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Collective synthesis of several 2,7′-cyclolignans and their correlation by chemical transformations†

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Collective synthesis of anti-malarial 2,7′-cyclolignans has been stereoselectively achieved employing (±)-cyclogalgravin (**2**) as a linchpin through a series of functional group conversions, including redox reactions. Interestingly, **2** can be correlated with the neolignan (±)-kadangustin J (**1**) isolated from a different plant source, through a highly efficient dehydrative cyclization reaction with excellent diastereotopic differentiation of the veratryl group and concomitant construction of the C1–C7 bond. It is noteworthy that the first total synthesis of stereodivergent (±)-8,8′-*epi*-aristoligone (**5**), (±)-8′-*epi*-aristoligone (**7**), (±)-8′-*epi*-8-OH-aristoligone (**8**) and (±)-8′-*epi*-aristoligol (**9**) was demonstrated.

Introduction

Lignans are a large class of secondary metabolites found in diverse plant families[1] generally and mammalian urine[2] occasionally. They are thought to be formed by the oxidative dimerization of two phenylpropanoid units in a C8–C8′ fashion, and have exhibited various plant defence functions such as antimicrobial, antifungal, and insecticidal ones. Moreover, their antitumor, anti-inflammatory, cardiovascular, and antioxidant biological properties have attracted significant interest from the synthetic community for further investigation of the structure–activity relationship.[3] Recently, we reported total synthesis of (±)-sacidumlignan D using Ueno–Stork radical cyclization as a key step for the biomimetic construction of the C8–C8′ bond (Scheme 1a),[4] and plausible biogenetic conversion of this rearranged tetrahydrofuran lignan to sacidumlignan A with a 7′-arylnaphthalene backbone. In this article, our attention was transferred to the structurally related but stereochemically more complex 2,7′-cyclolignan subclass such as 7′-aryl-7′,8′-dihydronaphthalene (DHN) and 7′-aryl-7,7′,8,8′-tetrahydro naphthalene (THN) that have been exemplified in Scheme 1b, and all of them (**2–9**)[5] demonstrate 2–4 consecutive all-carbon stereocenters.

Biosynthesis of these anti-malarial lignans from *Holostylis reniformis*[5h,i] was investigated, and detailed administration experiments suggested that this genus of plant exhibits regioselective control over C8–C8′ radical coupling of isoeugenol and diastereoselective control of subsequent C2–C7′ bond formation *in vivo*.[6a] However, the biomimetic synthesis of aryltetralins such as galbulin[5b,c] (**3**) by radical-cation-initiated Diels–Alder reaction of methylisoeugenol was unsuccessful.[6b] Thus, chemical synthesis of this typical THN molecule was achieved, *via* various approaches including Zr-mediated cyclization of a 1,7-diene,[7a] acid-catalyzed cyclization of diethyl *E*,*E*-dibenzylidenesuccinate[7b] and organocatalytic domino Michael–Michael–aldol condensation[7c] as the key steps. Herein, we disclose a distinctive strategy featuring unprecedented C1–C7 disconnection (Scheme 1b) for (±)-7,8-dehydrogalbulin [*i.e.*, cyclogalgravin[5a,i] (**2**)]. This aryltetralene is identified as a common intermediate[8] for other aryltetralones and aryltetralins [(**3–9**)], and could be available by the key diastereoselective dehydrative cyclization of the corresponding precursor derived from the neolignan (±)-kadangustin J (**1**) that was isolated from a different plant *Kadsura angustifolia* (Lem.) A. C. Smith.[9] The establishment of acyclic stereogenic centers at C8 and C8′ in **1** could be guaranteed through previously adopted Ueno–Stork radical cyclization/oxidation and subsequent alkylation reactions.[4] With sufficient quantities of (±)-cyclogalgravin (**2**) as a linchpin in hand, the collective synthesis[10] of stereodivergent 2,7′-cyclolignans (**3–9**) with *anti–anti* or (*anti–*)*syn–anti* arrangement of substituents in the THN skeleton could be implemented through a series of functional group conversions including redox reactions. In particular, the first syntheses of (±)-8,8′-*epi*-aristoligone (**5**), (±)-8′-*epi*-aristoligone (**7**), (±)-8′-*epi*-8-OH-aristoligone (**8**) and (±)-8′-*epi*-aristoligol (**9**) were accomplished during this endeavor, and their structures and relative configurations are confirmed accordingly.

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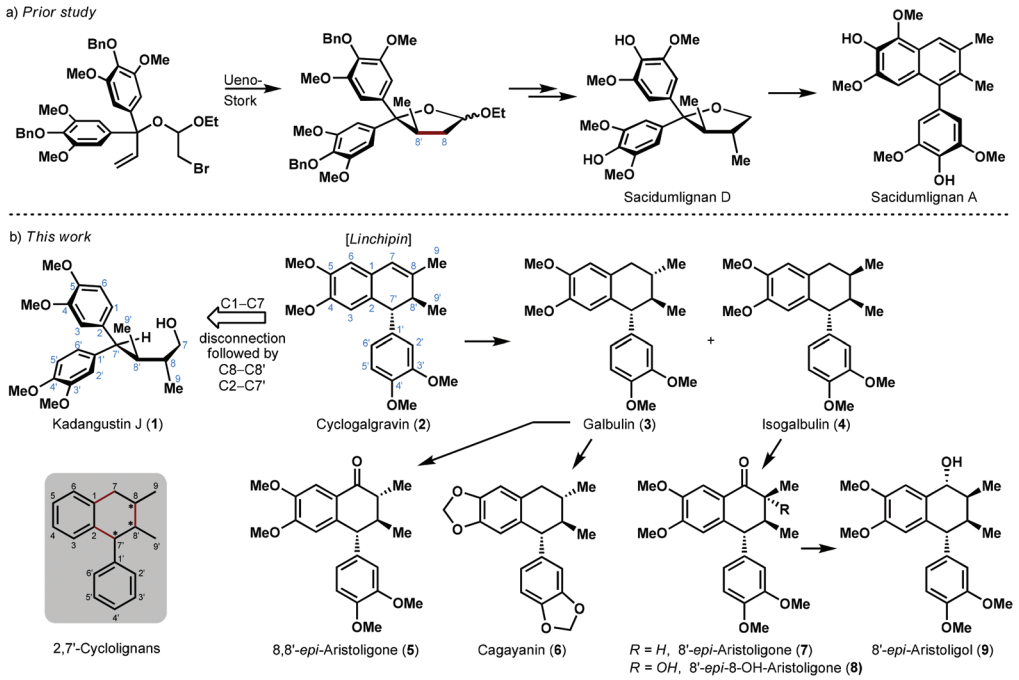
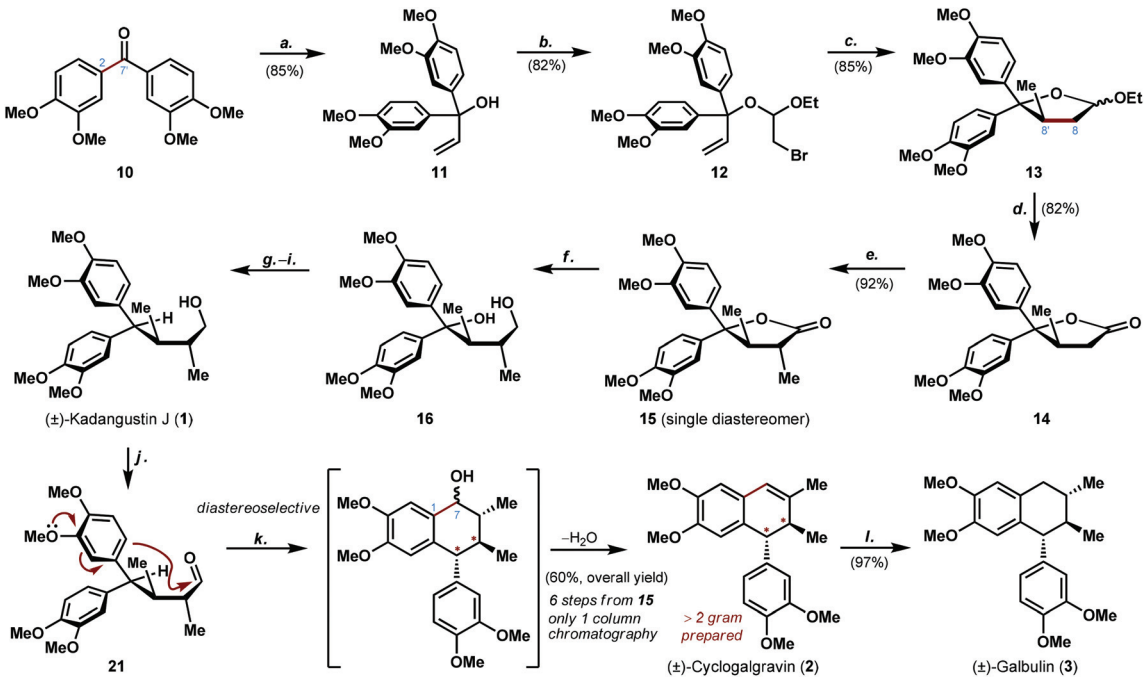


Scheme 1 Synthetic plan of 2,7′-cyclolignans and their correlation.



Scheme 2 Total syntheses of (±)-cyclogalgravin and (±)-galbulin *via* (±)-kadangustin J. *Reagents and conditions*: (a) vinylmagnesium bromide (1.1 equiv.), THF, 0 °C to rt, overnight, 85%; (b) Br_2 (8.0 equiv.), ethyl vinyl ether (10.0 equiv.), CH_2Cl_2, −78 °C, 30 min; then alcohol **11** (1.0 equiv.), *N*,*N*-dimethylaniline (15.0 equiv.), −78 to 0 °C, 2 h, then 15 °C, 10 h, 82%; (c) $(TMS)_3SiH$ (2.0 equiv.), AIBN (0.2 equiv.), PhMe, 90 °C, 2 h, 85% (d.r. = 2.2 : 1); (d) *m*-CPBA (2.0 equiv.), $BF_3{\cdot}Et_2O$ (1.5 equiv.), CH_2Cl_2, 0 °C, 20 min, 82%; (e) LiHMDS (3.0 equiv.), THF, −78 °C, 0.5 h, then MeOTf (3.0 equiv.), −78 °C, 3 h, 92%; (f) $LiAlH_4$ (2.0 equiv.), THF, 0 °C, 20 h; (g) TBDPSCl (1.1 equiv.), imidazole (2.0 equiv.), DMF, 0 °C to rt, 12 h; (h) Et_3SiH (5.0 equiv.), $BF_3{\cdot}Et_2O$ (2.0 equiv.), CH_2Cl_2, 0 °C, 20 min; (i) TBAF (5.0 equiv.), THF, 30 °C, 16 h; (j) IBX (1.2 equiv.), EtOAc, reflux, 4 h; (k) TsOH (0.2 equiv.), toluene, rt, 15 min, 60% (6 steps from **15**); (l) H_2 (balloon), 5% Pd/C, EtOH, 0 °C, 10 min, 97%.

