PREVIOUS SYNTHETIC APPROACHES

Herein, a brief account of the previous works carried out on the total synthesis of Pyrenophorol by various groups has been documented.

**Zwanenburg approach**

**Scheme 2 : Retrosynthetic approach of 1**

Zwanenburg et al,\(^{10}\) reported the first stereoselective synthesis of \((-)\)-pyrenophorol (1) using the photo induced rearrangement of an \(\alpha,\beta\)-epoxy diazomethyl ketone to 4-hydroxy-2-alkenoate as the key step. Their synthetic approach was based on the two successive lactonisation steps of acid 7, which could be in turn obtained from the allylic alcohol 8.

**Scheme 3 : Reagents and conditions:**

A. L-\((+)-DET, \, t\)-BuOOH, Ti(OiPr)$_2$, CH$_2$Cl$_2$, 77%; B. RuO$_4$, CH$_3$CN:CCl$_4$:H$_2$O = 2:2:3, ClCOO-i-Bu, Et$_3$N, CH$_2$N$_2$, 63%; C. \(hv\), MeOH, TBDMSCl, Imidazole, DMF, 60%; D. K$_2$CO$_3$, Allyl alcohol, 66%; E. NaOMe, MeOH, 0 °C, 87%; F. ethyl vinyl ether, PPTS, CH$_2$Cl$_2$, 98%; G. LiOH, THF:H$_2$O=1:1, 97%.

The key intermediate 9 was obtained from 8 by a chirality inducing Sharpless epoxidation, subsequent oxidation to the acid and further conversion into the corresponding epoxydiazomethyl ketone. Then a photo-induced rearrangement of this ketone gave the alkenoate which was protected as it silyl ether 7.
Allylic ester 10 was obtained by transesterification of 7, while the ethoxy ethyl protected acid 11 was obtained from 7 by the deprotection of 4-hydroxyl group, subsequent protection as ethoxy ethyl group and further hydrolysis of the ester.

Scheme 4 : Reagents and conditions:

A. DCC, DMAP, CH₂Cl₂, 75%; B. MgBr₂, Et₂O, 94%; C. Pd(PPh₃)₄, morpholin, THF, 77%; D. 2,6-Cl₂C₆H₃C(O)Cl, Et₃N, DMAP, toluene, reflux, 79%; E. n-Bu₄NF, THF, 95%.

The half-lactone 12 was obtained by the DCC coupling of fragments 10 and 11, which on removal of the ethoxy ethyl and allyl protecting functions gave the seco acid 13. Macrolactonisation and desilylation of 13 gave the target compound 1.

**Kibayashi approach**

Kibayashi and co-workers¹⁴ reported the second enantioselective synthesis of (–)-pyrenophorol 1 by the macrolactonisation of the seco acid 14 under mitsunobu conditions. The seco acid 14 could be obtained from the enantiopure (R R)-diepoxide 15.

Scheme 5 : Retrosynthetic approach of 1

Synthesis of the seco acid started with the addition of 1 eq of Vitride to the diepoxide 15 resulting in the corresponding epoxy alcohol which was protected as its silyl ether to furnish 16. Then a further epoxide opening by Grignard reagent gave the unsaturated alcohol 17.
O-mesylation of 17 followed by oxidation with RuO₄ gave the carboxylic acid which on treatment with KHCO₃ in aqueous methanol resulted in cyclisation to give the γ-lactone 18 as a single diastereomer. In this cyclization, the stereochemistry at C-4 was inverted due to SN₂ reaction.

Scheme 6: Reagents and conditions:

A. Vitride (1 mol), THF, 0 °C to rt; B. TBDPSCI, DMAP, CH₂Cl₂, rt; C. Vinyl magnesium chloride, Cul, THF, -15 °C; D. MsCl, Et₃N, CH₂Cl₂, 0 °C; E. RuO₄, CCl₄-CH₃CN-H₂O, rt; F. KHCO₃, MeOH-H₂O, rt, 10 min; G. 1 M LiN(SiMe₃)₂ in THF, THF-HMPA, -78 °C, then PhSSPh, THF, -78 °C; H. 20% aq NaOH, MeOH, rt, then CH₂N₂, Et₂O 0 °C; I. mCPBA, -20 °C; J. Py (2 equiv), toluene, reflux; K. 2,3-dihydropyron, CSA. CH₂C₁₂; L. 20% aq NaOH, MeOH, rt; M. t-Bu₄NF, THF, Reflux; N. Ph₃P. DEAD, Toluene-THF (10:1). -25 °C, 10 h; O. TsOH-H₂O, MeOH, rt.

Treatment of the enolate of 18 with diphenyl disulfide followed by hydrolysis and esterification resulted in the α-phenylthio-γ-hydroxyester 19. Oxidation of 19 to sulfoxide followed by pyrolysis gave the (E)-α, β-unsaturated hydroxy ester 20. Tetrahydropyranyl protection and subsequent hydrolysis and desilylation furnished the seco acid 14.

