Synthesis of (±)-Panduratin A and Related Natural Products Using the High Pressure Diels–Alder Reaction

Luke A. Pasfield, Laura de la Cruz, Junming Ho, Michelle L. Coote, Gottfried Otting, and Malcolm D. McLeod*^[a]

Panduratin A (**1**) is the prototypical member of a family of related cyclohexenyl natural products and is isolated as a racemic mixture from *Boesenbergia rotunda*, a perennial herb found in South East Asia (Figure 1).^[1–4] The plant has been used in traditional medicine to treat conditions such as diarrhea, asthma, indigestion, dysentery and many others.^[1–4] More recently studies have shown that these extracts have anti-HIV, anti-bacterial, anti-fungal and anti-tumor activity.^[3–6] Our particular interest in panduratin A (**1**) and its congeners stems from a report that they competitively inhibit the dengue virus NS2B-NS3 protease.^[7,8] Herein we report the synthesis of panduratin A (**1**) in 6 steps via a high pressure Diels–Alder reaction. This divergent sequence has also allowed for the synthesis of the related natural products 4-hydroxypanduratin A (**2**), panduratin H (**3**), panduratin I (**4**), nicolaioidesin B (**5**) and 2-hydroxyisopanduratin A (**6**).^[1–9] We investigated the binding of 4-hydroxypanduratin A (**2**) to the dengue virus NS2B-NS3 protease by NMR spectroscopy.

To date two syntheses of panduratin A (**1**) have been reported,^[10,11] both of which employed a cycloaddition reaction between a protected chalcone derivative **7** and *E*-ocimene (**8**) (Scheme 1). The first reported synthesis by Rahman and co-workers^[10] in 2010 was achieved by a thermally promoted Diels–Alder reaction between chalcone derivative **7** (P = MEM) and *E*-ocimene (**8**) followed by deprotection to afford a mixture of panduratin A and its regioisomer nicolaioidesin B. No regioisomer ratio was reported for this mixture, nor were the regioisomers separated. In the same year Porco and co-workers^[11] employed a silver nanoparticle catalyst developed in their laboratory to facilitate the cycloaddition between a chalcone **7** (P = Ac) and *E*-ocimene (**8**). This methodology afforded the adduct leading to panduratin A (**1**) with a small amount of the *exo* isomer corresponding to the isomeric natural product nicolaioidesin A.

Figure 1. Panduratin A (**1**) and related natural products.

Scheme 1. Rahman^[10] and Porco^[11] synthetic strategy and retrosynthetic analysis for this work.

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These efforts serve to highlight two key issues encountered in synthetic strategies targeting the panduratin natural product family. Firstly, the requisite chalcones are typically poor dienophiles in the Diels–Alder reaction due to their high level of substitution and moderate activation and require forcing conditions or special techniques to achieve high yields. Secondly, the diene *E*-ocimene (**8**) is known to be sensitive to Brønsted and Lewis acids resulting in polymerization and alkene isomerization.^[12] We instead envisaged an early stage high pressure Diels–Alder reaction^[13] to construct the cyclohexene core employing a sterically less encumbered and more active dienophile such as methyl cinnamate **9** with *E*-ocimene (**8**), followed by the construction of the phenylmethanone sidechain through organometallic addition (Scheme 1). This approach allows for late-stage access to different members of the panduratin family and is modular thereby providing avenues for the synthesis of analogues through the variation of building blocks.

The synthesis of panduratin A (**1**) began with the Diels–Alder cycloaddition of methyl cinnamate **9** and *E*-ocimene (**8**, see Supporting Information) performed under high pressure conditions (19 kbar) to afford the regioisomeric panduratin H (**3**) and I (**4**) in a 1:2.9 ratio (Scheme 2). Employing thermal conditions or Lewis acids failed to afford the Diels–Alder

Scheme 2. Synthesis of panduratin A (**1**) and 4-hydroxypanduratin A (**2**).

adduct. A combination of flash chromatography and HPLC separation afforded pure regioisomers that conformed to the reported literature data.^[4] In both isomers the orientation of the prenyl sidechain was *cis* to the adjacent ring substituent. Hydride reduction gave the alcohol products **10** and **11** that were readily separated by flash column chromatography, thus providing intermediates with the correct relative stereochemistry for the synthesis of panduratin A (**1**) and regioisomeric natural products. Subsequent oxidation of alcohol **10** with Dess–Martin periodinane provided aldehyde **12** as the branching point towards either panduratin A (**1**) or 4-hydroxypanduratin A (**2**). Addition of the organolithium reagent derived from bromobenzene **13** followed by Dess–Martin periodinane oxidation gave MOM protected ketone **14**. Removal of the MOM groups with acidic methanol cleanly afforded panduratin A (**1**). Using alternate bromobenzene **15** and following the same synthetic sequence via ketone **16** gave 4-hydroxypanduratin A (**2**) in a yield of 52% over 3 steps. The spectroscopic data for panduratin A (**1**) and 4-hydroxypanduratin A (**2**) agreed with that of literature.^[1,2]

To further explore the influence of structure on cycloaddition regioselectivity, various dienophiles **17** with differing electronic and steric attributes were paired with *E*-ocimene (**8**) in the high pressure Diels–Alder reaction (Table 1). After reaction the products were reduced to the corresponding alcohol or aldehyde which were easily separated and purified by flash column chromatography. In all cases the reactions afforded regioisomer **B** as the major product. Stronger activating groups such as the aldehyde or nitrile provided slightly higher ratios favouring regioisomer **B**. However, substitution of the ethyl ester for the more electron withdrawing 2,2,2-trifluoroethyl ester, a strong inductive electron withdrawing group, provided Diels–Alder adducts in a similar ratio.^[14,15]

Table 1. High pressure Diels–Alder reactions of different dienophiles **17** with *E*-ocimene (**8**).

X	Yield [%]	Ratio A:B ^[a]
CN	64 ^[b]	1:9.5
COO <i>t</i> Bu	63 ^[c]	1:8.9
CHO	62	1:7.2
COOEt	68 ^[c]	1:3.1
COOMe	73 ^[c]	1:2.9
COOCH ₂ CF ₃	56 ^[c]	1:2.4

[a] Ratio of regioisomers determined by 400 MHz ¹H NMR integration of the crude reaction mixture. [b] After reduction to aldehyde. [c] After reduction to alcohol.

The regiochemical outcome of the Diels–Alder cycloaddition between methyl cinnamate (**9**) with *E*-ocimene (**8**) was in accord with an analysis based on computationally-derived frontier

molecular orbitals (Figure 2). Alignment of the larger diene HOMO ($2p_z$ atomic) coefficient with that of the corresponding dienophile LUMO coefficient predicts formation of ester **4** as the major regioisomer.^[16] Orbital coefficients also predict the correct regiochemical outcomes for the other compounds studied in Table 1 (see the Supporting Information for further details).

Figure 2. Atomic orbital coefficients of the $2p$ orbitals of methyl cinnamate (**9**), and *E*-ocimene (**8**) calculated at the B3LYP/6-31G(d) level of theory (see computational methods in the Supporting Information for further details).

Employing cinnamaldehyde (**18**) in the high pressure Diels–Alder reaction afforded a separable 1:7.2 mixture of the two Diels–Alder regioisomers **12** and **19** (Scheme 3). Addition of the organolithium reagent derived from bromobenzene **13** to aldehyde **19** followed by oxidation afforded ketone **20** in 69% over two steps. Deprotection gave nicolaioidesin B (**5**) in 69% yield.^[9] Using alternate bromobenzene **15** and following the same synthetic sequence via ketone **21** gave 4-hydroxyisopanduratin A (**6**) in a yield of 50% over 3 steps. The spectroscopic data for nicolaioidesin B (**5**) and 4-hydroxyisopanduratin A (**6**) agreed with that of literature.^[3,9]

Scheme 3. Synthesis of nicolaioidesin B (**5**) and 4-hydroxyisopanduratin A (**6**).

The dengue virus NS2B-NS3 protease is crucial for viral replication and presents a target for the treatment of dengue virus infections. The hydrophilic NS2B fragment acts as a cofactor essential for full proteolytic activity. Recent NMR studies in association with pseudocontact shifts derived from paramagnetic lanthanide tags have shown that binding of an inhibitor at the

substrate-binding site can trigger a large conformational change of the NS2B cofactor, shifting the protein structure from an open to a closed conformation.^[17] Crystal structures of the NS2B-NS3 protease with bound inhibitors show that in the closed conformation, which is also thought to be the active conformation, NS2B lines the substrate binding site.^[18]

Both panduratin A (**1**) ($K_i = 25 \pm 8 \mu\text{M}$) and 4-hydroxypanduratin A (**2**) ($K_i = 21 \pm 6 \mu\text{M}$) have been reported, based on enzyme kinetic data, to inhibit the dengue virus NS2B-NS3 protease competitively, identifying them as important natural product lead structures.^[7,8] Thus NMR spectroscopy suggested itself as a suitable method to further define the nature of binding of these natural products at the NS2B-NS3 protease. To test whether panduratin A can induce a closed conformation we recorded ^{15}N -HSQC spectra of the uniformly ^{15}N -labelled NS2B-NS3 protease in the presence and absence of the compounds. No changes to the spectrum NS2B-NS3 protease were observed in the presence of panduratin A (**1**) or 4-hydroxypanduratin A (**2**), in contrast to the response to previously reported low molecular weight competitive inhibitors.^[17] Previous NMR and X-ray data showed, that binding of inhibitors at the substrate binding site can stabilize a closed conformation of the protease that resembles the enzymatically active state.^[17,18] The NMR spectra obtained in the presence of either panduratin A (**1**) or 4-hydroxypanduratin A (**2**) showed no evidence for such a conformational change. In our hands, panduratin A (**1**) and 4-hydroxypanduratin A (**2**) also proved to be poorly soluble in aqueous media. Addition of either of the two compounds from DMSO stock solutions to the protein sample caused precipitation of the panduratin. Panduratin A (**1**) precipitated even at a target concentration of $100 \mu\text{M}$ in 15% aqueous DMSO. These results highlight that some caution is warranted in adopting panduratin A (**1**) and 4-hydroxypanduratin A (**2**) as lead structures for the development of dengue virus NS2B-NS3 protease inhibitors.

In conclusion we have completed the synthesis of panduratin A (**1**) and five related natural products **2–6** using a high pressure Diels–Alder reaction as the key step. This flexible route provides rapid access to various members of the natural product family and is amenable to analogue synthesis. However, attempts to monitor the binding of panduratin A (**1**) and 4-hydroxypanduratin A (**2**) to the dengue virus NS2-NS3 protease by NMR failed to show the characteristic changes in protein conformation that have been observed for other known competitive inhibitors.

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Natural Products

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Under Pressure: Panduratin A (**1**) has been synthesized in 6 steps via a high pressure Diels–Alder reaction. This divergent sequence has also allowed for the synthesis of 4-hydroxypanduratin A (**2**), panduratin H (**3**), panduratin I (**4**), nicolaioidesin B (**5**) and 2-hydroxyisopanduratin A (**6**). The binding of panduratin A (**1**) to the dengue virus NS2B-NS3 protease has been investigated by NMR spectroscopy.

