Asymmetric total synthesis of eicosanoid

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Dedicated to Dr. A. V. Rama Rao on the occasion of his 70th birthday
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Abstract
An asymmetric total synthesis of eicosanoid 4 starting from 2,2-dimethyl-(R)-1,3-dioxolane-4-carbaldehyde is described. The key steps involved for the synthesis include modified Simmons-Smith cyclopropanation, stereoselective reduction, ring-closing metathesis (RCM) and Nozaki-Hiyama-Kishi coupling reaction.

Keywords: Eicosanoid, lipoxygenase inhibitors, stereoselective, cyclopropanation, ring-closing metathesis

Introduction
As a part of defense mechanism, marine organisms produce a fascinating range of secondary metabolites endowed with unusual and unexpected biological profiles. The arachidonic acid pathway in marine organisms provided a number of oxylipins such as 1-3 containing the cyclopropyl-lactone groups.1 Eicosanoid 4 was isolated by the incubation of arachidonic acid with an acetone powder of the Caribbean soft coral Plexaura homomalla.2 In conjunction with other marine fatty acid metabolites (Figure 1),3 eicosanoid 4 also incorporate a cyclopropane-lactone motif and lipoxygenase inhibiting activity and therefore provoked a considerable synthetic interest.4a,g It is likely that the origin of eicosanoid 4 might have occurred from transformation analogous to that as constanolactones 3.2 To expedite current pharmaceutical evaluations of this family, we describe herein an asymmetric total synthesis of eicosanoid 4. Our synthetic protocol involved modified Simmons-Smith cyclopropanation, stereoselective reduction of ketone, ring-closing metathesis (RCM) and Nozaki-Hiyama-Kishi coupling reaction (Scheme 1).
Figure 1. Some cyclopropyl-lactone containing oxylipins.

Our interest for the synthesis of natural products in a concise manner following our general synthetic protocol, described herein is an efficient chiral pool approach taking 2,2-dimethyl-(R)-1,3-dioxolane-4-carbaldehyde 8 as the starting material as depicted in the retro-synthetic analysis (Scheme 1).

Scheme 1. Retrosynthetic analysis of Eicosanoid 4.
Results and Discussion

Following our earlier related work, D-glyceraldehyde was converted to cyclopropyl aldehyde with good overall yield. Allyl Grignard reaction on the resulting aldehyde afforded compound in a 1:1 diastereomeric mixture separable with difficulty by repeated column chromatography in 87% yield.

Scheme 2. Reagents and conditions.

This problem was however circumvented by subjected the homoallyl alcohol mixture to oxidation under 2-iodoxybenzoic acid (IBX) condition and selective reduction of the keto-compound with K-selectride provided the diastereomers in the ratio of 9:1. The diastereomers were separated by column chromatography. The selectivity in reduction was rationalized on the basis of chelation controlled Cram's model.
Interaction between cyclopropyl C-C bonds and carbonyl π orbitals is maximized when the cyclopropyl and carbonyl groups are oriented orthogonally. Both the bisect (S)-(cis) and (S)-(trans) conformation are able to provide maximum stabilization. Mark Lautens et al. reported that treatment of tributylsilyl cyclopropyl ketone with LiBH₄ resulted in a diastereomeric mixture of 2.5:1 and explained the stereoselectivity by proposing the following (S)-(cis) model. But S. Shuto and co-workers reported the reverse stereoselectivity with diisobutylaluminium hydride (DIBAL-H) (Figure 2) and it was explained by (S)-(trans) model. When DIBAL-H is coordinated to the carbonyl group, due to steric repulsion between the two bulky isobutyl group and the substituent in the cyclopropyl group, (S)-(trans) conformation is preferred. The same argument holds true in the case of K-selectride, which demands a lot of steric repulsion due to its three sec-butyl groups. The newly created secondary hydroxyl group bearing center was assigned following modified Mosher’s method. According to the method, the minor isomer 14b was converted to its (R)- and (S)-2-methoxy-2-(trifluoromethyl)-2-phenylacetic acid (MTPA) ester with corresponding 2-methoxy-2-(trifluoromethyl)-2-phenylacetic acid which showed negative chemical shift differences ($\Delta\delta = \delta_S - \delta_R$) for protons on C₁ through C₅ while protons on C₇ through C₉ showed positive differences, which is consistent with C₆ bearing an (R)-configuration (Figure 3). The major S-isomer was the result of the hydride attack from the less hindered Re-face in the (S)-(trans) conformation. Although this manipulation gave the desired product 14a along with 14b, the undesired intermediate was easily converted into 14a in 76% yields over two steps via standard Mitsunobu protocol.
The next job was to construct the six-membered lactone ring. The required isomer 14a was then treated with acryloyl chloride in CH₂Cl₂ to afford the ester 16 in 92% yield.

