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Facile total synthesis of the antimalarial nonenolide

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Abstract—The facile total synthesis of the antimalarial nonenolide **1** is reported. The convergent strategy features the use of reactions such as Sharpless asymmetric dihydroxylation, aldol addition, Mitsunobu reaction, and ring-closing metathesis (RCM).

1. Introduction

The ascomycetous genus *Cordyceps* is a rich source of biologically active secondary metabolites[1] that has been widely used as food and herbal medicines in Asia.[2] Over the past years, these secondary metabolites attracted many synthetic chemists' attention due to their unique structure and special biological activity. Compound **1**, isolated as a white solid from the entomopathogenic fungus *Cordyceps militaries BCC2816* in 2004, shows good antimalarial activity.[3] Recently, the first synthesis of **1** has been reported by Grubbs.[4] As a part of our ongoing program on the synthesis of bioactive macrolides,[5] compound **1** attracted our interests because of its challenging medium ring size and special antimalarial activity. Herein, we report a shorter and facile total synthesis of nonenolide **1** featuring the use of one MOM-group as a constraint to confer *E*-selectivity of the RCM reaction, which is different to that reported by Grubbs.[4]

Compound **1**, a part of the 10-membered β-keto lactone families, has an *E*-olefin bond and possesses a total of three stereocenters. Although there are already some strategies for the construction of medium-sized rings, the synthesis of 10-membered lactones remains a difficult challenge where destabilizing nonbounded, transannular interactions and unfavorable entropic factors must be overcome.[6] Thinking of the effectiveness of ring-closing metathesis (RCM) in the synthesis of natural lactones,[7] we decided to use RCM as the key step in our synthesis. Our retrosynthetic planning is outlined in Scheme 1. A convergent strategy identified **2** and **3** as the key intermediates of a similar complexity, which would give the lactone via single Mitsunobu esterification[8] and ring-closing metathesis. Alcohol **2** could be obtained from commercially available (*S*)-propylene oxide by a simple nucleophilic attack with allyl magnesium bromide, while acid **3** was envisaged from **5** and **6** by the aldol addition.

2. Results and discussion

The synthesis of alcohol **2** began with (*S*)-propylene oxide **4** (Scheme 2). Regioselective ring opening of the epoxide ring by allyl magnesium bromide in the presence of CuI yielded the alcohol, which was protected as PMB ether **7** (85% yield, 2 steps). Asymmetric dihydroxylation of **7** with AD-mix-β gave diol **8**,[9] which was rapidly transformed to epoxide **9** using NaH and *N*-tosylimidazole in THF.[10] Epoxide **9** was then converted to one carbon homologated allylic alcohol **10** by dimethylsulfonium methylide.[11] Protection of the hydroxyl group as a MOM ether and removal of the PMB group accomplished the synthesis of alcohol **2**.

The synthesis of fragment **3** was started with an aldol addition between the enolate of known *N*-acyloxazolidinone **5**[5b] and acrolein under Crimmins' conditions[12] to deliver the protected Evans-*syn*[13] adduct **12** after silylation of the alcohol (Scheme 3). The methylsulfenyl group was essential for excellent diastereoselectivity of the aldol addition, and was removed with n-Bu_3SnH and AIBN in excellent yield.[14]

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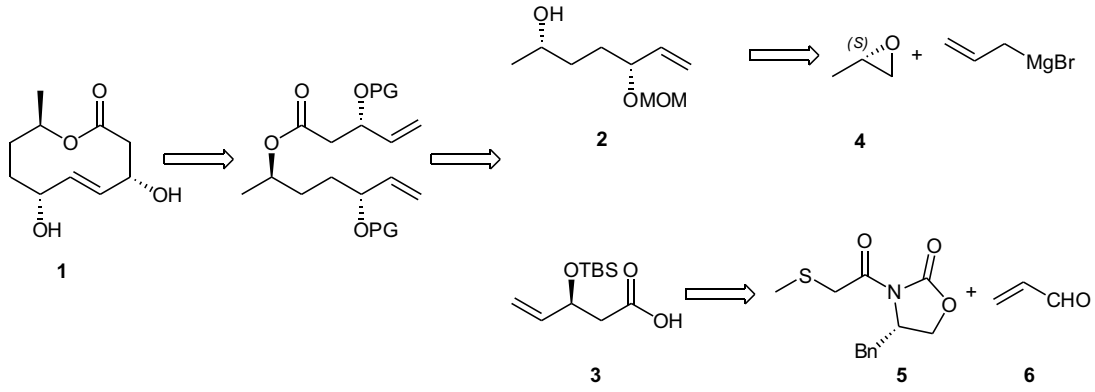
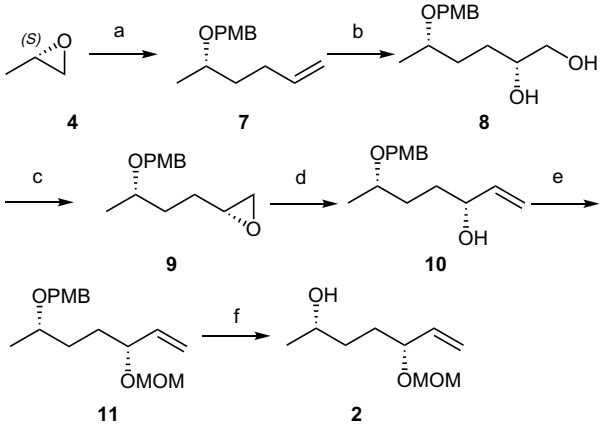
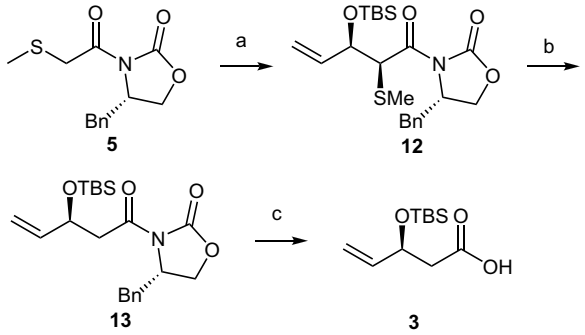


