Syntheses of dinor-cis/iso-12-oxo-phytodienoic acid (dn-cis/iso-OPDAs), ancestral jasmonate phytohormones of the bryophyte Marchantia polymorpha L., and their catabolites

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In recent years, the biology of the evolutionary origin of phytohormone signaling has made significant progress. Among them, the ligand-receptor co-evolution found in jasmonate signaling has attracted the attention of plant scientists. Dinor-cis-12-oxo-phytodienoic acid (dn-cis-OPDA, 4) and dn-iso-OPDA (5) are ancestral plant hormones of the bryophyte Marchantia polymorpha L. We succeeded in the first practical synthetic supply of these hormones as well as their possible catabolites. These compounds are expected to be useful in the study of ancestral jasmonate signaling in bryophytes.

(+)-Jasmonoyl-l-isoleucine (JA-Ile, 1) is a lipid-derived plant phytohormone, implicated in the regulation of plant growth, fertility, and defense against pathogens and insects1–3. JA-Ile-mediated signal transduction depends on the COI1-JAZ co-receptor system, composed of an F-box protein CORONATINE INSENSITIVE 1 (COI1) and JASMONATE ZIM-DOMAIN (JAZ) repressor protein4–6. After signal transduction, 1 is catabolized into 12-hydroxy-JA-Ile (12-OH-JA-Ile, 2) by CYP94B1/B3, then 12-carboxy-JA-Ile (12-COOH-JA-Ile, 3) by CYP94C1, and then deactivated within a few hours (Fig. 1)7–9. Biological studies of the evolution of phytohormone signaling is an important topic in plant science10–13, and recent achievements in the genomic sequencing of a myriad of plant species have enabled research into the evolutionary origins of phytohormones. Marchantia polymorpha L., a type of bryophyte, has attracted a great deal of attention due to its ancestral signaling module14, and its jasmonate signaling constitutes an intriguing example of ligand-receptor co-evolution, depending on the MpCOI1-MpJAZ co-receptor system (Fig. 1)15. However, JA-Ile, the usual ligand for the COI1-JAZ co-receptor system of vascular plants, cannot be perceived by MpCOI1-MpJAZ–dinor-cis-12-oxo-phytodienoic acid (dn-cis-OPDA, 4) and dn-iso-OPDA (5) are the ligands of MpCOI1-MpJAZ co-receptor instead (Fig. 1). Genetic studies have revealed that the ligand-receptor pair of dn-cis/iso-OPDA and MpCOI1-MpJAZ participates in all the jasmonate responses of M. polymorpha, including defense responses16–18. However, biological studies require samples of 4 and 5—in the past, 4 has been synthesized enzymatically19 but is now out of stock; and the only known synthesis of 5 entails an electroorganic reaction20 that cannot be accomplished using normal laboratory equipment (Scheme S1). Accordingly, we developed and report herein the first chemical synthesis of 4 and the first non-electroorganic synthesis of 5. In addition, we synthesized their potent catabolites 16-hydroxy-dinor-cis-OPDA (16-OH-dn-cis-OPDA, 6), 16-carboxy-dinor-cis-OPDA (16-COOH-dn-cis-OPDA, 7), 16-hydroxy-dinor-iso-OPDA (16-OH-dn-iso-OPDA, 8), 16-carboxy-dinor-iso-OPDA (16-COOH-dn-iso-OPDA, 9) (Fig. 1). These potent catabolites will enable further studies on the catabolism of ancestral plant hormones.

