

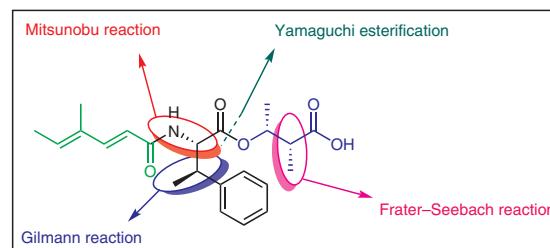
First Total Synthesis of Jomthonic Acid A¹

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Received: 14.10.2019

Accepted after revision: 07.11.2019

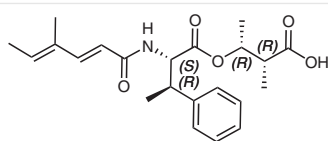
Published online: 29.11.2019

DOI: 10.1055/s-0039-1691503; Art ID: st-2019-d0549-l

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 β -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. BB47.² Compound **1** contains four stereocenters and several unusual structural features, such as the 4-methyl-(2*E*,4*E*)-hexa-2,4-dienoate and β -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 μ M.

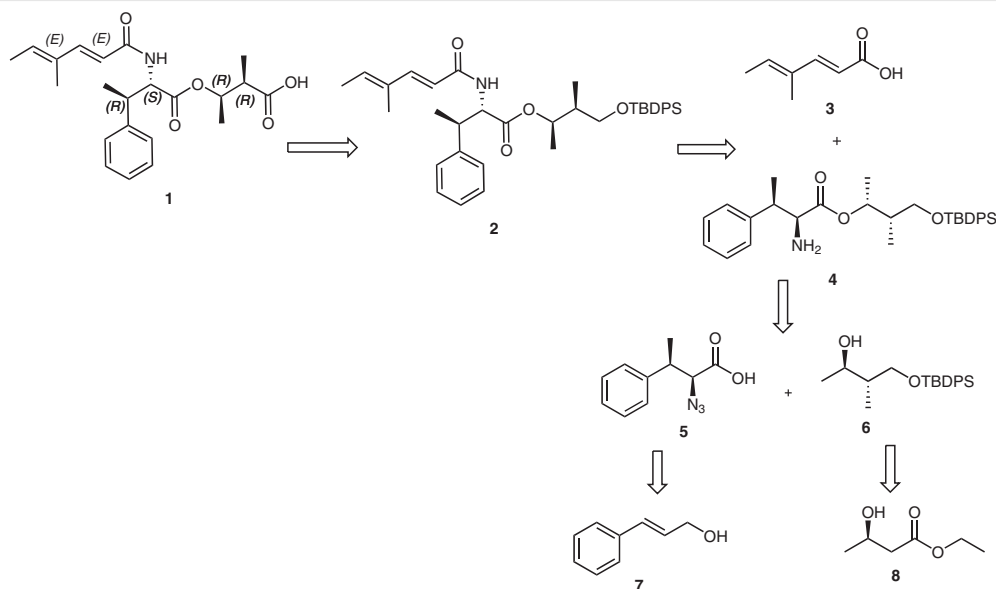
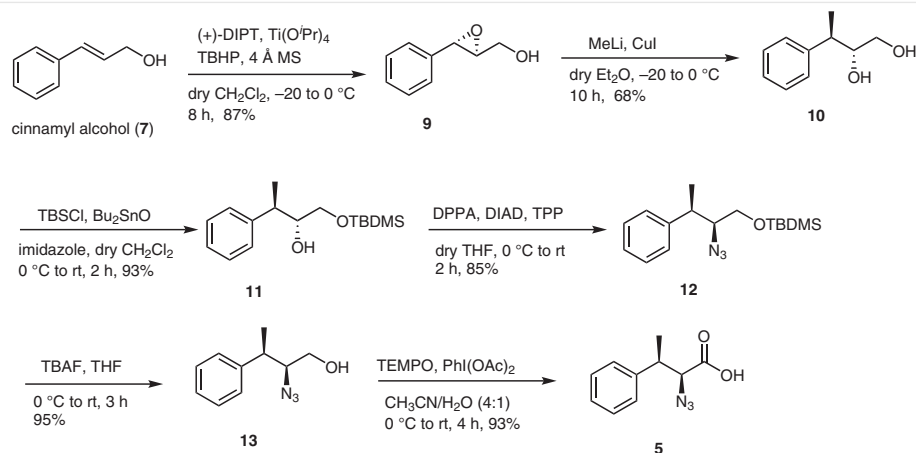


Jomthonic Acid A (**1**)

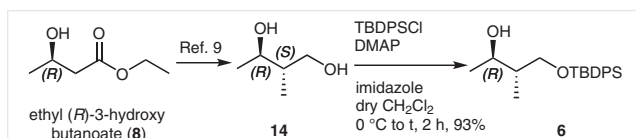
Figure 1

In continuation of our interest in the total synthesis of bioactive natural products,³ 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.⁴ Compound **4** might be assembled from azide **5** and alcohol **6** under Yamaguchi conditions.⁵ 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.⁶

