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Total synthesis of (+)-crocacin C

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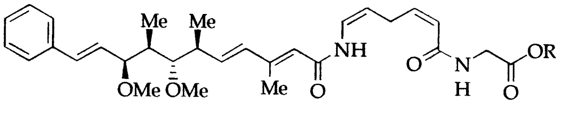
Abstract—The total synthesis of potent antifungal and cytotoxic agent (+)-crocacin C in optically pure form following a convergent strategy is described here in detail. The synthesis also established the absolute stereochemistry of the molecule having a (6*S*,7*S*,8*R*,9*S*) configuration. While C8 and C9 stereocenters were built following a Ti(IV)-mediated diastereoselective 'non-Evans' aldol reaction based on 2-oxazolidinethione chiral auxiliary, lithium dimethylcuprate opening of a C6–C7 chiral epoxide prepared by Sharpless epoxidation method established the remaining two stereocentres. © 2001 Elsevier Science Ltd. All rights reserved.

1. Introduction

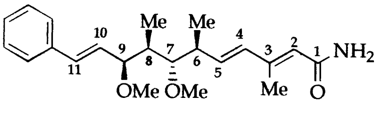
Many known biologically active metabolites were isolated from myxobacteria. Recently, four novel antifungal and highly cytotoxic metabolites, the crocacins A–D (**1**–**4**) were isolated by Jansen's group from the myxobacterial strains of *Chondromyces crocatus* (crocacins A–C) and *Chondromyces pediculatus* (crocacin D).[1,2] The biological activity of the major component crocacin A (**1**) consists of moderate growth inhibition of Gram-positive bacteria and an effective growth inhibition of fungi and yeasts, caused by the inhibition of electron flow within the cytochrome bc_1 segment (complex III) of the respiratory chain.[3] Crocacin D (**4**) shows a distinctly higher biological activity against *saccharomyces cerevisiae* and higher toxicity in L929 mouse fibroblast cell culture compared to other crocacins.

The crocacins represent a second novel group of modified peptides from *C. crocatus*. However, unlike the chondramides isolated earlier,[4] crocacins are linear dipeptides. Crocacin C (**3**) is a structural fragment of crocacins A, B and D. Although small amounts of **3** are regularly observed in the extracts of *C. crocatus*, it may additionally be formed during the isolation process by cleavage of the acid sensitive enamine bond.

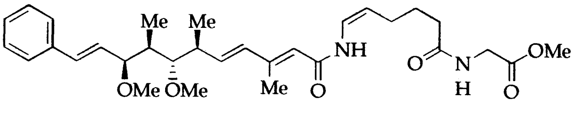
The main structural features of crocacin molecules are polyketide derived four consecutive stereocentres, unusual dipeptides of glycine and a 6-aminohexenoic (in crocacin



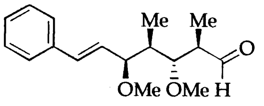
1: crocacin A (R = Me)
2: crocacin B (R = H)



3: crocacin C



4: crocacin D



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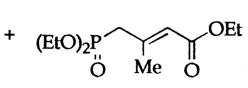

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Keywords: antifungals; cytotoxins; aldol reactions; katsuki-sharpless reactions.

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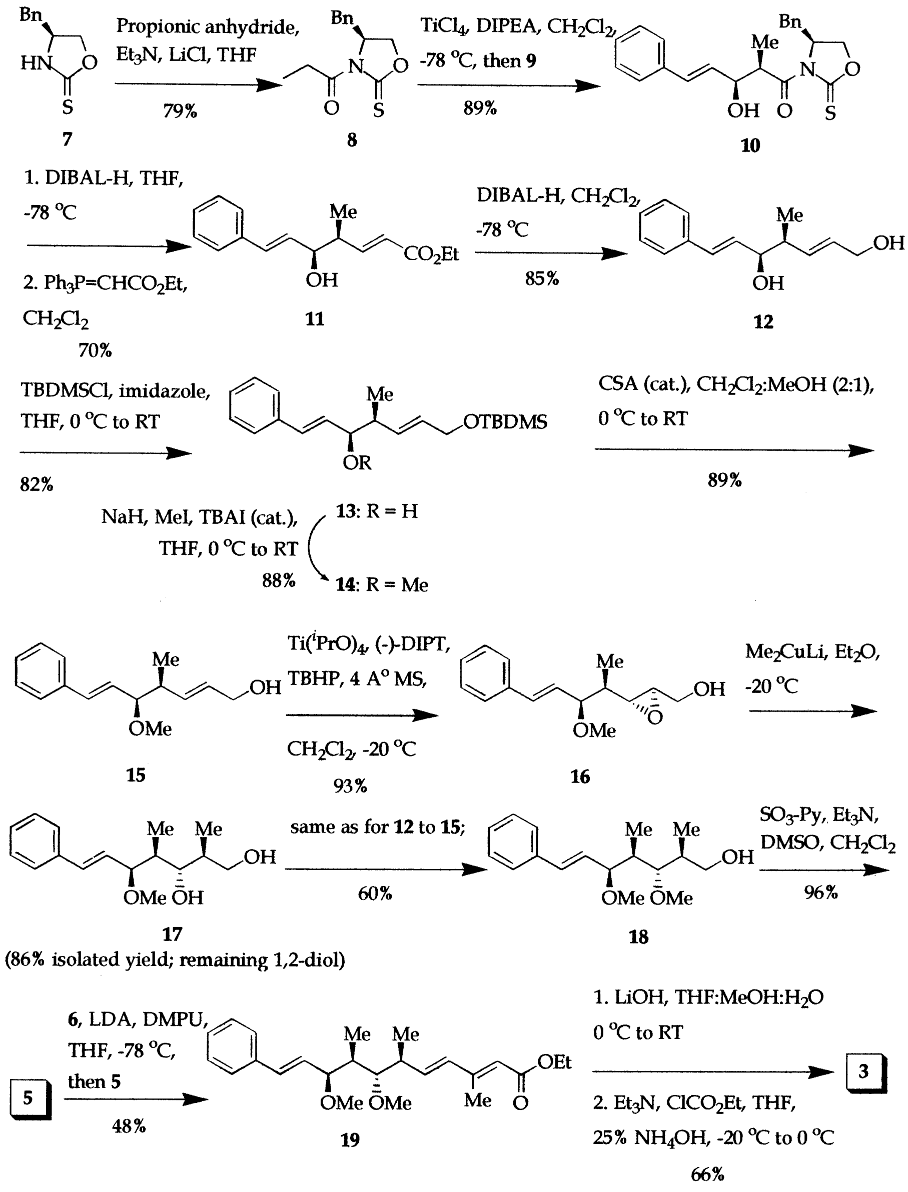

Scheme 1. Stereoselective synthesis of (+)-crocacin C.