Results and discussion

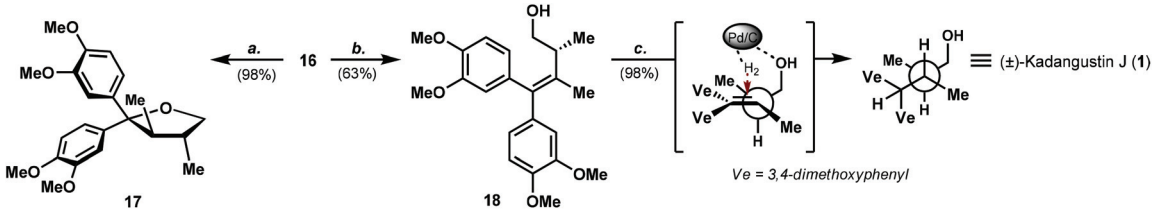
Guided by the above analysis, we started total syntheses of (±)-galbulin (**3**) *via* (±)-kadangustin J (**1**) and then (±)-cyclogalgravin (**2**) (Scheme 2). Upon subjection to aryl lithium reagent generated *in situ* from commercially available 4-bromoveratrole with *n*-BuLi at −78 °C, veratraldehyde could be smoothly transformed into diaryl carbinol in 84% isolated

yield on the deca-gram scale (see the Experimental section) with the construction of the C2–C7′ bond. Sufficient amounts of diveratryl ketone **10** resulting from oxidation could be converted to *gem*-diveratryl allyl alcohol **11** in 87% yield by the addition of vinylmagnesium bromide. The access to β-bromo acetal **12** with ethyl vinyl ether under our previous optimized conditions[4] proved to be smooth, and the desired Ueno–Stork radical cyclization precursor **12** could be obtained in 82% yield. The standard conditions (Bu_3SnH, AIBN, Δ) allowed the desired cyclization to proceed smoothly, affording cyclic acetal **13** as a mixture of inconsequential diastereomers (d.r. = 2.1 : 1) in 92% yield and gram-scale. This step for the construction of the C8–C8′ bond also easily took place under the less toxic $(TMS)_3SiH$/AIBN conditions,[11] and the desired **13** could be isolated in 85% yield as well. Oxidation of cyclic acetal **13** mediated by *m*-CPBA and $BF_3{\cdot}Et_2O$[12] can provide γ-lactone **14** in 82% isolated yield under carefully controlled conditions due to the existence of highly electron-donating aromatic rings. C8 methylation of γ-lactone **14** occurred with high diastereoselectivity, delivering **15** as a single diastereomer in 92% isolated yield under the shown conditions. The complete reduction of lactone **15** by $LiAlH_4$ afforded diol **16** in 95% yield, which set the stage for the synthesis of (±)-kadangustin J (**1**).

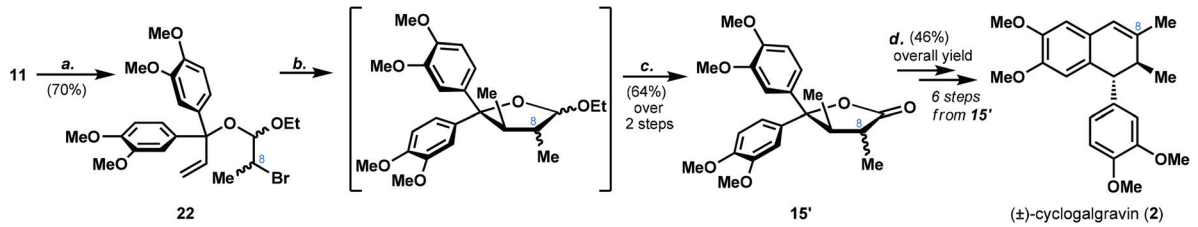
The initially attempted direct access to (±)-kadangustin J (**1**) was by chemoselective reduction of the tertiary alcohol group in **16** promoted by the combination of Et_3SiH and $BF_3{\cdot}Et_2O$.[13] Disappointingly, undesired tetrahydrofuran **17** was instead obtained in 98% yield (Scheme 3), which could be attributed to a more favorable intramolecular trap of the resulting benzylic carbonium by the primary alcohol group rather than the intermolecular trap from the hydride under this reductive deoxygenation condition. Thus, diol **16** was first converted to homoallylic alcohol **18** through selective dehydration under concentrated HCl conditions.[14] We were then pleased to find that the subsequent Pd/C-catalyzed, hydroxyl-directed hydrogenation[15] of this tetrasubstituted alkene proceeded with complete stereocontrol, and the desired (±)-kadangustin J (**1**) was obtained as a sole diastereoisomer in nearly quantitative yield. The NMR spectroscopic data of the synthetic sample are identical to those published for this natural product[9] and in the only previous synthesis[16] (see Table S1†) where the aza-Claisen rearrangement was utilized to establish the requisite *anti*-dimethyl configuration at C8 and C8′ stereocenters.

The alternative pathway for (±)-kadangustin J (**1**) that featured the retention of the original C8′ stereocenter, is continuously illustrated in Scheme 2. So, diol **16** was first selectively protected as its mono-silyl ether **19** in which the tertiary alcohol group was then removed by Et_3SiH without accident followed by deprotection of the resulting TBDPS ether **20**, to give **1** in 92% yield over four steps (from **15**) as well. With aldehyde **21**, generated from oxidation of **1** by IBX, in hand, the designed intramolecular Friedel–Crafts type,[17] dehydrative cyclization reaction[17a,b] was evaluated. To our delight, this key cascade triggered by the catalytic amount of TsOH demonstrated excellent diastereotopic differentiation of the veratryl group (*anti*-relationship with Me around dihydronaphthalene backbone) with concomitant construction of the C1–C7 bond, and eventually (±)-cyclogalgravin (**2**) with matched spectra data (see Table S2†)[5a,i,18] was produced in 66% yield over two steps. It is noteworthy that the relevant but more sophisticated spirocyclization catalyzed by palladium(0) has also been observed recently during the elegant synthesis of sesquilignan Tatanans B and C by Zakarian and co-workers.[19] Importantly, each step in the whole sequence (from **15** to **2**) was run in gram-scale, and more than 2 grams of (±)-cyclogalgravin (**2**) as a linchpin could be prepared in a single batch after only ONE column chromatography purification, which therefore enables the subsequent collective synthesis of stereodivergent 2,7′-cyclolignans (**3**–**9**) with three and four consecutive all-carbon stereocenters in the THN skeleton.

Early-stage installation of the C8 methyl group was also investigated (Scheme 4) regardless of the control of its stereochemistry since this stereogenic center will be destroyed in a later conversion to (±)-cyclogalgravin (**2**). Accordingly, commercially available ethyl propenyl ether (*E* : *Z* = 1.7 : 1) was utilized to give β-bromo acetal **22** as a mixture of diastereomers in 70% yield following the similar procedure for **12**. The analogous Ueno–Stork cyclization of **22** proceeded smoothly, and the generated cyclic acetal was subjected to oxidation with *m*-CPBA, affording **15′** in 64% yield over two steps. Following similar transformations starting from **15**, γ-lactone **15′** as a mixture of two inconsequential diastereoisomers could be converted to **2** indeed, and no other isomer can be detected, suggesting that the C8′ rather than the C8 methyl group dictates the *anti*-orientation of the C7′ veratryl group. Eventually, stereoselective hydrogenation of **2** mediated by 5% Pd/C (Scheme 2) can almost quantitatively lead to (±)-galbulin (**3**), whose NMR spectroscopic data well agree with those reported for this natural product[5c] and in the previous total syntheses.[7] Moreover, the structure assignment of synthetic (±)-galbulin (**3**) was



Scheme 3 Other approach to (±)-kadangustin J. *Reagents and conditions*: (a) Et_3SiH (5.0 equiv.), $BF_3{\cdot}Et_2O$ (2.0 equiv.), CH_2Cl_2, 0 °C, 2 min, 98%; (b) HCl (conc.), EtOH, reflux, 3 h, 63%; (c) H_2 (balloon), 5% Pd/C, EtOH, 16 °C, 1 h, 98%.



Scheme 4 Other approach to (±)-cyclogalgravin. *Reagents and conditions*: (a) Br_2 (8.0 equiv.), ethyl propenyl ether (10.0 equiv.), CH_2Cl_2, −78 °C, 30 min; then alcohol **11** (1.0 equiv.), *N*,*N*-dimethylaniline (15.0 equiv.), −78 to 0 °C, 2 h, then 15 °C, 10 h, 70% (d.r. = 2.1 : 1); (b) $(TMS)_3SiH$ (2.0 equiv.), AIBN (0.2 equiv.), PhMe, 90 °C, 2 h; (c) *m*-CPBA (2.0 equiv.), $BF_3{\cdot}Et_2O$ (1.5 equiv.), CH_2Cl_2, rt, 10 min, 64% over 2 steps (d.r. = 1.5 : 1); (d) as **15**→**2** in Scheme 2.

unambiguously confirmed by its single-crystal structure analysis (Fig. 1).[20]

At this stage, diastereoselective hydrogenation of (±)-cyclogalgravin (**2**) was further investigated (Scheme 5). The heterogeneous conditions with Pd/C favor the formation of (±)-galbulin (**3**), and higher diastereoselectivities could be observed in low temperature. 5% Pd/C provided superior results compared to 10% Pd/C under identical conditions, thus this protocol was applied in the synthesis of (±)-galbulin (**3**) (*vide supra*). Then, diastereodivergent hydrogenation of this unfunctionalized trisubstituted olefin in **2** through tuning conditions was also studied, in order to afford (±)-isogalbulin (**4**), which could be converted into subsequent (±)-8′-*epi*-aristoligone (**7**) and (±)-8′-*epi*-8-OH-aristoligone (**8**) with common *syn*–*anti* substituents in the tetrahydronaphthalene (THN) framework. Adams catalyst (PtO_2) proved to be a choice, and the ratio of (±)-galbulin (**3**) resulting from this hydrogenation condition decreased largely. Further optimization regarding solvent and temperature led to no significant improvement. Homogeneous hydrogenation conditions such as the utilization of Wilkinson catalyst [$RhCl(PPh_3)_3$] also provided no superior results. In any case, large scale hydrogenation under PtO_2 can provide the mixture of **3** and **4**, from which the desired (±)-isogalbulin (**4**) can be separated by fractional recrystallization in EtOAc and pentane (1 : 10), demonstrating identical spectroscopic data with those reported previously (see Table S3†).[5e,7a]

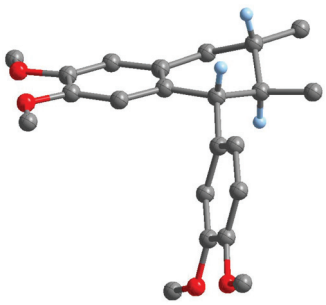
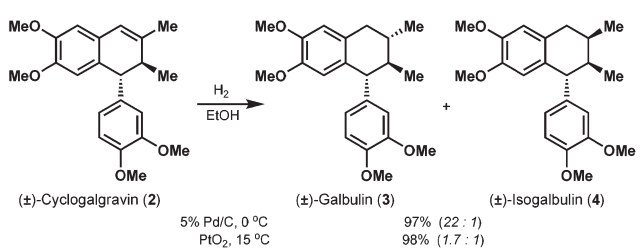


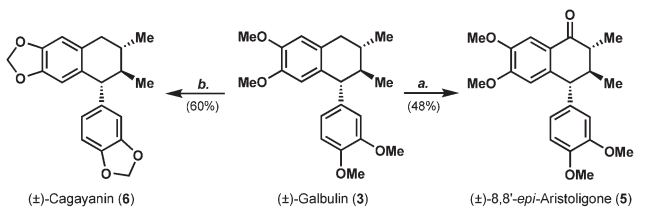
Fig. 1 X-ray crystal structure of (±)-galbulin (**3**).