When the hydroxyl acid 14 was exposed to Mitsunobu conditions, macrolactonization took place with complete inversion of chirality at C-4 to give the dimerised product 21, which on removal of O-protecting groups gave the target compound 1.
The promising biological properties and structural features of Pyrenophorol 1 have prompted us to develop a new and efficient synthetic route for the total synthesis of this macrolide.

The retrosynthetic route is outlined in scheme 7. (–)-Pyrenophorol (1) was foreseen to be synthesized by an intermolecular Mitsunobu cyclization of seco acid 22, which in turn could be obtained by olefin metathesis of allylic alcohol 23 with methyl acrylate. The allylic alcohol 23 could be derived via the Wittig olefination and Sharpless asymmetric epoxidation of the TBDPS ether 24 of the commercially available lactate ester.

**Scheme 7 : Retrosynthetic approach of 1**

The synthesis of pyrenophorol (1) began with the DIBAL-H reduction of the TBDPS ether 24 in dry CH₂Cl₂ at -78 °C that gave the corresponding aldehyde which was immediately subjected to 2-carbon Wittig olefination with Ph₃PCHCOOEt in benzene under reflux conditions to give the unsaturated ester 25 in 92% yield over two steps. A 95:5 mixture of E:Z isomers were formed which could be separated by column chromatography. Formation of 25 was confirmed from its ¹H NMR spectrum which showed a dd at 6.92 and a doublet at 6.08 integrating for one proton each that correspond to the protons attached to the olefinic carbons. Their coupling constant of $J_{CH-CH} = 15.1$ Hz ascertained the trans geometry of the olefin. ¹H NMR spectrum also showed the protons resonating at 4.09 as a quartet and at 1.25 as a triplet that correspond to the ester function. The ¹³C spectrum also displayed the peaks corresponding to olefinic carbons at 151.0 and 119.1. Formation of 25 was further confirmed by ESI-MS which showed the (M+H)+ peak at 383.

Reduction of the olefin 25 using NaBH₄ in the presence of NiCl₂ gave the saturated ester 26 in 90% yield. Formation of 26 was ascertained by the disappearance of signals at δ 6.92 and 6.08 in its ¹H NMR spectrum, and at 151.0 and 119.1 in its ¹³C
NMR that correspond to the unsaturation. ESI-MS spectrum also showed the (M+H)$^+$ peak at 385, thereby confirming the reduction of 26.

**Scheme 8 : Reagents and conditions:**

A. (i) DIBAL-H, CH$_2$Cl$_2$, -78 °C, 15 min; (ii) Ph$_3$PCHCOOEt, benzene, reflux, 1 h, 92% (2 steps); B. NaBH$_4$, NiCl$_2$·6H$_2$O, MeOH, 0 °C, 1 h, 90%; C. (i) DIBAL-H, CH$_2$Cl$_2$, -78 °C, 15 min; (ii) Ph$_3$PCHCOOEt, benzene, reflux, 1 h, 94% (2 steps).

Partial reduction of ester 26 with DIBAL-H in CH$_2$Cl$_2$ at -78 °C followed by another 2-carbon Wittig olefination of the resulting aldehyde with Ph$_3$PCHCOOEt in benzene gave the unsaturated ester 27 in 94% yield (E:Z=95:5). Formation of 27 was confirmed by its $^1$H NMR spectrum which displayed a multiplet in 6.81-6.92 region and a doublet at 5.73 corresponding to the protons attached to the olefinic carbons. $^{13}$C spectrum too revealed the peaks at 149.1 and 121.1 corresponding to these olefinic carbons. The FTIR spectrum showed the carbonyl absorption frequency at 1721 cm$^{-1}$ and the ESI-MS spectrum displayed the (M+H)$^+$ peak at 411 to confirm the product.

**Scheme 9 : Reagents and conditions:**

A. DIBAL-H, CH$_2$Cl$_2$, 0 °C, 1 h, 92%; B. (+)-DIPT, Ti(O$i$Pr)$_4$, Molecular sieves, TBHP, CH$_2$Cl$_2$, -20 °C, 7 h, 78%; C. (i) TPP, Imidazole, I$_2$, THF:CH$_3$CN (4:1), 30 min; (ii) Zn dust, MeOH, reflux, 12 h, 82% (2 steps).

DIBAL-H reduction of the unsaturated ester 27 in CH$_2$Cl$_2$ at 0 °C furnished the allylic alcohol 28 in 92% yield. Formation of 28 was confirmed by the disappearance of the peaks at 4.17 and 1.28 in its $^1$H NMR spectrum and of absorption at 1721 cm$^{-1}$ in its FTIR spectrum corresponding to the ester function. ESI-MS spectrum also confirmed this by displaying the (M+H)$^+$ peak at 369.

