Stereoselective synthesis of *epi*-jasmonic acid, tuberonic acid, and 12-oxo-PDA†

Hisato Nonaka, Narihito Ogawa, Noriaki Maeda, Yong-Gang Wang and Yuichi Kobayashi*

Received 6th June 2010, Accepted 6th August 2010
DOI: 10.1039/c0ob00218f

epi-Jasmonic acid (*epi*-JA) and tuberonic acid (TA) were synthesized from the key aldehyde, all *cis*-2-(2-hydroxy-5-vinylcyclopentyl)acetaldehyde (**14**), which was in turn prepared stereoselectively from the (1*R*)-acetate of 4-cyclopentene-1,3-diol (**10**) through S_N2-type allylic substitution with CH_2═CHMgBr followed by Mitsunobu inversion, Eschenmoser–Claisen rearrangement, and regioselective Swern oxidation of the corresponding bis-TES ether (**13**). Wittig reaction of the aldehyde **14** with $[Ph_3P(CH_2)Me]^+Br^-$ followed by oxidation afforded *epi*-JA (**3**) stereoselectivity over the *trans* isomer. Similarly, TA (**5**) was synthesized. Furthermore, the above findings were applied successfully to improve the total efficiency of the previous synthesis of 12-oxo-PDA (**1**).

Introduction

Plants metabolize linolenic acid to a class of cyclopentanones and -enones, which possess the two side chains at the α and β positions (Fig. 1).[1] Different from the well-known prostaglandins, the side chains are projected to the same direction (defined herein as the *cis* configuration),[2] which renders the metabolites susceptible to isomerization at the α carbon to produce the thermodynamically more stable *trans* isomers. Indeed, the metabolites isolated from natural sources through multi-step purifications have been contaminated with the *trans* isomers in varying ratios, whereas these materials have been used for biological studies.[3] The thermodynamic instability also restricts reactions for stereocontrolled synthesis of these metabolites. For example, the enolate reaction is ill-suited. Strongly acidic and basic conditions should be avoided as well. Consequently, stereoselective synthesis of the metabolites is a challenging subject in modern organic chemistry.[4]

Recently, we have established regio- and stereoselective allylic substitution of the monoacetate of *cis*-4-cyclopentene-1,3-diol with copper and borane reagents derived from organometallics such as RMgX and RLi.[5,6] This substitution was utilized to construct the intermediates with the upper chain of 12-oxo-PDA (**1**), OPC-8:0 (**2**), and related compounds, while the lower chain was attached through the Claisen rearrangement.[7] Later, 12-oxo-PDA was used to identify a peroxisomal acyl-activating enzyme[8] and to elucidate the expression of the specific DNA.[9]

Afterwards, we focused our attention on the synthesis of *epi*-JA (**3**) and TA (**5**). The former is the junction in the metabolic cascade leading to Me *epi*-JA (**4**)[1,2,10] and amino acid conjugates **7**,[11,12] though a mechanism regulating the two pathways is not fully clarified. The lack of a method to obtain *epi*-JA seems responsible for. So far, optically active *epi*-JA was once synthesized from diol **8** as a mixture with lactone **9** [eqn (1)].[13] On the other hand, several syntheses of optically active Me *epi*-JA have been reported,[13,14] though reaction conditions for hydrolysis to *epi*-JA are not established. Instead, chemically stable analogues of *epi*-JA has been synthesized.[15] TA (**5**)[16] and TAG (**6**)[17] have been isolated from the leaves of potato as the promoters of the tuber formation. The *cis* configuration for the two side chains of TAG

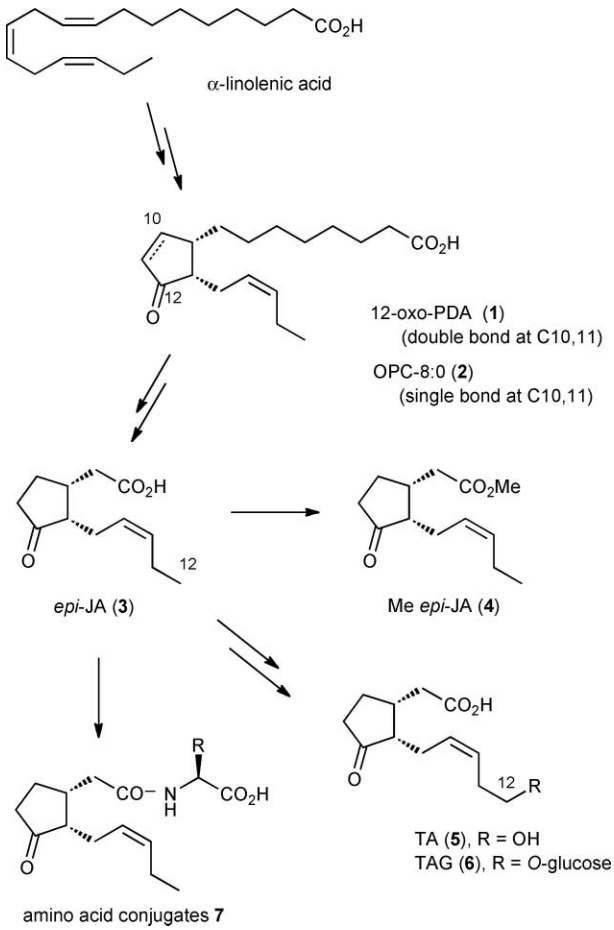


Fig. 1 The linolenic acid cascade in plants. 12-oxo-PDA, (15*Z*)-12-oxo-10,15-phytodienoic acid; OPC-8:0, (3-oxo-2-((2*Z*)-pentenyl)cyclopentyl)octanoic acid; *epi*-JA, *epi*-jasmonic acid; Me *epi*-JA, methyl *epi*-jasmonate; TA, tuberonic acid; TAG, tuberonic acid glucoside.

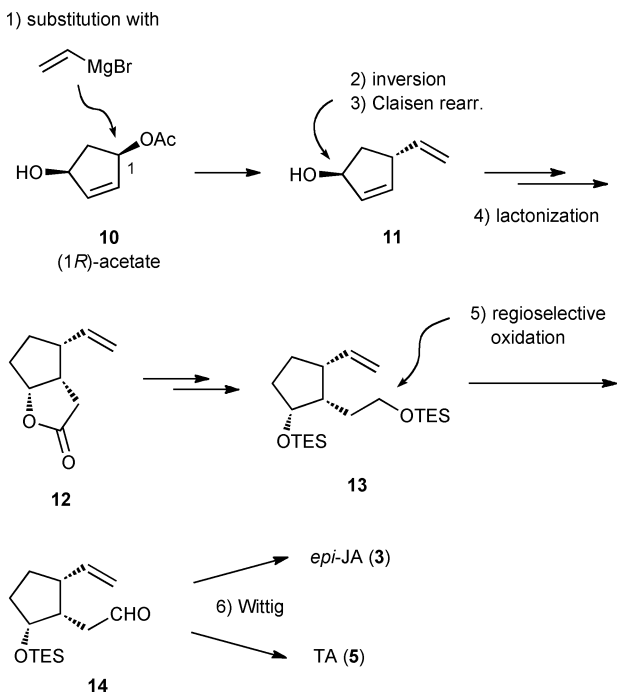
Department of Biomolecular Engineering, Tokyo Institute of Technology, B52, Nagatsuta-cho 4259, Midori-ku, Yokohama, 226-8501, Japan. E-mail: ykobayas@bio.titech.ac.jp

† Electronic supplementary information (ESI) available: Spectral data for the compounds described herein. See DOI: 10.1039/c0ob00218f

was determined by Koda on the basis of the time-dependent loss of the biological activity.[18,19] The assignment is consistent with the stereochemistry that is created by the cascade. By analogy, the *cis* configuration was assigned to TA (**5**). Previously, the methyl ester of TA has been synthesized as optically active and racemic forms by Kitahara[20] and Kiyota,[21] respectively. In these syntheses, they observed isomerization to the *trans* isomer during the removal of the THP, EE (ethoxyethyl), and TBDPS (*t*-BuPh$_2$Si) groups under acidic conditions, and hence changed these groups to the very unstable CF_3CO and TMS groups, respectively. Importantly, as was in the case of Me *epi*-JA, hydrolysis of the ester to TA is not reported.

(1)

With the above information on the stability in mind, we planed a synthesis of *epi*-JA (**3**) and TA (**5**), which is summarized in Scheme 1 with several key reactions. Aldehyde **14** was designed as a common key intermediate to be converted to targets **3** and **5** by using a Wittig reaction. The vinyl group chosen as a CH_2CO_2H equivalent[22] was expected to reduce steps for protection/deprotection manipulation. The realization of this strategy was communicated with the synthesis of **5**,[23] in which the conversion of lactone **12** to aldehyde **14** was accomplished quite efficiently and with operationally simple way through regioselective Swern oxidation[24] of bis-TES ether **13**. In addition, conversion of **11** to **12** was improved by using the Escenmosher–Claisen rearrangement, which is the mercury free version of the rearrangement. We then accomplished synthesis of *epi*-JA (**3**) along this line. Furthermore, the method was applied to the previous synthesis of 12-oxo-PDA (**1**) to improve the efficiency. Herein, we present a full account of the investigation.

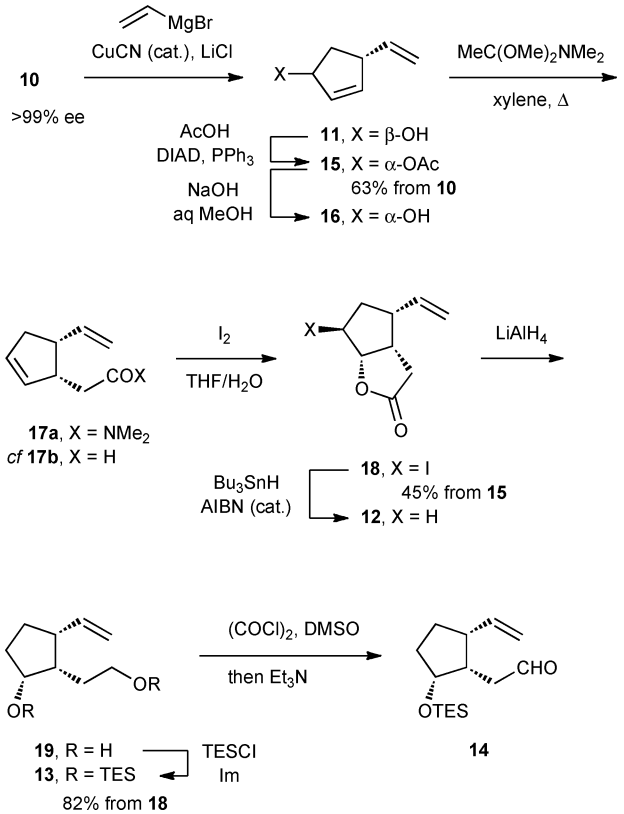


Scheme 1 An approach to *epi*-JA and TA.

Results and discussion

Synthesis of the key intermediate 14

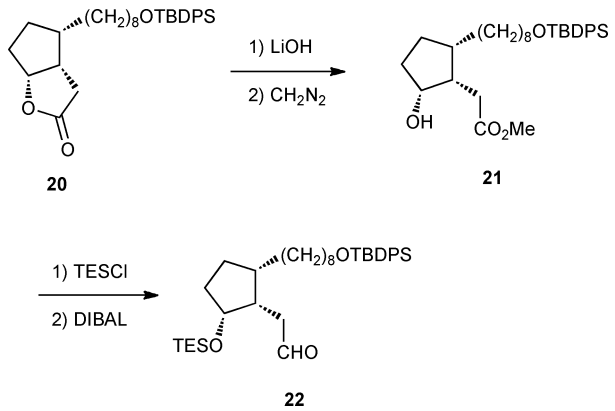
(1*R*)-Acetate **10** (>99% ee by chiral HPLC analysis) was prepared by the PPL-assisted hydrolysis of the corresponding diacetate (PPL, pig pancreatic lipase).[25] Allylic substitution of **10** with CH_2=CHMgBr was performed in the presence of CuCN and LiCl to afford **11** with 93% regioselectivity over the *anti* S_N2' isomer and with complete stereoselectivity (Scheme 2).[6c,d,26] Since the product is highly volatile, the 93 : 7 mixture was subjected to Mitsunobu inversion[27] with AcOH and DIAD in toluene at −78 °C to produce acetate **15** as a single product in 63% yield from **10**. Under these conditions the minor alcohol (regioisomer of **11**) remained unreacted probably due to the vinyl group obstacle. Acetate of **10** (stereoisomer of **15**) was not detected by ^{1}H NMR analysis (**15**, δ 3.21–3.32 ppm; acetate of **11**, δ 3.40–3.52 ppm). Hydrolysis of **15** afforded alcohol **16**, which was subjected to Claisen rearrangement using excess CH_2=CHOEt and $Hg(OAc)_2$ (cat.) in benzene at 180–200 °C according to the previous procedure.[7a] However, the reaction took place slowly to give, after 60 h, a mixture of aldehyde **17b** (22% yield) and alcohol **16** as minor and major components. Coordination of the vinyl group to the mercury catalyst is a likely reason for the low yield.[28] The Eschenmoser method[29] was next examined with $MeC(OMe)_2NMe_2$ in xylene under reflux. The reaction completed within 1 h to afford amide **17a**, which was then subjected to iodolactonization with I_2 in aqueous THF to



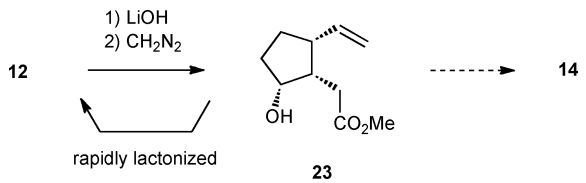
Scheme 2 Synthesis of the key intermediate **14**.

produce iodolactone **18** in 45% yield from acetate **15**. Inevitable loss of the volatile alcohol **16** during the isolation/purification might be responsible for the somewhat low yield (45%). The iodo group was then removed with Bu_3SnH and AIBN to afford lactone **12** without causing damage to the vinyl moiety.

