# Chemoenzymatic Approach to the Total Synthesis of (+)-Bourgeanic Acid

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**Abstract:** A highly stereoselective total synthesis of (+)-bourgeanic acid has been accomplished by an enzymatic desymmetrization approach to create two methyl chiral centers. Other key steps involved in this approach are a Wittig reaction, a Gilman reaction, and TEMPO/iodobenzene diacetate mediated selective oxidation of the 1,3-diol, Yamaguchi lactonization and lithium hydroxide mediated partial hydrolysis (saponification) of the eight-membered cyclic dilactone

**Key words:** enzymatic desymmetrization, aliphatic depside, (+)-bourgeanic acid, bourgeanic lactone, (–)-hemibourgeanic acid, Wittig reaction, Gilman reaction, Yamaguchi lactonization

Natural products derived from polydeoxypropionates are known to exhibit promising biological activity.[1–3] (+)-Bourgeanic acid (**1**), a structurally unique aliphatic depside, was isolated by the Bodo group in 1973 from the species of lichen *Ramalina*.[4] The structure of **1** was established by the same group, as an esterification product of two molecules of (–)-hemibourgeanic acid (**3**), i.e. (2*S*,3*S*,4*R*,6*R*)-2,4,6-trimethyl-3-hydroxyoctanoic acid, and was confirmed by saponification of **1**. The absolute configuration of **1** was proposed by X-ray analysis of its *p*-bromophenacyl ester.[5,6] The formation of an eight-membered dilactone **2** takes place rapidly from compound **1** under mild dehydrating conditions, which was noted by Bodo et al. Based on conformational analysis, the dilactone exists as eight-membered ring that adopts a crown shaped conformation with $C_2$ axis of symmetry and all the substituents positioned in equatorial orientation, which favors the formation of eight-membered structure (Figure 1).[7]

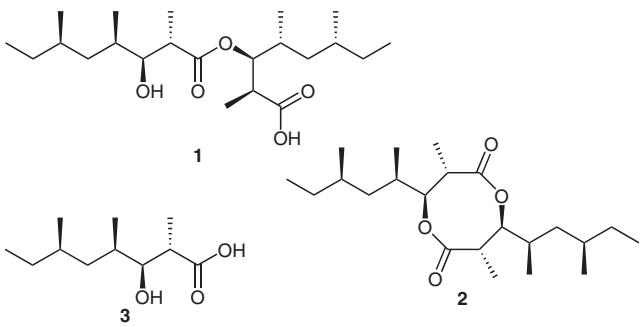
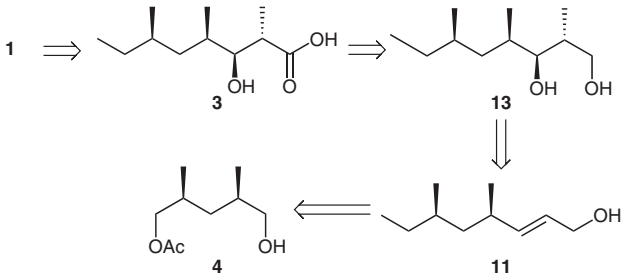



**Figure 1** Representative structures of (+)-bourgeanic acid (**1**), bourgeanic lactone (**2**), and (–)-hemibourgeanic acid (**3**)

The first total synthesis of (+)-bourgeanic acid (**1**) was reported by White et al. using methodology developed by Evans and Sonnet.[7] Subsequently, Breit et al. reported the total synthesis of **1** using *o*-DPPB [*o*-(diphenylphosphino)benzoyl]-directed copper-mediated allylic substitution as the key step.[8] Inspired by its fascinating structural features, recently we reported the total synthesis of (+)-bourgeanic acid (**1**).[9] In continuation of our research on total synthesis of polydeoxypropionate natural products,[10] we herein report a highly stereoselective total synthesis of (+)-bourgeanic acid (**1**) via an enzymatic desymmetrization approach.

The retrosynthetic route for the (+)-bourgeanic acid (**1**) is depicted in Scheme 1. (+)-Bourgeanic acid (**1**) was proposed to be synthesized from seco acid **3**, which could easily be prepared from diol **13**. The diol **13** was assumed to be prepared from compound **11** by Sharpless asymmetric epoxidation followed by epoxide ring opening. Compound **11** could in turn be obtained from known compound **4** by a sequence of reactions such as protection, deprotection, and Wittig olefination and diisobutylaluminum hydride reduction.