D) or -hexadienoic acid (in crocacins A and B) and a large number of double bonds with their respective geometric constraints. The relative configurations of these molecules were deduced using 2D NMR experiments and molecular modeling studies.[2]

Total synthesis of (+)-crocacin C (**3**) communicated recently by us[5] as well as by Rizzacasa et al.[6] confirmed the relative stereochemistry of the molecule deduced earlier[2] and also established the absolute configuration of the natural product as (6*S*,7*S*,8*R*,9*S*). In this paper we describe in detail the full account of the convergent strategy followed by us for the total synthesis of (+)-crocacin C.

2. Results and discussion

Retrosynthetically crocacin C can be dissected into two halves, an aldehyde component **5** and the diethylphosphonate **6**,[7] which could be coupled using the Horner–Wadsworth–Emmons olefination method.

The salient features of the synthesis is a Ti(IV)-mediated diastereoselective ‘non-Evans’ aldol reaction following the protocol of Crimmins et al.[8] using a 2-oxazolidinethione-based chiral auxilliary,[9] which was expected to fix the C_8 and C_9 stereocentres. The remaining two centers, C_6 and C_7, were to be constructed employing Sharpless asymmetric epoxidation followed by lithium dimethylcuprate opening of the epoxide. The entire route is depicted in Scheme 1.

For the asymmetric aldol reaction, the required propanoyl oxazolidinethione (**8**) was prepared by *N*-acylation of the chiral oxazolidinethione **7**[9] using propionic anhydride in presence of triethylamine and anhydrous LiCl in THF to furnish the desired product **8** in 79% yield. Addition of the titanium enolate derived from the propanoyl oxazolidinethione **8** to *trans*-cinnamaldehyde (**9**), following the reported procedure,[8] gave the non-Evans *syn* aldol product **10** as the only isolable diastereomer in 89% yield. The relative and absolute stereochemistries of the product were assigned on the basis of earlier reports.[8] The *syn*-relationship between the methyl and hydroxyl groups was supported by the relatively small value of vicinal coupling constant of 4.7 Hz.

Once the required diastereoselectivity in fixing the C_8–C_9 centers was achieved, the chiral auxiliary was removed by reduction using DIBAL-H. This controlled reduction of **10** using DIBAL-H in THF at −78°C gave an intermediate aldehyde[10,11] along with the oxazolidinethione **7**. After an aqueous work up, the aldehyde was used directly in the next step where it was treated with stabilized ylide, carbethoxymethylenetriphenylphosphorane. The product, α,β-unsaturated ester **11** was formed in 70% yield. The ^{1}H NMR spectrum of **11** showed signals for the newly formed *trans*-olefinic protons at δ 5.92 and 7.05 with 16.1 Hz coupling constant. The ester **11** in the next step was reduced to the diol **12** in 85% yield using DIBAL-H in dichloromethane at −78°C.

The primary hydroxyl group of diol **12** was protected selectively as the *tert*-butyldimethylsilyl ether **13**, by treatment with TBDMSCl and imidazole in THF. Next, the secondary hydroxyl in **13** was protected as methyl ether to furnish **14** in 88% yield by treatment with sodium hydride and methyl iodide in presence of catalytic amount of tetra-*n*-butylammonium iodide in THF. The TBDMS protective group in **14** was then removed by the addition of a catalytic amount of camphorsulfonic acid in MeOH/CH_2Cl_2 (1:2). The product *E*-allylic alcohol **15** was formed in 89% yield.

The *E*-allylic alcohol **15** was then subjected to Sharpless asymmetric epoxidation[12] using (−)-diisopropyl tartrate (DIPT) in presence of $Ti(O^iPr)_4$ and *tert*-butylhydroperoxide and 4 Å molecular sieves in CH_2Cl_2 at −20°C furnishing the desired epoxy alcohol **16** as the only diastereomer in 93% isolated yield.

Now the stage was set to carry out the regioselective opening of epoxy alcohol **16**, which is expected to fix the C_6–C_7 stereocentres. Accordingly, the regioselective opening of epoxide ring using lithium dimethylcuprate (Me_2CuLi) in ether at −20°C gave the required 1,3-diol **17** as the major product. The minor 1,2-diol could be removed easily by standard silica gel column chromatography to get 86% yield of **17**. The bulky substituent at the '3-position' of the '2,3-epoxy alcohol' moiety in **16** and also the electronic factor helped to open the epoxide ring more favourably at the less crowded '2-position' giving an excellent yield of the desired 1,3-diol.[13]

The secondary hydroxy group of **17** was methylated following the same three steps as described for the conversion of **12** to **15**, i.e. selective protection of the primary alcohol as the silyl ether, methylation of the secondary alcohol and finally deprotection of the primary hydroxyl protective group. The product primary alcohol **18** was obtained in an overall 60% yield in three steps.

