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Asymmetric synthesis of the constitutive C_{22}-carboxylic acid of macroviracin A

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Abstract: An efficient asymmetric synthesis of the C_{22}-trihydroxy fatty acid component of macroviracin A has been developed. The key steps were highly enantioselective (i) lipase-catalyzed acylation (ii) $InCl_3$-(*S*)-BINOL mediated allylation, and (iii) asymmetric dihydroxylation (ADH) reaction. The moderate diastereoselectivity of the ADH reaction was overridden by converting the resultant diol diastereomers to the required epoxide enantiomer.

Keywords: asymmetric synthesis • total synthesis • antiviral agent • macroviracin A • lipase catalyzed reaction

1. Introduction

Impressive progress notwithstanding, design of simple and efficient routes for the asymmetric synthesis of bioactive target compounds remains a challenging research area.[1] For the past several years, this has been the major focus of our research leading to the asymmetric syntheses of a diverse array of natural compounds.[2] The polyhydroxy acids and the macrolides derived from them are of wide occurrence in various natural sources, and several of these show impressive anti-cancer, antiviral, antifungal as well as vaccine adjuvant activities.[3] Some of the examples of this class of compounds include (i) pinellic acid, responsible for the anti-influenza activity of Kampo medicine,[4a] (ii) the pharmacophores of the glycosidase inhibitors such as the

schulzeines,[4b] penasulfate[4c] and the penarolides[4d], (iii) oxylipins, used by the AIDS patients as the immune-boosters etc.[4e-g] A new family of structurally related glycolipids, isolated from the mycelium of *Streptomyces sp*. BA 2836 exhibit a powerful and selective activity against various human pathogens including herpes simplex-, human immunodeficiency- and varicella-zoster viruses.[5] These compounds, designated as macroviracins are classified into eight types of congeners (A-D) differing in the length (C_{22} or C_{24}) of their constitutive fatty acid chains forming the central lactide ring, and the fatty acid appendages. Their antiviral activity is claimed to be 10 times that of acyclovir. Macroviracin A, a member of this family possesses a 42-membered macrodiolide core with D-glucose residues, and a long side chain attached to the core. Its structure resembles that of the sugar-fatty acid lactones, cycloviracins and fattiviracins.

The architectural complexity and therapeutic potential of these compounds make them synthetically challenging and attractive targets to the organic chemists. Earlier, the total syntheses of cycloviracin B_1,[6a-d] and cycloviracin D have been reported.[6e] Till today, the only synthesis of macroviracin A by Nakata's group also established the (3*R*,15*S*,21*R*)-configuration of its constituent fatty acid segment.[7] In the only reported synthesis of **2**, Nakata *et al*. used 22-26 steps to synthesize similar compounds like **17** bearing different hydroxyl protecting groups. The C-3 stereogenic centre was created using Sharpless asymmetric epoxidation followed by destruction of one of the newly created stereogenic centres. The C-15 stereogenic centre was installed by the Jacobsen protocol of hydrolytic kinetic resolution of terminal epoxides, while the C-21 stereogenic centre was inherited from the microbial product, (*R*)-3-hydroxybutanoate.[7b] In another longer synthesis,[7a] Sharpless asymmetric epoxidation and regioselective epoxide reduction were used to fix the C-15 stereogenic centre. Hence, the present work was focused on developing a simple and shorter synthesis of the C_{22}-trihydroxy acid derivative **2**. A

retrosynthetic analysis (Figure 1) revealed acid **2** as the precursor of the domain structure **1** of macroviracin A, because its intermolecular macrodimerization is already reported.[7] We paid particular attention to install an orthogonal protecting group on the C-15 hydroxyl group in **2** as this needs to be glycosylated later for the synthesis of **1**.

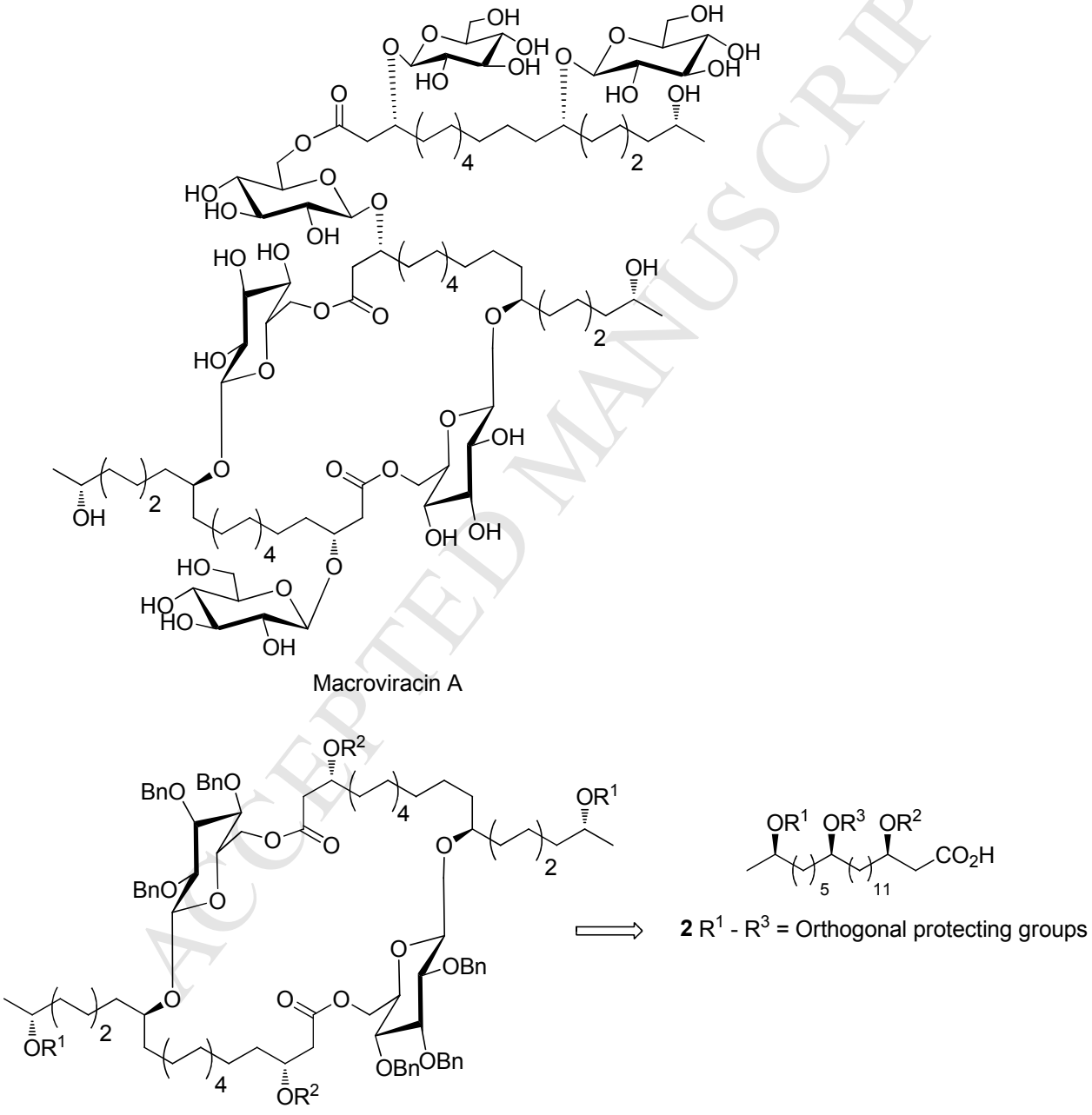


Figure 1. Retrosynthesis of compound **1**.

