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Total Synthesis of (+)-petromyroxol *via* tandem α-aminoxylation-allylation and asymmetric dihydroxylation-S_N2 cyclization approach†‡

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The total synthesis of (+)-petromyroxol, a tetrahydrofuran (THF)-diol fatty acid, isolated from sea lamprey larvae (Petromyzon marinus) is reported. The present synthesis employs a tandem α-aminoxylation-allylation, cross metathesis and tandem asymmetric dihydroxylation-S_N2 cyclization as key steps.

Acetogenins, an important class of compounds containing tetrahydrofuran ring systems (Fig 1), were isolated from Annonaceae plants. They are known to exhibit a wide range of biological activities such as antifeedant, antitumor, immunosuppressive and most significantly pesticidal and pheromonal activities.[1] This interesting biological profile along with varied structural features of the acetogenin family has aroused a lot of research interest in the synthesis of this class of compounds among the organic chemists worlwide.[2] Isolation of one such mono acetogenin, petromyroxol containing a single THF ring has been reported recently by Li *et al*.[3] Petromyroxol was known to have a possible biochemical role in study of communication among the sea lamprey, which are parasitic fish that have known to cause damage to the fish population especially in Great lakes area of North America. Significant efforts have been made to maintain the ecological balance and minimize the havoc caused by these invasive species.

Towards this, many strategies have been employed to control the growth of sea lamprey and one such study was to understand the olfactory responses in these species. A non-racemic mixture of petromyroxol (2.9 mg) has been isolated from >100 000 L of water conditioned with the larvae of *Petromyzon marinus*. The (+)-enantiomer was found to be just 0.9 mg (~ 36%) of the isolated mixture, nevertheless, was found to trigger a better olfactory response among the lamprey fish than it's (–)-antipode. The scarcity of the material has hampered further research in this area. The use of sex pheromones as a tool for biological control of pests has been under active consideration and along these lines petromyroxol is expected be a part of sex pheromones,[3] of sea lamprey and could possibly help in development of eco-friendly pest controlling agents.

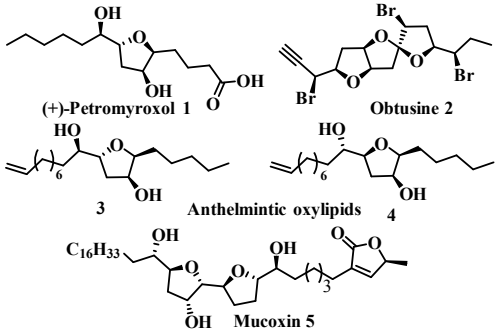

Figure 1: Some of the acetogenins based natural products

In recent years organocatalysis has emerged as a powerful tool box in the area of developing new methodologies and its application to the synthesis of biologically important natural products.[4] It compliments both the metal catalysis and expensive protein catalysis.[5] Proline is extensively used as organocatalyst since it is commercially available in both the enantiomeric forms.[6] It has an advantage of operational simplicity, moisture tolerance and often products are obtained with high *ee*.

Petromyroxol is structurally interesting molecule with trisubstituted tetrahydrofurandiol. The construction of stereochemically defined THF ring has always been a major challenge which is evident from various literature reports.[2] The attractive structural features of petromyroxol along with biological importance and its low abundance drew our attention towards its synthesis. Accordingly we devised a simple and efficient route to (+)-petromyroxol via organocatalytic tandem process. While, the first synthesis of petromyroxol was reported by Boyer[7a] using a protocol based on

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† Dedicated to Professor Richard R. Schmidt on the occasion of his 80th birthday

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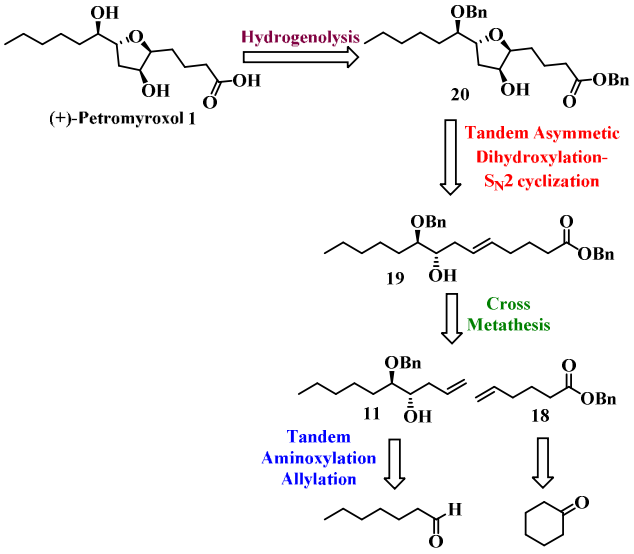
rhodium catalyzed denitrogenation and rearrangement of a 1-sulfonyl-1,2,3-triazole,[7b-c] Ramana *et al*. described its synthesis from carbohydrate using a chiral pool approach.[7d] Herein we report our successful endeavors towards the total synthesis of **1** employing proline catalyzed tandem α-aminoxylation-allylation, cross-metathesis and tandem asymmetric dihydroxylation-S_N2 cyclization as key steps.

