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Asymmetric total synthesis of 5′-*epi*-paecilomycin-F

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ABSTRACT

The asymmetric total synthesis of one of the stereoisomers of the naturally occurring 14-membered ring macrolide paecilomycin-F (5′-*epi*) has been reported in this article. The main highlight of the synthetic strategy involves the successful application of a ring closing metathesis (RCM) reaction at a late stage. Asymmetric Keck allylation, Sharpless asymmetric dihydroxylation, and Mitsunobu esterification have also been used successfully for the total synthesis of 5′-*epi*-paecilomycin-F.

1. Introduction

β-Resorcylic acid lactones (RALs) belong to a unique class of fungal polyketide derived secondary metabolites, which are β-resorcylic acid derivatives containing a C11 side chain.[1] In a majority of cases, these RALs have a 14-membered ring lactone as one of the core structural components. Their biological activity spans from estrogenic, antifungal, cytotoxic, antimalarial properties and they have also been shown to possess inhibitory effects against selective enzymes, such as ATPases and kinases.[2] Due to these important biological properties, RALs have attracted a great deal of attention from synthetic organic chemists. Recently six new β-RALs have been isolated from a mycelial solid culture of *Paecilomyces* sp. SC0924 (filamentous fungi found in South China Sea).[3] These compounds have been named as paecilomycins A–F **1**–**6**, and their structures have been elucidated by extensive NMR and X-ray analyses. In addition to these six new RALs, five known RALs have also been isolated from the same species; aigilomycin B **7**, zeaenol **8**, aigialomycin D **9**, aigialomycin F **10**, and aigialospirol (Fig. 1). There are numerous reports on the total synthesis of RALs,[4] but to the best of our knowledge there is only one synthetic report for the paecilomycins. Srihari et al.[4e] have reported the first total synthesis of paecilomycin-E **5** by a chiral pool approach. The best synthetic strategy reported for RALs involve a biomimetic synthesis featuring a late stage aromatization of properly substituted triketo esters as demonstrated by Barett et al. in their total synthesis.[4a,b] We have recently accomplished the total synthesis of cochliomycin-A and zeaenol.[5] Herein we report the asymmetric total synthesis of 5′-*epi*-paecilomycin-F **11**. It should be noted that the synthesis accomplished herein was not a target oriented synthesis, rather it could be better described as a strategy oriented synthesis as two hydroxyl stereocenters at C-5′ and C-6′ have been fixed by asymmetric dihydroxylation by AD-mix β which lead to 5′-*epi*-paecilomycin-F.

2. Results and discussion

The retrosynthetic analysis of compound **11** is shown in Scheme 1. We envisioned that the double bond between C-1′ and C-2′ could be constructed from ester **12** by adopting an RCM reaction. Ester **12** could be obtained from alcohol **13** and acid **14** with a pendant vinyl group by a Mitsunobu esterification reaction. Trisubstituted benzoic acid **14** with a pendant vinyl group was synthesized from 3,5-dihydroxy benzoic acid in seven steps.[5] The alcohol fragment **13** was prepared from 1,5-pentanediol by applying a stereoselective Keck allylation, Sharpless asymmetric dihydroxylation, and ME-DKR reaction (metal–enzyme combined dynamic kinetic resolution).

The synthesis of alcohol fragment **13** was initiated from 1,5-pentanediol as a starting material. Monoprotection with PMB-Br (*para*-methoxy benzyl bromide) afforded compound **15** in 82% yield. Swern oxidation[6] of compound **15** afforded aldehyde **16** in 90% yield. The addition of a freshly generated solution of MeMgBr to aldehyde **16** yielded racemic secondary alcohol **17** in 85% yield. The DKR of the secondary alcohol functionality in compound **17** was achieved by coupling an enzyme-catalyzed transesterification reaction with a metal-catalyzed (ruthenium based catalyst shown in Scheme 2) racemization method as reported by Kim et al.[7] Isopropenyl acetate was used as the acyl donor in the DKR reaction. The DKR reaction was highly efficient for compound **17** since it yielded the corresponding acetate **18** in 92% yield with excellent enantioselectivity (ee = 98%).[8] The acetate functionality was removed by treatment with K_2CO_3 in MeOH to yield enantiomerically pure (*R*)-**17** in 94% yield. This type of ME-DKR has already been successfully used[9] for the synthesis of valuable chiral intermediates. The free secondary hydroxy group in compound **17** was protected as its TBDPS (*tert*-butyldiphenylsilyl) ether by treatment with TBDPS-Cl and imidazole to produce

