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Asymmetric synthesis of unnatural (*Z*,*Z*,*E*)-octadecatrienoid and eicosatrienoid by lipoxygenase-catalyzed oxygenation

S. Nanda* and J. S. Yadav

Organic Division, Indian Institute of Chemical Technology, Hyderabad 500007, India

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Dedicated to Professor A. Ian Scott on his 75th Birthday.

Abstract—The asymmetric synthesis of unnatural 13-hydroxy-(6*Z*,9*Z*,11*E*,13*S*)-octadecatrienoid and 15-hydroxy-(8*Z*,11*Z*,13*E*,15*S*)-eicosatrienoid is described using a biomimetic oxidation route. The main highlights of this synthesis are the asymmetric hydroxylation of the substrate with soybean lipoxygenase and *cis* selective Wittig olefination. © 2003 Published by Elsevier Science Ltd.

1. Introduction

Fatty acids such as leukotrienes (eicosanoids) and unsaturated C-18 hydroxy fatty acids (octadecenoids) have been the subject of much interest because of the wide range of their biological properties. The leukotrienes are associated with the pharmacological activities related to immune hypertensive reactions such as asthma and inflammation,[1–3] whereas octadecenoids have an altogether different biological role such as ionophoric activity, self-defensive properties against blast disease in the rice plant etc. Coriolic and dimorphecolic acids, the two octadecenoids, which were isolated from beef heart mitochondria,[4] were shown to possess unique divalent cation ionophoric activity. These acids seem to inhibit the spore germination and germ tube growth of Conidia of rice blast fungus thus playing a self-defensive role in the rice plant against being infected by the disease.[5] Samuelson[6] established the presence of these two octadecenoids in the sera of patients with Familial Mediterranean Fever (FMF), an autosomal recessive disorder. The presence of these fatty acids in the lipid extract of sera of patients of FMF suggests that the defects formation features elimination of these compounds and might play a role in the pathogenesis of FMF. The presence of these fatty acids except the above-mentioned two octadecenoids in natural sources is in insignificant amounts.

Therefore there is a need for obtaining these products as well as their unnatural counterparts to study the physiological properties and to understand the mechanism of action, which in turn, may help in designing products with better therapeutic action. A large number of organic chemists[7–18] are engaged in the synthesis of these molecules mainly the octadecenoids. In view of their importance and rapid expansion, it is pertinent to synthesize these fatty acids and their analogues.

2. Results and discussion

Herein I describe for the first time a biomimetic approach to the total synthesis of unnatural unsaturated hydroxy fatty acids 13-*S*-HOTE and 15-*S*-HETrE. Both of these oxidative metabolites have anti-inflammatory properties.[19] 15-*S*-HETrE induces a concentration dependent inhibition or potentiation of platelet aggregation.[20–22] It has been shown to inhibit 5-LO and 12-LO. Hence formation of LTB_4 from arachidonic acid in A23187-stimulated neutrophils ($IC_{50} = 0.2$ μM) was blocked. The role of lipoxygenase in the biosynthesis of leukotrienes is well known, and in our previous communication we described the synthesis of some chiral (*Z*,*E*)-diene-diols by lipoxygenase catalyzed asymmetric oxygenation of unnatural substrates mimicking linoleic acid. A careful analysis revealed that the target compounds (*Z*,*Z*,*E*)-hydroxy fatty acids **1a**

* Corresponding author. Present address: Department of Chemistry, Texas A&M University, 3255 TAMU, College station, TX 77843, USA. Fax: +1-979-845-5992; e-mail: snanda@mail.chem.tamu.edu

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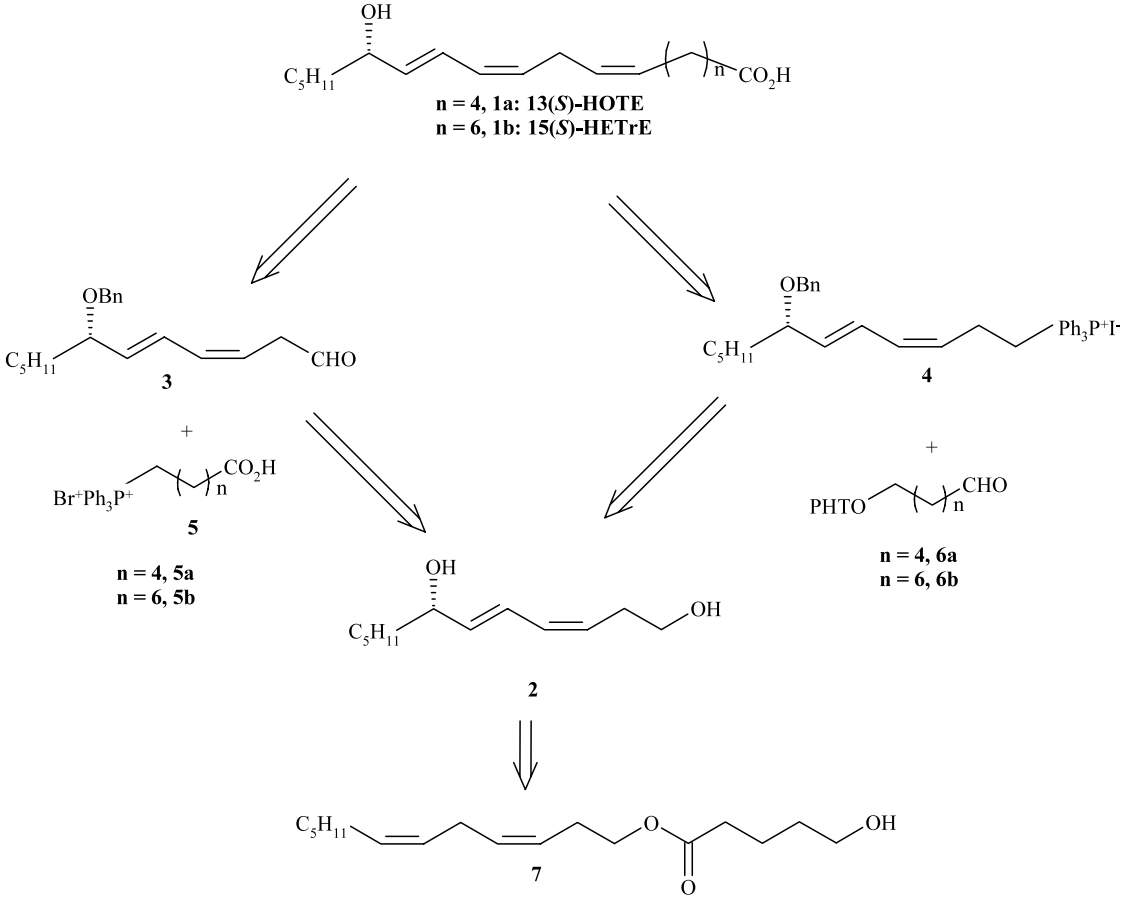
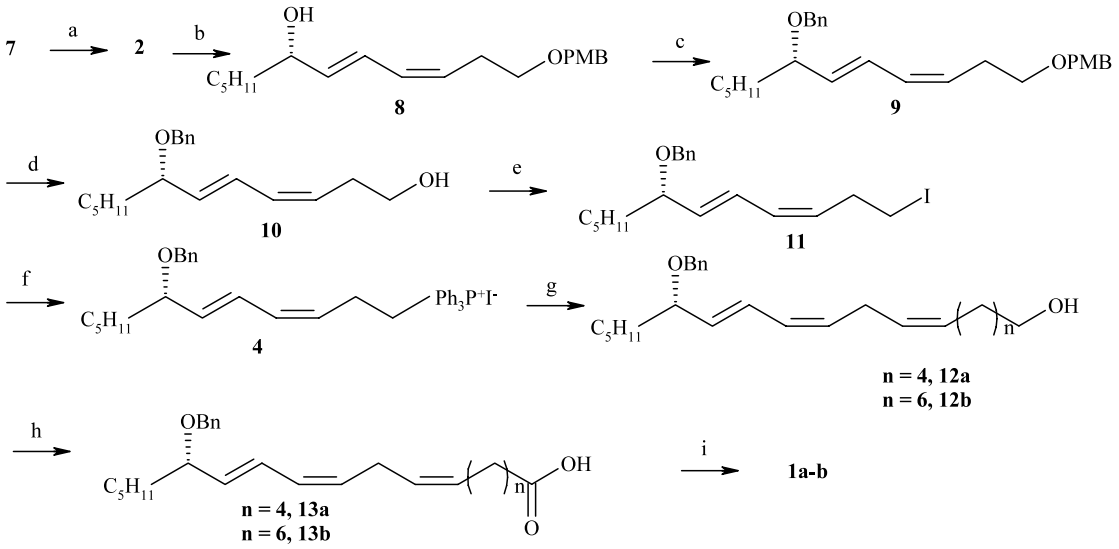
and **1b** can be constructed from the (*Z*,*E*)-diene-diol **2**. The C-6 to C-18 fragment in **1a** and C-9 to C-20 fragment in **1b** should remain intact as in the starting material and we need to construct an extra (*Z*)-double bond. A *cis* selective Wittig reaction was chosen for construction of the (6*Z* and 8*Z*) double bonds. The (*Z*,*E*)-diene-diol **2** was used as the aldehydic partner **3** as well as Wittig ylide **4** for the construction of the double bond (Scheme 1).