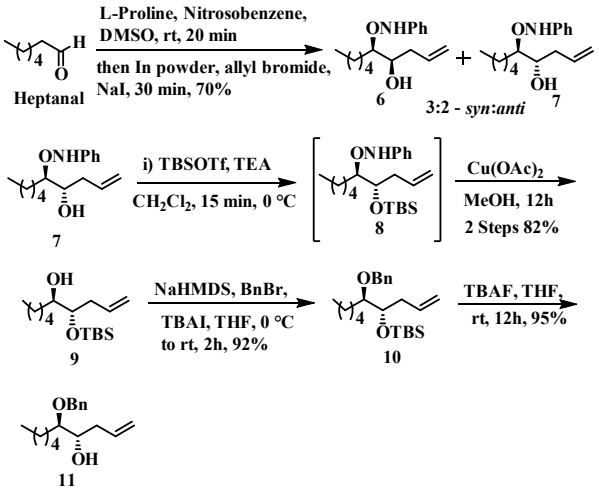


Scheme 1: Retrosynthetic analysis of (+)-petromyroxol **1**

Our synthetic strategy for the synthesis of **1** is outlined in scheme 1. We envisioned that the target molecule could be achieved by hydrogenolysis of THF diol **20**. The key tri-substituted THF moiety could be constructed diastereoselectively by using tandem asymmetric dihydroxylation-S_N2 cyclization of an olefin **19** which in turn could be derived from the cross metathesis of ester **18** and homoallylic alcohol **11**. The homo allylic alcohol **11** could be synthesized from commercially available heptanal via oragano catalytic tandem α-aminoxylation-allylation protocol[8] developed by Zhong. The ester fragment **18** could be readily accessible from cyclohexanone.

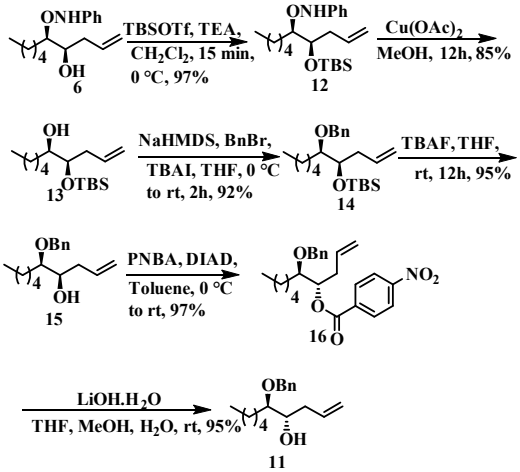
As illustrated in scheme 2, synthesis of petromyroxol started from commercially available heptanal, which was subjected to α-aminoxylation using L-proline as a catalyst and nitrosobenzene as an oxygen source to provide chiral O-N-phenylaminoxyaldehyde. This intermediate was then subjected to in situ indium mediated allylation (In/allylbromide/NaI) to afford a mixture of O-amino-substituted allylic alcohols **6** & **7** respectively with a diastereomeric ratio of 3:2 (*syn*:*anti*) in 70% overall yield with excellent enantioselectivities.[9] Both compounds **6** and **7** were cleanly separated by silica gel chromatography and fully characterized by spectroscopic means.

The *anti* compound **7** was then protected as its TBS ether using TBSOTf and NEt_3 to furnish the silyl ether **8**. The crude compound **8** was subjected to N-O bond cleavage[10] using copper (II) acetate in methanol to get compound **9** in 82% yield (2 steps). Further, the free alcohol was protected as its benzyl ether using NaHMDS and benzyl bromide at 0 °C to furnish the compound **10**, which was then desilylated using TBAF in THF to obtain homo allylic alcohol **11**.



Scheme 2: Synthesis of alcohol fragment **11**

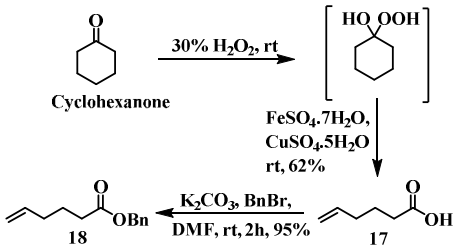
Our next task was to convert the major *syn* compound **6** into the required homoallylic alcohol **11** (scheme 3). Towards this end compound **15** was synthesized from **6** using a similar sequence of reactions as described in scheme 2. Subsequently compound **15** was smoothly converted to the required fragment **11** via Mitsunobu inversion.



Scheme 3: Conversion of *syn* isomer **6** to desired *anti* alcohol fragment **11**

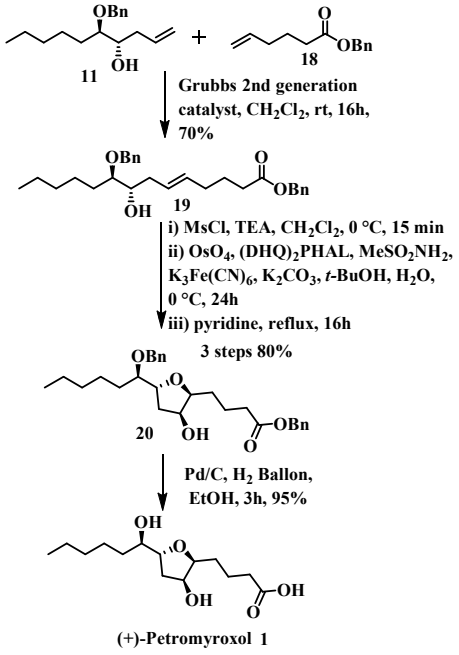
We then proceeded next to prepare the ester fragment, for that cyclohexanone was treated with 30% H_2O_2 to give hydroperoxide intermediate which was decomposed using ferrous sulfate-copper sulfate system to give the acid **17** in 62% yield[11] (scheme 4). The

olefinic acid **17** was subjected to esterification using K_2CO_3/BnBr to furnish the benzyl ester **18** in 95% yield.



Scheme 4: Synthesis of ester fragment **18**

After few optimizations with temperature and catalyst loading, the cross metathesis[12] reaction was performed between alcohol **11** (1 equiv) and **18** (5 equiv) in CH_2Cl_2 using 15 mol% Grubb's catalyst, resulting in the cross coupled **19** as major product in 70% yield (scheme 5).



