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Formal total synthesis of (−)-salicylihalamides A and B

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Dedicated to Prof. G. Mehta on his 60th birthday

Abstract—Formal total synthesis of (−)-salicylihalamides A and B is described starting with a nonracemic chiral epoxide obtained from Jacobsen's kinetic resolution. Sharpless asymmetric epoxidation, Diels Alder reaction, Mitsunobu coupling and ring closing metathesis are the other key steps involved.
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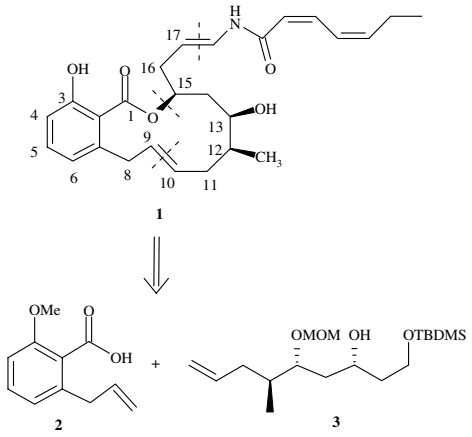
1. Introduction

Even though marine sponges supply compounds with high diversity and architectural complexity, the ability to obtain the same natural product repeatedly is highly uncertain. This is even more so when the natural product is isolated from an unidentified natural sponge. Salicylihalamide is one such macrolide isolated[1] from *Haliclona* genus (South-Western Australian coast), which exhibited cytotoxicity against a 60-cell line human tumor assay with GI_{50} of 15 nM. The mechanism of action of this compound has no correlation with known compounds and thus occupies an important status. Total synthesis was the only solution for this very important molecule and to study further the biological properties six syntheses have already been reported.[2,3] This clearly indicates that this target molecule has generated tremendous activity in the synthetic chemistry and medicinal chemistry groups not only as a complex target but also as a promising lead molecule. Our long standing interest in development of strategies for total synthesis of natural products having cytotoxic properties prompted us to look at the total synthesis of (−)-salicylihalamides A and B. Our retrosynthetic analysis revealed two key fragments viz., the functionalized benzoic acid derivative **2** and the chiral aliphatic fragment **3** (Scheme 1).

Herein, we report full details on the formal total synthesis of title compound involving a kinetic resolution using Jacobsen's complex, Sharpless asymmetric epoxidation and regioselective opening of an epoxide for elaborating the aliphatic part and a Diels Alder strategy for the aromatic part as the key steps. All these reactions are high yielding, clean, regio- and stereoselective and with this strategy by manoeuvering the reagents, other diastereomers/enantiomers would be easily synthesizable.



Scheme 1.

2. Results and discussion

Kinetic resolution of 2-(benzyloxyethyl)oxirane using Jacobsen's catalyst[4] (*R*,*R*)-(−)-*N*-*N*′-bis(3,5-di-*tert*-butylsalicylidene)-1,2-cyclohexanediaminocobalt (II) and water yielded (*R*)-2-(benzyloxyethyl)oxirane **4** in 44%

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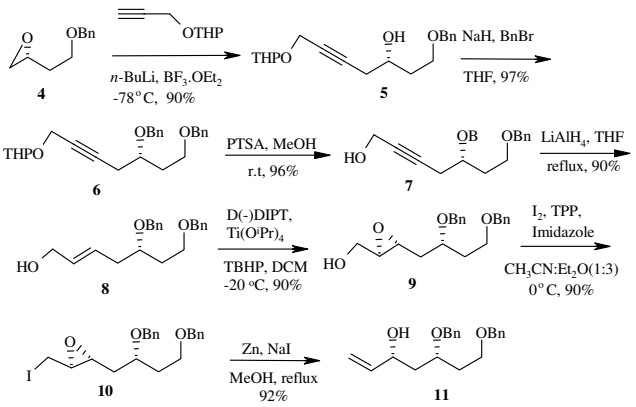
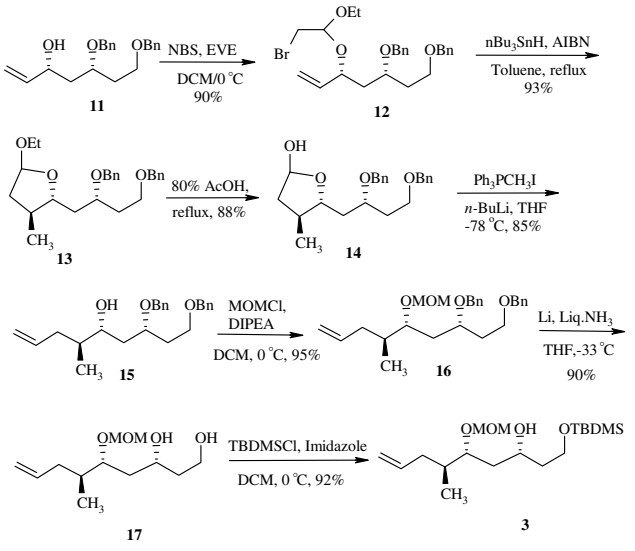
yield and 99% ee. $\{[\alpha]_D^{20} = +16.8$ (c 2.75, $CHCl_3$) Lit[5] $[\alpha]_D = +16.9$ (c 2.51, $CHCl_3$)$\}$.

Epoxide **4** was opened with propargyl alcohol –O-THP ether employing the Yamaguchi protocol[6] to produce the 2-heptyne-triol derivative **5** (Scheme 2). Protection of the alcohol **5** as its benzyl ether **6** followed by deprotection of the THP moiety afforded propargylic alcohol **7**, which was reduced to allyl alcohol **8** using $LiAlH_4$ in THF under reflux. Sharpless asymmetric epoxidation[7] of allyl alcohol **8** yielded epoxyalcohol **9**, which was converted to the corresponding iodide **10** by treating with I_2, TPP, and imidazole[8] at 0 °C. The compound **10** on treating with Zn, NaI in MeOH at reflux, yielded the secondary alcohol **11**.[9]



Scheme 2.

Treatment of **11** with NBS and ethylvinylether in dichloromethane yielded the prerequisite bromo acetal **12** for further manipulation (Scheme 3).[10] We anticipated a standard 5-*exo* trig cyclization on **11** with preferential *anti*-geometry of the resulting new stereogenic center using *n*-Bu_3SnH in refluxing toluene with catalytic AIBN as radical initiator to yield cyclic ethyl acetal **13**.[11]

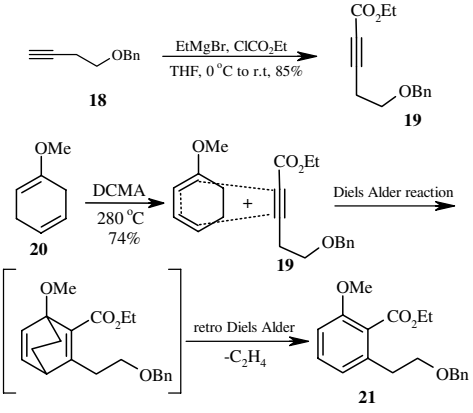


Scheme 3.

The absolute stereochemistry of this new stereogenic center was also unequivocally confirmed at a later stage after destroying the anomeric center.

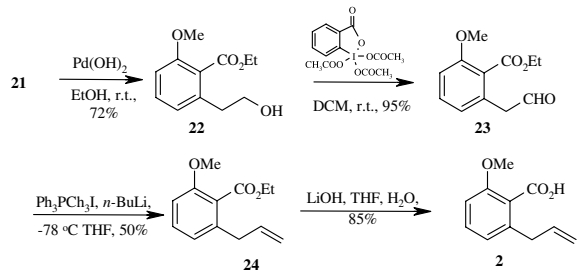
The hydrolysis of ethyl acetal **13** using 80% acetic acid under reflux conditions afforded the lactol **14**, which on one carbon Wittig olefination furnished the homologated triol derivative **15** in 85% yield. ^{13}C data and HPLC analysis of **15** ascertained the homogeneity of the new stereogenic center created during the free radical cyclization. The free hydroxyl group in **15** was protected as methoxymethylether to afford **16**. Selective debenzylation of **16** without affecting the olefinic functionality was achieved by lithium/liq. NH_3 to afford diol **17** in 90% yield. The diol **17** was monoprotected using TBDMSCl to furnish the required chiral aliphatic moiety **3**.