**Scheme 1** Retrosynthetic analysis of (+)-bourgeanic acid (**1**)

Our synthesis began with the known precursor **4** which was synthesized in four steps starting from *cis*-4,6-dimethylcyclohexane-1,3-dione.[11] Accordingly, *cis*-diketone was converted into the diacid using periodate oxidation.[12] Reduction of the diacid with lithium aluminum hydride in tetrahydrofuran at room temperature gave *meso*-2,4-dimethylpentane-1,5-diol in 98% yield. Desymmetrization of the *meso*-diol was achieved using a lipase (derived from porcine pancrease; PPL) and vinyl acetate in tetrahydrofuran at room temperature to afford the mono-acetate

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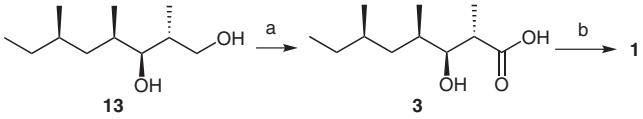
**4** in 47% yield with >95% ee along with the *meso*-diacetate.[13] It is noteworthy to mention that the *meso*-diacetate was again converted back into the *meso*-diol by treatment with sodium methoxide in methanol. The mono-acetate **4** was then protected as its silyl ether **5** using *tert*-butyldiphenylsilyl chloride and imidazole in dichloromethane. The mono-acetate **5** was treated with sodium methoxide in methanol to furnish the alcohol **6**, which was then protected as the tosylate **7** using tosyl chloride, triethylamine, and a catalytic amount of 4-(dimethylamino)pyridine. The tosylate **7** was then subjected to a Gilman reaction using lithium dimethylcuprate (6 equiv) to give the methyl derivative **8** in 92% yield.[14] Further desilylation of compound **8** using tetrabutylammonium fluoride in tetrahydrofuran gave the alcohol **9** in 95% yield. The resulting alcohol **9** was then subjected to Swern oxidation followed by Wittig olefination using ethyl (triphenylphosphoranylidene)acetate to afford the α,β-unsaturated ester **10**. Reduction of compound **10** using diisobutylaluminum hydride gave an allylic alcohol **11** in 92% yield, which was then subjected to Sharpless asymmetric epoxidation using titanium(IV) isopropoxide, (+)-diethyl tartrate, and *tert*-butyl hydroperoxide to afford epoxide **12** in 85% yield.[15] Ring opening of the epoxide **12** with dilithium cyano(dimethyl)cuprate gave 1,3-diol **13** in 84% yield (Scheme 2).[16]

Selective oxidation of 1,3-diol **13** using 2,2,6,6-tetramethylpiperidinoxyl (TEMPO) and iodobenzene diacetate afforded (2*S*,3*S*,4*R*,6*R*)-3-hydroxy-2,4,6-trimethyloctanal, which was further oxidized under Pinnick's conditions ($NaClO_2$, $NaH_2PO_4 \cdot 2\ H_2O$)[17] to give (–)-hemibourgeanic acid (**3**) in 75% yield.[18] The Yamaguchi macrolactonization of (–)-hemibourgeanic acid (**3**) using 2,4,6-trichlorobenzoyl chloride, triethylamine, and 4-(dimethylamino)pyridine under dilute conditions afforded bourgeanic lactone (**2**) in 85% yield.[19] Partial hydrolysis of **2** using 1.0 equivalents of lithium hydroxide in tetrahydrofuran–water (1:1) over 30 minutes gave the target natural product **1** in 54% yield as a white solid (Scheme 3). The analytical and spectral data of the target molecule **1** were in good agreement with the literature.[7–9]




**Scheme 3** *Reagents and conditions*: (a) (i) TEMPO, $PhI(OAc)_2$, $CH_2Cl_2$, 5 h, (ii) $NaClO_2$, $NaH_2PO_4 \cdot 2\ H_2O$, 2-methylbut-2-ene, *t*-BuOH–$H_2O$ (3:1), 75% over 2 steps; (b) (i) 2,4,6-$Cl_3C_6H_2COCl$, $Et_3N$, DMAP, 85%, (ii) LiOH, THF–$H_2O$ (1:1), 0.5 h, 54%.

In conclusion, we have demonstrated the total synthesis of (+)-bourgeanic acid (**1**) in a highly stereoselective manner. The synthesis involves very simple and straightforward reactions such as enzymatic desymmetrization of a *meso*-diol, Sharpless asymmetric epoxidation, Gilman's dimethylcuprate addition to an epoxide, 2,2,6,6-tetramethylpiperidinoxyl/iodobenzene diacetate oxidation of the primary alcohol, Yamaguchi lactonization, and lithium hydroxide mediated partial hydrolysis of the lactone as key steps.