The synthesis starts from the unnatural substrate **7** mimicking linoleic acid and having a hydroxy end group. Upon oxygenation with lipoxygenase, subsequent reduction of the peroxides with HRP and hydrolysis of the ester moiety **2** was obtained with excellent regio and stereocontrol.[23,24] The primary hydroxy functionality in **2** was selectively monoprotected as its PMB-ether by treatment with NaH and PMB-Br to yield **8**. The secondary alcohol group in **8** was protected as its benzyl ether by treating with benzylimidate [25] in the presence of CSA to give **9** in 82% yield. ^{1}H NMR spectrum of **9** showed peaks at δ 2.5 (q, =***CH$_2$***-CH$_2$-OPMB, 2H), 3.5 (t, -***CH$_2$***-OPMB, 2H), 5.2–6.4 (*olefinic protons*, 4H) and 6.8–7.2 (*aromatic protons*, 9H). Its ^{13}C NMR spectrum showed peaks at 130.5, 129.5, 128.2 and 127.6 indicates the presence of (*Z*,*E*)-double bonds. Deprotection of the PMB ether with DDQ[26] in the presence of the benzyl group yielded **10** in 80% yields. ^{1}H NMR spectrum of **10** showed peaks at δ 2.5 (q, =C***H$_2$***-CH$_2$-OH, 2H), 3.7 (t, -***CH$_2$***OH, 2H), 3.8 (m, -***CH***-OBn, 1H), 4.28 (d, *benzylic proton*, 1H), 4.6 (d, *benzylic proton*, 1H), 5.48–6.5 (*olefinic protons*, 4H), 7.2-7.4 (*aromatic protons*, 5H). The primary hydroxy group in **10** was converted to the corresponding iodo compound **11** by treatment with I_2/TPP/imidazole in 85% yield.[27] ^{1}H NMR spectrum of **11** showed peaks at δ 2.8 (q, =***CH$_2$***-CH$_2$I, 2H), 3.2 (t, -***CH$_2$***I, 2H). Compound **11**, when refluxed with TPP in acetonitrile, generated the phosphonium salt **4** as a white solid. Condensation of **4** with the appropriate monotetrahydropyranyl protected aldehyde (**6a**–**b**) in the presence of *n*-BuLi and subsequent removal of the tetrahydropyranyl group with methanolic PTSA afforded **12a**–**b** in 60% yield. Oxidation of **12a**–**b** under Jones conditions afforded the carboxylic acids **13a**–**b** in 75% yield. Finally removal of benzyl group with Li–NH_3 (l)[28] yielded the target compound **1a**–**b** in 60% and overall 12% yield starting from **7** (Scheme 2).

In another approach the primary alcohol group in **10** was subjected to oxidation under various conditions to obtain **3**. Several oxidation reactions were tested, e.g. PCC, Swern, TPAP/NMO, but in all the cases poor (10–25%) yields were obtained. Though it is well known that oxidation of homoallylic alcohols are problematic due to probable isomerization and migration of the double bond towards the more stable α,β-unsaturated aldehyde. The best result was obtained with the Dess–

