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Synthesis of 2*E*,4*E*,6*E*,11*Z*-octadecatetraenoic acid of the *Rhizobium leguminosarum* biovar *viciae* Nod factor

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Abstract—2*E*,4*E*,6*E*,11*Z*-Octadecatetraenoic acid was synthesized in a good yield and in a stereospecific manner by coupling a vinylborane compound and ethyl *trans*-3-iodoacrylate. The trienic system (*E*,*E*,*E*) was obtained by successive use of metal-catalyzed coupling and hydro-metallation reactions.

Several molecules are involved in the setting up of nitrogen-fixing symbiosis between leguminous plants and *Rhizobium* bacteria. One of these molecules (Nod factor) is produced by *Rhizobium* bacteria and elicits the morphogenesis of plant root nodules in which atmospheric nitrogen is reduced to ammonia.[1] The specific Nod factor of peas (*Pisum sativum*) was isolated by Spaink et al.[2] and since then, several authors[3,4] have carried out in-depth studies to establish its actual structure. As shown in Figure 1, it is a lipochitooligosaccharide. The unsaturated fatty acid attached to the nonreducing terminal glucosamine is 2*E*,4*E*,6*E*,11*Z*-octadecatetraenoic acid. The biological activity of this Nod factor is highly dependent on the geometry of this polyunsaturated system.

In order to test the effect of this molecule on crops in the field, its hemisynthesis has been planned using an oligosaccharide produced by metabolically engineered bacterial cells.[5] First, it was necessary to produce 2*E*,4*E*,6*E*,11*Z*-octadecatetraenoic acid in sufficient quantities and with the required double bond positions and geometry. Although the Wittig reaction is well known in organic chemistry, its low stereoselectivity does not make it well adapted to the preparation of such systems. To generate a trienic system via a highly stereoselective route, hydro-metallation[6,7] and cross-coupling reactions[8,9] were used to obtain pure configuration *E* olefins. Only the *Z* double bond was synthesized using the Wittig reaction under the conditions of Rollin and Pougny.[10] The compounds thus prepared do not require purification steps. Figure 2 shows the retrosynthetic route for this acid.

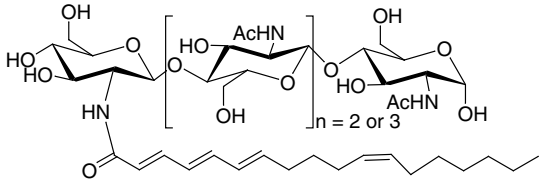

Figure 1. Structure of the Nod factor of *leguminosarum* by *viciae*.

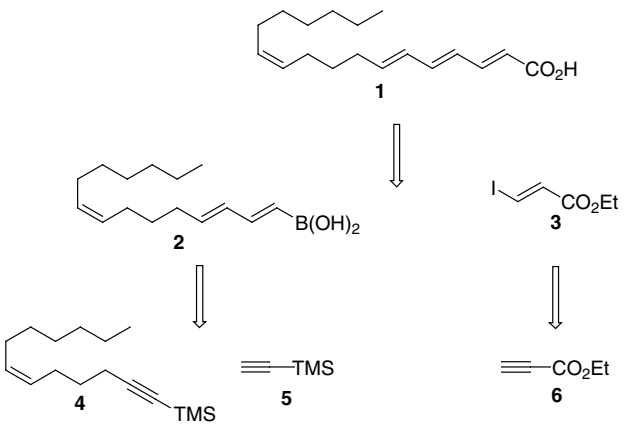

Figure 2. Retrosynthetic route for 2*E*,4*E*,6*E*,11*Z*-octadecatetraenoic acid.

