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First total syntheses of bicyclic marine sesquiterpenoids drechslerines A and B

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ABSTRACT

The first total syntheses of the bicyclic sesquiterpenoids drechslerines A (**1**) and B (**2**), which were isolated from the algicolous fungus *Drechslera dematioidea* in the marine red alga *Liagora viscida*, has been accomplished starting from (*S*)-carvone (**13**) via three palladium-catalyzed reactions, namely, diastereoselective allylation, conjugate reduction, and carbon monoxide insertion, as the key reactions.

1. Introduction

Marine organisms produce a large number of structurally interesting and biologically unique natural products.[1] Several polycyclic sesquiterpenoids were recently isolated from the algicolous fungus *Drechslera dematioidea* of leaf mold of the red algae *Liagora viscida*.[2] Among them were nor-sesquiterpenoids drechslerines A (**1**) and C (**3**), and sesquiterpenoids drechslerines B (**2**), D (**4**), E (**5**), F (**6**), and G (**7**). These compounds have the same carbon framework as helminthosporal (**8**) isolated from the terrestrial fungus, having a unique bicyclo[3.2.1]octane framework with an isopropyl group in common. However, the absolute stereochemistries of drechslerines have not been fully discussed.[2] Synthetic studies of sesquiterpenoids with the bicyclo[3.2.1]octane core have already been conducted: first, in the total synthesis of helminthosporal (**8**)[3] by Corey and Nozoe in 1965,[3a] and subsequently by other groups in the total synthesis of sativene (**9**),[4] which has an antipodal core of helminthosporal (**8**). Since then, synthetic studies in this area have been interrupted over two decades because new natural products have not been isolated. In the course of our synthetic study of bridged carbocyclic compounds,[4f,5] we re-visited the synthesis of the functionalized bicyclo[3.2.1]octane core and describe here the first total syntheses of drechslerines A (**1**) and B (**2**), thereby establishing their absolute stereochemistries.

2. Results and discussions

2.1. Synthesis of common intermediate 10

The retrosynthetic plan is outlined in Scheme 1. Enol triflate **10** was envisaged as an advanced common intermediate in the syntheses of drechslerines A (**1**) and B (**2**) by palladium-catalyzed conjugate reduction, and carbon monoxide insertion, respectively, which could be derived from bicyclic keto alcohol **11** via Wittig olefination. The keto alcohol **11** in turn could be obtained by regio- and diastereo-controlled allylation of optically active (*S*)-carvone (**13**), followed by an intramolecular aldol reaction. Carvone (**13**) is a classic but still useful chiral building block in the total synthesis of natural products.

The (*S*)-enantiomer of carvone (**13**) was chosen as the starting material. Reduction of the enone moiety of **13** with zinc in potassium hydroxide solution[6] and subsequent reduction of the isopropenyl group with platinum under hydrogen atmosphere led to tetrahydrocarvone (**14**) in 75% overall yield, although laborious workup to remove zinc circumvented large-scale preparation. On the other hand, hydrogenation of **13** with palladium on carbon resulted in partial isomerization to carvacrol along with partial epimerization of the isopropyl group, which was identified later by (*S*)-MTPA ester **23** (Fig. 2). These features made the hydrogenation protocols less attractive. Fortunately, the hydrogenation issue was solved by catalytic medium-pressure hydrogenation with rhodium on alumina to afford a diastereomeric mixture of tetrahydrocarvone (**14**) in 96%

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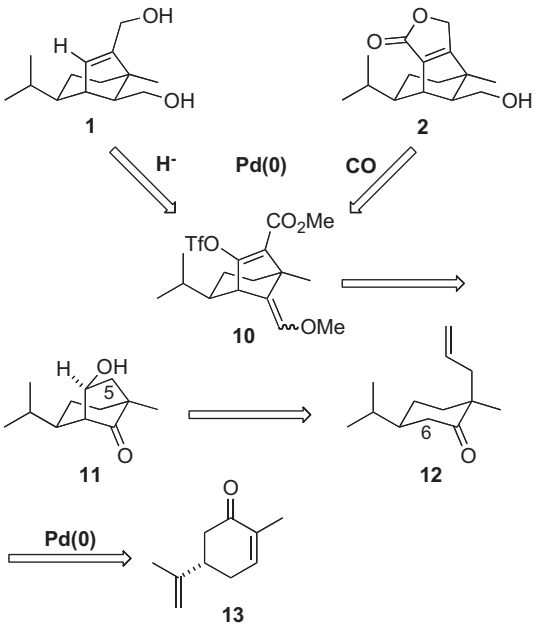


Scheme 1. Synthetic plan of drechslerines A (**1**) and B (**2**).

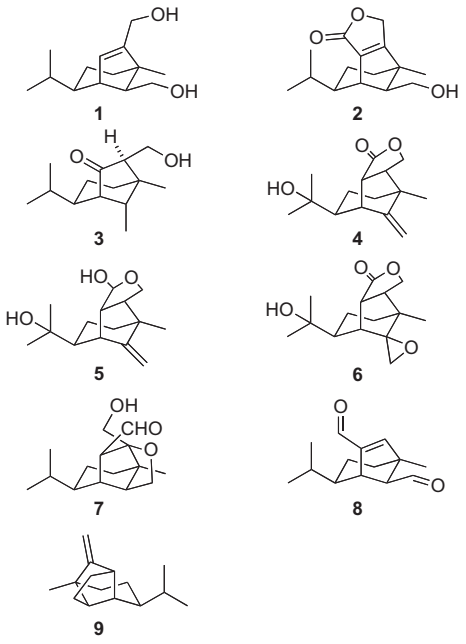


Fig. 1. Drechslerines A (**1**) and B (**2**) and their congeners.

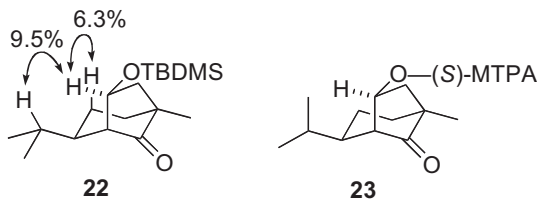
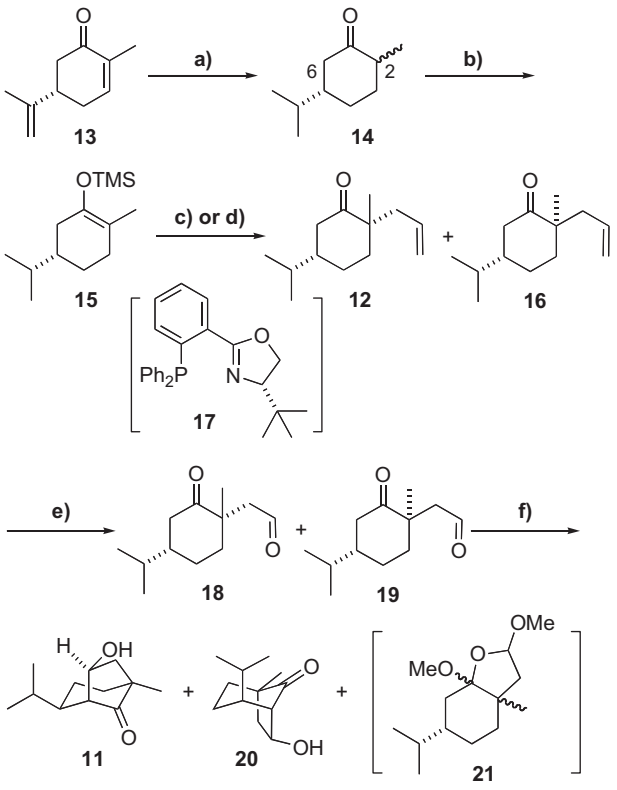


Fig. 2. Determination of the relative stereochemistry and enantiomeric excess of the intramolecular aldol product **11**.

yield. Moreover, the catalyst could be re-used without loss of catalytic activity (Scheme 2).

The control of regio- and diastereoselectivity in the alkylation of a monocyclic carbonyl compound is not an easy task due to



Scheme 2. Reagents and conditions: (a) H_2 (4 MPa), Rh/Al_2O_3 (0.1 mol %), EtOH, rt, 3.5 h, 96%. (b) TMSCl, NaI, Et_3N, MeCN, rt, 4 h, 99%. (c) MeLi, DME, −40 °C then allyliodide, THF, −50 °C, 22 h, 97% (**12**/**16**=3.4:1). (d) TBAT, $Pd_2(dba)_3$, **17**, THF, allyl carbonate, 78%, (**12**/**16**=55:1). (e) O_3, CH_2Cl_2, then Et_3N, −78 °C, 3 h, quant. (f) KOH, EtOH, 50 °C, 13 h, 80%, recrystallization.

