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Synthesis of juniperonic acid

Anders Vik [a,*], Trond Vidar Hansen [a], Anne Kristin Holmeide [b], Lars Skattebøl [b]

[a] School of Pharmacy, Department of Pharmaceutical Chemistry, University of Oslo, PO Box 1185 Blindern, N-0316, Oslo, Norway
[b] Department of Chemistry, University of Oslo, PO Box 1185 Blindern, N-0316, Oslo, Norway

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ABSTRACT

Synthesis of juniperonic acid [(all-*Z*)-5,11,14,17-eicosatetraenoic acid], has been achieved in eight steps and in 19% overall yield starting from eicosapentaenoic acid.

Juniperonic acid (**1**, Fig. 1), (all-*Z*)-5,11,14,17-eicosatetraenoic acid, belongs to a group of naturally occurring methylene-interrupted polyunsaturated fatty acids (PUFA). The seeds of the conifer *Juniperus communis* has a high content of this acid, hence the name juniperonic acid.[1] It was first found in the leaves and nuts of the conifer *Ginkgo biloba*.[2,3] It has since been found in other conifers,[4,5] flowering plants,[6,7] joint pine[8] and also in some marine invertebrates.[9–11] It is present in the seeds of the conifer *Biota orientalis*[4] which is used in traditional Chinese medicines.[12] This PUFA exhibits interesting biological activity[13,14] and it is converted into α-linoleic acid in animal models.[15] No synthesis has been reported; however, the synthesis of a tetradeuterated derivative of the methyl ester has been described.[16]

Juniperonic acid is actually a 8,9-dihydroderivative of EPA. Although there is no way we can selectively hydrogenate that particular double bond of EPA, this fatty acid seemed a good starting material. We have used EPA as a starting material for the synthesis of other natural products.[17–19] EPA is readily converted into the C-15 aldehyde **4** (Fig. 1).[20] Selective saturation of the α,β-double bond in **4** should then provide aldehyde **2**[21] which can participate in a Wittig reaction with 4-carboxybutyltriphenylphosphorane (**3**) to afford juniperonic acid. We anticipated the stereoselectivity of the Wittig reaction to be the crucial point in our synthesis. However, under appropriate conditions, a high *Z*:*E* ratio has been observed with non-stabilized Wittig reagents such as **3**.[22]

Aldehyde **4** was obtained as depicted in Scheme 1.[20] Iodolactonization of EPA and subsequent treatment of the resulting iodolactone **5** with potassium carbonate in methanol provided epoxide **6** in 79% overall yield. Oxidative cleavage of **6** with periodic acid in diethyl ether and subsequent selective double bond migration in **7** by treatment with DBU in diethyl ether furnished the α,β-unsaturated aldehyde **4** in 49% yield over the two steps. The α,β-double bond of this aldehyde was then selectively reduced with DIBAL/CuI in THF/HMPA at −20 °C, essentially as reported by Hamberg et al.,[21] to give aldehyde **2** in 74% yield.

A Wittig reaction between aldehyde **2** and the phosphonium bromide **3** using NaHMDS as base in dry THF at −100 °C provided juniperonic acid in a *Z*:*E* ratio of 93:7 and a moderate yield of 46% (Table 1, entry 3). This was not entirely satisfactory. Others have reported that the presence of anionic groups such as carboxyl in triphenylphosphonium ylides causes a shift in stereoselectivity towards the *E*-isomer. Although this effect is significantly stronger for aromatic aldehydes and seems more trivial for aliphatic aldehydes,[23] we decided to protect the carboxyl group. We were unable to obtain the methyl ester of **3** as a solid, and its use in a Wittig reaction with aldehyde **2** under conditions identical to those described above was not successful. We therefore prepared the phosphonium iodide **9** (Scheme 2). Finkelstein reaction of **8** followed by reaction with triphenylphosphine in refluxing acetonitrile afforded **9** as a colorless solid after recrystallisation from acetonitrile/ethyl acetate. The yield was only 42% because a substantial amount of the acetal was cleaved under these reaction conditions.

The Wittig reaction between aldehyde **2** and triphenylphosphonium iodide **9** was performed under identical conditions to those described above to provide acetal **10** in 87% yield with a *Z*:*E* ratio of 98:2 as determined by GLC analysis. We also investigated if addition of HMPA would improve the stereoselectivity as HMPA has provided very good *Z*-selectivity in similar reactions.[24,25] Changing the solvent to THF/HMPA (4:1) gave **10** with excellent

* Corresponding author. Tel.: +47 22857451; fax: +47 22855947.
E-mail address: anders.vik@farmasi.uio.no (A. Vik).

