

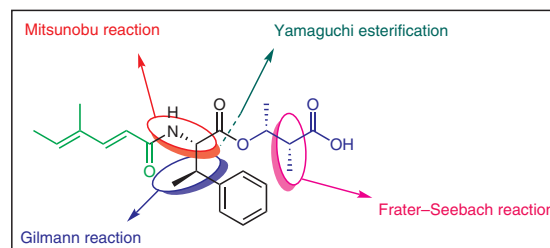
# First Total Synthesis of Jomthonic Acid A<sup>1</sup>

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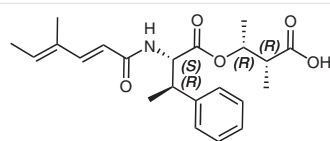
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**Abstract** A stereoselective total synthesis of jomthonic acid A is described. The key features of the synthetic strategy are a Sharpless asymmetric epoxidation, a Gilman reagent-induced methylation, a Mitsunobu reaction, a Yamaguchi esterification, and an *O*-(benzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium tetrafluoroborate (TBTU)-mediated amide coupling. Jomthonic acid A is an architecturally rare amino acid containing a  $\beta$ -methylphenylalanine residue and a 4-methyl-(2*E*,4*E*)-hexa-2,4-dienoate moiety. It shows antidiabetic and antiatherogenic activities when tested against mouse ST-13 preadipocytes.

**Key words** Gilman reaction, Mitsunobu reaction, Yamaguchi esterification, amide coupling, total synthesis, jomthonic acid A

Actinomycetes are a major source of structurally diverse secondary metabolites that exhibit antagonism to Gram-positive bacteria. Igarashi and co-workers recently reported the isolation and characterization of the modified amino acid derivative jomthonic acid A (**1**; Figure 1) from the culture broth of a soil-derived actinomycete of the genus *Streptomyces* sp. BB47.<sup>2</sup> Compound **1** contains four stereocenters and several unusual structural features, such as the 4-methyl-(2*E*,4*E*)-hexa-2,4-dienoate and  $\beta$ -methylphenylalanine fragments. Jomthonic acid A exhibits antidiabetic and antiatherogenic activities against mouse ST-13 preadipocytes and it also inhibits the differentiation of preadipocytes into mature adipocytes at 2–50  $\mu$ M.

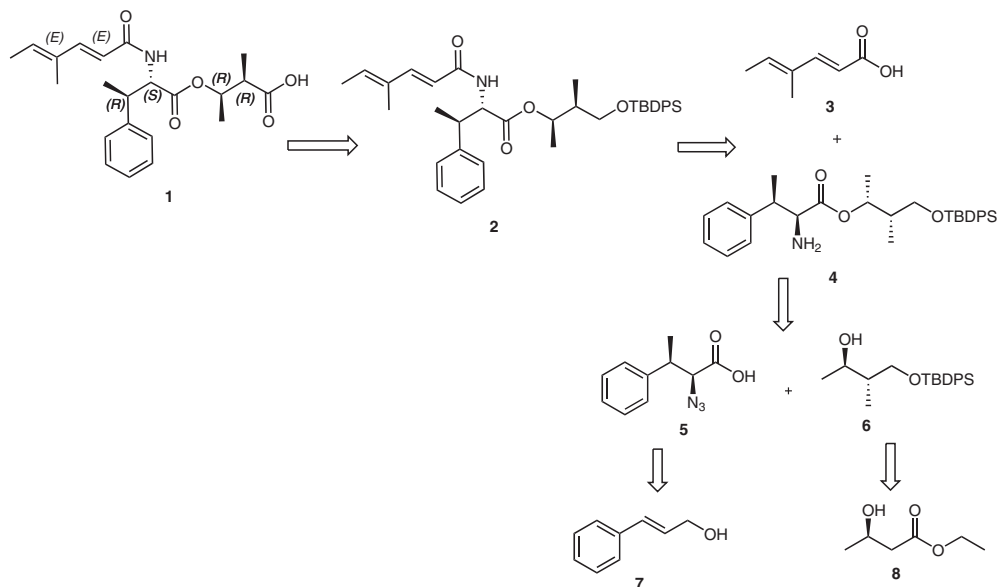


Jomthonic Acid A (1)