Scheme 5: Synthesis of (+)-petromyroxol **1**

After having substantial amounts of olefinic alcohol **19**, the time was set for the construction of *trans* trisubstituted tetrahydrofuran ring **20** via intramolecular tandem Sharpless asymmetric dihydroxylation-S_N2 cyclization according to Marshall's protocol.[13] Thus, the alcohol **19** was first converted into its mesylate and then subjected to Sharpless asymmetric dihydroxylation[14] using commercially available AD-mix-α in *t*-BuOH–H_2O (1:1), however the reaction did not work. So we considered to optimizing the dihydroxylation reaction conditions with respect to ligand and OsO_4. Initially we carried out the reaction with standard conditions of Sharpless asymmetric dihydroxylation using 1 mol% ligand $(DHQ)_2PHAL$ and 0.4mol% OsO_4, but reaction did not work even after prolonged reaction time for a week at 0 °C. This prompted us to increase the amount of OsO_4 to 5 mol% in phased manner and to our delight starting material was completely consumed to give the crude diol. This crude product, without any extensive characterization, was immediately subjected to cyclization using pyridine as solvent. Though the reaction did not proceed at room temperature, refluxing the same in pyridine for 16h furnished the desired cyclized compound **20** in 80% yield (3 steps) with excellent selectivity (single diastereomer, confirmed by ^1H and ^{13}C NMR). Finally debenzylation of compound **20** using 10% wt/wt Pd/C under hydrogen balloon pressure gave the target molecule (+)-petromyroxol **1** in 95% yield.

Conclusions

In summary, we achieved the asymmetric synthesis of (+)-petromyroxol in 10 steps with an overall yield of 26.6% from easily accessible starting materials. Depending upon the catalyst (D/L-proline) used in the tandem aminoxylation-allylation step along with variation in chain length and the ligands (DHQ/DHQD) in the Sharpless asymmetric dihydroxylation step, one can have easy access to various stereoisomers of petromyroxol and its synthetic analogues.

Acknowledgements

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Experimental section

(4*R*, 5*R*)-5-((Phenylamino)oxy)hept-1-en-4-ol 6:

To a stirred solution of heptanal (6.4 g, 56.0 mmol) and nitrosobenzene (5.0, 46.6 mmol) in DMSO (94 mL), L-proline (1.07 g, 9.3 mmol) was added. After being stirred for 20 min at rt (The endpoint of the reaction was monitored by its color change from green to orange), allyl bromide (6.05 ml, 70.0 mmol), NaI (10.5 g, 70.0 mmol), and indium powder (8.03 g, 70.0 mmol) were added at rt. The stirring was kept at room temperature for 30 min. The reaction mixture was quenched with 0.5 M aq HCl (50 mL) and the aqueous layer was extracted with CH_2Cl_2 (2 × 30 mL). The combined organic layers were washed with brine (30 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The crude was purified by flash column chromatography (EtOAc-petroleum ether, 3:97) to afford compound (4*R*, 5*R*)-5-((phenylamino)oxy)hept-1-en-4-ol **6** (5.1g, 42%) and the more quickly eluting (4*S*, 5*R*)-isomer **7** (3.5 g, 28%). The diastereomeric ratios of the products were determined by weighing the separated isomers. The enantiomeric excess of the *anti* and the *syn*-diastereomer

was measured by HPLC analysis after separation of the isomers using column chromatography.

***Syn* 6**: $[\alpha]_D^{26.6}$: +28.7° (*c* 1.58, $CHCl_3$); IR (neat, cm^{-1}) : ν_{max} 3394, 3275, 3074, 2929, 2863, 1640, 1600, 1484, 1459, 1375, 1320, 1041; ^{1}H NMR (500MHz, $CDCl_3$) δ = 7.28 (s, 2 H), 7.09 (s, 1 H), 7.02 - 6.97 (m, 3 H), 5.95 - 5.85 (m, 1 H), 5.21 - 5.14 (m, 2 H), 4.03 (t, *J* = 5.6 Hz, 1 H), 3.89 (td, *J* = 2.9, 8.5 Hz, 1 H), 2.57 (br. s., 1 H), 2.32 (t, *J* = 6.9 Hz, 2 H), 1.76 - 1.66 (m, 2 H), 1.65 - 1.56 (m, 2 H), 1.55 - 1.36 (m, 4 H), 0.93 - 0.90 (m, 3 H); ^{13}C NMR (125MHz, $CDCl_3$) δ = 148.3, 135.1, 129.0, 122.4, 117.7, 114.9, 85.8, 72.2, 36.9, 31.9, 28.2, 26.0, 22.5, 14.0; HRMS (ESI) for $C_{16}H_{25}O_2$ N (M + Na)$^+$ found 286.1782, calcd 286.1778. The enantioselectivity of compound **6** was determined as 98% *ee* using chiral HPLC {Chiralcel OD-H (250mm x 4.6 mm), iPrOH/hexane (10:90), flow rate 1 mL min^{-1}, λ = 230 nm, t_R = 5.40 (major), t_R = 6.31 (minor)}.

***Anti* 7**: $[\alpha]_D^{26.6}$: +20.4° (*c* 1.43, $CHCl_3$); IR (neat, cm^{-1}) : ν_{max} 3396, 3285,3075, 2929, 2863, 1640, 1600, 1480, 1459, 1375, 1320, 1041; ^{1}H NMR (500MHz, $CDCl_3$) δ = 7.31 - 7.27 (m, 2 H), 7.04 - 6.98 (m, 3 H), 5.98 - 5.82 (m, 1 H), 5.21 - 5.12 (m, 2 H), 3.87 (ddd, *J* = 4.1, 5.7, 8.2 Hz, 1 H), 3.79 (q, *J* = 5.8 Hz, 1 H), 2.51 - 2.38 (m, 1 H), 2.33 - 2.25 (m, 1 H), 1.75 - 1.61 (m, 2 H), 1.53 - 1.42 (m, 2 H), 1.38 - 1.30 (m, 4 H), 0.90 (t, *J* = 6.9 Hz, 3 H); ^{13}C NMR (125MHz, $CDCl_3$) δ = 148.0, 134.6, 129.0, 122.6, 117.9, 115.3, 85.4, 72.7, 38.2, 32.0, 29.4, 25.3, 22.5, 14.0; HRMS (ESI) for $C_{16}H_{25}O_2$ N (M + Na)$^+$ found 286.1782, calcd 286.1778; The enantioselectivity of compound **7** was determined as 98% *ee* using chiral HPLC {Chiralcel OD-H (250mm x 4.6 mm), iPrOH/hexane (10:90), flow rate 1 mL min^{-1}, λ = 230 nm, t_R = 6.32 (major), t_R = 7.35 (minor)}.

