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Chemoenzymatic Access to (+)-Artabotriol and its Application in Collective Synthesis of (+)-Grandiamide D, (–)-Tulipalin B, (+)-Spirathundiol, and (+)-Artabotriolcaffeate

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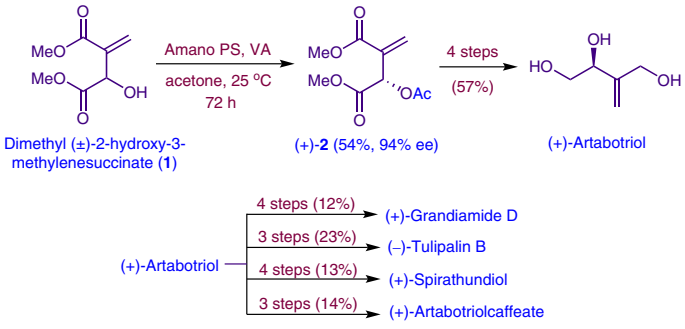

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Abstract Starting from dimethyl (±)-2-hydroxy-3-methylenesuccinate chemoenzymatic collective formal/total synthesis of enantiomerically pure bioactive natural products has been described via the advanced level common precursor (+)-artabotriol. An efficient enzymatic resolution with high enantiomeric purity, selective diester to diol reduction, and requisite dehydrative coupling reactions without any racemization are the significant topographies.

Key words dimethyl (±)-2-hydroxy-3-methylenesuccinate, enzymatic resolution, reduction, (+)-artabotriol, coupling reactions, collective synthesis, natural products

Nature derives large number of sugar monomers, which rejoin with other natural products to form broad range of structurally interesting and biologically important secondary metabolites; in addition to the formation of prime essential complex carbohydrates.[1] More specifically, the five carbon bearing sugar (–)-artabotriol has been isolated from *Artabostrys hexapetalus*.[2] Recently, the (+)-artabotriol derived natural product (+)-grandiamide D has been isolated from *Aglaia gigantean*;[3] whereas the (+)-artabotriolcaffeate has been isolated from *Ilex pubescens* (Figure 1).[4] The absolute configuration of (+)-artabotriolcaffeate has been established by using modified Mosher's method. The first total synthesis of (+)-grandiamide D has been recently reported in the literature;[5] although the synthesis of artabotriol is still awaited. Simple retrosynthetic analysis revealed that nature constructs them starting from enantiomerically pure artabotriol in a stepwise fashion via an appropriate sequence of coupling reactions utilizing the naturally occurring putrescine, cinnamic acid, and caffeaic acid. The science of collective total synthesis of bioactive natural products is very important for structure activity relationship studies from lead optimization and drug discovery point of view.[6] In continuation of our studies on both cyclic anhydrides and derivatives to bioactive natural products[7] and efficient enzymatic resolutions,[6a,8] we herein report a facile chemoenzymatic synthesis of the (+)-artabotriol and its application as a fundamental building block in collective formal/total synthesis of four other enantiomerically pure natural products (Schemes 1–3).

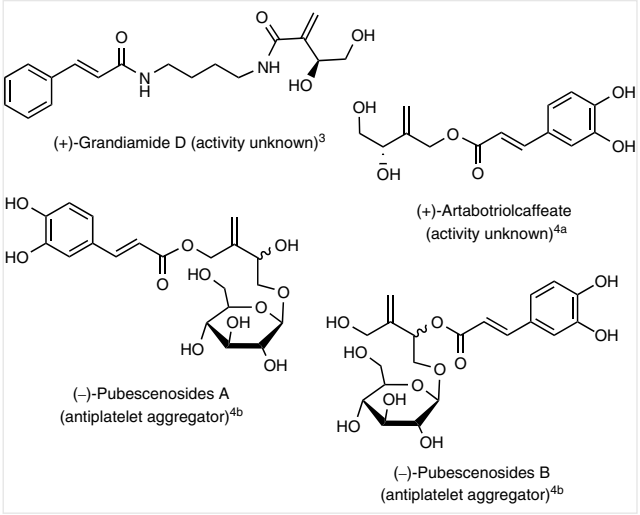
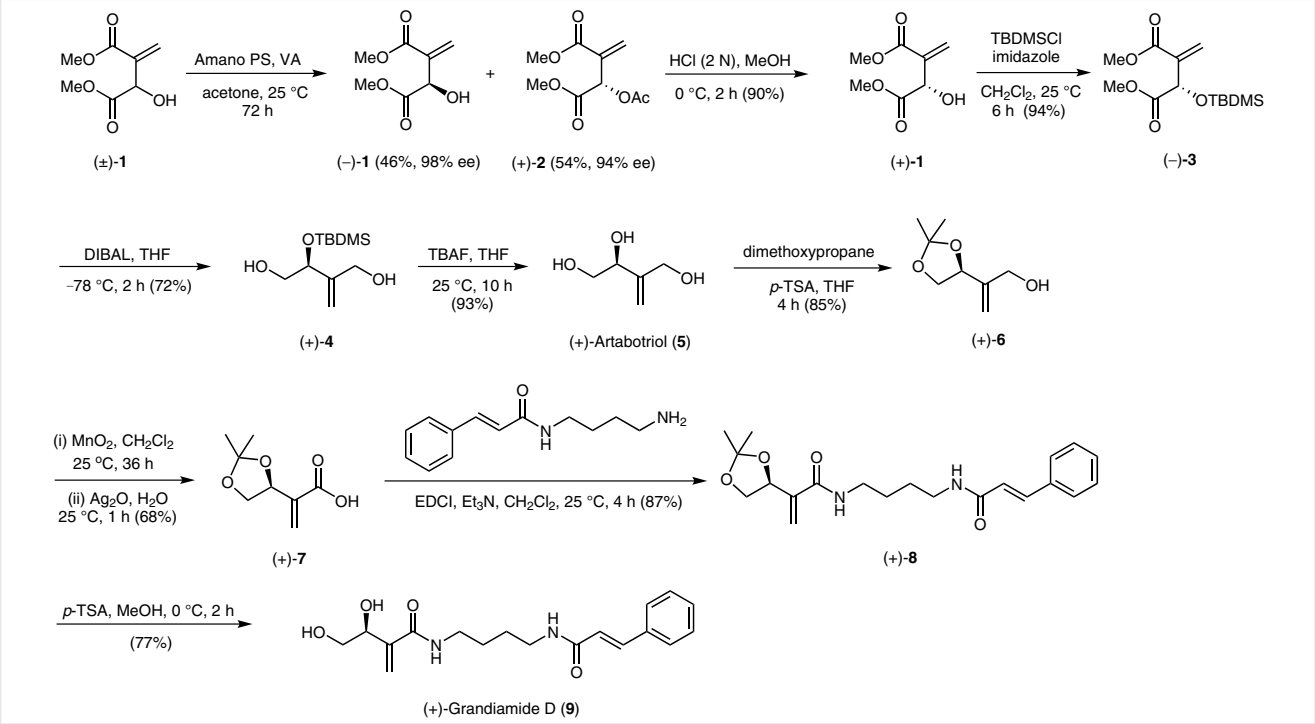