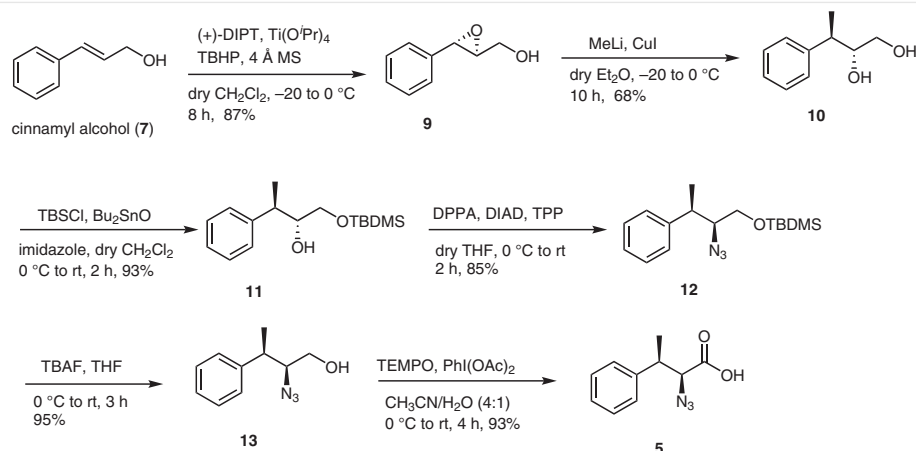
Figure 1

In continuation of our interest in the total synthesis of bioactive natural products,<sup>3</sup> we have developed a convergent synthesis of jomthonic acid A (**1**). Our retrosynthetic analysis of **1** (Scheme 1) suggested that it might be derived from the amido ester **2** through deprotection followed by oxidation. Compound **2** might be prepared from 4-methylhexa-2,4-dienoic acid (**3**) and amino ester **4** through amide coupling.<sup>4</sup> Compound **4** might be assembled from azide **5** and alcohol **6** under Yamaguchi conditions.<sup>5</sup> Compound **5** might, in turn, be obtained from *trans*-cinnamyl alcohol (**7**) by epoxidation, regioselective ring opening of the epoxide with the Gilman reagent, and Mitsunobu reaction followed by oxidation. Likewise, alcohol **6** might be obtained by Frater-Seebach alkylation of ethyl (3*R*)-3-hydroxybutanoate.<sup>6</sup>

Our synthetic approach began with commercially available *trans*-cinnamyl alcohol (**7**; Scheme 2). This was converted into the chiral epoxy alcohol **9** in 87% yield by Sharpless asymmetric epoxidation. Regioselective ring opening of epoxide **9** with the Gilman reagent gave diol **10** in 68% yield.<sup>7</sup> Next, selective protection of the primary hydroxy group of 1,2-diol **10** by TBDMSCl/imidazole/ $\text{Bu}_2\text{SnO}$  in  $\text{CH}_2\text{Cl}_2$  at 0 °C for two hours gave silyl ether **11** in 93% yield. Subsequently, **11** was converted into the corresponding azide **12** in 85% yield under Mitsunobu conditions by using diphenyl phosphorazidate (DPPA) and DIAD in anhydrous THF at 0 °C to room temperature.<sup>8,9</sup> Subsequent deprotection of silyl ether **12** with TBAF in THF afforded alcohol **13** (95% yield).<sup>10</sup> The purity of compound **13** was determined by LC/MS analysis, and the diastereomeric excess was found to be 98% (see Supporting Information). Compound **13**, on further oxidation with TEMPO and  $\text{PhI}(\text{OAc})_2$  in  $\text{CH}_2\text{Cl}_2$ - $\text{H}_2\text{O}$  (4:1) gave acid **5** in 93% yield.<sup>11</sup>