(4*S*, 5*R*)-4-((Tert-butyldimethylsilyl)oxy)dec-1-en-5-ol 9:

To a stirred solution of compound **7** (3.0 g, 10.48 mmol) in CH_2Cl_2 (30.0 mL) at 0 °C was added Et_3N (3.5 mL, 25.09 mmol), followed by TBDMSOTf (3.2 mL, 13.6 mmol) and the mixture was stirred for 15 min. The reaction mixture was quenched with sat. NH_4Cl solution (20 mL) and the aqueous layer was extracted with CH_2Cl_2 (2 × 30 mL). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4 and concentrated under reduced pressure to give the crude **8** as yellow oil.

To a stirred solution of the crude **8** in MeOH (50 mL) was added $Cu(OAc)_2$ (720 mg, 3.96 mmol). The mixture was stirred at rt for 16h. The reaction mixture was quenched with a cold sat. NH_4Cl solution and extracted with ethyl acetate (3 x 30 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under vacuum. The residue was purified by flash column chromatography on silica gel (EtOAc-pet ether, 2:98) to afford compound **9** as yellow colour oil (2.4 g, 2 steps 82%). $[\alpha]_D^{27.7}$: +0.24° (*c* 1.74, $CHCl_3$); IR (neat, cm^{-1}): ν_{max} 3566, 3460, 3076, 2942, 2862, 1462, 1392, 1258, 1080; ^{1}H NMR (400MHz, $CDCl_3$) δ = 5.90 - 5.77 (m, 1 H), 5.12 - 5.01 (m, 2 H), 3.70 - 3.64 (m, 1 H), 3.61 - 3.56 (m, 1 H), 2.35 - 2.26 (m, 1 H), 2.25 - 2.17 (m, 1 H), 1.92 (br. s., 1 H), 1.45 - 1.39 (m, 2 H), 1.37 - 1.29 (m, 6 H), 0.91 (s, 12H), 0.08 (s, 6 H); ^{13}C NMR (100MHz, $CDCl_3$) δ = 135.6, 116.8, 75.1, 74.6, 35.9, 31.9, 31.8, 25.8, 25.8, 22.6, 18.1, 14.0, -4.3, -4.6; HRMS (ESI) for $C_{16}H_{34}O_2$ Si (M + Na)$^+$ found 309.2228, calcd 309.2220.

(((4*S*, 5*R*)-5-(Benzyloxy)dec-1-en-4-yl)oxy)(tert-butyl)dimethylsilane 10:

Sodium bis(trimethylsilyl)amide (1M solution in THF, 10.48 mL, 10.48 mmol) was added to a stirred solution of **9** (2.0 g, 6.9 mmol), tetrabutylammonium iodide (258 mg, 0.69 mmol) and benzyl bromide (1.24 mL, 10.48 mmol) in THF (30 mL) at 0 °C. The mixture was stirred at ambient temperature for 2h. The reaction was quenched by the addition of saturated aqueous ammonium chloride (25 mL) and extracted with EtOAc (3 × 50 mL). The combined organic layers were dried over Na_2SO_4, and concentrated in vacuo. The crude product was purified by flash column chromatography (EtOAc-pet ether, 1.5:98.5) to yield compound **10** as colourless oil (2.37 g, 92%). $[\alpha]_D^{28.9}$: +15.67° (*c* 1.31, $CHCl_3$); IR (neat, cm^{-1}): ν_{max} 3075, 3029, 2940, 2861, 1462, 1370, 1317, 1252, 1208, 1095; ^{1}H NMR (400MHz, $CDCl_3$) δ = 7.38 - 7.28 (m, 5 H), 5.88 (tdd, *J* = 7.2, 10.1, 17.1 Hz, 1 H), 5.11 - 5.02 (m, 2 H), 4.71 (d, *J* = 11.5 Hz, 1 H), 4.51 (d, *J* = 11.5 Hz, 1 H), 3.79 (td, *J* = 4.3, 6.3 Hz, 1 H), 3.38 (td, *J* = 3.6, 7.5 Hz, 1 H), 2.45 - 2.36 (m, 1 H), 2.32 - 2.24 (m, 1 H), 1.54 - 1.48 (m, 2 H), 1.36 - 1.24 (m, 6H), 0.92 - 0.87 (m, 12 H), 0.07 (s, 6 H); ^{13}C NMR (100MHz, $CDCl_3$) δ = 139.1, 135.8, 128.2, 127.8, 127.4, 116.7, 82.3, 74.2, 72.5, 37.8, 32.0, 30.7, 25.9, 25.5, 22.6, 18.1, 14.1, -4.4, -4.4; HRMS (ESI) for $C_{23}H_{40}O_2$ Si (M + Na)$^+$ found 399.2699, calcd 399.2690.