For the Horner–Wadsworth–Emmons olefination reaction, the required diethyl-phosphonate **6** was prepared in two steps from ethyl 3-methylbut-2-enoate following reported procedures.[7] The oxidation of the primary hydroxy group of **18** was carried out using SO_3-Py/Et_3N in DMSO/CH_2Cl_2 to give the targeted aldehyde **5** in quantitative yield. Once the aldehyde **5** and the diethyl phosphonate **6** were ready, the crucial Horner–Wadsworth–Emmons olefination was carried out by adding the anion generated from **6** using lithium diisopropylamide (LDA) in presence of 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone (DMPU)[14] to the aldehyde **5** at −78°C. After stirring for 8 h at the same temperature, the reaction mixture was worked up in usual fashion. Chromatographic purification furnished the desired *E*-olefin **19** in 48% yield (60%, based on 20% recovered aldehyde). Although the olefination was slow at −78°C, the reaction temperature could not be raised due to the formation of considerable amount of eliminated product at higher temperatures. The exclusive formation of *E*-olefinic product was confirmed by ^{1}H NMR signal of C_4–H that appeared as a doublet at δ 6.04 with 15.8 Hz coupling constant.

The basic framework of crocacin C in **19** was finally converted to the natural product **3** in two steps in 66% yield. The ester group upon saponification using LiOH·H_2O in THF/MeOH/H_2O gave an acid intermediate. Reaction of the acid with ethyl chloroformate in THF in presence of triethyl amine at −20°C converted it to a mixed anhydride that was treated in situ with 25% aqueous NH_4OH at −20°C.[15] The reaction mixture was stirred for 20 min as the temperature was allowed to reach to 0°C. Aqueous work up was followed by chromatographic purification to furnish the target molecule crocacin C (**3**).

Our synthetic crocacin C (**3**) showed rotation $[\alpha]_D^{20}=+53.8$ (*c* 0.2, MeOH) [literature value[2] is +52.2 (*c* 0.3, MeOH)]. The ^{1}H and ^{13}C NMR data of synthetic **3** was in all respects identical with the reported data for the naturally occurring crocacin C.[2] Thus, the naturally occurring crocacin C has the (6*S*,7*S*,8*R*,9*S*) configuration of the synthetic product reported here. Since crocacin C is the biogenetic precursor of crocacins A, B and D, these compounds should also have the same absolute configuration.

In conclusion the total synthesis described here for (+)-crocacin C will help to achieve the synthesis of other congeners and will be useful for further studies with these molecules.

3. Experimental

3.1. General procedures

All reactions were carried out in oven or flame-dried glassware with magnetic stirring under nitrogen atmosphere using dry, freshly distilled solvents, unless otherwise noted. Reactions were monitored by thin layer chromatography (TLC) carried out on 0.25 mm silica gel plates with UV light, I_2, 7% ethanolic phosphomolybdic acid-heat and 2.5% ethanolic anisaldehyde (with 1% AcOH and 3.3% conc. H_2SO_4)-heat as developing agents. Silica gel finer than 200 mesh was used for flash column chromatography.

Yields refer to chromatographically and spectroscopically homogeneous materials unless otherwise stated. IR spectra were recorded as neat liquids or KBr pellets. NMR spectra were recorded on 200, 400 and 500 MHz spectrometers at room temperature of ~21°C in $CDCl_3$ or acetone-d_6 using tetramethylsilane as internal standard or the solvent signal as secondary standard and the chemical shifts are shown in δ scales. Multiplicities of NMR signals are designated as s (singlet), d (doublet), t (triplet), q (quartet), br (broad), m (multiplet, for unresolved lines), etc. ^{13}C NMR spectra were recorded with complete proton decoupling. Mass spectra were obtained under electron impact (EI) and liquid secondary ion mass spectrometric (LSIMS) techniques.

3.1.1. *N*-Propanoyl-(*S*)-4-benzyl-1,3-oxazolidine-2-thione (8). To a solution of oxazolidinethione **7**[9] (9.5 g, 49.20 mmol) in dry THF (150 mL), Et_3N (13.7 mL, 98.40 mmol) was added followed by the portionwise addition of anhydrous LiCl (3.34 g, 78.70 mmol). The reaction mixture was cooled to −20°C and propionic anhydride (7.56 mL, 59.04 mmol) was added dropwise, turning the reaction mixture slowly into a slurry. Stirring was continued for 3 h as the temperature slowly reached the room temperature. The reaction mixture was concentrated to remove the THF and then diluted with EtOAc (200 mL), washed with aqueous HCl (0.2 M, 50 mL), followed by saturated $NaHCO_3$ (50 mL), brine (50 mL), dried (Na_2SO_4) and concentrated in vacuo. Purification of the crude by column chromatography (SiO_2, 5–15% EtOAc in petroleum ether eluent) afforded acylated product **8** (9.7 g, 79%) as a white solid. R_f=0.5 (silica, 15% EtOAc in petroleum ether); $[\alpha]_D^{20}=+122$ (*c* 1, $CHCl_3$); mp 74–75°C; IR (KBr): ν_{max} 2988, 2949, 1709, 1357, 1302, 1192, 925, 706 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 7.40–7.20 (m, 5H, Ar*H*), 4.98–4.84 (m, 1H, C*H*CH_2Ph), 4.35–4.22 (m, 2H, CHCH_2O), 3.50–3.20 (m, 3H, C*H*Ph, CH_2CO), 2.75 (dd, *J*=14.5, 11.0 Hz, 1H, C*H'*Ph), 1.25 (t, *J*=7.2 Hz, 3H, CH_2CH_3); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 185.29, 174.71, 135.25, 129.26, 128.86, 127.24, 70.22, 59.83, 37.58, 31.22, 8.44; MS (EI): *m/z* (%): 249 (30) [M^+]; HRMS (EI): calcd for $C_{13}H_{15}NO_2S$ [M^+]: 249.0824, found: 249.0825.