Synthesis of (±)-Panduratin A and Related Natural Products Using the High Pressure Diels–Alder Reaction

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Chemistry Experimental

General

Infrared absorption (IR) spectra were obtained using with a Perkin–Elmer Spectrum One FTIR spectrometer. Compounds were prepared as a thin film between 0.5 cm sodium chloride plates. Absorption maxima ($\nu_{\max}$) are expressed in wavenumbers (cm^{-1}). ^1H Nuclear magnetic resonance spectra were recorded using a Varian Mercury 300 (300 MHz), Varian Mercury 400 (400 MHz) or Bruker 800 (800 MHz) spectrometer at 25°C , and are recorded in parts per million (ppm) downfield shift from tetramethylsilane ($\delta_{\text{TMS}} = 0$), using residual chloroform (δ 7.26) or methanol (δ 3.31) solvent as internal reference. The data is reported as chemical shift (δ_{H}), relative integral, multiplicity (s = singlet, br = broad, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constant (J Hz), and assignment. ^{13}C Nuclear magnetic resonance spectra were recorded using a Varian Mercury 300 (75 MHz) or Varian Mercury 400 (100 MHz) spectrometer at 25°C with complete proton decoupling. Data is expressed in parts per million (ppm) downfield relative to tetramethylsilane ($\delta_{\text{TMS}} = 0$) using deuterated chloroform (δ 77.00) solvent as an internal reference and is reported as chemical shift (δ_{C}). High and low resolution electron impact ionization (EI) mass spectra were recorded using a Micromass VG Autospec mass spectrometer. Low and high resolution electrospray ionization (ESI) mass spectra were recorded using a Micromass ZMD LR mass spectrometer or a Waters LCT Premier XE mass spectrometer respectively. Preparative HPLC was performed on a Waters preparative HPLC system consisting of a 600E solvent delivery system, in-line degasser and 2996 diode array detector. Samples were injected manually via a Rheodyne 7725i injection valve fitted with a 5 mL loop and separated on a Waters XBridge C18 $5\ \mu\text{m}$ $150\ \text{mm} \times 4.6\ \text{mm}$ eluted at $1\ \text{mL min}^{-1}$. The system was interfaced with Empower 2 software for instrument control and data acquisition. Analytical thin layer chromatography (TLC) was performed using 0.2 mm thick aluminum backed pre-coated silica gel plates (Merck Kieselgel 60 F254). Flash chromatography was carried out using Merck Kieselgel 60 (230–400 mesh ASTM), under a positive pressure of nitrogen. Solvent compositions were mixed v/v as specified. High pressure reactions were carried out in a PSIKA high pressure reactor. All solvents and reagents were purified according to standard literature procedures.^[1]

3-Methyl-2-(3-methylbut-2-en-1-yl)-2,5-dihydrothiophene 1,1-dioxide (22)^[2]

3-Methyl sulfolene (3.46 g, 26.2 mmol), prenyl bromide (1.53 mL, 13.1 mmol) and tetrahydrofuran (50 mL) were added to a flask and under a nitrogen atmosphere and cooled to -95°C with stirring.

LHMDS (26.2 mL, 1 M, 26.2 mmol) in tetrahydrofuran was then slowly added over 1 min and the reaction allowed to stir for a further 1 min. Quenching with a saturated solution of ammonium chloride (30 mL) was then followed by extraction with diethyl ether (3 × 20 mL). The combined organic layers were then dried over magnesium sulfate, filtered, concentrated under reduced pressure and purified via silica gel chromatography using diethyl ether : hexane (2:3) to afford 3-methyl-2-(3-methylbut-2-en-1-yl)-2,5-dihydrothiophene 1,1-dioxide **22** as a clear yellow oil (2.15 g, 82%); **R_f** (diethyl ether:hexane 2:3) 0.19; **¹H-NMR** (400 MHz, CDCl₃) δ 5.68 (1H, m, H4), 5.21 (1H, m, H2'), 3.73–3.60 (2H, m, H5), 3.50 (1H, t, *J* = 6.0 Hz, H2), 2.61–2.49 (2H, m, H1'), 1.85 (3H, s, CH₃), 1.72 (3H, s, CH₃), 1.66 (3H, s, CH₃); **¹³C-NMR** (100 MHz, CDCl₃) δ 138.6, 135.3, 118.3, 117.0, 67.2, 55.6, 26.4, 25.7, 18.1, 17.8; **IR** (thin film) ν_{max} = 2970 (m), 2920 (m), 2856 (m), 1730 (w), 1671 (w), 1442 (m) 1380 (m), 1303 (s) cm⁻¹; **LRMS** (EI⁺) *m/z* = 200 (M⁺, 10%), 135 ([M–SO₂–H]⁺, 100%); **HRMS** (EI⁺) calcd for C₁₀H₁₆O₂S (M⁺) 200.0871, found 200.0873, calcd for C₁₀H₁₅ ([M–SO₂H]⁺) 135.1174, found 135.1172.

(*E*)-Ocimene (8)^[2]

3-Methyl-2-(3-methylbut-2-en-1-yl)-2,5-dihydrothiophene 1,1-dioxide **22** (403 mg, 2.01 mmol) and pyridine (20 mL) were added to a flask and heated at reflux for 6 hours with stirring. After cooling to room temperature the reaction was extracted with 30–40 petroleum spirits (20 mL) and washed with 2 M hydrochloric acid solution (4 × 20 mL). The petroleum spirit layer was then washed through a silica gel plug and concentrated under reduced pressure to give *E*-ocimene **8** as a clear colorless oil (222 mg, 81%); **R_f** (diethyl ether:hexane 2:3) 0.75; **¹H-NMR** (300 MHz, CDCl₃) δ 6.37 (1H, dd, *J* = 17.4 & 11.1 Hz, H3), 5.46 (1H, t, *J* = 7.8 Hz, H5), 5.16–5.07 (2H, m, H2 & H7), 4.94 (1H, d, *J* = 10.5 Hz, H1), 2.84 (2H, t, *J* = 7.5 Hz, H6), 1.77 (3H, s, CH₃), 1.71 (3H, s, CH₃), 1.65 (3H, s, CH₃); **¹³C-NMR** (75 MHz, CDCl₃) δ 141.6, 133.8, 132.3, 131.9, 122.3, 110.7, 27.4, 25.8, 17.8, 11.7; **IR** (thin film) ν_{max} = 2975 (s), 2926 (s), 2857 (m), 1789 (w), 1640 (m), 1606 (m), 1448 (m), 1376 (m) cm⁻¹; **LRMS** (EI⁺) *m/z* = 136 (M⁺, 45%), 93 (100%).

(±)-Panduratin H (3) and (±)-panduratin I (4)^[3]

Methyl cinnamate **9** (601 mg, 3.71 mmol), *E*-ocimene **8** (2.02 g, 14.8 mmol) and dichloromethane (2 mL) were added to a pressure vessel, sealed and pressurized to 19 kbar for 3 days. The reactions was then diluted with dichloromethane (20 mL), evaporated on to silica and purified by column chromatography using diethyl ether : hexane (1:9) and then preparative HPLC on Waters Xbridge C18, 60% acetonitrile, 40% water: to afford (*R*_t 31.1 min) (±)-panduratin H **3** as a clear colorless oil (257 mg, 23%); *R*_f (diethyl ether:hexane 1:4) 0.44; ¹H-NMR (400 MHz, CDCl₃) δ 7.26 (2H, m, H3''), 7.20–7.13 (3H, m, H2''& H4''), 5.42 (1H, br s, H4), 5.06 (1H, m, H2'), 3.40 (3H, s, OCH₃), 3.19 (1H, ddd, *J* = 12.0, 10.4 & 6.4 Hz, H6), 3.08 (1H, dd, *J* = 12.4, 4.8 Hz, H1), 2.45 (1H, dd, *J* = 10.4 & 5.2 Hz, H2), 2.40–2.23 (2H, m, H5β & H1'a), 2.17 (1H, m, H1'b), 2.04 (1H, m, H5α), 1.78 (3H, s, CH₃), 1.67 (3H, s, CH₃), 1.60 (3H, s, CH₃); ¹³C-NMR (100 MHz, CDCl₃) δ 173.8, 145.9, 136.3, 132.0, 128.3, 127.1, 126.0, 123.8, 121.0, 51.0, 49.1, 42.6, 37.1, 35.1, 29.2, 25.9, 22.6, 17.9; IR (thin film) ν_{max} = 2966 (m), 2949 (m), 2914 (m), 1741 (vs), 1494 (w), 1434 (m), 1301 (w), 1157(s); LRMS (EI⁺) *m/z* = 298 (M⁺, 60%), 169 (100%); HRMS (EI⁺) calcd for C₂₀H₂₆O₂ (M⁺) 298.1933, found 298.1935. A further fraction from flash column chromatography gave (±)-panduratin I **4** as a colorless oil (772 mg, 70%); *R*_f (diethyl ether:hexane 1:4) 0.39; ¹H-NMR (400 MHz, CDCl₃) δ 7.26 (2H, m, H3''), 7.19–7.14 (3H, m, H2''& H4''), 5.45 (1H, br s, H4), 4.81 (1H, m, H2'), 3.49 (3H, s, OCH₃), 3.33 (1H, dd, *J* = 11.2 & 5.2 Hz, H1), 3.18 (1H, ddd, *J* = 11.2, 9.6 & 6.4 Hz, H6), 2.44 (1H, m, H5β), 2.32 (1H, m, H5α), 2.23 (1H, dd, *J* = 10.8 & 5.2 Hz, H2), 1.99–1.86 (2H, m, H1'), 1.74 (3H, s, CH₃), 1.57 (3H, s, CH₃), 1.34 (3H, s, CH₃); ¹³C-NMR (100 MHz, CDCl₃) δ 176.5, 142.3, 137.6, 131.0, 128.2, 128.1, 126.1, 123.4, 119.5, 51.5, 46.3, 44.5, 39.9, 29.5, 27.6, 25.8, 22.9, 17.7; IR (thin film) ν_{max} = 2966 (m), 2950 (m), 2913 (m), 1739 (vs), 1496 (w), 1435 (m), 1265 (m), 1162 (s); LRMS (EI⁺) *m/z* = 298 (M⁺, 60%), 169 (100%); HRMS (EI⁺) calcd for C₂₀H₂₆O₂ (M⁺) 298.1933, found 298.1935.

(±)-((1*R*,2*S*,6*R*)-3-Methyl-2-(3-methylbut-2-en-1-yl)-6-phenylcyclohex-3-en-1-yl)methanol (**10**) and (±)-((1*R*,5*S*,6*R*)-4-methyl-5-(3-methylbut-2-en-1-yl)-6-phenylcyclohex-3-en-1-yl)methanol (**11**)

To a solution of panduratin H **3** and panduratin I **4** (251 mg, 0.841 mmol) in tetrahydrofuran (20 mL) was added 1 M lithium aluminum hydride in tetrahydrofuran (3.37 mL, 3.37 mmol) dropwise over 5 minutes. After 1 h of stirring at room temperature the reaction was cooled to 0°C and ethyl acetate (10 mL) was added dropwise over 10 minutes. The reaction was then diluted with diethyl ether (80 mL) and a saturated solution of potassium sodium tartrate (80 mL) and stirred vigorously for 30 minutes. The diethyl ether layer was then separated and the aqueous layer re-extracted with diethyl ether (2 × 50 mL). The combined organic layers were washed with brine (50 mL) and evaporated on to silica with purification by column chromatography using diethyl ether : hexane (1:4) affording (3-methyl-2-(3-methylbut-2-en-1-yl)-6-phenyl-3-cyclohexene-1-yl)methanol **10** as a colorless oil (45.5 mg, 20%); **R_f** (diethyl ether:hexane 3:7) 0.20; **¹H-NMR** (400 MHz, CDCl₃) δ 7.27 (2H, m, H3'''), 7.20–7.17 (3H, t, *J* = 8.4 Hz, H2''' & H4'''), 5.45 (1H, br s, H4), 5.28 (1H, m, H2''), 3.38–3.26 (2H, m, H1'), 2.79 (1H, ddd, *J* = 10.8, 10.8 & 6.4 Hz, H6), 2.33–2.15 (6H, m, H1, H2 H5 & H1''), 1.78 (3H, s, CH₃), 1.71 (3H, s, CH₃), 1.68 (3H, s, CH₃), (OH not observed); **¹³C-NMR** (100 MHz, CDCl₃) δ 145.0, 137.2, 132.0, 128.5, 127.6, 126.3, 124.6, 121.2, 63.4, 45.0, 40.5, 39.0, 34.9, 27.7, 25.8, 22.7, 18.0; **IR** (thin film) *v*_{max} = 3350 (m), 2963 (s), 2911 (s), 1602 (w), 1452 (m), 1376 (w), 1048 (m), 757 (m); **LRMS** (ESI⁺) *m/z* = 293 ([M+Na]⁺, 58%), 102 (100%); **HRMS** (ESI⁺) calcd for C₁₉H₂₆ONa ([M+Na]⁺), 293.1881, found 293.1881. A second fraction afforded (4-methyl-5-(3-methylbut-2-en-1-yl)-6-phenylcyclohex-3-en-1-yl)methanol **11** as a colorless oil (134 mg, 59%); **R_f** (diethyl ether:hexane 3:7) 0.15; **¹H-NMR** (400 MHz, CDCl₃) δ 7.28 (2H, m, H3'''), 7.20–7.16 (3H, m, H2''' & H4'''), 5.48 (1H, s, H3), 4.90 (1H, m, H2''), 3.60 (1H, m, H1'a), 3.42 (1H, m, H1'b), 2.92 (1H, dd, *J* = 9.6 & 4.8 Hz, H6), 2.36–2.24 (2H, m, H1 & H2a), 2.15 (1H, m, H5), 2.06–1.99 (3H, m, H2b & H1''), 1.73 (3H, s, CH₃), 1.58 (3H, s, CH₃), 1.34 (3H, s, CH₃), (OH not observed); **¹³C-NMR** (100 MHz, CDCl₃) δ 142.4, 137.1, 130.9, 129.3, 128.0, 126.0, 123.6, 121.1, 66.1, 46.1, 44.1, 35.0, 28.1, 27.5, 25.8, 22.8, 17.7; **IR** (thin film) *v*_{max} = 3326 (m), 2962 (s), 2913 (s), 1494 (m), 1452 (s), 1376 (m), 1032 (m), 703 (s); **LRMS** (ESI⁺) *m/z* = 293 ([M+Na]⁺, 100%); **HRMS** (ESI⁺) calcd for C₁₉H₂₆ONa ([M+Na]⁺), 293.1881, found 293.1884.

