 (t, 1 H, CH=, J = 7 Hz); mass spectrum (70 eV), m/e 252 (M^+ − 18), 239 (M^+ − 31).

Anal. Calcd for $C_{16}H_{30}O_3$: C, 71.07; H, 11.18. Found: C, 70.78; H, 11.04.

Methyl 2-Methyl-5-hydroxytetradecanonate (4). The ester **3b** (6.75 g, 25 mmol) in methanol (50 mL) was hydrogenated over 10% Pd/C (250 mg) at atmospheric pressure until starting material disappeared on TLC analysis. After filtration from the catalyst and removal of the solvent, **4** was obtained as an oil in a quantitative yield: IR (neat) 3400 (OH), 1720 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.9 (t, 3 H, CH_3), 1.1–1.8 (m, 23 H, CH_2 and $CHCH_3$), 2.2–2.7 (m, 1 H, $CHCH_3$), 3.45 (s, 1 H, OH), 3.4–3.7 (m, 1 H, CHOH), 3.7 (s, 3 H, OCH_3); mass spectrum (70 eV), m/e 272 (M^+), 254 ($M^+ - H_2O$), 241 (M^+ − 31).

Methyl 2-Methyl-5-oxotetradecanoate (5). To a solution of **4** (5.44 g, 20 mmol) in acetone (40 mL, distilled over potassium permanganate) was added Jones reagent[6] dropwise until an orange-brown color persisted. Then water was added and the mixture was extracted with ether. The ether extracts were washed with H_2O and dried ($MgSO_4$). Removal of the solvent afforded a residue which was chromatographed on silica gel with hexane–ethyl acetate (8:2) to obtain **5** (4.59 g, 85% yield) as a colorless oil: IR (neat) 1730, 1720 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.9 (t, 3 H, CH_3), 1.15 (d, 3 H, CH_3, J = 7 Hz), 1.2–1.5 (m, 14 H, CH_2), 1.7–2 (m, 2 H, $CH_2CH(CH_3C$=O), 2.2–2.7 (m, 5 H, CH_2COCH_2 and $CH(CH_3)$), 3.7 (s, 3 H, OCH_3); mass spectrum (70 eV), m/e 270 (M^+), 239 (M^+ − 31), 155, 127.

Anal. Calcd for $C_{16}H_{30}O_3$: C, 71.07; H, 11.18. Found: C, 70.94; H, 11.10.

Methyl 2-Methyl-5-methylenetetradecanoate (6a). In a three-necked flask equipped with mechanical stirrer, Mg/Hg amalgam was prepared by stirring 200 g of Hg and 600 mg (25 mmol) of Mg turnings under argon. To the well-stirred amalgam were added dry ether (20 mL) and dry benzene (20 mL), followed by a solution containing methylene iodide (2.94 g, 11 mmol) and **5** (2.68 g, 10 mmol) in dry ether (20 mL) during 20 min at room temperature. The mixture was stirred at room temperature for 1 h; then ice–water and 2 N HCl were added and the solution was extracted with ether. Ether extracts were dried ($MgSO_4$) and, after removal of the solvent, the residue was chromatographed on silica gel with hexane–ether (95:5) to afford **6a** (2.14 g, 80% yield) as a colorless oil: IR (neat) 1730 (C=O),910 (C=CH_2) cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.9 (t, 3 H, CH_3), 1.15 (d, 3 H, CH_3, J = 7 Hz), 1.2–1.4 (m, 14 H, CH_2), 1.5–1.9 (m, 2 H, CH_2), 1.8–2.2 (m, 4 H, $CH_2(C$=$CH_2)CH_2$), 2.2–2.6 (m, 1 H, $CHCH_3$), 3.7 (s, 3 H, OCH_3), 4.75 (br s, 2 H, C=CH_2); mass spectrum (70 eV), m/e 268 (M^+), 157, 112.

2-Methyl-5-methylenetetradecanoic Acid (6b). Ester **6a** (2.14 g, 8 mmol) was dissolved in 10% methanolic KOH (20 mL) and stirred for 12 h at room temperature. After the solution was poured in ice–water, 2 N HCl was added. The aqueous layer was extracted with ether, dried ($MgSO_4$), and evaporated; **6b** was obtained in a quantitative yield as a clear oil: IR (neat) 1710 (C=O), 910 (C=CH_2) cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.9 (t, 3 H, CH_3), 1.15 (d, 3 H, CH_3, J = 7 Hz), 1.2–1.4 (m, 14 H, CH_2), 1.5–1.9 (m, 2 H, CH_2), 1.8–2.2 (m, 4 H, $CH_2C(=CH_2)CH_2$), 2.2–2.6 (m, 1 H, $CHCH_3$), 4.75 (br s, 2 H, C=CH_2), 10.10 (br s, 1 H, OH); mass spectrum (70 eV), m/e 254 (M^+), 142.