3.1.2. (2*R*,3*S*,4*E*)-1-[4-Benzyl-2-thioxo-(4*S*)-1,3-oxazolan-3-yl]-3-hydroxy-2-methyl-5-phenyl-pent-4-en-1-one (10). To a solution of propanoyl oxazolidinethione **8** (9 g, 36 mmol) in CH_2Cl_2 (100 mL) at 0°C, $TiCl_4$ (7.93 mL, 72 mmol) was added dropwise. The reaction mixture turned into yellowish slurry. It was stirred for 5 min at 0°C and then diisopropylethylamine (6.9 mL, 39.6 mmol) was added dropwise. The reaction mixture now turned deep reddish in color. Stirring was continued for another 20 min at 0°C. It was cooled to −78°C and freshly distilled cinnamaldehyde **9** (5 mL, 39.6 mmol) was added dropwise, during which the yellow color appeared again. Then it was stirred at −78°C for 1 h, warmed to 0°C and quenched by the addition of cold saturated NH_4Cl solution. It was then extracted with EtOAc (200 mL) and washed with brine (100 mL), dried (Na_2SO_4) and concentrated in vacuo. Purification by column chromatography (SiO_2, 20–40% EtOAc in petroleum ether eluent) afforded **10** (12.25 g, 88%) as a colorless solid. R_f=0.5 (silica, 30% EtOAc in petroleum ether); $[\alpha]_D^{20}=+98.8$ (*c* 1, $CHCl_3$); mp 83–85°C; IR (KBr): ν_{max} 3553, 3012, 2949, 1702, 1357, 1325, 1192, 965, 745, 690 cm^{-1}, ^1H NMR ($CDCl_3$, 200 MHz): δ 7.45–7.15 (m, 10H, Ar*H*), 6.70 (d, *J*=15.2 Hz, 1H, C5–*H*), 6.26 (dd, *J*=15.2, 4.7 Hz, 1H, C4–*H*), 5.10–4.90 (m, 2H, C2–*H*, C4′–*H*), 4.80 (m, 1H, C3–*H*), 4.34–4.25 (m, 2H, C5′–H_2), 3.30 (dd, *J*=12.7, 3.6 Hz, 1H, C*H*Ph), 2.75 (br, 1H, O*H*), 2.70 (dd, *J*=12.7, 10.0 Hz, 1H, C*H′*Ph), 1.25 (d, *J*=7.2 Hz, 3H, C2–CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 185.28, 176.77, 136.41, 135.03, 131.47, 129.22, 128.87, 128.58, 128.46, 127.63, 127.29, 126.46, 72.92, 70.15, 59.92, 42.59, 37.61, 11.25; MS (EI): *m/z* (%): 381 (5) [M^+]; HRMS (EI): calcd for $C_{22}H_{23}NO_3S$ [M^+]: 381.1399, found: 381.1381.

3.1.3. Ethyl 5-hydroxy-4-methyl-7-phenyl-(2*E*,4*S*,5*S*,6*E*)-2,6-heptadienoate (11). To a solution of **10** (10 g, 26.2 mmol) in dry THF (80 mL) at −78°C, a solution of DIBAL-H in toluene (1.2 M, 43.7 mL, 52.5 mmol) was added dropwise. After the addition was complete, the progress of the reaction was monitored regularly every 5 min. The reaction was complete in 15 min, and was quenched by the addition of few drops of MeOH, followed by saturated aqueous sodium potassium tartrate solution. It was warmed to 0°C and stirred for 0.5 h. The aqueous layer was extracted with EtOAc (200 mL) and washed with brine (50 mL), dried (Na_2SO_4) and concentrated in vacuo. The crude aldehyde was used directly in the next reaction.

To a solution of the aldehyde in CH_2Cl_2 (60 mL) cooled to 0°C, carbethoxymethylenetriphenylphosphorane (18.27 g, 52.6 mmol) was added in one portion and stirred at this temperature for 10 min. It was then diluted with EtOAc (100 mL), washed with brine (50 mL), dried (Na_2SO_4) and concentrated in vacuo. Purification by column chromatography (SiO_2, 20–30% EtOAc in petroleum ether eluent) afforded 11 (4.77 g, 70%) as a colorless oil. R_f=0.4 (silica, 20% EtOAc in petroleum ether); $[\alpha]_D^{20}=+2.79$ (*c* 1, $CHCl_3$); IR (Neat): ν_{max} 3443, 2988, 1710, 1270, 1184, 957, 753 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 7.45–7.25 (m, 5H, Ar*H*), 7.05 (dd, *J*=16.1, 7.2 Hz, 1H, C3–*H*), 6.62 (d, *J*=16.3 Hz, 1H, C7–*H*), 6.20 (dd, *J*=16.3, 5.4 Hz, 1H, C6–*H*), 5.92 (d, *J*=16.1 Hz, 1H, C2–*H*), 4.38–4.25 (m, 1H, C5–*H*), 4.20 (q, *J*=6.6 Hz, 2H, OCH_2CH_3), 3.75–3.58 (m, 1H, C4–*H*), 1.70 (d, *J*=3.5 Hz, 1H, C5–O*H*), 1.30 (t, *J*=6.6 Hz, 3H, OCH_2CH_3), 1.24 (d, *J*=6.6 Hz, 3H, C4–CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 166.58, 150.22, 136.35, 131.72, 129.31, 128.43, 127.63, 126.41, 121.74, 75.4, 60.23, 42.42, 14.25, 14.07; MS (LSIMS): *m/z* (%): 259 (10) [M^+−H], 243 (68) [M^+−OH], 169 (36) [M^+−Bn]; HRMS (LSIMS): calcd for $C_{16}H_{19}O_3$ [M^+−H]: 259.1334, found: 259.1335.