Allylic alcohol 28 was then subjected to Sharpless asymmetric epoxidation using (+)-DIPT, Ti(O$i$Pr)$_4$ and TBHP in anhydrous CH$_2$Cl$_2$ at -20 °C to get the epoxy alcohol 29 in 78% yield. Epoxidation was confirmed by the upfield shifting of the
multiplet in the $^1$H NMR spectrum from 5.50-5.56 region to the 2.79-2.87 region. $^{13}$C NMR spectrum also displayed a shift in resonances from 133.1 and 128.8 to 68.7 and 58.4 respectively. Further, ESI-MS spectrum showed a peak at 407 that corresponds to (M+Na)$^+$. 

Epoxy alcohol 29 was then treated with TPP, imidazole and iodine to get the iodo compound which was immediately subjected to epoxide opening with Zn dust in methanol under refluxing conditions to furnish the allylic alcohol 23 in 82% yield over 2 steps. The structure of 23 was confirmed on the basis of $^1$H NMR which showed two multiplets in 5.72-5.87 region and 5.04-5.21 region that correspond to the protons of the terminal olefin. $^{13}$C NMR spectrum too showed the presence of olefinic carbons as expected, while the ESI-MS spectrum displayed the (M+H)$^+$ peak at 369.

Scheme 10: Reagents and conditions:

A. Methyl acrylate, Grubbs II$^{nd}$ generation catalyst, CH$_2$Cl$_2$, reflux, 24h, 78%; B. (i) 3,4-dihydropyran, CSA, CH$_2$Cl$_2$, rt, 1h, 88%; (ii) 20% aq. NaOH, MeOH, rt, 30 min, 85%; C. Bu$_4$NF, THF, 60 °C,2h, 90%.

Alllylic alcohol 23 was subjected to olefin cross metathesis with methyl acrylate using Grubbs II$^{nd}$ generation catalyst in CH$_2$Cl$_2$ under reflux conditions to give the coupled enoate 30 in 78% yield. Use of Grubbs I$^{st}$ generation catalyst at this stage increased the reaction time and also reduced the yield of the product considerably. So the II$^{nd}$ generation catalyst was preferred for the cross metathesis. A negligible amount of cis isomer was formed which could be separated by column chromatography. Formation of 30 was confirmed by the ESI-MS spectrum which showed the (M+H)$^+$ peak at 427, while the $^1$H NMR spectrum displayed the signals corresponding to the
internal olefin at 6.90 and 6.02 and those of methyl ester at 3.75. The FTIR spectrum too displayed strong absorption corresponding to the carbonyl stretching at 1724 cm⁻¹.

The hydroxyl group in the enoate 30 was protected as its tetrahydropyranyl ether with CSA and then subjected to basic hydrolysis with 20% aq. NaOH in MeOH to furnish the acid 32 in 85% yield. The disappearance of the signal due to the methyl ester in ¹H NMR and the appearance of signals due to the THP group confirmed the product. The ¹³C NMR too showed the signals corresponding to the THP group, while the ESI-MS spectrum displayed the (M-H)⁺ peak at 495.

Then the desilylation of 32 was carried out with Bu₄NF in THF to afford the seco acid 22 in 90% yield which was now ready for the key Mitsunobu cyclization. The ¹H and ¹³C NMR spectra showed the absence of signals corresponding to the TBDPS group, while the ESI-MS spectrum displayed the (M+Na)⁺ peak at 281, thereby confirming the desilylation.

**Scheme 11 : Reagents and conditions:**

A. Ph₃P, DEAD, toluene:THF (10:1), -25 °C, 24 h, 60%; B. PTSA, MeOH, rt, 30 min, 96%.

The stage was now set for the intermolecular Mitsunobu cyclisation of 22 which was carried out by Gerlach’s procedure¹⁵ using TPP and DEAD in toluene:THF (10:1) resulting in macrolactonisation with complete inversion of configuration at C-4 to give 33. Formation of the cyclized product 33 was confirmed by the ESI-MS and ESI-HRMS spectra which showed the (M+Na)⁺ peak at 503.2601 as compared to the calculated mass of 503.2620. The FTIR spectrum too was devoid of any strong absorption due to free OH groups, thereby confirming the macrolactonisation.

Finally, removal of the THP group in 33 with PTSA in methanol furnished the target macrolide 1 as a white solid in 96% yield. The final product 33 was confirmed by the studying its ¹H NMR spectrum, which showed the absence of protons corresponding to THP protection and a strong absorption at 3382 cm⁻¹ in FTIR spectrum proved the presence of free hydroxyl.
groups. The spectral data and optical rotation of (−)-Pyrenophorol (1) were also compared with the literature values and were found to be identical in all respects.