(±)-((1*R*,2*S*,6*R*)-3-Methyl-2-(3-methylbut-2-en-1-yl)-6-phenylcyclohex-3-en-1-yl)methanal (**12**) and (±)-((1*R*,5*S*,6*R*)-4-methyl-5-(3-methylbut-2-en-1-yl)-6-phenylcyclohex-3-en-1-yl)methanal (**19**)

Cinnamaldehyde **18** (917 mg, 6.94 mmol), *E*-ocimene **8** (3.79 g, 27.8 mmol) and dichloromethane (3 mL) were added to a pressure vessel, sealed and pressurized to 19 kbar for 3 days. The reactions was then diluted with dichloromethane (20 mL), evaporated on to silica and purified by column chromatography using diethyl ether : hexane (1:9) to afford as (3-methyl-2-(3-methylbut-2-en-1-yl)-6-phenylcyclohex-3-en-1-yl)methanal **12** a clear colorless oil (144 mg, 8%); **R_f** (diethyl ether:hexane 1:4) 0.54; **¹H-NMR** (400 MHz, CDCl₃) δ 9.46 (1H, d, *J* = 3.6 Hz, CHO), 7.28 (2H, m, H2''), 7.21–7.16 (3H, m, H3''& H4''), 5.49 (1H, br s, H4), 5.05 (1H, m, H2'), 3.35 (1H, ddd, *J* = 10.8, 10.8 & 6.0 Hz, H6), 2.81 (1H, ddd, *J* = 10.8, 4.4 & 3.6 Hz, H1), 2.52–2.40 (2H, m, H2 & H5α), 2.31 (2H, t, *J* = 5.6 Hz, H1'), 2.14 (1H, m, H5β), 1.78 (3H, s, CH₃), 1.66 (3H, s, CH₃), 1.60 (3H, s, CH₃); **¹³C-NMR** (100 MHz, CDCl₃) δ 205.80, 144.0, 136.3, 132.3, 128.7, 127.7, 126.6, 123.7, 121.6, 55.3, 42.2, 36.9, 34.0, 28.9, 25.7, 22.2, 18.0; **IR** (thin film) ν_{max} = 2964 (m), 2914 (m), 1725 (s), 1604 (w), 1493 (m), 1447 (m), 1209 (w), 748 (m); **LRMS** (EI⁺) *m/z* = 268 (M⁺, 80%), 91 (100%); **HRMS** (EI⁺) calcd for C₁₉H₂₄O (M⁺) 268.1827, found 268.1824. A second fraction afforded (4-methyl-5-(3-methylbut-2-en-1-yl)-6-phenylcyclohex-3-en-1-yl)methanal **19** as a clear colorless oil (630 mg, 54%); **R_f** (diethyl ether:hexane 1:4) 0.48; **¹H-NMR** (400 MHz, CDCl₃) δ 9.42 (1H, d, *J* = 3.6 Hz, CHO), 7.27 (2H, m, H3''), 7.20–7.16 (3H, m, H2''& H4''), 5.50 (1H, m, H3), 4.85 (1H, m, H2'), 3.35 (1H, dd, *J* = 10.4 & 5.2 Hz, H6), 2.99 (1H, dddd, *J* = 10.4, 7.2, 7.2 & 3.2 Hz, H1), 2.28–2.22 (3H, m, H2 & H5), 1.97 (2H, dd, *J* = 11.6 & 6.4, H1'), 1.75 (3H, s, CH₃), 1.57 (3H, s, CH₃), 1.27 (3H, s, CH₃); **¹³C-NMR** (100 MHz, CDCl₃) δ 204.1, 141.1, 137.9, 131.42, 128.8, 128.2, 126.4, 122.9, 119.2, 46.5, 44.0, 43.5, 27.3, 25.7, 24.5, 22.7, 17.5; **IR** (thin film) ν_{max} = 2964 (m), 2913 (m), 1724 (s), 1602 (w), 1495 (m), 1452 (m), 1377 (m), 750 (m); **LRMS** (EI⁺) *m/z* = 268 (M⁺, 80%), 91 (100%); **HRMS** (EI⁺) calcd for C₁₉H₂₄O (M⁺) 268.1827, found 268.1824.

To a solution of (3-methyl-2-(3-methylbut-2-en-1-yl)-6-phenylcyclohex-3-en-1-yl)methanol **10** (171 mg, 633 μmol) in dichloromethane (20 mL) was added Dess–Martin periodinane (403 mg, 950

μmol) and the mixture was stirred at room temperature for 1 h. The reaction was then evaporated on to silica under reduced pressure and purified by column chromatography using diethyl ether : hexane (1:9) to afford 3-methyl-2-(3-methylbut-2-en-1-yl)-6-phenylcyclohex-3-en-1-yl)methanal **12** as a clear colorless oil (132 mg, 78%).

General procedure for high pressure reactions (Table 1)

Dienophile (917 mg, 6.94 mmol), *E*-ocimene **8** (3.79 g, 27.8 mmol) and dichloromethane (3 mL) were added to a pressure vessel, sealed and pressurized to 19 kbar for 3 days. The reactions were then diluted with dichloromethane (20 mL), evaporated onto silica and purified by column chromatography to afford the corresponding Diels–Alder adducts.

Reduction to alcohols. To a solution of Diels–Alder adducts (251 mg, 0.841 mmol) in tetrahydrofuran (20 mL) was added lithium aluminum hydride in tetrahydrofuran (3.37 mL, 1 M, 3.37 mmol) dropwise over 5 min. After 1 h of stirring at room temperature the reaction was cooled to 0°C and ethyl acetate (10 mL) was added dropwise over 10 minutes. The reaction was then diluted with diethyl ether (80 mL) and a saturated solution of potassium sodium tartrate (80 mL) and stirred vigorously for 30 min. The diethyl ether layer was then separated and the aqueous layer re-extracted with diethyl ether (2 $\times$ 50 mL). The combined organic layers were washed with brine (50 mL) and evaporated on to silica with purification by column chromatography to afford the corresponding alcohols.

Reduction to aldehydes. To a solution of Diels–Alder adducts (454 mg, 1.71 mmol) in dichloromethane (20 mL) was added diisobutylaluminum hydride in dichloromethane (5.13 mL, 1 M, 5.13 mmol) at –78°C. After 30 min, the reaction was quenched with saturated aqueous sodium potassium tartrate (50 mL), and stirred vigorously for 30 min. The dichloromethane layer was then separated and the aqueous layer re-extracted with dichloromethane (2 $\times$ 50 mL). The combined organic layers were washed with brine (50 mL) and evaporated on to silica with purification by column chromatography to afford the corresponding aldehydes.

2-Bromo-5-methoxybenzene-1,3-diol (**23**)^[4]

To a solution of 5-methoxyresorcinol (1.92 g, 13.7 mmol) in chloroform (100 mL) and dioxane (5 mL) at 0°C was added portion-wise over 1 h a solution of 2,4,4,6-tetrabromo-2,5-cyclohexadienone (6.79 g, 16.6 mmol) in chloroform (20 mL). The resulting reaction mixture was stirred at 0°C for 5 h and then concentrated under reduced pressure. Purification via silica gel chromatography using dichloromethane followed by recrystallization from dichloromethane gave 2-bromo-5-methoxybenzene-1,3-diol **23** as white crystals (1.60 g, 54%); R_f (DCM) 0.13; **m.p.** 73–75°C (lit.^[5] **m.p.** 73–75°C); $^1\text{H-NMR}$ (400 MHz, CDCl_3) δ 6.22 (2H, s, CH), 5.41 (2H, s, OH), 3.75 (3H, s, CH_3O); $^{13}\text{C-NMR}$ (100 MHz, CDCl_3) δ 160.7, 153.3, 94.7, 90.6, 55.5; **IR** (thin film) ν_{max} = 3453 (m), 2940 (w), 2849 (w), 1597 (vs), 1506 (m), 1444 (m), 1368 (m), 1323 (w) cm^{-1} ; **LRMS** (ESI^-) m/z = 217 ($\text{C}_7\text{H}_6\text{O}_3^{79}\text{Br}$, $[\text{M}-\text{H}]^-$, 22%), 219 ($\text{C}_7\text{H}_6\text{O}_3^{81}\text{Br}$, $[\text{M}-\text{H}]^-$, 21%), 122 (100%); **HRMS** (ESI^-) calcd for $\text{C}_7\text{H}_6\text{O}_3^{79}\text{Br}$ ($[\text{M}-\text{H}]^-$) 216.9500, found 216.9500, calcd for $\text{C}_7\text{H}_6\text{O}_3^{81}\text{Br}$ ($[\text{M}-\text{H}]^-$) 218.9480, found 218.9482.

2-Bromo-5-methoxy-1,3-bis(methoxymethoxy)benzene (**13**)^[6]

Sodium hydride 60% dispersion in mineral oil (557 mg, 13.9 mmol) and hexanes (60 mL) were added to a flask and stirred vigorously at room temperature for 30 min. The mixture was then allowed to settle and the majority of the hexane removed by pipette. Dimethylformamide (30 mL) was added to the flask followed by cooling to 0°C. 2-Bromo-5-methoxybenzene-1,3-diol **23** (1.02 g, 4.66 mmol) was then added portion wise over 20 min followed by methoxymethyl chloride (881 μL , 11.6 mmol) dropwise over 10 min. After warming to room temperature the resulting solution was stirred for 16 h and then diluted with water (60 mL). Extraction with ether (3×50 mL), drying over magnesium sulfate, concentration under reduced pressure and purification by silica gel chromatography using diethyl ether : hexane (1:4) gave 2-bromo-5-methoxy-1,3-bis(methoxymethoxy)benzene **13** as a clear colorless oil (946 mg, 66%); R_f (diethyl ether:hexane 3:7) 0.26; $^1\text{H-NMR}$ (400 MHz, CDCl_3) δ 6.46 (2H, s, CH), 5.22 (4H, s, $\text{CH}_3\text{OCH}_2\text{O}$), 3.77 (3H, s, CH_3O), 3.51 (6H, s, $\text{CH}_2\text{OCH}_2\text{O}$); $^{13}\text{C-NMR}$ (100 MHz, CDCl_3) δ 160.0, 155.1, 96.2, 95.0, 94.6, 56.2, 55.4; **IR** (thin film) ν_{max} = 2963 (s), 2911 (s), 2831 (m), 1605 (s), 1537 (w), 1482 (s), 1391 (m), 1303 (m) cm^{-1} ; **LRMS** (EI^+) m/z = 306 ($\text{C}_{11}\text{H}_{15}\text{O}_5^{79}\text{Br}$, $\text{M}^{+\bullet}$, 100%), 308 ($\text{C}_{11}\text{H}_{15}\text{O}_5^{81}\text{Br}$, $\text{M}^{+\bullet}$, 98%); **HRMS** (EI^+) calcd for $\text{C}_{11}\text{H}_{15}\text{O}_5^{79}\text{Br}$ ($\text{M}^{+\bullet}$) 306.0103, found 306.0103, calcd for $\text{C}_{11}\text{H}_{15}\text{O}_5^{81}\text{Br}$ ($\text{M}^{+\bullet}$) 308.0082, found 308.0066.