Previously, lactone **20** was converted to aldehyde **22** in the synthesis of OPC-8:0 through the hydroxy methyl ester **21** in four steps (Scheme 3), in which **21** was quickly semi-purified for the next reaction in order to prevent lactonization back to **20**.[7a] This conversion was also successful with a similar lactone leading to 12-oxo-PDA (**1**). However, the present hydroxy ester **23** derived from lactone **12** underwent rapid lactonization to **12** (Scheme 4), which led us to investigate another sequence of reactions. As delineated in Scheme 2, reduction of lactone **12** with $LiAlH_4$ followed by bis-silylation of the resulting diol **19** afforded bis-TES ether **13** in 82% yield from iodolactone **18**. Swern oxidation[24] of **13** at the primary $TESOCH_2$ group proceeded regioselectively to afford aldehyde **14** as a sole product. This conversion is one-step shorter than the attempted sequence through **23** (Scheme 4) and, furthermore, the overall yield is acceptable (77% yield at the stage of **24**). In addition, the intermediates in this three-step sequence are chemically quite stable to allow easy handling.



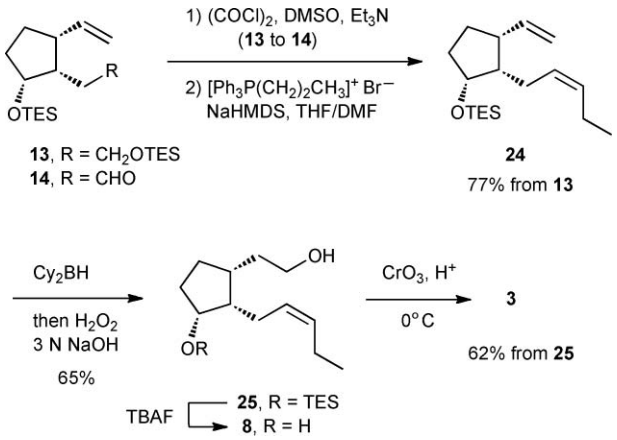
Scheme 3 The previous conversion of lactone **20** to aldehyde **22**.



Scheme 4 An attempted conversion of lactone **12** to aldehyde **14**.

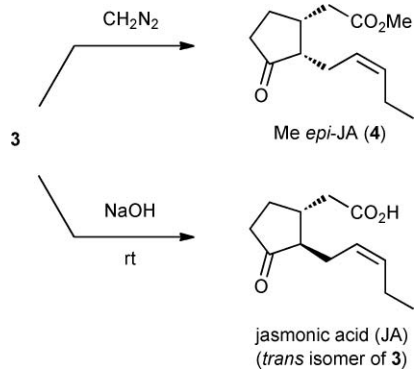
Synthesis of *epi*-JA

Aldehyde **14** prepared above was transformed to *epi*-JA (**3**) as delineated in Scheme 5. Wittig reaction with an ylide derived from $[Ph_3P(CH_2)_2Me]^+Br^-$ and NaHMDS ($NaN(TMS)_2$) in THF–DMF afforded *cis* olefin **24** stereoselectively. Hydroboration of **24** with Cy_2BH (Cy: *c*-C_6H_{11}) was regioselective to produce alcohol **25** in 65% yield after oxidative workup. Finally, desilylation of the TES group followed by Jones oxidation of the resulting diol **8** at 0 °C furnished *epi*-JA (**3**) in 62% yield from **25**. The lactone **9** produced previously[13] from **8** by the oxidation with PDC (eqn



Scheme 5 Synthesis of *epi*-JA (**3**).

(1)) was not detected. To confirm the structure of **3**, especially the *cis* configuration, **3** was converted (Scheme 6) to Me *epi*-JA (**4**) and the *trans* isomer (*i.e.*, JA), and the ^1H and ^{13}C NMR spectra of the products were found to be consistent with those reported.[13,14b,d,30] The chemical purity of **3** over the *trans* isomer was 98% by ^1H NMR spectroscopy (**3**, δ 2.77–2.91 ppm; the isomer, δ 2.71–2.83 ppm) (see page S13 of the ESI†).



Scheme 6 Conversion of **3** to the known compounds.

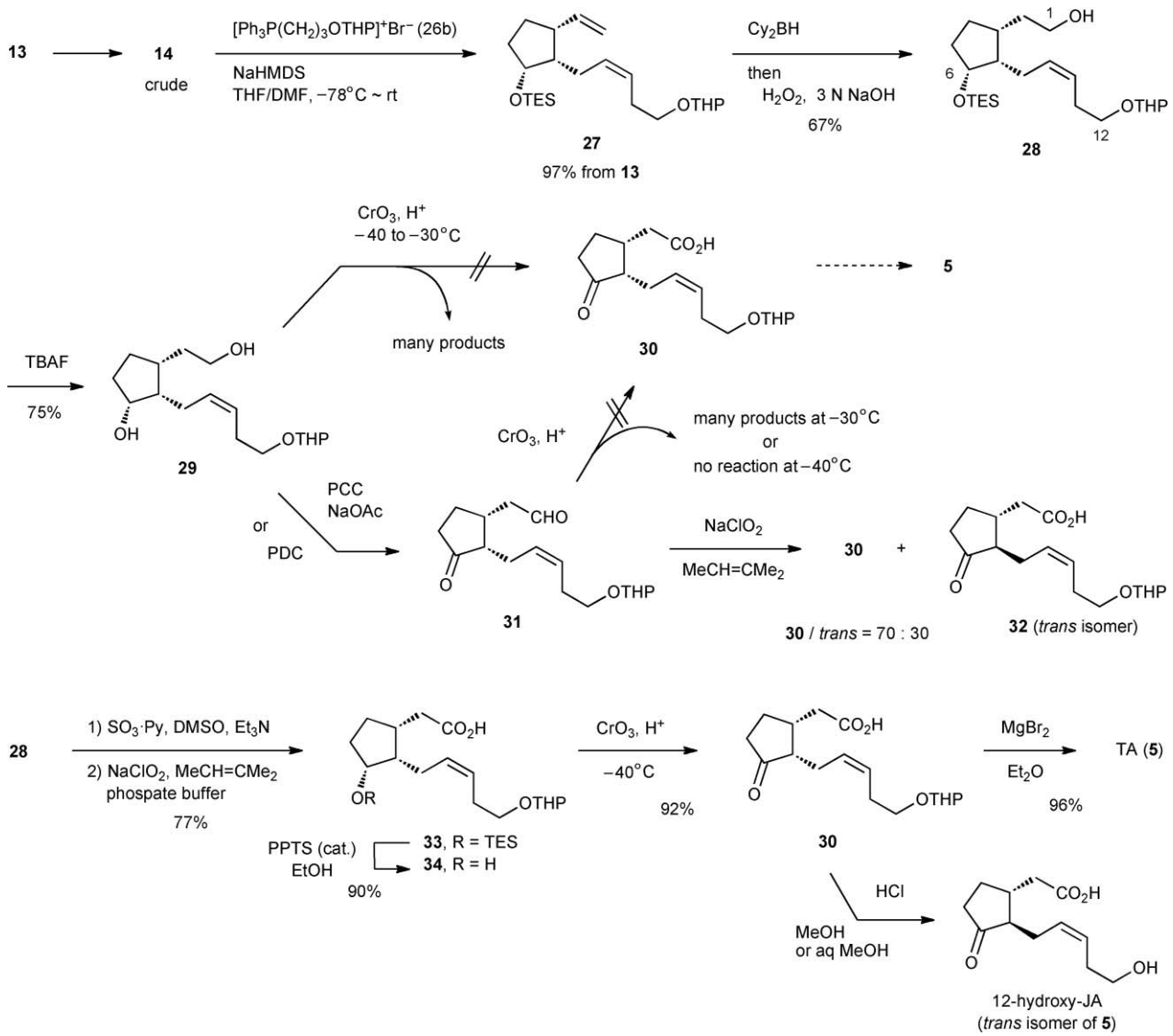
Synthesis of TA

Two phosphonium salts **26a,b** with PMB (*p*-$MeOC_6H_4CH_2$) and THP protective groups received attention as a Wittig partner of aldehyde **14**. Among them, **26a** was not examined for a specific reason found in a preliminary study using a model PMB ether derived from racemic Me JA.[31]

$[Ph_3P(CH_2)_3OR]+ Br-$

26 for R; **a**, PMB; **b**, THP

As shown in Scheme 7, Wittig reaction of aldehyde **14** with an anion derived from the THP ether **26b** afforded *cis* olefin **27**, which, upon hydroboration with Cy_2BH followed by oxidative workup, produced alcohol **28** in 67% yield. The remaining reactions at this stage were oxidation of the C1 and C6 carbons and deprotection of the THP group. First, desilylation of **28** afforded diol **29** in 75% yield. Jones oxidation was attempted between –40 and –30 °C in order to prevent unwanted deprotection of the THP protective group.[32] However, a mixture of products was produced. Next, the



Scheme 7 Synthesis of TA (**5**).

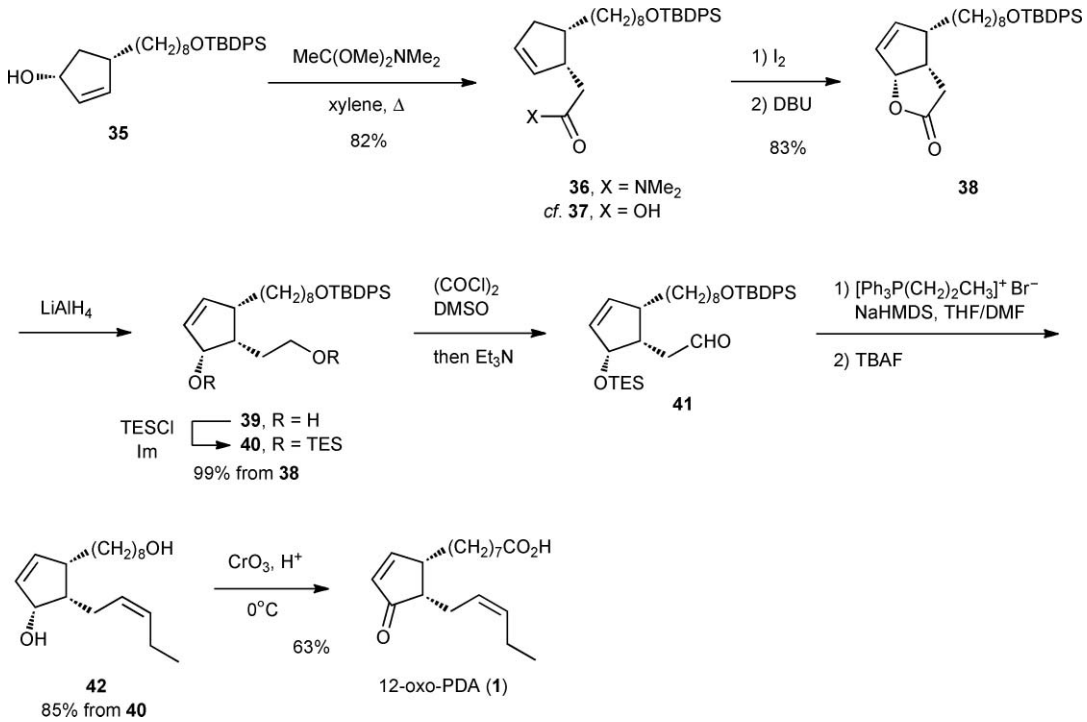
keto aldehyde **31** derived from diol **29** was subjected to Jones oxidation at −30 °C to give another mixture, whereas no oxidation took place at −40 °C. Oxidation of **31** with $NaClO_2$ proceeded with isomerization to afford a 70 : 30 mixture of **30** and the *trans* isomer **32**.[33]

The above results clearly suggested a sequential oxidation first at C1 and then at C6 is inevitable to prevent the competitive reactions and/or the isomerization. To this end, oxidation of alcohol **28** with SO_3·pyridine gave the corresponding aldehyde, which, upon further oxidation with $NaClO_2$ under neutral conditions,[34] afforded acid **33** in good yield. Selective removal of the TES group from **33** was accomplished with PPTS (*ca.* 0.3 equiv) in EtOH (rt, 1 h) to produce the acid alcohol **34** in 90% yield.[35] Finally, Jones oxidation of alcohol **34** at −40 °C produced the keto acid **30** without any cleavage of the THP group and isomerization to the *trans* isomer.

