A concise total synthesis of (±)-acutifolone A†

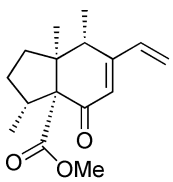
Ming-Tsang Hsieh,[a,c] Hsing-Jang Liu,*[a] Tai Wei Ly[b] and Kak-Shan Shia*[c]

Received 24th March 2009, Accepted 21st May 2009
First published as an Advance Article on the web 19th June 2009
DOI: 10.1039/b905910e

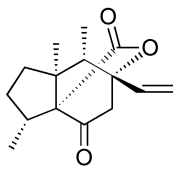
Starting from 4-methylcyclohexanone (**7**), a concise total synthesis of the pinguisane-type sesquiterpenoid acutifolone A, in racemic form, has been accomplished in 14 steps with an overall yield of 14.5%.

Introduction

Pinguisane-type sesquiterpenoids[1] possess an intriguing arrangement of several contiguously *cis*-oriented substituents along the perhydroindane core. Additionally, their carbon skeleton appears to be inconsistent with the isoprene rule, while biologically this family of natural products has been shown to possess a wide variety of interesting and/or medically relevant activities including piscicidal, antineoplastic, and microbicidal properties.[2,3] These aforementioned factors make them attractive targets for total synthesis, of which several have been documented.[4,5]



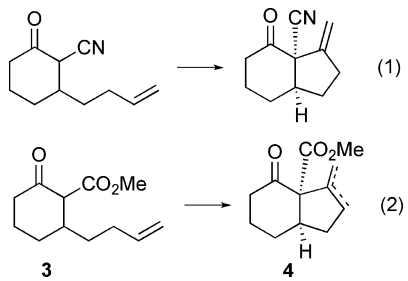
1



2

In 1998 and 2000, Asakawa and co-workers reported the structural elucidation of acutifolones A (**1**)[6] and B (**2**)[7] as members of the pinguisane family of natural products as isolated from the ether extracts of the Japanese liverwort *Porella acutifolia* subsp. *tosana*.[8] Recently, Nishiyama *et al.* reported the first total synthesis of acutifolone A in racemic form *via* a sequence involving more than thirty synthetic operations which also served to corroborate the structural assignments of Asakawa.[5]

Several years ago, our laboratories developed a novel approach to bicyclic systems[9] containing a cyclopentane ring appended with a methylene moiety (Scheme 1, Eq. 1). We extrapolated that the same process, with minor modifications to the starting substrate, would provide not only an effective route towards the bicyclo[4.3.0] core present in pinguisane sesquiterpenoids, but also allow for the establishment of the required *cis*-ring junction of these natural products in one step. This supposition was realized by a model reaction whereby keto ester **3** successfully furnished keto ester **4** (84%) in the presence of palladium acetate (Scheme 1, Eq. 2). Encouraged by this result, we embarked on the total synthesis of acutifolone A (**1**), culminating in the second total synthesis of this structurally complex natural product.

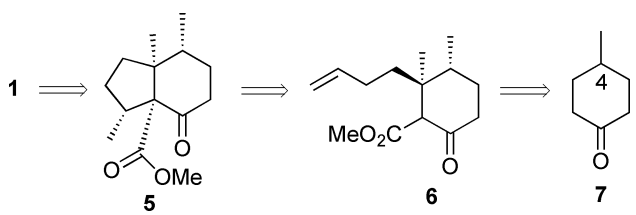


3 **4**

Scheme 1 Palladium(II) acetate mediated methylenecyclopentane annulation process.

Results and discussion

Our retrosynthetic strategy is outlined in Scheme 2. Target molecule **1** is anticipated to be derived from advanced intermediate **5**, the synthesis of which should be achieved from keto ester **6** *via* the aforementioned cyclopentene annulation followed by hydrogenation. The required keto ester **6** is projected to be readily prepared from 4-methylcyclohexanone (**7**) *via* a synthetic sequence of carbomethoxylation followed by two individual Michael addition reactions. Since the vicinal methyl groups need to be *cis*-oriented, the two Michael addition reactions would involve the addition of the methyl group first, followed by the 1-butenyl group. We surmised that this particular order of addition would lead to the desired stereochemical outcome as the methyl group on C-4 would serve to persuade the incoming 1-butenyl anion to attack from the face opposite to itself.



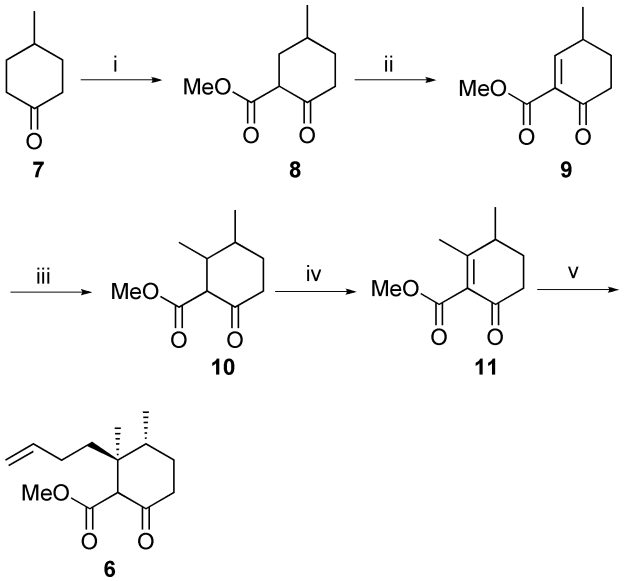
5 **6** **7**

Scheme 2 The retrosynthetic analysis of **1**.

