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Aphidicolin Synthesis (I)——Formal Synthesis of (±)-Aphidicolin By the Successive Intramolecular Diels-Alder Reactions

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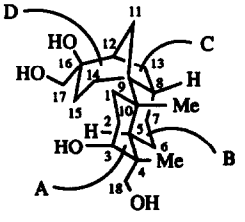
Abstract: Formal synthesis of an antitumor and antiviral diterpene aphidicolin (1) has been achieved. The key steps, **7** → **6** and **4** → **3**, involve intramolecular Diels-Alder reaction.

Introduction

Aphidicolin (**1**), isolated from the fungus *Cephalosporium aphidicola* Petch,[1] is an antibiotic that shows marked activity against Herpes simplex Type I virus, both *in vitro* and in the rabbit eye.[2] In addition to its antifeedant property,[3] aphidicolin (**1**) exhibits a considerable antitumor activity in the C6 mouse colon and B16 mouse melanosarcoma screens[4] and has been shown to inhibit the growth of leukemic T- and B-lymphocytes[5] with no discernible toxicity. Although the development of **1** as an antitumor agent has been hampered by the poor water solubility of the parent compound, a recent report[6] of enhanced antitumor activity associated with the more water-soluble aphidicolin-17-glycinate ester HCl salt, synthesized as a pro-drug, might revive interest in **1** and its analogues as a specific reversible inhibitor of DNA polymerase α.



Aphidicolin (**1**)

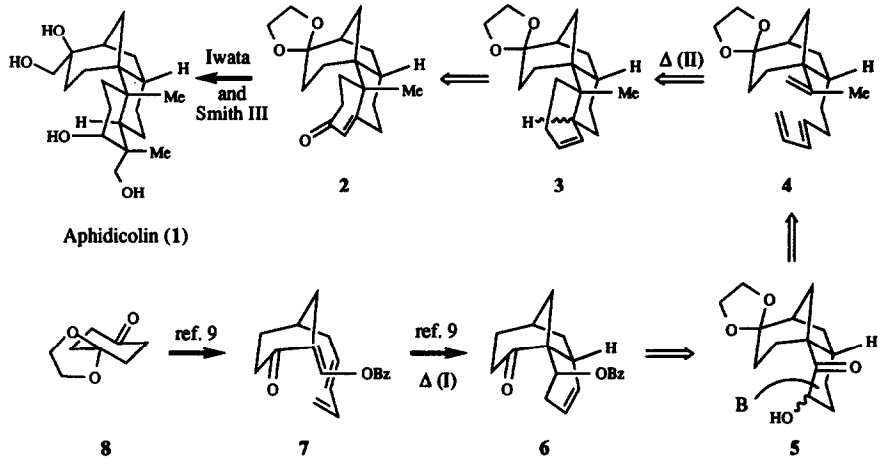
The unusual tetracyclic carbon skeleton of aphidicolin (**1**) incorporates eight stereogenic centers and a spiro fused bicyclo[3.2.1]octane moiety which comprises the C and D rings. Not only is C9 spiro center chiral, it is also next to another quaternary center, C10. The presence of these two adjacent chiral quaternary centers makes this region of aphidicolin quite crowded. After considerable efforts, eight total syntheses[7] and one formal synthesis have been reported to date. In addition, Holton and co-workers disclosed the first enantioselective construction of **1**, unambiguously confirming the absolute stereochemistry.[7g]

Herein, we describe an approach based upon a successive intramolecular Diels-Alder reaction strategy. Our approach to aphidicolin (**1**) is unlike ones[7,8] as it relies on the construction of A, B-*trans* ring juncture on the pre-formed bicyclo[3.2.1]octane ring system corresponding to the C, D ring part of **1**.

Synthetic Plan

For preparing aphidicolin (**1**), the novel synthetic strategy depicted in **Scheme I** was designed in which the successive intramolecular Diels-Alder reactions (I and II) are employed. Since the enone (**2**) has already been converted to the natural product (**1**) by Iwata and Smith III,[7h] the synthesis of the compound (**2**) completes the task. Access to **2** is provided through the intramolecular Diels-Alder reaction of the triene (**4**) followed by photosensitized oxygenation of the resulting olefin (**3**). The triene (**4**) is in turn available from regioselective bond cleavage reaction in ring B of **5** followed by introduction of diene and dienophile portions. 1,3-Transcarbonylation reaction and functionalization of the ketone (**6**), obtainable from the triene (**7**) using an intramolecular Diels-Alder reaction as previously,[9] afford the α-hydroxy ketone (**5**).

