A Short Synthesis of Natural (−)-Oblongolide via an Intramolecular or a Transannular Diels–Alder Reaction

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The absolute configuration of naturally occurring oblongolide is confirmed as (3a*S*,5a*R*,7*S*,9a*S*,9b*S*)-3a,5a,6,7,8,9,9a,9b-octahydro-7,9b-dimethylnaphtho[1,2-*c*]furan-1(3*H*)-one (**1**) on the basis of a six-stage or an eight-stage synthesis from (−)-citronellol involving a steric-controlled, regioselective reduction and an intramolecular Diels–Alder (IMDA) reaction or a transannular Diels–Alder (TDA) reaction as the key steps. (−)-Citronellol (**5**) was converted into methyl (2*E*,4*E*,10*E*)-(*S*)-(+)-11-(*tert*-butoxycarbonyl)-7-methylundeca-2,4,10-trienoate (**7**) by sequential Lemiuex–Johnson oxidation, Wittig olefination, pyridinium dichromate oxidation, and Wadsworth–Emmons–Horner alkenation. A regioselective reduction of the methoxycarbonyl group in **7** afforded *tert*-butyl (2*E*,8*E*,10*E*)-(*S*)-(+)-2,6-dimethyl-12-hydroxydodeca-2,8,10-trienoate (**8**) from which oblongolide (**1**) was obtained via an IMDA reaction. The macrocyclic (2*E*,8*E*,10*E*)-(*S*)-(+)-2,6-dimethyldodeca-2,8,10-trieno-1,12-lactone derived from **8** underwent a highly stereoselective TDA reaction to give **1** at a lower reaction temperature, in a shorter reaction time and in a better yield than the analogous IMDA reaction.

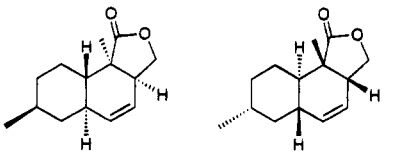
Introduction

Several years ago, a novel norsesquiterpene γ-lactone was isolated in low yield from the fungus *Phomopsis oblonga* (Desm) Trav., and was assigned the trivial name oblongolide.[1] Fungus *P. oblonga*, which is frequently found in the outer bark of healthy elm trees, can invade the phloem of stressed trees, primarily those infected by *Ceratocystis ulmi*, the causative agent of Dutch elm disease.[2,3] Elm bark beetles, the insect vector of the disease, reject *P. oblonga*-invaded phloem as being unsuitable for breeding, and such trees do not become brood trees. Using a laboratory bioassay in which the beetles were offered a choice between treated and untreated elm bark, oblongolide has been shown to be a boring/feeding deterrent for the beetles.[4]

The structure and the relative stereochemistry of oblongolide were shown to be **1** or its enantiomer *ent*-**1** by X-ray crystallography.[1] The absolute configuration of oblongolide was initially assigned as *ent*-**1** based on a circular dichroism study of its dihydro-derivative according to the lactone sector rule.[1] This assignment was subsequently proved to be incorrect by an unambiguous total synthesis of *ent*-**1** which was identical with the natural oblongolide except for the sign of the optical rotation, thereby demonstrating that the absolute configuration of oblongolide should be **1**.[5]

This paper now describes, starting from commercially available (−)-citronellol, involving minimum protecting group chemistry and a key intramolecular [4 + 2] cycloaddition, a short synthesis of (−)-oblongolide **1** which is identical in all respects with the natural material, thereby confirming its absolute configuration as illustrated.

Chart 1



1 *ent*-**1**

Results and Discussion

Retrosynthesis of oblongolide **1** indicates that it might be obtained by lactonization, following an intramolecular Diels–Alder (IMDA)[6] reaction of triene **2** or by a transannular Diels–Alder (TDA)[7] reaction of the macrolide **3** (Figure 1). The triene-ester **2** or the macrolide **3**, in turn, might be derived formally from bisaldehyde **4** or its equivalent *via* two sequential Wittig-type[8] homologations in which the dienophile would be introduced first. The bisaldehyde **4** should be readily accessible from (3*S*)-(−)-citronellol (**5**). The stereochemical outcome of the pivotal IMDA reaction deserves more detailed analysis. To this end, the four possible transition states leading to the four diastereoisomeric cycloadducts are illustrated in Figure 2. The attainment of the stereochemistry in **1** could only be realized if the IMDA reaction proceeded through (a) chair conformers with the C-6 methyl substituent disposed in an equatorial position and (b) an *endo*-mode[9] of cyclization. These requirements appeared to be readily achievable and prompted us to carry out

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(9) *endo*-IMDA reactions afford *trans*-fused adducts, see ref 6.