The aryl part was synthesized starting from 1-benzyloxy-3-butyne **18** (Scheme 4). This procedure involved a novel Diels Alder-retro Diels Alder sequence hitherto not reported for this fragment (Scheme 4). Treatment of alkyne **18** with ethyl magnesium bromide resulted in an acetylide that was quenched with ethylchloroformate to furnish the carboxylic ester **19**. Diels Alder reaction between **19** and 1-methoxy cyclohexa-1,4-diene[12] **20** using catalytic dichloromaleic anhydride[13] at 280 °C produced the disubstituted benzoic acid ethyl ester **21** in 74% yield.

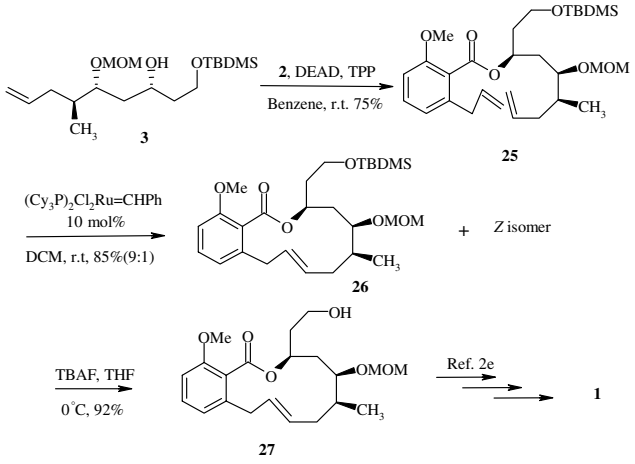


Scheme 4.

Functional group manipulation involving debenzylation of compound **21** with $Pd(OH)_2$ under a hydrogen atmosphere and oxidation of the resulting alcohol **22** under Dess Martin conditions[14] yielded the aldehyde **23**. The aldehyde **23** on 1C Wittig homologation afforded allyl derivative **24**, which was hydrolyzed with lithium hydroxide to obtain the key fragment allyl anisic acid **2**. Mitsunobu[15] reaction between chiral aliphatic alcohol **3** and allyl anisic acid **2** produced the ester **25**, which is set for ring closing metathesis reaction (Schemes 5 and 6). RCM with Grubb's catalyst[16] furnished the advanced *E*-intermediate **26** in 85% yield (9:1, E/Z) toward total synthesis of salicylihalamide.



Scheme 5.



Scheme 6.

Deprotection of silyl ether **26** with TBAF proceeded uneventfully to furnish the known alcohol **27**, which has already been converted to the target molecule by Furstner et al.[2e] Thus the present strategy completes the formal total synthesis.

3. Conclusions

Our synthesis enabled us to prepare intermediate **27** in multiple 100-mg quantity for introduction of modified sidechains, which is currently underway. Also introduction of stereogenic centers was achieved via Jacobsen's kinetic resolution and Sharpless epoxidation, which should allow us to synthesize other stereoisomers.

4. Experimental

4.1. General methods

Melting point was determined with a melting point apparatus (Polmon) and is uncorrected. Optical rotations were measured with an Jasco DIP-360 Polarimeter at 20 °C and IR spectra were recorded with a Perkin Elmer FTIR spectrophotometer. ^{1}H NMR spectra were carried out using a Varian Gemini 200 or Varian Unity 400 or Varian Inova 500 MHz or Bruker Avance 300 MHz spectrophotometer using TMS as an internal standard in $CDCl_3$. Mass spectra were recorded on Micro mass VG-7070H for EI, VG Autospec M for FABMS, and Kompact SEQ MALDITOF MS for MALDI mass spectrometers. The progress of all the reactions was monitored by thin-layer chromatography (TLC) using glass plates precoated with silica gel $60F_{254}$ to a thickness of 0.5 mm (Merck). Column chromatography was conducted by elution of columns with silica gel 60–120 mesh using ethyl acetate and hexane as the eluents. All reactions were carried out under inert atmosphere unless mentioned following standard syringe septa techniques. All the solvents were dried using a standard procedure.

4.2. 2-(2-Benzyloxyethyl)-(2*R*)-oxirane 4

A mixture of (*R*,*R*)-(−)-*N*-*N*′Bis(3,5-di*tert*-butyl salicylidene)-1,2-cyclohexanediaminocobalt II (0.695 g, 1.15 mmol) toluene (2 mL) and acetic acid (0.130 mL, 2.25 mmol) was stirred while open to the air for 1 h at room temperature. The solvent was removed by rotary evaporator under reduced temperature and the brown residue was dried over vacuum. The racemic 2-(2-benzyloxyethyl)-oxirane (41 g, 230 mmol) was added in one portion, and the stirred mixture was cooled in an ice water bath. Water (2.5 mL, 139 mmol) was slowly added and the temperature of the reaction mixture was maintained such a way that it never rises more than 20 °C. After 1 h, addition was complete. The icebath was removed and the reaction mixture was stirred for 24 h. The product **4** was isolated by column chromatography (18.0 g, 44%). $[\alpha]_D = +16.8$ (*c* 2.75, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.38–7.20 (m, 5H, aromatic-H), 4.50 (s, 2H, –OC*H*$_2$Ph), 3.60 (t, 2H, $J = 7.3$ Hz, –C*H*$_2$CH$_2$OBn), 3.05–2.95 (m, 1H, CH$_2$(O)C*H*CH$_2$ CH$_{2-}$), 2.75 (pseudo t, 1H, $J = 4.9$ Hz, one –CH$_2$CH(O)C*H*$_2$), 2.50–2.40 (m, 1H, one –CH$_2$CH(O) C*H*$_2$), 2.00–1.65 (m, 2H, –C*H*$_2$CH$_2$OBn). ^{13}C NMR ($CDCl_3$, 50 MHz): $\delta = 138.8$, 128.2, 127.4, 72.9, 66.9, 49.8, 46.8, 32.8. IR (neat) cm^{-1}: 3033, 2860, 1603, 1495, 1258, 1100, 1013, and 911. MS (EI): *m*/*z* 178 (M$^+$).

4.3. 1-Benzyloxy-7-tetrahydro-2*H*-2-pyranyloxy-(3*S*)-5-heptyn-3-ol 5

Under nitrogen atmosphere, a solution of *n*-butyl lithium in hexane (43.2 mL, 112 mmol, 2.6 M solution in hexane) was added to a solution of THP ether of propargyl alcohol (18.4 g, 112 mmol) in THF (80 mL) at −78 °C, and the mixture was stirred for 15 min. Then, $BF_3{\cdot}OEt_2$ (7 mL, 56 mmol) was added to the solution and the stirring was continued for 15 min at −78 °C. Finally a solution of epoxide **4** (10 g, 56 mmol) in dry THF (20 mL) was added, and after stirring the reaction mixture for 3 h at −78 °C, the reaction was quenched by adding saturated aqueous NH_4Cl solution (40 mL). The reaction mixture was extracted with ethyl acetate and dried over anhydrous Na_2SO_4. Evaporation of the

solvents resulted in crude alcohol, which was purified by column chromatography to afford pure alcohol **5** (15.45 g, 90% yield) as a colorless liquid. $[\alpha]_D = +3.1$ (*c* 11.65, $CHCl_3$). ^1H NMR ($CDCl_3$, 200 MHz): $\delta = 7.40$–7.20 (m, 5H, aromatic-*H*), 4.80–4.76 (m, 1H, –OC*H*O– of THP ring), 4.51 (s, 2H, –OCH_2Ph), 4.21–4.19 (m, 2H, –CH_2OTHP), 3.99–3.40 (m, 5H, –CH$_2$CH_2OBn, –CH$_2$C*H*C(OH)– and –OCH_2 of THP ring), 3.00–2.91 (br s, 1H, O*H*), 2.41–2.39 (m, 2H, –CH(OH)CH_2C≡C–), 1.90–1.42 (m, 8H, 3×CH_2 of THP ring and –CH_2CH$_2$OBn). IR (neat) cm^{-1}: 3420, 2922, 2231, 1602, 1498, 1352, 1078, 905. MS (FABMS): *m*/*z* 319 (M^++1). Anal. Calcd for $C_{19}H_{26}O_4$: C, 71.67; H, 8.23. Found C, 71.71; H, 8.21%.

