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Asymmetric total synthesis of Paecilomycin E, 10′-epi-Paecilomycin E and 6′-epi-Cochliomycin C

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Abstract: Asymmetric total synthesis of naturally occurring Resorcylic acid lactone paecilomycin E and two of its structural congeners have been reported in this article. The major highlight of the synthetic venture is the application of late stage Mitsunobu macrolactonization method (which seems to be difficult to proceed through standard carboxyl activation method) of a properly functionalized seco-acid. The macrolactonization precursor was synthesized by applying an “E”-selective Julia-Kocienski olefination of a highly functionalized aromatic aldehyde and the sulphone, which constitutes all the stereocenters (C4′, C5′, C6′ and C10′; 3S,7R,8R,9S) in the target molecule.

Introduction

Resorcylic acid lactones (RALs) are a class of mycotoxins isolated from various strains of fungi defined by the presence of a β-resorcylic acid ring and a 14-membered macrolactone core with a stereochemically pure methyl substituent at the C10'-position (Figure 1) in its structure. Radicicol was the first known molecule in this family was isolated from Monocillium nordinii in 1953 ¹ followed by zearalenone (Figure 1) in 1962, ² LL-Z1640-2 in 1978 ³ and hypothemycin in 1980. ⁴ Initially estrogen agonistic property is reported by zearalenone, which was unable to tempt synthetic organic chemist community towards the total synthesis of these molecules. Later on, in early 1990 the first report of kinase inhibition by radicicol kindled the interest in this molecule and in 1992 first synthesis of radicicol was reported by Lett et al. ⁵ Since the first isolation of radicicol, nearly 30 naturally occurring RALs have been reported till today. They have been shown to have estrogenic, antifungal, cytotoxic, antimalarial, and nematicidal properties and inhibitory activities against ATPases and kinases. RALs have attracted considerable interest from synthetic organic chemist community due to its broad spectrum of bioactivity and skeletal diversity as evident from several elegant publications.⁶
Recently six new RAL molecules named paecilomycins A-F \(^7\) (Figure 1) were isolated from the mycelial solid culture of *Paecilomyces* sp. SC0924 by Chen and Wei *et al*, along with other known RALs. Paecilomycin A possess 1´, 2´-epoxy linkage with three hydroxyl groups at 4´, 5´, 6´-position whereas paecilomycin C and D possesses 6-membered lactones instead of the 14-membered macrolactones seen in other RALs. Paecilomycin E exhibited antiplasmodial activity against *Plasmodium falciparum* line 3D7 with IC\(_{50}\) values of 20.0 nM. Paecilomycin E and F showed moderate activity against the *P. falciparum* line Dd2.

![Figure 1: General structural feature of RALs with newly isolated paecilomycins and cochliomycins (uncorrected).](image)

Of late two new 14-membered resorcylic acid lactones with a rare natural acetonide group, cochliomycins A and B, and one new 5-chlorosubstituted lactone, cochliomycin C, together with four known analogues, were obtained from the fungus *Cochliobolus lunatus* in the South China Sea.\(^8\) These lactones were evaluated against the larval settlement of barnacle *Balanus amphitrite*, \(\ldots\)
and antifouling activity was detected for the first time in this type of metabolites. Very recently two new brominated RALs (5-bromozaeanol and 3,5-dibromozaeanol) was isolated from the fungus *Cochliobolus lunatus* by chemical epigenetic manipulation approach.\(^8b\)

Later structural revision for paecilomycin F and cochliomycin C was reported.\(^9-10\) The stereochemistry of the hydroxyl containing C-6´ carbon is inverted in both the molecules in the corrected form, hence paecilomycin F became paecilomycin E which is also a natural product but the other one became 6´-epimer of the natural cochliomycin C (Figure 2).

**Figure 2:** Structural revision of paecilomycin E and F and cochliomycin C.

We have already reported the asymmetric total synthesis of several RALs such as cochliomycin A, zeaenol,\(^11\) 5´-epi-cochliomycin C and F (uncorrected)\(^12\) by successful exploration of several useful transformations e.g, ME-DKR (metal enzyme combined dynamic kinetic resolution), Keck asymmetric allylation, \(E\)-selective Julia-Kocienski olefination, RCM reaction and macrolactonization (Yamaguchi and Mitsunobu) reactions. Our main aim is to develop a general and flexible synthetic strategy for asymmetric total synthesis of several naturally occurring RALs and its structural analogues. Recently few other groups have also successfully completed the synthesis of cochliomycin A, cochliomycin B, paecilomycin E and other structurally related RAL molecules.\(^13\)
Present work

At the beginning we have two target molecules in our mind paecilomycin F and cochliomycin C (uncorrected) as both of them have similar stereochemical features and substitution patterns (C\textsubscript{1}-C\textsubscript{11}), the notable difference being the substitution pattern in the aromatic ring in cochliomycin C (contains an extra “Cl” atom at C\textsubscript{5} position). But the structural revision paper was published during midway of our synthetic venture, so we have decided to continue the remaining part of the synthesis. Eventually after structural revision paecilomycin F became paecilomycin E (another natural product) and cochliomycin C became 6’-epi-cochliomycin C. A close inspection of the previously reported synthesis of cochliomycins (A and B) and paecilomycins (F and its stereoisomers) reveals that (Scheme 1) “E” olefinic unsaturation between C\textsubscript{1’}-C\textsubscript{2’} was constructed by successful exploration of RCM or Suzuki or Stille reactions.