3.1.4. 4-Methyl-7-phenyl-(2*E*,4*S*,5*S*,6*E*)-2,6-heptadiene-1,5-diol (12). To a solution of **11** (4.7 g, 18.07 mmol) in CH_2Cl_2 (50 mL) at −78°C, a solution of DIBAL-H in toluene (1.2 M, 30 mL, 36.14 mmol) was added dropwise and stirred for 0.5 h at this temperature. The reaction was quenched by the addition of few drops of MeOH followed by saturated aqueous sodium potassium tartrate solution. It was warmed to 0°C and stirred for 0.5 h. The aqueous layer was extracted with EtOAc (100 mL) and washed with brine (50 mL), dried and concentrated in vacuo. Purification of the crude by column chromatography (SiO_2, 30–50% EtOAc in petroleum ether eluent) afforded **12** (3.35 g, 85%) as a colorless liquid. R_f=0.4 (silica, 50% EtOAc in petroleum ether); $[\alpha]_D^{20}=+10.77$ (*c* 1.01, $CHCl_3$); IR (Neat): ν_{max} 3325, 2965, 2898, 1502, 968, 753, 698 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 7.44–7.20 (m, 5H, Ar*H*), 6.60 (d, *J*=16.3 Hz, 1H, C7–*H*), 6.24 (dd, *J*=16.3, 5.4 Hz, 1H, C6–*H*), 5.88–5.66 (m, 2H, C2–*H*, C3–*H*), 4.25 (t, *J*=5.4 Hz, 1H, C5–*H*), 4.14 (d, *J*=4.5 Hz, 2H, C1–H_2), 2.60–2.45 (m, 1H, C4–*H*), 1.10 (d, *J*=6.6 Hz, 3H, C4–CH_3); ^{13}C NMR ($CDCl_3$, 100 Hz): δ 136.68, 133.81, 131.19, 130.33, 129.63, 128.45, 127.53, 126.33, 75.90, 63.19, 42.35, 14.92; MS (LSIMS): *m/z* (%): 241 (8) $[M^++Na]$, 217 (4) [M−H], 201 (34) $[M^+-OH]$; HRMS (LSIMS): calcd for $C_{14}H_{19}O_2$ $[M^++H]$: 219.1385, found: 219.1386.

3.1.5. 1-*tert*-Butyldimethylsilyloxy-4-methyl-7-phenyl-(2*E*,4*S*,5*S*,6*E*)-2,6-heptadiene-5-ol (13). To a solution of **12** (3.3 g, 15.13 mmol) in dry THF (40 mL) at 0°C, imidazole (1.34 g, 19.6 mmol) was added portionwise followed by TBDMSCl (2.5 g, 16.64 mmol) in one portion. The reaction mixture was stirred for 1 h with the temperature slowly reaching room temperature. It was quenched with saturated aqueous NH_4Cl solution (10 mL), diluted with EtOAc (100 mL), washed with brine (50 mL), dried (Na_2SO_4) and concentrated in vacuo. Purification by column chromatography (SiO_2, 20–30% EtOAc in petroleum ether eluent) of the crude afforded **13** (4.12 g, 82%) as a colourless oil. R_f=0.5 (silica, 30% EtOAc in petroleum ether); $[\alpha]_D^{20}=+5.95$ (*c* 0.5, $CHCl_3$); IR (Neat): ν_{max} 3443, 2918, 2863, 1459, 1239, 965, 831, 745 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 7.40–7.18 (m, 5H, Ar*H*), 6.55 (d, *J*=16.3 Hz, 1H, C7–*H*), 6.20 (dd, *J*=16.3, 5.4 Hz, 1H, C6–*H*), 5.74–5.54 (m, 2H, C2–*H*, C3–*H*), 4.25–4.04 (m, 3H, C1–H_2, C5–*H*), 2.55–2.38 (m, 1H, C4–*H*), 1.10 (d, *J*=6.6 Hz, 3H, C4–CH_3), 0.88 (s, 9H, $(CH_3)_3C$–Si), 0.02 (s, 6H, $(CH_3)_2Si$); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 136.87, 131.84, 131.12, 130.92, 130.23, 128.46, 127.47, 126.44, 75.98, 63.77, 42.60, 25.92, 18.35, 15.28, −5.13; MS (LSIMS): *m/z* (%): 331 (12) $[M^+-H]$, 315 (32) $[M^+-OH]$; HRMS (LSIMS): calcd for $C_{20}H_{31}O_2Si$ $[M^+-H]$: 331.2093, found: 331.2092.

3.1.6. 1-*tert*-Butyldimethylsilyloxy-5-methoxy-4-methyl-7-phenyl-(2*E*,4*S*,5*S*,6*E*)-2,6-heptadiene (14). To a solution of **13** (4.1 g, 12.35 mmol) in dry THF (30 mL) at 0°C, NaH (60% dispersion in oil, 1.0 g, 24.69 mmol) was added portionwise and stirred for 10 min. Then methyl iodide (0.84 mL, 13.58 mmol) was added dropwise followed by tetrabutylammonium iodide (0.45 g, 1.2 mmol) in one portion and the reaction mixture was stirred for 4 h. It was then cooled to 0°C and quenched with saturated aqueous NH_4Cl solution (10 mL) and diluted with EtOAc (100 mL), washed with saturated aqueous $Na_2S_2O_3$ solution (50 mL), brine (50 mL), dried (Na_2SO_4) and concentrated in vacuo. Column chromatographic purification (SiO_2, 5–15% EtOAc in petroleum ether eluent) of the crude afforded **14** (3.76 g, 88%) as a syrupy liquid. R_f=0.6 (silica, 20% EtOAc in petroleum ether); $[\alpha]_D^{20}=+12.11$ (*c* 0.3, $CHCl_3$); IR (Neat): ν_{max} 2941, 2870, 1223, 1114, 972, 824, 784 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 7.40–7.18 (m, 5H, Ar*H*), 6.48 (d, *J*=16.3 Hz, 1H, C7–*H*), 6.00 (dd, *J*=16.3, 7.3 Hz, 1H, C6–*H*), 5.72–5.46 (m, 2H, C2–*H*, C3–*H*), 4.10 (d, *J*=4.7 Hz, 2H, C1–H_2), 3.50 (dd, *J*=5.4, 4.7 Hz, 1H, C5–*H*), 3.30 (s, 3H, OCH_3), 2.52–2.38 (m, 1H, C4–*H*), 1.06 (d, *J*=6.6 Hz, 3H, C4–CH_3), 0.88 (s, 9H, $(CH_3)_3C$–Si), 0.02 (s, 6H, $(CH_3)_2Si$); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 136.79, 133.01, 132.49, 129.63, 128.48, 127.54, 126.49, 86.49, 64.02, 56.54, 41.26, 25.95, 18.36, 15.90, −5.08; MS (LSIMS): *m/z* (%): 345 (15) $[M^+-H]$, 315 (29) $[M^+-OMe]$; HRMS (LSIMS): calcd for $C_{21}H_{33}O_2Si$ $[M^+-H]$: 345.2249, found: 345.2244.