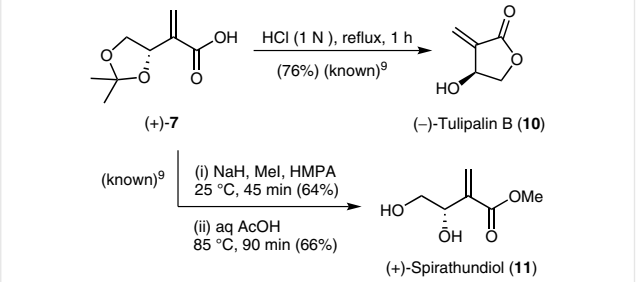
Figure 1 Artabotriol derived natural products

A careful analysis of (+)/(–)-artabotriol structure specified that the dimethyl (±)-2-hydroxy-3-methylenesuccinate (**1**)[8a] would be a potential precursor for their synthesis via enzymatic resolution followed by the reduction route (Scheme 1). The racemic dimethyl 2-hydroxy-3-methylenesuccinate (**1**) was prepared from dimethyl itaconate via allylic oxidation in two steps by using the known procedure.[8a] Accordingly, we systematically studied the Amano PS-catalyzed stereoselective acylation of (±)-alcohol **1** using vinyl



Scheme 1 Chemoenzymatic total synthesis of putrescine bisamide (+)-grandiamide D

acetate (VA) as an acyl donor and obtained the enantiomerically pure (–)-alcohol **1** in 46% yield (98% *ee*, by HPLC) and the corresponding (+)-acetate **2** in 54% yield (94% *ee*, by HPLC) (Table 1). The obtained stereochemical outcome was further confirmed by comparison with the reported analytical and spectral data for both the compounds (–)-**1** and (+)-**2**.[8a] Acid-catalyzed hydrolysis of (+)-acetate **2** to the corresponding (+)-alcohol **1** followed by TBDMS-protection provided (–)-silyl ether **3** in 85% yield over two steps. The DIBAL reduction of (–)-diester **3** to the corresponding (+)-diol **4** followed by TBAF induced desilylation supplied the desired enantiomerically pure (+)-artabotriol (**5**) in 67% yield over two steps. The analytical and spectral data obtained for synthetic (+)-artabotriol (**5**) was in complete agreement with the reported data for natural product (–)-artabotriol (**5**)[2] and the chemoenzymatic first synthesis of



Scheme 2 Formal synthesis of (–)-tulipalin B and (+)-spirathundiol

(+)-artabotriol (**5**) was accomplished in five steps in 31% overall yield. The selective protection of vicinal diol moiety in compound (+)-**5** resulted in (+)-ketal **6** in 85% yield. The MnO_2 oxidation of (+)-allylic alcohol **6** to the corresponding α,β-unsaturated aldehyde followed by its an immediate silver oxide-induced oxidation delivered the known α,β-unsaturated (+)-carboxylic acid **7** in 68% yield. In the above mentioned reaction, the formed intermediate α,β-unsaturated aldehyde was unstable and hence it was directly subjected to the next oxidation without any purification and characterization to obtain the corresponding known (+)-carboxylic acid **7**.[9] The (+)-acid **7** on EDCI-induced dehydrative coupling reaction with the known requisite putrescine amide[10] formed the corresponding (+)-putrescine diamide **8** in 87% yield. Finally, acid-catalyzed deprotection of a ketal moiety in (+)-diamide **8** furnished the desired natural product (+)-grandiamide D (**9**) in 77% yield (98% *ee* by HPLC). The analytical and spectral data obtained for synthetic product was in complete agreement with the reported data for natural product[3,5] and the chemoenzymatic synthesis of (+)-grandiamide D (**9**) was accomplished in nine steps in 12% overall yield. The natural products (–)-tulipalin B (**10**) and (+)-spirathundiol (**11**) have been isolated from *Tulipa gesneriana* and *Spiraea thunbergii* Sieb. respectively.[9,11] As depicted in Scheme 2, the acid-catalyzed ketal deprotection in (+)-acid **7** followed by in situ regioselective dehydrative γ-lactonization to form the (–)-tulipalin B (**10**) in one step in 76% yield and the esterification of (+)-acid **7** followed by

the controlled ketal deprotection to form the (+)-spirathundiol (**11**) in two steps in 42% overall yield are known in the literature.[9]

