First Stereoselective Total Synthesis of Tumonoic Acid A and its Derivatives

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Abstract An efficient protecting-group-free synthesis of tumonoic acid A and its derivatives has been accomplished. The synthesis started from commercially available n-octanal and employs the magnesium chloride catalysed anti-aldol reaction under the Evans protocol as the key step. Ethyl tumonoate A is a new tumonoic acid derivative with anti-inflammatory activity and inhibitory activity towards calcium oscillations in neocortical neurons.

Key words n-octanal, Wittig reaction, chiral auxiliary, hydrolysis, coupling

Marine natural product chemists have isolated and identified over 13,000 compounds, half of which show anticancer activity¹ and are often used as lead structures in the development of drugs.² Cyanobacteria represent a monophyletic bacterial phylum that are extraordinarily rich in bioactive molecules. Tumonoic acids A–C were isolated from the marine cyanobacteria (blue-green algae) Oscillatoria margaritifera, Lyngbya majuscule and Schizothrix calcicola (Figure 1).³ Ethyl tumonoate A exhibits anti-inflammatory activity in murine macrophage cells, inhibitory activity of calcium oscillations in neocortical neurons and in vitro anti-inflammatory activity in the RAW 264.7 murine macrophage cell-based nitric oxide assay with an IC₅₀ of 9.8 μM (3.6 μg/mL).⁴ Ethyl tumonoate A shares a structural resemblance to a number of other cyanobacterial secondary metabolites, such as the viridamides and the microcolins. These molecules are composed of 8–12 carbon fatty acid chains connected to amino acid moieties.

Retrosynthetic analysis (Scheme 1) shows that ethyl tumonoate A could be derived from the intermediate, (S)-4-benzyl-3-[(2R,3S,E)-3-hydroxy-2,4-dimethyldec-4-enoyl]oxazolidindin-2-one (8), which could, in turn, be obtained from n-octanal 2 through the Evans protocol without using protecting groups.

By using a Wittig protocol, octanal 2 underwent olefination with (carbethoxyethylidene)triphenyl phosphorane to give unsaturated ester 4 in 85% yield,⁵ which was then reduced to the allylic alcohol 5 in 92% yield by treating with

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Figure 1

Scheme 1
DIBAL-H (Scheme 2). Subsequent oxidation of alcohol 5 with MnO₂ in anhydrous hexane provided the corresponding aldehyde 6 in 97% yield. The (E)-2-methyldec-2-enal 6 was subjected to diastereoselective aldol reaction by following the Evans protocol, catalysed by magnesium chloride, using (S)-4-benzyl-3-propionyloxazolidin-2-one 7 as the chiral auxiliary to give anti-aldol product 8 in 67% yield, with excellent diastereoselectivity, as determined by ¹H NMR spectroscopy. The removal of the chiral auxiliary was achieved by oxidative hydrolysis with LiOH, H₂O₂ in THF-H₂O, furnishing the desired (2R,3S,E)-3-hydroxy-2,4-dimethyldeca-4-enoic acid (9). Finally, amide bond formation was achieved by coupling-acid 9 with L-proline ester in the presence of EDC·HCl and HOBT to give the target molecule, ethyl tumonoate A 1a, as a yellow liquid in 82% yield, with a specific rotation [α]₂⁵ = −78 (c = 0.4, CHCl₃) {Lit. [α]₂⁵ = −77.5 (c = 1, CHCl₃)}. Tumonoic acid A 1b was obtained as a pale-yellow liquid with a specific rotation [α]₀₂⁵ = −80 (c = 0.7, CHCl₃) {Lit [α]₀₂⁵ = −79 (c = 1.1, CHCl₃)} by hydrolysis of ethyl tumonoate A using EtOH and NaOH. Methyl tumonoate A 1c with specific rotation [α]₀₂⁵ = −52 (c = 1, CHCl₃) {Lit [α]₀₂⁵ = −51 (c = 1.3, CHCl₃)} was obtained by esterification of tumonoic acid A 1b using methyl iodide and potassium carbonate in DMF. All air- and moisture-sensitive reactions were carried out under an inert atmosphere (nitrogen or argon). Oven-dried glass apparatus was used to perform all reactions. Freshly distilled anhydrous solvents were used for air- and moisture-sensitive reactions. Commercially available reagents were used as purchased. Purification of compounds was carried out by column chromatography, using silica gel (60–120 mesh). ¹H NMR and ¹³C NMR spectra were recorded in CDCl₃ at 300 MHz, Bruker Avance II and 500 MHz, Bruker Avance III HD, using TMS as an internal standard. IR spectra were recorded with a Perkin–Elmer FTIR 240-c spectrophotometer using KBr / thin-film optics. Mass spectra were recorded with a Finnigan MAT 1020 mass spectrometer.