Ring-closing metathesis (RCM)¹⁰ was then attempted on 16. So, treatment of 16 with Grubbs’ first generation catalyst in refluxing CH₂Cl₂ provided after 36h the desired six-membered lactone 17 in 90% yield (Scheme 3). In ¹H NMR of compound 17, the frequency corresponding to olefinic protons appeared at 6.72 ppm as a multiplet and at 6.04 ppm as a doublet and other protons at their respective regions. ¹³C NMR was in consistent with the assigned structure and elemental analysis substantiated the proposed structure. Reduction of double bond, hydrolysis of acetonide ring followed by oxidation with NaIO₄ afforded the known intermediate 20 in good overall yield.⁴a

Scheme 3. Reagents and conditions.

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Figure 3. Δδ = (δ₅-δ₉) x 10³ for (R) - and (S)-MTPA esters of compound 14b.
Side chain C₁₀-C₂₀ of eicosanoid 4 was prepared starting from 1,4-butanediol. Following standard reaction conditions, (1E,5Z)-1-iodo-1,5-undecadiene 6 was obtained in six steps with 42% overall yield.¹¹

\[
\begin{align*}
\text{19} & \quad + \quad \text{6} \\
& \quad \xrightarrow{a} \quad \text{20} \\
& \quad \xrightarrow{b} \quad \text{4}
\end{align*}
\]

a) CrCl₂, NiCl₂ (catalytic), THF, 0°C, 24h, 82%. b) Dess-Martin periodinane, CH₂Cl₂, rt, 2h, 89%.

**Scheme 4.** Reagents and conditions.

The final job of our endeavor was the introduction of the side chain on the cyclopropyl-lactone main core which was achieved smoothly by subjecting compound 6 and 19 with chromium(II) chloride and catalytic amount of nickel(II) chloride to afford the corresponding allyl alcohol 20 in a 1:1 ratio (Scheme 4).¹² The total synthesis of eicosanoid 4 was completed by oxidation of the derived hydroxyl group with Dess-Martin periodinane¹³ in 89% yield and the obtained product was identical in all respect to the reported data of the eicosanoid 4.⁴g

**Conclusions**

In conclusion, we have achieved the total synthesis of eicosanoid 4 starting from 2,2-dimethyl-(R)-1,3-dioxolane-4-carbaldehyde. Modified Simmons-Smith cyclopropanation, stereoselective reduction, ring-closing metathesis (RCM) and Nozaki-Hiyama-Kishi reactions have been used successfully to construct the core cyclopropyl and lactone moiety. The strategy reported herein could be applied for getting different lactone as well as side chain motifs for a diversity oriented synthesis of the above natural products for pharmacological studies and work towards this end are underway in our laboratory and will be reported in due course.

