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Convergent radical-free synthesis of isoflavanquinones: Divergent total synthesis of abruquinones B, E, and P

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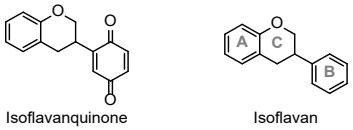
ABSTRACT

We report divergent total syntheses of isoflavanquinone natural products based on a new convergent synthetic strategy. A 3-chloro-2*H*-chromene, prepared by our originally developed Claisen rearrangement–cyclization cascade, was subjected to Suzuki-Miyaura cross coupling with three purposefully protected 2,5-dibenzyloxyarylboronic acids to afford isoflavenes with B rings as benzyl-protected hydroquinone moieties. The subsequent catalytic hydrogenation afforded isoflavenes, releasing unmasked hydroquinone moieties. Finally, these hydroquinone moieties were oxidized to quinones in the presence of palladium on carbon and air in one-pot to give three isoflavanquinone natural products, abruquinones B, E, and P quantitatively in all cases. Our newly developed method enabled the facile total syntheses of natural isoflavanquinones, including the first syntheses of abruquinones E and P.

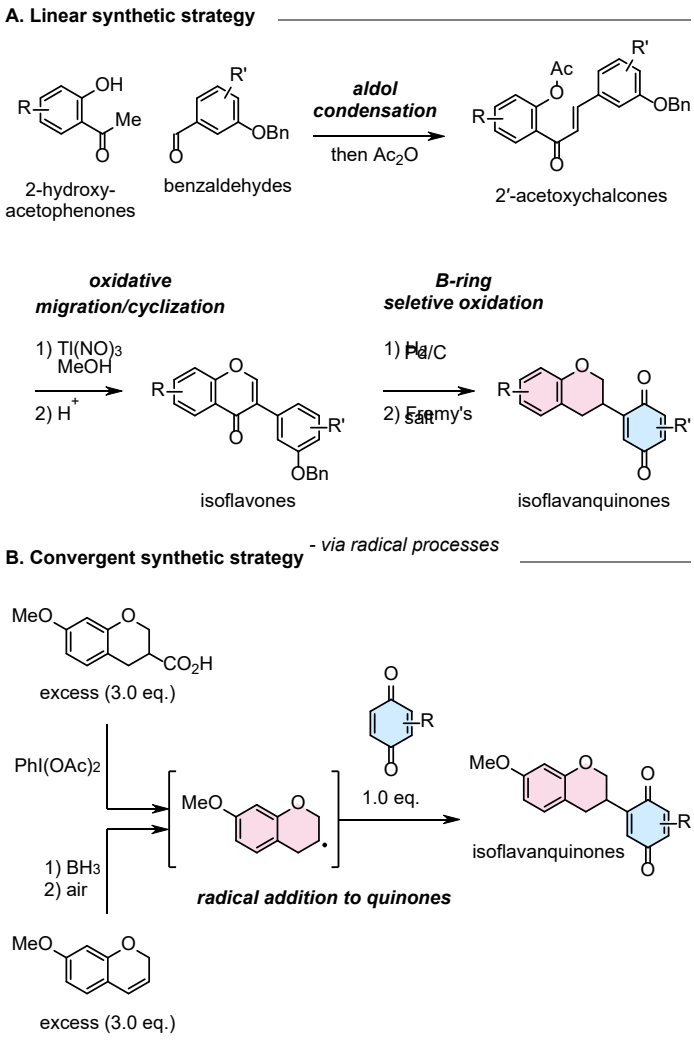
1. Introduction



Isoflavanquinone Isoflavan

Figure 1. Core structures of isoflavanquinones and isoflavans.

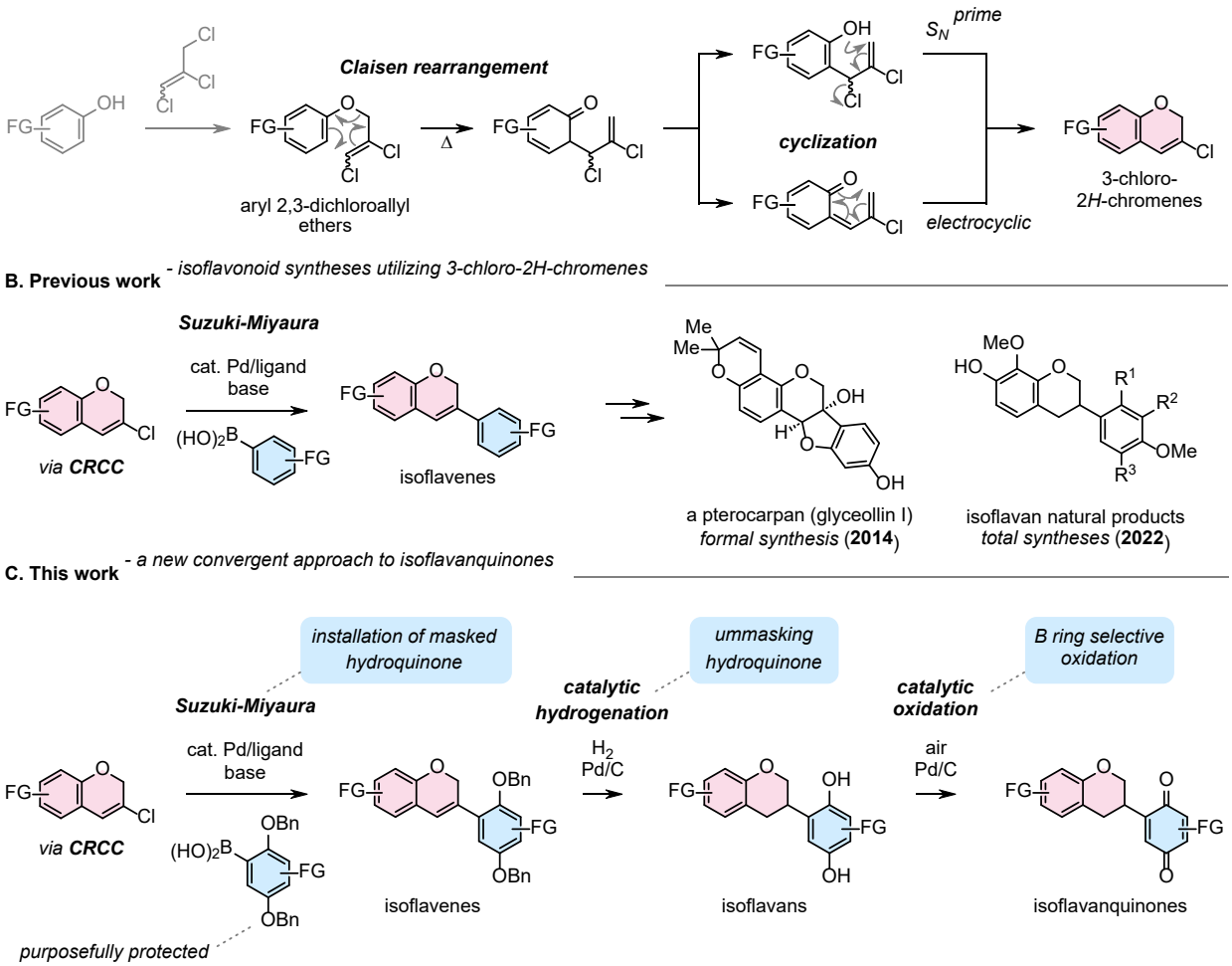
Isoflavonoids, compounds possessing a 3-arylchromane skeleton, are a large group of plant secondary metabolites mainly produced by Fabaceae and possess functions beneficial for human health.[1] In Fabaceae, isoflavonoids play a role in defense against pests and pathogens and symbiosis with rhizobia. Additionally, it has been reported that they function as phytoestrogens, antioxidants, and anticancer agents. Due to their usefulness and attractive functions, numerous synthetic approaches for isoflavonoids have been developed[2,3] over the past century.[4] However, a class of isoflavonoids, isoflavanquinone, is not always easy to access, even with the latest synthetic technology. Isoflavanquinones, which are isoflavan analogs with their B rings oxidized to quinones (**Figure 1**), are also found in many Fabaceae.[3] They show various bioactivities, including antifeedant activity against grass grub (*Costelytra zealandica*),[5] antifertility (implantation inhibitory) activity against rats,[6] antitumor activity against human cancer cells derived from various tissues,[7] and antibacterial activity against multidrug resistant *Staphylococcus aureus*.[8] The number of synthetic examples of isoflavanquinone natural products/derivatives remains at sixteen[9] despite these various attractive bioactivities accompanying potential usefulness in medicine and agriculture.



