First Stereoselective Total Synthesis of Tumonoic Acid A and its Derivatives

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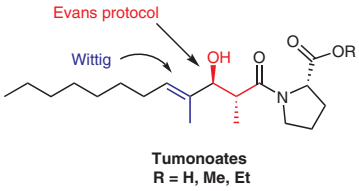

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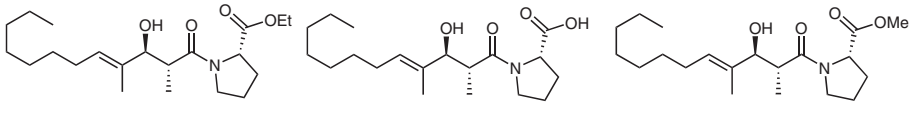
Abstract An efficient protecting-group-free synthesis of tumonoic acid A and its derivatives has been accomplished. The synthesis started from commercially available *n*-octanal and employs the magnesium chloride catalysed *anti*-aldol reaction under the Evans protocol as the key step. Ethyl tumonoate 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 activity[1] 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 IC_{50} 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.

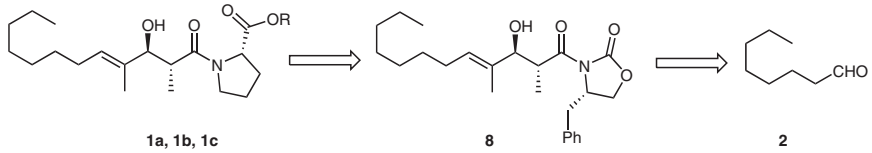
Retrosynthetic analysis (Scheme 1) shows that ethyl tumonoate A could be derived from the intermediate, (*S*)-4-benzyl-3-[(2*R*,3*S*,*E*)-3-hydroxy-2,4-dimethyldodec-4-enoyl]oxazolidindin-2-one (**8**), which could, in turn, be obtained from *n*-octanal **2** through the Evans protocol without using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



Ethyl tumonoate A (1a) Tumonoic acid A (1b) Methyl tumonoate A (1c)