(*4S*, 5*R*)-5-(Benzyloxy)dec-1-en-4-ol 11:

To a stirred solution of **10** (2.0 g, 5.3 mmol) in THF (10 mL) was added 1.0 M TBAF in THF (10.6 mL, 10.6 mmol) at 0 °C. After being stirred for 12 h at rt, the reaction mixture was quenched with H_2O (10 mL) and the aqueous layer was extracted with EtOAc (2 × 20 mL). The combined organic layer was washed with brine (20 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The crude residue was purified by flash column chromatography (EtOAc–pet ether, 5:95) to afford compound **11** as colourless oil (1.3 g, 95%). $[\alpha]_D^{28.9}$: -1.95° (*c* 0.6, $CHCl_3$); IR (neat, cm^{-1}): ν_{max} 3425, 3076, 3030, 2926, 2865, 1696, 1635, 1455, 1372, 1084, 1037; ^{1}H NMR (500MHz, $CDCl_3$) δ = 7.36 - 7.28 (m, 5 H), 5.95 - 5.79 (m, 1 H), 5.19 - 5.11 (m, 2 H), 4.64 - 4.56 (m, 2 H), 3.87 - 3.81 (m, 1 H), 3.44 - 3.38 (m, 1 H), 2.35 - 2.25 (m, 2 H), 1.93 (br. s., 1 H), 1.69 - 1.60 (m, 1 H), 1.50 (d, *J* = 7.6 Hz, 2 H), 1.38 - 1.25 (m, 5 H), 0.92 - 0.87 (m, 3 H); ^{13}C NMR (125MHz, $CDCl_3$) δ = 138.5, 135.1, 128.4, 127.8, 127.7, 117.6, 81.7, 77.3, 76.7, 72.1, 71.4, 36.9, 32.0, 29.1, 25.2, 22.6, 14.0; HRMS (ESI) for $C_{17}H_{26}O_2$ (M + Na)$^+$ found 285.1830, calcd 285.1825.

O-((4*R*, 5*R*)-4-((Tert-butyldimethylsilyl)oxy)dec-1-en-5-yl)-N-phenylhydroxylamine 12:

Procedure as described in the preparation of **9**. Yellow colour liquid. Yield: 5.57 g, 97%. $[\alpha]_D^{25.8}$: +22.7° (*c* 1.7, $CHCl_3$); IR (neat, cm^{-1}) : ν_{max} 3296, 3074, 2942, 2861, 1641, 1601, 1463, 1421, 1372, 1252, 1081, 1010, 913, 835, 772, 728, 687; ^{1}H NMR (500MHz, $CDCl_3$) δ = 7.32 - 7.26 (m, 3 H), 7.02 - 6.94 (m, 3 H), 5.90 (tdd, *J* = 7.2, 10.0, 17.1 Hz, 1 H), 5.15 - 5.06 (m, 2 H), 4.00 (ddd, *J* = 2.1, 5.0, 7.2 Hz, 1 H), 3.87 - 3.82 (m, 1 H), 2.41 (td, *J* = 7.1, 14.3 Hz, 1 H), 2.34 - 2.27 (m, 1 H), 1.73 - 1.62 (m, 2 H), 1.56 - 1.44 (m, 2 H), 1.42 - 1.34 (m, 4 H), 0.98 - 0.93 (m, 12 H), 0.13 (s, 6 H); ^{13}C NMR (125MHz, $CDCl_3$) δ = 148.8, 135.7, 128.8, 121.6, 116.9, 114.3, 86.6, 74.0, 37.6, 32.0, 29.4, 26.2, 25.9, 22.6, 18.2, 14.1, -4.3, -4.4; HRMS (ESI) for $C_{22}H_{39}O_2$ N Si $(M+H)^+$ found 378.2830, calcd 378.2823.

(4*R*, 5*R*)-4-((Tert-butyldimethylsilyl)oxy)dec-1-en-5-ol 13:

Procedure as described in the preparation of **9**. Yellow colour oil. Yield: 3.2 g, 85%. $[\alpha]_D^{26.0}$: -7.8° (*c* 1.61, $CHCl_3$); IR (neat, cm^{-1}): ν_{max} 3568, 3460, 3076, 2942, 2862, 1463, 1392, 1255, 1079; ^{1}H NMR (500MHz, $CDCl_3$) δ = 5.80 (tdd, *J* = 7.1, 10.1, 17.2 Hz, 1 H), 5.12 - 5.05 (m, 2 H), 3.56 (td, *J* = 4.3, 7.0 Hz, 1 H), 3.47 - 3.43 (m, 1 H), 2.43 (td, *J* = 7.1, 14.1 Hz, 1 H), 2.25 - 2.18 (m, 1 H), 1.91 (br. s., 1 H), 1.53 - 1.44 (m, 1 H), 1.43 - 1.39 (m, 2 H), 1.37 - 1.28 (m, 5 H), 0.92 - 0.89 (m, 12 H), 0.10 (d, *J* = 7.3 Hz, 6 H); ^{13}C NMR (125MHz, $CDCl_3$) δ = 134.4, 117.4, 74.6, 72.4, 38.7, 33.9, 31.9, 25.9, 25.5, 22.6, 18.1, 14.1, -4.1, -4.7; HRMS (ESI) for $C_{16}H_{34}O_2$ Si $(M + Na)^+$ found 309.2226, calcd 309.2220.