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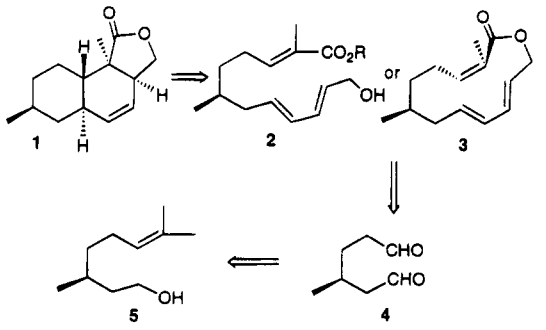


Figure 1. Retrosynthesis of oblongolide.

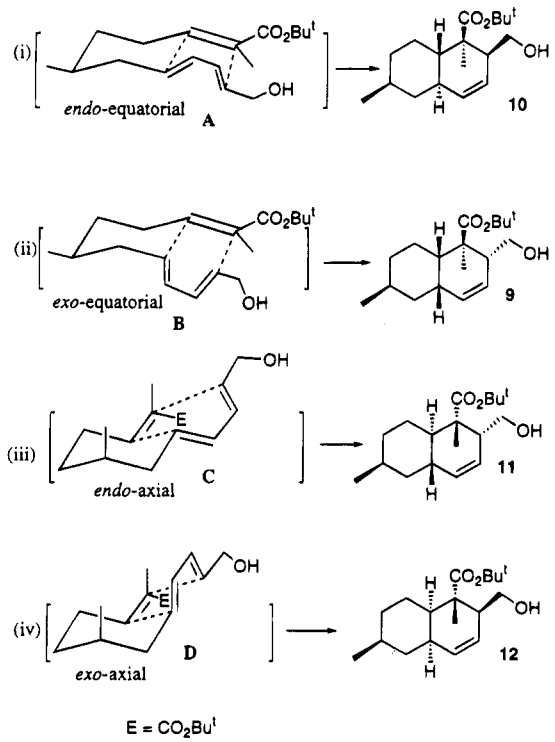
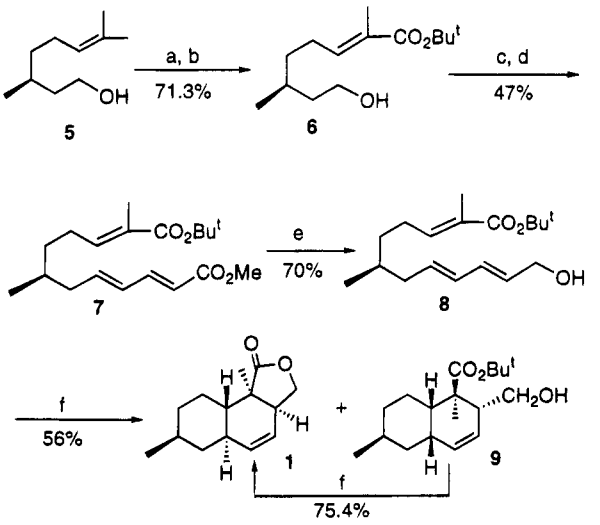


Figure 2. The four possible transition states of the IMDA reaction.

the synthesis since an example of using a methyl substituent to control the diastereofacial selectivity of an IMDA reaction has been reported.[10]

To prepare the Diels–Alder precursor **2**, the first objective was to cleave oxidatively the alkene moiety in **5** to form the corresponding aldehyde which then would undergo a Wittig olefination to give the dienophilic ester. Although the alkene moiety in a hydroxy-protected citronellol (as a silyl ether) had been successfully ozonized to give the corresponding aldehyde,[11] we decided to explore a shorter pathway which would avoid the hydroxy-protection and -deprotection steps. It was found that the Lemieux–Johnson reaction[12] (dihydroxylation followed by glycol cleavage) of **5** in aqueous dioxane occurred smoothly to give the corresponding aldehyde which reacted with Wittig reagent $Ph_3P{=}CMeCO_2Bu^t$,[13] affording the *E*-dienophilic ester **6** as the sole product (Scheme 1). The *Z*-isomer could not be detected on TLC

Scheme 1[a]



[a] Reagents and conditions: (a) cat. OsO_4, $NaIO_4$, dioxane–H_2O, rt; (b) $Ph_3P{=}C(CH_3)CO_2Bu^t$, CH_2Cl_2; (c) PDC, 3 Å molecular sieves, CH_2Cl_2; (d) $(OMe)_2P(O)CH_2CH{=}CHCO_2Me$, $NaN(SiMe_3)_2$, THF, −78 °C; (e) DIBALH (2 e equiv) THF, −78 °C; (f) 1,2-dichlorobenzene, sealed tube, 210 °C.

