Synthesis of the Marine Compound (2*R*,5*Z*,9*Z*)-2-Methoxyhexacosa-5,9-dienoic Acid via a Lipase-Catalyzed Resolution and a Novel O-Alkylation Protocol

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Abstract: The title compound has been synthesized by a facile route starting from 4-pentyn-1-ol. The enantioselectivity was attained by a strategy involving a lipase-catalyzed acetylation of a solid-phase immobilized long chain α-hydroxy acid. Another important feature of the synthesis was the formulation of an efficient HgO-catalyzed O-methylation of the α-hydroxy acids which proceeded without any racemization. The alkylation protocol was also highly efficient for selective mono-methylation/benzylation of symmetrical diols.

Key words: *O*-alkylation biocatalyst, enantioselective synthesis, demospongic acid

Phospholipids containing α-methoxy/hydroxy fatty acids are quite rare in nature but sponges have provided the most striking examples of these. Compounds of this class have been isolated up to C_{30}-chain length and are either saturated or contain one to three double bonds. After the first isolation[1a] from the marine sponge *Higginsia tethyoides*, a series of α-methoxy/hydroxy phospholipid bound fatty acids were obtained[1b] from the African sponge *H. tethyoides*. In addition, other closely related acids are also encountered in the sponges *Amphimedon compressa*,[1c,d] *Polymasita gleneni*[1e] and *Callyspongia fallax*.[1f] One such long chain compound *viz*. (5*Z*,9*Z*)-2-methoxyhexacosa-5,9-dienoic acid (**I**) has been isolated[2] from the sponge *Tropsentia roquensis*. The low natural abundance of these acids has so far precluded their bioassay and biosynthetic study which remain speculative. These compounds are known to possess (*R*)-configuration[1f] and some of them show antibacterial properties.[3] In this paper, we report an efficient enantiomeric synthesis of (*R*)-**I** which also involved a novel methodology for alkylation of alcohols under practically neutral, non-racemizing conditions.

Initially, we envisaged that the corresponding chiral cyanohydrins would be the suitable precursors for the synthesis of **I** and other related compounds. Thus, the most important task for the synthesis was the formulation of an efficient strategy for asymmetric cyanohydrination. Several chemical[4a–c] routes for preparing enantiomeric cyanohydrins are known which are most suited for aromatic substrates. Amongst the biochemical[5a–f] methods, chiral cyanohydrins can be obtained by oxynitrilase-mediated cyanohydrination of aldehydes or lipase-catalyzed resolution of racemic cyanohydrins. However, even these methods generally provide the aromatic cyanohydrins. Although the oxynitrilase obtained from almond meal accepts aliphatic substrates but these are limited to only small chain aldehydes.[5e,f] Hence, we envisaged that those may not be suitable for the long chain substrates used in the present synthesis as revealed in the subsequent discussion. Consequently, we devised a novel lipase-catalyzed protocol for the synthesis of the target molecule. Another requirement of the synthesis was the development of a new protocol for O-methylation of the chiral α-hydroxy esters/cyanide which are susceptible to racemization under the conventional base-catalyzed alkylation procedures. Hence, we developed a simple and efficient method for O-alkylation of carbinols, which could be used for the required methylation of a chiral α-hydroxy ester without affecting its chiral integrity.

At the outset, we felt that methylation of a chiral alcohol under non-racemizing conditions would meet our primary objective. For this, a combination of Ag_2O/MeI was appealing as this is widely used for the methylation of sugars.[6] However, this requires freshly prepared and dried Ag_2O which is often cumbersome. Therefore, we attempted the methylation of alcohols in the presence of commercially available HgO (Scheme 1). The results of the experiments are summarized in Table 1. First, we attempted the methylation of decan-1-ol (**1a**) with MeI (excess)/HgO in toluene which proceeded excellently furnishing product **2a** in 93% yield (Table 1, entry 1). Next, we turned our attention to explore the potential of the method for the selective methylation of some symmetrical diols **1b**–**e**.

