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Total Synthesis of (+)-Achalensolide Based on the Rh(I)-Catalyzed Allenic Pauson−Khand-Type Reaction

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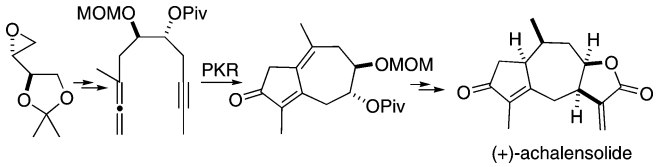

The first total synthesis of (+)-achalensolide was achieved from a commercially available D-(−)-isoascorbic acid. The known epoxide, derived from D-(−)-isoascorbic acid, was converted into the allenyne, the Rh(I)-catalyzed Pauson−Khand-type reaction of which directly provided the bicyclo[5.3.0]decane system, a core framework of the title natural product. The construction of the γ-lactone moiety and some chemical modifications resulted in the completion of the total synthesis of (+)-achalensolide.

Introduction

The $Co_2(CO)_8$-mediated intramolecular Pauson−Khand reaction,[1] the formal [2+2+1] cycloaddition of three components (an alkyne, an alkene, and carbon monoxide), has been well recognized as one of the most powerful and reliable tools for constructing bicyclo[3.3.0]octenone and bicyclo[4.3.0]nonenone frameworks. In general, this reaction efficiently produces the bicyclo[*m*.3.0] compounds ($m = 3, 4$) in good to high yields. However, application of this protocol to the construction of the larger-sized bicyclo[5.3.0]decenone framework could not be easily achieved except for a few specific substrates,[2] which have, for example, an aromatic ring as the template. Recent efforts in this laboratory[3] have disclosed an efficient method for the preparation of the 2-phenylsulfonylbicyclo[5.3.0]deca-1,7-dien-9-ones from the 3-phenylsulfonyl-1,2-nonadien-8-yne derivatives based on the Rh(I)-catalyzed allenic Pauson−Khand-type reaction (Scheme 1). Brummond and co-workers also reported the $[RhCl(CO)_2]_2$-catalyzed PKR of allenynes, which involves four successful examples of the formation of the bicyclo[5.3.0]-decadienone skeleton.[4]

As an extension of our program, we now focused on the application of the newly developed Rh(I)-catalyzed Pauson−

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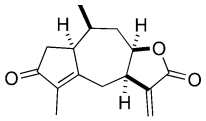
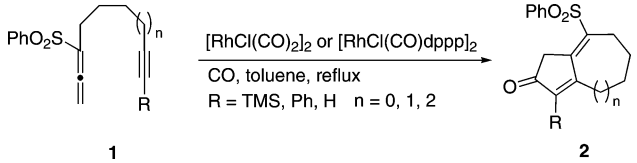


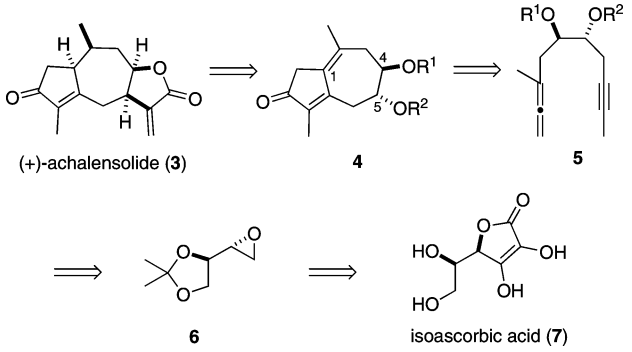
(+)-achalensolide (**3**)

FIGURE 1. Structure of (+)-achalensolide (3).

SCHEME 1. Rh-catalyzed Pauson−Khand-Type Reaction of Allenynes



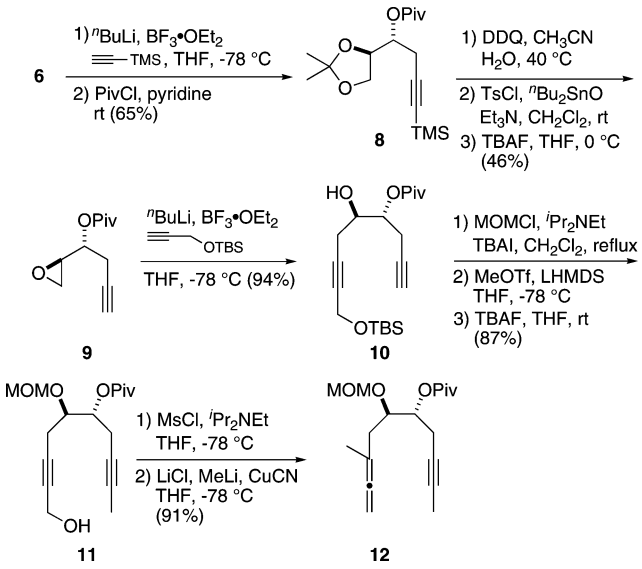
SCHEME 2. Retrosynthetic Analysis



Khand-type reaction of allenynes for the total synthesis of natural products. Many natural products possessing the bicyclo[5.3.0]decane ring system as the central carbon framework, exemplified by the guaianolide skeleton, have so far been isolated. We chose (+)-achalensolide (**3**), a simple guaianolide, as our first target natural product. In 1983, (+)-achalensolide (**3**) was isolated by Bohlmann[5] from the aerial parts of *Decachaeta thieleana* gathered in Turrucares, Costa Rica. Herz[6] also reported the isolation of **3** from *Stevia achalensis*, collected in Copina, Córdoba, Argentina, in the same year. The structure of **3** was unambiguously established by its X-ray analysis as depicted in Figure 1. Compound **3** was shown to be the potent inhibitor of aromatase enzyme activity in human placental microsomes similar to the other guaianolides.

