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Enantioselective synthesis of (10*S*)- and (10*R*)-methyl-anandamides

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ABSTRACT

For the development of novel endocannabinoid templates with potential resistance to hydrolytic and oxidative metabolism, we are targeting the bis-allylic carbons of the arachidonoyl skeleton. Toward this end, we recently disclosed the synthesis and preliminary biological data for the (13*S*)-methyl-anandamide. We report now the total synthesis of the (10*S*)- and (10*R*)-methyl-counterparts. Our synthetic approach is stereospecific, efficient, and provides the analogs without the need for resolution. Peptide coupling, P-2 nickel partial hydrogenation, and cis-selective Wittig olefination are the key steps.

1. Introduction

The endogenous arachidonic acid (**Ia**) derivatives *N*-arachidonoylethanolamine (AEA, anandamide, **Ib**) and 2-arachidonoyl glycerol (2-AG, **Ic**, Fig. 1) are synthesized on demand in response to elevations of intracellular calcium, and are the two key lipid modulators that act on CB1 and CB2 cannabinoid receptors.[1–3] Both CB1 and CB2 are members of the superfamily of G-protein-coupled receptors[4–7] and they are implicated in a wide array of pathophysiological processes including inflammation,[8] nociception,[9–11] neuroprotection,[12–15] memory,[16] anxiety,[17] feeding,[18,19] and cell proliferation.[20,21] Following their synthesis and release, the endocannabinoids AEA and 2-AG are removed from their sites of action by cellular uptake and degraded by enzymes. In most tissues, fatty acid amide hydrolase (FAAH) is the enzyme responsible for AEA hydrolysis, and monoacylglycerol lipase (MGL) is the major metabolizing enzyme for 2-AG.[22,23] In addition to hydrolysis, the presence of an arachidonoyl moiety in both AEA and 2-AG suggests the conspicuous possibility that endocannabinoids may be metabolized by the plethora of oxygenases that act on arachidonic acid. Investigations into this possibility have shown that a subset of oxidative enzymes of the arachidonate cascade, such as lipoxygenases (LOX), cyclooxygenase-2 (COX-2), and cytochrome P450 catalyze the biotransformation of AEA and 2-AG into eicosanoid-related metabolites.[24–29] Apart from the hydrolytic deactivation of AEA and 2-AG, the alternative COX-2 oxidative deactivation becomes important when FAAH or MGL are inhibited and when endocannabinoid biosynthesis is activated following tissue damage.[30,31] Also, in platelets, which lack significant COX-2 and FAAH activity a lipoxidative pathway of AEA deactivation predominates.[26]

As a part of our ongoing program in cannabinoid medicinal chemistry, we turned our attention into the development of novel endocannabinoid prototypes that possess CB receptor binding affinity as well as metabolic stability to the action of COX-2 and LOX. The novel analogs can enhance our understanding regarding the stereoelectronic requirements for CB receptor binding and aid in

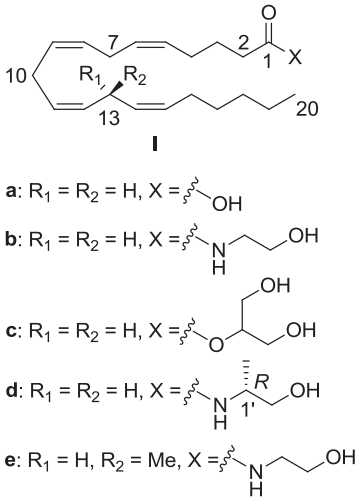

Fig. 1. Structures of arachidonic acid and endocannabinoid analogs.

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the discovery of more potent and selective cannabinergic drug candidates and fatty acid oxygenase (e.g., COX-2 and LOX) inhibitors. They can also serve as biochemical/pharmacological tools to explore the connection between the endocannabinoid and the COX-2 and LOX systems, and to define the physiological significance of the oxidative metabolism of endocannabinoids.

Earlier work from our laboratory has shown that one of the most successful and convenient ways to 'shut off' the enzymatic hydrolysis of AEA is the addition of a methyl substituent near the metabolic hot spot of the substrate (e.g., (*R*)-methanandamide, **Id**).[32–34] It has also been shown that COX-2 and LOX mediated metabolism of arachidonic acid and its derivatives begins with abstraction of a hydrogen radical from the bis-allylic carbons 7, 10, or 13 (Fig. 1).[35–38] Therefore, we considered that introduction of a methyl group at the bis-allylic positions might preserve cannabinoid activity while blocking the oxidative metabolism by COX-2 and LOX enzymes. In this regard, we recently described the synthesis and preliminary biological evaluation of (13*S*)-methyl anandamide (**Ie**).[39] With the aim of exploring all three bis-allylic positions and establishing structure–activity relationships (SAR) for the hitherto unknown, methyl-substituted arachidonoyl chain, we report here our efforts toward the total synthesis of the (10*S*)- and (10*R*)-methyl-anandamides. Our synthetic approach is stereospecific, efficient, and provides the analogs without the need for resolution. A detailed SAR study along with a full biological evaluation of the synthesized analogs will be reported in due course.

2. Results and discussion

Our retrosynthetic analysis involves methyl esters **2a** and **2b** as the key precursors from which (10*S*)- and (10*R*)-methyl-anandamides (**1a** and **1b**, respectively) would be produced through peptide coupling (Fig. 2). Retrosynthetic disconnection at the double bonds adjacent to the chiral center provides four convergent fragments: the phosphonium salts **5** and **6**, and the chiral aldehydes **3** and **4** that possess the *S* and *R* configuration corresponding to the C10 stereogenic centers of **1a** and **1b**, respectively. The synthetic direction could be completed through Wittig olefination reactions.

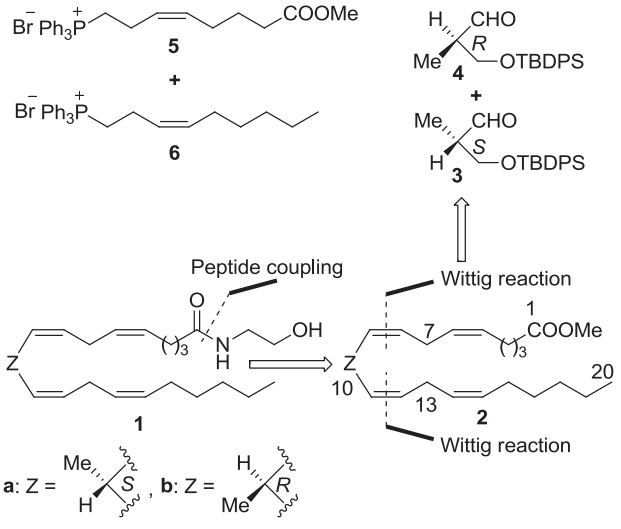
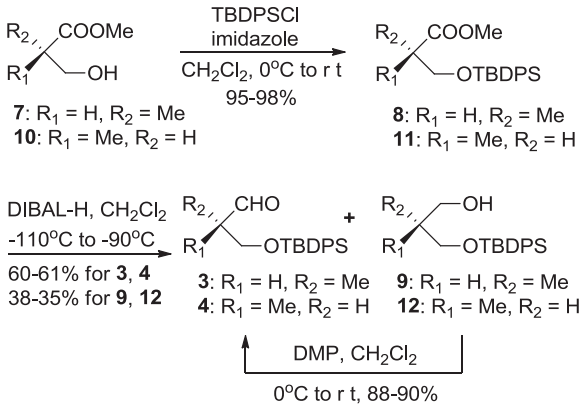


Fig. 2. Retrosynthetic analysis of (10*S*)- and (10*R*)-methyl-anandamides.

Synthesis of chiral aldehyde **3** was carried out by following our recently reported procedures (Scheme 1).[39] Briefly, silylation of commercially available methyl ester **7** gave the TBDPS ether **8** (95% yield), which upon reduction with diisobutylaluminum hydride led to aldehyde **3** (60% yield) and alcohol **9** (38% yield). Oxidation of **9** with Dess–Martin periodinane produced **3** in 88% yield. Similarly, the enantiomeric aldehyde **4**[40] was synthesized from Roche ester **10**.