Scheme 1. Existing linear and convergent synthesis of isoflavanquinones.

Isoflavanquinones have been chemically synthesized based on the following two synthetic strategies. The first one utilizes the aldol condensation of 2-hydoroxyacetophenones and benzaldehydes as a key early step (**Scheme 1A**).[9a–9d] The generating 2′-hydroxychalcones are further acetylated with acetic anhydride to increase their solubility and subjected to oxidative acetal-forming aryl group migration. The following acid-mediated intramolecular condensation of the resulting phenoxy acetals forms isoflavones. Catalytic hydrogenation of these isoflavone derivatives produces isoflavans. In the end, the oxidation of their B ring moieties affords isoflavanquinones. This aldol-based method could access isoflavanquinone derivatives with various A and B ring moieties by taking advantage of the readily available starting materials. However, this linear strategy introduces the A and B ring moieties at the early stages, which would cause more steps, cost, and time when obtaining multiple isoflavanquinones.

Later, Kraus and Kim developed alternative convergent approaches for isoflavanquinones that combine their AC ring units and B ring moieties at the late synthetic stages (**Scheme 1B**).[9e,9f] These approaches involve adding chromane-based radicals as AC ring units to quinones as B ring moieties. These radical-involving reactions consume



Scheme 2. (A) Our original Claisen rearrangement–cyclization cascade. (B) Syntheses of a pterocarpan and isoflavans using 3-chloro-2*H*-chromene. (C) This work, a new convergent synthetic strategy of isoflavanquinones.

large excess amounts (three equivalents) of chromane-based radical precursors, presumably because the generated radicals are consumed by undesirabe self-coupling and/or hydrogen abstraction. For the same reason, these systems do not generally tolerate functional groups vulnerable to radicals. As a complementary strategy, we decided to develop another convergent approach that does not use radical species in this study.

We have previously developed Claisen rearrangement–cyclization cascade (CRCC) reactions of aryl 2,3-dichloroallyl ethers, which could be readily synthesized from the corresponding phenols and commercially available 1,2,3-trichloropropene[10] (**Scheme 2A**). It is assumed that these reactions are involved by the Claisen rearrangement of the allyl aryl ethers, the subsequent dehydrochlorination, and the final S_N' and/or electrocyclic cyclization to yield 3-chloro-2*H*-chromenes. Importantly, the resulting 3-chloro-2*H*-chromenes were employed as electrophiles for Suzuki-Miyaura cross coupling reactions with different arylboronic acids to afford 3-aryl-2*H*-chromenes, i.e., isoflavenes (**Scheme 2B**). Taking advantage of the synthetic usefulness of CRCC, we have previously accomplished the formal and total syntheses of isoflavonoids, including one pterocarpan[10] and three isoflavan[11] natural products.

Based on CRCC, we envisioned that another complementary convergent synthesis of isoflavanquinones would also be realized (**Scheme 2C**). The newly developed synthetic method of isoflavanquinones is as follows: First, a 3-

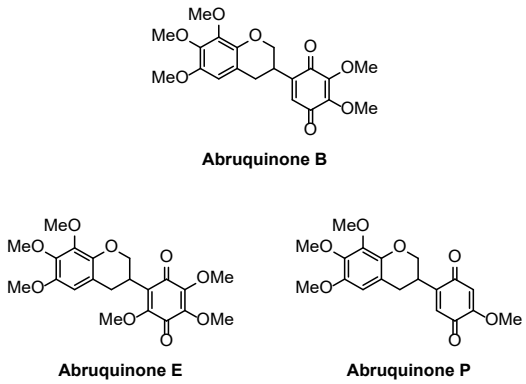
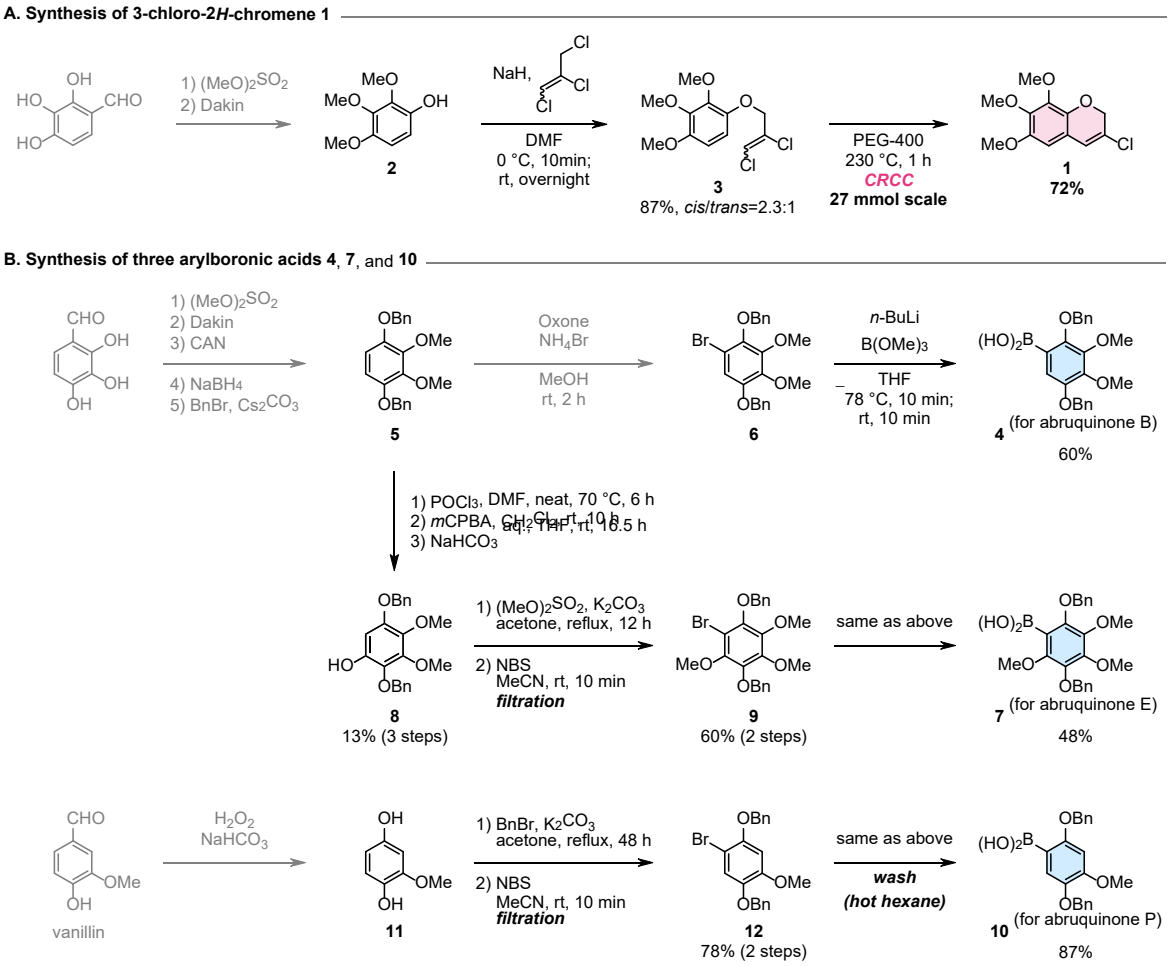


