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Synthesis of *trans*-vaccenic acid and *cis*-9-*trans*-11-conjugated linoleic acid

Patricia E. Duffy,[a] Sonia M. Quinn,[a] Helen M. Roche[b] and Paul Evans[a,*]

[a]*Centre for Synthesis and Chemical Biology, School of Chemistry, Trinity College, University of Dublin, Dublin 2, Ireland*
[b]*Nutrigenomics Research Group, Department of Clinical Medicine, Institute of Molecular Medicine, St. James' Hospital, Dublin 8, Ireland*

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Abstract—The preparation of the monounsaturated fatty acid, *trans*-vaccenic acid **4** (TVA), using both Wittig and one-pot Julia-Kocieński olefination protocol, was achieved in good yield. Similarly a Wittig approach was employed for the stereoselective synthesis of *cis*-9-*trans*-11-conjugated linoleic acid **2** from *trans*-2-nonenal and (8-carboxyoctyl)triphenylphosphonium bromide **12**.
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1. Introduction

Excessive dietary fatty acids, in particular saturated fatty acids, are associated with a number of chronic diet-related diseases including obesity, type 2 diabetes mellitus, cardiovascular disease and some cancers.[1] Together these conditions account for the majority of global mortality rates in the Western world. In contrast, unsaturated fatty acids, for example, linoleic acid (LA) **1**, are associated with reduced risk of these diet-related diseases.[1] Therefore, nutritional science is focussing on identifying 'healthy' fatty acids, which may be incorporated into functional foods or nutraceuticals. Recent evidence has demonstrated that a novel unsaturated fatty acid, conjugated linoleic acid (CLA) may have health promoting effects, inhibiting the development of cancer, atherosclerosis, diabetes and chronic inflammatory diseases.[2] Consequently CLA has become a popular health food supplement. CLA is a heterogeneous group of compounds, including a number of positional and geometrical isomers of linoleic acid (C18:2 *n*-6).[3] Significantly it has been demonstrated that the health effects of CLA are isomer specific, whereby the *cis*-9-*trans*-11 CLA (c9, t11-CLA) isomer **2** prevents disease processes that lead to atherosclerosis, diabetes, chronic inflammation and colon cancer.[4] However, the other main isomer, *trans*-10-*cis*-12 CLA **3** (t10, c12-CLA), appears to possess detrimental health effects including inducing a diabetic state, associated with hyperlipidaemia.[4] All commercially available supplements contain a mixture of these regioisomeric cis, trans-alkenes (**2** and **3**), since the current synthetic procedures used for their preparation are unselective. Therefore, any potential health benefit of *cis*-9-*trans*-11 CLA **2** is lost, due to the presence of the detrimental *trans*-10-*cis*-12 CLA **3** isomer.[5] A mixture of CLA (**2** and **3**) is obtained by following the base induced isomerisation of linoleic acid **1**.[3,6] However, this conversion leads to the mixture of regio- and stereoisomers that require lengthy and complicated separation (Fig. 1).

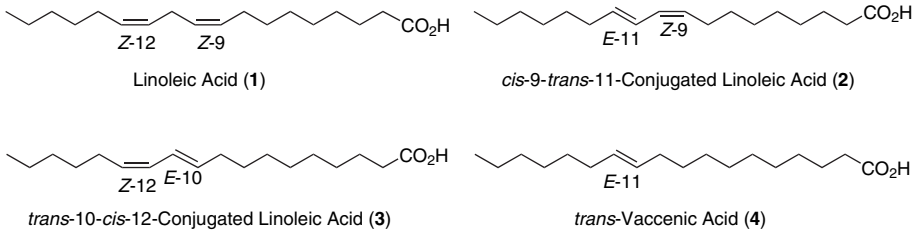

Figure 1. Structures of linoleic acid and related C-18 fatty acids.