Our retrosynthetic analysis of **3** is outlined in Scheme 2. The primary target was envisioned as the bicyclo[5.3.0]deca-1,7-dien-9-one derivative **4** with the two vicinal hydroxyl groups at suitable positions, which might be transformed into the *cis*-fused γ-lactone ring by proper manipulations at a later stage. The key intermediate **4** should be obtained from the 5,6-dioxygenated-3-methyldeca-1,2-dien-8-yne derivative **5** by the above-mentioned Rh(I)-catalyzed intramolecular Pauson−Khand-type reaction of allenyne **5**. The allenynes **5** must be prepared from the commercially available D-(−)-isoascorbic acid (**7**) via the known epoxide **6** by conventional procedures. On the basis of this simple retrosynthetic analysis, we investigated the total synthesis of **3**.

SCHEME 3. Preparation of Allene 12



Results and Discussion

Scheme 3 describes the preparation of the 5,6-dioxygenated-3-methyldeca-1,2-dien-8-yne derivative **5**, a key compound of this investigation, from D-(−)-isoascorbic acid (**7**). The known epoxide **6**, easily derived from **7** according to the literature,[7] reacted with the acetylide, which was prepared from the reaction of trimethylsilylacetylene with ^{n}BuLi in the presence of BF_3•OEt_2,[8] to furnish the homopropynyl alcohol derivative, the hydroxyl group of which was subsequently protected with a pivaloyl group to give **8** in 65% yield. Removal of the acetonide group of **8** with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ)[9] afforded the diol, which was transformed into the epoxy derivative **9** in 46% yield by successive activation of the primary hydroxyl group with tosyl chloride and ^{n}Bu$_2$SnO, and then treatment with tetra-*n*-butylammonium fluoride (TBAF). The (*tert*-butyldimethylsilyl)oxypropyne, an allenic moiety equivalent, was introduced into compound **9** by a procedure similar to the transformation of **6** into **8** to afford the alcohol **10** in 94% yield. Successive protection of the hydroxyl moiety of **10** with a methoxymethyl (MOM) group, introduction of a methyl group at the triple bond terminus, and desilylation furnished the propargyl alcohol derivative **11** in 87% yield. Transformation of **11** into the allenyl derivative **12** was realized as follows. Treatment of **11** with methanesulfonyl chloride (MsCl) afforded the corresponding mesylate. Exposure of the labile mesylate to organocuprate, prepared from copper cyanide, methyllithium, and lithium chloride, effected S_N2' addition[10] to produce the allenyne derivative **12** in 91% yield.

With the required allenyne **12** in hand, the Rh(I)-catalyzed Pauson−Khand-type reaction of **12** was carried out under several conditions. According to the previously established conditions ([RhCl(CO)$_2$]$_2$ or [RhCl(CO)dppp]$_2$, CO atmosphere, refluxing toluene)[3] for the construction of the 2-phenylsulfonyl-bicyclo[5.3.0]deca-1,7-dien-9-one, **12** was first treated with 10

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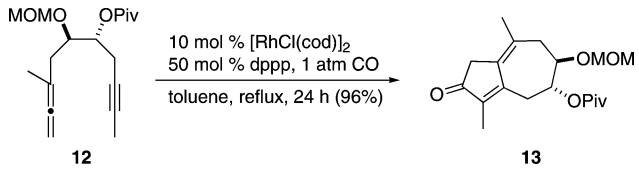
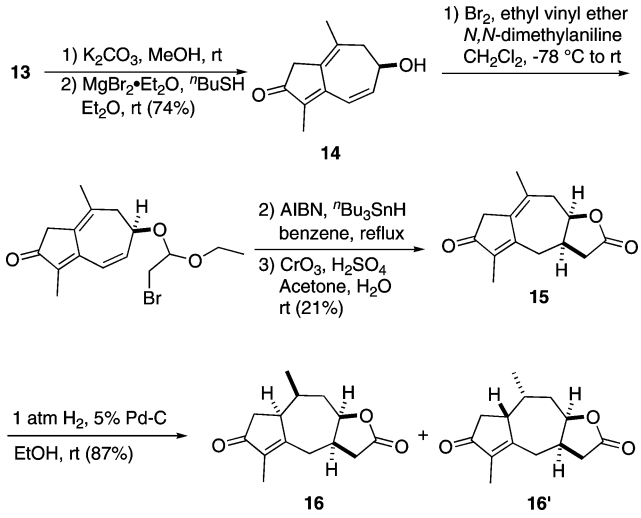
SCHEME 4. Rh-Catalyzed Pauson−Khand-type Reaction of 12



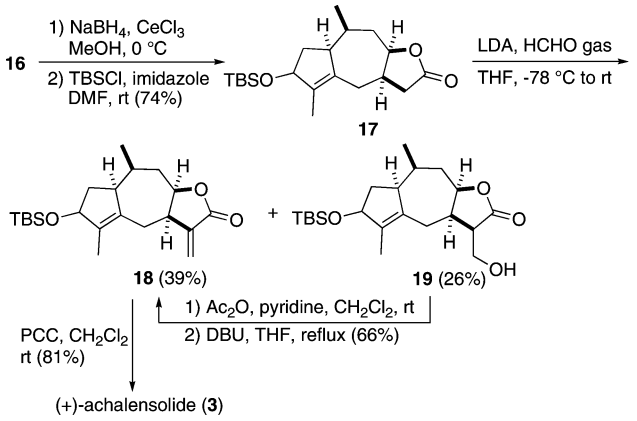
SCHEME 5. Preparation of γ-Lactone Derivative 16



mol % of $[RhCl(CO)_2]_2$ in refluxing toluene under a CO atmosphere for 1 h to produce the bicyclo[5.3.0] derivative **13** in 14% yield (Scheme 4). A significant improvement (61%) was observed when the reaction was carried out in the presence of $[RhCl(CO)dppp]_2$ instead of $[RhCl(CO)_2]_2$. A higher CO pressure led to an intractable mixture. The best result (96%) was obtained when **12** was refluxed in toluene under a CO atmosphere in the presence of $[\{Rh(CO)(dppp)_2\}Cl]$,[11] which was prepared in situ from 10 mol % of $[RhCl(cod)]_2$ and 50 mol % of 1,3-bis(diphenylphosphino)propane under CO atmosphere. The Wilkinson catalyst $[(Ph_3P)_3RhCl]$ was shown to be ineffective for this reaction.