To remove the THP group the keto acid **30** was exposed to dry HCl (5 mol%; derived from AcCl) in MeOH at room temperature, which unfortunately induced complete isomerization to the *trans* isomer (12-hydroxy-JA),[33] while exposure to 0.1 N HCl (5 mol%) in MeOH at 0 °C afforded a 27 : 73 mixture of TA (**5**) and the *trans* isomer. The facile isomerization is consistent with that reported previously for the deprotection of the THP, EE, and TBDPS ethers of the TA methyl ester in 70% AcOH at 60 °C and with HF in aqueous MeCN at −20 °C.[20,21] We then examined several protocols to finally find that $MgBr_2$ (3 equiv) in Et_2O[36] at room temperature for 2 h provided TA (**5**) in high yield with a minimum level of the isomerization (ratio of **5** to the *trans* isomer = 92 : 8 by ^{1}H NMR spectroscopy) (see page S23 of the ESI†). This step was repeated several times with similar selectivities.

Isomerization of TA

Time-dependency of the isomerization of TA (**5**) to the *trans* isomer was studied at room temperature in CD_3OD by monitoring the protons at δ 2.74–2.88 and 2.60–2.71 ppm for **5** and the *trans* isomer,[33] respectively. In contrast to the fairly rapid isomerization under acidic conditions (see above) and basic conditions,[33] little



Scheme 8 Synthesis of 12-oxo-PDA (**1**).

isomerization was detected even after 21 days! We then added K_2CO_3 (heterogeneous in CD_3OD), which catalyzed isomerization slowly to produce a 40 : 60 mixture after 7 days.

Synthesis of 12-oxo-PDA

Due to the demand for the biological study of 12-oxo-PDA,[8,9] the above findings were applied to the previous synthesis of 12-oxo-PDA.[7a, cf. 37] As shown in Scheme 8 Eschenmoser–Claisen rearrangement of alcohol **35**[7a] in xylene afforded amide **36** in 82% yield, which was subjected to iodolactonization with I_2 in aqueous THF and subsequent reaction with DBU to produce lactone **38** in 83% yield. In addition to the advantage of using the mercury-free method, the present method is superior in terms of yield, reaction time, operation, and steps to the original procedure [(1) CH_2═$CHOEt/Hg(OAc)_2$ cat., 170 °C, 61 h, a sealed tubing; (2) Jones oxidation of the resulting aldehyde to acid **37** in 79% yield over two steps]. Lactone **38** was converted successfully to aldehyde **41** through Swern oxidation of the bis-TES ether **40**. Subsequently, Wittig reaction and desilylation afforded diol **42** in 85% yield from lactone **38**. Finally, Jones oxidation of diol **42** furnished 12-oxo-PDA (**1**) in 63% yield. Diastereomeric purity of **1** was >95% by ^{1}H NMR spectroscopy, which was identical to that obtained previously. The overall yield of **1** from **35** was improved to be 36% (previously 19%).[38]

Conclusions

We have established a synthesis *epi*-JA (**3**) and TA (**5**), for the first time. Furthermore, the mercury-free Claisen rearrangement and the new method for conversion of lactone **12** to aldehyde **14** was applied to the previous synthesis of 12-oxo-PDA (**1**) to establish a new method to **1**. In addition, stability of **5** was studied under neutral conditions to establish no isomerization over an extended period. The stability of **5** established herein will be quite informative for modifying the isolation of **5** (and probably **3**) from the natural sources.

Experimental

General remarks

Infrared (IR) spectra are reported in wave numbers (cm^{-1}). The ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were measured in $CDCl_3$ using $SiMe_4$ (δ = 0 ppm) and the center line of $CDCl_3$ triplet (δ = 77.1 ppm) as internal standards, respectively. Signal patterns are indicated as br s, broad singlet; s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet. Coupling constants (J) are given in hertz (Hz). In some cases chemical shifts of carbons accompany plus (for C and CH_2) and minus (for CH and CH_3) signs of APT (Attached Proton Test) experiments. (1*R*)-acetate **10** of >99% ee (by chiral HPLC analysis) was prepared according to the literature procedure.[25] The following solvents were distilled before use: THF (from Na/benzophenone), Et_2O (from Na/benzophenone), and CH_2Cl_2 (from CaH_2).

(1*R*,4*R*)-4-Vinylcyclopent-2-enyl ethanoate (15). To an ice-cold solution of LiCl (1.20 g, 28.3 mmol) in THF (2.5 mL) was added CH_2═$CHMgBr$ (30 mL, 0.70 M in THF, 21 mmol) dropwise. After 20 min at 0 °C, CuCN (189 mg, 2.11 mmol) was added. The mixture was stirred at 0 °C for 15 min, and a solution of monoacetate **10** (1.0 g, 7.03 mmol, >99% ee) in THF (2.5 mL) was added. The reaction was carried out for 30 min and quenched by addition of saturated NH_4Cl and 28% NH_4OH with vigorous stirring. The resulting mixture was extracted with Et_2O twice. The combined extracts were washed with brine, dried over $MgSO_4$, and

concentrated to give alcohol **11** and the regioisomer in a 93 : 7 ratio, which was used for the next reaction without further purification: R_f (hexane–EtOAc 3 : 1) = 0.28 and 0.08 for **11** and **10**; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.65–2.05 (m, 3 H), 3.53 (br q, J = 7.5 Hz, 1 H), 4.89 (br s, 1 H), 4.93 (ddd, J = 10, 2, 1 Hz, 1 H), 5.03 (ddd, J = 17, 2, 1.5 Hz, 1 H), 5.66 (ddd, J = 17, 10, 8 Hz, 1 H), 5.88 (br s, 2 H).

To a solution of the above mixture in toluene (8 mL) at −78 °C were added PPh_3 (3.70 g, 14.1 mmol), AcOH (0.81 mL, 14.1 mmol), and DIAD (2.95 mL, 15.0 mmol). The mixture was stirred at −78 °C for 5 min, and diluted with saturated $NaHCO_3$ and hexane. The resulting mixture was filtered through a pad of Celite. The filtrate was washed with brine, dried over $MgSO_4$, and concentrated to afford a residue, which was purified by chromatography (hexane–EtOAc) to give acetate **15** (676 mg, 63% from **10**): R_f (hexane–EtOAc 3 : 1) = 0.70 and 0.27 for **15** and **11**; $[\alpha]_D^{23}$ = −53 (*c* 1.57, $CHCl_3$); IR (neat) 3079, 1738, 1239 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.57 (dt, J = 14, 5 Hz, 1 H), 2.04 (s, 3 H), 2.60 (dt, J = 14, 8 Hz, 1 H), 3.21–3.32 (m, 1 H), 4.98 (ddd, J = 10, 2, 1 Hz, 1 H), 5.07 (dt, J = 17, 1.5 Hz, 1 H), 5.61–5.68 (m, 1 H), 5.77 (ddd, J = 17, 10, 8 Hz, 1 H), 5.84 (dt, J = 5.5, 2 Hz, 1 H), 5.94 (ddd, J = 5.5, 2, 1 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 21.4 (–), 36.9 (+), 48.1 (–), 79.8 (–), 114.2 (+), 130.0 (–), 139.4 (–), 141.2 (–), 171.0 (+).

(1*S*,4*R*)-4-Vinylcyclopent-2-enyl ethanoate (acetate of 11). According to the above procedure, a solution of monoacetate **10** (500 mg, 3.52 mmol) in THF (2 mL) was added to an ice-cold mixture of CH_2=CHMgBr (16 mL, 0.66 M in THF, 11 mmol), CuCN (95 mg, 1.1 mmol), and LiCl (597 mg, 14.1 mmol) in THF (2 mL). The reaction was carried out at 0 °C for 1.5 h to afford alcohol **11**, which was used for the next reaction without further purification.

A solution of the above alcohol **11** and Ac_2O (0.50 mL, 5.3 mmol) in pyridine (2 mL) was stirred at room temperature overnight, and diluted with CH_2Cl_2 and 1 N NaOH with vigorous stirring. The organic phase was separated, and the aqueous phase was extracted with CH_2Cl_2 twice. The combined organic layers were washed with 1 N HCl and brine, dried over $MgSO_4$, and concentrated to afford a residue, which was purified by chromatography (hexane–EtOAc) to give acetate of **11** (403 mg, 75% from **10**): R_f (hexane–EtOAc 3 : 1) = 0.70 and 0.27 for the acetate and **11**; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.95 (s, 3 H), 1.85–2.14 (m, 2 H), 3.40–3.52 (m, 1 H), 4.90 (d, J = 10 Hz, 1 H), 4.98 (dt, J = 17, 1.5 Hz, 1 H), 5.53–5.67 (m, 2 H), 5.81 (dt, J = 6, 2 Hz, 1 H), 5.91 (dd, J = 6, 2 Hz, 1 H).

(3a*S*,4*R*,6*S*,6a*S*)-6-Iodo-4-vinylhexahydro-2*H*-cyclopenta-[*b*]furan-2-one (18). To a solution of acetate **15** (1.10 g, 7.22 mmol) in MeOH (7 mL) was added 3 N NaOH (7 mL). The mixture was stirred at room temperature for 15 min and diluted with Et_2O. The organic layer was separated, and the aqueous layer was extracted with Et_2O twice. The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated to give alcohol **16**, which was used for the next reaction without further purification: ^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.47 (dt, J = 14, 5 Hz, 1 H), 2.55 (ddd, J = 14, 8, 7 Hz, 1 H), 3.22 (br q, J = 7 Hz, 1 H), 4.77–4.85 (m, 1 H), 4.97 (d, J = 10 Hz, 1 H), 5.05 (dt, J = 17, 1.5 Hz, 1 H), 5.77–5.93 (m, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 40.6, 48.0, 65.9, 113.7, 134.2, 137.1, 142.2.

A solution of the above alcohol and $MeC(OMe)_2NMe_2$ (5.90 mL, 90% purity, 36.3 mmol) in xylene (24 mL) was stirred at 150 °C (oil bath temperature) for 1 h, cooled to room temperature, and concentrated. The residue was passed through a short column of silica gel (hexane–EtOAc) to give amide **17a**, which was used for the next reaction without further purification: R_f (hexane–EtOAc 1 : 1) = 0.35 and 0.57 for **17a** and **16**; $[\alpha]_D^{26}$ = −62.8 (*c* 1.13, $CHCl_3$); IR (neat) 1645, 1398, 1140 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 2.15 (dd, J = 16, 9 Hz, 1 H), 2.17–2.30 (m, 1 H), 2.35 (dd, J = 16, 7 Hz, 1 H), 2.43–2.58 (m, 1 H), 2.94 (s, 3 H), 2.97 (s, 3 H), 3.21–3.32 (m, 1 H), 4.96–5.08 (m, 2 H), 5.75 (br s, 1 H), 5.81 (ddd, J = 17, 10, 8 Hz, 1 H).