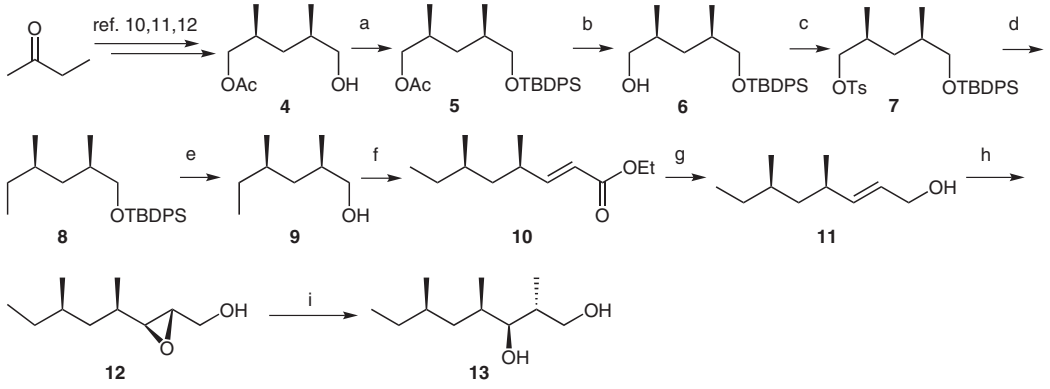
All solvents were purified by standard techniques. IR spectra were recorded on Perkin-Elmer FT-IR 240-c spectrophotometer using KBr optics. $^1H$ and $^{13}C$ NMR spectra were recorded on Bruker-300 spectrometer (300 MHz) and Varian Unity 500 spectrometer (500 MHz) in $CDCl_3$ using TMS as internal standard. Mass spectra were recorded on Finnigan MAT 1020 mass spectrometer operating at 70 eV. Column chromatography was performed using E. Merck 60–120, mesh silica gel. Melting points were recorded on Buchi R-535 apparatus and are uncorrected. Optical rotations were measured with JASCO DIP-370 polarimeter at 25 °C.

**(2*S*,4*R*)-5-Hydroxy-2,4-dimethylpentyl Acetate (4)**

To a stirred soln of *meso*-2,4-dimethylpentane-1,5-diol (4.0 g, 30.2 mmol) in THF (130 mL) and $H_2O$ (170 μL) were added PPL (11.6 gm) and vinyl acetate at r.t. The resulting mixture was stirred for 6 h at 25 °C. After complete conversion, the product was extracted with EtOAc. The organic extracts were dried ($Na_2SO_4$) and concentrated in vacuo and then purified by column chromatography (EtOAc–*n*-hexane, 1:5) to afford the monoacetate **4** (2.47 g, 47%) as a colorless liquid.

$[\alpha]_D^{25}$ +9.8 (*c* 0.6, $CHCl_3$).

IR (neat): 3431, 2957, 2924, 1738, 1462, 1391, 1371, 1243, 1030 $cm^{-1}$.




**Scheme 2** *Reagents and conditions*: (a) TBDPSCl, imidazole, $CH_2Cl_2$, 0 °C to r.t., 2 h, 98%; (b) NaOMe, MeOH, r.t., 1 h, 97%; (c) TsCl, $Et_3N$, DMAP, $CH_2Cl_2$, 0 °C to r.t., 4 h, 98%; (d) $Me_2LiCu$, –30 °C to 0 °C, 92%; (e) TBAF, THF, 3 h, 95%; (f) (1) $(COCl)_2$, DMSO, $Et_3N$, $CH_2Cl_2$, –78 °C, 3 h; (2) $Ph_3PCHCO_2Et$, benzene, 80 °C, 2 h, 80% over 2 steps; (g) DIBAL-H, $CH_2Cl_2$, 0 °C to r.t., 1 h, 92%; (h) L-(+)-DET, $Ti(Oi\text{-}Pr)_4$, TBHP, $CH_2Cl_2$, –20 °C, 6 h, 85%; (i) $Me_2Cu(CN)Li_2$, anhyd $Et_2O$, –78 °C to r.t., 3 h, 84%.

$^1$H NMR (300 MHz, $CDCl_3$): δ = 3.97 (dd, *J* = 10.5, 5.2 Hz, 1 H), 3.85 (dd, *J* = 10.5, 6.7 Hz, 1 H), 3.49 (dd, *J* = 10.5, 6.0 Hz, 1 H), 3.42 (dd, *J* = 10.5, 6.0 Hz, 1 H), 2.05 (s, 3 H), 1.82–1.96 (m, 1 H), 1.64–1.78 (m, 1 H), 1.43 (br, 1 H), 1.39–1.49 (m, 1 H), 1.15–1.30 (m, 1 H), 0.96 (d, *J* = 6.7 Hz, 3 H), 0.95 (d, *J* = 6.7 Hz, 3 H).

$^{13}$C NMR ($CDCl_3$, 75 MHz): δ = 171.3, 69.1, 67.9, 37.2, 32.9, 29.9, 20.9, 17.8, 17.2.

**(2*S*,4*R*)-5-(*tert*-Butyldiphenylsiloxy)-2,4-dimethylpentyl Acetate (5)**

To a stirred soln of alcohol **4** (2.35 g, 13.5 mmol), imidazole (1.47 g, 21.6 mmol), and DMAP (cat.) in $CH_2Cl_2$ (30 mL) was added TBDPSCl (4.45 g, 16.2 mmol) slowly at 0 °C. The resulting mixture was allowed to stir at r.t. for a further 2 h. Upon completion, the mixture was quenched with sat. $NH_4Cl$ soln and extracted with $CH_2Cl_2$ (3 × 20 mL). The combined organic layers were dried ($Na_2SO_4$) and concentrated in vacuo; the crude product was purified by column chromatography (EtOAc–*n*-hexane, 1:9) to give the silyl ether **5** (5.45 g, 98%) as a colorless oil.