As bicyclo[5.3.0]decadienone **13** could be prepared in a high yield, the next subject was the transformation of the two contiguous hydroxyl moieties into the *cis*-fused γ-lactone moiety (Scheme 5). As a result, we successfully applied the Ueno−Stork reaction[12] to the construction of the *cis*-fused γ-lactone group as follows. The elimination of the pivaloyloxy group of **13** with potassium carbonate produced the triene derivative, which was subsequently exposed to magnesium bromide and butanethiol[13] to furnish the allyl alcohol **14** in 74% yield. Compound **14** was then treated with bromine and ethyl vinyl ether in the presence of a base to afford the corresponding bromoacetal derivative, which was then exposed to the standard radical conditions (tributyltin hydride and azobisisobutyronitrile in refluxing benzene) to give the *5-exo*-mode ring-closed product. The resulting five-membered acetal moiety was converted into the γ-lactone functionality by Jones oxidation to provide the desired tricyclic compound **15** in 21% yield. Hydrogenation of **15** proceeded under an atmosphere of H_2 in the presence of 5% Pd−C in ethanol to furnish the desired **16** and its diastereoisomer **16′** in 87% yield in the ratio of 1 to 1. Although several typical catalysts and conditions were screened for the selective construction of **16**, the desired **16** could not be obtained in a selective manner. In most cases, an intractable mixture was detected by TLC. The stereochemical assignment of both compounds was made by an NMR spectral evaluation including NOE experiments.[14]

SCHEME 6. Completion of the Total Synthesis of 3



The construction of the exomethylene moiety on the γ-lactone ring remained prior to completing the total synthesis. However, the direct introduction of an exomethylene group at the α-position of the lactone functionality of **16** was unsuccessful presumably due to the presence of an α,β-unsaturated carbonyl functionality. Thus, compound **16** was first converted into the allyl alcohol derivative **17**[15] in 74% yield by $NaBH_4$ reduction[16] and protection of the resulting hydroxyl group by a TBS group. Exposure of **17** to lithium diisopropylamide (LDA) at −78 °C was followed by quenching of the resulting carbanion species with formaldehyde gas[17] to directly yield the exomethylene derivative **18** in 39% yield along with the hydroxymethyl derivative **19** in 26% yield (Scheme 6). Compound **19** could be converted into **18** in 66% yield by acetylation and elimination. Finally, pyridinium chlorochromate (PCC) effected the oxidation of the silyloxy group to give (+)-achalensolide (**3**) in 81% yield. The structure of synthetic **3** was unambiguously confirmed by comparison with the spectral data of the natural product.

In summary, we have completed the first total synthesis of (+)-achalensolide from a commercially available D-(−)-isoascorbic acid. The most significant feature of this synthesis involves the previously developed Rh(I)-catalyzed Pauson−Khand-type reaction of an allenyne, which enabled us to directly construct the bicyclo[5.3.0]decane system. Further studies on

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(14) See the Supporting Information.

(15) Compound **17** was obtained as a single isomer (based on ^1H and ^{13}C NMR spectral consideration), but its stereochemistry was not determined.

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(17) Several conditions including Eschenmoser salt were found to be fruitless for our purpose.

the total synthesis of other natural products having a bicyclo-[5.3.0]decane framework are now in progress.

Experimental Section

(4*R*,5*R*)-5,6-(Isopropylidenedioxy)-4-(pivaloyloxy)-1-(trimethylsilyl)hex-1-yne, (+)-(8). To a solution of trimethylsilylacetylene (0.29 mL, 2.0 mmol) in THF (8.0 mL) was gradually added ^{n}BuLi (1.46 M in hexane solution, 1.03 mL, 1.52 mmol) at −78 °C. After stirring for 1 h, BF_3·OEt_2 (1.00 M in THF solution, 1.01 mL, 1.01 mmol) was added dropwise to the reaction mixture, which was stirred for 1 h. Then a solution of **6** (146 mg, 1.01 mmol) in THF (2.0 mL) was added to the reaction mixture, which was stirred for 30 min. The reaction mixture was quenched by addition of saturated aqueous NH_4Cl and extracted with AcOEt. The extract was washed with water and brine, dried, and concentrated to dryness. The residue was passed through a short pad of silica gel with hexane−AcOEt (3:1) to afford crude alcohol. To a solution of alcohol in pyridine (10 mL) was added PivCl (0.19 mL, 1.5 mmol), which was stirred for 20 h. The reaction mixture was quenched by addition of 10% aqueous HCl and extracted with AcOEt. The extract was washed with water and brine, dried, and concentrated to dryness. The residue was chromatographed with hexane−AcOEt (15:1) to afford **8** (214 mg, 65% for 2 steps) as a colorless oil: $[\alpha]^{26}_D$ +3.2 (*c* 1.21, $CHCl_3$); IR 2179, 1724 cm^{-1}; ^{1}H NMR δ 5.03−4.95 (m, 1H), 4.32−4.26 (m, 1H), 4.00 (dd, 1H, *J* = 6.8, 8.5 Hz), 3.73 (dd, 1H, *J* = 5.6, 8.5 Hz), 2.61−2.50 (m, 2H), 1.41 (s, 3H), 1.32 (s, 3H), 1.21 (s, 9H), 0.11 (s, 9H); ^{13}C NMR δ 177.8, 109.5, 101.7, 86.8, 75.5, 70.5, 65.4, 38.9, 27.1, 26.3, 25.2, 22.1, −0.1; MS *m*/*z* 326 (M$^+$, 5.4); HRMS calcd for $C_{17}H_{30}O_4Si$ 326.1913, found 326.1921.