* Corresponding author. Tel.: +353 1 716 2291; e-mail addresses: hmroche@tcd.ie; paul.evans@ucd.ie

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CLA is a natural food component found in the lipid fraction of meat, milk and dairy products, and *cis*-9-*trans*-11 CLA **2** is the principal dietary isomeric form of CLA.[7] It is now evident that the major trans-fatty acid found in ruminant meat and milk is *trans*-vaccenic acid **4** (TVA, *trans*-11 C18:1) which has been found to protect against chemically-induced mammary cancer in rats.[8] Biosynthetic evidence indicates that TVA **4** is readily converted by the bacterial enzyme Δ^9-desaturase into *cis*-9-*trans*-11-conjugated linoleic acid **2**. Initially it was proposed that this was the major source of CLA synthesis in the bovine mammary gland but it is now clear that several human tissues, in particular the intestine, can convert TVA **4** to *cis*-9-*trans*-11 CLA **2**.[9] Therefore, the biopotency of CLA food sources can be enhanced in vivo by the co-existence of TVA **4** in several food products (milk, yoghurt, cheese, butter and meats). Nevertheless, the presence of both fatty acids in foods impedes investigation of the individual effects of CLA and TVA. Additionally, currently there are no stereoisomerically pure forms of TVA **4** is commercially available for nutritional studies to determine whether the nature of the health effects ascribed to TVA are due to the fatty acid alone or attributable to metabolic conversion of TVA **4** to CLA **2**. This data are essential to define the health implication of CLA and TVA enriched functional foods and nutraceuticals for the development and application of enhanced human nutrition and health products. Consequently, we became interested in the stereoselective preparation of both *trans*-vaccenic acid **4** and *cis*-9-*trans*-11-conjugated linoleic acid **2**.

2. Results and discussion

Since it was known that *cis*-vaccenic acid undergoes a facile isomerisation to *trans*-vaccenic acid **4** with a mixture of $NaNO_2$–HNO_3,[10] the preparation of *trans*-vaccenic acid was achieved by using Wittig chemistry (see Fig. 2).[11] Thus, commercially available carboxylic acid **5** was converted into the phosphonium salt **6**, the purification of which was achieved by taking up the crude mixture and treatment with boiling ethyl acetate. This operation also facilitates the handling of **6** since on addition of ethyl acetate, **6** formed a solid.[12] Treatment of a slurry of **6**, in THF at −78 °C, with 2.5 equiv of LHMDS and then warming this mixture to 0 °C over 2 h resulted in the formation of the ylide. Subsequent re-cooling to −78 °C and addition of heptanal gave the Wittig product *cis*-vaccenic acid in good yield (70%) and as a ratio of alkenyl stereoisomers (*Z*/*E*: ca. 82:18—estimated by integration of the respective alkenyl signals in the ^{1}H NMR spectrum [*cis*-CVA: δ_H 5.34–5.41 ppm; *trans*-CVA: δ_H 5.38–5.47 ppm]).

Under the so-called 'salt-free' Wittig conditions using KHMDS as the base slightly better yields and stereoselectivities were observed for this process (89%; *Z*/*E*, ca. 88:12).[11,13] Isomerisation was then effected by following the conditions reported and *trans*-vaccenic acid **4** was obtained by iterative recrystallisation of the crude product from acetone (*E*/*Z*, >95:5).[10] This overall synthetic sequence proved a robust method for the preparation of *trans*-vaccenic acid **4** and was performed on scales of ca. 30 g (Wittig product).

Although the melting point of our synthetic material was consistent with that reported in the literature[10] and additional spectroscopic evidence supported the assigned structure we were not able to observe the trans-alkenyl coupling by proton NMR spectroscopy since the two alkenyl protons in both the *cis*- and *trans*-vaccenic acid samples were coincident. Therefore, in order to probe the stereochemistry of the alkene formed in this sequence we investigated a complementary Julia-Kocieński one-pot olefination protocol, since this method has been reported to generate high levels of trans-stereoselectivity during alkene formation (particularly when K^+ counter ions are employed).[14] Thus, the sulfonyl tetrazole **7** was synthesised by following the alkylation of 1-phenyl-1*H*-tetrazole-5-thiol **8** with 11-bromoundecanoic acid methyl ester and the oxidation of the sulfide adduct with *m*-CPBA. Subsequently, a solution of the sulfone **7** in THF was treated with KHMDS at approximately −55 °C[14] and stirring was continued for 40 min before addition of heptanal at the same temperature. The resultant alkene **9** was isolated in 50% yield and with reasonable trans-stereoselectivity (*E*/*Z*, ca. 85:15). Subsequent ester hydrolysis with LiOH