4.4. 2-[5,7]-Di(benzyloxy)-(5*S*)-2-heptynyloxy]tetrahydro-2*H*-pyran 6

To a suspension of NaH (1.6 g, 66 mmol, 60% dispersion in mineral oil) in dry THF (35 mL) was added dropwise a solution of alcohol **5** (10.0 g, 32.6 mmol) in THF (20 mL) at 0 °C. To this reaction mixture TBAI (0.05 g) and benzyl bromide (4.3 mL, 35.9 mmol) were added subsequently and stirring was continued for 2 h at same temperature and overnight at room temperature. The reaction mixture was quenched by crushed ice flakes until a clear solution (biphasic) has been formed. The reaction mixture was extracted with ethyl acetate (2×100 mL). The organic extracts were washed with water (1×50 mL) brine (1×50 mL) and dried over anhydrous Na_2SO_4. Evaporation of the solvents followed by column chromatography afforded the pure product **6** (12.5 g, 97% yield) as a colorless liquid. $[\alpha]_D = +29.0$ (*c* 9.2, $CHCl_3$). ^1H NMR ($CDCl_3$, 200 MHz): $\delta = 7.40$–7.20 (m, 10H, aromatic-*H*), 4.81–4.79 (m, 1H, –OC*H*O of THP), 4.70–4.20 (m, 6H, 2× –OCH_2Ph, –CH_2OTHP), 3.90–3.40 (m, 5H, –CH$_2$CH_2OBn, –CH$_2$C*H*(OBn)– and –OCH_2 of THP ring), 2.52–2.40 (m, 2H, –CH_2CH(OBn)–), 1.98–1.41 (m, 8H, 3×–CH_2 of THP ring and –CH_2CH$_2$OBn). IR(neat) cm^{-1}: 2921, 2230, 1606, 1496, 1357, 1080, 903. MS (FABMS): *m*/*z* 409 (M^++1). Anal. Calcd for $C_{26}H_{32}O_4$: C, 76.44; H, 7.89. Found: C, 76.49; H, 7.86%.

4.5. 5,7-Di(dibenzyloxy)-(5*S*)-2-heptynyl alcohol 7

The compound **6** (12.0 g, 30.3 mmol) in MeOH (50 mL) was stirred along with the catalytic amount of *para*-toluenesulphonic acid (~200 mg) for 2 h. The mixture was quenched by addition of saturated aqueous $NaHCO_3$ solution (10 mL). MeOH was evaporated under reduced pressure and the aqueous phase was extracted with ethyl acetate (2×30 mL). The organic extracts were washed by brine (1×30 mL) dried over anhydrous Na_2SO_4. After evaporating the solvent the product was purified by column chromatography to afford pure alcohol **7** (9.5 g, 96.8% yield) as a colorless liquid. $[\alpha]_D = +27.9$ (*c* 7.0, $CHCl_3$). ^1H NMR ($CDCl_3$, 200 MHz): $\delta = 7.32$–7.15 (m, 10H, aromatic-*H*), 4.60–4.38 (m, 4H, 2×–OCH_2Ph), 4.15 (s, 2H, –CH_2OH), 3.75–3.60 (m, 1H, –C*H*(OBn)–), 3.60–3.45 (m, 2H, –CH_2OBn), 2.50–2.38 (m, 2H, –CH_2CHC(OBn)–), 1.95–1.80 (m, 2H, –CH_2CH$_2$OBn), 1.60–1.40 (br s, 1H, –O*H*). IR (neat) cm^{-1}: 3418, 3032, 2923, 2237, 1963, 1603, 1453, 1360, 1274 and 1099. MS (FABMS): *m*/*z* 325 (M^++1).

4.6. 5,7-Di(benzyloxy)-(E,5S)-2-hepten-1-ol 8

Under nitrogen atmosphere, propargylic alcohol **7** (12 g, 37.0 mmol) was added to the suspension of $LiAlH_4$ (4.2 g, 110 mmol) in dry THF (80 mL) at 0 °C and the mixture was heated to reflux for 8 h. The reaction mixture was cooled to 0 °C and quenched by ice-cooled water (5 mL), 20% NaOH solution (5 mL) and again water (15 mL). The mixture was filtered over a small pad of Celite to afford the crude allyl alcohol that was purified by column chromatography to afford pure **8** as a colorless liquid (10.8 g, 89.6% yield). $[\alpha]_D = +34.1$ (*c* 3.7, $CHCl_3$). ^1H NMR ($CDCl_3$, 200 MHz): $\delta = 7.40$–7.20 (m, 10H, aromatic-H), 5.70–5.59 (m, 2H, olefinic-H), 4.60–4.39 (m, 4H, 2×–OCH_2Ph), 4.02–3.98 (m, 2H, –CH_2OH), 3.70–3.41 (m, 3H, –CH$_2$CH_2OBn and –CH$_2$C*H*(OBn)–), 2.40–2.20 (m, 2H, –CH_2CH (OBn)–), 1.80 (q, 2H, *J* = 6.8, 12.0 Hz, –CH_2CH$_2$OBn), 1.26 (s, 1H, O*H*). ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta = 139.9$, 139.8, 133.2, 129.7, 129.2, 129.0, 128.0, 127.8, 76.8, 74.4, 72.7, 68.1, 66.4, 38.4, 35.8. IR (neat) cm^{-1}: 3438, 2862, 1641, 1452, 1095, and 918. MS (EI): *m*/*z* 326 (M^++1).

4.7. 3-[2,4-Di(benzyloxy)-(2*R*)-butyl]-(2*R*,3*R*)-oxiran-2-yl methanol 9

To a freshly flame dried double necked round bottomed flask equipped with activated molecular sieves (4 AA)(~5 g) and dry CH_2Cl_2 (120 mL) at −20 °C were added Ti(O^iPr)$_4$ (1 mL, 4.6 mmol), D(−)-diisopropyl tartrate (1.2 mL, 4.0 mmol) and the mixture was stirred for 20 min. Allyl alcohol **8** (10.5 g, 32.2 mmol) followed by an interval of 20 min. TBHP (23.6 mmol, 70.8 mmol, 3 M solution in isooctane) were added and stirring was continued for completion of the reaction (12 h). The reaction mixture was warmed to 0 °C and quenched by water (30 mL) and stirred vigorously for 30 min. Whole reaction mixture was filtered through sintered funnel and the filtrate was again stirred along with 20% aq NaOH solution (5 mL) saturated with solid NaCl. The biphasic solution was separated and aqueous layer was extracted with CH_2Cl_2 (2×50 mL). The combined organic extracts were dried over anhydrous Na_2SO_4 and concentrated under vacuum. The crude residue was purified by column chromatography to afford pure epoxide **9** as a colorless oil (9.9 g, 89.8% yield). $[\alpha]_D = +35.2$ (*c* 7.2, $CHCl_3$). ^1H NMR ($CDCl_3$, 200 MHz): $\delta = 7.30$–7.10 (m, 10H, aromatic-H), 4.50–4.32 (m, 4H, 2×–OCH_2Ph), 3.80–3.60 (m, 2H, –CH_2OH), 3.58–3.39 (m, 3H, –CH_2OBn and –C*H*(OBn)–), 3.00–2.90 (m, 1H, one epoxide-*H*), 2.80–2.70 (m, 1H, one epoxide-*H*), 2.50–2.20 (br s, 1H, –O*H*), 1.90–1.60 (m, 4H, –CH_2CH$_2$CH(OBn)–). ^{13}C NMR