Figure 1



1a, 1b, 1c 8 2

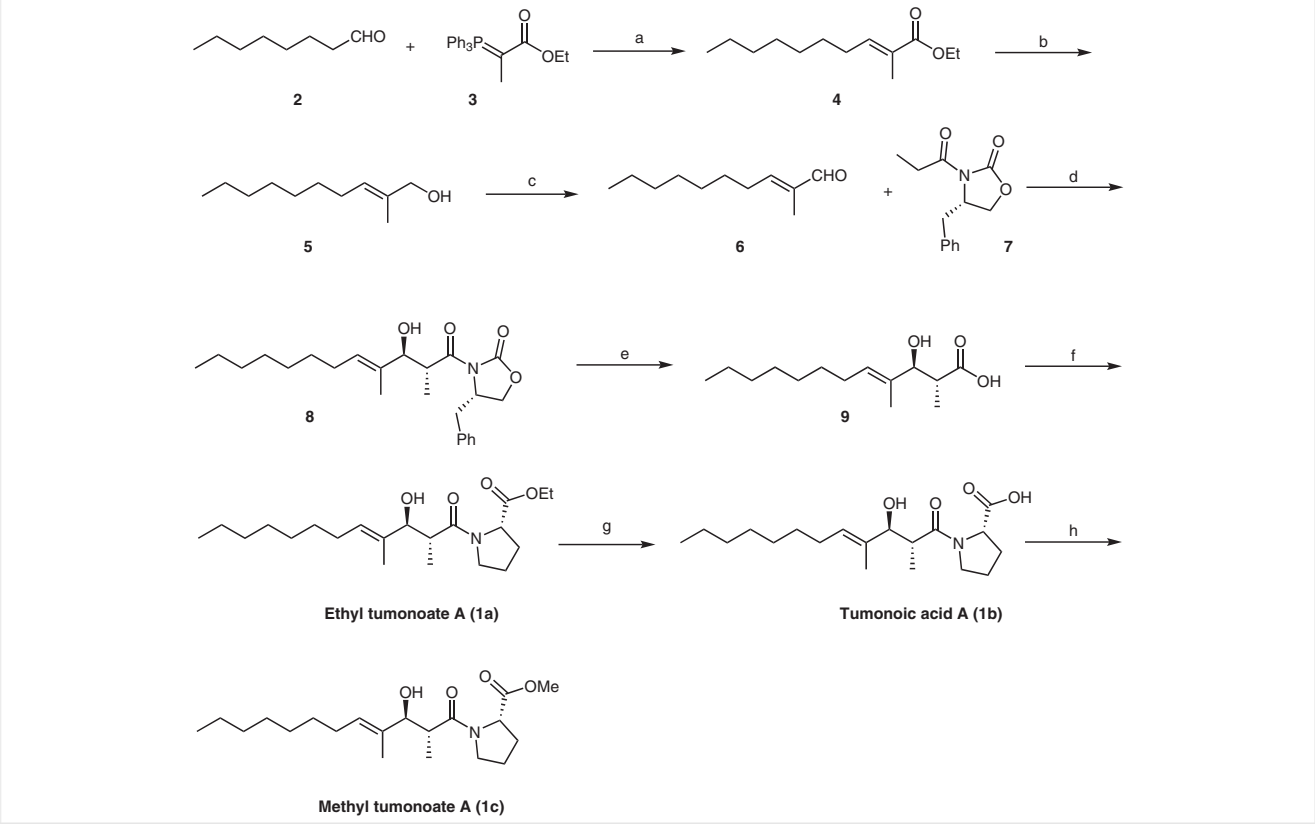
Scheme 1

DIBAL-H (Scheme 2). Subsequent oxidation of alcohol **5** with MnO_2 in anhydrous hexane provided the corresponding aldehyde **6** in 97% yield.[6]

The (*E*)-2-methyldec-2-enal **6** was subjected to diastereoselective aldol reaction by following the Evans protocol,[7] 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 ^{1}H NMR spectroscopy. The removal of the chiral auxiliary was achieved by oxidative hydrolysis with LiOH, H_2O_2 in THF-H_2O, furnishing the desired (2*R*,3*S*,*E*)-3-hydroxy-2,4-dimethyldodec-4-enoic acid (**9**).[8] 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,[9] with a specific rotation $[\alpha]_D^{25}$ = –78 (*c* = 0.4, $CHCl_3$) {Lit.[4] $[\alpha]_D^{25}$ = –77.5 (c = 1, $CHCl_3$)}. Tumonoic acid A (**1b**) was obtained as a pale-yellow liquid with a specific rotation $[\alpha]_D^{25}$ = –80 (c = 0.7, $CHCl_3$) {Lit[3] $[\alpha]_D^{25}$ = –79 (c = 1.1, $CHCl_3$)} by hydrolysis of ethyl tumonoate A using EtOH and NaOH. Methyl tumonoate A (**1c**) with specific rotation $[\alpha]_D^{25}$ = –52 (c = 1, $CHCl_3$) {Lit[3] $[\alpha]_D^{25}$ = –51 (c = 1.3, $CHCl_3$)} was obtained by esterification of tumonoic acid A (**1b**) using methyl iodide and potassium carbonate in DMF. The structures of all the products were confirmed by their spectroscopic data and by comparison with reported data.

In conclusion, we have accomplished the stereoselective total synthesis of naturally occurring tumonoic acid A and its derivatives, starting from *n*-octanal, without using any protection protocols. The synthetic strategy involves successful application of the magnesium chloride-catalysed *anti*-aldol reaction under the Evans protocol and amide coupling.