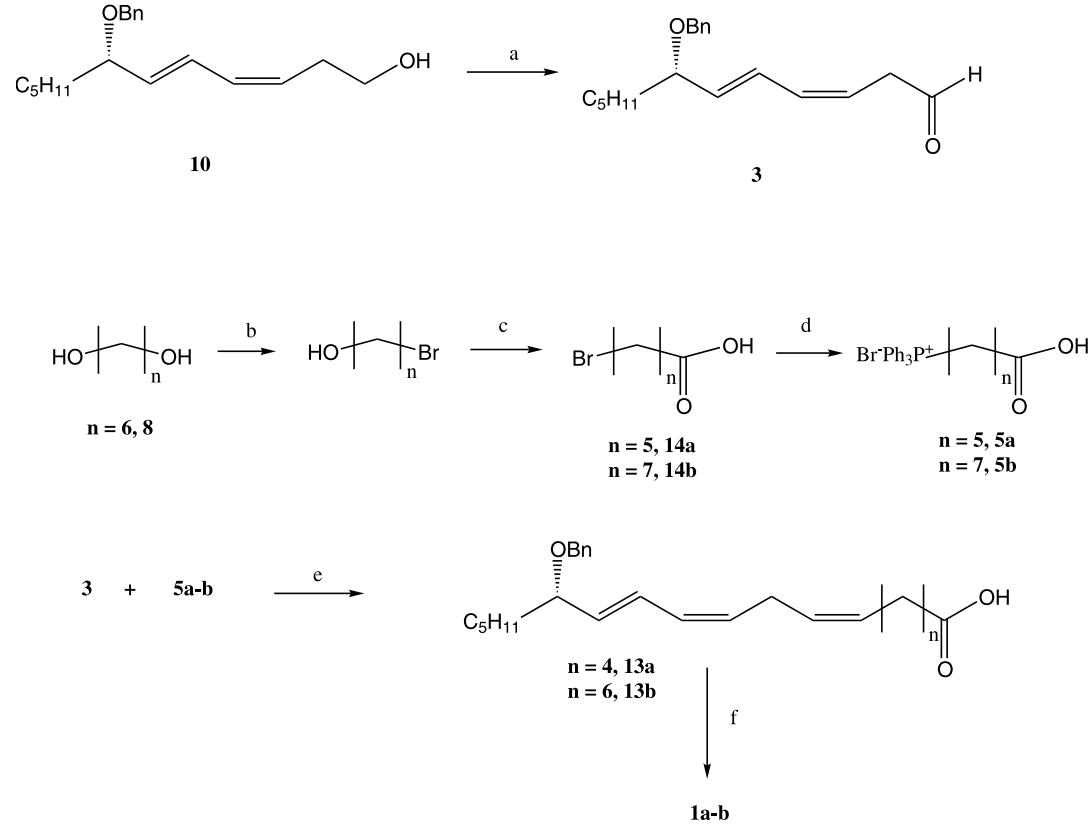


Scheme 1.



Scheme 2. *Reagents and conditions*: (a) SBLO, 0°C, sodium borate buffer, pH 9.0, HRP, sodium phosphate buffer, pH 6.5, KOH/MeOH, rt, 12 h; (b) NaH, PMB-Br, $^{n}Bu_4N^+I^-$; (c) BnO (-NH=CCl_3), CSA; (d) DDQ, DCM:H_2O (19:1); (e) I_2, TPP, imidazole, CH_3CH:ether (1:3); (f) TPP, CH_3CN, reflux, 48 h (g) ^{n}BuLi, THPO-$(CH_2)_n$CHO (n=5,7), MeOH, PTSA; (h) CrO_3–H_2O (8N); (i) $LiNH_3$ (l).

Martin periodinane[29] (65%). The corresponding Wittig ylide was generated from the appropriate diol. It was mono-brominated with 48% HBr[30] to yield the mono-bromo alkanol. Jones oxidation of the monobromo alkanol provides the corresponding acid **14a**–**b** in good yield. Treatment of **14a**–**b** with triphenyl phosphine in refluxing acetonitrile yielded the Wittig ylide **5a**–**b** as a white solid. A *cis* selective Wittig reaction of **5a**–**b** with aldehyde **3** in presence of NaHMDS as a base, and subsequent removal of benzyl functionality with Li/NH_3 (l) afforded **1a**–**b** in moderate yield (Scheme 3).



Scheme 3. *Reagents and conditions*: (a) DMP, DCM, 0°C, 1 h, 65%; (b) HBr, benzene, 60%; (c) CrO_3, H_2SO_4 (8N); (d) TPP, CH_3CN, reflux; (e) NaHMDS, −30°C, 40%; (f) Li/NH_3 (l).

3. Conclusion

An efficient asymmetric total synthesis of unsaturated hydroxy fatty acid has been established. The key step in the synthesis is to construct the asymmetric center by lipoxygenase-catalyzed oxygenation of the unnatural substrates. Currently we are actively engaged in the total synthesis of several unsaturated hydroxy fatty acids and their analogues, which have tremendous biological potential. Although numerous synthetic approaches have appeared after the isolation of these fatty acids, their mechanisms of self-defensive action against rice blast disease or other physiological properties are still to be understood. Further, how these compounds are synthesized by the plants under stress conditions remains to be studied.

4. Experimental

4.1. General

Unless otherwise stated, materials were obtained from commercial suppliers and used without further purification. THF and diethyl ether were distilled from sodium benzophenone ketyl. HMPA was distilled from BaO and stored over 3 Å molecular sieves. Dichloromethane (DCM) was distilled from calcium hydride. Lipoxygenase (type-1, activity = 127,000 u/mg protein) and peroxidase (from horseradish, type-VI-A, 1100 u/mg protein) were obtained from Sigma Co. (USA) and used as obtained. Reactions were monitored by thin-layer chromatography (TLC) carried out on 0.25 mm silica gel plates with UV light and 2.5% ethanolic anisaldehyde (with 1% AcOH and 3% conc. H_2SO_4) heat as developing agents. Silica gel 100–200 mesh was used for column chromatography. Yields refer to chromatographically and spectroscopically homogeneous materials unless otherwise stated. NMR spectra were recorded on 200 MHz spectrometers at rt in $CDCl_3$ using tetramethyl silane as internal standard and the chemical shifts are shown in δ. ^{13}C NMR spectra were recorded with a complete proton decoupling instrument. Infrared spectra were recorded on a Perkin–Elmer 1420 spectrometer. Optical rotations were measured on a JASCO Dip 360 digital polarimeter. TF denotes thin film. HPLC analysis was performed on a Shimadzu liquid chromatography LC-6A. The column was 4.6×250 mm, chiral cell OD column (Daicell). The eluents were hexane–^{i}PrOH (HPLC Grade, 85:15) at 0.5 mL/min flow rate and monitored at a wavelength of 240 nm. For compounds **1a**–**b** HPLC was performed on μ-porasil column at a flow rate 1 mL/min. The eluent used was hexane:^{i}PrOH:AcOH (991:8:1).