Figure 2. Abruquinones B, E, and P.

chloro-2*H*-chromene is subjected to Suzuki-Miyaura cross coupling with purposefully protected 2,5-dibenzyloxyarylboronic acids to afford isoflavenes with 2′,5′-dibenzyloxy-substituted B rings as masked hydroquinone moieties. The subsequent catalytic hydrogenation of the C3-C4 double bonds in the chromene C rings and hydrogenolytic removal of benzyl groups of these isoflavenes afford isoflavenes with 2′,5′-dihydroxylated B rings. Finally, these unmasked hydroquinone moieties are oxidized to quinones to give isoflavanquinones.

To implement this synthetic strategy, we planned the divergent total synthesis of three natural isoflavanquinones, abruquinones B, E, and P (**Figure 2**). They were all isolated from *Abrus precatorius*,[7,12,13] and abruquinone B has also been found in non-leguminous plants.[14] Several bioactivities,[7,13,15,16,17] including antiplatelet, anti-inflammatory, antitubercular, antileishmanial, anticancer activities have been reported for abruquinone B. Abruquinone E has been less investigated, and only its antiplatelet activity has been reported.[13] Abruquinone P was recently isolated, and its biological activity remains unknown.[7] Lupi and coworkers previously synthesized abruquinone B in 1980 using the above linear approach with the toxic thallium reagent.[9b] No synthetic approaches have not been established yet for abruquinones E and P.

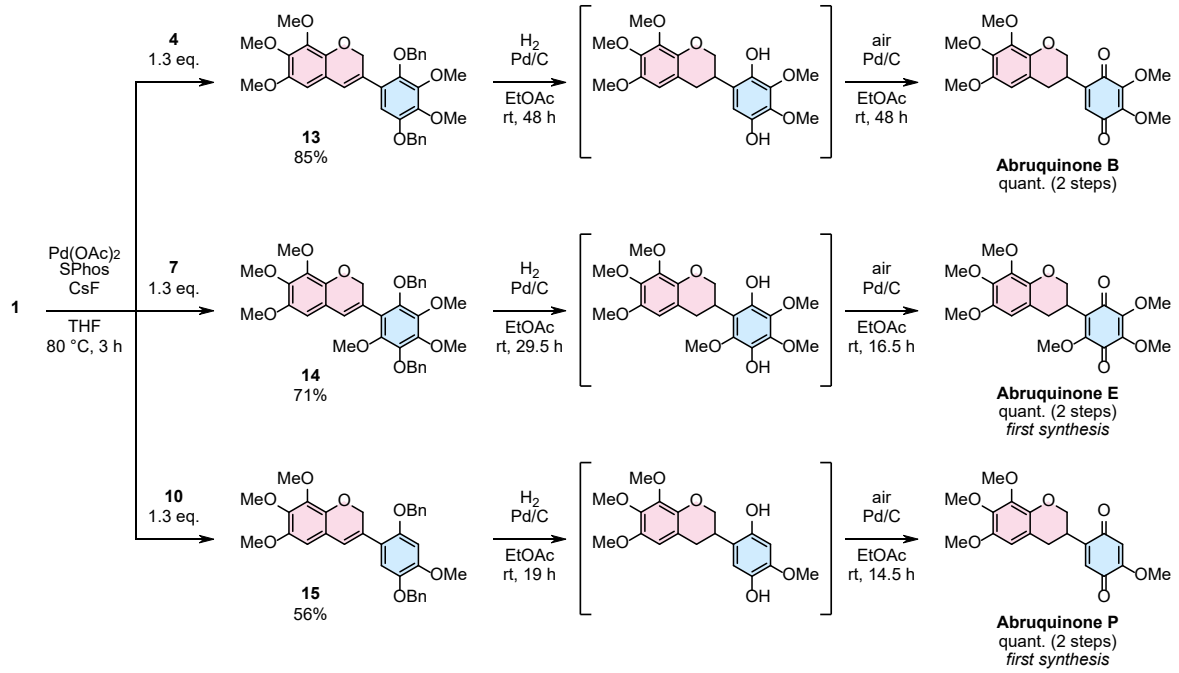
2. Results and Discussion



Scheme 3. Synthesis of (A) 3-chloro-6,7,8-trimethoxy-2*H*-chromene **1** and (B) three arylboronic acids **4**, **7**, and **10**.

We started this study by synthesizing 3-chloro-6,7,8-trimethoxy-2*H*-chromene **1** (**Scheme 3A**). Starting with commercially available 2,3,4-trimethoxybenzaldehyde, 2,3,4-trimethoxyphenol **2** was synthesized over two steps according to the reported procedure.[18] Phenol **2** was etherified with 1,2,3-trichloropropene (1:0.8 mixtures of *cis*- and *trans*-isomers) to give aryl 2,3-dichloroallyl ether **3** as a 2.3:1 mixture of *cis*- and *trans*-isomers. The CRCC was conducted by heating **3** in polyethylene glycol 400 (PEG-400) at 230 °C for 1 h. This key reaction proceeded without problems even with 27 mmol of substrate **3** to afford **1** in 72% yield.

After obtaining **1**, we went on to synthesize arylboronic acids for the desired Suzuki-Miyaura coupling reactions (**Scheme 3B**). Arylboronic acid **4** for abruquinone B was synthesized as follows: 2,3,4-Trimethoxybenzaldehyde was converted to **5** over five steps, and then to bromobenzene **6** according to the reported process.[19] Further, **6** was treated with $B(OMe)_3$ and *n*-BuLi to yield arylboronic acid **4**. The other two arylboronic acids were synthesized similarly: Arylboronic acid **7** for abruquinone E was synthesized from **5**, a precursor in common with **4**. Vilsmeier–Haack formylation and subsequent Dakin oxidation of **5** gave phenol **8**, albeit in a low yield of 13%. Phenol **8** was converted to arylboronic acid 7 via the following conventional 3 steps: methylation of hydroxy group, bromination, and



Scheme 4. Total syntheses of abruquinone B, E, and P by Suzuki-Miyaura cross coupling, catalytic hydrogenation, and hydroquinone oxidation.

borylation. Borylation of **6** and **9** succeeded by pre-addition of $B(OMe)_3$ before *n*-BuLi. To synthesize arylboronic acid **10** for abruquinone P, hydroquinone **11**, which was obtained by Dakin oxidation of vanillin,[20] was benzylated and then brominated. The resulting bromobenzene **12** was highly crystalline and able to be obtained simply by filtering the reaction solution. Arylboronic acid **10** generated in the next step was also highly crystalline and able to be purified by washing the crude product with hot hexane. All these highly oxygen-functionalized arylboronic acids **4**, **7**, and **10** were new compounds, and intriguingly **7** is the first example of an arylboronic acid derivative with carbons other than the boron-substituted carbon oxygen-functionalized.