(4*R*,5*R*)-5,6-Epoxy-4-(pivaloyloxy)hex-1-yne, (−)-(9). To a solution of **8** (4.27 g, 13.1 mmol) in CH_3CN−H_2O (9:1, 131 mL) was added DDQ (297 mg, 1.31 mmol). Then the reaction mixture was warmed to 40 °C, which was stirred for 10 h. The solvent was evaporated off, and the residue was extracted with AcOEt. The extract was washed with water and brine, dried, and concentrated to dryness. The residue was passed through a short pad of silica gel with hexane−AcOEt (1:1) to afford crude diol. To a solution of diol in CH_2Cl_2 (13 mL) were added Et_3N (2.74 mL, 19.7 mmol), ^{n}Bu_2SnO (326 mg, 1.31 mmol), and TsCl (2.75 g, 14.4 mmol), then the solution was stirred for 12 h. The reaction mixture was quenched by addition of water and extracted with CH_2Cl_2. The extract was washed with water and brine, dried, and concentrated to dryness. The crude tosylate was used for the next reaction without further purifications. To a solution of crude tosylate in THF (131 mL) was added TBAF (1.0 M in THF solution, 39 mL, 39 mmol) at 0 °C, then the solution was stirred for 2 h. The reaction mixture was quenched by addition of water and extracted with Et_2O. The extract was washed with water and brine, dried, and concentrated to dryness. The residue was chromatographed with hexane−AcOEt (8:1) to afford **9** (1.18 g, 46% for 3 steps) as a colorless oil: $[\alpha]^{26}_D$ −11.8 (*c* 1.71, $CHCl_3$); IR 3310, 2125, 1728 cm^{-1}; ^{1}H NMR δ 4.76 (q, 1H, *J* = 5.9 Hz), 3.23 (ddd, 1H, *J* = 2.7, 3.7, 6.2 Hz), 2.83 (dd, 1H, *J* = 4.2, 4.9 Hz), 2.67 (dd, 1H, *J* = 2.4, 4.9 Hz), 2.59 (ddd, 1H, *J* = 2.7, 7.1, 17 Hz), 2.53 (ddd, 1H, *J* = 2.7, 6.1, 17 Hz), 2.00 (t, 1H, *J* = 2.7 Hz), 1.20 (s, 9H); ^{13}C NMR δ 177.4, 78.5, 70.9, 70.8, 52.1, 44.7, 38.8, 27.0, 21.3; MS *m*/*z* 196 (M$^+$, 3.1); HRMS calcd for $C_{11}H_{16}O_3$ 196.1100, found 196.1097.

(4*R*,5*R*)- 9-(*tert*-Butyldimethylsiloxy)-4-(pivaloyloxy)nona-1,7-diyn-5-ol, (−)-(10). To a solution of 3-(*tert*-butyldimethylsiloxy)-prop-1-yne (1.91 g, 11.2 mmol) in THF (35 mL) was gradually added ^{n}BuLi (1.27 M in hexane solution, 8.82 mL, 11.2 mmol) at −78 °C. After stirring for 1 h, BF_3·OEt_2 (1.00 M in THF solution, 12.3 mL, 12.3 mmol) was added dropwise to the reaction mixture, which was stirred for 2 h. Then a solution of **9** (731 mg, 3.73 mmol) in THF (2.0 mL) was added to the reaction mixture, which was stirred for 4 h. The reaction mixture was quenched by addition of saturated aqueous NH_4Cl and extracted with AcOEt. The extract was washed with water and brine, dried, and concentrated to dryness. The residue was chromatographed with hexane−AcOEt (8:1) to afford **10** (1.26 g, 94%) as a colorless oil: $[\alpha]^{27}_D$ −4.3 (*c* 6.20, $CHCl_3$); IR 3429, 3308, 1728 cm^{-1}; ^{1}H NMR δ 4.93 (dt, 1H, *J* = 3.7, 6.6 Hz), 4.23 (s, 2H), 3.98 (br s, 1H), 2.62−2.47 (m, 3H), 2.39 (d, 2H, *J* = 6.6 Hz), 1.95 (t, 1H, *J* = 2.7 Hz), 1.16 (s, 9H), 0.83 (s, 9H), 0.04 (s, 6H); ^{13}C NMR δ 177.5, 81.2, 80.2, 79.1, 72.2, 70.6, 69.7, 51.7, 38.8, 27.0, 25.7, 23.9, 20.2, 18.1, −5.3; MS *m*/*z* 366 (M$^+$, 0.7); HRMS calcd for $C_{20}H_{34}O_4Si$ 366.2226, found 366.2223.

(5*R*,6*R*)-5-(Methoxymethoxy)-6-(pivaloyloxy)deca-2,8-diyn-1-ol, (+)-(11). To a solution of **10** (36.7 mg, 0.100 mmol) in CH_2Cl_2 (1.0 mL) were added ^{i}Pr_2NEt (0.07 mL, 0.4 mmol), TBAI (3.7 mg, 1.0×10^{-2} mmol), and MOMCl (0.02 mL, 0.3 mmol). Then the reaction mixture was refluxed for 13 h. The reaction mixture was quenched by addition of water and extracted with CH_2Cl_2. The extract was washed with water and brine, dried, and concentrated to dryness. The crude alkyne was used for the next reaction without further purifications. To a solution of crude alkyne in THF (1.0 mL) was gradually added LHMDS (1.0 M in THF solution, 0.30 mL, 0.30 mmol) at −78 °C. After stirring for 1 h, MeOTf (0.03 mL, 0.3 mmol) was added to the reaction mixture, which was stirred for 2.5 h. The reaction mixture was quenched by addition of saturated aqueous $NaHCO_3$ and extracted with AcOEt. The extract was washed with water and brine, dried, and concentrated to dryness. The crude silicate was used for the next reaction without further purifications. To a solution of crude silicate in THF (1.0 mL) was added TBAF (1.0 M in THF solution, 0.15 mL, 0.15 mmol), then the solution was stirred for 30 min. The solvent was evaporated off, and the residue was chromatographed with hexane−AcOEt (2:1) to afford **11** (26.9 mg, 87% for 3 steps) as a colorless oil: $[\alpha]^{27}_D$ +9.2 (*c* 2.39, $CHCl_3$); IR 3609, 3504, 2230, 1724 cm^{-1}; ^{1}H NMR δ 5.17 (dt, 1H, *J* = 4.2, 6.6 Hz), 4.73 (dd, 2H, *J* = 6.8, 10 Hz), 4.19 (d, 2H, *J* = 2.0 Hz), 3.99 (dt, 1H, *J* = 4.2, 6.8 Hz), 3.40 (s, 3H), 2.62−2.38 (m, 4H), 2.16 (br s, 1H), 1.74 (t, 3H, *J* = 2.2 Hz), 1.21 (s, 9H); ^{13}C NMR δ 177.9, 97.0, 81.6, 80.9, 77.9, 75.6, 73.8, 72.1, 55.8, 51.1, 39.0, 27.1, 21.7, 20.3, 3.4; MS *m*/*z* 310 (M$^+$, 1.8); HRMS calcd for $C_{17}H_{26}O_5$ 310.1780, found 310.1773.