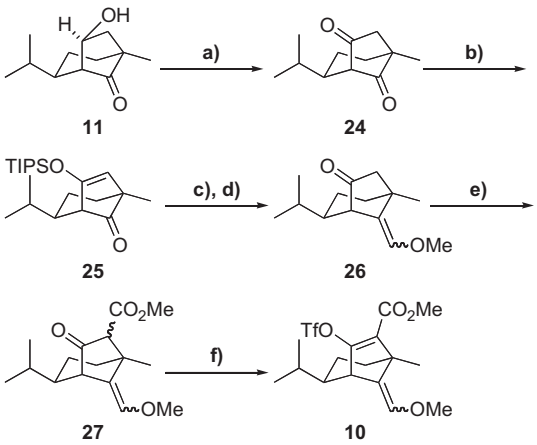
flexibility and the lack of steric constraints in a monocyclic ring. In the total synthesis of helminthosporal (**8**) by Corey and Nozoe,[3a] the stereoselectivity in the introduction of the side chain at C-2 of the tetrahydrocarvone derivative was 60% de. Although Mori et al. in their synthesis of (+)-sorokinianin already reported the synthesis of the 5-hydroxy isomer of **11** by allylation at C-6 of tetrahydrocarvone (**14**) followed by ozonolysis and intramolecular aldol reaction, an undesired diastereomer also appeared in 26% yield, even under thermodynamically forced reaction conditions.[7] On the basis of these results, we anticipated that the allyl group could be initially introduced to the thermodynamically stable enolate of tetrahydrocarvone **14** from the same side of the isopropyl group by kinetically controlled axial alkylation. Then, thermodynamically stable tetrasubstituted silylenol ether **15** was prepared quantitatively by treatment with chlorotrimethylsilane in the presence of sodium iodide and triethylamine. Silylenol ether **15** was cleaved with methyllithium in dimethoxymethane (DME) at −40 °C to give the regioselective enolate. After fine tuning a variety of reaction conditions, the chemical yield and diastereoselectivity of allylation was optimized when allyliodide was employed and the reaction mixture was allowed to stand at −50 °C for 22 h. Fortunately, the desired 2*S*-isomer **12** predominated in 78% de as an inseparable mixture with 2*R*-isomer **16**, in which the ratio of diastereomers was estimated by the tertiary methyl peaks in NMR. The stereochemistry of the major 2*S*-isomer **12** was determined by NOE measurement of silyl ether **22** after several subsequent transformations (Fig. 2). A reversal of diastereoselectivity was observed when hexamethylphosphoric triamide was added. Allylation proceeded very slowly in diethyl ether.

The issue regarding diastereoselective allylation was solved via palladium-catalyzed diastereoselective Tsuji allylation developed by Behenna and Stoltz.[8] In the presence of a catalytic amount of

bispalladium tris(benzylidene)acetone $Pd_2(dba)_3$, chiral ligand (*S*)-*tert*-ButylPHOX **17**, and tetrabutylammonium difluorotriphenylsilicate (TBAT), allylation of the silylenol ether **15** with allyl carbonate proceeded under mild reaction conditions to give 2*R*-isomer **12** and 2*S*-isomer **16** in 78% yield with 98% diastereoselectivity in favor of the desired 2*R*-**12**.

Ozonolysis of the double bond of **12** and **16** was effected by adding triethylamine to decompose ozonide.[9] Without purification of unstable aldehydes **18** and **19**, an intramolecular aldol reaction with potassium hydroxide in ethanol at 50 °C afforded bicyclic hydroxyketones **11** and **20** in 80% yield. In contrast, the aldol reaction in methanol led to acetal **21**, which regenerated keto aldehydes **18** and **19** by acid-catalyzed hydrolysis. The desired hydroxy ketone **11** was separated by recrystallization from the diastereomer **20**, in which the relative stereochemistry of the hydroxyl group of **11** was established (Fig. 2) by NOE measurement of ether **22**. The keto alcohol **11** was enantiomerically pure as evaluated by the NMR spectrum of (*S*)-MTPA ester **23**.

With key keto alcohol **11** in hand, we investigated its transformation into an advanced common intermediate (Scheme 3). Jones oxidation of keto alcohol **11** provided 1,3-dicarbonyl compound **24** in 95% yield, in which the carbonyl group at C-6 of the diketone **24** was protected for the next transformation with sodium bistrimethysilylamide (NaHMDS) and triisopropylsilylchloride as triisopropylsilylenol ether **25** in 98% yield.

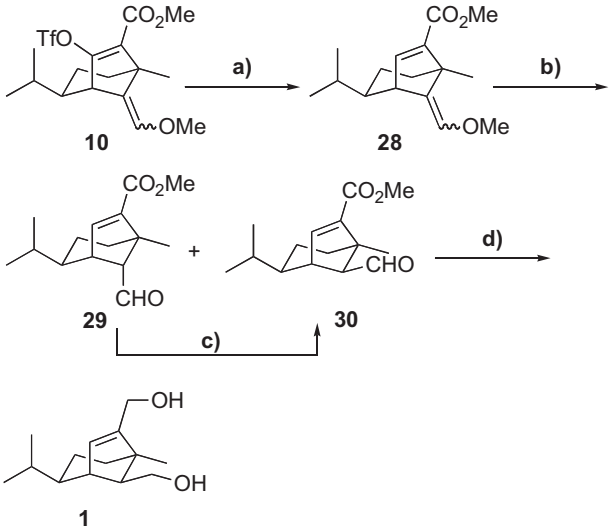


Scheme 3. Reagents and conditions: (a) Jones reagent, acetone, rt, 15 min, 95%. (b) TIPSCl, NaHMDS, THF, −78 °C, 1.5 h, 98%. (c) $Ph_3PCH_2(OMe)$ Cl, *n*-BuLi, THF, 60 °C, 4 h. (d) TBAF, THF, 0 °C, 1 h, 73% in two steps. (e) NaHMDS, $CNCO_2Me$, THF, −78 °C, 30 min, 87%. (f) NaHMDS, Tf_2O, Et_2O, −78 °C, 1.5 h, 94%.

Wittig methoxymethylenation of the remaining carbonyl group at C-8 gave methyl enol ether, which was subsequently deprotected by treatment with tetrabutylammonium fluoride to give ketone **26** in 73% yield in two steps. Methoxycarbonylation of **26** with methyl cyanoformate[10] selectively afforded *C*-acylated product **27** in 88% yield, whereas methoxycarbonylation of diketone **24** under various reaction condition gave a mixture of by-products. Treatment of β-keto ester **27** with NaHMDS and triflic anhydride furnished the advanced common intermediate, enol triflate **10** as a mixture of *E*/*Z* isomers, in 95% yield.

2.2. Synthesis of drechslerine A (1)

The advanced common intermediate, enol triflate **10**, was reduced with formic acid in the presence of palladium acetate, triphenylphosphine, and tri-*n*-butylamine to give unsaturated ester **28** in 96% yield (Scheme 4).[11] Hydrolysis of the enol ether with ethereal perchloric acid provided 8*R*-aldehyde **29** and 8*S*-aldehyde **30** in 28% and 69% yields, respectively, in which the relative stereochemistry of **30** was determined by NOE measurements (Fig. 3). The axial aldehyde **29** was epimerized into the equatorial aldehyde **30** by treatment with morpholine and *p*-toluenesulfonic acid (PTSA) in acetonitrile.[12] Reduction of aldehyde **30** with diisobutylaluminum hydride in dichloromethane gave drechslerine A (**1**), of which the spectral data and optical rotation value were consistent with those of the natural product (**1**).



Scheme 4. Reagents and conditions: (a) $Pd(OAc)_2$, HCO_2H, PPh_3, *n*-Bu_3N, DMF, 50 °C, 0.5 h, 96%. (b) $HClO_4$, Et_2O, rt, 97% (**29**/**30**=1:2.5). (c) Morpholine, PTSA, MeCN, rt, 14.5 h, 94% (**29**/**30**=1:2.3). (d) DIBAL, CH_2Cl_2, −78 °C, 1 h, 89%.

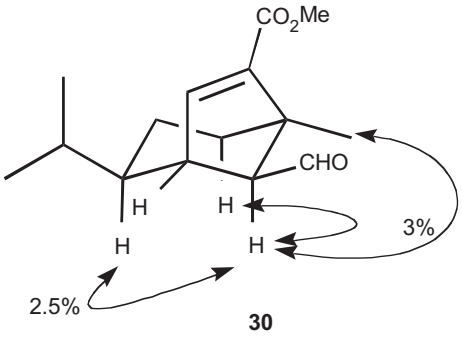


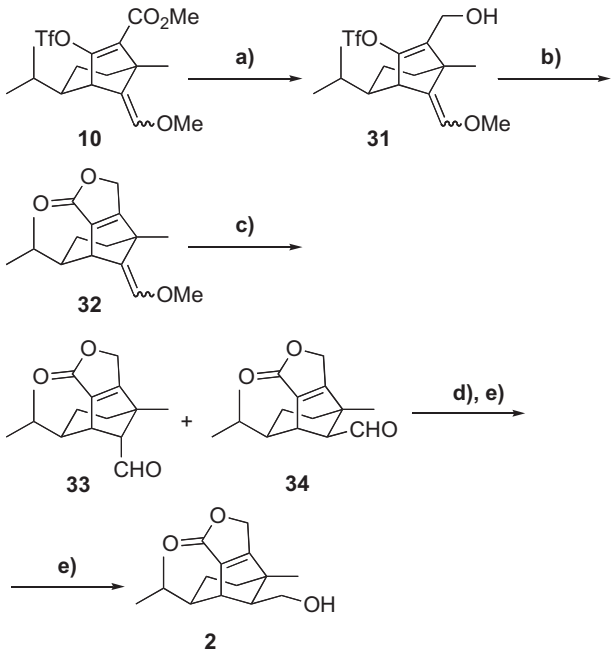
Fig. 3. Relative stereochemistry of aldehyde **30**.