Now 3-chloro-2*H*-chromene **1** and arylboronic acids **4**, **7**, and **10** were prepared, so we addressed Suzuki-Miyaura coupling (**Scheme 4**). The condition was based on that employed in the isoflavan synthesis we previously reported.[11] As before, SPhos was selected as a ligand since alkenyl chloride **1** would be poorly reactive in Pd-catalyzed cross coupling conditions using classical ligands. Divergent coupling reactions of **1** with **4**, **7**, and **10** successfully proceeded to give isoflavene derivatives **13**, **14**, and **15** in 85, 71, and 56% yield, respectively. The C=C reduction and benzyl deprotection of **13**, **14**, and **15** were carried out under H_2 with Pd/C catalyst. Initially, we planned to isolate the resulting isoflavenes and oxidize their hydroquinone moieties in the following step. To our surprise and delight, on our early attempt of catalytic hydrogenation with substrate **15**, deprotected hydroquinone moiety was spontaneously oxidized to quinones to generate abruquinone P. With this result in mind, in later trials, we replaced H_2 in balloons with air[21] after confirming the consumption of the starting isoflavenes **13**, **14**, and **15** by thin layer chromatography (TLC). Hydroquinone moieties were, as envisioned, oxidized to quinones after 14.5–48 h stirring at room temperature, yielding the targeting natural isoflavanquinones, abruquinones B, E, and P quantitatively. The

spectral data of these isoflavanquinone natural products were in good agreement with those reported in the literature (see **Tables S1–S3** in Supplementary data).[7,13,17]

3. Conclusion

In conclusion, we developed a new convergent synthetic method of isoflavanquinones that does not require a radical process and is complementary to the existing approaches. This approach features the CRCC, divergent Suzuki-Miyaura cross coupling, and one-pot catalytic hydrogenation/oxidation as key steps. In the early stage, the CRCC was conducted in PEG-400 by heating the allyl ether **3**, which is obtained by Williamson etherification of known phenol **2** with trichloropropene (27 mmol scale, 72%). The resulting chlorochromene **1** was combined with three appropriately protected arylboronic acid derivatives **4**, **7**, and **10** using Suzuki-Miyaura coupling to give isoflavene derivatives **13**, **14**, and **15** with benzyl-masked hydroquinone moieties as B rings. The subsequent C=C bond reduction and benzyl group removal were achieved by homogeneous catalytic hydrogenation to afford isoflavenes, releasing unmasked hydroquinone moieties. Finally, these hydroquinone moieties were oxidized to quinone rings in one-pot to accomplish the total syntheses of three isoflavanquinone natural products, abruquinones B, E, and P. Our newly developed method enabled the facile total syntheses of natural isoflavanquinones, including the first syntheses of abruquinones E and P. This new method would facilitate access to isoflavanquinones and contribute to the exploration of biologically active substances. Development of an asymmetric version of our method based on enantioselective hydrogenation[22] of isoflavene intermediates is currently underway.

4. Experimental section

4.1. General experimental details

For reactions that required heating, a heat block and an oil bath were used as the heat source. Column chromatography was performed on Silica Gel 60 N (spherical, neutral), 100–210 μm (purchased from Kanto Chemical Company, Incorporated). Reactions and chromatography fractions were analyzed by TLC on Silica gel 70 F254 TLC Plate-Wako (purchased from FUJIFILM Wako Pure Chemical Corporation), with visualization by UV irradiation at 254 nm, anisaldehyde, 2,4-dinitrophenylhydrazine and/or $FeCl_3$ staining. ^1H and ^{13}C nuclear magnetic resonance (NMR) spectra were recorded on a JEOL JNM-ECZ-400S instrument at 400 and 101 MHz, respectively. Chemical shifts (δ) and coupling constants (*J*) are presented in ppm (relative to internal standards), and Hz, respectively. For internal standard on ^1H NMR spectroscopy, Me_4Si (δ 0.00) or CD_3HOD (δ 3.31) was used. For internal standard on ^{13}C NMR spectroscopy, Me_4Si (δ 0.00) or CD_3OD (δ 49.00) was used. ^{13}C NMR spectra were recorded with ^1H NMR decoupling. To distinguish mono- (CH_3), di- (CH_2), tri- (CH), and tetra-substituted (C) carbon atoms, distortionless enhancement by polarization transfer (DEPT) spectra were obtained by variation of selection angle (90° and 135°) parameters (DEPT90 and DEPT135). High-resolution mass spectrometry (HRMS) data were obtained by a JEOL JMS-T100LP instrument for electrospray ionization (ESI). HRMS data were obtained after

calibration with PEG-400. Fourier transform (FT)-IR spectra were recorded with a ThermoFisher Nicolet iS5 instrument with an iD5 attenuated total reflection (ATR) attachment and are reported in terms of frequency absorption (cm^{-1}). All reagents and solvents were purchased from chemical companies and used as received unless otherwise mentioned. Dry solvents were purchased for the reactions and used without purification.

4.2. Synthesis and characterization of compounds

The NMR data for the natural products (abruquinones B,[17] E,[13] and P[7]) were in good agreement with the literature values (see Supplementary data for the spectra, and **Tables S1**, **S2**, and **S3**). The analytical data for the new compounds are as follows.

*4.2.1. 1-(2,3-dichloroallyloxy)-2,3,4-trimethoxybenzene (**3**)*

To a solution of **2**[18] (8.65 g, 47.0 mmol) in dry *N,N*-dimethylformamide (DMF) (135 mL) was added NaH (3.20 g, 80.0 mmol, 60 wt% in mineral oil) at 0 °C under N_2 atmosphere. After stirring the mixture for 10 min, 1,2,3-trichloropropene (10.1 mL, 99.3 mmol, *cis*/*trans* = *1.2:1*) was added at 0 °C and the reaction mixture was stirred overnight at room temperature. The reaction mixture was quenched with sat. NH_4Cl aq. (115 mL) and extracted with hexane/EtOAc = 8:1 (100 mL × 4). The combined organic layer was washed with brine, dried over Na_2SO_4, decolorized with charcoal, filtered through Celite, and concentrated under reduced pressure. The crude product was purified by column chromatography (SiO_2 100 g; hexane/EtOAc = 4:1) to afford the *title compound* (12.0 g, 87%) as a 2.3:1 mixture of *cis*- and *trans*-isomers. Analytically pure sample of each isomer ***trans*-3** and ***cis*-3** was obtained by preparative TLC.