CONCLUSION

In conclusion, we have developed an efficient new route for the synthesis of (−)-Pyrenophorol (1) featuring Sharpless asymmetric epoxidation, olefin cross metathesis and intermolecular Mitsunobu cyclization starting from the readily available lactate ester, following a simple an efficient route ensuring no compromise in the yield of the target molecule at any stage.
(S,E)-ethyl 4-(tert-butyldiphenylsilyloxy)pent-2-enoate (25):

DIBAL-H (11.6 mL, 11.6 mmol, 1.0M solution in toluene) was added dropwise to a solution of ester 24 (3.60 g, 10.51 mmol) in CH$_2$Cl$_2$ (45 mL) at -78 °C and stirred for 15 min at the same temperature. The reaction mixture was then quenched by adding saturated aqueous sodium potassium tartrate solution (20 mL) followed by vigorous stirring for 1 h. The aqueous phase was then extracted with CH$_2$Cl$_2$ (3 × 30 mL) and the combined organic layers were washed with brine (10 mL), dried over Na$_2$SO$_4$ and the solvent removed in vacuo. The crude aldehyde thus obtained was dissolved in benzene (50 mL) and Ph$_3$PCHCOOEt (4.35g, 12.5 mmol) was added and the reaction mixture was refluxed for 1 h. Then the reaction was quenched by adding H$_2$O (20 mL), and the aqueous phase was extracted with EtOAc (3 × 30 mL). The combined organic layers were dried over Na$_2$SO$_4$, solvent removed in vacuo and the residue was purified by SiO$_2$ gel flash chromatography (1% EtOAc/hexane) to give 25 (3.66 g, 92% yield) as a colorless oil.

$[\alpha]_D^{25}$ : $-39.6$ (c 2.0, CHCl$_3$);

IR (Neat) : $\nu_{\text{max}}$ 3071, 2965, 2931, 2860, 1736, 1473, 1427, 1376, 1267, 1177, 1135, 1110, 1029, 997, 822, 742, 701 cm$^{-1}$;

$^1$H NMR (CDCl$_3$, 300 MHz) : $\delta$ 7.66-7.73 (m, 4H), 7.33-7.44 (m, 6H), 6.92 (dd, $J = 15.1$, 4.7 Hz, 1H), 6.08 (d, $J = 15.1$ Hz, 1H), 4.40-4.44 (m, 1H), 4.09 (q, $J = 7.5$ Hz, 2H), 1.25 (t, $J = 7.1$ Hz, 3H), 1.04-1.08 (m, 12H);

$^{13}$C NMR (CDCl$_3$, 75 MHz) : $\delta$ 166.4, 151.0, 135.6, 134.1, 129.8, 129.4, 127.5, 127.4, 119.1, 68.6, 60.2, 26.9, 23.2, 19.2, 14.2;

ESI-MS : $m/z$: 383 (M+H)$^+$;

(S)-ethyl 4-(tert-butyldiphenylsilyloxy)pentanoate (26):

To a solution of 25 (3.542 g, 9.27 mmol) in anhydrous MeOH (30 mL) at 0 °C was added NiCl$_2$.6H$_2$O (0.66 g, 2.78 mmol) and NaBH$_4$ (0.70 g, 18.54 mmol) portion wise,
and was stirred at same temperature for 1h. Then the reaction mixture was filtered through celite, organic phase was concentrated and the residue was purified by SiO2 gel flash chromatography (1% EtOAc/hexane) to give 26 3.205 g, 90% yield) as a colorless oil.

\[ \alpha \] D<sub>25</sub> : -6.2 (c 2.0, CHCl₃);

IR (Neat) : \( \nu_{\text{max}} \) 3071, 2959, 2931, 2856, 1722, 1656, 1472, 1428, 1367, 1272, 1152, 1110, 1051, 980, 822, 740, 702 cm⁻¹;

\(^1\)H NMR (CDCl₃, 300 MHz) : \( \delta \) 7.66-7.73 (m, 4H), 7.33-7.44 (m, 6H), 4.10 (q, \( J = 7.5 \) Hz, 2H), 3.92-3.94 (m, 1H), 2.38 (t, \( J = 7.5 \) Hz, 1H), 2.37 (t, \( J = 7.5 \) Hz, 1H), 1.78 (m, 2H), 1.23 (t, \( J = 7.1 \) Hz, 3H), 1.03-1.08 (m, 12H);

\(^13\)C NMR (CDCl₃, 75 MHz) : \( \delta \) 173.6, 136.2, 134.0, 129.6, 129.4, 127.5, 127.4, 68.4, 60.0, 34.5, 30.0, 27.2, 23.0, 19.2, 14.1;

ESI-MS : m/z: 385 (M+H)<sup>+</sup>;

(S,E)-ethyl 6-(tert-butyldiphenylsilyloxy)hept-2-enoate (27):

DIBAL-H (9.5 mL, 9.5 mmol, 1.0M solution in toluene) was added dropwise to a solution of ester 26 (3.083 g, 8.03 mmol) in CH₂Cl₂ (35 mL) at -78 °C and stirred for 15 min at the same temperature. The reaction mixture was then quenched by adding saturated aqueous sodium potassium tartrate solution (20 mL) followed by vigorous stirring for 1h. The aqueous phase was then extracted with CH₂Cl₂ (3 x 30 mL) and the combined organic layers were washed with brine (10 mL), dried over MgSO₄ and the solvent removed in vacuo. The crude aldehyde thus obtained was dissolved in benzene (30 mL) and Ph₃PCHCOOEt (3.436 g, 9.875 mmol) was added and the reaction mixture was refluxed for 1h. Then the reaction was quenched by adding H₂O (15 mL), and the aqueous phase was extracted with EtOAc (3 x 20 mL). The combined organic layers were dried over MgSO₄, solvent removed in vacuo and the residue was purified
by SiO$_2$ gel flash chromatography (1% EtOAc/hexane) to give 27 (2.53 g, 94% yield) as a colorless oil.