or by ^1H NMR spectroscopy. PDC oxidation (with molecular sieves)[14] of the alcohol in **6** followed by a Wadsworth–Emmon–Horner alkenation[8] furnished the diester **7**. The *E*-geometry of all the double bonds in **7** was confirmed by chemical evidence: heating a solution of **7** with a catalytic amount of iodine in benzene, the conditions for thermodynamically controlled isomerization of *Z*-alkenes to *E*-alkenes,[15] did not afford any new compound and only **7** was recovered quantitatively. The methyl ester in **7** could be selectively reduced with DIBAL-H in the presence of the *tert*-butyl ester to give the desired Diels–Alder precursor **8** as the major product and a trace amount of the regioisomeric allyl alcohol. This differentiation of the two ester carbonyls by steric-controlled hydride reduction is noteworthy because it reduces the protecting group chemistry involved in setting up such a Diels–Alder triene[10,16] system.

With the triene **8** readily at hand, we set out to perform the IMDA reaction. In general, the *endo*- versus *exo*-preference in an intermoleculer Diels–Alder reaction is attributable to nonbonding secondary orbital interactions of the dienophile with the diene.[17] However, this is not the case for IMDA reactions. Work carried out in Roush's laboratories demonstrated that thermal cyclizations of undeca-2,8,10-trienoates generally afforded *cis*-fused products (*exo*-mode of cyclization) preponderantly and suggested that IMDA reactions which occurred at temperatures in excess of 100 °C were not governed by secondary orbital interactions, and the product selectivity was dominated by subtle steric interactions of the transition states.[18]

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(11) Tapolczay, D. J.; Thomas, E. J.; Whitehead, J. W. F. *J. Chem. Soc., Chem. Commun.* **1985**, 143.
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(13) Commercially available $(Ph)_3P{=}CHCO_2Bu^t$ was alkylated with an excess of MeI in THF at rt. The resulting phosphonium iodide was dissolved in aqueous EtOH, and the pH of the solution adjusted to pH = 9 with 1 N NaOH to give $(Ph)_3P{=}C(Me)CO_2Bu^t$ in 70% overall yield: mp 148–50 °C; ^1H NMR δ 0.91 (12H, s), 1.23 (3H, d, *J* = 16.5 Hz), 7.3–7.8 (15H, m).
(14) Czernecki, S.; Georgoulis, C.; Stevens, C. L.; Vijayakumaran, K. *Tetrahedron Lett.* **1985**, *26*, 1699.
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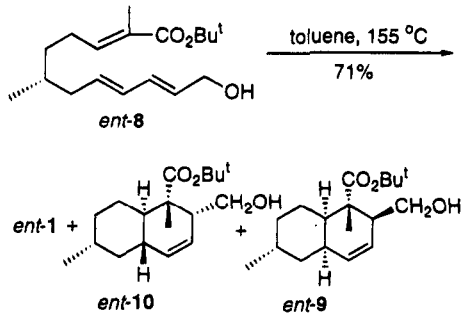
Scheme 2

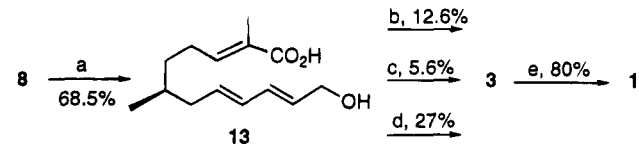


Our previous work[5] on the synthesis of *ent*-(+)-**1** indicated that heating the triene *ent*-**8** in toluene at 155 °C afforded a mixture of *cis*- and *trans*-fused decalins in roughly equal amounts (*ent*-**1**:*ent*-**10**:*ent*-**9** = 12:24:38) as illustrated in Scheme 2. Attempts to ameliorate the stereoselectivity of the IMDA reaction via Lewis acid catalysis[19] met with failures, attributable to the instability of unreactive *ent*-**8**.