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). ^{1}H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$ 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, CH_2Cl_2, 30 min, 92%; (c) MnO_2, anhydrous hexane, 3 h, 97%; (d) (i) $MgCl_2$, TMS-Cl, Et_3N, EtOAc, 24 h; (ii) *p*-TsOH, MeOH, 67%; (e) LiOH, H_2O_2, THF-H_2O (4:1), Na_2SO_3, 2 h, 75%; (f) (*S*)-ethyl pyrrolidine-2-carboxylate, EDC·HCl, 1-hydroxybenzotriazole (HOBt), CH_2Cl_2, Et_3N, 1 h, 82%; (g) NaOH, MeOH-THF (1:1), 1 h, 80%; (h) K_2CO_3, CH_3I, 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 (carbethoxy ethylidene)triphenyl phosphorane (8.50 g, 27.0 mmol) and 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): 2851, 1711, 1639, 1549, 1462, 1449, 1377, 1216, 1093, 771 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 6.80–6.72 (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).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 168.2, 142.3, 127.5, 60.2, 31.7, 29.3, 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 CH_2Cl_2 (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 CH_2Cl_2 (2 × 30 mL), washed with brine, dried over Na_2SO_4, 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): 3450, 2924, 2854, 1601, 1641, 1498, 1460, 1260, 1175, 1023, 756 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 5.41 (t, *J* = 6.9 Hz, 1 H), 4.00 (s, 2 H), 2.09–1.97 (m, 2 H), 1.67 (s, 3 H), 1.38–1.20 (m, 10 H), 0.88 (t, *J* = 6.5 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): 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 $[M + H]^+$.

(*E*)-2-Methyldec-2-enal (6)

To a stirred solution of compound **5** (1.60 g, 9.4 mmol) in anhydrous hexane (20 mL) was added activated MnO_2 (8.20 g, 94 mmol). After stirring at r.t. for 3 h, the reaction mixture was filtered through a bed of Celite®. The filtrate was concentrated under reduced pressure and the residue was purified by column chromatography, eluting with EtOAc–hexane (5:95) mixture to afford **6** (1.53 g, 97%) as a pale-yellow liquid.

IR (neat): 2923, 2853, 1689, 1644, 1461, 1419, 1379, 1279, 1219, 933, 772 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 9.40 (s, 1 H), 6.50 (t, *J* = 7.3 Hz, 1 H), 2.35 (q, *J* = 7.2 Hz, 2 H), 1.75 (s, 3 H), 1.38–1.20 (m, 10 H), 0.88 (t, *J* = 6.7 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 195.4, 155.1, 139.2, 31.7, 29.2, 29.0, 28.9, 28.3, 22.6, 14.0, 9.1.

MS (ESI): *m*/*z* = 169 $[M + H]^+$.

(*S*)-4-Benzyl-3-[(2*R*,3*S*,*E*)-3-hydroxy-2,4-dimethyldodec-4-enoyl]oxazolidin-2-one (8)

To a stirred solution of (*S*)-4-benzyl-3-propionyloxazolidin-2-one **7** (2.08 g, 11.8 mmol) in anhydrous EtOAc (20 mL) was added anhydrous $MgCl_2$ (0.17 g, 1.7 mmol), triethylamine (1.6 mL, 11.8 mmol) and trimethylsilyl chloride (1.12 mL, 9.0 mmol) sequentially. The reaction mixture was stirred for 10 min and then aldehyde **6** (1 g, 5.9 mmol), dissolved in anhydrous EtOAc (10.0 mL), was added to the reaction mixture. After 24 h, the reaction mixture was filtered through a plug of silica-gel using EtOAc as the eluent. The solvent was removed *in vacuo*, then MeOH (20 mL) was added to the residue, along with *p*-TsOH (1.69 g, 8.8 mmol). After 15 min, desilylation was complete as monitored by TLC. After concentration *in vacuo* the desilylated mixture was purified by column chromatography, eluting with EtOAc–hexane (2:8). The pure product **8** (1.20 g, 67%) was obtained as a yellow liquid, with 19:1 diastereoselectivity.

$[\alpha]_D^{25}$ = +20 (c = 0.6, $CHCl_3$).