Scheme I



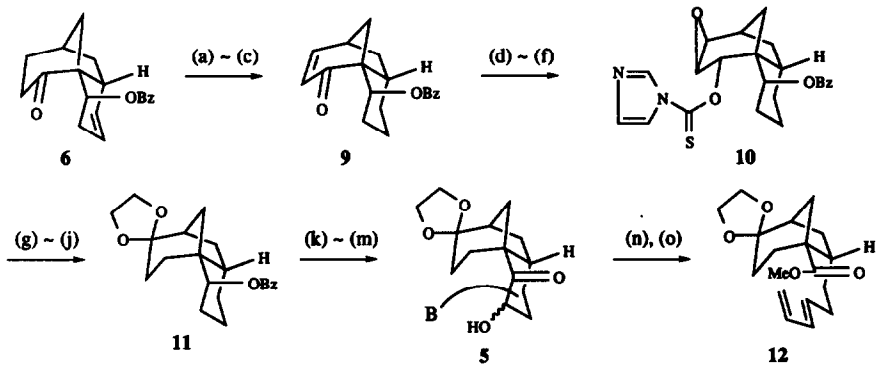
Results and Discussion

Although minor product, the tricyclic ketone (**6**) was obtained by means of the initial intramolecular Diels-Alder reaction of the triene (**7**) available from 1,4-cyclohexanedione monoethylene ketal (**8**).[9] Catalytic hydrogenation of **6** in the presence of 10% palladium-charcoal led to the corresponding ketone (94%), which was subjected to bromination reaction (86%) with pyridinium bromide perbromide in acetic acid at room temperature followed by dehydrobromination of the resulting α-bromo ketone with 1,8-diazabicyclo-[5.4.0]undec-7-ene (DBU) in benzene under reflux to give rise to the enone (**9**) in 82% yield. Epoxidation of **9** with 30% hydrogen peroxide in the presence of sodium hydroxide in methanol was next performed to furnish the epoxy ketone (91%), which was reduced to the epoxy alcohol (100%) with sodium borohydride in the presence of cerium (III) chloride heptahydrate. Upon treatment of the resulting epoxy alcohol with 1,1'-

thiocarbonyldiimidazole in the presence of 4-dimethylaminopyridine (DMAP) in dichloromethane, the thioimidazolide (**10**) was produced in quantitative yield. Radical-mediated epoxide fragmentation[10] of **10** was conducted with tributyltin hydride in the presence of 2,2'-azobisisobutyronitrile (AIBN) in benzene under reflux to afford the allylic alcohol (91%), which was allowed to react with manganese (IV) oxide, giving the corresponding enone in 88% yield. Catalytic hydrogenation of the resulted enone gave rise to the corresponding ketone (99%), which was converted into **11** after ketalization (ethylene glycol, TsOH, benzene, reflux, 98%).

With the efficient synthesis of the highly functionalized tricyclic benzoate (**11**) realized, we then examined on the regioselective bond cleavage reaction in ring B of the α-hydroxy ketone (**5**). Toward this end, the benzoate (**11**) was subjected to hydrolysis (lithium hydroxide monohydrate, MeOH-H_2O (3 : 1 v/v), reflux, 93%) and pyridinium chlorochromate (PCC) oxidation (88%) in the presence of sodium acetate and Florisil® in dichloromethane followed by α-hydroxylation reaction of the resulting ketone with oxodiperoxymolybdenum(pyridine)(hexamethylphosphoric triamide)[11] in the presence of lithium diisopropylamide at -30 °C in THF to furnish **5** in 81% yield as a 3 : 1 diastereomeric mixture. Without separation, **5** was treated with lead tetraacetate in MeOH-C_6H_6 (1 : 3 v/v) at 0 °C to give the corresponding aldehyde, in 79% yield, which was allowed to Yamamoto reaction[12] ($Ph_2P(O)CH_2CH{=}CH_2$, n-BuLi, HMPA, THF, -78 °C → room temperature, 61%) to yield the diene ester (**12**) (**Scheme II**).

Scheme II



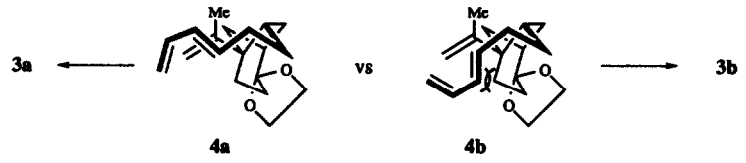
Reagents and Conditions: (a) H_2, 10% Pd-C, EtOAc, (b) Py·HBr_3, AcOH, (c) DBU, C_6H_6, reflux, (d) 30% H_2O_2, NaOH, MeOH, 0 °C → room temperature, (e) $NaBH_4$, $CeCl_3 \cdot 7H_2O$, MeOH, 0 °C, (f) 1,1'-thiocarbonyldiimidazole, DMAP, CH_2Cl_2, reflux, (g) n-Bu_3SnH, AIBN, C_6H_6, reflux, (h) MnO_2, CH_2Cl_2, (i) H_2, 10% Pd-C, EtOAc, (j) ethylene glycol, TsOH, C_6H_6, reflux, (k) LiOH·H_2O, MeOH-H_2O (3 : 1 v/v), reflux, (e) PCC, NaOAc, CH_2Cl_2, (m) LDA, THF; MoOPH, -30 °C, (n) $Pb(OAc)_4$, MeOH-C_6H_6 (1 : 3 v/v), (o) $Ph_2P(O)CH_2CH{=}CH_2$, n-BuLi, HMPA, THF, -78 °C → room temperature