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Results and discussion

Synthesis of dn-cis-OPDA (4) and its potent catabolites (6 and 7). Our plan for the synthesis of dn-cis-OPDA (4) and its catabolites (6 and 7) is outlined in Scheme 1. A major initial concern in the syntheses of 4, 6 and 7 was the avoidance of epimerization at C11 which was anticipated to be facile in the presence of either acid or base based on the ready epimerization of the structurally similar 1 to give the more thermodynamically stable trans-1 in a ratio of trans:cis = 95:5 \(^{21}\). We therefore planned to synthesize 4 according to a procedure similar to that used to synthesize OPDA (10), a congener of 4, developed by Kobayashi et al.\(^{22}\). They avoided epimerization by introducing the ketone at the late stage of synthesis\(^{24}\). Compounds 4 and 6 would be obtained from a common intermediate 11 by Wittig reaction using a different phosphonium salt (Scheme 1), and 7 would be obtained by oxidation of 6.
Our synthesis of dn-cis-OPDA (4) is summarized in Scheme 2. Allylic substitution of monoacetate 15, prepared by enzymatic reaction, with TBDPS(CH₃)₆MgCl, was performed in the presence of CuCN to afford 16. The Mitsunobu reaction of 16, hydrolysis of resulting acetate and Eschenmoser–Claisen rearrangement gave dimethylamide 17. Iodolactonization, elimination with DBU and subsequent reduction with LiAlH₄ afforded diol 18. In the iodolactonization step, use of water in place of buffer resulted in the removal of TBDPS group. TES
diastereomeric ratio were in good accordance with previous literature (trans:cis = ca. 94:6 by NMR). This epimerization and observed diastereomeric ratio were in good accordance with previous literature (trans:cis = ca. 94:6 by NMR). This epimerization and observed diastereomeric ratio were in good accordance with previous literature (trans:cis = ca. 94:6 by NMR). This epimerization and observed diastereomeric ratio were in good accordance with previous literature (trans:cis = ca. 94:6 by NMR). This epimerization and observed diastereomeric ratio were in good accordance with previous literature (trans:cis = ca. 94:6 by NMR). This epimerization and observed diastereomeric ratio were in good accordance with previous literature (trans:cis = ca. 94:6 by NMR). This epimerization and observed diastereomeric ratio were in good accordance with previous literature (trans:cis = ca. 94:6 by NMR). This epimerization and observed diastereomeric ratio were in good accordance with previous literature (trans:cis = ca. 94:6 by NMR). This epimerization and observed diastereomeric ratio were in good accordance with previous literature (trans:cis = ca. 94:6 by NMR). This epimerization and observed diastereomeric ratio were in good accordance with previous literature (trans:cis = ca. 94:6 by NMR). This epimerization and observed diastereomeric ratio were in good accordance with previous literature (trans:cis = ca. 94:6 by NMR). This epimerization and observed diastereomeric ratio were in good accordance with previous literature (trans:cis = ca. 94:6 by NMR). This epimerization and observed diastereomeric ratio were in good accordance with previous literature (trans:cis = ca. 94:6 by NMR). This epimerization and observed diastereomeric ratio were in good accordance with previous literature (trans:cis = ca. 94:6 by NMR). This epimerization and observed diastereomeric ratio were in good accordance with previous literature (trans:cis = ca. 94:6 by NMR). This epimerization and observed diastereomeric

Scheme 3. Synthesis of 16-OH-dn-cis-OPDA (6) and 16-COOH-dn-cis-OPDA (7). Reagents and conditions: (a) (COCl)2, DMSO, NEt3, CH2Cl2; (b) [THPO(CH2)3PPh3]+Br−, NaHMDS, THF, 76% (2 steps); (c) TBAF, THF 72%; (d) Jones reagent, acetone, −20 °C; (e) MgBr2, Et2O, 72% (2 steps); (f) PPTS, MeOH, 35 °C, 54%; (g) Jones reagent, acetone, −20 °C, 73%.

Synthesis of dn-iso-OPDA (5) and its potent catabolites (8 and 9). Our plan for the synthesis of dn-iso-OPDA (5) and its potent catabolites (8 and 9) is shown in Scheme 4. In the synthesis of [3H2]-tetrahydrodicanenone (iso-OPDA), Lauchli and Boland introduced the C1–8 side chain by the 1,4-addition using an organozinc reagent and CuCN28. However, organozinc reagents are difficult to prepare and less toxic than CuCN. And potent catabolites 16-OH-dn-iso-OPDA (8) and 16-COOH-dn-iso-OPDA (9) could be obtained from the same starting material 24 by using a different allyl bromide.

Our synthesis of dn-iso-OPDA (5) is summarized in Scheme 5. Allylation of 1,3-cyclopentanedione 24 followed by methylation of the resulting 27 gave cyclopentenone 28. After the Grignard reaction of 28, dilution of the reaction mixture with hydrochloric acid promoted hydrolysis of the enol ether and the deprotection of the THP group, to give alcohol 30. Finally, Jones oxidation of 30 gave 61 mg of dn-iso-OPDA (5) in only 4 steps from 24.