IR (neat): 3451, 2924, 2853, 1780, 1636, 1458, 1385, 1261, 1103, 1016, 926, 853 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.38–7.20 (m, 5 H, ArH), 5.49 (t, *J* = 6.9 Hz, 1 H), 4.70 (ddd, *J* = 10.1, 6.9, 3.3 Hz, 1 H), 4.27–4.00 (m, 4 H), 3.32 (dd, *J* = 13.4, 3.2 Hz, 1 H), 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), 1.06 (d, *J* = 6.4 Hz, 3 H), 0.88 (t, *J* = 6.6 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): 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.

MS (ESI): *m*/*z* = 424 $[M + Na]^+$.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{24}H_{36}O_4N$: 402.26389; found: 402.26404.

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

To a stirred solution of compound **8** (1.10 g, 2.7 mmol) in THF-H_2O (4:1, 18 mL) at 0 °C was added aqueous H_2O_2 (30%, 1.86 mL, 16.4 mmol) followed by LiOH·H_2O (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 Na_2SO_3 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 CH_2Cl_2 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 Na_2SO_4, 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.

$[\alpha]_D^{25}$ = –23 (c = 0.8, $CHCl_3$).

IR (neat): 3445, 2924, 2854, 1550, 1713, 1459, 1379, 1258, 1219, 1200, 1009, 915, 848, 771 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 5.46 (t, *J* = 7.0 Hz, 1 H), 4.12 (d, *J* = 9.4 Hz, 1 H), 2.74–2.60 (m, 1 H), 2.04 (q, *J* = 6.8 Hz, 2 H), 1.61 (s, 3 H), 1.38–1.20 (m, 10 H), 1.05 (d, *J* = 6.9 Hz, 3 H), 0.88 (t, *J* = 6.6 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 180.1, 133.4, 130.8, 80.1, 42.9, 31.8, 29.6, 29.2, 29.1, 27.5, 22.6, 14.1, 14.0, 10.4.

MS (ESI): *m*/*z* = 265 $[M + Na]^+$.

HRMS (ESI): *m*/*z*$[M + Na]^+$ calcd for $C_{14}H_{26}O_3Na$: 265.17742; found: 265.17751.

(*S*)-Ethyl-1-[(2*R*,3*S*,*E*)-3-hydroxy-2,4-dimethyldodec-4-enoyl]-pyrolidine-2-carboxylate (Ethyl tumonoate A; 1a)

To a stirred solution of **9** (0.40 g, 1.6 mmol) in anhydrous CH_2Cl_2 (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 (*S*)-ethyl pyrrolidine-2-carboxylate (0.28 g, 1.9 mmol) and triethylamine (0.69 mL, 4.9 mmol) in CH_2Cl_2 (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 CH_2Cl_2 (60 mL) and water (20 mL). The organic layer was separated and washed with HCl (1 M, 5 mL), water (15 mL), saturated aqueous $NaHCO_3$ (10 mL) and brine (15 mL). The organic layer was dried over Na_2SO_4, 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.

$[\alpha]_D^{25}$ = –78 (c = 0.4, $CHCl_3$).[4]

IR (neat): 3420, 2925, 2854, 1743, 1626, 1565, 1461, 1373, 1274, 1187, 1095, 1024, 917, 754, 703 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): 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), 3.65 (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).

^{13}C NMR (125 MHz, $CDCl_3$): 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, 29.0, 27.5, 24.7, 22.6, 14.4, 14.1, 11.4.

MS (ESI): *m*/*z* = 368 $[M + H]^+$.

HRMS (ESI): *m*/*z*$[M + H]^+$ calcd for $C_{21}H_{38}O_4N$: 368.27954; found: 368.27962.