2. Results and Discussion

The synthesis commenced by α-alkylation of the ketoester **3** with 6-bromo-1-hexene followed by Krapcho decarboxylation to furnish the ketone **4**, which on reduction with $LiAlH_4$ afforded the alcohol (±)-**5**. For its resolution, the alcohol (±)-**5** was subjected to a lipase-catalyzed *trans*-acetylation with vinyl acetate in different solvents. Amongst the tested lipases, Novozym 435® produced the best result, furnishing the acetate (*R*)-**6** (96% ee) and (*S*)-**5** (91% ee) after 50% conversion (*cf*. GC, 2 h) in diisopropyl ether solvent. The resolved alcohol (*S*)-**5** was enantiomerically enriched to 98% ee by a second Novozym 435®-catalyzed acetylation (10% conversion) as above. Alkaline hydrolysis of the acetate (*R*)-**6** with KOH/MeOH furnished the alcohol (*R*)-**5**. The % ees of the enantiomeric alcohols (*R*)-**5** and (*S*)-**5** were determined from the relative intensities of the methoxyl resonances of the corresponding α-methoxytrifluoromethyl phenyl acetates (MTPA), prepared using (*R*)-MTPA chloride.[8] The configurations of the alcohols were assigned by converting a small aliquot of the respective alkenol enantiomers into known compounds-(*R*)- and (*S*)-nonan-2-ols.[9] To offset the limitation of a resolution-based protocol, the alcohol (*S*)-**5** was converted to its enantiomer (*R*)-**5** under the Mitsunobu conditions (Ph_3P/DEAD/*p*-nitrobenzoic acid/THF; K_2CO_3/MeOH/25 ^oC/8 h, 91%).[10]

The alcohol (*R*)-**5** was silylated with *tert*-butyldiphenylsilyl chloride (TBDPSCl) in the presence of imidazole and 4-dimethylaminopyridine (DMAP) to furnish **7** (**Scheme 1.**). Asymmetric dihydroxylation[11] of the alkene function in **7** with AD-mix β reagent gave a mixture of C-2 epimers, **8a** and **8b** in 91:9 ratio, which could be isolated in pure forms by column chromatography. Reaction of **8a** with *para*-toluene sulphonyl chloride (*p*-TsCl)/Bu_2SnO/Et_3N proceeded regioselectively at the primary carbinol function to furnish the corresponding monotosylate. This was converted to the epoxide **9** by treatment with K_2CO_3/MeOH. To make

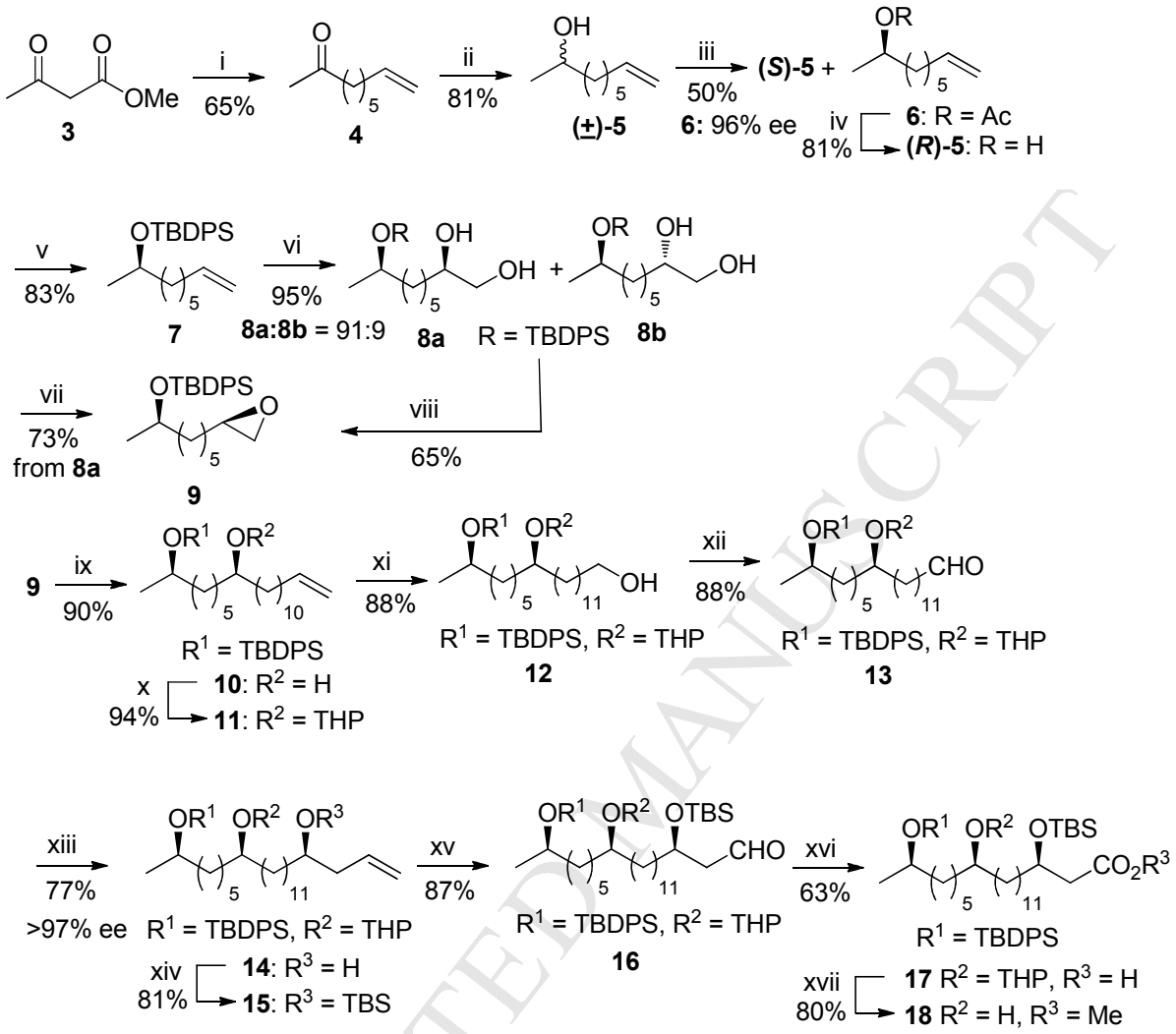
the synthesis enantioconvergent, the diol **8b** was monosilylated at its primary carbinol site with trimethylchlorosilane (TMSCl), the adjacent hydroxyl function mesylated with methanesulphonyl chloride (MsCl) and subsequently desilylated in one pot. The resultant hydroxymesyl compound was treated with K_2CO_3/MeOH to furnish the epoxide **9**.[12] This was reacted with the Grignard reagent, prepared from 11-bromo-1-undecene in the presence of CuBr as the catalyst to furnish the alcohol **10**. The carbinol function in **10** was protected with 3,4-dihydropyran (DHP) in the presence of pyridinium *p*-toluenesulphonate (PPTS) in CH_2Cl_2 to furnish **11**, which on hydroboration-oxidation with $BH_3.Me_2S$ afforded compound **12**. Its Swern oxidation proceeded uneventfully to furnish the aldehyde **13**. For installing the third stereogenic center, we preferred an $InCl_3$-mediated allylation of **13** with allyl$(Bu)_3Sn$ in the presence of (*S*)-BINOL and activated 4Å molecular sieves in CH_2Cl_2 to obtain the alcohol **14** as a single enantiomer in good yield.[13] Consistent with our previous observation,[14] the present result suggested that the stereochemistry of the allylation reaction was dictated exclusively by the reagent chirality, without a significant contribution from that present in the substrate. The alcohol **14** was silylated with *tert*-butyldimethylsilyl chloride (TBSCl) in the presence of imidazole and DMAP to furnish **15**. Lemieux-Johnson oxidation (OsO_4/NMO; $NaIO_4$) of the olefin function in **15** afforded the aldehyde **16** in 87% yield. Finally, this was subjected to Pinnick oxidation with $NaClO_2$ to furnish the desired acid **17** (compound **2** equivalent).