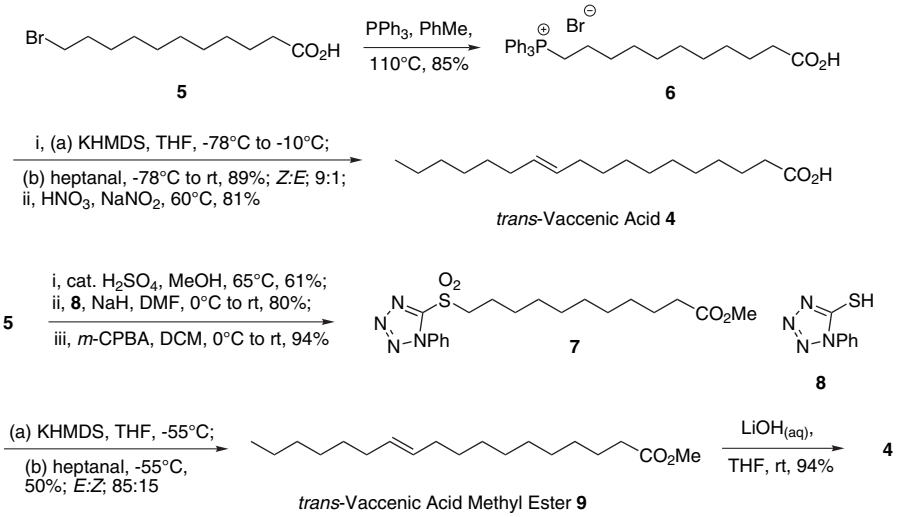

Figure 2. Synthesis of *trans*-vaccenic acid **4**.

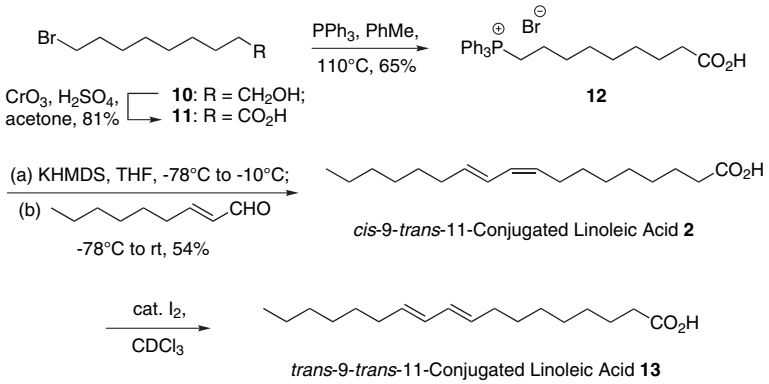

Figure 3. Synthesis of *cis*-9-*trans*-11-conjugated linoleic acid **4**.

gave the corresponding acid **2** and the spectroscopic data of the predominant stereoisomer were identical to that obtained from *trans*-vaccenic acid **2** accessed via the Wittig-isomerisation route.

Following these studies we then investigated the stereo- and regioselective preparation of *cis*-9-*trans*-11-conjugated linoleic acid **2**.[6] Arguably the most widely used method to synthesise this type of conjugated *cis*, *trans*-dienyl system present in CLA is based on the reduction of a *trans*-enyne.[6a,15] However, in their classical synthesis of the insect pheromone bombykol, Bestmann and co-workers demonstrated that the Wittig reaction between a non-stabilised ylide and a *trans*-α,β-unsaturated aldehyde affords the adduct in good levels with cis-stereoselectivity.[16] Therefore, we chose to employ a similar Wittig approach to construct the cis, trans-dienyl architecture present in *cis*-9-*trans*-11-CLA **2** (Fig. 3).

Jones oxidation of 9-bromononanol **10** gave the carboxylic acid **11**, which was converted into phosphonium bromide **12**.[17] As described for **6**, this material was purified by stirring in boiling ethyl acetate, removing the unreacted starting materials and also facilitating the formation of the phosphonium salt **12** as an amorphous solid. The subsequent Wittig reaction of **12** was performed using KHMDS as a base in an identical fashion to the previous synthesis of TVA **4**. Thus, *cis*-9-*trans*-11-conjugated linoleic acid **2** was isolated in 54% yield and the new double bond was formed with reasonable cis-selectivity (*Z*/*E*, ca. 85:15). The stereochemical integrity of the predominantly formed geometric isomer was confirmed by comparison with the commercially available material.[6e,18] In addition its isomerisation to *trans*-9-*trans*-11-conjugated linoleic acid **13** was achieved using approximately 5 mol % of I_2, as described[6a] and consequently we were able to confirm the identity of the minor impurity in the Wittig reaction.

