


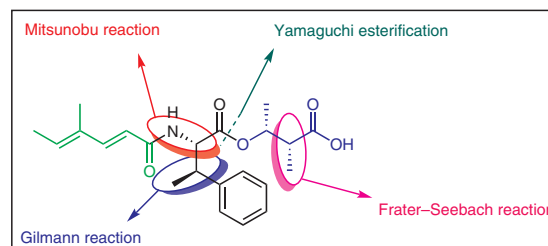
First Total Synthesis of Jomthonic Acid A¹

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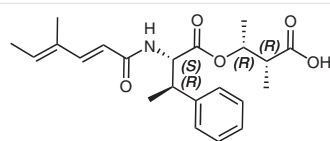
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Abstract A stereoselective total synthesis of jomthonic acid A is described. The key features of the synthetic strategy are a Sharpless asymmetric epoxidation, a Gilman reagent-induced methylation, a Mitsunobu reaction, a Yamaguchi esterification, 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 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.

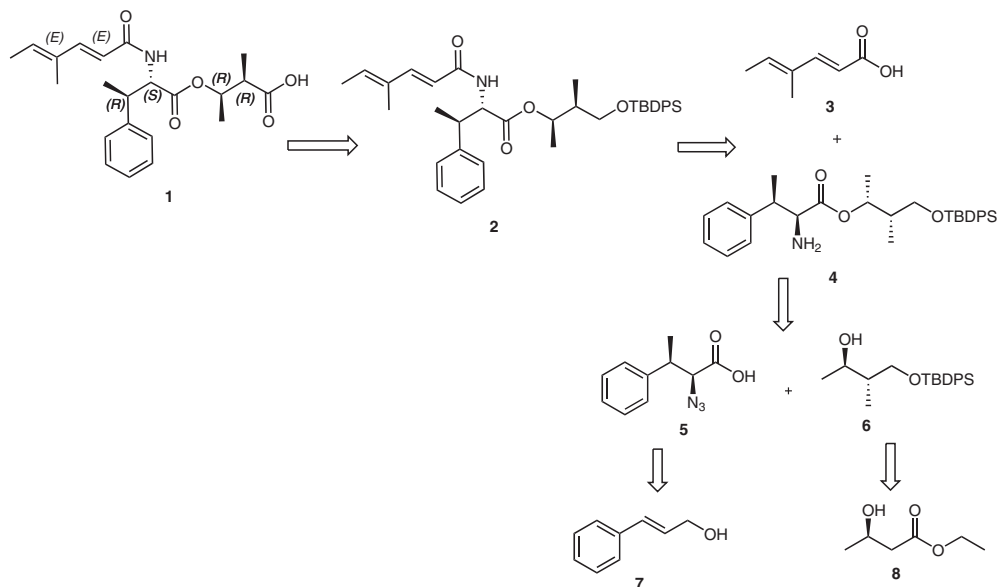


Jomthonic Acid A (**1**)

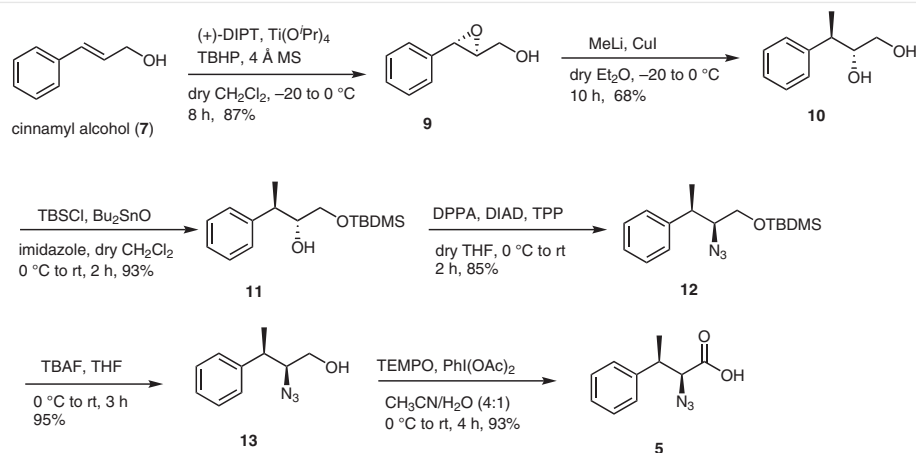
Figure 1

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

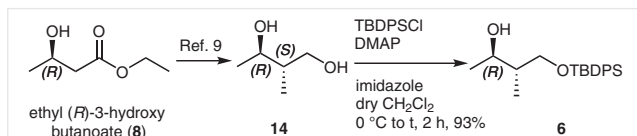


Scheme 1 Retrosynthetic analysis of jomthonic acid A (**1**)