$[\alpha]_D^{25}$ +7.9 (*c* 1.0, $CHCl_3$).

IR (neat): 3061, 2955, 2860, 1737, 1465, 1389, 1376, 1240, 1112 cm$^{-1}$.

$^1$H NMR (300 MHz, $CDCl_3$): δ = 0.88 (d, *J* = 6.8 Hz, 3 H), 0.94 (m, 1 H), 0.95 (d, *J* = 6.8 Hz, 3 H), 1.05 (s, 9 H), 1.46–1.55 (m, 1 H), 1.68–1.86 (m, 2 H), 2.0 (s, 3 H), 3.44 (ddd, *J* = 17.4, 9.8, 6.0 Hz, 2 H), 3.74–3.78 (m, 1 H), 3.87–3.92 (m, 1 H), 7.32–7.40 (m, 6 H), 7.65 (dd, *J* = 7.5, 1.5 Hz, 4 H).

$^{13}$C NMR (75 MHz, $CDCl_3$): δ = 17.6, 19.3, 20.9, 26.8, 29.9, 33.0, 37.3, 68.5, 69.3, 127.5, 129.5, 133.9, 135.6, 171.3.

MS (ESI): *m*/*z* = 435 [M + Na].

HRMS (ESI): *m*/*z* [M + Na] calcd for $C_{25}H_{36}NaO_3Si$: 435.2331; found: 435.2340.

**(2*S*,4*R*)-5-(*tert*-Butyldiphenylsiloxy)-2,4-dimethylpentan-1-ol (6)**

To a stirred soln of acetate **5** (5.41 g, 13.13 mmol) in MeOH (20 mL) was added NaOMe (1.4 g, 26.26 mmol). The resulting mixture was allowed to stir for 1.5 h at r.t. It was then quenched with sat. $NH_4Cl$ soln and extracted with $CH_2Cl_2$ (3 × 30 mL). The combined organic layers were washed with sat. NaCl soln and then dried (anhyd $Na_2SO_4$). Removal of the solvent followed by purification by column chromatography (silica gel, EtOAc–*n*-hexane, 3:7) gave the alcohol **6** (4.71 g, 97%) as a colorless oil.

$[\alpha]_D^{25}$ +1.1 (*c* 1.3, $CHCl_3$).

IR (neat): 3353, 3073, 3053, 2954, 2849, 1461, 1421, 1077, 813 cm$^{-1}$.

$^1$H NMR (300 MHz, $CDCl_3$): δ = 0.87 (d, *J* = 6.8 Hz, 3 H), 0.91 (m, 1 H), 0.94 (d, *J* = 6.8 Hz, 3 H), 1.05 (s, 9 H), 1.42–1.50 (m, 1 H), 1.55–1.63 (m, 1 H), 1.68–1.76 (m, 1 H), 3.28–3.34 (m, 1 H), 3.39–3.51 (m, 3 H), 7.34–7.41 (m, 6 H), 7.60–7.64 (m, 4 H).

$^{13}$C NMR (75 MHz, $CDCl_3$): δ = 135.6, 133.9, 129.5, 127.6, 68.7, 68.3, 37.1, 33.1, 26.9, 26.5, 19.3, 17.9, 17.4.

MS (ESI): *m*/*z* = 393 [M + Na].

HRMS (ESI): *m*/*z* [M + Na] calcd for $C_{23}H_{34}NaO_2Si$: 393.2225; found: 393.2223.

**(2*S*,4*R*)-5-(*tert*-Butyldiphenylsilyloxy)-2,4-dimethylpentyl 4-Methylbenzenesulfonate (7)**

To a stirred soln of alcohol **6** (4.62 g, 12.48 mmol) in $CH_2Cl_2$ at 0 °C were added $Et_3N$ (2.25 mL, 16.23 mmol), DMAP (cat.), and TsCl (2.61 g, 13.7 mmol) successively. The resulting mixture was stirred at r.t. for 4 h and then quenched with $H_2O$ and extracted with $CH_2Cl_2$ (3 × 25 mL). The combined organic layers were washed with sat. NaCl soln, dried ($Na_2SO_4$), and concentrated in vacuo. The crude product was then purified by column chromatography (EtOAc–*n*-hexane, 1:9) to give the tosylate **7** (6.42 g, 98%) as a colorless oil.

$[\alpha]_D^{25}$ +3.8 (*c* 1.7, $CHCl_3$).