3.1.7. 5-Methoxy-4-methyl-7-phenyl-(2*E*,4*S*,5*S*,6*E*)-2,6-heptadiene-1-ol (15). To a solution of **14** (3.7 g, 10.69 mmol) in MeOH/CH_2Cl_2 (1:2, 30 mL) at 0°C, camphor sulfonic acid (2.48 g, 10.69 mmol) was added portionwise and stirred for 1 h, while the temperature was allowed to rise from 0°C to room temperature. The reaction mixture was cooled to 0°C and neutralized by the addition of saturated aqueous $NaHCO_3$, diluted with EtOAc (100 mL), washed with brine (50 mL), dried (Na_2SO_4) and concentrated in vacuo. Column chromatographic purification (SiO_2, 20–30% EtOAc in petroleum ether eluent) of the crude afforded **15** (2.2 g, 89%) as a colourless liquid. R_f=0.4 (silica, 30% EtOAc in petroleum ether); $[\alpha]_D^{20}=+5.78$ (*c* 1.04, $CHCl_3$); IR (Neat): ν_{max} 3404, 2933, 1451, 1090, 965, 753, 690 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 7.40–7.20 (m, 5H, Ar*H*), 6.50 (d, *J*=16.3 Hz, 1H, C7–*H*), 6.00 (dd, *J*=16.3, 7.3 Hz, 1H, C6–*H*), 5.80–5.58 (m, 2H, C2–*H*, C3–*H*), 4.10 (d, *J*=4.7 Hz, 2H, C1–H_2), 3.52 (dd, *J*=5.4, 4.0 Hz, 1H, C5–*H*), 3.30 (s, 3H, OCH_3), 2.55–2.38 (m, 1H, C4–*H*), 1.08 (d, *J*=6.6 Hz, 3H, C4–CH_3); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 136.55, 133.78, 133.20, 129.61, 128.44, 127.98, 127.55, 126.37, 86.27, 63.35, 56.41, 41.12, 15.81; MS (LSIMS): *m/z* (%): 231 (8) $[M^+-H]$; HRMS (LSIMS): calcd for $C_{15}H_{19}O_2$ $[M^+-H]$: 231.1385, found: 231.1387.

3.1.8. 3-[2-Methoxy-1-methyl-4-phenyl-(1*S*,2*S*,3*E*)-3-butenyl]-(2*R*,3*R*)-oxiran-2-yl methanol (16). To dichloromethane (20 mL) containing flame-dried 4 Å molecular sieves powder (0.4 g) at −20°C, $Ti(O^iPr)_4$ (2.5 mL, 8.6 mmol) and (−)-DIPT (1.8 mL, 8.6 mmol) were added sequentially and stirred for 20 min. The allylic alcohol **15** (2 g, 8.62 mmol) in CH_2Cl_2 (5 mL) was then added dropwise and the reaction stirred for another 0.5 h. Next, TBHP (3.3 M in toluene, 6.5 mL, 21.5 mmol) was added dropwise and stirring continued at −20°C for 1 h. A few drops of water were added to the reaction mixture and stirred for 20 min. It was then warmed to 0°C and 1 M NaOH (1 mL) was added and stirred at this temperature for 0.5 h. The reaction mixture was diluted with EtOAc (100 mL), washed with brine (50 mL), dried (Na_2SO_4) and concentrated in vacuo. Column chromatography (SiO_2, 25–35% EtOAc in petroleum ether eluent) of the crude afforded 16 (1.98 g, 93%) as a syrupy liquid. R_f=0.45 (silica, 50% EtOAc in petroleum ether); $[\alpha]_D^{20}=+20.8$ (*c* 1.05, $CHCl_3$); IR (Neat): ν_{max} 3427, 2925, 1435, 1074, 965, 745, 690 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz, numbering started from primary hydroxy group attached carbon): δ 7.42–7.20 (m, 5H, Ar*H*), 6.58 (d, *J*=16.3 Hz, 1H, C7–*H*), 6.12 (dd, *J*=16.3, 7.3 Hz, 1H, C6–*H*), 3.95–3.82 (m, 2H, C1–*H*, C5–*H*), 3.62 (dd, *J*=12.7, 5.0 Hz, 1H, C1–*H′*), 3.36 (s, 3H, OCH_3), 3.04 (dd, *J*=9.0, 2.7 Hz, 1H, C3–*H*), 2.90 (m, 1H, C2–*H*), 1.60 (m, 1H, C4–*H*), 1.00 (d, *J*=6.7 Hz, 3H, C4–CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 136.44, 132.81, 128.52, 127.76, 127.67, 126.43, 83.75, 61.92, 57.48, 57.35, 56.76, 41.07, 10.75; MS (LSIMS): *m*/*z* (%): 271 (10) [M$^+$+Na], 247 (10) [M$^+$−H], 217 (26) [M$^+$−OMe]; HRMS (LSIMS): calcd for $C_{15}H_{19}O_3$ [M$^+$−H]: 247.1334, found: 247.1333.