(((4*R*, 5*R*)-5-(Benzyloxy)dec-1-en-4-yl)oxy)(tert-butyl)dimethylsilane 14:

Procedure as described in the preparation of **10**. Colourless oil. Yield: 3.4 g, 92 %. $[\alpha]_D^{27.6}$: +22.3° (*c* 2.8, $CHCl_3$); IR (neat, cm^{-1}): ν_{max} 3074, 3029, 2941, 2862, 1462, 1370, 1319, 1253, 1208, 1094; ^{1}H NMR (500MHz, $CDCl_3$) δ = 7.37 - 7.28 (m, 5 H), 5.84 (tdd, *J* = 7.2, 10.0, 17.2 Hz, 1 H), 5.09 - 5.01 (m, 2 H), 4.62 (d, *J* = 11.9 Hz, 1 H), 4.55 (d, *J* = 11.6 Hz, 1 H), 3.81 (td, *J* = 3.9, 8.3 Hz, 1 H), 3.33 (ddd, *J* = 2.9, 4.4, 9.2 Hz, 1 H), 2.41 (dddd, *J* = 1.8, 3.4, 5.1, 14.0 Hz, 1 H), 2.17 - 2.10 (m, 1 H), 1.67 - 1.61 (m, 1 H), 1.55 - 1.48 (m, 1 H), 1.42 (dtd, *J* = 4.6, 9.0, 13.5 Hz, 1 H), 1.34 - 1.27 (m, 5 H), 0.89 (s, 12 H), 0.02 (s, 3 H), 0.04 (s, 3 H); ^{13}C NMR (125MHz, $CDCl_3$) δ = 139.3, 136.7, 128.5, 128.1, 127.8, 116.7, 82.3, 77.3, 72.8, 72.6, 36.7, 32.2, 29.0, 26.3, 26.1, 22.9, 18.3, 14.3, -4.2, -4.2; HRMS (ESI) for $C_{23}H_{40}O_2$ Si $(M + Na)^+$ found 399.2699, calcd 399.2690.

(4*R*, 5*R*)-5-(Benzyloxy)dec-1-en-4-ol 15:

Procedure as described in the preparation of **11**. Colourless oil. Yield: 1.3 g, 95%. $[\alpha]_D^{28.8}$: -18.6° (*c* 2.27, $CHCl_3$); IR (neat, cm^{-1}): ν_{max} 3421, 3073, 3030, 2927, 2862, 1638, 1695, 1457, 1373, 1080; ^{1}H NMR (400MHz, $CDCl_3$) δ = 7.38 - 7.29 (m, 5 H), 5.88 (tdd, *J* = 7.0, 10.3, 16.9 Hz, 1 H), 5.16 - 5.07 (m, 2 H), 4.67 (d, *J* = 11.2 Hz, 1 H), 4.52 (d, *J* = 11.2 Hz, 1 H), 3.65 (td, *J* = 4.8, 7.8 Hz, 1 H), 3.35 (q, *J* = 5.5 Hz, 1 H), 2.40 - 2.31 (m, 1 H), 2.30 - 2.21 (m, 1 H), 2.16 (br. s., 1 H), 1.72 - 1.53 (m, 2 H), 1.43 - 1.28 (m, 6 H), 0.91 (t, *J* = 6.8 Hz, 3 H); ^{13}C NMR (100MHz, $CDCl_3$) δ = 138.4, 135.0, 128.4, 127.8, 127.7, 117.3, 81.4, 72.3, 72.0, 38.1, 32.1, 30.1, 24.8, 22.6, 14.0; HRMS (ESI) for $C_{17}H_{26}O_2$ $(M + Na)^+$ found 285.1831, calcd 285.1825.

(4*S*, 5*R*)-5-(Benzyloxy)dec-1-en-4-yl 4-nitrobenzoate 16:

To a stirred solution of alcohol **15** (1.0 g, 3.8 mmol) in dry toluene (15 mL) were added PPh_3 (0.393 g, 15.2 mmol), p-nitrobenzoic acid (PNBA) (0.143 g, 19.0 mmol) and diisopropylazodicarboxylate (DIAD) (0.29 ml, 15.2 mmol) at 0 °C and it was stirred for 2h at rt. Toluene was concentrated and directly transferred into silica gel column and it was purified by silica gel column chromatography using (EtOAc-petroleum ether, 3 : 97) as eluent to furnish **16** as a yellow colour oil (1.5 g, 97%). $[\alpha]_D^{28.9}$: +9.13° (*c* 1.18, $CHCl_3$); IR (neat, cm^{-1}): ν_{max} 3074, 3027, 2937, 2863, 1724, 1643, 1641, 1530, 1456, 1348, 1275; ^{1}H NMR (400MHz, $CDCl_3$) δ = 8.32 - 8.26 (m, *J* = 8.8 Hz, 2 H), 8.22 - 8.16 (m, *J* = 8.8 Hz, 2 H), 7.38 - 7.27 (m, 5 H), 5.82 (tdd, *J* = 7.0, 10.0, 17.1 Hz, 1 H), 5.41 (td, *J* = 4.0, 8.4 Hz, 1 H), 5.17 - 5.04 (m, 2 H), 4.70 (d, *J* = 11.5 Hz, 1 H), 4.55 (d, *J* = 11.5 Hz, 1 H), 3.64 (td, *J* = 3.7, 7.8 Hz, 1 H), 2.66 - 2.56 (m, 1 H), 2.56 - 2.48 (m, 1 H), 1.73 - 1.48 (m, 4 H), 1.46 - 1.29 (m, 4 H), 0.89 (t, *J* = 6.8 Hz, 3 H); ^{13}C NMR (100MHz, $CDCl_3$) δ = 164.2, 150.5, 138.2, 135.8, 133.6, 130.7, 128.4, 127.9, 127.7, 123.5, 118.1, 79.6, 75.7, 72.4, 34.2, 31.8, 30.5, 25.3, 22.5, 14.0; HRMS (ESI) for $C_{24}H_{29}O_5$ N $(M + Na)^+$ found 434.1949, calcd 434.1938.