To an ice-cold solution of the above amide in THF (5 mL) were added I_2 (1.80 g, 7.09 mmol) and H_2O (5 mL). The resulting mixture was stirred at room temperature overnight and diluted with aqueous $Na_2S_2O_3$ and EtOAc. The organic phase was separated, and the aqueous phase was extracted with EtOAc twice. The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated to afford a residue, which was purified by chromatography (hexane–EtOAc) to give iodolactone **18** (889 mg, 45% from **15**): R_f (hexane–EtOAc 3 : 1) = 0.45 and 0.15 for **18** and **17a**; $[\alpha]_D^{25}$ = +11 (*c* 1.16, $CHCl_3$); IR (neat) 3079, 1781, 1167, 1010 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.97 (ddd, J = 15, 12, 5 Hz, 1 H), 2.12 (dd, J = 15, 7 Hz, 1 H), 2.54 (dd, J = 19, 4 Hz, 1 H), 2.58 (dd, J = 19, 9 Hz, 1 H), 3.15–3.27 (m, 1 H), 3.34–3.49 (m, 1 H), 4.49 (d, J = 5 Hz, 1 H), 5.12 (dt, J = 17, 1.5 Hz, 1 H), 5.22 (dt, J = 10.5, 1.5 Hz, 1 H), 5.28 (d, J = 6.5 Hz, 1 H), 5.77 (ddd, J = 17, 10.5, 6.5 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 27.7 (–), 29.8 (+), 38.4 (+), 39.6 (–), 44.1 (–), 92.4 (–), 118.0 (+), 135.5 (–), 176.4 (+). HRMS (FAB) calcd for $C_9H_{11}IO_2Na$ [(M+Na)$^+$] 300.9701, found 300.9699.

(1*R*,2*S*,3*R*)-2-(2-Hydroxyethyl)-3-vinylcyclopentanol (19). A solution of iodolactone **18** (650 mg, 2.24 mmol), Bu_3SnH (1.20 mL, 4.47 mmol), and AIBN (4 mg, 0.024 mmol) in benzene (5 mL) was stirred at 85 °C (oil bath temperature) for 30 min, cooled to room temperature, and diluted with CH_2Cl_2. The solution was washed with 1 N NaOH and with brine. The aqueous solutions used were extracted with CH_2Cl_2 twice. The CH_2Cl_2 solutions were combined, dried over $MgSO_4$, and concentrated. The residue was passed through a short column of silica gel (hexane–EtOAc) to give lactone **12**, which was used for the next reaction without further purification: R_f (hexane–EtOAc 3 : 1) = 0.43 for **12** and **18**; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.39–1.58 (m, 1 H), 1.62–1.80 (m, 2 H), 1.99 (dd, J = 13, 7 Hz, 1 H), 2.36 (dd, J = 19, 5 Hz, 1 H), 2.43 (dd, J = 19, 10.5 Hz, 1 H), 2.53–2.67 (m, 1 H), 2.90–3.03 (m, 1 H), 4.95–5.03 (m, 1 H), 5.01 (dt, J = 17, 1.5 Hz, 1 H), 5.08 (dt, J = 11, 1.5 Hz, 1 H), 5.71 (ddd, J = 17, 11, 6.5 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 26.9 (+), 29.7 (+), 32.7 (+), 40.9 (–), 46.1 (–), 85.8 (–), 116.7 (+), 136.9 (–), 177.7 (+).

To an ice-cold suspension of $LiAlH_4$ (255 mg, 6.71 mmol) in THF (6 mL) was added the above lactone in THF (6 mL) dropwise. After 5 min of stirring at 0 °C, excess hydride was quenched with H_2O. The resulting mixture was diluted with EtOAc and 1 N HCl, and stirred vigorously at room temperature until the layers became clear. The organic layer was separated and washed with brine. The combined aqueous layers were extracted with EtOAc twice. The organic layers were combined, dried over $MgSO_4$, and concentrated to give diol **19**, which was used for the next reaction

without further purification. The reaction was repeated to obtain analytically pure **19**: R_f (hexane–EtOAc 1 : 1) = 0.24 and 0.66 for **19** and **12**; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.52–1.99 (m, 7 H), 2.54–2.68 (m, 1 H), 3.61 (ddd, J = 10, 9, 4.5 Hz, 1 H), 3.78 (dt, J = 10, 5 Hz, 1 H), 3.89 (br s, 2 H), 4.23–4.33 (m, 1 H), 4.87–4.99 (m, 2 H), 5.89 (dt, J = 18, 9 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 28.5 (+), 29.5 (+), 33.2 (+), 46.0 (–), 47.2 (–), 62.2 (+), 74.4 (–), 113.9 (+), 141.8 (–). HRMS (FAB) calcd for $C_9H_{16}O_2Na$ [(M+Na)$^+$] 179.1048, found 179.1050.

(1*R*,2*S*,3*R*)-1-(Triethylsilyloxy)-2-(2-(triethylsilyloxy)-ethyl)-3-vinylcyclopentane (13). A solution of the above diol, TESCl (1.13 mL, 6.70 mmol), and imidazole (610 mg, 8.96 mmol) in DMF (1.1 mL) was stirred at room temperature overnight and directly subjected to chromatography (hexane–EtOAc) to give the TES ether **13** (704 mg, 82% from **18**): R_f (hexane–EtOAc 1 : 1) = 0.95 and 0.25 for **13** and **19**; $[\alpha]_D^{25}$ = –6 (c 0.99, $CHCl_3$); IR (neat) 3079, 1414, 1239, 1095 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 0.53–0.64 (m, 12 H), 0.94 (t, J = 8 Hz, 18 H), 1.50–1.94 (m, 7 H), 2.57 (dq, J = 4, 9 Hz, 1 H), 3.62 (t, J = 7 Hz, 2 H), 4.12–4.19 (m, 1 H), 4.80–4.90 (m, 2 H), 5.92 (dt, J = 17, 10 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 4.5 (+), 5.1 (+), 6.9 (–), 7.0 (–), 29.4 (+), 30.2 (+), 34.7 (+), 45.26 (–), 45.34 (–), 62.0 (+), 75.8 (–), 113.1 (+), 143.4 (–). HRMS (FAB) calcd for $C_{21}H_{44}O_2Si_2Na$ [(M+Na)$^+$] 407.2778, found 407.2781.

(1*R*,2*S*,3*R*)-1-(Triethylsilyloxy)-2-((*Z*)-pent-2-enyl)-3-vinylcyclopentane (24). To a solution of $(COCl)_2$ (0.11 mL, 1.26 mmol) in CH_2Cl_2 (2 mL) was added DMSO (0.19 mL, 2.68 mmol) at –78 °C. After 15 min, TES ether **13** (100 mg, 0.260 mmol) in CH_2Cl_2 (3 mL) was added dropwise. The suspension was stirred below –60 °C for 40 min, and Et_3N (0.36 mL, 2.60 mmol) was added. The resulting mixture was stirred vigorously below –60 °C for 20 min and then at room temperature for 10 min before dilution with CH_2Cl_2. The solution thus obtained was washed with saturated $NaHCO_3$ and then with brine. The aqueous solutions were extracted with CH_2Cl_2 twice. The extracts were combined, dried over $MgSO_4$, and concentrated to give aldehyde **14**, which was used for the next reaction without further purification: ^{1}H NMR (300 MHz, $CDCl_3$) δ = 0.56 (q, J = 8 Hz, 6 H), 0.92 (t, J = 8 Hz, 9 H), 1.56–1.88 (m, 4 H), 2.33–2.58 (m, 3 H), 2.62–2.74 (m, 1 H), 4.22–4.28 (m, 1 H), 4.84–4.94 (m, 2 H), 5.79 (ddd, J = 17, 11, 9 Hz, 1 H), 9.79 (br s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 4.9 (+), 6.9 (–), 28.7 (+), 33.9 (+), 40.7 (+), 43.6 (–), 44.7 (–), 75.1 (–), 114.6 (+), 141.7 (–), 203.0 (–).

To an ice-cold suspension of $[Ph_3P(CH_2)_2Me]^+Br^-$ (331 mg, 0.859 mmol) in THF (3 mL) was added NaHMDS (0.78 mL, 1 M in THF, 0.78 mmol). The resulting orange-red mixture was stirred at room temperature for 40 min and cool to –78 °C. To this solution were added DMF (0.5 mL) and a solution of the above aldehyde in THF (3 mL) dropwise. The resulting solution was stirred at –78 °C for 2 h, allowed to warm to room temperature, and stirred overnight. Saturated NH_4Cl and EtOAc were added with vigorous stirring. The mixture was separated, and the aqueous layer was extracted with EtOAc twice. The combined organic layers were dried over $MgSO_4$ and concentrated to afford a residue, which was purified by chromatography (hexane–EtOAc) to give olefin **24** (59 mg, 77% from **13**): R_f (hexane–EtOAc 5 : 1) = 0.76; $[\alpha]_D^{22}$ = –18 (c 0.98, $CHCl_3$); IR (neat) 3073, 1075, 1005 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 0.59 (q, J = 8 Hz, 6 H), 0.95 (t, J = 7.5 Hz, 3 H), 0.96 (t, J = 8 Hz, 9 H), 1.56–1.80 (m, 4 H), 1.80–1.93 (m, 1 H), 1.96–2.19 (m, 4 H), 2.59 (dq, J = 4, 18 Hz, 1 H), 4.16–4.21 (m, 1 H), 4.80–4.91 (m, 2 H), 5.26–5.45 (m, 2 H), 5.94 (dt, J = 17, 10 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 5.1 (+), 7.0 (–), 14.4 (–), 20.8 (+), 23.9 (+), 30.1 (+), 34.7 (+), 45.6 (–), 50.1 (–), 75.4 (+), 113.1 (+), 129.0 (–), 131.5 (–), 143.3 (–). HRMS (EI) calcd for $C_{18}H_{34}OSi$ [M$^+$] 294.2379, found 294.2382.

2-((1*R*,2*S*,3*R*)-2-((*Z*)-Pent-2-enyl)-3-(triethylsilyloxy)-cyclopentyl)ethanol (25). To an ice-cold solution of olefin **24** (40 mg, 0.136 mmol) in THF (2 mL) was added freshly prepared Cy_2BH (0.82 mL, 0.5 M in THF, 0.41 mmol). After 15 min at 0 °C, 3 N NaOH (2 mL) and 35% H_2O_2 (2 mL) were added to the solution. The resulting mixture was stirred at room temperature for 1 h and diluted with EtOAc. The organic phase was separated, and the aqueous phase was extracted EtOAc twice. The combined organic phases were washed with brine, dried over $MgSO_4$, and concentrated. The residue was purified by chromatography (hexane–EtOAc) to give alcohol **25** (27 mg, 65%): R_f (hexane–EtOAc 5 : 1) = 0.33 and 0.74 for **25** and **24**; $[\alpha]_D^{24}$ = –2 (c 1.45, $CHCl_3$); IR (neat) 3350, 1053, 1016 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 0.57 (q, J = 8 Hz, 6 H), 0.95 (t, J = 8 Hz, 9 H), 0.97 (t, J = 7.5 Hz, 3 H), 1.18–1.87 (m, 8 H), 1.93–2.28 (m, 5 H), 3.51–3.62 (m, 1 H), 3.67 (ddd, J = 10.5, 8, 5 Hz, 1 H), 4.11–4.19 (m, 1 H), 5.28–5.50 (m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 5.0 (+), 7.0 (–), 14.3 (–), 20.8 (+), 22.7 (+), 28.6 (+), 33.8 (+), 35.0 (+), 35.9 (–), 48.8 (–), 62.5 (+), 75.3 (–), 129.3 (–), 131.6 (–). HRMS (FAB) calcd for $C_{18}H_{37}O_2Si$ [(M+H)$^+$] 313.2563, found 313.2570.

***epi*-Jasmonic acid (3).** To an ice-cold solution of alcohol **25** (32 mg, 0.102 mmol) in THF (1 mL) was added TBAF (0.30 mL, 1 M in THF, 0.30 mmol). The solution was stirred at room temperature for 2 h and concentrated. The residue was passed through a short column of silica gel (hexane–EtOAc) to give diol **8**, which was used for the next reaction without further purification: R_f (hexane–EtOAc 1 : 1) = 0.27; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 0.98 (t, J = 8 Hz, 3 H), 1.1–1.9 (m, 9 H), 1.97–2.21 (m, 4 H), 2.22–2.35 (m, 1 H), 3.59 (dt, J = 10, 7 Hz, 1 H), 3.70 (ddd, J = 10, 8, 5 Hz, 1 H), 4.17–4.26 (m, 1 H), 5.35–5.47 (m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 14.3 (–), 20.8 (+), 22.9 (+), 28.9 (+), 33.3 (+), 34.8 (+), 36.1 (–), 47.8 (–), 62.2 (+), 75.1 (–), 128.4 (–), 132.4 (–). These data were consistent with those reported.[13]

To an ice-cold solution of the above diol in acetone (0.5 mL) was added Jones reagent (4 M solution) dropwise until the color of the reagent persisted (a few drops). After 30 min of stirring at 0 °C, *i*-PrOH was added, and the mixture was diluted with Et_2O. The organic layer was passed through a plug of silica gel with Et_2O. The filtrate was concentrated, and the residue was purified by chromatography (CH_2Cl_2–MeOH) to furnish *epi*-JA (**3**) (13 mg, 62% from **25**), which was 98% pure over the *trans* isomer (see below for preparation) by ^{1}H NMR spectroscopy: R_f (hexane–EtOAc 1 : 1) = 0.17 and 0.26 for **3** and **8**; $[\alpha]_D^{30}$ = +24 (c 1.08, $CHCl_3$); IR (neat) 3100, 1738, 1712 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 0.97 (t, J = 7.5 Hz, 3 H), 1.89 (ddt, J = 13, 8, 5.5 Hz, 1 H), 1.97–2.45 (m, 9 H), 2.49 (dd, J = 16, 5.5 Hz, 1 H), 2.77–2.91 (m, 1 H), 5.26–5.52 (m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 14.1, 20.8, 23.1, 25.8, 33.7, 35.4, 35.5, 52.6, 125.4, 133.8, 177.7, 218.8.