Table 1 Lipase-Catalyzed Resolution of Dimethyl (±)-2-Hydroxy-3-methylenesuccinate

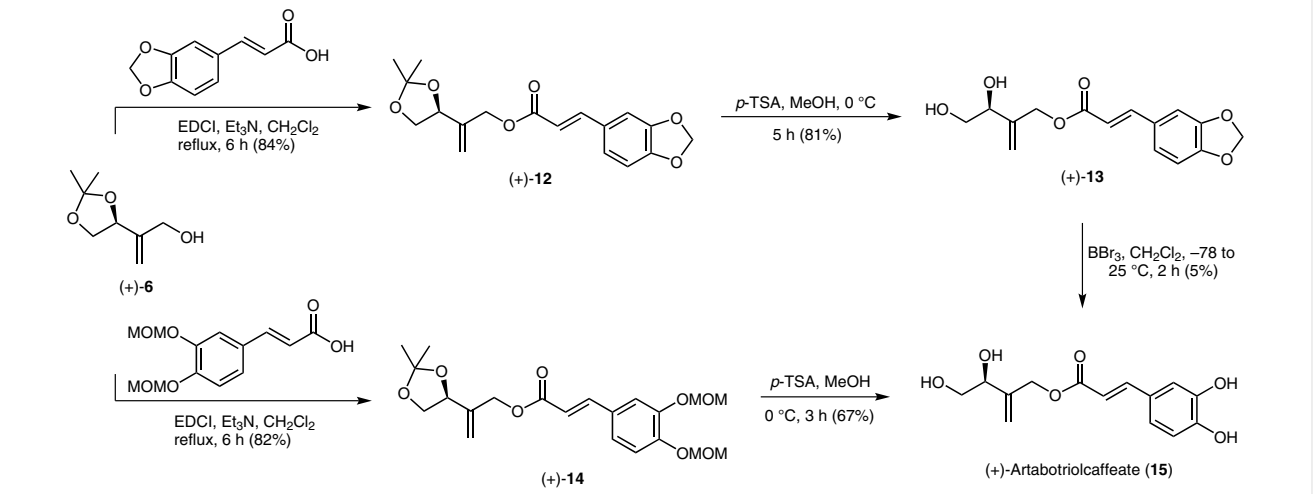
Entry	Solvent	Temp (Time)[a]	(–)-**1**: Yield (%) (*ee*)[b]	(+)-**2**: Yield (%) (*ee*)[b]
1	Benzene–PE	25 °C (24 h)	74 (ND)[c]	24 (ND)[c]
2	Benzene–PE	25 °C (48 h)	40 (72)	60 (51)
3	Acetone	25 °C (48 h)	72 (ND)[c]	28 (ND)[c]
4	Acetone	25 °C (72 h)	46 (98)	54 (94)
5	Acetone	25 °C (80 h)	44 (100)	56 (92)

[a] Reactions were monitored by HPLC.
[b] Chiral HPLC.
[c] ND: Not determined.

In the next part of studies, it was envisioned to synthesize natural product (+)-artabotriolcaffeate starting from (+)-artabotriol (**5**) (Scheme 3). Accordingly, the EDCI-persuaded dehydrative coupling of (+)-allylic alcohol **6** with the methylenedioxy-protected caffeaic acid provided the corresponding (+)-ester **12** in 84% yield. Acid-catalyzed deprotection of ketal moiety in compound (+)-**12** resulted into the essential product (+)-**13** in 81% yield. Though the final step of BBr_3-promoted deprotection of methylenedioxy bridge in product (+)-**13** was not very clean, the desired natural product (+)-artabotriolcaffeate (**15**) was obtained in ~5% yield. Plausibly the free vicinal diol system in compound (+)-**13**/(+)-**15** was responsible for the noticed excessive decomposition. However, the alternatively performed EDCI-prompted dehydrative coupling of (+)-allylic alcohol **6** with the double OMOM protected caffeaic acid delivered the corresponding (+)-ester **14** in 82% yield. The (+)-ester **14** on treatment with *p*-TSA in methanol directly furnished the desired natural product (+)-artabotriolcaffeate (**15**) in 67% yield. In the above specified reaction, fortunately both the deprotection of ketal moiety and the two OMOM groups took place in one pot and the formed product with four free hydroxyl groups was quite stable under the set of our reaction conditions. The analytical and spectral data obtained for synthetic product was in complete agreement with the reported data for natural product[4a] and the chemoenzymatic synthesis of (+)-artabotriolcaffeate (**15**) was accomplished in eight steps in 14% overall yield (Scheme 3).

In summary, we have completed the chemoenzymatic first synthesis of (+)-artabotriol sugar and used it as a potential starting material to accomplish the collective synthesis of enantiomerically pure bioactive natural products employing a chiral pool strategy. Synthesis of those multifunctional natural products is noteworthy from their stability point of view. Application of enzymatic resolution pathway also provides an access to antipodes of all the synthesized natural products. The present approach on collective total synthesis of enantiomerically pure natural and unnatural products will be highly useful for the rational design of focused mini-libraries of their analogues and congeners for SAR-studies.