2-Methyl-5-nonyl-5-(iodomethyl)pentanolide (7). Iodine (4 g, 16 mmol) was added at room temperature to a solution of **6b** (2 g, 8 mmol) in acetonitrile (30 mL) and the solution was stirred for 2.5 h. The reaction mixture was diluted with ether and 10% aqueous $Na_2S_2O_3$ and the organic layer was dried ($MgSO_4$). The organic phase was concentrated and the residue was chromatographed on silica gel with hexane–ethyl acetate 9:1 to give **7** (2.7 g, 90% yield) as a clear oil. The product was a mixture of diastereomers in 4:6 ratio, as indicated by two distinct signals, at δ 3.37 and 3.40, for CH_2I protons in the ^1H NMR spectrum: IR (neat) 1730 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.9 (t, 3 H, CH_3), 1.1–1.5 (m, 19 H, CH_2), 1.6–2 (m, 4 H, CH_2), 2.1–2.6 (m, 1 H, $CHCH_3$), 3.37 and 3.40 (2 s, 2 H, CH_2I); mass spectrum (70 eV), m/e 253 (M^+ − 127), 239 (M^+ − 141).

2-Methyl-5-nonyl-5-(hydroxymethyl)pentanolide (Malyngolide, 1). Mercury(II) oxide (1.1 g, 5 mmol) was added to a mixture of dimethoxyethane (10 mL) and 1.5 mL of 60% aqueous $HClO_4$, until all mercury(II) oxide was dissolved. The solution was cooled to room temperature and 1 mL of distilled water, followed by **7** (1.9 g, 5 mmol) in dimethoxyethane (5 mL), was added. The reaction mixture was stirred at 50 °C for 30 min, cooled to room temperature, diluted with H_2O, and extracted with ether. The ether extracts were dried ($MgSO_4$) and evaporated. The residue was chromatographed on silica gel with hexane–ethyl acetate (7:3) and 1 (1.22 g, 91% yield) was obtained in an approximate 4:6 mixture of diastereomers with R_f 0.47 and 0.35 in TLC, respectively, using hexane–ethyl acetate (6:4) as solvent. The product with R_f 0.47 presents the following ^1H NMR data ($CDCl_3$): δ 0.9 (t, 3 H, CH_3), 1.1–1.45 (m, 19 H, CH_2 and CH_3), 1.45–2.15 (m, 4 H, CH_2), 2.15–2.6 (m, 1 H, $CHCH_3$), 3.62 (s, 2 H, CH_2OH), 3.9 (br s, 1 H, OH). The product with R_f 0.35 has a ^1H NMR spectrum corresponding to that of the reported natural product:[1] ^1H NMR ($CDCl_3$) δ 0.9 (t, 3 H, CH_3), 1.1–1.45 (m, 19 H, CH_2 and CH_3), 1.45–2.15 (m, 4 H, CH_2), 2.15–2.6 (m, 1 H, $CHCH_3$), 3.46 (d, 1 H, CH_2OH, J_{gem} = 12 Hz), 3.71 (d, 1 H, CH_2OH, J_{gem} = 12 Hz); IR (neat) 3430 (OH), 1725 (C=O), cm^{-1}; mass spectrum (70 eV), m/e 239 ($M^+ - CH_2OH$), 211, 155, 143.

Anal. Calcd for $C_{16}H_{30}O_3$: C, 71.07; H, 11.18. Found: C, 70.71; H, 11.13.

1-Diazoundecan-2-one (8). A solution of decanoyl chloride (5.7 g, 30 mmol) in dry ether (30 mL) was slowly dropped into an ethereal solution of 0.2 M diazomethane (350 mL) at −5 °C during 30 min. After all the acid chloride was added, the solution was allowed to stand at room temperature for 1 h. Removal of the ether afforded a yellow oil which crystallized on standing at room temperature to give **8** in quantitative yield as yellow crystals: mp 34 °C; IR (neat) 3000, 2100 (CHN_2), 1640 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.9 (t, 3 H, CH_3), 1–1.5 (m, 14 H, CH_2), 2.1–2.5 (m, 2H, CH_2C=O), 5.25 (s, 1 H, CHN_2); mass spectrum (70 eV), m/e 196 (M^+), 155 ($M^+ - CHN_2$).