Scheme 1. Retrosynthetic analysis.



Scheme 2. Reagents and conditions: (a) (i) Allyl magnesium bromide, CuI, THF, −40 °C–rt; (ii) PMBCl, NaH, TBAI, THF, reflux, 8 h, 85%, 2 steps; (b) AD-mix-β, *t*-BuOH/H_2O = 1:1, 0 °C, 48 h, 87%, 67% de; (c) NaH, *N*-Tosylimidazole, THF, 0 °C–rt, 10 h, 83%; (d) *n*-BuLi, $Me_3S^+I^-$, THF, −20 °C–rt, 85%; (e) MOMCl, DIPEA, NaI, DCM, reflux, 5 h, 98%; (f) DDQ, DCM, Buffer, 0 °C, 3 h, 98%.



Scheme 3. Reagents and conditions: (a) (i) $TiCl_4$, DIPEA, NMP, acrolein, DCM, −78 °C; (ii) TBSCl, Imidazole, DMF, 35 °C, overnight, 74%, 2 steps; (b) *n*-Bu_3SnH, AIBN, benzene, 80 °C, 1 h, 95%; (c) LiOH, H_2O_2 (aq), THF, H_2O, 0 °C, 20 min, 97%.

The oxidative removal of the auxiliary by LiOOH directly gave the desired acid **3**.[15]

With compounds **2** and **3** in hand (Scheme 4), a Mitsunobu reaction was used to invert the stereogenic center of C-9 to furnish the diene ester **14**. Next, we attempted to construct a 10-membered ring by RCM reaction. Although not unprecedented,[4] the ability to perform the RCM reactions in the presence of two hydroxy groups α- to both the double bounds was expected to be a significant challenge. As shown in Figure 1, we explored the use of Grubbs' second generation catalyst **19**, Hoveyda–Grubbs' second generation catalyst **20** and various protecting groups for the hydroxy groups. Unfortunately, this proved unsuccessful.

Interestingly, the removal of the TBS-group of **14** using HF-Py in THF produced **15** (Scheme 5), which was treated with Grubbs' second generation catalyst in 1 mM of degassed DCM at reflux to furnish the desired *E*-isomer **16** as the major product. The result that *E*-selectivity of RCM can also be obtained from mono protected diene ester **15** is different to that reported by Grubbs.[4] Deprotection of the MOM group using Dowex-50W-x8 in MeOH and H_2O at reflux produced the target compound **1**.[16]

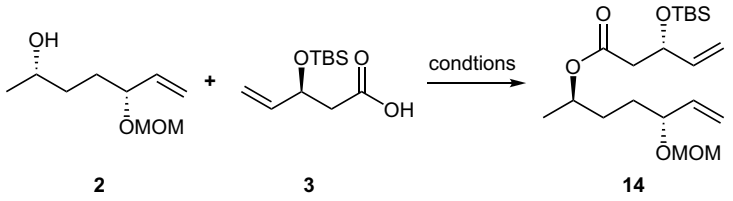
3. Conclusion

In conclusion, a facile and effective synthesis of nonenolide **1** has been achieved from commercially available (*S*)-propylene oxide and **5**[5b] was easily achieved in 12% overall yield. The notable feature of the synthesis was the use of reactions such as the Sharpless asymmetric dihydroxylation, aldol addition, Mitsunobu reaction, and ring-closing metathesis (RCM). Although our ring-closing strategy is similar to that of Grubbs, the synthesis of the precursor is more efficient, while the mono protected diene was found to give the desired *E*-olefin in the RCM step.

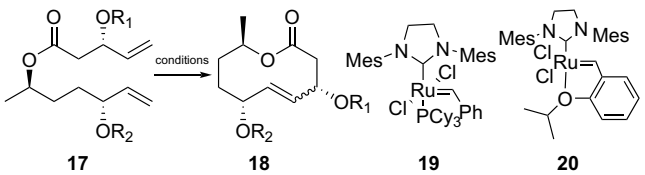
4. Experimental

4.1. General methods

Oxygen- and moisture-sensitive reactions were carried out under an argon atmosphere. Solvents were purified and dried by standard methods prior to use. All commercially available reagents were used without further purification unless otherwise noted. Column chromatography was performed on silica gel (200–300 mesh). Optical rotations were