The synthesis of the annulation precursor **6** began with the 4-methylcyclohexanone (**7**) which was carbomethoxylated in the

[a]*Department of Chemistry, National Tsing Hua University, Hsinchu, Taiwan 30013, R.O.C*
[b]*Axikin Pharmaceuticals, Inc., 10835 Road to the Cure, Suite 250, San Diego, CA 92121, USA*
[c]*Division of Biotechnology and Pharmaceutical Research, National Health Research Institutes, Miaoli County 35053, Taiwan, R.O.C. E-mail: ksshia@nhri.org.tw; Fax: +886-37-586456; Tel: +886-37-246166 ext:35709*
† Electronic supplementary information (ESI) available: ^{1}H and ^{13}C spectra for all new compounds and an X-ray crystallographical picture of **5a**.[13] CCDC reference number 706353. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/b905910e

presence of dimethyl carbonate and sodium hydride to furnish keto ester **8** (Scheme 3). Intermediate **8** thus obtained was treated with phenylselenyl chloride in the presence of pyridine followed by oxidative elimination with hydrogen peroxide at 0 °C[10] to yield enone ester **9** which in turn, without purification,[11] underwent the first 1,4-conjugate addition with freshly prepared lithium dimethylcuprate to afford the desired keto ester **10** in 77% yield over three steps. Subsequently, compound **10** was transformed to enone **11** in 91% overall yield using the same process as that utilized to oxidize ketone **8** to enone **9**. Exposure of enone ester **11** to the magnesium organocuprate freshly generated from 4-bromo-1-butene, magnesium turnings and cuprous iodide, provided keto ester **6** in 76% yield. Even though all the spectroscopic evidence for **6** was in agreement with the proposed structure, the critical issue of relative stereochemistry between all the appendages could not be unequivocally established due to facile keto–enol tautomerization. The indicated stereochemistry followed from the subsequent transformations (*vide infra*).

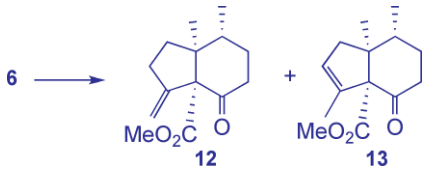


Scheme 3 *Reagents and conditions*: (i) NaH, $CO(OMe)_2$, THF, reflux, 2 h, 87%; (ii) PhSeCl, pyridine, CH_2Cl_2, 0 °C, 1 h then 30% H_2O_2, 0 °C, 8 min; (iii) MeLi, CuI, THF, −78 °C, 30 min, 77% over three steps; (iv) PhSeCl, pyridine, CH_2Cl_2, rt, 3 h then 30% H_2O_2, 0 °C, 10 min, 91% over two steps; (v) 3-butenylmagnesium bromide, CuI, THF/Me_2S (20:1), −78 °C, 30 min, 76%.

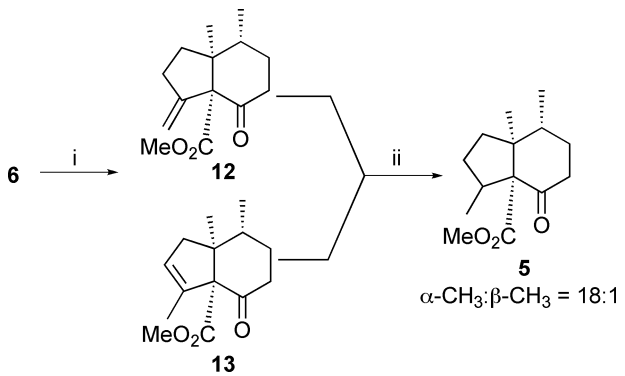
With the synthetic sequence towards the annulation precursor **6** mapped out and achieved, we were ready to tackle the key transformation in our retrosynthetic strategy towards acutifolone A. Initial attempts at the annulation reaction using previously established reaction conditions (1.0 equiv. $Pd(OAc)_2$, THF, rt) yielded unspectacular results. Gratifyingly, after a brief investigation into this reaction during which various parameters such as reagents, solvents, additives ($Cu(OAc)_2$ or K_2CO_3), and time were systematically varied, we arrived at a satisfactory set of reaction conditions (Table 1, Entry 5) to achieve this key annulation process.

Although the annulation process identified furnished a mixture of product **12** and its isomer **13**, these were readily separated and both are amenable for our total synthesis of acutifolone A. As indicated in Scheme 4, hydrogenation of ketones **12** and

Table 1 Palladium(II) mediated annulation process of **6** under various reaction conditions



Entry	Conditions	Time	Yield (%) 12	13
1	1.0 eq. $Pd(OAc)_2$, THF, rt	3 h	25	32
2	1.0 eq. $Pd(OAc)_2$, DMSO, rt	5 h	22	28
3	1.0 eq. $Pd(OAc)_2$, THF, rt	8 h	19	29
4	1.2 eq. $Pd(OAc)_2$, THF, rt	10 h	22	43
5	1.4 eq. $Pd(OAc)_2$, THF, rt	16 h	30	54
6	1.0 eq. $Cu(OAc)_2$, 0.1 eq. $Pd(OAc)_2$, THF, rt	60 h	11	39
7	1.5 eq. $Cu(OAc)_2$, 0.25 eq. $Pd(OAc)_2$, THF, rt	52 h	16	41



Scheme 4 *Reagents and conditions*: (i) $Pd(OAc)_2$ (1.4 equiv.), THF, rt, 16 h, 84%, (**12**/**13** = 0.56); (ii) H_2, 10% Pd/C, MeOH, rt, 90%.

13, individually, over a catalytic amount of 10% Pd/C furnished keto ester **5** as a mixture consisting predominantly of the product with the desired stereochemistry, contaminated with a trace of the undesired β-isomer.[12] Interestingly, it was observed that even though both olefins **12** and **13** furnished the reduced product **5** in excellent yield, there was a remarkable difference in reaction rate with ketone **12** being reduced much faster than ketone **13**. The relative stereochemistry of the major component of **5** was confirmed by the single crystal X-ray crystallography of its corresponding 2,4-DNP derivative **5a** (Fig. 1).[13] This experiment not only served to confirm the stereochemical outcome of the hydrogenation reaction, but also validated our design of the sequence of the double Michael addition reactions (*vide supra*).

