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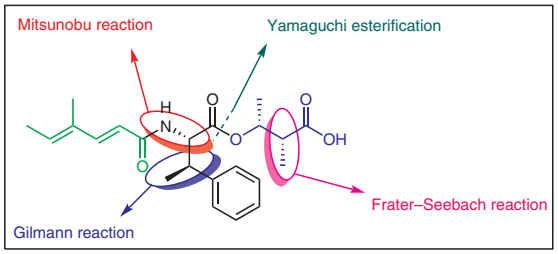
First Total Synthesis of Jomthonic Acid A[1]

Mohan Dumpala
Batthula Srinivas
Palakodety Radha Krishna*

D-211, Discovery Laboratory, Organic Synthesis and Process Chemistry Division, CSIR-Indian Institute of Chemical Technology, Hyderabad-500 007, India
prkgenius@iict.res.in



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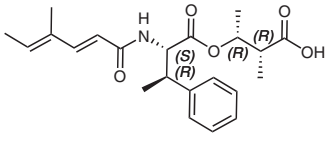
Abstract A stereoselective total synthesis of jomthonic acid A is described. The key features of the synthetic strategy are a Sharpless asymmetric epoxidation, a Gilmann reagent-induced methylation, a Mitsunobu reaction, a Yamaguchi esterification, and an *O*-(benzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium 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 preadiopocytes.

Key words Gilmann 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 preadiopocytes and it also inhibits the differentiation of preadipocytes into mature adipocytes at 2–50 μM.



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 Gilmann 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 Gilmann 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 $PhI(OAc)_2$ in CH_2Cl_2–H_2O (4:1) gave acid **5** in 93% yield.[11]

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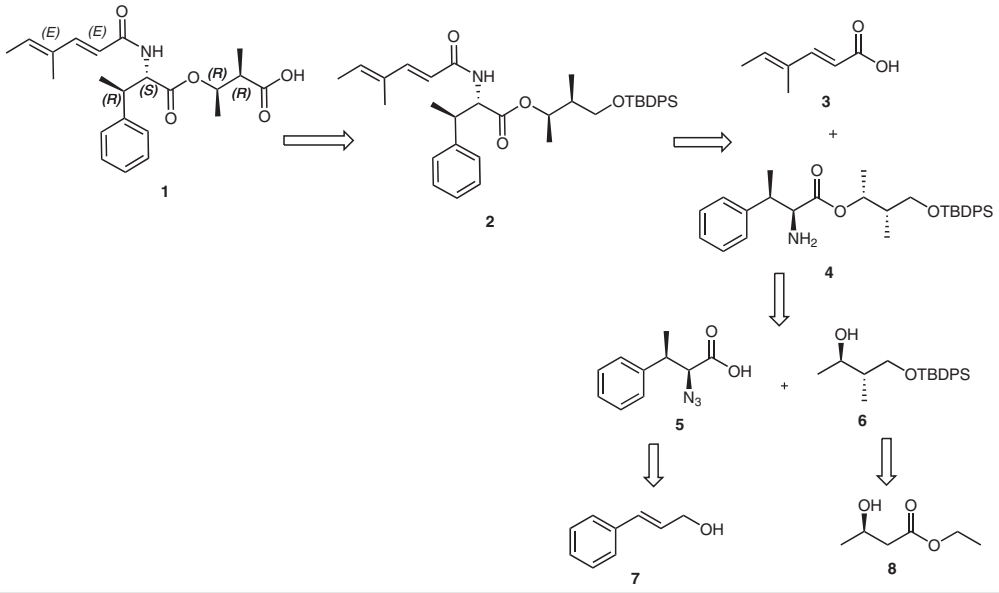
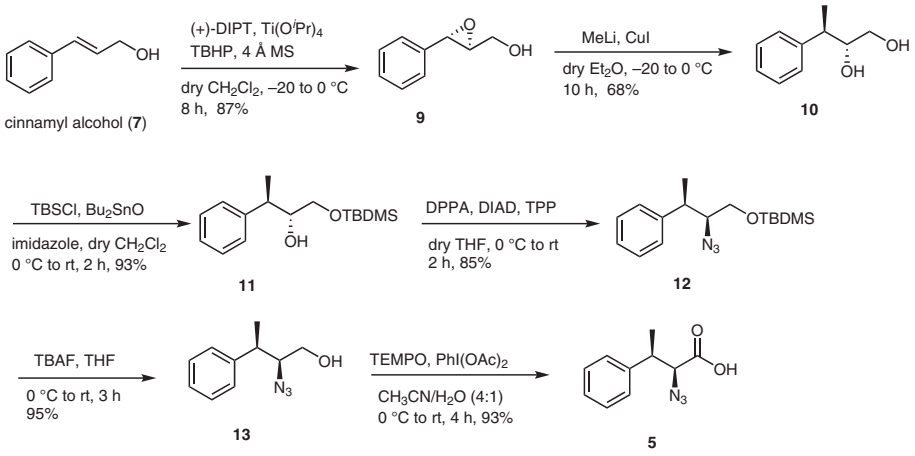
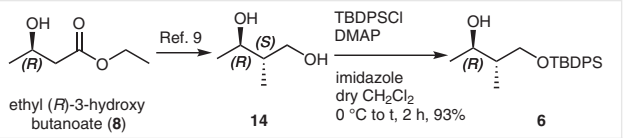