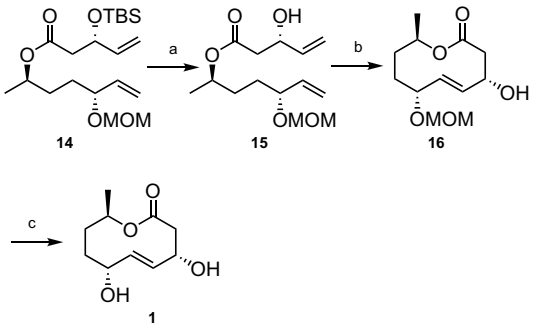


Scheme 4. Reagents and conditions: PPh_3, DIAD, benzene, rt, overnight, 87%.



entry	diene	R_1	R_2	results
1[a]	**14**	TBS	MOM	no reaction
2[a]	**17-a**	TBS	TBS	no reaction
3[a]	**17-b**	MOM	MOM	no reaction
4[b]	**17-b**	MOM	MOM	decomposition
5[a]	**17-c**	H	H	50%, ***Z*-18**

Figure 1. Reagents and conditions: (a) **20**, DCM, 1 mM, reflux, 24 h; (b) **19**, toluene, 1 mM, reflux, 24 h.



Scheme 5. Reagents and conditions: (a) HF-Py, THF, rt, 4 days, 79%; (b) Grubbs' 2nd catalyst, DCM, 1 mM, reflux, 2 days, 50%; (c) Dowex-50W-x8, MeOH, H_2O, reflux, 69%.

measured on a precision automated polarimeter. ^{1}H NMR and ^{13}C NMR spectra were recorded on a 300 MHz spectrometer and a 400 MHz spectrometer. Chemical shifts are reported as δ values relative to internal chloroform-D (δ 7.26 for ^{1}H and 77.0 for ^{13}C) or methanol-d_4. High resolution mass spectra (HRMS) were recorded on a Bruker Daltonics APEX II47e instrument.

4.2. PMB ether 7

A 100 mL three-necked flask containing magnesium turnings (1.58 g, 66 mmol) and a stirring bar was dried in an oven at 100 °C for 2 h and cooled to room temperature under a stream of dry Ar. A portion of allyl bromide (5.5 mL, 60 mmol) in anhydrous THF (80 mL) was introduced, the reaction was initiated with a small crystal of iodine, and the remaining solution added over 1 h at 0 °C. Stirring was continued for a further 2 h at room temperature, and the mixture was cooled to −40 °C. CuI (1.14 g, 6 mmol) was added and the mixture stirred for 30 min. Epoxide **4** (2.1 mL, 30 mmol) in dry THF was added dropwise over 10 min. It was stirred at −40 °C for 1 h, then warmed to room temperature over 2 h. The mixture was quenched by saturated aqueous NH_4Cl and extracted by ether, washed with water and brine, dried over Na_2SO_4, and then ether evaporated below 10 °C to give the (*S*)-5-heptene-2-ol as colorless oil, which was used directly in the next step.

Sodium hydride (60% dispersion in mineral oil, 2.43 g, 60.93 mmol) was washed three times with hexanes, dried under a stream of argon, suspended in 20 mL of THF, and cooled to 0 °C. (*S*)-5-Heptene-2-ol in 10 mL of THF was added dropwise via an addition funnel to the reaction flask. The reaction mixture was allowed to stir at 0 °C for 1 h before *p*-methoxybenzylchloride (4.1 mL, 30.5 mmol) was added dropwise. The reaction mixture was then refluxed for 6 h. The reaction mixture was quenched with saturated NH_4Cl, extracted three times with ethyl acetate, and dried over Na_2SO_4. Concentration in vacuo and purification by flash column chromatography (hexane/EtOAc = 50/1) gave 5.6 g (85% yield) of protected *p*-methoxybenzyl ether **7**. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.28$ (d, $J = 12$ Hz, 2H), 6.89 (d, $J = 12$ Hz, 2H), 5.76–5.87 (m, 1H), 4.94–5.06 (m, 2H), 4.52 (d, $J = 11.4$ Hz, 1H), 4.39 (d, $J = 11.4$ Hz, 1H), 3.81 (s, 3H), 3.49–3.56 (m, 1H), 2.10–2.21 (m, 2H), 1.48–1.58 (m, 1H), 1.64–1.74 (m, 1H), 1.19–1.21 (d, $J = 6$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 138.7$, 131.1, 129.3, 129.2, 114.4, 113.7,73.9, 70.0, 55.2, 35.9, 29.8, 19.6; $[\alpha]_D = +22$ (*c* 2.0, $CHCl_3$).

4.3. Diol 8

A mixture of AD-mix-β (6.5 g) in *t*-BuOH/H_2O = 25 mL/25 mL was stirred at room temperature for 15 min and then cooled to 0 °C. To this solution was added the above compound **7** (1.1 g, 5 mmol). The reaction mixture was stirred at 0 °C for 2 days and then quenched with saturated aqueous Na_2SO_3 at 0 °C for 0.5 h. Next EtOAc was added to the reaction mixture, and after separation of the layers, the aqueous layer was further extracted with EtOAc twice. The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. Purification by flash column chromatography (EtOAc/hexane = 1/1) afforded the corresponding diol **8** (1.1 g, 87% yield) as a clear oil. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.26$ (d, $J = 12$ Hz, 2H), 6.88 (d, $J = 12$ Hz, 2H), 4.54 (d, $J = 11.4$ Hz, 1H), 4.35 (d,

$J = 11.4$ Hz, 1H), 3.81 (s, 3H), 3.60 (m, 1H), 3.51–3.60 (m, 2H), 3.37–3.42 (m, 1H), 3.18 (b, 1 H), 2,29 (b, 1H), 1.48–1.57 (m, 2H), 1.61–1.68 (m, 2H), 1.20–1.22 (d, $J = 6$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 159.1$, 130.4, 129.4, 113.7, 74.5, 72.1, 70.0, 66.7, 55.2, 32.7, 29.1, 19.3; $[\alpha]_D = +28$ (c 2.3, $CHCl_3$).