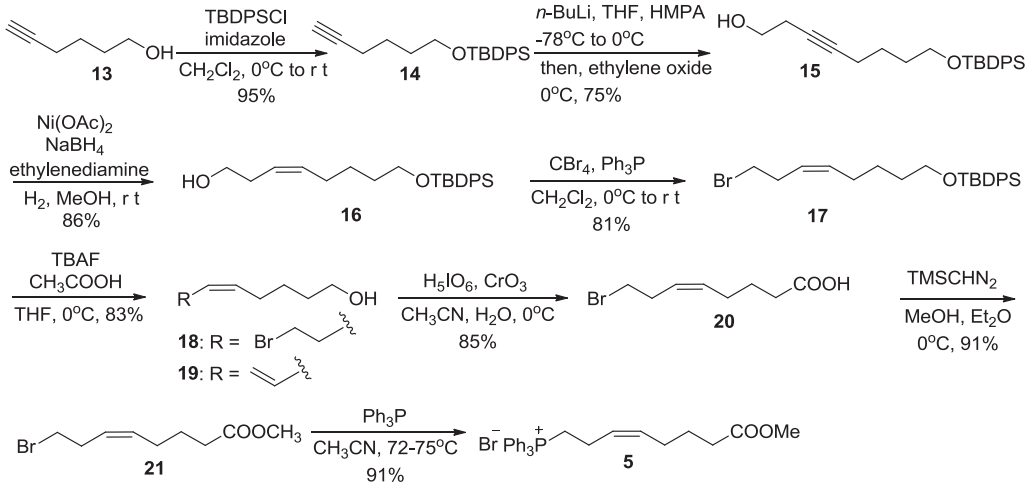


Scheme 1. Synthesis of chiral aldehydes **3** and **4**.

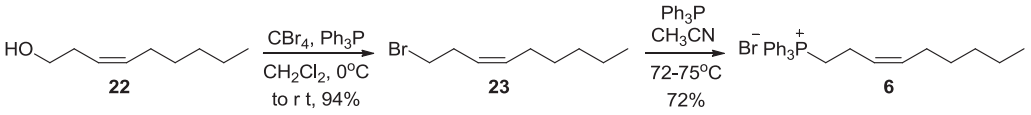
Construction of the required alkenyl phosphonium salt **5** is summarized in Scheme 2. Protection of the acetylenic alcohol **13** afforded terminal alkyne **14** (95% yield), which was metalated with *n*-BuLi and quenched with excess ethylene oxide to give the two carbon homologated alcohol **15** in 75% yield. As reported earlier,[41] we also observed that ethylene oxide opening with lithium acetylides (e.g., TBDPSO$(CH_2)_4C{\equiv}CLi$) in the presence of boron trifluoride etherate has low reproducibility, especially on large scale, and requires freshly distilled catalyst. Use of hexamethylphosphoramide,[42] which strongly coordinates to lithium cations, is a robust alternative to carry out this conversion. Partial hydrogenation of alkyne **15** over P-2 nickel catalyst[39] afforded the corresponding *Z* alkene **16** in 86% yield ($^3J_{3H-4H}$=10.5 Hz). Treatment of this material with the PPh_3/CBr_4 system gave bromide **17** (81% yield). However, deprotection with TBAF at 0 °C produced the desirable bromide **18** (R_f=0.32, 30% AcOEt in hexane, 41% yield) along with significant amounts of the elimination byproduct **19** (R_f=0.27, 30% AcOEt in hexane, 32% yield). We also observed that large excess of TBAF reagent and elevated temperature favor the formation of **19**. After our experimental exercise, the problem was solved by carrying out the reaction in the presence of acetic acid at 0 °C. Under these neutral conditions, **18** was produced in 83% yield without any contamination with **19**. Oxidation of the primary alcohol **18** to the carboxylic acid **20** employing Zhao's elegant method,[43] followed by $TMSCHN_2$ esterification gave methyl ester **21**[44,45] in 77% yield over two steps. A lower overall yield (63%) was obtained when conversion of **18** to **20** was carried out using Jones oxidation. Heating of **21** (72–75 °C) with triphenylphosphine in dry acetonitrile for four days furnished phosphonium salt **5**[44] in 91% yield after purification.

Similarly the requisite C12–C20 fragment **6**[45] was synthesized in two steps and high overall yield (Scheme 3) through conversion of alcohol **22** to bromide **23** (94% yield) and reaction with triphenylphosphine in refluxing acetonitrile for seven days (72% yield). The reaction time for the synthesis of phosphonium salt **6**, is longer when compared to the time required for the preparation of **5**. Perhaps, this is due to slightly different solubility of bromides **21** and **23** in acetonitrile. Our attempts to minimize the reaction time during the preparation of phosphonium salts **5** and **6** using microwave heating[46] resulted in reduction of the purity of the products.

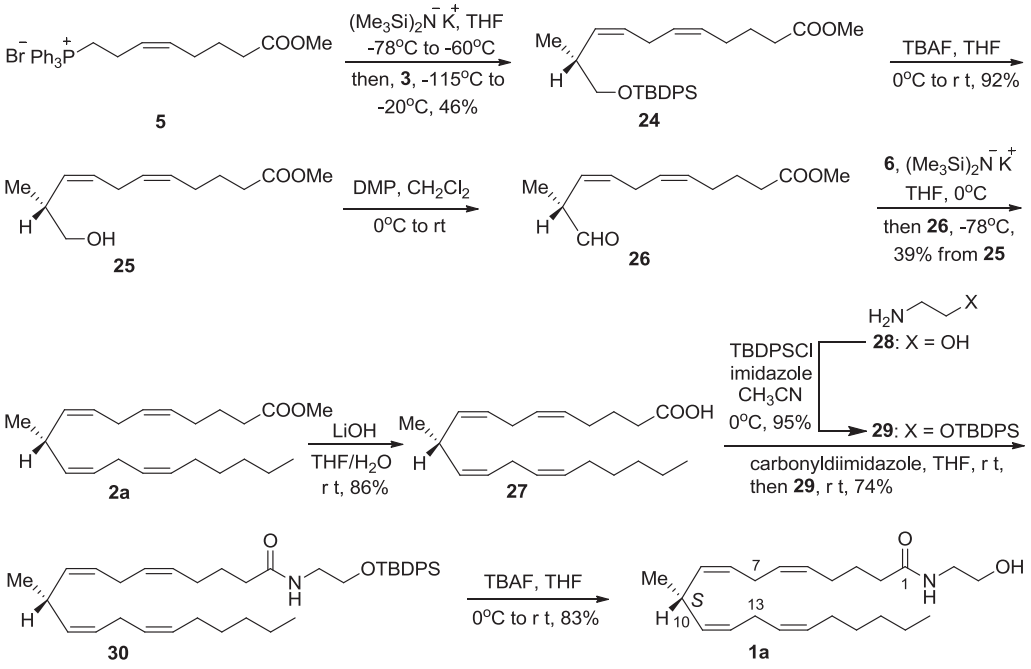
The assembly of the phosphonium salts **5** and **6** with chiral aldehyde **3** into (10*S*)-methyl-anandamide **1a** is outlined in Scheme 4. Treatment of **5** with KHMDS at −78 to −60 °C and coupling of the resulting ylide with aldehyde **3** at −115 °C gave TBDPS ether **24** (46% yield). Based on ^{1}H NMR analysis (see Supplementary data), this Wittig reaction afforded the *Z* olefin exclusively with



Scheme 2. Synthesis of alkenyl phosphonium salt **5**.



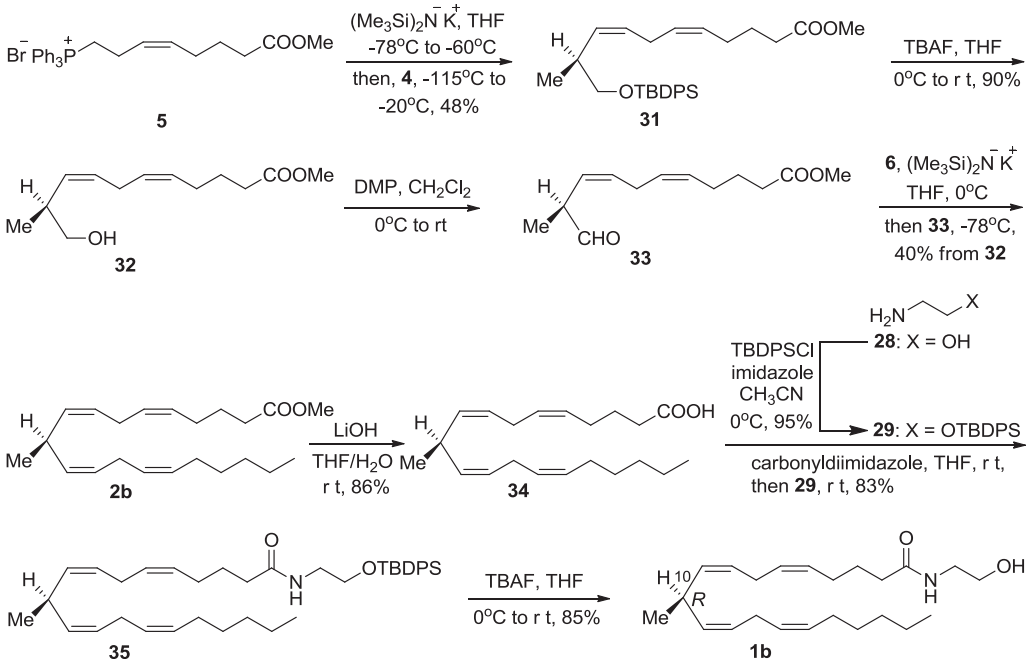
Scheme 3. Synthesis of alkenyl phosphonium salt **6**.