The retrosynthetic analysis of the targeted RALs was presented in Scheme 1. We have planned to construct the 14-membererd ring by late stage macrolactonization (carboxylic acid activation method) reaction from the seco-acid \textit{3}. It was envisioned that as Julia-Kocienski (JK) olefination is known to be very efficient in generating \textit{E}-alkene selectively, the internal “E” double bond between C\textsubscript{1’}-C\textsubscript{2’} could be achieved by JK-olefination between sulfone \textit{4} and aldehyde \textit{5} to furnish compound \textit{3}. Aldehyde \textit{5} could be accessed from commercially available 3,5-dihydroxy benzoic acid (7). Wittig reaction or Z-selective JK-olefination between enantiopure aldehyde \textit{10} and 9/8 should lead to olefinic compound \textit{7} which upon substrate directed dihydroxylation and acetonide protection was thought to produce compound \textit{4}. Compound \textit{10} was synthesized from 1,3-propanediol by applying a ME-DKR (metal enzyme combined dynamic kinetic resolution) strategy as reported earlier from our group. The sulphone \textit{8} and phosphonium salt \textit{9}, was thought to be accessed from 1,5 pentane diol and its stereo center could be fixed by enzymatic kinetic resolution (EKR) coupled with Mitsunobu inversion reaction as depicted in Scheme 1.
Previously reported synthesis of paecilomycins (E,F) and cochliomycins (A, B)

General structures of paecilomycins (E, F) and cochliomycins (A-C).
* X = stereochemically pure hydroxy groups or protected as its acetonides
* R = Cl in case of cochliomycin-C (otherwise R = H)
* "E"-olefinic unsaturation (C7'-C8') in case of cochliomycin A and B

Present work

Yamaguchi macrolactonization

1. Julia-Kocienski or Cross metathesis for cochliomycin A (Ref: 11, 13c)
2. RCM for cochliomycin B (13b)
3. Suzuki for cochliomycin B (Ref: 13b)
4. Stille for cochliomycin A (Ref: 13c)

Present work

Scheme 1: Retrosynthetic analysis of Paecilomycin E and related RALs.

Result and discussion

Synthesis of the sulphone 8 and phosphonium salt 9 required for JK and Wittig olefination:
The synthesis was initiated from known racemic hexane-1,5-diol (11). Enzymatic Kinetic resolution (EKR) of 11 was performed using vinyl acetate as active acyl donor and CAL-B (Candida antartica lipase ) as a biocatalyst in DIPE solvent to afford corresponding (R)-acetate
12 (yield = 48%, ee = 98%) and (S)-alcohol 13 (yield = 48%, ee > 99%) according to Kazlauskas empirical rule. The unwanted acetate 12 was then hydrolysed with 1% NaOH in MeOH and the resulting alcohol was inverted by applying Mitsunobu inversion strategy to give desired compound (S)-13 (over all yield 90% after three steps with ee = 98%). Free hydroxyl group of 13 was protected as its TBS (tert-butyl dimethylsilyl) ether by treatment with imidazole and TBS-Cl to afford compound 14 in 95% yield. Deprotection of the PMB group was achieved by treating compound 14 with DDQ furnished the primary alcohol 15 which is then subsequently converted to its corresponding methanesulfonate 16, by treatment with Ms-Cl (methanesulfonyl chloride) and Et$_3$N. The Compound 16 was then converted to the corresponding iodo compound 17 by treatment with NaI in acetone in presence of NaHCO$_3$ and DIPEA (catalytic) in 92% yield (Scheme 2).

Scheme 2: Synthesis of the sulphone 8 and phosphonium salt 9.
The iodo compound 17 was then refluxed with Ph₃P in toluene along with Hunig's base (DIPEA) to furnish the Wittig salt 9 in 91% yield. Addition of DIPEA is necessary as it stops the deprotection of TBS group under the reaction condition. Compound 17 was also converted to its corresponding sulfide 18 by treatment with 2-mercaptopyridine sulfide through SN₂ reaction and subsequent Mo(IV)-catalyzed oxidation of the sulfide produced the desired sulfone 8 in 85% yield (Scheme 2).

**Synthesis of the aldehyde 10:** For the synthesis of the aldehyde 10 we have started our journey from the known alcohol 19. TBDS protection of this alcohol with TBDPS-Cl and imidazole afforded compound 20 in 95% yield. Dihydroxylation and oxidative cleavage of olefin under Lemieux-Johnson condition of compound 20 afforded the aldehyde 10 in a single pot operation with 80% yield (Scheme 3).

![Scheme 3: Synthesis of aldehyde 10.](image)

**Synthesis of the sulfone 4:** For the “Z”-selective JK-olefination reaction, initially 2-pyridylsulfone 8 was reacted with aldehyde 10 under different reaction conditions (different solvent and different bases) but to our utter disappointment the desired “Z” olefinic compound 21 was isolated in very less yield. In all the cases the starting sulfone was completely consumed, but the aldehyde 10 was isolated as a major component after usual work-up procedure. The reason for this unusual low reactivity of aldehyde 10 towards “Z” selective JK olefination is not very clear to us, but presence of a bulky TBDPS group at the α-position cannot be ruled out, which might block the nucleophilic attack to the –CHO functionality. The detail for this optimization was provided in table-1. As the “Z”-selective JK-olefination reaction did not proceed well, we switched over our attention to the “Z” selective Wittig olefination reaction. For that purpose the Wittig salt 9 was treated with KHMDS to generate the required anion which was then subsequently reacted with the aldehyde 10 to afford the “Z”-olefin 7 in 76% yield as a single product. The base KHMDS was found to provide best result for this reaction. Dihydroxylation of the cis olefin 7 furnished two diastereomeric diols 21 and 22 in 1:8 ratio. The origin of this high diastereoselection can be explained by Kishi model which utilizes A³-strain as a deciding factor. The diol functionality in compound 22 was then protected as its acetonide by treatment...
with 2,2-DMP and PPTS (catalytic amount) to furnish compound 23 in 94% yield. Subsequent removal of PMB-group was achieved by treating compound 23 with DDQ afforded compound 24 in 96% yield. Compound 24 was then transformed into the corresponding 1-phenyl-1H-tetrazol-5-yl sulfide through a Mitsunobu reaction, and subsequent Mo(IV)-catalyzed oxidation of sulfide produced the desired sulfone 4 in a yield of 82% over two steps (Scheme 4).