1,3,5-Tris(methoxymethoxy)benzene (**24**)^[7]

Sodium hydride 60% dispersion in mineral oil (5.70 g, 143 mmol) and hexane (40 mL) were added to a flask and stirred vigorously at room temperature for 30 min. The mixture was then allowed to settle and the majority of the hexane removed by pipette. Dimethylformamide (80 mL) was added to the flask followed by cooling to 0°C. Phloroglucinol (4.50 g, 35.7 mmol) was then added portion wise over 10 min followed by methoxymethyl chloride (8.97 mL, 118 mmol) dropwise over 10 min. After warming to room temperature the resulting solution was stirred for 16 h and then diluted with water (100 mL). Extraction with ether (3 × 50 mL), drying over magnesium sulfate, concentration under reduced pressure and purification by silica gel chromatography using ethyl acetate : hexane (1:4) afforded 1,3,5-tris(methoxymethoxy)benzene **24** as a clear colorless oil (5.68 g, 62%); **R_f** (ethyl acetate:hexane 1:4) 0.22; **¹H-NMR** (400 MHz, CDCl₃) δ 6.41 (3H, s, CH), 5.13 (6H, s, CH₃OCH₂O), 3.47 (9H, s, CH₃OCH₂O); **¹³C-NMR** (100 MHz, CDCl₃) δ 158.9, 98.4, 94.5, 56.1; **IR** (thin film) ν_{max} = 2955 (w), 2901 (m), 2827 (m), 1598 (s), 1471 (m), 1439 (w), 1399 (m), 1314 (w) cm⁻¹; **LRMS** (EI⁺) *m/z* = 258 (M⁺, 55%), 45 (CH₃OCH₂⁺, 100%); **HRMS** (EI⁺) calcd for C₁₂H₁₈O₆ (M⁺) 258.1103, found 258.1116.

2-Bromo-1,3,5-tris(methoxymethoxy)benzene (**15**)^[7]

To a solution of 1,3,5-tris(methoxymethoxy)benzene **24** (5.68 g, 22.0 mmol) in dichloromethane (60 mL) was added *N*-bromosuccinimide (4.11 g, 23.1 mmol) followed by stirring at room temperature for 1 h. The reaction was then evaporated on to silica under reduced pressure and purified by silica gel chromatography using ethyl acetate : hexane (3:17) to give 2-bromo-1,3,5-tris(methoxymethoxy)benzene **15** as a white solid (7.34 g, 98%); **R_f** (ethyl acetate:hexane 1:4) 0.20; **m.p.** 35–40°C; **¹H-NMR** (400 MHz, CDCl₃) δ 6.60 (2H, s, CH), 5.23 (4H, s, CH₃OCH₂O), 5.14 (2H, s, CH₃OCH₂O), 3.52 (6H, s, CH₃OCH₂O), 3.47 (3H, s, CH₃OCH₂O); **¹³C-NMR** (100 MHz, CDCl₃) δ 157.7, 155.2, 98.5, 96.1, 95.1, 94.6, 56.4, 56.1; **IR** (thin film) ν_{max} = 2957 (m), 2907 (m), 2828 (m), 1588 (vs), 1469 (m), 1392 (s), 1307 (w), 1232 (m) cm⁻¹; **LRMS** (EI⁺) *m/z* = 336 (C₁₂H₁₇O₆⁷⁹Br, M⁺, 100%), 338 (C₁₂H₁₇O₆⁸¹Br, M⁺, 100%); **HRMS** (EI⁺) calcd for C₁₂H₁₇⁷⁹BrO₆ (M⁺) 336.0208, found 336.0208, calcd for C₁₂H₁₇⁸¹BrO₆ (M⁺) 338.0188, found 338.0192.

(±)-((1*R*,2*S*,6*R*)-3-Methyl-2-(3-methylbut-2-en-1-yl)-6-phenylcyclohex-3-en-1-yl) (4-methoxy-2,6-bis(methoxymethoxy) phenyl) methanone (14**)**

2-Bromo-5-methoxy-1,3-bis(methoxymethoxy)benzene **13** (230 mg, 748 μ mol) and tetrahydrofuran (15 mL) were added to a flask and cooled to -78°C under a nitrogen atmosphere. Butyl lithium (575 μ L, 1.6 M, 748 μ mol) was then added dropwise over 5 min and the resulting solution stirred for 30 min. A solution of (3-methyl-2-(3-methylbut-2-en-1-yl)-6-phenylcyclohex-3-en-1-yl)methanal **12** (66.9 mg, 249 μ mol) in tetrahydrofuran (5 mL) was then added dropwise over 5 min followed by stirring at -78°C for 15 min. After this the reaction was allowed to warm to room temperature and stirred for a further 30 minutes followed by quenching with a saturated solution of ammonium chloride (30 mL). Extraction with diethyl ether (3×30 mL), drying over magnesium sulfate and purification by column chromatography using diethyl ether : hexane (3:7) gave a mixture of the alcohol diastereomer products; **R_f** (diethyl ether:hexane 1:1) 0.11 & 0.22; The alcohol products, Dess–Martin periodinane (211 mg, 498 μ mol) and dichloromethane (15 mL) were added to a flask and stirred at room temperature for 1 h. The reaction was then evaporated on to silica under reduced pressure and purified by column chromatography using diethyl ether : hexane (3:7) to afford (3-methyl-2-(3-methylbut-2-en-1-yl)-6-phenylcyclohex-3-en-1-yl) (4-methoxy-2,6-bis(methoxymethoxy)phenyl)methanone **14** as colorless oil (87.5 mg, 71% over 2 steps); **R_f** (diethyl ether:hexane 1:1) 0.19; **¹H-NMR** (400 MHz, CDCl_3) δ 7.31 (2H, d, $J = 8.0$ Hz, H2'''), 7.23 (2H, t, $J = 8.0$ Hz, H3'''), 7.10 (1H, t, $J = 7.2$ Hz, H4'''), 6.36 (2H, s, H3), 5.40 (1H, br s, H4'), 5.11 (1H, m, H2''), 5.01 (4H, s, CH_2OCH_3), 3.84 (1H, dd, $J = 10.8$ & 3.2 Hz, H1'), 3.77 (3H, s, OCH_3), 3.48 (1H, m, H6'), 3.38 (6H, s, CH_2OCH_3), 2.51 (1H, m, H5' β), 2.36–2.34 (3H, m, H2' & H1''), 2.17 (1H, m, 5' α), 1.72 (3H, s, CH_3), 1.67 (3H, s, CH_3), 1.61 (3H, s, CH_3); **¹³C-NMR** (100 MHz, CDCl_3) δ 203.3, 161.8, 156.5, 146.8, 138.3, 130.9, 128.2, 127.7, 125.5, 124.6, 120.6, 114.8, 94.9, 94.5, 58.2, 56.1, 55.4, 40.7, 36.8, 34.5, 29.6, 25.8, 23.6, 18.0; **IR** (thin film) ν_{max} = 2960 (m), 2912 (m), 1695 (m), 1605 (vs), 1452 (m), 1391 (w), 1215 (m), 1151 (vs); **LRMS** (EI^+) m/z = 494 (M^{++} , 2%), 197 (100%); **HRMS** (EI^+) calcd for $\text{C}_{30}\text{H}_{38}\text{O}_6$ (M^{++}) 494.2668, found 494.2669.

(±)-Panduratin A (1**)**^[8]

(3-Methyl-2-(3-methylbut-2-en-1-yl)-6-phenylcyclohex-3-en-1-yl) (4-methoxy-2,6-bis(methoxymethoxy)phenyl)methanone **14** (83.4 mg, 169 μ mol), methanol (10 mL) and 2 drops of concentrated hydrochloric acid were added to a flask and heated at 50°C with stirring for 2 h. The reaction mixture was then neutralized with saturated sodium bicarbonate solution, extracted with ethyl acetate (2 $\times$ 30 mL) and dried over magnesium sulfate. Filtration, concentration under reduced pressure and purification via silica gel chromatography using diethyl ether : hexane (3:7) afforded (±)-panduratin A **1** as a yellow solid (48.3 mg, 70%); **R_f** (diethyl ether:hexane 1:1) 0.35; **m.p.** 154–156°C (lit.^[8] m.p. 157–157.5°C); **¹H-NMR** (400 MHz, CD₃OD) δ 7.18–7.16 (4H, m, H2''' & H3'''), 7.05 (1H, m, H4'''), 5.88 (2H, s, H3), 5.41 (1H br s, H4'), 4.88 (1H, obscured by HOD, H2''), 4.77 (1H, dd, J = 11.6 & 4.4, H1'), 3.74 (3H, s, OMe), 3.38 (1H, ddd, J = 10.8, 10.8, 6.4 Hz, H6'), 2.65 (1H, m, H2'), 2.36–2.24 (2H, m, H5'a & H1''a), 2.08–1.95 (2H, m, H5'b & H1''b), 1.77 (3H, s, CH₃), 1.50 (6H, s, CH₃); **¹³C-NMR** (100 MHz, CD₃OD) δ 208.1, 167.0, 165.4, 148.5, 138.4, 132.4, 129.2, 128.3, 126.4, 125.7, 122.0, 107.2, 94.4, 55.76, 55.0, 43.4, 38.4, 37.1, 29.8, 25.9, 23.0, 18.1; **IR** (thin film) ν_{max} = 3401 (s), 2964 (w), 2914 (w), 1627 (s), 1581 (m), 1424 (w), 1231 (m), 1162 (m) cm⁻¹; **LRMS** (ESI⁻) m/z = 405 ([M-H]⁻, 100%); **HRMS** (ESI⁻) calcd for C₂₆H₂₉O₄ ([M-H]⁻) 405.2066, found 405.2066.

(±)-((1*R*,2*S*,6*R*)-3-Methyl-2-(3-methylbut-2-en-1-yl)-6-phenylcyclohex-3-en-1-yl) (2,4,6-tris-(methoxymethoxy)phenyl)methanone (16**)**

2-Bromo-1,3,5-tris(methoxymethoxy)benzene **15** (277 mg, 822 μ mol) and tetrahydrofuran (15 mL) were added to a flask and cooled to -78°C under a nitrogen atmosphere. Butyl lithium (514 μ L, 1.6M, 823 μ mol) was then added dropwise over 5 min and the resulting solution stirred for 30 min.