Scheme 4. Synthesis of (10*S*)-methyl-anandamide **1a**.

$^{3}J_{8H-9H}$=10.5 Hz. Cleavage of the silyl ether **24** with TBAF produced alcohol **25** in 92% yield. Interestingly, in the ^{1}H NMR spectrum of **25**, all four double bond protons are well separated with coupling constants $^{3}J_{5H-6H}$ and $^{3}J_{8H-9H}$ equal to 10.5 Hz (see Supplementary data), which confirms a *Z* relationship between the hydrogen atoms of the 5H–6H and 8H–9H spin systems. Exposure of **25** to Dess–Martin periodinane delivered aldehyde **26**, which was used immediately, without purification, in a Wittig reaction with phosphonium bromide **6**, under salt free conditions, to give (10*S*)-methyl-arachidonate **2a** (39% yield from **25**). Saponification of **2a** with lithium hydroxide in THF/H_2O led to acid **27** (86% yield), which was coupled with 2-(*tert*-butyldiphenylsilyloxy)ethanamine (**29**) to give amide **30** (74% yield) by using the carbonyldiimidazole activation procedure. Desilylation of **30** with TBAF produced the requisite (10*S*)-methyl-anandamide (**1a**) in 83% yield. The structure of **1a** was established using 1D and 2D NMR experiments (COSY, HSQC and NOESY, given under Supplementary data). NOESY interactions between 10H and 13H confirm the *Z* stereochemistry for the C11=C12 double bond, which was installed earlier in the arachidonate structure during the synthesis of the methyl ester **2a**.

The enantiomer (10*R*)-methyl-anandamide (**1b**) was synthesized in a similar fashion (Scheme 5). Thus, Wittig olefination of aldehyde **4** with phosphonium bromide **5** gave the *Z* product **31**. Deprotection with TBAF followed by oxidation with Dess–Martin periodinane led to intermediate aldehyde **33**, which was used immediately in the next step. Combination of **33** and the ylide derived from **6** and KHMDS, resulted in the formation of the methyl ester precursor **2b**. The synthesis of **1b** was completed by following: (a) methyl ester hydrolysis, (b) coupling with protected ethanolamine **29** and (c) desilylation using TBAF.



Scheme 5. Synthesis of (10*R*)-methyl-anandamide **1b**.

3. Conclusion

In summary, to explore the bio-actions, the receptor-appropriate conformation(s), and the metabolic stability of a novel arachidonoyl chain substituted with methyl groups at the bis-allylic positions, we report here the enantioselective total synthesis of (10*S*)- and (10*R*)-methyl-anandamides. Our approach involves P-2 nickel partial hydrogenation, cis-selective Wittig olefination and peptide coupling as the key steps. A detailed SAR study and a full biological evaluation of the analogs described here are currently underway.

4. Experimental

4.1. General

All reagents and solvents were purchased from Aldrich Chemical Company, unless otherwise specified, and used without further purification. All anhydrous reactions were performed under a static argon or nitrogen atmosphere in flame-dried glassware using scrupulously dry solvents. Flash column chromatography employed silica gel 60 (230–400 mesh). All compounds were demonstrated to be homogeneous by analytical TLC on pre-coated silica gel TLC plates (Merck, 60 F_{245} on glass, layer thickness 250 μm), and chromatograms were visualized by phosphomolybdic acid or $KMnO_4$ staining. Melting points were determined on a micro-melting point apparatus and are uncorrected. Optical rotations were recorded on a Rudolph DigiPol 781 polarimeter. NMR spectra were recorded in $CDCl_3$, unless otherwise stated, on a Bruker Ultra Shield 400WB plus (^{1}H at 400 MHz, ^{13}C at 100 MHz), or on a Varian 500 (^{1}H at 500 MHz, ^{13}C at 125 MHz), or on a Varian 600 (^{1}H at 600 MHz, ^{13}C at 150 MHz), or on a Bruker Ultra Shield 700WB plus (^{1}H at 700 MHz, ^{13}C at 175 MHz) spectrometers and chemical shifts are reported in units of δ relative to internal TMS. Multiplicities are indicated as br (broadened), s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet) and coupling constants (*J*) are reported in hertz (Hz). Low and high-resolution mass spectra were performed in School of Chemical Sciences, University of Illinois at Urbana-Champaign. Mass spectral data are reported in the form of *m*/*z* (intensity relative to base=100). Elemental analyses were obtained in Baron Consulting Co., Milford, CT.

*4.1.1. 6-[(tert-Butyldiphenylsilyl)oxy]hex-1-yne (**14**).*[47] To a solution of 5-hexyn-1-ol (**13**) (14.2 g, 144.7 mmol) and dried imidazole (12.8 g, 188.1 mmol) in anhydrous CH_2Cl_2 (180 mL) at 0 °C under an argon atmosphere, was added a solution of *tert*-butyldiphenylsilyl chloride (43.8 g, 159.2 mmol) in 10 mL CH_2Cl_2 dropwise. The reaction mixture was stirred for 1 h at 0 °C and 1 h at room temperature. On completion, the reaction was quenched with saturated aqueous sodium bicarbonate solution and extracted with CH_2Cl_2. The combined organic extracts were washed with brine, dried ($MgSO_4$) and concentrated under reduced pressure. Purification by flash column chromatography on silica gel (10–20% diethyl ether in hexanes) gave 44.1 g (95% yield) of **14** as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.68 (d, *J*=7.2 Hz, 4H, 2-H, 6-H, Ph), 7.42 (t, *J*=7.2 Hz, 2H, 4-H, Ph), 7.38 (t, *J*=7.2 Hz, 4H, 3-H, 5-H, Ph), 3.68 (t, *J*=6.0 Hz, 2H, $-CH_2O-$), 2.19 (td, *J*=7.0, 2.5 Hz, 2H, $-CH_2-C\equiv CH$), 1.93 (t, *J*=2.5 Hz, 1H, $-CH_2-C\equiv CH$), 1.71–1.60 (m, 4H, $-CH_2-CH_2-$), 1.05 (s, 9H, $-C(CH_3)_3-$). ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.8 (Ph), 134.2 (=C(Si)–), 129.8 (Ph), 127.8 (Ph), 84.7 (*C*≡CH), 68.5 (≡CH), 63.5 ($-CH_2O-$), 31.8, 27.2 ($-C(CH_3)_3$), 25.7, 19.4, 18.4. Mass spectrum (ESI) *m*/*z* (relative intensity) 359 (M^++Na, 37), 337 (M^++H, 100), 239 (95), 135 (42). Exact mass (ESI) calculated for $C_{22}H_{29}OSi$ (M^++H), 337.1988; found, 337.1992.

*4.1.2. 8-[(tert-Butyldiphenylsilyl)oxy]oct-3-yn-1-ol (**15**).* To a stirred solution of **14** (5.0 g, 15.6 mmol) in dry THF (78 mL) at −78 °C under an argon atmosphere, was added *n*-BuLi (12.5 mL, 31.2 mmol, 2.5 M

solution in hexanes) dropwise followed by the addition of HMPA (previously dried over 4 Å molecular sieves). The reaction temperature was raised to 0 °C and stirring was continued for 1.5 h. Ethylene oxide (7.7 mL, 156 mmol) was added at the same temperature and the reaction mixture was stirred for an additional 5 h. On completion, the mixture was quenched by the addition of saturated aqueous NH_4Cl at −78 °C, then warmed at room temperature, and extracted with diethyl ether. The combined organic extracts were washed with brine, dried ($MgSO_4$), and concentrated under reduced pressure at 30 °C. Purification by flash column chromatography on silica gel (20–50% diethyl ether in hexanes) afforded 4.45 g (75% yield) of **15** as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.66 (d, J=7.2 Hz, 4H, 2-H, 6-H, Ph), 7.42 (t, J=7.2 Hz, 2H, 4-H, Ph), 7.38 (t, J=7.2 Hz, 4H, 3-H, 5-H, Ph), 3.67 (t, J=6.0 Hz, 2H, $-CH_2OH$ or $-CH_2OTBDPS$), 3.66 (t, J=6.0 Hz, 2H, $-CH_2OTBDPS$ or $-CH_2OH$), 2.42 (tt, J=6.5, 2.5 Hz, 2H, $-CH_2-C\equiv C-$), 2.17 (tt, J=6.5, 2.5 Hz, 2H, $-C\equiv C-CH_2-$), 1.72 (t, J=6.5 Hz, 1H, OH), 1.68–1.56 (m, 4H, $-CH_2-CH_2-$), 1.05 (s, 9H, $-C(CH_3)_3-$). ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.8 (Ph), 134.2 (=C(Si)–), 129.8 (Ph), 127.8 (Ph), 84.5 ($-C\equiv CH$), 77.2 ($\equiv CH$),63.6 ($-CH_2O-$), 61.6 ($-CH_2O-$), 32.0, 27.1 ($-C(CH_3)_3$), 25.6, 23.4, 19.4, 18.7. Mass spectrum (ESI) m/z (relative intensity) 403 (M^++Na, 100), 303 (15). Exact mass (ESI) calculated for $C_{24}H_{32}O_2NaSi$ (M^++Na), 403.2069; found, 403.2068.