Next, we synthesized 16-OH-dn-iso-OPDA (8) and 16-COOH-dn-iso-OPDA (9) (Schemes 6, 7). Introduction of the C12–C16 side chain of 24 was first attempted by allylation, but the side chain could not be directly introduced using allylation in order to O-alkylation. Accordingly, we abandoned this approach and sought to construct the C12–C16 side chain by Z-selective cross metathesis29–31. Pd-mediated allylation25 of 24 and subsequent methylation gave allylcyclopentenone 32. Introduction of the C1–C6 side chain using THP(CH2)3MgBr followed by hydrolysis and deprotection of THP group gave alcohol 33. Finally, Jones oxidation of 33 followed by
cross metathesis with CH2=CHCH2CH2OAc and deprotection of the acetyl group gave 16-OH-dn-iso-OPDA (8, 15.6 mg in 7 steps and 11% overall yield from 24) as a Z/E mixture (10:1 Z/E). Z/E isomers were easily separated by chiral HPLC using a CHIRALPAK IA column to obtain pure Z-8 (2.4 mg). 16-COOH-dn-iso-OPDA (9, 12:1 Z/E, 6.3 mg) was also obtained from allylcyclopentenone 33 by cross metathesis with CH2=CHCH2CH2OAc, hydrolysis of acetyl group and Jones oxidation (total 7 steps and 3.4% overall yield from 24). Z/E isomers were easily separated by HPLC to obtain pure Z-9 (2.6 mg).

Conclusions
A synthetic supply of jasmonates is indispensable if their study is to be advanced \(^{20,30,33,34}\), and this work finally enables dn-cis/iso-OPDAs (4 and 5) and their potent catabolites (6–9) to be readily obtained. Our work is expected to accelerate biological studies of the signaling mechanisms of bryophyte hormones, which should lead to a better understanding of the evolutionary origins of phytohormone signaling. In particular, study of the catabolism of 4 and 5 should provide insights into the deactivation mechanism of ancestral plant hormones. Biological studies using synthetic 4–9 are now in progress.
Method

Synthesis of dn-cis-OPDA (4). To a solution of 20 (57.2 mg, 94.5 µmol) in THF (20 mL) was added 1 M TBAF in THF (1.6 mL, 1.60 mmol). After being stirred at reflux temperature for 1.5 h, the solvent was removed under reduced pressure. The residue was purified by medium-pressure chromatography (Isolera, eluent: 93:7 n-hexane/EtOAc to 40:60 n-hexane/EtOAc) to give a diol intermediate (22.3 mg, 94%) as a colorless oil. [α]D 22 + 63.6 (c 1.09, CHCl3). 1H NMR (400 MHz, CDCl3) δH: 6.22 (dd, J = 5.8, 2.6 Hz, 1H), 5.96 (brd, J = 5.8 Hz, 1H), 5.49–5.38 (m, 2H), 4.51 (dd, J = 5.8, 2.6 Hz, 1H), 3.63 (t, J = 6.6 Hz, 2H), 2.52–2.43 (m, 1H), 2.37–2.27 (m, 1H), 2.04–1.94 (m, 4H), 1.66–1.52 (m, 3H), 1.47–1.20 (m, 7H), 0.99 (t, J = 7.5 Hz, 3H); 13C NMR (100 MHz, CDCl3) δC: 141.64, 132.46, 132.01, 127.88, 76.55, 62.99, 46.13, 46.00, 33.52, 32.73, 29.70, 28.05, 25.69, 23.08, 20.78, 14.26; IR (neat) cm⁻¹: 3356, 2931, 2861, 1458, 1053; HRMS (ESI, positive) m/z [M + Na]+ Calcd. for C16H28NaO2: 275.1987, Found: 275.1976.

To a solution of diol intermediate (15.3 mg, 60.6 µmol) in acetone (5.2 mL) was added Jones reagent (4.0 M solution) at −20 °C until the orange color of the reagent persisted (30 drops). After 10 min of stirring at −20 °C, i-PrOH was added to quench the remaining reagent. Then, EtOAc/n-hexane (1/1, 20 mL) and H2O (20 mL) were added and the water layer was extracted with EtOAc. The combined organic layers were washed with saturated aqueous NaCl, dried over Na2SO4 and concentrated under reduced pressure. The residue was purified by medium-pressure chromatography (Isolera, eluent: 0.1:88:12 AcOH/n-hexane/EtOAc to 0.1:99.9 AcOH/EtOAc) to give 4 (116 mg, 97%) as a colorless oil. Diastereomeric purity of 4 was >99% by 1H NMR spectroscopy (δH = 7.72 (dd, J = 5.8, 2.7 Hz, 1H) for 4; 7.59 (dd, J = 5.8, 2.6 Hz, 1H) for the trans isomer). [α]D 22 + 135.5 (c 0.75, CHCl3). 1H NMR (400 MHz, CDCl3) δH: 7.72 (dd, J = 5.8, 2.7 Hz, 1H), 6.18 (dd, J = 5.8, 1.6 Hz, 1H), 5.48–5.31 (m, 2H), 3.04–2.94 (m, 2H), 2.36 (brt, J = 7.1 Hz, 2H), 2.13 (dt, J = 15.8, 7.5 Hz, 2H), 2.05 (quintet, J = 7.5 Hz, 2H), 1.80–1.69 (m, 1H), 1.63 (brt, J = 7.1 Hz, 2H), 1.52–1.29 (m, 4H), 1.23–1.11 (m, 1H), 0.97 (t, J = 7.5 Hz, 3H); 13C NMR (100 MHz, CDCl3) δC: 210.86, 179.32, 166.96, 133.02, 132.50, 126.82, 49.79, 44.20, 33.84, 30.58, 29.18, 27.32, 24.49, 23.76, 20.78, 13.99; HRMS (ESI, positive) m/z [M + Na]+ Calcd. for C16H24NaO3: 287.1623, Found: 287.1618.