Stereochemical assignments are based on the optical rotation of the known compounds. Melting points are uncorrected. The ^1H NMR spectra were recorded on 200 MHz, 400 MHz, or 500 MHz NMR spectrometer using TMS as an internal standard. The ^{13}C NMR spectra were recorded on 200 (50 MHz), 400 (100 MHz), or 500 (125 MHz) NMR spectrometer. Mass spectra were taken on MS-TOF mass spectrometer. HRMS (ESI) were taken on Orbitrap (quadrupole plus ion trap) and TOF mass analyzer. The IR spectra were recorded on an FT-IR spectrometer. Column chromatographic separations were carried out on silica gel (60–120 mesh). Commercially available TBDMSCl,



Scheme 3 Synthesis of (+)-artabotriolcaffeate

DIBAL, EDCI, DMAP, TBAF solution in THF (1.0 M), dimethoxypropane, cinnamic acid, Boc-protected diamines were used. Amano PS enzyme from Sigma-Aldrich was used.

Amano PS-Catalyzed Resolution of Dimethyl (±)-2-Hydroxy-3-methylenesuccinate [(±)-1]

To a stirred solution of dimethyl (±)-2-hydroxy-3-methylenesuccinate (**1**; 2.00 g, 9.25 mmol) and vinyl acetate (3.98 g, 46.25 mmol) in acetone (25 mL) was added the enzyme Amano PS (100 mg, Sigma-Aldrich). The resulting reaction mixture was stirred at 25 °C for 72 h with monitoring of the reaction progress by HPLC. The reaction mixture was filtered through a Celite bed and washed with EtOAc (30 mL). Concentration of organic layer in vacuo, followed by silica gel (60–120 mesh) column chromatographic purification of the resulting residue using EtOAc–PE (1:3) as an eluent afforded the pure product (–)-**1** as a viscous oil;[8a] yield: 920 mg (46%) and (+)-**2** as a viscous oil;[8a] yield: 1.36 g (54%).

(–)-1

$[\alpha]_D^{25}$ –18.5 (*c* 0.30 EtOH, 98% *ee*).

IR ($CHCl_3$): 3503, 1746, 1726, 1636 cm^{-1}.

^1H NMR ($CDCl_3$, 200 MHz): δ = 3.58 (br s, 1 H), 3.79 (s, 6 H), 4.88 (br s, 1 H), 5.97 (s, 1 H), 6.39 (s, 1 H).

^{13}C NMR ($CDCl_3$, 50 MHz): δ = 52.1, 53.0, 71.2, 129.2, 137.8, 165.6, 172.7.

MS (ESI): *m*/*z* =175 $[M + H]^+$, 197 $[M + Na]^+$.

(+)-2

$[\alpha]_D^{25}$ +48.6 (*c* 0.19 EtOH, 94% *ee*).

IR ($CHCl_3$): 1755, 1747, 1732, 1638 cm^{-1}.

^1H NMR ($CDCl_3$, 200 MHz): δ = 2.18 (s, 3 H), 3.77 (s, 3 H), 3.82 (s, 3 H), 6.00 (s, 1 H), 6.02 (s, 1 H), 6.51 (s, 1 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 20.6, 52.4, 52.7, 70.2, 130.7, 134.7, 164.8, 168.3, 169.7.

MS (ESI): *m*/*z* = 217 $[M + H]^+$, 239 $[M + Na]^+$, 255 $[M + K]^+$.

Dimethyl (*S*)-(+)-2-Hydroxy-3-methylenesuccinate [(+)-1]

To a stirred solution of acetate (+)-**2** (1.20 g, 5.55 mmol) in MeOH (10 mL) was added aq 2 N HCl (5 mL) at 0 °C and the reaction mixture was stirred for 2 h. The mixture was concentrated in vacuo and the obtained residue was diluted with EtOAc (20 mL). The organic layer was washed with H_2O (15 mL), brine (15 mL), and dried (Na_2SO_4). Concentration of organic layer in vacuo, followed by silica gel (60–120) column chromatographic purification of the resulting residue using EtOAc–PE (1:3) as an eluent afforded the pure product (+)-**1** as a viscous oil; yield: 760 mg (90%); $[\alpha]_D^{25}$ +18.0 (*c* 0.28 EtOH). The obtained spectroscopic data were identical with the data for (–)-**1**.

Dimethyl (*S*)- (–)-2-[(*tert*-Butyldimethylsilyl)oxy]-3-methylenesuccinate [(–)-3]

To a stirred solution of alcohol (+)-**1** (700 mg, 4.02 mmol) in CH_2Cl_2 (20 mL) were added imidazole (301 mg, 4.42 mmol) and TBDMSCl (666 mg, 4.42 mmol) at 0 °C under argon atmosphere. The reaction mixture was stirred at 25 °C for 6 h. The mixture was concentrated in vacuo and the obtained residue was diluted with EtOAc (40 mL). The organic layer was washed with H_2O (30 mL) and brine (30 mL), and dried (Na_2SO_4). Concentration of organic layer in vacuo, followed by silica gel (60–120 mesh) column chromatographic purification of the resulting residue using EtOAc–PE (1:19) as an eluent afforded the pure product (–)-**3** as a viscous oil; yield: 1.09 g (94%); $[\alpha]_D^{25}$ –20.9 (*c* 0.40 EtOH).