*4.1.3. (Z)–8-[(tert-Butyldiphenylsilyl)oxy]oct-3-en-1-ol (**16**).* To a stirred solution of $Ni(OAc)_2$ (2.24 g, 9.0 mmol) in dry MeOH (178 mL) at room temperature under an argon atmosphere, was added $NaBH_4$ (0.4 g, 10.6 mmol) portionwise. Following the addition, the argon atmosphere was replaced with hydrogen. To the black suspension was added ethylenediamine (0.9 mL), stirring was continued for 5 min and then a solution of **15** (2.0 g, 5.3 mmol) in dry MeOH (20 mL) was added. The reaction mixture was hydrogenated until the TLC analysis indicated total consumption of the starting material (2 h). The catalyst was filtered off through Celite pad, and the filtrate was diluted with diethyl ether and brine. The organic phase was separated and the aqueous phase extracted five times with diethyl ether, and the combined organic layer was washed with brine. Then, the aqueous phases were reextracted with diethyl ether and the ethereal layer was washed with brine. The combined organic phase was dried ($MgSO_4$) and evaporated under reduced pressure at 38 °C. The residue was again diluted with diethyl ether/brine and the organic phase was separated. The aqueous phase was extracted with diethyl ether and the combined organic layer was washed with brine, dried ($MgSO_4$) and concentrated in vacuo (38 °C). Purification by flash column chromatography on silica gel (10–30% diethyl ether in hexanes) afforded 1.73 g (86% yield) of **16** as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.66 (d, J=7.2 Hz, 4H, 2-H, 6-H, Ph), 7.42 (t, J=7.2 Hz, 2H, 4-H, Ph), 7.38 (t, J=7.2 Hz, 4H, 3-H, 5-H, Ph), 5.54 (dtt, J=10.5, 7.0, 1.5 Hz, 1H, =$CH(CH_2)_2O-$), 5.36 (dtt, J=10.5, 7.0, 1.5 Hz, 1H, $-CH=$), 3.66 (t, J=6.5 Hz, 2H, $-CH_2O-$), 3.62 (t, J=6.5 Hz, 2H, $-CH_2OH$), 2.30 (dt, J=7.0, 7.0 Hz, 2H, $-CH_2CH_2OH$), 2.05 (dt, J=7.0, 7.0 Hz, 2H, $-CH_2-CH=$), 1.57 (quintet, J=6.5 Hz, 2H, $-CH_2-$), 1.44 (quintet, J=6.5 Hz, 2H, $-CH_2-$), 1.04 (s, 9H, $-C(CH_3)_3-$). ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.8 (Ph), 134.3 (=C(Si)–), 133.50 ($-CH=CH-$), 129.7 (Ph), 127.8 (Ph), 125.4 ($-CH=CH-$), 64.0 ($-CH_2O-$), 62.6 ($-CH_2O-$), 32.4, 31.0, 27.3, 27.1 ($-C(CH_3)_3$), 26.1, 19.5. Mass spectrum (ESI) m/z (relative intensity) 405 (M^++Na, 100). Exact mass (ESI) calculated for $C_{24}H_{34}O_2NaSi$ (M^++Na), 405.2226; found, 405.2229.

*4.1.4. (Z)-[(8-Bromooct-5-en-1-yl)oxy](tert-butyl)diphenylsilane (**17**).* To a solution of **16** (1.64 g, 4.3 mmol) and carbon tetrabromide (2.85 g, 8.6 mmol) in dry CH_2Cl_2 (21 mL) at 0 °C under an argon atmosphere, was added dried triphenylphosphine (2.25 g, 8.6 mmol) portionwise. The reaction mixture was stirred for 1 h at 0 °C and for 2 h at room temperature. On completion, the solvent was removed under reduced pressure at 30 °C and the residue was purified by flash column chromatography on silica gel (1–2% diethyl ether in hexanes) to give 1.54 g (81% yield) of **17** as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.66 (d, J=7.2 Hz, 4H, 2-H, 6-H, Ph), 7.42 (t, J=7.2 Hz, 2H, 4-H, Ph), 7.38 (t, J=7.2 Hz, 4H, 3-H, 5-H, Ph), 5.51 (dtt, J=10.5, 7.0, 1.5 Hz, 1H, =$CH(CH_2)_2Br$), 5.36 (dtt, J=10.5, 7.0, 1.5 Hz, 1H, $-CH=$), 3.66 (t, J=6.3 Hz, 2H, $-CH_2O-$), 3.35 (t, J=6.3 Hz, 2H, $-CH_2Br$), 2.58 (dt, J=7.0, 7.0 Hz, 2H, $-CH_2CH_2Br$), 2.03 (dt, J=7.0, 7.0 Hz, 2H, $-CH_2-CH=$), 1.57 (quintet, J=6.5 Hz, 2H, $-CH_2-$), 1.44 (quintet, J=6.5 Hz, 2H, $-CH_2-$), 1.05 (s, 9H, $-C(CH_3)_3-$). ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.8 (Ph), 134.3 (=C(Si)–), 133.1 ($-CH=CH-$), 129.7 (Ph), 127.8 (Ph), 126.2 ($-CH=CH-$), 63.9 ($-CH_2O-$), 32.7, 32.3, 31.0, 27.3, 27.1 ($-C(CH_3)_3$), 25.9, 19.4. Mass spectrum (EI) m/z (relative intensity) 389 (M^++2-$C(CH_3)_3$, 22), 387 ($M^+-C(CH_3)_3$, 22), 263 (25), 261 (25), 109 (100). Mass spectrum (ESI) m/z (relative intensity) 469 (M^++2+Na, 100), 467 (M^++Na, 100). Exact mass (ESI) calculated for $C_{24}H_{33}BrOSiNa$ (M^++Na), 467.1382; found, 467.1396.

*4.1.5. (Z)-8-Bromooct-5-en-1-ol (**18**).* To a solution of **17** (1.5 g, 3.36 mmol) in dry THF (67 mL) at 0 °C, under an argon atmosphere, was added acetic acid (1.78 mL, 31.2 mmol), followed by tetra-*n*-butylammonium fluoride (4.37 mL, 1 M solution in THF) dropwise. The reaction mixture was stirred at 0 °C until completion of the reaction (12 h) and then it was quenched with saturated aqueous NH_4Cl, and extracted with diethyl ether. The combined organic extracts were washed with brine, dried ($MgSO_4$) and the solvent was evaporated under reduced pressure at 33 °C. The residue was purified by flash column chromatography on silica gel (20–40% ethyl acetate in hexanes) to give 578 mg of **18** as a colorless oil in 83% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.53 (dtt, J=10.5, 7.0, 1.5 Hz, 1H, =$CH(CH_2)_2Br$), 5.38 (dtt, J=10.5, 7.0, 1.5 Hz, 1H, $-CH=$), 3.66 (t, J=6.5 Hz, 2H, $-CH_2OH$), 3.37 (t, J=7.0 Hz, 2H, $-CH_2Br$), 2.63 (dt, J=7.0, 7.0 Hz, 2H, $-CH_2CH_2Br$), 2.09 (dt, J=7.0, 7.0 Hz, 2H, $-CH_2-CH=$), 1.59 (m as quintet, J=7.0 Hz, 2H, $-CH_2-$), 1.46 (m as quintet, J=7.0 Hz, 2H, $-CH_2-$). ^{13}C NMR (100 MHz, $CDCl_3$) δ 132.8 ($-CH=CH-$), 126.4 ($-CH=CH-$), 63.0 ($-CH_2O-$), 32.6, 32.5, 31.0, 27.3, 25.8. Mass spectrum (CI) m/z (relative intensity) 207 (M^++H, 2%), 189 (M^+−OH, 5%), 188 (3), 187 (3), 127 (M^++H-Br, 10), 109 (100). Exact mass (ESI) calculated for $C_8H_{16}BrO$ (M^++H), 207.0385; found, 207.0395.