Our synthetic efforts were next focused on the introduction of dienophile portion for the second intramolecular Diels-Alder reaction. The requisite triene (**4**) was readily prepared as described below. Addition of large excess amount of methyllithium in n-hexane at -78 °C (60%) followed by dehydration of the resulting alcohol with thionyl chloride and pyridine at -30 °C provided **4** in 89% yield.

With the efficient synthesis of triene (**4**) realized, the stage was now set for the construction of aphidicolane-type ring system. An intramolecular Diels-Alder reaction was performed in the presence of methylene blue[13] in toluene at 210 °C for 120 h in a sealed tube to produce the desired tricyclic compound (**3**), in 57% yield as a 3 : 1 diastereomeric mixture at C5, which was used directly in the next step without separation.

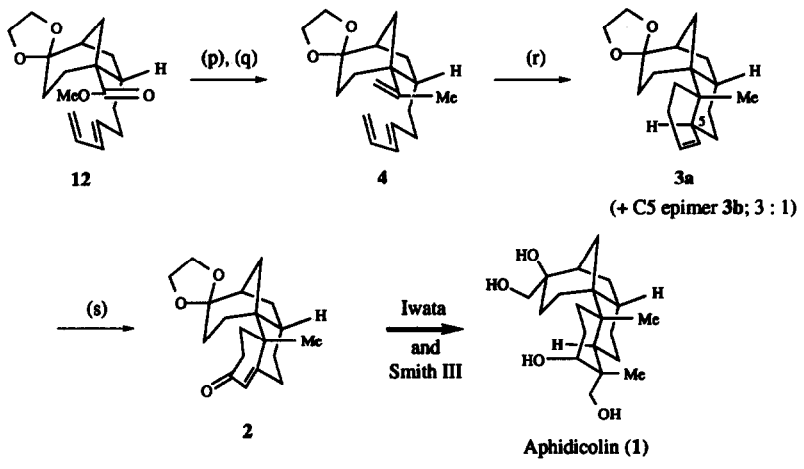
The stereochemistry of **3a** was deduced on the preference of the conformer (**4a**) in the transition state, in which the nonbonding interactions are minimized (**Figure I**).

Figure I



Finally, consecutive irradiation[14] of **3** in pyridine in the presence of hematoporphyrin under oxygen atmosphere with a halogen lamp, reductive work-up of the resulting hydroperoxides with sodium iodide in the presence of acetic acid in Et_2O-EtOH (5 : 1 v/v) and MnO_2 oxidation provided, in 57% overall yield, the enone (**2**), which displayed spectral properties identical with those reported by Iwata and Smith III in a total synthesis of aphidicolin (**1**), thus completing a formal total synthesis of **1** (**Scheme III**).

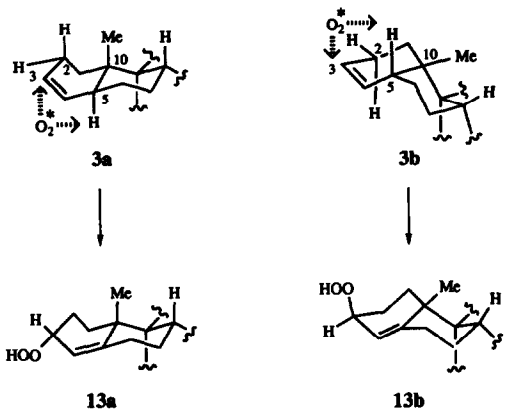
Scheme III



Reagents and Conditions: (p) MeLi, n-hexane, -78 °C, (q) $SOCl_2$, Py, -30 °C, (r) 210 °C, toluene, sealed tube, (s) O_2, hv, hematoporphyrin, Py; NaI, AcOH, Et_2O-EtOH (5 : 1 v/v); MnO_2, CH_2Cl_2

An important advantage of the present strategy is that each diastereomer (**3a** and **3b**), isomeric only at C5, yields the same product (**2**). The consumption of both cycloadducts (**3a** and **3b**) was deduced from the TLC analysis during the transformation (**3**→**2**). In **3a** (boat conformer), attack by oxygen at C3 from α-side is relatively unhindered, and the *quasi*-axial hydrogen at C5 is appropriately oriented for cyclic transfer to the oxygen leading to the hydroperoxide (**13a**). On the other hand, geometric factors in **3b** (half chair conformer) favor β-oxygenation at C3 because there is no serious steric hindrance and because the C5 hydrogen is *quasi*-axial and therefore suitably oriented for abstraction (**Figure II**).