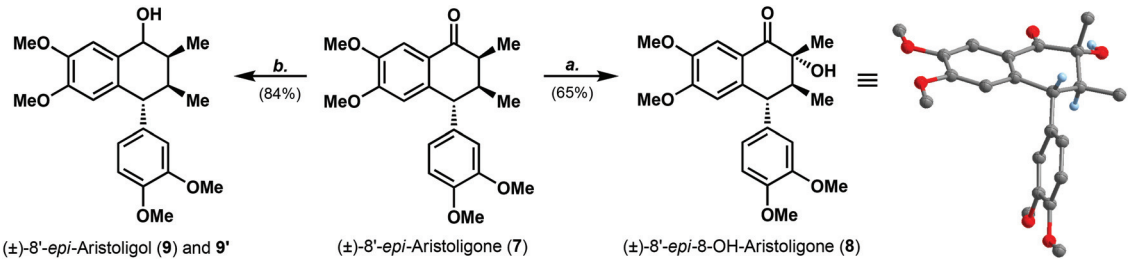
Scheme 5 Diastereoselective hydrogenation of (±)-cyclogalgravin.

The next focus was the syntheses of (±)-8,8′-*epi*-aristoligone (**5**) and (±)-cagayanin (**6**) with common *anti*–*anti* substituents appended to the THN framework, *via* (±)-galbulin (**3**) through C–H oxidation at C7 and the conversion of methoxy to methylenedioxy group, respectively. As shown in Scheme 6, benzylic C–H oxidation at C7 in **3** was achieved under the conditions of PCC and Celite,[21a] and the desired (±)-8,8′-*epi*-aristoligone (**5**) was obtained in 48% isolated yield. The NMR spectroscopic data of synthetic **5** well agree with those reported for this natural product (see Table S4†).[5h] Other oxidation methods such as CrO_3/3,5-dimethylpyrazole[21b,c] and CrO_3/Bu_4NIO_4 [21d] provided inferior results. The global cleavage of methoxy groups in **3** with BBr_3 and subsequent double methylenation of the resulting bis-catechol with CH_2Br_2 under basic conditions afforded (±)-cagayanin (**6**) in 60% yield over two steps. The NMR spectroscopic data of the synthetic **6** are consistent with those reported for the natural product[5f,g] and in the sole previous synthesis (see Table S5†).[7b,22] It is noteworthy that the present route is featured in step-economic, late-stage functional group conversion instead of previous parallel synthesis[7b] starting from the respective precursor with methylenedioxy group, that is the usual strategy utilized to access this kind of lignans.

Similar to **5**, regioselective C–H oxidation of (±)-isogalbulin (**4**) (see the Experimental section) can give rise to (±)-8′-*epi*-aristoligone (**7**), which was identical spectroscopically to the



Scheme 6 Conversion of (±)-galbulin into (±)-8,8′-*epi*-aristoligone and (±)-cagayanin. *Reagents and conditions*: (a) PCC (3.0 equiv.), Celite, benzene, 90 °C, 4 h, 48%; (b) (1) BBr_3 (6.0 equiv.), CH_2Cl_2, −78 °C, 20 min; (2) CH_2Br_2 (8.5 equiv.), NaOH (11.0 equiv.), DMSO, 35 °C, 2.0 h, 60%, over two steps.



(±)-8′-*epi*-Aristoligol (**9**) and **9′** (±)-8′-*epi*-Aristoligone (**7**) (±)-8′-*epi*-8-OH-Aristoligone (**8**)

Scheme 7 Conversion of (±)-8′-*epi*-aristoligone into (±)-8′-*epi*-8-OH-aristoligone and (±)-8′-*epi*-aristoligol. *Reagents and conditions*: (a) KHMDS (5.0 equiv.), THF, −78 °C, 0.5 h, then (+)-(2*R*,8a*S*)-camphorylsulfonyl oxaziridine (4.0 equiv.), −78 °C to rt, 4 h, 65% (d.r. = 20 : 1); (b) $NaBH_4$ (5.0 equiv.), MeOH, 0 °C, 15 min, 84% (d.r. = 1.9 : 1).

isolation report (see Table S6†)[5h] and paved the way for the syntheses of (±)-8′-*epi*-8-OH-aristoligone (**8**) and (±)-8′-*epi*-aristoligol (**9**) with two *syn*-methyls. After careful optimization, highly diastereoselective (d.r. = 20 : 1) hydroxylation of ketone **7** could be realized in 65% yield under the condition of KHMDS and Davis reagent [(+)-(2*R*,8a*S*)-camphorylsulfonyl oxaziridine,[23] Scheme 7], thus completing the first total synthesis of this natural product. The NMR spectroscopic data of the synthetic **8** are matched with those reported in the isolation literature (see Table S7†),[5i,24] and the structure assignment of synthetic sample was verified again by its single-crystal structure analysis.[20] Finally, the synthesis of (±)-8′-*epi*-aristoligol (**9**) with 4 continuous stereocenters was also achieved in 29% yield from **7** by $NaBH_4$ reduction, accompanied by the formation of its 7-epimer (**9′**) in 55% yield. The synthetic **9** displayed identical spectral properties to those reported for this natural product (see Table S8†).[5i]

Conclusions

In summary, we have demonstrated the application of the Ueno–Stork radical cyclization strategy in the stereoselective synthesis of neolignan (±)-kadangustin J (**1**), which can be converted to (±)-cyclogalgravin (**2**) through the facile dehydrative cyclization reaction with excellent diastereotopic differentiation of the veratryl group. Starting from (±)-cyclogalgravin (**2**) as a relay linchpin, collective synthesis of stereodivergent 2,7′-cyclolignans (**3–9**) with an *anti–anti* or (*anti–*)*syn–anti* arrangement of substituents in the tetrahydronaphthalene skeleton was stereoselectively achieved through a series of redox reactions. These molecules (**1–9**), albeit from different plant sources, demonstrate interesting and non-biomimetic correlation by chemical transformations in the laboratory. The current result would be valuable in accessing other members of the 2,7′-cyclolignan family.

Experimental section

General

For product purification by flash column chromatography, silica gel (200–300 mesh) and petroleum ether (bp. 60–90 °C) were used. All solvents were purified and dried by standard techniques, and distilled prior to use. All experiments were conducted under an argon or nitrogen atmosphere in an oven-dried or flame-dried glassware with magnetic stirring, unless otherwise specified. NMR spectra were measured using Bruker AM-400 and 600 MHz instruments. All ^1H chemical shifts (δ) are relative to residual $CHCl_3$ (7.26 ppm), and all ^{13}C chemical shifts (δ) are relative to $CHCl_3$ (77.00 ppm). Mass spectra data were measured using a Bruker Daltonics APEX II 47e FT-ICR spectrometer with ESI or APCI positive ion mode. Infrared spectra were recorded using a Nicolet FT-170SX spectrophotometer. The X-ray diffraction data of **3** and **8** were measured using a Bruker SMART Apex CCD area detector diffractometer with the graphite-monochromated Mo-Kα radiation source (λ = 0.71073 Å).

Bis(3,4-dimethoxyphenyl)methanone (10). In a 200 mL, two-necked, round-bottom flask, 4-bromoveratrole (10.85 g, 50 mmol) was dissolved in anhydrous THF (100 mL) and cooled to −78 °C. The resulting solution was treated with *n*-BuLi (2.5 M in THF, 22.0 mL, 55 mmol, 1.1 equiv.) dropwise *via* a syringe over a 15 min period and the mixture was stirred for 0.5 h at this temperature followed by the addition of the solution of veratraldehyde (9.97 g, 60 mmol, 1.2 equiv.) in THF (40 mL). The reaction mixture was stirred for 20 min at −78 °C, then allowed to slowly warm to room temperature, and stirred further for 4 h. The reaction was carefully quenched by saturated aqueous NH_4Cl (5 mL), and extracted with CH_2Cl_2 (2 × 150 mL). The combined organic layers were separated and washed with water (3 × 50 mL) and brine (50 mL) respectively, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The resulting crude residue was purified by flash column chromatography (petroleum ether–EtOAc = 10 : 1 → 2 : 1 → 1 : 1) on silica gel to afford the desired diarylcarbinol (14.0 g, 92% yield) as a colorless oil. R_f = 0.30 (petroleum ether–EtOAc = 1 : 1); IR (film): ν_{max} = 3508, 3066, 2999, 2955, 2936, 2835, 1593, 1513, 1463, 1417, 1259, 1137, 1027, 914, 860, 744, 643 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 6.91 (d, J = 1.6 Hz, 2H), 6.85 (dd, J = 1.6, 8.0 Hz, 2H), 6.80 (d, J = 8.0 Hz, 2H), 5.70 (d, J = 2.4 Hz, 1H), 3.84 (s, 6H), 3.82 (s, 6H), 2.56 (d, J = 2.8 Hz, 1H, –O*H*) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 148.8 (2C), 148.2 (2C), 136.6 (2C), 118.7 (2C), 110.8 (2C), 109.7 (2C), 75.5, 55.8 (2C), 55.7 (2C) ppm; HRMS (ESI): calcd for $C_{17}H_{19}O_4^+$ [M − OH − e]$^+$: 287.1278, found: 287.1273. To a

stirred solution of the above diarylcarbinol (14.0 g, 46.0 mmol) in CH_2Cl_2 (100 mL) was added PDC (25.9 g, 69.0 mmol, 1.5 equiv.) portionwise at 0 °C. The resulting mixture was stirred further for 24 h at 15 °C, and then filtered and concentrated under reduced pressure to afford the desired **10** (12.8 g, 92% yield) as a white solid. This resulting material could be used directly for the next Grignard addition reaction without further purification. R_f = 0.47 (petroleum ether–EtOAc = 1 : 1); Mp. 141–142 °C; IR (film): ν_{max} = 3081, 3006, 2961, 2937, 2838, 1643, 1596, 1514, 1463, 1417, 1337, 1268, 1172, 1137, 1024, 915, 878, 731, 623 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.44 (d, J = 2.0 Hz, 2H), 7.39 (dd, J = 2.0 Hz, 8.4 Hz, 2H), 6.91 (d, J = 8.4 Hz, 2H), 3.97 (s, 6H), 3.95 (s, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 194.4, 152.6 (2C), 148.9 (2C), 130.8 (2C), 124.7 (2C), 112.3 (2C), 109.7 (2C), 56.0 (4C) ppm; HRMS (ESI): calcd for $C_{17}H_{19}O_5^+$ $[M + H]^+$: 303.1227, found: 303.1223.