($CDCl_3$, 50 MHz): $\delta = 138.3, 137.1, 129.2, 127.9, 127.5, 75.0, 73.9, 66.9, 63.9, 62.8, 48.9, 37.3, 35.9$. IR (neat) cm^{-1}: 3460, 2929, 2860, 1602, 1453, 1276, 1096, 912, and 699. MS (FABMS): m/z 343 (M^++1). Anal. Calcd for $C_{21}H_{26}O_4$: C, 73.66; H, 7.65. Found: C, 73.58; H, 7.66%.

4.8. 2,4-Di(benzyloxy)-1-[3-iodomethyl-(2*R*,3*S*)-oxiran-2-yl]-(2*R*)-butane 10

To a solution of alcohol **9** (10 g, 29.2 mmol) in acetonitrile: ether (1:3, 400 mL) at 0 °C under nitrogen atmosphere were added imidazole (4.9 g, 71.9 mmol), iodine (14.8 g, 58.2 mmol), and triphenylphosphine (15.3 g, 58.6 mmol) successively. The mixture was stirred for 20 min. The resulting solution was diluted by cool ether (200 mL) and was filtered over a sintered funnel. The residue was washed by anhydrous ether (2×50 mL). The combined filtrate was concentrated under reduced temperature and the crude was passed through a pad of silica gel to afford pure iodo product **10** (12.5 g, 95%) as a colorless liquid. $[\alpha]_D = +6.5$ (c 5.1, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 200 MHz): $\delta = 7.34–7.20$ (m, 10H, aromatic-*H*), 4.59–4.42 (m, 4H, 2×–OCH_2Ph), 3.80–3.78 (m, 1H, –C*H*(OBn)–), 3.60–3.50 (m, 2H, –CH_2OBn), 3.20–3.18 (m, 1H, CH_2I), 3.00–2.92 (m, 2H, one –CH_2I, one epoxy-*H*), 2.36–2.30 (m, 1H, one epoxy-*H*), 2.00–1.78 (m, 4H, –CH_2CH(OBn)–, –C$H_2$$CH_2$OBn). IR (neat) cm^{-1}: 3087, 2921, 1496, 1455, 1092, 1027, and 894.

4.9. 5,7-Di(benzyloxy)-(3*R*,5*R*)-1-hepten-3-ol 11

A mixture of iodo compound **10** (20 g, 44.2 mmol), NaI (13.2 g, 88 mmol) and freshly activated zinc (7.2 g, 110 mmol) in anhydrous MeOH (120 mL) was refluxed for 8 h under nitrogen atmosphere. The solution was filtered and the residue was washed with MeOH (2×25 mL). The filtrates were combined and concentrated. The residue was taken in ethylacetate (50 mL) and washed with water (2×30 mL), brine (1×30 mL) and dried over anhydrous Na_2SO_4. Evaporation of the solvent and purification by column chromatography afforded pure alcohol **11** (13.2 g, 91.6% yield) as a colorless liquid. $[\alpha]_D = -23.8$ (c 5.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta = 7.38–7.20$ (m, 10H, aromatic-H), 5.83–5.72 (m, 1H, –CH(OH)C*H*=CH_2), 5.20 (d, 1H, $J = 15.0$ Hz, olefinic-*H*), 5.01 (d, 1H, $J = 8.6$ Hz, olefinic-*H*), 4.60 (d, 1H, $J = 14.2$ Hz, one from 2° –OCH_2Ph), 4.50–4.40 (m, 3H, –CH_2OCH_2Ph and one from 2° –OCH_2Ph), 4.30–4.20 (m, 1H, –C*H*(OH)–), 3.89–3.80 (m, 1H, –C*H*(OBn)–), 3.60–3.42 (m, 2H, –CH_2OBn), 2.00–1.80 (m, 2H, –CHCH_2CH(OBn)–), 1.78–1.61 (m, 2H, –C$H_2$$CH_2$OBn). ^{13}C NMR ($CDCl_3$, 50 MHz): $\delta = 139.9, 136.9, 136.7, 127.7, 126.8, 126.2, 113.8, 74.9, 74.0, 70.1, 64.3, 62.9, 42.6, 36.4$. IR (neat) cm^{-1}: 3440, 3031, 2862, 1954, 1602, 1493, 1207, and 1091. MS (FABMS): m/z 327 (M^++1). Anal. Calcd for $C_{21}H_{26}O_3$: C, 77.27; H, 8.03. Found: C, 77.32; H, 8.06%.

4.10. 5,7-Di(benzyloxy)-3-(2-bromo-1-ethoxyethoxy)-(3*R*,5*R*)-1-heptene 12

Freshly recrystallised NBS (7.6 g, 42.6 mmol) was added to a stirred solution of ethylvinylether (9.2 g, 127 mmol) and allyl alcohol **11** (14.0 g, 42.9 mmol) in anhydrous CH_2Cl_2 (120 mL) at 0 °C. After stirring the mixture for 5 h, the mixture was washed with water (2×30 mL) followed by brine (1×30 mL) and dried over anhydrous Na_2SO_4. Filtration followed by evaporation of the solvent and chromatographic purification of he crude residue afforded pure bromo acetal **12** (18.4 g, 89.8% yield) as a colorless liquid. ^{1}H NMR ($CDCl_3$, 300MHz): $\delta = 7.32–7.18$ (m, 10H, aromatic-*H*), 5.80–5.60 (m, 1H, –C*H*=CH_2), 5.21–5.02 (m, 2H, –CH=CH_2), 4.69–4.60 (m, 1H, –C*H*CH_2Br), 4.50–4.40 (m, 4H, 2×–OCH_2Ph), 4.22–4.00 (m, 1H, –CH_2C*H*(O)CH=CH_2), 3.70–3.40 (m, 4H, –CH_2OBn, –OC$H_2$$CH_3$), 3.30–3.25 (d, 2H, $J = 4.9$ Hz, –CH_2Br), 2.01–1.60 (m, 4H, –CH(O)CH_2-CH(OBn)–, –CHC$H_2$$CH_2$OBn), 1.18 (t, 3H, $J = 7.5$ Hz, –OCH_2CH_3). IR (neat) cm^{-1}: 2959, 2925, 2872, 1456, 1376, 1101, and 876. MS (EI): m/z 478 (M^++1).