IR ($CHCl_3$): 1759, 1736, 1686 cm^{-1}.

^1H NMR ($CDCl_3$, 200 MHz): δ = 0.10 (s, 3 H), 0.13 (s, 3 H), 0.91 (s, 9 H), 3.72 (s, 3 H), 3.78 (s, 3 H), 5.08 (dd, *J* = 2, 2 Hz, 1 H), 6.07 (dd, *J* = 2, 2 Hz, 1 H), 6.38 (dd, *J* = 2, 2 Hz, 1 H).

^{13}C NMR ($CDCl_3$, 50 MHz): δ = –5.4, –5.2, 18.3, 25.6, 52.0, 52.3, 70.9, 126.4, 138.7, 165.9, 171.2.

MS (ESI): *m*/*z* = 289 $[M + H]^+$, 311 $[M + Na]^+$.

(+)-(*S*)-2-[(*tert*-Butyldimethylsilyl)oxy]-3-methylenebutane-1,4-diol [(+)-4]

To a stirred solution of diester (–)-**3** (1.00 g, 3.46 mmol) in THF (10 mL) was added DIBAL solution (0.16 mL, 0.16 mmol, 1 M in hexane) in dropwise fashion at –78 °C and the reaction mixture was stirred under argon atmosphere for 2 h. The reaction was quenched with sat. aq NH_4Cl and the reaction mass was concentrated in vacuo. The obtained residue was diluted with EtOAc (20 mL) and the organic layer was washed with brine (15 mL) and dried (Na_2SO_4). Concentration of organic layer in vacuo, followed by silica gel (60–120 mesh) column chromatographic purification of the resulting residue using EtOAc–PE (2:3) as an eluent afforded the pure product (+)-**4** as a viscous oil; yield: 580 mg (72%); $[\alpha]_D^{25}$ +6.3 (*c* 0.50 EtOH).

IR ($CHCl_3$): 3456, 1652 cm^{-1}.

^1H NMR ($CDCl_3$, 200 MHz): δ = 0.07 (s, 3 H), 0.10 (s, 3 H), 0.91 (s, 9 H), 2.46 (br s, 2 H), 3.54–3.70 (m, 2 H), 4.10 (d, *J* = 12 Hz, 1 H), 4.21 (d, *J* = 12 Hz, 1 H), 4.34 (t, *J* = 6 Hz, 1 H), 5.18 (br s, 1 H), 5.20 (br s, 1 H).

^{13}C NMR ($CDCl_3$, 50 MHz): δ = –5.1, –4.8, 18.1, 25.7, 63.1, 66.5, 75.2, 114.2, 148.1.

MS (ESI): *m*/*z* = 255 $[M + Na]^+$.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{11}H_{24}O_3NaSi$: 255.1392; found: 255.1383.

(+)-(*S*)-3-Methylenebutane-1,2,4-triol [(+)-Artabotriol, (+)-5]

To a stirred solution of diol (+)-**4** (550 mg, 2.36 mmol) in anhyd THF (10 mL) was added slowly a solution of Bu_4NF (2.60 mL, 2.60 mmol, 1 M in THF) at 0 °C and the reaction mixture was stirred for 10 h at 25 °C. The reaction was quenched with sat. aq NH_4Cl and the mixture was concentrated in vacuo. The obtained residue was diluted with EtOAc (20 mL) and the organic layer was washed with brine (20 mL) and dried (Na_2SO_4). Concentration of organic layer in vacuo, followed by silica gel (60–120) column chromatographic purification of the resulting residue using MeOH–EtOAc (1:19) as an eluent afforded the pure product (+)-**5** as a viscous oil; yield: 260 mg (93%); $[\alpha]_D^{25}$ +4.5 (*c* 0.28 MeOH).

IR ($CHCl_3$): 3355 cm^{-1}.

^1H NMR (200 MHz, acetone-d_6): δ = 3.40–4.35 (m, 8 H), 5.13 (s, 2 H).

^{13}C NMR (50 MHz, acetone-d_6): δ = 64.2, 68.0, 75.7, 112.0, 152.2.

(+)-(*S*)-2-(2,2-Dimethyl-1,3-dioxolan-4-yl)prop-2-en-1-ol [(+)-6]

To a stirred solution of triol (+)-**5** (250 mg, 2.11 mmol) in anhyd THF (5 mL) was added 2,2-dimethoxypropane (242 mg, 2.33 mmol) at 0 °C and the reaction mixture was stirred for 4 h at 25 °C. The mixture was concentrated in vacuo and the obtained residue was diluted with EtOAc (20 mL). The organic layer was washed with H_2O (20 mL) and brine (15 mL), and dried (Na_2SO_4). Concentration of organic layer in vacuo, followed by silica gel (60–120) column chromatographic puri-

fication of the resulting residue using EtOAc–PE (1:4) as an eluent afforded the pure product (+)-**6** as a viscous oil; yield: 284 mg (85%); $[\alpha]_D^{25}$ +35.9 (*c* 0.30 $CHCl_3$).

IR ($CHCl_3$): 3419, 1656 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 1.40 (s, 3 H), 1.46 (s, 3 H), 2.25 (br s, 1 H), 3.72 (t, *J* = 8 Hz, 1 H), 4.05–4.30 (m, 3 H), 4.68 (t, *J* = 8 Hz, 1 H), 5.21 (s, 2 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 25.4, 26.3, 63.3, 68.9, 77.7, 109.4, 113.4, 145.7.

