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Characterization and synthesis of (−)-7-methoxydodec-4(*E*)-enoic acid, a novel fatty acid isolated from *Lyngbya majuscula*

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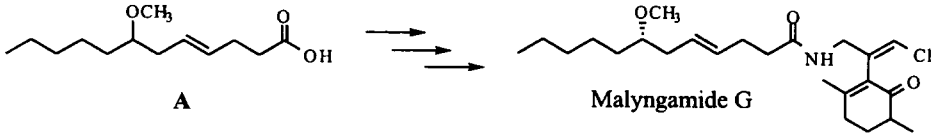
Abstract

The isolation and characterization of (−)-7-methoxydodec-4(*E*)-enoic acid, a novel fatty acid isolated from the marine Cyanophyte *Lyngbya majuscula* collected off the French Mediterranean coast are described. The synthesis of this acid and three of its isomers is reported. © 1999 Published by Elsevier Science Ltd. All rights reserved.

Keywords: natural product; *Lyngbya majuscula*; fatty acid; Wittig reaction.

The marine Cyanophyte *Lyngbya majuscula* is the source of a wide variety of biologically active marine metabolites, such as Malyngamides.[1] In 1993, Praud et al. reported the isolation of Malyngamide G[2] from this cyanobacterium collected off the French Mediterranean coast. We report herein the isolation and synthesis of the first dodecenoic acid from *L. majuscula*: (−)-7-methoxydodec-4(*E*)-enoic acid **A**, which is the probable precursor of Malyngamide G (Scheme 1).



Scheme 1.

Re-investigation of the ether extract of *L. majuscula* collected at Le Brusc (Var, France) and containing Malyngamide G, led to isolation of **A** (7.5% of the extract).[3] Both compounds show potent immunosuppressive properties.[4]

The chemical structure[5] of **A** was confirmed by spectral analysis (^{1}H NMR, ^{13}C NMR, UV, IR, MS) and comparison with literature data.[1,2] The comparison of the ^{13}C NMR spectra of **A** and Malyngamide G showed significant differences in chemical shifts for the carbon atoms close to the amide moiety (C-1: 178.9 ppm for **A** vs 171.2 ppm and C-2: 33.9 ppm for **A** vs 35.3 ppm).

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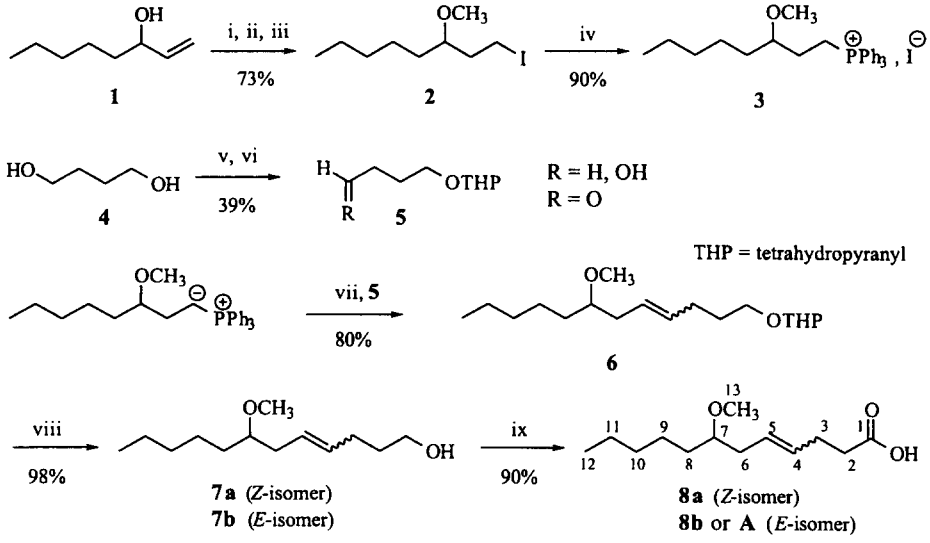
The synthesis of the *Z*- and *E*-isomers of **A** was achieved by a Wittig reaction as outlined in Scheme 2.

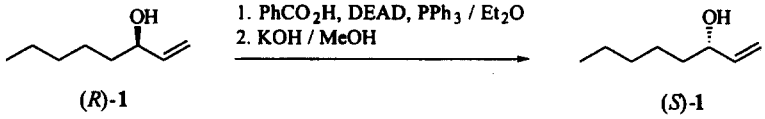


Scheme 2. (i) NaH, CH_3I/THF reflux; (ii) BH_3·THF then NaOH, H_2O_2; (iii) I_2, PPh_3, imidazole, diisopropylamine/CH_3CN, Et_2O, 25°C; (iv) PPh_3/CH_3CN reflux; (v) DHP, Amberlyst 15 cat., 25°C; (vi) PDC/CH_2Cl_2, 25°C; (vii) LiHMDS/THF (–78°C then 25°C); (viii) Amberlyst 15 cat./MeOH, 25°C; (ix) PDC/DMF, 25°C

Oct-1-en-3-ol **1** was converted into its iodo derivative **2** in 73% yield by a three-step sequence: protection of the hydroxyl group, hydroboration of the double bond with the BH_3·THF complex,[6] followed by halogenation with iodine.[7] Treatment of **2** with triphenylphosphine in acetonitrile led to formation of the corresponding phosphonium salt **3** in 90% yield.