**Scheme 2** Reagents and conditions: (a) Benzene, reflux, 3 h, 85%; (b) DIBAL-H, –78 °C, CH₂Cl₂, 30 min, 92%; (c) MnO₂, anhydrous hexane, 3 h, 97%; (d) MgCl₂, TMS-Cl, Et₃N, EtOAc, 24 h; (e) p-TsOH, MeOH, 67%; (f) LiOH, H₂O₂, THF-H₂O (4:1), Na₂SO₃, 2 h, 75%; (g) (S)-ethyl pyrrolidine-2-carboxylate, EDC·HCl, 1-hydroxybenzotriazole (HOBt), CH₂Cl₂, Et₃N, 1 h, 82%; (h) NaN₃, MeOH-THF (1:1), 1 h, 80%; (i) K₂CO₃, CH₃I, DMF, 90 °C, 2 h, 78%;
operating at 70 eV. Specific rotation values were recorded with a Horiba sepa 300 polarimeter. High-resolution mass spectra (HRMS) [ESI+] were obtained with an Orbitrap, Thermo Scientific.

(E)-Ethyl 2-methyldec-2-enoate (4)

To a stirred solution of n-octanal (2.00 g, 15.6 mmol) in benzene (30 mL) was added (carboxethoxy ethylidene)trimethyl phosphorane (8.50 g, 27.0 mmol). The reaction mixture was heated to reflux for 3 h. After completion of reaction, the solvent was removed under reduced pressure and the crude product was purified by column chromatography, eluting with EtOAc–hexane (5:95). The pure product 4 (2.80 g, 85%) was obtained as a yellow liquid.

IR (neat): 3451, 2924, 2853, 1780, 1636, 1585, 1438, 1385, 1261, 1103, 853 cm–1.

1H NMR (300 MHz, CDCl3): δ = 6.81–6.72 (m, 1 H), 4.19 (q, J = 7.0 Hz, 2 H), 2.16 (q, J = 7.2 Hz, 2 H), 1.83 (s, 3 H), 1.38–1.20 (m, 13 H), 0.88 (t, J = 6.7 Hz, 3 H).

13C NMR (75 MHz, CDCl3): δ = 168.2, 142.3, 127.5, 60.2, 31.7, 29.6, 29.0, 28.6, 28.5, 22.5, 14.2, 14.0, 12.2.

MS (ESI): m/z = 213 [M + H]+.

(E)-2-Methyldec-2-en-1-ol (5)

To a stirred solution of compound 4 (2.30 g, 10.8 mmol) in anhydrous CH2Cl2 (30 mL), DIBAL-H (1 M in toluene, 23.7 mL, 23.7 mmol) was added at –78 °C. After 30 min, the reaction mixture was quenched with MeOH (1 mL) and a saturated solution of Rochelle’s salt (50 mL) and allowed to stir for 1 h. The mixture was extracted with CH2Cl2 (2 × 30 mL), washed with brine, dried over Na2SO4, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography, eluting with EtOAc–hexane (1:9) mixture to furnish compound 5 (1.70 g, 92%) as a yellow liquid.

IR (neat): 3445, 2924, 2854, 1601, 1498, 1460, 1260, 1175, 1023, 756 cm–1.

1H NMR (300 MHz, CDCl3): δ = 5.41 (t, J = 6.7 Hz, 3 H), 1.83–1.78 (m, 2 H), 1.67 (s, 3 H), 1.38–1.20 (m, 10 H), 0.88 (t, J = 6.5 Hz, 3 H).

13C NMR (75 MHz, CDCl3): δ = 134.4, 126.3, 68.7, 31.7, 29.4, 29.2, 29.1, 27.5, 22.5, 13.9, 13.4.

MS (ESI): m/z = 171 [M + H]+.