IR (neat): 3063, 2958, 2930, 2859, 2360, 1463, 1361, 1179, 1104, 965, 701 cm$^{-1}$.

$^1$H NMR (300 MHz, $CDCl_3$): δ = 7.79–7.74 (m, 4 H), 7.61 (m, 2 H), 7.42–7.34 (m, 6 H), 7.29 (m, 2 H), 3.85–3.80 (m, 1 H), 3.71–3.66 (m, 1 H), 3.44–3.33 (m, 2 H), 2.43 (s, 3 H), 1.85–1.77 (m, 1 H), 1.66–1.59 (m, 1 H), 1.44–1.38 (m, 1 H), 1.04 (s, 9 H), 0.92 (m, 1 H), 0.89 (d, *J* = 6.6 Hz, 3 H), 0.85 (d, *J* = 6.6 Hz, 3 H).

$^{13}$C NMR (75 MHz, $CDCl_3$): δ = 144.5, 135.5, 134.7, 133.7, 129.7, 129.5, 127.8, 127.5, 75.1, 68.3, 36.7, 32.7, 30.3, 26.8, 21.5, 19.2, 17.5, 17.1.

MS (ESI): *m*/*z* = 547 [M + Na].

HRMS (ESI): *m*/*z* [M + Na] calcd for $C_{30}H_{40}O_4NaSiS$: 547.2314; found: 547.2325.

***tert*-Butyl[(2*R*,4*R*)-2,4-dimethylhexyloxy]diphenylsilane (8)**

To a solution of $Me_2CuLi$, prepared from CuI (13.8 g, 72.6 mmol) and MeLi (96.7 mL, 145.1 mmol, 1.5 M in $Et_2O$) in $Et_2O$ (60 mL) at –25 °C was added tosylate **7** (6.35 g, 12.1 mmol) in $Et_2O$ and the reaction mixture was slowly warmed to 0 °C. After 3 h stirring at r.t., the mixture was quenched with sat. aq $NH_4Cl$ and extracted with $Et_2O$ (2 × 100 mL). The combined organic extract was washed with brine and dried over anhyd $Na_2SO_4$. Solvent removal then gave the crude product which was purified by column chromatography (EtOAc–hexane, 1:19) to give compound **8** (4.09 g, 92%) as a colorless oil.

$[\alpha]_D^{25}$ +4.9 (*c* 1.3, $CHCl_3$).

IR (neat): 3069, 2959, 2858, 1465, 1385, 1108, 703 cm$^{-1}$.

$^1$H NMR (500 MHz, $CDCl_3$): δ = 7.7 (m, 4 H), 7.45–7.38 (m, 6 H), 3.56–3.42 (m, 2 H), 1.76 (m, 1 H), 1.42–1.29 (m, 3 H), 1.08 (s, 9 H), 0.96 (d, *J* = 7 Hz, 3 H), 0.93–0.89 (m, 2 H), 0.76 (d, *J* = 7 Hz, 3 H), 0.74 (t, *J* = 6 Hz, 3 H).

$^{13}$C NMR (75 MHz, $CDCl_3$): δ = 135.6, 133.9, 129.5, 127.6, 68.7, 40.3, 33.1, 31.8, 29.1, 26.8, 19.7, 19.3, 17.7, 11.1.

MS (ESI): *m*/*z* = 391 [M + Na]$^+$.

**(2*R*,4*R*)-2,4-Dimethylhexan-1-ol (9)**

To a stirred soln of compound **8** (3.91 g, 10.62 mmol) in THF (20 mL) was added 1.0 M TBAF in THF (17 mL, 17 mmol) dropwise. The resulting mixture was allowed to stir at r.t. for 6 h. Removal of the solvent followed by purification by column chromatography (silica gel, EtOAc–hexane, 2:8) gave the alcohol **9** (1.31 g, 95%) as a colorless oil.

$[\alpha]_D^{25}$ +4.1 (*c* 2.3, $CHCl_3$).

IR (neat): 3380, 2959, 2925, 1686, 1461, 1031 cm$^{-1}$.

$^1$H NMR (300 MHz, $CDCl_3$): δ = 3.51–3.31 (m, 2 H), 1.74–1–64 (m, 1 H), 1.46–1.28 (m, 3 H), 1.14–1.05 (m, 1 H), 0.91 (d, *J* = 6.8 Hz, 3 H), 0.88 (t, *J* = 6.9 Hz, 3 H), 0.87 (d, *J* = 6.8 Hz, 3 H).

$^{13}$C NMR (100 MHz, $CDCl_3$): δ = 68.4, 40.6, 33.1, 31.5, 29.0, 19.8, 17.3, 11.1.