4.11. 5-[2,4-Di(benzyloxy)-(2*R*)-butyl]-2-ethoxy-4-methyl-(4*S*,5*R*)-2*H*,3*H*,4*H*-furan 13

To a solution of bromo acetal **12** (8.0 g, 16.7 mmol) in dry toluene (50 mL) at reflux temperature under nitrogen atmosphere was added a solution of *n*-tributyltinhydride (4.5 mL, 16.7 mmol), azobisisobutyronitrile (0.04 g, 0.16 mmol) in toluene (15 mL). After 2 h, the solution was cooled to room temperature and passed through a pad of silica gel to afford pure cyclic acetal **13** as colorless oil (6.2 g, 93%). ^{1}H NMR ($CDCl_3$, 200 MHz): $\delta = 7.40–7.20$ (m, 10H, aromatic-H), 5.10–4.94 (m, 1H, –CH_2C*H*(OEt)O–), 4.60–4.40 (m, 4H, 2×–OCH_2Ph), 3.80–3.62 (m, 3H, –OC$H_2$$CH_3$, –CH($CH_3$)C*H*(O)$CH_2$–), 3.60 (t, 2H, $J = 7.0$ Hz, –CH_2OBn), 3.45–3.32 (m, 1H, –C*H*(OBn)CH_2–), 2.02–1.60 (m, 6H, –CHCH_2CH(CH_3)–, –CHCH_2CH(OBn)–, CHC$H_2$$CH_2$OBn), 1.20 (t, 3H, $J = 6.2$ Hz, –OCH_2CH_3), 1.10–0.98 (m, 3H, –CH(CH_3)–). IR (neat) cm^{-1}: 2929, 2870, 1606, 1455, 1372, 1097, 991, 795, and 697. MS (FABMS): m/z 353 (M^+−OEt). Anal. Calcd for $C_{25}H_{34}O_4$: C, 75.34; H, 8.60. Found: C, 75.39; H, 8.51%.

4.12. 5-[2,4-Di(benzyloxy)-(2*R*)-butyl]-4-methyl-(4*S*,5*R*)-2*H*,3*H*,4*H*-2-furanol 14

The solution of ethyl acetal **13** (3.0 g, 7.5 mmol) in 80% aq AcOH (30 mL) solution was refluxed for 4 h. The mixture was cooled to 0 °C, neutralized by solid $NaHCO_3$ and extracted with ethyl acetate (2×50 mL). The organic extracts were washed by water (2×25 mL) followed by brine (1×25 mL) and dried over anhydrous Na_2SO_4. Filtration and evaporation of the solvent followed by purification (column chromatography) afforded pure lactol **14** (2.5 g, 89.9% yield) as a syrupy liquid. ^{1}H NMR ($CDCl_3$, 200 MHz): $\delta = 7.32–7.20$ (m, 10H, aromatic-*H*), 5.45–5.30 (m, 1H, –CH_2C*H*(OH)O–), 4.60–4.36 (m, 4H, 2× –OCH_2Ph), 3.80–3.62 (m, 1H,

–CH(CH_3)C*H*(O)CH_2–), 3.60–3.42 (m, 3H, –CH_2OBn, –C*H*(OBn)–), 2.80–2.60 (br m, 1H, O*H*), 2.40–1.62 (m, 6H, –CHCH_2CH(CH_3)–, –CHCH_2CH(OBn)–, CHC$H_2$$CH_2$OBn), 1.60–1.40 (m, 1H, –C*H*(CH_3)-CH(O)–), 1.00 (t, 3H, $J = 7.1$ Hz, CH(CH_3)–). IR (neat) cm^{-1}: 3421, 3030, 2926, 1496, 1095, and 989. MS (FABMS): m/z 371 (M^++1). Anal. Calcd for $C_{23}H_{30}O_4$: C, 74.57; H, 8.16. Found: C, 74.49; H, 8.14%.

4.13. 7,9-Di(benzyloxy)-4-methyl-(4*S*,5*R*,7*R*)-1-nonen-5-ol 15

To methyltriphenylphosphoniumiodide (8.75 g, 21.6 mmol) in dry THF (40 mL) under nitrogen atmosphere at −78 °C was added *n*-BuLi (6.3 mL, 21.5 mmol, 3.4 M solution in hexane). After 30 min, to the resulting orange yellow turbid mixture was added lactol **14** (2.0 g, 5.4 mmol) in dry THF (5 mL) via a canula and stirring was continued for 8 h allowing the temperature to warm to 0 °C. The reaction mixture was quenched with saturated aqueous NH_4Cl solution (15 mL). The mixture was filtered over a sintered funnel and the residue was washed with ether (3×25 mL). The combined organic filtrates were evaporated after washing with water (1×25 mL), brine (1×25 mL), and drying over anhydrous Na_2SO_4. The product **15** was purified by column chromatography to afford a colorless liquid (1.7 g, 85.8%). $[\alpha]_D = +31.1$ (c 0.75, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 200 MHz): $\delta = 7.40$–7.20 (m, 10H, aromatic-H), 5.90–5.68 (m, 1H, –CH_2C*H*=CH_2), 5.10–4.92 (m, 2H, –CH=CH_2), 4.66–4.40 (m, 4H, 2×–OCH_2Ph), 3.90–3.80 (m, 1H, –CHC*H*(OH)CH_2–), 3.62–3.58 (m, 3H, –C*H*(OBn), –CH_2CH_2OBn), 2.30–2.16 (m, 1H, –C*H*(CH_3)–), 2.00–1.80 (m, 4H, –CH(CH_3)CH_2CH=), –CH(OH)CH_2CH(OBn)–), 1.70–1.50 (m, 2H, –CH(OBn)CH_2–), 0.90 (d, 3H, $J = 5.5$ Hz, –CH(CH_3)–). ^{13}C NMR ($CDCl_3$, 50 MHz): $\delta = 138.2$, 137.9, 137.5, 128.3, 127.7, 127.5, 115.6, 77.8, 74.3, 73.8, 71.5, 66.5, 38.7, 36.9, 34.1, and 14.9. IR (neat) cm^{-1}: 3480, 2926, 1640, 1454, and 1093. MS (FABMS): m/z 369 (M^++1). Anal. Calcd for $C_{24}H_{32}O_3$: C, 78.22; H, 8.75. Found: C, 78.16; H, 8.74%.

4.14. 7,9-Di(benzyloxy)-5-methoxymethoxy-4-methyl-(4*S*,5*R*,7*R*)-1-nonene 16

To alcohol **15** (1.6 g, 4.3 mmol) in anhydrous CH_2Cl_2 (12 mL) at 0 °C were added diisopropylethyl amine (1.4 g, 10.8 mmol) and MOMCl (0.46 g, 5.6 mmol) successively and the mixture was stirred for 3 h. The reaction mixture was quenched by adding water (4 mL) and extracted with CH_2Cl_2. The organic extracts were washed with brine, dried over anhydrous Na_2SO_4 and concentrated under vacuum to yield the crude product, which was purified by column chromatography to afford the pure product **16** (1.65 g, 92.2%). $[\alpha]_D = +34.3$ (c 5.4, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 200 MHz): $\delta = 7.38$–7.15 (m, 10H, aromatic-*H*), 5.80–5.60 (m, 1H, –C*H*=CH_2), 5.00–4.90 (m, 2H, –CH=CH_2), 4.60–4.32 (m, 6H, –OCH_2O–, 2× –OCH_2Ph), 3.80–3.60 (m, 1H, –C*H*O-MOM), 3.60–3.42 (m, 3H, –C*H*(OBn)–, –CH_2OBn), 3.30 (s, 3H, –OCH_3), 2.10–1.90 (m, 1H, –C*H*(CH_3)–), 1.89–1.46 (m, 6H, –CHCH_2CH(CH_3)–, –CHCH_2CH(OBn)–, –CHCH_2-CH_2OBn), 0.86 (d, 3H, $J = 6.6$ Hz, –CH(CH_3)–). IR (neat) cm^{-1}: 3064, 2931, 2882, 1640, 1496, 1098, 1039, and 916. MS (FABMS): m/z 413 (M^++1).