[$\alpha$]$_D^{25}$: $-19.4$ (c 2.75, CHCl$_3$);

IR (Neat): $\nu_{\text{max}}$ 2953, 2859, 1721, 1269, 1172, 1045, 738, 703, 618 cm$^{-1}$;

$^1$H NMR (CDCl$_3$, 300 MHz): $\delta$ 7.64-7.69 (m, 4H), 7.33-7.46 (m, 6H), 6.81-6.92 (m, 1H), 5.73 (d, $J = 15.6$ Hz, 1H), 4.17 (q, $J = 14.3$, 7.1 Hz, 2H), 3.82-3.91 (m, 1H), 2.16-2.26 (m, 2H), 1.50-1.66 (m, 2H), 1.28 (t, $J = 7.1$ Hz, 3H), 1.03-1.08 (m, 12H);

$^{13}$C NMR (CDCl$_3$, 75 MHz): $\delta$ 149.1, 149.0, 135.8, 129.6, 129.4, 127.5, 127.4, 121.1, 68.7, 60.3, 37.4, 27.8, 27.0, 23.1, 14.2;

ESI-MS: $m/z$: 411 (M+H)$^+$;

**(S,E)-6-(tert-butyldiphenylsilyloxy)hept-2-en-1-ol (28):**

A solution of compound 27 (2.30 g, 5.609 mmol) in CH$_2$Cl$_2$ (25 mL) was cooled to 0 °C and DIBAL-H (1M solution in toluene, 14.0 mL, 14.0 mmol) was slowly added over 10 min under N$_2$ atmosphere. After addition was complete, stirring was continued for 1h at 0 °C. The reaction mixture was then carefully quenched with saturated aqueous solution of potassium sodium tartrate solution (25 mL) and the mixture was stirred vigorously for 1h. The aqueous phase was then extracted with CH$_2$Cl$_2$ (3 × 30 mL) and the combined organic layers were washed with brine (10 mL), dried over MgSO$_4$, the solvent removed in vacuo and the crude product was subjected to SiO$_2$ gel flash chromatography (10% EtOAc/hexane) to give the alcohol 28 (1.899 g, 92%) as a colorless liquid.

[$\alpha$]$_D^{25}$: $-11.4$ (c 2.5, CHCl$_3$);
Chapter III, Section B, Experimental Section

IR (Neat) : $\nu_{\text{max}}$ 3380, 3069, 2930, 2857, 1665, 1464, 1427, 1375, 1188, 1107, 1050, 1003, 972, 821, 739, 703, 611, 507 cm$^{-1}$;

$^1$H NMR (CDCl$_3$, 300 MHz) : $\delta$ 7.63-7.70 (m, 4H), 7.34-7.45 (m, 6H), 5.50-5.56 (m, 2H), 3.98-4.03 (m, 2H), 3.79-3.89 (m, 1H), 1.99-2.09 (m, 2H), 1.40-1.63 (m, 2H), 1.00-1.11 (m, 12H);

$^{13}$C NMR (CDCl$_3$, 75 MHz) : $\delta$ 135.9, 133.1, 129.4, 128.8, 127.5, 127.4, 68.9, 63.7, 38.7, 27.9, 27.0, 23.1, 19.2;

ESI-MS : $m/z$: 369 (M+H)$^+$;

((2S,3R)-3-((S)-3-(tert-butyldiphenylsilyloxy)butyl)oxiran-2-yl)methanol (29):

To a stirred suspension of 4Å molecular sieves (10 g) in dry CH$_2$Cl$_2$ (250 mL) under N$_2$ was added L-(+)-diisopropyl tartrate (0.127 mL, 0.606 mmol, 0.12 equiv) in one portion. The mixture was cooled to -20 °C and Ti(OiPr)$_4$ (0.148 mL, 0.502 mmol, 0.1 equiv) was added in one portion. After 10 min, t-BuO$_2$H (8.69 M solution in CH$_2$Cl$_2$, 1.16 mL, 10.04 mmol, 2 equiv) was added dropwise over 5 min. The mixture was stirred at -20 °C for 30 min whereafter a solution of allylic alcohol 28 (1.858 g, 5.05 mmol) in dry CH$_2$Cl$_2$ (50 mL) was added dropwise over 30 min. The reactants were stirred at -20 °C for 7h and then quenched with H$_2$O (10 mL). EtOAc (100 mL) was added and the reaction mixture was allowed to warm to room temperature. The organic layer was separated and washed with H$_2$O (50 mL), dried over anhydrous MgSO$_4$, and filtered. Following evaporation of the solvent in vacuo, the residue was purified by SiO$_2$ flash chromatography (15% EtOAc/hexane) to give 29 (1.51 g, 78%) as a colorless oil.

