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Aphidicolin Synthesis (II)——An Expeditious and Efficient Formal Synthesis of (±)-Aphidicolin

Masahiro Toyota, Youichi Nishikawa and Keiichiro Fukumoto*

Pharmaceutical Institute, Tohoku University, Aobayama, Sendai 980-77, Japan

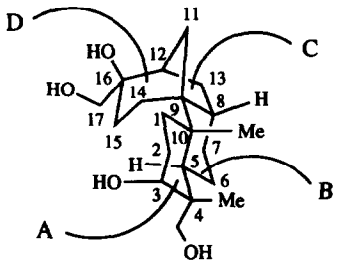
Abstract: An expeditious and efficient formal total synthesis of an antiviral and antitumor tetracyclic diterpene aphidicolin (**1**) has been achieved. An intramolecular Heck reaction (**7**→**6**) and an intramolecular Diels-Alder reaction (**4**→**3**) were utilized for the key steps of the sequence.

Introduction

Aphidicolin (**1**) is a diterpenoid tetraol produced by the mold *Cephalosporium aphidicola*. Since its structure was unveiled in 1972 by Hesp and co-workers,[1] the molecule has captured the imagination of synthetic chemists because of its unique network of rings and stereogenic centers, which presents formidable challenges to current synthetic methodology.

The first syntheses of aphidicolin (**1**) were reported independently by McMurry[2a] and by Trost[2b] and their colleagues in 1979. After considerable efforts, eight total syntheses[2] and one formal synthesis[3] have been reported to date. In addition, Holton and co-workers disclosed the first enantioselective construction of **1**, unambiguously confirming the absolute stereochemistry.[2g]

Aphidicolin (**1**) incorporates three structural features which have posed long-standing synthetic problems: (i) a spiro fused bicyclo[3.2.1]octane moiety which comprises C and D rings, (ii) adjacent quaternary stereogenic centers (C9 and C10), and (iii) A, B-*trans* ring juncture.



Aphidicolin (**1**)

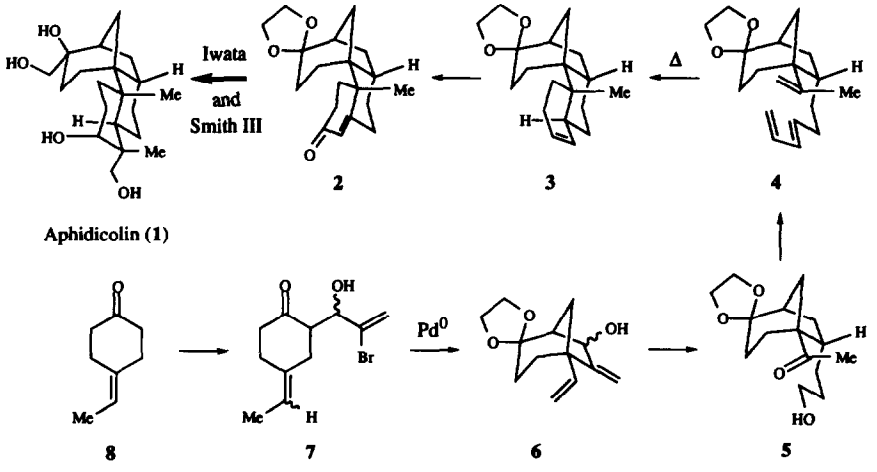
Rather surprisingly in view of its simple functionality, aphidicolin (**1**) shows marked activity against Herpes simplex Type I virus, both *in vitro* and in the rabbit eyes.[4] Apart from its antifeedant property,[5] **1** exhibits considerable antitumor activity in the C6 mouse colon and B16 mouse melanosarcoma screens[6] and has

been shown to inhibit the growth of leukemia T- and B-lymphocytes[7] 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[8] of enhanced antitumor activity associated with the more water-soluble aphidicolin-17-glycinate HCl salt, synthesized as a pro-drug, might revive interest in **1** and its analogues as a specific reversible inhibitor of DNA polymerase α.

Herein, we describe conceptually distinct approach to **1** featuring methodologies designed to address the above-mentioned outstanding topological issues confronted during the total synthesis of **1**, *viz.*, (a) intramolecular Heck reaction for the construction of CD ring system, and (b) intramolecular Diels-Alder reaction affording AB *trans* ring juncture.

Synthetic Plan

Since the enone (**2**) has already been converted to the natural product (**1**) by Iwata[2h] and Smith III,[9] the synthesis of **2** completes the task. The novel synthetic strategy contemplated for the present diastereoselective approach to **1** is shown in **Scheme I**. Aldol reaction of the ketone (**8**) followed by an intramolecular Heck reaction and protection was expected to establish the bicyclo[3.2.1]octane (**6**). [3,3] Sigmatropic rearrangement of the vinyl enol ether of **6** followed by hydride reduction, Wacker oxidation, and hydrogenation would make the keto alcohol (**5**) available. Modest functional group manipulation would lead to the triene (**4**). Finally, access to the enone (**2**) was expected *via* intramolecular Diels-Alder reaction of **4** followed by photosensitized oxygenation of the resulting olefin (**3**).



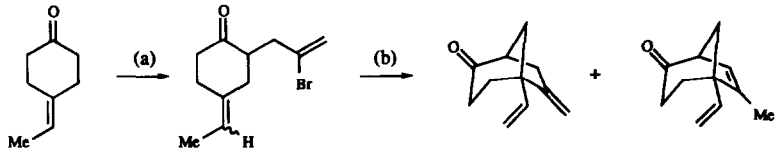
Scheme I

Results and Discussion

In order to explore feasibility of the designed synthetic strategy, the intramolecular Heck reaction[10] of **9**, the model compound of **7**, was first studied. In this connection, the development of efficient routes for the synthesis of functionalized bicyclo[3.2.1]octane ring systems continues to attract attention due to the wide variety

of natural products containing this structural unit. The requisite vinyl bromide (**9**) for the intramolecular Heck reaction was readily prepared by means of alkylation of **8** with 2,3-dibromopropene in the presence of LDA.