4.15. 5-Methoxymethoxy-6-methyl-(3*R*,5*R*,6*S*)-8-nonene-1,3-diol 17

To a solution of lithium (0.51 g, 72.8 mmol) in liq. NH_3 (50 mL) was added compound **16** (1.5 g, 3.6 mmol) in dry THF (4 mL). The mixture was stirred for 1 h, after cooling the mixture to −78 °C solid NH_4Cl (1.6 g) was added. NH_3 was allowed to evaporate and the residual mixture was taken in ethylacetate (20 mL) and washed with water (2×10 mL), brine (1×20 mL) and dried over anhydrous Na_2SO_4. Evaporation of the solvent and chromatography of the crude afforded pure diol **17** (0.510 g, 90.6% yield) as a colorless liquid. $[\alpha]_D = +43.4$ (c 8.75, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta = 5.80$–5.60 (m, 1H, –C*H*=CH_2), 5.00–4.90 (m, 2H, –CH=CH_2), 4.72 (d, 1H, $J = 6.8$ Hz, one –OC$H_2$$OCH_3$), 4.61 (d, 1H, $J = 6.4$ Hz, one –OC$H_2$$OCH_3$), 4.02–3.97 (m, 1H, –C*H*OH), 3.80–3.65 (m, 3H, –C*H*OMOM, –CH_2OH), 3.40 (s, 3H, –OCH_3), 1.98–1.80 (m, 3H, =CHCH_2C*H*(CH_3)–), 1.70–1.40 (m, 4H, –C$H_2$$CH_2$OH, –CH(OMOM)C$H_2$CH–), 0.90 (d, 3H, $J = 6.0$ Hz, –CH(CH_3)–). IR (neat) cm^{-1}: 3390, 3077, 2934, 1640, 1442, 1378, 1215, 1150, 1097, 1038, and 915. MS (EI): m/z 232 (M^+). Anal. Calcd for $C_{12}H_{24}O_4$: C, 62.04; H, 10.41. Found: C, 62.08; H, 10.40%.

4.16. 1-(*tert*-Butyldimethylsilyloxy)-5-methoxymethoxy-6-methyl-(3*R*,5*R*,6*S*)-8-nonen-3-ol 3

To a solution of diol **17** (0.5 g, 2.15 mmol) in dry CH_2Cl_2 (5 mL) and imidazole (0.29 g, 4.26 mmol) at 0 °C under nitrogen atmosphere was added TBDMSCl (0.32 g, 2.15 mmol) and stirred for 6 h allowing the mixture to warm to room temperature. The reaction mixture was diluted with water (3 mL) and extracted with CH_2Cl_2 (2×5 mL). The combined organic layers was washed with brine (1×5 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under vacuum to afford the crude product. Column chromatography of the crude product afforded **3** as a colorless liquid (0.685 g, 91.9%). $[\alpha]_D = +22.3$ (c 3.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 200 MHz): $\delta = 5.80$–5.58 (m, 1H, –C*H*=CH_2), 5.07–4.85 (m, 2H, –CH=CH_2), 4.60 (q, 2H, $J = 6.8$, 13.6 Hz, –OC$H_2$$OCH_3$), 3.97–3.54 (m, 4H, –C$H_2$OTBDMS, –CHC*H*(OMOM)–, –C*H*(OH)CH_2–), 3.31 (s, 3H, –OCH_3), 2.12–1.77 (m, 3H, =CHCH_2C*H*(CH_3)–), 1.70–1.48 (m, 2H, –CH(OMOM)CH_2–), 1.40–1.20 (m, 2H, –CH(OH)CH_2–), 0.94–0.79 (m, 12H, –C(CH_3)$_3$), –CH(CH_3)–), 0.06 (s, 6H, –Si(CH_3)$_2$C(CH_3)$_3$). ^{13}C NMR ($CDCl_3$, 300 MHz) δ 137.1, 115.9, 95.5, 80.1, 69.5, 55.9, 39.0, 37.4, 36.7, 35.4, 25.8, 18.2, 14.1, −5.2. IR (neat) cm^{-1}: 3514, 2933, 1468, 1754, 1095, 1039, and 915. MS (FABMS): m/z 347 (M^++1).

4.17. 1-(3-Butynyloxymethyl)benzene 18

Product **18** was prepared using similar procedure as given to compound **6** to afford 21.7 g in 95.1% yield as a colorless liquid from 10 g of 3-butyne-1-ol. ^{1}H NMR ($CDCl_3$, 200 MHz): $\delta = 7.40$–7.20 (m, 5H, aromatic-*H*), 4.59 (s, 2H, –OCH_2Ph), 3.60 (t, 2H, $J = 6.4$ Hz, –CH_2OBn), 2.55–2.40 (m, 2H, –CH_2CH_2OBn), 0.98–0.92 (m, 1H, acetylene-*H*). IR (neat) cm^{-1}: 3031, 2862, 2121, 1455, 1104, 909. MS (EI): m/z 160 (M^+).

4.18. Ethyl 5-benzyloxy-2-pentynoate 19

To a freshly prepared ethyl magnesium bromide solution [from ethyl bromide (9.3 mL, 124 mmol) and magnesium (3.0 g, 125 mmol) in dry THF (100 mL)] under nitrogen atmosphere at 0 °C was added alkyne **18** (10.0 g, 62.5 mmol) and allowed to stir at room temperature for 1 h. To this reaction mixture, at 0 °C freshly distilled ethyl chloroformate (12 mL, 125 mmol) was added slowly. After the addition was complete, the mixture was further stirred overnight at room temperature. The reaction mixture was quenched with saturated aqueous NH_4Cl solution (25 mL) and extracted with ethyl acetate. The organic extract was washed with water (2×50 mL), brine (1×50 mL), dried over anhydrous Na_2SO_4, filtered and concentrated under vacuum. Purification of the crude by column chromatography afforded the ester **19** (12.3 g, 84.8% yield) as a colorless syrupy liquid. ^{1}H NMR ($CDCl_3$, 200 MHz): $\delta = 7.40$–7.22 (m, 5H, aromatic-*H*), 4.58 (s, 2H, –OCH_2Ph), 4.20 (q, 2H, $J = 6.7$ Hz, –OCH_2CH$_3$), 3.62 (t, 2H, $J = 7.4$ Hz, –CH_2OBn, 1.34 (t, 2H, $J = 6.7$ Hz, –OCH$_2$CH_3). IR (neat) cm^{-1}: 2983, 2870, 2241, 1711, 1454, 1366, 1255, 1076, 1019, and 746. MS (EI): m/z 232 (M^+).

4.19. Ethyl 2-(2-benzyloxyethyl)-6-methoxybenzoate 21

A neat solution of 1-methoxycyclohexa-1,4-diene **20** (4.75 g, 43.1 mmol) and ester **19** (5.0 g, 21.5 mmol) along with a catalytic amount of dichloromaleic anhydride (5 mg) was heated at 280 °C for 8 h in a sealed tube. The reaction mixture was cooled to room temperature diluted with ethylacetate (25 mL) and washed with 20% $NaHCO_3$ solution followed by brine (1×25 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered and evaporated to give the crude oil which was purified by column chromatography to afford **21** (5.0 g, 73.9%) as a pale yellow liquid. ^{1}H NMR ($CDCl_3$, 200 MHz): $\delta = 7.38$–7.20 (m, 6H, 5 from phenyl, one subs.aryl-H), 6.82 (d, 2H, $J = 7.8$ Hz, sub.aryl-*H*), 6.75 (d, 1H, $J = 7.8$ Hz, sub.aryl-*H*), 4.48 (s, 2H, –OCH_2Ph), 4.32 (q, 2H, $J = 7.4$ Hz, –OCH_2CH$_3$), 3.80 (s, 3H, –OCH$_3$), 3.60 (t, 2H, $J = 7.4$ Hz, –CH_2OBn), 2.86 (t, 2H, $J = 7.4$ Hz, –CH_2CH$_2$OBn), 1.36 (t, 3H, $J = 7.4$ Hz, –OCH$_2$CH_3). ^{13}C NMR ($CDCl_3$, 50 MHz): $\delta = 167.9$, 156.2, 138.2, 136.9, 130.0, 128.1, 127.4, 127.3, 122.1, 109.0, 72.7, 70.5, 60.9, 55.7, 33.7, 14.1. IR (neat) cm^{-1}: 3030, 2859, 1727, 1599, 1585, 1471, 1364, 1267, 1072, 1028, and 913. MS (FABMS): m/z 315 (M^++1). Anal. Calcd for $C_{19}H_{22}O_4$: C, 72.59; H, 7.05. Found: C, 72.53; H, 7.07%.