When the above procedure was carried out without acetic acid, two major compounds were isolated and identified: (a) (Z)-8-bromooct-5-en-1-ol (**18**, 41% yield, R_f=0.32, 30% AcOEt in hexane) and (b) (*Z*)-octa-5,7-dien-1-ol[48] (**19**, 32% yield, R_f=0.27, 30% AcOEt in hexane). (*Z*)-Octa-5,7-dien-1-ol (**19**) ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.63 (ddd, J=16.5, 11.0, 10.5 Hz, 1H, 7-H), 6.02 (dd, J=11, 10.5 Hz, 1H, 6-H), 5.45 (dtd, J=10.5, 8.0, 1.0 Hz, 1H, 5-H), 5.18 (dd, J=16.5, 1.5 Hz, 1H, 8-H), 5.09 (d, J=10.5 Hz, 1H, 8-H), 3.65 (t, J=6.5 Hz, 2H, $-CH_2O-$), 2.23 (dt, J=8.0, 7.5 Hz, 2H, 4-H), 1.65–1.57 (m, 2H, $-CH_2-$), 1.51–1.42 (m, 2H, $-CH_2-$).

*4.1.6. (Z)-8-Bromooct-5-enoic acid (**20**).* To a stirred mixture of **18** (512 mg, 2.5 mmol) in acetonitrile (9 mL) and water (3 mL) at 0 °C was added 1 mL of Zhao's reagent every 30 min until completion of reaction (3.5 h). A stock solution of Zhao's reagent was prepared by dissolving 0.63 g H_5IO_6 and 1.27 g CrO_3 in 1.9 mL H_2O and 4.4 mL CH_3CN. The reaction was quenched with Na_2HPO_4 (20 mg in 1 mL H_2O) and diluted with diethyl ether. The organic phase was separated and the aqueous phase extracted with diethyl ether. The combined organic layer was washed with brine, dried ($MgSO_4$) and the solvent was evaporated under reduced pressure at 33 °C. Purification by flash column chromatography on silica gel (30–40% ethyl acetate in hexanes) gave 464 mg (85% yield) of **20**[44,45] as an oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.53 (dtt, J=11.0, 7.0, 1.5 Hz, 1H, =$CH(CH_2)_2Br$), 5.38 (dtt, J=11.0, 7.0, 1.5 Hz, 1H, $-CH=$), 3.37 (t, J=7.0 Hz, 2H, $-CH_2Br$), 2.63 (dt, J=7.0, 7.0 Hz, 2H, $-CH_2CH_2Br$),

2.38 (t, J=7.0, 7.0 Hz, 2H, $-CH_2-$COOH), 2.12 (dt, J=7.0, 7.0 Hz, 2H, $-CH_2-$CH=), 1.73 (quintet, J=7.0 Hz, 2H, $-CH_2-CH_2-$COOH). ^{13}C NMR (100 MHz, $CDCl_3$) δ 179.7 (−COOH), 131.7 (−CH=CH−), 127.4 (−CH=CH−), 33.5, 32.6, 31.0, 26.9, 24.6. Mass spectrum (EI) m/z (relative intensity) 222 (M^++2, 0.2), 220 (M^+, 0.2), 204 (M^++2-H_2O, 1), 202 (M^+-H_2O, 1), 176 (M^++2-H_2O-CO, 2), 174 (M^+-H_2O, −CO, 2), 162 (M^++2-H_2O, −CO, $-CH_2$, 18), 160 (M^+-H_2O, −CO, $-CH_2$, 18), 140 (M^+−Br, 86), 123 (39), 81 (100). Mass spectrum (ESI) m/z (relative intensity) 245 (M^++2+Na, 100), 243 (M^++Na, 100), 127 (45), 125 (45). Exact mass (ESI) calculated for $C_8H_{13}BrO_2Na$ (M^++Na), 242.9997; found, 243.0004.

*4.1.7. (5Z)-8-Bromo-5-octenoic methyl ester (**21**).* To a stirred solution of **20** (0.35 g, 1.58 mmol) in 1:4 mixture of methanol (4 mL) and diethyl ether (16 mL) at 0 °C under an argon atmosphere, was added trimethylsilyldiazomethane (1.02 mL, 2.05 mmol, 2.0 M solution in hexane). After 20 min, the reaction was quenched with saturated aqueous NH_4Cl and diluted with diethyl ether. The organic phase was separated and the aqueous layer was extracted with diethyl ether. The combined organic layer was washed with brine, dried ($MgSO_4$) and concentrated under reduced pressure at 25 °C. Purification by flash column chromatography on silica gel (0–10% diethyl ether in hexanes) afforded 338 mg (91% yield) of **21**[44,45] as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.50 (dtt, J=11.0, 7.0, 1.5 Hz, 1H, =$CH(CH_2)_2$Br), 5.42 (dtt, J=11.0, 7.0, 1.5 Hz, 1H, −CH=), 3.68 (s, 3H, $-COOCH_3$), 3.39 (t, J=7.0 Hz, 2H, $-CH_2$Br), 2.61 (dt, J=7.0, 7.0 Hz, 2H, $-CH_2CH_2$Br), 2.33 (t, J=7.5 Hz, 2H, $-CH_2-$COO−), 2.10 (dt, J=7.0, 7.0 Hz, 2H, $-CH_2-$CH=), 1.71 (quintet, J=7.0 Hz, 2H, $-CH_2-CH_2-$COO−). ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.1 (>C=O), 131.8 (−CH=CH−), 127.2 (−CH=CH−), 51.7 ($-OCH_3$), 33.5, 32.6, 30.9, 26.9, 24.8. Mass spectrum (EI) m/z (relative intensity) 236 (M^++2, 1), 234 (M^+, 1), 205 (M^++2-MeO, 5), 204 (M^++2-MeOH, 3), 203 (M^+−MeO, 5), 202 (M^+−MeOH, 3), 176 (M^++2-MeOH, −CO, 4), 174 (M^+−MeOH, −CO, 4), 162 (M^++2-MeOH, −CO, $-CH_2$, 11), 160 (M^+−MeOH, −CO, $-CH_2$, 11), 160 (M^+−MeOH, −CO, $-CH_2$, 11), 155 (M^++H−Br, 42), 154 (M^+−Br, 32), 123 (M^+−Br, −OMe, 79), 74 (100). Exact mass (ESI) calculated for $C_9H_{15}BrO_2$ (M^+), 234.0255; found, 234.0244.

*4.1.8. [(3Z)-8-Methoxy-8-oxo-3-octen-1-yl]triphenylphosphonium bromide (**5**).* A stirred mixture of **21** (300 mg, 1.27 mmol) and dried triphenylphosphine (667 mg, 2.54 mmol) in anhydrous acetonitrile (6 mL) was heated (72–75 °C) for four days under argon. Solvent evaporation and purification by flash column chromatography on silica gel (0–15% methanol in methylene chloride) gave 576 mg (91% yield) of **5**[44] as a colorless gum. The product was rigorously dried in high vacuo for 6 h at 40–42 °C, and used in the next step. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.88 (m as dd, J=12.6, 7.8 Hz, 6H, 2-H, 6-H, $-PPh_3$), 7.81 (m as td, J=7.8, 1.8 Hz, 3H, 4-H, $-PPh_3$), 7.71 (m as td, J=7.8, 4.2 Hz, 6H, 3-H, 5-H, $-PPh_3$), 5.65 (dtt, J=11.0, 7.0, 1.5 Hz, 1H, =$CH(CH_2)_2P^+Ph_3$), 5.37 (dtt, J=11.0, 7.0, 1.5 Hz, 1H, −CH=), 3.96 (dt, J=12.0, 8.0 Hz, 2H, $-CH_2P^+Ph_3$), 3.61 (s, 3H, $-COOCH_3$), 2.48–2.46 (m, 2H, $-CH_2-CH_2P^+Ph_3$), 2.21 (t, J=7.5 Hz, 2H, $-CH_2-$COO−), 1.87 (dt, J=7.0, 7.0 Hz, 2H, $-CH_2-$CH=), 1.58 (quintet, J=7.5 Hz, 2H, $-CH_2-CH_2-$COO−). ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.1 (>C=O), 135.2 (C4′, Ph), 134.1 (d, J=9.2 Hz, C2′, C6′, Ph), 131.3 (−CH=CH−$(CH_2)_2$P Ph$_3$), 130.7 (d, J=11.5 Hz, C3′, C5′, Ph), 127.5 (d, J=13.8 Hz, −CH=CH−$(CH_2)_2$P), 118.6 (d, J=85.5 Hz, C1′, Ph), 51.7 ($-OCH_3$), 33.5, 26.8, 24.7, 23.0 (d, J=49 Hz, $-CH_2$P), 20.7. Mass spectrum (ESI) m/z (relative intensity) 417 (M^+−Br, 100). Exact mass (ESI) calculated for $C_{27}H_{30}O_2P(M^+-Br)$, 417.1983; found, 417.1973.