Synthesis of 16-OH-dn-cis-OPDA (6). To a solution of 22 (71.0 mg, 201 µmol) in acetone (20 mL) was added Jones reagent (4.0 M solution, 400 µL, 1.60 mmol) at −20 °C. After 20 min of stirring at −20 °C, i-PrOH was added to quench the remaining reagent. Then, EtOAc/n-hexane (1/1, 10 mL) and H2O (20 mL) were added...
and the water layer was extracted with EtOAc. The combined organic layers were washed with saturated aqueous NaCl, dried over Na2SO4, and filtered. The residue was purified by medium-pressure chromatography (Isolera, eluent: 0.5:99.5 AcOH/CHCl3/MeOH to 0.5:99.5 AcOH/CHCl3/MeOH) to give 7 (8.3 mg, 73%) as a colorless oil. Diastereomeric purity of 7 was > 98% by 1H NMR spectroscopy (δH, 7.74 (dd, J = 5.9, 2.7 Hz, 1H) for 7; 7.62 (dd, J = 5.9, 2.4 Hz, 1H) for the trans isomer), [α]D21 +117.6 (c 0.24, CHCl3). 1H NMR (400 MHz, CDCl3) δH: 7.74 (dd, J = 5.9, 2.7 Hz, 1H) for 7; 7.62 (dd, J = 5.9, 2.4 Hz, 1H) for the trans isomer). [α]D21 +117.6 (c 0.24, CHCl3). 1H NMR (400 MHz, CDCl3) δH: 7.74 (dd, J = 5.9, 2.7 Hz, 1H) for 7; 7.62 (dd, J = 5.9, 2.4 Hz, 1H) for the trans isomer).

Synthesis of 16-COOH-dn-cis-OPDA (7). To a solution of 23 (10.3 mg, 38.4 µmol) in acetone (6.0 mL) was added Jones reagent (4.0 M solution) at −20 °C until the orange color of the reagent persisted (37 drops). After 20 min of stirring at −20 °C, i-ProOH was added to quench the remaining reagent. Then, EtOAc (10 mL) and H2O (60 mL) were added and the water layer was extracted with EtOAc. The combined organic layers were washed with saturated aqueous NaCl, dried over Na2SO4, and filtered. After evaporation, the residue was purified by medium-pressure chromatography (Isolera, eluent: 0.5:99.5 AcOH/CHCl3/MeOH to 0.5:99.5 AcOH/CHCl3/MeOH) to give 7 (8.3 mg, 73%) as a colorless oil. Diastereomeric purity of 7 was > 98% by 1H NMR spectroscopy (δH, 7.74 (dd, J = 5.9, 2.7 Hz, 1H) for 7; 7.62 (dd, J = 5.9, 2.4 Hz, 1H) for the trans isomer), [α]D21 +117.6 (c 0.24, CHCl3). 1H NMR (400 MHz, CDCl3) δH: 7.74 (dd, J = 5.9, 2.7 Hz, 1H) for 7; 7.62 (dd, J = 5.9, 2.4 Hz, 1H) for the trans isomer).