A solution of (3-methyl-2-(3-methylbut-2-en-1-yl)-6-phenylcyclohex-3-en-1-yl)methanal **12** (55.2 mg, 206 μmol) in tetrahydrofuran (5 mL) was then added dropwise over 5 min followed by stirring at -78°C for 15 min. After this the reaction was allowed to warm to room temperature and stirred for a further 30 min followed by quenching with a saturated solution of ammonium chloride (30 mL). Extraction with diethyl ether (3×30 mL), drying over magnesium sulfate and purification by column chromatography using diethyl ether : hexane (3:7) gave a mixture of the alcohol diastereomer products; R_f (diethyl ether:hexane 1:1) 0.20 & 0.28; The alcohol products, Dess–Martin periodinane (131 mg, 309 μmol) and dichloromethane (15 mL) were added to a flask and stirred at room temperature for 1 h. The reaction was then evaporated on to silica under reduced pressure and purified by column chromatography using diethyl ether : hexane (3:7) to afford (3-methyl-2-(3-methylbut-2-en-1-yl)-6-phenylcyclohex-3-en-1-yl) (2,4,6-tris(methoxymethoxy)phenyl) methanone **16** as colorless oil (78.9 mg, 73% over 2 steps); R_f (diethyl ether:hexane 1:1) 0.37; $^1\text{H-NMR}$ (400 MHz, CDCl_3) δ 7.31 (2H, d, $J = 7.6$ Hz, H_2'''), 7.23 (2H, t, $J = 7.2$ Hz, H_3'''), 7.11 (1H, t, $J = 7.2$ Hz, H_4'''), 6.48 (2H, s, H_3), 5.41 (1H, br s, H_4'), 5.13 (3H, s, H_2'' & CH_2OCH_3), 5.00 (4H, s, CH_2OCH_3), 3.81 (1H, dd, $J = 11.2$ & 3.2 Hz, H_1'), 3.52–3.47 (4H, m, H_6' & CH_2OCH_3), 3.37 (6H, s, CH_2OCH_3), 2.51 (1H, m, $\text{H}_5'\beta$), 2.36–2.33 (3H, m, H_2' & H_1''), 2.17 (1H, m, $\text{H}_5'\alpha$), 1.73 (3H, s, CH_3), 1.67 (3H, s, CH_3), 1.61 (3H, s, CH_3); $^{13}\text{C-NMR}$ (100 MHz, CDCl_3) δ 203.3, 159.4, 156.3, 146.7, 138.3, 130.9, 128.3, 127.7, 125.5, 124.6, 120.7, 115.9, 97.0, 94.5, 94.4, 58.3, 56.3, 56.2, 40.6, 36.7, 34.4, 29.6, 25.8, 23.6, 18.0; **IR** (thin film) ν_{max} = 2959 (m), 2911 (m), 1697 (m), 1605 (s), 1451 (w), 1217 (w), 1155 (s), 1050 (vs); **LRMS** (EI^+) m/z = 524 (M^{+} , 3%), 389 (100%); **HRMS** (EI^+) calcd for $\text{C}_{31}\text{H}_{40}\text{O}_7$ (M^{+}) 524.2774, found 524.2794.

($\pm$)-4-Hydroxypanduratin A (**2**)^[9]

(3-Methyl-2-(3-methylbut-2-en-1-yl)-6-phenylcyclohex-3-en-1-yl) (2,4,6-tris(methoxymethoxy)-phenyl) methanone **16** (69.7 mg, 141 μmol), methanol (10 mL) and 2 drops of concentrated hydrochloric acid were added to a flask and heated at 50°C with stirring for 2 h. The reaction mixture was then neutralized with saturated sodium bicarbonate solution, extracted with ethyl acetate (2×30 mL) and dried over magnesium sulfate. Filtration, concentration under reduced pressure and purification via silica gel chromatography using diethyl ether : hexane (2:3) afforded

(±)-4-hydroxy panduratin A **2** as a pale yellow oil (39.3 mg, 71%); **R_f** (diethyl ether:hexane 1:1) 0.17; **¹H-NMR** (400 MHz, CD₃OD) δ 7.18–7.17 (4H, m, H2''' & H3'''), 7.05 (1H, m, H4'''), 5.78 (2H, s, H3), 5.40 (1H, br s, H4'), 4.91 (1H, obscured by HOD, H2''), 4.76 (1H, dd, *J* = 12.0, 4.8 Hz, H1'), 3.37 (1H, ddd, *J* = 10.4, 10.4, 6.4, H6'), 2.65 (1H, m, H2'), 2.36–2.22 (2H, m, H5'a & H1''a), 2.08–1.94 (2H, m, H5'b & H1''b), 1.77 (3H, s, CH₃), 1.51 (6H, s, CH₃); **¹³C-NMR** (100 MHz, CD₃OD) δ 207.8, 165.5, 148.6, 138.4, 132.2, 129.1, 128.2, 126.4, 125.7, 121.9, 106.5, 95.8 (2 × C), 54.8, 43.8, 38.4, 37.1, 29.9, 25.9, 23.0, 18.0; **IR** (thin film) ν_{max} = 3400 (vs), 2958 (w), 2913 (w), 1623 (s), 1597 (m), 1492 (w), 1436 (w), 1216 (w) cm⁻¹; **LRMS** (ESI⁻) *m/z* = 391 ([M-H]⁻, 100%); **HRMS** (ESI⁻) calcd for C₂₅H₂₇O₄ ([M-H]⁻) 391.1909, found 391.1909.

(±)-((1*R*,5*S*,6*R*)-4-Methyl-5-(3-methylbut-2-en-1-yl)-6-phenylcyclohex-3-en-1-yl) (4-methoxy-2,6-bis(methoxymethoxy)phenyl) methanone (20**)**

2-Bromo-5-methoxy-1,3-bis(methoxymethoxy)benzene **13** (229.7 mg, 748 μmol) and tetrahydrofuran (20 mL) were added to a flask and cooled to -78°C under a nitrogen atmosphere. Butyl lithium (575 μL, 1.3 M, 748 μmol) was then added dropwise over 5 min and the resulting solution stirred for 30 min. A solution of (3-methyl-2-(3-methylbut-2-en-1-yl)-6-phenylcyclohex-3-en-1-yl)methanal **19** (66.9 mg, 249 μmol) in tetrahydrofuran (5 mL) was then added dropwise over 5 min followed by stirring at -78°C for 15 min. After this the reaction was allowed to warm to room temperature and stirred for a further 30 min followed by quenching with a saturated solution of ammonium chloride (30 mL). Extraction with diethyl ether (3 × 20 mL), drying over magnesium sulfate and purification by column chromatography using diethyl ether : hexane (1:3) gave a mixture of the alcohol diastereomer products; **R_f** (diethyl ether:hexane 1:1) 0.11 & 0.19; The alcohol products, Dess–Martin periodinane (158 mg, 374 μmol) and dichloromethane (10 mL) were added to a flask and stirred at room temperature for 1 h. The reaction was then evaporated on to silica under reduced pressure and purified by column chromatography using diethyl ether : hexane (3:7) to afford (3-methyl-2-(3-methylbut-2-en-1-yl)-6-phenylcyclohex-3-en-1-yl) (4-methoxy-2,6-bis(methoxymethoxy)phenyl) methanone **20** as colorless oil (85.0 mg, 69% over 2 steps); **R_f** (diethyl ether:hexane 1:1) 0.39; **¹H-NMR** (400 MHz, CDCl₃) δ 7.23–7.08 (5H, m, H2''', H3''', H4'''), 6.37 (2H, s, H3), 5.48 (1H, s, H3'), 5.06–4.98 (4H, m, CH₂OCH₃), 4.87 (1H, t, *J* = 6.4 Hz, H2''),

3.79 (3H, s, OMe), 3.71 (1H, dd, $J = 16.0$ & 7.2 Hz, H6'), 3.47–3.42 (7H, m, H1' & CH₂OCH₃), 2.35–2.32 (3H, m, H2' & H5'), 2.04–1.90 (2H, m, H1''), 1.74 (3H, s, CH₃), 1.55 (3H, s, CH₃), 1.25 (3H, s, CH₃); ¹³C-NMR (100 MHz, CDCl₃) δ 204.8, 162.0, 156.2, 143.2, 137.2, 130.9, 129.0, 127.6, 125.6, 123.6, 120.6, 115.1, 94.8, 94.7, 56.2, 55.4, 48.4, 45.5, 43.5, 27.8, 27.0, 25.7, 22.7, 17.5; IR (thin film) $\nu_{\max} = 2960$ (w), 2913 (w), 1698 (m), 1606 (s), 1452 (w), 1153 (s), 1048 (s), 924 (w) cm⁻¹; LRMS (EI⁺) $m/z = 494$ (M⁺, 2%), 255 (100%); HRMS (EI⁺) calcd for C₃₀H₃₈O₆ (M⁺) 494.2668, found 494.2673.

(±)-Nicolaoidesin B (5)^[10]

(3-Methyl-2-(3-methylbut-2-en-1-yl)-6-phenylcyclohex-3-en-1-yl) (4-methoxy-2,6-bis(methoxymethoxy)phenyl) methanone **20** (71.3 mg, 175 μ mol), methanol (10 mL) and 4 drops of concentrated hydrochloric acid were added to a flask and heated at 50°C with stirring for 2 h. The reaction mixture was then neutralized with saturated sodium bicarbonate solution, extracted with ethyl acetate (2 $\times$ 20 mL) and dried over magnesium sulfate. Filtration, concentration under reduced pressure and purification via silica gel chromatography using diethyl ether : hexane (35:65) afforded (±)-nicolaoidesin B **5** as a pale yellow oil (49.1 mg, 69%); R_f (diethyl ether:hexane 2:3) 0.07; ¹H-NMR (400 MHz, CD₃OD) δ 7.18–7.11 (4H, m, H2''' & H3'''), 7.07 (1H, m, H4'''), 5.93 (2H, s, H3), 5.49 (1H, s, H4'), 4.92 (1H, m, H6'), 4.88 (1H, m, H2''), 3.77 (3H, s, OMe), 3.51 (1H, dd, $J = 11.6$ & 5.2 Hz, H1'), 2.61 (1H, m, H5'a), 2.24 (1H, m, H2'), 2.07–1.83 (3H, m, H5'b & H1''), 1.75 (3H, s, CH₃), 1.57 (3H, s, CH₃), 1.34 (3H, s, CH₃); ¹³C-NMR (100 MHz, CD₃OD) δ 211.2, 167.4, 165.5, 144.9, 138.6, 131.4, 129.4, 129.0, 126.7, 124.8, 121.4, 106.8, 94.5, 55.8, 47.6, 47.0, 44.6, 31.9, 29.0, 26.1, 23.3, 18.0; IR (thin film) $\nu_{\max} = 3292$ (w), 2964 (w), 2913 (w), 1625 (vs), 1575 (s), 1377 (w), 1211 (s), 1079 (w) cm⁻¹; LRMS (ESI⁻) $m/z = 405$ ([M-H]⁻, 40%), 113 (100%); HRMS (ESI⁻) calcd for C₂₆H₂₉O₄ ([M-H]⁻) 405.2066, found 405.2067.

(±)-((1*R*,5*S*,6*R*)-4-Methyl-5-(3-methylbut-2-en-1-yl)-6-phenylcyclohex-3-en-1-yl) (2,4,6-tris(methoxymethoxy)phenyl) methanone (21**)**

2-Bromo-1,3,5-tris(methoxymethoxy)benzene **15** (136 mg, 406 μ mol) and tetrahydrofuran (10 mL) were added to a flask and cooled to -78°C under a nitrogen atmosphere. Butyl lithium (162 μ L, 1.6 M, 406 μ mol) was then added dropwise over 5 min and the resulting solution stirred for 30 min. A solution of (4-methyl-5-(3-methylbut-2-en-1-yl)-6-phenylcyclohex-3-ene-1-yl)methanal **19** (36.3 mg, 135 μ mol) in tetrahydrofuran (5 mL) was then added dropwise over 5 min followed by stirring at -78°C for 15 min. After this the reaction was allowed to warm to room temperature and stirred for a further 30 min followed by quenching with a saturated solution of ammonium chloride (30 mL). Extraction with diethyl ether (3×20 mL), drying over magnesium sulfate and purification by column chromatography using diethyl ether : hexane (1:3) gave a mixture of the alcohol diastereomer products; **R_f** (diethyl ether:hexane 1:1) 0.11 & 0.19; The alcohol products, Dess–Martin periodinane (83.2 mg, 196 μ mol) and dichloromethane (5 mL) were added to a flask and stirred at room temperature for 1 h. The reaction was then evaporated on to silica under reduced pressure and purified by column chromatography using diethyl ether : hexane (3:7) to afford (4-methyl-5-(3-methylbut-2-en-1-yl)-6-phenylcyclohex-3-en-1-yl) (2,4,6-tris(methoxymethoxy)phenyl) methanone **21** as colorless oil (50.3 mg, 71% over 2 steps); **R_f** (diethyl ether:hexane 2:3) 0.17; **¹H-NMR** (400 MHz, CDCl_3) δ 7.24–7.16 (4H, m, H2''' & H3'''), 7.11 (1H, m, H4'''), 6.50 (2H, s, H3), 5.47 (1H, s, H3'), 5.15 (2H, s, CH_2OCH_3), 5.07–4.99 (4H, m, CH_2OCH_3), 4.87 (1H, m, H2''), 3.69 (1H, dd, $J = 8.4$ & 7.2 Hz, H6'), 3.50–3.42 (10H, m, H1' & CH_2OCH_3), 2.35–2.34 (3H, m, H2' & H5'), 2.04–1.90 (2H, m, H1''), 1.75 (3H, s, CH_3), 1.55 (3H, s, CH_3), 1.24 (3H, s, CH_3); **¹³C-NMR** (100 MHz, CDCl_3) δ 204.7, 159.6, 155.9, 143.2, 137.3, 131.0, 129.0, 127.6, 125.6, 123.6, 120.5, 116.0, 96.8, 94.7, 94.4, 56.3 ($2 \times \text{C}$), 48.5, 45.3, 43.4, 27.8, 26.8, 25.7, 22.7, 17.5; **IR** (thin film) $\nu_{\text{max}} = 2959$ (m), 2912 (m), 1700 (m), 1605 (s), 1451 (m), 1216 (m), 1155 (s), 1050 (s) cm^{-1} ; **LRMS** (EI^+) $m/z = 524$ (M^{+} , 1%), 285 (100%); **HRMS** (EI^+) calcd for $\text{C}_{31}\text{H}_{40}\text{O}_7$ (M^{+}) 524.2774, found 524.2790.