Selective mono-protection of symmetrical diols is an important exercise as the products are important synthons in organic synthesis.[7a,b] Earlier, good selectivities for monosilylation,[8a] acetylation[8b] and tetrahydropyranylation[8c] of diols have been reported. However, their selective monoalkylation often leads to a statistical mixture of products. In the present investigation, when the diols **1b**–**e** were treated with MeI (1.25 equiv) and HgO (1.5 equiv), the monomethylated products **2b**–**e** were obtained exclusively in good yields (Table 1, entries 2–5). In view of the poor solubilities of the diols, the reactions were carried out in CH_2Cl_2. Alkylation of **1e** with an increased amount

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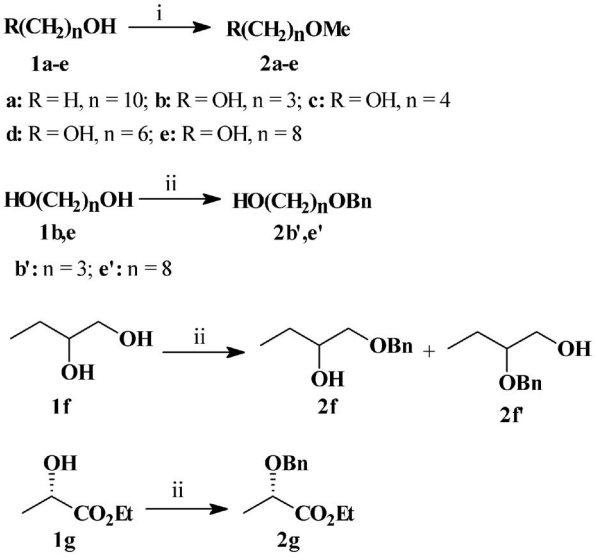


Scheme 1 *Reagents and conditions:* (i) HgO/MeI/CH_2Cl_2 or toluene; (ii) HgO/BnBr/Bu_4NI/ CH_2Cl_2 or toluene.

Table 1 HgO-Catalyzed O-Alkylation of Carbinols

Entry	Substrate	Reaction Conditions	Time	Product (% yield)[b]
1	**1a**	MeI (1.25 equiv)/toluene	12 h	**2a** (93)
2	**1b**	MeI (1.25 equiv)/CH_2Cl_2	28 h	**2b** (72)
3	**1c**	MeI (1.25 equiv)/CH_2Cl_2	28 h	**2c** (78)
4	**1d**	MeI (1.25 equiv)/CH_2Cl_2	18 h	**2d** (88)
5	**1e**	MeI (1.25 equiv)/CH_2Cl_2	18 h	**2e** (83)
6	**1e**	MeI (1.6 equiv)/CH_2Cl_2	18 h	**2e** (81)
7	**1f**	MeI (1.25 equiv)/CH_2Cl_2	24 h	**2f + 2f′** (71)[c]
8	**1b**	BnBr (1.25 equiv)/CH_2Cl_2[a]	24 h	**2b′** (77)
9	**1e**	BnBr (1.25 equiv)/CH_2Cl_2[a]	20 h	**2e′** (78)
10	**1g**	BnBr (1.25 equiv)/CH_2Cl_2 [a]	28 h	**2g** (69)

[a] The reaction was carried out in the presence of Bu_4NI (10 mole%).
[b] Isolated yields.
[c] Combined isolated yields. The ratio of the individual products was 3:2, as determined by GLC.

of MeI (1.6 equiv) also did not alter the course of the reaction and only **2e** was obtained (Table 1, entry 6). In order to assess the chemoselectivity, the reaction was attempted with the unsymmetrical diol **1f** which has both a primary and a secondary hydroxyl group. In this case also, the reaction proceeded up to monomethylation, but without any chemoselectivity and a 3:2 mixture of monomethyl products **2f** and **2f′** (Table 1, entry 7) was obtained, as revealed by GLC analysis. Subsequently, the method was extended for benzylation using **1b** and **1e** as the substrates. The reactions carried out with BnBr (1.25 equiv) in the presence of Bu_4NI (10 mole%) also proceeded well furnishing the products **2b′** and **2e′** respectively (Table 1, entries 8, 9). All the products **2a**–**2e**, **2b′** and **2e′** were characterized from their ^1H NMR spectra and microanalyses.