With the desired stereochemistry of keto ester **5** established, we approached the concluding phase of the total synthesis of target **1**. Although keto ester **5** was an advanced intermediate in the only previously reported total synthesis of acutifolone A,[5b,c] we were of the belief that a more concise sequence of events could be experimentally realized to convert keto ester **5** into **1**. A key operation in this would be to identify a short process for installation of an α,β-unsaturated enone system into keto ester **5**. Towards this end, the corresponding trimethylsilyl enol ether of ketone **5** obtained under standard conditions[14] was oxidized by $Pd(OAc)_2$ in refluxing acetonitrile[15] to furnish the desired enone **14** in 67% yield over two steps (Scheme 5). Subsequent treatment

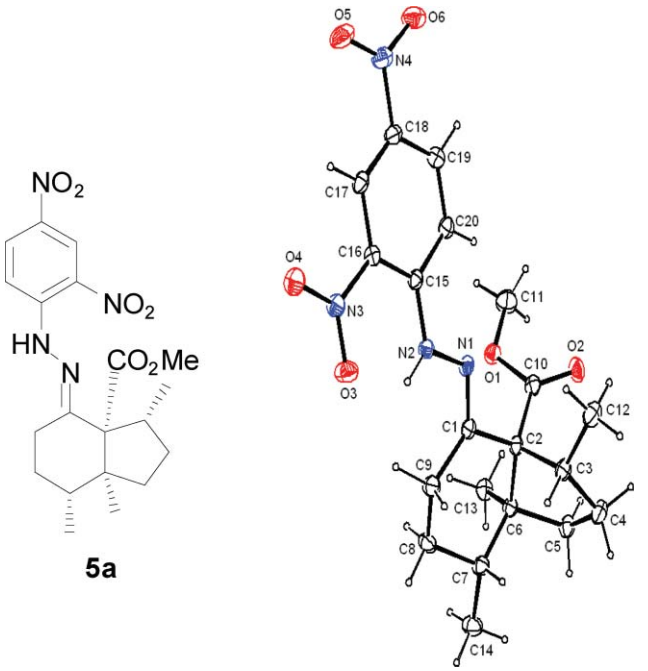
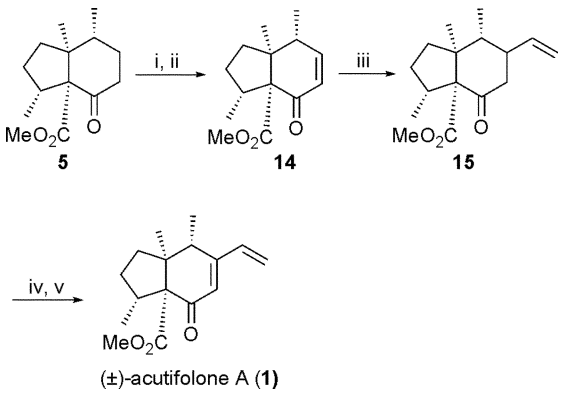


Fig. 1 The X-ray crystal structure of **5a** (thermal ellipsoids are shown at 50% probability).



Scheme 5 *Reagents and conditions:* (i) LHMDS, THF, −78 °C, 15 min then Me_3SiCl, 3 h; (ii) $Pd(OAc)_2$, CH_3CN, reflux, 50 h, 67% over two steps; (iii) vinylmagnesium bromide, CuI, THF/Me_2S (20:1), −78 °C to 0 °C, 2 h, 87%; (iv) LHMDS, THF, −78 °C, 15 min then Me_3SiCl, 3 h; (v) $Pd(OAc)_2$, CH_3CN, reflux, 52 h, 66% over two steps.

of enone **14** with the magnesium organocuprate reagent, readily prepared by the addition of vinylmagnesium bromide to a mixture of cuprous iodide and dimethyl sulfide (cat.) in THF at −78 °C, gave Michael adduct **15** in good yield (87%). Finally, following the same protocol for the transformation of ketone **5** to enone **14**, acutofolone A was achieved from enone **15** in 66% yield over two steps, the spectroscopic results of which were found to be identical to those reported in the literature.[5b,c,6]

Conclusions

In conclusion, a total synthesis of the pinguisane-type sesquiterpenoid acutifolone A, in racemic form, is reported. Not only is this the most concise (14 steps) and efficient (14.5% overall yield) total synthesis of acutifolone A, but this work also serves to demonstrate the utility of our previously developed annulation reaction as an efficient approach to the indanyl systems highly prevalent in nature.

Experimental

General

All reactions were performed under an atmosphere of argon or nitrogen unless otherwise stated. All solvents were dried prior to use and reagents were employed as received. Analytical thin layer chromatography was performed on SiO_2 60 F-254 plates and flash column chromatography was carried out using SiO_2 60 (particle size 0.040–0.055 mm, 230–400 mesh), both of which are available from E. Merck. Visualization was performed under UV irradiation at 254 nm followed by staining with vanillin (60 g of vanillin in 1 L of 95% ethanol containing 10 mL of conc. H_2SO_4) and charring by heat gun. Fourier transform infrared spectra (IR) were recorded on Bomen MR-100 and expressed in cm^{-1}. ^1H and ^{13}C NMR spectra were recorded on Bruker Avance EX 400 FT NMR or Bruker DMX-600. Chloroform-*d* was used as the solvent and TMS (δ = 0.00 ppm) as an internal standard. Chemical shifts are reported as δ values in ppm as referenced to TMS. Multiplicities are recorded as s (singlet), d (doublet), t (triplet), q (quartet), quint (quintet), sext (sextet), sept (septet), dd (doublet of doublet), dt (doublet of triplet), br (broadened), m (multiplet). Coupling constants (J) are expressed in Hz. HRMS were measured by JEOL JMS-HX110 spectrometer and spectral data were recorded as m/z values.