(±)-4-Hydroxyisopanduratin A (6)^[11]

(3-Methyl-2-(3-methylbut-2-enyl)-6-phenylcyclohex-3-enyl)(2,4,6-tris(methoxymethoxy)phenyl)-methanone **21** (40.0 mg, 76.2 μmol), methanol (10 mL) and 4 drops of concentrated hydrochloric acid were added to a flask and heated at 50°C with stirring for 2 h. The reaction mixture was then neutralized with saturated sodium bicarbonate solution, extracted with ethyl acetate (2 $\times$ 20 mL) and dried over magnesium sulfate. Filtration, concentration under reduced pressure and purification via silica gel chromatography using diethyl ether : hexane (35:65) afforded (±)-4-hydroxyisopanduratin A **6** as a pale yellow oil (21.1 mg, 71%); **R_f** (diethyl ether:hexane 2:3) 0.07; **¹H-NMR** (800 MHz, CD₃OD) δ 7.19–7.06 (5H, m, H2''', H3''' & H4'''), 5.81 (2H, s, H3), 5.49 (1H, s, H4'), 4.92 (1H, ddd, J = 11.1, 11.1 & 6.1 Hz, H6'), 4.88 (1H, obscured by HOD, H2''), 3.50 (1H, dd, J = 11.7 & 5.0 Hz, H1'), 2.60 (1H, m, H5'β), 2.24 (1H, m, H2'), 2.05–1.96 (2H, m, H1''), 1.86 (1H, m, 5'α), 1.75 (3H, s, CH₃), 1.57 (3H, s, CH₃), 1.34 (3H, s, CH₃); **¹³C-NMR** (200 MHz, CD₃OD) δ 210.8, 166.1, 145.0, 138.6, 131.4, 129.5, 129.0, 126.7, 124.9, 121.5, 106.1, 95.9 (2 $\times$ C), 47.6, 47.1, 44.4, 31.9, 29.1, 26.1, 23.3, 17.9; **IR** (thin film) ν_{max} = 3235 (w), 2918 (w), 2853 (w), 1627 (s), 1599 (s), 1451 (m), 1202 (m), 1073 (m) cm⁻¹; **LRMS** (ESI⁻) m/z = 392 ([M-H]⁻, 10%), 153 (100%); **HRMS** (ESI⁻) calcd for C₂₅H₂₇O₄ ([M-H]⁻) 391.1909, found 391.1899.

Panduratin H (**3**) ¹H NMR Comparison.

Proton	δ_L (Lit., ^[3] 400 MHz, CDCl ₃)	δ_3 (Compound 3 , 400 MHz, CDCl ₃)	$\Delta\delta$ ($\delta_L - \delta_3$)
H3''	7.25 (m)	7.26 (m)	-0.01
H2'', H4''	7.15 (m)	7.17 ^a (m)	0.02
H4	5.42 (s)	5.42 (s)	0.00
H2'	5.06 (t, 6.8)	5.06 (m)	0.00
OCH ₃	3.40 (s)	3.40 (s)	0.00
H6	3.19 (ddd, 11.2, 10.0, 6.0)	3.19 (ddd, 12.0, 10.4, 6.4)	0.00
H1	3.09 (dd, 11.2, 5.4)	3.08 (dd, 12.4, 4.8)	0.01
H2	2.45 (dd, 10.2, 5.4)	2.45 (dd, 10.4, 5.2)	0.00
H5 β	2.34 (dt, 18.3, 6.0, 1.9)	2.32 ^a (m)	—
H1'a	2.26 (m)	—	—
H1'b	2.18 (m)	2.17 (m)	0.01
H5 α	2.04 (m)	2.04 (m)	0.00
CH ₃	1.77 (s)	1.78 (s)	-0.01
CH ₃	1.67 (s)	1.67 (s)	0.00
CH ₃	1.59 (s)	1.60 (s)	-0.01

^aCalculated from midpoint of multiplet.

Panduratin H (**3**) ¹³C NMR Comparison.

Carbon	δ_L (Lit., ^[3] 100 MHz, CDCl ₃)	δ_3 (Compound 3 , 100 MHz, CDCl ₃)	$\Delta\delta$ ($\delta_L - \delta_3$)
<u>C</u> OOCH ₃	173.7	173.8	-0.1
C1''	145.9	145.9	0.0
C3	136.3	136.3	0.0
C3'	131.9	132.0	-0.1
C3'', C5''	128.3	128.3	0.0
C2'', C6''	127.1	127.1	0.0
C4''	125.9	126.0	-0.1
C2'	123.0	123.8	-0.8
C4	121.1	121.0	0.1
COO <u>C</u> H ₃	51.0	51.0	0.0
C1	49.2	49.1	0.1
C2	42.7	42.6	0.1
C6	37.2	37.1	0.1
C5	35.1	35.1	0.0
C1'	29.2	29.2	0.0
C4'	25.9	25.9	0.0
3-CH ₃	22.6	22.6	0.0
C5'	17.9	17.9	0.0

Panduratin I (**4**) ¹H NMR Comparison.

Proton	δ_L (Lit., ^[3] 400 MHz, CDCl ₃)	δ_3 (Compound 4 , 400 MHz, CDCl ₃)	$\Delta\delta$ ($\delta_L - \delta_4$)
H3''	7.25 (m)	7.26 (m)	-0.01
H2'', H4''	7.15 (m)	7.17 ^a (m)	-0.02
H4	5.45 (s)	5.45 (s)	0.00
H2'	4.80 (t, 7.6)	4.81 (m)	-0.01
OCH ₃	3.49 (s)	3.49 (s)	0.00
H1	3.33 (dd, 11.2, 5.6)	3.33 (dd, 11.2, 5.2)	0.00
H6	3.18 (ddd, 11.2, 9.6, 6.1)	3.18 (ddd, 11.2, 9.6, 6.4)	0.00
H5 β	2.43 (dt, 18.0, 6.1, 1.9)	2.44 (m)	-0.01
H5 α	2.34 (m)	2.32, (m)	0.02
H2	2.21 (dd, 10.2, 5.6)	2.23 (dd, 10.8, 5.2)	-0.02
H1'	1.93 (m)	1.93 ^a (m)	0.00
CH ₃	1.74 (s)	1.74 (s)	0.00
CH ₃	1.56 (s)	1.57 (s)	-0.01
CH ₃	1.34 (s)	1.34 (s)	0.00

^aCalculated from midpoint of multiplet.

Panduratin I (**4**) ¹³C NMR Comparison.

Carbon	δ_L (Lit., ^[3] 100 MHz CDCl ₃)	δ_3 (Compound 3 , 100 MHz, CDCl ₃)	$\Delta\delta$ ($\delta_L - \delta_4$)
<u>C</u> OOCH ₃	176.5	176.5	0.0
C1''	142.4	142.3	0.1
C3	137.7	137.6	0.1
C3'	131.0	131.0	0.0
C2'', C4'', C6''	128.2	128.2	–
		128.1	–
C3'', C5''	126.2	126.1	0.1
C2'	123.4	123.4	0.0
C4	119.5	119.5	0.0
COO <u>C</u> H ₃	51.5	51.5	0.0
C1	46.3	46.3	0.0
C2	44.6	44.5	0.1
C6	39.9	39.9	0.0
C5	29.5	29.5	0.0
C1'	27.7	27.6	0.1
C4'	25.8	25.8	0.0
3-CH ₃	22.9	22.9	0.0
C5'	17.7	17.7	0.0

Panduratin A (**1**) ¹H NMR Comparison.

Proton	δ_L (Lit., ^[8] 500 MHz, CDCl ₃)	δ_3 (Compound 1 , 400 MHz, CD ₃ OD)	$\Delta\delta$ ($\delta_L - \delta_1$)
H2'', H3''	7.21 (m)	7.17 ^a (m)	0.04
H4''	7.10 (m)	7.05 (m)	0.05
H3	5.87 (s)	5.88 (s)	-0.01
H4'	5.43 (s)	5.41 (s)	0.02
H2''	4.87 (t, 6.7)	4.88 ^b	-0.01
H1'	4.66 (dd, 11.3, 4.6)	4.77 (dd, 11.6, 4.4)	-0.11
OMe	3.74 (s)	3.74 (s)	0.00
H6'	3.43 (ddd, 11.0, 11.0, 6.3)	3.38 (ddd, 10.8, 10.8, 6.4)	0.05
H2'	2.63 (m)	2.65 (m)	-0.02
H5'a, H1''a	2.40 (m)	2.30 ^a (m)	0.10
H5'b, H1''b	2.03 (m)	2.02 ^a (m)	0.01
CH ₃	1.78 (s)	1.77 (s)	0.01
CH ₃	1.52 (s)	1.50 (s)	0.02

^aCalculated from midpoint of multiplet.

^bObscured by HOD peak, chemical shift determined from COSY.

Panduratin A (**1**) ^{13}C NMR Comparison.

Carbon	δ_{L} (Lit., ^[8] 125 MHz, CDCl_3)	δ_3 (Compound 1 , 100 MHz, CD_3OD)	$\Delta\delta$ ($\delta_{\text{L}}-\delta_1$)
C=O	206.4	208.1	-1.7
C2	165.0	167.0	-2.0
C4	165.0	165.4	-0.4
C1'''	147.0	148.5	-1.5
C3'	137.1	138.4	-1.3
C3''	131.9	132.4	-0.5
C3'''	128.3	129.2	-0.9
C2'''	127.0	128.3	-1.3
C4'''	125.6	126.4	-0.6
C2''	124.2	125.7	-1.5
C4'	121.1	122.0	-0.9
C1	105.7	107.2	-1.5
C3	94.5	94.4	0.1
OMe	55.4	55.8	-0.4
C1'	53.9	55.0	-1.1
C2'	42.6	43.4	-0.6
C6'	37.0	38.4	-1.4
C5'	35.9	37.1	-1.2
C1''	28.8	29.8	-1.0
9'-CH ₃	25.6	25.9	-0.3
3'-CH ₃	22.7	23.0	-0.3
9'-CH ₃	17.9	18.1	-0.2

4-Hydroxypanduratin A (**2**) ¹H NMR Comparison.

Proton	δ_L (Lit., ^[9] 600 MHz, CD ₃ OD)	δ_3 (Compound 2 , 400 MHz, CD ₃ OD)	$\Delta\delta$ ($\delta_L - \delta_2$)
H2'', H3''	7.17 (m)	7.18 ^a (m)	-0.01
H4''	7.05 (m)	7.05 (m)	0.00
H3	5.76 (s)	5.78 (s)	-0.02
H4'	5.41 (ddd, 4.5, 2.8, 1.9)	5.40 (s)	0.01
H2''	4.90 (dd, 7.1, 7.1)	4.91 ^b	-0.01
H1'	4.75 (dd, 11.6, 4.7)	4.76 (dd, 12.0, 4.8)	-0.01
H6'	3.36 (ddd, 11.6, 10.6, 6.4)	3.37 (ddd, 10.4, 10.4, 6.4)	-0.01
H2'	2.64 (dddd, 7.2, 4.7, 4.5, 1.6)	2.65 (m)	-0.01
H5'a	2.33 (dddq, 18.1, 6.4, 4.5, 1.9)	2.29 ^a (m)	-
H1''a	2.25 (ddd, 15.2, 7.2, 7.1)		-
H1b''	2.05 (ddd, 15.2, 7.1, 4.5)		-
H5'b	1.98 (dddq, 10.6, 2.8, 1.9, 1.6)	2.01 (m)	-0.03
CH ₃	1.77 (ddd, 1.9, 1.9, 1.9)	1.77 (s)	0.00
CH ₃	1.51 (s)	1.51 (s)	0.00

^aCalculated from midpoint of multiplet.