**Experimental Section**

**General Procedures.** Solvents were purified and dried by standard procedures before use. Column chromatography was carried out with silica gel (60-120 mesh). NMR spectra were recorded on Bruker AC-200 and Bruker DRX-500 machine in CDCl₃ with TMS as internal standard. Mass spectra were obtained with Finningen MAT 1210 mass spectrometer. Optical rotations were measured with digital polarimeter. Elemental analysis was done on elemental analyzer model 1108 EA. All reactions were monitored on 0.25 mm E-Merck pre-coated silica gel (TLC) plates (60F-254) with UV or I₂, anisaldehyde reagent in ethanol. Petroleum ether refers to mixture of hexanes with bp 60-80 °C.
3-[2,2-Dimethyl-(4S)-1,3-dioxolan-4-yl]-(E)-2-propen-1-ol (10). To a solution of 9 (8.0g, 40.0 mmol) in CH₂Cl₂ was added DIBAL-H (40.84 ml, 1M solution in toluene) at –78 °C. The solution was stirred for 1h at same temperature and allowed to warm to 0 °C slowly. After completion of the reaction (monitored by TLC), MeOH (20 ml) was added slowly followed by the addition of cold aqueous saturated sodium potassium tartrate (50 ml). The biphasic mixture was stirred for further 2h and then partitioned. Aqueous layer was extracted with CH₂Cl₂ (2x70 ml). Combined organic extracts were dried over Na₂SO₄ and purified by silica gel column chromatography using ethyl acetate/petroleum ether (1:4) to obtain 5.43 g (86%) of pure allyl alcohol 10 as colorless viscous liquid. [$\alpha$]D = +32.5 (c 3.5, CHCl₃); ¹H NMR (200MHz): δ 1.35 (s, 3H), 1.40 (s, 3H), 2.80(br s, 1H), 3.56 (t, J = 6.2 Hz, 1H), 4.12 (m, 3H), 4.52 (m, 1H), 5.65 (m, 1H), 5.88 (m, 1H); Anal. Calcd for C₈H₁₄O₃ (158.20): C, 60.73; H, 8.91. Found: C, 60.24; H, 8.96.

(1E,4S)-tert-Butyl[3-(2,2-dimethyl-1,3-dioxolan-4-yl)-2-propenyl]oxydiphenylsilane (11). To a solution of allyl alcohol 10 (5.0g, 31.6 mmol) in CH₂Cl₂ (40 ml) was added imidazole (6.45g, 94.9 mmol) at 0 °C. The reaction mixture was then stirred for 15 min at the same temperature and tert-butylidiphenylchlorosilane (TBDPSCl) (9.65 ml, 38.0 mmol) was added. The reaction mixture was allowed to warm to room temperature and stirred overnight. After completion of the reaction (monitored by TLC), water (20 ml) was added to it. Organic layer was separated and aqueous layer was extracted with CH₂Cl₂ (2x50 ml). Combined organic extracts were washed successively with water and brine, dried over Na₂SO₄ and purified by silica gel column chromatography using 5% ethyl acetate/petroleum ether to afford 10.0g (80%) of pure silyl ether 11 as colorless liquid. [$\alpha$]D = +22.4 (c 1.2, CHCl₃); ¹H NMR (200 MHz): δ 0.98 (s, 9H), 1.25 (s, 3H), 1.34 (s, 3H), 3.46 (t, J = 6.7 Hz, 1H), 3.98 (m, 1H), 4.12 (d, J = 5.7 Hz, 2H), 4.30 (q, J = 6.6 Hz, 1H), 5.67 (m, 2H), 7.30 (m, 6H), 7.54 (m, 4H); Anal. Calcd for C₂₄H₃₂O₃Si (396.61): C, 72.68; H, 8.13. Found: C, 72.94; H, 8.42.

(1R,2R,4S)-tert-Butyl[2-(2,2-dimethyl-1,3-dioxolan-4-yl)cyclopropyl]methoxydiphenylsilane (12). Et₂Zn (142.5 ml, 115.9 mmol, 1M solution in hexane) was added dropwise to a clear solution of 11 (9.5g, 23.2 mmol) in CH₂Cl₂ (200 ml) at -78 °C. After 10 min, CH₂I₂ (9.3 ml, 115.9 mmol) was added through syringe. The reaction mixture was stirred at the same temperature for 4h and then at -10 °C for 20h. The reaction mixture was poured into a saturated solution of NH₄Cl. Organic layer was separated and aqueous layer was extracted with CH₂Cl₂ (2x100 ml). Combined organic extracts were washed successively with water and brine, dried over Na₂SO₄ and purified by silica gel column chromatography using ethyl acetate/petroleum ether (1:19-1:9) to give 9.34g (95%) of pure compound 12 as colorless liquid. [$\alpha$]D = -7.7 (c 1.4, CHCl₃); lit. ⁵ [$\alpha$]D = -7.9 (c 1.15, CHCl₃); ¹H NMR (200 MHz): δ 0.54 (m, 2H), 0.72 (m, 1H), 0.96 (m, 1H), 1.05 (s, 9H), 1.35 (s, 3H), 1.40 (s, 3H), 3.46 (m, 2H), 3.68 (m, 2H), 4.05 (m, 1H), 7.36 (m, 6H), 7.64 (m, 4H); Anal. Calcd for C₂₅H₃₄O₃Si (410.64): C, 73.12; H, 8.34. Found: C, 72.94; H, 8.76.