5-Methyl-2-oxocyclohexanecarboxylic acid methyl ester (8). To a stirred suspension of sodium hydride (60%, 3.42 g, 85.58 mmol) in dimethyl carbonate (50 mL, 597.36 mmol) at room temperature was added 4-methylcyclohexanone (6.00 g, 53.49 mmol) in dimethyl carbonate (5 mL, 59.74 mmol) dropwise. The reaction mixture was heated to reflux for 2 h and then cooled to 0 °C. 2 N HCl (30 mL) was added cautiously to quench the reaction. The aqueous layer was separated and extracted with diethyl ether (3 × 50 mL). The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered and concentrated to give the crude product, which was purified by flash chromatography on silica gel with EtOAc/*n*-hexane (1:10) to afford compound **8** (7.92 g, 87% yield) as a colorless oil: IR (CH_2Cl_2, cast) ν_{max} 2925, 2854, 1734, 1669, 1625 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 12.10 (br s, 1H), δ 3.71 (s, 3H), 2.36–2.26 (m, 4H), 1.75–1.69 (m, 3H), 1.65–1.61 (m, 2H), 1.28–1.22 (m, 2H), 1.01–0.90 (m, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 172.9 (C), 171.9 (C), 97.0 (C), 51.3 (CH_2), 30.7 (CH_2), 29.8 (CH_2), 28.9 (CH_2), 28.5 (CH_2), 21.3 (CH_3); HRMS (EI) calcd. for $C_9H_{14}N_3$: 170.1943; found: 170.1945.

2,3-Dimethyl-6-oxocyclohexanecarboxylic acid methyl ester (10). To a stirred solution of phenylselenyl chloride (0.63 g, 3.27 mmol) in CH_2Cl_2 (15 mL) at 0 °C was added pyridine (0.4 mL, 5.13 mmol) dropwise. After stirring for 20 min, compound **8** (0.50 g, 2.93 mmol) in CH_2Cl_2 (8 mL) was added. The resulting mixture was stirred at room temperature for 1 h and then washed with 1 N HCl solution (5 mL) to remove pyridine. The organic layer was separated and H_2O_2 (30%, 0.9 mL, 9.34 mmol) was introduced dropwise at 0 °C. The resulting mixture was kept stirring for 8 min at the same temperature and saturated $NaHCO_3$ solution (10 mL) was added to quench the reaction. The aqueous layer was

separated and extracted with CH_2Cl_2 (2 × 15 mL). The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered and concentrated to give the crude compound **9**, which was dried under vacuum and used without further purification.

To a stirred suspension of copper(I) iodide (0.62 g, 3.16 mmol) in anhydrous THF (15 mL) was added methyllithium (4.6 mL, 7.35 mmol) dropwise at 0 °C. The resulting colorless solution was stirred at the same temperature for 40 min and then cooled to −78 °C, at which time a solution of the crude compound **9** in anhydrous THF (10 mL) was introduced dropwise. After reaction was complete (ca. 30 min), saturated NH_4Cl solution (10 mL) was added. The aqueous layer was separated and extracted with diethyl ether (3 × 20 mL). The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered and concentrated to give the crude product, which was purified by flash chromatography on silica gel with EtOAc/*n*-hexane (1:9) to afford compound **10** (0.42 g, 77% yield over three steps) as a colorless oil: IR (CH_2Cl_2, cast) ν_{max} 2954, 2927, 2872, 1748, 1714, 1651, 1614 cm^{-1}; ^1H NMR ($CDCl_3$, 600 MHz) a mixture of enol and keto forms in a ratio of 2:3 δ 12.25 (br s, 0.44H), 3.73 (s, 3H), 3.06 (d, J = 12.0 Hz, 0.56H), 2.43 (ddd, J = 14.1, 4.2, 2.9 Hz, 1H), 2.39–2.33 (m, 1H), 2.31–2.24 (m, 1H), 2.15 (dt, J = 3.3, 18.7 Hz, 1H), 1.99–1.95 (m, 1H), 1.53–1.37 (m, 1H), 1.05–1.00 (m, 3H), 0.98–0.91 (m, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 206.0 (C), 173.5 (C), 171.6 (C), 170.4 (C), 101.3 (C), 64.4 (CH), 51.9 (CH_2), 51.2 (CH_2), 42.2 (CH), 41.2 (CH_2), 36.8 (CH), 34.3 (CH_2), 33.8 (CH), 33.2 (CH), 25.4 (CH_2), 23.4 (CH_2), 22.0 (CH_3), 18.9 (CH_3 × 2), 18.7 (CH_3); HRMS (EI) calcd. For $C_{10}H_{16}O_3$: 184.1099; found: 184.1096.

2,3-Dimethyl-6-oxocyclohex-1-enecarboxylic acid methyl ester (11). To a stirred solution of phenylselenyl chloride (0.46 g, 2.39 mmol) in CH_2Cl_2 (15 mL) at 0 °C was added pyridine (0.3 mL, 3.87 mmol) slowly. After stirring for 20 min at the same temperature, compound **10** (0.40 g, 2.17 mmol) in CH_2Cl_2 (8 mL) was added. The resulting mixture was stirred at 0 °C for 3 h and then washed with 1 N HCl solution (5 mL) to remove pyridine. The organic layer was separated and H_2O_2 (30%, 0.8 mL, 8.30 mmol) was added dropwise at 0 °C. The resulting mixture was kept stirring for 10 min at the same temperature and saturated $NaHCO_3$ solution (5 mL) was added to quench the reaction. The aqueous layer was separated and extracted with CH_2Cl_2 (2 × 15 mL). The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered and concentrated to give the crude product, which was purified by flash chromatography on silica gel with EtOAc/*n*-hexane (1:4) to afford compound **11** (0.36 g, 91% yield for two steps) as a yellow oil: IR (CH_2Cl_2, cast) ν_{max} 2952, 2925, 1748, 1714, 1653, 1614, 1457 cm^{-1}; ^1H NMR ($CDCl_3$, 600 MHz) δ 3.79 (s, 3 H), 2.51 (ddd, J = 12.0, 10.4, 6.0 Hz, 1H), 2.36 (ddd, J = 17.0, 7.1, 4.9 Hz, 1H), 2.47–2.43 (m, 1H), 2.15–2.09 (m, 1H), 1.94 (s, 3H), 1.78–1.73 (m, 1H), 1.22 (d, J = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 194.9 (C), 167.6 (C), 163.9 (C), 132.6 (C), 52.1 (CH_3), 34.7 (CH), 33.9 (CH_2), 29.1 (CH_2), 20.4 (CH_3), 17.4 (CH_3); HRMS (EI) calcd. for $C_{10}H_{14}O_3$: 182.0943; found: 182.0942.