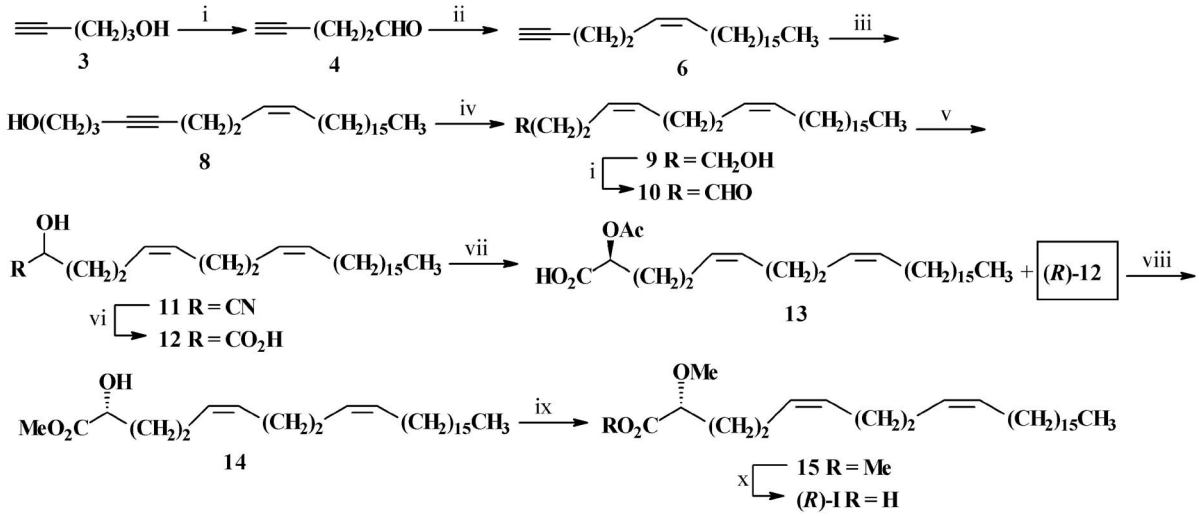
Finally, we applied the method for benzylation of (*S*)-ethyl lactate **1g** in order to assess its efficacy for the alkylation of a chiral α-hydroxy ester without any racemization. The benzylation of **1g** was slow but proceeded smoothly furnishing the benzylated ester **2g** (Table 1, entry 10). Its enantiomeric purity was assessed by converting it to 2-benzyloxypropanal and comparing the optical rotation with that reported.[9] The reaction protocol was found to preserve the stereochemical integrity of the starting substrate.

Thus, an efficient HgO-catalyzed protocol for the alkylation of carbinols has been developed which also showed remarkable selectivity with symmetrical diols. The method works in practically neutral conditions and, hence, can preserve the chiral integrity of the substrates. This might be beneficial in its application for the alkylation of chiral α-hydroxy acids/esters/carbonyls/cyanides.

Having designed the above strategy for the O-alkylation of α-hydroxy esters, we attempted the synthesis of the target compound **I**. For this, the required aldehyde **10** was prepared by a simple sequence of reactions using easily available materials (Scheme 2). Thus, alcohol **3** was oxidized with pyridinium chlorochromate (PCC) to give aldehyde **4** which upon *Z*-selective Wittig reaction with the C_{17}-phosphonium salt **5**[10] furnished enyne **6**. Terminal C-alkylation of **6** with the C_3-bromo derivative **7**[11] and subsequent acid-catalyzed deprotection afforded alcohol **8**. Subjecting this to semi-hydrogenation over a P-2 Ni catalyst gave **9** which was oxidized with PCC to furnish the required aldehyde **10**.