1,1-Bis(3,4-dimethoxyphenyl)prop-2-en-1-ol (11). To a stirred solution of diarylketone **10** (12.8 g, 42.4 mmol) in anhydrous THF (75 mL) was added vinylmagnesium bromide (0.7 M in THF, 66.6 mL, 46.6 mmol, 1.1 equiv.) dropwise (1 drop per second) *via* a syringe at 0 °C. The resulting mixture was warmed to room temperature and further stirred for 12 h. The reaction was carefully quenched by saturated aqueous NH_4Cl (10 mL), and extracted with EtOAc (2 × 100 mL). The combined organic layers were separated and washed with water (3 × 50 mL) and brine (50 mL), respectively, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The resulting crude residue was purified by flash column chromatography (petroleum ether–EtOAc = 2 : 1) on silica gel to afford the desired **11** (11.9 g, 85% yield) as a white solid. R_f = 0.23 (petroleum ether–EtOAc = 2 : 1); Mp. 111–112 °C; IR (film): ν_{max} = 3503, 3082, 3002, 2934, 2836, 1595, 1511, 1463, 1412, 1329, 1257, 1140, 1027, 917, 862, 807, 764, 732, 646 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 6.96 (d, J = 2.0 Hz, 2H), 6.86 (dd, J = 2.0, 8.4 Hz, 2H), 6.80 (d, J = 8.4 Hz, 2H), 6.45 (dd, J = 10.4, 17.0 Hz, 1H), 5.30 (dd, J = 0.8, 17.2 Hz, 1H), 5.29 (dd, J = 0.8, 10.4 Hz, 1H), 3.87 (s, 6H), 3.82 (s, 6H), 2.24 (s, 1H, –O*H*) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 148.6 (2C), 148.2 (2C), 143.7, 138.4 (2C), 119.3 (2C), 113.6, 110.4 (4C), 79.2, 55.8 (4C) ppm; HRMS (ESI): calcd for $C_{19}H_{22}O_5Na^+$ $[M + Na]^+$: 353.1359, found: 353.1355.

4,4′-(1-(2-Bromo-1-ethoxyethoxy)prop-2-ene-1,1-diyl)bis-1,2-dimethoxybenzene) (12). In a 200 mL round-bottom flask, Br_2 (3.0 mL, 58 mmol, 8.0 equiv.) was dissolved in anhydrous CH_2Cl_2 (80 mL) and cooled to −78 °C. To the resulting solution was added ethyl vinyl ether (7.0 mL, 72.7 mmol, 10.0 equiv.) dropwise over a 5 min period, and the mixture was stirred for 30 min at −78 °C. To this system was added *via* a cannula the solution of allyl alcohol **11** (2.40 g, 7.26 mmol) and *N*,*N*-dimethylaniline (13.8 mL, 108.9 mmol, 15.0 equiv.) in CH_2Cl_2 (20 mL) at −78 °C. The resulting mixture was gradually warmed to 0 °C over a 2 h period and further stirred for 10 h at 15 °C. Eventually, the reaction mixture was directly diluted with CH_2Cl_2 (200 mL). The combined organic layers were separated and washed with 10% HCl (3 × 30 mL), water (3 × 30 mL) and brine (30 mL) respectively, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The resulting crude residue was purified by flash column chromatography (petroleum ether–EtOAc = 4 : 1) on basic Al_2O_3 to afford the desired **12** (2.87 g, 82% yield) as a colorless oil. R_f = 0.46 (petroleum ether–EtOAc = 2 : 1); IR (film): ν_{max} = 3084, 2973, 2935, 2835, 1634, 1601, 1511, 1463, 1412, 1333, 1260, 1143, 1028, 914, 865, 807, 765, 732, 648 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 6.95–6.90 (m, 3H), 6.83–6.78 (m, 3H), 6.61 (dd, J = 10.8, 17.2 Hz, 1H), 5.36 (dd, J = 0.8, 10.8 Hz, 1H), 4.95 (dd, J = 1.2, 17.2 Hz, 1H), 4.76 (t, J = 5.6 Hz, 1H), 3.90 (s, 3H), 3.88 (s, 3H), 3.81 (s, 6H), 3.49–3.40 (m, 2H), 3.40–3.33 (m, 2H), 1.10 (t, J = 7.2 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 148.4 (2C), 148.1 (2C), 141.1, 136.4, 135.4, 121.0, 120.6, 117.9, 111.9, 111.7, 109.9, 109.8, 96.7, 85.3, 60.4, 55.9, 55.80, 55.77 (2C), 32.8, 15.0 ppm; HRMS (ESI): calcd for $C_{23}H_{29}O_6{}^{79}BrNa^+$ $[M + Na]^+$: 503.1040, found: 503.1033.

2,2-Bis(3,4-dimethoxyphenyl)-5-ethoxy-3-methyltetrahydrofuran (13). In a 50 mL, two-necked, round-bottom flask, α-bromo acetal **12** (67 mg, 0.14 mmol) was dissolved in anhydrous toluene (6 mL) followed by the addition of the solution of $(TMS)_3SiH$ (90 μL, 0.28 mmol, 2.0 equiv.) and AIBN (5 mg, 0.03 mmol, 0.2 equiv.) in toluene (2 mL) dropwise under argon. The resulting mixture was heated to 90 °C and stirred for 2 h. Then the reaction mixture was cooled to room temperature and directly concentrated under reduced pressure. The resulting crude residue was diluted with CH_2Cl_2 (20 mL), and washed with water (3 × 5 mL) and brine (5 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The resulting crude residue was purified by flash column chromatography (petroleum ether–EtOAc = 10 : 1) on silica gel to afford the mixture **13** of two inconsequential diastereoisomers (47 mg, 85% yield, d.r. = 2.2 : 1) as a colorless oil. R_f = 0.42 (petroleum ether–EtOAc = 2 : 1); IR (film): ν_{max} = 3068, 2967, 2934, 2834, 1604, 1590, 1511, 1463, 1410, 1325, 1259, 1140, 1028, 978, 919, 805, 763 cm^{-1}; (*major isomer*) ^1H NMR (400 MHz, $CDCl_3$): δ = 7.04 (dd, J = 1.6, 8.4 Hz, 1H), 6.99 (d, J = 1.6 Hz, 1H), 6.82 (d, J = 8.4 Hz, 1H), 6.75 (d, J = 8.4 Hz, 1H), 6.72 (d, J = 2.0 Hz, 1H), 6.63 (dd, J = 2.0, 8.4 Hz, 1H), 5.42 (d, J = 4.4 Hz, 1H), 3.89 (s, 3H), 3.84 (s, 3H), 3.82 (s, 3H), 3.80 (s, 3H), 3.74–3.65 (m, 1H), 3.50–3.42 (m, 1H), 3.31–3.20 (m, 1H), 2.10 (dd, J = 6.4, 12.4 Hz, 1H), 1.86 (ddd, J = 5.2, 10.4, 12.6 Hz, 1H), 1.02 (t, J = 6.8 Hz, 3H), 0.82 (d, J = 6.8 Hz, 3H), ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 148.4, 147.9, 147.7, 147.5, 140.1, 136.7, 119.4, 117.8, 110.8, 110.5, 110.1, 109.8, 102.5, 90.5, 62.4, 55.7 (4C), 40.9, 39.8, 17.3, 15.0 ppm; HRMS (ESI): calcd for $C_{23}H_{31}O_6^+$ $[M + H]^+$: 403.2115, found: 403.2120.

(Alternative gram-scale procedure for **13**) In a 250 mL, two-necked, round-bottom flask, α-bromo acetal **12** (2.45 g, 5.1 mmol) was dissolved in anhydrous toluene (80 mL) followed by the addition of *n*-Bu_3SnH (2.1 mL, 7.65 mmol, 1.5 equiv.) and AIBN (167 mg, 1.02 mmol, 0.2 equiv.) under argon. The resulting mixture was heated to 85 °C and stirred for 4 h. Then the reaction mixture was cooled to room temperature and directly concentrated under reduced pressure. The resulting crude residue was dissolved in Et_2O (20 mL) and 30% aqueous $KF{\cdot}2H_2O$ (30 mL) was added. The mixture was stirred

for 0.5 h and the *n*-Bu_3SnF precipitate was filtered. The filtrate was extracted with CH_2Cl_2 (2 × 50 mL), and the combined organic layers were washed with water (3 × 20 mL) and brine (20 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The resulting crude residue was purified by flash column chromatography (petroleum ether–EtOAc = 10 : 1) on silica gel to afford **13** (1.89 g, 92% yield, d.r. = 2.1 : 1).

5,5-Bis(3,4-dimethoxyphenyl)-4-methyldihydrofuran-2(3*H*)-one (14). To a stirred solution of acetal **13** (1.89 g, 4.7 mmol) in CH_2Cl_2 (10 mL) was added *m*-CPBA (77%, 2.11 g, 9.4 mmol, 2.0 equiv.) at room temperature followed by the addition of $BF_3{\cdot}Et_2O$ (0.88 mL, 7.05 mmol, 1.5 equiv.). After 20 min, the reaction mixture was quenched by saturated aqueous Na_2SO_3 (5 mL) and extracted with CH_2Cl_2 (100 mL). The organic layers were washed with saturated aqueous $NaHCO_3$ (2 × 20 mL), water (3 × 20 mL) and brine (30 mL), then dried over $MgSO_4$, filtered and concentrated under reduced pressure. The resulting crude residue was purified by flash column chromatography (petroleum ether–EtOAc = 4 : 1) on silica gel to afford the desired **14** (1.43 g, 82% yield) as a colorless oil. R_f = 0.32 (petroleum ether–EtOAc = 1 : 1); IR (film): ν_{max} = 2924, 2853, 1779, 1642, 1594, 1514, 1462, 1414, 1264, 1144, 1025, 927, 806, 765 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.10 (dd, J = 2.0, 8.4 Hz, 1H), 6.91 (d, J = 2.0 Hz, 1H), 6.85 (d, J = 8.4 Hz, 1H), 6.80 (d, J = 8.4 Hz, 1H), 6.78 (d, J = 2.0 Hz, 1H), 6.74 (dd, J = 2.0, 8.4 Hz, 1H), 3.89 (s, 3H), 3.86 (s, 3H), 3.83 (s, 3H), 3.82 (s, 3H), 3.36 (sext, J = 6.8 Hz, 1H), 2.74 (dd, J = 7.2, 17.2 Hz, 1H), 2.33 (dd, J = 4.8, 17.2 Hz, 1H), 0.91 (d, J = 7.2 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 176.0, 149.0, 148.8, 148.4, 148.1, 135.3, 133.2, 118.1, 117.3, 110.6, 110.4, 110.2, 109.0, 92.2, 55.8 (2C), 55.7 (2C), 38.1, 37.6, 17.1 ppm; HRMS (ESI): calcd for $C_{21}H_{25}O_6^+$ $[M + H]^+$: 373.1646, found: 373.1649.

