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Synthesis of deuterated 5(*Z*),11(*Z*)-eicosadienoic acid as a biomarker for trophic transfer

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ABSTRACT

The poly-methylene interrupted fatty acid 5(*Z*),11(*Z*)-eicosadienoic acid and its tetradeuterated analogue were prepared via a convergent synthetic sequence.

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Fatty acids (FAs) are recognized as important tools in ecology,[1] toxicology[2] and conservation biology.[3] While they have been utilized previously as trophic markers,[4–6] their use is hampered by the fact that they exhibit species-specific bioconversion rates and also because many FAs are ubiquitous and abundant in aquatic food webs. In contrast, poly-methylene interrupted fatty acids[7] (PMI-FAs) possess an unusual methylene substitution pattern and, as such, occur much less frequently in nature. In the marine environment, it is thought that PMI-FAs are synthesized de novo primarily in bivalves and carnivorous gastropods[8–10] and further accumulate, to varying extents (depending on diet), in marine mammals.[9]

Our interest in PMI-FAs stems from their potential as biomarkers for zebra (*Dreissena polymorpha*) and quagga (*D. bugensis*) mussels (termed dreissenids). Since their introduction in the Laurentian Great Lakes, their adaptability, rapid life cycle, and high reproductive potential have ensured their continued invasion success[11,12] and has resulted in extensive ecosystem impact and damage.[13,14] New methods designed to enable researchers to better track the passage of dreissenid-derived carbon to both native and introduced consumers at different trophic levels through the food web are required in an effort to understand the extent to which dreissenids alter the function and stability of aquatic ecosystems. The PMI-FA 5(*Z*),11(*Z*)-eicosadienoic acid (**1**) was identified as a useful biomarker for these studies and the present paper describes the synthesis of a deuterated analogue applicable for analytical studies using isotopic dilution.[15]

Despite having been isolated from a variety of natural sources, the synthesis of 5(*Z*),11(*Z*)-eicosadienoic acid (**1**) has not been described in the literature. The synthetic route developed appears in Schemes 1 and 2. The approach was designed so as to insure *cis* stereochemistry at C5=C6 and C11=C12 by taking advantage of an alkyne reduction using Lindlar's catalyst. Furthermore, the route offers the opportunity to introduce deuterium at either alkene or both as desired.

Initial development of the synthesis focused on preparation of the non-deuterated fatty acid. The route to the C7–C20 fragment appears in Scheme 1 (R = H). While 4-bromo-1-butanol (**3**) is commercially available, a convenient synthesis has been described previously wherein tetrahydrofuran (**2**) is treated with HBr.[16] The resulting bromo-alcohol was then protected as its THP ether (**4**)[17] before coupling with 1-decyne (**5**) in THF at −78 °C to give **6**. Heterogeneous hydrogenation of the alkyne to the alkene (**7**) is carried out in the presence of Lindlar's catalyst. Inspection of the ^{1}H NMR (at 700 MHz) allowed for resolution of the alkenic protons and revealed only a single isomer. Furthermore, coupling of the alkenic protons to each other with a J = 6.9 Hz was consistent with the desired *cis* geometry. Removal of the THP protecting group affords the free alcohol **8** that was subsequently tosylated (to give **9**). Finally, treatment with NaI in acetone provides **10**, the required C7–C20 synthon.

Synthesis of the C1–C6 synthon along with its coupling to the C7–C20 fragment appears in Scheme 2 (R = H). Commercially available 5-hexyn-1-ol (**11**) was protected as its THP ether (**12**)[18] before coupling to iodo-alkene **10** to yield alkene-alkyne **13**. It should be noted that attempts to couple **12** with the tosylate **9** failed prompting the use of the iodo compound **10**. Reduction to the bisalkene (**14**) once again took advantage of the H_2/Lindlar's catalyst system with *cis* geometry at the newly formed C5=C6 alkene confirmed via ^{1}H NMR. Deprotection of the THP ether **14** to the alcohol **15** is followed by oxidation using pyridinium dichromate in DMF to yield the desired 5(*Z*),11(*Z*)-eicosadienoic acid (**1**: R = H).