(*S*)-1-((2*R*,3*S*,*E*)-3-Hydroxy-2,4-dimethyldodec-4-enoyl)pyrrolidine-2-carboxylic Acid (Tumonoic acid A; 1b)

To a stirred solution of compound **1a** (0.40 g, 1.08 mmol) in methanol-THF (1:1, 8 mL) aq. NaOH (2 M, 1.6 mL) was added and the reaction mixture was stirred at r.t. for 1 h. After completion of the reaction, as monitored by TLC, the solvent was removed *in vacuo*. The residue was diluted with water (2 mL) and HCl (2 M, 1.6 mL) and the precipitated product was extracted with EtOAc (2 × 10 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography, eluting with methanol-chloroform (2:8) to furnish pure **1b** (0.29 g, 80%) as a pale-yellow liquid.

$[\alpha]_D^{25}$ = –80 (c = 0.7, $CHCl_3$).[3]

IR (neat): 3418, 2924, 2855, 1731, 1618, 1458, 1262, 1217, 1192, 1017, 927, 771 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 5.46 (t, *J* = 7.0 Hz, 1 H), 4.65–4.58 (m, 1 H), 4.17 (d, *J* = 8.5 Hz, 1 H), 3.75–3.66 (m, 1 H), 3.64–3.57 (m, 1 H), 2.80 (p, *J* = 7.3 Hz, 1 H), 2.45–2.28 (m, 2 H), 2.07–1.99 (m, 4 H), 1.62 (s, 3 H), 1.38–1.20 (m, 10 H), 1.03 (d, *J* = 6.8 Hz, 3 H), 0.88 (t, *J* = 6.8 Hz, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 177.8, 177.6, 133.7, 130.3, 80.4, 60.3, 47.9, 41.3, 31.8, 29.6, 29.2, 29.1, 27.6, 27.4, 24.7, 22.6, 14.3, 14.0, 10.9.

MS (ESI): *m*/*z* = 338 $[M – H]^+$.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{19}H_{34}O_4N$: 340.24824; found: 340.24841.

(*S*)-Methyl-1-((2*R*,3*S*,*E*)-3-hydroxy-2,4-dimethyldodec-4-enoyl)pyrrolidine-2-carboxylate (Methyl tumonoate A; 1c)

A stirred solution of tumonoic acid A (0.20 g, 0.5 mmol) in DMF (3 mL) was cooled to 0 °C and K_2CO_3 (0.13 g, 0.9 mmol) was added, followed by iodomethane (0.04 mL, 0.7 mmol). The reaction mixture was allowed to warm to r.t. and stirred for 1 h, when it became a yellow heterogeneous solution. The mixture was then heated to 90 °C for 1 h and cooled to r.t. The reaction mixture was extracted with EtOAc (2 × 10 mL) and the combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude compound was purified by column chromatography, eluting with EtOAc–hexane (3:7). Pure product **1c** (0.17 g, 78%) was obtained as a yellow liquid.

$[\alpha]_D^{25}$ = –52 (c = 1, $CHCl_3$).[3]

IR (neat): 3449, 2924, 2853, 1744, 1629, 1459, 1169, 766 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 5.44 (t, *J* = 7.0 Hz, 1 H), 4.52 (dd, *J* = 8.7, 4.1 Hz, 1 H), 4.15 (d, *J* = 7.7 Hz, 1 H), 3.73 (s, 3 H), 3.66 (t, *J* = 6.6 Hz, 2 H), 2.76 (p, *J* = 7.1 Hz, 1 H), 2.38–2.28 (m, 2 H), 2.24–1.94 (m, 4 H), 1.62 (s, 3 H), 1.36–1.20 (m, 10 H), 1.10 (d, *J* = 7.0 Hz, 3 H), 0.88 (t, *J* = 6.8 Hz, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 175.0, 172.6, 134.0, 129.2, 79.9, 58.5, 52.2, 47.0, 41.1, 31.9, 29.6, 29.4, 29.2, 29.0, 27.5, 24.7, 22.6, 14.3, 14.0, 11.4.

MS (ESI): *m*/*z* = 354 $[M + H]^+$.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{20}H_{36}O_4N$: 354.26389; found: 354.26431.

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0037-1610365.

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