2-But-3-enyl-2,3-dimethyl-6-oxocyclohexanecarboxylic acid methyl ester (6). To a stirred suspension of CuI (0.28 g, 1.49 mmol) in THF (10 mL) were sequentially added Me_2S (0.5 mL) and freshly prepared 3-butenylmagnesium bromide solution (10.5 mL, 0.36 M in THF, 3.80 mmol) dropwise at −78 °C. After stirring for 30 min at the same temperature, a solution of compound **11** (0.25 g, 1.37 mmol) in anhydrous THF (6 mL) was introduced. The resulting mixture was stirred for another 1 h at 0 °C. Saturated NH_4Cl solution (8 mL) was added to quench the reaction. The aqueous layer was separated and extracted with diethyl ether (3 × 15 mL). The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered and concentrated to give the crude residue, which was purified by flash chromatography on silica gel with EtOAc/*n*-hexane (1:9) to afford compound **6** (0.25 g, 76% yield) as a yellow oil: IR (CH_2Cl_2, cast) ν_{max} 3077, 2969, 2950, 2877, 1752, 1715, 1641 cm^{-1}; ^1H NMR ($CDCl_3$, 600 MHz): a mixture of enol and keto forms in a ratio of 1:5 was observed. δ 13.05 (s, 0.17H), 5.76–5.71 (m, 1H), 4.99–4.90 (m, 2H), 3.69–3.63 (m, 3H), 3.26 (s, 0.83H), 2.86 (dq, J = 20.0, 7.3 Hz, 1H), 2.41–2.37 (m, 1H), 2.32–2.28 (m, 2H), 2.03–1.99 (m, 1H), 1.95–1.87 (m, 2H), 1.63–1.55 (m, 1H), 1.52–1.49 (m, 1H), 0.99–0.97 (m, 3H), 0.90–0.76 (m, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 207.0 (C), 169.2 (C), 138.6 (CH), 114.4 (CH_2), 65.4 (CH), 52.0 (CH_3), 43.6 (C), 38.6 (CH_2), 37.4 (CH_2), 33.5 (CH), 30.3 (CH_2), 27.3 (CH_2), 17.7 (CH_3), 14.9 (CH_3); HRMS (EI) calcd. for $C_{14}H_{22}O_3$: 238.1569; found: 238.1569.

(3a*R,7*R**,7a*S**)-Methyl 7,7a-dimethyl-3-methylene-4-oxo-octahydro-1*H*-indene-3a-carboxylate (12) and (3a*R**,7*R**,7a*S**)-methyl 3,7,7a-trimethyl-4-oxo-3a,4,5,6,7,7a-hexahydro-1*H*-indene-3a-carboxylate (13).** To a solution of compound **6** (120 mg, 0.50 mmol) in THF (8 mL) was added $Pd(OAc)_2$ (0.16 g, 0.71 mmol) at room temperature. The resulting mixture was stirred at the same temperature for 16 h. H_2O (10 mL) was added to quench the reaction. The aqueous layer was separated and extracted with Et_2O (3 × 15 mL). The combined organic extracts were washed with brine, dried over $MgSO_4$, filtered and concentrated to give the crude product, which was purified by flash chromatography on silica gel with EtOAc/*n*-hexane (1:5) to afford compound **12** (36 mg, 30% yield) as a colorless oil: IR (CH_2Cl_2, cast) ν_{max} 2956, 2933, 1742, 1715, 1641, 1462 cm^{-1}; ^1H NMR ($CDCl_3$, 600 MHz): δ 5.10 (t, J = 2.2 Hz, 1H), 4.88 (t, J = 2.5 Hz, 1H), 3.68 (s, 3H), 2.66–2.61 (m, 1H), 2.52–2.45 (m, 1H), 2.44–2.36 (m, 2H), 1.87 (ddd, J = 13.1, 8.5, 1.8 Hz, 1H), 1.74–1.67 (m, 3H), 1.50 (dt, J = 13.4, 10.3 Hz, 1H), 0.96 (s, 3H), 0.95 (m, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 206.9 (C), 171.5 (C), 150.2 (C), 111.6 (CH_2), 75.5 (C), 52.9 (C), 52.0 (CH_3), 38.1 (CH_2), 34.6 (CH_2), 33.1 (CH), 29.7 (CH_2), 28.5 (CH_2), 17.4 (CH_3), 16.4 (CH_3); HRMS (EI) calcd. for $C_{14}H_{20}O_3$: 236.1412; found: 236.1416.