(3*R,4*R**)-5,5-Bis(3,4-dimethoxyphenyl)-3,4-dimethyldihydrofuran-2(3*H*)-one (15).** A 25 mL round-bottom flask was charged with LiHMDS (1.07 M in THF, 2.8 mL, 2.94 mmol, 3.0 equiv.) under argon and the resulting solution was cooled to −78 °C. To this precooled base, a solution of γ-lactone **14** (365 mg, 0.98 mmol) in THF (10 mL) was added dropwise *via* a syringe and stirring was continued for 0.5 h at this temperature. Then resulting enolate was treated with MeOTf (0.33 mL, 2.94 mmol, 3.0 equiv.) at −78 °C, and the methylation reaction was continued for 3 h at the same temperature; it was then quenched by saturated aqueous NH_4Cl (2 mL). The reaction mixture was allowed to warm to room temperature, diluted with EtOAc (30 mL) and poured into a separatory funnel. The combined organic layers were separated and washed with water (3 × 10 mL) and brine (10 mL) respectively, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The resulting crude residue was purified by flash column chromatography (petroleum ether–EtOAc = 2 : 1) on silica gel to afford the desired **15** (348 mg, 92% yield) as a white solid. R_f = 0.54 (petroleum ether–EtOAc = 1 : 1); Mp. 121–122 °C; IR (film): ν_{max} = 2965, 2934, 2837, 1770, 1595, 1514, 1461, 1411, 1329, 1259, 1212, 1145, 1026, 980, 806, 732 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.06 (dd, J = 2.4, 8.4 Hz, 1H), 6.86 (d, J = 8.4 Hz, 1H), 6.85 (d, J = 2.0 Hz, 1H), 6.79 (d, J = 8.4 Hz, 1H), 6.63 (dd, J = 2.0, 8.4 Hz, 1H), 6.55 (d, J = 2.4 Hz, 1H), 3.90 (s, 3H), 3.86 (s, 3H), 3.79 (s, 3H), 3.77 (s, 3H), 2.89 (sext, J = 6.8 Hz, 1H), 2.39 (sext, J = 6.8 Hz, 1H), 1.27 (d, J = 7.2 Hz, 3H), 1.05 (d, J = 6.8 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 178.7, 149.0 (2C), 148.4, 148.3, 135.6, 132.6, 119.2, 117.9, 111.2, 110.4, 110.1, 109.9, 90.6, 55.9 (3C), 55.8, 46.2, 41.0, 16.0, 13.1 ppm; HRMS (ESI): calcd for $C_{22}H_{27}O_6^+$ $[M + H]^+$: 387.1802, found: 387.1808.

(2*R,3*R**)-1,1-Bis(3,4-dimethoxyphenyl)-2,3-dimethylbutane-1,4-diol (16).** To a stirred solution of γ-lactone **15** (3.75 g, 9.7 mmol) in anhydrous THF (80 mL) at 0 °C was added $LiAlH_4$ (737 mg, 19.4 mmol, 2.0 equiv.) portionwise. The reaction mixture was stirred for 20 h at this temperature and quenched carefully by water (10 mL) and aqueous NaOH (10%, 20 mL). After stirring for 30 min, the resulting precipitate was then filtered with a short plug of silica gel (elution with 200 mL of Et_2O) and the filtrate was extracted with Et_2O (100 mL). The combined organic layers were washed with water (3 × 30 mL) and brine (50 mL) respectively, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The resulting crude diol **16** (3.79 g) as a colorless oil could be used directly without further purification. The small amount of this sample was isolated for characterization. R_f = 0.23 (petroleum ether–EtOAc = 1 : 1); IR (film): ν_{max} = 3516, 3371, 2930, 2836, 1591, 1512, 1463, 1411, 1256, 1136, 1027, 860, 807, 763, 735 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.14 (d, J = 2.0 Hz, 1H), 7.07 (d, J = 2.0 Hz, 1H), 7.04 (dd, J = 2.0, 8.4 Hz, 2H), 6.79 (d, J = 8.4 Hz, 2H), 3.86 (s, 3H), 3.854 (s, 3H), 3.845 (s, 3H), 3.839 (s, 3H), 3.43 (br, 2H), 2.95 (q, J = 6.0 Hz, 1H), 2.26 (br, 1H, –O*H*), 1.88 (q, J = 6.8 Hz, 1H), 1.29 (br, 1H, –O*H*), 0.86 (d, J = 7.2 Hz, 3H), 0.83 (d, J = 7.2 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 148.44, 148.41, 147.29, 147.26, 140.0, 139.6, 117.9, 117.7, 110.6, 110.5, 109.5 (2C), 81.6, 67.4, 55.8 (2C), 55.7 (2C), 39.4, 35.4, 12.9, 9.4 ppm; HRMS (ESI): calcd for $C_{22}H_{29}O_5$ $[M - H_2O + H]^+$: 373.2010, found: 373.2004.

(2*R,3*R**)-4-(*tert*-Butyldiphenylsilyloxy)-1,1-bis(3,4-dimethoxyphenyl)-2,3-dimethylbutan-1-ol (19).** In a 100 mL, two-necked, round-bottom flask, the above crude diol **16** (3.79 g, 9.72 mmol) was dissolved in anhydrous DMF (40 mL) and cooled to 0 °C. Then imidazole (1.32 g, 19.4 mmol, 2.0 equiv.) was added and stirring was continued for 10 min followed by the addition of TBDPSCl (2.94 g, 10.7 mmol, 1.1 equiv.). The resulting mixture was warmed to 25 °C and stirred for 12 h. Eventually, the mixture was diluted with CH_2Cl_2 (200 mL) and poured into a separatory funnel. The organic layers were washed with water (10 × 30 mL) and brine (50 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The resulting crude tertiary alcohol **19** (5.8 g) as a colorless oil could be used directly without further purification. The small amount of this sample was isolated for characterization. R_f = 0.41 (petroleum ether–EtOAc = 1 : 1); IR (film): ν_{max} = 3536, 3070, 2955, 2931, 2857, 1590, 1512, 1463, 1411, 1256, 1136, 1111, 1079, 1029, 819, 763, 741, 704, 613 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.64 (t, J = 6.4 Hz, 4H), 7.42 (q, J = 7.2 Hz, 2H), 7.37 (t, J = 7.2 Hz, 4H), 7.09 (d, J = 2.8 Hz, 2H), 7.04 (d, J = 7.2 Hz, 2H), 6.80 (d, J = 8.0 Hz, 1H), 6.71 (d, J

= 9.2 Hz, 1H), 3.85 (s, 3H), 3.83 (s, 6H), 3.77 (s, 3H), 3.46–3.38 (m, 2H), 3.16 (q, J = 6.8 Hz, 1H), 2.19 (br, 1H, –O*H*), 2.07 (q, J = 6.8 Hz, 1H), 1.10 (s, 9H), 0.80 (d, J = 6.8 Hz, 3H), 0.76 (d, J = 6.8 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 148.5 (2C), 147.3 (2C), 140.7, 139.6, 135.6 (2C), 135.5 (2C), 133.7, 133.6, 129.7, 129.6, 127.7 (2C), 127.6 (2C), 118.1, 117.5, 110.6, 110.5, 109.4, 109.3, 81.7, 67.9, 55.8 (4C), 38.5, 34.7, 26.9 (3C), 19.3, 12.3, 8.5 ppm; HRMS (ESI): calcd for $C_{38}H_{48}O_6SiNa^+$ $[M + Na]^+$: 651.3112, found: 651.3101.

((2*R,3*S**)-4,4-Bis(3,4-dimethoxyphenyl)-2,3-dimethyl butoxy)-(*tert*-butyl)diphenylsilane (20).** To a stirred solution of the above tertiary alcohol **19** (5.8 g, 9.24 mmol) in CH_2Cl_2 (70 mL) was added Et_3SiH (7.4 mL, 46.2 mmol, 5.0 equiv.) at 0 °C followed by the addition of $BF_3{\cdot}Et_2O$ (2.3 mL, 18.5 mmol, 2.0 equiv.) dropwise. After 20 min, the reaction was quenched by saturated aqueous Na_2SO_3 (10 mL) and extracted with CH_2Cl_2 (200 mL). The organic layers were washed with water (3 × 30 mL) and brine (50 mL), then dried over Na_2SO_4, filtered and concentrated under reduced pressure. The resulting crude *O*-silyl ether **20** (5.6 g) as a colorless oil could be used directly without further purification. The small amount of this sample was isolated for characterization. R_f = 0.53 (petroleum ether–EtOAc = 1 : 1); IR (film): ν_{max} = 3066, 2957, 2930, 2857, 1590, 1513, 1463, 1262, 1143, 1111, 1078, 1029, 817, 742, 704 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.64 (t, J = 8.0 Hz, 4H), 7.41 (q, J = 7.2 Hz, 2H), 7.35 (t, J = 7.2 Hz, 4H), 6.91 (d, J = 8.4 Hz, 1H), 6.85 (d, J = 9.2 Hz, 1H), 6.84 (s, 2H), 6.80 (d, J = 9.2 Hz, 1H), 6.78 (d, J = 7.6 Hz, 1H), 3.86 (s, 3H), 3.84 (s, 3H), 3.83 (s, 3H), 3.78 (s, 3H), 3.54 (d, J = 11.6 Hz, 1H), 3.48 (d, J = 7.6 Hz, 2H), 2.88–2.81 (m, 1H), 1.93 (q, J = 7.2 Hz, 1H), 1.09 (s, 9H), 0.66 (d, J = 7.2 Hz, 3H), 0.63 (d, J = 6.8 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 148.9, 148.8, 147.2, 147.1, 138.1, 137.3, 135.6 (2C), 135.5 (2C), 134.0, 133.8, 129.6, 129.5, 127.60 (2C), 127.57 (2C), 119.7 (2C), 111.22 (2C), 111.18, 110.9, 67.1, 55.9, 55.8 (2C), 55.7 (2C), 35.4, 35.3, 26.9 (3C), 19.4, 11.6, 9.3 ppm; HRMS (ESI): calcd for $C_{38}H_{48}O_5SiNa^+$ $[M + Na]^+$: 635.3163, found: 635.3155.

(±)-Kadangustin J (1). To a stirred solution of the above *O*-silyl ether **20** (5.6 g, 9.15 mmol) in THF (60 mL) was added *n*-Bu_4NF (11.9 g, 45.7 mmol, 5.0 equiv.) portionwise at 30 °C. After 16 h, the reaction mixture was diluted with CH_2Cl_2 (300 mL) and poured into a separatory funnel. The organic layers were washed with water (3 × 50 mL) and brine (50 mL), then dried over Na_2SO_4, filtered and concentrated under reduced pressure. The resulting crude (±)-kadangustin J (**1**) (3.38 g) as a colorless oil could be used directly without further purification. The small amount of this sample was isolated for characterization. R_f = 0.28 (petroleum ether–EtOAc = 1 : 1); IR (film): ν_{max} = 3513, 2960, 2935, 2835, 1591, 1514, 1464, 1417, 1380, 1263, 1144, 1028, 912, 732 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.88 (dd, J = 1.6, 8.0 Hz, 1H), 6.86 (dd, J = 1.6, 8.0 Hz, 1H), 6.84 (d, J = 1.6 Hz, 1H), 6.81 (d, J = 1.6 Hz, 1H), 6.78 (d, J = 8.0 Hz, 1H), 6.77 (d, J = 8.0 Hz, 1H), 3.87 (s, 3H), 3.86 (s, 3H), 3.82 (s, 6H), 3.54 (d, J = 12.0 Hz, 1H), 3.50–3.43 (m, 2H), 2.66–2.58 (m, 1H), 1.82–1.72 (m, 1H), 1.39 (br, 1H, –O*H*), 0.76 (d, J = 7.2 Hz, 3H), 0.69 (d, J = 6.8 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 148.8, 148.7, 147.13, 147.10, 137.6, 137.1, 119.6, 119.5, 111.2, 111.1, 111.03, 110.98, 66.9, 55.8 (3C), 55.7 (2C), 36.0, 35.9, 11.8, 9.6 ppm; HRMS (ESI): calcd for $C_{22}H_{30}O_5Na^+$ $[M + Na]^+$: 397.1985, found: 397.1979.