**Ethyl (4*R*,6*R*,*E*)-4,6-Dimethyloct-2-enoate (10)**

To a stirred soln of oxalyl chloride (1.85 mL, 19.38 mmol) in anhyd $CH_2Cl_2$ (20 mL) at –78 °C was added DMSO (2.06 mL, 29.07 mmol) slowly dropwise under a $N_2$ atmosphere. After 15 min stirring, a soln of alcohol **9** (1.26 g, 9.69 mmol) in anhyd $CH_2Cl_2$ (20 mL) was added. After 45 min of stirring at –78 °C, $Et_3N$ (6.7 mL,

48.46 mmol) was added and the mixture was stirred for 0.5 h at –78 °C and then 0.5 h at 0 °C. The mixture was then quenched with sat. $NH_4Cl$ soln (300 mL) and extracted with $CH_2Cl_2$ (2 × 800 mL). The combined organic layers were washed with $H_2O$ (500 mL), followed by brine (300 mL) soln, dried ($Na_2SO_4$), and concentrated in vacuo. To a stirred soln of the above crude aldehyde in benzene was added stabilized ylide, $Ph_3PCHCO_2Et$ (4.52 g, 8.12 mmol) and the mixture was allowed to reflux for 2 h. It was then concentrated in vacuo. Purification of the crude ester by column chromatography (silica gel, EtOAc–hexane, 1:9) gave the pure unsaturated ester **10** (1.53 g, 80% over 2 steps) as a colorless liquid.

$[\alpha]_D^{25}$ –40.2 (*c* 0.4, $CHCl_3$).

IR (neat): 2962, 2921, 1722, 1651, 1460, 1181 $cm^{-1}$.

$^1H$ NMR (300 MHz, $CDCl_3$): δ = 0.83 (d, *J* = 6.4 Hz, 3 H), 0.85 (t, *J* = 7.3 Hz, 3 H), 0.97 (d, *J* = 6.7 Hz, 3 H), 1.05–1.15 (m, 4 H), 1.22–1.40 (m, 3 H), 1.57 (br s, 1 H), 2.24 (m, 1 H), 4.10 (dd, *J* = 5.8, 0.6 Hz, 2 H), 5.51 (ddt, *J* = 15.4, 7.6, 1.0 Hz, 1 H), 5.60 (dtd, *J* = 15.4, 5.8, 0.6 Hz, 1 H).

$^{13}C$ NMR (100 MHz, $CDCl_3$): δ = 11.3, 19.1, 21.5, 30.0, 31.9, 34.1, 44.2, 64.0, 127.2, 139.3.

HRMS (ESI): *m*/*z* [M + Na] calcd for $C_{12}H_{22}NaO_2$: 221.1517; found: 221.1525.

**(4*R*,6*R*,*E*)-4,6-Dimethyloct-2-en-1-ol (11)**

To a stirred soln of ester **10** (1.47 g, 7.42 mmol) in anhyd $CH_2Cl_2$ (20 mL) at 0 °C was added 1.0 M DIBAL-H in toluene (8.9 mL, 8.9 mmol) dropwise. The resulting mixture was stirred for 1 h at r.t. and then quenched with MeOH and sat. sodium potassium tartarate soln (15 mL) at 0 °C. The organic layer was washed with brine, dried (anhyd $Na_2SO_4$), and purified by column chromatography (EtOAc–hexane, 3:7) to give the allyl alcohol **11** (1.06 g, 92%) as oil.

$[\alpha]_D^{25}$ –25.3 (*c* 0.5, $CHCl_3$).

IR (neat): 3357, 2960, 2917, 2872, 1459 $cm^{-1}$.

$^1H$ NMR (300 MHz, $CDCl_3$): δ = 0.83 (d, *J* = 6.4 Hz, 3 H), 0.85 (t, *J* = 7.3 Hz, 3 H), 0.97 (d, *J* = 6.6 Hz, 3 H), 1.04–1.16 (m, 2 H), 1.22–1.38 (m, 3 H), 1.59 (br s, 1 H), 2.24 (m, 1 H), 4.08 (dd, *J* = 5.1, 0.6 Hz, 2 H), 5.47–5.64 (m, 2 H).

$^{13}C$ NMR (75 MHz, $CDCl_3$): δ = 11.2, 18.9, 21.3, 29.8, 31.8, 33.9, 44.1, 63.8, 127.1, 139.1.

LC-MS: *m*/*z* = 174 [$M + NH_4$].

**{(2*S*,3*S*)-3-[(2*R*,4*R*)-4-Methylhexan-2-yl]oxiran-2-yl}methanol (12)**

To a stirred suspension of powdered 4Å molecular sieves in $CH_2Cl_2$ (15 mL) at –20 °C were added L-(+)-DET (0.15 mL, 0.86 mmol) and $Ti(O\textit{i}\text{-}Pr)_4$ (0.2 mL, 0.69 mmol). After 30 min, a soln of allylic alcohol **11** (0.9 g, 5.77 mmol) in $CH_2Cl_2$ (10 mL) was added to the above suspension, and then 4–5 M TBHP in toluene (2.5 mL, 11.5 mmol) was added. The resulting mixture was stirred at –20 °C for 6 h and then quenched with $H_2O$ (20 mL). The above mixture was treated with 3 M NaOH and then saturated with solid NaCl and the resulting mixture was stirred vigorously for 30 min. The layers were separated, and the aqueous layer was extracted with $CH_2Cl_2$ (3 × 10 mL). The combined organic layers were dried ($Na_2SO_4$) and concentrated under reduced pressure. The crude product was purified by column chromatography (EtOAc–*n*-hexane, 3:7) to afford the epoxy alcohol **12** (0.86 g, 85%) as a colorless liquid.