With **9** in hand, the crucial intramolecular Heck reaction for the construction of the CD ring system of aphidicolin (**1**) was examined (**Scheme II**). Some of conditions and yields examined for Heck reaction of **9** are listed in **Table I**. All reactions employed 10 mol % $Pd(OAc)_2$ and 20 mol % ligand. As a result of testing, the intramolecular Heck reaction in MeCN under reflux in the presence of K_2CO_3 proceeded quite nicely to provide **10** in 86% yield (entry 10).



8 **9** **10** **11**

(a) LDA, THF, HMPA, -78 °C; 2,3-Dibromopropene, -78 °C, (b) Reagent ratios and experimental details can be found in the experimental section.

Scheme II

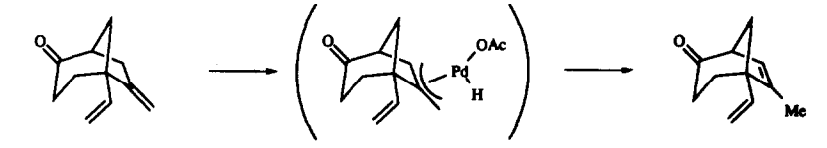
Conditions and Yields of the Intramolecular Heck Reaction of Compound (**9**)

entry	ligand	base	solvent	temperature (°C)	time (h)	yield (%)	ratio	
							10	**11**
1	PPh_3	Et_3N	MeCN	reflux	6	48	14	1
2	PPh_3	Et_3N	DMF	130 [c]	56	—	—	—
3	PPh_3	Et_3N	none	100 [c]	89	29	14	1
4	P(*o*-tolyl)$_3$	Et_3N	none	100 [c]	89	51	1	9
5	PPh_3	Et_3N	MeCN	100 [c]	31	39	13	1
6	P(*o*-tolyl)$_3$	Et_3N	MeCN	100 [c]	31	75	1	4
7	PPh_3	Et_3N	toluene	120 [c]	133	42	8	1
8	P(*o*-tolyl)$_3$	Et_3N	toluene	120 [c]	133	51	9	2
9	P(*o*-tolyl)$_3$	Et_3N	aq. MeCN	110 [c]	158	trace	—	—
10	P(*o*-tolyl)$_3$	K_2CO_3	MeCN	reflux	5	86	> 99	< 1
11 [a]	P(*o*-tolyl)$_3$	K_2CO_3	MeCN	r. t.	4.5	—	—	—
12 [b]	P(*o*-tolyl)$_3$	K_2CO_3	MeCN	r. t.	12	—	—	—

a) The reaction mixture was kept in an ultrasonic bath. b) Plus 1.0 eq. of n-$Bu_4N^+Cl^-$ was used. c) The reaction was performed in a sealed tube.

Table I

Interestingly, in entries 4 and 6, extensive isomerization of the exocyclic double bond to an endo cyclic position occurred. In order to provide some understanding of the above result, MMX steric energy calculations[11] were performed on the two compounds (**10** and **11**). These calculations (**Figure I**) suggested that the endo-olefin (**11**) is considerably lower in energy than the exo-olefin (**10**). Probably, **10** represents the kinetic product that is equilibrated *via* the π-allylpalladium complex (**12**) under the reaction conditions in entries 4 and 6 (**Figure I**).

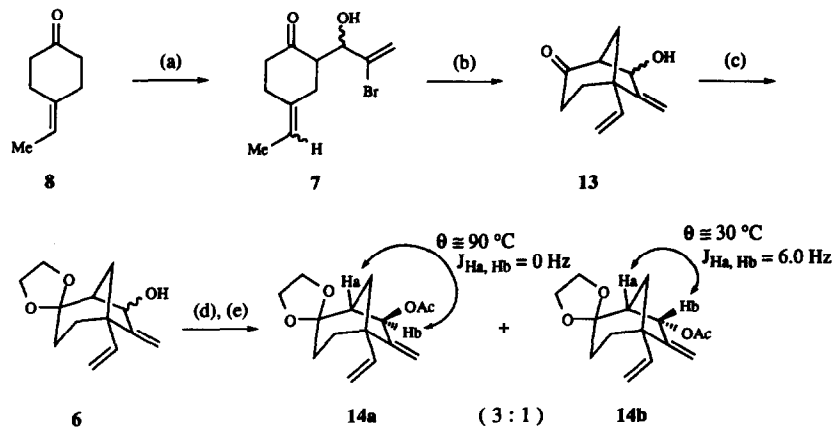


10 **12** **11**

MMXrel = 2.63 Kcal/mol MMXrel = 0 Kcal/mol

Figure I

Being encouraged by this result, the intramolecular Heck reaction was next examined employing **7** which bears a hydroxyl group at the allylic position. Toward this end, first of all, the requisite allylic alcohol (**7**) was synthesized as a diastereomeric mixture by using aldol reaction of **8** with α-bromoacrolein in the presence of LDA at - 78 °C (89%). The critical Heck reaction of **7** proceeded cleanly in refluxing MeCN in the presence of 10 mol % $Pd(OAc)_2$, 20 mol % P(*o*-tolyl)$_3$ and 2 eq. of K_2CO_3 to give rise to, in 90% yield, the highly functionalized bicyclo[3.2.1]octane derivative (**13**), which was transformed into **6** after ketalization (89%). Although the stereochemical assignment of **6** was not possible at this stage, successful elaboration of **6** to the acetates (**14a** and **14b**) definitely confirmed their stereochemistry as shown in **Scheme III**. The major diastereoisomer was assigned structure (**14a**) by a high-field NMR analysis. The 0 Hz coupling constant for $J_{Ha,\,Hb}$ defines the structure of major product to be **14a** (**Scheme III**).