Conversion of nitrobenzoate 16 to alcohol fragment 11:

To a stirred solution of p-nitro benzoate ester **16** (1.1 g, 2.6 mmol) in THF:MeOH:H_2O (3:2:1, 12 mL) was added LiOH.H_2O (0.168 g, 4.0 mmol) and stirred at rt for 1h. After completing the starting material (monitored by TLC), reaction was quenched with water and extracted with EtOAc (3 x 10 ml). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated in vacuum. The crude was purified by column chromatography using an eluent (EtOAc-petroleum ether, 5:95) to give **11** as colourless oil (659 mg, 95%).

Hex-5-enoic acid 17:

To a stirred solution of cyclohexanone (20.0 g, 203.7 mmol) in MeOH (20 mL), hydrogen peroxide (46 mL, 407.4 mmol) was added slowly at rt. The mixture was then added to a stirred solution of $FeSO_4.7H_2O$ (56.7 g, 203.7 mmol) and $CuSO_4.5H_2O$ (51 g, 203.7 mmol) in water (370 mL), maintaining the reaction temperature at 18-20 °C. The aqueous phase was separated and extracted with Et_2O (3 x 40 mL). The combined Et_2O extracts were washed with 20% NaOH (3 x 20 mL). The alkaline extract was acidified with 20% H_2SO_4 to pH 2 and extracted with Et_2O (3 x 40 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The crude residue was purified by flash column chromatography (EtOAc–petroleum ether, 10:90) to afford compound **17** as colourless oil (14.4 g, 62%). IR (neat, cm^{-1}): ν_{max} 3077, 2933, 2670, 1711, 1420, 1251, 1110; ^{1}H NMR (200MHz, $CDCl_3$) δ = 5.95 - 5.67 (m, 1 H), 5.14 - 4.96 (m, 2 H),

2.45 - 2.33 (m, 2 H), 2.13 (q, *J* = 7.1 Hz, 2 H), 1.75 (quin, *J* = 7.4 Hz, 2 H).

Benzyl hex-5-enoate 18:

To a stirred solution of compound **17** (4.0 g, 35.04 mmol), in DMF (50 mL), K_2CO_3 (12.1 g, 87.6 mmol) was added under argon atmosphere at 0 °C. After 10 min stirring at 0 °C, BnBr (6.2 mL, 52.5 mmol) was added to the reaction mixture and stirred for 2h at rt. After completion of reaction cold water was added into the reaction mixture and extracted with EtOAc (2 x 50 mL). The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. The crude product was purified by flash column chromatography (EtOAc-petrolium ether, 5:95) to yield compound **18** as colourless oil (6.8 g, 95%). IR (neat, cm^{-1}): ν_{max} 3074, 2940, 1737, 1638, 1596, 1451, 1234, 1162, 1111; ^{1}H NMR (200MHz, $CDCl_3$) δ = 7.47 - 7.32 (m, 5 H), 5.91 - 5.65 (m, 1 H), 5.13 (s, 2 H), 5.09 - 4.94 (m, 2 H), 2.39 (t, *J* = 7.5 Hz, 2 H), 2.10 (q, *J* = 7.3 Hz, 2 H), 1.88 - 1.65 (m, 2 H); ^{13}C NMR (50MHz , $CDCl_3$) δ = 173.4, 137.6, 136.0, 128.5, 128.2, 115.4, 66.1, 33.5, 33.0, 24.0; HRMS (ESI) for $C_{13}H_{16}O_2$ (M + Na)$^+$ found 227.1047, calcd 227.1043.

Benzyl (8*S*, 9*R*, *E*)-9-(benzyloxy)-8-hydroxytetradec-5-enoate 19:

To a stirred solution of **11** (600 mg, 2.28 mmol) in CH_2Cl_2 (7.0 mL) was added compound **18** (2.3 g, 11.44 mmol) and degassed for 15 min. Then Grubb's II catalyst (290 mg, 15 mol %) was added to the reaction mixture and stirred for 16h at rt. After completion of reaction solvent was removed under reduced pressure. The crude material was purified by flash column chromatography (EtOAc–petroleum ether, 8:92) to afford compound **19** as yellow colour oil (700 mg, 70%). $[\alpha]_D^{28.9}$: -1.11° (*c* 1.64, $CHCl_3$); IR (neat, cm^{-1}): ν_{max} 3456, 3030, 2930, 2861, 1734, 1598, 1454, 1378, 1219, 1155, 1083; ^{1}H NMR (400MHz, $CDCl_3$) δ =7.42 - 7.28 (m, 10 H), 5.56 - 5.40 (m, 2 H), 5.15 - 5.10 (m, 2 H), 4.64 - 4.53 (m, 2 H), 3.82 - 3.72 (m, 1 H), 3.45 - 3.33 (m, 1 H), 2.41 - 2.34 (m, 2 H), 2.29 - 2.16 (m, 2 H), 2.14 - 2.01 (m, 2 H), 1.92 - 1.84 (m, 1 H), 1.74 (quin, *J* = 7.5 Hz, 2 H), 1.68 - 1.57 (m, 1 H), 1.54 - 1.45 (m, 2 H), 1.36 - 1.28 (m, 5 H), 0.89 (t, *J* = 6.8 Hz, 3 H); ^{13}C NMR (100MHz, $CDCl_3$) δ = 173.4, 138.5, 136.0, 132.5, 131.4, 128.5, 128.4, 128.2, 127.8, 127.6, 127.4, 126.7, 81.7, 72.1, 71.6, 66.1, 35.6, 33.6, 32.0, 31.9, 29.1, 25.2, 24.5, 22.6, 14.0; HRMS (ESI) for $C_{28}H_{38}O_4$ (M + Na)$^+$ found 461.2672, calcd 461.2662.