$[\alpha]_D^{25}$ –34.8 (*c* 2.0, $CHCl_3$).

IR (neat): 3424, 2962, 2922, 2874, 1461 $cm^{-1}$.

$^1H$ NMR (300 MHz, $CDCl_3$): δ = 0.87 (t, *J* = 7.4 Hz, 3 H), 0.88 (d, *J* = 6.4 Hz, 3 H), 1.01 (d, *J* = 6.4 Hz, 3 H), 1.05–1.16 (m, 2 H), 1.26 1.50 (m, 4 H), 1.89 (br s, 1 H), 2.64 (dd, *J* = 7.4, 2.3 Hz, 1 H), 2.92 (dt, *J* = 4.5, 2.4 Hz, 1 H), 3.53–3.62 (m, 1 H), 3.83–3.91 (m, 1 H).

$^{13}C$ NMR (75 MHz, $CDCl_3$): δ = 11.1, 17.7, 19.4, 29.4, 31.6, 32.8, 40.9, 58.7, 60.7, 61.8.

HRMS (ESI): *m*/*z* [M + Na] calcd for $C_{10}H_{20}NaO_2$: 195.1360; found: 195.1368.

**(2*R*,3*S*,4*R*,6*R*)-2,4,6-Trimethyloctane-1,3-diol (13)**

A soln $Me_2Cu(CN)Li_2$ was prepared by addition of 1.5 M MeLi in $Et_2O$ (36.7 mL, 55.1 mmol) to a suspension of anhyd CuCN (2.46 g, 27.5 mmol) in anhyd $Et_2O$ (10 mL) at –78 °C under argon. The mixture was stirred at –30 °C until it became homogeneous. To this soln was added a soln of the epoxy alcohol **12** (0.79 g, 4.59 mmol) in $Et_2O$ (5 mL) at –78 °C. The resulting mixture was allowed to warm slowly to r.t. over 3 h. Upon completion, the mixture was treated with sat. $NH_4Cl$ (28 mL), aq 25% $NH_3$ (7 mL), $H_2O$ (50 mL), and $Et_2O$ (90 mL). The resulting mixture was then allowed to stir for 30 min. The layers were separated and the aqueous phase was saturated with NaCl and extracted with $Et_2O$ (4 × 50 mL). The combined organic layers were dried ($Na_2SO_4$) and concentrated in vacuo. The residue was dissolved in $CH_2Cl_2$ (20 mL) and treated with $NaIO_4$ (0.5 g, 2.3 mmol) at r.t. for 1 h. The mixture was filtered and the filtrate was concentrated in vacuo. The residue was purified by column chromatography (EtOAc–*n*-hexane, 3:7) to furnish the diol **13** (0.72 g, 84%) as a colorless oil.

$[\alpha]_D^{25}$ –9.5 (*c* 0.6, $CHCl_3$).

IR (neat): 3372, 2960, 2924, 1460, 1379, 1278, 1076, 1027, 979 $cm^{-1}$.

$^1H$ NMR (300 MHz, $CDCl_3$): δ = 0.81 (d, *J* = 7.5 Hz, 3 H), 0.86 (d, *J* = 6.8 Hz, 3 H), 0.87 (d, *J* = 6.8 Hz, 3 H), 0.88 (t, *J* = 7.5 Hz, 3 H), 1.0–1.15 (m, 2 H), 1.30–1.47 (m, 3 H), 1.71–1.81 (m, 1 H), 1.83–1.93 (m, 2 H), 3.46 (dd, *J* = 9.1, 2.5 Hz, 1 H), 3.66 (dd, *J* = 10.6, 7.5 Hz, 1 H), 3.72 (dd, *J* = 10.6, 3.8 Hz, 1 H).

$^{13}C$ NMR (75 MHz, $CDCl_3$): δ = 11.2, 12.7, 13.5, 19.5, 29.4, 31.4, 32.1, 37.5, 40.9, 68.9, 79.7.

MS (EI): *m*/*z* = 188 [M].

HRMS: *m*/*z* [M] calcd for $C_{11}H_{24}O_2$: 188.1776; found: 188.1781.