2.3. Synthesis of drechslerine B (2)

Then, we turned our attention on the synthesis of drechslerine B (**2**). The enol triflate **10** was reduced with diisobutylalminum hydride in dichloromethane to give hydroxy-triflate **31** in 95% yield (Scheme 5). Palladium-catalyzed insertion of carbon monoxide to the hydroxy-triflate **31** was not trivial, and we were forced to tune the reaction conditions, which are summarized in Table 1.

An optimized result was obtained in the reaction with tetrakis(triphenylphosphine) palladium {$Pd(PPh_3)_4$} as a catalyst in the presence of tri-*n*-butylamine in acetonitrile[13] to give butenolide **32** in 88% yield (Table 1, entry 1). The addition of an external ligand, such as 1,1-bis(diphenylphosphino)ferrocene (DPPF) was not effective (Table 1, entries 3 and 5). Palladium acetate gave moderate yield (Table 1, entry 5).

Hydrolysis of the enol ether **32** by ethereal perchloric acid proceeded preferentially from the *exo*-face of the enol ether to give 8*R*-aldehyde **33** and 8*S*-aldehyde **34** in 91% yield in a 14:1 ratio, in which the relative stereochemistry of the 8*R*-aldehyde **33** was



Scheme 5. Reagents and conditions: (a) DIBAL, CH_2Cl_2, −78 °C, 45 min, 95%. (b) $Pd(PPh_3)_4$, CO atmosphere, LiCl, *n*-Bu_3N, MeCN, 60 °C, 4 h, 88%. (c) $HClO_4$, Et_2O, rt, 2 h, 91% (**33**/**34**=14:1). (d) K_2CO_3, MeOH, rt, 3 h, 70% (**33**/**34**=1:2.6). (e) $NaBH_4$, MeOH, 0 °C, 2 h, 44%.

Table 1
Insertion of carbon monoxide to triflate **31**[a]

Entry	Catalyst (equiv)	Base (equiv)	LiCl (equiv)	Time (h)	Yield (%)	
					Butenolide **32**	Triflate **31**
1	$Pd(PPh_3)_4$ (0.1)	*n*-Bu_3N (3)	1.5	4	88	n.d.
2[b]	$Pd(PPh_3)_4$ (0.1)	*n*-Bu_3N (2)	1	18	40	36
3[c]	$Pd(PPh_3)_4$ (0.2)	*n*-Bu_3N (2)	1	18	43	Trace
4	$Pd(PPh_3)_4$ (0.2)	DIPEA[d] (3)	1	18	3	25
5[c]	$Pd(OAc)_2$ (0.5)	Et_3N (4.5)	None	17	63	22

[a] Reaction was carried out in acetonitrile at 60–65 °C.
[b] Reaction was carried out in DMF.
[c] DPPF was added.
[d] Diisopropylethylamine.

determined rigorously by NOE measurement (Fig. 4). Although 8*S*-aldehyde **34** is 3.44 kJ more stable than 8*R*-aldehyde **33**, as estimated by PM3 calculations, isomerization was sensitive due to the instability of the aldehydes. The attempt at isomerization to give the thermodynamically more stable 8*S*-aldehyde **34** is compiled in Table 2. Treatment of a mixture of aldehydes **33** and **34** with potassium carbonate in methanol led to an equilibrium mixture of 1:2.6 (entry 1). Prolonged reaction time or elevated temperature

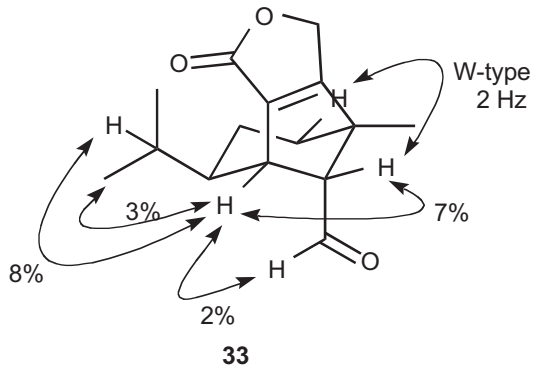


Fig. 4. Determination of relative stereochemistry of **33**.

Table 2
Isomerization of the 8*R*-aldehyde **33**[a]

Entry	Reagent (equiv)	Solvent	Time (h)	Yield (%)	8*R* **33**/8*S* **34**[c]
1	K_2CO_3 (0.2)	MeOH	3	70	1:2.6
2[b]	K_2CO_3 (0.2)	MeOH	3	60	1:3.1
3	K_2CO_3 (0.2)	MeOH	18	26	1:2.7
4	K_2CO_3 (1)	H_2O/THF	12	11	5:1
5	Morpholine (0.3)/ PTSA (0.1)	CH_2Cl_2	21	58	1:1
6	Morpholine (0.1)/ PTSA (0.1)	MeCN	17	57	1:5

[a] Reaction was carried out at rt.
[b] Reaction was carried out at 45 °C.
[c] Ratio was determined by ^1H NMR.

decreased yields without changing the isomeric ratio. Although treatment with morpholine and *p*-toluenesulfonic acid (PTSA) in acetonitrile[12] at room temperature provided 8*S*-aldehyde **34** preferentially at a ratio of 5:1 (entry 6), the reaction was unpredictable. Finally, reduction of a mixture of aldehydes **33** and **34** with sodium borohydride provided a mixture of drechslerine B **2**[14] and its C-8 epimer in 90%, which were separated by medium-pressure LC repeatedly to afford drechslerine B **2** in 44% yield. The spectral data of synthetic **2** including optical rotation was completely identical with that of natural **2**, which unambiguously established the absolute stereochemistry of **2** (Fig. 1).

3. Conclusion

In summary, we have completed the first total syntheses of drechslerines A (**1**) and B (**2**) by employing palladium-catalyzed transformations of enol triflates **10** prepared from (*S*)-carvone **13**, which established the absolute stereostructures as described in Fig. 1.

4. Experimental section

4.1. General

^1H spectra were recorded on a Varian Unity 500 plus (500 MHz), a Varian MR (400 MHz), or a JNM-Excalibur (270 MHz) spectrometer. ^{13}C NMR spectra were obtained for solutions in deuteriochloroform with a Varian MR (100 MHz). ^1H and ^{13}C chemical shifts are reported in parts per million downfield from tetramethylsilane (TMS, δ scale) as an internal standard. The following abbreviations were used to explain the multiplicities: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad. IR spectra were recorded on a JASCO FT/IR-4200. Melting points (mp) were recorded on a Yanaco hot stage apparatus and were uncorrected. Optical rotations were measured on a Horiba SEPA-200 spectrophotometer. Mass spectra were recorded on JMS GC-mate using EI method. Analytical TLC was carried out on Kieselgel 60 F_{254} plates employing *n*-hexane/ethyl acetate as the mobile phase. THF was distilled from sodium/benzophenone ketyl. Toluene was distilled from sodium. Acetonitrile and dimethylformamide were distilled from CaH_2.

*4.1.1. (5S)-2-Methyl-5-(methylethyl)cyclohexan-1-one (**14**).*

4.1.1.1. Reduction with zinc followed by hydrogenation catalyzed by Pd/C. A solution of carvone (**13**) (53.6 g) in methanol (70 mL) was slowly added to a refluxing solution of potassium hydroxide (24.9 g) and zinc powder (69.8 g) in aqueous methanol (1:6, 400 mL) over 11 h. After being refluxed for 62 h, the reaction was quenched by aqueous ammonium chloride. Extraction with *n*-hexane, followed by evaporation to dryness provided crude dihydrocarvone.

A solution of dihydrocarvone in ethyl acetate (100 mL) was stirred in the presence of 10% palladium on carbon (1.50 g) under hydrogen atmosphere at room temperature for 2 days. The catalyst

was removed by filtration through a silica gel column. Jones reagent (6 mL) was added at 0 °C. After being stirred for 20 min, the reaction was quenched by the addition of sodium sulfite. Product was extracted with *n*-hexane twice. The organic layer was washed with dilute aqueous sodium hydroxide, water, and brine, and then dried over anhydrous sodium sulfate. Evaporation of the solvent followed by Kugelrohr distillation (95–100 °C, 25 mmHg) provided tetrahydrocarvone (**14**) (39.39 g, 72%).