4.2. (3*Z*,5*E*,7*S*)-3,5-Dodecadiene-1,7-diol 2

To a homogeneous solution of 100 mg (0.35 mmol) of **7** in 20 mL of 0.2 M sodium borate buffer (pH 9.0), at 0°C was added 50 mg of Lipoxygenase type-1. While O_2 was bubbled through the solution at such a rate to produce minimum of foaming. After 1 h the reaction mixture was acidified with citric acid to pH 5.0, and then extracted several times with ether, dried (Na_2SO_4) and evaporated to afford the crude hydroperoxide. The crude hydroperoxide (105 mg) was taken in 5 mL of 0.1 M phosphate buffer and to this solution HRP (50 mg) was added and the reaction mixture was agitated for 1 h at rt. After the completion of reaction (indicated by TLC) it was extracted with ether. Evaporation of the ethereal solution and chromatographic separation 44 mg (40%) of the diol was obtained. IR (γ, TF): 3400, 1740 cm^{-1}. $[\alpha]_D^{25} = +11.0$ (*c* 0.5, $CHCl_3$). ^1H NMR: 0.9 (t, $J = 7.0$ Hz, 3H), 1.3 (brs, 6H), 1.5–1.8 (m, 4H), 2.3 (t, $J = 7.0$ Hz, 2H), 2.4 (t, $J = 7.0$ Hz, 2H), 2.5 (brs, 2H, -OH), 3.6 (m, 2H), 4.1 (m, 3H), 5.46 (dd, $J = 7.0$, 10.4 Hz, 1H), 5.73 (dd, $J = 7.0$, 15 Hz, 1H), 6.15 (dd, $J =$ 10.0, 10.4 Hz, 1H), 6.52 (dd, $J = 10.0$, 15 Hz, 1H). ^{13}C NMR: 14, 20.9, 22.5, 26, 26.9, 27.1, 29.4, 31.6, 34, 62.1, 64, 72, 124, 127.4, 128.5, 130.2, 173. EIMS (*m*/*z*): 298 (M^+).

For the removal of the prosthetic modifier the compound obtained in the previous step (44 mg, 0.147 mmol) was dissolved in 2 mL of methanol, followed by addition of KOH (1 g), and the mixture was stirred for 12 h at rt. The mixture was diluted with water and extracted several times with EtOAc. Evaporation and purification by column chromatography gave (30 mg) the diol **2** as yellow oil in 90% yield. Enantioselection (Ee) was 97% as determined from Chiral HPLC measurement. IR (γ, TF): 3400, 980 cm^{-1}. $[\alpha]_D^{25} = +52.0$ (*c* 1.0, $CHCl_3$). ^1H NMR: 0.85 (t, $J = 7.0$ Hz, 3H), 1.26 (m, 6H), 1.44 (m, 2H), 2.2 (brs, 2H, -OH), 2.4 (q, $J = 7.0$ Hz, 2H), 3.69 (t, $J = 7.0$ Hz, 2H), 4.1 (q $J = 7.0$ Hz, 1H), 5.46 (dd, $J = 7.0$, 10.4 Hz, 1H), 5.73 (dd, $J = 7.0$, 15 Hz, 1H), 6.15 (dd, $J = 10.0$, 10.4 Hz, 1H), 6.52 (dd, $J = 10.0$, 15 Hz, 1H). ^{13}C NMR: 130.3, 128.6, 127.5, 124.3, 65.0, 62.5, 32.0, 29.5, 27.0, 26.0, 22.5, 13.9. EIMS (*m*/*z*): 198 (M^+).

4.3. 12-(4-Methoxybenzyloxy)-1-pentyl (1*S*,2*E*,4*Z*)-2,4-heptadienyl alcohol 8

(3*Z*,5*E*,7*S*)-3,5-Dodecadiene-1,7-diol **2** (0.5 g, 2.5 mmol) was taken in 8 mL of dry THF and NaH (60% dispersion in mineral oil, 0.1 g, 4.2 mmol) was added to it portionwise at 0°C. The reaction mixture was stirred at 0°C for 1 h under a nitrogen atmosphere. Tetrabutylammoniumiodide (catalytic) was added to it followed by the addition of 4-methoxybenzylbromide (0.5 g, 2.5 mmol). Stirred for a further 2 h at rt. Water was added to the reaction mixture and extracted with EtOAc. Washed with brine and dried (Na_2SO_4). Purification by means of column chromatography gave the product **8** (0.64 g) in 80% yield. $[\alpha]_D^{25} = +19.1$ (*c* 1.1, $CHCl_3$). ^1H NMR: 0.9 (m, 3H), 1.2–1.6 (m, 8H), 2.5 (q, $J = 7.0$ Hz, 2H), 3.5 (t, $J = 7.0$ Hz, 2H), 3.9 (s, 3H), 4.0 (m, 1H), 4.4 (s, 2H), 5.4–5.7 (m, 2H), 6.15 (dd, $J = 10.0$, 10.4 Hz, 1H), 6.4 (dd, $J = 10.0$, 15.0 Hz, 1H), 6.8 (d, $J = 6.2$ Hz, 2H), 7.2 (d, $J = 6.2$ Hz, 2H). ^{13}C NMR: 159.2, 130.3, 130, 129, 128.6, 127.5, 124.3, 114, 72.5, 69.4, 65.0, 55.2, 32, 29.5, 27, 26, 22.5, 14. FABMS (*m*/*z*): 318 (M^+)

4.4. 1-[7-Benzyloxy-(3*Z*,5*E*,7*S*)-3,5-dodecadienyloxy-methyl]-4-methoxy benzene 9

NaH (0.1 g, 4.2 mmol) was suspended in anhydrous ether (4 mL) and a solution of benzyl alcohol (4.5 g, 42 mmol) in ether (6 mL) was added drop wise with stirring under nitrogen. After 20 min the solid had dissolved and the solution was cooled to 0°C. TCA (5.78 g, 40 mmol) was then added dropwise during 5 min and the mixture was allowed to warm at rt for 1 h. A small amount of brown ppt formed during the addition of TCA but did not appear to influence the course of the reaction. The reaction mixture was concentrated to syrup and pentane containing anhyd. MeOH (4 mL+0.2 mL) was added, followed by vigorous shaking, filtration and concentration of the filtrate. The resulting imidate was obtained as a colorless liquid.

To a solution of **8** (0.64 g, 2 mmol) in 5 mL of cyclohexane and 2.5 mL of DCM was added benzyl 2,2,2-trichloro acetamide (0.632 g, 2.5 mmol) followed by addition of CSA (0.2 mmol). The solution was stirred overnight at rt. After 24 h the mixture was filtered, and the filtrate was washed with water, aq. $NaHCO_3$ and brine. The organic extract was dried (Na_2SO_4) and purified by column chromatography to afford the compound **9** (0.67 g) in 82% yield. $[\alpha]_D^{25}=+33.6$ (*c* 1.3, $CHCl_3$). ^{1}H NMR: 0.9 (m, 3H), 1.2–1.6 (m, 8H), 2.52 (q, $J=7.0$ Hz, 2H), 3.5 (t, $J=7.0$ Hz, 2H), 3.9 (m, 4H), 4.25 (d, $J=6.0$ Hz, 1H), 4.45 (s, 2H), 4.52 (d, $J=6.0$ Hz, 1H), 5.2–5.7 (m, 2H), 6.18 (dd, $J=10.0$, 10.4 Hz, 1H), 6.4 (dd, $J=10$, 15.0 Hz, 1H), 6.8 (d, $J=6.2$ Hz, 2H), 7.2–7.4 (m, 7H). ^{13}C NMR: 159.2, 138.8, 134.8, 130.5, 129.5, 129.1, 128.2, 128.05, 127.65, 127.4, 127.27, 113.75, 79.8, 72.5, 70.03, 69.34, 55.2, 35.7, 31.7, 28.5, 25.04, 22.5, 13.9. FABMS: 408 (M^+).