4.20. Ethyl 2-(2-hydroxyethyl)-6-methoxybenzoate 22

To compound **21** (2.0 g, 6.36 mmol) in absolute ethanol (20 mL) was added $Pd(OH)_2$ (0.15 g) and stirred at room temperature under hydrogen atmosphere for 20 h. The mixture was diluted by adding $CHCl_3$ (5 mL) and filtered through a small pad of Celite. Evaporation of the solvent and purification of the crude mixture by column chromatography afforded pure alcohol **22** (1.02 g, 71.5%) as a colorless liquid. ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta = 7.27$ (t, 1H, $J = 7.9$ Hz, one aromatic H), 6.84 (d, 1H, $J = 7.6$ Hz, one aromatic *H*), 6.77 (d, 1H, $J = 7.6$ Hz, one aromatic *H*), 4.38 (q, 2H, $J = 7.2$, 14.3 Hz, –OCH_2CH$_3$), 3.85–3.76 (m, 5H, –OCH_3, –CH_2OH), 2.79 (t, 2H, $J = 6.4$ Hz, –CH_2CH$_2$OH), 1.90 (br s, 1H, –O*H*), 1.39 (t, 3H, $J = 7.2$ Hz, –OCH$_2$CH_3). IR (neat) cm^{-1}: 3418, 2946, 2842, 1730, 1588, 1469, 1266, 1189, 1072, and 952. MS (EI): m/z 224 (M^+).

4.21. Ethyl 2-formylmethyl-6-methoxybenzoate 23

Dess Martin Periodinane (0.22 g, 0.53 mmol) was added to a solution of alcohol **22** (0.1 g, 0.44 mmol) in dry CH_2Cl_2 (15 mL) at 0 °C under nitrogen atmosphere. The turbid solution was allowed to warm to room temperature and stirred for 14 h. The reaction was diluted with ethyl acetate (17 mL) and quenched with saturated aqueous $NaHCO_3$ (20 mL), and saturated aqueous $Na_2S_2O_3$ (20 mL). The mixture was vigorously stirred until a clear solution resulted. The aqueous layer was extracted with ethyl acetate (2×25 mL). The combined organic extracts were washed with brine (1×20 mL), dried over anhydrous Na_2SO_4 and concentrated to give the crude aldehyde. Purification by column chromatography afforded the pure aldehyde **23** (0.094 g, 94.9%) as a colorless oil. ^{1}H NMR ($CDCl_3$, 200 MHz): $\delta = 9.60$ (m, 1H, –C*H*O), 7.28–7.20 (m, 1H, one aromatic-*H*), 6.90–6.78 (m, 2H, aromatic-*H*), 4.38 (q, 2H, $J = 7.2$, 14.2 Hz, –OCH_2CH$_3$), 3.80 (s, 3H, –OCH_3), 3.60 (s, 2H, –CH_2CHO), 1.40 (t, 3H, $J = 7.3$ Hz, –OCH$_2$CH_3). IR (neat) cm^{-1}: 2981, 2841, 2728, 1729, 1706, 1586, 1471, 1266, 1072, and 795.

4.22. Ethyl 2-allyl-6-methoxybenzoate 24

To a mixture of methyltriphenylphosphonium iodide (0.109 g, 0.26 mmol) and ^{t}BuOK (0.020 g, 0.178 mmol) in dry THF (5 mL) at −78 °C was added 18 crown 6 (~3 mg) and the solution was stirred for half an hour. Aldehyde **33** (0.050 g, 0.225 mmol) in dry THF (1 mL) was added to this solution and stirring was continued until the starting material had been consumed. The reaction mixture was quenched by addition of water (1 mL) and the solvent was evaporated. The residue was taken in ethyl acetate and the organic layer was washed with water (1×5 mL) followed by brine (1×5 mL) and dried over anhydrous Na_2SO_4. The solvent was

evaporated under reduced pressure. Purification by flash chromatography afforded the pure product **24** (0.025 g, 50% yield). ^{1}H NMR ($CDCl_3$, 200 MHz): $\delta = 7.30$–7.18 (m, 1H, aromatic-H), 6.82–6.72 (m, 2H, aromatic-H), 6.10–5.70 (m, 1H, –C*H*=CH_2), 5.10–4.98 (m, 2H, –CH=C*H*$_2$), 4.38 (q, 2H, $J = 7.3$, 14.1 Hz, –OC*H*$_2$CH$_3$), 3.80 (s, 3H, –OC*H*$_3$), 3.34 (d, 2H, $J = 6.8$ Hz, –C*H*$_2$CH=CH_2), 1.40 (t, 3H, $J = 7.3$ Hz, –OCH$_2$C*H*$_3$). IR (neat) cm^{-1}: 2923, 2853, 1715, 1599, 1580, 1470, 1265, 1109, and 1072. MS (EI): m/z 220 (M^+).

4.23. 2-Allyl-6-methoxybenzoic acid 2

To a solution of ester **24** (1.0 g, 4.5 mmol) in MeOH/water (3:1; 10 mL) was added LiOH·H_2O (1.6 g, 36.3 mmol) and the mixture was heated to 70 °C for 48 h. The solvent was evaporated and the residue in water was washed with ether (2×5 mL). The aqueous solution was acidified by 2 N HCl (20 mL) and extracted with ethyl acetate. The organic layer was washed with brine, dried over Na_2SO_4 and concentrated to get the crude acid. The product was purified over silica gel column chromatography to afford colorless solid **2** (0.74 g, 85% yield). Melting point 105–107 °C. ^{1}H NMR ($CDCl_3$, 200 MHz): $\delta = 7.32$ (t, 1H, $J = 16.3$ Hz, aromatic-*H*), 6.80 (t, 2H, $J = 16.3$ Hz, aromatic-*H*), 6.00–5.80 (m, 1H, –C*H*=CH_2), 5.20–5.00 (m, 2H, —CH=C*H*$_2$), 3.90 (s, 3H, –OC*H*$_3$), 3.50 (d, 2H, $J = 6.2$ Hz, Aryl-C*H*$_2$–), 1.25 (s, 1H, acid-O*H*). ^{13}C NMR ($CDCl_3$, 75MHz): $\delta = 162.8$, 157.1, 139.6, 136.0, 131.5, 122.5, 121.6, 116.5, 108.9, 55.8, 37.2. IR (KBr) cm^{-1}: 2940, 1704, 1598, 1471, 1267, 1219, 1077, and 910. MS (EI): m/z 192 (M^+). Anal. Calcd for $C_{11}H_{12}O_3$: C, 68.74; H, 6.29. Found: C, 68.72; H, 6.27%.