Keywords: Hydrozirconation; Hydroboration; Palladium; Cross-coupling reaction; Polyunsaturated acid; Nod factor.
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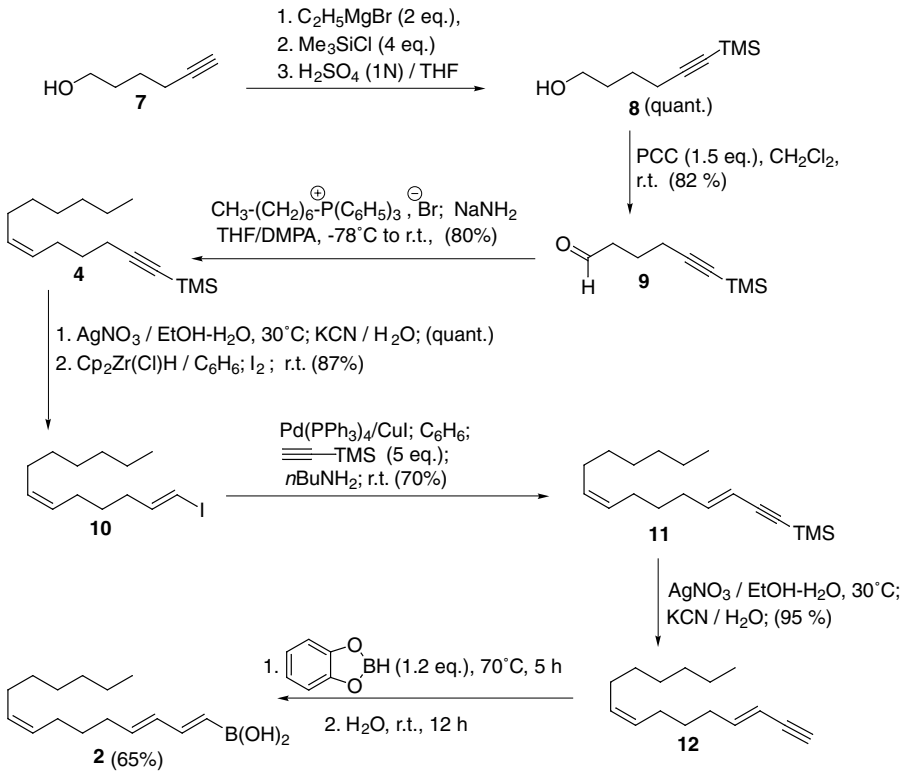


Scheme 1. Synthesis of vinylborane **2**.

Construction of vinylborane **2** begins with 5-hexyn-1-ol **7**. As seen in Scheme 1, successive action of ethylmagnesium bromide, trimethylsilyl chloride and sulfuric acid results in the formation of 6-trimethylsilyl-5-hexyn-1-ol **8**.[11] The oxidation of this alcohol by pyridinium chlorochromate[12] generated aldehyde **9**, which was directly condensed with heptyltriphenylphosphonium bromide under the conditions of Rollin and Pougny[10] (−78 °C, THF/HMPA: 9/1) gives compound **4** (isomeric purity > 95%) in 80% yield. This product was purified by flash chromatography and the double bond geometry was confirmed by ^{1}H NMR ($^3J_{cis}$ = 11 Hz).

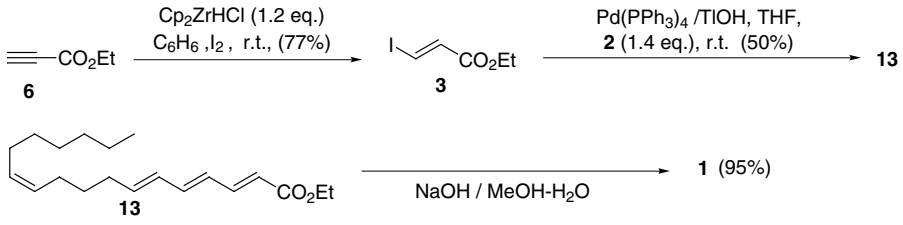
The desilylation of this compound by silver nitrate and potassium cyanide[13] was quantitative. It was followed by a hydrozirconation using Schwartz's reagent (bis(cyclopentadienyl)zirconium chloride hydride), and an iodolysis[14,15] to give vinyl iodide **10** (1*E*,6*Z*) by a *cis*-addition mechanism in 87% yield.

Vinyl iodide **10** was directly involved in the coupling reaction with the trimethylsilylacetylene in the presence of tetrakis(triphenylphosphine)palladium ($Pd(PPh_3)_4$) and copper iodide.[15,16] Thus trimethylsilylpentadeca-3*E*,8*Z*-dien-1-yne **11** was obtained in 70% yield. Deprotection of this gave alkyne **12**, which reacted with catechol borane[17] to give the vinylborane **2** after hydrolysis.