4.1.1.2. Catalytic hydrogenation catalyzed by Rh/Al_2O_3. A solution of carvone (**13**) (7.49 g, 50 mmol) in ethanol (55 mL) was hydrogenated in the presence of Rh/Al_2O_3 (0.203 g, 0.025 mmol) at 4.2 MPa in an autoclave at room temperature for 3.5 h. After filtration of the catalyst, evaporation of the solvent followed by Kugelrohr distillation gave tetrahydrocarvone (**14**) (7.60 g, 99%). $[\alpha]_D^{21}$ −37.8 (*c* 1.32, $CHCl_3$); IR ($CHCl_3$) ν_{max}/cm^{-1} 3013, 2963, 1702, 1457, 1369, 1315; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 2.48–2.31 (m, 2H), 2.09 (m, 1H), 1.87 (m, 1H), 1.72–1.25 (m, 4H), 1.29 (ddd, 1H, *J* 25.8, 12.8, 3.2 Hz), 1.09 (d, 1.5H, *J* 6.8 Hz), 1.01 (d, 1.5H, *J* 6.4 Hz), 0.90 (dd, 3H, *J* 6.8, 6.0 Hz), 0.89 (dd, 3H, *J* 6.4, 3.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 214.3, 212.8, 46.2, 44.9, 44.5, 44.4, 43.9, 42.6, 34.7, 32.4, 31.0, 30.2, 28.5, 24.7, 19.7, 19.6, 19.2, 19.0, 15.4, 14.0; HRMS *m*/*z* calcd for $C_{10}H_{18}O$ 154.1358, found 154.1359.

*4.1.2. 1-[(5S)-2-Methyl-5-(methylethyl)cyclohex-1-enyloxy]-1,1-dimethyl-1-silaethane (**15**).* Tetrahydrocarvone (**14**) (16.0 g, 0.10 mol) in acetonitrile (60 mL) was added to a solution of sodium iodide (31.2 g, 0.21 mol), chlorotrimethylsilane (26.5 mL, 0.21 mol), and triethylamine (43.5 mL, 0.31 mol) in acetonitrile (100 mL), at room temperature under nitrogen atmosphere. After being stirred for 4 h, the reaction was quenched by the addition of water at 0 °C. Product was extracted with *n*-hexane. The extract was dried over anhydrous sodium sulfate and evaporated to dryness. Purification by column chromatography (eluent: ethyl acetate/*n*-hexane=1:10) provided silylenol ether **15** (23.4 g, 99%). $[\alpha]_D^{21}$ −68.6 (*c* 0.966, $CHCl_3$); IR ($CHCl_3$) ν_{max}/cm^{-1} 2959, 2924, 2877, 2836, 1691, 1464, 1173, 846; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 2.03–1.87 (m, 3H), 1.78 (m, 1H), 1.67 (ddt, 1H, *J* 13.2, 7.2, 1.6 Hz), 1.53 (s, 3H), 1.44 (dt, 1H, *J* 13.2, 6.4 Hz), 1.34 (m, 1H), 1.12 (ddd, 1H, *J* 24.0, 12.0, 6.4 Hz), 0.87 (d, 3H, *J* 3.6 Hz), 0.86 (d, 3H, *J* 3.6 Hz), 0.15 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 142.71, 111.43, 41.63, 34.01, 32.08, 30.24, 26.47, 19.95, 19.71, 16.09, 0.711; HRMS *m*/*z* calcd for $C_{13}H_{26}OSi$ 226.1753, found 226.1768.

*4.1.3. (2S,5S)-2-Methyl-5-(methylethyl)-2-prop-2-enylcyclohexan-1-one (**12**) and (2R,5S)-2-methyl-5-(methylethyl)-2-prop-2-enylcyclohexan-1-one (**16**).*

4.1.3.1. Diastereoselective Tsuji allylation. A solution of tetrabutylammonium difluorotriphenylsilicate (59 mg, 0.1 mmol), $Pd_2(dba)_3$ (18 mg, 0.03 mmol), and (*S*)-*tert*-butylPHOX (**17**) (36 mg, 0.063 mmol) in THF (3 mL) was stirred at room temperature under nitrogen for 25 min. Diallyl carbonate (160 mL, 1.1 mmol) and then the silylenol ether **15** (227 mg, 1 mmol) in THF were added. After stirring for 5 h, the solvent was evaporated to dryness. Column chromatography (eluent: ethyl acetate/*n*-hexane=1:30) of the residue provided a mixture of allyl derivative **12** and **16** (201 mg) at a ratio of 55:1 (calculated from NMR of 2-methyl peaks) in favor of **12**. $[\alpha]_D^{26}$ −113.2 (*c* 0.618, $CHCl_3$); IR ($CHCl_3$) ν_{max}/cm^{-1} 3020, 2963, 2873, 1698, 1208; ^1H NMR (270 MHz, $CDCl_3$) δ (ppm) 5.54–5.72 (m, 1H), 5.08 (s, 1H), 5.03 (m, 1H), 2.44 (dd, 1H, *J* 13.8, 7.2 Hz), 2.28 (br s, 1H), 2.25 (m, 1H), 2.15 (dd, 1H, *J* 13.8, 7.5 Hz), 1.87 (dd, 1H, *J* 13.4, 3.2 Hz), 1.36–1.76 (m, 5H), 1.01 (s, 3H), 0.91 (d, 3H, *J* 6.4 Hz), 0.90 (d, 3H, *J* 6.4 Hz); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ (ppm) 215.2, 132.8, 117.9, 48.1, 46.0, 42.2, 41.4, 37.9, 32.6, 24.4, 22.1, 19.7, 19.5; HRMS *m*/*z* calcd for $C_{13}H_{22}O$ 194.1671, found 194.1669.

4.1.3.2. Allylation of thermodynamic enolate. Methyllithium (3 M solution in dimethoxyethane, 13.5 mL, 39 mmol) was added to a stirred solution of silylenol ether **15** (6.65 g, 30 mmol) in THF (70 mL) at −40 °C. After stirring for 1 h, allyliodide (8.23 mL, 90 mmol) was added at −50 °C and the resulting solution was stirred at −50 °C for 19 h. The reaction was quenched by aqueous ammonium chloride and extracted with ethyl acetate. The extract was dried over anhydrous sodium sulfate and evaporated to dryness. Column chromatography followed to give an inseparable mixture of **12** and **16** (5.51 g, 97%) at 3.4:1 (calculated from NMR of 2-methyl peaks).

*4.1.4. (6S)-6-Hydroxy-1-methyl-4-(methylethyl)bicyclo[3.2.1]octan-8-one (**11**).* Ozone/oxygen was passed through a solution of **12** and **16** (201 mg) in dichloromethane (13 mL) at −78 °C for 3 h, until the color of the solution was blue. The reaction was quenched by addition of triethylamine (0.42 mL, 3 mmol), and the solution was left to stand until it reached room temperature. Evaporation of the solvent followed by short column chromatography of the residue (eluent: ethyl acetate/*n*-hexane=1:3) provided 2-[(1*S*,4*S*)-1-methyl-4-(methylethyl)-2-oxocyclohexyl]ethanal (**18**) (149 mg, 75% in two steps). $[\alpha]_D^{26}$ −30.4 (*c* 1.05, $CHCl_3$); IR ($CHCl_3$) ν_{max}/cm^{-1} 3024, 2963, 2873, 1719, 1704; ^1H NMR (270 MHz, $CDCl_3$) δ (ppm) 9.71 (t, 1H, *J* 2.2 Hz), 2.67 (dd, 1H, *J* 15.6, 1.8 Hz), 2.53 (dd, 1H, *J* 15.6, 2.7 Hz), 2.26–2.49 (m, 2H), 1.90–2.04 (m, 1H), 1.72–1.86 (m, 1H), 1.44–1.69 (m, 4H), 1.22 (s, 3H), 0.92 (s, 3H), 0.90 (s, 3H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ (ppm) 213.6, 200.6, 50.3, 46.8, 45.4, 41.8, 37.5, 31.6, 24.1, 23.0, 19.8, 19.7; HRMS *m*/*z* calcd for $C_{12}H_{20}O_2$ 196.1463, found 196.1468.

A solution of aldehyde **18** (1.43 g, 7.3 mmol) and potassium hydroxide (335 mg, 5.1 mmol) in ethanol (100 mL) was heated at 50 °C for 13 h. After evaporation of ethanol in vacuo, aqueous ammonium chloride was added. Product was extracted with ethyl acetate and dried over anhydrous sodium sulfate. Evaporation of the solvent followed by column chromatography of the residue (eluent: ethyl acetate/*n*-hexane=1:1) gave the desired diastereomer **11** (1.43 g, 80%). Aldol **11** has mp 85.0–85.6 °C; $[\alpha]_D^{23}$ −25.88 (*c* 0.800, $CHCl_3$); IR ($CHCl_3$) ν_{max}/cm^{-1} 3601, 2963, 2930, 1741, 1456, 1206, 1018; ^1H NMR (270 MHz, $CDCl_3$) δ (ppm) 4.30 (dd, 1H, *J* 7.8, 1.7 Hz), 2.43 (s, 1H), 2.40 (dd, 1H, *J* 14.2, 8.0 Hz), 2.09 (br s, 1H), 1.46–1.83 (m, 6H), 1.25 (td, 1H, *J* 13.4, 6.1 Hz), 1.06 (s, 3H), 0.94 (d, 3H, *J* 6.5 Hz), 0.93 (d, 3H, *J* 6.5 Hz); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ (ppm) 221.6, 66.1, 58.3, 52.5, 47.7, 44.5, 42.0, 31.2, 24.4, 21.3, 19.0, 18.8; HRMS *m*/*z* calcd for $C_{12}H_{20}O_2$ 196.1463, found 196.1459.