The transformation of **17** to **1** would require (i) chemoselective deprotection of the OTHP group of its ester under neutral conditions to avoid any desilylation; (ii) glycolyzation of the resultant alcohol; and (iii) macrolactonization after ester hydrolysis and removal of the TBS group. Hence we converted compound **17** to the hydroxyester **18** by its esterification with CH_2N_2 and its depranylation with $CuCl_2.2H_2O$ in MeOH at room temperature.[15] The subsequent

conversion of **18** to **1** can be achieved following Nakata's protocol[7b] and some routine synthetic steps.

3. Conclusion

Overall, we have developed an enantioconvergent synthesis of the C_{22}-trihydroxy acid segment of macroviracin A in ~4.5% overall yield in 16 steps. A chemoselective protocol for its conversion the corresponding C-15 hydroxy ester, an advanced precursor of **1** was also demonstrated. The required stereogenic centres in the target compound were installed using a lipase-catalyzed acetylation, an asymmetric dihydroxylation and a reagent-controlled asymmetric allylation. Compared to the reported procedures of **2**,[7] our synthesis is much shorter, does not involve destruction of any stereogenic centre, employs highly enantioselective transformations, and is enantioconvergent. Besides, like the previous reported procedure,[7a] our synthesis can also be used to synthesize all the stereoisomers of **17** or **18** by using the suitable enantiomer of **5** and proper choice of the chiral auxiliaries for asymmetric dihydroxylation and allylation.



Scheme 1

i) (a) NaOMe/MeOH/6-bromo-1-hexene/65 ^{o}C/3.5 h; (b) aqueous NaOH/25 ^{o}C/2 h; (c) aqueous H_2SO_4/80 ^{o}C/3 h, ii) $LiAlH_4$/Et_2O/25 ^{o}C/2 h, iii) Vinyl acetate/diisopropyl ether/Novozym 435®/25 ^{o}C/1.5 h, iv) KOH/aqueous MeOH/25 ^{o}C/3 h, v) TBDPSCl/imidazole/ DMAP/CH_2Cl_2/25 ^{o}C/7 h, vi) AD-mix β/*tert*-BuOH-H_2O (1:1)/0 ^{o}C/72 h, vii) (a) *p*-TsCl/ Bu_2SnO/Et_3N/CH_2Cl_2/25 ^{o}C/3 h; (b) K_2CO_3/MeOH/25 ^{o}C/3 h, viii) (a) TMSCl/ Et_3N/EtOAc/-20 ^{o}C/30 min; (b) MsCl/Et_3N/ -20 ^{o}C/30 min; (c) aqueous 2N HCl/25 ^{o}C/1 h; (d) K_2CO_3/MeOH/25 ^{o}C/3 h, ix) CH_2=$CH(CH_2)_9MgBr$/THF/CuBr/-60 ^{o}C/1.5 h; 25 ^{o}C/3 h, x) DHP/PPTS/CH_2Cl_2/25 ^{o}C/3 h, xi) (a) $BH_3.Me_2S$/THF/0 to 25 ^{o}C/1.5 h; (b) aqueous NaOH/H_2O_2/0 ^{o}C/1 h; 25 ^{o}C/3 h, xii)

$(COCl)_2$/DMSO/Et_3N/CH_2Cl_2/-78 ^oC/0.5 h; 25 ^oC/2 h, xiii) $AllylSn(Bu)_3$/$InCl_3$/4Å molecular sieve/(*S*)-BINOL/CH_2Cl_2/-78 ^oC/4 h then 25 ^oC/16 h, xiv) TBSCl/imidazole/DMAP/CH_2Cl_2/25 ^oC/4 days, xv) (a) OsO_4/NMO/*tert*-BuOH/acetone-H_2O (8:1)/25 ^oC/12 h; (b) $NaIO_4$/MeCN-H_2O/25 ^oC/2 h, xvi) $NaClO_2$/NaH_2PO_4/30%H_2O_2 /MeCN-H_2O /0 ^oC/0.5 h; 15 ^oC/6 h, xvii) (a) CH_2N_2/Et_2O/0 ^oC/2 h; (b) $CuCl_2.2H_2O$/MeOH/25 ^oC/12 h.

4. Experimental Section

4.1 General Details

All chemicals (Fluka and Lancaster) were used as received. Other reagents were of AR grade. The anhydrous reactions were carried out under an Ar atmosphere, using freshly dried solvents. The organic extracts were dried over anhydrous Na_2SO_4. The IR spectra as thin films were scanned with a Jasco model A-202 FT-IR spectrometer. The ^1H NMR (200 MHz) and ^{13}C (50 MHz) NMR spectra were recorded with Bruker AC-200 spectrometers in $CDCl_3$. The optical rotations were recorded with a Jasco DIP 360 digital polarimeter. The CHN analyses were carried out with a vario Micro cube Elementar analyzer.

4.2 8-Nonen-2-one 4

To a stirred solution of NaOMe [prepared from Na (2.37 g, 10.29 mmol) in MeOH (15 mL)] was dropwise added **3** (10.86 g, 9.35 mmol) at room temperature. After refluxing the mixture for 0.5 h, 6-bromo-1-hexene (1.83 g, 11.22 mmol) was added into it, and refluxing continued for an additional 3 h. The mixture was concentrated in vacuo and the residue taken in EtOAc (50 mL). The organic extract was washed with H_2O (3 × 15 mL) and brine (1 × 5 mL), dried and concentrated in vacuo. The residue was column chromatographed (silica gel, 0-5% EtOAc/hexane) to afford the α-alkylated ketoester (13.4 g, 72%) as a colorless oil; [Found: C, 66.69; H, 9.27. $C_{11}H_{18}O_3$ requires C, 66.64; H, 9.15%]; R_f (15% EtOAc/hexane) 0.72; $\bar{\upsilon}$ (liquid

film) 1745 cm^{-1}; δ_H 1.24-1.43 (m, 4H), 1.81-1.86 (m, 2H), 1.98-2.04 (m, 2H), 2.22 (s, 3H), 3.40 (t, *J* = 7.3 Hz, 1H), 3.72 (s, 3H), 4.90-5.01 (m, 2H) 5.69-5.78 (m, 1H); δ_C 26.5, 27.7, 28.2, 28.4, 33.0, 51.9, 59.2, 114.2, 138.1, 169.9, 202.5.

A mixture of the above compound (10.4 g, 52.52 mmol) and aqueous 5% NaOH (100 mL) was stirred for 2 h at room temperature, acidified by dropwise addition of aqueous 50% H_2SO_4 (50 mL) at 0 ^oC, and subsequently heated at 80 ^oC for 3 h. The mixture was extracted with Et_2O (3 × 30 mL), the combined organic extracts washed with H_2O (3 × 15 mL) and brine (1 × 5 mL), dried and concentrated in vacuo. The residue was column chromatographed (silica gel, 0-5% EtOAc/hexane) to furnish pure **4** (6.7 g, 91%) as a colorless liquid; [Found: C, 77.22; H, 11.86. $C_9H_{16}O$ requires C, 77.09; H, 11.50%]; R_f (10% Et_2O/hexane) 0.81; $\bar{\upsilon}$ (liquid film) 1715, 1641 cm^{-1}; δ_H 1.28-1.34 (m, 2H), 1.38-1.42 (m, 2H), 1.56-1.61 (m, 2H), 2.02-2.05 (m, 2H), 2.13 (s, 3H), 2.42 (t, *J* = 7.2 Hz, 2H), 4.92-5.00 (m, 2H), 5.74-5.84 (m, 1H); δ_C 23.5, 28.4, 28.5, 29.6, 33.4, 43.5, 114.2, 138.6, 208.8.