Table 1: “Z” selective JK-olefination of sulfone 8 with aldehyde 10

<table>
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<tr>
<th>Entry</th>
<th>Sulfone</th>
<th>Aldehyde</th>
<th>Base</th>
<th>Temperature (°C)</th>
<th>Solvent</th>
<th>Yield (%)</th>
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<td>10</td>
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<td>THF</td>
<td>~8</td>
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<tr>
<td>4</td>
<td>8</td>
<td>10</td>
<td>KHMDS</td>
<td>-78</td>
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<td>8</td>
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<td>nBuLi</td>
<td>-78</td>
<td>THF/HMPA b</td>
<td>~5</td>
</tr>
</tbody>
</table>

nr: No significant reaction was observed; b: THF/HMPA (6:1) was used as a solvent. c: THF/DMPU (8:1) was used as a solvent. HMPA: hexamethylphosphoramide; DMPU: N,N'-Dimethylpropyleneurea.
Scheme 4: Synthesis of sulphone 4 by “Z”-selective Wittig olefination.

Synthesis of the highly functionalized aromatic aldehyde 5 and corresponding “Cl” derivative 6: The synthesis was initiated from known 3,5-dimethoxybenzaldehyde (26). Regioselective electrophilic bromination of 26 was performed using Br₂ in AcOH to afford compound 27 in 85% yield as a sole product. The aldehyde functionality of the compound 27 was protected as its corresponding ketal by using ethylene glycol to furnish compound 28 in 98% yield. Lithium exchange of the bromo compound 28 with n-BuLi and subsequent reaction of the generated organo-Li species with ethyl chloroformate furnished the desired compound 5 in a satisfactory 80% yield. ²⁴ We have installed the chlorine atom in the C-3 position (C5-position in the natural product cochliomycin C) of the aldehyde 5 using SO₂Cl₂ in DCM in 72% yield to prepare the corresponding chloro aldehyde 6 ²⁵ as a sole regioisomer (Scheme 5). The structure of aldehyde 6 was confirmed by 1D-nOe analysis (¹H-NMR spectrum; see the supporting information).
Scheme 5: Synthesis of aldehyde 5 and 6.

Fragment assembly for the synthesis of the seco-acid 3: The sulfone (4) was now reacted with the aromatic aldehyde 5 in presence KHMDS at -78°C to afford the trans olefin 29 exclusively in 80% yield. Attempted hydrolysis of the ester functionality in compound 29 was a bit problematic than we really expected. After refluxing with LiOH in THF/water (1:1) for 5 days the starting material was recovered completely. In another reaction the hydrolysis was attempted with KOH in refluxing MeOH, which afforded the hydrolyzed product with subsequent removal of the TBDPS group also took place. Use of tBuOK in THF as an alternate reagent only removes the TBDPS group in 2h without affecting the CO₂Et functionality (Scheme 7). We assume that due to presence of two -OMe groups in the aromatic ring (o and p to -CO₂Et group), the electrophilicity of the carbonyl carbon is substantially reduced, and the ester group becomes inert towards hydrolysis. As an alternative arrangement, reduction of compound 29 with DIBAL-H furnished the benzylic alcohol 30 in 95% yield. Benzylic oxidation was performed with an excess of MnO₂ to furnish the aldehyde 31, which on further oxidation by Pinnick condition 27 furnished the carboxylic acid 32 in 80% yield. Compound 39 was then treated with PPTS in presence of 2,2-DMP and MeCN which subsequently removed the TBS group in presence of
acetonide and TBDPS groups to furnish the seco-acid 3 in 85% yield (Scheme 6).

Scheme 6: Synthesis of the seco-acid 3.

Macrolactonization and the synthesis of 10'-epi-Paecilomycin E: The seco-acid 3 was then subjected to different intramolecular ring closing protocols viz. Yamaguchi macrolactonization,\textsuperscript{28} Shiina macrolactonization,\textsuperscript{29} Keck macrolactonization\textsuperscript{30} to prepare the anticipated macrolactone 33. But the failure in all three cases made us doubtful about the success of acid activating macrolactonization strategy for our compound. We anticipate that presence of the two -OMe groups in the aromatic ring substantially deactivates the -CO_2H functionality, hence mixed anhydride formation is inhibited (which is the prerequisite for all of the above carboxylic activation macrolactonization protocol). So we went for Mitsunobu macrolactonization (hydroxyl activation method) reaction, and with our delight macrolactone 33 was obtained in 65% yield (with inversion at the C-10 stereocenter as Mitsunobu reaction is associated with clean $S_N2$ inversion).\textsuperscript{31} Acetonide protection in compound 33 was then removed by treatment with PPTS to furnish the diol 34 in 90% yield. Selective demethylation with BBr\textsubscript{3} \textsuperscript{32} afforded compound 35 in 85% yield. Compound 35 was then treated with HF-Pyridine \textsuperscript{33} in THF for 10 h to furnish the 10'-epi-paecliomycin E in 80% yield (Scheme 7; overall yield is 3.5% from 1,5 hexane diol and 13.5% from compound 19).
Scheme 7: Synthesis of 10′-epi-paecilomycin E.