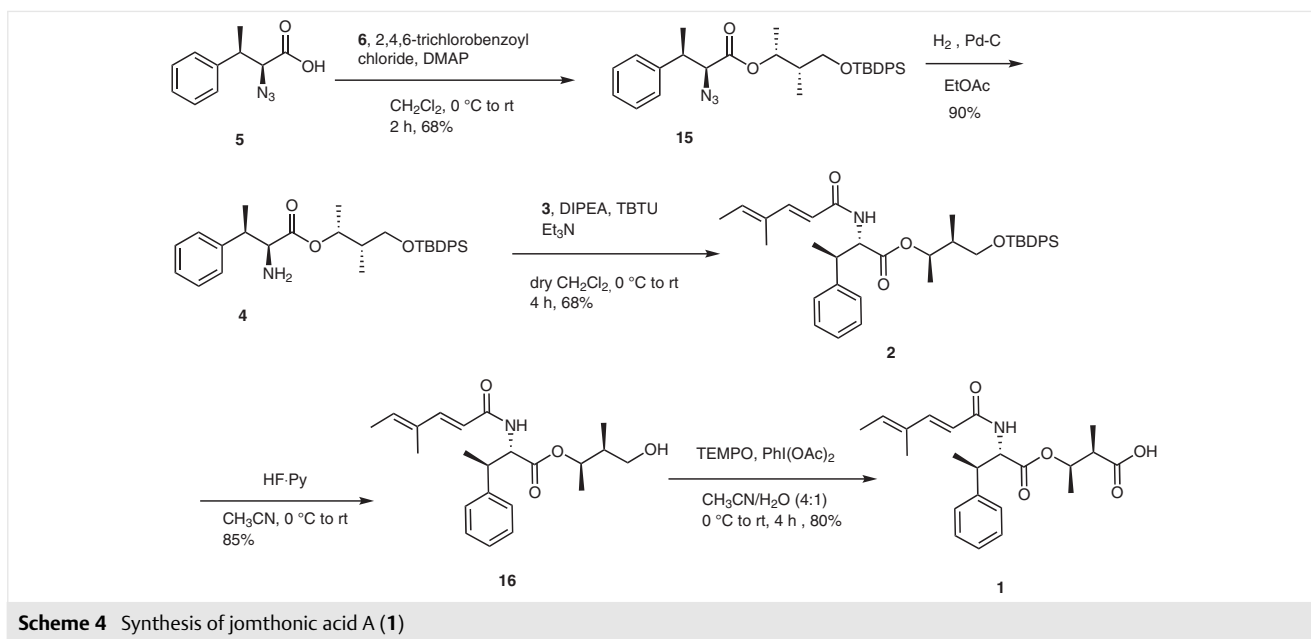
Scheme 2 Synthesis of fragment **5**

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-*S*Cl/imidazole/*Bu*₂SnO in CH₂Cl₂ 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 H₂ (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 CH₃CN at 0 °C to room temperature to afford the alcohol **16** in 85% yield.¹⁵ Finally oxidation of **16** with TEMPO and PhI(OAc)₂ in CH₂Cl₂–H₂O (4:1) gave the target compound **1**. Spectroscopic data for this product were consistent with the reported values.²



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

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Supporting Information

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

References and Notes

- (1) Communication No. IICT/Pubs./2019/237.
- (2) (a) Igarashi, Y.; Yu, L.; Ikeda, M.; Oikawa, T.; Kitani, S.; Nihira, T.; Bayanmunkh, B.; Panbangred, W. *J. Nat. Prod.* **2012**, *75*, 986. (b) García-Salcedo, R.; Álvarez-Álvarez, R.; Olano, C.; Cañedo, L.; Braña, A. F.; Méndez, C.; De la Calle, F.; Salas, J. A. *Mar. Drugs* **2018**, *16*, 259. (c) Yu, L.; Oikawa, T.; Kitani, S.; Nihira, T.; Bayanmunkh, B.; Panbangred, W.; Igarashi, Y. *J. Antibiot.* **2014**, *67*, 345.
- (3) Bérdy, J. *J. Antibiot.* **2012**, *65*, 385.
- (4) Markworth, C. J.; Marron, B. E.; Swain, N. A. WO 2010035166, **2010**.
- (5) Dhimitruka, I.; SantaLucia, J. *Org. Lett.* **2006**, *8*, 47.
- (6) Fráter, G.; Müller, U.; Günther, W. *Tetrahedron* **1984**, *40*, 1269.

- (7) (a) Radha Krishna, P.; Arun Kumar, P. V.; Mallula, V. S.; Ramakrishna, K. V. S. *Tetrahedron* **2013**, *69*, 2319. (b) Simmons, B.; Walji, A. M.; MacMillan, D. W. C. *Angew. Chem. Int. Ed.* **2009**, *48*, 4349.
- (8) (a) Shioiri, T. *Diphenyl Phosphorazide (DPPA): More Than Three Decades Later, TCI Mail No. 134*. Tokyo Tokyo Chemical Industry Co. Ltd **2007**, <https://www.tcichemicals.com/en/kr/support-download/tcimail/backnumber/article/134drE.pdf> (accessed Nov 19, 2019) (b) Thompson, A. S.; Grabowski, E. J. J. WO 1995001970, **1995**. (c) Pastó, M.; Moyano, A.; Pericàs, M. A.; Riera, A. *J. Org. Chem.* **1997**, *62*, 8425.
- (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 $[\text{M} + \text{NH}_4]^+$.

(11) Zhao, M.; Li, J.; Song, Z.; Desmond, R.; Tschaen, D. M.; Grabowski, E. J. J.; Reider, P. J. *Tetrahedron Lett.* **1998**, 39, 5323.

(12) (a) Micoine, K.; Fürstner, A. *J. Am. Chem. Soc.* **2010**, 132, 14064. (b) AnkiReddy, S.; AnkiReddy, P.; Sabitha, G. *Synthesis* **2015**, 47, 2860. (c) Gallenkamp, D.; Fürstner, A. *J. Am. Chem. Soc.* **2011**, 133, 9232.

(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 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.

(14) Matsumoto, A.; Sada, K.; Tashiro, K.; Miyata, M.; Tsubouchi, T.; Tanaka, T.; Odani, T.; Nagahama, S.; Tanaka, T.; Inoue, K.; Saragai, S.; Nakamoto, S. *Angew. Chem. Int. Ed.* **2002**, 41, 2502.

(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.