In summary, we have achieved a straightforward stereoselective synthesis of *cis*-9-*trans*-11-conjugated linoleic acid **2**. The preparation of its bioprecursor, the monounsaturated fatty acid, *trans*-vaccenic acid **4**, was also performed using both Wittig and Julia-Kocieński olefination approaches. Significantly, these reaction sequences are scalable, enabling the preparation of multi-gram amounts of these biologically important fatty acids.

3. Experimental

3.1. General

Starting materials were purchased from commercial sources and were used without further purification. Anhydrous THF was distilled under nitrogen from the sodium-benzophenone ketyl radical. ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded using a Bruker AMX400 spectrometer. Infrared spectroscopy was performed on a Perkin–Elmer Paragon 1000 FTIR spectrometer. Flash column chromatography, under moderate pressure was performed using silica gel—ICN 32–63, 60 Å. Melting points were recorded on an Electrothermal IA9000 digital melting point apparatus and were uncorrected.

3.1.1. (10-Carboxydecyl)triphenylphosphonium bromide 6. Under nitrogen a solution of 11-bromoundecanoic acid **5** (40.0 g, 0.15 mol, 1 equiv) and triphenylphosphine (43.42 g, 0.165 mol, 1.1 equiv) in toluene (250 mL) were heated to reflux for 24 h. On cooling the two phases were apparent and the upper phase was decanted and DCM (ca. 250 mL) was added to the viscous residue before the solvent was stripped in vacuo. The resultant solid was washed with boiling EtOAc (3×ca. 250 mL) and the white solid (67.4 g, 85%) was collected by filtration and dried in vacuo. Mp 103–105 °C; υ_{max} (Nujol/cm^{-1}) 3010, 2925, 2855, 1711, 1465, 1287; δ_H (400 MHz, $CDCl_3$) 1.19–1.35 (10H, m, CH_2), 1.57–1.69 (6H, m, CH_2), 2.46 (2H, t, *J* 7.0 Hz, CH_2), 3.70–3.81 (2H, m, CH_2), 7.66–7.78 (6H, m, ArH), 7.78–7.84 (9H, m, ArH); δ_C (100 MHz, $CDCl_3$) 22.3 (d, *J* 5.0 Hz), 22.8 (d, *J* 49.5 Hz), 24.4, 28.25, 28.3, 29.9 (d, *J* 15.5 Hz), 34.3, 118.4 (d, *J* 85.5 Hz), 130.5 (d, *J* 12.5 Hz), 133.6 (d, *J* 9.5 Hz), 135.0, 177.4; δ_P (162 MHz, $CDCl_3$) 25.65.

3.1.2. *cis*-Octadec-12-enoic acid (*cis*-vaccenic acid)

(a) Under nitrogen hexamethyldisilazane (28.8 mL, 0.138 mol, 3 equiv) in dry THF (250 mL) was cooled to −78 °C and treated with 1.6 M BuLi in hexane (72 mL, 0.115 mol, 2.5 equiv). Stirring was continued for 0.5 h before this solution of LHMDS was added to a slurry of the phosphonium salt **6** (24.25 g, 0.046 mol, 1 equiv) in THF (350 mL) at −78 °C via cannula. The resultant yellow–orange mixture was stirred between

−78 and 0 °C for 2 h before the solution was re-cooled to −78 °C and heptanal (8.4 mL, 0.06 mol, 1.3 equiv) was added dropwise. The mixture was stirred for 48 h during which period room temperature was gradually reached. EtOAc (250 mL) and 1 M HCl (250 mL) were added and the resultant aqueous phase was further extracted with EtOAc (2×250 mL). The combined organic phases were dried over $MgSO_4$ before filtration and solvent evaporation under reduced pressure gave the crude cis-alkene. Purification by flash column chromatography (Hex–EtOAc, 6:1) afforded the product (9.03 g, 70%) as a viscous yellow oil. R_f=0.3 (Hex–EtOAc, 6:1); υ_{max} (neat/cm^{-1}) 3005, 2925, 2855, 1713, 1586, 1464; δ_H (400 MHz, $CDCl_3$) 0.89 (3H, t, *J* 7.0 Hz, CH_3), 1.23–1.39 (20H, m, CH_2), 1.64 (2H, pent, *J* 7.5 Hz, CH_2), 1.98–2.07 (4H, m, CH_2), 2.36 (2H, t, *J* 7.5 Hz, CH_2), 5.34–5.41 (2H, m, CH), 11.20 (1H, br s, CO_2H); δ_C (100 MHz, $CDCl_3$) 14.1, 22.6, 24.7, 27.15, 27.2, 29.0, 29.05, 29.2, 29.4, 29.5, 29.7, 31.8, 34.1, 129.8, 129.9, 179.9.