(5*R*,6*R*)-3-Methyl-5-(methoxymethoxy)-6-(pivaloyloxy)deca-1,2-dien-8-yne, (+)-(12). To a solution of **11** (496 mg, 1.60 mmol) in THF (16 mL) were added ^{i}Pr_2NEt (1.12 mL, 8.00 mmol) and MsCl (0.49 mL, 6.4 mmol) at −78 °C, then the solution was stirred for 5 h. The reaction mixture was quenched by addition of saturated aqueous $NaHCO_3$ and extracted with AcOEt. The extract was washed with water and brine, dried, and concentrated to dryness. The residue was passed through a short pad of silica gel to afford crude mesylate. To a solution of CuCN (573 mg, 6.40 mmol) and LiCl (542 mg, 12.8 mmol) in THF (14 mL) was gradually added MeLi (0.98 M in Et_2O, 6.5 mL, 6.4 mmol) at −78 °C. Then the reaction mixture was warmed to −20 °C, and the solids were dissolved at this temperature. The reaction mixture was cooled to −78 °C again, and the crude mesylate was added to the reaction mixture, which was stirred for 2 h. The reaction mixture was quenched by addition of saturated aqueous NH_4Cl and extracted with AcOEt. The extract was washed with water and brine, dried, and concentrated to dryness. The residue was chromatographed with hexane−AcOEt (8:1) to afford **12** (450 mg, 91% for 2 steps) as a colorless oil: $[\alpha]^{28}_D$ +11.6 (*c* 4.17, $CHCl_3$); IR 2233, 1961, 1724 cm^{-1}; ^{1}H NMR δ 4.97 (dt, 1H, *J* = 3.4, 6.6 Hz), 4.69 (dd, 2H, *J* = 6.6, 15 Hz), 4.56 (d, 2H, *J* = 2.7 Hz), 3.94 (dt, 1H, *J* = 3.4, 6.6 Hz), 3.37 (s, 3H), 2.52−2.37 (m, 2H), 2.22−2.10 (m, 2H), 1.71 (t, 3H, *J* = 2.4 Hz), 1.67 (t, 3H, *J* = 3.2 Hz), 1.18 (s, 9H); ^{13}C NMR δ 207.1, 177.4, 96.7, 94.3, 77.4, 75.0, 74.3, 74.1, 72.2, 55.7, 38.8, 34.8, 27.1, 20.1, 18.7, 3.3; MS *m*/*z* 308 (M$^+$, 26.7); HRMS calcd for $C_{18}H_{28}O_4$ 308.1988, found 308.1986.

(4*R*,5*R*)-2,8-Dimethyl-4-(methoxymethoxy)-5-(pivaloyloxy)-bicyclo[5.3.0]deca-1,7-dien-9-one, (−)-(13). To a solution of **12** (100 mg, 0.324 mmol) in toluene (3.2 mL) were added dppp (66.8 mg, 0.162 mmol) and $[RhCl(cod)]_2$ (16.0 mg, 3.24×10^{-2} mmol).

Then the reaction mixture was refluxed for 24 h under CO atmosphere. The solvent was evaporated off, and the residue was chromatographed with hexane−AcOEt (2:1) to afford **13** (105 mg, 96%) as colorless needles: mp 73−74 °C (hexane−AcOEt); $[\alpha]^{25}_D$ −123.4 (*c* 0.97, $CHCl_3$); IR 1718, 1684 cm^{-1}; ^1H NMR δ 5.21−5.15 (m, 1H), 4.64 (s, 2H), 3.87 (ddd, 1H, *J* = 2.7, 5.4, 9.8 Hz), 3.34 (s, 3H), 3.05 (dd, 1H, *J* = 5.1, 16 Hz), 2.90 (d, 2H, *J* = 2.4 Hz), 2.86−2.77 (m, 2H), 2.42 (dd, 1H, *J* = 2.7, 16 Hz), 1.90 (s, 3H), 1.71 (s, 3H), 1.14 (s, 9H); ^{13}C NMR δ 204.3, 177.6, 162.0, 139.6, 133.4, 130.6, 95.8, 79.2, 75.9, 55.6, 39.5, 38.7, 37.5, 30.0, 27.0, 24.1, 8.1; MS *m*/*z* 336 (M^+, 3.1). Anal. Calcd for $C_{19}H_{28}O_5$: C, 67.83; H, 8.39. Found: C, 67.61; H, 8.38.