2-Oxoundecan-1-ol (9a). The diazo ketone **8** (5.9 g, 30 mmol) was dissolved in dioxane (60 mL) and 2 N H_2SO_4 (100 mL) was slowly added; the solution was warmed to 50 °C for 3 h under vigorous magnetic stirring, allowed to cool to room temperature, and then saturated with NaCl. After extraction with ether, the organic layer was dried ($MgSO_4$) and removal of the solvent afforded a residue which was chromatographed on silica gel with hexane–ether (8:2) to give (**9a**)(4.63 g, 83% yield) as white crystals: mp 47 °C; IR (Nujol) 3200 (OH), 1710 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.9 (t, 3 H, CH_3), 1–1.5 (m, 12 H, CH_2), 1.6–1.8 (m, 2 H, CH_2), 2.45 (br t, 2 H, CH_2C=O, J = 6 Hz), 3.15 (t, 1 H, OH, J = 5 Hz), 4.15 (d, 2 H, CH_2OH, J = 5 Hz); mass spectrum (70 eV), m/e 155 ($M^+ - CH_2OH$), 143, 85.

Anal. Calcd for $C_{11}H_{22}O_2$: C, 70.92; H, 11.90. Found: C, 70.83; H, 11.89.

2-[(2-Oxoundec-1-yl)oxy]tetrahydropyran (9b). A solution of 2-oxoundecan-1-ol (**9a**; 3.7 g, 20 mmol) and 3,4-dihydro-2*H*-pyran (1.85 g, 22 mmol) in dichloromethane (20 mL) was added to a suspension of Amberlyst H 15 (Rohm and Haas, 0.5 g, 1 mequiv) in dichloromethane (20 mL) and the mixture was stirred for 30 min at 0 °C. The resin was then filtered off and removal of the solvent afforded a residue which was chromatographed on silica gel with hexane–ether (8:2) as eluant to give **9b** (4.9 g, 92% yield) as a clear oil: IR (neat) 1720 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.9 (t, 3 H, CH_3), 1.1–1.5 (m, 12 H, CH_2), 1.55–1.9 (m, 8 H, CH_2),

2.45 (br t, 2 H, $CH_2C{=}O$, J = 6 Hz), 3.3–3.9 (m, 2 H, CH_2O in pyran ring) 4.00 (d, 2 H, CH_2OTHP, J_{gem} = 1 Hz), 4.6 (m, 1 H, O–CH–O); mass spectrum (70 eV), m/e 155 ($M^+ - CH_2OTHP$), 85.

(*E*)-2-Methyl-5-hydroxy-5-[(tetrahydropyranyloxy)-methyl]tetradec-2-enoic Acid (10). To a suspension of NaH (480 mg of a 50% dispersion in oil, 10 mmol) in dry THF (30 mL) at 0 °C under argon was added tiglic acid (1 g, 10 mmol) in dry THF (20 mL) and the mixture was stirred at 40 °C for 3 h. The solution was cooled to 0 °C and then lithium diisopropylamide, prepared from 1.41 mL (1.01 g, 10 mmol) of diisopropylamine and 6.6 mL of a 1.5 M solution of *n*-BuLi (10 mmol) in *n*-hexane, in dry THF (10 mL) was slowly added. The mixture was stirred for 0.5 h at 0 °C and then allowed to warm to 40 °C for 1.5 h. After the mixture was cooled to −78 °C, dry HMPA (3 mL) was added and **9b** (2.7 g, 10 mmol) in THF (20 mL) was slowly dropped in over a 50-min period; the reaction mixture was stirred overnight at −78 °C and then warmed at 50 °C for 6 h. Ice–water and 2 N HCl were added and the mixture was extracted with ether. The ether extracts were washed with water and dried ($MgSO_4$). Removal of the solvent afforded a residue which was chromatographed on silica gel with hexane–methanol (98:2) to give **10** (2.51 g, 68% yield) as a colorless oil: IR (neat) 3400 (OH), 1690 (C=O), 1640 (C=C) cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.9 (t, 3 H, CH_3), 1.05–1.5 (m, 12 H, CH_2), 1.5–1.9 (m, 8 H, CH_2), 1.8 (s, 3 H, $CH_3C{=}C$), 3.2–3.9 (m, 4 H, CH_2O in pyran ring, CH_2OTHP), 4.55 (m, 1 H, O–CH–O), 6.05 (br s, 2 H, OH) 6.9 (t, 1 H, CH=C, J = 6.5 Hz); mass spectrum (70 eV), m/e 370 (M^+), 255 ($M^+ - CH_2OTHP$), 237 ($M^+ - CH_2OTHP - H_2O$), 187, 85.