3.1.9. 5-Methoxy-2,4-dimethyl-7-phenyl-(2*S*,3*S*,4*S*,5*S*,6*E*)-6-heptene-1,3-diol (17). To a stirred solution of CuI (2.92 g, 15.32 mmol) in dry ether (20 mL) at 0°C, MeLi (2 M in ether, 15.32 mL, 30.64 mmol) was added dropwise until the color of the emulsion turned from yellowish to a light green clear solution. Then it was cooled to −20°C and epoxy alcohol **16** (1.9 g, 7.66 mmol) in dry ether (5 mL) was added dropwise. The color of the reaction mixture turned to yellowish slurry again. Stirring was continued at −20°C for another 2 h. It was then quenched by the addition of saturated aqueous NH_4Cl solution (2 mL). The excess CuI was quenched by the addition of 25% aqueous NH_4OH solution. The bluish aqueous layer was extracted with EtOAc (100 mL), washed with water (50 mL), brine (50 mL), dried (Na_2SO_4) and concentrated in vacuo. Column chromatography (SiO_2, 40–50% EtOAc in petroleum ether eluent) of the crude afforded **17** (1.74 g, 86%) as a thick syrup. R_f=0.4 (silica, 50% EtOAc in petroleum ether); $[\alpha]_D^{20}$=+35.4 (*c* 1, $CHCl_3$); IR (Neat): ν_{max} 3404, 2933, 1443, 1074, 965, 745, 690 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.45–7.25 (m, 5H, Ar*H*), 6.58 (d, *J*=16.3 Hz, 1H, C7–*H*), 6.18 (dd, *J*=16.3, 7.2 Hz, 1H, C6–*H*), 4.15 (dd, *J*=7.2, 4.5 Hz, 1H, C5–*H*), 3.80 (m, 1H, C3–*H*), 3.70–3.50 (m, 2H, C1–H_2), 3.35 (s, 3H, OCH_3), 2.05 (m, 1H, C2–*H*), 1.85 (m, 1H, C4–*H*), 1.20 (d, *J*=6.7 Hz, 3H, C2–CH_3), 0.88 (d, *J*=6.6 Hz, 3H, C4–CH_3); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 136.26, 133.38, 128.56, 127.86, 126.83, 126.48, 84.34, 80.80, 66.79, 56.37, 39.77, 37.46, 14.48, 12.14; MS (LSIMS): *m*/*z* (%): 287 (10) [M$^+$+Na], 265 (2) [M$^+$+H], 233 (26) [M$^+$−OMe]; HRMS (LSIMS): calcd for $C_{16}H_{25}O_3$ [M$^+$+H]: 265.1803, found: 265.1802.

3.1.10. 3,5-Dimethoxy-2,4-dimethyl-7-phenyl-(2*S*, 3*S*, 4*R*, 5*S*, 6*E*)-6-hepten-1-ol (18). Following the same procedure as described above for the conversion of **12** to **15**, the alcohol **18** was obtained in 60% yield (from 3 steps) from the diol **17**. R_f=0.4 (silica, 30% EtOAc in petroleum ether); $[\alpha]_D^{20}$=−6.5 (*c* 1, $CHCl_3$); IR (Neat): ν_{max} 3450, 2975, 2940, 2875, 2825, 1450, 1100 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.36–7.17 (m, 5H, Ar*H*), 6.54 (d, *J*=16.0 Hz, 1H, C7–*H*), 6.14 (dd, *J*=16.0, 7.2 Hz, 1H, C6–*H*), 4.04 (dd, *J*=7.2, 2.0 Hz, 1H, C5–*H*), 3.79 (dd, *J*=11.2, 3.4 Hz, 1H, C1–*H*), 3.53 (s, 3H, OCH_3), 3.49 (dd, *J*=11.2, 4.3 Hz, 1H, C1–*H*′), 3.30 (s, 3H, OCH_3), 3.25 (dd, *J*=9.5, 2.6 Hz, 1H, C3–*H*), 2.60 (br s, 1H, O*H*), 1.85 (m, 2H, C2–*H* and C4–*H*), 1.19 (d, *J*=6.9 Hz, 3H, C2–CH_3), 0.89 (d, *J*=7.2 Hz, 3H, C4–CH_3); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 136.72, 132.09, 129.29, 128.51, 127.51, 126.33, 88.24, 81.16, 64.40, 61.41, 56.28, 42.22, 35.98, 16.10, 10.34; MS (LSIMS): *m*/*z* (%): 301 (4) [M$^+$+Na]; HRMS (LSIMS): calcd for $C_{17}H_{25}O_3$ [M$^+$−H]: 277.1804, found: 277.1817.

3.1.11. Ethyl 7,9-dimethoxy-3,6,8-trimethyl-11-phenyl-(2*E*,4*E*,6*S*,7*S*,8*R*,9*S*,10*E*)-2,4,10-undecatrienoate (19). To a solution of **18** (0.1 g, 0.36 mmol) in DMSO/CH_2Cl_2 (1:1, 2 mL) at 0°C, triethylamine (0.25 mL, 1.8 mmol) was added dropwise and stirred for 5 min. Then SO_3-py (0.28 g, 1.8 mmol) was added portionwise and stirred for 20 min. Next, the reaction mixture was diluted with ether (50 mL), washed with saturated NH_4Cl (25 mL), brine (25 mL), dried (Na_2SO_4) and concentrated in vacuo. Purification by column chromatography (SiO_2, 10–20% EtOAc in petroleum ether eluent) afforded the pure aldehyde **5** (0.095 g, 96%) as colorless oil. The aldehyde was used directly in the next reaction without characterization.