(b) Under nitrogen, a stirred slurry of (10-carboxydecyl)triphenylphosphonium bromide **6** (10.0 g, 18.98 mmol, 1 equiv) in THF (120 mL) was cooled to −78 °C. Potassium bis(trimethylsilyl)amide (101 mL of 0.5 M solution in toluene, 50.49 mmol, 2.7 equiv) was added and the mixture was warmed to room temperature over 2 h. The deep red solution was then re-cooled to −78 °C before heptanal (3.66 mL, 26.22 mmol, 1.4 equiv) was added dropwise. The reaction was warmed to room temperature and stirred for 12 h. Work-up and purification was carried out as above and *cis*-vaccenic acid (4.76 g, 89%) was obtained whose data corresponded to the above data.

3.1.3. *trans*-Octadec-12-enoic acid (*trans*-vaccenic acid 4). With stirring *cis*-vaccenic acid (9.03 g, 32.02 mmol, 1 equiv) was treated with a solution of $NaNO_2$ (0.47 g, 6.81 mmol, 0.2 equiv) in water (1.8 mL), which was heated to 60 °C. After 0.5 h a solution of concd HNO_3 (2.3 mL) in water (2.3 mL) was added. The mixture was further stirred for 0.3 h before being removed from the oil bath. After reaching room temperature (ca. 1 h) Et_2O (30 mL) and water (30 mL) were added. The resultant aqueous phase was further extracted with Et_2O (4×30 mL) and the combined organic phases were dried over $MgSO_4$ before filtration and solvent evaporation under reduced pressure gave the crude trans-alkene. Purification by three repetitive recrystallisations from acetone afforded the product **4** (7.31 g, 81%) as a white solid. Mp 43.5–44 °C (acetone); R_f=0.25 (Hex–EtOAc, 6:1); υ_{max} (Nujol/cm^{-1}) 2954, 2923, 2852, 1712, 1462, 1414, 1377; δ_H (400 MHz, $CDCl_3$) 0.90 (3H, t, *J* 6.5 Hz, CH_3), 1.24–1.39 (20H, m, CH_2), 1.65 (2H, pent, *J* 7.5 Hz, CH_2), 1.95–2.04 (4H, m, CH_2), 2.36 (2H, t, *J* 7.5 Hz, CH_2), 5.38–5.47 (2H, m, CH_2), 10.05 (1H, br s, CO_2H); δ_C (100 MHz, $CDCl_3$) 14.1, 22.6, 24.6, 28.8, 29.0, 29.1, 29.2, 29.35, 29.4, 29.6, 31.7, 32.55, 32.6, 34.1, 130.3, 130.4, 180.3; *m/z* (CI) 300 (MNH_4^+, 100%); found 300.28983, $C_{18}H_{38}O_2N$ requires 300.29025 (−1.5 ppm); found C, 76.67; H, 11.85%; $C_{18}H_{34}O_2$ requires C, 76.54; H, 12.13%.

3.1.4. 11-Bromoundecanoic acid methyl ester.[19] A solution of 11-bromoundecanoic acid (5.0 g, 19.00 mmol, 1 equiv) and methanol (50 mL) was treated with concd H_2SO_4 (0.5 mL) and heated to reflux for 12 h. On cooling Et_2O (80 mL) and 1 M KOH (80 mL) were added. The resultant aqueous phase was further extracted with Et_2O (2×80 mL) and the combined organic phases were dried over $MgSO_4$. Filtration and solvent removal under reduced pressure gave the crude methyl ester which was purified by flash column chromatography (Hex–EtOAc, 19:1). Thus the methyl ester (2.734 g, 61%) was isolated as a colourless liquid. R_f=0.25 (Hex–EtOAc, 19:1); υ_{max} (neat/cm^{-1}) 2926, 2854, 1737, 1436, 1246, 1196, 1169; δ_H (400 MHz, $CDCl_3$) 1.22–1.31 (10H, m, CH_2), 1.42 (2H, pent, *J* 7.0 Hz, CH_2), 1.63 (2H, pent, *J* 7.0 Hz, CH_2), 1.84 (2H, pent, *J* 7.5 Hz, CH_2), 2.31 (2H, t, *J* 7.5 Hz, CH_2), 3.39 (2H, t, *J* 7.0 Hz, CH_2), 3.66 (3H, s, CH_3); δ_C (100 MHz, $CDCl_3$) 24.9, 28.1, 28.6, 29.0, 29.1, 29.2, 29.3, 32.7, 33.95, 34.0, 51.4, 174.2.