In this work, molecular mechanics calculations according to the MM2 force field of Allinger[20] showed that if the thermal cycloaddition proceeded through a product-like transition state, the *endo*-equatorial product **10** would be favored (Figure 2); on the other hand, a reactant-like transition state would afford a mixture of *endo*-equatorial and *exo*-equatorial products **10** and **9** since the respective transition states **A** and **B** were similar in energy whereas transition states **C** and **D** leading to cycloadducts **11** and **12** were energetically less favorable. The calculated differences between the transition states **A/B** and **C/D** are roughly 3 kcal mol^{-1}. The actual formation of a mixture of *ent*-**9** and *ent*-**10** thus indicated that the IMDA reaction proceeded through early and equatorial transition states. The spontaneous formation of *ent*-**1** is also in accord with molecular mechanics calculations that show that the E_{steric} of *ent*-**1** is roughly 8 kcal mol^{-1} less than that of *ent*-**10**. In view of this finding, we reasoned that raising the reaction temperature of the cycloaddition might give us the target lactone **1** directly. To our expectation, heating a solution of the triene **8** in a sealed tube at 210 °C for 56 h afforded a mixture of oblongolide (**1**) (38.8%) and *cis*-decalin **9** (17.2%), but the hydroxy-ester **10** could not be detected. Extending the reaction time to 76 h surprisingly gave oblongolide **1** (55%) as the sole product! Resubjection of the *cis*-decalin **9** to the IMDA reaction conditions for 56 h furnished **1** in 75.4% yield, thus providing evidence for a reversible IMDA reaction. The high reaction temperature and long reaction time led us to believe that the product-selectivity of the IMDA reaction was simply thermodynamically controlled. Synthetic **1** displayed all spectral data in accord with the reported values,[1] and its optical rotation after one recrystallization from hexane had $[\alpha]^{20}_D$ −181.5 (96% ee, since the reported[1] $[\alpha]^{20}_D$ was −190).[21] The absolute configuration of the natural oblongolide is confirmed as **1**.

Since examples of TDA reactions have been reported to be much more facile than the conventional IMDA reactions,[7] we next turned our attention to an alternative route to **1** along this strategy as indicated in our retrosynthetic analysis (Figure 1). Hydrolysis of the *tert*-butyl ester group in **8** with aqueous TFA or LiOH was unsuccessful, but the reaction went smoothly with aqueous NaOH in EtOH to give hydroxy-acid **13**. However, all the yields for the conversion of the hydroxy-acid **13** into the macrolide **3** were disappointingly low, and among the methods[22-25] of macrolactonization attempted, the Yamaguchi[24] protocol proved to be the most efficient (Scheme 3). It is interesting that lactonization under the Mitsunobu conditions[25] was unsuccessful, and no macrolide **3** could be isolated. Heating a solution of **3** in toluene under reflux for 25 h afforded oblongolide (**1**) in 80% yield, and no other stereoisomers were detected. The oblongolide obtained was identical in all respects to the one prepared by the IMDA cyclization.

Scheme 3[a]



[a] Reagents and conditions: (a) 10% NaOH/EtOH-H_2O; (b) 2-chloro-1-methylpyridinium iodide, Et_3N, CH_2Cl_2, reflux; (c) DCC, DMAP, CH_2Cl_2, 25 °C; (d) 2,4,6-trichlorobenzoyl chloride, Et_3N, DMAP; (e) toluene, reflux.

Conclusions

In summary, natural oblongolide (**1**) was synthesized from commercially available (3*S*)-(−)-citronellol (**5**) in six steps with an overall 13% yield via a thermodynamically controlled IMDA reaction as the key step. This synthetic sequence was rendered short because minimum protecting group chemistry was involved. The differentiation between a methyl ester and a *tert*-butyl ester carbonyl with a steric-controlled, regioselective hydride reduction is noteworthy. Also, we have demonstrated the first example that a macrolide **3** underwent a facile, efficient, and highly stereoselective TDA reaction, in contrast to the acyclic IMDA precursor **8** that only cyclized under forcing conditions with poor stereoselectivity. However, owing to the poor yield of the macrolactonization step, the overall yield for the eight-step synthesis of **1** involving the TDA cyclization was only 3.5%, and more efficient avenues for the preparation of macrolides are currently under investigation.

Experimental Section

Melting points are reported in degrees Celsius and are uncorrected. Optical rotations were measured with an automatic digital polarimeter at 589 nm. Infrared (IR) spectra were recorded on a FT-IR spectrometer as thin films on NaCl disks. Unless stated to the contrary, nuclear magnetic resonance (NMR) spectra were measured in solutions of $CDCl_3$ at 250 MHz (^1H) or at 62.9 MHz (^{13}C) . Spin−spin coupling constants (*J*) were measured directly from the spectra. Carbon and hydrogen elemental analyses were carried out at either the Shanghai Institute of Organic Chemistry, The