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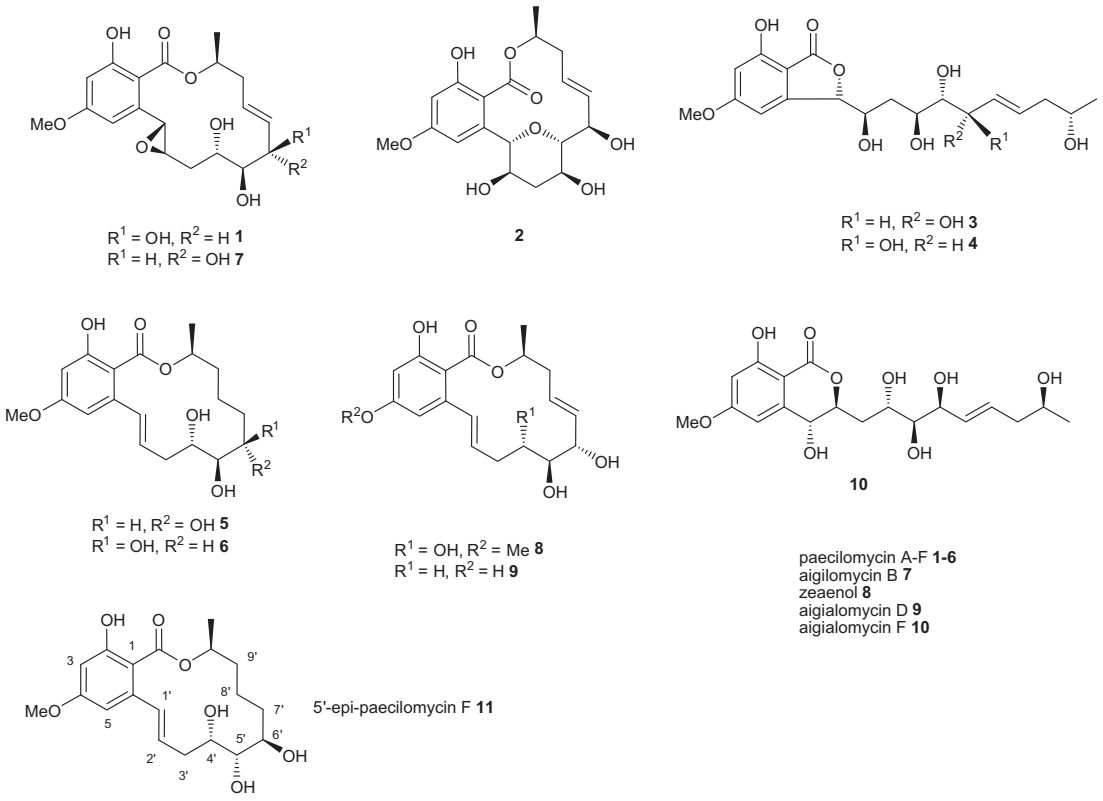
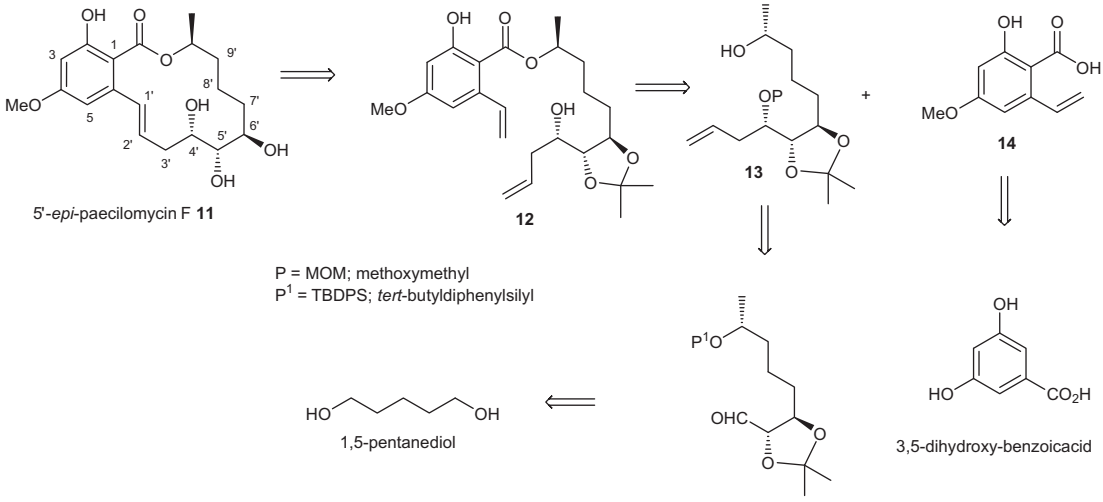


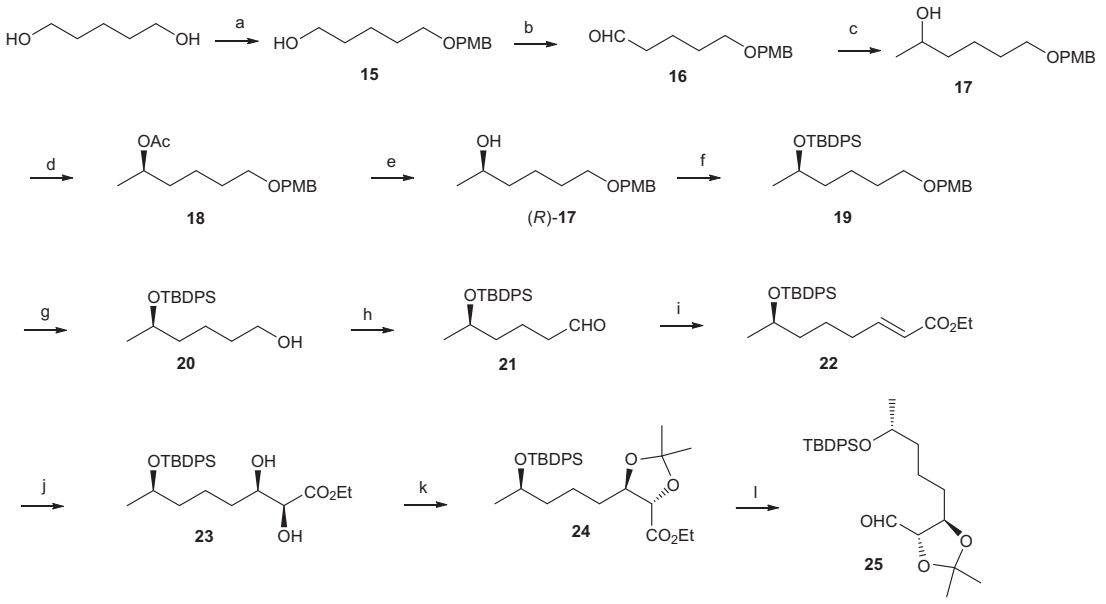
Figure 1. Structures of the paecilomycins and other related RALs.



Scheme 1. Retrosynthetic analysis of 5′-*epi*-paecilomycin F.

compound **19** in 90% yield. Removal of the PMB group was achieved with DDQ[10] to afford compound **20** in 83% yield. The primary hydroxy group in compound **20** was transformed into its corresponding aldehyde by another round of Swern oxidation to afford aldehyde **21** in 88% yield. The *trans*-selective HWE olefination of aldehyde **21** with triethyl phosphonoacetate yielded the *E*-ester **22** in 88% yield (*Z*:*E* = 1:20). Dihydroxylation of ester **22** with AD mix-β[11] produced the required diol **23** in 75% yield. Diol **23** was protected as its acetonide by treatment with 2,2-DMP[12] (2,2-dimethoxy propane) in the presence of a catalytic amount of CSA (camphoresulfonic acid) to afford **24** in 92% yield. Selective reduction of the ester functionality in compound **24** with DIBAL-H afforded aldehyde **25** in 80% yield (Scheme 2).