8 **7** **13**

6 **14a** (3 : 1) **14b**

(a) LDA, THF, CH_2=CBrCHO, -78 °C, (b) $Pd(OAc)_2$, P(*o*-tolyl)$_3$, K_2CO_3, MeCN, reflux, (c) Ethylene glycol, PPTS, C_6H_6, reflux, (d) Chromatographical separation, (e) Ac_2O, Pyridine, DMAP, room temperature.

Scheme III

The stereoselectivity of the aldol process (**8**→**7**) is consistent with the rule, based on the Zimmerman-Traxler cyclic transition state model[12] depicted in **Figure II**, that E-enolates should selectively produce *threo* aldol products. Since only E-enolate can arise from the cyclic structure (**8**), the reaction outcome is not distorted by possible E⇄Z isomerization. Hence, the ratio of products (**16**) and (**18**) reflects exclusively the behavior of the E-enolate. Of the two transition states (**15**) and (**17**), the former will produce the *threo*-aldol (**16**), while the latter will afford the *erythro*-isomer (**18**). Since the transition state (**15**) is sterically less congested, the *threo* adduct predominated in the reaction mixture.

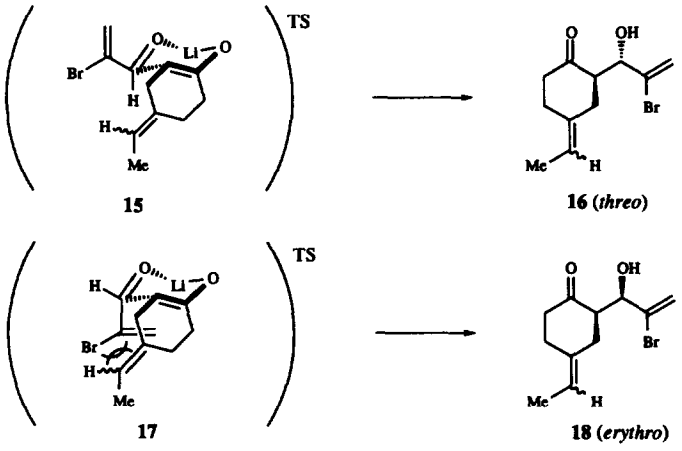


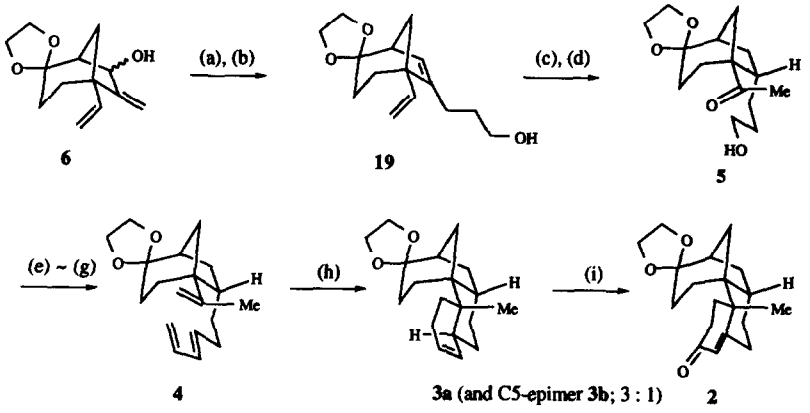
Figure II

With a secure supply of **6** in hand, our efforts were next directed toward the introduction of C_2 carbon unit. The conversion of **6** to the alcohol (**19**) was achieved in three steps (82% overall yield), including vinyl etherification[13] (CH_2=CHOEt, $Hg(OCOCF_3)_2$, Et_3N), the Claisen rearrangement[14] of the vinyl ether (toluene, 140 °C, sealed tube) and $NaBH_4$ reduction of the resulting aldehyde. In order to confirm that the Claisen rearrangement of both diastereoisomers (**6**) proceeds, the allylic alcohols (**6**) were separated and each was subjected to the same transformational conditions, which yielded the same product (**19**) in both instances. Wacker oxidation[15] of **19** was next conducted with O_2, $PdCl_2$ and CuCl in DMF-H_2O (7 : 1) at 40 °C to furnish the corresponding methyl ketone in 70% yield, which was treated with 10% palladium-charcoal under a hydrogen atmosphere to give rise to the saturated ketone (**5**) in 82% yield. As a consequence of steric congestion on the endo surface of the bicyclo[3.2.1]octane subunit, the above hydrogenation provided the compound (**5**) as a sole product.

Our synthetic efforts were next focused on the introduction of diene and dienophile portions for the intramolecular Diels-Alder reaction. Wittig methylenation ($Ph_3P^+MeBr^-$, n-BuLi, THF, reflux, 81%) of **5** provided the olefinic alcohol, which was converted to the corresponding aldehyde (92%) by using PCC in the presence of NaOAc. Subsequent transformation into the triene (**4**) was accomplished in 62% yield by means of Yamamoto reaction.[16]

With the efficient synthesis of **4** realized, the stage was now set for the construction of aphidicolan-type skeleton. An intramolecular Diels-Alder reaction was performed in the presence of methylene blue[17] in toluene

230 °C for 120 h in a sealed tube to produce the desired tetracyclic compound (**3**), in 67% yield as a 3 : 1 diastereomeric mixture at C5, which was used directly in next step without separation (**Scheme IV**).