4.5. 7-Benzyloxy-(3*Z*,5*E*,7*S*)-3,5-dodecadiene-1-ol 10

Compound **9** (0.67 g, 1.6 mmol) was taken in 10 mL of dichloromethane: water (19:1). DDQ (0.56 g, 2.46 mmol) was added to it, and the solution stirred for 1 h at rt. The reaction mixture was filtered off, and the filtrate was washed with 5% $NaHCO_3$ solution, brine and dried (Na_2SO_4). Purification by chromatography gave **10** (0.387 g) in 80% yield. $[\alpha]_D^{25}=+13.9$ (*c* 1.25, MeOH). ^{1}H NMR: 0.9 (m, 3H), 1.2–1.8 (m, 8H), 2.5 (q, $J=7.0$ Hz, 2H), 3.7 (t, $J=7.0$ Hz, 2H), 3.8 (m, 1H), 4.28 (d, $J=6.0$ Hz, 1H), 4.6 (d, $J=6.0$ Hz, 1H), 5.48 (dd, $J=7.0$, 10.4 Hz, 1H), 5.7 (dd, $J=7.0$, 15.0 Hz, 1H), 6.15 (dd, $J=10.0$, 10.4 Hz, 1H), 6.52 (dd, $J=10.0$, 15.0 Hz, 1H), 7.2–7.4 (m, 5H). ^{13}C NMR: 138.8, 130.5, 129.5, 129.1, 128.2, 128.05, 127.65, 124.27, 72.5, 69.34, 65.2, 35.7, 31.7, 28.5, 25.04, 22.5, 13.9. FABMS (*m*/*z*): 288 (M^+).

4.6. 1-[7-Iodo-1-pentyl-(1*S*,2*E*,4*Z*)-2,4-heptadienyloxy-methyl] benzene 11

Compound **10** (0.378 g, 1.3 mmol) was taken in 7.5 mL acetonitrile: ether (3:1). Imidazole (0.133 g, 1.96 mmol) was added to it at rt, followed by addition of I_2 (0.5 g, 1.96 mmol) and triphenylphosphine (0.515 g, 1.96 mmol). The reaction mixture was stirred for 45 min at rt. After that it was filtered and the filtrate was concentrated to give a semisolid mass, which was purified through column chromatography to give the pure iodide **11** (0.44 g) in 85% yield. $[\alpha]_D^{25}=+69.0$ (*c* 2.0, $CHCl_3$). ^{1}H NMR: 0.9 (t, $J=7.0$ Hz, 3H), 1.2–1.4 (m, 4H), 1.5–1.8 (m, 4H), 2.8 (q, $J=7.0$ Hz, 2H), 3.2 (t, $J=7.0$ Hz, 2H), 3.78 (m, 1H), 4.3 (d, $J=6.0$ Hz, 1H), 4.58 (d, $J=6.0$ Hz, 1H), 5.38 (dd, $J=7.0$, 10.4 Hz, 1H), 5.6 (dd, $J=7.0$, 15.0 Hz, 1H), 6.12 (dd, $J=10.0$, 10.4 Hz, 1H), 6.38 (dd, $J=10.0$, 15.0 Hz, 1H), 7.2–7.4 (m, 5H). FABMS: 398 (M^+).

4.7. Phosphonium salt 4

Compound **11** (0.44 g, 1.1 mmol) was taken in 8 mL dry acetonitrile. Triphenylphosphine (0.29 g, 1.1 mmol) was added to it, and the reaction mixture was heated at 60°C for 48 h under a nitrogen atmosphere. Acetonitrile was evaporated and dry ether 30 mL was added to the semisolid mass and shaken vigorously. Evaporation of the ether gave the phosphonium salt **4** (0.6 g) as a white solid.

4.8. 8-Tetrahydro-2*H*-pyranyloxy-1-octanol[31]

1,8-Octanediol (2 g, 13.7 mmol) was taken in 25 mL anhyd. DCM. 3, 4-dihydro-2*H*-pyran (1 g, 13 mmol) was added to it dropwise followed by addition of catalytic amount of PTSA. After 30 min, the reaction mixture was washed with satd $NaHCO_3$ and brine. The organic extract was dried (Na_2SO_4) and purified through column chromatography to yield 1.9 g in 60% yield. ^{1}H NMR: 1.2–1.4 (m, 8H), 1.42–1.6 (m, 8H), 1.6–1.8 (m, 2H), 3.3 (m, 1H), 3.45 (m, 1H), 3.6 (t, $J=7.0$ Hz, 2H), 3.7 (m, 1H), 3.8 (m, 1H), 4.58 (t, $J=4.0$ Hz, 1H).

4.9. 6-Tetrahydro-2*H*-pyranyloxy-1-hexanol[31]

Prepared in the same way as described above from 1, 6-hexanediol. ^{1}H NMR: 1.2–1.4 (m, 6H), 1.45–1.62 (m, 6H), 1.7–1.83 (m, 2H), 3.34 (m, 1H), 3.46 (m, 1H), 3.62 (t, $J=7.0$ Hz, 2H), 3.7 (m, 1H), 3.82 (m, 1H), 4.6 (t, $J=4.0$ Hz, 1H).

4.10. 8-Tetrahydro-2*H*-pyranyloxy-1-octanal 6b[32]

To oxallylchloride (0.72 mL, 8.2 mmol) and DMSO (1.2 mL, 16.4 mmol) in DCM (50 mL) at −78°C was added monoprotected 1,8-octanediol (1.9 g, 8.2 mmol) in DCM and the temperature was allowed to maintain the same for a further 1 h. Triethylamine (5.3 mL, 41 mmol) was added and after 5 min the temperature was allowed to raise to 25°C. Stirred for a further 30 min at the same temperature. Water was added to the solution, extracted with DCM. Washed with water, brine and dried (Na_2SO_4). Evaporation and purification by means of column chromatography gave corresponding aldehyde in 90% yield (1.7 g). ^{1}H NMR: 1.2–1.4 (m, 8H), 1.4–1.8 (m, 8H), 2.4 (t, $J=7.0$ Hz, 2H), 3.32 (m, 1H), 3.5 (m, 1H), 3.65 (m, 1H), 3.8 (m, 1H), 4.58 (t, $J=4.0$ Hz, 1H), 9.8 (s, 1H).