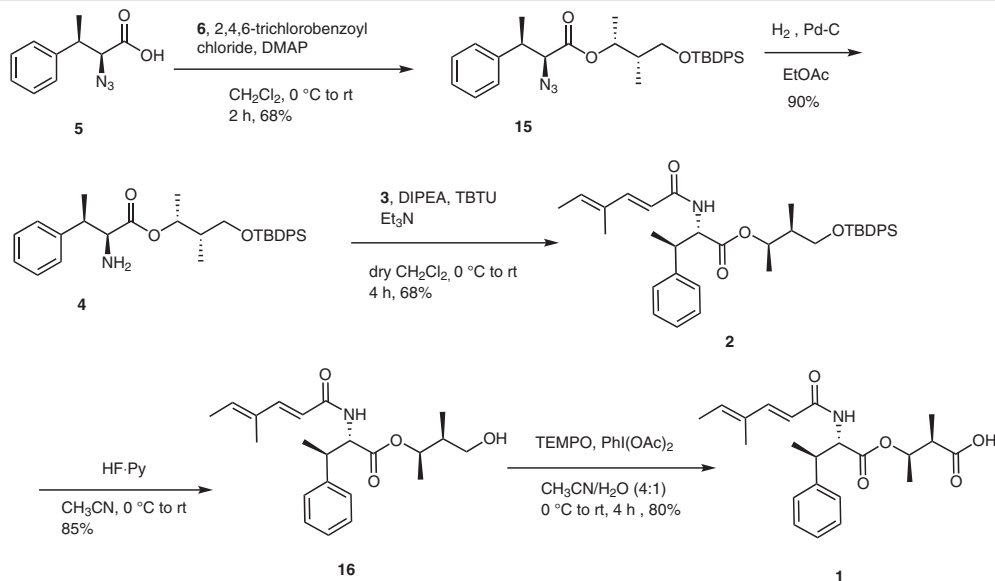
Our synthetic approach began with commercially available *trans*-cinnamyl alcohol (**7**; Scheme 2). This was converted into the chiral epoxy alcohol **9** in 87% yield by Sharpless asymmetric epoxidation. Regioselective ring opening of epoxide **9** with the Gilman reagent gave diol **10** in 68% yield.⁷ Next, selective protection of the primary hydroxy group of 1,2-diol **10** by TBDMSCl/imidazole/ Bu_2SnO in CH_2Cl_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.^{8,9} Subsequent deprotection of silyl ether **12** with TBAF in THF afforded alcohol **13** (95% yield).¹⁰ 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 CH_2Cl_2 - H_2O (4:1) gave acid **5** in 93% yield.¹¹

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 (3*R*)-3-hydroxybutanoate (**8**; Scheme 3). Frater–Seebach alkylation of **8** gave 1,3-diol **14**.^{6,12} Selective protection of the primary hydroxy group of this 1,3-diol with TBDP-SCI/imidazole/ Bu_2SnO in CH_2Cl_2 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).^{5,13} Reduction of azide **15** with H_2 (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.^{4,14} Subsequently, the silyl group was removed by treatment with HF-Py in CH_3CN at 0 °C to room temperature to afford the alcohol **16** in 85% yield.¹⁵ Finally oxidation of **16** with TEMPO and $\text{PhI}(\text{OAc})_2$ in CH_2Cl_2 - H_2O (4:1) gave the target compound **1**. Spectroscopic data for this product were consistent with the reported values.²



Scheme 4 Synthesis of jomthonic acid A (1)

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.

Acknowledgment

M.D. and B.S. are grateful to the UGC, New Delhi for the financial support in the form of fellowships.

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%).
¹H NMR (400 MHz, CDCl₃): 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). ¹³C NMR (100 MHz, CDCl₃): 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* + NH₄]⁺.
- (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 H₂O (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 (Na₂SO₄). 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*]_D²⁵ –9.1 (c 0.7, CHCl₃).

^1H NMR (400 MHz, CDCl_3): δ = 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}C NMR (100 MHz, CDCl_3): δ = 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)silyl]oxy]-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 Et_3N (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 NaHCO_3 and washed with brine. The organic layer was dried (Na_2SO_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, CHCl_3).

^1H NMR (500 MHz, CDCl_3): δ = 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}C NMR (100 MHz, CDCl_3):

δ = 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 CH_3CN (2 mL) at 0 °C, and the mixture was stirred for 12 h. The reaction was then quenched by adding sat. aq NaHCO_3 (1 mL) and the mixture was extracted with EtOAc (3 × 5 mL). The organic extracts were washed with brine (5 mL), dried (Na_2SO_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, CHCl_3).

^1H NMR (500 MHz, CDCl_3): δ = 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}C NMR (100 MHz, CDCl_3): δ = 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.