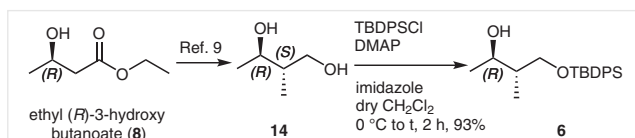


**Scheme 1** Retrosynthetic analysis of jomthonic acid A (**1**)



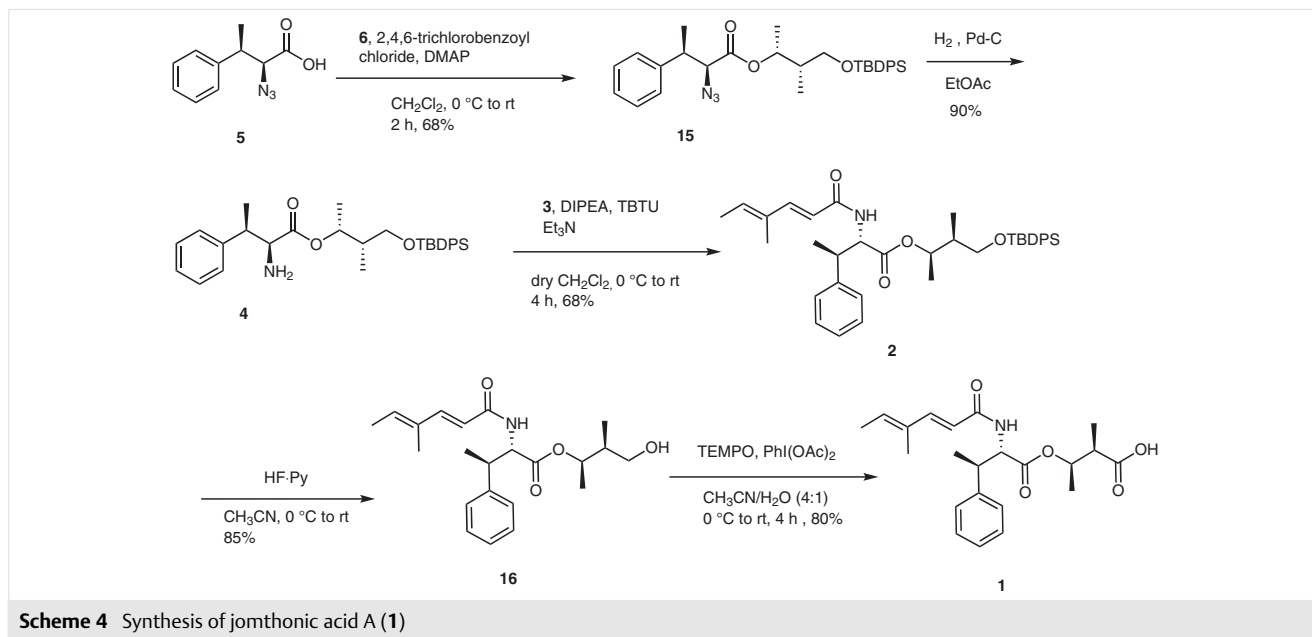
**Scheme 2** Synthesis of fragment **5**

In parallel, compound **6**, required for the Yamaguchi esterification, was prepared from commercially available ethyl (*3R*)-3-hydroxybutanoate (**8**; Scheme 3). Frater–Seebach alkylation of **8** gave 1,3-diol **14**.<sup>6,12</sup> Selective protection of the primary hydroxy group of this 1,3-diol with TBDP-*S*Cl/imidazole/*Bu*<sub>2</sub>SnO in CH<sub>2</sub>Cl<sub>2</sub> at 0 °C to room temperature gave silyl ether **6** in 93% yield.



**Scheme 3** Synthesis of fragment **6**

Having both coupling partners in hand, we performed a Yamaguchi esterification of acid **5** with silyl ether **6** to give the azide derivative **15** in 68% yield (Scheme 4).<sup>5,13</sup> Reduction of azide **15** with H<sub>2</sub> (1 atm) over Pd/C gave amine **4** in 90% yield. Compound **2** was obtained in 68% yield by *O*-(benzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium tetrafluoroborate (TBTU)-mediated coupling of amine **4** with acid **3**, prepared from tiglic aldehyde by a reported procedure.<sup>4,14</sup> Subsequently, the silyl group was removed by treatment with HF·Py in CH<sub>3</sub>CN at 0 °C to room temperature to afford the alcohol **16** in 85% yield.<sup>15</sup> Finally oxidation of **16** with TEMPO and PhI(OAc)<sub>2</sub> in CH<sub>2</sub>Cl<sub>2</sub>–H<sub>2</sub>O (4:1) gave the target compound **1**. Spectroscopic data for this product were consistent with the reported values.<sup>2</sup>



In conclusion, the first stereoselective total synthesis of jomthonic acid A was achieved by a convergent approach with an 8.0% overall yield by employing a Sharpless asymmetric epoxidation, a Gilman reaction, a Mitsunobu azidation, hydrogenation, a Yamaguchi esterification, and amide coupling as the key steps.