*4.1.5. (1S,4R,5R)-1-Methyl-4-(methylethyl)bicyclo[3.2.1]octane-6,8-dione (**24**).* Jones reagent (11 mL, 2.67 M solution, 29.4 mmol) was added drop wise to a stirred solution of keto alcohol **11** (1.71 g, 8.69 mmol) in acetone (20 mL) at 0 °C, and the resulting solution was stirred at room temperature for 15 min. The solution was diluted with *n*-hexane and the reaction was quenched by the addition of isopropyl alcohol. Product was extracted with ethyl acetate and dried over anhydrous sodium sulfate. Evaporation of the solvent followed by column chromatography of the residue (eluent: ethyl acetate/*n*-hexane=1:3) afforded diketone **24** (1.60 mg, 95%) as colorless crystals. Mp 31.0 °C; $[\alpha]_D^{25}$ −87.6 (*c* 1.05, $CHCl_3$); IR ($CHCl_3$) ν_{max}/cm^{-1} 3026, 2968, 2931, 2872, 1766, 1727, 1456, 1231, 1185; ^1H NMR (270 MHz, $CDCl_3$) δ (ppm) 2.95 (s, 1H), 2.61 (d, 1H, *J* 19.2 Hz), 2.41 (d, 1H, *J* 19.2 Hz), 1.80–2.10 (m, 4H), 1.58–1.78 (m, 1H), 1.30–1.48 (m, 1H), 1.20 (s, 3H), 1.00 (d, 3H, *J* 6.5 Hz), 0.90 (d, 3H, *J* 6.5 Hz); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ (ppm) 216.3, 209.0, 61.6, 56.8, 51.0, 49.6, 42.0, 30.6, 24.7, 21.2, 20.6, 18.5; HRMS *m*/*z* calcd for $C_{12}H_{18}O_2$ 194.1307, found 194.1307.

*4.1.6. (1S,4R,5R)-6-[1,1-Bis(methylethyl)-2-methyl-1-silapropoxy]-1-methyl-4-(methylethyl)bicyclo[3.2.1]oct-6-en-8-one (**25**).* Sodium bistrimethylsilylamide (1 M solution in THF, 1.43 mL, 14.3 mmol) was added to a stirred solution of diketone **24** (2.55 g, 13 mmol) and triisopropylsilylchloride (4.2 mL, 20.0 mmol) in THF (40 mL) at

−78 °C under nitrogen atmosphere. After being stirred for 1.5 h, the reaction was quenched by aqueous ammonium chloride. Ether was added and the organic layer was separated by decantation, and dried over anhydrous sodium sulfate. Evaporation of the solvents followed by medium-pressure LC of the residue (eluent: ethyl acetate/*n*-hexane=1:10) gave TIPS enol ether **25** (4.52 g, 98%). $[\alpha]_D^{24}$−80.8 (*c* 1.15, $CHCl_3$); IR ($CHCl_3$) ν_{max}/cm^{-1} 2962, 2928, 2869, 1748, 1617, 1463, 1353, 1285, 1262, 1214, 883, 821; ^1H NMR (270 MHz, $CDCl_3$) δ (ppm) 4.66 (s, 1H), 2.86 (d, 1H, *J* 1.6 Hz), 1.70–1.80 (m, 1H), 1.50–1.70 (m, 2H), 1.30–1.50 (m, 3H), 1.05–1.30 (m, 21H), 1.05 (s, 3H), 1.01 (d, 3H, *J* 6.5 Hz), 0.84 (d, 3H, *J* 6.5 Hz); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ (ppm) 215.8, 151.2, 104.2, 55.4, 51.5, 47.8, 36.5, 32.3, 24.7, 21.2, 21.0, 18.0, 17.2, 12.5; HRMS *m*/*z* calcd for $C_{23}H_{42}O_2Si$ 350.2641, found 350.2645.

*4.1.7. (1S,4R,5S)-8-(Methoxymethylene)-1-methyl-4-(methylethyl) bicyclo[3.2.1]octan-6-one (**26**).* *n*-Butyllithium (1.63 M solution in *n*-hexane, 1.9 mL, 3.10 mmol) was added to a stirred suspension of methoxymethyltriphenylphosphonium chloride (1.27 g, 3.70 mmol) in THF (5 mL) at 0 °C under nitrogen atmosphere. After being stirred for 50 min at room temperature, a solution of crude TIPS enol ether 25 (350 mg, 1.00 mmol) in THF (5 mL) was added. The resulting solution was stirred at 60 °C for 4 h. The reaction was quenched by aqueous ammonium chloride. Product was extracted with *n*-hexane twice. The organic layer was dried over anhydrous sodium sulfate and evaporated to dryness. Residue was passed through a short silica gel column. Products were mixtures of *E*/*Z* isomers (6:1 by ^1H NMR), in which major the isomer separated by medium-pressure LC had $[\alpha]_D^{19}$ −95.6 (*c* 0.861, $CHCl_3$); IR ($CHCl_3$) ν_{max}/cm^{-1} 2945, 2867, 1708, 1619, 1462, 1253, 1163, 883; ^1H NMR (270 MHz, $CDCl_3$) δ (ppm) 5.49 (s, 0.14H), 5.43 (s, 0.86H), 4.36 (s, 0.86H), 4.28 (s, 0.14H), 3.51 (s, 2.6H), 3.46 (s, 0.4H), 3.41 (br s, 1H), 1.75 (dd, 1H, *J* 13.0, 5.9 Hz), 1.52–1.16 (m, 7H), 1.14 (m, 21H), 1.02 (s, 3H), 1.01 (d, 3H, *J* 7.0 Hz), 0.84 (d, 3H, *J* 7.0 Hz); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ (ppm) 155.0, 135.8, 128.9, 106.8, 59.5, 45.8, 45.6, 44.0, 38.0, 32.0, 26.1, 21.7, 21.2, 21.1, 18.1, 12.5; HRMS *m*/*z* calcd for $C_{23}H_{42}O_2Si$ 378.2954, found 378.2958.

TBAF (1.5 mL) was added to a solution of the crude methyl enol ether in THF (5 mL) at room temperature. After being stirred for 1 h, the reaction was quenched by addition of aqueous ammonium chloride and the product was extracted with *n*-hexane twice. The organic layer was washed with water and brine, and then dried over anhydrous sodium sulfate. Evaporation of the solvent followed by medium-pressure LC (eluent: ethyl acetate/*n*-hexane=1:10) provided ketone **26** (174 mg, 73% in two steps) as a mixture of *E*/*Z* isomers, in which the major enol ether has $[\alpha]_D^{27}$−274.0 (*c* 1.89, $CHCl_3$); IR ($CHCl_3$) ν_{max}/cm^{-1} 3027, 3011, 2960, 2931, 2871, 1735, 1456, 1251, 1172, 1123; ^1H NMR (270 MHz, $CDCl_3$) δ (ppm) 5.80 (s, 1H), 3.57 (s, 3H), 3.42 (s, 1H), 2.12 (d, 1H, *J* 18.1 Hz), 2.01 (d, 1H, *J* 18.1 Hz), 1.88 (dt, 1H, *J* 18.3, 5.1 Hz), 1.74 (dd, 1H, *J* 12.7, 5.7 Hz), 1.44–1.64 (m, 2H), 1.28–1.44 (m, 1H), 1.18 (s, 3H), 1.05–1.26 (m, 1H), 1.05 (d, 1H, *J* 6.7 Hz), 0.84 (d, 1H, *J* 6.8 Hz); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ (ppm) 216.5, 135.6, 127.2, 59.7, 52.2, 51.1, 51.0, 41.6, 40.1, 30.3, 25.7, 22.3, 21.5, 20.5; HRMS *m*/*z* calcd for $C_{14}H_{22}O_2$ 222.1620, found 222.1621.

*4.1.8. Methyl (1S,2R,5S)-8-(methoxymethylene)-5-methyl-2-(methylethyl)-7-oxobicyclo[3.2.1]octane-6-carboxylate (**27**).* Sodium bistrimethylsilylamide (1.0 M solution in THF, 0.33 mL, 0.33 mmol) was added to a stirred solution of ketone **26** (48 mg, 0.22 mmol, a mixture of *E*/*Z* isomer) in THF (1 mL) at −78 °C under nitrogen atmosphere. After being stirred for 10 min, methyl cyanoformate (0.026 mL, 0.33 mmol) was added. The reaction was quenched by aqueous ammonium chloride after being stirred for 30 min. Product was extracted with ethyl acetate twice. The organic layer was washed with water and brine, and then dried over anhydrous sodium sulfate. After evaporation of the solvent, the residue was separated with medium-pressure LC (eluent: ethyl acetate/*n*-hexane=1:3) to provide keto ester **27** (53 mg, 87%). $[\alpha]_D^{27}$−204.4 (*c* 1.09, $CHCl_3$); IR ($CHCl_3$) ν_{max}/cm^{-1} 3010, 2933, 2871, 1748, 1727, 1435, 1120; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 5.85 (s, 1H), 3.67 (s, 3H), 3.59 (s, 3H), 3.55 (s, 1H), 3.00 (s, 1H), 1.91 (ddd, 1H, *J* 12.8, 5.3, 5.2 Hz), 1.90 (ddd, 1H, *J* 13.2, 6.1, 6.0 Hz), 1.62 (td, 2H, *J* 13.2, 6.0 Hz), 1.52 (m, 1H), 1.42 (m, 1H), 1.15 (s, 3H), 1.06 (d, 3H, *J* 6.4 Hz), 0.84 (d, 3H, *J* 6.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 210.3, 169.4, 137.0, 124.8, 64.7, 59.7, 51.7, 51.6, 50.6, 43.9, 43.3, 30.3, 25.3, 21.2, 20.3, 18.8; HRMS *m*/*z* calcd for $C_{16}H_{24}O_4$ 280.1674, found 280.1675.