(+)-(*S*)-2-(2,2-Dimethyl-1,3-dioxolan-4-yl)acrylic Acid [(+)-7]

To a stirred solution of (+)-**6** (100 mg, 0.63 mmol) in CH_2Cl_2 (2 mL) was added active MnO_2 (1.37 g, 15.75 mmol) at 25 °C and the reaction mixture was stirred for 36 h. The inorganic materials from the mixture were filtered off through a Celite bed, which was thoroughly washed with CH_2Cl_2 (10 mL). The combined filtrates were evaporated to give the crude α,β-unsaturated aldehyde, which was used in the next step without any purification. A suspension of Ag_2O prepared from $AgNO_3$ (115 mg, 0.69 mmol) and NaOH (100 mg, 2.52 mmol) in H_2O (3 mL) was added to the above crude aldehyde at 0 °C and the reaction mixture was stirred at 25 °C for 1 h. The mixture was filtered through a Celite bed and the filtrate was acidified with sat. aq oxalic acid followed by extraction with EtOAc. Concentration of organic layer in vacuo, followed by silica gel (60–120) column chromatographic purification of the resulting residue using EtOAc–PE (2:3) as an eluent afforded the pure product (+)-**7** as a white solid; yield: 74 mg (68%); mp 60–62 °C; $[\alpha]_D^{25}$ +37.2 (*c* 0.60 $CHCl_3$) {Lit.[9] $[\alpha]_D^{25}$ +47.3 (*c* 1.12 $CHCl_3$)}.

IR ($CHCl_3$): 3684, 3620, 1701, 1633 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 1.44 (s, 3 H), 1.47 (s, 3 H), 3.65 (t, *J* = 10 Hz, 1 H), 4.38 (t, *J* = 10 Hz, 1 H), 4.87 (t, *J* = 10 Hz, 1 H), 6.18 (s, 1 H), 6.45 (s, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 25.5, 26.3, 70.1, 73.8, 109.6, 127.1, 138.7, 170.7.

(+)-(*S*)-*N*-(4-Cinnamamidobutyl)-2-(2,2-dimethyl-1,3-dioxolan-4-yl)acrylamide [(+)-8]

To a stirred solution of acid (+)-**7** (40 mg, 0.23 mmol) in CH_2Cl_2 (5 mL) were added amine (56 mg, 0.25 mmol), EDCI (48 mg, 0.25 mmol), Et_3N (25 mg, 0.25 mmol), and a catalytic amount of DMAP at 0 °C under argon atmosphere. The reaction mixture was allowed to reach 25 °C and stirred for 4 h. The reaction was quenched with H_2O (5 mL) and the mixture was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic layers were washed with brine (10 mL) and dried (Na_2SO_4). Concentration of organic layer in vacuo, followed by silica gel (60–120) column chromatographic purification of the resulting residue using EtOAc as an eluent afforded the pure product (+)-**8** as a white solid; yield: 75 mg (87%); mp 110–112 °C; $[\alpha]_D^{25}$ +15.3 (*c* 0.20 $CHCl_3$).

IR ($CHCl_3$): 3688, 3621, 1732, 1663, 1623 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 1.42 (s, 3 H), 1.48 (s, 3 H), 1.63 (s, 2 H), 1.80 (s, 2 H), 3.37 (d, *J* = 5 Hz, 2 H), 3.43 (d, *J* = 5 Hz, 2 H), 3.75 (t, *J* = 10 Hz, 1 H), 4.29 (t, *J* = 10 Hz, 1 H), 4.86 (t, *J* = 10 Hz, 1 H), 5.70 (s, 1 H), 5.93 (s, 1 H), 6.20 (br s, 1 H), 6.43 (d, *J* = 20 Hz, 1 H), 6.80 (br s, 1 H), 7.36 (s, 3 H), 7.50 (d, *J* = 5 Hz, 2 H), 7.62 (d, *J* = 15 Hz, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 25.2, 26.4, 26.8, 27.0, 39.0, 39.2, 69.4, 75.6, 109.6, 120.6, 120.7, 127.7, 128.8, 129.6, 134.8, 140.9, 141.8, 166.1, 166.6.

MS (ESI): *m*/*z* = 395 $[M + Na]^+$.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{21}H_{28}N_2O_4Na$: 395.1941; found: 395.1933.

(+)-(*S*)-*N*-(4-Cinnamamidobutyl)-3,4-dihydroxy-2-methylenebutanamide [(+)-Grandiamide D, (+)-9]

To a stirred solution of (+)-**8** (50 mg, 0.13 mmol) in anhyd MeOH (2 mL) was added a catalytic amount of *p*-TSA (5 mg) at 0 °C under argon atmosphere and the reaction mixture was stirred for 2 h. The mixture was concentrated in vacuo and the obtained residue was diluted with EtOAc (10 mL). The organic layer was washed with brine (10 mL) and dried (Na_2SO_4). Concentration of organic layer in vacuo, followed by silica gel (60–120) column chromatographic purification of the resulting residue using MeOH–EtOAc (1:19) as an eluent afforded the pure product (+)-**9** as a white solid; yield: 34 mg (77%); mp 105–107 °C; $[\alpha]_D^{25}$ +2.7 (*c* 0.60 MeOH, 98% *ee*) {Lit.[5] $[\alpha]_D^{25}$ +4.76 (*c* 0.50 MeOH)}.