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## Supporting Information

Supporting information for this article is available online at <https://doi.org/10.1055/s-0039-1691503>.

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- (9) **[[{(2S,3R)-2-Azido-3-phenylbutyl}oxy](tert-butyl)dimethylsilane (12)**  
To a solution of compound **11** (1.7 g, 6.0 mmol) in THF (20 mL) at 0 °C were added DIAD (2.39 mL, 12.1 mmol) and TPP (3.1 g, 12.1 mmol), and the mixture was stirred for 5 min. DPPA (2.61 g, 9.5 mmol) was added at 0 °C, and the mixture was allowed to warm to rt, stirred for 3 h, then warmed to 35 °C for 24 h. The mixture was then concentrated and purified by flash column chromatography [silica gel, EtOAc–hexane (8:92)] to give a pale-yellow oil; yield: 1.48 g (80%).  
<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ = 7.33–7.26 (m, 2 H), 7.24–7.16 (m, 3 H), 3.60 (dd, *J* = 10.4, 3.1 Hz, 1 H), 3.4–3.40 (m, 1 H), 3.39–3.33 (m, 1 H), 2.91 (dq, *J* = 14.1, 7.0 Hz, 1 H), 1.35 (d, *J* = 7.0 Hz, 3 H), 0.88 (s, 9 H), –0.02 (s, 6 H). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ = 143.5, 128.6, 127.55, 126.5, 69.2, 64.9, 40.3, 25.8, 18.4, 18.2, –5.6. EI-ESI: *m/z* = 323 [M + NH<sub>4</sub>]<sup>+</sup>.
- (10) **(2S,3R)-2-Azido-3-phenylbutan-1-ol (13)**  
A 1.0 M solution of TBAF in THF (1.54 g, 8.85 mL, 5.9 mmol) was added to a solution of compound **12** (1.2 g, 3.9 mmol) in anhyd THF (10 mL) at 0 °C, and the mixture was stirred at rt for 2 h. When the reaction was complete, the mixture was diluted with H<sub>2</sub>O (5 mL), and the mixture was extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with brine (2 × 10 mL) and dried (Na<sub>2</sub>SO<sub>4</sub>). Filtration, and evaporation of the solvent under reduced pressure, followed by column chromatography [silica gel, EtOAc–hexane (20:80)] gave a colorless liquid; yield: 0.676 g (90%); [α]<sub>D</sub><sup>25</sup> –9.1 (*c* 0.7, CHCl<sub>3</sub>).

$^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 7.37–7.30 (m, 2 H), 7.27–7.19 (m, 3 H), 3.60–3.50 (m, 2 H), 3.46–3.37 (m, 1 H), 2.94–2.83 (m, 1 H), 1.40 (d,  $J$  = 6.9 Hz, 3 H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 142.8, 128.7, 127.3, 127.0, 70.3, 64.0, 41.4, 18.4. EI-ESI:  $m/z$  = 209  $[\text{M} + \text{NH}_4]^+$ .

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(13) **(1R,2S)-3-[[tert-Butyl(diphenyl)silyloxy]-1,2-dimethylpropyl (2S,3R)-2-Azido-3-phenylbutanoate (15)**

To a stirred solution of azide **5** (0.200 g, 0.9 mmol), alcohol **6** (0.333 g, 0.9 mmol), and  $\text{Et}_3\text{N}$  (0.4 mL, 2.9 mmol) in THF (5 mL) was added 2,4,6-trichlorobenzoyl chloride (0.2 mL, 1.1 mmol) at rt, and the mixture was stirred for 2 h. DMAP (0.238 g, 1.6 mmol) was added at rt, and the mixture was stirred for 6 h. When the reaction was complete, the mixture was quenched with sat. aq  $\text{NaHCO}_3$  and washed with brine. The organic layer was dried ( $\text{Na}_2\text{SO}_4$ ), filtered, and concentrated in vacuo. The residue was purified by column chromatography [silica gel, EtOAc–hexane (20:80)] to give a colorless oil; yield: 0.349 g, (68%);  $[\alpha]_{\text{D}}^{25}$  +22.0 (c 0.5,  $\text{CHCl}_3$ ).