Aldehyde **25** was then subjected to a Keck asymmetric allylation[13] reaction to produce allylic alcohol **26** in 78% yield with a 19:1 diastereomeric ratio. The protection of the free hydroxyl group as its MOM (methoxy-methyl) ether[14] was achieved by treating compound **26** with DIPEA, MOM-Cl and a catalytic amount of TBAI (tetra-*n*-butyl ammonium iodide, yield = 92%) to afford compound **27**. Deprotection of the TBDPS group in compound **27** by TBAF[15] afforded alcohol **13** in 86% yield. With the vinyl substituted benzoic acid **14** and properly functionalized alcohol **13** in hand, the esteri-



Scheme 2. Reagents and conditions: (a) PMB-Br, NaH, TBAI (cat.), THF, rt, 2 h,(80%); (b) $(COCl)_2$, DMSO, Et_3N, −78 °C, 86%; (c) MeMgI, Et_2O, −78 °C to rt, 2 h, 92%; (d) CAL-B, isopropenyl acetate, chlorodicarbonyl(1-(isopropylamino)-2,3,4,5-tetraphenylcyclopentadienyl) ruthenium(II) [DKR catalyst], K_2CO_3, KO^{t}Bu, 92%; (e) K_2CO_3, MeOH, 94%; (f) imidazole, TBDPS-Cl, DCM, rt, 95%; (g) DDQ, DCM/H_2O (19:1), 86%; (h) $(COCl)_2$, DMSO, Et_3N, −78 °C, 84%; (i) triethylphosphano acetate, NaH, Et_2O, −5 °C to rt, 96%; (j) AD-mix-β, $MeSO_2NH_2$, *t*BuOH/H_2O (1:1), 78%; (k) 2,2-dimethoxy propane, PTSA, DCM, rt, 80%; (l) DIBAL-H, DCM, −78 °C, 1 h, 70%.

fication reaction of the two fragments under Mitsunobu conditions[16] proceeded cleanly to generate ester **12** in 85% yield. In order to complete the total synthesis, macrocyclization by RCM and deprotection was required. Compound **12** with two terminal olefins, upon treatment with Grubbs-II catalyst[17] furnished macrolactone **28** in 68% yield. Global deprotection of the MOM and acetonide functionality was achieved by treating compound **28** with 2 M HCl to afford 5′-*epi*-paecilomycin-F in 88% yield (overall yield = 5.5% from 1,5-pentanediol, Scheme 3).

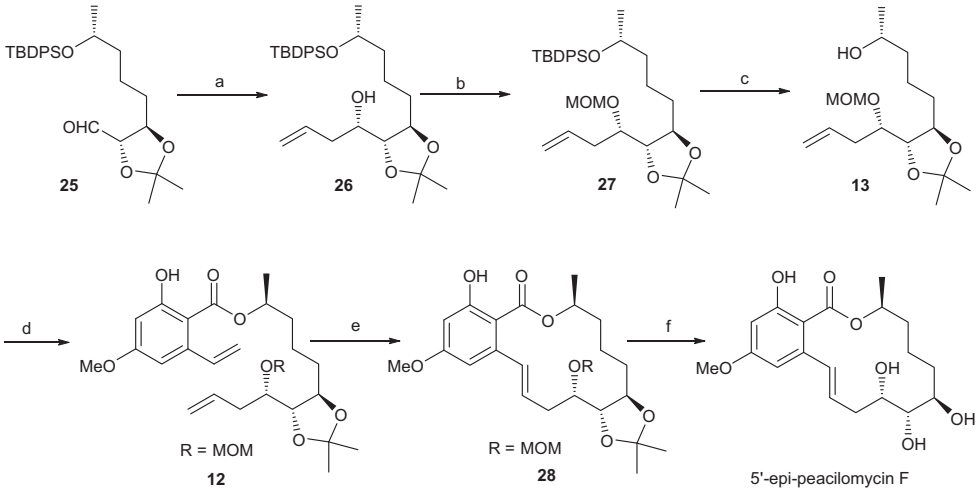
3. Conclusion

In conclusion, we have synthesized a new RAL 5′-*epi*-paecilomycin-F starting from the commercially available, inexpensive starting materials 3,5-dihydroxy benzoic acid and 1,5-pentanediol. The key steps of our synthesis include a metal–enzyme combined DKR, an effective Keck asymmetric allylation on an acetonide protected aldehyde, an asymmetric dihydroxylation reaction by the Sharpless protocol and a late stage RCM reaction. Synthetic studies toward several structurally related RALs (cochliomycin B and C, paecilomycin F) are still under investigation.

4. Experimental

4.1. General

Unless stated otherwise, materials were obtained from commercial suppliers and used without further purification. THF and diethyl ether were distilled from sodium benzophenone ketyl. Dichloromethane (DCM), dimethylformamide (DMF), and dimethylsulfoxide (DMSO) were distilled from calcium hydride. Diisopropylether (DIPE) was refluxed over P_2O_5 and distilled prior to use. Vinyl acetate was freshly distilled prior to use. CAL-B (*Candida antartica* lipase-B, Novozym-435, immobilized on acrylic resin)



Scheme 3. Reagent and conditions: (a) allyltributyltin, Ti(OPr)$_4$, (*S*)-BINOL, toluene, −78 °C then −20 °C 72 h, 76%; (b) MOM-Cl, DIPEA, DCM, rt, overnight, 90%; (c) TBAF, THF, rt, 4 h, 92%; (d) **14**, DIAD, PPh_3, toluene, 1.5 h, 85%; (e) Grubbbs II, DCM, 40 °C, 6 h, 72%; (f) 2 M HCl, THF, 20 h, 90%.

were obtained from Sigma and used as obtained. Reactions were monitored by thin-layer chromatography(TLC) carried out on 0.25 mm silica gel plates (Merck) with UV light, ethanolic anisaldehyde and phosphomolybdic acid/heat as developing agents. Silica gel 100–200 mesh was used for column chromatography. Yields refer to chromatographically and spectroscopically homogeneous materials unless otherwise stated. NMR spectra were recorded on Bruker 400 and 200 MHz spectrometers at 25 °C in $CDCl_3$ using TMS as the internal standard. Chemical shifts are shown in δ. ^{13}C NMR spectra were recorded with a complete proton decoupling environment. The chemical shift value is listed as δ_H and δ_C for ^1H and ^{13}C, respectively. Optical rotations were measured on a JASCO P-1020 digital polarimeter. Chiral HPLC was performed using a Chiral AS-H column (0.46 × 25 cm, Daicel industries) with a Shimadzu Prominence LC-20AT chromatograph coupled with a UV–vis detector (254 nm). The eluting solvent used was different ratio of hexane and 2-propanol. Mass spectral analysis was performed at IICT, Hyderabad, India.