(4*R*)-2,8-Dimethyl-4-hydroxybicyclo[5.3.0]deca-1,5,7-trien-9-one, (+)-(14). To a solution of **13** (263 mg, 0.781 mmol) in MeOH (7.8 mL) was added K_2CO_3 (162 mg, 1.17 mmol), then the solution was stirred for 2 h. The solvent was evaporated off, and the residue was diluted with water and extracted with AcOEt. The extract was washed with water and brine, dried, and concentrated to dryness. The residue was passed through a short pad of silica gel with hexane−AcOEt (2:1) to afford crude triene. To a solution of triene in Et_2O (6.9 mL) were added ^{n}BuSH (0.19 mL, 1.7 mmol) and $MgBr_2{\cdot}OEt_2$ (535 mg, 2.07 mmol), then the solution was stirred for 24 h. The reaction mixture was quenched by addition of water and extracted with CH_2Cl_2. The extract was washed with water and brine, dried, and concentrated to dryness. The residue was chromatographed with hexane−AcOEt−CH_2Cl_2 (10:10:1) to afford **14** (110 mg, 74% for 2 steps) as colorless needles: mp 158−160 °C (hexane−AcOEt); $[\alpha]^{26}_D$ +169.9 (*c* 0.97, $CHCl_3$); IR 3421, 1678 cm^{-1}; ^1H NMR δ 6.42 (dd, 1H, *J* = 2.2, 12 Hz), 6.34−6.27 (m, 1H), 4.63 (ddd, 1H, *J* = 2.9, 5.5, 11 Hz), 2.98 (s, 2H), 2.87−2.78 (m, 1H), 2.51−2.44 (m, 1H), 2.44−2.37 (m, 1H), 1.90 (s, 3H), 1.84 (s, 3H); ^{13}C NMR δ 204.7, 157.3, 144.1, 139.6, 130.0, 129.9, 121.1, 68.4, 43.7, 40.3, 24.5, 8.2; MS *m*/*z* 190 (M^+, 100). Anal. Calcd for $C_{12}H_{14}O_2$: C, 75.76; H, 7.42. Found: C, 75.42; H, 7.46.

(3*R*,7*R*)-9,13-Dimethyl-6-oxatricyclo[8.3.0.0^{3,7}]tetradecan-9,-13-dien-5,12-dione, (−)-(15). To a solution of Br_2 (0.26 mL, 5.0 mmol) in CH_2Cl_2 (9.0 mL) was added ethyl vinyl ether (0.72 mL, 7.5 mmol) at −78 °C. After stirring for 2 h, *N*,*N*-dimethylaniline (0.95 mL, 7.5 mmol) was added to the reaction mixture, which was stirred for 10 min. Then **14** (95.0 mg, 0.500 mmol) in CH_2Cl_2 (1.0 mL) was added to the reaction mixture. The reaction mixture was warmed to room temperature, then stirred for 2 h. The reaction mixture was quenched by addition of saturated aqueous $Na_2S_2O_3$ and $NaHCO_3$ and extracted with CH_2Cl_2. The extract was washed with water and brine, dried, and concentrated to dryness. The residue was passed through a short pad of silica gel to afford crude acetal. To a solution of crude acetal in benzene (5.0 mL) were added AIBN (32.9 mg, 0.200 mmol) and ^{n}Bu_3SnH (0.15 mL, 0.55 mmol). Then the reaction mixture was refluxed for 3 h. The solvent was evaporated off, and the residue was passed through a short pad of silica gel to afford crude acetal. To a solution of crude acetal in acetone (5.0 mL) was added Jones reagent, prepared from CrO_3 (150 mg, 1.50 mmol), concentrated H_2SO_4 (0.13 mL, 2.4 mmol), and H_2O (0.6 mL), until the orange color of reagent remained. The reaction mixture was quenched by addition of 2-propanol and $NaHCO_3$ and extracted with AcOEt. The extract was washed with water and brine, dried, and concentrated to dryness. The residue was chromatographed with hexane−AcOEt (1:2) to afford **15** (23.9 mg, 21% for 3 steps) as colorless needles: mp 176−177 °C (hexane−CH_2Cl_2); $[\alpha]^{28}_D$ −134.1 (*c* 0.24, $CHCl_3$); IR 1772, 1688 cm^{-1}; ^1H NMR δ 4.87−4.78 (m, 1H), 2.97−2.81 (m, 6H), 2.74 (dd, 1H, *J* = 10, 15 Hz), 2.62 (dd, 1H, *J* = 3.2, 15 Hz), 2.40−2.30 (m, 1H), 1.92 (s, 3H), 1.79 (s, 3H); ^{13}C NMR δ 204.1, 175.4, 163.2, 139.2, 134.0, 128.8, 80.8, 39.3, 36.2, 34.7, 34.5, 30.2, 24.3, 8.2; MS *m*/*z* 232 (M^+, 100). Anal. Calcd for $C_{14}H_{16}O_3$: C, 72.39; H, 6.94. Found: C, 72.08; H, 6.94,

(3*R*,7*R*,9*S*,10*S*)-9,13-Dimethyl-6-oxatricyclo[8.3.0.0^{3,7}]tetradec-13-en-5,12-dione, (+)-(16), and (3*R*,7*R*,9*R*,10*R*)-9,13-Dimethyl-6-oxatricyclo[8.3.0.0^{3,7}]tetradec-13-en-5,12-dione, (−)-(16′). To a solution of **15** (23.2 mg, 0.100 mmol) in EtOH (1.0 mL) was added 5% Pd−C (24.0 mg), then the solution was stirred for 9 h under H_2 atmosphere. The reaction mixture was filtered through celite, and the filtrate was concentrated. The residue was chromatographed with hexane−AcOEt−CH_2Cl_2 (10:10:1) to afford **16** and **16′** (20.4 mg, 87%, dr = 1:1) as a mixture of diastereomers. The diastereomeric ratio was determined by ^1H NMR analysis. Both pure samples were separated by preparative TLC with Et_2O−hexane (9:1, 5 times).