Completion of the synthesis of paecilomycin E: From the above discussion it was clear that, if we initiate our synthetic journey from ent-9, naturally occurring paecilomycin E can be synthesized by following the above route. We have started our journey from compound (R)-12, which was earlier synthesized in our group $^{12a}$ by adopting a ME-DKR (metal enzyme dynamic kinetic resolution) strategy. By following a similar reaction sequences depicted in Scheme 2, ent-9 was synthesized in good yield. Wittig olefination of aldehyde 10 with ent-9 afforded compound 36 as a single diastereomer. Compound 36 was then synthetically elaborated to sulphone 42 as depicted in Scheme 8.
Scheme 8: Synthesis of the sulphone 42.

With sulphone 42 in our hand, the stage is now ready for the crucial JK-olefination reaction with aldehyde 5 and 6. Stereoselective JK-olefination with sulphone 42 and aldehyde 5/6 furnished the compound 43 and 44 in 82% and 78% yield respectively. Reduction of the –CO₂Et functionality with DIBAL-H afforded the benzyl alcohols 45 and 46, and subsequent oxidation with activated MnO₂ furnished the corresponding aldehydes 47 and 48. Pinnick oxidation of aldehydes 47 and 48 under similar condition as depicted earlier yielded corresponding carboxylic acids 49 and 50. Selective removal of TBS group afforded the seco-acids 51 and 52 in 85% and 82% yield respectively (Scheme 9).
Scheme 9: Synthesis of the seco-acids 51 and 52.

Completion of the synthesis through late stage Mitsunobu macrolactonization method: The seco-acids 51 and 52 were subjected to Mitsunobu macrolactonization method as shown in Scheme 10, which afforded the ring closed products 53 and 54 in 68% and 65% yield respectively. Acetone deprotection and selective demethylation with BBr₃ furnished the compounds 57 and 58, which on desilylation with HF-pyridine afforded paecilomycin E and 6’-epi-cochliomycin C in 80% and 82% yield respectively (overall yield for paecilomycin E is 3.2% from 1,5 hexane diol). The spectral ($^1$H-NMR, $^{13}$C-NMR, HSQC, $^1$H-$^1$H COSY) characteristic of our synthesized paecilomycin E matches perfectly with the naturally occurring one (Table 2). In the previous article, NMR spectrum ($^1$H and $^{13}$C) of paecilomycins E, F and cochliomycin C was reported in CDCl₃ solvent. We have also recorded the $^1$H-NMR spectrum of paecilomycin E and 6’-epi-cochliomycin C in acetone (d₆) as a solvent, and we observe sharp resolution in the corresponding spectrum (see the supporting information) when compared to the spectrum obtained in CDCl₃.
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**Scheme 10:** Completion of the synthesis for paecilomycin E and 6'-epi-cochliomycin C.

**Conclusion:** In conclusion we have disclosed the asymmetric total synthesis of naturally occurring paecilomycin E and other two of its close structural congeners 10'-epi-paecilomycin E and 6'-epi-cochliomycin C. The synthetic strategy involves successful application of late stage Mitsunobu macrolactonization (through hydroxyl group activation by $S_N2$ inversion), $E$-stereoseleltive JK-olefination, substrate directed stereoselective dihydroxylation and $Z$-selective Wittig olefination. Further studies directed towards novel and efficient strategies for the total synthesis of several structurally related RALS are currently under investigation in our laboratory and will be reported later.

**General Information:** Unless otherwise stated, materials were obtained from commercial suppliers and used without further purification. THF and diethylether were distilled from sodiumbenzophenone ketyl. Dichloromethane (CH$_2$Cl$_2$), dimethylformamide (DMF) and dimethylsulfoxide (DMSO) were distilled from CaH$_2$. 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. Silicagel 100-200 mesh was used for column chromatography. Yields refer to chromatographically and spectroscopically homogeneous materials unless otherwise stated. Proton nuclear magnetic resonance ($^1$H-NMR) and carbon nuclear magnetic resonance ($^{13}$C-NMR) spectra were acquired in CDCl$_3$ unless otherwise mentioned. Chemical shifts are reported in parts per million (ppm, $\delta$), downfield from
tetramethylsilane (TMS, δ = 0.00 ppm), and are referenced to residual solvent (CDCl₃, δ = 7.26 ppm (1H), 77.16 ppm (13C) and CD₃COCD₃, δ = 2.09 ppm (¹H)). Coupling constants (J) are reported in hertz (Hz) and the resonance multiplicity abbreviations used are: s, singlet; d, doublet; t, triplet; q, quartet; dt, doublet of triplets; dd, doublet of doublets; ddd, doublet of doublet of doublets; m, multiplet; comp, overlapping multiplets of magnetically non-equivalent protons. Optical rotations were measured on a JASCO P1020 digital polarimeter. Mass spectrometric analysis was performed in the CRF, IIT-Kharagpur (TOF analyzer). HPLC analysis was performed with the help of PDA detector (200-800 nm)

(5S,11S,Z)-5-(2-(4-methoxybenzyl)ethyl)-2,2,11,13,13,14,14-heptamethyl-3,3-diphenyl-4,12-dioxo-3,13-disilapentadec-6-ene (7)