Figure II



In conclusion, we have established a novel strategy for the synthesis of aphidicolin (**1**) with repeating intramolecular Diels-Alder reaction.

Experimental Section

General: Unless otherwise noted, materials were obtained from commercial suppliers and used without further purification. Tetrahydrofuran (THF) was distilled under argon from sodium benzophenone immediately prior to use. Dichloromethane (CH_2Cl_2), pyridine, benzene (C_6H_6), toluene, and diisopropylamine were distilled under argon from CaH_2 and used immediately. The concentration of commercially available n-butyllithium in n-hexane was checked by titration using diphenylacetic acid. All reactions involving organometallic reagents or strong bases (e.g. LDA) were conducted under an argon atmosphere in dry flasks. Unless otherwise noted, reagents and solvents were added by syringe, and organic extracts were dried by being stirred over anhydrous $MgSO_4$, filtered through Celite, and concentrated under reduced pressure (aspirator) with the aid of a rotary evaporator. Chromatography was carried out using Merck 60 (230-400 mesh) silica gel according to the procedure described by Still. Reactions and chromatography fractions were analyzed using precoated silica gel 60 F_{254} plates (Merck). Infrared spectra were recorded as films on NaCl plates unless otherwise noted. ^1H NMR spectra were measured as $CDCl_3$ solutions at 300 MHz. Chemical shifts are expressed in ppm downfield from internal tetramethylsilane. *J* values are in hertz.

Enone (9)

A mixture of the olefin (**6**) (1.61 g, 5.44 mmol) and 10% palladium-charcoal (30 mg) in EtOAc (30 mL) was stirred at room temperature under an atmosphere of hydrogen until absorption of hydrogen had ceased. After filtration through Celite, the filtrate was evaporated and the residue was chromatographed. Elution with a 10 : 1 mixture of n-hexane-EtOAc gave rise to the saturated ketone (1.524 g, 94%) as a colorless oil. IR: 1710 and 1690 cm^{-1}. ^1H NMR: δ 5.79 (1H, dd, J = 2.9 and 2.6), 7.40 - 7.49 (2H, m), 7.51 - 7.60 (1H, m) and 8.01 - 8.08 (2H, m). HRMS: calcd for $C_{19}H_{22}O_3$ 298.1569, found 298.1569. *Anal.* Calcd for $C_{19}H_{22}O_3$: C, 76.48; H, 7.43. Found: C, 76.27; H, 7.41.

To a stirred solution of the above ketone (2.684 g, 9.007 mmol) in acetic acid (30 mL) was added pyridinium bromide perbromide (2.880 g, 9.005 mmol) at room temperature, whereupon it was continued to stir at the same temperature for an additional 6 h. The reaction mixture was neutralized with saturated $NaHCO_3$ solution at 0 °C, then the aqueous layer was extracted with CH_2Cl_2 (2 × 150 mL). The organic layers were washed with saturated $KHSO_4$ solution, brine, dried and evaporated to leave a crude bromide. Chromatography (elution with a 10 : 1 mixture of n-hexane-EtOAc) afforded the bromide (2.928 g, 86%) as needles, mp 147 - 148 °C. IR ($CHCl_3$): 1722 cm^{-1}. ^1H NMR: δ 4.64 (1H, dd, J = 12.1 and 8.4), 5.91 (1H, dd, J = 2.9 and 2.6), 7.42 - 7.50 (2H, m), 7.54 - 7.62 (1H, m) and 8.01 - 8.08 (2H, m). HRMS: calcd for $C_{19}H_{21}BrO_3$ 376.0674, found 376.0673. *Anal.* Calcd for $C_{19}H_{21}BrO_3$: C, 60.49; H, 5.61; Br, 21.18. Found: C, 60.40; H, 5.65; Br, 21.00.

To a stirred solution of the above α-bromo ketone (2.928 g, 7.767 mmol) in C_6H_6 (60 mL) was added DBU (11.60 mL, 77.57 mmol) at room temperature, whereupon the mixture was refluxed for 10 h. After cooling to room temperature, the mixture was poured into saturated $KHSO_4$ solution (100 mL) at 0 °C, then the resulting mixture was extracted with Et_2O (2 × 100 mL). The organic layers were successively washed with saturated $KHSO_4$ solution, K_2CO_3 solution and brine. Drying of the organic layers, and evaporation of the solvent gave a crude material, which was chromatographed. Elution with a 10 : 1 mixture of n-hexane-EtOAc afforded the enone (**9**) (1.673 g, 82%) as needles, mp 107 - 109 °C. IR ($CHCl_3$): 1710 cm^{-1}. ^1H NMR: δ 5.71 (1H, dd, J = 2.9 and 2.6) 5.86 (1H, d, J = 9.2), 7.42 - 7.50 (2H, m), 7.53 - 7.62 (2H, m) and 8.03 - 8.09 (2H, m). HRMS: calcd for $C_{19}H_{20}O_3$ 296.1412, found 296.1412. *Anal.* Calcd for $C_{19}H_{20}O_3$: C, 77.00; H, 6.80. Found: C, 76.99; H, 6.83.