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(21) The ee of the product is limited by the ee of the starting material, i.e., (−)-citronellol.
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Chinese Academy of Sciences, China, or the MEDAC Ltd, Department of Chemistry, Brunel University, Uxbridge, England. All reactions were monitored by analytical thin-layer chromatography (TLC) on aluminum precoated with silica gel $60F_{254}$ (E. Merck), and compounds were visualized with a spray of 5% w/v dodecamolybdophosphoric acid in ethanol and subsequent heating. All columns were packed wet using E. Merck silica gel 60 (230–400 mesh) as the stationary phase and eluted using flash[26] chromatographic technique. Et_3N was distilled over barium oxide and stored in the presence of potassium hydroxide pellets. THF was distilled from sodium benzophenone ketyl under a nitrogen atmosphere. CH_2Cl_2 was distilled over phosphorus pentoxide and stored in the presence of 4 Å molecular sieves.

***tert*-Butyl (*E*)-(*S*)-(−)-2,6-Dimethyl-8-hydroxyoct-2-enoate (6).** To a solution of (*S*)-(−)-citronellol (**5**) (2 g, 12.8 mmol) in 40 mL of dioxane was added 0.5 mL of a solution of OsO_4 in dioxane (100 mg/5 mL) at rt. The mixture was stirred for 10 min and then was added a solution of $NaIO_4$ (8 g, 37.4 mmol) in 50 mL of water. The mixture was stirred for 16 h at rt and filtered, and the filtrate was poured into saturated aqueous NH_4Cl (40 mL). The aqueous phase was extracted with $CHCl_3$ (4 × 25 mL), and the combined extracts were dried ($MgSO_4$) and passed through a thin layer of silica gel. Concentration of the filtrate gave an oil which was dissolved in CH_2Cl_2 (5 mL). The resulting solution was then added to a solution of $Ph_3P{=}C(Me)CO_2Bu^t$ (5.2 g, 13.3 mmol) in CH_2Cl_2 (20 mL) and was stirred for 4 h at rt. Solvent removal gave an oil which was flash chromatographed (hexanes–diethyl ether 1:1) to yield the hydroxy-ester **6** (2.21 g, 9.13 mmol, 71.3%) as a colorless oil; TLC R_f 0.54 (hexanes-diethyl ether 1:2); $[\alpha]^{27}_D$ −10.7 (*c* 1.1, $CHCl_3$); IR (film) 3500 (OH), 1704 cm^{-1} (conjugated ester C=O); UV (EtOH) λ_{max} 215 nm; ^1H NMR δ 0.93 (3H, d, J = 6.4 Hz), 1.47 (9H, s), 1.4–1.6 (5H, m), 1.77 (3H, s), 1.83 (1H, bs), 2.14 (2H, m), 3.68 (2H, m), 6.63 (1H, t, J = 7.5 Hz); MS *m*/*z* (EI) 186 (5.7%, $M^+ - CH_3C(CH_3){=}CH_2$), 168 (25.1, $M^+ - CH_3C(CH_3){=}CH_2 - H_2O$,), 57 (100, $C_4H_9^+$). Anal. Calcd for $C_{14}H_{26}O_3$: C, 69.4; H, 10.8. Found: C, 69.6; H, 10.4.