(a) CH_2=CHOEt, $Hg(OCOCF_3)_2$, Et_3N, room temperature, (b) Toluene, 140 °C, sealed tube; $NaBH_4$, MeOH, 0 °C, (c) O_2, $PdCl_2$, CuCl, DMF-H_2O, 40 °C, (d) H_2, 10% Pd-C, EtOAc, (e) $Ph_3P^+MeBr^-$, n-BuLi, THF, reflux, (f) PCC, NaOAc, Florisil®, CH_2Cl_2, (g) $Ph_2P(O)CH_2CH_2$=CH_2, n-BuLi, HMPA, THF, -78 °C→room temperature, (h) Methylene blue, Toluene, 230 °C, sealed tube, (i) ref. 19.

Scheme IV

The stereochemistry of **3a** was deduced on the preference of the conformer (**4a**) in the transition state, in which the nonbonding interactions are minimized. MMX steric energy calculations were performed on the two transition states available to **4**. The transition state (**4a**) can lead to **3a**, while **4b** can generate **3b**. A bond order[18] of 0.3 was used to define the C1-C2 and C5-C10 distances in the transition structure. These calculations suggested that the transition state (**4a**) is considerably lower in energy than the alternative one (**4b**). This analysis therefore also supports the tentative assignment of **3a** as the major product of the intramolecular Diels-Alder reaction of the triene (**4**) (**Figure III**).

4a MMXrel = 0 Kcal/mol

4b MMXrel = 1.97 Kcal/mol

Figure III

With ready access to the olefin (**3**) (11 steps) and our previous experience[19] with the photosensitized oxygenation of **3**, the completion of the synthesis seemed imminent. The pivotal transformation (**3**→**2**) was

occasioned, 81% overall yield for 3 steps, under standard conditions[20] (i; O_2, hv, hematoporphyrin, pyridine, ii; NaI, AcOH, Et_2O-EtOH, iii; MnO_2, CH_2Cl_2). An important advantage of the present synthetic strategy is that each diastereoisomers (**3a** and **3b**), isomeric only at C5 position, gives rise to the same enone (**2**),[21] which displayed the same spectra with those provided[2h] by Iwata and co-workers in a total synthesis of aphidicolin (**1**), thus completing a formal synthesis of **1**.

In conclusion, we have established expeditious and highly stereocontrolled methodology for the formal total synthesis of aphidicolin based on intramolecular Heck cyclization reaction and intramolecular Diels-Alder reaction. The success of the above procedure rests on the extremely high regio- and stereoselectivities observed through the overall sequences.

Experimental Section

General: Unless otherwise noted, materials were obtained from commercial suppliers and used without further purification. Tetrahydrofuran (THF) and Et_2O were distilled under argon from sodium benzophenone immediately prior to use. Dichloromethane (CH_2Cl_2), acetonitrile (MeCN), pyridine and Et_3N were distilled under argon from CaH_2 and used immediately. Toluene and benzene (C_6H_6) were distilled under argon from phosphorus pentoxide (P_2O_5). Dimethylformamide (DMF) was distilled under argon from $MgSO_4$ prior to use. Diisopropylamine, HMPA and MeOH were distilled under argon and used immediately. The concentration of commercially available n-butyllithium in n-hexane was checked by titration by using diphenylacetic acid.[22] 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 by using Merck 60 (230-400 mesh) silica gel according to the procedure described by Still.[23] Reactions and chromatography fractions were analyzed by using precoated silica gel 60 F_{254} plates (Merck). IR spectra were recorded as films on NaCl plates unless otherwise noted. ^1H NMR spectra were measured as $CDCl_3$ solutions at 300 and 500 MHz. Chemical shifts are expressed in ppm downfield from internal tetramethylsilane or relative internal $CHCl_3$, *J* values are in hertz.

Vinyl Bromide (**9**)

To a stirred solution of LDA, prepared from diisopropylamine (0.15 mL, 1.08 mmol) and 10% n-hexane solution of n-butyllithium (0.67 mL, 1.05 mmol) in THF (8 mL), at -78 °C were added dropwise a THF solution (2 mL) of 4-ethylidenecyclohexanone (100 mg, 0.806 mmol) and HMPA (0.18 mL, 1.03 mmol), whereupon the mixture was stirred at the same temperature for 40 min. After the addition of 2,3-dibromopropene (0.12 ml, 1.16 mmol) at -78 °C, the resulting mixture was allowed to warm to room temperature over a period of 0.5 h. After 18 h of stirring at the same temperature, the reaction was quenched with saturated NH_4Cl solution, then extracted with Et_2O (10 mL). The ethereal layer was washed with brine, dried and evaporated to leave a crude material, which was chromatographed. Elution with a 17 : 1 mixture of n-hexane-EtOAc afforded the compound (**9**) (65.0 mg, 78%; based upon recovered starting material) and **6** (58.0 mg) as an oil. IR: 1710 cm^{-1}. ^1H NMR (300 MHz): δ 1.61 (1.5H, d, *J* = 5.1), 1.66 (1.5H, d, *J* = 6.6), 1.99 - 2.20 (9H, m), 5.20 - 5.70 (3H, m). HRMS: calcd for $C_{11}H_{15}O$ (M^+ -79) 163.1123, found 163.1127.

Heck Reaction of 9

(entry 1) A mixture of the bromide (**9**) (28.0 mg, 0.115 mmol), triphenylphosphine (PPh_3) (6.0 mg, 0.0230 mmol), $Pd(OAc)_2$ (2.6 mg, 0.0115 mmol) and Et_3N (0.03 mL, 0.215 mmol) in MeCN (0.5 mL) was refluxed for 6 h. After filtration through Celite, the filtrate was evaporated and the residue was chromatographed. Elution with a 20 : 1 mixture of n-hexane-EtOAc gave rise to the bicyclic compound (9.0 mg, 48%) as a 14 : 1 isomeric mixture. IR: 1700 cm^{-1}. ^1H NMR (300 MHz): δ 4.95 - 4.98 (0.933H, m) and 5.59 - 5.64 (0.067H, m). HRMS: calcd for $C_{11}H_{14}O$ 162.1045, found 162.1035.