[2-(2,2-Dimethyl-(4S)-1,3-dioxolan-4-yl)-(1R,2R)-cyclopropyl]methanol (7). To a stirred solution of 12 (9.0g, 22.0 mmol) in THF (50 ml) at 0 °C, was added Bu₄NF (32.9 ml, 32.9 mmol, 1M solution in THF) dropwise and stirring was continued for 1h at 0 °C. The reaction mixture was then brought to room temperature and stirred overnight. The solvent was removed under reduced pressure and the crude product was purified by silica gel column chromatography using
ethyl acetate/petroleum ether (1:4) to afford 3.25g (86%) of pure compound 7 as colorless viscous liquid. \([\alpha]_D^0 = +16.5 (c 1.25, \text{CHCl}_3); \]^1H NMR (200 MHz): \(\delta 0.63 (m, 2H), 0.87 (m, 1H), 1.01 (m, 1H), 1.33 (s, 3H), 1.37 (s, 3H), 2.68(br s, 1H), 3.34 (m, 1H), 3.55 (m, 3H), 4.05 (m, 1H);\) Anal. Calcd for C_9H_{16}O_3 (172.23): C, 62.76; H, 9.36. Found: C, 62.84; H, 9.72.

\(2-[2,2-\text{Dimethyl-(4S)-1,3-dioxolan-4-yl}]-[1R,2R]-\text{cyclopropanecarbaldehyde} (13).\) To a stirred solution of 2-iodoxybenzoic acid (IBX) (7.81g, 27.9 mmol) in DMSO (20 ml), was added a solution of 7 (3.2g, 18.6 mmol) in THF (10 ml) at room temperature and stirring was continued for further 4h. After completion of the reaction (monitored by TLC), water (10 ml) was added to the reaction mixture, precipitated solid was filtered off and the filtrate was diluted with water (50 ml) and extracted with ether (4x50 ml). The combined organic layers were washed successively with aqueous NaHCO_3, water, brine and dried over Na_2SO_4. The solvent was removed under reduced pressure and the crude product was purified by silica gel column chromatography using ethyl acetate/petroleum ether (1:6) to afford 2.97g (94%) of pure cyclopropyl aldehyde 13 as colorless liquid. \[^1H\text{NMR (200 MHz): }\delta 1.25 (m, 2H), 1.35 (s, 3H), 1.40 (s, 3H), 1.65 (m, 1H), 1.87 (m, 1H), 3.68 (t, \(J = 6.2\) Hz, 1H), 3.84 (m, 1H), 4.10 (m, 1H), 9.18 (d, \(J = 6.2\) Hz, 1H);\) Anal. Calcd for C_9H_{14}O_3 (170.21): C, 63.50; H, 8.28. Found: C, 62.94; H, 8.36.

**Grignard reaction.** To an ice cooled solution of aldehyde 13 (2.9g, 17.0 mmol) in ether (20 ml) was added dropwise to an ethereal solution of allyl magnesium bromide [prepared from allyl bromide (2.94 ml, 34.0 mmol) and Mg (1.22g, 51.0 mmol) in ether (50 ml)] and stirring was continued for 3h at room temperature. The reaction mixture was then quenched with 5% HCl (20 ml) and extracted with ethyl acetate (3x50 ml). The combined organic layers were washed successively with aqueous NaHCO_3, water, brine and dried over Na_2SO_4. The solvent was removed under reduced pressure and the crude product was purified by silica gel column chromatography using ethyl acetate/petroleum ether (1:4) to afford 3.14g (87%) of homoallyl alcohol diastereomers 14.