Methyl (2*E*,4*E*,10*E*)-(*S*)-(+)-11-(*tert*-Butoxycarbonyl)-7-methylundeca-2,4,10-trienoate (7). To a suspension of PDC (4.66 g, 12.4 mmol) and 3 Å molecular sieves (6.6 g) in dry CH_2Cl_2 (20 mL) was added a solution of the alcohol **6** (2.0 g, 8.26 mmol) in CH_2Cl_2 (15 mL) at rt. After the mixture was stirred for 35 min at rt, Celite (4.2 g) was added. The resulting slurry was stirred for a further 20 min and then filtered. Solvent removal from the filtrate gave a dark brown residue which was triturated with diethyl ether (2 × 30 mL). The combined ethereal solutions were passed through a thin layer of silica gel topped with anhydrous $MgSO_4$. Solvent removal from the filtrate gave the corresponding aldehyde (1.5 g, 6.27 mmol, 75.9%) as a pale yellow oil. To a solution of trimethyl 4-phosphonocrotonate (1.56 g, 7.5 mmol) in dry THF (50 mL) was added a 1.0 M solution of sodium bis(trimethylsilyl)amide in THF (7.5 mL, 7.5 mmol) at −78 °C. After the mixture was stirred for 10 min at −78 °C, a solution of the aldehyde (1.5 g, 6.27 mmol) in dry THF (15 mL) was added. The mixture was then stirred for 20 min at − 78 °C, quenched with saturated aqueous NH_4Cl (25 mL), and extracted with $CHCl_3$ (4 × 25 mL). The combined extracts were washed with brine (10 mL), dried with anhydrous $MgSO_4$, and filtered. Solvent removal from the filtrate gave an oil which was flash chromatographed (hexanes–diethyl ether 3:1) to yield the diester **7** (1.216 g, 60.2%) as a colorless oil; TLC R_f 0.5 (hexanes–diethyl ether 3:1); $[\alpha]^{26}_D$ +13.0 (*c* 0.8, $CHCl_3$); IR (film) 1720 (dienoate C=O), 1702 (enoate C=O), 1645 cm^{-1} (conjugated C=C); UV (EtOH) λ_{max} 215 nm, 260 nm; ^1H NMR δ 0.92 (3H, d, J = 6.5 Hz), 1.49 (9H, s), 1.2–1.65 (3H, m), 1.78 (3H, s), 2.07–2.17 (4H, m), 3.74 (3H, s), 5.80 (1H, d, J = 15.4 Hz), 6.14 (2H, m), 6.63 (1H, t, J = 7.5 Hz), 7.28 (1H, m); MS *m*/*z* (EI) 266 (9.8%, $M^+ - C_4H_9$), 235 (6.1, M^+ − *tert*-butyl − OMe), 221 (4, $M^+ - CH_3C(CH_3){=}CH_2$ − OMe − Me), 57 (100, $C_4H_9^+$). Anal. Calcd for $C_{19}H_{30}O_4$: C, 70.8; H, 9.4. Found: C, 70.7; H, 9.7.

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***tert*-Butyl (2*E*,4*E*,10*E*)-(*R*)-(+)-2,6-Dimethyl-12-hydroxyundeca-2,8,10-trienoate (8).** To a solution of the diester **7** (163.6 mg, 0.507 mmol) in dry THF (6 mL) was added dropwise a 1.5 M solution of DIBAL-H in toluene (1.0 mL, 1.5 mmol) at −78 °C. The mixture was stirred for 30 min at −78 °C and then quenched with saturated aqueous NH_4Cl (4 mL) and 1 N H_2SO_4 (1 mL). The aqueous phase was extracted with diethyl ether (4 × 10 mL), and the combined extracts were washed with brine (5 mL), dried ($MgSO_4$), and filtered. Solvent removal gave an oil which was flash chromatographed (hexanes–diethyl ether 1:1) to give the hydroxy-ester **8** (87.6 mg, 70%) as a colorless oil and also the starting material **7** (25.8 mg); TLC R_f 0.34 (hexanes–diethyl ether 1:1); $[\alpha]_D^{27}$ + 9.9 (*c* 1.6, $CHCl_3$), IR (film) 3420 (OH), 1708 (conjugated ester C=O), 1648 cm^{-1} (conjugated C=C); UV (EtOH) λ_{max} 225 nm; ^1H NMR δ 0.90 (3H, d, J = 6.5 Hz), 1.2–1.56 (2H, m), 1.48 (9H, s), 1.78 (3H, s), 1.81–2.20 (6H, m), 4.17 (2 H, d, J = 5.8 Hz), 5.71 (2H, m), 6.04 (1H, dd, J = 10.1, 4.9 Hz), 6.23 (1H, dd, J = 10.4, 4.5 Hz), 6.63 (1H, t, J = 7.4 Hz); MS *m*/*z* (EI) 238 (2.60%, $M^+ - (CH_3)_2C{=}CH_2$), 220 (6.5, $C_{14}H_{20}O_2^+$), 175 (12.5, $C_{13}H_{19}^+$), 57 (100, $C_4H_9^+$). Anal. Calcd for $C_{18}H_{30}O_3$: C, 73.4; H, 10.3. Found: C, 73.4; H, 10.0.