***Thioimidazolide* (10)**

To a stirred solution of the enone (**9**) (1.162 g, 5.463 mmol) in MeOH (50 mL) were added 30% H_2O_2 solution (1.690 mL, 14.912 mmol) and NaOH (47 mg, 1.175 mmol) at 0 °C, whereupon it was allowed to warm to room temperature. After 2 h of stirring at the same temperature, the mixture was diluted with H_2O (50 mL) and extracted with EtOAc (3 × 50 mL). The organic phases were washed with brine, dried and evaporated to leave a crude product. Chromatography (elution with a 10 : 1 mixture of n-hexane-EtOAc) furnished the epoxy ketone (1.551 g, 91%) as needles, mp 120 - 121 °C. IR ($CHCl_3$) 1712 and 1700 cm^{-1}. ^1H NMR: δ 2.02 (1H, d, J = 12.1), 2.20 - 2.36 (2H, m), 2.42 - 2.60 (1H, m), 2.77 - 2.86 (1H, m), 3.11 (1H, d, J = 4.0), 3.50 (1H, dd, J = 4.0 and 4.0), 5.53 (1H, dd, J = 2.9 and 2.9), 7.41 - 7.49 (2H, m), 7.53 - 7.61 (1H, m) and 7.99 - 8.16 (2H, m). HRMS: calcd for $C_{19}H_{20}O_4$ 312.1362, found 312.1388.

To a stirred solution of the above epoxy ketone (1.500 g, 4.808 mmol) and $CeCl_3 \cdot 7H_2O$ (2.150 g, 5.771 mmol) in MeOH (100 mL) was added $NaBH_4$ (195 mg, 5.155 mmol) in *ca.* 50 mg portions at 0 °C over a period of 5 min. After 0.5 h of stirring, the mixture was diluted with H_2O (100 mL) and extracted with CH_2Cl_2 (3 × 100 mL). The organic layers were washed with brine, dried and concentrated to give an oil, which was chromatographed with a 10 : 3 mixture of n-hexane-EtOAc to yield the epoxy alcohol (1.509 g, 100%) as prisms, mp 164 - 165 °C. IR ($CHCl_3$): 3600 and 1710 cm^{-1}. ^1H NMR: δ 2.93 (1H, d, J = 4.0), 3.25 (1H, dd, J = 4.0 and 3.7), 4.17 (1H, d, J = 5.9), 5.29 (1H, dd, J = 2.9 and 2.6), 7.41 - 7.50 (2H, m), 7.52 - 7.60 (1H, m) and 8.00 - 8.08 (2H, m). HRMS: calcd for $C_{19}H_{22}O_4$ 314.1518, found 314.1518.

To a stirred solution of the above epoxy alcohol (2.010 g, 6.401 mmol) in CH_2Cl_2 (40 mL) were added DMAP (1.180 g, 9.659 mmol) and 90% 1,1'-thiocarbonyldiimidazole (1.980 g, 9.999 mmol) at room

temperature, whereupon it was heated under reflux for 144 h. After removal of the solvent, the residue was chromatographed. Elution with a 1 : 1 mixture of n-hexane-EtOAc gave rise to the compound (**10**) (2.714 g, 100%) as a colorless oil. IR ($CHCl_3$): 1710 and 1392 cm^{-1}. ^1H NMR: δ 2.13 - 2.28 (1H, m), 2.31 - 2.46 (1H, m), 2.58 - 2.68 (1H, m), 2.94 (1H, d, J = 4.4), 3.28 (1H, dd, J = 4.0 and 4.0), 5.31 (1H, br dd, J = 2.1 and 2.0), 6.70 (1H, s), 7.09 - 7.13 (1H, m), 7.42 - 7.50 (2H, m), 7.54 - 7.62 (1H, m), 7.67 - 7.71 (1H, m) and 8.38 (1H, br s). HRMS: calcd for $C_{23}H_{24}N_2O_4S$ 424.1457, found 424.1456.

***Ketal* (11)**

To a degassed solution of the compound (**10**) (501 mg, 1.18 mmol) in C_6H_6 (45 mL) was added dropwise a degassed C_6H_6 solution (15 ml) of 97% n-Bu_3SnH (0.425 mL, 1.53 mmol) and AIBN (19 mg, 0.116 mmol) under reflux. After 2 h of stirring, to the mixture was added 25% NH_4OH solution (30 mL), then the resulting mixture was continued to stir for 0.5 h. The aqueous layer was neutralized with saturated NH_4Cl solution, whereupon the aqueous layer was extracted with Et_2O (2 × 50 mL). The ethereal layers were washed with brine, dried and evaporated to leave a crude material (321 mg, 91%), which without purification was used directly in the next step.