3.1.5. 11-(1-Phenyl-1*H*-tetrazole-5-sulfanyl)undecanoic acid methyl ester. Under nitrogen at 0 °C 60% w/w NaH (0.48 g, 12.0 mmol, 1.1 equiv) was added in one portion to a solution of 1-phenyl-1*H*-tetrazole-5-thiol **8** (1.96 g, 11.0 mmol, 1 equiv) in dry DMF (25 mL). After stirring for 0.5 h the methyl ester (2.56 g, 11.0 mmol, 1 equiv) was added. Stirring was maintained for 12 h. Et_2O (50 mL) and water (50 mL) were added and the resultant aqueous layer was further extracted with Et_2O (3×50 mL). The combined ethereal extracts were dried over $MgSO_4$. Filtration, solvent removal in vacuo and purification by flash column chromatography (Hex–EtOAc, 4:1) gave the sulfide (3.29 g, 80%) as a colourless waxy solid. Mp 34–36 °C; R_f=0.3 (Hex–EtOAc, 4:1); υ_{max} (neat/cm^{-1}) 2925, 1736, 1598, 1500, 1386, 1242, 1170; δ_H (400 MHz, $CDCl_3$) 1.25–1.38 (10H, m, CH_2), 1.44 (2H, pent, *J* 7.5 Hz, CH_2), 1.62 (2H, pent, *J* 7.5 Hz, CH_2), 1.83 (2H, pent, *J* 7.0 Hz, CH_2), 2.34 (2H, t, *J* 7.5 Hz, CH_2), 3.42 (2H, t, *J* 7.0 Hz, CH_2), 3.69 (3H, s, CH_3), 7.52–7.66 (5H, m, ArH); δ_C (100 MHz, $CDCl_3$) 24.9, 28.6, 29.0, 29.05, 29.1, 29.2, 29.3, 29.35, 33.3, 34.1, 51.5, 123.8, 129.8, 130.1, 133.7, 154.5, 174.3; *m/z* (ES^+) 399 (MNa^+, 100%), 377 (MH^+, 20%); found 377.1996, $C_{19}H_{29}N_4O_2S$ requires 377.2011 (−4.0 ppm).

3.1.6. 11-(1-Phenyl-1*H*-tetrazole-5-sulfonyl)undecanoic acid methyl ester 7. At 0 °C *m*-CPBA (1.38 g, 7.98 mmol, 3 equiv) was added in one portion to a solution of the sulfide (1.00 g, 2.66 mmol, 1 equiv) in DCM (40 mL). Stirring was maintained for two days. DCM (50 mL) and satd Na_2SO_3 (50 mL) were added and the mixture was partitioned for 1 h. The resultant aqueous layer was further extracted with DCM (50 mL) and the combined organic extracts were washed with satd $NaHCO_3$ (100 mL). The resultant aqueous layer was washed with DCM (3×50 mL) before drying over $MgSO_4$. Filtration and solvent removal in vacuo gave the sulfone **7** (1.02 g, 94%) as a colourless solid whose ^1H NMR spectrum indicated sufficient purity for further use. Mp 47–49 °C; R_f=0.2 (Hex–EtOAc, 4:1); υ_{max} (neat/cm^{-1}) 2918, 2848, 1725, 1595, 1437, 1341, 1155; δ_H (400 MHz, $CDCl_3$) 1.22–1.40 (10H, m, CH_2), 1.46–1.55 (2H, m, CH_2), 1.64 (2H, pent, *J* 7.5 Hz, CH_2), 1.96 (2H, pent, *J* 8.0 Hz, CH_2), 2.34 (2H, t, *J* 7.5 Hz, CH_2), 3.68 (3H, s, CH_3), 3.74 (2H, t, *J* 8.0 Hz, CH_2), 7.60–7.67 (3H, m, ArH), 7.72 (2H, d, *J* 7.5 Hz, ArH); δ_C (100 MHz, $CDCl_3$) 21.9, 24.9, 28.1, 28.8, 29.0, 29.05, 29.1, 29.2, 34.1, 51.5,

56.0, 125.0, 129.7, 131.4, 133.0, 153.4, 174.3; *m/z* (ES^+) 431 (MNa^+, 100%), 409 (MH^+, 15%); found 409.1913, $C_{19}H_{29}N_4O_4S$ requires 409.1910 (+0.8 ppm).