*4.1.9. (3Z)-1-Bromo-3-nonene (**23**).* To a stirred solution of (3Z)-3-nonen-1-ol (5 g, 35.15 mmol) and carbon tetrabromide (11.6 g, 35.15 mmol) in dry CH_2Cl_2 (170 mL) at 0 °C under an argon atmosphere, was added dried triphenylphosphine (9.17 g, 35.15 mmol) portionwise. The reaction mixture was stirred for 1 h at 0 °C and for 2 h at room temperature. On completion, the solvent was removed under reduced pressure at 30 °C and the residue was purified by flash column chromatography on silica gel (1–2% diethyl ether in hexanes) to give 6.8 g (94% yield) of **23**[49] as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.53 (dtt, J=10.5, 7.0, 1.5 Hz, 1H, 3-H), 5.36 (dtt, J=10.5, 7.0, 1.5 Hz, 1H, 4-H), 3.36 (t, J=7.0 Hz, 2H, $-CH_2$Br), 2.61 (dt, J=7.0, 7.0 Hz, 2H, $-CH_2-CH_2$Br), 2.03 (dt, J=7.0, 7.0 Hz, 2H, =CH−$CH_2-(CH_2)_3-CH_3$), 1.40–1.24 (m and sextet overlapping, 6H, 6-H, 7-H, 8-H, especially 1.36 sextet, J=7.0 Hz, 2H), 0.89 (t, J=7.5 Hz, 3H, $-CH_2CH_3$). Mass spectrum (ESI) m/z (relative intensity) 205 (M^++H, 15), 163 (15), 123 (92), 55 (100). Exact mass (EI) calculated for $C_7H_{17}Br(M^+)$, 204.0514; found, 204.0504.

*4.1.10. [(3Z)-3-Nonen-1-yl]triphenylphosphonium bromide (**6**).* A stirred mixture of **23** (5 g, 24.37 mmol) and dried triphenylphosphine (12.78 g, 48.74 mmol) in anhydrous acetonitrile (48 mL) was heated (72–75 °C) for 7 days under argon. Solvent evaporation and purification by flash column chromatography on silica gel (3% methanol in methylene chloride) gave 8.2 g (72% yield) of **6**[45] as a colorless gum. The product was rigorously dried in high vacuo for 6 h at 40–42 °C, and used in the next step. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.88 (m as dd, J=12.5, 7.5 Hz, 6H, 2-H, 6-H, $-PPh_3$), 7.80 (m as td, J=7.5, 1.8 Hz, 3H, 4-H, $-PPh_3$), 7.70 (m as td, J=7.5, 4.2 Hz, 6H, 3-H, 5-H, $-PPh_3$), 5.57 (dtt, J=11.0, J=7.0, 1.5 Hz, 1H, =$CH(CH_2)_2P^+Ph_3$), 5.39 (dtt, J=11.0, 7.0, 1.5 Hz, 1H, −CH=), 3.95 (dt, J=12.0, 8.0 Hz, 2H, $-CH_2P^+Ph_3$), 2.49–2.41 (m, 2H, $-CH_2-CH_2-P^+Ph_3$), 1.75 (quintet, J=7.0 Hz, 2H, −CH=CH−CH_2-), 1.26–1.17 (m, 4H, $-CH_2-$), 1.16–1.10 (m, 2H, $-CH_2-$), 0.84 (t, J=7.0 Hz, 3H, $-CH_2-CH_3$). Mass spectrum (ESI) m/z (relative intensity) 387 (M^+−Br, 100). Exact mass (ESI) calculated for $C_{27}H_{32}P(M^+-Br)$, 387.2242; found, 387.2249.

*4.1.11. (10R,5Z,8Z)-11-[(tert-Butyldiphenylsilyl)oxy]-10-methyl-undeca-5,8-dienoic methyl ester (**24**).* To a solution of **5** (415 mg, 0.834 mmol) in dry THF (4 mL) at −78 °C under an argon atmosphere was added potassium bis(trimethylsilyl)amide (0.79 mL, 1.0 M solution in THF) dropwise. The mixture was stirred at −78 °C to −60 °C for 45 min, to ensure complete formation of the orange ylide, and then it was cooled to −115 °C. Subsequently, a solution of aldehyde **3** (136 mg, 0.417 mmol) in dry THF (1 mL) was added dropwise. The reaction mixture was stirred for 15 min at −115 °C, and then it was warmed to −20 °C over a period of 2.5 h. The reaction mixture was then cooled to −78 °C and quenched with a saturated aqueous sodium bicarbonate solution. The mixture was warmed to room temperature, extracted with diethyl ether and the combined organic extracts were washed with brine, dried ($MgSO_4$) and concentrated in vacuo. Purification by flash column chromatography on silica gel (5–7% diethyl ether in hexane) gave **24** as colorless oil in 46% yield (89 mg). $[\alpha]_D^{26}$ −17.48 (c 0.2 g/100 mL in $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.66 (d, J=7.8 Hz, 4H, 2-H, 6-H, Ph), 7.44 (t, J=7.2 Hz, 2H, 4-H, Ph), 7.37 (t, J=7.2 Hz, 4H, 3-H, 5-H, Ph), 5.37–5.28 (m, 3H, 5-H, 6-H, 8-H), 5.19 (tdd, J=10.5, 9.5, 1.0 Hz, 1H, 9-H), 3.66 (s, 3H, $-COOCH_3$), 3.46 (dd, J=10.0, 6.0 Hz, 1H, 11-H), 3.46 (dd, J=10.0, 7.0 Hz, 1H, 11-H), 2.81–2.73 (m, 1H, 10-H), 2.72–2.64 (m, 2H, 7-H), 2.30 (t, J=7.5 Hz, 2H, 2-H), 2.07 (dt, J=6.5, 6.5 Hz, 2H, 4-H), 1.69 (quintet, J=7.5 Hz, 2H, 3-H), 1.05 (s, 9H, $-C(CH_3)_3$), 1.00 (d, J=6.5 Hz, 3H, >CH−CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.23 (>C=O), 135.9, 134.2, 133.3, 129.7, 129.5, 128.9, 128.3, 127.8, 68.8, 51.6, 35.0, 33.7, 27.1, 26.8, 26.1, 25.0, 19.5, 17.7. Mass spectrum (ESI) m/z (relative intensity) 465 (M^++H, 23), 387 (M^+−Ph, 100). Exact mass (ESI) calculated for $C_{29}H_{41}O_3Si$ (M^++H), 465.2825; found, 465.2827.

*4.1.12. (10R,5Z,8Z)-11-Hydroxy-10-methyl-undeca-5,8-dienoic methyl ester (**25**).* To a stirred solution of **24** (85 mg, 0.183 mmol) in dry THF (3 mL), under an argon atmosphere at 0 °C, was added TBAF

(0.25 mL, 0.25 mmol, 1 M solution in THF) dropwise. Stirring was continued for 10 min at 0 °C and for 1.5 h at room temperature. The reaction mixture was quenched with a saturated aqueous NH_4Cl solution at 0 °C and extracted with AcOEt. The combined organic extracts were washed with brine, dried ($MgSO_4$) and concentrated under reduced pressure at 37 °C. The crude material was purified by flash column chromatography on silica gel (15–45% ethyl acetate in hexane) to afford **25** (38 mg, 92% yield) as a colorless viscous liquid. $[\alpha]_D^{26}$ 83.11 (*c* 0.139 g/100 mL in $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.49 (dtd, *J*=10.5, 7.5, 1.2 Hz, 1H, 8-H), 5.40 (td, *J*=10.5, 7.0 Hz, 1H, 6-H or 5-H), 5.35 (td, *J*=10.5, 7.0 Hz, 1H, 5-H or 6-H), 5.16 (tdd, *J*=10.5, 10.0, 1.5 Hz, 1H, 9-H), 3.67 (s, 3H, $-COOCH_3$), 3.49 (ddd, *J*=12.0, 8.0, 6.0 Hz, 1H, 11-H), 3.35 (ddd, *J*=12.0, 8.5, 4.5 Hz, 1H, 11-H), 2.83 (dd, *J*=7.5, 7.5 Hz, 2H, 7-H), 2.73 (m as septet, *J*=6.5 Hz, 1H, 10-H), 2.33 (t, *J*=7.0 Hz, 2H, 2-H), 2.11 (dt, *J*=7.5, 7.5 Hz, 2H, 4-H), 1.70 (quintet, *J*=7.5 Hz, 2H, 3-H), 1.51 (dd, *J*=6.0, 4.5 Hz, 1H, OH), 0.96 (d, *J*=6.5 Hz, 3H, >CH−C*H*$_3$). ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.1 (>C=O), 132.8 (C-9 or C-8), 130.4 (C-8 or C-9), 129.4 (C-6 or C-5), 129.2 (C-5 or C-6), 68.1 (CH_2OH), 51.8 (OCH_3), 35.4, 33.9, 27.0, 26.4, 25.1, 17.4. Mass spectrum (ESI) *m*/*z* (relative intensity) 249 (M^++Na, 100). Exact mass (ESI) calculated for $C_{13}H_{22}O_3Na$ (M^++Na), 249.1465; found, 249.1468.