4.4. Epoxide 9

Sodium hydride (60% oil dispersion) (70 mg, 1.6 mmol) was suspended in 8 mL of THF, and cooled to 0 °C. Diol **8** (102 mg, 0.4 mmol) in 2 mL of THF was added dropwise via an addition funnel to the reaction flask. The reaction mixture was allowed to stir at 0 °C for 1 h. *N*-Tosylimidazole (110 mg, 0.48 mmol) was then added and the suspension was stirred overnight at room temperature. The reaction was quenched with saturated NH_4Cl, extracted three times with ethyl acetate, and dried over Na_2SO_4. Concentration in vacuo and purification by flash column chromatography (10% ethyl acetate in hexane) gave 78 mg (83%) of epoxide **9** as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.26$ (d, $J = 11.7$ Hz, 2H), 6.86 (d, $J = 11.7$ Hz, 2H), 4.52 (d, $J = 11.1$ Hz, 1H), 4.37 (d, $J = 11.7$ Hz, 1H), 3.79 (s, 3H), 3.52–3.57 (m, 1H), 2.88–2.92 (m, 1H), 2.71–2.74 (m, 1H), 2.43–2.47 (m, 1H), 1.55–1.73 (m, 4H), 1.18–1.20 (d, $J = 6$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 159.0$, 130.9, 129.1, 113.7, 73.6, 69.8, 55.2, 52.1, 47.0, 32.5, 28.2, 19.4; $[\alpha]_D = +21$ (c 2.5, $CHCl_3$).

4.5. Allylic alcohol 10

To a −20 °C suspension of trimethylsulfonium iodide (755 mg, 3.7 mmol) in anhydrous tetrahydrofuran (15 mL) was added a solution of *n*-BuLi (1.9 M in *n*-hexane, 1.6 mL, 2.96 mmol). After the addition of *n*-BuLi was complete, the resulting solution was stirred at −20 °C for 45 min. Epoxide **9** (174 mg, 0.74 mmol) in 2 mL of THF was then introduced. The suspension was stirred for 30 min at −20 °C and 4 h at room temperature, after which it was quenched with water and diluted with ethyl acetate. The organic layer was separated and the aqueous layer was extracted with ethyl acetate three times. The combined organic fractions were washed with water and dried over Na_2SO_4. After removing the solvent, the crude oil was purified by flash column chromatography (15% ethyl acetate in hexane) to afford the allylic alcohol **10** (157 mg, 85%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.26$ (d, $J = 12$ Hz, 2H), 6.87 (d, $J = 12$ Hz, 2H), 5.79–5.90 (m, 1H), 5.20 (d, $J = 18$ Hz, 1H), 5.08 (d, $J = 12$ Hz, 1H), 4.51 (d, $J = 11.1$ Hz, 1H), 4.37 (d, $J = 11.1$ Hz, 1H), 4.06 (b, 1H), 3.79 (s, 3H), 3.50–3.56 (m, 1H), 2.39 (b, 1H), 1.54–1.68 (m, 4H), 1.18–1.20 (d, $J = 6$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 159.2$, 141.2, 130.7, 129.3, 114.4, 113.7, 74.2, 72.9, 69.9, 55.2, 32.9, 32.3, 19.4; $[\alpha]_D = +15$ (c 2.1, $CHCl_3$).

4.6. MOM ether 11

To a solution of alcohol **10** (36 mg, 0.15 mmol) in dry DCM (3 mL) at room temperature, Hunig's base (0.54 mL, 3 mmol), MOMCl (0.07 mL, 0.8 mmol), and a catalytic amount of NaI were added. After stirring for 7 h at reflux, water was added. The organic layer was separated and the aqueous layer was extracted twice with DCM. The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated in vacuo. Purification by flash column chromatography gave ether **11** (43 mg, 98% yield) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.26$ (d, $J = 12$ Hz, 2H), 6.87 (d, $J = 12$ Hz, 2H), 5.60–5.72 (m, 1H), 5.19 (d, $J = 15.3$ Hz, 1H), 5.18 (d, $J = 11.7$ Hz, 1H), 4.69 (d, $J = 7.2$ Hz, 1H), 4.53 (d, $J = 7.2$ Hz, 1H), 4.49 (d, $J = 11.7$ Hz, 1H), 4.38 (d, $J = 11.1$ Hz, 1H), 3.93–3.99 (m, 1H), 3.72 (s, 3H), 3.47–3.55 (m, 1H), 3.39 (s, 3H), 1.45–1.79 (m, 4H), 1.17–1.19 (d, $J = 6$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 159.0$, 138.3, 131.1, 129.1, 117.2, 113.7, 93.7, 76.6, 74.1, 69.9, 55.4, 55.2, 32.1, 31.1, 19.5; $[\alpha]_D = +37$ (c 0.55, $CHCl_3$).