(Alternative procedure for **kadangustin J**)

(3*R,4*R**)-2,2-Bis(3,4-dimethoxyphenyl)-3,4-dimethyl tetrahydrofuran (17).** To a stirred solution of the above tertiary alcohol **16** (28 mg, 0.072 mmol) in CH_2Cl_2 (2 mL) was added Et_3SiH (0.06 mL, 0.36 mmol, 5.0 equiv.) at 0 °C followed by the addition of $BF_3{\cdot}Et_2O$ (0.02 mL, 0.144 mmol, 2.0 equiv.) dropwise. After 2 min, the reaction was quenched by saturated aqueous Na_2CO_3 (1 mL) and extracted with CH_2Cl_2 (20 mL). The organic layers were washed with water (3 × 5 mL) and brine (5 mL), then dried over Na_2SO_4, filtered and concentrated under reduced pressure. The resulting crude residue was purified by flash column chromatography (petroleum ether–EtOAc = 1 : 1) on silica gel to afford the undesired tetrahydrofuran **17** (26 mg, 98% yield) as a colorless oil. R_f = 0.60 (petroleum ether–EtOAc = 1 : 1); IR (film): ν_{max} = 2998, 2958, 2932, 2871, 2835, 1604, 1590, 1511, 1463, 1409, 1327, 1258, 1240, 1168, 1141, 1029, 913, 859, 803, 763, 732, 647 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.02 (dd, J = 2.0, 8.4 Hz, 1H), 6.91 (d, J = 2.0 Hz, 1H), 6.84 (d, J = 8.4 Hz, 1H), 6.75 (d, J = 2.0 Hz, 1H), 6.73 (d, J = 8.4 Hz, 1H), 6.62 (dd, J = 2.0, 8.4 Hz, 1H), 4.31 (t, J = 8.0 Hz, 1H), 3.89 (s, 3H), 3.84 (s, 3H), 3.81 (s, 3H), 3.80 (s, 3H), 3.46 (dd, J = 8.4, 10.8 Hz, 1H), 2.41 (qd, J = 2.8, 10.8 Hz, 1H), 2.07–1.95 (m, 1H), 1.01 (d, J = 6.4 Hz, 3H), 0.86 (d, J = 6.8 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 148.7, 148.0, 147.8, 147.5, 139.8, 137.7, 119.8, 118.4, 110.9 (2C), 109.93, 109.87, 90.3, 73.8, 55.83 (2C), 55.76 (2C), 49.4, 40.6, 15.6, 14.5 ppm; ESI-MS: m/z 373.3 $[M + H]^+$; HRMS (ESI): calcd for $C_{22}H_{29}O_5^+$ $[M + H]^+$: 373.2010, found: 373.2007.

4,4-Bis(3,4-dimethoxyphenyl)-2,3-dimethylbut-3-en-1-ol (18). To a stirred solution of the above diol **16** (200 mg, 0.51 mmol) in EtOH (10 mL) was added conc. HCl (0.8 mL) dropwise at reflux. After 3 h, the reaction mixture was cooled to room temperature and diluted with CH_2Cl_2 (60 mL). The organic layers were washed with saturated aqueous Na_2CO_3 (10 mL), water (3 × 10 mL) and brine (10 mL), then dried over Na_2SO_4, filtered and concentrated under reduced pressure. The resulting crude residue was purified by flash column chromatography (petroleum ether–EtOAc = 1 : 1) on silica gel to afford 3-butene-1-ol **18** (120 mg, 63% yield) as a colorless oil. R_f = 0.20 (petroleum ether–EtOAc = 1 : 1); IR (film): ν_{max} = 3523, 3000, 2958, 2935, 2871, 2835, 1601, 1581, 1511, 1464, 1408, 1316, 1251, 1167, 1184, 1138, 1029, 913, 863, 802, 760, 733 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.80 (d, J = 7.6 Hz, 2H), 6.71 (dd, J = 3.2, 8.0 Hz, 2H), 6.70 (s, 1H), 6.64 (s, 1H), 3.86 (s, 6H), 3.82 (s, 3H), 3.81 (s, 3H), 3.62 (t, J = 10.0 Hz, 1H), 3.50 (dd, J = 6.4, 10.8 Hz, 1H), 2.93 (sext, J = 6.8 Hz, 1H), 1.71 (s, 3H), 1.34 (br, 1H, –O*H*), 1.03 (d, J = 7.2 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 148.4, 148.3, 147.44, 147.38, 139.9, 135.9, 135.7, 134.8, 121.9, 121.5, 112.8, 112.7, 110.8, 110.6, 66.0, 55.81 (2C), 55.75 (2C), 39.7, 15.5, 14.0 ppm; ESI-MS: m/z 373.4 $[M + H]^+$; HRMS (ESI): calcd for $C_{22}H_{29}O_5^+$ $[M + H]^+$: 373.2010, found: 373.2004.

3-Butene-1-ol **18** (80 mg, 0.215 mmol) was dissolved in EtOH (3 mL) followed by the addition of 5% Pd/C (54 mg) at 25 °C. The whole system with a three-way Teflon stopcock connected to a standard balloon was evacuated and backfilled with H_2, and this protocol was repeated three times. Then the heterogeneous mixture was allowed to stir at 16 °C under a positive pressure of hydrogen. After 1 h, the hydrogenation reaction finished, and the reaction mixture was filtered directly through silica gel, washed with EtOAc (4 × 5 mL), and concentrated under reduced pressure. The resulting crude residue was purified by flash column chromatography (petroleum ether–EtOAc = 2 : 1) on silica gel to afford the desired kadangustin J (**1**) (78 mg, 98% yield).

(2*R,3*S**)-4,4-Bis(3,4-dimethoxyphenyl)-2,3-dimethyl butanal (21).** To a stirred solution of kadangustin J (3.38 g, 9.04 mmol) in EtOAc (75 mL) was added IBX (3.04 g, 10.8 mmol, 1.2 equiv.) portionwise at 25 °C. The resulting reaction mixture was stirred for 4 h at 80 °C then filtered directly through silica gel. The filter cake was washed with EtOAc (5 × 60 mL), and the combined organic phase was washed with water (3 × 40 mL) and brine (30 mL), then dried over Na_2SO_4, filtered and concentrated under reduced pressure. The resulting crude aldehyde **21** (2.75 g) as a colorless oil could be used directly without further purification. The small amount of this sample was isolated for characterization. R_f = 0.38 (petroleum ether–EtOAc = 1 : 1); IR (film): ν_{max} = 2959, 2926, 2846, 1718, 1651, 1591, 1512, 1460, 1263, 1144, 1027, 755 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 9.65 (s, 1H), 6.91 (d, J = 8.4 Hz, 2H), 6.84–6.81 (m, 2H), 6.81 (d, J = 2.4 Hz, 1H), 6.79 (d, J = 2.4 Hz, 1H), 3.88 (s, 3H), 3.86 (s, 3H), 3.84 (s, 3H), 3.83 (s, 3H), 3.56 (d, J = 11.6 Hz, 1H), 3.06–2.96 (m, 1H), 2.40 (qd, J = 2.4, 7.2 Hz, 1H), 1.05 (d, J = 6.8 Hz, 3H), 0.72 (d, J = 6.8 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 205.4, 149.1, 148.9, 147.6, 147.5, 136.2 (2C), 119.6, 119.4, 111.5, 111.3, 111.1, 111.0, 55.9 (2C), 55.8 (2C), 55.4, 47.9, 35.6, 13.6, 6.5 ppm; HRMS (ESI): calcd for $C_{22}H_{28}O_5Na^+$ $[M + Na]^+$: 395.1829, found: 395.1830.

(±)-Cyclogalgravin (2). To a stirred solution of the above aldehyde **21** (2.75 g, 7.39 mmol) in toluene (75 mL) was added *p*-TsOH·H_2O (282 mg, 1.47 mmol, 0.2 equiv.) at 25 °C. After 15 min, the reaction mixture was quenched by saturated aqueous $NaHCO_3$ (5 mL) and directly concentrated under reduced pressure in order to remove toluene. Then CH_2Cl_2 (200 mL) was added and washed with water (3 × 20 mL) and brine (30 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The resulting crude residue was purified by flash column chromatography (petroleum ether–EtOAc = 2 : 1) on silica gel to afford the desired (±)-cyclogalgravin **2** (2.06 g, 60% overall yield, 6 steps from **15**) as a colorless oil. R_f = 0.48 (petroleum ether–EtOAc = 2 : 1); IR (film): ν_{max} = 2955, 2924, 2853, 1660, 1604, 1511, 1463, 1263, 1230, 1142, 1028, 870, 759 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 6.72 (d, J = 8.0 Hz, 1H), 6.67 (d, J = 2.0 Hz, 1H), 6.63 (s, 1H), 6.56 (s, 1H), 6.56 (dd, J = 2.0, 8.0 Hz, 1H), 6.15 (br s, 1H), 3.89 (s, 3H), 3.83 (s, 3H), 3.793 (s, 3H), 3.790 (s, 3H), 3.69 (d, J = 2.8 Hz, 1H), 2.40 (qd, J = 3.2, 6.8 Hz, 1H), 1.80 (s, 3H), 1.09 (d, J = 7.2 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 148.6, 147.6, 147.5, 147.3, 138.8, 138.1, 127.3, 127.1, 121.1, 119.6, 112.8, 110.9, 110.8, 108.9, 55.9 (2C), 55.7 (2C), 50.8, 42.0, 22.2, 18.7 ppm; HRMS (ESI): calcd for $C_{22}H_{27}O_4^+$ $[M + H]^+$: 355.1904, found: 355.1909.