3.1.7. *trans*-Octadec-12-enoic acid methyl ester 9. At −55 °C a solution of the sulfone (0.644 g, 1.58 mmol, 1 equiv) in THF (10 mL) was treated with a 0.5 M solution of potassium bis(trimethylsilyl)amide in toluene (3.56 mL, 1.78 mmol, 1.1 equiv). Stirring was continued for 40 min at −55 °C before heptanal (0.29 mL, 2.054 mmol, 1.3 equiv) was added. The mixture was further stirred for 1 h at −55 °C before water (25 mL) and Et_2O (25 mL) were added. The mixture was extracted with Et_2O (3×25 mL) and the combined organic extracts were dried over $MgSO_4$. Filtration and solvent removal under reduced pressure and purification by flash column chromatography (Hex−EtOAc, 19:1) gave the alkene **9** (0.237 g, 50%) as a colourless oil. R_f=0.6 (Hex–EtOAc, 4:1); υ_{max} (neat/cm^{-1}) 2925, 2855, 1744, 1693, 1464, 1436; δ_H (400 MHz, $CDCl_3$) 0.91 (3H, t, *J* 6.5 Hz, CH_3), 1.22–1.39 (20H, m, CH_2), 1.63 (2H, pent, *J* 7.5 Hz, CH_2), 1.93–2.01 (4H, m, CH_2), 2.32 (2H, t, *J* 7.5 Hz, CH_2), 3.69 (3H, s, CH_3), 5.38–5.44 (2H, m, CH); δ_C (100 MHz, $CDCl_3$) 14.1, 22.7, 24.9, 28.8, 29.1, 29.2, 29.4, 29.45, 29.6, 31.8, 32.6, 34.1, 51.5, 130.3, 130.4, 174.4.

3.1.8. *trans*-Octadec-12-enoic acid (*trans*-vaccenic acid 4). A solution of the methyl ester (100 mg, 0.337 mmol, 1 equiv) in THF (3 mL) was treated with a solution of LiOH (24 mg, 1.01 mmol, 3 equiv) in water (3 mL). Stirring was continued for 48 h before Et_2O (20 mL) and 0.5 M HCl (20 mL) were added. The resultant aqueous layer was further extracted with Et_2O (3×20 mL) and the combined organic extracts were dried over $MgSO_4$. Filtration and solvent removal under reduced pressure gave the alkene (89 mg, 94%) as a white solid whose data was identical to that described above.

3.1.9. 9-Bromononanoic acid 11.[17] Chromium trioxide (1.34 g, 13.4 mmol, 1.5 equiv) and water (1.3 mL) was cooled to ca. 0 °C and concd H_2SO_4 (1.0 mL, 17.92 mmol, 2 equiv) was cautiously added followed by water (2.5 mL). After 5 min a solution of 9-bromo-1-nonanol **10** (2.0 g, 8.96 mmol, 1 equiv) in acetone (7 mL) was added dropwise. The reaction mixture was stirred for 2 h at 0 °C before warming to room temperature and stirring for 12 h. Et_2O (50 mL) and H_2O (50 mL) were added and the aqueous layer was further extracted with Et_2O (3×50 mL). The combined organic phases were then washed with a brine solution (100 mL) and the resultant organic phase was dried over $MgSO_4$, filtered and reduced in vacuo. The crude acid was purified by flash column chromatography (DCM; 0.5% AcOH) affording the product **11** (1.71 g, 81%) as a white solid. Mp 35–37 °C; R_f=0.25 (DCM); υ_{max} (Nujol/cm^{-1}) 2928, 2855, 1706, 1464, 1430, 1412, 1243, 1209, 936; δ_H (400 MHz, $CDCl_3$) 1.41 (8H, m, CH_2), 1.66 (2H, m, CH_2), 1.88 (2H, m, CH_2), 2.38 (2H, t, *J* 7.5 Hz, CH_2), 3.43 (2H, t, *J* 7.0 Hz, CH_2); δ_C (100 MHz, $CDCl_3$) 24.6, 28.0, 28.5, 28.9, 29.0, 32.7, 34.0, 180.1.