*4.1.13. (10R,5Z,8Z)-10-Methyl-11-oxo-undeca-5,8-dienoic methyl ester (**26**).* To a solution of alcohol **25** (38 mg, 0.168 mmol) in dry CH_2Cl_2 (3.5 mL) at 0 °C under an argon atmosphere, was added Dess–Martin periodiane (DMP) (142 mg, 0.336 mmol) and the resulting suspension was warmed to room temperature and stirred for 45 min. An additional amount of DMP (21 mg, 0.05 mmol) was added at 0 °C and stirring was continued for 30 min at room temperature to ensure total consumption of alcohol **25**. The reaction mixture was quenched by adding a mixture of $Na_2S_2O_3$ (10% in H_2O) and saturated $NaHCO_3$ (1:1) and diluted with diethyl ether. The slurry was filtered through Celite, the organic phase separated and the aqueous phase was extracted with diethyl ether. The combined organic layer was washed with saturated $NaHCO_3$, brine, and dried ($MgSO_4$). Solvent evaporation under reduced pressure at 36–40 °C provided the sensitive crude product **26** as a colorless oil, which was used in the next step immediately. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.53 (d, *J*=1.5 Hz, 1H, −CHO), 5.64 (dtd, *J*=10.5, 7.5 Hz, 1.2 Hz, 1H, 8-H), 5.42–5.34 (m, 2H, 6-H, 5-H), 5.25 (ttd, *J*=10.5, 10.0, 1.5 Hz, 1H, 9-H), 3.67 (s, 3H, $-COOCH_3$), 3.37 (m as quintet, *J*=8.0 Hz, 1H, 10-H), 2.86–2.78 (m, 2H, 7-H), 2.33 (t, *J*=7.0 Hz, 2H, 2-H), 2.11 (dt, *J*=7.5, 7.5 Hz, 2H, 4-H), 1.71 (quintet, *J*=7.5 Hz, 2H, 3-H), 1.19 (d, *J*=6.5 Hz, 3H, >CH−C*H*$_3$). Mass spectrum (ESI) *m*/*z* (relative intensity) 247 (M^++Na, 100), 225 (M^++H, 10), 175 (34). Exact mass (ESI) calculated for $C_{13}H_{20}O_3Na$ (M^++Na), 247.1310; found, 247.1309.

*4.1.14. (10S,5Z,8Z,11Z,14Z)-10-Methyl-eicosa-5,8,11,14-tetraenoic methyl ester (**2a**).* To a stirred solution of phosphonium bromide **6** (395 mg, 0.845 mmol) in dry THF (4 mL) at 0 °C under an argon atmosphere, was added potassium bis(trimethylsilyl)amide (0.83 mL, 1.0 M solution in THF) dropwise. The mixture was stirred for 30 min at 0 °C to ensure complete formation of the orange ylide and then it was cooled to −78 °C. A solution of crude aldehyde **26** in dry THF (1 mL) was added dropwise, the reaction mixture was stirred for 1 h at −78 °C and then it was quenched by the addition of saturated aqueous sodium bicarbonate. The mixture was warmed to room temperature, extracted with diethyl ether, and the combined organic extracts were washed with brine, dried ($MgSO_4$) and concentrated in vacuo. Purification by flash column chromatography on silica gel (0–8% diethyl ether in hexane) gave 21 mg (39% yield from alcohol **25**) of ester **2a** as a colorless oil. $[\alpha]_D^{26}$ 351.92 (*c* 0.087 g/100 mL in $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.43–5.31 (m, 4H, −CH=CH−), 5.31–5.21 (m, 4H, −CH=CH−), 3.67 (s, 3H, $-COOCH_3$), 3.49 (ddq as sextet, *J*=6.5 Hz, 1H, 10-H), 2.88–2.75 (m, 4H, 7-H, 13-H), 2.32 (t, *J*=7.0 Hz, 2H, 2-H), 2.11 (dt, *J*=7.0, 7.0 Hz, 2H, 4-H), 2.05 (dt, *J*=7.5, 7.5 Hz, 2H, 16-H), 1.71 (quintet, *J*=7.5 Hz, 2H, 3-H), 1.39–1.24 (m, 6H, 18-H, 19-H, 17-H), 1.02 (d, *J*=7.0 Hz, 3H, >CH−C*H*$_3$), 0.89 (t, *J*=7.0 Hz, 3H, 20-H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.2 (>C=O), 135.0 (−CH=), 134.7 (−CH=), 130.7 (−CH=), 129.3 (−CH=), 129.1 (−CH=), 127.9 (−CH=), 126.6 (−CH=), 126.2 (−CH=), 51.6 (OCH_3), 33.7, 31.7, 30.8, 29.9, 29.5, 27.4, 26.8, 26.0, 25.0, 22.7, 22.1, 14.2 (C-20). Mass spectrum (ESI) *m*/*z* (relative intensity) 355 (M^++Na, 100), 333 (M^++H, 72). Exact mass (ESI) calculated for $C_{22}H_{36}O_2Na$ (M^++Na), 355.2613; found, 355.2618, and calculated for $C_{22}H_{37}O_2$ (M^++H), 333.2794; found, 333.2797.

*4.1.15. (10S,5Z,8Z,11Z,14Z)-10-Methyl-eicosa-5,8,11,14-tetraenoic acid (**27**).* To a stirred solution of **2a** (15 mg, 0.045 mmol) in dry THF (1 mL) at room temperature, under an argon atmosphere, was added 1 M aqueous LiOH solution (0.09 mL). Stirring was continued for 24 h, and then the reaction mixture was acidified with 5% HCl to pH 3, and lipophilic products were extracted with Et_2O. The combined organic extracts were washed with brine and dried ($MgSO_4$). Solvent evaporation under reduced pressure at 37–40 °C gave pure acid **27** (12.4 mg, 86% yield) as a colorless oil, which was used in the next step without further purification. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.43–5.31 (m, 4H, −CH=CH−), 5.31–5.21 (m, 4H, −CH=CH−), 3.48 (ddq as sextet, *J*=6.5 Hz, 1H, 10-H), 2.88–2.76 (m, 4H, 7-H, 13-H), 2.38 (t, *J*=7.5 Hz, 2H, 2-H), 2.13 (dt, *J*=7.5, 7.5 Hz, 2H, 4-H), 2.05 (dt, *J*=7.0, 7.0 Hz, 2H, 16-H), 1.72 (quintet, *J*=7.5 Hz, 2H, 3-H), 1.39–1.24 (m, 6H, 18-H, 19-H, 17-H), 1.03 (d, *J*=7.0 Hz, 3H, >CH−C*H*$_3$), 0.89 (t, *J*=7.0 Hz, 3H, 20-H). Mass spectrum (ESI) *m*/*z* (relative intensity) 341 (M^++Na, 100), 319 (M^++H, 45). Exact mass (ESI) calculated for $C_{21}H_{34}O_2Na$ (M^++Na), 341.2457; found, 341.2456, and calculated for $C_{21}H_{35}O_2$ (M^++H), 319.2637; found, 319.2638.

*4.1.16. 2-[(tert-Butyldiphenylsilyl)oxy]ethanamine (**29**).* To a solution of ethanolamine (**28**) (1 g, 16.4 mmol) and dried imidazole (2.44 mg, 36.1 mmol) in anhydrous CH_3CN (80 mL) at 0 °C under an argon atmosphere, was added *tert*-butyldiphenylsilyl chloride (4.95 mg, 18.0 mmol) dropwise. The reaction mixture was stirred for 30 min at 0 °C and then quenched with a saturated aqueous sodium bicarbonate solution, diluted with water and extracted with CH_2Cl_2. The combined organic extracts were washed with brine, dried ($MgSO_4$) and concentrated in vacuo. The crude oil was purified by flash column chromatography on silica gel (10% MeOH in CH_2Cl_2) to afford **29**[39] (4.64 g, 95%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.68 (d, *J*=7.2 Hz, 4H, 2-H, 6-H, PhH), 7.43 (t, *J*=7.2 Hz, 2H, 4-H, PhH), 7.39 (t, *J*=7.2 Hz, 4H, 3-H, 5-H, PhH), 3.70 (t, *J*=5.4 Hz, 2H, $-CH_2-$OTBDPS), 2.83 (t, *J*=5.4 Hz, 2H, −C*H*$_2$−NH−), 2.41 (br s, 2H, $-NH_2$), 1.07 (s, 9H, $-C(CH_3)_3$).