4.24. 1-[2-(*tert*-Butyldimethylsilyloxy)ethyl]-3-methoxymethoxy-4-methyl-(1*S*,3*R*,4*S*)-6-heptenyl 2-allyl-6-methoxybenzoate 25

To a well-stirred solution of alcohol **3** (0.15 g, 0.60 mmol) and triphenylphosphine (0.24 g, 0.91 mmol) in dry benzene (4 mL) at room temperature was added prestirred solution of acid **2** (0.117 g, 0.60 mmol) and DEAD (0.160 g, 0.91 mmol) in benzene (4 mL). The mixture was stirred for 14 h. Solvent was evaporated and the residue was washed with dry ether and filtered through a sintered funnel. The filtrates were dried over anhydrous Na_2SO_4 and evaporation of the solvent followed by chromatography of the crude residue afforded pure ester **25** (0.235 g, 74.3% yield) as a pale pink colored viscous liquid. $[\alpha]_D = -3.5$ (*c* 4.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 200 MHz): $\delta = 7.30$–7.20 (m, 1H, aromatic-H), 6.76 (t, 2H, $J = 8.9$ Hz aromatic-H), 6.00–5.60 (m, 2H, 2× –C*H*=CH_2), 5.40–5.30 (m, 1H, –C*H*(OCO)–), 5.10–4.84 (m, 4H, –CH=C*H*$_2$), 4.73–4.65 (m, 2H, –OC*H*$_2$OCH$_3$), 3.83 (s, 3H, –OC*H*$_3$), 3.78–3.62 (m, 2H, –C*H*$_2$OTBDMS), 3.41–3.30 (m, 4H, –CH$_2$OC*H*$_3$, –C*H*(OMOM)–), 1.95–1.79 (m, 4H, ArC*H*$_2$-CH=CH_2, –C*H*$_2$CH$_2$OTBDMS), 1.74–1.65 (m, 2H, –CH(CH$_3$)C*H*$_2$CH=CH_2), 0.92–0.82 (m, 12H, *tert*-butyl-*H*), 0.05 (s, 6H, –Si(C*H*$_3$)$_2$–). IR (neat) cm^{-1}: 2931, 1725, 1586, 1469, 1265, 1098, 1039, and 913. MS (MALDI): m/z 543 (M^++Na).

4.25. 3-[2-(*tert*-Butyldimethylsilyloxy)ethyl]-14-methoxy-5-methoxymethoxy-6-methyl-(3*S*,5*R*,6*S*)-1*H*,4*H*,5*H*,6*H*,7*H*,10*H*-benzo[*c*]oxacyclododecin-1-one 26

To a solution of the Grubb's catalyst $(Cy_3P)_2Cl_2$ Ru = CHPh (0.025 g, 0.03 mmol) in dry CH_2Cl_2 (40 mL) was added a solution of compound **25** (0.130 g, 0.25 mmol) in CH_2Cl_2 (2 mL). The reaction mixture was stirred for 3 h at ambient temperature and poured into water (20 mL). The organic phase was washed with brine (1×20 mL), dried over anhydrous Na_2SO_4, filtered and concentrated. Column chromatography of the crude residue afforded pure product **26** (0.104 g, 85% yield (9:1) $E:Z$ isomer) as a light brown colored viscous liquid. $[\alpha]_D = -58.5$ (*c* 3.0, MeOH). ^{1}H NMR ($CDCl_3$, 500 MHz): $\delta = 7.22$ (t, 1H, $J = 7.8$ Hz, aromatic-*H*), 6.77 (dd, 2H, $J = 8.4$, 22.5 Hz, aromatic-*H*), 5.52–5.42 (m, 2H, –C*H*(OCO)–, one olefinic-*H*), 5.37–5.30 (q, 1H, $J = 9.5$, 15.2 Hz, olefinic-*H*), 4.92 (d, 1H, $J = 6.2$ Hz, one –OC*H*$_2$OCH$_3$), 4.79 (d, 1H, $J = 6.7$ Hz, one –OC*H*$_2$OCH$_3$), 4.15 (dd, 1H, $J = 3.4$, 9.0 Hz, –C*H*(O-MOM)–), 3.80–3.65 (m, 6H, –OC*H*$_3$, –OC*H*$_2$OTBDMS, one Ar–C*H*$_2$–CH=CH–), 3.45 (s, 3H, –OCH$_2$OCH$_3$), 3.31 (d, 1H, $J = 16.3$ Hz, one Ar–C*H*$_2$–CH=CH–), 2.30 (d, 1H, $J = 13.5$ Hz, one –C*H*$_2$CH$_2$OTBDMS), 2.18–2.09 (m, 1H, –C*H*(CH$_3$)–), 2.00–1.90 (m, 1H, one –C*H*$_2$CH$_2$OTBDMS), 1.82–1.65 (m, 3H, =CH–C*H*$_2$–CH(CH$_3$)–, one –C*H*$_2$–CH(OMOM)–), 1.51–1.41 (m, 1H, one –C*H*$_2$CH(OMOM)–), 0.90 (s, 9H, *tert*.butyl-*H*), 0.87 (d, 3H, $J = 6.7$ Hz, –CH(C*H*$_3$)–), 0.06 (s, 6H, –SiC*H*$_3$)$_2$–). ^{13}C NMR($CDCl_3$, 50 MHz): $\delta = 168.1$, 156.6, 139.1, 131.3, 129.8, 128.5, 122.7, 109.2, 96.9, 79.3, 72.0, 59.3, 55.4, 39.5, 37.7, 37.6, 35.7, 34.1, 25.8, 18.1, 13.3, −5.2. IR (neat) cm^{-1}: 2954, 2928, 2856, 1725, 1597, 1584, 1469, 1438, 1275, 1254, 1088, 1041, 970, and 951. MS (FABMS): m/z 493 (M^++1).

4.26. 3-(2-Hydroxyethyl)-14-methoxy-5-methoxymethoxy-6-methyl-(3*S*,5*R*,6*S*)-1*H*,4*H*,5*H*,6*H*,7*H*,10*H*-benzo-[*c*]oxacyclododecin-1-one 27

TBAF (0.44 mL, 0.44 mmol, 1 M in THF) was added at 0 °C to a solution of TBDMS ether **26** (0.12 g, 0.24 mmol) in THF (4 mL). After stirring the mixture for 3 h at ambient temperature the mixture was quenched with water (3 mL). The aqueous layer was extracted with ethyl acetate (2×5 mL). The combined organic phases were dried over anhydrous Na_2SO_4 and evaporated. Column chromatography of the crude residue afforded the pure alcohol **27** (0.085 g, 92.4%) as a viscous liquid. $[\alpha]_D = -52.6$ (*c* 5.5, MeOH), −38.8 (*c* 1.0, $CHCl_3$), lit.[2e] $[\alpha]_D = -34.5$ (*c* 1.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta = 7.24$–7.15 (m, 1H, aromatic-H), 6.81–6.73 (m, 2H, aromatic-H), 5.53–5.41 (m, 2H, one olefinic-*H* and –C*H*(OCO)–), 5.37–5.26 (m, 1H, olefinic-H), 4.82 (Ab quartet, 2H, $J = 6.8$, 18.1 Hz, –OC*H*$_2$OCH$_3$), 4.18–4.10 (m, 1H, –C*H*OMOM), 3.84 (s, 3H, –OC*H*$_3$), 3.78–3.66 (m, 4H, –C*H*$_2$OH, aryl-C*H*$_2$CH=CH_2), 3.43

(s, 3H, –OCH_2OCH_3), 2.35–2.23 (m, 2H, $CH(CH_3)$-$CH_2CH{=}CH_2$–), 2.15–2.05 (m, 1H, –$CH(CH_3)$–), 1.93–1.62 (m, 4H, –$CH(OCO)CH_2CH(OMOM)$–, –CH_2-CH_2OH), 0.85 (d, 3H, $J = 6.8$ Hz, –$CH(CH_3)$–). ^{13}C NMR ($CDCl_3$, 75 MHz): $\delta = 168.2$, 156.0, 139.0, 131.0, 129.9, 128.2, 124.2, 122.9, 109.1, 96.7, 79.3, 72.7, 59.1, 55.5, 55.4, 38.8, 37.6, 35.7, 33.9, and 13.2. IR (neat) cm^{-1}: 3438, 2924, 1722, 1585, 1467, 1275, 1039, 973, 913, and 731. MS (FABMS): m/z 379 (M^++1). Anal. Calcd for $C_{21}H_{30}O_6$: C, 66.65; H, 7.99. Found: C, 66.59; H, 8.01%.

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