4.7. Alcohol 2

To a stirred biphasic solution of ether **11** (154 mg, 0.52 mmol) in CH_2Cl_2 (20 mL) and pH 7 Buffer (0.8 mL) at 0 °C was added DDQ (131 mg, 0.58 mmol) and the reaction mixture was allowed to warm to 20 °C. The reaction mixture was stirred for 1 h and the layers were then separated. The aqueous layer was extracted with DCM (3×10 mL) and the combined organic extracts were dried over Na_2SO_4, filtered through a plug of silica with EtOAc, and concentrated in vacuo. Purification by flash column chromatography gave ether **2** (88 mg, 98% yield) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 5.62$–5.73 (m, 1H), 5.21 (d, $J = 17.1$ Hz, 1H), 5.2 (d, $J = 9.9$ Hz, 1H), 4.71 (d, $J = 6.6$ Hz, 1H), 4.54 (d, $J = 7.2$ Hz, 1H), 4.15 (m, 1H), 3.83 (m, 1H), 3.38 (s, 3H), 1.79 (b, 1H), 1.51–1.74 (m, 4H), 1.19–1.21 (d, $J = 6$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 138.0$, 117.5, 93.7, 76.6, 67.9, 55.6, 34.9, 31.6, 23.5; $[\alpha]_D = +13$ (c 0.3, $CHCl_3$); HRMS: m/z $[M+Na]^+$ calcd: 197.1148; found: 197.1143.

4.8. Amide 12

To a dry round-bottomed flask under argon was added 2.32 g (8.76 mmol) of the *N*-acyloxazolidone **5** and 90 mL of DCM. After cooling to −78 °C, $TiCl_4$ (1.01 mL, 9.2 mmol) was added dropwise and the solution was allowed to stir for 15 min. Diisopropylethylamine (3.84 mL, 21.9 mmol) was added dropwise to the mixture and the solution was allowed to stir for 2 h. 1-Methyl-2-pyrrolidinone (0.85 mL, 8.8 mmol) was added at −78 °C and the mixture was stirred for an additional 10 min. Freshly distilled acrolein (2.4 mL, 36 mmol) was then added directly to the enolate. The reaction mixture was allowed to stir for 3 h at −78 °C and then warmed to −40 °C for 2 h followed by the addition of half-satd NH_4Cl. The organic layer was separated and the aqueous layer extracted twice with DCM. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated. The initial product mixture was analyzed by purification by flash column chromatography. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.23$–7.35 (m, 5H), 5.81–5.93 (m, 1H), 5.38–5.45 (d, $J = 19$ Hz, 1H), 5.21–5.55 (d, $J = 11.7$ Hz, 1H), 4.77 (d, $J = 8.1$ Hz, 1H), 4.66–4.73 (m, 1H), 4.52 (t, $J = 7.5$ Hz, 1H), 4.18 (d,

$J = 6.6$ Hz, 2H), 3.25 (dd, $J = 9.6$ Hz, 13.5 Hz, 1H), 3.11 (b, 1H), 2.55 (dd, $J = 9.3$ Hz, 13.5 Hz, 1H), 2.20 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 169.1$, 152.7, 136.3, 134.8, 129.4, 128.9, 127.3, 118.2, 69.5, 65.9, 54.9, 50.0, 37.5, 12.7; $[\alpha]_D = +44.6$ (c 6.95, $CHCl_3$).

To a solution of the above-mentioned alcohol product in DMF (18 mL) were added imidazole (1.23 g, 18 mmol) and TBSCl (1.6 g, 10.5 mmol). After stirring for 17 h at rt, EtOAc was added and the mixture washed with water twice. The organics were dried over Na_2SO_4, filtered, and concentrated in vacuo. Purification by flash column chromatography gave the protected alcohol **12** in 74% yield (2 steps). ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.24$–7.34 (m, 5H), 5.85–5.96 (m, 1H), 5.26 (d, $J = 17.1$ Hz, 1H), 5.15 (d, $J = 10.8$ Hz, 1H), 4.90 (d, $J = 9$ Hz, 1H), 4.62–4.70 (m, 1H), 4.49 (t, $J = 8.4$ Hz, 15.9 Hz, 1H), 4.14 (d, $J = 6$ Hz, 2H), 3.27 (dd, $J = 3.6$ Hz, 12.9 Hz, 1H), 2.79 (dd, $J = 9.3$ Hz, 13.5 Hz, 1H), 2.24 (s, 3H), 0.90 (s, 9H), 0.06 (s, 3H), 0.09 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 169.7$, 152.9, 138.4, 135.1, 129.5, 128.9, 127.3, 117.4, 73.8, 65.8, 55.2, 37.6, 25.8, 25.6, 18.2, 14.8, −4.34, −4.86; $[\alpha]_D = +28.6$ (c 3.45, $CHCl_3$); HRMS: m/z $[M+Na]^+$ calcd: 458.1792; found: 458.1785.