A mixture of the above allyl alcohol (31 mg, 0.104 mmol) and MnO_2 (321 mg) in CH_2Cl_2 (3 mL) was stirred at room temperature for 2 h. After filtration through Celite, the filtrate was concentrated to yield a crude product, which was chromatographed. Elution with a 2 : 1 mixture of n-hexane-EtOAc afforded the enone (27 mg, 88%) as a colorless oil. IR: 1718 and 1680 cm^{-1}. ^1H NMR: δ 2.30 - 2.51 (2H, m), 2.79 - 2.88 (1H, m), 5.47 (1H, dd, J = 2.6 and 2.5), 6.00 (1H, dd, J = 10.3 and 1.8), 6.91 (1H, dd, J = 10.3 and 1.8), 7.42 - 7.51 (2H, m), 7.55 - 7.63 (1H, m) and 8.02 - 8.09 (2H, m). HRMS: calcd for $C_{19}H_{20}O_3$ 296.1412, found 296.1412. *Anal.* Calcd for $C_{19}H_{20}O_3$: C, 77.00; H, 6.80. Found C, 76.90; H, 6.85.

A mixture of the above enone (131 mg, 0.443 mmol) and 10% palladium-charcoal (5 mg) in EtOAc (5 mL) was stirred at room temperature under an atmosphere of hydrogen until absorption of hydrogen had ceased. After filtration through Celite, the filtrate was evaporated and chromatographed. Elution with a 2 : 1 mixture of n-hexane-EtOAc gave rise to the ketone (131 mg, 99%) as a colorless oil. IR ($CHCl_3$): 1712 cm^{-1}. ^1H NMR: δ 5.24 (1H, dd, J = 2.6 and 2.5), 7.42 - 7.50 (2H, m), 7.54 - 7.61 (1H, m) and 8.02 - 8.08 (2H, m). HRMS: calcd for $C_{19}H_{22}O_3$ 298.1569, found 298.1569.

A solution of the above ketone (108 mg, 0.36 mmol), ethylene glycol (225 mg, 3.63 mmol) and toluene-*p*-sulfonic acid (5 mg, 0.026 mmol) in C_6H_6 (8 mL) was refluxed under a Dean-Stark water separator for 2 h. The solution was cooled to room temperature, and the solvent was removed under reduced pressure. The residue was taken up in CH_2Cl_2 (10 mL) and washed with saturated $NaHCO_3$ solution and brine. The organic layer was dried and evaporated to afford an oil. Chromatography (elution with a 1 : 1 mixture of n-hexane-EtOAc) gave the compound (**11**) (121 mg, 98%) as a colorless oil. IR: 1712 cm^{-1}. ^1H NMR: δ 3.77 - 3.99 (4H, m), 5.11 - 5.17 (1H, m), 7.40 - 7.49 (2H, m), 7.51 - 7.59 (1H, m) and 8.01 - 8.08 (2H, m). HRMS: calcd for $C_{21}H_{26}O_4$ 342.1831, found 342.1832.

***α-Hydroxy ketone* (5)**

To a stirred solution of the compound (**11**) (42 mg, 0.123 mmol) in MeOH (3 mL) were added $LiOH{\cdot}H_2O$ (52 mg, 1.24 mmol) and H_2O (1 mL), whereupon the mixture was heated under reflux for 8 h. After cooling to room temperature, the solution was neutralized with saturated NH_4Cl solution. The aqueous layer was

extracted with CH_2Cl_2 (2 ×10 mL), then the organic phases were dried and evaporated to yield a crude material. Chromatography (elution with a 1 : 1 mixture of n-hexane-EtOAc) gave rise to the alcohol (27 mg, 93%) as prisms, mp 113 - 114 °C. IR ($CHCl_3$): 3620 cm^{-1}. ^1H NMR: δ 3.74 (1H, br s) and 3.80 - 4.03 (4H, m). HRMS: calcd for $C_{14}H_{22}O_3$ 238.1569, found 238.1569. *Anal.* Calcd for $C_{14}H_{22}O_3$: C, 70.56; H, 9.30. Found: C, 70.49; H, 9.29.