To confirm the structure, *epi*-JA (**3**) (7 mg, 0.033 mmol, 98% purity) in Et_2O (0.3 mL) was treated with excess CH_2N_2 for 5 min, and the solution was passed through a short column of silica gel

with Et_2O as an eluent to give Me *epi*-JA (**4**) (91% purity over the *trans* isomer (Me JA)): R_f (hexane–EtOAc 1 : 1) = 0.70 and 0.16 for the ester and **3**; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 0.96 (t, J = 7.5 Hz, 3 H), 1.76–1.89 (m, 1 H), 1.94–2.48 (m, 10 H), 2.77–2.91 (m, 1 H), 3.69 (s, 3 H), 5.24–5.58 (m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 14.1, 20.7, 23.0, 25.7, 33.8, 35.3, 35.6, 51.8, 52.8, 125.5, 133.6, 173.0, 219.0 ppm. The ^{1}H NMR and ^{13}C NMR spectra were identical to the data reported.[13,14b,d,30]

Isomerization of *epi*-jasmonic acid (3) to jasmonic acid. A mixture of *epi*-JA (**3**) (10 mg, 0.048 mmol) in MeOH (2 mL) and 6 N NaOH (0.5 mL) was stirred at room temperature for 3 h, neutralized with AcOH (0.1 mL), and concentrated to afford a residue, which was purified by chromatography (CH_2Cl_2–MeOH) to give JA (10 mg, 100%): R_f (hexane–EtOAc 1 : 1) = 0.17 for JA and **3**; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 0.96 (t, J = 7.5 Hz, 3 H), 1.43–1.63 (m, 1 H), 1.86–2.46 (m, 10 H), 2.71–2.83 (m, 1 H), 5.20–5.33 (m, 1 H), 5.41–5.53 (m, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 14.2, 20.7, 25.6, 27.3, 37.81, 37.83, 38.8, 53.9, 124.9, 134.3, 178.1, 219.0. The ^{1}H NMR and ^{13}C NMR data were identical with those reported.[39]

(1*R*,2*S*,3*R*)-1-Triethylsilyloxy-2-((*Z*)-5-(tetrahydro-2*H*-pyran-2-yloxy)pent-2-enyl)-3-vinylcyclopentane (27). To a solution of $(COCl)_2$ (0.11 mL, 1.26 mmol) in CH_2Cl_2 (2 mL) was added DMSO (0.19 mL, 2.68 mmol) at −78 °C, and, after 15 min, a solution of TES ether **13** (100 mg, 0.260 mmol) in CH_2Cl_2 (2 mL). After 40 min of stirring below −60 °C, Et_3N (0.36 mL, 2.58 mmol) was added to the mixture, which was stirred vigorously at the same temperature for 20 min and at room temperature for 10 min. The mixture was diluted with CH_2Cl_2 and washed with saturated $NaHCO_3$ and with brine. The aqueous solutions were combined and extracted with CH_2Cl_2 twice. The combined extracts were dried over $MgSO_4$ and concentrated to give aldehyde **14**, which was used for the next reaction without further purification.

To a suspension of $[Ph_3P(CH_2)_3OTHP]^+Br^-$ (**26b**) (416 mg, 0.857 mmol) in THF (3 mL) at 0 °C was added NaHMDS (0.78 mL, 1 M in THF, 0.78 mmol). The resulting orange-red mixture was stirred at room temperature for 40 min and cooled to −78 °C. DMF (0.5 mL) and a solution of the above aldehyde in THF (3 mL) were added to the mixture. The reaction was conducted at −78 °C for 2 h and at room temperature overnight and quenched with saturated NH_4Cl. The product was extracted with EtOAc three times. The combined extracts were washed with brine, dried over $MgSO_4$, and concentrated. The residue was purified by chromatography (hexane–EtOAc) to give olefin **27** (100 mg, 97% from **13**): R_f (hexane–EtOAc 5 : 1) = 0.76; $[\alpha]_D^{22}$ = −20.3 (*c* 1.43, $CHCl_3$); IR (neat) 3073, 3008, 1077, 1034 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 0.59 (q, J = 8 Hz, 6 H), 0.95 (t, J = 8 Hz, 9 H), 1.43–1.92 (m, 11 H), 1.88–2.21 (m, 2 H), 2.35 (q, J = 7 Hz, 2 H), 2.59 (dq, J = 17, 4 Hz, 1 H), 3.40 (dt, J = 9, 7 Hz, 1 H), 3.44–3.55 (m, 1 H), 3.72 (dt, J = 9, 7 Hz, 1 H), 3.87 (ddd, J = 11, 7.5, 3.5 Hz, 1 H), 4.15–4.22 (m, 1 H), 4.57–4.63 (m, 1 H), 4.80–4.91 (m, 2 H), 5.30–5.58 (m, 2 H), 5.93 (dt, J = 17, 10 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 5.0 (+), 7.0 (−), 19.6 (+), 24.1 (+), 25.6 (+), 28.2 (+), 30.0 (+), 30.8 (+), 34.6 (+), 45.5 (−), 50.0 (−), 62.3 (+), 67.1 (+), 75.3 (−), 98.7 (−), 113.1 (+), 125.4 (−), 131.6 (−), 143.2 (−). HRMS (FAB) calcd for $C_{23}H_{42}O_3SiNa$ [(M+Na)$^+$] 417.2801, found 417.2805.

2-((1*R*,2*S*,3*R*)-2-((*Z*)-5-(Tetrahydro-2*H*-pyran-2-yl-oxy)pent-2-enyl)-3-(triethylsilyloxy)cyclopentyl)ethanol (28). To an ice-cold solution of olefin **27** (77 mg, 0.195 mmol) in THF (2 mL) was added Cy_2BH (1.2 mL, 0.5 M in THF, 0.60 mmol). After 15 min at 0 °C, 3 N NaOH (2 mL) and 35% H_2O_2 (2 mL) were added. The resulting mixture was stirred at room temperature for 2 h and diluted with EtOAc. The organic phase was separated, and the aqueous phase was extracted with EtOAc twice. The combined organic layers were washed with brine and concentrated. The residue was purified by chromatography (hexane–EtOAc) to give alcohol **28** (53 mg, 67%): R_f (hexane–EtOAc 5 : 1) = 0.22 and 0.76 for **28** and **27**; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 0.57 (q, J = 8 Hz, 6 H), 0.94 (t, J = 8 Hz, 9 H), 1.45–2.08 (m, 15 H), 2.10–2.30 (m, 2 H), 2.33–2.49 (m, 2 H), 3.45–3.94 (m, 6 H), 4.10–4.20 (m, 1 H), 4.46–4.65 (m, 1 H), 5.31–5.60 (m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 5.5 (+), 7.0 (−), 19.60 (+) and 19.63 (+), 22.9 (+), 25.5 (+), 28.1 (+) and 28.2 (+), 28.6 (+), 30.7 (+), 33.7 (+), 35.0 (+), 35.9 (−), 48.6 (−), 62.33 (+), 62.37 (−), 67.0 (+) and 67.2 (+), 75.3 (−), 98.7 (−) and 98.9 (−), 125.4 (−) and 125.5 (−), 132.0 (−) and 132.03 (−).

2-((1*R*,2*S*,3*R*)-2-((*Z*)-5-(Tetrahydro-2*H*-pyran-2-yloxy)-pent-2-enyl)-3-(triethylsilyloxy)cyclopentyl)ethanoic acid (33). To an ice-cold solution of alcohol **28** (80 mg, 0.194 mmol) in CH_2Cl_2/DMSO (1 : 1, v/v, 2 mL) were added Et_3N (0.14 mL, 1.01 mmol) and SO_3·pyridine (123 mg, 0.773 mmol). After being stirred at 0 °C for 20 min, the mixture was diluted first with H_2O and then with saturated NH_4Cl and EtOAc. The organic phase was separated, and the aqueous phase was extracted EtOAc twice. The combined organic layers were dried over $MgSO_4$ and concentrated to afford a residue, which was passed through a short column of silica gel (hexane–EtOAc) to give the corresponding aldehyde, which was used for the next reaction without further purification: R_f (hexane–EtOAc 3 : 1) = 0.63 and 0.26 for the aldehyde and **28**; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 0.58 (q, J = 8 Hz, 6 H), 0.95 (t, J = 8 Hz, 9 H), 1.43–1.96 (m, 12 H), 2.04–2.27 (m, 2 H), 2.37 (q, J = 7 Hz, 2 H), 2.42–2.62 (m, 2 H), 3.42 (ddt, J = 10, 2, 7 Hz, 1 H), 3.45–3.56 (m, 1 H), 3.75 (ddt, J = 10, 2.5, 7 Hz, 1 H), 3.87 (ddd, J = 11, 7, 3.5 Hz, 1 H), 4.12–4.22 (m, 1 H), 4.56–4.64 (m, 1 H), 5.34–5.57 (m, 2 H), 9.75 (s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 5.0 (+), 7.0 (−), 19.7 (+), 23.5 (+), 25.5 (+), 28.2 (+), 29.5 (+), 30.8 (+), 33.6 (−), 34.2 (+), 47.1 (+), 48.5 (−), 62.4 (+), 67.0 (+), 75.2 (−), 98.8 (−), 126.4 (−), 130.8 (−), 203.7 (−).

To a solution of the above aldehyde in *t*-BuOH (2 mL) were added 2-methyl-2-butene (0.21 mL, 1.98 mmol), phosphate buffer (1 mL, pH 7), and aqueous $NaClO_2$ (33 mg, 80% purity, 0.292 mmol) dissolved in H_2O (1 mL). After being stirred at room temperature for 1 h, the mixture was acidified to pH 6 with 1 N HCl and the product was extracted with EtOAc three times. The combined extracts were washed with brine, dried over $MgSO_4$, and concentrated to afford a residue, which was purified by chromatography (hexane–EtOAc) to give acid **33** (63 mg, 77% from **28**): R_f (hexane–EtOAc 3 : 1) = 0.38 and 0.61 for **33** and the aldehyde; $[\alpha]_D^{26}$ = −2 (*c* 1.66, $CHCl_3$); IR (neat) 3000, 1707, 1077, 1034 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 0.58 (q, J = 8 Hz, 6 H), 0.96 (t, J = 8 Hz, 9 H), 1.46–1.96 (m, 12 H), 2.06–2.27 (m, 2 H), 2.28–2.54 (m, 4 H), 3.36–3.57 (m, 2 H), 3.69–3.81 (m, 1 H), 3.83–3.94 (m, 1 H), 4.12–4.22 (m, 1 H), 4.58–4.66 (m, 1 H), 5.34–5.58 (m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 5.0 (+), 7.0 (−),

19.55 (+) and 19.58 (+), 23.3 (+), 25.5 (+), 28.2 (+), 29.3 (+), 30.7 (+), 34.0 (+), 36.0 (–), 36.9 (+), 48.6 (–), 62.2 (+) and 62.3 (+), 67.0 (+) and 67.1 (+), 75.3 (–), 98.7 (–) and 98.8 (–), 126.26 (–) and 126.30 (–), 130.9 (–), 180.1 (+) and 180.2 (+).