Wittig salt 9 (3.59 g, 5.95 mmol) was dissolved in 30 mL anhydrous THF and the temperature was made -78 ºC. A solution of KHMDS (0.5 M in THF, 13.1 mL, 6.54 mmol) was added to this solution drop wise and the resulting orange red solution was stirred for 40 minute. The aldehyde 10 (2.5 g, 5.41 mmol) in 15 mL anhydrous THF was added to this orange red solution at -78 ºC and the temperature was allowed to reach to the room temperature slowly. The reaction is quenched with saturated aq. NH₄Cl solution (35 mL) and further 50 mL diethyl ether was added. The organic layer was separated and the aqueous layer was farther washed with diethyl ether (2×30 mL). The combined organic part was washed with water (40 mL), brine solution (40 mL) and dried over anhydrous MgSO₄ and concentrated under reduced pressure. Purification by means of flash column chromatography (EtOAc/hexane = 1:20) furnished the Z-alkene 7 as colorless oil (2.71 g, 4.1 mmol) in 76% yield.

Rf = 0.65 (EtOAc/hexane, 1:20).

¹H NMR (200 MHz, CDCl₃): δ: 7.67-7.64 (m, 4H), 7.42- 7.31 (m, 6H), 7.16 (d, J = 8.4 Hz, 2H), 6.84 (d, J = 8.4 Hz, 2H), 5.42-5.37 (m, 1H), 5.21- 5.16 (m, 1H), 4.62- 4.60 (m,1H), 4.29 (s, 2H), 3.80 (s, 3H), 3.64- 3.60 (m, 1H), 1.75- 1.60 (m, 1H), 1.42-1.16 (m, 6H), 1.03 (s, 3H), 1.03 (s, 9H), 0.88 (s, 9H), 0.02 (s, 6H).

¹³C NMR (50 MHz, CDCl₃): δ: 159.2, 136.2, 136.1, 134.5, 132.7, 130.9, 130.3, 129.6, 129.5, 129.2, 127.7, 127.5, 113.8, 72.5, 68.6, 67.4, 66.8, 55.5, 39.5, 38.5, 31.8, 29.9, 27.6, 27.2, 26.1, 25.8, 23.9, 19.5, 18.4, -4.2, -4.5.

[α]D²⁸ = 12.16 (c = 1.16, CHCl₃).

HRMS (ESI) for C₄₀H₆₀O₄Si₂Na [M + Na]⁺, calculated: 683.3927, found: 683.3920.
(5S,6R,7R,11S)-5-(2-(4-methoxybenzyloxy)ethyl)-2,2,11,13,14,14-heptamethyl-3,3-diphenyl-4,12-dioxa-3,13-disilapentadecane-6,7-diol (22) and (5S,6S,7S,11S)-5-(2-(4-methoxybenzyloxy)ethyl)-2,2,11,13,14,14-heptamethyl-3,3-diphenyl-4,12-dioxa-3,13-disilapentadecane-6,7-diol (21)

Compound 7 (5.42 g, 8.2 mmol) was dissolved in 32 mL THF and the solution was cooled to 0 °C. To this solution NMO (1.4 g, 12.3 mmol) and 0.05 M solution of OsO₄ in toluene (16 mL, 0.82 mmol) was added consecutively and the reaction was protected from light by covering the reaction flask with black paper. The mixture was stirred for 12 h at the same temperature. The reaction was quenched by the addition of saturated aq. Na₂SO₃ solution (8mL) and further stirred for 1 h at room temperature. Further 20 mL water and 40 mL EtOAc was added to this mixture and the organic layer was separated. The aqueous part was washed with EtOAc (2×50 mL). The combined organic part was washed with brine solution (40 mL) and dried over anhydrous MgSO₄ and concentrated under reduced pressure. Two diastereomeric diols (compound 21 and compound 22) were purified by flash column chromatography (EtOAc/hexane = 1:20) to afford diol 22 (4.5 g, 6.49 mmol) and diol 21 (563 mg, 0.81 mmol) in 8:1 ratio.

Rf of 22 = 0.31 (EtOAc/hexane, 1:5).

1H NMR of compound 22 (400 MHz, CDCl₃): δ: 7.71- 7.61 (m, 4H), 7.44- 7.34 (m, 6H), 7.14 (d, J = 8.4 Hz, 2H), 6.84 (d, J = 8.4 Hz, 2H), 4.31 (d, J = 2.8 Hz, 2H), 4.01- 3.98 (m, 1H), 3.79 (s, 3H), 3.75- 3.71 (m, 1H), 3.57- 3.65 (m, 2H), 3.24 (s, 1H), 3.20- 3.13 (m, 1H), 1.93-1.82 (m, 1H), 1.81- 1.71 (m, 1H), 1.41- 1.23 (m, 6H), 1.09 (d, J = 6 Hz, 3H), 1.05 (s, 9H), 0.88 (s, 9H), 0.04 (d, J = 2.4 Hz, 6H).

13C NMR of compound 22 (50 MHz, CDCl₃): δ: 159.3, 135.8, 133.8, 133.2, 129.8, 129.7, 129.5, 129.4, 127.7, 127.6, 113.7, 77.0, 72.8, 72.4, 71.8, 68.7, 66.2, 55.2, 39.9, 32.5, 32.2, 27.0, 25.9, 23.7, 21.9, 19.3, 18.1, -4.4, -4.7.

[α]D²⁸ = 11.1 (c = 0.8, CHCl₃).

HRMS (ESI) for C₄₀H₆₂O₆Si₂Na [M + Na]⁺, calculated: 717.3982, found: 717.3973.