\(1-\{2-[2,2-\text{Dimethyl-(4S)-1,3-dioxolan-4-yl}]-[1R,2R]-\text{cyclopropyl}\}-3\text{-buten-1-one} (15).\) To a stirred solution of 2-iodoxybenzoic acid (IBX) (4.95g, 17.7 mmol) in DMSO (30 ml), was added a solution of homoallyl alcohol 14 (2.50g, 11.8 mmol) in THF (20 ml) at room temperature and stirring was continued for further 3h. After completion of the reaction (monitored by TLC), water (10 ml) was added to the reaction mixture, precipitated solid was filtered off and the filtrate was diluted with water (50 ml) and extracted with ether (4x50 ml). The combined organic layers were washed successively with aqueous NaHCO_3, water, brine and dried over Na_2SO_4. The solvent was removed under reduced pressure and the crude product was purified by silica gel column chromatography using ethyl acetate/petroleum ether (1:9) to afford 2.23g (90%) of pure cyclopropyl ketone 15 as colorless liquid. \([\alpha]_D^0 = -59.7 (c 1.30, \text{CHCl}_3); \]^1H NMR (200 MHz): \(\delta 1.08 (m, 1H), 1.26 (m, 1H), 1.34 (s, 3H), 1.40 (s, 3H), 1.63 (m, 1H), 1.98 (m, 1H), 3.32 (dd, \(J = 1.5, 6.2\) Hz, 2H), 3.66 (t, \(J = 7.4\) Hz, 1H), 3.87 (dd, \(J = 6.6, 8.1\) Hz, 1H), 4.08 (dd, \(J = 6.6, 8.1\) Hz, 1H), 5.19 (m, 2H), 5.93 (m, 1H); \[^{13}C\text{NMR (50 MHz): }\delta 14.2, 24.2, 25.6, 26.5, 26.6, 48.5, 69.1, 76.2, 109.3, 118.9, 130.5, 206.7;\) Anal. Calcd for C_{12}H_{18}O_3 (210.27): C, 68.54; H, 8.63. Found: C, 69.22; H, 8.45.

\(1-\{2-[2,2-\text{Dimethyl-(4S)-1,3-dioxolan-4-yl}]-[1R,2R]-\text{cyclopropyl}\}-3\text{-buten-1-ol} (14a \text{ and } 14b).\) To a stirred solution of 15 (1.0g, 4.8 mmol) in THF (30 ml), was added K-selectride (7.42
ml, 7.4 mmol, 1M solution in THF) at −78 °C, and stirred for 2h at the same temperature. Methanol was added and the reaction mixture was brought to room temperature. After removal of the solvent at reduced pressure, the residue was treated with 2M NaOH solution (15 ml), extracted with ethyl acetate (2×50 ml). Combined organic layers were dried over Na₂SO₄ and concentrated to afford the crude product, which on flash chromatographic separation using ethyl acetate/petroleum ether (1:4) to afford 792mg of major isomer 14a and 88mg of minor isomer 14b.

1-{2-[(2,2)-Dimethyl-(4S)-1,3-dioxolan-4-yl]-(1R,2R)-cyclopropyl}-(1S)-3-buten-1-ol (14a). 1H NMR (200 MHz): δ 0.40-0.70 (m, 2H), 0.77-1.06 (m, 2H), 1.28 (s, 3H), 1.44 (s, 3H), 2.19 (br s, 1H), 2.30 (m, 2H), 3.05 (m, 1H), 3.65 (m, 2H), 4.06 (m, 1H), 5.10 (m, 2H), 5.84 (m, 1H); 13C NMR (50 MHz): δ 7.9, 18.7, 21.6, 25.6, 26.7, 41.7, 69.2, 73.8, 79.1, 108.9, 118.0, 134.3; Anal. Calcd for C₁₂H₂₀O₃ (212.29): C, 67.89; H, 9.49. Found: C, 68.24; H, 9.57.