Further elution gave compound **13** (64 mg, 54% yield) as a yellow oil: IR (CH_2Cl_2, cast) ν_{max} 2987, 2911, 1739, 1711, 1644 cm^{-1}; ^1H NMR ($CDCl_3$, 600 MHz): δ 5.65 (s, 1H), 3.67 (s, 3H), 2.57–2.52 (m, 1H), 2.39–2.35 (m, 1H), 2.22–2.16 (m, 1H), 2.14–2.11 (m, 1H), 1.87–1.77 (m, 2H), 1.69–1.66 (m, 1H), 1.61 (q, J = 1.8 Hz, 3H), 0.99 (m, 3H), 0.98 (s, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 208.0 (C), 171.4 (C), 137.5 (C), 130.3 (CH), 77.5 (C), 51.8 (C), 51.7 (CH_3), 45.6 (CH_2), 37.7 (CH), 37.1 (CH_2), 26.5 (CH_2), 20.4 (CH_3), 16.6 (CH_3), 15.0 (CH_3); HRMS (EI) calcd. for $C_{14}H_{20}O_3$: 236.1412; found: 236.1412.

(3*R,3a*R**,7*R**,7a*S**)-Methyl 3,7,7a-trimethyl-4-oxooctahydro-1*H*-indene-3a-carboxylate (5).** To a stirred solution of compound **12** (88 mg, 0.37 mmol) in MeOH (6 mL) was added Pd/C (0.01 g, 10% w/w) in one portion. The resulting mixture was hydrogenated under 1 atmosphere of H_2 at room temperature. After reaction was complete (*ca.* 8 h), the mixture

was filtered by celite and concentrated to give the crude product, which was purified by flash chromatography on silica gel with EtOAc/*n*-hexane (1:5) to afford the major component (α-CH_3) of compound **5** (80 mg, 90% yield) as a colorless oil: IR (CH_2Cl_2, cast) ν_{max} 2956, 2933, 2876, 1731, 1712 cm^{-1}; ^1H NMR ($CDCl_3$, 600 MHz): δ 3.65 (s, 3H), 2.57 (ddd, $J = 16.7$, 7.5, 4.4 Hz, 1H), 2.42–2.34 (m, 2H), 1.80–1.71 (m, 4H), 1.66–1.59 (m, 3H), 1.06 (d, $J = 6.8$ Hz, 3H), 0.95 (s, 3H), 0.92 (d, $J = 6.5$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 210.1 (C), 171.0 (C), 72.5 (C), 51.3 (C), 51.0 (CH_3), 41.6 (CH), 37.8 (CH_2), 37.2 (CH_2), 36.0 (CH), 30.8 (CH_2), 28.1 (CH_2), 18.0 (CH_3), 16.4 (CH_3), 15.4 (CH_3); HRMS (EI) calcd. for $C_{14}H_{22}O_3$: 238.1569; found: 238.1565.

Alternatively, compound **5** could be achieved using **13** as the starting material in a longer reaction time: to a stirred solution of compound **13** (102 mg, 0.43 mmol) in MeOH (6 mL) was added Pd/C (0.01 g, 10% w/w) in one portion. The resulting mixture was hydrogenated under 1 atmosphere of H_2 at room temperature. After reaction was complete (*ca.* 15 h), the mixture was filtered by celite and concentrated to give the crude product, which was purified by flash chromatography on silica gel with EtOAc/*n*-hexane (1:5) to afford the major component (α-CH_3) of compound **5** (90 mg, 88% yield) as a colorless oil.

(3*R,3a*R**,7*R*,7a*S**)-4-[(2,4-Dinitrophenyl)-hydrazono]-3,7,7a-trimethyl-octahydroindene-3a-carboxylic acid methyl ester (5a).** A two-neck round bottom flask equipped with a Dean-Stark and a condenser, was charged with compound **5** (49 mg, 0.25 mmol), *p*-TSA (2 mg, 0.01 mmol) and benzene (10 mL). The reaction mixture was heated to reflux for 5 days with azeotropic removal of water and then cooled to room temperature. Saturated $NaHCO_3$ solution (5 mL) was added. The resulting aqueous solution was extracted with Et_2O (3 × 15 mL). The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered and concentrated to give the crude product, which was purified by flash chromatography on silica gel with EtOAc/*n*-hexane (1:9) to afford compound **5a** (46 mg, 90% yield) as an orange solid, which was further recrystallized from ethyl acetate and *n*-hexane to afford a crystalline compound in bright-orange color.

Mp 139–141 °C; IR (CH_2Cl_2, cast) ν_{max} 3321, 2950, 1729, 1618, 1592, 1518 cm^{-1}; ^1H NMR ($CDCl_3$, 600 MHz): δ 11.18 (br s, 1H), 9.11 (d, $J = 2.6$ Hz, 1H), 8.28 (dd, $J = 8.8$, 2.5 Hz, 1 H), 7.83 (d, $J = 9.6$ Hz, 1H), 3.67 (s, 3H), 2.56 (ddd, $J = 16.8$, 7.7, 3.7 Hz, 2 H), 2.56–2.50 (m, 2H), 1.88–1.79 (m, 2H), 1.72–1.63 (m, 4H), 1.25 (d, $J = 6.8$ Hz, 3H), 0.96–0.94 (m, 6H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 172.5 (C), 161.0 (C), 145.4 (C), 137.8 (C), 130.1 (CH), 129.2 (C), 123.5 (CH), 116.4 (CH), 67.2 (C), 51.3 (C), 51.0 (CH_3), 43.9 (CH), 38.9 (CH_2), 37.7 (CH), 31.4 (CH_2), 26.4 (CH_2), 24.6 (CH_2), 18.3 (CH_3), 16.5 (CH_3), 16.0 (CH_3); HRMS (EI) calcd. For $C_{20}H_{26}N_4O_6$: 418.1852; found: 418.1852. X-ray crystallographic data of compound **5a** (CCDC 706353) are available *via* www.ccdc.cam.ac.uk/conts/retrieving.html or mailto:deposit@ccdc.cam.ac.uk.†

(3*R,3a*R**,7*R**,7a*S**)-Methyl 3,7,7a-trimethyl-4-oxo-2,3,3a,4,7,7a-hexahydro-1*H*-indene-3a-carboxylate (14).** To a solution of compound **5** (45 mg, 0.19 mmol) in THF (6 mL) was added LHMDS (0.4 mL, 1 M in THF, 0.40 mmol) dropwise at –78 °C. The resulting mixture was stirred at the same temperature for 15 min, and then TMSCl (45 mg, 0.42 mmol) in anhydrous THF (6 mL) was added in one portion. The reaction mixture was allowed to warm to room temperature and stirred for another 3 h. H_2O (6 mL) was added to quench the reaction. The aqueous layer was separated and extracted with Et_2O (3 × 15 mL). The combined organic extracts were washed brine, dried over $MgSO_4$, filtered and concentrated. The crude silyl enol ether thus obtained was further dried under vacuum and used without purification in the following transformation.