4.2. 5-(4-Methoxybenzyloxy)pentan-1-ol 15

Pentane-1,5-diol (8 g, 77 mmol) was taken in 200 mL of dry THF. NaH (60% dispersion in mineral oil, 3.11 g, 111 mmol) was added portionwise at 0 °C. The reaction mixture was then stirred at 0 °C for 1 h. Tetrabutylammonium iodide (TBAI, 5 mmol) was then added to it followed by the addition of 4-methoxybenzylbromide. The reaction mixture was stirred for a further 2 h at room temperature. Water was then carefully added to the reaction mixture to quench any excess NaH. The reaction mixture was extracted with a large volume of EtOAc. The organic solution was washed with water and brine. Evaporation and purification by means of silica gel chromatography (2.5:1, hexane/EtOAc) afforded the mono-PMB protected alcohol **15** in 80% yield. δ_H ($CDCl_3$, 200 MHz): 7.24 (d, J = 8.0 Hz, 2H), 6.85 (d, J = 8.0 Hz, 2H), 4.42 (s, 2H), 3.78 (s, 3H), 3.60–3.41 (m, 4H), 1.65–1.36 (m, 6H). δ_C ($CDCl_3$, 50 MHz): 159.1, 130.6, 129.3 (*C*H), 113.8 (*C*H), 72.6 (*C*H_2), 70.0 (*C*H_2), 62.7 (*C*H_2), 55.3 (*C*H_3), 32.5 (*C*H_2), 29.4 (*C*H_2), 22.4 (*C*H_2).

4.3. 6-(4-Methoxybenzyloxy)hexan-2-ol 17

Monoprotected alcohol **15** was oxidized under Swern oxidation conditions in a dry, 250 ml, two-necked, round-bottomed flask charged with an excess of Mg (1.2 g) and 100 ml of anhydrous Et_2O. To the stirred mixture was added dropwise a solution of methyl iodide (6.25 g, 2.75 ml, 44 mmol) at such a rate to maintain a gentle reflux. After the addition was complete, the mixture was stirred for 30 min. To this a solution of crude aldehyde **16** (6.5 g, 29.2 mmol) in ether (30 ml) at −78 °C was added dropwise. The resulting mixture was then stirred for 1 h at −78 °C, after which it was allowed to warm to room temperature over 1 h. The reaction mixture was quenched by adding cold saturated NH_4Cl solution and extracted with ethyl acetate. The organic phase was washed with brine and dried over $MgSO_4$. The crude reaction mixture was filtered and concentrated under reduced pressure. Purification by silica gel chromatography (5:1, hexane/EtOAc) afforded the racemic alcohol **17** in 78% yield over two steps. δ_H ($CDCl_3$, 200 MHz): 7.30 (d, J = 8.0 Hz, 2H), 6.88 (d, J = 8.0 Hz, 2H), 4.46 (s, 2H), 3.83 (s, 3H), 3.85–3.83 (m, 1H), 3.48 (t, J = 6.4 Hz, 2H), 1.69–1.44 (m, 6H), 1.22 (d, J = 7.2 Hz, 3H). δ_C ($CDCl_3$, 50 MHz): 159.1, 130.7, 129.3 (*C*H), 113.8 (*C*H), 72.5 (*C*H_2), 69.9 (*C*H_2), 67.9 (*C*H), 55.2 (*C*H_3), 39.0 (*C*H_2), 29.6 (*C*H_2), 23.4 (*C*H_3), 22.4 (*C*H_2).

4.4. (*R*)-6-(4-Methoxybenzyloxy)hexan-2-yl acetate 18

In a 100 mL round bottomed flask attached with a grease free high vacuum stopcock, chlorodicarbonyl(1-(isopropylamino)-2,3,4,5-tetraphenylcyclopentadienyl) ruthenium(II) [DKR catalyst, 142 mg, 0.228 mmol] was added. The flask was successively charged with alcohol **17** (1.36 g, 5.7 mmol) in 20 mL of dry toluene, Na_2CO_3 (5.7 mmol), CAL-B (65 mg), and KO*t*Bu (0.28 mmol) followed by isopropenyl acetate (5 mmol). The reaction mixture was stirred at room temperature under an argon atmosphere. After 6 h the reaction mixture was filtered off and the solution was evaporated to afford the crude acetate, which was subsequently purified by silica gel chromatography (7:1, hexane/EtOAc) to afford the pure acetate **18** in 92% yield. δ_H ($CDCl_3$, 200 MHz): 7.23 (d, J = 8.0 Hz, 2H), 6.85 (d, J = 8.0 Hz, 2H), 4.95–4.79 (m, 1H), 4.41 (s, 2H), 3.78 (s, 3H), 3.42 (t, J = 6.4 Hz, 2H), 2.03 (s, 3H), 1.62–1.37 (m, 6H), 1.18 (d, J = 6.2 Hz, 3H). δ_C ($CDCl_3$, 50 MHz): 170.7, 159.1, 130.7, 129.2 (CH), 113.7 (CH), 72.5 (*C*H_2), 70.9 (*C*H), 69.8 (*C*H_2), 55.2 (*C*H_3), 35.7 (*C*H_2), 29.6 (*C*H_2), 22.1 (*C*H_2), 21.3 (*C*H_3), 19.9 (*C*H_3). $[\alpha]_D^{30} = -1.9$ (c 2.0, MeOH). HRMS (ESI) for $C_{16}H_{24}O_4Na$ $[M+Na]^+$, calculated: 303.1572, found: 303.1579.

4.5. (*R*)-6-(4-Methoxybenzyloxy)hexan-2-ol 17

The pure acetate **18** (3 g, 10.7 mmol) was taken in MeOH (50 ml) followed by the addition of K_2CO_3 (1.48 g, 10.7 mol) and the solution was stirred at room temperature for 2 h, after which MeOH was evaporated and the residue was taken in DCM, and washed successively with water and brine. The organic layer was dried ($MgSO_4$) and purified through silica gel chromatography (5:1, hexane/EtOAc) to yield the (*R*)-alcohol **17**. $[\alpha]_D^{30} = +7.6$ (c 2.0, MeOH).