For the asymmetric cyanohydrination of **10**, we first attempted a chemical route developed by Hayashi et al.[6] However, this led to a very poor yield (ca. 10–12%) of the product with equally disappointing enantioselectivity (ca. 15–20% ee). Consequently, an enzymatic protocol involving oxynitrilase was explored. The enzyme, available from various sources, is known to carry out cyanohydrination of especially aromatic aldehydes in a stereospecific fashion. For aliphatic substrates, however, only the almond meal derived oxynitrilase acts as an efficient catalyst. Hence, for the present study, we attempted the cyanohydrination of **10** with two different cyanide donors (HCN and acetone cyanohydrin) in the presence of crude almond meal as the oxynitrilase source. Unfortunately, however, there was no reaction in this case. Clearly the enzyme could not accommodate the chosen long chain substrate.

Against the above background, it seemed prudent to follow a lipase-catalyzed resolution strategy for the synthesis. The resolution could be attempted either by acylation of the racemic cyanohydrin, prepared chemically or by es-



Scheme 2 *Reagents and conditions:* (i) PCC/CH_2Cl_2/NaOAc (71%); (ii) $CH_3(CH_2)_{16}PPh_3Br$ (**5**)/$NaCH_2SOCH_3$ (49%); (iii) *n*-BuLi/THF/HMPA/THPO$(CH_2)_3$Br (**7**)/–78 °C, MeOH/PTS/Δ (70%); iv) H_2/P-2 Ni/ethylene diamine/EtOH (90%); v) $NaHSO_3$/NaCN/H_2O (62%); vi) HCl/Δ (91%); vii) Silica gel, vinyl acetate/PCL/CH_2Cl_2 (47%); viii) CH_2N_2/Et_2O (nearly quantitative); ix) MeI/HgO/toluene (71%); x) Alcoholic KOH (74%).

terification/acylation of the corresponding hydroxy acid/ester. Initially we decided to follow the former route. Consequently, the racemic cyanohydrin **11** was prepared[12] via an in situ reaction of the bisulfite adduct of **10** with NaCN. However, attempted acylation of **11** with vinyl acetate in the presence of *Pseudomonas cepacia* lipase (PCL) as the catalyst was abortive even in different solvents (hexane, THF and CH_2Cl_2).

Finally, we resorted to a lipase-catalyzed acylation of the hydroxy acid **12** which was prepared by hydrolysis of **11** with concentrated HCl. Compound **12** was not soluble even in moderately polar organic solvents like CH_2Cl_2, THF etc. which are good media for PCL-catalyzed acylation. Hence, we adopted a substrate immobilization strategy for its acylation. Earlier, similar protocols were used by us[13a] and Berger et al.[13b] for the acylation of sugars and diols, respectively. For this, **12** was first pre-adsorbed on silica gel and subjected to PCL-catalyzed acylation with vinyl acetate in CH_2Cl_2. This reaction furnished (*S*)-acetate **13** and (*R*)-**12** in 68% and 97% ee's, respectively. Earlier, PCL-catalyzed acetylation of a long chain 2-hydroxy acid has been reported[14] to furnish the (*S*)-acetate which showed a negative optical rotation. In the present case also, acetate **13** was levorotatory. Hence, in analogy with the previous report it was assigned *S*-configuration. The stereochemical assignment is in congruence with the Kazalauskas rule[15] which is used extensively for predicting the stereochemical outcome of lipase-catalyzed resolution of secondary alcohols. For the determination of % ee's, **12** was esterified to **14** with diazomethane and subsequently converted into its (*R*)-MTPA ester which was analyzed by ^{1}H NMR spectroscopy. From the integrations of its OMe singlets at δ = 3.61 and δ = 3.65, the % ee was determined. Likewise, the % ee of **13** was also determined after converting it into (*S*)-**12**. Consequently, using the method described earlier, compound **14** was methylated to give **15** which on alkaline hydrolysis gave the target acid (*R*)-**I**.