IR ($CHCl_3$): 3374, 1658, 1607 cm^{-1}.

^1H NMR (200 MHz, CD_3OD): δ = 1.61 (br s, 4 H), 3.20–3.40 (m, 4 H), 3.49 (dd, *J* = 11, 8 Hz, 1 H), 3.65 (dd, *J* = 10, 4 Hz, 1 H) 4.53 (t, *J* = 6 Hz, 1 H), 5.63 (s, 1 H), 5.80 (s, 1 H), 6.61 (d, *J* = 16 Hz, 1 H), 7.30–7.45 (m, 3 H), 7.45–7.60 (m, 3 H).

^{13}C NMR (100 MHz, CD_3OD): δ = 27.8, 27.9, 40.0, 40.2, 66.7, 73.3, 119.9, 121.9, 128.8, 129.9, 130.8, 136.3, 141.60, 146.3, 168.6, 170.4.

MS (ESI): *m*/*z* = 355 $[M + Na]^+$.

(+)-(*S*)-2-(2,2-Dimethyl-1,3-dioxolan-4-yl)allyl (*E*)-3-(Benzo[*d*][1,3]dioxol-5-yl)acrylate [(+)-12]

To a stirred solution of 3,4-(methylenedioxy)cinnamic acid (100 mg, 0.52 mmol) in CH_2Cl_2 (10 mL) were added alcohol (+)-**6** (74 mg, 0.47 mmol), EDCI (97 mg, 0.52 mmol), Et_3N (105 mg, 1.04 mmol), and a catalytic amount of DMAP at 0 °C under argon atmosphere. The reaction mixture was allowed to gradually reach to 25 °C and further refluxed for 6 h. The reaction was quenched with H_2O (10 mL) and the mixture was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic layers were washed with brine (10 mL) and dried (Na_2SO_4). Concentration of organic layer in vacuo, followed by silica gel (60–120) column chromatographic purification of the resulting residue using EtOAc–PE (1:3) as an eluent afforded the pure product (+)-**12** as a viscous oil; yield: 176 mg (84%); $[\alpha]_D^{25}$ +28.6 (*c* 0.64 $CHCl_3$).

IR ($CHCl_3$): 1708, 1632, 1608 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.41 (s, 3 H), 1.46 (s, 3 H), 3.77 (t, *J* = 8 Hz, 1 H), 4.19 (t, *J* = 8 Hz, 1 H), 4.64 (t, *J* = 8 Hz, 1 H), 4.75 (dd, *J* = 20, 16 Hz, 2 H), 5.28 (s, 1 H), 5.39 (s, 1 H), 6.01 (s, 2 H) 6.28 (d, *J* = 16 Hz, 1 H), 6.82 (d, *J* = 12 Hz, 1 H), 7.01 (d, *J* = 8 Hz, 1 H), 7.04 (s, 1 H), 7.61 (d, *J* = 16 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 25.6, 26.2, 64.0, 69.1, 77.1, 101.6, 106.5, 108.5, 109.4, 114.8, 115.4, 124.6, 128.6, 141.6, 145.0, 148.3, 149.7, 166.6.

MS (ESI): *m*/*z*= 355 $[M + Na]^+$.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{18}H_{20}O_6Na$: 355.1152; found: 355.1142.

(+)-(*S*)-3,4-Dihydroxy-2-methylenebutyl (*E*)-3-(Benzo[*d*][1,3]dioxol-5-yl)acrylate [(+)-13]

To a stirred solution of (+)-**12** (50 mg, 0.15 mmol) in anhyd MeOH (5 mL) was added a catalytic amount of *p*-TSA (5 mg) at 0 °C under argon atmosphere and the reaction mixture was stirred for 5 h. The mixture was concentrated in vacuo and the obtained residue was diluted with EtOAc (10 mL). The organic layer was washed with brine (10 mL) and

dried (Na_2SO_4). Concentration of organic layer in vacuo, followed by silica gel (60–120) column chromatographic purification of the resulting residue using EtOAc–PE (3:2) as an eluent afforded the pure product (+)-**13** as a viscous oil; yield: 36 mg (81%); $[\alpha]_D^{25}$ +3.7 (*c* 0.90 $CHCl_3$).

IR ($CHCl_3$): 3390, 1700, 1629, 1606 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 2.47 (br s, 1 H), 2.89 (br s, 1 H), 3.67 (dd, *J* = 12, 6 Hz, 1 H), 3.79 (dd, *J* = 12, 4 Hz, 1 H), 4.36 (dd, *J* = 6, 4 Hz, 1 H), 4.75 (s, 2 H), 5.32 (s, 1 H), 5.36 (s, 1 H), 6.01 (s, 2 H), 6.28 (d, *J* = 16 Hz, 1 H), 6.82 (d, *J* = 10 Hz, 1 H), 7.01 (d, *J* = 8 Hz, 1 H), 7.03 (s, 1 H), 7.62 (d, *J* = 16 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 64.3, 65.6, 73.2, 101.6, 106.5, 108.5, 115.2, 115.4, 124.7, 128.5, 143.3, 145.4, 148.3, 149.8, 167.0.

MS (ESI): *m*/*z* = 315 $[M + Na]^+$.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{15}H_{16}O_6Na$: 315.0839; found: 315.0833.