*4.1.9. Methyl (1S,2R,5R)-8-(methoxymethylene)-5-methyl-2-(methylethyl)-7-[(trifluoromethyl)sulfonyloxy]bicyclo[3.2.1]oct-6-ene-6-carboxylate (**10**).* Sodium bistrimethylsilylamide (1 M solution in THF, 1.67 mL, 1.67 mmol) was added to a stirred solution of keto ester **27** (335 mg, 1.19 mmol) in ether (5 mL) at −78 °C under nitrogen. After being stirred for 20 min, triflic anhydride (313 μL, 1.91 mmol) was added. The solution was stirred for an additional 1.5 h. The reaction was quenched by aqueous sodium hydrogencarbonate. After being stirred for 5 h until room temperature, the product was extracted with ethyl acetate twice. The organic layer was washed with water and brine, and then dried over anhydrous sodium sulfate. Evaporation of the solvent and subsequent medium-pressure LC (eluent: ethyl acetate/*n*-hexane=1:3) provided enol triflate **10** (463 mg, 94%). Due to the instability of enol triflate **10**, optical rotation and IR spectrum were not measured. $[\alpha]_D^{23}$+165.0 (*c* 0.552, $CHCl_3$); IR ($CHCl_3$) ν_{max}/cm^{-1} 2955, 2934, 1714, 1631, 1427, 1300, 1119; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 5.64 (s, 1H), 3.85 (s, 1H), 3.78 (s, 3H), 3.57 (s, 3H), 1.95–1.88 (m, 2H), 1.40 (m, 1H), 1.29 (s, 3H), 1.31–1.10 (m, 3H), 1.03 (d, 3H, *J* 6.4 Hz), 0.85 (d, 3H, *J* 6.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 162.2, 154.7, 132.8, 127.9, 126.9, 123.1, 119.9, 116.7, 113.5, 59.7, 51.4, 46.5, 45.1, 44.4, 35.6, 31.4, 25.0, 20.9, 20.6, 17.7; HRMS *m*/*z* calcd for $C_{17}H_{23}O_6SF_3S$ 412.1167, found 412.1162.

*4.1.10. Methyl (1R,2R,5R)-8-(methoxymethylene)-5-methyl-2-(methylethyl)bicyclo[3.2.1]oct-6-ene-6-carboxylate (**28**).* Formic acid (0.37 mL, 9.8 mmol) was added to a stirred solution of enol triflate **10** (406 mg, 0.98 mmol), palladium acetate (67 mg, 0.30 mmol), triphenylphosphine (157 mg, 0.60 mmol), and tri-*n*-butylamine (2.3 mL, 9.8 mmol) in dimethylformamide (15.0 mL) and the resulting solution was heated at 50 °C for 0.5 h. The reaction was quenched by water. Product was extracted with ethyl acetate twice. The organic layer was washed with water and brine, and then dried over anhydrous sodium sulfate, before being passed through a short silica gel column and evaporated to dryness. The residue was purified by medium-pressure LC (eluent: ethyl acetate/*n*-hexane=1:5) to afford unsaturated ester **28** (481 mg, 96%). $[\alpha]_D^{19}$ −122.0 (*c* 0.718, $CHCl_3$); IR ($CHCl_3$) ν_{max}/cm^{-1} 2957, 2933, 2874, 2847, 1704, 1597, 1458, 1436, 1258, 1119; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 6.82 (d, 1H, 3.0 Hz), 5.56 (s, 1H), 3.72 (s, 3H), 3.61 (t, 1H, *J* 1.0 Hz), 3.55 (s, 3H), 1.74 (dd, 1H, *J* 11.6, 6.4 Hz), 1.63 (dt, 1H, *J* 13.6, 4.8 Hz), 1.31–1.20 (m, 3H), 1.27 (s, 3H), 1.08 (ddd, 1H, *J* 12.8, 11.2, 5.6 Hz), 1.06 (d, 3H, *J* 6.4 Hz), 0.84 (d,3H, *J* 6.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 165.0, 143.0, 139.6, 134.3, 131.2, 59.5, 51.0, 46.4, 44.8, 42.7, 35.3, 32.6, 24.8, 21.0, 20.8, 17.8; HRMS *m*/*z* calcd for $C_{16}H_{24}O_3$ 264.1725, found 264.1726.

*4.1.11. Methyl (1R,2R,5R,8R)-8-formyl-5-methyl-2-(methylethyl)bicyclo[3.2.1]oct-6-ene-6-carboxylate (**29**) and (1R,2R,5R,8S)-8-formyl-5-methyl-2-(methylethyl)bicyclo[3.2.1]oct-6-ene-6-carboxylate (**30**).* Ethereal perchloric acid (2.0 mL), prepared by mixing perchloric acid and ether at a ratio of 1:7, was added to a stirred solution of enol ether **28** (248 mg, 0.94 mmol) in ether (10.0 mL). The resulting solution was stirred at room temperature for 1 h. Extra ethereal perchloric acid (0.5 mL) was added three times at 1 h intervals. The reaction was quenched by the addition of sodium hydrogencarbonate powder. Product was triturated with ethyl acetate twice. The organic layer was passed through a short silica gel

column and evaporated to dryness. Medium-pressure LC of the residue (eluent: ethyl acetate/*n*-hexane=1:5) gave a mixture of aldehyde **29** and **30** (89 mg, 97%). Axial aldehyde **29** partially separated by medium-pressure LC had $[\alpha]_D^{19}$+147.3 (*c* 0.260, $CHCl_3$); IR ($CHCl_3$) ν_{max}/cm^{-1} 3027, 2958, 2872, 1712, 1602, 1460; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 9.89 (d, 1H, *J* 0.8 Hz), 6.83 (d, 1H, *J* 3.2 Hz), 3.75 (s, 3H), 3.18 (ddd, 1H, *J* 5.2, 2.8, 2.8 Hz), 2.55 (dd, 1H, 5.2, 0.8 Hz), 1.71 (ddd, 1H, *J* 13.2, 8.8, 3.6 Hz), 1.59 (dd, 1H, *J* 10.0, 3.6 Hz), 1.58 (dd, 1H, *J* 7.6, 2.0 Hz), 1.45 (s, 3H), 1.26 (m, 2H), 1.06 (m, 1H), 0.94 (d, 3H, *J* 6.4 Hz), 0.83 (d, 3H, *J* 6.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 203.2, 164.9, 142.8, 140.9, 64.7, 51.2, 46.2, 42.6, 37.4, 32.5, 27.1, 24.6, 21.3, 20.9, 20.7; HRMS *m*/*z* calcd for $C_{15}H_{22}O_3$ 250.1569, found 250.1565.

*4.1.12. Methyl (1R,2R,5S,8S)-8-formyl-5-methyl-2-(methylethyl)bicyclo[3.2.1]oct-6-ene-6-carboxylate (**30**).* A solution of aldehyde **29** (89 mg, 0.36 mmol), morpholine (15.5 mg, 0.18 mmol), and *p*-toluenesulfonic acid (6.8 mg, 0.036 mmol) in acetonitrile (1 mL) was stirred at room temperature for 14.5 h. The solution was diluted with ethyl acetate and dried over anhydrous sodium sulfate, which was filtered through a short silica gel column. Evaporation of the solvent gave a residue, in which the ratio of **29** to **30** was determined to be 1:0.2 by NMR measurement.

The residue (89 mg, 0.36 mmol) in acetonitrile (1 mL) was again treated with morpholine (15.5 mg, 0.18 mmol) and *p*-toluenesulfonic acid (6.8 mg, 0.036 mmol) at 40 °C for 12.5 h. The solution was diluted with ethyl acetate and the organic layer was passed through a short silica gel column. Evaporation of the solvent followed by medium-pressure LC (eluent: ethyl acetate/*n*-hexane=1:3) produced an inseparable mixture of aldehydes **29** and **30** (84 mg, 94%) at a ratio of 1:2.3. Repeated medium-pressure LC produced pure **30**. IR ($CHCl_3$) ν_{max}/cm^{-1} 2959, 2874, 1713, 1605, 1453, 1279; ^1H NMR (270 MHz, $CDCl_3$) δ (ppm) 9.69 (d, 1H, *J* 3.9 Hz), 6.78 (d, 1H, *J* 2.4 Hz), 3.73 (s, 3H), 3.01 (br s, 1H), 2.11 (d, 3H, *J* 3.9 Hz), 1.71–1.82 (m, 1H), 1.66 (dd, 1H, *J* 13.2, 6.1 Hz), 1.36 (s, 3H), 0.97–1.42 (m, 4H), 0.95 (d, 3H, *J* 6.6 Hz), 0.86 (d, 3H, *J* 6.6 Hz). Due to the instability of aldehyde **30**, optical rotation and ^{13}C spectrum were not measured.