4.6. ((*R*)-6-(4-Methoxybenzyloxy)hexan-2-yloxy)(*tert*-butyl) diphenylsilane 19

Compound **17** (5.5 g, 23.1 mmol) was taken in 100 mL of anhydrous DCM. Imidazole (3.13 g, 46.2 mmol) was then added to it at room temperature. The reaction mixture was stirred for 15 min, after which TBDPS-Cl (7.2 mL, 27.73 mmol) was added and the reaction mixture was stirred overnight. After completion of the reaction, water was added to the reaction mixture and the organic layer was washed with excess water and brine. The organic layer was dried ($MgSO_4$) and evaporated to dryness to afford the crude silylated compound **19**, which was purified by silica gel chromatography (15:1, hexane/EtOAc). δ_H ($CDCl_3$, 200 MHz): 7.75–7.70 (m, 4H), 7.45–7.31 (m, 6H), 7.27 (d, J = 8.0 Hz, 2H), 6.89 (d, J = 8.0 Hz, 2H), 4.44 (s, 2H), 3.91–3.85 (m, 1H), 3.88 (s, 3H), 3.41 (t, J = 6.4 Hz, 2H), 1.67–1.42 (m, 6H), 1.10 (12H). δ_C ($CDCl_3$, 50 MHz): 159.1, 135.9, 135.0, 134.6, 133.8, 130.8, 129.5, 129.4, 129.3, 127.6, 127.5, 113.8, 72.6, 70.1, 69.6, 55.3, 39.3, 29.8, 27.1, 23.2, 21.9, 19.3. $[\alpha]_D^{30} = +8.4$ (c 1.8, MeOH). HRMS (ESI) for $C_{30}H_{40}O_3NaSi$ $[M+Na]^+$, calculated: 499.2644, found: 499.2649.

4.7. (*R*)-5-*tert*-Butyldiphenylsilyloxy-hexan-1-ol 20

Compound **19** (10.95 g, 23 mmol) was taken in 100 mL of DCM/H_2O (19:1). Next, DDQ (7.83 g, 34.5 mmol) was added to it in one portion. The reaction mixture was stirred at room temperature for 1 h. The reaction mixture was filtered off, and the filtrate was washed with 5% $NaHCO_3$ solution, water, and brine. The organic layer was dried ($MgSO_4$) and evaporated. Purification by silica gel chromatography (3:1, hexane/EtOAc) afforded pure alcohol **20** in 86% yield. δ_H ($CDCl_3$, 200 MHz): 7.74–7.69 (m, 4H), 7.44–7.34 (m, 6H), 3.92–3.83 (m, 1H), 3.55 (t, J = 6.4 Hz, 2H), 1.56–1.39 (m, 6H), 1.28–1.1 (12H). δ_C ($CDCl_3$, 50 MHz): 135.9, 134.9, 134.6, 129.5, 129.4, 127.6, 127.5, 127.4, 69.5 (CH), 62.8 (*C*H_2), 39.1 (*C*H_2), 32.7 (*C*H_2), 27.1 (*C*H_3), 23.2 (*C*H_3), 21.4 (*C*H_2), 19.3. $[\alpha]_D^{30} = +4.6$ (c 1.3, MeOH). HRMS (ESI) for $C_{22}H_{32}O_2NaSi$ $[M+Na]^+$, calculated: 379.2069, found: 379.2063.

4.8. (*R*)-5-*tert*-Butyldiphenylsilanyloxy-hexanal 21

Oxallyl chloride (2.6 mL, 29.6 mmol) was taken in anhydrous DCM (100 mL). Then DMSO (4.2 mL, 59.1 mmol) was added to the solution and kept at −78 °C. After 15 min, alcohol **20** (7 g, 19.7 mmol) was added to it, and the solution was stirred at the same temperature for a further 45 min, after which Et_3N (16.6 mL, 118.2 mmol) was added slowly to the reaction mixture at the same temperature. The reaction mixture was then allowed to return to room temperature. Water was added to the solution, and the mixture was extracted with DCM. The organic extract was washed with water, $NaHCO_3$ solution and brine. The organic layer was dried ($MgSO_4$) and evaporated. Purification by silica gel chromatography yielded aldehyde **21** in 84% yield. δ_H ($CDCl_3$, 200 MHz): 9.7 (t, *J* = 1.6 Hz, 1H), 7.74–7.69 (m, 4H), 7.47–7.36 (m, 6H), 3.97–3.68 (m, 1H), 2.47–2.23 (m, 2H), 1.69–1.55 (m, 4H), 1.13 (12H). δ_C ($CDCl_3$, 50 MHz): 202.8 (*C*H), 136.0 (*C*H), 135.7 (*C*H), 134.8, 134.6, 129.7 (*C*H), 129.6 (*C*H), 127.7 (*C*H), 127.6 (*C*H), 69.2 (*C*H), 43.9 (CH_2), 38.8 (CH_2), 27.2 (CH_3), 23.3 (CH_3), 19.4, 17.9 (CH_2). $[\alpha]_D^{30} = +8.2$ (*c* 1.6, MeOH).

4.9. (*R*,*E*)-Ethyl 7-*tert*-butyldiphenylsilanyloxy-oct-2-enoate 22

To a stirred suspension of sodium hydride (796 mg, 19.9 mmol, of a 60% dispersion in mineral oil) in freshly dried ether (60 ml) at −5 °C was dropwise added diethylphosphono acetate (3.95 ml, 19.9 mmol). The yellowish suspension was then stirred for another 10 min until hydrogen evolution ceased. A solution of aldehyde **21** (6.7 g, 18.92 mmol) in 10 ml of freshly dried ether was dropwise added to the Wadsworth–Horner–Emmons reagent, after which the cooling bath was removed, and the mixture was stirred for an additional 4 h. The non-volatile components of the reaction mixture were then absorbed on silica by evaporation under reduced pressure and purified by column chromatography (15:1, hexane/EtOAc) to give the target unsaturated ester **22** as a colorless oil in 96% yield. δ_H ($CDCl_3$, 200 MHz): 7.70–7.66 (m, 4H), 7.43–7.28 (m, 6H), 6.98–6.83 (m, 1H), 5.75 (d, *J* = 15.6 Hz, 1H), 4.18 (q, *J* = 7.2 Hz, 2H), 3.89–3.81 (m, 1H), 2.1–2.06 (m, 2H), 1.48–1.44 (m, 4H), 1.29 (t, *J* = 7.2 Hz, 3H), 1.08 (12H). δ_C ($CDCl_3$, 50 MHz): 166.9, 149.4 (*C*H), 136.1 (*C*H), 135.8 (*C*H), 135.0, 134.6, 129.7 (*C*H), 129.6 (*C*H), 127.7 (*C*H), 127.6 (*C*H), 121.5 (*C*H), 69.4 (*C*H), 60.3 (CH_2), 39.0 (CH_2), 32.3 (CH_2), 27.2 (CH_3), 23.8 (CH_2), 23.4 (CH_3), 19.5, 14.5 (CH_3). $[\alpha]_D^{30} = +11.5$ (*c* 2.0, MeOH). HRMS (ESI) for $C_{26}H_{36}O_3NaSi$ $[M+Na]^+$, calculated: 447.2331, found: 447.2338.