4,4′-(1-(2-Bromo-1-ethoxypropoxy)prop-2-ene-1,1-diyl)bis-1,2-dimethoxybenzene) (22). In a 50 mL, round-bottom flask, Br_2 (0.15 mL, 3.0 mmol, 5.0 equiv.) was dissolved in dry CH_2Cl_2 (16 mL) and cooled to −78 °C. To the resulting solution was added ethyl propenyl ether (E : Z = 1.7 : 1, 0.4 mL, 3.6 mmol, 6.0 equiv.) dropwise, and the mixture was stirred for 30 min at −78 °C. This system was transferred *via* a cannula to another round bottom flask where the solution of allyl alcohol **5** (200 mg, 0.6 mmol) and *N*,*N*-dimethylaniline (0.61 mL, 4.8 mmol, 8.0 equiv.) in CH_2Cl_2 (4 mL) had been prepared. The resulting mixture was warmed to 0 °C and further stirred for 2 h and then for 10 h at 15 °C. Eventually, the reaction mixture was carefully quenched by water (2 mL) and poured into a separatory funnel. The combined organic layers were washed with aqueous HCl (1.0 M, 3 × 10 mL), water (3 × 10 mL) and brine (10 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The resulting crude residue was purified by flash column chromatography (petroleum ether–EtOAc = 4 : 1) on silica gel to afford the desired **22** (207 mg, 70% yield, d.r. = 2 : 1) as a pale yellow oil. R_f = 0.46 (petroleum ether–EtOAc = 2 : 1); IR (film): ν_{max} = 3059, 2956, 2908, 2835, 1633, 1602, 1587, 1511, 1464, 1411, 1334, 1259, 1142, 1028, 863, 807, 765 cm^{-1}; (*major isomer*) ^1H NMR (400 MHz, $CDCl_3$): δ = 7.02 (d, J = 2.0 Hz, 1H), 6.97–6.90 (m, 2H), 6.87–6.77 (m, 3H), 6.59 (dd, J = 10.8, 17.2 Hz, 1H), 5.37 (dd, J = 1.2, 10.8 Hz, 1H), 4.99 (dd, J = 1.2, 17.2 Hz, 1H), 4.59 (d, J = 4.0 Hz, 1H), 4.16–4.04 (m, 1H), 3.90 (s, 3H), 3.88 (s, 3H), 3.82 (s, 3H), 3.80 (s, 3H), 3.41–3.19 (m, 2H), 1.72 (d, J = 6.8 Hz, 3H), 1.07 (t, J = 6.8 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 148.3, 148.2, 148.1, 148.0, 141.1, 136.6, 135.5, 121.0, 120.6, 118.1, 112.2, 111.8, 109.8 (2C), 99.8, 84.8, 63.7, 55.8 (4C), 50.4, 19.6, 15.0 ppm; (*minor isomer*) ^1H NMR (400 MHz, $CDCl_3$): δ = 7.04 (d, J = 1.6 Hz, 1H), 6.97–6.90 (m, 2H), 6.87–6.77 (m, 3H), 6.64 (dd, J = 10.4, 16.0 Hz, 1H), 5.33 (dd, J = 1.6, 10.8 Hz, 1H), 5.03 (dd, J = 1.6, 17.2 Hz, 1H), 4.51 (d, J = 4.0 Hz, 1H), 4.16–4.04 (m, 1H), 3.90 (s, 3H), 3.89 (s, 3H), 3.82 (s, 3H), 3.80 (s, 3H), 3.41–3.19 (m, 2H), 1.76 (d, J = 6.8 Hz, 3H), 1.05 (t, J = 6.8 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 148.4, 148.3, 148.0, 147.9, 141.4, 136.9, 135.1, 121.3, 120.6, 117.4, 112.5, 111.7, 109.8, 109.7, 99.5, 85.0, 62.1, 55.8 (4C), 49.6, 20.1, 15.1 ppm; HRMS (ESI): calcd for $C_{19}H_{21}O_4^+$ $[M - C_5H_{10}O_2Br - e]^+$: 313.1434, found: 313.1438.

5,5-Bis(3,4-dimethoxyphenyl)-3,4-dimethyldihydrofuran-2(3*H*)-one (15′). In a 50 mL, two-necked, round-bottom flask, α-bromo acetal **22** (69 mg, 0.14 mmol) was dissolved in anhydrous toluene (6 mL) followed by the addition of the solution of $(TMS)_3SiH$ (86 μL, 0.28 mmol, 2.0 equiv.) and AIBN (5 mg, 0.028 mmol, 0.2 equiv.) in toluene (2 mL) dropwise under argon. The resulting mixture was heated to 90 °C and stirred for 2 h. Then the reaction mixture was cooled to room temperature and directly concentrated under reduced pressure. The

resulting crude residue was diluted with CH_2Cl_2 (20 mL), and washed with water (3 × 10 mL) and brine (10 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The resulting crude residue was purified by flash column chromatography (petroleum ether–EtOAc = 10 : 1) on silica gel to afford the mixture of cyclic acetal (48 mg) as a colorless oil. To a stirred solution of this diastereoisomeric cyclic acetal in CH_2Cl_2 (10 mL) was added *m*-CPBA (77%, 53.6 mg, 0.24 mmol, 2.0 equiv.) at room temperature followed by the addition of $BF_3{\cdot}Et_2O$ (0.02 mL, 0.18 mmol, 1.5 equiv.). After 10 min, the reaction mixture was quenched by saturated aqueous Na_2SO_3 (3 mL) and extracted with CH_2Cl_2 (3 × 10 mL). The organic layers were washed with saturated aqueous $NaHCO_3$ (2 × 10 mL), water (3 × 10 mL) and brine (10 mL), then dried over $MgSO_4$, filtered and concentrated under reduced pressure. The resulting crude residue was purified by flash column chromatography (petroleum ether–EtOAc = 4 : 1) on silica gel to afford the desired **15′** (**15** : C8 isomer = 1.5 : 1, 36 mg, 64% yield over two steps) as a colorless oil. R_f = 0.33 (petroleum ether–EtOAc = 1 : 1) (C8 isomer of **15**) ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.14 (dd, J = 2.0, 8.4 Hz, 1H), 6.98 (d, J = 2.0 Hz, 1H), 6.92 (s, 1H), 6.88–6.75 (m, 3H), 3.87 (s, 3H), 3.86 (s, 3H), 3.84 (s, 3H), 3.83 (s, 3H), 3.30 (quint, J = 7.2 Hz, 1H), 2.93–2.83 (m, 1H), 1.18 (d, J = 7.6 Hz, 3H), 0.72 (d, J = 6.8 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 178.4, 149.2, 148.7, 148.6, 147.7, 135.4, 133.9, 117.7, 116.9, 110.8, 110.4, 109.9, 108.5, 90.3, 55.9 (4C), 42.5, 40.3, 11.7, 10.2 ppm; HRMS (ESI): calcd for $C_{22}H_{27}O_6^+$ $[M + H]^+$: 387.1802, found: 387.1808.

(±)-Galbulin (3). (±)-Cyclogalgravin **2** (46 mg, 0.13 mmol) was dissolved in EtOH (3 mL) followed by the addition of 5% Pd/C (3 mg) at 0 °C. The whole system with a three-way Teflon stopcock connected to a standard balloon was evacuated and backfilled with H_2, and this protocol was repeated three times. Then the heterogeneous mixture was allowed to stir at 0 °C under a positive pressure of hydrogen. After 20 min, the hydrogenation reaction finished, and the reaction mixture was filtered directly through silica gel. The filter cake was washed with EtOAc (4 × 5 mL), and the filtrate was concentrated under reduced pressure. The resulting crude residue was purified by flash column chromatography (petroleum ether–EtOAc = 2 : 1) on silica gel to afford the desired (±)-galbulin **3** (45 mg, 97% yield, d.r. = 22 : 1) as a white solid. This product was dissolved in EtOAc and pentane (1 : 10). After a few days, colorless single crystals were obtained by slow evaporation of the solvent at room temperature. R_f = 0.52 (petroleum ether–EtOAc = 2 : 1); Mp. 113–114 °C; IR (film): ν_{max} = 3056, 2958, 2926, 2854, 1607, 1591, 1514, 1464, 1417, 1353, 1261, 1140, 1108, 1029, 861, 803, 766, 736, 703, 644 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.81 (d, J = 8.0 Hz, 1H), 6.71 (dd, J = 1.6, 8.0 Hz, 1H), 6.58 (s, 1H), 6.57 (d, J = 1.6 Hz, 1H), 6.16 (s, 1H), 3.89 (s, 3H), 3.85 (s, 3H), 3.81 (s, 3H), 3.56 (s, 3H), 3.43 (d, J = 10.0 Hz, 1H), 2.76 (dd, J = 4.4, 16.4 Hz, 1H), 2.62 (dd, J = 12.2, 15.4 Hz, 1H), 1.70–1.60 (m, 1H), 1.56–1.47 (m, 1H), 1.08 (d, J = 6.4 Hz, 3H), 0.87 (d, J = 6.4 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 148.8, 147.3, 147.0, 146.9, 139.0, 132.4, 129.1, 121.9, 112.8, 112.0, 110.7, 110.6, 55.9, 55.79 (2C), 55.76, 54.3, 43.8, 39.0, 35.6, 20.0, 17.2 ppm; HRMS (ESI): calcd for $C_{22}H_{32}O_4N^+$ $[M + NH_4]^+$: 374.2326, found: 374.2332.

(±)-Isogalbulin (4). (±)-Cyclogalgravin **2** (100 mg, 0.28 mmol) was dissolved in EtOH (10 mL) followed by the addition of PtO_2 (12 mg, 0.2 equiv.) at 15 °C. The whole system with a three-way Teflon stopcock connected to a standard balloon was evacuated and backfilled with H_2, and this protocol was repeated three times. Then the heterogeneous mixture was allowed to stir at 15 °C under a positive pressure of hydrogen. After 5 min, the hydrogenation reaction finished, and the reaction mixture was filtered directly through silica gel. The filter cake was washed with EtOAc (4 × 10 mL), and the filtrate was concentrated under reduced pressure. The resulting crude residue was purified by flash column chromatography (petroleum ether–EtOAc = 2 : 1) on silica gel to afford (±)-galbulin **3** and (±)-isogalbulin **4** (99 mg, 98% yield, d.r. = 1.7 : 1) as a white solid. The desired (±)-isogalbulin **4** could be obtained through fractional recrystallization in EtOAc and pentane (1 : 10). R_f = 0.52 (petroleum ether–EtOAc = 2 : 1); Mp. 98–100 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.75 (d, J = 8.4 Hz, 1H), 6.60 (s, 1H), 6.58 (d, J = 2.0 Hz, 1H), 6.51 (dd, J = 2.0, 8.4 Hz, 1H), 6.34 (s, 1H), 3.87 (s, 3H), 3.85 (s, 3H), 3.80 (s, 3H), 3.69 (d, J = 6.0 Hz, 1H), 3.67 (s, 3H), 2.86 (dd, J = 5.2, 16.8 Hz, 1H), 2.46 (dd, J = 8.0, 16.8 Hz, 1H), 2.07–1.98 (m, 1H), 1.97–1.90 (m, 1H), 0.92 (d, J = 6.8 Hz, 3H), 0.91 (d, J = 6.8 Hz, 3H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$): δ = 148.6, 147.3, 147.1 (2C), 139.8, 129.5, 128.5, 121.3, 113.3, 112.2, 111.2, 110.6, 55.9, 55.81, 55.77, 55.7, 50.9, 40.8, 34.7, 28.6, 16.5, 15.4 ppm; HRMS (ESI): calcd For $C_{22}H_{28}O_4Na^+$ $[M + Na]^+$: 379.1880, found: 379.1879.

(±)-8,8′-*epi*-Aristoligone (5). A 25 mL, two-necked, round-bottom flask was charged with PCC (91 mg, 0.42 mmol, 5.0 equiv.), Celite (270 mg), benzene (4 mL) and stirring was continued for 5 min followed by the addition of (±)-galbulin **3** (30 mg, 0.084 mmol) in benzene (1 mL). The reaction mixture was stirred for 24 h at reflux, then cooled to room temperature and filtered through silica gel. The resulting filter cake was washed with EtOAc (4 × 5 mL), and the filtrate was concentrated under reduced pressure. The resulting crude residue was purified by flash column chromatography (petroleum ether–EtOAc = 2 : 1) on silica gel to afford the desired (±)-8,8′-*epi*-aristoligone **5** (15 mg, 48% yield) as a white solid. R_f = 0.45 (petroleum ether–EtOAc = 2 : 1); Mp. 149–151 °C; IR (film): ν_{max} = 3059, 2963, 2928, 2873, 1672, 1600, 1513, 1464, 1418, 1407, 1364, 1316, 1266, 1235, 1212, 1182, 1160, 1141, 1077, 1028, 880, 804, 769, 736 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.54 (s, 1H), 6.87 (d, J = 8.0 Hz, 1H), 6.76 (dd, J = 1.6, 8.0 Hz, 1H), 6.58 (d, J = 1.6 Hz, 1H), 6.19 (s, 1H), 3.93 (s, 3H), 3.92 (s, 3H), 3.82 (s, 3H), 3.71 (d, J = 11.2 Hz, 1H), 3.63 (s, 3H), 2.39 (dq, J = 6.4, 12.0 Hz, 1H), 2.14–2.00 (m, 1H), 1.32 (d, J = 6.4 Hz, 3H), 0.94 (d, J = 6.4 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 198.8, 153.1, 149.1, 147.9, 147.8, 141.5, 136.1, 125.6, 122.1, 111.6, 111.0, 110.8, 108.0, 56.0, 55.9, 55.8 (2C), 53.3, 48.5, 43.7, 18.0, 12.6 ppm; ESI-MS: *m*/*z* 371.3 $[M + H]^+$; HRMS (APCI): calcd for $C_{22}H_{27}O_5^+$ $[M + H]^+$: 371.1853, found: 371.1853.