To a solution of the crude silyl enol ether in CH_3CN (4 mL) was added $Pd(OAc)_2$ (51 mg, 0.23 mmol) in one portion. The reaction mixture was heated to reflux for 50 h and then cooled to room temperature. H_2O (5 mL) was added to quench the reaction. The resulting aqueous solution was separated and extracted with Et_2O (3 × 15 mL). The combined organic extracts were washed brine, dried over $MgSO_4$, filtered and concentrated to give the crude residue, which was purified by flash chromatography on silica gel with EtOAc/*n*-hexane (1:6) to afford compound **14** (30 mg, 67% yield over two steps) as a yellow oil: IR (CH_2Cl_2 cast) ν_{max} 2956, 2932, 2870, 1723, 1683, 1628 cm^{-1}; ^1H NMR ($CDCl_3$, 600 MHz): δ 6.52 (dd, $J = 10.2$, 2.0 Hz, 1H), 6.00 (dd, $J = 10.2$, 2.9 Hz, 1H), 3.60 (s, 3H), 2.57–2.52 (m, 1H), 2.41–2.34 (m, 1H), 2.01–1.95 (m, 1H), 1.85–1.73 (m, 2H), 1.66–161 (m, 1H), 1.12 (d, $J = 6.2$ Hz, 3H), 1.10 (d, $J = 5.6$ Hz, 3H), 0.85 (s, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 195.7 (C), 171.2 (C), 151.9 (CH), 127.5 (CH), 70.4 (C), 53.2 (C), 51.1 (CH_3), 39.2 (CH), 35.4 (CH), 34.9 (CH_2), 30.8 (CH_2), 17.9 (CH_3), 15.4 (CH_3), 14.5 (CH_3); HRMS (EI) calcd. for $C_{14}H_{20}O_3$: 236.1412; found: 236.1413.

(3*R,3a*R**,7*R**,7a*S**)-Methyl 3,7,7a-trimethyl-4-oxo-6-vinyl-octahydro-1*H*-indene-3a-carboxylate (15).** To a suspension of copper(I) iodide (28 mg, 0.15 mmol) in anhydrous THF (5 mL) was added vinylmagnesium bromide (0.3 mL, 0.30 mmol) dropwise at –78 °C. The resulting mixture was stirred at the same temperature for 30 min, at which time a solution of compound **14** (28 mg, 0.12 mmol) in anhydrous THF (5 mL) was introduced dropwise. The resulting mixture was warmed and kept stirring at 0 °C for 2 h. H_2O (5 mL) and saturated $NaHCO_3$ solution (5 mL) was added to quench the reaction. The aqueous layer was separated and extracted with Et_2O (3 × 15 mL). The combined organic extracts were washed brine, dried over $MgSO_4$, filtered and concentrated to give the crude residue, which was purified by flash chromatography on silica gel with EtOAc/*n*-hexane (1:9) to afford compound **15** (27 mg, 87% yield) as a colorless oil: IR (CH_2Cl_2 cast) ν_{max} 2967, 2911, 2881, 1723, 1686, 1641 cm^{-1}; ^1H NMR ($CDCl_3$, 600 MHz): δ 5.58–5.54 (m, 1H), 4.99–4.95 (m, 2H), 3.67 (s, 3H), 2.76 (dd, $J = 16.1$, 7.7 Hz, 1H), 2.45–2.36 (m, 2H), 2.23 (dd, $J = 16.1$, 7.6 Hz, 1H), 1.82–1.76 (m, 3 H), 1.66–163 (m, 1H), 1.42–1.37 (m, 1H), 1.08 (d, $J = 6.8$ Hz, 3H), 1.01 (s, 3H), 0.89 (d, $J = 6.7$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 209.1 (C), 170.9 (C), 141.2 (CH), 114.8 (CH_2), 72.6 (C), 52.7 (C), 51.1 (CH_3), 43.9 (CH), 43.6 (CH_2), 41.4 (CH), 40.4 (CH), 38.2 (CH_2), 30.7 (CH_2), 18.8 (CH_3), 15.1 (CH_3), 14.4 (CH_3); HRMS (EI) calcd. for $C_{16}H_{24}O_3$: 264.1725; found: 264.1725.

(±)-Acutifolone A (1)

To a solution of compound **15** (21 mg, 0.08 mmol) in THF (2.5 mL) was added LHMDS (0.2 mL, 0.20 mmol) dropwise at –78 °C. The resulting mixture was stirred at the same temperature for 15 min, and then TMSCl (22 mg, 0.20 mmol) in anhydrous THF (2 mL) was added in one portion. The reaction mixture was warmed and

kept stirring at room temperature for 3 h. H_2O (6 mL) was added to quench the reaction. The aqueous layer was extracted with Et_2O (3 × 15 mL). The combined organic extracts were washed brine, dried over $MgSO_4$, filtered and concentrated to give the crude silyl enol ether, which was further dried under vacuum and used without further purification in the following transformation.