Compound **16**: colorless oil; $[\alpha]^{30}_D$ +48.7 (*c* 0.28, $CHCl_3$); IR 1772, 1697 cm^{-1}; ^1H NMR δ 4.71 (ddd, 1H, *J* = 4.2, 7.7, 12 Hz), 3.15−3.06 (m, 1H), 2.98 (br s, 1H), 2.81 (dd, 1H, *J* = 6.3, 15 Hz), 2.66 (dd, 1H, *J* = 4.2, 15 Hz), 2.50 (dd, 1H, *J* = 8.5, 17 Hz), 2.42 (dd, 1H, *J* = 6.3, 18 Hz), 2.25 (dd, 1H, *J* = 11, 17 Hz), 2.20−2.12 (m, 1H), 2.09 (dd, 1H, *J* = 3.4, 18 Hz), 1.76 (td, 1H, *J* = 3.7, 14 Hz), 1.69 (d, 3H, *J* = 2.2 Hz), 1.35 (ddd, 1H, *J* = 9.8, 12, 14 Hz), 0.96 (d, 3H, *J* = 7.1 Hz); ^{13}C NMR δ 207.6, 175.2, 168.6, 139.6, 81.4, 45.8, 37.3, 36.4, 33.7, 31.7, 27.9, 27.8, 18.7, 8.4; MS *m*/*z* 234 (M^+, 100), HRMS calcd for $C_{14}H_{18}O_3$ 234.1256, found 234.1256.

Compound **16′**: colorless needles, mp 164−166 °C (hexane−AcOEt); $[\alpha]^{30}_D$ −14.1 (*c* 0.25, $CHCl_3$); IR 1771, 1693 cm^{-1}; ^1H NMR δ 4.64−4.58 (m, 1H), 2.96 (br s, 1H), 2.94−2.86 (m, 1H), 2.71−2.61 (m, 1H), 2.54−2.36 (m, 5H), 2.06 (dd, 1H, *J* = 3.2, 19 Hz), 1.87 (dd, 1H, *J* = 6.3, 15 Hz), 1.72 (d, 3H, *J* = 2.2 Hz), 1.72−1.66 (m, 1H), 0.94 (d, 3H, *J* = 7.1 Hz); ^{13}C NMR δ 208.3, 175.8, 170.8, 138.0, 80.9, 47.3, 38.4, 37.6, 36.9, 32.4, 30.6, 25.6, 17.8, 7.7; MS *m*/*z* 234 (M^+, 91.6), HRMS calcd for $C_{14}H_{18}O_3$ 234.1256, found 234.1257.

(3*R*,7*R*,9*S*,10*S*)-12-(*tert*-Butyldimethylsiloxy)-9,13-dimethyl-6-oxatricyclo[8.3.0.0^{3,7}]tetradec-13-en-5-one, (−)-(17). To a solution of **16** (12.2 mg, 5.21×10^{-2} mmol) in MeOH (0.5 mL) was added $CeCl_3{\cdot}7H_2O$ (38.7 mg, 0.104 mmol) at 0 °C. After stirring for 10 min, $NaBH_4$ (3.9 mg, 0.10 mmol) was added to the reaction mixture, which was then stirred for 10 min. The reaction mixture was quenched by addition of saturated aqueous NH_4Cl and extracted with AcOEt. The extract was washed with water and brine, dried, and concentrated to dryness. The crude alcohol was used for the next reaction without further purifications. To a solution of crude alcohol in DMF (0.5 mL) were added imidazole (7.1 mg, 0.10 mmol) and TBSCl (15.7 mg, 0.104 mmol), then the solution was stirred for 2 h. The reaction mixture was quenched by addition of water and extracted with AcOEt. The extract was washed with water and brine, dried, and concentrated to dryness. The residue was chromatographed with hexane−AcOEt (6:1) to afford **17** (13.6 mg, 74% for 2 steps) as colorless needles: mp 84−85 °C (hexane); $[\alpha]^{31}_D$ −22.7 (*c* 0.24, $CHCl_3$); IR 1767 cm^{-1}; ^1H NMR δ 4.56−4.49 (m, 2H), 2.97−2.87 (m, 1H), 2.57−2.47 (m, 2H), 2.43 (dd, 1H, *J* = 3.9, 14 Hz), 2.26−2.10 (m, 3H), 1.94−1.84 (m, 1H), 1.65−1.55 (m, 4H), 1.41 (dd, 1H, *J* = 4.4, 14 Hz), 1.13 (ddd, 1H, *J* = 8.1, 9.9, 12 Hz), 0.93 (d, 3H, *J* = 7.1 Hz), 0.92 (s, 9H), 0.09 (s, 3H), 0.08 (s, 3H); ^{13}C NMR δ 176.9, 140.7, 132.9, 83.0, 78.5, 49.3, 38.1, 35.9, 32.6, 30.6, 27.9, 25.9, 24.0, 19.6, 18.2, 11.4, −4.3, −4.7; MS *m*/*z* 350 (M^+, 9.9); HRMS calcd for $C_{20}H_{34}O_3Si$ 350.2277, found 350.2277.

(3*R*,7*R*,9*S*,10*S*)-12-(*tert*-Butyldimethylsiloxy)-9,13-dimethyl-4-methylene-6-oxatricyclo[8.3.0.0^{3,7}]tetradec-13-en-5-one, (+)-(18), and (3*R*,7*R*,9*S*,10*S*)-12-(*tert*-Butyldimethylsiloxy)-9,13-dimethyl-4-hydroxymethyl-6-oxatricyclo[8.3.0.0^{3,7}]tetradec-13-en-5-one, (+)-(19). To a solution of **17** (3.5 mg, 1.0×10^{-2} mmol) in THF (1.0 mL) was gradually added LDA (1.0 M in THF solution, 0.10 mL, 0.10 mmol) at −78 °C. After stirring for 1.5 h, HCHO gas, generated by heating $(HCHO)_n$ at 150 °C in a N_2 stream was bubbled through the reaction mixture for 5 min. Then the reaction mixture was warmed to room temperature and stirred for 30 min. The reaction mixture was quenched by addition of saturated aqueous NH_4Cl and extracted with AcOEt. The extract was washed with water and brine, dried, and concentrated to dryness. The residue

was chromatographed with hexane−AcOEt (6:1) to afford **18** (1.4 mg, 39%) as a colorless oil and **19** (1.0 mg, 26%) as colorless needles.