Having established the viability of the synthetic route, attention was turned to the preparation of the deuterated analogue (Schemes 1 and 2 where R = D). Use of D_2 gas in place of H_2 in the hydrogenations of **6** to **7** and **13** to **14** allowed for the incorporation of deuterium into the newly generated *cis* alkenes. [$^2H_4$]-

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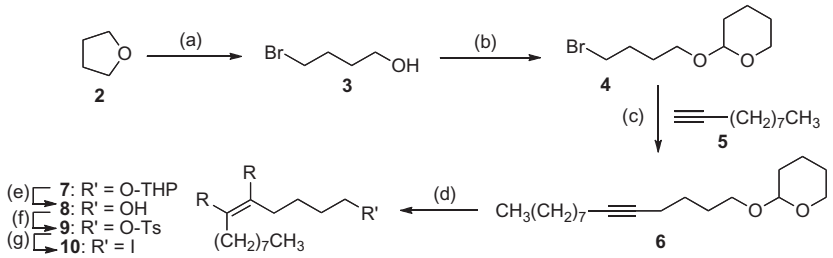
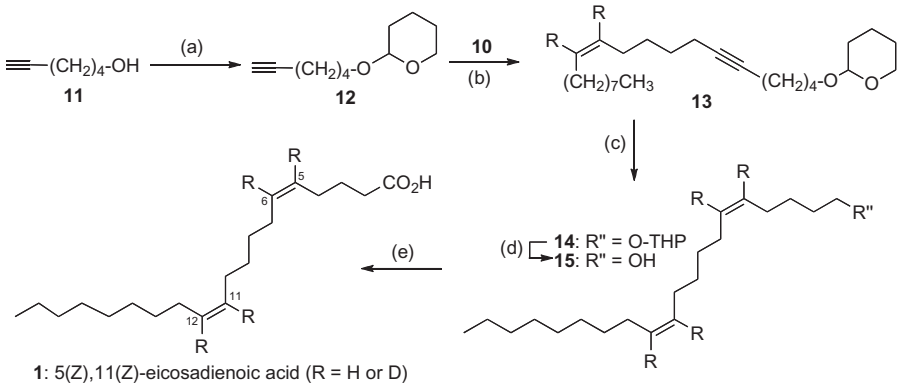


Scheme 1. Synthesis of the C7–C20 synthon. Reagents and conditions: (a) HBr, H_2SO_4 (90%); (b) DHP, *p*-TsOH, DCM (72%); (c) (i) **5**, *n*-BuLi, THF, −78 °C; (ii) dropwise addition of **4** then heat (85%); (d) 1 atm H_2, Lindlar's catalyst (72%); (e) *p*-TsOH, MeOH (68%); (f) *p*-TsCl, DCM, pyridine (73%); (g) NaI, acetone (71%).



Scheme 2. Synthesis of the C1–C6 synthon and coupling to the C7–C20 fragment. Reagents and conditions: (a) DHP, *p*-TsOH, DCM (92%); (b) (i) **12**, *n*-BuLi, HMPA, THF, −78 °C; (ii) dropwise addition of **10** then heat (65%); (c) 1 atm H_2, Lindlar's catalyst (62%); (d) *p*-TsOH, MeOH (92%); (e) PDC, DMF (45%).

5(*Z*), 11(*Z*)-Eicosadienoic acid (**1**: R = D) was completely characterized by ^{1}H NMR, ^{13}C NMR and HRMS.[19] Furthermore, gas chromatographic analysis of the deuterated PMI-FA with an authentic standard revealed that both samples had similar retention times.[20]

In conclusion, 5(*Z*),11(*Z*)-eicosadienoic acid and its tetradeuterated analogue were prepared via a convergent 12-step synthesis. The nature of the route is such that other PMI-FAs can be prepared in this fashion. Work describing the use of the deuterated standard as a biomarker for trophic transfer will be described elsewhere.

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19. ^{1}H NMR (600 MHz, $CDCl_3$): 2.36 (t, 2H, J = 7 Hz), 2.09 (t, 2H, J = 7 Hz), 2.01–1.94 (m, 6H), 1.69 (m, 2H), 1.30–1.26 (m, 16H), 0.87 (t, 3H, J = 7 Hz); ^{13}C NMR (120 MHz, $CDCl_3$): 178.8, 131.2, 131.0, 129.6, 128.2, 33.3, 32.0, 29.9, 2 × 29.6, 2 × 29.5, 29.4, 27.2, 27.1, 27.1, 26.4, 24.7, 22.8, 14.2; ES-HRMS: Calculated for $C_{20}H_{31}O_2D_4$ $[M-H]^-$ 311.2888; observed: 311.2884.
20. The PMI-FAs were analysed by GC–MS (Agilent 6890N GC) equipped with a DB-23 polar capillary column (Agilent; #122-2361; 60 m × 0.25 mm id × 0.15 μm film thickness), an Agilent 7683B injector, and a mass selective quadrupole detector (Agilent 5973N). Helium was used as the carrier gas at a constant pressure (~180 kPa at 33 cm s^{-1} at 50 °C). Samples were injected at an oven temperature of 50 °C. After 1 min, the oven temperature was raised to 175 °C at a rate of 25 °C min^{-1}, then to 235 °C at 4 °C min^{-1} and held for 5 min. The retention times for 5(*Z*),11(*Z*)-eicosadienoic acid and [$^2H_4$]-5(*Z*),11(*Z*)-eicosadienoic acid were 18.1 and 18.2 min, respectively.