4.3 (±)-8-Nonen-2-ol 5

To a stirred suspension of $LiAlH_4$ (2.72 g, 71.58 mmol) in Et_2O (100 mL) was dropwise added **4** (6.30 g, 45.00 mmol) in Et_2O (100 mL) and the mixture stirred for 2 h at room temperature till completion of the reaction (*cf*. TLC). The mixture was treated with aqueous saturated Na_2SO_4, filtered through a pad of celite, and the filtrate concentrated in vacuo to obtain a residue, which on column chromatography (silica gel, 0-5% Et_2O/hexane) afforded pure **5** (5.2 g, 81%) as a colorless liquid; [Found: C, 75.78; H, 13.05. $C_9H_{18}O$ requires C, 76.00; H, 12.76%]; R_f (15% EtOAc/hexane) 0.56; $\bar{\upsilon}$ (liquid film) 3363, 992 cm^{-1}; δ_H 1.17 (d, *J* = 6.6 Hz, 3H), 1.38-1.48 (m, 7H), 1.58-1.67 (m, 2H), 2.02-2.06 (m, 2H), 3.77-3.81 (m, 1H), 4.92-5.01 (m, 2H), 5.76-5.83 (m, 1H); δ_c 23.3, 28.8, 29.0, 33.6, 39.1, 68.1, 114.1, 138.9.

4.4 (*R*)-8-Acetoxynon-1-ene 6

A mixture of **(±)-5** (4.6 g, 32.39 mmol) and Novozym 435® (1.0 g) in vinyl acetate (10.0 mL) was agitated on an orbital shaker at 110 rpm for 1.5 h. The reaction mixture was diluted with Et_2O (15 mL), filtered, and the filtrate concentrated in vacuo to get a residue, which on column chromatography (silica gel, 0-10% Et_2O/hexane) gave pure (*R*)-**6** (2.6 g, 44%) and (*S*)-**5** (1.9 g, 41%) as colorless liquids. (*S*)-**5**: $[\alpha]_D^{23}$ +5.4 (*c* 1.36, $CHCl_3$); (*R*)-**6**: [Found: C, 71.81; H, 11.05. $C_{11}H_{20}O_2$ requires C, 71.70; H, 10.94%]; R_f (10% Et_2O/hexane) 0.80; $[\alpha]_D^{23}$ -0.8 (*c* 1.7, $CHCl_3$); $\bar{\upsilon}$ (liquid film) 1738, 911 cm^{-1}; δ_H 1.19 (d, *J* = 6.0 Hz, 3H), 1.27-1.38 (m, 5H), 1.40-1.48 (m, 1H), 1.55-1.64 (m, 2H), 2.02-2.06 (m containing a s at δ 2.04, 5H), 4.87-5.01 (m, 3H), 5.77-5.82 (m, 1H); δ_C 19.9, 21.3, 25.2, 28.8, 33.6, 35.8, 70.9, 114.2, 138.9, 170.7.

4.5 (*R*)-8-Nonen-2-ol 5

A mixture of (*R*)-**6** (2.00 g, 10.87 mmol) and KOH (0.700 g, 12.50 mmol) in MeOH (25 mL) was stirred at room temperature for 3 h. The mixture was filtered, concentrated in vacuo, diluted with H_2O (30 mL) and extracted with Et_2O (2 × 20 mL). The organic extracts were washed with H_2O (2 × 10 mL) and brine (1 × 5 mL), and dried. Removal of solvent in vacuo followed by column chromatography of the residue (silica gel, 0-10% Et_2O/hexane) afforded pure (*R*)-**5** (1.3 g, 81%) as a colorless liquid; [Found: C, 75.78; H, 12.72. $C_9H_{18}O$ requires C, 76.00; H, 12.76%]; R_f (15% EtOAc/hexane) 0.56; $[\alpha]_D^{25}$ -6.7 (*c* 1.35, $CHCl_3$); $\bar{\upsilon}$ (liquid film) 3363, 992, 909 cm^{-1}; δ_H 1.17 (d, *J* = 6.2 Hz, 3H), 1.22-1.46 (m, 9H), 2.00-2.10 (m, 2H), 3.75-3.89 (m, 1H), 4.89-5.00 (m, 2H), 5.70-5.84 (m, 1H); δ_C 23.4, 28.4, 28.9, 33.5, 38.9, 67.8, 114.1, 138.8.

4.6 (*R*)-8-*tert*-Butyldiphenylsilyloxynon-1-ene 7

A solution of (*R*)-**5** (1.12 g, 7.88 mmol), TBDPSCl (2.60 g, 9.46 mmol), imidazole (0.805 g, 11.83 mmol) and DMAP (catalytic) in CH_2Cl_2 (20 mL) was stirred for 7 h at room temperature. The mixture was poured into ice-cold H_2O (20 mL), the organic layer separated, and the aqueous portion extracted with $CHCl_3$ (3 × 10 mL). The combined organic extracts were washed with water (2 × 10 mL), and brine (1 × 5 mL), and dried. Removal of solvent in vacuo followed by column chromatography (silica gel, 0-5% EtOAc/hexane) of the residue afforded pure **7** (2.5 g, 83%) as a colorless liquid; $[\alpha]_D^{25}$ +16.0 (*c* 1.10, $CHCl_3$); [Found: C, 78.52; H, 9.73. $C_{25}H_{36}OSi$ requires C, 78.89; H, 9.53%]; R_f (10% Et_2O/hexane) 0.90; $[\alpha]_D^{25}$ +16.0 (*c* 1.10, $CHCl_3$); $\bar{\upsilon}$ (liquid film) 1641, 997 cm^{-1}; δ_H 1.09 (merged s and d, *J* = 6.0 Hz, 12H), 1.25-1.36 (m, 8H), 1.98-2.09 (m, 2H), 3.83-3.92 (m, 1H), 4.94-5.07 (m, 2H), 5.77-5.90 (m, 1H), 7.38-7.47 (m, 6H), 7.71-7.75 (m, 4H); δ_C 19.4, 23.3, 25.2, 27.1, 28.9, 29.2, 29.8, 33.8, 39.5, 69.7, 114.2, 127.5, 129.5, 134.7, 135.1, 136.0, 139.3. Anal. Calcd. for $C_{25}H_{36}OSi$: C, 78.89; H, 9.53%. Found: C, 78.52; H, 9.73%.