The IR spectra were scanned with a Nicolet 410 FT-IR spectrometer. The ^{1}H NMR spectra were recorded in $CDCl_3$ with a Bruker AC-200 (200 MHz) instrument. The optical rotations were measured using a Jasco DIP 360 polarimeter. The GLC analyses were carried out with a Shimadzu GC-16A chromatograph fitted with a stainless steel column and flame ionization detector using 3% OV-17 (2 m × 0.5 mm) column and a N_2 flow rate of 40 cm^3/min. Anhydrous reactions were carried out under Ar using freshly dried solvents. The organic extracts were dried over anhydrous Na_2SO_4.

O-Alkylation of Alcohols; General Procedure

A mixture of alcohol **1a–g** (1 mmol), electrophile (MeI or BnBr, 1.25 mmol) and HgO (1.5 mmol) in a solvent (15 mL, as specified in Table 1) was stirred at r.t. for the time specified in Table 1. For benzylation, Bu_4NI (10 mole%) was also added. The mixture was diluted with Et_2O, decanted and the organic solution concentrated in vacuo to obtain a residue which on column chromatography (silica gel) gave the pure alkylated products **2a–g**.

Pent-4-ynal (4)

To a stirred and cooled (0 °C) suspension of PCC (11.52 g, 0.053 mol) and anhyd NaOAc (0.435 g, 5.30 mmol) in CH_2Cl_2 (50 mL) was added alcohol **3** (3.0 g, 0.036 mol) in one portion. After stirring for 2 h, the mixture was diluted with anhyd Et_2O (50 mL), the supernatant was passed through a pad (2″) of silica gel and the column was eluted with Et_2O. The combined eluent was concentrated to give **4** which was sufficiently pure (cf. TLC) to be used as such for the next step; yield: 2.08 g (71%).

IR (film): 3300, 2725, 2100, 1730 cm^{-1}.

^{1}H NMR: δ = 2.18 (t, *J* = 1.5 Hz, 1 H), 2.3–2.6 (m, 4 H), 9.7 (t, *J* = 1.5 Hz, 1 H).

(5*Z*)-Docos-5-en-1-yne (6)

To a stirred solution of dimsyl anion (0.029 mol) [prepared from NaH (1.39 g, 50% suspension in oil, 0.029 mol)] in DMSO (60 mL) was added compound **5** (16.85 g, 0.029 mol) at r.t. After 1 h, the al-

dehyde **4** (2.0 g, 0.024 mol) in THF (30 mL) was added dropwise to the solution at 0 °C. Stirring was continued at r.t. for 24 h. The mixture was poured in ice-cooled water, extracted with hexane, the organic layer washed thoroughly with H_2O and brine, and concentrated in vacuo. The residue was re-dissolved in hexane, cooled to 0 °C, the solution filtered and the precipitate washed with cold hexane. The hexane solution was concentrated again in vacuo and the residue subjected to column chromatography (silica gel, hexane) to furnish **6**; yield: 3.63 g (49%).

IR (film): 3320, 3010, 2100, 1660 cm^{-1}.

^1H NMR: δ = 0.9 (dist. t, 3 H), 1.32 (br s, 28 H), 2.1–2.5 (m, 7 H), 5.3–5.5 (m, 2 H).

Anal. Calcd for $C_{22}H_{40}$: C, 86.76; H, 13.24. Found: C, 86.95; H, 13.44.

3-Bromo-1-tetrahydropyranyloxypropane (7)
Following a reported procedure,[16] propane-1,3-diol (15.0 g, 0.197 mol) was monobrominated with 48% aq HBr (33.30 mL, 0.197 mol) in C_6H_6 (200 mL) to give the bromohydrin; yield: 18.89 g (69%).