4.10. (2*S*,3*R*,7*R*)-Ethyl 2,3-dihydroxy-7-*tert*-butyldiphenylsilanyloxy-octanoate 23

To a vigorously stirring mixture of AD-mix-β (10 g) in *t*BuOH/H_2O (50 mL) at room temperature was added methanesulfonamide (1.2 g, 12.7 mmol). Stirring was then continued for a further 15 min. after which olefinic ester **22** was added. After vigorous stirring for 8–10 h, sodium sulfite (10 g) was added and stirring was continued for a further 60 min. The mixture was then treated with H_2O (30 ml) and extracted with ethyl acetate, washed with 2 M KOH, water, brine, dried over anhydrous $MgSO_4$, and concentrated. The residue was purified by silica gel column chromatography (hexane/EtOAc, 1:3) to afford the dihydroxy compound **23** (78%). δ_H ($CDCl_3$, 400 MHz): 7.69–7.67 (m, 4H), 7.43–7.35 (m, 6H), 4.28 (q, *J* = 6.4 Hz, 2H), 3.99–3.80 (m, 3H), 1.53–1.34 (m, 6H), 1.3 (t, *J* = 6.4 Hz, 3H), 1.08 (12H). δ_C ($CDCl_3$, 100 MHz): 173.6, 135.8 (*C*H), 135.5 (*C*H), 134.8, 134.4, 129.5 (*C*H), 129.3 (*C*H), 127.5 (*C*H), 127.3 (*C*H), 72.9 (*C*H), 72.4 (*C*H), 69.3 (*C*H), 62.0 (CH_2), 39.1 (CH_2), 33.7 (CH_2), 26.9 (CH_3), 23.1 (CH_3), 21.3 (CH_2), 19.2, 14.1 (CH_3). $[\alpha]_D^{30} = +13.2$ (*c* 1.6, MeOH). HRMS (ESI) for $C_{26}H_{38}O_5NaSi$ $[M+Na]^+$, calculated: 481.2386, found: 481.2383.

4.11. (4*S*,5*R*)-Ethyl-5-((*R*)-4-*tert*-butyldiphenylsilanyloxy-pentyl)-2,2-dimethyl-1,3-dioxolane-4-carboxylate 24

To a stirred solution of diol **23** (4.3 g, 9.42 mmol) in DCM (50 ml), 2,2-dimethoxypropane (1.96 g, 18.84 mmol) and 4-methylbenzenesulfonic acid (179 mg, 0.942 mmol) were added at room temperature. After stirring for 1 h at rt, saturated $NaHCO_3$ (aq.) was added and the mixture was stirred for an additional 10 min. The organic layer was separated and the aqueous layer was extracted with DCM. The combined organic layers was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (10:1, hexane/EtOAc) to give acetonide protected ester **24** (95%) as a colorless liquid. δ_H ($CDCl_3$, 400 MHz): 7.73–7.71 (m, 4H), 7.45–7.38 (m, 6H), 4.28–4.24 (m, 2H), 4.11–4.09 (m, 2H), 3.97–3.93 (m, 1H), 1.65–1.52 (m, 6H), 1.5 (s, 6H), 1.32 (t, *J* = 7.2 Hz, 3H), 1.12 (12H). δ_C ($CDCl_3$, 100 MHz): 170.9, 135.9 (*C*H), 135.5 (*C*H), 134.7, 134.4, 129.5 (*C*H), 129.3 (*C*H), 127.5 (*C*H), 127.3 (*C*H), 110.6, 79.0 (*C*H), 78.8 (*C*H), 69.3 (*C*H), 61.2 (CH_2), 39.2 (CH_2), 33.4 (CH_2), 27.1 (CH_3), 26.5 (CH_3), 25.6 (CH_3), 23.1 (CH_2), 21.2 (CH_3), 19.2, 14.1 (CH_3). $[\alpha]_D^{30} = +13.0$ (*c* 1.7, MeOH). HRMS (ESI) for $C_{29}H_{42}O_5NaSi$ $[M+Na]^+$, calculated: 521.2699, found: 521.2694.

4.12. (4*S*,5*R*)-5-((*R*)-4-*tert*-Butyldiphenylsilanyloxy-pentyl)-2,2-dimethyl-1,3-dioxolane-4-carbaldehyde 25

To a solution of ester **24** (4.4 g, 8.83 mmol) in dry DCM (30 mL) at −78 °C was added DIBAL-H (1 M solution in toluene, 9.7 mL, 9.7 mmol). After 1 h, the excess DIBAL-H was quenched with a saturated solution of sodium potassium tartarate. The solid was filtered off, and the filtrate was concentrated to give a residue, which was purified by silica gel column chromatography (hexane/EtOAc, 10:1) to give aldehyde **25** (70%) as a colorless oil. δ_H ($CDCl_3$, 400 MHz): 9.68 (d, *J* = 2.4 Hz, 1H), 7.69–7.67 (m, 4H), 7.44–7.35 (m, 6H), 3.99–3.94 (m, 1H), 3.88–3.84 (m, 2H), 1.64–1.51 (m, 6H), 1.43 (s, 6H), 1.07 (12H). δ_C ($CDCl_3$, 100 MHz): 200.9 (*C*H), 135.83 (*C*H), 135.81 (*C*H), 134.7, 134.4, 129.4 (*C*H), 129.3 (*C*H), 127.4 (*C*H), 127.3 (*C*H), 110.8, 84.6 (*C*H), 77.3 (*C*H), 69.2 (*C*H), 39.1 (CH_2), 33.2 (CH_2), 27.0 (CH_3), 26.9 (CH_3), 26.1 (CH_3), 23.1 (CH_3), 21.2 (CH_2), 19.2. $[\alpha]_D^{30} = +5.2$ (*c* 1.2, MeOH).