4.9. Compound 13

First n-Bu_3SnH (8.4 mL, 31 mmol) and AIBN (120 mg, 0.7 mmol) were added to the solution of **12** (2.7 g, 6.2 mmol) in anhydrous benzene (30 mL) under Ar. The solution was then warmed to 80 °C and stirred for 1 h. The mixture was allowed to cool to rt, and the solvent was evaporated in vacuo. Flash column chromatography on silica gel afforded **13** (2.18 g, 90%). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.30$–7.34 (m, 2H), 7.25–7.28 (m, 1H), 7.20 (d, $J = 7.2$ Hz, 2H), 5.85–5.94 (m, 1H), 5.25 (d, $J = 16$ Hz, 1H), 5.09 (d, $J = 9.2$ Hz, 1H), 4.71–4.73 (m, 1H), 4.63–4.67 (m, 1H), 4.14–4.16 (m, 2H), 3.23–3.30 (m, 2H), 3.07 (dd, $J = 5.2$ Hz, 16 Hz, 1H), 2.74 (dd, $J = 10$ Hz, 13.2 Hz, 1H), 0.89 (s, 9H), 0.09 (s, 3H), 0.07 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 170.3$, 153.3, 140.4, 135.2, 129.4, 128.9, 127.3, 114.7, 70.1, 66.0, 55.1, 44.1, 37.8, 27.0, 18.1, −4.48, −4.97; $[\alpha]_D = +27.8$ (c 6.42, $CHCl_3$); HRMS: m/z $[M+Na]^+$ calcd: 412.1915; found: 412.1920.

4.10. Acid 3

A solution of 2 g (5.1 mmol) **13** in 60 mL of THF and 20 mL of water, stirred at 0 °C under Ar, was treated with 2.7 g (21 mmol) of 30% H_2O_2 followed by 330 mg (7.7 mmol, 2.0 equiv) of LiOH–H_2O. The resulting mixture was stirred at 0 °C for 20 min, and treated with 2.7 g (40.8 mmol, 10 equiv) of Na_2SO_3. After most of the THF was evaporated in vacuo, the mixture was acidified to pH 4 with 1 M HCl and extracted with four 75 mL portions of DCM. The extracts were combined, dried over Na_2SO_4, and evaporated in vacuo. The residue was purified by flash column chromatography on silica gel (hexane/EtOAc/AcOH, 40:10:1) to afford acid **3** (1.1 g, 94%), which was used directly in the next reaction.

4.11. Ester 14

At room temperature, to a solution of 35 mg (0.2 mmol) of **2** and 60 mg (0.22 mmol) of triphenylphosphine in 1 mL of benzene was added a solution of 45 mg (0.22 mmol) of DIAD and 92 mg (0.4 mmol) of acid **3** in 2 mL of benzene over 5 min. The reaction mixture was stirred overnight, then quenched with 5 mL of H_2O. This mixture was extracted with 10 mL of $CHCl_3$ three times, washed with 5.0 mL of brine, dried over Na_2SO_4, filtered, and concentrated. Chromatography (5% EtOAc/hexane) provided 67 mg of **14** (87% yield). ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 5.76$–5.88 (m, 1H), 5.57–5.69 (m, 1H), 5.15–5.23 (m, 3H), 5.04 (d, $J = 12$ Hz, 1H), 4.85–4.90 (m, 1H), 4.68 (d, $J = 6.9$ Hz, 1H), 4.54–4.58 (m, 1H), 4.51 (d, $J = 6.6$ Hz, 1H), 3.91–3.97 (m, 1H), 3.35 (s, 3H), 2.45 (dd, $J = 7.8$ Hz, 14.7 Hz, 1H), 2.39 (dd, $J = 5.1$ Hz, 14.4 Hz, 1H), 1.51–1.67 (m, 4H), 1.19–1.21 (d, $J = 6$ Hz, 3H), 0.89 (s, 9H), 0.01 (d, $J = 10.5$ Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 170.6$, 140.3, 132.0, 117.5, 114.6, 93.7, 77.1, 71.0, 70.7, 55.4, 43.8, 31.8, 31.3, 25.7, 19.9, 18.1, −4.44, −5.02; $[\alpha]_D = +39.6$ (c 4, $CHCl_3$); HRMS: m/z $[M+Na]^+$ calcd: 409.2381; found: 409.2375.

4.12. Compound 15

HF/pyridine (20% solution purchased from Acros, 0.5 mL) was added to a 0 °C solution of ester **14** (42 mg, 0.11 mmol) in 2 mL of THF in a plastic vial. The reaction mixture was allowed to warm to room temperature and stirred for 48 h. The reaction mixture was carefully quenched by the addition of saturated $NaHCO_3$ at 0 °C. The mixture was extracted three times with EtOAc, and the combined organic layers were washed with a cold solution of 1 M $NaHSO_4$ and dried over Na_2SO_4. Concentration in vacuo and purification by flash column chromatography gave 23.7 mg (79%) of alcohol **15** and 7 mg (17%) of ester **14**. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 5.84$–5.93 (m, 1H), 5.61–5.70 (m, 1H), 5.32 (d, $J = 17.2$ Hz, 1H), 5.14–5.24 (m, 3H),4.96–5.00 (m, 1H), 4.70 (d, $J = 6.8$ Hz, 1H), 4.53 (d, $J = 6.8$ Hz, 1H), 4.52–4.57 (m, 1H), 3.97–4.00 (m, 1H), 3.37 (s, 3H), 3.04 (d, $J = 5.6$ Hz, 1H), 2.48–2.60 (m, 2H), 1.52–1.68 (m, 4H), 1.24–1.28 (d, $J = 6$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 172.2$, 139.0, 138.1, 118.0, 115.6, 93.9, 75.2, 71.7, 69.2, 55.7, 41.6, 31.9, 31.4, 20.3; $[\alpha]_D = +42$ (c 1.9, $CHCl_3$); HRMS: m/z $[M+Na]^+$ calcd: 295.1516; found: 295.1513.