4.7 (2*R*,8*R*)/(2*S*,8*R*)-8-*tert*-Butyldiphenylsilyloxynonane-1,2-diol 8a/8b

To a cooled (0 °C) and stirred solution of **7** (2.40 g, 6.32 mmol) in aqueous 50% *tert*-BuOH (100 mL) was added AD-mix β (8.84 g, 1.4 g/mmol), and the mixture stirred till completion of the reaction (*cf.* TLC, ~ 72 h). Aqueous saturated Na_2SO_3 was added to the mixture, the organic layer separated and the aqueous portion extracted with $CHCl_3$ (3 × 10 mL). The combined organic extracts were washed with H_2O (3 × 10 mL) and brine (1 × 5 mL), dried and concentrated in vacuo. The residue was purified by column chromatography (silica gel, 0-10% Et_2O/hexane) to afford pure **8a** (2.23 g, 85%) and **8b** (0.24 g**,** 9%) as colorless liquids. **8a: [**Found: C, 72.67; H, 9.54. $C_{25}H_{38}O_3Si$ requires C, 72.41; H, 9.24%]; R_f (5% MeOH/$CHCl_3$) 0.40; $[\alpha]_D^{23}$ +11.3 (*c* 1.04, $CHCl_3$); $\bar{\upsilon}$ (liquid film) 3428, 3071 cm^{-1}; δ_H 1.06 (merged s and d, *J* =

6.2 Hz, 12H), 1.17-1.39 (m, 10H), 1.78 (broad s, 2H), 3.42-3.45 (m, 1H), 3.64-3.67 (m, 2H), 3.80-3.84 (m, 1H), 7.37-7.41 (m, 6H), 7.67-7.70 (m, 4H); δ_C 19.3, 19.5, 23.3, 25.5, 27.1, 29.7, 33.1, 39.4, 66.8, 69.5, 72.3, 127.5, 129.4, 135.9. **8b:** $[\alpha]_D^{25}$ +17.6 (*c* 1.06, $CHCl_3$); [Found: C, 72.55; H, 9.04. $C_{25}H_{38}O_3Si$ requires C, 72.41; H, 9.24%]; R_f (5% MeOH/$CHCl_3$) 0.42; $[\alpha]_D^{25}$ +17.6 (*c* 1.06, $CHCl_3$); $\bar{\upsilon}$ (liquid film) 3401, 3071 cm^{-1}; δ_H 1.08 (merged s and d, *J* = 6.2 Hz, 12H), 1.18-1.43 (m, 10H), 1.80 (broad s, 2H), 3.25-3.28 (m, 1H), 3.47-3.85 (m, 3H), 7.31-7.40 (m, 6H), 7.63-7.68 (m, 4H); δ_C 19.2, 19.4, 23.1, 25.2, 25.5, 27.0, 33.1, 39.2, 69.4, 70.7, 76.0, 127.3, 127.4, 129.3, 129.4, 134.4, 134.7, 135.8.

4.8 (2*R*,8*R*)-8-*tert*-Butyldiphenylsilyloxy-1,2-epoxynonane 9 (from 8a)

To a stirred solution of **8a** (2.23 g, 5.39 mmol) in CH_2Cl_2 (50 mL) were added Bu_2SnO (0.040 g, 0.16 mmol), Et_3N (0.93 mL, 6.68 mmol) and *p*-TsCl (1.08 g, 5.66 mmol). After stirring for 3 h at room temperature, brine (10 mL) was added and the mixture extracted with $CHCl_3$ (2 × 20 mL). The combined organic extracts were washed with H_2O (1 × 10 mL), and brine (1 × 5 mL), and dried. Solvent removal followed by column chromatography (silica gel, 0-15% EtOAc-hexane) of the residue furnished the corresponding monotosylate (2.5 g, 83%) as a colorless liquid; [Found: C, 67.55; H, 7.84. $C_{32}H_{44}O_5SSi$ requires C, 67.57; H, 7.80%]; R_f (20% EtOAc/hexane) 0.45; $[\alpha]_D^{22}$ +8.6 (*c* 1.00, $CHCl_3$); $\bar{\upsilon}$ (liquid film) 3500, 1362, 1177 cm^{-1}; δ_H 1.03-1.06 (merged s and d, 12H), 1.15-1.34 (m, 10H), 1.81 (broad s, 1H), 2.44 (s, 3H), 3.76-3.89 (m, 3H), 3.98-4.04 (m, 1H), 7.33-7.41 (m, 8H), 7.64-7.67 (m, 4H), 7.78-7.82 (m, 2H); δ_C 19.2, 21.6, 23.2, 25.0, 27.0, 29.3, 32.5, 39.2, 69.3, 69.4, 73.9, 127.3, 127.4, 127.9, 129.3, 129.4, 129.9, 132.6, 134.5, 134.8, 135.8, 144.9.

A mixture of the above compound (2.50 g, 4.40 mmol) and anhydrous K_2CO_3 (1.22 g, 8.80 mmol) in MeOH (10 mL) was stirred for 3 h at room temperature. The supernatant was decanted,

concentrated in vacuo, diluted with H_2O (20 mL) and extracted with EtOAc (3 × 10 mL). The organic extract was washed with H_2O (3 × 10 mL), and brine (1 × 5 mL), and dried. Solvent removal followed by column chromatography (silica gel, 0-15% EtOAc/hexane) of the residue gave pure **9** (1.53 g, 88%) as a colorless liquid; [Found: C, 75.91; H, 9.09. $C_{25}H_{36}O_2Si$ requires C, 75.70; H, 9.15%]; R_f (10% EtOAc/hexane) 0.84; $[\alpha]_D^{22}$ +13.8 (*c* 1.05, $CHCl_3$); υ (liquid film) 1241, 822 cm^{-1}; δ_H 1.03 (merged s and d, *J* = 6.0 Hz, 12H), 1.29-1.48 (m, 10H), 2.41-2.45 (m, 1H), 2.71-2.75 (m, 1H), 2.82-2.91 (m, 1H), 3.77-3.86 (m, 1H), 7.32-7.41 (m, 6H), 7.64-7.70 (m, 4H); δ_C 19.0, 23.0, 24.9, 25.6, 26.8, 29.1, 32.1, 39.0, 46.6, 51.9, 63.2, 127.2, 129.2, 134.2, 134.5, 135.3, 135.6.

4.9 (2*R*,8*R*)-8-*tert*-Butyldiphenylsilyloxy-1,2-epoxynonane 9 (from 8b)

To a cooled (-20 ^oC) and stirred solution of **8b** (0.240 g, 0.58 mmol) and Et_3N (0.3 mL, 2.03 mmol) in EtOAc (2 mL) was added TMSCl (0.074 mL, 0.58 mmol). After stirring for 0.5 h, Et_3N (0.13 mL, 0.93 mmol) and MsCl (0.05 mL, 0.69 mmol) were successively added into the mixture. After stirring for another 0.5 h, the mixture was brought to 25 °C, aqueous 2M HCl (2 mL) was added and stirring continued for 1 h. The organic layer was separated, the aqueous portion extracted with EtOAc (3 × 10 mL) and the combined organic extracts washed successively with H_2O (3 × 10 mL), aqueous 2M HCl (2 × 10 mL), H_2O (2 × 10 mL) and brine (1 × 5 mL), and dried. Solvent removal afforded the corresponding 1-hydroxy-2-mesylate, which was used as such for the next step.

A mixture of the above compound (0.238 g, 0.50 mmol) and anhydrous K_2CO_3 (0.139 g, 1.01 mmol) in MeOH (5 mL), was stirred for 3 h at room temperature. The supernatant was decanted, the solid residue washed with EtOAc (20 mL) and the combined organic extracts concentrated in vacuo. The residue was taken in EtOAc (20 mL) washed with water (2 × 10 mL)

and brine (1 × 5 mL), and dried. Removal of solvent in vacuo followed by column chromatography (silica gel, 0-10% EtOAc/hexane) of the residue afforded pure **9** (0.149 g, 65%) as a colorless oil. $[\alpha]_D^{24}$ +13.6 (*c* 1.01, $CHCl_3$). R_f (10% EtOAc/hexane) 0.83. Its IR and NMR spectral data were similar to that synthesized from **8a**.