To a solution of diisopropylamine (0.09 mL, 0.65 mmol) in dry THF (2 mL) at −78°C, ^{n}BuLi (1.6 M in hexane, 0.4 mL, 0.65 mmol) was added dropwise and stirred at the same temperature for 30 min. Then DMPU (0.5 mL, 1.5 mL/mmol) was added to the reaction mixture and stirred for 5 min. Next, diethylphosphonate **6** (0.17 g, 0.65 mmol) in dry THF (0.3 mL) was added to the reaction mixture followed immediately by the addition of freshly prepared aldehyde **5** (0.095 g, 0.33 mmol) in dry THF (0.3 mL). The stirring was continued at −78°C for 8 h. The reaction mixture was quenched by the addition of saturated aqueous NH_4Cl solution (2 mL). It was allowed to reach room temperature and diluted with EtOAc (50 mL), washed with brine (25 mL), dried (Na_2SO_4) and concentrated in vacuo. Column chromatography (SiO_2, 5–10% EtOAc in petroleum ether eluent) of the crude afforded pure 19 (0.061 g) in 48% Yield (60% based on 20% recovered aldehyde) as a colourless oil. R_f=0.5 (silica, 5% EtOAc in petroleum ether); $[\alpha]_D^{20}$=−7.91 (*c* 0.2, $CHCl_3$); IR (Neat): ν_{max} 2925, 1710, 1624, 1153, 1090, 750, 690 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.32 (d, *J*=8.2 Hz, 2H, aromatic *ortho*-protons), 7.24 (dd, *J*=8.2, 7.3 Hz, 2H, aromatic *meta*-protons), 7.16 (br dd, 1H, aromatic *para*-proton), 6.48 (d, *J*=16.2 Hz, 1H, C11–*H*), 6.08 (m, 2H, C5–*H*, C10–*H*), 6.04 (d, *J*=15.8 Hz, 1H, C4–*H*), 5.60 (s, 1H, C2–*H*), 4.06 (q, *J*=6.8 Hz, 2H, OCH_2CH$_3$), 4.00 (ddd, *J*=7.3, 2.2, 1.0 Hz, 1H, C9–*H*), 3.47 (s, 3H, C7–OCH_3), 3.25 (s, 3H, C9–OCH_3), 3.12 (dd, *J*=9.8, 1.9 Hz, 1H, C7–*H*), 2.49 (m, 1H, C6–*H*), 2.18 (d, *J*=1.1 Hz, 3H, C3–CH_3), 1.47 (m, 1H, C8–*H*), 1.2 (t, *J*=6.8 Hz, 3H, OCH$_2$CH_3), 1.16 (d, *J*=6.7 Hz, 3H, C6–CH_3), 0.88 (d, *J*=6.8 Hz, 3H, C8–CH_3); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 167.19, 152.53, 138.04, 136.79, 133.94, 132.01, 129.25, 128.55, 127.52, 126.39, 118.06, 86.43, 81.07, 61.42, 59.54, 56.41, 42.65, 40.11, 18.69, 14.31, 13.97, 9.74; MS (LSIMS): *m*/*z* (%): 355 (2) [M$^+$−OMe], 341 (2) [M$^+$−CH_3CH_2O].

3.1.12. 7,9-Dimethoxy-3,6,8-trimethyl-11-phenyl-(2*E*,4*E*,6*S*,7*S*,8*R*,9*S*,10*E*)-2,4,10-undecatrienamide (3). To a solution of **19** (0.06 g, 0.15 mmol) in THF/MeOH/H_2O (3:1:1, 1.0 mL) at 0°C, LiOH/H_2O (0.06 g, 1.5 mmol) was added in one portion and stirred from 0°C to room temperature for 1 h. It was then acidified with 1 M HCl at 0°C up to pH 2 and diluted with EtOAc (10 mL) and washed with brine (5 mL), dried (Na_2SO_4) and concentrated in vacuo. The crude acid was used directly in the next reaction.

To the acid (0.04 g, 0.12 mmol) in dry THF (1.0 mL) at −20°C, triethylamine (0.02 mL, 0.13 mmol) was added and stirred for 5 min. Ethyl chloroformate (0.012 mL, 0.13 mmol) was added next to the reaction mixture and stirring continued at −20°C for 0.5 h. This was followed by the dropwise addition of 25% aqueous NH_4OH solution

(0.05 mL, 0.72 mmol). After stirring at 0°C for 20 min, the reaction mixture was quenched by the addition of saturated NH_4Cl solution (5 mL), extracted with EtOAc (10 mL), washed with brine (5 mL), dried (Na_2SO_4) and concentrated in vacuo. Column chromatography (SiO_2, 40–60% EtOAc in petroleum ether eluant) afforded pure amide **3** (0.036 g, 66%) as a colourless semi solid. R_f=0.5 (silica, 50% EtOAc in petroleum ether); $[\alpha]_D^{20}=+53.8$ (*c* 0.2, MeOH); IR (Neat): ν_{max} 2925, 1655, 1600, 1190 cm^{-1}; ^1H NMR (acetone-d_6, 500 MHz): δ 7.45 (d, *J*=8.0 Hz, 2H, aromatic *ortho*-protons), 7.31 (dd, *J*=8.0, 7.4 Hz, 2H, aromatic *meta*-protons), 7.22 (t, *J*=7.4 Hz, 1H, aromatic *para*-proton), 6.58 (d, *J*=16.1 Hz, 1H, C11–*H*), 6.23 (d, *J*=16.1, 7.24 Hz, 1H, C10–*H*), 6.09 and 6.07 (m, 2H, C4–*H* and C5–*H*), 5.79 (d, *J*=1.1 Hz, 1H, C2–*H*), 4.07 (ddd, *J*=7.24, 2.4, 1.0 Hz, 1H, C9–*H*), 3.51 (s, 3H, C7–OCH_3), 3.29 (s, 3H, C9–OCH_3), 3.16 (dd, *J*=9.5, 2.3 Hz, 1H, C7–*H*), 2.82 (br s, 2H, NH_2), 2.58 (m, 1H, C6–*H*), 2.21 (d, *J*=1.1 Hz, 3H, C3–CH_3), 1.56 (m, 1H, C8–*H*), 1.16 (d, *J*=6.95 Hz, 3H, C6–CH_3), 0.84 (d, *J*=7.1 Hz, 3H, C8–CH_3); ^{13}C NMR (acetone-d_6, 125 MHz): δ 169.19, 148.2, 137.89, 137.12, 135.0, 132.56, 130.49, 129.38, 128.27, 127.25, 121.88, 87.21, 81.83, 61.44, 56.47, 43.63, 40.77, 19.26, 13.52, 10.16; MS (LSIMS): *m/z* (%): 380 (30) $[M^++Na]$, 358 (10) $[M^++H]$; 326 (44) $[M^++H-CH_3OH]$, 294 (16) $[M^++H-2CH_3OH]$, HRMS (LSIMS): calcd for $C_{22}H_{32}NO_3$ $[M^++H]$: 358.2382, found: 358.2384.

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