*4.2.1.1. (E)-1-(2,3-dichloroallyloxy)-2,3,4-trimethoxybenzene (**trans-3**)*

Pale yellow oil; ν_{max} 3071, 2993, 2962, 2936, 2831, 1488, 1433, 1419, 1260, 1093, 1074, 1055, 1015; δ_H ($CDCl_3$) 6.63 (1H, d, *J* 9.2), 6.58 (1H, d, *J* 1.0), 6.56 (1H, d, *J* 9.2), 4.64 (2H, s), 3.92 (3H, s), 3.90 (3H, s), 3.83 (3H, s); δ_C ($CDCl_3$) 149.2 (C), 145.4 (C), 144.7 (C), 143.4 (C), 132.1 (C), 118.1 (CH), 110.9 (CH), 106.4 (CH), 72.1 (CH_2), 61.4 (CH_3), 61.2 (CH_3), 56.2 (CH_3); HRMS (ESI): MNa^+, found 315.0173. $C_{12}H_{14}Cl_2NaO_4^+$ requires 315.0162.

*4.2.1.2. (Z)-1-(2,3-dichloroallyloxy)-2,3,4-trimethoxybenzene (**cis-3**)*

Pale yellow oil; ν_{max} 3077, 2992, 2936, 2830, 1488, 1433, 1419, 1259, 1242, 1092, 1015; δ_H ($CDCl_3$) 6.66 (1H, d, *J* 9.1), 6.56 (1H, d, *J* 9.1), 6.40 (1H, s), 4.85 (2H, s), 3.94 (3H, s), 3.90 (3H, s), 3.83 (3H, s); δ_C ($CDCl_3$) 149.0 (C), 145.4 (C), 144.7 (C), 143.4 (C), 131.8 (C), 118.3 (CH), 110.3 (CH), 106.2 (CH), 67.3 (CH_2), 61.4 (CH_3), 61.2 (CH_3), 56.2 (CH_3); HRMS (ESI): MNa^+, found 315.0167. $C_{12}H_{14}Cl_2NaO_4^+$ requires 315.0162.

*4.2.2. 3-Chloro-6,7,8-trimethoxy-2H-chromene (**1**)*

A solution of **3** (*E*/*Z* = 1:2.3 mixture, 7.91 g, 27.0 mmol) in PEG-400 (270 mL) was stirred at 230 °C (oil bath

temperature) for 1 h under N_2 atmosphere. The resulting mixture was diluted with toluene (250 mL) and washed with water (250 mL; 100 mL × 2). The combined aqueous layer was extracted with toluene (50 mL × 3). The combined organic layer (totally 400 mL) was washed with brine (100 mL), dried over Na_2SO_4, decolorized with charcoal, filtered through Celite, and concentrated under reduced pressure. The crude product was purified by column chromatography (SiO_2 75 g; hexane/EtOAc = 4:1) to give the *title compound* (4.97 g, 72%) as a yellow oil; ν_{max} 3062, 2993, 2937, 2829, 1487, 1464, 1418, 1348, 1272, 1217, 1194, 1133, 1108, 1041; δ_H ($CDCl_3$) 6.46 (1H, s), 6.29 (1H, s), 4.78 (2H, d, *J* 1.2), 3.90 (3H, s), 3.89 (3H, s), 3.81 (3H, s); δ_C ($CDCl_3$) 148.0 (C), 143.1 (C), 142.2 (C), 139.2 (C), 124.8 (C), 121.7 (CH), 117.4 (C), 104.6 (CH), 68.6 (CH_2), 61.4 (CH_3), 61.3 (CH_3), 56.5 (CH_3); HRMS (ESI): MNa^+, found 279.0385. $C_{12}H_{13}ClNaO_4^+$ requires 279.0395.

*4.2.3. 2,5-dibenzyloxy-3,4-dimethoxyphenylboronic acid (**4**)*

To a solution of **6**[19] (429 mg, 1.00 mmol) in dry tetrahydrofuran (THF) (8 mL) was added $B(OMe)_3$ (225 μL, 2.02 mmol) under N_2 atmosphere. The solution was cooled to −78 °C, and *n*-BuLi (1.25 mL, 2.00 mmol, 1.6 M in hexane) was added. After stirred at room temperature for 10 min, the reaction mixture was quenched with 1 M HCl aq. (8 mL) and extracted with EtOAc (8 mL × 3). The combined organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by column chromatography (SiO_2 10 g; hexane/EtOAc = 2:1) to yield the *title compound* (238 mg, 60%) as a white solid; mp 85 °C; ν_{max} 3443, 3089, 3064, 3031, 2937, 2881, 2830, 1450, 1417, 1368, 1346, 1218, 1113, 1042; δ_H ($CDCl_3$) 7.51 – 7.30 (10H, m), 7.18 (1H, s), 5.80 (2H, s), 5.12 (2H, s), 5.09 (2H, s), 3.98 (3H, s), 3.97 (3H, s); δ_C ($CDCl_3$) 152.1 (C), 149.0 (C), 146.7 (C), 146.1 (C), 137.0 (C), 136.4 (C), 128.9 (CH), 128.8 (CH), 128.7 (CH), 128.5 (CH), 127.9 (CH), 127.5 (CH), 114.4 (CH), 76.7 (CH_2 observed by DEPT135), 71.1 (CH_2), 61.4 (CH_3), 61.3 (CH_3); HRMS (ESI): $[M – 2OH + 2Ome + Na]^+$, found 445.1831. $C_{24}H_{27}BnaO_6^+$ requires 445.1793.

*4.2.4. 2,5-dibenzyloxy-3,4-dimethoxyphenol (**8**)*

A mixture of $POCl_3$ (6.00 mL, 65.7 mmol) and dry DMF (5.10 mL, 65.9 mmol) was stirred for 10 min at 0 °C. To the resulting mixture was added **5**[19] (4.58 g, 13.1 mmol), and the mixture was stirred at 70 °C (oil bath temperature) for 6 h. The resulting mixture was quenched with water (130 mL) and extracted with EtOAc (130 mL). The organic layer was washed with 1 M NaOH aq. (130 mL) and brine (130 mL), dried over Na_2SO_4, and concentrated under reduced pressure. To a solution of the resulting residue in CH_2Cl_2 (13 mL) was added *m*-chloroperbenzoic acid (2.94 g, ≤ 13.1 mmol, ≤ 77% purity). After stirred at room temperature for 10 h, the resulting mixture was filtered. The filtrate was quenched with sat. $Na_2S_2O_3$ aq. (20 mL), and CH_2Cl_2 was removed under reduced pressure. A mixture of the resulting residue, THF (13 mL), and sat. $NaHCO_3$ aq. (13 mL) was stirred at room temperature for 16.5 h. The reaction mixture was extracted with EtOAc (13 mL × 3). The combined organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by column chromatography (SiO_2 75 g;

hexane/EtOAc = 9:1) to yield the *title compound* (627 mg, 13%) as a yellow oil, and the starting **5** (1.42 g, 31%) was recovered; ν_{max} 3522, 3420, 3088, 3063, 3031, 2935, 2878, 2828, 1596, 1488, 1470, 1376, 1304, 1232, 1175, 1129, 1090, 1027; δ_H ($CDCl_3$) 7.47 – 7.28 (10H, m), 6.33 (1H, s), 5.34 (1H, s), 5.04 (2H, s), 5.03 (2H, s), 4.00 (3H, s), 3.87 (3H, s); δ_C ($CDCl_3$) 149.0 (C), 146.9 (C), 145.0 (C), 137.0 (C), 136.9 (C), 136.4 (C), 132.5 (C), 128.8 (CH), 128.6 (CH), 128.53 (CH), 128.49 (CH) 127.9 (CH), 127.3 (CH), 96.5 (CH), 76.0 (CH_2), 71.0 (CH_2), 61.5 (CH_3), 61.3 (CH_3); HRMS (ESI): Mna^+, found 389.1362. $C_{22}H_{22}NaO_5^+$ requires 389.1360.