^bObscured by HOD peak, chemical shift determined from COSY.

4-Hydroxypanduratin A (**2**) ¹³C NMR Comparison.

Carbon	δ_L (Lit., ^[9] 150MHz, DMSO- <i>d</i> ₆)	δ_3 (Compound 2 , 100 MHz, CD ₃ OD)	$\Delta\delta$ ($\delta_L - \delta_2$)
C=O	205.7	207.8	-2.1
C4	164.3	165.5	—
C2	164.1		—
C1'''	^a	148.6	—
C1''	137.1 ^b	138.4	-1.3
C3''	130.6	132.2	-1.6
C3'''	128.1	129.1	-1.0
C2'''	126.9	128.2	-1.3
C4'''	125.3	126.4	-1.1
C2''	124.3	125.7	-1.4
C4'	120.9	121.9	-1.0
C1	104.7	106.5	-1.8
C3	94.8	95.8	-1.0
C1'	52.8	54.8	-2.0
C2'	42.1	43.8	-1.7
C6'	36.4	38.4	-2.0
C5'	35.7	37.1	-1.4
C1''	28.4	29.9	-1.5
CH ₃	25.5	25.9	-0.4
CH ₃	22.6	23.0	-0.4
CH ₃	17.6	18.0	-0.4

^aNot reported in isolation paper

^bReported as 7.1 and assumed to be a typographical error

Nicolaoidesin B (**5**) ¹H NMR Comparison.

Proton	δ_L (Lit., ^[10] 500 MHz, CDCl ₃)	δ_3 (Compound 5 , 400 MHz, CD ₃ OD)	$\Delta\delta$ ($\delta_L - \delta_5$)
H	7.16 ^a (m)	7.15 ^a (m)	0.01
H	7.08 (m)	7.07 (m)	0.01
H3	5.92 (s)	5.93 (s)	-0.01
H4'	5.49 (s)	5.49 (s)	0.00
H6'	4.86 (t, 5.9)	4.92 (m)	-0.06
H2''	4.76 (ddd, 11.0, 11.0, 6.1)	4.88 ^b (m)	-0.12
OMe	3.76 (s)	3.77 (s)	-0.01
H1'	3.57 (dd, 11.0, 5.1)	3.51 (dd, 11.6, 5.2)	0.06
H5'a	2.62 (dt, 18.0, 4.2)	2.61 (m)	0.01
H2'	2.27 (dt, 5.0, 4.9)	2.24 (m)	0.03
H1'', H5'b	1.97 (m)	1.95 ^a (m)	0.02
3-CH ₃	1.76 (s)	1.75 (s)	0.01
3''-CH ₃	1.56 (s)	1.57 (s)	-0.01
3''-CH ₃	1.33 (s)	1.34 (s)	-0.01

^aCalculated from midpoint of multiplet.

^bObscured by HOD peak, chemical shift determined from COSY.

Nicolaoidesin B (**5**) ^{13}C NMR Comparison.

Carbon	δ_{L} (Lit., ^[10] 125 MHz, CDCl_3)	δ_3 (Compound 5 , 100 MHz, CD_3OD)	$\Delta\delta$ ($\delta_{\text{L}}-\delta_5$)
C=O	209.2	211.2	-2.0
4	165.4	167.4	-2.0
2	162.7	165.5	-2.8
1'''	143.4	144.9	-1.5
3'	137.6	138.6	-1.0
3''	130.4	131.4	-1.0
2'''	128.1	129.4	-1.3
3'''	128.1	129.0	-0.9
4'''	125.7	126.7	-1.0
2''	123.8	124.8	-1.0
4'	120.1	121.4	-1.3
1	105.2	106.8	-1.6
3	94.6	94.5	-0.9
OMe	55.5	55.8	-0.3
1'	46.0	47.6	-1.6
2'	45.6	47.0	-1.4
6'	43.8	44.6	-0.8
5'	30.9	31.9	-1.0
1''	28.0	29.0	-1.0
3''-CH ₃	25.9	26.1	-0.2
3'-CH ₃	22.9	23.3	-0.4
3''-CH ₃	17.8	18.0	-0.2

4-Hydroxyisopanduratin A (**6**) ¹H NMR Comparison.

Proton	δ_L (Lit., ^[11] 400 MHz, CD ₃ OD)	δ_3 (Compound 6 , 800 MHz, CD ₃ OD)	$\Delta\delta$ ($\delta_L - \delta_6$)
H2'''	7.16 ^a (m)	7.17 ^a (m)	-0.01
H3''', H4'''	7.06 (m)	7.07 (m)	-0.01
H3	5.80 (s)	5.81 (s)	-0.01
H4'	5.47 (s)	5.49 (s)	-0.02
H2''	4.80 (t, 7.0)	4.91 (m)	-0.11
H6'	4.77 (ddd, 11.9, 11.9, 6.0)	4.87 ^b	-0.10
H1'	3.49 (dd, 11.9, 5.1)	3.50 (dd, 11.7, 5.0)	-0.01
H5'b	2.61 (ddd, 17.3, 6.0, 1.9)	2.60 (d, 17.3)	0.01
H2'	2.23 (dd, 9.8, 5.1)	2.24 (m)	-0.01
H5'a	2.04 (ddd, 17.3, 11.9, 1.9)	2.00 (m)	0.04
H1''	1.94 ^a (m)	1.86 ^a (m)	-0.07
CH ₃	1.74 (s)	1.75 (s)	-0.01
CH ₃	1.57 (s)	1.57 (s)	0.00
CH ₃	1.42 (s)	1.34 (s)	0.08

^aCalculated from midpoint of multiplet.

^bObscured by HOD peak, chemical shift determined from COSY.

4-Hydroxyisopanduratin A (**6**) ^{13}C NMR Comparison.

Carbon	δ_{L} (Lit., ^[11] 100 MHz, CD_3OD)	δ_3 (Compound 6 ppm, 200 MHz, CD_3OD)	$\Delta\delta$ ($\delta_{\text{L}}-\delta_3$)
C7	210.7	210.8	-0.1
C2, C4	165.9	166.1	-0.2
C1'''	144.9	145.0	-0.1
C3'	138.5	138.6	-0.1
C3''	131.3	131.4	-0.1
C3'''	129.4	129.5	-0.1
C2'''	128.9	129.0	-0.1
C4'''	126.6	126.7	-0.1
C2''	124.9	124.9	0.0
C4'	121.4	121.5	-0.1
C1	106.1	106.1	0.0
C3	95.9	95.9	0.0
C1'	47.5	47.6	-0.1
C2'	47.0	47.1	-0.1
C6'	44.4	44.4	0.0
C5'	31.9	31.9	0.0
C1''	29.1	29.1	0.0
C4''	26.1	26.1	0.0
3'CH ₃	23.3	23.3	0.0
C5''	17.9	17.9	0.0

Computational Details

The geometries of all compounds were optimized at the B3LYP/6-31+G(d) level of theory. Systematic conformer searching was carried out to locate the lowest energy conformer of each compound, and vibrational frequencies were computed at the same level of theory to confirm that these are indeed global minimum energy structures. Geometry optimization and frequency calculations were performed using the Gaussian09 program.^[12] The atomic coefficients of the p orbitals were calculated at the B3LYP/6-31G(d) level of theory and these were carried out using the GAMESSPLUS package.^[13]

Table S1. The B3LYP/6-31G(d) orbital coefficients of the 2p_z and 3p_z atomic orbitals on carbon atoms C2 and C3 in the LUMO^a of the dienophile.

<p style="text-align: center;">17</p>	X=		C3	C2
	C(O)OMe	2Pz	0.297	−0.259
		3Pz	0.333	−0.317
	C(O)OEt	2Pz	0.295	−0.260
		3Pz	0.332	−0.318
	C(O)OCH ₂ CF ₃	2Pz	0.308	−0.249
		3Pz	0.342	−0.305
	C(O)OtBu	2Pz	0.293	−0.260
		3Pz	0.330	−0.317
	C(O)H	2Pz	0.308	−0.228
		3Pz	0.319	−0.268
	CN	2Pz	0.306	−0.288
		3Pz	0.341	−0.344

^aThe HOMO(diene)/LUMO(dienophile) pair has the smaller HOMO-LUMO energy gap.