In a parallel sequence, butan-1,4-diol **4** was monoprotected by treatment with DHP[8] (68%) and oxidized with PDC[9] to obtain the aldehyde **5** in 58% yield. The Wittig reaction between **5** and the phosphorane derived from **3** led to an unseparable mixture of olefins *Z*/*E* **6** (80%).[10] Removal of the tetrahydropyranyl group by methanolysis in the presence of a catalytic amount of Amberlyst 15 afforded a mixture of the *Z*-isomer **7a** and the *E*-isomer **7b** in a 75:25 ratio and 98% yield. Compounds **7a** and **7b** were separated by preparative HPLC and unambiguously characterized by ^1H NMR spectroscopy of the coupling constants of the olefinic protons (10.3 and 15.4 Hz, respectively, for the *Z*- and *E*-isomers). Infrared spectroscopy allowed distinction of the *Z*-isomer by two characteristic absorption bands at 1406 and 724 cm^{-1} while the *E*-isomer showed absorption bands at 1260 and 872 cm^{-1}. On the other hand, the HMBC sequence, ^1H and ^{13}C NMR analysis allowed assignment of the structure of the two isomers. Thus, the chemical shifts affected by the change of isomery concerned the C-4 and C-5 atoms and also the vicinal carbon atoms 3 and 6 (the values of the chemical shifts were, respectively, 24.0 and 31.9 ppm for the *Z*-isomer and 29.4 and 36.5 ppm for the *E*-isomer). Treatment of each of these alcohols **7a**[11] and **7b**[12] with PDC in DMF led to the corresponding acids **8a**[13] and **8b**[14] in 90% yield. Only an absorption band in IR spectrum of *E*-isomer **8b** at 972 cm^{-1} distinguished it from the *Z*-isomer **8a**. In NMR spectroscopy, the most important difference may be noticed in chemical shifts of the H-3 and H-6 atoms and C-3 to C-6 atoms.

Since the only stereocenter of **A** is the C-7 atom, a method to produce and incorporate optically active (*R*)- and (*S*)-oct-1-en-3-ol was explored. Commercial (*R*)-oct-1-en-3-ol was submitted to Mitsunobu's asymmetric transformation (Scheme 3) and led to the (*S*)-benzoic ester.[15] This reaction was followed by an alcaline hydrolysis (without allylic rearrangement) and led to (*S*)-**1** in up to 95% ee.



Scheme 3.

Optically active (*R*)-**1** and (*S*)-**1** could now be incorporated into the above synthesis to produce the natural optically active (–)-7-methoxydodec-4(*E*)-enoic acid **A**, and its enantiomer.

These results allowed confirmation of the structure and geometry of the natural metabolite **A** and of its synthetic *Z*-isomer. The synthesis of Malyngamide G and its isomers from this new fatty acid is under current investigation.