*4.1.13. [(1S,2R,5R,8S)-7-(Hydroxymethyl)-1-methyl-4-(methylethyl)bicyclo[3.2.1]oct-6-en-8-yl]methan-1-ol=drechslerin A (**1**).* Diisobutylaluminum hydride (0.90 M solution in toluene, 0.58 mL, 0.52 mmol) was added to a stirred solution of aldehyde **30** (26 mg, 0.104 mmol) in dichloromethane (3 mL) at −78 °C under nitrogen atmosphere. After being stirred for 30 min, extra diisobutylaluminum hydride (0.23 mL) was added. After being stirred for 30 min, the reaction was quenched by adding aqueous ammonium chloride. Product was extracted with ethyl acetate twice. The organic layer was washed with water and brine, and then dried over anhydrous sodium sulfate. Evaporation of the solvent and subsequent medium-pressure LC purification of the residue (eluent: ethyl acetate/*n*-hexane=4:1) afforded drechslerine A **1** (21 mg, 89%). Mp 128.1–128.9 °C, lit.[2] 125 °C; $[\alpha]_D^{25}$−27.6 (*c* 0.098, $CHCl_3$), lit.[2] $[\alpha]_D^{22}$−25.0 (*c* 0.10, EtOH); IR ($CHCl_3$) ν_{max}/cm^{-1} 3612, 3446 (br), 2957, 2929, 1458, 1009; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 5.55 (br d, 1H, *J* 1.6 Hz), 4.05 (d, 1H, *J* 14.4 Hz), 4.02 (dd, 1H, *J* 14.4, 1.2 Hz), 3.64 (dd, 1H, *J* 10.4, 6.4 Hz), 3.36 (dd, 1H, *J* 10.4, 10.0 Hz), 2.80 (br s, 1H), 1.65 (m, 1H), 1.54 (dd, 1H, *J* 9.2, 4.8 Hz), 1.38 (m, 1H), 1.30–1.20 (m, 3H), 1.05 (m, 1H), 0.96 (s, 3H), 0.95 (d, 3H, *J* 6.4 Hz), 0.85 (d, 3H, *J* 6.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 147.1, 124.2, 63.9, 62.7, 59.9, 47.7, 45.4, 43.9, 35.8, 33.8, 26.3, 21.6, 21.3, 19.0; HRMS *m*/*z* calcd for $C_{14}H_{24}O_2$ 224.1776, found 224.1776.

*4.1.14. (1R,4R,5S)-7-(Hydroxymethyl)-8-(methoxymethylene)-1-methyl-4-(methylethyl)bicyclo[3.2.1]oct-6-en-6-yl (trifluoromethyl) sulfonate (**31**).* Diisobutylaluminum hydride (0.99 M solution in toluene, 1.2 mL, 1.2 mmol) was added to a stirred solution of enol-ester **10** (206 mg, 0.50 mmol) in dichloromethane (10 mL) at −78 °C under nitrogen atmosphere. After being stirred for 45 min, the reaction was quenched by aqueous ammonium chloride. Product was extracted with ethyl acetate twice. The organic layer was washed with water and brine, and then dried over anhydrous sodium sulfate. Evaporation of solvent followed by medium-pressure LC of the residue (eluent: ethyl acetate/*n*-hexane=1:3) afforded alcohol **31** (72 mg, 95%). Due to the instability of enol triflate, optical rotation and IR spectrum were not measured. ^1H NMR (270 MHz, $CDCl_3$) δ (ppm) 5.58 (s, 1H), 4.21 (s, 2H), 3.74 (s, 1H), 3.56 (s, 3H), 1.85 (m, 1H), 1.71–1.57 (m, 1H), 1.31–1.13 (m, 4H), 1.21 (s, 3H), 1.04 (d, 3H, *J* 6.5 Hz), 0.85 (d, 3H, *J* 6.5 Hz); HRMS *m*/*z* calcd for $C_{16}H_{23}O_5F_3S$ 384.1218, found 384.1219.

*4.1.15. (1S,7R,10R)-11-(Methoxymethylene)-7-methyl-10-(methylethyl)-4-oxatricyclo[5.3.1.0^{2,6}]undec-2(6)-en-3-one (**32**).* A solution of alcohol **31** (73 mg, 0.19 mmol), lithium chloride (13 mg, 0.29 mmol), palladium tetrakistriphenylphosphine (23 mg, 0.02 mmol), and tri-*n*-butylamine (0.136 mL, 0.57 mmol) in acetonitrile (2 mL) was evacuated under water aspirator. After the introduction of carbon monoxide, the solution was heated at 60 °C for 4 h. After aqueous ammonium chloride was added, the product was triturated with *n*-hexane twice. The organic layer was dried over anhydrous sodium sulfate and passed through a short silica gel column. Evaporation of the solvent followed by medium-pressure LC (eluent: ethyl acetate/*n*-hexane=1:3) gave butenolide **32** (44 mg, 88%). $[\alpha]_D^{19}$ −89.6 (*c* 0.170, $CHCl_3$); IR ($CHCl_3$) ν_{max}/cm^{-1} 3017, 2961, 2872, 1749, 1635, 1454, 1120, 999; ^1H NMR (270 MHz, $CDCl_3$) δ (ppm) 5.61 (s, 1H), 4.86 (dd, 1H, *J* 18.1, 1.2 Hz), 4.74 (d, 1H, *J* 18.1 Hz), 3.88 (s, 1H), 3.58 (s, 3H), 1.84 (dt, 1H, *J* 14.1, 4.8 Hz), 1.66 (dd, 1H, *J* 12.5, 6.1 Hz), 1.48 (td, 1H, *J* 12.5, 6.0 Hz), 1.24 (s, 3H), 1.17–1.34 (m, 2H), 1.09 (d, 3H, *J* 6.0 Hz), 0.84–0.96 (m, 1H), 0.82 (d, 3H, *J* 6.0 Hz); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ (ppm) 117.6, 170.0, 135.9, 134.4, 132.2, 67.3, 59.8, 46.4, 44.7, 39.3, 36.3, 32.5, 25.7, 21.4, 20.7, 17.4; HRMS *m*/*z* calcd for $C_{16}H_{22}O_3$ 262.1569, found 262.1572.

*4.1.16. (1R,7S,8R,11R)-1-Methyl-8-(methylethyl)-4-oxa-5-oxotricyclo[5.3.1.0^{2,6}]undec-2(6)-ene-11-carbaldehyde (**33**) and (1R,7S,8S,11R)-1-methyl-8-(methylethyl)-4-oxa-5-oxotricyclo[5.3.1.0^{2,6}]undec-2(6)-ene-11-carbaldehyde (**34**).* Ethereal perchloric acid (0.2 mL), which was prepared from perchloric acid and ether at a ratio of 1:7, was added to a stirred solution of enol ether **32** (48 mg, 0.18 mmol) in ether (0.5 mL). After being stirred for 2 h at room temperature, the reaction was quenched by adding sodium bicarbonate powder. After the addition of ethyl acetate and subsequent decantation, the organic layer was dried over anhydrous sodium sulfate and passed through a short silica gel column. Evaporation of the solvent followed by medium-pressure LC (eluent: ethyl acetate/*n*-hexane=1:1) provided aldehydes **33** and **34** (14:1) (41 mg, 91%). Axial aldehyde **33** has IR ($CHCl_3$) ν_{max}/cm^{-1} 3030, 2962, 2870, 1753, 1720, 1642, 1003; ^1H NMR (270 MHz, $CDCl_3$) δ (ppm) 9.82 (s, 1H), 4.90 (d, 1H, *J* 18.1 Hz), 4.78 (d, 1H, *J* 18.1 Hz), 3.51 (d, 1H, *J* 4.6 Hz), 3.02 (dd, 1H, *J* 4.9, 2.2 Hz), 1.76–1.99 (m, 2H), 1.35–1.48 (m, 1H), 1.42 (s, 3H), 1.16–1.31 (m, 2H), 1.05 (d, 3H, *J* 5.1 Hz), 0.84–0.96 (m, 1H), 0.82 (d, 3H, *J* 5.1 Hz); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ (ppm) 200.8, 178.4, 169.6, 134.3, 68.6, 67.1, 45.8, 39.2, 38.3, 32.2, 27.4, 25.2, 21.1, 20.5, 20.5; HRMS *m*/*z* calcd for $C_{15}H_{20}O_3$ 248.1412, found 248.1414. Due to the instability of **33**, optical rotation was not measured.