Rf of 21 = 0.32 (EtOAc/hexane, 1:5).

1H NMR of compound 21 (400 MHz, CDCl₃): δ: 7.71-7.66 (m, 4H), 7.44-7.34 (m, 6H), 7.09 (d, J = 8.8 Hz, 2H), 6.82 (d, J = 8.8 Hz, 2H), 4.20 (s, 2H), 4.16- 4.13 (m, 1H), 3.79 (s, 3H), 3.78-
3.75 (m, 1H), 3.51-3.49 (m, 1H), 3.37-3.35 (m, 1H), 3.28-3.27 (m, 1H), 3.21-3.18 (m, 1H), 2.06-2.00(m, 2H), 1.68-1.66 (m,2H), 1.65-1.64 (m, 2H), 1.49-1.41 (m, 2H), 1.11(d, J = 6 Hz, 3H), 1.06 (s, 9H), 0.88 (s, 9H), 0.04 (s, 6H).

$^{13}$C NMR of compound 21 (100 MHz, CDCl$_3$): $\delta$: 159.2, 136.0, 135.9, 133.6, 132.9, 130.4,127.2, 130.0, 129.9, 129.3, 127.9, 127.9, 127.7, 113.8, 74.9, 72.4, 72.2, 72.0, 68.6, 66.3, 55.3, 39.7, 33.4, 33.6, 29.7, 27.1, 26.0, 23.7, 21.6, 19.4, 18.2, -4.3, -4.6.

$[\alpha]_{D}^{28}$ = 1.3 (c = 0.8, CHCl$_3$).

HRMS (ESI) for C$_{40}$H$_{62}$O$_6$Si$_2$Na $[M + Na]^{+}$, calculated: 717.3982, found: 717.3988.

*tert*-butyl((S)-1-((4R,5R)-5-((S)-4-(tert-butyldimethylsilyloxy)pentyl)-2,2-dimethyl-1,3-dioxolan-4-yl)-3-(4 methoxybenzyloxy)propoxy)diphenylsilane (23)

To a stirring solution of the desired diol 22 (4.5 g, 6.49 mmol) in anhydrous acetone (26 mL), 2,2’ DMP (1.6 mL, 12.98 mmol) and catalytic amount of PPTS were added at room temperature and the reaction mixture was stirred for 5 h. The solvent was then evaporated in vacuo and the residue was purified by flash column chromatography (EtOAc/hexane = 1:20) to afford compound 23 (4.47 g, 6.1 mmol) as colorless oil in 94% yield.

$R_f = 0.25$ (EtOAc/hexane, 1:20).

$^{1}$H NMR of compound 23 (400 MHz, CDCl$_3$): $\delta$: 7.69- 7.64 (m, 4H), 7.43-7.32 (m, 6H), 7.15 (d, $J = 8.4$ Hz, 2H), 6.84 (d, $J = 8.4$ Hz, 2H), 4.26 (s, 2H), 4.07-4.04 (m, 1H), 3.97-3.89 (m, 2H), 3.8 (s, 3H), 3.66-3.63 (m, 1H), 3.55-3.48 (m, 2H), 1.97- 1.83 (m, 2H), 1.34 (s, 3H), 1.29 (s, 6H), 1.20-1.07 (m, 2H), 1.04 (d, $J = 5.2$ Hz, 3H), 1.02 (s, 9H), 0.88- 0.87 (m,2H), 0.87 (s, 9H), 0.02-0.00 (m,6H).

$^{13}$C NMR of compound 21 (100 MHz, CDCl$_3$): $\delta$: 159.3, 136.2, 134.1, 129.8, 129.3, 127.7, 113.9, 107.7, 80.7, 72.6, 69.9, 68.6, 66.6, 55.4, 39.8, 34.9, 30.1, 29.9, 27.9, 27.2, 26.1, 27.8, 23.9, 22.5, 19.6, 18.3, -4.2, -4.2.

$[\alpha]_{D}^{28}$ = 9.2 (c = 0.6, CHCl$_3$).

HRMS (ESI) for C$_{43}$H$_{66}$O$_6$Si$_2$Na $[M + Na]^{+}$, calculated: 757.4295, found: 757.4283.

*(S)-3-((4R,5R)-5-((S)-4-(tert-butyldimethylsilyloxy)pentyl)-2,2-dimethyl-1,3-dioxolan-4-yl)-3-(tertbutyldiphenylsiloxyl) propan-1-ol (24)

Compound 23 (4.47 g, 6.1 mmol) was dissolved in 24 mL of CH$_2$Cl$_2$/ phosphate buffer (pH = 7; 19:1) and the solution was cooled to 0 °C. DDQ (1.38 g, 7.32 mmol) was added portion wise
to it and the mixture was stirred at this temperature for 1 h. Then, the reaction mixture was filtered through a pad of celite. The residue was washed with 65 mL of CH$_2$Cl$_2$. The combined organic solution was washed successively with 5% NaHCO$_3$ solution, water and brine solution. The organic layer was then dried with anhydrous MgSO$_4$ and evaporated in vacuo. Purification by flash column chromatography (EtOAc:hexane = 1:10) afforded compound 24 (3.59 g, 5.85 mmol) as colorless oil in 96% yield.

R$_f$ = 0.20 (EtOAc/hexane, 1:10).