To a stirred solution of the above alcohol (23 mg, 0.097 mmol), Florisil® (50 mg) and NaOAc (10 mg, 0.116 mmol) in CH_2Cl_2 (3 mL) was added PCC (31 mg, 0.144 mmol) at ambient temperature. The resulting mixture was continued to stir at room temperature for 2 h. Filtration and evaporation of the filtrate gave a residue which was chromatographed. Elution with a 1 : 1 mixture of n-hexane-EtOAc yielded the ketone (20 mg, 88%) as prisms, mp 56 - 57 °C. IR: 1702 cm^{-1}. ^1H NMR: δ 2.50 - 2.65 (1H, m), 3.79 - 4.03 (4H, m). HRMS: calcd for $C_{14}H_{20}O_3$ 236.1412, found 236.1412.

To a stirred solution of LDA, prepared from diisopropylamine (0.140 mL, 0.999 mmol) and n-butyllithium (1.6 M solution in n-hexane; 0.610 mL, 0.976 mmol) in THF (5 mL), was added dropwise a THF solution (3 mL) of the above ketone (116 mg, 0.492 mmol) at -78 °C, whereupon the mixture was stirred at -35 °C for 1 h. After addition of MoOPH (470 mg, 1.083 mmol) at -35 °C the resulting mixture was continued to stir for an additional 0.5 h. The reaction was quenched with saturated Na_2CO_3 solution (10 mL) at 0 °C, then the reaction mixture was extracted with Et_2O (2 × 10 mL). The aqueous layer was acidified to pH 4 with 5% HCl solution, then the resulting solution was re-extracted with CH_2Cl_2 (15 mL). Each organic layer was washed with brine, then combined. The combined organic layers were dried and evaporated to leave an oil, which was chromatographed. Elution with a 1 : 1 mixture of n-hexane-EtOAc afforded the α-hydroxy ketone (**5**) (100 mg, 81%) as a 3 : 1 diastereomeric mixture as a colorlss oil. IR: 3450 and 1710 cm^{-1}. ^1H NMR: δ 3.78 - 4.03 (4H, m), 4.30 - 4.39 (0.25H, m) and 4.46 - 4.57 (0.75H, m). HRMS: calcd for $C_{14}H_{20}O_4$ 252.1362, found 252.1362.

***Diene* (12)**

To a stirred solution of the compound (**5**) (39 mg, 0.155 mmol) in C_6H_6 (3 mL) were added MeOH (1 mL) and $Pb(OAc)_4$ (82 mg, 0.185 mmol) at 0 °C. After 1 h of stirring, to the mixture was added saturated $NaHCO_3$ solution (15 mL) at 0 °C, whereupon the resulting mixture was extracted with EtOAc (2 × 15 mL). The organic phases were dried and evaporated to give a crude material (34 mg, 79%), which without purification was used in the next reaction. IR: 1730 and 1725 cm^{-1}. ^1H NMR: δ 3.67 (3H, s), 3.80 - 4.02 (4H, m) and 9.76 (1H, t, J = 1.5). HRMS: calcd for $C_{15}H_{22}O_5$ 282.1467, found 282.1452.

To a stirred solution of allyldiphenylphosphine oxide (34 mg, 0.141 mmol) in THF (2 mL) was added HMPA (0.03 mL, 0.172 mmol), then the mixture was cooled to -78 °C. To the mixture was added dropwise n-butyllithium (1.6 M solution in n-hexane; 0.08 mL, 0.127 mmol) with stirring . After 10 min, to the resulting mixture was added THF solution (1 mL) of the above aldehyde (20 mg, 0.071 mmol) at -78 °C. The mixture was stirred at the same temperature for 0.5 h, then allowed to come to room temperature. To the mixture was added saturated NH_4Cl solution at 0 °C, whereupon the resulting mixture was extracted with Et_2O (2 × 15 mL). The organic layers were washed with brine, dried and concentrated to give a crude product, which was chromatographed. Elution with a 20 : 1 mixture of benzene-acetone yielded the diene (**12**) (13 mg, 61%) as a colorless oil. IR ($CHCl_3$): 1720 cm^{-1}. ^1H NMR: δ 3.66 (3H, s), 3.80 - 3.99 (4H, m), 4.96 (1H, br dd, J = 9.9

and 1.1), 5.08 (1H, br d, J = 16.8), 5.67 (1H, dt, J = 15.0 and 7.0), 6.04 (1H, br dd, J = 15.0 and 9.9). and 6.30 (1H, dt, J = 16.8 and 9.9). HRMS: calcd for $C_{18}H_{26}O_4$ 306.1831, found 306.1837.

***Triene* (4)**

To a stirred solution of the compound (**12**) (6.0 mg, 0.0196 mmol) in n-hexane (1.5 mL) was added methyllithium (1.4 M solution in Et_2O; 0.3 mL, 0.4192 mmol) at 0 °C, whereupon it was continued to stir at the same temperature for 20 min. To the mixture was added saturated NH_4Cl solution (15 mL) at 0 °C, then the resulting mixture was extracted with EtOAc (2 × 5 mL). The organic phases were washed with brine, dried and evaporated to leave an oil, which was chromatographed. Elution with a 2 : 1 mixture of n-hexane-EtOAc furnished the alcohol (3.6 mg, 60%) as a colorless oil. ^{1}H NMR: δ 1.23 (6H, s), 3.80 - 4.02 (4H, m), 4.95 (1H, br d, J = 10.0), 5.08 (1H, br d, J = 17.0), 5.70 (1H, dt, J = 15.0 and 7.0), 6.05 (1H, br dd, J = 15.0 and 10.0 Hz) and 6.30 (1H, dt, J = 17.0 and 10.0).