4.11. 6-Tetrahydro-2*H*-pyranyloxy-1-hexanal 6a[31]

It was prepared by the Swern oxidation of mono tetrahydropyranyl protected 1,6-hexane di-ol as described in Section 4.10. ^{1}H NMR: 1.2–1.4 (m, 6H), 1.42–1.8 (m, 6H), 2.38 (t, $J=7.0$ Hz, 2H), 3.35 (m, 1H), 3.5 (m, 1H), 3.68 (m, 1H), 3.85 (m, 1H), 4.6 (t, $J=4.0$ Hz, 1H), 9.78 (s, 1H).

4.12. 15-Benzyloxy-(8*Z*,11*Z*,13*E*,15*S*)-8, 11, 13-eicosatriene-1-ol 12b

Ylide (**4**, 0.6 g, 0.9 mmol) was taken in 5 mL THF: HMPA (6:1). *n*-BuLi (0.4 mL, 3.0 M in hexane) was added to it at 0°C. The orange colored solution was stirred at the same temperature for 1 h. 8-Tetrahydropyranyl octanal (0.2 g, 0.9 mmol) in 1 mL THF was added and the reaction mixture stirred for a further 2 h at the same temperature. Quenched with satd NH_4Cl solution and then extracted with ether. Washed with water, brine and dried (Na_2SO_4). The crude product was dissolved in 5 mL of methanol and catalytic amount of PTSA was added to it, stirred for 1 h at rt. Evaporation of methanol and purification by column chromatography afforded the (*Z*,*Z*,*E*) trienol **12b** in 60% yield. $[\alpha]_D^{25}=+39.2$ (*c* 1.8, $CHCl_3$). ^{1}H NMR: 0.9 (m, 3H), 1.2–1.75 (m, 18H), 2.1 (m, 2H), 2.8 (t, $J=7.0$ Hz, 2H), 3.6 (t, $J=7.0$ Hz, 2H), 4.1 (m, 1H), 4.4 (s, 2H), 5.3 (m, 2H), 5.6 (m, 1H), 5.9–6.12 (m, 2H), 6.38 (m, 1H), 7.2–7.4 (m, 5H). ^{13}C NMR: 138.8, 134.0, 130.2, 128.6, 128.2, 127.7, 127.5, 127.3, 126.5, 124.3, 72, 69.5, 65, 32.5, 31, 29.2, 27, 26.3, 26, 25.4, 24.1, 23.2, 22.5, 21.6, 14. FABMS (*m*/*z*): 398 (M^+).

4.13. 13-Benzyloxy-(6*Z*,9*Z*,11*E*,13*S*)-6,9,11-octadecatriene-1-ol 12a

Comound **12a** was prepared from ylide **4** and 6-tetrahydropyranyl hexanal **6b** as described in the previous step. ^{1}H NMR: 0.9 (m, 3H), 1.2–1.8 (m, 14H), 2.15 (m, 2H), 2.8 (t, $J=7.0$ Hz, 2H), 3.62 (t, $J=7.0$ Hz, 2H), 4.1 (m, 1H), 4.4 (s, 2H), 5.3 (m, 2H), 5.6 (m, 1H), 5.9–6.12 (m, 2H), 6.38 (m, 1H), 7.2–7.4 (m, 5H). ^{13}C NMR: 138.8, 134.2, 130.4, 128.5, 128.1, 127.9, 127.4, 127.1, 126.5, 124.5, 72.6, 69.4, 65, 33.5, 31, 29.4, 26.3, 25.4, 24.1, 23.4, 22.8, 21.7, 14.1. FABMS (*m*/*z*): 370 (M^+).

4.14. 15-Benzyloxy-(8*Z*,11*Z*,13*E*,15*S*)-8,11,13-eicosatrienoicacid 13b

Compound **12b** (0.2 g, 0.5 mmol) was taken in 5 mL of distilled acetone at 0°C. Freshly prepared Jones reagent was added dropwise at the same temperature until the orange brown color persists. The reaction mixture was allowed to attain rt and stirred for a further 30 min. Water was added, and it was extracted with EtOAc. Purification by chromatography gave the acid **13b** as a gummy white solid (0.15 g) in 75% yield. $[\alpha]_D^{25}=+39.2$ (*c* 1.8, $CHCl_3$). ^{1}H NMR: 0.9 (m, 3H), 1.2–1.8 (m, 16H), 2.0 (m, 2H), 2.5 (t, $J=7.0$ Hz, 2H), 2.8 (t, $J=7.0$ Hz, 2H), 4.1 (m, 1H), 4.6 (s, 2H), 5.3 (m, 1H), 5.6 (m, 1H), 5.9–6.12 (m, 3H), 6.38 (m, 1H), 7.2–7.4 (m, 5H). ^{13}C NMR: 180.5, 138.8, 134.0, 130.2, 128.6, 128.2, 127.7, 127.5, 127.3, 126.5, 124.3, 72, 69.5, 33.6, 32.5, 31, 29.2, 27, 26.3, 26, 25.4, 23.2, 22.5, 21.6, 14. FABMS: 412 (M^+).

4.15. 13-Benzyloxy-(6*Z*,9*Z*,11*E*,13*S*)-6,9,11-octadecatrienoicacid 13a

Compound **13a** was prepared by Jones oxidation of **12a** as described in Section 4.14. $[\alpha]_D^{25}=+15.8$ (*c* 1.8, $CHCl_3$). ^{1}H NMR: 0.9 (m, 3H), 1.2–1.75 (m, 12H), 2.1 (m, 2H), 2.5 (t, $J=7.0$ Hz, 2H), 2.8 (t, $J=7.0$ Hz, 2H), 4.1 (m, 1H), 4.6 (s, 2H), 5.3 (m, 1H), 5.6 (m, 1H), 5.9–6.12 (m, 3H), 6.38 (m, 1H), 7.2–7.4 (m, 5H). ^{13}C NMR: 181.2, 138.8, 134.2, 130.4, 128.5, 128.1, 127.9, 127.4, 127.1, 126.5, 124.5, 72.6, 69.4, 33.6, 32.0, 31, 29.4, 26.3, 25.4, 23.4, 22.8, 21.7, 14.1. FABMS (*m*/*z*): 384 (M^+).