3.1.10. (8-Carboxyoctyl)triphenylphosphonium bromide 12.[17] 9-Bromononanoic acid **11** (2.00 g, 8.41 mmol, 1 equiv) and triphenylphosphine (2.21 g, 8.41 mmol, 1 equiv) were dissolved in toluene (15 mL). This mixture was heated to reflux for 24 h. On cooling, the upper layer was decanted and the lower layer was dissolved in DCM (3×20 mL) and reduced in vacuo. The resulting brown solid was washed in boiling EtOAc (3×50 mL), and a white solid (2.72 g, 65%) was collected by filtration and dried in vacuo. Mp 82–84 °C; υ_{max} (Nujol/cm^{-1}) 3058, 2930, 2857, 1718, 1644, 1439, 1113; δ_H (400 MHz, $CDCl_3$) 1.20 (6H, m, CH_2), 1.49 (6H, m, CH_2), 2.28 (2H, t, *J* 7.0 Hz, CH_2), 3.56 (2H, m, CH_2), 7.67–7.78 (15H, m, ArH); δ_C (100 MHz, $CDCl_3$) 22.2 (d, *J* 7.0 Hz), 22.4 (d, *J* 50.0 Hz), 24.4, 28.25, 28.3, 29.9 (d, *J* 15.5 Hz), 34.2, 117.9 (d, *J* 85.0 Hz), 130.4 (d, *J* 12.5 Hz), 133.4 (d, *J* 10.0 Hz), 134.9 (d, *J* 3.0 Hz), 176.8; δ_P (162 MHz, $CDCl_3$) 25.65.

3.1.11. *cis*-9-*trans*-11-Octadecdienoic acid (*cis*-9-*trans*-11-CLA) 2. Under nitrogen, a slurry of **12** (2.00 g, 4.00 mmol, 1 equiv) in THF (30 mL) was stirred at −78 °C and potassium bis(trimethylsilyl)amide (20 mL of a 0.5 M solution in toluene, 10.00 mmol, 2.5 equiv) was added dropwise. This mixture was warmed to room temperature over 2 h before re-cooling to −78 °C. *trans*-2-Nonenal (0.86 mL, 5.20 mmol, 1.3 equiv) was added dropwise and the mixture was stirred for 12 h during which room temperature was reached. EtOAc (50 mL) and 1 M HCl (50 mL) were added and the aqueous layer was further extracted with EtOAc (2×50 mL). The combined organic phases were dried over $MgSO_4$ before filtration and solvent evaporation under reduced pressure. The crude product was purified via flash column chromatography (Hex–EtOAc, 5:1) affording the title compound **2** (0.60 g, 54%) as a viscous yellow oil. R_f=0.25 (Hex–EtOAc, 5:1); υ_{max} (Nujol/cm^{-1}) 3019, 2955, 2926, 2855, 1711, 1465, 1465, 1411, 1259, 983; δ_H (400 MHz, $CDCl_3$) 0.90 (3H, t, *J* 7.0 Hz, CH_3), 1.23–1.45 (16H, m, CH_2), 1.65 (2H, pent, *J* 7.5 Hz, CH_2), 2.04–2.20 (4H, m, CH_2), 2.37 (2H, t, *J* 7.5 Hz, CH_2), 5.31 (1H, dt, *J* 7.5, 11.0 Hz, CH-9), 5.68 (1H, dt, *J* 7.0, 14.75 Hz, CH-12), 5.96 (1H, dd, app. t, *J* 11.0 Hz, CH-10), 6.31 (1H, dd, *J* 11.0, 14.75 Hz, CH-11); δ_C (100 MHz, $CDCl_3$) 14.1, 22.6, 24.6, 27.6, 28.9, 29.0, 29.1, 29.3, 29.4, 29.6, 31.7, 32.9, 125.52, 128.7, 129.9, 134.8, 179.8; *m/z* (ES^-) 279 ($M-H^-$, 100%); found 279.2314, $C_{18}H_{31}O_2$ requires 279.2324 (−3.6 ppm).

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