Anal. Calcd for $C_{21}H_{38}O_5$: C, 68.07; H, 10.34. Found: C, 67.88; H, 10.26.

2-Methyl-5-hydroxy-5-[(tetrahydropyranyloxy)methyl]-tetradecanoic Acid (11). The acid **10** (1.85 g, 5 mmol) in methanol (20 mL) was hydrogenated over 10% Pd–C (150 mg) at atmospheric pressure until starting material disappeared on TLC analysis. After filtration from the catalyst and removal of the solvent, **11** was obtained as a colorless oil in almost quantitative yield: IR (neat) 3350 (OH), 1720 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.9 (t, 3 H, CH_3), 1.1–1.5 (m, 23 H, CH_2 and CH_3), 1.5–2 (m, 6 H, CH_2), 2.1–2.65 (m, 1 H, $CHCH_3$), 3.1–4.1 (m, 4 H, CH_2O in pyran ring, CH_2OTHP) 4.6 (m, 1 H, O–CH–O), 7.2 (br s, 2 H, OH); mass spectrum (70 eV), m/e 372 (M^+), 257 ($M^+ - CH_2OTHP$), 239 ($M^+ - CH_2OTHP - H_2O$), 117, 85.

2-Methyl-5-nonyl-5-(hydroxymethyl)pentanolide (Malyngolide, 1). The acid **11** (1.48 g, 4 mmol) was dissolved in methanol (15 mL), 3 mL of 6 N HCl was added, and the mixture was warmed at 45° C for 30 min. The mixture was then poured into ice–water and extracted with ether. The ether extracts were dried ($MgSO_4$) and evaporated. The residue was chromatographed on silica gel with hexane–ethyl acetate (7:3) and **1** (930 mg, 87% yield) was obtained as a 1:1 mixture of diastereomers, with R_f 0.47 and 0.35 in TLC, respectively, using hexane–ethyl acetate (6:4) as eluant. These diastereomers had the same spectral properties (IR, ^1H NMR and mass spectra) as those previously reported for Malyngolide (**1**) obtained by path A.

Anal. Calcd for $C_{16}H_{30}O_3$: C, 71.07; H, 11.18. Found: C, 70.76; H, 11.11.

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Registry No. (±)-**1** (isomer 1), 74742-19-1; (±)-**1** (isomer 2), 76984-84-4; (±)-**3b**, 76917-10-7; **4**, 76917-11-8; (±)-**5**, 76984-85-5; (±)-**6a**, 76917-12-9; (±)-**6b**, 74709-66-3; (±)-**7** (isomer 1), 76917-13-0; (±)-**7** (isomer 2), 76917-14-1; **8**, 76917-15-2; **9a**, 76917-16-3; **9b**, 76917-17-4; **10**, 76917-18-5; **11**, 76917-19-6; tiglic acid, 80-59-1; decanal, 112-31-2; decanoyl chloride, 112-13-0; diazomethane, 334-88-3.

Total Synthesis of (±)-Albene

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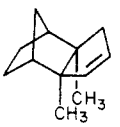
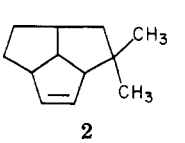
The exo Diels–Alder adduct of 2,3-dimethylmaleic anhydride and cyclopentadiene has been converted to (±)-albene, a hydrocarbon found in plants of the genera *petasites* and *adenostyles*, through an efficient eight-step sequence of reactions. The synthesis includes a simple four-step process for transforming a succinic anhydride moiety into the corresponding cyclopentenone.

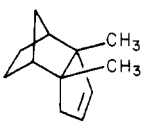
The structure of (−)-albene, a crystalline tricyclic $C_{12}H_{18}$ compound first isolated in 1962 from *petasites albus*,[1] has been conclusively established, largely through the efforts of Kreiser, Janitschke, and coworkers:[2-6] formula **1** is (−)-albene, with absolute stereochemistry as depicted.



1



2



3

The earliest provisional structural hypothesis for this natural product,[7] the tetrahydrotriquinacene **2**, was abandoned when spectral data and direct chemical correlations with (+)-camphene appeared to support the

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