(±)-Cagayanin (6).[5g,7b] To a stirred solution of (±)-galbulin **3** (24 mg, 0.067 mmol) in CH_2Cl_2 (3 mL) was added BBr_3 (1.0 M in CH_2Cl_2, 0.4 mL, 0.4 mmol, 6.0 equiv.) dropwise over a 2 min period at −78 °C. The reaction mixture was then stirred at this temperature for 3 h and quenched by ice-water (0.5 mL). After stirring for 20 min, the resulting mixture was extracted with CH_2Cl_2 (2 × 20 mL). The combined organic layers were washed with 10% aqueous HCl (2 mL), ice-water (2 × 2 mL) and brine (2 mL), then dried over Na_2SO_4, filtered and concentrated under reduced pressure. The resulting labile bis-catechol was dissolved in DMSO (1 mL) at 25 °C followed by the addition of CH_2Br_2 (40 μL, 0.57 mmol, 8.5 equiv.) dropwise over a 30 second period and NaOH (29 mg, 0.73 mmol, 11 equiv.). The resulting mixture was stirred at 35 °C for 2 h and then quenched by water (1 mL) and extracted with CH_2Cl_2 (3 × 20 mL). The organic layers were washed with saturated water (6 × 6 mL) and brine (6 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The resulting crude residue was purified by flash column chromatography (petroleum ether–EtOAc = 2 : 1) on silica gel to afford the desired (±)-cagayanin **6** (13 mg, 60% yield over two steps) as a white solid. R_f = 0.55 (petroleum ether–EtOAc = 2 : 1); Mp. 127–128 °C; IR (film): ν_{max} = 2964, 2881, 2773, 1609, 1503, 1484, 1459, 1440, 1374, 1292, 1232, 1190, 1156, 1125, 1096, 1041, 939, 866, 803, 790, 738 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 6.74 (d, J = 7.6 Hz, 1H), 6.62 (dd, J = 1.6, 8.0 Hz, 1H), 6.52 (s, 2H), 6.16 (s, 1H), 5.92 (s, 2H), 5.81 (d, J = 1.2 Hz, 2H), 3.38 (d, J = 10.4 Hz, 1H), 2.70 (dd, J = 4.4, 16.4 Hz, 1H), 2.57 (dd, J = 11.6, 16.0 Hz, 1H), 1.65–1.53 (m, 1H), 1.51–1.42 (m, 1H), 1.05 (d, J = 6.4 Hz, 3H), 0.87 (d, J = 6.0 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 147.8, 145.9, 145.6, 145.4, 140.5, 133.4, 130.1, 122.8, 109.6, 109.2, 107.7, 107.6, 100.8, 100.5, 54.6, 43.9, 39.5, 35.4, 19.9, 17.1 ppm; EI-MS: m/z 324.0 $[M]^+$.

(±)-8′-*epi*-Aristoligone (7). This tetralone as a white solid was prepared from (±)-isogalbulin (**4**) *via* a similar oxidation procedure as for **5**. R_f = 0.45 (petroleum ether–EtOAc = 2 : 1); Mp. 136–138 °C; IR (film): ν_{max} = 3070, 2966, 2933, 2872, 2834, 1672, 1599, 1512, 1463, 1417, 1407, 1364, 1268, 1235, 1212, 1159, 1142, 1077, 1028, 880, 826, 768, 736 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.57 (s, 1H), 6.78 (d, J = 8.4 Hz, 1H), 6.62 (d, J = 1.6 Hz, 1H), 6.55 (dd, J = 1.6, 8.0 Hz, 1H), 6.43 (s, 1H), 3.98 (d, J = 5.2 Hz, 1H), 3.95 (s, 3H), 3.87 (s, 3H), 3.81 (s, 3H), 3.78 (s, 3H), 2.82–2.74 (m, 1H), 2.46–2.40 (m, 1H), 1.14 (d, J = 6.8 Hz, 3H), 0.99 (d, J = 6.8 Hz, 3H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$): δ = 200.0, 153.6, 149.0, 148.1, 147.7, 138.7, 136.2, 125.5, 121.1, 111.8 (2C), 110.9, 108.1, 56.0 (2C), 55.9 (2C), 50.3, 42.7, 42.5, 15.9, 11.9 ppm; HRMS (ESI): calcd for $C_{22}H_{26}O_5Na^+$ $[M + Na]^+$: 393.1672, found: 393.1657.

(±)-8′-*epi*-8-Hydroxy-aristoligone (8). A 10 mL round-bottom flask was charged with KHMDS (1.0 M in THF, 80 μL, 80 μmol, 5.0 equiv.) under argon and the resulting solution was cooled to −78 °C. To this precooled base, a solution of **7** (5.9 mg, 16 μmol) in THF (1.0 mL) was added dropwise *via* a syringe and stirring was continued for 0.5 h at this temperature. Next, the resulting enolate was treated with (+)-(2*R*,8a*S*)-camphorylsulfonyl oxaziridine (15 mg, 64 μmol, 4.0 equiv.) at −78 °C, and this hydroxylation reaction was allowed to slowly warm to room temperature and was stirred for 4 h and quenched by water (1 mL). The mixture was diluted with CH_2Cl_2 (20 mL) and poured into a separatory funnel. The combined organic layers were separated and washed with water (3 × 5 mL) and brine (5 mL) respectively, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The resulting crude residue was purified by flash column chromatography (petroleum ether–EtOAc = 4 : 1) on silica gel to afford the desired **8** (4 mg, 65% yield, d.r. = 20 : 1) as a white solid. R_f = 0.50 (petroleum ether–EtOAc = 1 : 1); Mp. 179–180 °C; IR (film): ν_{max} = 3446, 3057, 2956, 2924, 2853, 1670, 1600, 1513, 1464, 1408, 1368, 1276, 1260, 1239, 1214, 1188, 1157, 1141, 1123, 1095, 1020, 928, 878, 854, 813, 768, 736 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.49 (s, 1H), 6.85 (d, J = 8.4 Hz, 1H), 6.76 (d, J = 6.4 Hz, 1H), 6.54 (br, 1H), 6.23 (s, 1H), 4.07 (s, 1H, –O*H*), 3.94 (s, 3H), 3.91 (s, 3H), 3.79 (s, 3H), 3.69 (d, J = 11.2 Hz, 1H), 3.65 (s, 3H), 2.37 (dq, J = 6.4, 11.2 Hz, 1H), 1.31 (s, 3H), 0.99 (d, J = 6.8 Hz, 3H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$): δ = 201.3, 154.1, 149.3, 148.4, 148.0, 141.6, 135.5, 122.7, 122.1, 111.3 (2C), 110.9, 108.3, 75.6, 56.0, 55.9, 55.8 (2C), 51.0, 46.6, 19.3, 12.4 ppm; ESI-MS: m/z 387.0 $[M + H]^+$; HRMS (ESI): calcd for $C_{22}H_{26}O_6Na^+$ $[M + Na]^+$: 409.1622, found: 409.1603.

(±)-7,8′-*epi*-Aristoligol (9′).[5i] **and (±)-8′-*epi*-aristoligol (9).** To a stirred solution of the above ketone **7** (3.8 mg, 10.3 μmol) in MeOH (1 mL) was added $NaBH_4$ (2 mg, 51 μmol, 5 equiv.) at 0 °C. After 15 min, the reaction mixture was directly concentrated under reduced pressure in order to remove MeOH. Then the residue was diluted with EtOAc (10 mL) and water (3 mL) was added. The organic layers were separated and the aqueous layers were extracted with EtOAc (2 × 5 mL). The combined organic layers were washed with water (2 × 3 mL) and brine (3 mL), then dried over Na_2SO_4, filtered and concentrated under reduced pressure. The resulting crude residue was purified by flash column chromatography (petroleum ether–EtOAc = 4 : 1 → 2 : 1) on silica gel to afford the desired **9′** (2.1 mg, 55% yield) and **9** (1.1 mg, 29% yield) as a white solid, respectively. **9′**: R_f = 0.38 (petroleum ether–EtOAc = 1 : 1); Mp. 152–154 °C; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.14 (s, 1H), 6.79 (d, J = 8.0 Hz, 1H), 6.64 (dd, J = 8.0, 1.6 Hz, 1H), 6.54 (d, J = 1.6 Hz, 1H), 6.22 (s, 1H), 5.00 (dd, J = 7.2, 6.0 Hz, 1H), 3.90 (s, 3H), 3.87 (s, 3H), 3.80 (s, 3H), 3.61 (s, 3H), 3.54 (d, J = 10.4 Hz, 1H), 2.26–2.18 (m, 1H), 2.12–2.03 (m, 1H), 1.70 (d, J = 8.4 Hz, 1H, –O*H*), 0.93 (d, J = 7.2 Hz, 3H), 0.90 (d, J = 7.2 Hz, 3H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$): δ = 148.8, 147.9, 147.8, 147.5, 138.2, 131.4, 130.6, 121.7, 112.3, 112.1, 110.8, 108.6, 72.5, 55.91, 55.82, 55.80, 55.77, 49.3, 39.9, 39.4, 17.7, 6.7 ppm; ESI-MS: m/z 355.3 $[M - H_2O + H]^+$. **9**: R_f = 0.31 (petroleum ether–EtOAc = 1 : 1); Mp. 52–53 °C; ^1H NMR (400 MHz, $CDCl_3$): δ = 6.88 (s, 1H), 6.79 (d, J = 8.0 Hz, 1H), 6.64 (dd, J = 8.4, 1.8 Hz, 1H), 6.62 (d, J = 2.4 Hz, 1H), 6.28 (s, 1H), 4.46 (d, J = 4.0 Hz, 1H), 3.90 (s, 3H), 3.88 (s, 3H), 3.81 (s, 3H), 3.63 (s, 3H), 3.50 (d, J = 9.2 Hz, 1H), 2.41–2.32 (m, 1H), 2.10–2.02 (m, 1H), 0.93 (d, J = 7.2 Hz, 3H), 0.92 (d, J = 6.8 Hz, 3H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$): δ = 148.8, 148.7, 147.8, 147.4, 138.2, 131.9,

129.3, 121.7, 112.5, 112.1, 111.7, 110.7, 74.0, 55.92, 55.83 (2C), 55.75, 49.3, 39.2, 35.8, 16.8, 12.0 ppm; HRMS (ESI): calcd for $C_{22}H_{27}O_4^+$ $[M - H_2O + H]^+$: 355.1904, found: 355.1909.

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