(entry 2) A mixture of **9** (43.0 mg, 0.177 mmol), PPh_3 (4.8 mg, 0.0183 mmol), $Pd(OAc)_2$ (4.0 mg, 0.0177 mmol) and Et_3N (0.05 mL, 0.359 mmol) in DMF (0.5 mL) was heated at 130 °C in a sealed tube for 56 h. Under the above conditions, no identifiable compound could be obtained.

(entry 3) A mixture of **9** (58.0 mg, 0.239 mmol), PPh_3 (13.0 mg, 0.0496 mmol), $Pd(OAc)_2$ (5.4 mg, 0.0241 mmol) and Et_3N (0.10 mL, 0.717 mmol) was heated at 100 °C in a sealed tube for 89 h. Work-up in the same way furnished the bicyclic compound (7.0 mg, 29%) as a 14 : 1 isomeric mixture.

(entry 4) A mixture of **9** (109 mg, 0.449 mmol), tri-*o*-tolylphosphine (TOTP) (27.0 mg, 0.0887 mmol), $Pd(OAc)_2$ (10.1 mg, 0.0450 mmol) and Et_3N (0.30 mL, 2.15 mmol) was heated at 100 °C in a sealed tube for 89 h. Work-up in the same way gave rise to the bicyclic compound (31.0 mg, 51%) as a 1 : 9 isomeric mixture.

(entry 5) A mixture of **9** (77.0 mg, 0.317 mmol), PPh_3 (17.0 mg, 0.0649 mmol), $Pd(OAc)_2$ (7.1 mg, 0.0316 mmol) and Et_3N (0.09 mL, 0.657 mmol) in MeCN (3 mL) was heated at 100 °C in a sealed tube for 31 h. Work-up in the same way yielded the bicyclic compound (20.0 mg, 39%) as a 13 : 1 isomeric mixture.

(entry 6) A mixture of **9** (54.0 mg, 0.222 mmol), TOTP (13.5 mg, 0.0443 mmol), $Pd(OAc)_2$ (5.0 mg, 0.0223 mmol) and Et_3N (0.06 mL, 0.430 mmol) in MeCN (2 mL) was heated at 100 °C in a sealed tube for 31 h. Work-up in the same way afforded the bicyclic compound (27.0 mg, 75%) as a 1 : 4 isomeric mixture.

(entry 7) A mixture of **9** (47.0 mg, 0.193 mmol), PPh_3 (10.4 mg, 0.0396 mmol), $Pd(OAc)_2$ (4.3 mg, 0.0192 mmol) and Et_3N (0.05 mL, 0.359 mmol) in toluene (2 mL) was heated at 120 °C in a sealed tube for 133 h. Work-up in the same way gave the bicyclic compound (13.0 mg, 42%) as an 8 : 1 isomeric mixture.

(entry 8) A mixture of **9** (91.0 mg, 0.374 mmol), TOTP (22.7 mg, 0.0746 mmol), $Pd(OAc)_2$ (8.4 mg, 0.0374 mmol) and Et_3N (0.10 mL, 0.717 mmol) in toluene (3.5 mL) was heated at 120 °C in a sealed tube for 133 h. Work-up in the same way yielded the bicyclic compound (31.0 mg, 51%) as a 9 : 2 isomeric mixture.

(entry 9) A mixture of **9** (68.0 mg, 0.280 mmol), TOTP (17.0 mg, 0.0558 mmol), $Pd(OAc)_2$ (6.3 mg, 0.0281 mmol) and Et_3N (0.08 mL, 0.574 mmol) in MeCN-H_2O (2 mL; 10 : 1) was heated at 110 °C in a sealed tube for 158 h. Work-up in the same way furnished trace amount of the bicyclic compound.

(entry 10) A mixture of **9** (36.0 mg, 0.148 mmol), TOTP (9.0 mg, 0.0296 mmol), $Pd(OAc)_2$ (3.3 mg, 0.0147 mmol) and K_2CO_3 (40.9 mg, 0.296 mmol) in MeCN (2 mL) was refluxed for 5 h. Work-up in the same way gave rise to **10** (12.0 mg, 86%: based upon recovered starting material) as a colorless oil along with **9** (15.0 mg). Compound (**10**), IR: 1700 cm^{-1}. ^1H NMR (300 MHz): δ 1.79 - 1.91 (3H, m), 2.01 - 2.09 (1H, m), 2.26 - 2.58 (4H, m), 2.66 - 2.82 (1H, m), 4.95 - 4.98 (1H, m), 5.07 - 5.10 (1H, m), 5.12 (1H, dd, J = 17.6 and 1.1), 5.16 (1H, dd, J = 10.6 and 1.1) and 5.95 (1H, dd, J = 17.6 and 10.6).

(entry 11) A mixture of **9** (44.0 mg, 0.181 mmol), TOTP (11.0 mg, 0.0361 mmol), $Pd(OAc)_2$ (4.1 mg, 0.0168 mmol) and K_2CO_3 (50.0 mg, 0.362 mmol) in MeCN (2 mL) was kept in an ultrasonic bath at room temperature for 4.5 h. No reaction proceeded at all.

(entry 12) A mixture of **9** (44.0 mg, 0.181 mmol), TOTP (11.0 mg, 0.0361 mmol), $Pd(OAc)_2$ (4.1 mg, 0.0183 mmol), K_2CO_3 (50.0 mg, 0.362 mmol) and n-$Bu_4N^+Cl^-$ (50.3 mg, 0.181 mmol) was stirred at room temperature for 12 h. No reaction was judged by TLC analysis.