1-{2-[(2,2)-Dimethyl-(4S)-1,3-dioxolan-4-yl]-(1S,2S)-cyclopropyl}-(1R)-3-buten-1-ol (14b). 1H NMR (200 MHz) δ 0.60 (m, 2H), 0.86 (m, 2H), 1.28 (s, 3H), 1.42 (s, 3H), 1.68 (br s, 1H), 2.30 (m, 2H), 3.07 (m, 1H), 3.60 (m, 2H), 4.16 (m, 1H), 5.15 (m, 2H), 5.84 (m, 1H); 13C NMR (50 MHz): δ 7.5, 18.6, 21.3, 25.6, 26.7, 41.7, 69.1, 73.5, 79.1, 108.9, 117.9, 134.4; Anal. Calcd for C₁₂H₂₀O₃ (212.29): C, 67.89; H, 9.49. Found: C, 67.55; H, 9.26.

Mitsunobu reaction. To a solution of 14b (1.2g, 5.66 mmol) in THF (30 ml) was added PPh₃ (4.45g, 17.0 mmol) and p-nitrobenzoic acid (2.84g, 17.0 mmol) and the resultant mixture was cooled to 0 °C. To it, diethyl azodicarboxylate (DEAD) (3.13 ml, 19.8 mmol) diluted with THF (5 ml) was added dropwise. The reaction mixture was then brought to room temperature and stirred overnight. After removal of the solvent, the residue was taken in CH₂Cl₂ and was washed successively with aqueous NaHCO₃, water, brine, and dried over Na₂SO₄. The solvent was removed under reduced pressure and the crude product was dissolved in MeOH and treated with K₂CO₃ (0.3g). The solid was then filtered off, filtrate concentrated and the residue was purified by silica gel column chromatography using ethyl acetate/petroleum ether (1:4) to afford 0.91g (76% after two steps) of pure homoallyl alcohol 14a.

(S)-2-Methoxy-2-(trifluoromethyl)-2-phenylacetic acid (MTPA) ester. To a solution of 14b (20mg, 0.1 mmol) in CH₂Cl₂ (2 ml) was added (S)-2-methoxy-2-(trifluoromethyl)-2-phenylacetic acid (S-MTPA) (35mg, 0.16 mmol) N, N-dicyclohexyl carbodiimide (DCC) (30 mg, 0.17 mmol) and catalytic amount of 4-dimethylaminopyridine (DMAP). The reaction mixture was stirred overnight at room temperature. The solid was filtered off, filtrate concentrated and the residue was purified by silica gel column chromatography using ethyl acetate/petroleum ether (1:5) to afford 0.91g (76% after two steps) of pure homoallyl alcohol 14a.

(R)-2-Methoxy-2-(trifluoromethyl)-2-phenylacetic acid (MTPA) ester. To a solution of 14b (20mg, 0.1 mmol) in CH₂Cl₂ (2 ml) was added (R)-2-methoxy-2-(trifluoromethyl)-2-phenylacetic acid (R-MTPA) (35mg, 0.16 mmol), DCC (30mg, 0.17 mmol) and catalytic amount of DMAP. The reaction mixture was stirred overnight at room temperature. The solid was filtered off, filtrate concentrated and the residue was purified by silica gel column chromatography using ethyl acetate/petroleum ether (1:19) to afford 35mg (80%) of pure (R)-
MTPA ester. $^1$H NMR (200 MHz): $\delta$ 0.74 (m, 1H), 0.80 (m, 1H), 1.06 (m, 2H), 1.32 (s, 3H), 1.41 (s, 3H), 2.44 (m, 2H), 3.61 (m, 5H), 4.03 (m, 1H), 4.60 (m, 1H), 5.06 (m, 2H), 5.61 (m, 1H), 7.40 (m, 3H), 7.54 (m, 2H).

1[2-(2,2-Dimethyl-1,3-dioxolan-4-yl)cyclopropyl]-3-butenyl acrylate (16). Acryloyl chloride (0.12 ml, 1.4 mmol) was added dropwise to a solution of allyl alcohol 14a (0.2 g, 0.9 mmol) and triethylamine (0.4 ml, 2.8 mmol) in CH$_2$Cl$_2$ (15 ml) at 0 °C. After stirring for 2h at 0 °C, the reaction was quenched with saturated aqueous NaHCO$_3$ (5 ml), poured into brine (10 ml) and extracted with dichloromethane (2x15 ml). The combined extracts were dried over Na$_2$SO$_4$, concentrated under reduced pressure, and the residue was purified over neutral alumina using ethyl acetate/petroleum ether (1:9) to furnish ester 16 (0.196 g, 92%) as a colorless oil.