4.10 (2*R*,8*S*)-2-*tert*-Butyldiphenylsilyloxy-19-eicosen-8-ol 10

To a cooled (-60 °C) and stirred solution of the Grignard reagent prepared from 11-bromoundec-1-ene (1.80 g, 7.73 mmol) and Mg (0.222 g, 9.27 mmol) in THF (80 mL) was added CuBr (catalytic) followed by **9** (1.53 g, 3.86 mmol) in THF (20 mL) after 0.5 h. Stirring was continued for 1 h at -60 °C and 3 h at room temperature. The mixture was treated with aqueous saturated NH_4Cl, the organic layer separated and the aqueous portion extracted with Et_2O (3 × 20 mL). The combined organic extracts were washed with water (2 × 10 mL) and brine (1 × 5 mL), dried, concentrated in vacuo, and the residue column chromatographed (silica gel, 0-10% Et_2O/hexane) to obtain pure **10** (1.9 g, 90%) as a colorless liquid; [Found: C, 78.11; H, 10.90. $C_{36}H_{58}O_2Si$ requires C, 78.48; H, 10.61%]; R_f (10% EtOAc/hexane) 0.54; $[\alpha]_D^{23}$ +10.7 (*c* 1.03, $CHCl_3$); ῡ (liquid film) 3358, 909 cm^{-1}; δ_H 1.03 (merged s and d, *J* = 6.0 Hz, 12H), 1.26-1.49 (m, 29H), 1.97-2.07 (m, 2H), 3.47-3.67 (s, 1H), 3.74-3.85 (m, 1H), 4.88-5.03 (m, 2H), 5.70-5.90 (m, 1H), 7.34-7.39 (m, 6H), 7.64-7.68 (m, 4H); δ_C 19.1, 23.2, 25.1, 25.5, 25.6, 26.9, 28.8, 29.1, 29.4, 29.5, 29.6, 29.7, 33.7, 37.3, 37.4, 39.3, 69.4, 71.7, 114.1, 127.3, 129.2, 129.3, 134.5, 134.8, 135.8, 139.0.

4.11 (13*S*,19*R*)-19-*tert*-Butyldiphenylsilyloxy-13-tetrahydropyranyloxyeicosene 11

A solution of **10** (1.20 g, 2.18 mmol), DHP (0.275 g, 3.27 mmol) and PPTS (catalytic) in CH_2Cl_2 (20 mL) was stirred for 3 h at room temperature. The mixture was poured into aqueous 5% $NaHCO_3$ (20 mL), the organic layer separated and the aqueous portion extracted with $CHCl_3$

(3 × 10 mL). The combined organic extracts were washed with water (2 × 10 mL) and brine (1 × 5 mL), and dried. Removal of solvent in vacuo followed by column chromatography (silica gel, 0-10% EtOAc/hexane) of the residue afforded pure **11** (1.3 g, 94%) as a colorless liquid; [Found: C, 77.31; H, 10.35. $C_{41}H_{66}O_3Si$ requires C, 77.54; H, 10.48%]; R_f (10% EtOAc/hexane) 0.84; $[\alpha]_D^{22}$ +9.4 (*c* 1.13, $CHCl_3$); $\bar{\upsilon}$ (liquid film) 1375, 999 cm^{-1}; δ_H 1.05 (merged s and d, 12H), 1.26-1.63 (m, 34H), 1.97-2.08 (m, 2H), 3.43-3.59 (m, 2H), 3.77-3.93 (m, 2H), 4.63 (broad s, 1H), 4.89-5.03 (m, 2H), 5.70-5.91 (m, 1H), 7.34-7.41 (m, 6H), 7.64-7.68 (m, 4H); δ_C 19.2, 19.9, 23.2, 24.9, 25.0, 25.2, 25.6, 27.0, 28.9, 29.1, 29.5, 29.6, 29.8, 31.2, 33.4, 33.5, 33.8, 34.9, 35.0, 39.4, 62.6, 69.6, 76.6, 97.4, 114.1, 127.4, 127.5, 129.3, 129.4, 134.6, 134.9, 135.5, 135.8, 139.1.

4.12 (13*S*,19*R*)-19-*tert*-Butyldiphenylsilyloxy-13-tetrahydropyranyloxyeicosan-1-ol 12

To a cooled (0 °C) and stirred solution of **11** (1.10 g, 1.74 mmol) in THF (25 mL) was injected $BH_3.Me_2S$ (0.58 mL, 2M in THF, 1.16 mmol). After 0.5 h, the solution was brought to room temperature, stirred for 1 h at room temperature and treated with aqueous 3N NaOH (1 mL). After cooling to 0 °C, H_2O_2 (1 mL) was added slowly, stirring continued for 1 h at 0 °C and for 3 h at room temperature. The mixture was poured into H_2O (20 mL), the organic layer separated and the aqueous portion extracted with EtOAc (3 × 10 mL). The combined organic extracts were washed with water (2 × 10 mL) and brine (1 × 5 mL), and dried. Removal of solvent in vacuo followed by column chromatography (silica gel, 0-10% EtOAc/hexane) of the residue afforded pure **12** (1.0 g, 88%) as a colorless liquid; [Found: C, 75.23; H, 10.62. $C_{41}H_{68}O_4Si$ requires C, 75.40; H, 10.50%]; R_f (15% EtOAc/hexane) 0.45; $[\alpha]_D^{27}$ +7.9 (*c* 1.10, $CHCl_3$); $\bar{\upsilon}$ (liquid film) 3409, 1023 cm^{-1}; δ_H 1.05 (merged s and d, 12H), 1.24-1.60 (m, 39H), 3.49-3.65 (m, 4H), 3.76-3.89 (m, 2H), 4.61 (broad s, 1H), 7.31-7.46 (m, 6H), 7.62-7.74 (m, 4H);

δ_C 19.2, 19.9, 21.0, 23.2, 25.0, 25.5, 25.6, 25.7, 27.0, 29.4, 29.6, 29.8, 31.2, 32.8, 33.4, 35.0, 39.4, 60.4, 62.6, 63.0, 69.5, 76.7, 97.4, 127.3, 127.4, 129.3, 129.4, 134.6, 134.9, 135.8.

4.13 (13*S*,19*R*)-19-*tert*-Butyldiphenylsilyloxy-13-tetrahydropyranyloxyeicosanal 13

To a cooled (-78 °C) and stirred solution of oxalyl chloride (0.119 g, 0.94 mmol) in CH_2Cl_2 (20 mL) was added DMSO (0.15 mL, 2.15 mmol). After stirring for 10 min, **12** (0.560 g, 0.86 mmol) was added, followed by Et_3N (0.60 mL, 4.29 mmol) after 20 min. After stirring for 2 h at room temperature, the reaction mixture was poured into H_2O (20 mL), the organic layer separated and the aqueous portion extracted with $CHCl_3$ (3 × 10 mL). The combined organic extracts were washed with water (2 × 10 mL) and brine (1 × 5 mL), and dried. Removal of solvent in vacuo followed by column chromatography (silica gel, 0-10% EtOAc/hexane) of the residue afforded pure **13** (0.490 g, 88%) as a colorless oil; [Found: C, 75.91; H, 10.12. $C_{41}H_{66}O_4Si$ requires C, 75.64; H, 10.22%]; R_f (10% EtOAc/hexane) 0.75; $[\alpha]_D^{22}$ +9.8 (*c* 1.00, $CHCl_3$); $\bar{\upsilon}$ (liquid film) 2719, 1720 cm^{-1}; δ_H 1.04 (merged s and d, 12H), 1.24-1.81 (m, 36H), 2.36-2.45 (m, 2H), 3.44-3.64 (m, 2H), 3.77-3.90 (m, 2H), 4.62 (broad s, 1H), 7.32-7.41 (m, 6H), 7.64-7.68 (m, 4H), 9.75 (t, *J* = 1.8 Hz, 1H); δ_C 19.1, 19.9, 21.9, 23.1, 23.7, 24.9, 25.1, 25.5, 26.8, 26.9, 29.0, 29.2, 29.3, 29.4, 29.5, 29.7, 31.1, 33.3, 33.4, 34.8, 34.9, 39.2, 39.3, 43.6, 43.8, 62.7, 69.4, 76.5, 97.3, 127.3, 129.2, 134.5, 134.8, 135.4, 135.7, 202.6, 209.1.