4.13. (*S*)-1-((4*R*,5*R*)-5-((*R*)-4-*tert*-Butyldiphenylsilanyloxy-pentyl)-2,2-dimethyl-1,3-dioxolan-4-yl)but-3-en-1-ol 26

A mixture of (*S*)-BINOL (114.4 mg, 0.398 mmol), 1 M $Ti(O^iPr)_4$ in DCM (0.398 mL, 0.398 mmol), and oven-dried powdered 4 Å sieves (800 mg) in DCM (8 mL) was heated at reflux for 1 h. The red-brown mixture was cooled to room temperature and aldehyde **25** (1.79 g, 3.94 mmol) was added. After being stirred for 10 min, the contents were cooled to −78 °C, and allyltri-*n*-butylstannane (1.45 g, 4.38 mmol) was added. The reaction mixture was then stirred for 10 min and then placed in a −20 °C freezer for 72 h. Next, saturated $NaHCO_3$ (1 mL) was added, and the contents were stirred for 1 h, then poured over Na_2SO_4 and filtered through a plug of Celite. The crude material was purified by flash chromatography, eluting with hexane/EtOAc (15:1) to give (*S*)-allylic alcohol **26** (76%). δ_H ($CDCl_3$, 200 MHz): 7.63–7.59 (m, 4H), 7.37–7.28 (m, 6H), 5.88–5.68 (m, 1H), 5.14–5.02 (m, 2H), 3.97–3.77 (m, 4H), 2.30–2.18 (m, 2H), 1.68–1.5 (m, 6H), 1.44 (s, 6H), 1.01 (12H). δ_C ($CDCl_3$, 50 MHz): 136.0 (*C*H), 135.9 (*C*H), 135.8 (*C*H), 134.7, 134.4, 129.5 (*C*H), 129.4 (*C*H), 127.5 (*C*H), 127.4 (*C*H), 118.6 (CH_2), 108.4, 82.7 (*C*H), 78.1 (*C*H), 71.0 (*C*H), 69.5 (*C*H), 39.3 (CH_2), 37.8 (CH_2), 34.4 (CH_2), 27.5 (CH_3), 27.1 (CH_3), 26.8 (CH_3), 23.2 (CH_3), 21.8 (CH_2), 19.3. $[\alpha]_D^{30} = +17.5$ (*c* 1.8, MeOH). HRMS (ESI) for $C_{30}H_{44}O_4NaSi$ $[M+Na]^+$, calculated: 519.2907, found: 519.2912.

4.14. ((*R*)-5-((4*R*,5*R*)-5-((*S*)-1-(Methoxymethoxy)but-3-enyl)-2,2-dimethyl-1,3-dioxolan-4-yl)pentan-2-yloxy)(*tert*-butyl) diphenylsilane 27

To a solution of allylic alcohol **26** (2.5 g, 5.04 mmol) in DCM (30 mL) at 0 °C were added diisopropylethylamine (8.78 mL, 50.4 mmol) and chloromethylmethyl ether (1.95 mL, 25.2 mmol). The reaction mixture was immediately allowed to warm to rt. After 10 h of stirring, saturated $NaHCO_3$ (aq.) was added. The organic layer was separated and the aqueous layer was extracted with DCM. The combined organic layers was washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography to afford compound **27** in 88% yield. δ_H ($CDCl_3$, 400 MHz): 7.73–7.71 (m, 4H), 7.45–7.37 (m, 6H), 5.94–5.88 (m, 1H), 5.19–5.12 (m, 2H), 4.71 (s, 2H), 3.95–3.89 (m, 2H), 3.76–3.70 (m, 2H), 3.4 (s, 3H), 2.43–2.40 (m, 2H), 1.52–1.30 (m, 6H), 1.40 (s, 6H), 1.11 (12H). δ_C ($CDCl_3$, 100 MHz): 136.1 (*C*H), 135.9 (*C*H), 134.9 (*C*H), 134.6, 134.5, 129.5 (*C*H), 129.4 (*C*H), 127.5 (*C*H), 127.4 (*C*H), 117.6 (CH_2), 108.5, 96.2 (CH_2), 81.6 (*C*H), 78.6 (*C*H), 77.3 (*C*H), 69.5 (*C*H), 55.8 (CH_3), 39.4 (CH_2), 35.7 (CH_2), 34.5 (CH_2), 27.5 (CH_3), 27.2 (CH_3), 27.1 (CH_3), 23.1 (CH_3), 21.7 (CH_2), 19.3. $[\alpha]_D^{30} = +28.3$ (*c* 0.8, MeOH). HRMS (ESI) for $C_{32}H_{48}O_5NaSi$ $[M+Na]^+$, calculated: 563.3169, found: 563.3162.

4.15. (*R*)-5-((4*R*,5*R*)-5-((*S*)-1-(Methoxymethoxy)but-3-enyl)-2,2-dimethyl-1,3-dioxolan-4-yl)pentan-2-ol 13

Compound **27** (850 mg, 1.57 mmol) was taken in dry THF (10 mL). Next, TBAF (1 M in THF, 3.14 mL, 2 equiv) was added, and the reaction mixture was stirred for 24 h at room temperature. After this time, the THF was evaporated, and water (5 mL) was added to it. The reaction mixture was then extracted with EtOAc (50 mL). The organic layer was washed with dilute $NaHCO_3$ solution, and brine, dried over $MgSO_4$, and purified by flash chromatography with ethyl acetate/petroleum ether (1:3) to afford compound **13** in 92% yield. δ_H ($CDCl_3$, 400 MHz): 5.81–5.75 (m, 1H), 5.07–4.99 (m, 2H), 4.58 (s, 2H), 4.04–3.61 (m, 4H), 3.3 (s, 3H), 2.32–2.30 (m, 2H), 1.61–1.46 (m, 6H), 1.40 (s, 6H), 1.15 (d, J = 6.8 Hz, 3H). δ_C ($CDCl_3$, 100 MHz): 134.3 (*C*H), 117.5 (CH_2), 108.5, 96.1 (CH_2), 81.5 (*C*H), 78.5 (*C*H), 76.5 (*C*H), 67.7 (*C*H), 55.7 (CH_3), 38.9 (CH_2), 35.6 (CH_2), 34.2 (CH_2), 27.3 (CH_3), 27.0 (CH_3), 23.2 (CH_3), 22.2 (CH_2). $[\alpha]_D^{30} = +8.3$ (*c* 0.8, MeOH). HRMS (ESI) for $C_{16}H_{30}O_5Na$ $[M+Na]^+$, calculated: 325.1991, found: 325.1996.