Oblongolide (1). Method A (from triene **8**). A Pyrex resealable tube was charged with a solution of the triene **8** (150 mg, 0.51 mmol) and methylene blue (0.2 mg) in dry 1,2-dichlorobenzene (45 mL). After three freeze-pump-thaw cycles, the tube was sealed in vacuo and then maintained at 210 °C (bath temp) for 76 h. The tube was then cooled to rt, and the contents were concentrated. The residue was fractionated by flash chromatography on silica gel (hexanes–diethyl ether 4:1) to give the crude oblongolide **1** (62 mg, 55%) as a white solid. Recrystallization from hexane at −18 °C gave white crystals: mp 101–103 °C (lit.,[1] 105–106 °C); $[\alpha]^{26}_D$ −181.5 (*c* 0.2, $CHCl_3$), 95.5% ee (lit.,[1] $[\alpha]_D$ −190); IR (film) 1766 cm^{-1} (lactone C=O); ^1H NMR δ 0.91 (3H, d, J = 6.5 Hz), 1.14 (3H, s), 0.87–1.89 (9H, m), 2.73 (1H, m), 3.84 (1H, dd, J = 10.96, 8.76 Hz), 4.39 (1H, t, J = 8.63 Hz), 5.57 (1H, m), 5.62 (1H, d, J = 10.1 Hz); ^{13}C NMR δ 180.04, 134.58, 121.47, 70.25, 45.12, 41.72, 39.37, 36.28, 35.20, 32.87, 25.52, 22.25, 16.17; MS *m*/*z* (EI) 220 (22.8%, M^+), 205 (4.8, $M^+ - CH_3$), 175 (100, $M^+ - CO_2 - C_{13}H_{19}^+$), 147 (50.3, $C_{11}H_{15}^+$), 133 (11.5), 119 (53.2), 105 (67.7), 91 (70). Anal. Calcd for $C_{14}H_{20}O_2$: C, 76.3; H, 9.2. Found: C, 76.3; H, 9.1.

Method B (from *cis*-decalin **9**). In a similar manner, the *cis*-decalin **9** (7.1 mg) was dissolved in 1,2-dichlorobenzene (2 mL) containing a catalytic amount of methylene blue. The resulting solution was charged into a Pyrex tube and heated at 210 °C for 56 h to give oblongolide **1** (4 mg, 75.4%), identical with the one prepared in the above experiment.

Method C (from acid **13**). To a solution of the acid **13** (9.8 mg, 0.04 mmol) in 1,2-dichlorobenzene (100 mL) was added a catalytic amount of methylene blue, and the mixture was refluxed under nitrogen for 7 days. Solvent removal gave a blue residue which was chromatographed (hexanes–diethyl ether 4:1) to afford oblongolide (**1**) (4.5 mg, 49.7%) as white crystals.

Method D (from macrolide **3**). To a solution of the lactone **3** (2 mg) in dry toluene (1 mL) was added a catalytic amount of methylene blue, and the mixture was refluxed at 130 °C under nitrogen for 25 h. Solvent removal gave a blue residue which was flash chromatographed (hexanes–diethyl ether 4:1) to afford oblongolide (**1**) (1.6 mg, 80%).

***cis*-Decalin 9.** A Pyrex resealable tube was charged with a solution of triene **8** (100 mg, 0.34 mmol) and methylene blue (0.2 mg) in dry 1,2-dichlorobenzene (30 mL). After three freeze-pump-thaw cycles, the tube was sealed in vacuo and then maintained at 210 °C (bath temp) for 56 h. The workup was the same as in Method A to give oblongolide (**1**) (29 mg, 48.8%) as a white solid and the *cis*-decalin **9** (17.2 mg, 17.2%); TLC R_f 0.22 (hexanes–diethyl ether 2:1); $[\alpha]^{22}_D$ −28.2 (*c* 0.7, $CHCl_3$); IR (film) 3430 (OH), 1748 cm^{-1} (ester C=O); ^1H NMR δ 0.85 (3H, d, J = 6.5 Hz), 0.97–1.94 (9H, m), 1.23 (3H, s), 1.30 (9H, s), 2.3 (1H, s), 2.90 (1H, m), 3.60 (1H, dd, J = 10.8, 3.4 Hz), 3.76 (1H, dd, J = 10.8, 4.4 Hz), 5.47 (1H, d, J = 10.2 Hz), 5.77 (1H, dt, J = 10.2, 4.4, 3.4 Hz); MS *m*/*z* (EI) 234 (27.6%, $M^+ - (CH_3)_2C{=}CH_2$), 221 (37.2, $C_{14}H_{20}O_2^+$), 221 (35.2,

$C_{14}H_{20}O_2^+$), 161 (100, $C_{13}H_{19}^+$), 105 (88.2, $C_{11}H_{15}^+$). Anal. Calcd for $C_{18}H_{30}O_3$: C, 73.4; H, 10.3. Found: C, 73.5; H, 10.6.