$[\alpha]_D^{25}$ : $-6.0$ (c 1.0, CHCl$_3$)

IR (Neat) : $\nu_{\text{max}}$ 3424, 3069, 2927, 2856, 1740, 1463, 1427, 1376, 1262, 1107, 1047, 1002, 877, 821, 739, 703, 611 cm$^{-1}$;
1H NMR (CDCl₃, 300 MHz) : δ 7.64-7.71 (m, 4H), 7.32-7.47 (m, 6H), 3.80-3.95 (m, 2H), 3.51-3.59 (m, 1H), 2.79-2.87 (m, 2H), 1.49-1.66 (m, 2H), 1.30-1.33 (m, 2H), 1.01-1.10 (m, 12H);

13C NMR (CDCl₃, 75 MHz) : δ 135.8, 129.6, 129.5, 127.5, 127.4, 69.0, 68.7, 61.6, 58.4, 35.2, 29.7, 27.0, 23.1, 19.2;

ESI-MS : m/z: 385 (M+H)+;

(3S,6S)-6-(tert-butyldiphenylsilyloxy)hept-1-en-3-ol (23):

To a vigorously stirred solution of epoxy alcohol 29 (1.5 g, 3.90 mmol) in dry THF:CH₃CN (4:1, 30 mL) was added imidazole (1.59 g, 23.4 mmol), Ph₃P (2.93 g, 11.2 mmol) and I₂ (2.84 g, 11.2 mmol) in successive single portions. Stirring was continued at rt for 30 min whereupon Et₂O (20 mL) was added to precipitate out Ph₃P=O. The solids were filtered through a short pad of SiO₂ and the filtrate was concentrated in vacuo to obtain the crude iodo epoxide. To a vigorously stirred solution of this iodo epoxide in MeOH (25 mL) was added Zn dust (2.61 g, 40 mmol) and the reaction mixture was refluxed for 12h. After cooling to rt, it was filtered through a short pad of celite, washed well with MeOH and the filtrate was concentrated in vacuo. Purification of the residue by SiO₂ gel flash chromatography (10% EtOAc/hexane) furnished allylic alcohol 23 (1.08 g, 82%) as a colorless oil.

[α]D²⁵ : -5.8 (c 1.0, CHCl₃);

IR (neat) : νmax 3420, 3067, 2926, 2859, 1108, 871, 844, 819, 737, 704, 665, 610 cm⁻¹;

1H NMR (CDCl₃, 300 MHz) : δ 7.63-7.72 (m, 4H), 7.34-7.45 (m, 6H), 5.72-5.87 (m, 1H), 5.04-5.21 (m, 2H), 4.16-4.23 (m, 1H), 3.46-3.56 (m, 1H), 1.46-1.81(m, 7H), 1.05 (s, 9H);

13C NMR (CDCl₃, 75 MHz) : δ 139.1, 135.6, 129.4, 127.5, 127.3, 115.7, 73.5, 71.2, 33.1, 31.4, 28.6, 26.9, 21.2;
(4S,7S,E)-methyl 7-(tert-butyldiphenylsilyloxy)-4-hydroxyoct-2-enoate (30):

To a solution of 23 (0.505 g, 1.372 mmol) in CH₂Cl₂ (50 mL), Grubbs II nd generation catalyst (0.058 g, 0.067 mmol) was added and the reaction mixture was refluxed for 24 h under N₂ atmosphere. Most of the solvent was then distilled off and the concentrated solution left to stir at room temperature for 2h under open air in order to decompose the catalyst. The reaction mixture was evaporated to dryness to give a brown residue, which was purified by SiO₂ flash chromatography (15% EtOAc/hexane) to give 30 as colorless syrup (0.456 g, 78% yield).

[α]D⁰ : −15.5 (c 0.35, CHCl₃);

IR (Neat) : \( \nu_{\text{max}} \) 3447, 2925, 2855, 1724, 1657, 1461, 1432, 1376, 1272, 1168, 1108, 1045, 820, 738, 703, 611, 506 cm⁻¹;

\(^1\)H NMR (CDCl₃, 300 MHz) : \( \delta \) 7.65-7.70 (m, 4H), 7.34-7.44 (m, 6H), 6.90 (ddd, \( J = 1.5, 15.8 \) Hz, 1H), 6.02 (dt, \( J = 1.5, 15.8 \) Hz, 1H), 4.18-4.26 (m, 1H), 3.91 (q, \( J = 12.0, 6.0 \) Hz, 1H), 3.75 (s, 3H), 1.52-1.64 (m, 4H), 1.2 (d, \( J = 6.2Hz \) 3H), 1.05 (s, 9H);

\(^13\)C NMR (CDCl₃, 75 MHz) : \( \delta \) 150.4, 150.3, 135.8, 129.6, 127.6, 127.4, 119.7, 71.1, 69.1, 51.6, 34.2, 31.6, 29.7, 27.0, 22.3;