*4.1.17. (10S,5Z,8Z,11Z,14Z)-10-Methyl-eicosa-5,8,11,14-tetraenoic acid N-{2-[(tert-butyldiphenylsilyl) oxy]ethyl}amide (**30**).* A mixture of acid **27** (10 mg, 0.031 mmol), and fresh carbonyldiimidazole (15 mg, 0.093 mmol) in dry THF (1 mL) at room temperature under an argon atmosphere, was stirred for 2 h and then protected ethanolamine **29** (37 mg, 0.125 mmol) in THF (0.5 mL) was added. The reaction mixture was stirred for 1 h and then diluted with water and ethyl acetate. The organic phase was separated and the aqueous phase extracted with AcOEt. The combined organic layer was washed with brine, dried ($MgSO_4$) and concentrated in vacuo. The crude product obtained after work up was purified by flash column chromatography on silica gel (15–25% acetone in hexane), and gave 14 mg (74% yield) of **30** as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.63 (d, *J*=7.5 Hz, 4H, 2-H, 6-H, Ph), 7.43 (t, *J*=7.5 Hz, 2H, 4-H, Ph), 7.38 (t, *J*=7.5 Hz, 4H, 3-H, 5-H, Ph), 5.73 (br s, 1H, >NH), 5.43–5.32 (m, 4H, −CH=CH−), 5.31–5.19 (m, 4H, −CH=CH−), 3.74 (t, *J*=6.5 Hz, 2H, $-CH_2-$OTBDPS), 3.48 (m as sextet, *J*=7.0 Hz, 1H, 10-H),

3.40 (dt, J=6.5, 6.5 Hz, 2H, $-CH_2-NH-$), 2.88–2.76 (m, 4H, 7-H, 13-H), 2.16–2.08 (t and dt overlapping, 4H, 2-H, 4-H), 2.04 (dt, J=7.2, 7.2 Hz, 2H, 16-H), 1.68 (quintet, J=8.0 Hz, 2H, 3-H), 1.38–1.24 (m, 6H, 18-H, 19-H, 17-H), 1.07 (s, 9H, $-C(CH_3)_3$), 1.02 (d, J=8.5 Hz, 3H, $>CH-CH_3$), 0.88 (t, J=7.0 Hz, 3H, 20-H). Mass spectrum (ESI) m/z (relative intensity) 600 (M^++H, 100), 522 (M^+−Ph, 52). Exact mass (ESI) calculated for $C_{39}H_{58}NO_2Si$ (M^++H), 600.4237; found, 600.4238.

*4.1.18. (10S,5Z,8Z,11Z,14Z)-10-Methyl-eicosa-5,8,11,14-tetraenoic acid N-(2-hydroxyethyl)amide (**1a**).* The synthesis was carried out as described for **25**, using **30** (10 mg, 0.0166 mmol) and TBAF (0.02 mL, 0.02 mmol, 1 M solution in THF) in dry THF (1 mL). The reaction was completed in 1 h and the crude oil obtained after work up was purified by flash column chromatography on silica gel (57:40:3, ethyl acetate/hexane/MeOH) to afford **1a** (5 mg, 83% yield) as a colorless oil. $[\alpha]_D^{26}$ 99.27 (c 0.108 g/100 mL in $CHCl_3$). ^{1}H NMR (700 MHz, $CDCl_3$) δ 5.87 (br s, 1H, >NH), 5.43–5.32 (m, 4H, −CH=), 5.30–5.19 (m, 4H, −CH=), 3.73 (t, J=5.1 Hz, 2H, $-CH_2-O-$), 3.48 (qdd as sextet, J=7.2 Hz, 1H, 10-H), 3.42 (dt, J=5.5, 5.5 Hz, 2H, $-CH_2-NH-$), 2.87–2.75 (m, 4H, 7-H, 13-H), 2.22 (t, J=7.6 Hz, 2H, 2-H), 2.12 (dt, J=7.0, 7.0 Hz, 2H, 4-H), 2.05 (dt, J=7.4, 7.4 Hz, 2H, 16-H), 1.73 (quintet, J=7.5 Hz, 2H, 3-H), 1.52 (br s, 1H, OH), 1.38–1.33 (sextet, J=7.1 Hz, 2H, 17-H), 1.32–1.24 (m, 4H, 18-H, 19-H), 1.02 (d, J=6.7 Hz, 3H, $>CH-CH_3$), 0.88 (t, J=7.1 Hz, 3H, 20-H). ^{13}C NMR (175 MHz, $CDCl_3$) δ 174.2 (>C=O), 134.8 (−CH=), 134.4 (−CH=), 130.5 (−CH=), 129.01 (−CH=), 128.99 (−CH=), 127.7 (−CH=), 126.4 (−CH=), 126.0 (−CH=), 62.7 ($-CH_2OH$), 42.5 ($-NH-CH_2-$), 35.9 (C-2), 31.5 (C-18 or C-19), 30.6 (C-10), 29.3 (C-17), 27.2 (C-16), 26.6 (C-4), 25.9 (C-7, C-13), 25.5 (C-3), 22.6 (C-19 or C-18), 22.0 (C_{10}-Me), 14.1 (C-20). Mass spectrum (ESI) m/z (relative intensity) 362 (M^++H, 100), 301 ($M^+-NH(CH_2)_2OH$, 11). Exact mass (ESI) calculated for $C_{23}H_{40}NO_2$ (M^++H), 362.3059; found, 362.3061. Elemental analysis calculated for $C_{23}H_{39}NO_2$: C, 76.40; H, 10.87; N, 3.87. Found: C, 76.11; H, 11.17; N, 4.21.

*4.1.19. (10S,5Z,8Z)-11-[(tert-Butyldiphenylsilyl)oxy]-10-methyl-undeca-5,8-dienoic methyl ester (**31**).* The synthesis was carried out as described for **24** and gave the title compound in 48% yield. Spectroscopic and physical data were identical to those of the enantiomer **24**.

*4.1.20. (10S,5Z,8Z)-11-Hydroxy-10-methyl-undeca-5,8-dienoic methyl ester (**32**).* The synthesis was carried out as described for **25** and gave the title compound in 90% yield. Spectroscopic and physical data were identical to those of the enantiomer **25**.

*4.1.21. (10S,5Z,8Z)-10-Methyl-11-oxo-undeca-5,8-dienoic methyl ester (**33**).* The synthesis was carried out as described for **26** and the product was used in the next step immediately without further purification. Spectroscopic and physical data were identical to those of the enantiomer **26**.

*4.1.22. (10R,5Z,8Z,11Z,14Z)-10-Methyl-eicosa-5,8,11,14-tetraenoic methyl ester (**2b**).* The synthesis was carried out as described for **2a** and gave the title compound in 40% yield from alcohol **32**. Spectroscopic and physical data were identical to those of the enantiomer **2a**.

*4.1.23. (10R,5Z,8Z,11Z,14Z)-10-Methyl-eicosa-5,8,11,14-tetraenoic acid (**34**).* The synthesis was carried out as described for **27** and gave the title compound in 86% yield. Spectroscopic and physical data were identical to those of the enantiomer **27**.

*4.1.24. (10R,5Z,8Z,11Z,14Z)-10-Methyl-eicosa-5,8,11,14-tetraenoic acid N-{2-[(tert-butyldiphenylsilyl) oxy]ethyl}amide (**35**).* The synthesis was carried out as described for **30** and gave the title compound in 83% yield. Spectroscopic and physical data were identical to those of the enantiomer **30**.

*4.1.25. (10R,5Z,8Z,11Z,14Z)-10-Methyl-eicosa-5,8,11,14-tetraenoic acid N-(2-hydroxyethyl)amide (**1b**).* The synthesis was carried out as described for **1a** and gave the title compound in 85% yield. Spectroscopic and physical data were identical to those of the enantiomer **1a**.

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Supplementary data

Experimental procedures and spectroscopic and physical data for all compounds. Reproductions of ^{1}H NMR spectra of compounds **24** and **25** in $CDCl_3$ solutions and reproductions of ^{1}H NMR, ^{13}C NMR, COSY, HSQC and NOESY spectra of compound **1a** in $CDCl_3$ solutions. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2012.05.010.

References and notes

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