* The ester was found to be unstable in CDCl$_3$ and was used directly for the next reaction.

6-[2-(2,2-Dimethyl-1,3-dioxolan-4-yl)cyclopropyl]-5,6-dihydro-2H-pyran-2-one (17). To a stirred solution of 16 (0.17 g, 0.6 mmol) in CH$_2$Cl$_2$ (80 ml) was added Ti(i-OPr)$_4$ (0.3 mL, 0.3 mmol) and refluxed for 1h. Then the temperature of the reaction mixture was brought to room temperature and a solution of bis-(tricyclohexylphosphine)[benzylidene]ruthenium(IV) dichloride (18 mg, 0.06 mmol) in dichloromethane was added dropwise over 15 min at the same temperature. After refluxing for 36h, the solvent was removed under vacuum and the residue was purified by silica gel column chromatography using ethyl acetate/petroleum ether (1:9) to afford six-membered lactone 17 (0.136 g, 90%) as a colorless liquid. $[^{25}\alpha]D$ = -55.00 (c 0.95, CHCl$_3$); $^1$H NMR (200 MHz): $\delta$ 0.62 (m, 1H), 0.78 (m, 1H), 1.12 (m, 2H), 1.33 (s, 3H), 1.41 (s, 3H), 2.47 (m, 2H), 3.68 (m, 1H), 3.78 (m, 2H), 4.10 (dd, 1H, $J$ = 5.9, 8.0 Hz), 6.02 (d, 1H, $J$ = 9.5 Hz), 6.87 (dt, 1H, $J$ = 4.4, 9.5 Hz). $^{13}$C NMR (50 MHz): $\delta$ 6.7, 18.8, 19.2, 25.4, 26.5, 29.2, 69.0, 69.0, 77.7, 80.6, 108.6, 121.3, 144.5, 163.5; Anal. Calcd for C$_{13}$H$_{18}$O$_4$ (238.28): C, 65.53; H, 7.61. Found: C, 65.32; H, 8.07.

6-[2-(2,2-Dimethyl-1,3-dioxolan-4-yl)cyclopropyl]tetrahydro-2H-pyran-2-one (5). Palladium charcoal (20 mg) was added to a stirred solution of 17 (0.2 g, 0.84 mmol) in ethyl acetate (15 ml) under hydrogen atmosphere at room temperature. After completion of the reaction (monitored by TLC), the reaction mixture was passed through a pad of silica gel and the solvent was evaporated to dryness under reduced pressure to afford pure reduced product 5 (0.19 g, 94%) as a colorless oil. $[^{25}\alpha]D$ = +8.45 (c 1.15, CHCl$_3$); $^1$H NMR (500 MHz): $\delta$ 0.60 (dt, 1H, $J$ = 5.0, 8.2 Hz), 0.74 (dt, 1H, $J$ = 5.5, 8.7 Hz), 0.99 (m, 1H), 1.32 (s, 3H), 1.08 (m, 1H), 1.40 (s, 3H), 1.67 (m, 1H), 1.81 (m, 1H), 1.94 (m, 1H), 2.02 (m, 1H), 2.44 (ddd, 1H, $J$ = 6.9, 8.7, 1.8 Hz), 2.55 (dt, 1H, $J$ = 17.4, 6.9 Hz), 3.66 (m, 2H), 3.75 (t, 1H, $J$ = 7.8 Hz), 4.09 (dd, 1H, $J$ = 6.4, 8.3 Hz); $^{13}$C NMR (125 MHz): $\delta$ 6.6, 18.2, 19.2, 19.7, 25.4, 26.5, 27.7, 29.2, 69.0, 77.8, 83.0, 108.6, 170.6; Anal. Calcd for C$_{13}$H$_{20}$O$_4$ (240.30): C, 65.53; H, 8.71. Found: C, 64.63; H, 8.48.