4.13. Compound 16

To a solution of Grubbs' second generation catalyst (13 mg, 0.015 mmol) in 160 mL of anhydrous DCM under Ar at reflux was added 42 mg of **15** in 20 mL of anhydrous DCM during 10 min and the mixture was stirred at reflux for 24 h. After that, DCM was removed under vacuo and the residue was purified by flash column chromatography on silica gel to afford **16** (14 mg, 50%), and 7.6 mg (18%) of starting material **15**. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 5.76$ (dd, $J = 2.8$ Hz and 16 Hz, 1H), 5.55 (dd, $J = 9.6$ Hz and 16 Hz, 1H), 4.91–4.95 (m, 1H), 4.67–4.70 (m, 2H), 4.50 (d, $J = 6.8$ Hz, 1H), 4.14 (m, 1H), 3.34 (s, 3H), 2.59–2.63 (m, 2H), 2.50–2.55 (m, 1H), 1.57–1.93 (m,

4H), 1.18 (d, $J = 6.4$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 170.5$, 135.0, 128.7, 93.5, 72.9, 69.7, 67.6, 55.3, 44.2, 34.4, 31.3, 21.6; $[\alpha]_D = +39$ (*c* 0.61, $CHCl_3$). HRMS: *m*/*z* $[M+Na]^+$ calcd: 267.1203; found: 267.1201.

4.14. Compound 1

To a solution of **16** (10 mg, 0.04 mmol) in 2.5 mL of MeOH and 0.5 mL of water was added 30 mg of Dowex-50W-X8, which was treated according to the method reported.[16] After the reaction mixture was refluxed for 5 h, the resin was removed by filtration and washed with MeOH. The solvent was evaporated, and the residual material was chromatographed (hexane/EtOAc = 1/2) to give compound **1** as a white solid (69% yield). ^{1}H NMR (400 MHz, CD_3OD): $\delta = 5.76$ (dd, $J = 2.4$ Hz and 15.6 Hz, 1H), 5.64 (dd, $J = 8$ Hz and 15.6 Hz, 1H), 4.76–4.80 (m, 1H), 4.63–4.64 (m, 1H), 4.09–4.14 (m, 1H), 2.54 (dd, $J = 3.6$ Hz and 11.6 Hz, 1H), 2.49 (dd, $J = 3.6$ Hz and 12 Hz, 1H), 1.93–1.98 (m, 1H), 1.75–1.80 (m, 1H), 1.58–1.68 (m, 2H), 1.16 (d, $J = 6.8$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 170.4$, 133.2, 130.5, 74.4, 73.0, 67.0, 44.2, 37.2, 31.4, 20.8; $[\alpha]_D = -51$ (*c* 0.3, MeOH). HRMS: *m*/*z* $[M+Na]^+$ calcd: 223.0941; found: 223.0943.

4.15. Diene 17a

To a solution of known diol **17c**[4] (38 mg, 0.17 mmol) in DMF (3 mL) were added imidazole (116 mg, 1.7 mmol) and TBSCl (103 mg, 0.68 mmol). After stirring overnight at rt, EtOAc was added and the mixture was washed with water twice. The organic was dried over Na_2SO_4, filtered and concentrated in vacuo. Purification by flash column chromatography gave protected diene **17a** (70 mg) as a colorless oil in 90% yield. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 5.70$–5.89 (m, 2H), 5.01–5.24 (m, 4H), 4.83–4.89 (m, 1H), 4.53–4.60 (m, 1H), 4.07–4.09 (m, 1H), 2.51 (dd, $J = 7.5$ Hz, 14.4 Hz, 1H), 2.40 (dd, $J = 6.3$ Hz, 14.7 Hz, 1H), 1.41–1.59 (m, 4H), 1.20 (d, $J = 6$ Hz, 3H), 0.81–0.84 (m, 18H), 0.02–0.05 (m, 12H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 170.6$, 141.3, 140.3, 114.6, 113.9, 73.5, 71.2, 70.7, 43.9, 33.7, 31.4, 27.4, 25.8, 20.0, 18.2, 13.7, −4.4, −4.9; $[\alpha]_D = -4$ (*c* 2.2, $CHCl_3$); HRMS: *m*/*z* $[M+Na]^+$ calcd: 479.2983; found: 479.2985.