*4.2.5. 2,5-dibenzyloxy-3,4,6-trimethoxybromobenzene (**9**)*

To a mixture of **8** (627 mg, 1.71 mmol) in acetone (6.8 mL) were added K_2CO_3 (473 mg, 3.42 mmol) and dimethyl sulfate (324 μL, 3.42 mmol). After refluxed for 12 h, the reaction mixture was filtered through Celite and concentrated under reduced pressure. To a solution of the resulting residue in MeCN (3.4 mL) was added *N*-bromosuccinimide (NBS) (304 mg, 1.71 mmol). After stirred at room temperature for 10 min, the reaction mixture was concentrated under reduced pressure. The resulting solid was washed with hexane and water/MeOH=1:1 to afford the *title compound* (474 mg, 60%) as a pale yellow solid; mp 71−72 °C; ν_{max} 3064, 3031, 2937, 2872, 1457, 1427, 1404, 1368, 1090, 1048, 1029; δ_H ($CDCl_3$) 7.56 (2H, d, *J* 6.9), 7.50 (2H, d, *J* 7.1), 7.44 – 7.32 (6H, m), 5.04 (2H, s), 5.03 (2H, s), 3.91 (3H, s), 3.89 (3H, s), 3.88 (3H, s); δ_C ($CDCl_3$) 147.6 (C), 147.4 (C), 146.3 (C), 144.4 (C), 143.1 (C), 137.2 (C), 136.9 (C), 128.50 (CH), 128.46 (CH) 128.4 (CH), 128.3 (CH), 128.21 (CH), 128.17 (CH), 107.8 (C), 75.9 (CH_2), 75.4 (CH_2), 61.63 (CH_3), 61.60 (CH_3), 61.3 (CH_3); HRMS (ESI): Mna^+, found 481.0634. $C_{23}H_{23}BrNaO_5^+$ requires 481.0622.

*4.2.6. 2,5-dibenzyloxy-3,4,6-trimethoxyphenylboronic acid (**7**)*

To a solution of **9** (459 mg, 1.00 mmol) in dry THF (8 mL) was added $B(OMe)_3$ (222 μL, 2.02 mmol) under N_2 atmosphere. The solution was cooled to −78 °C, and *n*-BuLi (1.25 mL, 2.00 mmol, 1.6 M in hexane) was added. After stirring the reaction mixture at room temperature for 10 min, it was quenched with 1 M HCl aq. (8 mL) and extracted with EtOAc (8 mL × 3). The combined organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by column chromatography (SiO_2 20 g; hexane/EtOAc = 2:1) to yield the *title compound* (205 mg, 48%) as a white solid; mp 98−100 °C; ν_{max} 3481, 1463, 1431, 1336, 1313, 1044; δ_H ($CDCl_3$) 7.48 (4H, dd, *J* 7.8, 1.4), 7.44 – 7.33 (6H, m), 7.30 (2H, s), 5.09 (2H, s), 5.00 (2H, s), 3.98 (3H, s), 3.94 (3H, s), 3.90 (3H, s); δ_C ($CDCl_3$) 154.6 (C), 153.0 (C), 151.0 (C), 143.1 (C), 141.7 (C), 137.0 (C), 135.8 (C), 129.1 (CH), 128.9 (CH), 128.8 (CH), 128.5 (CH), 128.33 (CH), 128.27 (CH), 76.9 (CH_2), 75.7 (CH_2), 62.1 (CH_3), 61.5 (CH_3), 61.4 (CH_3); HRMS (ESI): $[M - 2OH + 2OMe + Na]^+$, found 475.1853. $C_{25}H_{29}BNaO_7^+$ requires 475.1899.

*4.2.7. 2,5-dibenzyloxy-4-methoxybromobenzene (**12**)*

11[20] (6.45g, 46.0 mmol), K_2CO_3 (25.4 g, 184 mmol) and BnBr (12.0 mL, 101 mmol) were refluxed in acetone (184 mL) for 48 h. The resulting mixture was filtered through Celite and concentrated under reduced pressure. The

residue was dissolved in EtOAc (180 mL) and washed with water/brine = 5:1 (180 mL × 4). The combined aqueous layer was extracted with EtOAc (100 mL × 3). The combined organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The resulting residue and NBS (8.19 g, 46.0 mmol) were stirred in MeCN (92 mL) at room temperature for 10 min. The resulting suspension was filtered. The filtered solid was washed with hexane/EtOAc = 2:1 and water/MeOH = 1:1 to give the *title compound* (14.3 g, 78%) as a slightly pale yellow solid; mp 145 °C; ν_{max} 3062, 3034, 3006, 2948, 2933, 2916, 2875, 2847, 1506, 1373, 1197, 1173, 1003; δ_H ($CDCl_3$) 7.52 – 7.27 (10H, m), 7.10 (1H, s), 6.57 (1H, s), 5.09 (2H, s), 5.05 (2H, s), 3.79 (3H, s); δ_C ($CDCl_3$) 149.91 (C), 149.86 (C), 143.4 (C), 136.8 (C), 136.7 (C), 128.6 (CH), 128.0 (CH), 127.5 (CH), 127.4 (CH), 119.5 (CH), 102.4 (C), 101.7 (CH), 72.4 (CH_2), 72.1 (CH_2), 56.3 (CH_3); HRMS (ESI): MNa^+, found 421.0370. $C_{21}H_{19}BrNaO_3^+$ requires 421.0410.

*4.2.8. 2,5-dibenzyloxy-4-methoxyphenylboronic acid (**10**)*

To a solution of **12** (2.00 g, 5.00 mmol) in dry THF (40 mL) at −78 °C was added *n*-BuLi (3.45 mL, 5.52 mmol, 1.6 M in hexane) and stirred for 15 min. $B(OMe)_3$ (1.65 mL, 14.8 mmol) was added and stirred for 10 min at room temperature. The reaction mixture was quenched with 1 M HCl (20 mL) and extracted with EtOAc (3 × 20 mL). The combined organic layer was washed with brine (30 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The crude product was washed with hot hexane to afford the *title compound* (1.58 g, 87%) as a pale yellow solid; mp 112−114 °C; ν_{max} 3468, 3383, 3063, 3032, 3010, 2952, 2918, 2859, 1602, 1509, 1448, 1406, 1311, 1263, 1204, 1190, 1113, 1011; δ_H ($CDCl_3$) 7.48 – 7.27 (11H, m), 6.58 (1H, s), 5.66 (2H, s), 5.12 (2H, s), 5.10 (2H, s), 3.87 (3H, s); δ_C ($CDCl_3$) 159.6 (C), 153.3 (C), 142.7 (C), 137.3 (C), 136.0 (C), 129.0 (CH), 128.6 (CH), 128.5 (CH), 127.8 (CH), 127.6 (CH), 121.6 (CH), 97.7 (CH), 71.8 (CH_2), 71.6 (CH_2), 56.0 (CH_3); HRMS (ESI): $[M – 2OH + 2OMe + Na]^+$, found 415.1676. $C_{23}H_{25}BNaO_5^+$ requires 415.1688.