ESI-MS : \( m/z \) 427 (M+H)⁺;


3,4-Dihydropyran (0.414 g, 4.93 mmol) was added to a solution of 30 (0.42 g, 0.98 mmol) in CH₂Cl₂ (10 mL) followed by CSA (0.023 g, 0.1mmol) and the reaction mixture was stirred at rt for 1h. The solvent and excess dihydropyran were removed \textit{in vacuo} and the crude product was purified by SiO₂ flash chromatography (5%
EtOAc/hexane) to give the protected alcohol, 31 as colorless syrup. This was then dissolved in MeOH (10 mL) and treated with 20% aqueous NaOH (2 mL) for 30 min. Then the reaction mixture was neutralized by the addition of dil HCl, MeOH was evaporated in vacuo and the aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with brine (10 mL), dried over MgSO₄ and the solvent removed in vacuo. The crude product was then subjected to SiO₂ gel flash chromatography (40% EtOAc/hexane) to give acid 32 (0.363 g, 85%) as a colorless liquid.

\[ \alpha_d^{25} \]: −10 (c 0.65, CHCl₃);

IR (neat) : \( \nu_{\text{max}} \) 3424, 2923, 2854, 1703, 1655, 1460, 1376, 1265, 1122, 1108, 1072, 1044, 1026, 980, 811, 771, 738, 705, 609 cm⁻¹;

\(^1\)H NMR (CDCl₃, 300 MHz) : \( \delta \) 7.60-7.67 (m, 4H), 7.29-7.41 (m, 6H), 6.75-6.83 (m, 1H), 5.85 (d, \( J = 15.8 \) Hz, 1H), 4.49-4.61 (m, 1H), 4.14-4.20 (m, 1H), 3.69-3.89 (m, 2H), 3.36-3.47 (m, 1H), 1.38-1.86 (m, 10H), 1.07 (d, \( J = 6.1 \) Hz, 3H), 1.04 (s, 9H);

\(^13\)C NMR (CDCl₃, 75 MHz) : \( \delta \) 170.5, 150.4, 135.8, 129.5, 129.4, 129.3, 127.3, 127.2, 121.6, 95.9, 74.6, 74.3, 74.1, 69.1, 62.2, 62.1, 34.6, 30.9, 30.7, 30.5, 30.4, 29.6, 29.0, 27.0, 25.4, 25.3, 23.0, 19.2;

ESI-MS : \( m/z \): 495 (M-H)⁺;


To a solution of 32 (0.350 g, 0.709 mmol) in dry THF (40 mL) was added Bu₄NF (1.0 M in THF, 0.85 mL, 0.85 mmol) at 0 °C, and then the mixture was stirred for 2h at room temperature. The reaction was quenched with saturated aqueous NH₄Cl. The organic layer was separated, and the aqueous layer was extracted with EtOAc (3 × 30 mL). The combined organic layers were dried over anhydrous MgSO₄, filtered, and
concentrated in vacuo. The crude product was purified by SiO₂ gel flash chromatography (70% EtOAc/hexane) to afford 22 (0.164 g, 90% yield) as a yellow liquid.

\[ \alpha \] \text{D}^{25} : +4.0 \ (c \ 0.5, \ CHCl₃);

IR (Neat) : \( \nu_{\text{max}} \) 3424, 2923, 2852, 1702, 1459, 1378, 1266, 1122, 1072, 1026, 982, 810, 771 cm\(^{-1}\);

\(^1\)H NMR (CDCl₃, 300 MHz) : \( \delta \) 6.79-7.07 (m, 1H), 5.94-6.13 (m, 1H), 4.73-4.77 (m, 1H), 4.55-4.59 (m, 1H), 4.33-4.44 (m, 1H), 3.9 (t, J=7.36 Hz, 2H), 1.97-2.11 (m, 2H), 1.46-1.88 (m, 8H), 1.2 (d, J= 6.2Hz, 3H);

\(^{13}\)C NMR (CDCl₃, 75 MHz) : \( \delta \) 170.5, 150.8, 120.1, 97.3, 74.8, 67.9, 60.3, 33.9, 30.6, 29.9, 25.2, 23.4, 19.2;

ESI-MS : m/z: 281 (M+Na);

\((3E,5S,8R,11E,13S,16R)-8,16$\text{-dimethyl-5,13-bis(tetrahydro-2H-pyran-2-yloxy)-1,9-dioxacyclohexadeca-3,11-diene-2,10-dione (33)}:\)

To a solution of 22 (0.130 g, 0.503 mmol) in dry toluene:THF (20:1, 80 mL), was added triphenylphosphine (0.660 g, 2.515 mmol) at -40 °C under argon atmosphere. To this mixture was added DEAD (0.437 g, 2.515 mmol) at same temperature and the reaction mixture was stirred at -25 °C for 24h. Then the solvent was removed in vacuo and the residue was subjected to SiO₂ gel flash chromatography (25% EtOAc/hexane) to afford 33 (0.072 g, 60%) as a yellow liquid.
[α]D$^{25}$ : +7.5 (c 0.75, CHCl₃);