$^1$H NMR of compound 24 (400 MHz, CDCl$_3$): δ: 7.69-7.67 (m, 4H), 7.46-7.39 (m, 6H), 4.16-4.11 (m, 2H), 3.91-3.89 (m, 1H), 3.72-3.66 (m, 2H), 3.53-3.47 (m, 4H), 2.31-2.30 (m, 1H), 1.90-1.87 (m, 2H), 1.44 (s, 3H), 1.41 (s, 3H), 1.39-1.20 (m, 6), 1.08-1.05 (m, 3H), 0.94 (s, 9H), 0.91 (s, 9H), 0.05-0.02 (m, 6H).

$^{13}$C NMR of compound 24 (100 MHz, CDCl$_3$): δ: 136.0, 136.0, 134.0, 133.6, 130.1, 127.8, 108.2, 80.6, 78.4, 70.8, 68.7, 59.2, 39.8, 38.7, 30.1, 28.3, 27.4, 27.2, 26.1, 23.8, 22.2, 19.4, 18.3, -4.2, -4.5.

[$\alpha$]$_D^{28}$ = 12.2 (c = 0.7, CHCl$_3$).

HRMS (ESI) for C$_{35}$H$_{58}$O$_5$Si$_2$Na [M + Na]$^+$, calculated: 637.3720, found: 637.3711.

5-(S)-3-((4R,5R)-5-(S)-4-(tert-butyldimethylsilyloxy)pentyl)-2,2-dimethyl-1,3-dioxolan-4-yl)-3-(tert-butyldiphenylsilyloxy)propylthio)-1-phenyl-1H-tetrazole (25)

To a stirring solution of compound 24 (3.59 g, 5.85 mmol) in anhydrous THF (20 mL) was added triphenylphosphine (2.19 g, 8.37 mmol) and 1-phenyl-5-mercapto-1H-tetrazole [PT-SH] (1.66 g, 9.36 mmol) at -5 ºC. After stirring 15 minute at this temperature DIAD (2.3 mL, 11.7 mmol) in 8 mL of anhydrous THF was added drop wise and the reaction was left to stir for 12 h. Water (60 mL) and 40 mL of EtOAc was added to this mixture and the organic layer was separated. The aqueous part was then washed with EtOAc (2×50 mL). The combined organic part was washed with saturated aq. NaHCO$_3$ solution and brine solution (40 mL). The organic solution was then dried over anhydrous MgSO$_4$ and concentrated under reduced pressure to furnish the crude product, which on purification by flash column chromatography (EtOAc:hexane = 1:20) afforded compound 25 (4.3 g, 5.55 mmol) as colorless oil in 95% yield.

R$_f$ = 0.45 (EtOAc/hexane, 1:10).
$^1$H NMR of compound 25 (400 MHz, CDCl$_3$): $\delta$: 7.69-7.66 (m, 4H), 7.60-7.52 (m, 5H), 7.42-7.32 (m, 6H), 4.16-4.13 (m, 1H), 4.04-4.01 (m, 1H), 3.90-3.89 (m, 1H), 3.69-3.67 (m, 1H), 3.51-3.46 (m, 2H), 2.22-2.11 (m, 1H), 2.09-2.01 (m, 1H), 1.37 (s, 3H), 1.30 (s, 3H), 1.28-1.21 (m, 4H), 1.18-1.14 (m, 2H), 1.08 (d, $J = 6.8$ Hz, 3H), 1.05 (s, 9H), 1.09 (s, 9H), 0.07 (s, 6H).

$^{13}$C NMR of compound 25 (50 MHz, CDCl$_3$): $\delta$: 154.3, 136.0, 133.9, 133.5, 130.0, 129.8, 127.8, 127.7, 123.8, 107.9, 80.4, 70.73, 68.57, 39.7, 34.2, 30.1, 29.4, 27.9, 27.1, 26.0, 25.7, 23.8, 22.3, 19.4, 18.2, -4.2, -4.5.

$[^{\alpha}]D^{28}$ = 6.2 (c = 0.3, CHCl$_3$).

HRMS (ESI) for C$_{42}$H$_{62}$N$_4$O$_4$SSi$_2$Na $[M + Na]^+$, calculated: 797.3927, found: 797.3935.

5-((S)-3-(((4R,5R)-5-((S)-4-(tert-butyldimethylsilyloxy)pentyl)-2,2-dimethyl-1,3-dioxolan-4-yl)-3-(tert-butyldiphenylsilyloxy)propylsulfonyl)-1-phenyl-1H-tetrazole (4)

To a stirring solution of sulfide 25 (4.3 g, 5.55 mmol) in ethanol (60 mL) was added a mixture of (NH$_4$)$_6$Mo$_7$O$_{24}$,4H$_2$O (1.236 g, 1.0 mmol) and 30% H$_2$O$_2$ solution (7.3 mL) at 0 °C. The mixture was then stirred at room temperature for 6 h, and after that the reaction mixture was poured into 10% Na$_2$S$_2$O$_3$ solution and extracted with ethyl acetate (200 mL). The organic layer was washed with saturated NaHCO$_3$ solution and brine, dried over anhydrous MgSO$_4$ and concentrated in vacuo to afford the crude sulphone. The crude product was then purified by flash column chromatography (EtOAc/hexane = 1:20) to furnish pure sulphone 4 (3.85g, 4.77 mmol) as colorless gummy oil in 86% yield.

$R_f = 0.45$ (EtOAc/hexane, 1:10).