(2*E*,4*E*,10*E*)-(*R*)-(+)-2,6-Dimethyl-12-hydroxyundeca-2,8,10-trienoic acid (13). To a solution of the hydroxy-ester **8** (580 mg, 1.97 mmol) in 95% ethanol (12 mL) was added 10% aqueous NaOH (10 mL). The mixture was heated under reflux for 6.5 h, cooled, and then washed with *n*-hexane (3 × 4 mL). The aqueous layer was acidified with 1 N H_2SO_4 to pH = 1 and extracted with chloroform (5 × 10 mL), and the combined chloroformic extracts were dried with $MgSO_4$. Filtration followed by concentration of the filtrate gave an oil which was flash chromatographed (hexanes−diethyl ether 1:2) to yield the hydroxy-acid **13** (321 mg, 68.5%) as white crystals: TLC R_f 0.26 (hexanes−diethyl ether 2:1); $[\alpha]^{25}_D$ 13.4 (*c* 0.32, $CHCl_3$); mp 43−45 °C; IR 3500 (OH), 1687 cm^{-1} (C=O); UV (EtOH) λ_{max} 225.8 nm; ^1H NMR δ 0.91 (3H, d, J = 6.5 Hz), 1.28 (1H, m), 1.51 (2H, m), 1.84 (3H, s), 1.93−2.26 (4H, m), 4.17 (2H, d, J = 6.0 Hz), 5.22 (1 H, dd, J = 10.4, 4.7 Hz), 5.64−5.79 (2H, m), 6.04 (1H, dd, J = 10.4, 4.4 Hz), 6.89 (1H, t, J = 7.2 Hz); MS *m*/*z* (EI) 220 (27.4%, $M^+ - H_2O$), 205 (100, $M^+ - H_2O - CH_3$), 175 (17.8), 145 (30), 119 (30), 105(64), 91 (70). Anal. Calcd for $C_{14}H_{22}O_3$: C, 70.6; H, 9.3. Found: C, 70.2; H, 9.6.

(2*E*,8*E*,10*E*)-(*S*)-(+)-2,6-Dimethyldodeca-2,8,10-trieno-1,12-lactone (3). Method A.[21] To a solution of the hydroxy-acid **13** (100 mg, 0.42 mmol) in dry CH_2Cl_2 (80 mL) were added 2-chloro-1-methylpyridinium iodide (430 mg, 1.68 mmol) and Et_3N (0.34 g, 3.36 mmol). The mixture was heated at reflux under nitrogen for 12 h. Solvent removal followed by flash chromatography (hexanes−diethyl ether 8:1) gave the lactone **3** (11.6 mg, 12.6%) as white crystals.

Method B.[22] To a solution of **13** (42.8 mg, 0.179 mmol) in CH_2Cl_2 (10 mL) was added DMAP (23 mg, 0.179 mmol) and DCC (40 mg, 0.198 mmol). The mixture was stirred at 25 °C for 65 h and similar workup as in method A furnished lactone **3** (2.2 mg, 5.6%).

Method C.[23] To a solution of **13** (24 mg, 0.10 mmol) and triethylamine (11 mg, 0.11 mmol) in dry THF (1 mL) was added 2,4,6-trichlorobenzoyl chloride. The mixture was stirred at rt for 1 h. After removal of the triethylamine hydrochloride by filtration, the filtrate was diluted with toluene (50 mL) and added dropwise to a refluxing solution of 4-(dimethylamino)-pyridine (73.2 mg, 0.6 mmol) in toluene (10 mL) over 3 h. After the addition, the mixture was refluxed under nitrogen for 2 h. Then the reaction solution was washed with 3% aqueous hydrochloric acid (2 mL), water (2 mL), 10% aqueous $NaHCO_3$ (2 mL), and water (2 mL) and dried with $MgSO_4$. Solvent removal gave a yellow residue which was flash chromatographed (hexanes−diethyl ether 10:1) to afford the lactone **3** (6 mg, 27%); TLC R_f 0.75 (hexanes−diethyl ether 3:1), $[\alpha]^{21}_D$ +57.1 (*c* 1.2, $CHCl_3$); mp 90−92 °C; IR (thin film) 1732 cm^{-1} (lactone C=O); UV (EtOH) λ_{max} 236.5 nm; ^1H NMR δ 0.91 (3H, d, J = 6.5 Hz), 1.23 (3H, m), 1.58 (3H, s), 1.72−2.0 (4H, m), 4.65 (2H, d, J = 6.5 Hz), 5.71 (2H, m), 6.04 (1H, dd, J = 10.5, 4.8 Hz), 6.28 (1H, dd, J = 10.5, 4.8 Hz), 6.75 (1H, t, J = 6.75 Hz); MS *m*/*z* (EI) 220 (41.2%, M^+), 175 (100, $M^+ - COOH$), 147 (35), 133 (7.5), 105 (39), 91 (21). Anal. Calcd for $C_{14}H_{20}O_2$: C, 76.3; H, 9.2. Found: C, 76.3; H, 9.3.

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