4.16. Diene 17b

To a solution of alcohol **15** (55 mg, 0.2 mmol) in dry DCM (5 mL) at room temperature, Hunig's base (0.23 mL, 1.2 mmol), MOMCl (0.09 mL, 1 mmol), and a catalytic amount of NaI were added. After stirring for 8 h at rt, water was added. The organic layer was separated and the aqueous layer was extracted twice with DCM. The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated in vacuo. Purification by flash column chromatography gave ether **17b** (60 mg, 97% yield) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 5.56$–5.76 (m, 2H), 5.15–5.31 (m, 4H), 4.89–4.95 (m, 1H), 4.67 (d, $J = 6.9$ Hz, 2H), 4.52 (d, $J = 6.9$ Hz, 2H), 4.42–4.49 (m, 1H), 3.93–3.97 (m, 1H), 3.33 (s, 3H), 3.32 (s, 3H), 2.59 (dd, $J = 9.6$ Hz, 15 Hz, 1H), 2.45 (dd, $J = 5.4$ Hz, 15 Hz, 1H), 1.53–1.64 (m, 4H), 1.23 (d, $J = 6$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 170.2$, 138.0, 136.7, 118.1, 117.5, 93.9, 93.6, 76.8, 73.8, 71.1, 55.5, 55.4, 41.1, 31.7, 31.2, 19.9; $[\alpha]_D = -3$ (*c* 2, $CHCl_3$); HRMS: *m*/*z* $[M+Na]^+$ calcd: 339.1779; found: 339.1782.

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References

1. (a) Kittakoop, P.; Punya, J.; Kongsaeree, P.; Lertwerawat, Y.; Jintasirikul, A.; Tanticharoen, M.; Thebtaranonth, Y. *Phytochemistry* **1999**, *52*, 453–457; (b) Isaka, M.; Tanticharoen, M.; Kongsaree, P.; Thebtaranonth, Y. *J. Org. Chem.* **2001**, *66*, 4803–4808; (c) Bok, J. W.; Lermer, L.; Chilton, J.; Klingeman, H. G.; Towers, G. H. N. *Phytochemistry* **1999**, *51*, 891–898.
2. (a) Huang, L. F.; Liang, Y. Z.; Guo, F. Q.; Zhou, Z. F.; Chang, B. M. *J. Pharm. Biomed. Anal.* **2003**, *33*, 1155–1162; (b) Weng, S. C.; Chou, C. J.; Lin, L. C.; Tsai, W. J.; Kuo, Y. C. *J. Ethnopharmacol.* **2002**, *83*, 79–85.
3. Rukachaisirikul, V.; Pramjit, S.; Pakawatchai, C.; Isaka, M.; Supothina, S. *J. Nat. Prod.* **2004**, *67*, 1953–1955.
4. Mohapatra, D. K.; Ramesh, D. K.; Giardello, M. A.; Chorghade, M. S.; Gurjara, M. K.; Grubbs, R. H. *Tetrahedron Lett.* **2007**, *48*, 2621–2625.
5. (a) Lu, J.; Xie, X.; Chen, B.; She, X.; Pan, X. *Tetrahedron: Asymmetry* **2006**, *17*, 1066–1073; (b) Liang, Q.; Zhang, J.; Quan, W.; Sun, Y.; She, X.; Pan, X. *J. Org. Chem.* **2007**, *72*, 2694–2697.
6. (a) Rousseau, G. *Tetrahedron* **1995**, *51*, 2777–2849; (b) Ferraz, M. C.; Bombonato, F. I.; Longo, L. S., Jr. *Synthesis* **2007**, *3261–3430*.
7. For review of RCM, see (a) Nicolaou, K. C.; Bulger, P. G.; Sarlah, D. *Angew. Chem., Int. Ed.* **2005**, *44*, 4490–4527; (b) Deiters, A.; Martin, S. F. *Chem. Rev.* **2004**, *104*, 2199–2238.
8. (a) Mitsunobu, O. *Synthesis* **1981**, 1–28; (b) Hanessian, S.; Sahoo, S. P.; Botta, M. *Tetrahedron Lett.* **1987**, *28*, 1143–1146.
9. (a) Xu, D.; Crispino, G. A.; Sharpless, K. B. *J. Am. Chem. Soc.* **1992**, *114*, 7570–7571; (b) Becker, H.; Soler, M. A.; Sharpless, K. B. *Tetrahedron* **1995**, *51*, 1345–1376.
10. Hicks, D. R.; Fraser-Reid, B. *Synthesis* **1974**, 203.
11. Alcaraz, L.; Harnett, J. J.; Mioskowski, C.; Martel, J. P.; Le Gall, T.; Shin, D. S.; Falck, J. R. *Tetrahedron Lett.* **1994**, *35*, 5449–5452.
12. Crimmins, M. T.; She, J. *Synlett* **2004**, 1371–1374.
13. (a) Evans, D. A.; Nelson, J. V.; Vogel, E.; Taber, T. R. *J. Am. Chem. Soc.* **1981**, *103*, 3099–3111; (b) Evans, D. A.; Takacs, J. M.; McGee, L. R.; Ennis, M. D.; Mathre, D. J.; Bartroli, J. *Pure Appl. Chem.* **1981**, *53*, 1109–1127.
14. Boger, D. L.; Honda, T.; Menezes, R. F.; Colletti, S. L.; Dang, Q.; Yang, W. *J. Am. Chem. Soc.* **1994**, *116*, 82–92.
15. (a) Evans, D. A.; Britton, T. C.; Ellman, J. A. *Tetrahedron Lett.* **1987**, *28*, 6141–6144; (b) Evans, D. A.; Chapman, K. T.; Bisaha, J. *J. Am. Chem. Soc.* **1988**, *110*, 1238–1256.
16. Seto, H.; Mander, L. N. *Synth. Commun.* **1992**, *22*, 2823–2828.