***Aldol adducts* (7)**

To a stirred solution of LDA, prepared from diisopropylamine (2.10 mL, 15.0 mmol) and 10% n-hexane solution of n-buthyllithium (9.4 mL, 14.7 mmol) in THF (60 mL), was added dropwise a THF solution (20 mL) of 4-ethylidenecyclohexanone (**8**) (1.40 g, 11.3 mmol) at -78 °C, whereupon the mixture was stirred at the same temperature for 1 h. After the addition of α-bromoacrolein (1.52 g, 12.4 mmol) in THF (20 mL) at -78 °C, the resulting mixture was continued to stir at the same temperature for 0.5 h. The mixture was quenched with saturated NH_4Cl solution, then extracted with EtOAc. The organic phase was washed with brine, dried and evaporated to yield a crude material, which was chromatographed. Elution with a 3 : 1 mixture of n-hexane-EtOAc provided **7** (1.49 g, 89%: based on recovered starting material) as a colorless oil along with **8** (0.556 g). IR: 3440 and 1700 cm^{-1}. ^1H NMR (300 MHz): δ 1.66 (3H, d, J = 7.0), 2.34 - 2.98 (6H, m), 4.80 - 4.89 (1H, m), 5.40 - 5.50 (1H, m), 5.68 - 5.70 (1H, m), 6.04 - 6.12 (1H, m). HRMS: calcd for $C_{11}H_{16}BrO_2$ (M^+ +1) 259.0334, found 259. 0324.

***Bicyclic Alcohol* (13)**

A mixture of **7** (240 mg, 0.972 mmol), TOTP (59.2 mg, 0.194 mmol), $Pd(OAc)_2$ (21.8 mg, 0.0892 mmol) and K_2CO_3 (268 mg, 1.94 mmol) in MeCN (12 mL) was refluxed for 2 h. After filtration through Celite, the filtrate was evaporated to give rise to a crude material, which was chromatographed. Elution with a 2 : 1 mixture of n-hexane-EtOAc afforded a solid, which was recrystallized from petroleum ether-Et_2O to yield the bicyclic compound (**13**) (155 mg, 90%) as prisms, m.p. 76.5 - 77.5 °C. IR: 3430 and 1710 cm^{-1}. ^1H NMR (300 MHz): δ 1.80 - 2.00 (4H, m), 2.30 - 2.60 (2H, m), 2.77 - 2.81 (0.25H, m), 2.92 - 2.99 (0.75H, m), 4.52 (0.25H, br s), 4.80 - 4.89 (0.75H, m), 5.09 - 5.24 (3H, m), 5.30 - 5.48 (1H, m) and 5.89 - 6.04 (1H, m). *Anal.* Calcd for $C_{11}H_{14}O_2$: C, 74.13; H, 7.92. Found: C, 74.08; H, 7.90.

***Ketals* (6)**

A solution of **13** (217 mg, 1.22 mmol), ethylene glycol (1.0 mL, 17.7 mmol) and pyridinium *p*-toluenesulfonate (PPTS) (103 mg, 0.410 mmol) in C_6H_6 (10 mL) was refluxed under a Dean-Stark water separator for 2 h. The solution was cooled to room temperature and the solvent was evaporated. The residue was taken up in CH_2Cl_2 and washed with saturated $NaHCO_3$ solution and brine. The organic layer was dried and evaporated to leave a crude material, which was chromatographed. Elution with a 2 : 1 mixture of n-hexane-EtOAc gave the minor isomer (60.0 mg, 22%) and the major one (181 mg, 67%) respectively.

minor isomer; needles, m.p. 96 °C (recrystallized from petroleum ether). IR: 3400 cm^{-1}. ^1H NMR (300 MHz): δ 1.50 - 1.94 (6H, m), 2.24 - 2.37 (1H, m), 3.46 (1H, d, J = 6.6), 3.84 - 4.09 (4H, m), 4.25 - 4.62 (1H, m), 4.95 (1H, br d, J = 2.6), 5.06 (1H, dd, J = 16.8 and 2.6), 5.07 (1H, dd, J = 11.7 and 2.6), 5.30 (1H, br d, J = 2.6) and 5.89 (1H, dd, J = 16.8 and 11.7). *Anal.* Calcd for $C_{13}H_{18}O_3$: C, 70.24; H, 8.16. Found: C, 69.98; H, 8.12.

major isomer; colorless oil. IR: 3400 cm^{-1}. ^1H NMR (300 MHz): δ 1.40 - 1.72 (4H, m), 1.78 (1H, br d, J = 11.8), 2.02 (1H, br ddd, J = 11.8, 5.4 and 2.9), 2.15 (1H, br d, J = 5.0) 2.49 (1H, br s), 3.85 - 4.04 (4H,

m), 4.47 (1H, br s), 5.01 (1H, d, J = 1.1), 5.10 (1H, dd, J = 16.8 and 1.1), 5.11 (1H, dd, J = 11.0 and 1.1), 5.31 (1H, br s) and 5.90 (1H, dd, J = 16.8 and 11.0). HRMS: calcd for $C_{13}H_{18}O_3$ 222.1256, found 222.1264.

***Acetate* (14a *and* 14b)**

A mixture of the major isomer of **6** (1.5 mg, 0.00676 mmol), Ac_2O (0.5 mL, 5.3 mmol) and 4-dimethylaminopyridine (DMAP) (0.1 mg, catalytic amount) in pyridine (1.0 mL) was stirred at room temperature for 0.5 h. The mixture was diluted with Et_2O (2 mL), whereupon the ethereal layer was washed with saturated $KHSO_4$ solution, saturated $NaHCO_3$ solution, brine, dried and evaporated to give a crude material which was chromatographed. Elution with a 4 : 1 mixture of n-hexane-EtOAc furnished a solid, which was recrystallized from petroleum ether to give rise to the acetate (**14a**) (1.7 mg, 95%) as needles, m.p. 96 °C. IR ($CHCl_3$): 1710 cm^{-1}. ^1H NMR (300 MHz): δ 2.05 (3H, s), 3.90 - 4.04 (4H, m), 5.06 (1H, dd, J = 11.0 and 1.0), 5.06 (1H, dd, J = 11.0 and 1.0), 5.07 (1H, dd, J = 17.5 and 1.0), 5.13 (1H, br d, J=1.0), 5.37 (1H, br s), 5.57 (1H, br d, J = 1.0) and 5.91 (1H, dd, J = 17.5 and 11.0). *Anal.* Calcd for $C_{15}H_{20}O_4$: C, 68.16; H, 7.63. Found: C, 68.10; H, 7.60.