*4.2.9. 6,7,8-Trimethoxy-3-(2,5-dibenzyloxy-3,4-dimethoxyphenyl)-2H-chromene (**13**)*

A mixture of dried CsF (168 mg, 1.11 mmol), $Pd(OAc)_2$ (6.7 mg, 30 μmol), SPhos (25.4 mg, 60.0 μmol, 97% purity), **4** (154 mg, 390 μmol), **1** (75.7 mg, 295 μmol), and dry THF (3 mL) was stirred at 80 °C (heat block temperature) for 3 h. The reaction mixture was quenched with water (5 mL) and extracted with EtOAc (5 mL × 3). The combined organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by column chromatography (SiO_2 10 g; hexane/EtOAc = 4:1) to yield the *title compound* as a sticky yellow oil (144 mg, 85%); ν_{max} 3087, 3061, 3030, 2990, 2935, 2877, 2841, 1487, 1466, 1432, 1417, 1358, 1135, 1110, 1053; δ_H ($CDCl_3$) 7.49 – 7.28 (10H, m), 6.65 (1H, s), 6.48 (1H, br s), 6.38 (1H, s), 5.11 (2H, s), 4.95 (2H, d, *J* 1.0), 4.91 (2H, s), 3.96 (3H, s), 3.96 (3H, s), 3.92 (3H, s), 3.92 (3H, s), 3.83 (3H, s); δ_C ($CDCl_3$) 148.8 (C), 147.64 (C), 147.55 (C), 144.5 (C), 143.7 (C), 142.9 (C), 142.0 (C), 140.8 (C), 137.1 (C), 136.9 (C), 130.9 (C), 128.6 (CH), 128.38 (CH), 128.36 (CH), 128.0 (CH), 127.5 (CH), 127.4 (CH), 122.7 (CH), 119.1 (C), 108.5 (CH), 105.1 (CH), 75.6 (CH_2), 71.4

(CH_2), 68.2 (CH_2), 61.5 (CH_3), 61.4 (CH_3), 56.5 (CH_3); HRMS (ESI): MNa^+, found 593.2159. $C_{34}H_{34}NaO_8^+$ requires 593.2146.

*4.2.10. 6,7,8-Trimethoxy-3-(2,5-dibenzyloxy-3,4,6-trimethoxyphenyl)-2H-chromene (**14**)*

A mixture of dried CsF (134 mg, 882 μmol), $Pd(OAc)_2$ (4.5 mg, 20 μmol), SPhos (16.9 mg, 39.9 μmol, 97% purity), **7** (110 mg, 259 μmol), **1** (51.3 mg, 200 μmol), and dry THF (2.0 mL) was stirred at 80 °C (heat block temperature) for 3 h. The reaction mixture was quenched with water (5 mL) and extracted with EtOAc (5 mL × 3). The combined organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by column chromatography (SiO_2 10 g; hexane/EtOAc = 9:1−4:1) to yield the *title compound* (84.9 mg, 71%) as a yellow oil; ν_{max} 3061, 3030, 2935, 2842, 1488, 1465, 1428, 1411, 1367, 1135, 1110, 1055; δ_H ($CDCl_3$) 7.54 – 7.48 (2H, m), 7.43 – 7.32 (5H, m), 7.29 – 7.24 (3H, m), 6.51 (1H, t, *J* 1.1), 6.37 (1H, s), 5.06 (2H, s), 4.93 (2H, s), 4.83 (2H, d, *J* 1.2), 3.96 (3H, s), 3.95 (3H, s), 3.93 (3H, s), 3.91 (3H, s), 3.82 (3H, s), 3.77 (3H, s); δ_C ($CDCl_3$) 147.8 (C), 147.54 (C), 147.49 (C), 146.3 (C), 143.7 (C), 142.8 (C), 142.4 (C), 142.1 (C), 140.9 (C), 137.5 (C), 137.1 (C), 128.6 (CH), 128.4 (CH), 128.30 (CH), 128.25 (CH), 128.1 (CH), 128.0 (CH), 125.45 (CH), 125.41 (C), 122.3 (C), 119.2 (C), 105.1 (CH), 75.8 (CH_2), 75.7 (CH_2), 68.6 (CH_2), 61.6 (CH_3), 61.5 (CH_3), 61.4 (CH_3), 56.4 (CH_3); HRMS (ESI): MNa^+, found 623.2295. $C_{35}H_{36}NaO_9^+$ requires 623.2252.

*4.2.11. 6,7,8-Trimethoxy-3-(2,5-dibenzyloxy-4-methoxyphenyl)-2H-chromene (**15**)*

A mixture of dried CsF (456 mg, 3.00 mol), $Pd(OAc)_2$ (22.5 mg, 100 μmol), SPhos (84.6 mg, 200 μmol, 97% purity), **10** (474 mg, 1.30 mmol), **1** (257 mg, 1.00 mmol), and dry THF (10 mL) in a flask was stirred at reflux temperature for 3 h. The reaction mixture was quenched with water (10 mL) and extracted with EtOAc (10 mL × 3). The organic layer was dried over Na_2SO_4, filtered through Celite, and concentrated under reduced pressure. The crude product was purified by column chromatography (SiO_2 20 g; hexane/EtOAc = 4:1) to yield the *title compound* (303 mg, 56%) as a pale yellow solid; mp 102 °C; ν_{max} 3061, 3031, 2993, 2935, 2842, 1506, 1487, 1466, 1351, 1233, 1194, 1135, 1109, 1053, 1017; δ_H ($CDCl_3$) 7.47 – 7.26 (10H, m), 6.93 (1H, s), 6.57 (1H, s), 6.44 (1H, s), 6.38 (1H, s), 5.10 (2H, s), 5.02 (2H, s), 4.96 (2H, s), 3.91 (3H, s), 3.89 (3H, s), 3.85 (3H, s), 3.81 (3H, s); δ_C ($CDCl_3$) 151.3 (C), 150.5 (C), 147.6 (C), 142.5 (C), 142.3 (C), 141.9 (C), 140.7 (C), 137.2 (C), 136.6 (C), 131.3 (C), 128.6 (CH), 128.5 (CH), 128.1 (CH), 127.9 (CH), 127.6 (CH), 127.5 (CH), 121.3 (CH), 119.7 (C), 119.4 (C), 115.7 (CH), 104.9 (CH), 99.3 (CH), 72.1 (CH_2), 71.5 (CH_2), 68.3 (CH_2), 61.3 (CH_3), 56.4 (CH_3), 56.2 (CH_3). HRMS (ESI): MNa^+, found 563.2021, $C_{33}H_{32}NaO_7^+$ requires 563.2041.