(+)-(*S*)-2-(2,2-Dimethyl-1,3-dioxolan-4-yl)allyl (*E*)-3-[3,4-Bis(methoxymethoxy)phenyl]acrylate [(+)-14]

To a stirred solution of (*E*)-3-[3,4-bis(methoxymethoxy)phenyl]acrylic acid (100 mg, 0.37 mmol) in CH_2Cl_2 (10 mL) were added alcohol (+)-**6** (52 mg, 0.33 mmol), EDCI (71 mg, 0.37 mmol), Et_3N (75 mg, 0.74 mmol) and a catalytic amount of DMAP at 0 °C under argon atmosphere. The reaction mixture was allowed to reach to 25 °C and further refluxed for 6 h. The reaction was quenched with H_2O (10 mL) and the mixture was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic layers were washed with brine (10 mL) and dried (Na_2SO_4). Concentration of organic layer in vacuo, followed by silica gel (60–120) column chromatographic purification of the resulting residue using EtOAc–PE (2:5) as an eluent afforded the pure product (+)-**14** as a viscous oil; yield: 176 mg (84%); $[\alpha]_D^{25}$ +7.5 (*c* 0.52, MeOH).

IR ($CHCl_3$): 3685, 3618, 1710, 1635, 1601 cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 1.41 (s, 3 H), 1.46 (s, 3 H), 3.52 (s, 3 H), 3.53 (s, 3 H), 3.77 (t, *J* = 8 Hz, 1 H), 4.19 (t, *J* = 8 Hz, 1 H), 4.65 (t, *J* = 8 Hz, 1 H), 4.75 (s, 2 H), 5.26 (s, 2 H), 5.27 (s, 2 H), 5.29 (s, 1 H), 5.39 (s, 1 H), 6.34 (d, *J* = 16 Hz, 1 H), 7.16 (s, 2 H), 7.37 (s, 1 H) 7.63 (d, *J* = 16 Hz, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 25.6, 26.3, 56.30, 56.32, 64.0, 69.1, 77.0, 95.1, 95.5, 109.5, 114.9, 115.7, 116.1, 116.2, 123.6, 128.8, 141.7, 144.9, 147.4, 149.3, 166.6.

MS (ESI): *m*/*z* = 431 $[M + Na]^+$.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{21}H_{28}O_8Na$: 431.1676; found: 431.1667.

(+)-(*S*)-3,4-Dihydroxy-2-methylenebutyl (*E*)-3-(3,4-Dihydroxyphenyl)acrylate [(+)-Artabotriolcaffeate, [(+)-15]

Method A: To a stirred solution of (+)-**13** (50 mg, 0.17 mmol) in CH_2Cl_2 (5 mL) was added a solution of BBr_3 (0.68 mL, 0.68 mmol, 1 M in CH_2Cl_2) in dropwise fashion at –78 °C and the reaction mixture was stirred under argon atmosphere for 30 min. The mixture was allowed to reach to 25 °C and stirred for 2 h. The reaction was quenched with ice cold H_2O (5 mL) and the mixture was extracted with CH_2Cl_2 (2 × 7 mL) and the organic layer was washed with brine (10 mL) and dried (Na_2SO_4). Concentration of organic layer in vacuo, followed by silica gel (60–120) column chromatographic purification of the resulting residue using EtOAc as an eluent afforded the pure product (+)-**15** as a white solid; yield: 2 mg (5%).

Method B: To a stirred solution of (+)-**14** (100 mg, 0.24 mmol) in anhyd MeOH (5 mL) were added a catalytic amount of *p*-TSA (5 mg) at 0 °C under argon atmosphere. The reaction mixture was stirred for 3 h. The mixture was concentrated in vacuo and the obtained residue was diluted with EtOAc (10 mL). The organic layer was washed with brine (5 mL) and dried (Na_2SO_4). Concentration of organic layer in vacuo, followed by silica gel (60–120) column chromatographic purification of the resulting residue using EtOAc as an eluent afforded the pure product (+)-**15** as a white solid; yield: 46 mg (67%); mp 168–169 °C; $[\alpha]_D^{25}$ +1.2 (*c* 0.80 MeOH) {Lit.[4a] $[\alpha]_D^{25}$ +2.3 (*c* 0.13 MeOH)}.

IR ($CHCl_3$): 3383, 1690, 1602 cm^{-1}.

^1H NMR (400 MHz, DMSO-d_6): δ = 3.35–3.50 (m, 2 H), 4.07 (q, *J* = 4 Hz, 1 H), 4.64 (t, *J* = 4 Hz, 1 H), 4.68 (s, 2 H), 5.01 (d, *J* = 8 Hz, 1 H), 5.11 (s, 1 H), 5.18 (s, 1 H), 6.30 (d, *J* = 16 Hz, 1 H), 6.77 (d, *J* = 8 Hz, 1 H), 7.02 (dd, *J* = 8, 4 Hz, 1 H), 7.07 (d, *J* = 4 Hz, 1 H), 7.50 (d, *J* = 16 Hz, 1 H), 9.15 (s, 1 H), 9.61 (s, 1 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 63.6, 65.3, 72.8, 112.0, 113.8, 114.9, 115.8, 121.5, 125.5, 145.4, 145.5, 145.6, 148.5, 166.2.

MS (ESI): *m*/*z* = 303 $[M + Na]^+$.

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Supporting Information

^1H NMR, ^{13}C NMR and DEPT spectra of compounds **1**–**9** and **12**–**15** as well as HPLC data for the enantiomeric purity of the compounds **1**, **2**, and **9** are available free of charge online at http://dx.doi.org/10.1055/s-0035-1561588.

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