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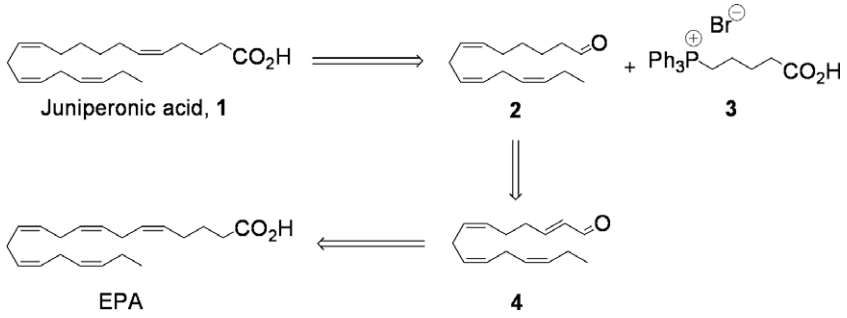
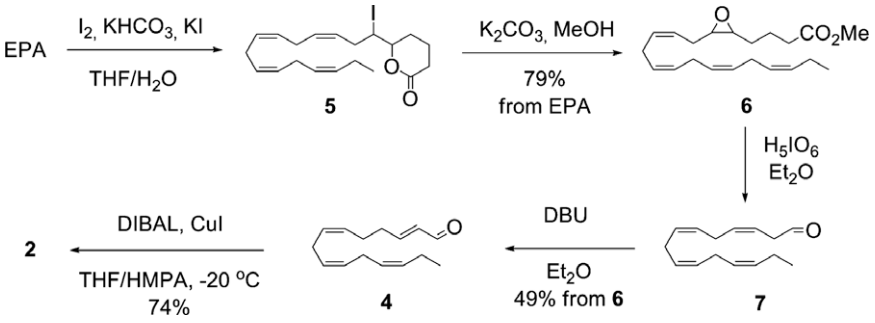


Figure 1. Retrosynthetic analysis of juniperonic acid.

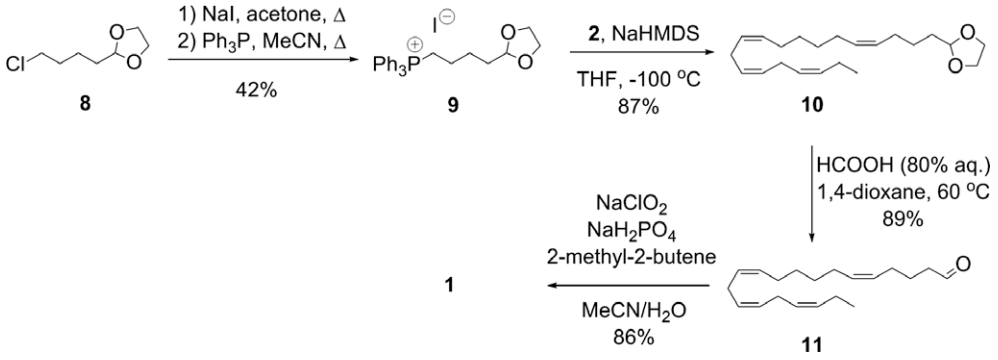


Scheme 1.

Table 1
Wittig reactions with **2**

Entry	Phosphonium halide	Solvent	Temp[a] (°C)	% Yield[b]	*Z*:*E* ratio[c]
1	**3**	Toluene/THF (10:1)	−100	82	85:15
2	**3**	THF	−78	47	90:10
3	**3**	THF	−100	46	93:7
4	**9**	THF	−78	60	94:6
5	**9**	THF:HMPA (4:1)	−100	74[d]	99:1[d]
6	**9**	THF	−100	87	98:2

NaHMDS was used as the base in all experiments.
[a] Temperature during addition of the aldehyde. The cooling bath was removed after complete addition and the mixture was allowed to reach rt and stirred until full conversion of **2** as judged by TLC.
[b] Isolated yield.
[c] Determined by GLC analysis of the resulting methyl ester in entries 1–3 and the acetal in entries 4–6.
[d] Contained 10% of an unidentified inseparable by-product containing a conjugated double bond.



Scheme 2.

Z-selectivity (*Z*:*E* ratio 99:1), but unfortunately some of the product had isomerized to form an inseparable unidentified by-product containing a conjugated double bond. We therefore avoided the use of HMPA.

Acetal **10** was cleaved with 80% aqueous formic acid in 1,4-dioxane to give aldehyde **11** in 89% yield. The conversion was very slow at room temperature, but when the mixture was heated at 60 °C, full conversion was achieved in one hour. Oxidation of **11**

using sodium chlorite in aqueous acetonitrile at room temperature with 2-methyl-2-butene as scavenger afforded juniperonic acid (**1**) in 86% yield.