4.16. 15-Hydroxy-(8*Z*,11*Z*,13*E*,15*S*)-8,11,13-eicosatrienoicacid 1b

Compound **13b** (0.15 g) in anhydrous THF (2 mL) was added to liq. NH_3 (10 mL). Finely chopped metallic lithium was added to it until the blue color persists. The mixture was stirred for a further 2 h at the same temperature. NH_4Cl was added to it and the ammonia was allowed to evaporate. Extracted with ether, washed with brine and dried (Na_2SO_4). After purification by column chromatography (MeOH/$CHCl_3$, 1:4) at −20°C in a cold room and lypholization of the organic solvents afforded polyunsaturated hydroxy fatty acid **1b** in 60% yield (0.07 g). The acid was obtained as a yellow oil and can be stored in ethanol at −70°C. $[\alpha]_D^{25}=+9.2$ (*c* 1.8, $CHCl_3$). ^{1}H NMR: 0.9 (m, 3H), 1.2–1.75 (m, 16H), 2.1 (m, 2H), 2.5 (t, $J=7.0$ Hz, 2H), 2.75 (t, $J=7.0$ Hz, 2H), 4.1 (m, 1H), 5.3 (m, 1H), 5.6 (m, 1H), 5.9–6.12 (m, 3H), 6.38 (m, 1H). ^{13}C NMR: 180.5, 130.2, 128.6, 128.2, 127.5, 126.5, 124.3, 69.5, 33.6, 32.5, 31, 29.2, 27, 26.3, 26, 25.4, 23.2, 22.5, 21.6, 14. FABMS: 322 (M^+).

4.17. 13-Hydroxy-(6*Z*,9*Z*,11*E*,13*S*)-6,9,11-octadecatrienoicacid 1a

Compound **1a** was obtained as described in Section 4.16 from debenzylation of **13a** in 60% yield. $[\alpha]_D^{25}=+9.2$ (*c* 1.8, $CHCl_3$). ^{1}H NMR: 0.9 (m, 3H), 1.2–1.75 (m, 12H), 2.1 (m, 2H), 2.5 (t, $J=7.0$ Hz, 2H), 2.75 (t, $J=7.0$ Hz, 2H), 4.1 (m, 1H), 5.3 (m, 1H), 5.6 (m, 1H), 5.9–6.12 (m, 3H), 6.38 (m, 1H). ^{13}C NMR: 181.2, 130.4, 128.5, 128.1, 127.4, 126.5, 124.5, 69.4, 33.6, 32.0, 31, 29.4, 26.3, 25.4, 23.4, 22.8, 21.7, 14.1. FABMS: 294 (M^+).

4.18. 8-Bromo-octan-1-ol[30]

1,8-Octane diol (2 g, 13.7 mmol) was taken in benzene (30 mL), and the solution was heated to reflux by addition of 48% aq. HBr (2 mL) for 18 h. While trapping the water formed was performed using a Dean–Stark water separator. The mixture was washed with 6N NaOH, 10% HCl, water and brine. The organic layer was dried with Na_2SO_4 and evaporated under reduced pressure. The residue was purified by

Kugelrohr distillation (bp = 110–120°C/2 torr) to yield 1.7 g of the monobromo compound (60%). IR (γ, TF): 3500, 2900, 1040 cm^{-1}. ^1H NMR: 1.2–2.0 (m, 12H), 3.40 (t, $J = 7.0$ Hz, 2H), 3.65 (t, $J = 7.0$ Hz, 2H). EIMS (m/z): 209 (M^+).

4.19. 6-Bromo-hexan-1-ol[30]

This was prepared from 1,6-hexane diol by treatment with aq. HBr as described in Section 4.18.

IR (γ, TF): 3500, 2900, 1040 cm^{-1}. ^1H NMR: 1.2–2.1 (m, 8H), 3.40 (t, $J = 7.0$ Hz, 2H), 3.65 (t, $J = 7.0$ Hz, 2H). EIMS (m/z): 181 (M^+).

4.20. 8-Bromo-octanoic acid 14b[9]

8-Bromo-octan-1-ol (1.7 g, 8.2 mmol) was dissolved in 25 mL distilled acetone at 0°C. Freshly prepared Jones reagent was added dropwise at the same temperature until the orange brown color persisted. The reaction mixture was allowed to attain rt and stirred for a further 30 min. Water was added, and it was extracted with EtOAc. Purification by chromatography gave the acid (1.45 g, 80%) as a heavy viscous liquid. ^1H NMR: 1.2–1.4 (m, 6H), 1.42–1.8 (m, 4H), 2.48 (t, $J = 7.0$ Hz, 2H), 3.6 (t, $J = 7.0$ Hz, 2H). EIMS (m/z): 223 (M^+).

4.21. 6-Bromo-hexanoic acid 14a[33]

Compound **14a** was obtained from 6-bromohexan-1-ol by Jones oxidation as described in Section 4.20. ^1H NMR: 1.2–1.4 (m, 4H), 1.6–1.8 (m, 2H), 2.51 (t, $J = 7.0$ Hz, 2H), 3.66 (t, $J = 7.0$ Hz, 2H). EIMS (m/z): 195 (M^+).

4.22. Phosphonium salt 5b

8-Bromo-octanoic acid (1.45 g, 6.5 mmol) was taken in 20 mL of dry CH_3CN. TPP (1.7 g, 6.5 mmol) was added to the solution and it was refluxed under argon atmosphere for 48 h. CH_3CN was evaporated and the viscous liquid was shaken with 20 mL of anhydrous ether and evaporated. This was continued for four times. Then the gummy white solid was dried in vacuo to yield white phosphonium salt **5b**.

4.23. 7-Benzyloxy-dodeca(3*Z*,5*E*,7*S*)-dien-1-al 3

Compound **10** (200 mg, 0.7 mmol) was dissolved in 7 mL of anhydrous DCM. To this solution was added DMP (372 mg, 0.91 mmol) at 0°C. After 10 min, it was allowed to warm at rt and stirred for a further 1 h. The white suspension was rapidly filtered off through a pad of silica gel by eluting with ether. The organic layer was evaporated at 0°C under vacuum. The aldehyde obtained (130 mg, 65%) was pure enough for the next reaction. $[\alpha]_D^{25} = +13.9$ (c 1.25, MeOH). ^1H NMR: 0.9 (m, 3H), 1.2–1.8 (m, 8H), 3.2 (br ddd, $J = 7.0$, 2.0, 1.5 Hz, 2H), 3.8 (m, 1H), 4.28 (d, $J = 6.0$ Hz, 1H), 4.6 (d, $J = 6.0$ Hz, 1H), 5.5 (dd, $J = 7.0$, 10.4 Hz, 1H), 5.72 (dd, $J = 7.0$, 15.0 Hz, 1H), 6.2 (dd, $J = 10.0$, 10.4 Hz, 1H), 6.58 (dd, $J = 10.0$, 15.0 Hz, 1H), 7.2–7.4 (m, 5H), 9.5 (t, $J = 2.0$ Hz, 1H). ^{13}C NMR: 200, 130.5, 129.1, 128.2, 128.05, 127.65, 127.4, 127.27, 118.5, 70.03, 68.34, 42.5, 31.7, 28.5, 25.04, 22.5, 13.9. FABMS (m/z): 286 (M^+).