A solution of the above compound (18.0 g, 0.129 mol), dihydropyran (DHP) (10.88 g, 0.129 mol) and pyridinium *p*-toluenesulfonate (PPTS, 0.1 g) in CH_2Cl_2 (200 mL) was stirred at r.t. for 6 h. The reaction was quenched with 10% aq $NaHCO_3$, the organic layer separated and the aqueous portion extracted with $CHCl_3$. The combined organic extracts were washed with H_2O and brine, and dried. Removal of the solvent followed by column chromatography (silica gel, Et_2O–hexane, 0–5%) of the residue gave pure **7**;[11] yield: 25.02 g (87%).

IR (film): 1085, 1020, 990, 810 cm^{-1}.

^1H NMR: δ = 1.2–1.3 (m, 2 H), 1.6–1.9 (m, 6 H), 3.2–3.8 (m, 6 H), 4.6 (br s, 1 H).

(8*Z*)-Pentacos-8-en-4-yn-1-ol (8)
To a stirred and cooled (–25 °C) solution of **6** (3.5 g, 0.012 mol) in THF (30 mL) was added *n*-BuLi (7.7 mL, 1.5 M in hexane, 0.012 mol). After 0.5 h, HMPA (5 mL) was added at –78 °C, the mixture stirred for 15 min and bromide **7** (2.68 g, 0.012 mol) in THF (20 mL) was added. Stirring was continued at the same temperature for 4 h and at r.t. for 16 h. The mixture was poured in ice-cooled water, extracted with Et_2O, the organic layer washed with H_2O and brine, and concentrated in vacuo. The crude product was dissolved in MeOH (30 mL), *p*-toluenesulfonic acid (PTS, 0.05 g) was added and the solution was refluxed for 4 h. Most of the solvent was removed in vacuo, the residue taken up in Et_2O and washed with 10% aq $NaHCO_3$, H_2O and brine, and dried. Removal of the solvent followed by column chromatography (silica gel, EtOAc–hexane, 0–15%) of the residue gave pure **8**; yield: 2.93 g (70%).

IR (film): 3440, 3010, 1660 cm^{-1}.

^1H NMR: δ = 0.9 (dist t, 3 H), 1.38 (br s, partially D_2O exchangeable, 31 H), 2.14–2.32 (m, 4 H), 2.42–2.63 (m, 4 H), 3.65 (t, *J* = 6 Hz, 2 H), 5.3–5.5 (m, 2 H).

Anal. Calcd for $C_{25}H_{46}O$: C, 82.80; H, 12.78. Found: C, 82.63; H, 12.93.

(4*Z*,8*Z*)-Pentacosa-4,8-dien-1-ol (9)
To a mixture of P-2 Ni [prepared from $Ni(OAc)_2 \cdot 4H_2O$ (0.222 g, 8.83 mmol) and $NaBH_4$ (0.2 g, 5.26 mmol)] and ethylenediamine (EDA, 0.2 mL) in EtOH (15 mL) was added compound **8** (2.9 g, 8.01 mmol). The mixture was shaken under a slight positive pressure of hydrogen and after the required uptake of H_2, the mixture was passed through a pad of silica gel (2″) and the pad eluted with Et_2O. The combined eluents were concentrated to furnish pure **9**; yield: 2.62 g (90%).

IR (film): 3380, 3010, 1660 cm^{-1}.

^1H NMR: δ = 0.89 (dist t, 3 H), 1.37 (br s, 30 H), 1.9–2.3 (m, 8 H), 2.5 (s, D_2O exchangeable, 1 H), 3.68 (t, *J* = 6 Hz, 2 H), 5.2–5.5 (m, 4 H).

Anal. Calcd for $C_{25}H_{48}O$: C, 82.34; H, 13.27. Found: C, 82.59; H, 13.48.