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2. Praud, A.; Valls, R.; Piovetti, L.; Banaigs, B. *Tetrahedron Lett.* **1993**, *34*, 5437–5440.
3. Isolation of (4*E*,7*S*)-**A**: 35 g of a freeze-dried sample of *Lyngbya majuscula* collected at Le Brusc (Var, France) gave 1 g of the ether extract (3% of the dried weight). HPLC Chromatography on semi-preparative column, 3 mL min^{-1}, EtOAc:isooctane, 60:40, gave 75 mg of (4*E*,7*S*)-**A** as a pale yellow oil: $[\alpha]_D^{20}$=–8 (*c* 1.8, $CHCl_3$); IR (ν_{max}, cm^{-1}, film): 3400–3200, 2950–2800, 1742, 1719, 1452, 1380, 1102, 977; HRMS: $[MH]^+$ 229.18041 (calcd for $C_{13}H_{25}O_3$: 229.18037); EIMS *m/z* (relative intensity) 229 (1%, $[MH]^+$), 197 (2%, $[MH]^+$, CH_3OH), 157 (3%, $C_8H_{13}O_3$), 115 (100%, $C_7H_{15}O$), 83 (89%, C_6H_{11}), 71 (16%, C_5H_{11}), 60 (2%, $C_2H_4O_2$), 55 (50%, C_4H_7); ^1H NMR (400 MHz, $CDCl_3$) δ 5.46 (m, 2H, H-4, H-5), 3.33 (s, 3H, OCH_3), 3.14 (m, 1H, H-7), 2.28 (m, 2H, H-3), 2.18 (m, 4H, H-2, H-6), 1.42 (m, 2H, H-8), 1.42–1.29 (m, 2H, H-9), 1.29 (m, 4H, H-10, H-11), 0.89 (t, 3H, H-12); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.9 (C, C-1), 130.2 (CH, C-4), 127.7 (CH, C-5), 80.8 (CH, C-7), 56.5 (CH_3, OCH_3), 36.3 (CH_2, C-6), 33.9 (CH_2, C-2), 33.2 (CH_2, C-8), 32.0 (CH_2, C-10), 27.6 (CH_2, C-3), 24.9 (CH_2, C-9), 22.6 (CH_2, C-11), 14.0 (CH_3, C-12).
4. Compound **A** and Malyngamide G are non-cytotoxic to KB cells in tissue culture and show immunosuppressive activity (ED_{50}=6 μg mL^{-1} on culture cells with concanavaline K and LPS).
5. Compound **A** has elemental composition $C_{13}H_{24}O_3$ (HRMS). The EIMS spectrum gave a major ion at *m/z* 115 ($C_7H_{15}O$) followed by *m/z* 83 (C_6H_{11}) that confirmed the presence of a C-7-methoxy group. The IR spectrum showed bands at 1742 and 1719 cm^{-1} for non-conjugated carboxylic carbonyl, a band at 1102 cm^{-1} for methoxy group and a band at 977 cm^{-1} characteristic of *trans* disubstituted alkene.
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11. Spectral data of **7a**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.39 and 5.42 (AB system, 2H, H-4, H-5, J=10.3 Hz), 3.59 (t, 2H, H-1), 3.29 (s, 3H, OCH_3), 3.15 (m, 1H, H-7), 2.22 (m, 2H, H-6), 2.16 (m, 2H, H-3), 1.59 (m, 2H, H-2), 1.42 (m, 2H, H-8), 1.30–1.22 (m, 6H, H-9, H-10, H-11), 0.84 (t, 3H, H-12); ^{13}C NMR (100 MHz, $CDCl_3$) δ 131.5 (C, C-4), 127.0 (CH, C-5), 81.6 (CH, C-7), 62.2 (CH_2, C-1), 57.3 (CH_3, C-13), 33.9 (CH_2, C-8), 32.6 (2 CH_2, C-2, C-10), 31.9 (CH_2, C-6), 25.5 (CH_2, C-9), 24.0 (CH_2, C-3), 23.2 (CH_2, C-11), 14.6 (CH_3, C-12).
12. Spectral data of **7b**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.47 and 5.43 (AB system, 2H, H-4, H-5, J=15.4 Hz), 3.63 (t, 2H, H-1), 3.30 (s, 3H, OCH_3), 3.14 (m, 1H, H-7), 2.18 (m, 2H, H-6), 2.09 (m, 2H, H-3), 1.63 (m, 2H, H-2), 1.42 (m, 2H, H-8), 1.32–1.23 (m, 6H, H-9, H-10, H-11), 0.86 (t, 3H, H-12); ^{13}C NMR (100 MHz, $CDCl_3$) δ 132.3 (C, C-4), 127.0 (CH, C-5), 80.9 (CH, C-7), 62.7 (CH_2, C-1), 56.6 (CH_3, C-13), 36.5 (CH_2, C-6), 33.4 (CH_2, C-8), 32.4 (CH_2, C-2), 32.2 (CH_2, C-10), 29.4 (CH_2, C-3), 25.1 (CH_2, C-9), 22.8 (CH_2, C-11), 14.2 (CH_3, C-12).
13. Spectral data of **8a**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.42 (m, 2H, H-4, H-5), 3.31 (s, 3H, OCH_3), 3.17 (quint., 1H, H-7), 2.35 (m, 4H, H-2, H-3), 2.25 (m, 2H, H-6), 1.40 (m, 2H, H-8), 1.20–1.35 (m, 6H, H-9, H-10, H-11), 0.85 (t, 3H, H-12); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.8 (C, C-1), 129.0 (CH, C-4), 127.3 (CH, C-5), 80.9 (CH, C-7), 56.6 (CH_3, OCH_3), 34.0 (CH_2, C-2), 33.6 (CH_2, C-8), 32.0 (CH_2, C-10), 31.1 (CH_2, C-6), 25.1 (CH_2, C-9), 22.8 (CH_2, C-3), 22.6 (CH_2, C-11), 14.1 (CH_3, C-12).
14. Spectral data of **8b**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.46 (m, 2H, H-4, H-5), 3.30 (s, 3H, OCH_3), 3.14 (quint., 1H, H-7), 2.37 (m, 2H, H-2), 2.30 (m, 2H, H-3), 2.15 (m, 2H, H-6), 1.40 (m, 2H, H-8), 1.20-1.35 (m, 6H, H-9, H-10, H-11), 0.87 (t, 3H, H-12); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.4 (C, C-1), 130.2 (CH, C-4), 127.7 (CH, C-5), 80.8 (CH, C-7), 56.5 (CH_3, OCH_3), 36.3 (CH_2, C-6), 33.9 (CH_2, C-2), 33.2 (CH_2, C-8), 32.0 (CH_2, C-10), 27.7 (CH_2, C-3), 24.9 (CH_2, C-9), 22.6 (CH_2, C-11), 14.0 (CH_3, C-12).
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