Scheme 1 Retrosynthetic analysis of jomthonic acid A (**1**)



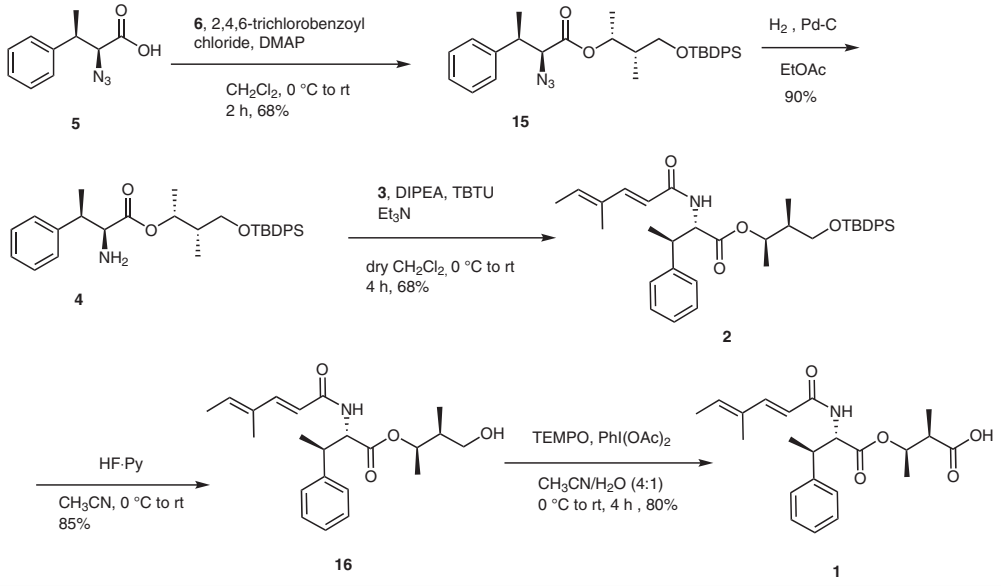
Scheme 2 Synthesis of fragment **5**

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 TBDPSCl/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 $PhI(OAc)_2$ 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 Gilmann 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.

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(9) **{[(2*S*,3*R*)-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%).
^{1}H NMR (400 MHz, $CDCl_3$): 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). ^{13}C NMR (100 MHz, $CDCl_3$): 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 $[M + NH_4]^+$.
(10) **(2*S*,3*R*)-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_2O (5 mL), and the mixture was extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with brine (2 x 10 mL) and dried (Na_2SO_4). 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%); $[\alpha]_D^{25}$ –9.1 (*c* 0.7, $CHCl_3$).

^{1}H 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 [M + NH_4]$^+$.

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(13) **(1*R*,2*S*)-3-{[*tert*-Butyl(diphenyl)silyl]oxy}-1,2-dimethylpropyl (2*S*,3*R*)-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%); $[\alpha]_D^{25}$ +22.0 (*c* 0.5, $CHCl_3$).

^{1}H 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* [M + NH_4]$^+$ calcd for $C_{31}H_{43}N_4O_3Si$: 547.3104; found: 547.3104.

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(15) **(1*R*,2*S*)-3-Hydroxy-1,2-dimethylpropyl (β*R*)-β-Methyl-*N*-[(2*E*,4*E*)-4-methylhexa-2,4-dienoyl]-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%); $[\alpha]_D^{25}$ +20.33 (*c* 0.3, $CHCl_3$).

^{1}H 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* [M + H]$^+$ calcd for $C_{22}H_{32}NO_4$: 374.2331; found: 374.2328.