To a stirred solution of the above alcohol (2.4 mg, 0.0078 mmol) in pyridine (1.5 mL) was added dropwise thionyl chloride (0.010 mL, 0.1371 mmol) at -30 °C. After 0.5 h of stirring at the same temperature, H_2O (5 mL) was added to the mixture at 0 °C, whereupon the resulting mixture was extracted with Et_2O (2 × 10 mL). The ethereal layer was washed with saturated $KHSO_4$ solution, brine, dried and evaporated to give an oil, which was chromatographed. Elution with a 10 : 1 mixture of n-hexane-EtOAc afforded the triene (**4**) (2.0 mg, 89%) as a colorless oil. IR ($CHCl_3$): 1630 cm^{-1}. ^{1}H NMR: δ 1.72 (3H, s), 3.80 - 4.01 (4H, m), 4.72 (1H, br s), 4.79 (1H, d, J = 1.1) 4.94 (1H, br d, J = 10.6), 5.07 (1H, br d, J = 16.8), 5.68 (1H, dt, J = 14.7 and 7.3), 5.97 - 6.10 (1H, m) and 6.28 (1H, ddd, J = 16.8, 10.6 and 10.6). HRMS: calcd for $C_{19}H_{28}O_2$ 288.2090, found 288.2076.

***Cycloadduct* (3)**

A mixture of the triene (**4**) (24.8 mg, 0.0861 mmol) and methylene blue (0.5 mg, 0.0013 mmol) in toluene (1 mL) was heated at 210 °C in a sealed tube for 120 h. After cooling to room temperature, the solvent was removed under reduced pressure, whereupon the residue was chromatographed. Elution with a 20 : 1 mixture of n-hexane-EtOAc provided the compound (**3**) (14.1 mg, 57%) as a 3 : 1 diastereoisomeric mixture. The cycloadducts were used without further separation. IR ($CHCl_3$): 1632 cm^{-1}. ^{1}H NMR: δ 0.83 (0.75H, s), 0.87 (2.25H, s), 3.80 - 4.03 (4H, m) and 5.32 - 5.69 (2H, m). HRMS: calcd for $C_{19}H_{28}O_2$ 288.2090, found 288.2065.

***Enone* (2)**

A stirred solution of the olefins (**3**) (27.0 mg, 0.0938 mmol) and hematoporphyrin (4.0 mg, 0.0067 mmol) in pyridine (9 mL) was irradiated by 700-W halogen lamp through a Pyrex® filter with oxygen bubbling for 88 h. To the mixture were added active charcoal (20 mg) and Et_2O (10 mL), whereupon the resulting mixture was stirred at room temperature for 15 min. After filtration through Celite, the filtrate was concentrated to leave a crude material (30.0 mg), which without purification was used in the next step.

To a stirred solution of the above product (30.0 mg) in a mixture of Et_2O (15 mL) and EtOH (3 mL) were added acetic acid (2 drops) and NaI (260 mg, 1.73 mmol) at ambient temperature, whereupon the resulting mixture was continued to stir at room temperature for 10.5 h. After removal of the solvent, the residue was dissolved in Et_2O (20 mL), then the ethereal layer was washed with saturated $Na_2S_2O_3$ solution, brine and

evaporated to yield a crude material (25.0 mg), which was taken up in CH_2Cl_2 (3 mL). MnO_2 (350 mg, 4.03 mmol) was added to the above solution, whereupon the resulting mixture was stirred at room temperature for 1.5 h. After filtration through Celite, the filtrate was concentrated to give an oil, which was chromatographed. Elution with a 15 : 1 mixture of benzene-acetone afforded the enone (**2**) (16.2 mg, 57% form **3**) as a colorless oil. IR ($CHCl_3$): 1661 cm^{-1}. ^1H NMR: δ 1.25 (3H, s), 1.32 - 1.40 (2H, m), 1.49 - 1.62 (5H, m), 1.68 - 1.86 (4H, m), 1.95 (1H, ddd, J = 13.5, 12.0, 7.9), 2.19 (1H, br dd, J = 6.2 and 6.2), 2.29 - 2.53 (5H, m), 3.81 - 4.01 (4H, m) and 5.82 (1H, d, J = 1.8). HRMS: calcd for $C_{19}H_{26}O_3$ 302.1882, found 302.1877.

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