4.16. (*S*)-5-((4*R*,5*R*)-5-((*S*)-1-(Methoxymethoxy)but-3-enyl)-2,2-dimethyl-1,3-dioxolan-4-yl)pentan-2-yl 2-hydroxy-4-methoxy-6-vinylbenzoate 12

Triphenylphosphine (135.3 mg, 0.516 mmol) and DIAD (102 μL, 0.516 mmol) were added sequentially to a stirred solution of acid **14** (50 mg, 0.258 mmol) and alcohol **13** (78 mg, 0.516 mmol) in dry toluene (5 mL). After 1 h, EtOAc (10 mL) and H_2O (5 mL) were added. The layers were separated and the aqueous phase extracted with EtOAc (2 × 10 mL). The combined organic portions were washed with brine solution, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (1:20, hexane/EtOAc) to give ester **12** as a colorless syrup (85%). δ_H ($CDCl_3$, 400 MHz): 11.80 (s, 1H), 7.28 (dd, J = 17.2, 10.8 Hz, 1H), 6.47 (d, J = 2.4 Hz, 1H), 6.41 (d, J = 2.4 Hz, 1H), 5.88–5.81 (m, 1H), 5.40 (d, J = 17.2 Hz, 1H), 5.42–5.06 (m, 4H), 4.67 (dd, J = 11.6, 6.8 Hz, 2H), 3.93–3.92 (m, 1H), 3.82 (s, 3H), 3.73–3.66 (m, 2H), 3.34 (s, 3H), 2.37–2.35 (m, 2H), 1.79–1.5 (m, 6H), 1.35 (9H). δ_C ($CDCl_3$, 100 MHz): 170.9, 165.1, 164.1, 143.9, 138.8 (*C*H), 134.4 (*C*H), 117.8 (CH_2), 115.5 (CH_2), 108.8, 108.5 (*C*H), 104.2, 100.3 (*C*H), 96.3 (CH_2), 81.6 (*C*H), 78.6 (*C*H), 76.8 (*C*H), 72.9 (*C*H), 56.0 (CH_3), 55.6 (CH_3), 36.0 (CH_2), 35.8 (CH_2), 34.4 (CH_2), 27.5 (CH_3), 27.2 (CH_3), 22.3 (CH_2), 20.2 (CH_3). $[\alpha]_D^{30} = +42.1$ (*c* 0.5, MeOH). HRMS (ESI) for $C_{26}H_{38}O_8Na$ $[M+Na]^+$, calculated: 501.2464, found: 501.2458.

4.17. Compound 28

Ester **12** (90 mg, 0.188 mmol) was taken in anhydrous degassed DCM (100 mL). Grubbs-second generation metathesis catalyst (12 mg, 0.013 mmol, 7 mol %) was then added and the reaction mixture was allowed to stir at 40 °C for 16 h. The solution was then evaporated off and the contents of the flask were directly loaded on a silica gel column. Purification by flash column chromatography with hexane/EtOA (10:1) afforded RCM product **28** in 72% yield as a white solid. δ_H ($CDCl_3$, 400 MHz): 11.65 (s, 1H), 6.84 (d, J = 15.2 Hz, 1H), 6.6 (d, J = 2.4 Hz, 1H), 6.55 (d, J = 2.4 Hz, 1H), 6.0–5.96 (m, 1H), 5.22–5.18 (m, 1H), 4.93–4.88 (m, 2H), 4.34–4.3 (m, 1H), 4.22–4.18 (m, 1H), 4.0–3.94 (m, 1H), 3.88 (s, 3H), 3.43 (s, 3H), 2.43–2.2 (m, 2H), 1.81–1.63 (m, 6H), 1.42 (9H). δ_C ($CDCl_3$, 100 MHz): 170.5, 164.8, 163.8, 141.6, 133.0 (*C*H), 126.7 (*C*H), 108.3 (*C*H), 106.8, 100.1 (*C*H), 96.8 (CH_2), 77.6 (*C*H), 74.5 (*C*H), 73.7 (*C*H), 72.8 (*C*H), 55.5 (CH_3), 55.4 (CH_2), 36.5 (CH_2), 34.5 (CH_2), 31.0 (CH_2), 29.6, 27.0 (CH_3), 26.7 (CH_3), 22.4 (CH_2), 17.8 (CH_3). $[\alpha]_D^{30} = +52.7$ (*c* 0.7, MeOH). HRMS (ESI) for $C_{25}H_{36}O_7Na$ $[M+Na]^+$, calculated: 471.2359, found: 471.2351.

4.18. (*E*,7*S*,11*R*,12*S*,13*S*)-7,8,9,10,11,12,13,14-Octahydro-4,11,12,13-tetrahydroxy-2-methoxy-7-methylbenzo[14]annulen-5(6*H*)-one 11

To a solution of compound **28** (50 mg, 0.11 mmol) in THF (5 mL) was added HCl (2 N, 5 mL) and stirred for 20 h. The reaction was quenched with saturated aqueous $NaHCO_3$ solution and extracted with EtOAc. The organic layers were combined, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced vacuum. The crude was purified by flash column chromatography with ethyl acetate/petroleum ether (3:2) to yield *epi*-peacilomycin as a white powder (36 mg, 90%). δ_H ($CDCl_3$, 400 MHz): 11.02 (s, 1H), 6.71 (d, J = 15.6 Hz, 1H), 6.5 (s, 1H), 6.4 (s, 1H), 6.03–5.96 (m, 1H), 5.13 (br, 1H), 4.21–4.11 (m, 2H), 3.74 (s, 3H), 3.55–3.54 (m, 1H), 3.0 (br, 3H, –OH), 2.64–2.47 (m, 2H), 2.04–1.92 (m, 2H), 1.70–1.62 (m, 4H), 1.3 (d, J = 7.2 Hz, 3H). δ_C ($CDCl_3$, 100 MHz): 170.2, 163.0, 161.2, 140.0, 128.3, 127.2, 108.0, 105.1, 99.6, 74.8 (*C*H), 73.7 (*C*H), 72.8 (*C*H), 68.2 (*C*H), 54.6 (CH_3), 38.0 (CH_2), 34.5 (CH_2), 33.7 (CH_2), 31.0 (CH_2), 17.2 (CH_3). $[\alpha]_D^{30} = +30.7$ (*c* 0.5, MeOH). HRMS (ESI) for $C_{20}H_{28}O_6Na$ $[M+Na]^+$, calculated: 387.1784, found: 387.1782.

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