(4*Z*,8*Z*)-Pentacosa-4,8-dienal (10)
As described earlier, compound **9** (2.7 g, 7.42 mmol) was oxidized with PCC (2.40 g, 11.14 mmol) in CH_2Cl_2 (30 mL) to give aldehyde **10**; yield: 2.15 g (80%).

IR (film): 3010, 2720, 1730, 1660 cm^{-1}.

^1H NMR: δ = 0.89 (dist. t, 3 H), 1.34 (br s, 28 H), 2.16–2.32 (m, 8 H), 2.39–2.45 (m, 2 H), 5.2–5.5 (m, 4 H), 9.78 (t, *J* = 1.5 Hz, 1 H).

Anal. Calcd for $C_{25}H_{46}O$: C, 82.80; H, 12.79. Found: C, 82.72; H, 12.94.

(5*Z*,9*Z*)-2-Hydroxyhexacosa-5,9-dienenitrile (11)
To a stirred solution of $NaHSO_3$ (0.775 g, 7.45 mmol) in H_2O (10 mL) was added aldehyde **10** (1.8 g, 4.97 mmol) in CH_2Cl_2 (30 mL). Immediately a white crystalline solid formed which was dissolved by adding H_2O (10 mL). To this solution was slowly added NaCN (0.365 g, 7.45 mmol) in H_2O (10 mL) so that the reaction temperature maintained at 0–5 °C. After stirring for 16 h at r.t. (cf. TLC), the mixture was extracted with $CHCl_3$, the organic layer washed with H_2O and brine, and dried. The residue obtained on concentration in vacuo was purified by column chromatography (silica gel, EtOAc–hexane, 0–15%) to give **11**; yield: 1.2 g (62%).

IR (film): 3420, 3020, 2220, 1660 cm^{-1}.

^1H NMR: δ = 0.88 (dist. t, 3 H), 1.36 (br s, partially D_2O exchangeable, 31 H), 2.1–2.4 (m, 8 H), 4.32 (t, *J* = 6 Hz, 1 H), 5.3–5.5 (m, 4 H).

Anal. Calcd for $C_{26}H_{47}NO$: C, 80.14; H, 12.16; N, 3.59. Found: C, 80.29; H, 12.24; N, 3.43.

(5*Z*,9*Z*)-2-Hydroxyhexacosa-5,9-dienoic Acid (12)
A solution of **11** (1.2 g, 3.08 mmol) and concd HCl (8.0 mL) was stirred for 16 h at r.t. and at 80 °C for 8 h. The residue was extracted with Et_2O, the extract was carefully washed with ice-cold water and brine, and dried. Removal of the solvent followed by column chromatography (silica gel, EtOAc–hexane, 0–10%) of the residue gave **12**; yield: 1.14 g (91%); mp 83–85 °C (Et_2O).

IR: 3700–3500, 3380, 1710 cm^{-1}.

^1H NMR: δ = 0.9 (dist. t, 3 H), 1.29 (br s, 30 H), 1.9–2.2 (m, 8 H), 2.6 (br s, D_2O exchangeable, 1 H), 4.45 (t, *J* = 6 Hz, 1 H), 5.2–5.4 (m, 4 H), 8.9 (br s, D_2O exchangeable, 1 H).

(2*S*,5*Z*,9*Z*)-2-(Acetyloxy)hexacosa-5,9-dienoic Acid (13)
A slurry of (+)-**12** (0.816 g, 2.0 mmol) and column grade silica gel (2.0 g) in Et_2O (10 mL) was shaken and the solvent evaporated in vacuo. A mixture of the resultant immobilized substrate, vinyl acetate (2.0 mL) and PCL (0.250 g) in CH_2Cl_2 (20 mL) was stirred at r.t. for 48 h. The reaction mixture was filtered and the residue thoroughly washed with Et_2O. The combined organic extracts were concentrated in vacuo and the residue chromatographed (silica gel, EtOAc–hexane, 0–10%) to furnish pure (*R*)-**12** and (*S*)-**13**.