A mixture of the minor isomer of **6** (4.5 mg, 0.0203 mmol), Ac_2O (2.0 mL, 21.2 mmol) and DMAP (0.1 mg, catalytic amount) in pyridine (4.0 mL) was stirred at room temperature for 0.5 h. Work-up in the same way afforded the acetate (**14b**) (3.3 mg, 62%) as a colorless oil. IR ($CHCl_3$): 1715 cm^{-1}. ^1H NMR (300 MHz): δ 2.10 (3H, s), 3.75 - 4.00 (4H, m), 5.00 (1H, br d, J = 2.5), 5.09 (1H, dd, J = 17.5 and 1.0), 5.10 (1H, dd, J = 11.0 and 1.0), 5.17 (1H, br d, J = 2.5), 5.35 (1H, dt, J = 6.0 and 2.5) and 5.87 (1H, br dd, J = 17.5 and 11.0). HRMS: calcd for $C_{15}H_{20}O_4$ 264.1362, found 264.1351.

***Alcohol* (19)**

A mixture of the ketals (**6**) (82.0 mg, 0.369 mmol), mercuric trifluoroacetate (62.2 mg, 0.146 mmol) and Et_3N (0.04 mL, 0.287 mmol) in freshly distilled ethyl vinyl ether (4.0 mL, 41.9 mmol) was stirred at room temperature for 60 h. After removal of the solvent, the residue was taken up into petroleum ether, and the extract was washed with 10% KOH solution, saturated $NaHCO_3$ solution, dried and evaporated to yield a yellow oil which was chromatographed on activity III basic alumina. Elution with a 5 : 1 mixture of n-hexane-EtOAc afforded the vinyl ether (78.4 mg, 97%: based upon recovered starting material) along with **6** (20.4 mg).

A toluene solution (18 mL) of the above vinyl ether (430 mg, 1.73 mmol) was heated at 140 °C in sealed tube for 17 h, then the solvent was removed under reduced pressure. The residual oil (418 mg) was dissolved in MeOH (20 mL), whereupon to the above solution was gradually added $NaBH_4$ (142 mg, 3.76 mmol) at 0 °C. After 10 min, the reaction mixture was diluted with H_2O and extracted with CH_2Cl_2 (30 mL). The organic layer was dried and evaporated to leave a crude material, which was chromatographed. Elution with a 1 : 3 mixture of n-hexane-EtOAc afforded the alcohol (**19**) (349 mg, 84% for 2 steps) as a colorless oil. IR: 3400 cm^{-1}. ^1H NMR (300 MHz): δ 1.26 - 1.33 (1H, m), 1.44 - 2.13 (8H, m), 2.44 - 2.50 (1H, m), 3.67 (2H, dt, J = 6.2 and 5.5), 3.83 - 4.03 (4H, m), 5.04 (1H, dd, J = 17.6 and 1.5), 5.09 (1H, dd, J = 10.6 and 1.5), 5.64 - 5.69 (1H, m) and 5.92 (1H, dd, J = 17.6 and 10.6). *Anal.* Calcd for $C_{15}H_{22}O_3$: C, 71.97; H, 8.86. Found: C, 71.79; H, 8.74.

***Keto alcohol* (5)**

The reactor was charged with $PdCl_2$ (8.7 mg, 0.0492 mmol), CuI (13.8 mg, 0.177 mmol), DMF (0.4 mL) and H_2O (0.1 mL). The mixture was stirred at 40 °C for 3 h, whereupon a DMF solution (0.4 mL) of the olefinic alcohol (**19**) (24.6 mg, 0.0984 mmol) was added, and then the resulting mixture was stirred at 50 °C for 10 h under oxygen. After removal of the solvent under reduced pressure, the residue was chromatographed on activity III basic alumina. Elution with a 2 : 1 mixture of benzene-acetone gave rise to the corresponding ketone (18.3 mg, 70%) as a colorless oil. IR: 3400 and 1700 cm^{-1}. ^1H NMR (300 MHz): 1.32 - 1.42 (1H, m), 1.66 - 2.24 (7H, m), 2.15 (3H, s), 2.27 - 2.39 (1H, m), 2.56 - 2.61 (1H, m), 3.62 - 3.73 (2H, m), 3.84 - 4.01 (4H, m), 5.81 (1H, br s). HRMS: calcd for $C_{15}H_{22}O_4$ 266.1518, found 266.1520.

A mixture of the above keto alcohol (264 mg, 0.992 mmol) and 10% palladium-charcoal (5 mg) in EtOAc (2 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 3 : 1 mixture of benzene-acetone afforded the compound (**5**) (219 mg, 82%) as a colorless oil. IR: 3440 and 1690 cm^{-1}. ^1H NMR (300 MHz): δ 1.29 - 1.91 (11H, m), 1.96 - 2.04 (1H, m), 2.05 - 2.24 (1H, m), 2.15 (3H, s), 3.64 (2H, t, J = 6.0) and 3.80 - 4.02 (4H, m). HRMS: calcd for $C_{15}H_{24}O_4$ 268.1675, found 268.1676.