In conclusion, juniperonic acid was obtained from EPA in 19% overall yield over eight steps.[26] The particular advantage of our method is the conservation of the all-*Z*-configuration of the methylene-interrupted double bonds. We believe this strategy competes well with other procedures for synthesizing an assembly of methylene-interrupted double bonds.

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26. *Spectroscopic data of selected compounds*: Juniperonic acid (**1**): ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.55 (br s, 1H), 5.48–5.25 (m, 8H), 2.81 (t, J = 5.7 Hz, 4H), 2.36 (t, J = 7.5 Hz, 2H), 2.15–1.98 (m, 8H), 1.70 (p, J = 7.5 Hz, 2H), 1.45–1.30 (m, 4H), 0.98 (t, J = 7.5 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 179.86 (CO_2H), 132.11 (CH), 131.26 (CH), 130.29 (CH), 128.44 (2 × CH), 128.38 (CH), 127.96 (CH), 127.26 (CH), 33.51 (CH_2), 29.45 (CH_2), 29.42 (CH_2), 27.28 (2 × CH_2), 26.59 (CH_2), 25.78 (CH_2), 25.68 (CH_2), 24.75 (CH_2), 20.71 (CH_2), 14.42 (CH_3). MS (EI) m/z: 304 (M^+, 7), 121 (34), 108 (61), 95 (57), 79 (100) and 67 (84). HRMS (EI) $C_{20}H_{32}O_2$ requires 304.2402, found 304.2396. *Compound* **2**:[21] ^{1}H NMR ($CDCl_3$, 300 MHz): δ 9.75 (t, J = 1.8 Hz, 1H), 5.46–5.15 (m, 6H), 2.86–2.74 (m, 4H), 2.42 (td, J = 7.3 and 1.8 Hz, 2H), 2.20–1.92 (m, 4H), 1.65 (dt, J = 15.2 and 7.3 Hz, 2H), 1.52–1.28 (m, 2H) and 0.97 (t, J = 7.5 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 202.63 (CHO), 132.11 (CH), 129.54 (CH), 128.54 (CH), 128.48 (CH), 128.13 (CH), 127.15 (CH), 43.88 (CH_2), 29.44 (CH_2), 27.04 (CH_2), 25.74 (CH_2), 25.65 (CH_2), 21.80 (CH_2), 20.67 (CH_2), 14.38 (CH_3). MS (EI) m/z: 220 (M^+, 9), 108 (39), 95 (63), 79 (100) and 67 (79). HRMS (EI) $C_{15}H_{24}O$ requires 220.1827, found 220.1821. *Compound* **10**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.46–5.20 (m, 8H), 4.85 (t, J = 4.7 Hz, 1H), 4.01–3.76 (m, 4H), 2.88–2.70 (m, 4H), 2.17–1.92 (m, 8H), 1.72–1.56 (m, 2H), 1.55–1.28 (m, 6H), 0.97 (t, J = 7.5 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 132.07 (CH), 130.37 (CH), 130.31 (CH), 129.43 (CH), 128.41 (CH), 128.37 (CH), 127.89 (CH), 127.24 (CH), 104.70 (CH), 64.97 (2×CH_2), 33.59 (CH_2), 29.48 (CH_2), 29.41 (CH_2), 27.26 (2×CH_2), 27.17 (CH_2), 25.76 (CH_2), 25.66 (CH_2), 24.23 (CH_2), 20.68 (CH_2), 14.41 (CH_3). MS (EI) m/z: 332 (M^+, 9), 108 (43), 99 (72), 79 (58) and 73 (100). HRMS (EI) $C_{22}H_{36}O_2$ requires 332.2715, found 332.2709. *Compound* **11**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.76 (t, J = 1.7 Hz, 1H), 5.57–5.15 (m, 8H), 2.90–2.68 (m, 4H), 2.43 (td, J = 7.3, 1.7 Hz, 2H), 2.16–1.94 (m, 8H), 1.69 (p, J = 7.4 Hz, 2H), 1.44–1.28 (m, 4H), 0.97 (t, J = 7.5 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.66 (CHO), 132.09 (CH), 131.26 (CH), 130.23 (CH), 128.50 (CH), 128.44 (CH), 128.34 (CH), 127.97 (CH), 127.23 (CH), 43.42 (CH_2), 29.40 (CH_2), 29.39 (CH_2), 27.26 (CH_2), 27.24 (CH_2), 26.60 (CH_2), 25.75 (CH_2), 25.66 (CH_2), 22.19 (CH_2), 20.68 (CH_2), 14.40 (CH_3). MS (EI) m/z: 288 (M^+, 5), 108 (61), 95 (63), 79 (100) and 67 (88). HRMS (EI) $C_{20}H_{32}O$ requires 288.2453, found 288.2446.