$^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 7.67–7.62 (m, 4 H), 7.45–7.35 (m, 6 H), 7.25–7.17 (m, 5 H), 5.02–4.95 (m, 1 H), 3.80 (dd,  $J$  = 7.2, 14.9 Hz, 1 H), 3.56–3.40 (m, 2 H), 3.28–3.20 (m, 1 H), 1.93–1.74 (m, 1 H), 1.34 (d,  $J$  = 7.0 Hz, 3 H), 1.05 (d,  $J$  = 5.1 Hz, 3 H), 1.04 (s, 9 H), 0.87 (d,  $J$  = 6.4 Hz, 3 H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):

$\delta$  = 169.1, 141.4, 135.5, 129.6, 128.5, 127.7, 127.6, 127.2, 73.6, 67.6, 65.1, 41.7, 39.9, 26.8, 19.2, 17.0, 15.7, 12.3. HRMS (ESI):  $m/z$   $[\text{M} + \text{NH}_4]^+$  calcd for  $\text{C}_{31}\text{H}_{43}\text{N}_4\text{O}_3\text{Si}$ : 547.3104; found: 547.3104.

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(15) **(1R,2S)-3-Hydroxy-1,2-dimethylpropyl (βR)-β-Methyl-N-[(2E,4E)-4-methylhexa-2,4-dienyl]-L-phenylalaninate (16)** HF-pyridine (0.09 mL) was added dropwise to a stirred solution of **2** (0.070 g, 0.1 mmol) in anhyd  $\text{CH}_3\text{CN}$  (2 mL) at 0 °C, and the mixture was stirred for 12 h. The reaction was then quenched by adding sat. aq  $\text{NaHCO}_3$  (1 mL) and the mixture was extracted with EtOAc (3 × 5 mL). The organic extracts were washed with brine (5 mL), dried ( $\text{Na}_2\text{SO}_4$ ), filtered, and concentrated in vacuo. The residue was purified by column chromatography [silica gel, EtOAc–hexane (25:75)] to give a pale-yellow liquid; yield: 0.030 g (85%);  $[\alpha]_{\text{D}}^{25}$  +20.33 (c 0.3,  $\text{CHCl}_3$ ).

$^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 7.33–7.23 (m, 5 H), 7.23 (d,  $J$  = 7.0 Hz, 1 H), 5.95 (q,  $J$  = 7.0 Hz, 1 H), 6.15–6.10 (m, 1 H), 5.77 (d,  $J$  = 15.2 Hz, 1 H), 4.82–4.70 (m, 2 H), 3.54 (dd,  $J$  = 7.0, 11.4 Hz, 1 H), 3.40 (dd,  $J$  = 6.7, 11.4 Hz, 1 H), 3.26–3.20 (m, 1 H), 3.13 (dq,  $J$  = 7.4, 7.7 Hz, 1 H), 1.86–1.80 (m, 1 H), 1.80 (d,  $J$  = 7.0 Hz, 3 H), 1.76 (s, 3 H), 1.40 (d,  $J$  = 7.1 Hz, 3 H), 0.87 (d,  $J$  = 7.0 Hz, 3 H), 0.78 (d,  $J$  = 6.4 Hz, 3 H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 172.0, 166.7, 146.9, 141.2, 135.6, 133.3, 128.4, 127.9, 127.2, 116.6, 73.6, 64.2, 58.2, 43.0, 40.4, 18.1, 16.8, 14.4, 13.2, 11.8. HRMS (ESI):  $m/z$   $[\text{M} + \text{H}]^+$  calcd for  $\text{C}_{22}\text{H}_{32}\text{NO}_4$ : 374.2331; found: 374.2328.