Compound **18**: colorless oil; $[\alpha]^{28}_D$ +98.0 (*c* 0.41, $CHCl_3$); IR 1757 cm^{-1}; ^1H NMR δ 6.32 (d, 1H, J = 3.2 Hz), 5.63 (d, 1H, J = 2.7 Hz), 4.80 (ddd, 1H, J = 3.4, 8.7, 12 Hz), 4.47 (t, 1H, J = 6.3 Hz), 3.34−3.24 (m, 1H), 2.62−2.42 (m, 3H), 2.11 (td, 1H, J = 7.6, 14 Hz), 1.98−1.89 (m, 2H), 1.64 (s, 3H), 1.53−1.42 (m, 1H), 1.32−1.24 (m, 1H), 0.93−0.85 (m, 12H), 0.07 (s, 3H), 0.06 (s, 3H); ^{13}C NMR δ 170.0, 138.3, 137.9, 134.1, 122.3, 80.0, 79.4, 48.0, 40.7, 36.0, 35.6, 29.4, 27.4, 25.9, 18.2, 17.8, 12.1, −4.4, −4.8; MS *m*/*z* 362 (M^+, 13.6); HRMS calcd for $C_{21}H_{34}O_3Si$ 362.2277, found 362.2269.

Compound **19**: colorless needles, mp 158−160 °C (hexane−MeOH); $[\alpha]^{30}_D$ +24.7 (*c* 0.60, $CHCl_3$); IR 3674, 3502, 1757 cm^{-1}; ^1H NMR δ 4.56−4.47 (m, 2H), 4.05 (dd, 1H, J = 3.2, 12 Hz), 3.75 (dd, 1H, J = 5.1, 11 Hz), 2.89−2.80 (m, 1H), 2.60 (td, 1H, J = 4.6, 13 Hz), 2.53 (br s, 1H), 2.44 (dd, 1H, J = 3.2, 14 Hz), 2.22−2.09 (m, 2H), 1.97−1.85 (m, 1H), 1.64−1.52 (m, 5H), 1.45 (dd, 1H, J = 5.1, 14 Hz), 1.10 (q, 1H, J = 10 Hz), 0.94 (d, 3H, J = 7.1 Hz), 0.91 (s, 9H), 0.09 (s, 3H), 0.07 (s, 3H); ^{13}C NMR δ 178.6, 140.8, 133.2, 81.8, 76.7, 59.2, 49.3, 42.6, 38.7, 35.9, 33.2, 27.9, 25.9, 23.0, 19.6, 18.2, 11.6, −4.3, −4.7; MS *m*/*z* 380 (M^+, 97); HRMS calcd for $C_{21}H_{36}O_4Si$ 380.2383, found 380.2380.

Compound 18 from Compound 19. To a solution of **19** (15.9 mg, 4.18 × 10^{-2} mmol) in CH_2Cl_2 (1.0 mL) were added pyridine (0.02 mL, 0.3 mmol) and Ac_2O (0.02 mL, 0.2 mmol), then the solution was stirred for 8 h. The reaction mixture was quenched by addition of water and extracted with CH_2Cl_2. The extract was washed with water and brine, dried, and concentrated to dryness. The residue was passed through a short pad of silica gel to afford crude acetate. To a solution of crude acetate in THF (1.0 mL) was added DBU (0.03 mL, 0.2 mmol). Then the reaction mixture was refluxed for 1 h. The reaction mixture was quenched by addition of saturated aqueous NH_4Cl and extracted with AcOEt. The extract was washed with water and brine, dried, and concentrated to dryness. The residue was chromatographed with hexane−AcOEt (7:1) to afford **18** (10.0 mg, 66% for 2 steps) as a colorless oil.

(+)-Achalensolide (3). To a solution of **18** (10.0 mg, 2.76 × 10^{-2} mmol) in CH_2Cl_2 (1.0 mL) was added PCC (17.8 mg, 8.28 × 10^{-2} mmol), then the solution was stirred for 5 h. The reaction mixture was quenched by addition of 2-propanol and saturated aqueous $NaHCO_3$ and extracted with CH_2Cl_2. The extract was washed with water and brine, dried, and concentrated to dryness. The residue was chromatographed with hexane−AcOEt−CH_2Cl_2 (10:10:1) to afford **3** (5.5 mg, 81%) as colorless needles: mp 175−177 °C (Et_2O−MeOH) (lit.[6] mp 176−177 °C); $[\alpha]^{26}_D$ +236.8 (*c* 0.22, $CHCl_3$) [lit.[6] $[\alpha]_D$ +226.8 (*c* 0.34, $CHCl_3$)]; IR 1761, 1695, 1641, 1603 cm^{-1}; ^1H NMR (270 MHz) δ 6.39 (d, 1H, J = 3.0 Hz), 5.72 (d, 1H, J = 2.6 Hz), 4.96 (ddd, 1H, J = 3.0, 8.5, 13 Hz), 3.58−3.44 (m, 1H), 3.05−2.97 (m, 1H), 2.93 (dd, 1H, J = 4.3, 19 Hz), 2.68 (dd, 1H, J = 12, 18 Hz), 2.40 (dd, 1H, J = 6.4, 19 Hz), 2.35−2.19 (m, 3H), 1.75−1.71 (m, 3H), 1.51−1.39 (m, 1H), 0.74 (d, 3H, J = 6.3 Hz); ^{13}C NMR (67.8 MHz) δ 208.1, 169.0, 168.3, 138.3, 138.2, 123.6, 77.9, 42.7, 38.4, 38.0, 36.6, 32.0, 30.0, 14.9, 8.2; MS *m*/*z* 246 (M^+, 50.2); HRMS calcd for $C_{15}H_{18}O_3$ 246.1256, found 246.1250.

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Supporting Information Available: ^1H and ^{13}C NMR spectra for compounds **3**, **8**−**19**, and **16′**. This material is available free of charge via the Internet at http://pubs.acs.org.

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