Synthesis of dn-iso-OPDA (5). To a solution of THPO(CH2)6MgBr (0.85 M in THF, 3.3 mL, 2.80 mmol) was added a solution of 28 (198 mg, 1.10 mmol) in THF (6.5 mL) at reflux under argon atmosphere. After being stirred at 60 °C for 3 h, the reaction mixture was allowed to cool to rt and 2 M HCl aq. (7 mL) was added. After 1.5 h of stirring, the water layer was extracted with EtOAc. The combined organic layers were washed with saturated aqueous NaCl, dried over Na2SO4, and filtered. After evaporation, the residue was purified by medium-pressure chromatography (Isolera, eluent: 40:60 n-hexane/EtOAc to EtOAc) to give the oxidized compound. The compound was carried on to the next step. To a solution of the mixture (79.6 mg) in acetone (6 mL) was added Jones reagent (4.0 M solution, 200 µL, 800 µmol) at 0 °C. After 3.5 h of stirring at 0 °C, i-ProOH was added to quench the remaining reagent. Then, H2O (20 mL) was added and the water layer was extracted with EtOAc. The combined organic layers were washed with saturated aqueous NaCl, dried over Na2SO4, and filtered. The residue was purified by medium-pressure chromatography (Isolera, eluent: 0.5:99.5 AcOH/n-hexane/EtOAc to 0.5:99.5 AcOH/EtOAc) to give 5 (61.4 mg, 89%) as a colorless oil. 1H NMR (400 MHz, CDCl3) δH: 7.15 (dd, J = 15.8, 7.8 Hz, 1H), 7.08 (dt, J = 17.2, 5.9 Hz, 1H), 4.08 (dd, J = 17.2, 5.9 Hz, 1H), 2.93 (d, J = 7.2 Hz, 2H), 2.50 (t, J = 4.4 Hz, 2H), 2.44 (t, J = 7.6 Hz, 2H), 2.39–2.35 (m, 4H), 2.15 (quin, J = 7.6 Hz, 2H), 1.68 (quin, J = 6.4 Hz, 2H), 1.58 (quin, J = 8.0 Hz, 2H), 1.44–1.36 (m, 2H), 0.99 (t, J = 7.6 Hz, 3H); 13C NMR (100 MHz, CDCl3) δC: 210.45, 179.82, 177.53, 167.19, 132.47, 131.97, 121.59, 49.21, 44.26, 33.82, 32.94, 30.48, 29.03, 27.30, 24.24, 24.15; IR (neat) cm⁻¹ : 2948, 2405, 3031, 2935, 1708 (br); HRMS (ESI, positive) m/z [M + Na]+ Calcd. for C38H32O3N: 537.2155. Found: 537.2153.

Synthesis of 16-OH-dn-iso-OPDA (8). A 5 mL pear-shaped flask was charged with 33 (31.2 mg, 140 µmol), CH3=CHCH2CH2OAc (165 mg, 144 mmol) and Hoveyda–Grubbs Catalyst M2001 Umicro (4.6 mg, 7.27 µmol). After 24 h of stirring, the residue was roughly purified by medium-pressure chromatography (Isolera, eluent: 0.1:99.1 AcOH/CHCl3/MeOH to 0.1:90.10 AcOH/CHCl3/MeOH) to give a mixture (58.2 mg). The crude mixture was used for the next reaction without further purification. To a solution of the mixture (58.2 mg) in acetone (10 mL) was added Jones reagent (4.0 M solution, 95 µL, 380 µmol) at −20 °C. After 30 min of stirring at −20 °C, i-ProOH was added to quench the remaining reagent. Then, EtOAc and H2O were added and the water layer was extracted with EtOAc. The combined organic layers were washed with saturated aqueous NaCl, dried over Na2SO4, and filtered. The crude mixture (33.0 mg) was used for the next reaction without further purification. To a solution of the mixture (33.0 mg) in THF (4.5 mL) was added 1 M-LiOH solution (510 µL, 510 µmol) and the mixture was stirred for 1.5 h. The reaction mixture was quenched with 1 M HCl aq. and the aqueous layer was extracted with EtOAc. The organic layer was washed with saturated aqueous NaCl, dried over Na2SO4, and filtered. After evaporation, the residue was purified medium-pressure chromatography (Isolera, eluent: 0.1:85:15 AcOH/n-hexane/EtOAc to 0.1:99.9 AcOH/EtOAc) to give 16-OH-dn-iso-OPDA (8) (15.6 mg, 40% in 3 steps) as a Z/E mixture (Z/E = 10/1). Z/E isomers were separated by
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Author contributions
M.U. conceived, designed, and coordinated the research project. N.K. designed the synthetic route of all compounds. M.U., N.K. and T.K. wrote the main manuscript text and all figures. J.W. T.K. and N.K. synthesized dn-cis-12-OPDA and the derivatives, and H.S. and N.K. synthesized dn-iso-12-OPDA and the derivatives. All authors reviewed the manuscript.

Competing interests
The authors declare no competing interests.

Additional information
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