Benzyl 4-((2*S*, 3*S*, 5*R*)-5-((*R*)-1-(benzyloxy)hexyl)-3-hydroxytetrahydrofuran-2-yl)butanoate 20:

To a stirred solution of compound **19** (72 mg, 0.164 mmol) in dry CH_2Cl_2 was added triethylamine (0.057 ml, 0.41 mmol), followed by slow addition of mesyl chloride (0.018 ml, 0.246 mmol) at 0 °C, with further stirring for 15 min at the room temperature. The reaction mixture was quenched with addition of cold water at 0 °C. The two phases were separated and the aqueous phase was extracted with CH_2Cl_2 (3 x 5 mL). The combined organic layers were washed with water (3 x 5 mL), brine, dried over Na_2SO_4 and concentrated to give crude mesylate.

To a mixture of $K_3Fe(CN)_6$ (0.192 g, 0.580 mmol), K_2CO_3 (0.081 g, 0.58 mmol) and $(DHQ)_2PHAL$ (1.5 mg, 0.002 mmol, 1 mol%) in *t*-BuOH–H_2O (1:1, 10 mL) at 0 °C was added osmium tetroxide (95 μL, 0.1 M solution in toluene, 5 mol%), followed by methane sulfonamide (0.079 g, 0.83 mmol). After stirring for 5 min at 0 °C, the crude mesylate (0.100 g, 0.19 mmol) was added in one portion. The reaction mixture was stirred at 0 °C for 24h and then quenched with solid sodium sulphite (286 mg, 1.48 mg/mmol). Stirring was continued for an additional 15 min and then the solution was extracted with EtOAc (3 × 10 mL). The combined extracts were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure to give the crude diol.

The crude diol was refluxed in pyridine at 150 °C for 16h gave the cyclized compound. After completion of the reaction 10% $CuSO_4.5H_20$ solution was added to the reaction mixture and extracted with EtOAc. The combined organic layers were washed with water (2 x 5 mL), brine, dried over Na_2SO_4 and concentrated to give crude cyclized compound. The crude material was purified by flash column chromatography (EtOAc–petroleum ether, 15:85) to give compound **20** as colourless oil (59 mg, 80%). $[\alpha]_D^{24.8}$: +15.2° (*c* 1.49, $CHCl_3$); IR (neat, cm^{-1}): ν_{max} 3441, 2928, 2861, 1733, 1455, 1249, 1161, 1083; ^{1}H NMR (400MHz, $CDCl_3$) δ = 7.38 - 7.28 (m, 10 H), 5.13 (s, 2 H), 4.70 (d, *J* = 11.7 Hz, 1 H), 4.63 (d, *J* = 11.7 Hz, 1 H), 4.32 (td, *J* = 6.2, 9.1 Hz, 1 H), 4.27 (t, *J* = 2.9 Hz, 1 H), 3.81 (dt, *J* = 2.6, 6.5 Hz, 1 H), 3.34 - 3.28 (m, 1 H), 2.53 - 2.38 (m, 2 H), 2.05 - 1.83 (m, 5 H), 1.83 - 1.57 (m, 6 H), 1.53 - 1.41 (m, 4 H), 0.88 (s, 3 H); ^{13}C NMR (100MHz, $CDCl_3$) δ = 173.7, 139.0, 135.9, 128.5, 128.2, 127.9, 127.4, 82.1, 81.1, 79.3, 72.9, 72.7, 66.3, 37.5, 33.9, 32.0, 30.6, 28.4, 25.3, 22.6, 21.3, 14.0; HRMS (ESI) for $C_{28}H_{38}O_5$ (M + Na)$^+$ found 477.2621, calcd 477.2611.

(+)-Petromyroxol 1:

To a stirred solution of **20** (14 mg, 0.03 mmol) in EtOH (3 mL) was added 10% w/w Pd/C (2 mg, 0.1 w/w) and the mixture was stirred for 3h under H_2 atmosphere. Then, the Pd/C was filtered off and the solvent was evaporated under reduced pressure. The residue was purified by flash column chromatography (MeOH:CH_2Cl_2, 15:85) to afford compound **1** as a colourless liquid (8 mg, 95%). $[\alpha]_D^{25.9}$: +8.5° (*c* 0.64, $CHCl_3$), {(lit^3. $[\alpha]_D^{25}$ = +17° (*c* 0.36, $CHCl_3$)}; IR (neat, cm^{-1}): ν_{max} 3400, 2935, 2861, 1710, 1408, 1248, 1072, 1065; ^{1}H NMR (500MHz, $CDCl_3$) δ = 4.32 - 4.27 (dd, *J* = 3.5, 3.5, 1 H), 4.10 - 4.04 (ddd, *J* = 6.4, 6.7, 8.9, 1 H), 3.82 - 3.77 (ddd, *J* = 2.4, 6.5, 6.5, 1 H), 3.43 - 3.37 (ddd, *J* = 4.0, 6.4, 7.3, 1 H), 2.49 - 2.37 (m, 2 H), 2.04 (dd, J = 6.6, 13.3 Hz, 1 H), 1.89 (ddd, *J* = 4.6, 9.1, 13.5 Hz, 1 H), 1.80 - 1.63 (m, 4 H), 1.55 - 1.47 (m, 1 H), 1.44 - 1.28 (m, 7 H), 0.89 (t, *J* = 6.9 Hz, 3 H). ^{13}C NMR (125MHz, $CDCl_3$) δ = 177.7, 82.4, 80.5, 74.1, 73.3, 37.6, 33.5, 33.1, 31.8, 28.2, 25.2, 22.6, 21.2, 14.0; HRMS (ESI) for $C_{14}H_{26}O_5$ (M + Na)$^+$ found 297.1678, calcd 297.1672.

Notes and references

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‡Electronic Supplementary Information (ESI) available: Copies of NMR spectra (^{1}H & ^{13}C) of all compounds. See DOI: 10.1039/c000000x/

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Total Synthesis of (+)-petromyroxol *via* tandem α-aminoxylation-allylation and asymmetric dihydroxylation-S_N2 cyclization approach†‡

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