2-((1*R*,2*S*,3*R*)-3-Hydroxy-2-((*Z*)-5-(tetrahydro-2*H*-pyran-2-yloxy)pent-2-enyl)cyclopentyl)ethanoic acid (34). A solution of acid **33** (30 mg, 0.0648 mmol) and PPTS (5 mg, 0.02 mmol) in EtOH (1 mL) was stirred at room temperature for 1 h. Et_3N (0.30 mL, 2.15 mmol) was added and the solution was concentrated to afford a residue, which was purified by chromatography (hexane–EtOAc) to give alcohol **34** (18 mg, 90%): R_f (hexane–EtOAc 1 : 1) = 0.22 and 0.64 for **34** and **33**; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.4–2.8 (m, 19 H), 3.34–3.58 (m, 2 H), 3.73–3.94 (m, 2 H), 4.10–4.24 (m, 1 H), 4.55–4.66 (m, 1 H), 5.34–5.60 (m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 19.5 (+) and 19.6 (+), 23.5 (+) and 23.6 (+), 25.4 (+), 28.1 (+), 29.8 (+) and 30.0 (+), 30.36 (+) and 30.45 (+), 33.2 (+) and 33.3 (+), 36.46 (–) and 36.52 (–), 36.8 (+), 47.7 (–), 62.3 (+) and 62.6 (+), 67.0 (+) and 67.4 (+), 73.9 (–), 99.0 (–) and 99.5 (–), 127.4 (–), 130.5 (–) and 130.7 (–), 179.4 (+).

2-((1*R*,2*S*)-3-Oxo-2-((*Z*)-5-(tetrahydro-2*H*-pyran-2-yloxy)-pent-2-enyl)cyclopentyl)ethanoic acid (30). To a solution of alcohol **34** (6 mg, 0.019 mmol) in acetone (0.2 mL) was added Jones reagent (1 drop, 4 M solution) at –40 °C. The mixture was stirred at –40 °C for 30 min and excess reagent was quenched by addition of *i*-PrOH. The mixture was stirred at –40 °C for 10 min and diluted with Et_2O. The organic layer was passed through a plug of silica gel with Et_2O. Concentration of the filtrate afforded a residue, which was purified by chromatography (hexane–EtOAc) to give keto acid **30** (6 mg, 92%): R_f (EtOAc) = 0.30; $[\alpha]_D^{27}$ = +10 (*c* 1.43, $CHCl_3$); IR (neat) 3000, 1733, 1031 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.3–2.6 (m, 17 H), 2.78–2.93 (m, 1 H), 3.35–3.58 (m, 2 H), 3.67–3.95 (m, 2 H), 4.56–4.66 (m, 1 H), 5.32–5.62 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 19.6 and 19.7, 23.16 and 23.21, 25.5, 25.90 and 25.93, 28.1 and 28.2, 30.7 and 30.8, 34.1, 35.39 and 35.44, 35.6 and 35.7, 52.6, 62.4 and 62.6, 66.8 and 67.1, 98.8 and 99.0, 99.2, 127.8 and 128.0, 128.2 and 128.3, 177.0 and 177.1, 218.9.

Tuberonic acid (5). To a solution of the keto acid **30** (7 mg, 0.023 mmol) in Et_2O (0.5 mL) was added $MgBr_2$ (13 mg, 0.071 mmol). The solution was stirred at room temperature for 2 h and diluted with Et_2O and MeOH. Most of the solvents were removed to afford a residue, which was purified by chromatography (CH_2Cl_2–MeOH) to furnish TA (**5**) (5 mg, 96%), which was 92% pure over the *trans* isomer (12-hydroxy-JA) by ^{1}H NMR spectroscopy: R_f (CH_2Cl_2–MeOH 9 : 1) = 0.17 and 0.51 for **5** and **30**; $[\alpha]_D^{25}$ = +11 (*c* 0.26, MeOH); ^{1}H NMR (300 MHz, CD_3OD) δ = 1.77–1.95 (m, 1 H), 1.9–2.5 (m, 10 H), 2.74–2.88 (m, 1 H), 3.55 (t, *J* = 7 Hz, 2 H), 5.37–5.62 (m, 2 H); ^{13}C NMR (75 MHz, CD_3OD) δ = 24.1, 26.6, 31.8, 36.1, 41.8, 62.5, 132.3.

Isomerization of TA (5) to the *trans* isomer, 12-hydroxy-JA. Additionally, TA (**5**) (14 mg, 0.062 mmol) was subjected to isomerization with 6 N NaOH (0.6 mL) in MeOH (2 mL) at room temperature for 2 h. The mixture was neutralized with AcOH (0.1 mL), and most of the solvents were evaporated. A residue thus obtained was purified by chromatography (CH_2Cl_2–MeOH) to afford 12-hydroxy-JA (11 mg, 79%): R_f (CH_2Cl_2–MeOH 9 : 1) = 0.17; IR (neat) 1722, 1119 cm^{-1}; ^{1}H NMR (300 MHz, CD_3OD) δ = 1.44–1.64 (m, 1 H), 1.93–2.04 (m, 1 H), 2.08 (ddd, *J* = 18, 11, 9 Hz, 1 H), 2.17–2.45 (m, 8 H), 2.60–2.71 (m, 1 H), 3.55 (t, *J* = 7 Hz, 2 H), 5.37–5.54 (m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 26.4, 28.3, 31.8, 38.7, 39.6, 55.3, 62.6, 128.9, 129.2, 222.2. The ^{1}H and ^{13}C NMR spectra were consistent with the data reported in the literature.[7a,19c]

2-((1*S*,5*S*)-5-(8-(*tert*-Butyldiphenylsilyloxy)octyl)cyclopent-2-enyl)-*N*,*N*-dimethyl acetamide (36). A solution of alcohol **35** (190 mg, 0.422 mmol) and $MeC(OMe)_2NMe_2$ (0.34 mL, 90% purity, 2.1 mmol) in xylene (5 mL) was stirred at 150 °C for 5 h, cooled to room temperature, and concentrated. The residue was purified by chromatography (hexane–EtOAc) to afford amide **36** (181 mg, 82%): R_f (hexane–EtOAc 5 : 1) = 0.16 and 0.32 for **36** and **35**; $[\alpha]_D^{26}$ = –73 (*c* 1.16, $CHCl_3$); IR (neat) 1654, 1395, 1112, 823 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.05 (s, 9 H), 1.2–1.5 (m, 11 H), 1.50–1.62 (m, 2 H), 1.96 (ddq, *J* = 16, 8, 2 Hz, 1 H), 2.12 (dd, *J* = 14, 10 Hz, 1 H), 2.21–2.46 (m, 4 H), 2.95 (s, 3 H), 2.98 (s, 3 H), 3.04–3.16 (m, 1 H), 3.66 (t, *J* = 6 Hz, 2 H), 5.67–5.77 (m, 1 H), 5.79–5.86 (m, 1 H), 7.34–7.46 (m, 6 H), 7.65–7.72 (m, 4 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 19.3 (+), 25.8 (+), 26.9 (–), 28.8 (+), 29.4 (+), 29.7 (+), 29.9 (+), 30.6 (+), 32.6 (+), 33.2 (+), 35.5 (–), 37.3 (+), 37.5 (–), 41.4 (–), 43.6 (–), 64.0 (+), 127.6 (–), 129.5 (–), 130.4 (–), 134.2 (+), 135.6 (–), 135.7 (–), 172.8 (+). HRMS (FAB) calcd for $C_{33}H_{50}NO_2Si$ [(M+H)$^+$] 520.3611, found 520.3610.

(3a*S*,4*S*,6a*R*)-4-(8-(*tert*-Butyldiphenylsilyloxy)octyl)-3,3a,4,6a-tetrahydro-2*H*-cyclopenta[*b*]furan-2-one (38). A mixture of amide **36** (369 mg, 0.710 mmol) and I_2 (360 mg, 1.42 mmol) in THF (5 mL) and H_2O (5 mL) was stirred at room temperature for 5 h and diluted with aqueous $Na_2S_2O_3$ and EtOAc. The organic phase was separated, and the aqueous phase was extracted with EtOAc twice. The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated to give the corresponding iodolactone, which was used for the next reaction without further purification: R_f (hexane–EtOAc 5 : 1) = 0.44 and 0.17 for the iodolactone and **36**; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.05 (s, 9 H), 1.17–1.74 (m, 15 H), 2.03–2.16 (m, 1 H), 2.42–2.78 (m, 3 H), 3.01–3.20 (m, 1 H), 3.66 (t, *J* = 6.5 Hz, 2 H), 4.45 (d, *J* = 5 Hz, 1 H), 5.26 (d, *J* = 7 Hz, 1 H), 7.29–7.51 (m, 6 H), 7.63–7.78 (m, 4 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 19.4, 25.9, 27.0, 28.4, 28.6, 28.7, 29.4, 29.6, 29.8, 30.2, 32.7, 39.0, 40.3, 40.5, 64.0, 92.8, 127.5, 129.5, 134.1, 135.5, 176.4. The ^{1}H and ^{13}C NMR spectra were identical to those reported.[7a]

A solution of the above iodolactone and DBU (0.28 mL, 1.9 mmol) in THF (7 mL) was heated under reflux for 7 h, cooled to room temperature, and diluted with saturated NH_4Cl. The mixture was extracted with EtOAc three times. The combined extracts were washed with brine and concentrated to leave an oil, which was purified by chromatography (hexane–EtOAc) to afford lactone **38** (288 mg, 83% from amide **36**); R_f (hexane–EtOAc 5 : 1) = 0.26 and 0.44 for **38** and the iodolactone; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.05 (s, 9 H), 1.18–1.63 (m, 14 H), 2.42 (dd, *J* = 15, 9 Hz, 1 H), 2.49 (dd, *J* = 15, 9 Hz, 1 H), 2.74–2.88 (m, 1 H), 3.19 (tt, *J* = 9, 8 Hz, 1 H), 3.66 (t, *J* = 6.5 Hz, 2 H), 5.46 (dm, *J* = 8 Hz, 1 H), 5.82 (ddd, *J* = 6, 2.5, 1.5 Hz, 1 H), 5.95 (dt, *J* = 6, 1 Hz, 1 H), 7.32–7.48 (m, 6 H), 7.64–7.73 (m, 4 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 19.4, 25.9, 27.0, 28.3, 29.4, 29.5, 29.6, 29.7, 31.2, 32.7, 39.9, 46.5, 64.1,

89.1, 127.5, 128.1, 129.5, 134.1, 135.5, 140.0, 177.2. The ^{1}H and ^{13}C NMR spectra were identical to those reported.[7a]

(3*R*,4*S*,5*S*)-5-(8-(*tert*-Butyldiphenylsilyloxy)octyl)-3-triethylsilyloxy-4-(2-(triethylsilyloxy)ethyl)cyclopent-1-ene (40). To an ice-cold suspension of $LiAlH_4$ (60 mg, 1.6 mmol) in Et_2O (7 mL) was added lactone **38** (260 mg, 0.530 mmol) in Et_2O (3 mL) dropwise. The mixture was stirred at room temperature for 1 h, and excess hydride was quenched by addition of 10% NaOH. The resulting mixture was filtered through a pad of Celite, and the filtrate was concentrated to afford diol **39**, which was used for the next reaction without further purification: R_f (hexane–EtOAc 3 : 1) = 0.21 and 0.66 for **39** and **38**; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 1.05 (s, 9 H), 1.16–1.46 (m, 10 H), 1.48–1.98 (m, 6 H), 2.00–2.30 (m, 3 H), 2.42–2.52 (m, 1 H), 3.65 (t, J = 6.5 Hz, 2 H), 3.76 (ddd, J = 10, 9, 4 Hz, 1 H), 3.89 (t, J = 10, 5 Hz, 1 H), 4.61 (dd, J = 6, 2.5 Hz, 1 H), 5.96 (dm, J = 6 Hz, 1 H), 6.20 (dd, J = 6, 2.5 Hz, 1 H), 7.32–7.47 (m, 6 H), 7.63–7.71 (m, 4 H). The spectrum was identical to that reported.[7a]

A solution of the above diol, TESCl (0.27 mL, 1.6 mmol), and imidazole (144 mg, 2.12 mmol) in DMF (10 mL) was stirred at room temperature overnight and diluted with saturated $NaHCO_3$ with vigorous stirring. The product was extracted with EtOAc three times. The combined extracts were washed with brine, dried over $MgSO_4$, and concentrated to afford an oil, which was purified by chromatography (hexane–EtOAc) to give bis-TES ether **40** (381 mg, 99% from lactone **38**): R_f (hexane–EtOAc 3 : 1) = 0.86 and 0.19 for **40** and **39**; $[\alpha]_D^{26}$ = 0 (c 1.03, $CHCl_3$); IR (neat) 1238, 1112, 1008, 739 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 0.51–0.66 (m, 12 H), 0.90–1.01 (m, 18 H), 1.04 (s, 9 H), 1.1–1.9 (m, 16 H), 1.98–2.13 (m, 1 H), 2.31–2.42 (m, 1 H), 3.55–3.75 (m, 4 H), 4.70 (dd, J = 6, 2 Hz, 1 H), 5.83 (dq, J = 6, 1 Hz, 1 H), 6.12 (dd, J = 6, 3 Hz, 1 H), 7.34–7.46 (m, 6 H), 7.64–7.72 (m, 4 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 4.5 (+), 5.3 (+), 6.9 (–), 7.0 (–), 19.3 (+), 25.9 (+), 27.0 (–), 28.1 (+), 28.9 (+), 29.5 (+), 29.7 (+), 30.1 (+), 32.7 (+), 42.9 (–), 46.2 (–), 62.2 (+), 64.1 (+), 76.3 (–), 127.6 (–), 129.5 (–), 132.7 (–), 134.3 (–), 135.7 (+), 140.4 (–). HRMS (FAB) calcd for $C_{43}H_{73}O_3Si_3$ [(M – H)$^+$] 721.4868, found 721.4885.