(2R,3S,E)-3-Hydroxy-2,4-dimethyldec-4-enoic Acid (9)

To a stirred solution of compound 8 (1.10 g, 2.7 mmol) in THF-H2O (4:1, 18 mL) at 0 °C was added aqueous H2O2 (30%, 1.86 mL, 16.4 mmol) followed by LiOH·H2O (0.34 g, 8.2 mmol). The reaction mixture was then warmed to r.t. and stirred for 2 h. After completion of reaction, as monitored by TLC, the excess peroxide was quenched with Na2SO3 solution (1 M, 10.90 mL) and the mixture was stirred for an additional 20 min. The solvent was removed under reduced pressure and the chiral auxiliary was recovered by CH2Cl2 extraction (3 × 10 mL). The aqueous phase was acidified with HCl (1 M) to pH 2 and then extracted with EtOAc (3 × 15 mL). The combined organic layers were washed with brine, dried over Na2SO4, filtered, and concentrated in vacuo. The crude product was purified by column chromatography, eluting with EtOAc–hexane (4:6) to afford pure 9 (0.50 g, 75%) as a pale-yellow liquid.

IR (neat): 3435, 2924, 2853, 1550, 1713, 1459, 1379, 1258, 1216, 1016, 926, 853 cm–1.

1H NMR (300 MHz, CDCl3): δ = 7.38–7.20 (m, 5 H, ArH), 2.84–2.74 (m, 1 H), 2.10–1.99 (m, 2 H), 1.68 (s, 3 H), 1.38–1.20 (m, 10 H), 0.88 (d, J = 6.4 Hz, 3 H).

13C NMR (75 MHz, CDCl3): δ = 176.7, 153.8, 135.3, 134.1, 130.1, 129.4, 128.9, 127.2, 81.4, 66.0, 55.6, 40.6, 37.7, 31.8, 29.6, 29.3, 29.1, 27.6, 22.6, 14.7, 14.0, 10.7.

(5)-Ethyl-1-[(2R,3S,5E)-3-hydroxy-2,4-dimethyldec-4-enoyl]-pyrrolidine-2-carboxylic acid (Ethyl tumonate A; 1a)

To a stirred solution of 9 (0.40 g, 1.6 mmol) in anhydrous CH₂Cl₂ (5 mL) was added EDC·HCl (0.35 g, 1.8 mmol) and HOBT (0.25 g, 1.8 mmol). After 10 min, a mixture of (5)-ethyl pyrrolidine-2-carboxylate (0.28 g, 1.9 mmol) and triethylamine (0.69 mL, 4.9 mmol) in CH₂Cl₂ (2 mL) was added dropwise, and the reaction mixture was stirred for 1 h. After completion of the reaction, as monitored by TLC, the mixture was diluted with CH₂Cl₂ (60 mL) and water (20 mL). The organic layer was separated and washed with HCl (1 M, 5 mL), saturated aqueous NaHCO₃ (10 mL) and brine (15 mL). The organic layer was dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography, eluting with EtOAc–hexane (3:7) mixture to afford the pure product 1a (0.5 g, 82%) as a yellowish liquid.

[a]ᵦ²⁵ = –78 (c = 0.4, CHCl₃).³

IR (neat): 3420, 2925, 2854, 1743, 1626, 1565, 1461, 1373, 1274, 1187, 1095, 924, 715, 703 cm⁻¹.

1H NMR (500 MHz, CDCl₃): δ = 5.44 (t, J = 7.0 Hz, 1 H), 4.50 (dd, J = 8.6, 4.2 Hz, 1 H), 4.24–4.12 (m, 3 H), 3.49 (t, J = 6.6 Hz, 2 H), 2.75 (p, J = 7.1 Hz, 1 H), 2.39–2.15 (m, 3 H), 2.10–1.94 (m, 3 H), 1.62 (s, 3 H), 1.38–1.20 (m, 13 H), 1.10 (d, J = 7.0 Hz, 3 H), 0.88 (t, J = 6.9 Hz, 3 H).

13C NMR (125 MHz, CDCl₃): δ = 174.9, 172.1, 134.0, 129.1, 79.8, 61.0, 58.6, 47.0, 41.1, 31.8, 29.6, 29.4, 29.1, 20.9, 27.5, 24.7, 22.6, 14.4, 14.1, 11.4.


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