4.14 (4*R*,16*S*,22*R*)-22-*tert*-Butyldiphenylsilyloxy-16-tetrahydropyranyloxytricos-1-en-4-ol 14

A mixture of azeotropically dried $InCl_3$ (0.037 g, 0.16 mmol), (*S*)-BINOL (0.047 g, 0.16 mmol) and molecular sieve 4Å (0.04 g) in CH_2Cl_2 (20 mL) was stirred for 2 h followed by slow addition of allylBu_3Sn (0.46 mL, 1.51 mmol). After 10 min, the reaction mixture was cooled to -78 °C and **13** (0.490 g, 0.75 mmol) added dropwise. After stirring at -78 °C for 4 h and at room

temperature for 16 h, the reaction mixture was treated with aqueous saturated NH_4Cl. The organic layer was separated and the aqueous portion extracted with $CHCl_3$ (2 × 10 mL). The combined organic extracts were washed with water (2 × 10 mL) and brine (1 × 5 mL), dried and concentrated in vacuo. The residue was purified by column chromatography (silica gel, 0-10% Et_2O/hexane) to afford pure **14** (0.400 g, 77%) as a colorless oil; [Found: C, 76.39; H, 10.68. $C_{44}H_{72}O_4Si$ requires C, 76.24; H, 10.47%]; R_f (10% EtOAc/hexane) 0.67; $[\alpha]_D^{25}$ +9.4 (*c* 1.20, $CHCl_3$); $\bar{\upsilon}$ (liquid film) 3457, 998 cm^{-1}; δ_H 1.02 (merged s and d, *J* = 6.0 Hz, 12H), 1.25-1.79 (m, 39H), 2.07-2.32 (m, 2H), 3.49-3.66 (m, 3H), 3.76-3.85 (m, 2H), 4.61 (broad s, 1H), 5.08-5.15 (m, 2H), 5.71-5.85 (m, 1H), 7.33-7.40 (m, 6H), 7.63-7.67 (m, 4H); δ_C 19.2, 19.9, 23.2, 24.9, 25.2, 25.5, 25.6, 27.0, 29.6, 29.8, 31.1, 33.3, 35.0, 36.7, 37.3, 39.3, 41.9, 62.5, 69.5, 70.6, 76.4, 97.3, 117.9, 127.3, 129.3, 134.5, 134.9, 135.5, 135.8.

4.15 (4*R*,16*S*,22*R*)-4-*tert*-Butyldimethylsilyloxy-22-*tert*-butyldiphenylsilyloxy-16-tetrahydropyranyloxytricos-1-ene 15

A mixture of **14** (0.300 g, 0.43 mmol), TBSCl (0.098 g, 0.65 mmol), imidazole (0.044 g, 0.65 mmol) and DMAP (catalytic) in CH_2Cl_2 (20 mL) was stirred at room temperature for 4 days. It was poured into ice-cold water (20 mL), the organic layer was separated and the aqueous portion extracted with $CHCl_3$ (3 × 10 mL). The combined organic extracts were washed with water (2 × 10 mL) and brine (1 × 5 mL), and dried. Removal of solvent in vacuo followed by column chromatography (silica gel, 0-5% EtOAc/hexane) of the residue afforded pure **15** (0.283 g, 81%) as a colorless liquid; [Found: C, 74.20; H, 10.89. $C_{50}H_{86}O_4Si_2$ requires C, 74.38; H, 10.74%]; R_f (10% EtOAc/hexane) 0.81; $[\alpha]_D^{24}$ +8.5 (*c* 1.17, $CHCl_3$); $\bar{\upsilon}$ (liquid film) 1640, 912 cm^{-1}; δ_H 0.03 and 0.05 (two s, 6H), 0.87 (s, 9H), 1.03 (merged s and d, 12H), 1.25-1.83 (m, 38H), 2.15-2.33 (m, 2H), 3.44-3.69 (m, 3H), 3.76-3.92 (m, 2H), 4.63-4.65 (m, 1H), 4.97-5.09 (m, 2H),

5.73-5.81 (m, 1H), 7.31-7.40 (m, 6H), 7.64-7.68 (m, 4H); δ_C -4.6, -4.4, 18.1, 19.2, 19.8, 19.9, 23.2, 25.0, 25.2, 25.3, 25.5, 25.6, 25.9, 27.0, 29.6, 29.7, 29.8, 31.2, 33.3, 34.7, 35.0, 36.8, 37.9, 39.4, 39.8, 41.9, 62.6, 69.6, 72.0, 75.3, 96.8, 97.4, 116.5, 116.9, 127.3, 127.4, 129.3, 134.6, 134.9, 135.5, 135.8.

4.16 (3*R*,15*S*,21*R*)-3-*tert*-Butyldimethylsilyloxy-21-*tert*-butyldiphenylsilyloxy-15-tetrahydropyranyloxydocosanal 16

To a stirred solution of **15** (0.200 g, 0.25 mmol) in acetone:water (8:1, 20 mL) were added NMO (0.067 g, 0.50 mmol) and OsO_4 (0.004 g, 0.012 mmol) in *tert*-BuOH (1 mL). After stirring overnight, the mixture was treated with aqueous saturated Na_2SO_3, the organic layer separated and the aqueous portion extracted with Et_2O (3 × 10 mL). The combined organic extracts were washed with water (2 × 10 mL) and brine (1 × 5 mL), and dried. Removal of solvent in vacuo followed by preparative thin layer chromatography (silica gel, 10% EtOAc/hexane) of the residue afforded the pure diol (0.200 g, 99%) as a colorless thick oil; [Found: C, 71.62; H, 10.86. $C_{50}H_{88}O_6Si_2$ requires C, 71.37; H, 10.54%]; R_f (5% MeOH/$CHCl_3$) 0.55; $[\alpha]_D^{24}$ +1.4 (*c* 1.02, $CHCl_3$); $\tilde{\upsilon}$ (liquid film) 3413, 1463 cm^{-1}; δ_H 0.08 and 0.1 (two s, 6H), 0.89 (s, 9H), 1.04 (merged s and d, 12H), 1.26-1.75 (m, 40H), 2.84 (broad, 2H), 3.38-3.65 (m, 4H), 3.77-4.12 (m, 4H), 4.63 (broad s, 1H), 7.31-7.43 (m, 6H), 7.64-7.68 (m, 4H); δ_C -3.8, -3.4, -3.2, 18.6, 20.0, 20.8, 24.0, 25.5, 26.0, 27.5, 27.8, 30.7, 31.9, 34.2, 35.7, 37.1, 38.2, 38.4, 39.8, 40.1, 63.3, 67.6, 67.9, 69.7, 70.4, 71.9, 73.4, 98.1, 128.1, 130.1, 135.3, 135.6, 136.6.