To a solution of the crude silyl enol ether in CH_3CN (4 mL) was added $Pd(OAc)_2$ (22 mg, 0.10 mmol). The reaction mixture was heated to reflux for 52 h and then cooled to room temperature. H_2O (5 mL) was added to quench the reaction. The aqueous layer was extracted with Et_2O (3 × 15 mL). The combined organic extracts were washed brine, dried over $MgSO_4$, filtered and concentrated to give the crude residue, which was purified by flash chromatography on silica gel with EtOAc/*n*-hexane (1:6) to afford synthetic product **1** (14 mg, 66% yield over two steps) as a yellow oil: IR (CH_2Cl_2 cast) ν_{max} 2966, 2878, 1728, 1711, 1663, 1460 cm^{-1}; ^1H NMR ($CDCl_3$, 600 MHz): δ 6.43 (dd, J = 17.5, 10.8 Hz, 1H), 5.97 (s, 1H), 5.67 (d, J = 17.5 Hz, 1H), 5.43 (d, J = 10.9 Hz, 1H), 3.65 (s, 3H), 2.60 (q, J = 7.1 Hz, 1H), 2.20-2.16 (m, 1H), 1.72–1.57 (m, 3H), 1.48–1.51 (m, 1H), 1.23 (d, J = 6.9 Hz, 3H), 1.16 (d, J = 7.1 Hz, 3H), 1.08 (s, 3 H); ^{13}C NMR ($CDCl_3$, 150 MHz): δ 197.2 (C), 171.2 (C), 160.4 (C), 136.8 (CH), 124.4 (C), 120.2 (CH_2), 67.3 (C), 51.1 (CH_3), 49.8 (C), 45.8 (CH), 40.9 (CH_2), 38.4 (CH), 31.4 (CH_2), 23.3 (CH_3), 18.1 (CH_3), 15.6 (CH_3); HRMS (EI) calcd. for $C_{16}H_{22}O_3$: 262.1569; found: 262.1575.

Acknowledgements

We are grateful to the National Science Council and the National Health Research Institutes of the Republic of China for financial support.

References

1 Y. Asakawa, *Progress in the Chemistry of Organic Natural Products*, W. Herz, G. W. Kirby, R. E. Moore, W. Steglich and Ch. Tamm, Eds.; Springer, Wien, New York, 1995; Vol. 65, pp. 1–562.
2 Y. Asakawa, *J. Hattori Bot. Lab.*, 1998, **84**, 91.
3 Y. Asakawa, *Bryophytes: Their Chemistry and Chemotaxonomy*, Clarendon, Oxford, 1990, pp 369–410.
4 (*a*) E. Piers and H. L. A. Tse, *Can. J. Chem.*, 1993, **71**, 983; (*b*) D. Schinzer, K. Ringe, P. G. Jonse and D. Doring, *Tetrahedron Lett.*, 1995, **36**, 4051; (*c*) A. Srikrishna and D. Vijaykumar, *J. Chem. Soc., Perkin Trans. 1*, 1997, **22**, 3295; (*d*) A. Srikrishna and D. Vijaykumar, *J. Chem. Soc., Perkin Trans. 1*, 1999, **22**, 1265; (*e*) C. K. Sha, H. W. Liao, P. C. Chen and S. C. Yen, *J. Org. Chem.*, 2003, **68**, 8704; (*f*) C. H. Jiang, A. Bhattacharyya and C. K. Sha, *Org. Lett.*, 2007, **17**, 3241.
5 (*a*) J. Shiina and S. Nishiyama, *Tetrahedron Lett.*, 2004, **45**, 9033; (*b*) J. Shiina and S. Nishiyama, *Tetrahedron Lett.*, 2005, **46**, 7683; (*c*) J. Shiina, M. Oikawa, K. Nakamura, R. Obata and S. Nishiyama, *Eur. J. Org. Chem.*, 2007, **31**, 5190.
6 T. Hashimoto, H. Irita, M. Tanaka, S. Takaoka and Y. Asakawa, *Tetrahedron Lett.*, 1998, **39**, 2977.
7 T. Hashimoto, H. Irita, M. Tanaka, S. Takaoka and Y. Asakawa, *Phytochemistry*, 2000, **53**, 593.
8 M. Toyota, A. Ueda and Y. Asakawa, *Phytochemistry*, 1991, **30**, 567.
9 L. R. Kung, C. H. Tu, K. S. Shia and H. J. Liu, *Chem. Commun.*, 2003, **20**, 2490.
10 D. Liotta, C. Barnum, R. Puleo, G. Zima, C. Bayer and H. S. Kezar, *J. Org. Chem.*, 1981, **46**, 2920.
11 This compound was found to be rather unstable. Attempted purification by flash chromatography resulted in substantial loss of material.
12 The ratio of a pair of epimers of **5** (α-CH_3:β-CH_3 = 18:1) was determined by GC-MS analysis, wherein two distinct peaks displayed the same formula weight. The minor component, unavailable by chromatographic purification, was tentatively assigned as the β isomer after the major component was unambiguously identified as the α isomer[13].
13 CCDC 706353 (**5a**) contains the supplementary crystallographic data for this paper.† These data can be obtained free of charge *via* http://www.ccdc.cam.ac.uk/conts/retrieving.html or deposit@ccdc.cam.ac.uk. Single crystals of **5a** were recrystallized from EtOAc/*n*-hexane and mounted in the 150 K N_2 stream of Siemens Smart CCD diffractometer equipped with a Mo K_α radiation source (λ = 0.71073 Å). Crystal data: $C_{20}H_{26}N_4O_6$, M = 418.45, Monoclinic, a = 10.3756(6), b = 12.6325(7), c = 16.2827(9) Å, V = 2058.0(2) $Å^3$, space group P2(1)/n, Z = 4, a total of 15394 reflections were collected in the range 2.07 < 2θ < 25.03. Of these, 3635 were independent; for the observed data, $wR2$ = 0.0888, R = 0.0334.
14 E. Colvin, *Silicon in Organic Synthesis*, Butterworths, Boston, 1981, pp. 198–287.
15 T. Saegusa, Y. Ito and T. Hirao, *J. Org. Chem.*, 1978, **43**, 1011.