***Triene* (4)**

A stirring suspension of methyltriphenylphosphonium bromide (1.34 g, 3.75 mmol) in THF (10 mL) was treated dropwise n-butyllithium (10% n-hexane solution, 2.4 mL, 3.74 mmol) at ambient temperature. After 2.5 h of reflux, the mixture was cooled to room temperature. This orange-brown ylide solution was treated dropwise with a THF solution (10 mL) of **5** (201 mg, 0.750 mmol). The mixture was refluxed for 16 h, at which time the mixture was diluted with Et_2O. The reaction was quenched with saturated NH_4Cl solution, then extracted with Et_2O. The ethereal layer was washed with brine, dried and evaporated to leave a crude material, which was chromatographed. Elution with a 6 : 1 mixture of benzene-acetone afforded the exo-olefin (161 mg, 81%) as a colorless oil. IR: 3400 cm^{-1}. ^1H NMR (300 MHz): δ 1.20 - 1.90 (9H, m), 1.73 (3H, s), 1.90 - 2.18 (3H, m), 3.59 - 3.69 (2H, m), 3.80 - 4.01 (4H, m), 4.73 (1H, br d, J = 1.1) and 4.80 (1H, br dd, J = 1.5 and 1.1). HRMS: calcd for $C_{16}H_{26}O_3$ 266.1882, found 266.1843.

To a stirred solution of the above alcohol (39.6 mg, 0.149 mmol), Florisil® (100 mg) and NaOAc (36.7 mg, 0.447 mmol) in CH_2Cl_2 (1.5 mL) was added PCC (96.0 mg, 0.447 mmol) at ambient temperature. The resulting mixture was continued to stir at room temperature for 1.5 h. Filtration and evaporation of the filtrate gave a residue which was chromatographed. Elution with a 15 : 1 mixture of benzene-acetone furnished the aldehyde (36.3 mg, 92%) as a colorless oil. IR ($CHCl_3$): 1720 cm^{-1}. ^1H NMR (300 MHz): δ 1.20 - 1.35 (2H, m), 1.44 - 1.87 (7H, m), 1.73 (3H, s), 1.90 - 2.16 (3H, m), 2.33 - 2.59 (2H, m), 3.79 - 4.01 (4H, m), 4.76 (1H, br d, J = 0.7), 4.83 (1H, br dd, J = 1.5 and 1.5) and 9.76 (1H, t, J = 1.5). HRMS: calcd for $C_{16}H_{24}O_3$ 264.1725, found 264.1739.

To a stirred solution of allyldiphenylphosphine oxide (37.3 mg, 0.166 mmol) in THF (1 mL) was added HMPA (0.06 mL, 0.343 mmol), whereupon the mixture was cooled to -78 °C. To the mixture was added n-butyllithium (10% solution of n-hexane; 0.11 mL, 0.172 mmol) with stirring. After 10 min, to the resulting mixture was added THF solution (1 mL) of the above aldehyde (36.3 mg, 0.138 mmol) at -78 °C. The reaction mixture was stirred at the same temperature for 10 min, 0 °C for 0.5 h and finally room temperature for 2 h. To

the mixture was added saturated NH_4Cl solution at 0 °C, whereupon the resulting mixture was extracted with Et_2O. The organic layers were washed with brine, dried and evaporated to give a crude material, which was chromatographed. Elution with a 40 : 1 mixture of benzene-acetone yielded the triene (**4**) (24.8 mg, 62%) as a colorless oil. IR ($CHCl_3$): 1630 cm^{-1}. ^1H NMR (300 MHz): δ 1.24 - 1.41 (2H, m), 1.48 - 1.83 (6H, m), 1.73 (3H, s), 1.91 - 2.25 (6H, m), 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.

***Cycloadducts* (3)**

A mixture of the triene (**4**) (24.8 mg, 0.0861 mmol) and methylene blue (0.1 mg, catalytic amount) in toluene (1 mL) was heated at 230 °C in a sealed tube for 120 h. After removal of the solvent under reduced pressure, the residue was chromatographed. Elution with a 20 : 1 mixture of n-hexane-EtOAc gave the cycloadducts (**3**) (16.6 mg, 67%) as a 3 : 1 diastereoisomeric mixture. IR ($CHCl_3$): 1632 cm^{-1}. ^1H NMR (500 MHz): δ 0.83 (0.75H, s), 0.87 (2.25H, s), 1.19 - 2.25 (18H, m), 2.34 - 2.49 (1H, m), 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 above cycloadducts (**3**) (11.0 mg, 0.0382 mmol) and hematoporphyrin (2.0 mg, 0.0034 mmol) in pyridine (5 mL) was irradiated by 700-W halogen lamp through a Pyrex® filter with oxygen bubbling for 114 h. To the mixture were added active charcoal (10 mg) and Et_2O (10 mL), whereupon the resulting mixture was stirred at room temperature for 5 min. After filtration through Celite, the filtrate was evaporated to leave a crude material (20 mg), which was used in the next step without purification.

To a stirred solution of the above product (20 mg) in a mixture of Et_2O (7.5 mL) and EtOH (1.5 mL) were added acetic acid (2 drops) and NaI (130 mg, 0.865 mmol) at ambient temperature, whereupon the resulting mixture was continued to stir at room temperature for 23 h. After removal of the solvent, the residue was dissolved in Et_2O (30 mL), whereupon the ethereal layer was washed with saturated $Na_2S_2O_3$ solution, brine and evaporated to give rise to a crude material (35.1 mg), which was taken up in CH_2Cl_2 (3 mL). MnO_2 (350 mg) was added to the above solution, and then the resulting mixture was stirred at room temperature for 1.5 h. After filtration through Celite, the filtrate was evaporated to afford an oil, which was chromatographed. Elution with a 20 : 1 mixture of benzene-acetone gave rise to the enone (**2**) (6.2 mg, 81% for 3 steps: based upon recovered starting material (3.7 mg)) as a colorless oil. IR ($CHCl_3$): 1660 cm^{-1}. ^1H NMR (500 MHz): 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 and 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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