(1*R*,4*S*,5*S*)-4-(8-Hydroxyoctyl)-5-((*Z*)-pent-2-enyl)cyclo-pent-2-enol (42). To a solution of $(COCl)_2$ (0.087 mL, 0.10 mmol) in CH_2Cl_2 (3 mL) was added DMSO (0.14 mL, 2.0 mmol) at –78 °C. After 40 min, TES ether **40** (144 mg, 0.199 mmol) in CH_2Cl_2 (2 mL) was added dropwise. The suspension was stirred at –78 °C for 1 h, and Et_3N (0.28 mL, 2.0 mmol) was added. The resulting mixture was stirred vigorously at –78 °C for 20 min and then at room temperature for 1 h, and diluted with saturated $NaHCO_3$. The mixture was extracted with CH_2Cl_2 twice. The combined extracts were dried over $MgSO_4$ and concentrated to give aldehyde **41**, which was used for the next reaction without further purification: R_f (hexane–EtOAc 5 : 1) = 0.16 and 0.60 for **41** and **40**; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 0.57 (q, J = 8 Hz, 6 H), 0.94 (t, J = 8 Hz, 9 H), 1.05 (s, 9 H), 1.15–1.63 (m, 14 H), 2.38 (dd, J = 15, 4 Hz, 1 H), 2.48–2.60 (m, 1 H), 2.61–2.82 (m, 2 H), 3.65 (t, J = 6.5 Hz, 2 H), 4.68 (dm, J = 6 Hz, 1 H), 5.77 (dt, J = 6, 2 Hz, 1 H), 5.98 (dd, J = 6, 2 Hz, 1 H), 7.33–7.48 (m, 6 H), 7.63–7.72 (m, 4 H), 9.87 (t, J = 1 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 5.2, 7.1, 19.4, 26.0, 27.0, 28.1, 29.5, 29.7, 30.0, 32.3, 32.7, 40.2, 41.7, 45.9, 64.1, 76.8, 127.5, 129.4, 132.6, 134.2, 135.6, 138.1, 202.8. The ^{1}H NMR spectrum was thus revised, while the ^{13}C NMR spectrum was identical to that reported.[7a]

To an ice-cold suspension of $[Ph_3P(CH_2)_2Me]^+Br^-$ (220 mg, 0.571 mmol) in THF (5 mL) was added NaHMDS (0.63 mL, 1.0 M in THF, 0.63 mmol). The resulting orange-red mixture was stirred at room temperature for 1 h and cooled to –78 °C. To this solution was added a solution of the above aldehyde in THF (2 mL) dropwise. The resulting solution was stirred at –78 °C for 2 h and then at room temperature for 12 h, diluted with saturated NH_4Cl and EtOAc with vigorous stirring. The mixture was separated, and the aqueous layer was extracted with EtOAc twice. The combined organic layers were dried over $MgSO_4$ and concentrated to afford olefin, which was passed through a short silica gel before the next reaction: R_f (hexane–EtOAc 5 : 1) = 0.85 and 0.68 for the olefin and **41**; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 0.57 (q, J = 8 Hz, 6 H), 0.95 (q, J = 8 Hz, 9 H), 0.98 (t, J = 7 Hz, 3 H), 1.05 (s, 9 H), 1.14–1.62 (m, 14 H), 1.91–2.30 (m, 5 H), 2.34–2.46 (m, 1 H), 3.65 (t, J = 6.5 Hz, 2 H), 4.50 (dd, J = 6, 3 Hz, 1 H), 5.26–5.58 (m, 2 H), 5.78–5.94 (m, 1 H), 6.12 (dd, J = 6, 3 Hz, 1 H), 7.32–7.47 (m, 6 H), 7.64–7.73 (m, 4 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 5.4, 7.2, 14.5, 19.4, 21.0, 23.4, 26.0, 27.0, 28.2, 29.6, 29.8, 30.2, 32.6, 32.8, 46.2, 47.4, 64.1, 76.4, 127.5, 128.7, 129.5, 131.6, 132.7, 134.2, 135.6, 140.2. The ^{1}H and ^{13}C NMR spectra were identical to those reported.[7a]

To a solution of the above olefin in THF (5 mL) was added TBAF (1.0 mL, 1.0 M in THF, 1.0 mmol). The solution was stirred at 55 °C for 1 h, cooled to room temperature, and diluted with saturated NH_4Cl. The mixture was extracted with EtOAc three times. The combined extracts were washed with brine, dried over $MgSO_4$, and concentrated. The residue was purified by chromatography (hexane–EtOAc) to give diol **42** (49 mg, 85% from the TES ether **40**): R_f (hexane–EtOAc 5 : 1) = 0.05 and 0.87 for **42** and the olefin; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 0.99 (t, J = 7.5 Hz, 3 H), 1.16–1.68 (m, 15 H), 1.96–2.39 (m, 6 H), 2.42–2.54 (m, 1 H), 3.63 (t, J = 6.5 Hz, 2 H), 4.51 (dd, J = 6, 2 Hz, 2 H), 5.33–5.59 (m, 2 H), 5.96 (ddd, J = 6, 4, 2 Hz, 1 H), 6.23 (dd, J = 6, 3 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 14.4, 20.9, 23.2, 25.9, 28.2, 29.5, 29.7, 30.0, 32.9, 33.7, 46.2, 46.3, 63.1, 76.7, 127.9, 132.0, 132.4, 141.7. The ^{1}H and ^{13}C NMR spectra were identical to those reported.[7a]

12-oxo-PDA (1). To an ice-cold solution of diol **42** (9.8 mg, 0.053 mmol) in acetone (1 mL) was added Jones reagent (4.0 M solution) dropwise until the color of the reagent persisted (four drops). After 30 min of stirring at 0 °C, *i*-PrOH was added to quench the remaining reagent. The mixture was passed through a plug of silica gel with hexane–EtOAc (1 : 1). The filtrate was concentrated, and the residue was purified by chromatography (hexane–EtOAc) to furnish 12-oxo-PDA (**1**) (6.3 mg, 63%), which was of >95% purity over the *trans* isomer by ^{1}H NMR spectroscopy (δ = 7.74 (dd, J = 6, 3 Hz, 1 H) for **1**; 7.61 (dd, J = 6, 2.5 Hz, 1 H) for the *trans* isomer). R_f (hexane–EtOAc 1 : 1) = 0.377 and 0.48 for **1** and **42**; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.97 (t, J = 7.5 Hz, 3 H), 1.04–1.82 (m, 12 H), 1.97–2.22 (m, 3 H), 2.35 (t, J = 7.5 Hz, 2 H), 2.39–2.57 (m, 2 H), 2.92–3.04 (m, 1 H), 5.26–5.54 (m, 2 H), 6.19 (dd, J = 6, 1.5 Hz, 1 H), 7.74 (dd, J = 6, 3 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.2, 20.9, 23.9, 24.8, 27.7, 29.1, 29.2, 29.7, 30.9, 34.1, 44.4, 50.0, 126.9, 132.4, 132.9, 167.2, 179.4, 210.9. The ^{1}H and ^{13}C NMR spectra were identical to those reported.[40,7a]

Acknowledgements

Racemic Me JA was kindly provided by Zeon Co. Ltd., Japan. This work was supported by a Grant-in-Aid for Scientific Research from the Ministry of Education, Science, Sports, and Culture, Japan. The authors thank Ms. M. Ishikawa of Center for Advanced Materials Analysis, Technical Department, Tokyo Institute of Technology, for HRMS analysis.

Notes and references

1 (*a*) Reviews: A. Schaller and A. Stintzi, *Phytochemistry*, 2009, **70**, 1532–1538; (*b*) T. Durand, V. Bultel-Ponce, A. Guy, S. Berger, M. J. Mueller and J.-M. Galano, *Lipids*, 2009, **44**, 875–888; (*c*) K. Kazan and J. M. Manners, *Plant Physiol.*, 2008, **146**, 1459–1468; (*d*) R. Lauchli and W. Boland, *Chem. Rec.*, 2003, **3**, 12–21; (*e*) M. H. Beale and J. L. Ward, *Nat. Prod. Rep.*, 1998, **15**, 533–548; (*f*) R. A. Creelman and J. E. Mullet, *Annu. Rev. Plant Physiol. Plant Mol. Biol.*, 1997, **48**, 355–381; (*g*) G. Sembdner and B. Parthier, *Annu. Rev. Plant Physiol. Plant Mol. Biol.*, 1993, **44**, 569–589; (*h*) Y. Koda, *Int. Rev. Cytol.*, 1992, **135**, 155–199; (*i*) M. Hamberg and H. W. Gardner, *Biochim. Biophys. Acta, Lipids Lipid Metab.*, 1992, **1165**, 1–18.

2 For example, (*a*) Y. Koda, Y. Kikuta, T. Kitahara, T. Nishi and K. Mori, *Phytochemistry*, 1992, **31**, 1111–1114; (*b*) F. Schaller, C. Biesgen, C. Müssig, T. Altmann and E. W. Weiler, *Planta*, 2000, **210**, 979–984; (*c*) B. Schuze, P. Dabrowska and W. Boland, *ChemBioChem*, 2007, **8**, 208–216; (*d*) Y. Seto, S. Hamada, H. Matsuura, M. Matsushige, C. Satou, K. Takahashi, C. Masuta, H. Ito, H. Matsui and K. Nabeta, *Phytochemistry*, 2009, **70**, 370–379.

3 For example, (*a*) E. Demole, E. Lederer and D. Mercier, *Helv. Chim. Acta*, 1962, **45**, 675–685; (*b*) E. Demole and M. Stoll, *Helv. Chim. Acta*, 1962, **45**, 692–703; (*c*) J. L. Ward and M. H. Beale, *J. Chem. Soc., Perkin Trans. 1*, 1993, 2379–2381.

4 The same stereochemical situation is found in isoprostanes. Recent syntheses: (*a*) U. Jahn and E. Dinca, *Chem.–Eur. J.*, 2009, **15**, 58–62; (*b*) C.-T. Chang, P. Patel, N. Kang, J. A. Lawson, W.-L. Song, W. S. Powell, G. A. FitzGerald and J. Rokach, *Bioorg. Med. Chem. Lett.*, 2008, **18**, 5523–5527; (*c*) C. Oger, Y. Brinkmann, S. Bouazzaoui, T. Durand and J.-M. Galano, *Org. Lett.*, 2008, **10**, 5087–5090; (*d*) B. A. Pandya and M. L. Snapper, *J. Org. Chem.*, 2008, **73**, 3754–3758; (*e*) D. F. Taber, P. G. Reddy and K. O. Arneson, *J. Org. Chem.*, 2008, **73**, 3467–3474; (*f*) E. Pinot, A. Guy, A. Fournial, L. Balas, J.-C. Rossi and T. Durand, *J. Org. Chem.*, 2008, **73**, 3063–3069; (*g*) S. H. Jacobo, C.-T. Chang, G.-J. Lee, J. A. Lawson, W. S. Powell, D. Pratico, G. A. FitzGerald and J. Rokach, *J. Org. Chem.*, 2006, **71**, 1370–1379.

5 (*a*) Y. Kobayashi, in *Modern Organonickel Chemistry*, ed. Y. Tamaru, Wiley-VCH, Weinheim, 2005, Chapter 3; (*b*) Y. Kobayashi, *Curr. Org. Chem.*, 2003, **7**, 133–147.

6 (*a*) M. Ito, M. Matsuumi, M. G. Murugesh and Y. Kobayashi, *J. Org. Chem.*, 2001, **66**, 5881–5889; (*b*) Y. Kobayashi, M. G. Murugesh, M. Nakano, E. Takahisa, S. B. Usmani and T. Ainai, *J. Org. Chem.*, 2002, **67**, 7110–7123; (*c*) T. Ainai, M. Ito and Y. Kobayashi, *Tetrahedron Lett.*, 2003, **44**, 3983–3986; (*d*) Y. Kobayashi, K. Nakata and T. Ainai, *Org. Lett.*, 2005, **7**, 183–186; (*e*) K. Nakata and Y. Kobayashi, *Org. Lett.*, 2005, **7**, 1319–1322; (*f*) K. Nakata, Y. Kiyotsuka, T. Kitazume and Y. Kobayashi, *Org. Lett.*, 2008, **10**, 1345–1348; (*g*) Y. Kobayashi, Y. Tani, K. Nakata and Y. Kaneko, *Synlett*, 2010, 325–328.