4.2.12. Abruquinone B

A mixture of **13** (29.5 mg, 51.7 μmol), Pd/C (5.4 mg, 5.1 μmol, 10 wt%), and EtOAc (2.0 mL) was stirred under H_2 atmosphere at room temperature for 48 h, and then stirred under air atmosphere at the same temperature for additional 48 h. The resulting mixture was filtered through Celite and concentrated under reduced pressure to yield

the *title compound* (20.2 mg, quant.) as a sticky dark red oil; sticky dark red oil; ν_{max} 2989, 2939, 2840, 1653, 1602, 1490, 1472, 1457, 1419, 1217, 1196, 1130, 1107, 1054; δ_H ($CDCl_3$) 6.35 (1H, br s), 6.34 (1H, s), 4.25 (1H, dd, *J* 10.7, 2.8), 4.11 (1H, dd, *J* 10.7, 5.9), 4.021 (3H, s), 4.015 (3H, s), 3.885 (3H, s), 3.880 (3H, s), 3.81 (3H, s), 3.45 (1H, qd, *J* 5.9, 2.8), 3.08 (1H, dd, *J* 16.5, 6.1), 2.72 (1H, dd, *J* 16.5, 6.1); δ_C ($CDCl_3$) 184.0 (C), 183.5 (C), 147.5 (C), 146.5 (C), 145.1 (C), 144.7 (C), 142.4 (C), 141.7 (C), 131.0 (CH), 114.9 (C), 106.9 (CH), 68.1 (CH_2), 61.35 (CH_3), 61.26 (CH_3), 56.3 (CH_3), 30.8 (CH), 29.3 (CH_2); δ_H (CD_3OD) 6.50 (1H, s), 6.40 (1H, d, *J* 1.0), 4.26 (1H, ddd, *J* 10.6, 2.9, 1.1), 4.01 (1H, dd, *J* 10.6, 7.4), 3.99 (3H, s), 3.98 (3H, s), 3.81 (3H, s), 3.80 (3H, s), 3.77 (3H, s), 3.40 – 3.33 (1H, m), 2.98 (1H, br dd, *J* 16.3, 5.7), 2.79 (1H, dd, *J* 16.3, 8.0); δ_C (CD_3OD) 185.5 (C), 184.8 (C), 148.6 (C), 147.9 (C), 146.6 (C), 146.0 (C), 143.3 (C), 142.9 (C), 142.7 (C), 131.9 (CH), 117.5 (C), 108.7 (CH), 69.3 (CH_2), 61.7 (CH_3), 61.64 (CH_3), 61.63 (CH_3), 61.61 (CH_3), 56.8 (CH_3), 32.3 (CH), 30.5 (CH_2); HRMS (ESI): MNa^+, found 413.1244. $C_{20}H_{22}NaO_8^+$ requires 413.1207.

4.2.13. Abruquinone E

A mixture of **14** (29.0 mg, 48.3 μmol), Pd/C (5.0 mg, 4.7 μmol, 10 wt%), and EtOAc (1.0 mL) was stirred under H_2 atmosphere at room temperature for 29.5 h, and then stirred under air atmosphere at the same temperature for additional 16.5 h. The resulting mixture was filtered through Celite and concentrated under reduced pressure to yield the *title compound* (20.3 mg, quant.) as a sticky dark red oil; ν_{max} 2989, 2941, 2840, 1646, 1604, 1490, 1462, 1430, 1419, 1277, 1217, 1195, 1130, 1094, 1050, 1019; δ_H ($CDCl_3$) 6.32 (1H, s), 4.37 (1H, t, *J* 10.5), 4.20 (1H, ddd, *J* 10.5, 3.3, 2.0), 4.05 (3H, s), 4.00 (3H, s), 3.98 (3H, s), 3.92 (3H, s), 3.88 (3H, s), 3.80 (3H, s), 3.65 – 3.54 (1H, m), 3.15 (1H, dd, *J* 15.6, 12.1), 2.64 (1H, ddd, *J* 15.6, 5.1, 2.0); δ_C ($CDCl_3$) 183.4 (C), 180.2 (C), 155.4 (C), 146.9 (C), 144.6 (C), 142.39 (C), 142.38 (C), 142.1 (C), 141.4 (C), 128.1 (C), 116.7 (C), 107.0 (CH), 67.6 (CH_2), 61.7 (CH_3), 61.4 (CH_3), 61.31 (CH_3), 61.27 (CH_3), 56.4 (CH_3), 30.8 (CH), 29.5 (CH_2); HRMS (ESI): MNa^+, found 443.1311. $C_{21}H_{24}NaO_9^+$ requires 443.1313.

4.2.14. Abruquinone P

A mixture of **15** (54.1 mg, 100 μmol), Pd/C (10.6 mg, 10.0 μmol, 10 wt%), and EtOAc (2.0 mL) was stirred under H_2 at room temperature for 19 h, and then stirred under air atmosphere at the same temperature for additional 14.5 h. The resulting mixture was filtered through Celite and concentrated under reduced pressure to yield the *title compound* (36.0 mg, quant.) as a sticky dark red oil; ν_{max} 2937, 2842, 1674, 1646, 1601, 1490, 1472, 1419, 1247, 1196, 1173, 1129, 1095, 1053; δ_H ($CDCl_3$) 6.47 (1H, d, *J* 1.2), 6.35 (1H, s), 5.98 (1H, s), 4.27 (1H, dd, *J* 10.9, 2.6), 4.12 (1H, ddd, *J* 10.9, 5.9, 0.9), 3.88 (3H, s), 3.88 (3H, s), 3.84 (3H, s), 3.81 (3H, s), 3.54 – 3.44 (1H, m), 3.09 (1H, dd, *J* 16.5, 6.1), 2.74 (1H, dd, *J* 16.5, 6.1); δ_C ($CDCl_3$) 186.6 (C), 182.1 (C), 158.5 (C), 149.2 (C), 147.4 (C), 142.3 (C), 141.7 (C), 141.6 (C), 130.8 (CH), 114.9 (C), 107.9 (CH), 106.8 (CH), 68.1 (CH_2), 61.3 (CH_3), 56.34 (CH_3), 56.27 (CH_3), 30.9 (CH), 29.3 (CH_2); δ_H (CD_3OD) 6.51 (1H, s), 6.51 (1H, s), 6.09 (1H, s), 4.28 (1H, ddd, *J* 10.6, 2.9, 1.1), 4.02 (1H, dd,

J 10.6, 7.3), 3.83 (3H, s), 3.81 (3H, s), 3.80 (3H, s), 3.78 (3H, s), 3.44 – 3.36 (1H, m), 3.00 (1H, dd, *J* 16.4, 5.7), 2.82 (1H, dd, *J* 16.4, 8.0); δ_C (CD_3OD) 188.1 (C), 183.4 (C), 160.1 (C), 150.2 (C), 148.5 (C), 143.3 (C), 143.0 (C), 142.7 (C), 131.9 (CH), 117.5 (C), 108.8 (CH), 108.7 (CH), 69.4 (CH_2), 61.7 (CH_3), 61.6 (CH_3), 56.9 (CH_3), 56.8 (CH_3), 32.4 (CH), 30.5 (CH_2); HRMS (ESI): MNa^+, found 383.1130. $C_{19}H_{20}NaO_{7+}$ requires 383.1102.

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Appendix A. Supplementary data

Supplementary data for this article can be found online at https://doi.org/10.1016/j.tet.2023.xxxxxx.

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