6-[2-(1,2)-Dihydroxyethyl)cyclopropyl]tetrahydro-2H-pyran-2-one (18). A solution of 5 (0.25 g, 1.0 mmol) in 80% aqueous AcOH: H$_2$O (3:3 ml) was stirred at room temperature for 3h. The reaction mixture was then diluted with CH$_2$Cl$_2$ (20 ml) cooled to 0 °C and neutralized to pH 7 by adding solid NaHCO$_3$ in small portions. The layers were then separated, aqueous layer extracted with CH$_2$Cl$_2$ (2x15 ml) and the combined organic extracts were washed sequentially with water and brine. After drying over Na$_2$SO$_4$ and removal of solvent under reduced pressure, the residue was column chromatographed using ethyl acetate/petroleum ether (1:1) to afford the diol 18 (0.16 g, 75%) as a colorless viscous liquid.
2-(6-Oxotetrahydro-2H-pyran-2-yl)cyclopropanecarbaldehyde (19). To a vigorously stirred solution of 18 (0.1g, 0.5 mmol) in CH₂Cl₂ (10 ml), added in one lot suspension of NaIO₄ supported on silica gel (1.5g) in CH₂Cl₂ (10 ml) at 0 °C. After stirring at the same temperature for 0.5h, the solid was removed by filtration, washed with CH₂Cl₂ (10 ml), combined filtrates were concentrated under vacuum and the residue filtered through a pad of silica gel column using ethyl acetate/petroleum ether (1:3) to afford the aldehyde 19 (0.08g, 94%) as a colorless liquid.

* This aldehyde was found to decompose on storage and was used immediately for the next reaction.

6-[2-(1-Hydroxy-2,6-dodecadienyl)cyclopropyl]tetrahydro-2H-pyran-2-one (20). To a mixture of 19 (0.04g, 0.2 mmol) and 6 (0.4g, 1.4 mmol), which had been thoroughly dried, were added degassed dimethyl formamide (10 ml), chromium(II) chloride (0.18g, 1.4 mmol), and nickel(II) chloride (catalytic). The green colored solution was stirred at room temperature for 24h and was poured into saturated NH₄Cl. Ether was then added to the resulting mixture and extracted with ether (2x20 ml), the combined organic phases were dried over Na₂SO₄ and the solvent was removed under reduced pressure.

* Compound 20 was found to be unstable at room temperature, so we proceeded for the next reaction without purification.

6-[2-(2,6-Dodecadienoyl)cyclopropyl]tetrahydro-2H-pyran-2-one (4). To a stirred solution of 20 (0.09g, 0.28 mmol) in CH₂Cl₂ (10 ml) was added Dess-Martin periodinane (0.24g, 0.56 mmol) at 0 °C and the suspension was stirred at room temperature for 2h. The reaction mixture was quenched with water and filtered through a sintered funnel. The residue was washed with CH₂Cl₂ (2x5 ml). The organic layer was separated and aqueous layer was extracted with CH₂Cl₂ (2x5 ml). The combined extracts were dried over Na₂SO₄, and the solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography using ethyl acetate and petroleum ether (1:9) to afford 4 (0.078g, 89%) as a colorless liquid. [α]D₂⁵ = -25.76 (c 0.60, CHCl₃); lit.⁴g [α]D = -27.40 (c 0.46, CHCl₃); ¹H NMR (500 MHz): δ 0.89 (t, 3H, J = 6.5 Hz), 0.97 (m, 1H), 1.29 (m, 7H), 1.71 (m, 2H), 1.83 (m, 1H), 1.95 (m, 1H), 2.03 (m, 3H), 2.26 (m, 5H), 2.48 (m, 1H), 2.55 (m, 1H), 3.88 (m, 1H), 5.33 (m, 1H), 5.43 (m, 1H), 6.25 (d, 1H, J = 16.0 Hz), 6.94 (dt, 1H, J = 15.6, 6.9 Hz); ¹³C NMR (125 MHz): δ 13.9, 14.1, 18.5, 22.6, 23.5, 25.9, 27.3, 28.2, 28.3, 29.5, 29.6, 31.6, 32.7, 81.5, 127.8, 130.8, 131.5, 147.5, 170.5, 197.8; MS: m/z (%) 351(M⁺ + MeOH, 90), 337(M⁺ + H₂O, 100); Anal. Calcd for C₂₀H₃₀O₃ (318.42): C, 75.43; H, 9.50. Found: C, 75.12; H, 9.83.

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References