B3LYP/6-31+G(d) Optimized Geometries

(*E*)-Ocimene 8

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1\1\GINC-X99\FOpt\RB3LYP\Gen\C10H16\JMH502\22-Nov-2011\0\#\B3LYP/gen
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.0053161552\C,-0.0442948282,0.1664628127,1.3377679647\H,0.9215610749,-
```

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-0.9689966901,0.2416491764,1.9055077407\C,-1.2287195827,-0.0503967268,
-0.8766232606\C,-2.2967446031,0.7421459353,-0.6488334183\C,-1.10425571
88,-1.0309566721,-2.0233016309\C,-3.60857321,0.7953604735,-1.397199929
9\H,-2.2330346664,1.437434396,0.1884548776\H,-0.2038744121,-0.81592322
2,-2.6154786821\H,-0.9951238907,-2.0577121945,-1.6481110559\H,-1.96019
63824,-1.0105401052,-2.7018793014\H,-3.7676063685,1.8162141509,-1.7659
833268\H,-3.5774946959,0.1492196623,-2.2828318228\C,-4.761283379,0.363
427998,-0.5158688005\C,-5.8030781834,1.0927884071,-0.0786041533\H,-4.7
053029023,-0.6777392625,-0.1930509066\C,-6.8581639933,0.4729943067,0.8
099671274\C,-6.0440187583,2.5479564662,-0.4045343435\H,-7.0077173851,2
.6744489057,-0.9184022331\H,-6.1031850757,3.144183093,0.5172299229\H,-
5.2685482369,2.9877962368,-1.0364832721\H,-7.852657732,0.5354209961,0.
3449275467\H,-6.6477189415,-0.5807292124,1.0209930472\H,-6.9284141122,
1.0053285449,1.7696192395\\Version=EM64L-G03RevE.01\State=1-A\HF=-390.
662807\RMSD=4.610e-09\RMSF=3.957e-06\Thermal=0.\Dipole=-0.1884948,0.04
73043,-0.1222158\PG=C01 [X(C10H16)]\@

17, X = CN

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,3,cc4,2,ccc4,1,dih4,0\C,4,cc5,3,ccc5,2,dih5,0\C,1,cc6,2,ccc6,3,dih6,0
\H,2,hc7,1,hcc7,6,dih7,0\H,3,hc8,2,hcc8,1,dih8,0\H,4,hc9,3,hcc9,2,dih9
,0\H,5,hc10,4,hcc10,3,dih10,0\H,6,hc11,1,hcc11,2,dih11,0\C,1,cc12,2,cc
c12,3,dih12,0\C,12,cc13,1,ccc13,2,dih13,0\H,12,hc14,1,hcc14,2,dih14,0\
C,13,cc15,12,ccc15,1,dih15,0\H,13,hc16,12,hcc16,1,dih16,0\X,15,1.,13,9
0.,12,180.,0\N,15,nc18,17,ncxx18,13,dih18,0\cc2=1.40972775\cc3=1.3920
2365\ccc3=120.69522174\cc4=1.40078177\ccc4=120.34102277\dih4=0.\cc5=1.
39668263\ccc5=119.68737746\dih5=0.\cc6=1.40809063\ccc6=118.25289198\di
h6=0.\hc7=1.08622795\hcc7=120.19034854\dih7=180.\hc8=1.08678972\hcc8=1
19.65619899\dih8=180.\hc9=1.08671384\hcc9=120.09408092\dih9=180.\hc10=
1.08668184\hcc10=120.23013944\dih10=180.\hc11=1.08770529\hcc11=119.213
57822\dih11=180.\cc12=1.46394125\ccc12=123.38454357\dih12=180.\cc13=1.
35207371\ccc13=127.1302215\dih13=0.\hc14=1.08889079\hcc14=115.31291014
\dih14=180.\cc15=1.42528951\ccc15=122.12993471\dih15=180.\hc16=1.08690
591\hcc16=122.2071591\dih16=0.\nc18=1.16567148\ncxx18=88.83624971\dih1
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e-09\RMSF=2.509e-05\Dipole=1.9149371,0.,1.0754856\Quadrupole=-6.466058
6,1.1711651,5.2948935,0.,-9.1619617,0.\PG=CS [SG(C9H7N1)]\@

17, X = CHO

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\C,2.511401109,0.,1.3600981269\C,2.4197895056,0.,-0.0339656025\C,1.167
7659125,0.,-0.6490286164\H,-0.8014935685,0.,2.1333144299\H,1.409319515
7,0.,3.217746443\H,3.4846411761,0.,1.8437423773\H,3.3210379443,0.,-0.6
412202033\H,1.1001538185,0.,-1.7347988936\C,-1.3025437611,0.,-0.585033
8796\C,-2.544757744,0.,-0.0509745077\H,-1.2315654148,0.,-1.6746930639\
C,-3.7273303853,0.,-0.9135582026\H,-2.7315685261,0.,1.0201983024\O,-4.
8798497167,0.,-0.5081965743\H,-3.5176191337,0.,-2.0063642731\Version=
EM64L-G03RevE.01\State=1-A'\HF=-422.9953337\RMSD=9.955e-09\RMSF=1.935e
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```

17, X = COOMe

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maxdisk=262144000\meo-dienophile.a2.freq\0,1\C,-0.0568095831,0.,0.15
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\C,2.5274114944,0.,1.2846284521\C,2.3711524675,0.,-0.1034466023\C,1.09
17580884,0.,-0.6606262285\H,-0.7466318282,0.,2.2085510619\H,1.51072631
07,0.,3.1904279658\H,3.5217725036,0.,1.7234239674\H,3.2432761814,0.,-0
.7520375516\H,0.9733917023,0.,-1.7418507797\C,-1.371778403,0.,-0.49149
98435\C,-2.5816600072,0.,0.1023383845\H,-1.3646056408,0.,-1.5810972077
\C,-3.8130148347,0.,-0.7112101162\H,-2.7136941481,0.,1.1796187731\O,-3
.8732136702,0.,-1.9291851961\O,-4.9138700359,0.,0.0833950251\C,-6.1790
798991,0.,-0.5992415626\H,-6.9324328767,0.,0.1891723536\H,-6.274260244
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7494471,-3.4348697,0.,-1.7454724,0.\PG=CS [SG(C10H8O2),X(H2)]\@
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17, X = COOEt

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maxdisk=262144000\eto-dienophile.a2.global.freq\0,1\C,-0.10162945,0.
,0.1418276683\C,0.1123673626,0.,1.5352812671\C,1.4030566227,0.,2.05758
31085\C,2.512459711,0.,1.2023454413\C,2.3185726265,0.,-0.1809455986\C,
1.0245575452,0.,-0.7033808495\H,-0.7354934204,0.,2.2142095494\H,1.5476
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-0.8528990589\H,0.8769739952,0.,-1.7810106509\C,-1.4338151997,0.,-0.46
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17, X = COOCH₂CF₃

1\1\GINC-V1280\FOpt\RB3LYP\Gen\C11H9F3O2\JMH502\22-Oct-2012\0\#\B3LYP/
 gen 6D INT(grid=ultrafine) OPT IOP(2/17=4) Freq=noraman
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 44,0.,0.1489573233\C,0.1164207957,0.,1.5413073614\C,1.410658703,0.,2.0
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 , -0.4504547748\C,-2.6303438756,0.,0.1853491083\H,-1.4703300956,0.,-1.5
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 872\O,-4.0007026814,0.,-1.797899421\O,-4.963587941,0.,0.252082391\C,-6
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 719549,0.8903775336,-1.0166196854\H,-6.3566719549,-0.8903775336,-1.016
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17, X = COO^tBu

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 , -0.373390542\C,-2.5928527927,0.,0.3128328381\H,-1.5126977181,0.,-1.46
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 64\O,-4.0207626394,0.,-1.6161881662\O,-4.9080658414,0.,0.4889704209\C,
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,1.9922416457\H,-6.8130565019,0.8881935582,1.9922416457\H,-7.713825392
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\H,-6.1123977731,1.2858983222,-1.6852839419\H,-7.7138253929,-1.3288702
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=CS [SG(C11H8O2),X(C2H8)]\\@

```

Binding Studies by NMR Spectroscopy

The construct of the dengue virus NS2B-NS3 protease used in this work was described previously.^[14] The protein was expressed *in vivo* in the *E. coli* strain Rosetta:: λDE3/pRARE using a high-cell density method.^[15] The pelleted cells were re-suspended in 50 mL lysis buffer A (50 mM HEPES, pH 7.5, 300 mM NaCl), disrupted by French press lysis at 12000 psi and centrifuged at 16000 × *g* for 45 min. at 4°C to remove the cell debris. The supernatant was filtered (Sartorius 0.45 μm filter) and loaded onto a 5-mL HisTrap HP column (GE Healthcare) equilibrated with buffer A. After washing the column with 20 mL buffer A at a flow rate of 1 mL/min, a gradient from 15–500 mM imidazole was applied over 60 min. The dengue virus protease eluted at 200 mM imidazole. Fractions containing the protease were pooled, dialyzed against NMR buffer (20 mM Tris, pH 6.9, 50 mM NaCl) and loaded onto a 50 mL Toyopearl DEAE-650M column equilibrated with the same buffer. After washing the column with 50 mL of NMR buffer, a gradient from 50 mM to 1 M NaCl was applied over 200 mL. The dengue virus protease eluted at 300 mM NaCl. Fractions containing the dengue virus protease were pooled, dialyzed against NMR buffer and concentrated in a centrifugal filter device (Millipore, MWCO 10000) for NMR experiments.

All NMR spectra were recorded at 25°C on a Bruker 800 MHz NMR spectrometer equipped with a cryoprobe. 0.1 mM samples of the dengue virus protease were prepared in NMR buffer (20 mM Tris, pH 6.9, 50 mM NaCl). In different experiments, panduratin A **1** and 4-hydroxypanduratin A **2** were individually added in equimolar ratio and in five-fold molar excess to the protein from a 100 mM stock solution in DMSO-*d*₆.

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panduratin H 3

^1H -NMR spectrum, 400MHz, CDCl_3

panduratin H 3

^{13}C -NMR spectrum, 100MHz, CDCl_3

panduratin I 4

$^1\text{H-NMR}$ spectrum, 400MHz, CDCl_3

panduratin I 4

^{13}C -NMR spectrum, 100MHz, CDCl_3

(±)-((1*R*,2*S*,6*R*)-3-methyl-2-(3-methylbut-2-en-1-yl)-
-6-phenylcyclohex-3-en-1-yl)methanol **10**
¹H-NMR spectrum, 400MHz, CDCl₃

(±)-((1*R*,2*S*,6*R*)-3-methyl-2-(3-methylbut-2-en-1-yl)-
-6-phenylcyclohex-3-en-1-yl)methanol **10**
¹³C-NMR spectrum, 100MHz, CDCl₃

(±)-((1*R*,5*S*,6*R*)-4-methyl-5-(3-methylbut-2-en-1-yl)-6-phenylcyclohex-3-en-1-yl)methanol **11**
¹H-NMR spectrum, 400MHz, CDCl₃

(±)-((1*R*,5*S*,6*R*)-4-methyl-5-(3-methylbut-2-en-1-yl)-6-phenylcyclohex-3-en-1-yl)methanol **11**
¹³C-NMR spectrum, 100MHz, CDCl₃

(±)-((1*R*,2*S*,6*R*)-3-methyl-2-(3-methylbut-2-en-1-yl)-6-phenylcyclohex-3-en-1-yl)methanal **12**
¹H-NMR spectrum, 400MHz, CDCl₃

(±)-((1*R*,2*S*,6*R*)-3-methyl-2-(3-methylbut-2-en-1-yl)-6-phenylcyclohex-3-en-1-yl)methanal **12**
¹³C-NMR spectrum, 100MHz, CDCl₃

(±)-((1*R*,5*S*,6*R*)-4-methyl-5-(3-methylbut-2-en-1-yl)-
-6-phenylcyclohex-3-en-1-yl)methanal **19**
¹H-NMR spectrum, 400MHz, CDCl₃

(±)-((1*R*,5*S*,6*R*)-4-methyl-5-(3-methylbut-2-en-1-yl)-
-6-phenylcyclohex-3-en-1-yl)methanal **19**
¹³C-NMR spectrum, 100MHz, CDCl₃

(±)-((1*R*,2*S*,6*R*)-3-methyl-2-(3-methylbut-2-en-1-yl)-6-phenylcyclohex-3-en-1-yl) (4-methoxy-2,6-bis(methoxymethoxy) phenyl) methanone **14**
¹H-NMR spectrum, 400MHz, CDCl₃

(±)-((1*R*,2*S*,6*R*)-3-methyl-2-(3-methylbut-2-en-1-yl)-6-phenylcyclohex-3-en-1-yl) (4-methoxy-2,6-bis(methoxymethoxy) phenyl) methanone **14**
¹³C-NMR spectrum, 100MHz, CDCl₃

panduratin A 1

^1H -NMR spectrum, 400MHz, CD_3OD

panduratin A 1

^{13}C -NMR spectrum, 100MHz, CD_3OD

(±)-((1R,2S,6R)-3-methyl-2-(3-methylbut-2-en-1-yl)-6-phenylcyclohex-3-en-1-yl) (2,4,6-tris(methoxymethoxy) phenyl) methanone **16**

¹H-NMR spectrum, 400MHz, CDCl₃

(±)-((1*R*,2*S*,6*R*)-3-methyl-2-(3-methylbut-2-en-1-yl)-6-phenylcyclohex-3-en-1-yl) (2,4,6-tris(methoxymethoxy) phenyl) methanone **16**

^{13}C -NMR spectrum, 100MHz, CDCl_3

4-hydroxypanduratin A 2
 ^1H -NMR spectrum, 400MHz, CD_3OD

4-hydroxypanduratin A **2**

^{13}C -NMR spectrum, 100MHz, CD_3OD

(±)-((1*R*,5*S*,6*R*)-4-methyl-5-(3-methylbut-2-en-1-yl)-6-phenylcyclohex-3-en-1-yl) (4-methoxy-2,6-bis(methoxymethoxy)phenyl) methanone **20**
¹H-NMR spectrum, 400MHz, CDCl₃

(±)-((1*R*,5*S*,6*R*)-4-methyl-5-(3-methylbut-2-en-1-yl)-6-phenylcyclohex-3-en-1-yl) (4-methoxy-2,6-bis(methoxymethoxy)phenyl) methanone **20**
¹³C-NMR spectrum, 100MHz, CDCl₃

nicolaioidesin B 5
 ^1H -NMR spectrum, 400MHz, CD_3OD

nicolaioidesin B **5**

^{13}C -NMR spectrum, 100MHz, CD_3OD

(±)-((1*R*,5*S*,6*R*)-4-methyl-5-(3-methylbut-2-en-1-yl)-6-phenylcyclohex-3-en-1-yl) (2,4,6-tris(methoxymethoxy) phenyl) methanone **21**

¹H-NMR spectrum, 400MHz, CDCl₃

(±)-((1*R*,5*S*,6*R*)-4-methyl-5-(3-methylbut-2-en-1-yl)-6-phenylcyclohex-3-en-1-yl) (2,4,6-tris(methoxymethoxy) phenyl) methanone **21**

^{13}C -NMR spectrum, 100MHz, CDCl_3

4-hydroxyisopanduratin A **6**
 ^1H -NMR spectrum, 400MHz, CD_3OD

4-hydroxyisopanduratin A 6
 ^{13}C -NMR spectrum, 100MHz, CD_3OD