**(2*S*,3*S*,4*R*,6*R*)-3-Hydroxy-2,4,6-trimethyloctanoic Acid (3)**

$PhI(OAc)_2$ (0.77 g, 2.39 mmol) and TEMPO (54 mg, 0.32 mmol) were added sequentially to a stirred soln of the diol **12** (0.30 g, 1.59 mmol) in $CH_2Cl_2$ (6 mL) at r.t. After completion, the mixture was treated with sat. $Na_2S_2O_3$. The separated organic phase was washed with sat. $NaHCO_3$ soln and brine soln, followed by dried (anhyd $Na_2SO_4$), and concentrated under reduced pressure. The crude aldehyde was used in next step without purification. The aldehyde was dissolved in *t*-BuOH–$H_2O$ (3:1). To the mixture were added $NaH_2PO_4 \cdot 2\,H_2O$ (0.44 g, 3.22 mmol) and 2-methylbut-2-ene (0.11 g, 1.61 mmol) followed by $NaClO_2$ (0.29 g, 3.22 mmol). The resulting mixture was stirred at 0 °C. After completion, the solvent was evaporated under reduced pressure and the residue was diluted with EtOAc. The organic layer was washed once with brine and dried ($Na_2SO_4$) and concentrated to afford the crude acid which was purified by column chromatography (silica gel, EtOAc–*n*-hexane, 1:1) to give the pure β-hydroxy acid **3** (0.24 g, 75%).

$[\alpha]_D^{25}$ –3.5 (*c* 1.0, $CHCl_3$).

IR (neat): 3439, 2961, 2923, 1712, 1459, 1380, 1262, 1212, 982, 769 $cm^{-1}$.

$^1H$ NMR (300 MHz, $CDCl_3$): δ = 3.64 (dd, *J* = 8.4, 3.0 Hz, 1 H), 2.7–2.60 (m, 1 H), 1.78–1.69 (m, 1 H), 1.47–1.23 (m, 5 H), 1.18 (d, *J* = 7.1 Hz, 3 H), 1.13–1.01 (m, 1 H), 0.87 (m, 9 H).

$^{13}C$ NMR (75 MHz, $CDCl_3$): δ = 181.2, 75.1, 43.2, 40.8, 31.6, 31.3, 29.2, 19.4, 14.1, 12.9, 11.1.

MS (ESI): *m/z* = 201 [M – H].

HRMS: *m/z* [M – H] calcd for $C_{11}H_{21}O_3$: 201.1490; found: 201.1486.

**(+)-Bourgeanic Acid (1)**

To a stirred solution of bourgeanic lactone **2** (60 mg, 0.163 mmol) in THF–$H_2O$ (1:1; 4 mL) was added LiOH (3.8 mg, 0.163 mmol) at r.t. After 30 min, the formation of the required acid was observed by TLC. The mixture was then acidified to pH 2 with 2 M HCl and then THF was removed under reduced pressure. The combined organic phase was dried over $Na_2SO_4$, and the solvent was removed under vacuum. The resulting aqueous layer was extracted with EtOAc (3 × 10 mL), concentrated under vacuum, and the residue was purified by silica gel chromatography (EtOAc–hexane, 1:1) to afford **1** (33 mg, 54%) as a white solid; mp 123–124 °C.

$[\alpha]_D^{25}$ +7.0 (*c* 1.0, $CHCl_3$).

IR (KBr): 3446, 2923, 2854, 1728, 1639, 1460 $cm^{-1}$.

$^1H$ NMR (300 MHz, $CDCl_3$): δ = 5.16 (dd, *J* = 9.0, 3.0 Hz, 1 H), 3.70 (dd, *J* = 9.8, 2.2 Hz, 1 H), 2.86–2.74 (m, 1 H), 2.67–2.54 (m, 1 H), 1.96–1.85 (m, 1 H), 1.79–1.59 (m, 2 H), 1.54–1.38 (m, 2 H), 1.34–1.23 (m, 3 H), 1.18 (d, *J* = 6.7 Hz, 3 H), 1.10 (d, *J* = 7.5 Hz, 3 H), 1.14–1.01 (m, 3 H), 0.94 (d, *J* = 7.5 Hz, 3 H), 0.96–0.90 (m, 1 H), 0.89 (t, *J* = 6.7 Hz, 3 H), 0.87 (d, *J* = 6.0 Hz, 3 H), 0.85 (d, *J* = 6.0 Hz, 3 H), 0.84 (t, *J* = 7.5 Hz, 3 H), 0.82 (d, *J* = 6.7 Hz, 3 H).

$^{13}C$ NMR (75 MHz, $CDCl_3$): δ = 177.1, 175.7, 76.5, 74.8, 44.0, 41.9, 41.0, 40.6, 31.2, 30.9, 30.9, 29.4, 29.2, 19.4, 19.3, 14.4, 13.8, 12.7, 11.2, 11.1.

MS (ESI): *m/z* = 385 [M – H].

HRMS: *m/z* [M – H] calcd for $C_{22}H_{42}O_5$: 385.2953; found: 385.2966.

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