7 (*a*) T. Ainai, M. Matsuumi and Y. Kobayashi, *J. Org. Chem.*, 2003, **68**, 7825–7832; (*b*) K. Yagi, H. Nonaka, H. P. Acharya, K. Furukawa, T. Ainai and Y. Kobayashi, *Tetrahedron*, 2006, **62**, 4933–4940.

8 (*a*) C. Li, A. L. Schilmiller, G. Liu, G. I. Lee, S. Jayanty, C. Sageman, J. Vrebalov, J. J. Giovannoni, K. Yagi, Y. Kobayashi and G. A. Howe, *Plant Cell*, 2005, **17**, 971–986; (*b*) A. J. K. Koo, H. S. Chung, Y. Kobayashi and G. A. Howe, *J. Biol. Chem.*, 2006, **281**, 33511–33520.

9 N. Taki, Y. Sasaki-Sekimoto, T. Obayashi, A. Kikuta, K. Kobayashi, T. Ainai, K. Yagi, N. Sakurai, H. Suzuki, T. Masuda, K. Takamiya, D. Shibata, Y. Kobayashi and H. Ohta, *Plant Physiol.*, 2005, **139**, 1268–1283.

10 (*a*) T. C. Baker, R. Nishida and W. L. Roelofs, *Science*, 1981, **214**, 1359–1361; (*b*) R. Nishida, T. C. Baker and W. L. Roelofs, *J. Chem. Ecol.*, 1982, **8**, 947–959; (*c*) R. Nishida and T. E. Acree, *J. Agric. Food Chem.*, 1984, **32**, 1001–1003; (*d*) R. Nishida, T. E. Acree and H. Fukami, *Agric. Biol. Chem.*, 1985, **49**, 769–772; (*e*) T. E. Acree, R. Nishida and H. Fukami, *J. Agric. Food Chem.*, 1985, **33**, 425–427; (*f*) H. Seto, E. Nomura, S. Fujioka, H. Koshino, T. Suenaga and S. Yoshida, *Biosci., Biotechnol., Biochem.*, 1999, **63**, 361–367; (*g*) J. Wang, *Plant Sci.*, 2009, **176**, 279–285.

11 (*a*) O. Miersch, B. Brückner, J. Schmidt and G. Sembdner, *Phytochemistry*, 1992, **31**, 3835–3837; (*b*) O. Miersch, H. Bohlmann and C. Wasternack, *Phytochemistry*, 1999, **50**, 517–523; (*c*) R. Kramell, O. Miersch, G. Schneider and C. Wasternack, *Chromatographia*, 1999, **49**, 42–46; (*d*) R. Kramell, J. Schmidt, G. Herrmann and W. Schliemann, *J. Nat. Prod.*, 2005, **68**, 1345–1349; (*e*) N. Ogawa and Y. Kobayashi, *Tetrahedron Lett.*, 2008, **49**, 7124–7127; (*f*) S. Fonseca, A. Chini, M. Hamberg, B. Adie, A. Porzel, R. Kramell, O. Miersch, C. Wasternack and R. Solano, *Nat. Chem. Biol.*, 2009, **5**, 344–350.

12 Biological studies using racemic *trans* isomer of **7**: (*a*) T. Krumm, K. Bandemer and W. Boland, *FEBS Lett.*, 1995, **377**, 523–529; (*b*) E. A. Schmelz, J. Engelberth, H. T. Alborn, P. O'Donnell, M. Sammons, H. Toshima and J. H. Tumlinson III, *Proc. Natl. Acad. Sci. U. S. A.*, 2003, **100**, 10552–10557; (*c*) P. E. Staswick and I. Tiryaki, *Plant Cell*, 2004, **16**, 2117–2127; (*d*) E. E. Farmer, *Nature*, 2007, **448**, 659–660; (*e*) B. Thines, L. Katsir, M. Melotto, Y. Niu, A. Mandaokar, G. Liu, K. Nomura, S. Y. He, G. A. Howe and J. Browse, *Nature*, 2007, **448**, 661–665; (*f*) A. Walter, C. Mazars, M. Maitrejean, J. Hopke, R. Ranjeva, W. Boland and A. Mithöfer, *Angew. Chem., Int. Ed.*, 2007, **46**, 4783–4785.

13 K. Weinges and U. Lernhardt, *Liebigs Ann. Chem.*, 1990, **1990**, 751–754.

14 (*a*) C. Fehr and J. Galindo, *Angew. Chem., Int. Ed.*, 2000, **39**, 569–573; (*b*) T. K. Sarkar, B. Mukherjee and S. K. Ghosh, *Tetrahedron*, 1998, **54**, 3243–3254; (*c*) G. J. Roth, S. Kirschbaum and H. J. Bestmann, *Synlett*, 1997, 618–620; (*d*) H. Stadtmüller, A. Vaupel, C. E. Tucker, T. Stüdemann and P. Knochel, *Chem.–Eur. J.*, 1996, **2**, 1204–1220; (*e*) C. Borm and E. Winterfeldt, *Liebigs Ann.*, 1996, 1209–1212; (*f*) T. Kitahara, T. Nishi and K. Mori, *Tetrahedron*, 1991, **47**, 6999–7006; (*g*) G. Helmchen, A. Goeke, G. Lauer, M. Urmann and J. Fries, *Angew. Chem., Int. Ed. Engl.*, 1990, **29**, 1024–1025; (*h*) F.-P. Montforts, I. Gesing-Zibulak, W. Grammenos, M. Schneider and K. Laumen, *Helv. Chim. Acta*, 1989, **72**, 1852–1859, and references cited therein; (*i*) Synthesis of the enantiomer: K. Suzuki, K. Inomata and Y. Endo, *Org. Lett.*, 2004, **6**, 409–411.

15 (*a*) H. Kiyota, S. Takigawa and S. Kuwahara, *Helv. Chim. Acta*, 2004, **87**, 1854–1859; (*b*) N. Kitaoka, E. Fukushi, Y. Koda, K. Nabeta and H. Matsuura, *Biosci., Biotechnol., Biochem.*, 2009, **73**, 1872–1876.

16 (*a*) Y. Koda, E.-S. A. Omer, T. Yoshihara, H. Shibata, S. Sakamura and Y. Okazawa, *Plant Cell Physiol.*, 1988, **29**, 1047–1051; (*b*) T. Yoshihara, E.-S. A. Omer, H. Koshino, S. Sakamura, Y. Kikuta and Y. Koda, *Agric. Biol. Chem.*, 1989, **53**, 2835–2837; (*c*) H. Matsuura, T. Yoshihara, A. Ichihara, Y. Kikuta and Y. Koda, *Biosci., Biotechnol., Biochem.*, 1993, **57**, 1253–1256; (*d*) H. Matsuura, F. Ohmori, M. Kobayashi, A. Sakurai and T. Yoshihara, *Biosci., Biotechnol., Biochem.*, 2000, **64**, 2380–2387.

17 (*a*) M. Wang, H. Kikuzaki, N. Zhu, S. Sang, N. Nakatani and C.-T. Ho, *J. Agric. Food Chem.*, 2000, **48**, 235–238; (*b*) I. Šimko, E. A. Omer, E. E. Ewing, S. McMurry, J. L. Koch and P. J. Davies, *Phytochemistry*, 1996, **43**, 727–730; (*c*) B. Cui, M. Nakamura, J. Kinjo and T. Nohara, *Chem. Pharm. Bull.*, 1993, **41**, 178–182.

18 See ref. 1*h*, pages 167–168.

19 In contrast, isolation of the *trans* isomer of TAG and its property have been reported: (*a*) O. Miersch, G. Schneider and G. Sembdner, *Phytochemistry*, 1991, **30**, 4049–4051; (*b*) M. Ueda, M. Okazaki, K. Ueda and S. Yamamura, *Tetrahedron*, 2000, **56**, 8101–8105; (*c*) T. Fujita, K. Terato and M. Nakayama, *Biosci., Biotechnol., Biochem.*, 1996, **60**, 732–735.

20 M. Inoue and T. Kitahara, *Tetrahedron*, 1999, **55**, 4621–4630.

21 H. Kiyota, D. Nakashima and T. Oritani, *Biosci., Biotechnol., Biochem.*, 1999, **63**, 2110–2117.

22 J. Tsuji, Y. Kobayashi, H. Kataoka and T. Takahashi, *Tetrahedron Lett.*, 1980, **21**, 1475–1478.

23 A preliminary report: H. Nonaka, Y.-G. Wang and Y. Kobayashi, *Tetrahedron Lett.*, 2007, **48**, 1745–1748.

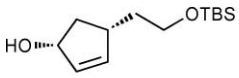
24 C. M. Afonso, M. T. Barros and C. D. Maycock, *J. Chem. Soc., Perkin Trans. 1*, 1987, 1221–1223.

25 (*a*) T. Sugai and K. Mori, *Synthesis*, 1988, 19–22; (*b*) K. Laumen and M. P. Schneider, *J. Chem. Soc., Chem. Commun.*, 1986, 1298–1299.

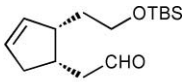
26 Regioselectivity in the absence of LiCl was 63%.

27 O. Mitsunobu, *Synthesis*, 1981, 1–28.

28 Claisen rearrangement of alcohol **i** under the same conditions produced aldehyde **ii** in 80% yield.

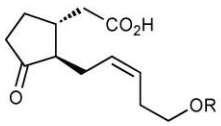


i

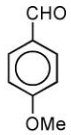


ii

29 (*a*) A. E. Wick, D. Felix, K. Steen and A. Eschenmoser, *Helv. Chim. Acta*, 1964, **47**, 2425–2429; (*b*) S. N. Gradl, J. J. Kennedy-Smith, J. Kim and D. Trauner, *Synlett*, 2002, 411–414.
30 H. C. Hailes, B. Isaac and M. H. Javaid, *Tetrahedron*, 2001, **57**, 10329–10333.
31 Deprotection of **iii** with DDQ in wet CH_2Cl_2 proceeded as usual. However, separation of 12-hydroxy-JA (**iv**) and aldehyde **v** by chromatography on silica gel was unsuccessful due to the close mobilities. In contrast, a mixture of ethyl ester of **iv** and **v** produced from ethyl ester of **iii** was separated easily, affording the ethyl ester in 79% yield.



iii, R = PMB
iv, R = H



v

32 E. J. Corey, T. K. Schaaf, W. Huber, U. Koelliker and N. M. Weinshenker, *J. Am. Chem. Soc.*, 1970, **92**, 397–398.
33 The authentic *trans* isomers, **32** and 12-hydroxy-JA (**iv**), were synthesized from acids **30** and **5**, respectively, by exposing them to NaOH in aqueous MeOH. The diagnostic signals for **30** *vs.* **32** and for **5** *vs.* **iv** in the ^{1}H NMR spectra (300 MHz, the former two in $CDCl_3$ and the latter two in CD_3OD) are (δ, ppm): **30**, 2.78–2.93; **32**, 2.54–2.73; **5**, 2.74–2.88; **iv**, 2.60–2.71. In addition, the ^{1}H NMR spectrum of **iv** was consistent with that reported[19c].
34 H. P. Acharya and Y. Kobayashi, *Tetrahedron Lett.*, 2005, **46**, 8435–8438.
35 The use of TBAF (6 equiv) in THF (rt, 4 h) produced **34** in 71% yield.
36 S. Kim and J. H. Park, *Tetrahedron Lett.*, 1987, **28**, 439–440.
37 Other syntheses of 12-oxo-PDA: (*a*) P. A. Grieco and N. Abood, *J. Org. Chem.*, 1989, **54**, 6008–6010; (*b*) M. Ernst and G. Helmchen, *Angew. Chem., Int. Ed.*, 2002, **41**, 4054–4056.
38 Overall yields and steps involved in the syntheses: 26.7% and 12 steps from acetate **10** by us; 4.9% and 8 steps from benzoquinone-cyclopentadiene adduct by Grieco;[37a] 6.5% and 11 steps from cyclopentenyl chloride by Helmchen[37b].
39 K. Weinges, H. Gethöffer, U. Huber-Patz, H. Rodewald and H. Irngartinger, *Liebigs Ann. Chem.*, 1987, **1987**, 361–366.
40 S. W. Baertschi, C. D. Ingram, T. M. Harris and A. R. Brash, *Biochemistry*, 1988, **27**, 18–24.