Ethyl *trans*-3-iodoacrylate **3** was prepared using Schwartz's reagent, followed by iodolysis of the ethylpropiolate **6** (Scheme 2).

Compound **2** coupled cleanly with iodide **3**, in the presence of thallium hydroxide (TlOH) and tetrakis-(triphenylphosphine)palladium in THF at room temperature.[18,19] After purification, 2*E*,4*E*,6*E*,11*Z*-ethyl octadecatetraenoate **13** was isolated in 50% yield. The hydrolysis of this compound under alkaline conditions gave the polyunsaturated fatty acid of the Nod factor of *Rhizobium leguminosarum* biovar *viciae* in quantitative yield.

The geometry of the unsaturated system is completely controlled and the resulting acid **1** does not show any



Scheme 2. Synthesis of 2*E*,4*E*,6*E*,11*Z*-octadecatetraenoic acid.

geometric isomers at all. This was confirmed by the spectral data ^{1}H and ^{13}C NMR, 2D NMR, MS and IR.[20]

In conclusion, the successive use of the Wittig reaction under special conditions, in addition to the hydro-metallation and metal-catalyzed coupling reactions have allowed 2*E*,4*E*,6*E*,11*Z*-octadecatetraenoic acid to be synthesized in good yield and high stereoselectivity. This acid is essential to induce nodule primordial and preinfection thread structures on the host plant.

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20. Chemical shifts of ^{1}H, ^{13}C and 2D NMR (400 MHz, $CDCl_3$) were recorded in ppm (δ). Compound **10**: 5.38 (m, 2H, C_{6-7}–H); 6.01 (d, 1H, C_1–H); 6.52 (dt, 1H, C_2–H); compound **2**: 5.39 (m, 2H, C_{8-9}–H); 5.77 (d, 1H, C_1–H, J_{1-2} = 16.7 Hz); 6.07 (m, 1H, C_3–H); 6.27 (dd, 1H, C_2–H); 6.86 (dm, 1H, C_4–H); **3**: 6.9 (d, 1H, C_2–H, J_{2-3} = 15.2 Hz); 7.9 (d, 1H, C_3–H, J_{3-2} = 15.2 Hz); compound **1**: ^{1}H NMR: 0.90 (t, 3H, C_{18}–H); 1.32 (m, 8H, C_{14}–H to C_{17}–H); 1.49 (m, 2H, C_9–H); 2.03 (m, 4H, C_{13}–H and C_8–H); 2.17 (m, 2H, C_{10}–H); 5.35 (dd, 1H, C_{11}–H, J_{11-12} = 10.83 Hz, J_{11-10} = 6.75 Hz); 5.41 (dd, 1H, C_{12}–H, J_{12-11} = 10.83 Hz, J_{12-13} = 6,25 Hz); 5.86 (d, 1H, C_2–H, J_{2-3} = 15.25 Hz); 5.95 (m, 1H, C_7–H, J_{7-6} = 15.10 Hz, J_{7-8} = 6.91 Hz); 6.25 (dd, 1H, C_4–H, J_{4-5} = 14.81 Hz, J_{4-3} = 10.87 Hz); 6.15 (dd, 1H, C_6–H, J_{6-7} = 15.10 Hz, J_{6-5} = 10.82 Hz); 6.55 (dd, 1H, C_5–H, J_{5-4} = 14.81 Hz, J_{5-6} = 10.72 Hz); 7.34 (dd, 1H, C_3–H, J_{3-2} = 15.25 Hz, J_{3-4} = 8.32 Hz); ^{13}C NMR: 14.32 (CH_3); 22.87–32.71 ($8CH_2$ in chain); 172.32 (COOH); 145.00 (C_3); 141.39 (C_5); 140.46 (C_7); 130.84 (C_{12}); 128.05 (C_4); 129.22 (C_{11}); 130.25 (C_6); 120.28 (C_2); Exact mass (ESI Q-Tof Ultima Waters) for $[M-H]^-$ = $C_{18}H_{27}O_2$: calculated: 275.2010. Found: 275.2037. IR (CaF_2): 1618 (C=C conj.) and 1711 (COOH conj.) cm^{-1}; UV (MeOH) 291.4 nm.