(*S*)-**13**

Yield: 0.423 g (47%); mp 79 °C (Et_2O); $[\alpha]_D^{22}$ –5.95 (*c* 1.18, Et_2O).

IR (film): 3700–3500, 2884, 1740 cm^{-1}.

^1H NMR: δ = 0.9 (dist. t, 3 H), 1.32 (br s, 30 H), 2.07–2.24 (m containing a s at δ = 2.1, 7 H), 2.32–2.45 (m, 4 H), 4.78 (t, *J* = 6 Hz, 1 H), 5.2–5.4 (m, 4 H), 8.4 (br s, D_2O exchangeable, 1 H).

(*R*)-**12**

Yield: 0.286 g (35%); mp 89 °C (Et_2O); $[\alpha]_D^{22}$ +8.39 (*c* 0.93, Et_2O).

The spectral data were similar with those for the racemic sample.

Methyl (2*R*,5*Z*,9*Z*)-2-Hydroxyhexacosa-5,9-dienoate (14)
To a solution of CH_2N_2 in Et_2O was added drop wise (*R*)-**12** (0.2 g, 0.49 mmol) in Et_2O (10 mL) at 0 °C. Removal of solvent gave pure **14**; yield: 0.2 g (nearly quant.); mp 81–83 °C (Et_2O); $[\alpha]_D^{22}$ +8.12 (*c* 0.84, Et_2O).

IR (film): 3440, 2980, 1735 cm^{-1}.

^1H NMR: δ = 0.9 (dist t, 3 H), 1.29 (br s, 30 H), 1.9–2.2 (m, 8 H), 2.4 (br s, D_2O exchangeable, 1 H), 3.78 (s, 3 H), 4.41 (t, *J* = 6 Hz, 1 H), 5.2–5.4 (m, 4 H).

(2*R*,5*Z*,9*Z*)-2-Methoxyhexacosa-5,9-dienoic Acid (I)
A stirred suspension of HgO (0.204 g, 0.94 mmol), (*R*)-**14** (0.2 g, 0.47 mmol) and MeI (1.34 g, 9.49 mmol) in toluene (10 mL) was stirred at r.t. until the reaction was complete (38 h, cf. TLC). The mixture was diluted with Et_2O, filtered and the filtrate concentrated in vacuo. Preparative TLC (silica gel, EtOAc–hexane, 5%) of the residue gave pure **15**; yield: 0.147 g (71%).

IR (film): 2880, 1740, 1620, 1240 cm^{-1}.

^1H NMR: δ = 0.9 (dist. t, 3 H), 1.29 (br s, 30 H), 1.9–2.2 (m, 8 H), 3.65 (s, 3 H), 3.78 (s, 3 H), 4.42 (t, *J* = 6 Hz, 1 H), 5.2–5.4 (m, 4 H).

MS (70 eV): *m*/*z* (%) = 436 (M^+), 404 (M^+ – MeOH, 2.2), 377 (M^+ – CO_2Me, 3.4), 345 (3.1), 104 (100).

A mixture of **15** (0.140 g, 0.32 mmol) and alcoholic KOH (2 N, 7 mL) was stirred for 18 h at r.t. Most of the solvent was removed in vacuo, the residue dissolved in Et_2O and washed with H_2O and brine, and dried. Removal of solvent followed by preparative TLC (silica gel, EtOAc–hexane, 5%) of the residue gave pure (*R*)-**I**.

Yield: 0.100 g (74%); mp 78 °C (from Et_2O); $[\alpha]_D^{22}$ +8.62 (*c* 1.1, Et_2O).

IR (film): 3700–3500, 2880, 1708, 1220 cm^{-1}.

^1H NMR: δ = 0.9 (dist. t, 3 H), 1.29 (br s, 30 H), 1.9–2.2 (m, 8 H), 3.65 (s, 3 H), 4.45 (t, *J* = 6 Hz, 1 H), 5.2–5.4 (m, 4 H), 8.8 (br s, D_2O exchangeable, 1 H).

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