4.24. 15-Benzyloxy-(8*Z*,11*Z*,13*E*,15*S*)-8, 11, 12-eicosatrienoicacid 13b

Wittig salt **5b** (0.230 g, 0.5 mmol) was dissolved in 3 mL of THF: HMPA (6:1). The solution was cooled at −30°C. A 1 M solution of NaHMDS (0.5 mL in THF, 0.5 mmol) was added to it dropwise to produce an orange colored solution. The reaction mixture was kept at the same temperature for 1 h, after that aldehydic partner **3** (0.045 g, 0.017 mmol) was added to it. The reaction was allowed to attain rt. The reaction mixture was quenched with satd NH_4Cl and extracted with EtOAc. The organic layer was washed with water and brine and dried over Na_2SO_4. Evaporation and purification through column chromatography afforded **13b** in 40% yield.

4.25. 3-Benzyloxy-(6*Z*,9*Z*,11*E*,13*S*)-6,9,11-octadecaatrienoicacid 13a

Compound **13a** was obtained as described in Section 4.24 from Wittig ylide **5a** and aldehyde **3** in 38% yield.

References

1. Green, R. H.; Lambeth, P. F. *Tetrahedron* **1987**, *39*, 1687.
2. Georgiev, In *Survey of Drug Research in Immunological Diseases*, *Aliphatic derivatives-1*; S. Karges: Basel, London, 1984; p. 182.
3. Evstignecva, R. P.; Myagkova, G. I. *Russ. Chem. Rev.* **1986**, *55*, 455.
4. Blondin, G. A. *Ann N.Y. Acad. Sci.* **1975**, *264*, 98.
5. Kato, T.; Yamaguchi, Y.; Hirano, T.; Yokoyama, T.; Uyehara, T.; Namai, T.; Yamanaka, S.; Harada, N. *Chem. Lett.* **1984**, 409.
6. Aisen, P. S.; Haines, K. A.; Given, W.; Aramson, S.b.; Pras, M.; Serhan, C.; Hamberg, M.; Samuelson, B.; Weissmann, W. *Proc. Natl. Acad. Sci.* **1985**, *82*, 1232.
7. Rama Rao, A. V.; Rajarathnam Reddy, E.; Sharma, G. V. M.; Yadgiri, P.; Yadav, J. S. *Tetrahedron. Lett.* **1985**, *26*, 465.
8. Rama Rao, A. V.; Rajarathnam Reddy, E.; Sharma, G. V. M.; Yadgiri, P.; Yadav, J. S. *Tetrahedron* **1986**, *42*, 4523.
9. Rama Rao, A. V.; Pullareddy, S.; Rajarathnam Reddy, E. *J. Org. Chem.* **1986**, *51*, 4158.
10. Gunn, B. *Heterocycles* **1985**, *23*, 3061.
11. Suemune, H.; Hayash, N.; Funakoshi, K.; Akita, H.; Oishi, T.; Sakai, K. *Chem. Pharm. Bull.* **1985**, *33*, 2168.
12. Moustakis, C. A.; Weerasinghe, D. K.; Mosset, P.; Falck, J. R. *Tetrahedron Lett.* **1986**, *27*, 303.
13. Tsuboi, S.; Han Wu, X.; Maeda, S.; Ono, S.; Kuroda, A.; Kawazu, K.; Takeda, A. *Bull. Chem. Soc. Japan* **1987**, *60*, 1103.
14. Kobayashi, Y.; Okamuto, S.; Shimazaki, T.; Ochiai, Y.; Sato, F. *Tetrahedron Lett.* **1987**, *28*, 3959.
15. Tsuboi, S.; Maeda, S.; Takeda, A. *Bull. Chem. Soc. Japan* **1986**, *59*, 2050.

16. Tsuboi, S.; Maeda, S.; Takeda, A. *J. Org. Chem.* **1982**, *47*, 4478.
17. Rama Rao, A. V.; Rajarathnam Reddy, E. *Tetrahedron Lett.* **1986**, *27*, 2279.
18. Rama Rao, A. V.; Rajarathnam Reddy, E.; Purandare, A. V.; Varaprasad, Ch. V. N. S. *Tetrahedron* **1987**, *43*, 4385.
19. Guichardant, M. *Biochim. Biophys. Acta* **1988**, *962*, 149.
20. Chapkin, R. S. *Biochem. Biophys. Res. Commun.* **1988**, *153*, 799.
21. Miller, C. C.; McCreedy, C. A.; Jones, A. D.; Ziboh, V. A. *Prostaglandin* **1988**, *35*, 917.
22. Iversen, L.; Fogh, K.; Bojesen, G.; Kragballe, K. *Agents and Actions* **1991**, *33*, 286.
23. Yadav, J. S.; Nanda, S.; Rao, A. B. *Synlett* **2001**, 787.
24. Yadav, J. S.; Nanda, S.; Rao, A. B. *Tetrahedron: Asymmetry* **2001**, *12*, 2129.
25. White, J. D.; Reddy, G. N.; Spessard, G. O. *J. Am. Chem. Soc.* **1988**, *110*, 1624.
26. Horita, K.; Yoshioka; Tanaka, T.; Olikawa, Y.; Yonemitsu, O. *Tetrahedron* **1986**, *42*, 3021.
27. Garegg, P. J.; Samuelson, B. *J. Chem. Soc., Perkin Trans. 1* **1980**, 2866.
28. Resist, J.; Bartuska, V. J.; Goodman, L. *J. Org. Chem.* **1964**, *29*, 3725.
29. Wavrin, L.; Viala, J. *Synthesis* **2002**, 226.
30. Kang, S.-K.; Kim, W.-S.; Moon, B.-H. *Synthesis* **1985**, 2161.
31. Sakane, S.; Maruoka, K.; Yamamoto, H. *Tetrahedron* **1986**, *42*, 2203.
32. Kiyoshi, N.; Masashi, I.; Koji, Y. *Chem. Pharm. Bull.* **1990**, *38*, 28.
33. Sankaranarayanan, S.; Chattopadhyay, S. *Tetrahedron: Asymmetry* **1998**, *9*, 1345.