IR (neat) : $\nu_{\text{max}}$ 2924, 2854, 1749, 1718, 1647, 1459, 1373, 1271, 1073, 1271, 1073, 1026, 987, 868, 764 cm⁻¹;

$^1$H NMR (CDCl₃, 300 MHz) : δ 6.54-6.81 (m, 2H), 5.78-5.88 (m, 2H), 4.99-5.09 (m, 2H), 4.65-4.70 (m, 1H), 4.45-4.49 (m, 1H), 3.99-4.18 (m, 4H), 3.69-3.85 (m, 1H), 3.36-3.47 (m, 1H), 1.72-1.84 (m, 4H), 1.41-1.56 (m, 4H), 1.12-1.32 (m, 18H);

$^{13}$C NMR (CDCl₃, 75 MHz) : δ 165.0, 146.3, 122.8, 96.5, 73.9, 69.5, 64.0, 30.7, 29.7, 28.8, 25.3, 19.2, 18.4, 14.3, 14.1;

ESI-MS : m/z: 503 (M+Na)$^+$;

HRMS : calcd for C$_{26}$H$_{40}$O$_8$Na : 503.2620, found : 503.2601;


To a stirred suspension of 15 (0.026 g, 0.054 mmol) in CH₃OH (1.5 mL) was added PTSA (0.001 g, 0.005 mmol) and the reaction mixture was stirred at room temperature for 30 min. Then the solvent was evaporated in vacuo and the crude product was purified by SiO₂ gel flash chromatography (40% EtOAc/hexane) to afford 1 (0.015 g, 96% yield) as a white solid.

Mp : 136-138 °C;

[α]D$^{25}$ : −3.2 (c 0.25, Acetone);

IR (KBr) : $\nu_{\text{max}}$ 3382, 2924, 2854, 1713, 1647, 1274, 1173, 1119 cm⁻¹
$^1$H NMR (CDCl$_3$, 300 MHz) : $\delta$ 6.83 (dd, $J=15.6$ Hz, 2H), 5.89 (dd, $J = 15.6$ Hz, 2H), 5.01-5.10 (m, 2H), 4.16-4.24 (m, 2H), 2.48-2.69 (m, 2H), 1.53-2.01 (m, 8H), 1.20 (dd, $J = 6.8$ Hz, 6H);

$^{13}$C NMR (CDCl$_3$, 75 MHz) : $\delta$ 165.0, 149.3, 122.0, 70.3, 69.7, 30.4, 28.8, 18.2;

ESI- MS : m/z : 335 (M+Na)$^+$;


$^1$H NMR SPECTRUM OF COMPOUND 25

$^{13}$C NMR SPECTRUM OF COMPOUND 25
ESI-MS SPECTRUM OF COMPOUND 25
$^1$H NMR SPECTRUM OF COMPOUND 26

$^{13}$C NMR SPECTRUM OF COMPOUND 26
ESI-MS SPECTRUM OF COMPOUND 26
$^1$H NMR SPECTRUM OF COMPOUND 27

$^{13}$C NMR SPECTRUM OF COMPOUND 27
$^1$H NMR SPECTRUM OF COMPOUND 28

$^{13}$C NMR SPECTRUM OF COMPOUND 28
FTIR SPECTRUM OF COMPOUND 28

User: Admin
Sample: YVR-V-10
Inj. Volume: 5.000
Data Name: C:\LCMSolution\User\Data\YVR-V-10-APCI-POS1.qld
Method Name: C:\LCMSolution\User\Method\esi.lnpm

LC-MS SPECTRUM OF COMPOUND 28
$^1$H NMR SPECTRUM OF COMPOUND 29

$^{13}$C NMR SPECTRUM OF COMPOUND 29
FTIR SPECTRUM OF COMPOUND 29

ESI-MS SPECTRUM OF COMPOUND 29
$^1$H NMR SPECTRUM OF COMPOUND 23

$^{13}$C NMR SPECTRUM OF COMPOUND 23
LC-MS SPECTRUM OF COMPOUND 23
$^1$H NMR SPECTRUM OF COMPOUND 32

$^{13}$C NMR SPECTRUM OF COMPOUND 32
LCMS SPECTRUM OF COMPOUND 32
$^1$H NMR SPECTRUM OF COMPOUND 22

$^{13}$C NMR SPECTRUM OF COMPOUND 22
FTIR SPECTRUM OF COMPOUND 22

ESI-MS SPECTRUM OF COMPOUND 22
$^1$H NMR SPECTRUM OF COMPOUND 33

$^{13}$C NMR SPECTRUM OF COMPOUND 33
FTIR SPECTRUM OF COMPOUND 33

ESI-MS SPECTRUM OF COMPOUND 33
$^1$H NMR SPECTRUM OF COMPOUND 1

$^{13}$C NMR SPECTRUM OF COMPOUND 1
FTIR SPECTRUM OF COMPOUND 1

ESI-MS SPECTRUM OF COMPOUND 1