*4.1.17. (1R,7S,8R,11S)-1-Methyl-8-(methylethyl)-4-oxa-5-oxotricyclo[5.3.1.0^{2,6}]undec-2(6)-ene-11-carbaldehyde (**34**).* A solution of aldehydes **33** and **34** (23 mg, 0.09 mmol) and potassium carbonate (2.5 mg, 0.018 mmol) in methanol (1.5 mL) was stirred at room temperature for 3 h. After the addition of ammonium chloride powder, the organic layer was dried over anhydrous sodium sulfate and passed through a short silica gel column. Evaporation of

the solvent followed by medium-pressure LC (eluent: ethyl acetate/*n*-hexane=1:1) gave an inseparable mixture of aldehydes (16 mg, 70%, **33**/**34**=1:2.6). NMR peaks of major isomer **34** are as follows: ^{1}H NMR (270 MHz, $CDCl_3$) δ (ppm) 9.69 (d, 1H, *J* 3.2 Hz), 4.91 (d, 1H, *J* 18.3 Hz), 4.76 (d, 1H, *J* 18.3 Hz), 3.33 (s, 1H), 2.52 (d, 1H, *J* 3.2 Hz), 1.84–2.01 (m, 2H), 1.58 (dd, 2H, *J* 9.5, 3.4 Hz), 1.17–1.36 (m, 1H), 1.32 (s, 3H), 1.06 (d, 3H, *J* 6.4 Hz), 0.86–1.13 (m, 1H), 0.85 (d, 3H, *J* 6.4 Hz); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ (ppm) 202.2, 176.6, 169.4, 134.4, 75.3, 67.2, 47.0, 42.9, 39.3, 34.2, 32.1, 25.7, 21.4, 20.6, 18.4; HRMS *m*/*z* calcd for $C_{15}H_{22}O_3$ 250.1569, found 250.1571. Due to the instability of **33** and **34**, only NMR and mass spectra were measured.

*4.1.18. (1S,7R,10R,11S)-11-(Hydroxymethyl)-7-methyl-10-(methylethyl)-4-oxatricyclo[5.3.1.0^{2,6}]undec-2(6)-en-3-one (**2**)=drechslerin B.* A solution of sodium borohydride (0.13 M in methanol, 1 mL, 0.13 mmol) was added to a stirred solution of aldehydes **33** and **34** (32 mg, 0.13 mmol) in methanol (1.0 mL) at 0 °C under nitrogen atmosphere. Extra methanol solution of sodium borohydride was added (1 mL and then 2 mL at 15 min intervals). After the addition of ammonium chloride powder, the mixture was diluted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate and passed through a short silica gel column. Evaporation of the solvent followed by medium-pressure LC (eluent: ethyl acetate/*n*-hexane=2:1) afforded drechslerine B **2** and C-8 epimer (29 mg, 90%). Repeated medium-pressure LC afforded pure drechslerine B **2** (14 mg, 44%). $[\alpha]_D^{20}$ −40.6 (*c* 0.18, EtOH), lit.[2] −42.0 (*c* 0.10, EtOH); IR ($CHCl_3$) ν_{max}/cm^{-1} 3624, 2928, 2873, 1747; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 4.90 (dd, 1H, *J* 19.2, 1.2 Hz), 4.87 (d, 1H, *J* 18.3 Hz), 3.71 (dd, 1H, *J* 10.8, 5.2 Hz), 3.35 (dd, 1H, *J* 11.2, 9.6 Hz), 3.14 (br s, 1H), 2.01 (dd, 1H, *J* 9.6, 5.2 Hz), 1.88 (dddd, 1H, *J* 14.0, 7.2, 4.1, 4.0 Hz), 1.58 (m, 1H), 1.56 (m, 1H), 1.24 (m, 1H), 1.19 (m, 1H), 1.13 (s, 3H), 1.03 (d, 3H, *J* 6.0 Hz), 0.88 (m, 1H), 0.84 (d, 3H, *J* 6.4 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) 180.9, 173.8, 134.9, 69.3, 68.1, 61.8, 45.3, 41.3, 35.5, 33.7, 27.0, 21.8, 21.0, 17.8; HRMS *m*/*z* calcd for $C_{15}H_{22}O_3$ 250.1569, found 248.1568.

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Supplementary data

Supplementary data associated with this article can be found in online version at doi:10.1016/j.tet.2011.04.007.

References and notes

1. For example, Kornprobst, J.-M. *Encyclopedia of Marine Natural Products*; Wiley-VCH: Weinheim, Germany, 2010.
2. Osterhage, C.; König, G. M.; Höller, U.; Wright, A. D. *J. Nat. Prod.* **2002**, *65*, 306–313.
3. (a) Corey, E. J.; Nozoe, S. *J. Am. Chem. Soc.* **1965**, *87*, 5728–5733; (b) Piers, E.; Isenring, H. P. *Can. J. Chem.* **1977**, *55*, 1039–1044; (c) Shizuri, Y.; Suyama, K.; Yamamura, S. *J. Chem. Soc., Chem. Commun.* **1986**, 63–64; (d) Nagaoka, H.; Baba, A.; Yamada, Y. *Tetrahedron Lett.* **1991**, *32*, 6741–6744.
4. (a) McMurry, J. E. *J. Am. Chem. Soc.* **1968**, *90*, 6821–6825; (b) McMurry, J. E. *J. Org. Chem.* **1971**, *36*, 2826–2832; (c) Piers, E.; Geraghty, M. B.; Soucy, M. *Synth. Commun.* **1973**, *3*, 401–405; (d) Eck, C. R.; Hodgson, G. L.; MacSweeney, D. F.; Mills, R. W.; Money, T. *J. Chem. Soc., Perkin Trans. 1* **1974**, 1938–1943; (e) Piers, E.; Geraghty, M. B.; Smillie, R. D.; Soucy, M. *Can. J. Chem.* **1975**, *53*, 2849–2864; (f) Hagiwara, H.; Miyashita, M.; Yoshikoshi, A.; Uda, H. *Bull. Chem. Soc. Jpn.* **1975**, *48*, 3723–3726; (g) Bakuzis, P.; Campos, O. O. S.; Bakuzis, M. L. F. *J. Org. Chem.* **1976**, *41*, 3261–3264; (h) Yanagiya, M.; Kaneko, K.; Kaji, T.; Matsumoto, T. *Tetrahedron Lett.* **1979**, 1761–1764; (i) Snowden, R. L. *Tetrahedron Lett.* **1981**, *22*, 101–102; (j) Oppolzer, W.; Godel, T. *Helv. Chim. Acta* **1984**, *67*, 1154–1167; (k) Sigrist, R.; Rey, M.; Dreiding, A. S. *Helv. Chim. Acta* **1988**, *71*, 788–807; (l) Wenkert, E.; Bookser, B. C.; Arrhenius, T. S. *J. Am. Chem. Soc.* **1992**, *114*, 644–654; (m) Hatsui, T.; Hashiguchi, T.; Takeshita, H. *Chem. Lett.* **1994**, 1415–1416; (n) Karimi, S. *J. Nat. Prod.* **2001**, *64*, 406–410.
5. Fukushima, M.; Morii, A.; Hoshi, T.; Suzuki, T.; Hagiwara, H. *Tetrahedron* **2007**, *63*, 7154–7164; Fukushima, M.; Endou, S.; Hoshi, T.; Suzuki, T.; Hagiwara, H. *Tetrahedron Lett.* **2005**, *46*, 3287–3290; Hagiwara, H.; Endou, S.; Fukushima, M.; Hoshi, T.; Suzuki, T. *Org. Lett.* **2004**, *6*, 1115–1118; Hagiwara, H.; Morii, A.; Yamada, Y.; Hoshi, T.; Suzuki, T. *Tetrahedron Lett.* **2003**, *44*, 1595–1597; Hagiwara, H.; Sakai, H.; Uchiyama, T.; Ito, Y.; Morita, N.; Hoshi, T.; Suzuki, T.; Ando, M. *J. Chem. Soc., Perkin Trans. 1* **2002**, 583–591.
6. De Faria, M. L.; Magalhaes, R. A.; Silva, F. C.; Matias, L. G. O.; Ceschi, M. A.; Brocksom, U.; Brocksom, T. *Tetrahedron: Asymmetry* **2000**, *11*, 4093–4103.
7. Watanabe, H.; Onoda, T.; Kitahara, T.; Mori, K. *Tetrahedron Lett.* **1997**, *38*, 6015–6018.
8. (a) Behenna, D. C.; Stoltz, B. M. *J. Am. Chem. Soc.* **2004**, *126*, 15044–15045; (b) Seto, M.; Roizen, J. L.; Stoltz, B. M. *Angew. Chem., Int. Ed.* **2008**, *47*, 6873–6876; (c) Krout, M. R.; Mohr, J. T.; Stoltz, B. M. *Org. Synth.* **2009**, *86*, 181–193.
9. Hon, Y.-S.; Lin, S.-W.; Lu, L.; Chen, Y.-J. *Tetrahedron* **1995**, *51*, 5019–5034.
10. Mander, L. N.; Sethi, S. P. *Tetrahedron Lett.* **1983**, *24*, 5425–5428.
11. Cacchi, S.; Morera, E.; Ortar, G. *Tetrahedron Lett.* **1984**, *25*, 4821–4824; Inoue, M.; Lee, N.; Kasuya, S.; Sato, T.; Hirama, M.; Moriyama, M.; Fukuyama, Y. *J. Org. Chem.* **2007**, *72*, 3065–3075.
12. Ley, S. V.; Brown, D. S.; Clase, J. A.; Fairbanks, A. J.; Lennon, I. C.; Osborn, H. M. I.; Stokes, E. S. E.; Wadsworth, D. J. *J. Chem. Soc., Perkin Trans. 1* **1998**, 2259–2276.
13. Crisp, G. T.; Meyer, A. G. *J. Org. Chem.* **1992**, *57*, 6972–6975.
14. Preliminary communication: Hagiwara, H.; Fukushima, M.; Kinugawa, K.; Matsui, M.; Hoshi, T.; Suzuki, T. *Nat. Prod. Commun.* **2011**, *6*, 311–313.