To a cooled (10 ^oC) and stirred solution of the above diol (0.170 g, 0.20 mmol) in aqueous 60% CH_3CN (20 mL) was added $NaIO_4$ (0.052 g, 0.24 mmol) in portions. After stirring for 2 h, the mixture was filtered, the filtrate treated with aqueous 10% $NaHSO_3$ and thoroughly extracted with $CHCl_3$ (2 × 10 mL). The organic layer was washed with water (2 × 10 mL) and

brine (1 × 5 mL), and concentrated in vacuo to get a residue, which on preparative thin layer chromatography (silica gel, 7% EtOAc/hexane) furnished pure **16** (0.144 g, 88%) as a colorless oil; [Found: C, 72.55; H, 10.64. $C_{49}H_{84}O_5Si_2$ requires C, 72.71; H, 10.46%]; R_f (10% EtOAc/hexane) 0.64; $[\alpha]_D^{24}$ +7.6 (*c* 1.00, $CHCl_3$); $\bar{\upsilon}$ (liquid film) 2712, 1727 cm^{-1}; δ_H 0.04 and 0.08 (two s, 6H), 0.84 (s, 9H), 1.02 (broad s, 12H), 1.24-1.74 (m, 38H), 2.47-2.50 (m, 2H), 3.48-3.55 (m, 2H), 3.75-3.84 (m, 2H), 4.12-4.17 (m, 1H), 4.61 (broad s, 1H), 7.30-7.36 (m, 6H), 7.64-7.66 (m, 4H), 9.78 (broad d, *J* = 2.2 Hz, 1H); δ_C -4.9, -4.6, 18.0, 19.2, 19.9, 23.2, 25.1, 25.2, 25.5, 25.7, 27.0, 29.6, 29.9, 31.2, 34.9, 37.8, 39.4, 50.8, 62.6, 68.2, 69.5, 76.7, 97.4, 127.3, 127.4, 129.4, 134.6, 134.9, 135.8, 202.5

4.17 (3*R*,15*S*,21*R*)-3-*tert*-Butyldimethylsilyloxy-21-*tert*-butyldiphenylsilyloxy-15-tetrahydropyranyloxydocosanoic acid 17

To a stirred solution of **16** (0.120 g, 0.15 mmol) in CH_3CN (0.5 mL) was added NaH_2PO_4 (6.2 mg, 0.04 mmol) in water (0.5 mL) and 30% H_2O_2 (185 µL, 0.16 mmol). The mixture was cooled to 0 ºC, and $NaClO_2$ (21.5 mg, 0.24 mmol) in water (1 mL) was added dropwise over 0.5 h. The reaction mixture was stirred at 15 ºC till completion of the reaction (~6 h, monitored by gas evolution), Na_2SO_4 (0.25 g) added, and the mixture extracted with EtOAc (3 × 10 mL). The organic layer was washed with water (2 × 5 mL) and brine (1 × 2 mL), and concentrated in vacuo to get a residue, which on preparative thin layer chromatography (silica gel, 10% EtOAc/hexane) furnished pure **17** (0.077 g, 63%) as a colorless thick oil; [Found: C, 71.20; H, 10.39. $C_{49}H_{84}O_6Si_2$ requires C, 71.31; H, 10.26%]; R_f (5% MeOH/$CHCl_3$) 0.25; $[\alpha]_D^{24}$ +6.6 (*c* 1.00, $CHCl_3$); $\bar{\upsilon}$ (liquid film) 3500-2500, 1712 cm^{-1}; δ_H 0.08 and 0.09 (two s, 6H), 0.88 (s, 9H), 1.04 (s, 12H), 1.20-1.69 (m, 38H), 2.48-2.51 (m, 2H), 3.65-3.95 (m, 4H), 4.06-4.11 (m, 1H), 4.64 (broad s, 1H), 7.35-7.41 (m, 6H), 7.65-7.68 (m, 4H); δ_C -4.9, -4.6, 14.1, 17.9, 19.2, 19.9, 22.7,

23.2, 25.1, 25.2, 25.5, 25.7, 27.0, 29.7, 29.8, 31.2, 31.9, 33.4, 34.9, 37.3, 39.4, 41.9, 50.7, 62.6, 69.5, 69.6, 76.8, 97.3, 127.3, 127.4, 129.4, 134.6, 135.8, 139.2, 175.5.

4.18 Methyl (3*R*,15*S*,21*R*)-3-*tert*-Butyldimethylsilyloxy-21-*tert*-butyldiphenylsilyloxy-15-hydroxydocosanoate 18

To a cooled (0 ^{o}C) solution of **17** (0.120 g, 0.15 mmol) in Et_2O (10 mL) was added CH_2N_2 in Et_2O in portions till the starting material was consumed (2 h). The reaction mixture was purged with N_2 (g) to remove the solvent. The residue was dissolved in MeOH (10 mL), $CuCl_2.2H_2O$ (10 mol%) added, and the mixture stirred at room temperature till completion of the reaction (*cf*. TLC, ~12 h). The mixture was diluted with Et_2O (20 mL), filtered, and concentrated in vacuum. The residue was purified by column chromatography (silica gel, 0-15% EtOAc/hexane) to get **18** (0.087 g, 80%) as a colorless oil; [Found: C, 71.45; H, 10.48. $C_{45}H_{78}O_5Si_2$ requires C, 71.56; H, 10.41%]; R_f (5% MeOH/$CHCl_3$) 0.59; $[\alpha]_D^{24}$ +6.1 (*c* 0.814, $CHCl_3$); $\bar{\upsilon}$ (liquid film) 3448, 1731 cm^{-1}; δ_H 0.08 (s, 6H), 0.89 (s, 9H), 1.04 (s, 12H), 1.25-1.53 (m, 33H), 2.40-2.44 (m, 1H), 2.50-2.55 (m, 1H), 3.54-3.57 (m, 1H), 3.71 (s, 3H), 3.79-3.83 (m, 1H), 3.98-4.02 (m, 1H), 7.35-7.42 (m, 6H), 7.67-7.69 (m, 4H); δ_C -4.6, 14.4, 19.3, 19.5, 22.9, 23.4, 25.4, 25.7, 27.2, 29.3, 29.6, 29.8, 30.4, 31.6, 32.1, 36.7, 37.6, 39.6, 41.3, 51.9, 68.2, 69.8, 72.2, 127.5, 127.6, 129.5, 129.6, 134.8, 135.8, 136.1, 173.7.

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Graphical abstract

Asymmetric synthesis of the constitutive C_{22}-carboxylic acid of macroviracin A

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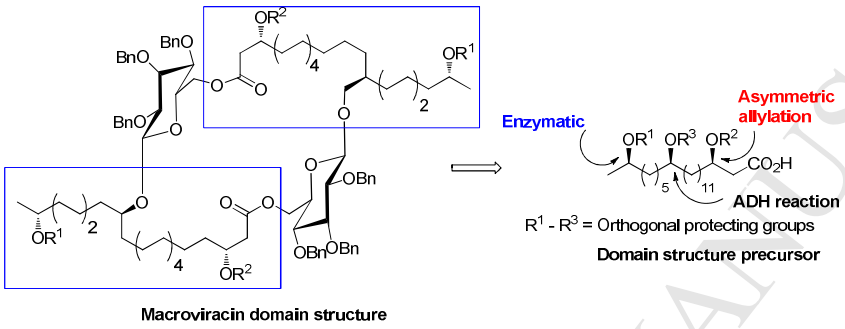

An enantioconvergent synthesis of the advanced intermediate of macroviracin A has been developed, using enantioselective lipase-catalyzed acylation, asymmetric allylation, and asymmetric dihydroxylation reaction to install the required stereogenic centres. The key reactions proceeded with good to excellent stereoselectivity.