$^1$H NMR of compound 4 (400 MHz, CDCl$_3$): $\delta$: 7.68-7.63 (m, 5H), 7.62-7.60 (m, 4H), 7.46-7.38 (m, 6H), 4.09-4.06 (m, 1H), 4.02-3.98 (m, 1H), 3.93-3.83 (m, 3H), 3.68-3.65 (m, 1H), 2.26-2.16 (m, 2H), 1.36 (s, 3H), 1.31 (s, 3H), 1.21 (comp. 6H), 1.10 (s, 3H), 1.07 (s, 9H), 0.90 (s, 9H), 0.04 (s, 6H).

$^{13}$C NMR of compound 4 (50 MHz, CDCl$_3$): $\delta$: 153.5, 136.1, 135.9, 133.5, 133.1, 132.9, 131.5, 130.3, 130.2, 129.8, 128.1, 127.9, 125.3, 108.2, 80.5, 69.8, 68.6, 52.6, 39.6, 30.2, 29.8, 29.9, 27.6, 27.1, 26.1, 25.8, 23.8, 22.8, 22.3, 19.4, 18.3, -4.2, -4.5.

$[^{\alpha}]D^{28}$ = 9.5 (c = 0.8, CHCl$_3$).

HRMS (ESI) for C$_{42}$H$_{62}$N$_4$O$_6$SSi$_2$Na $[M + Na]^+$, calculated: 829.3826, found: 829.3815.
Ethyl 2-((S,E)-4-((4R,5R)-5-((S)-4-(tert-butyldimethylsilyloxy)pentyl)-2,2-dimethyl-1,3-dioxolan-4-yl)-4-(tert-butyldiphenylsilyloxy)but-1-enyl)-4,6-dimethoxybenzoate (29)

Sulfone 4 (0.96 g, 1.19 mmol) was dissolved in anhydrous THF (10 mL) and the solution was cooled to -78 ºC. To this solution 0.5 M KHMDs in toluene (2.6 mL) was added drop wise and stirred for 40 min. Aldehyde 5 (339 mg, 1.42 mmol) in anhydrous THF (5 mL) was then added to the reaction solution at -78 ºC and the temperature was allowed to attain room temperature slowly. The reaction was then quenched with saturated NH₄Cl and extracted with diethyl ether (150 mL). The organic layer was washed with brine solution and dried with anhydrous MgSO₄ and concentrated in vacuo to furnish the crude olefin. The crude product was then purified by flash column chromatography (EtOAc/hexane = 1:15) to give E-olefin 29 (778 mg, 0.95 mmol) as colorless gummy oil in 80% yield.

R_f = 0.30 (EtOAc/hexane, 1:1).

1H NMR of compound 29 (400 MHz, CDCl₃): δ: 7.68- 7.43 (m, 4H), 7.41-7.33 (m, 6H), 6.45 (d, J = 2.4 Hz, 1H), 6.34 (d, J = 2 Hz, 1H), 6.29 (d, J = 15.2 Hz, 1H), 6.30-6.15 (m, 1H), 4.35- 4.30 (m, 2H), 4.09-4.07 (m, 1H), 4.04- 4.00 (m, 1H), 3.95-3.90 (m, 1H), 3.88 (s, 3H), 3.86 (s, 3H), 3.66-3.65 (m, 1H), 2.46- 2.45 (m, 2H), 1.43-1.41 (compm. 6H), 1.35 (s, 3H), 1.30 (s, 3H), 1.29-1.22 (comp. 3H), 1.10 (d, J = 6.4 Hz, 3H), 1.04 (s, 9H), 0.88 (s, 9H), 0.04 (s, 9H).

13C NMR of compound 29 (50 MHz, CDCl₃): δ: 168.1, 161.4, 158.2, 137.8, 136.2, 136.1, 133.9, 133.7, 129.9, 129.1, 128.1, 127.8, 125.3, 116.0, 107.8, 101.5, 97.7, 79.9, 78.0, 71.9, 68.7, 61.2, 56.1, 55.5, 39.9, 38.6, 32.1, 31.8, 30.4, 29.8, 28.3, 27.2, 26.1, 23.83, 22.8, 22.3, 19.5, 18.3, 14.5, -4.2, -4.5.

[α]D²⁸ = 25.3 (c = 0.1, CHCl₃).


(2-((S,E)-4-((4R,5R)-5-((S)-4-(tert-butyldimethylsilyloxy)pentyl)-2,2-dimethyl-1,3-dioxolan-4-yl)-4-(tert-butyldiphenylsilyloxy)but-1-enyl)-4,6-dimethoxyphenyl)methanol (30)

To a stirring solution of compound 29 (778 mg, 0.95 mmol) in anhydrous THF (7 mL) was added 1 M DIBAL solution in THF (2.37 mL, 2.37 mmol) at – 40 ºC and the temperature was slowly increased to 0 ºC. The reaction was stirred for further 3 h at the same temperature and then quenched with saturated solution of sodium potassium tartrate. Diethyl ether was added to the reaction mixture and then it was filtered through a pad of celite. The celite bed was washed with another 80 mL of diethyl ether. The combined organic solvent was dried over anhydrous...
MgSO₄ and concentrated in *vacuo*. The crude product was then purified by flash column chromatography (EtOAc/hexane = 1:10) to afford the alcohol 30 (700 mg, 0.90 mmol) as colorless oil in 95% yield.

R<sub>f</sub> = 0.20 (EtOAc/hexane, 1:10).

1H NMR of compound 30 (400 MHz, CDCl₃): δ: 7.69-7.65 (m, 4H), 7.42-7.33 (m, 6H), 6.59 (d, J = 15.6 Hz, 1H), 6.43 (s, 1H), 6.36 (s, 1H), 6.12 (td, J = 15.2, 7.6, 1H), 4.62 (d, J = 3.2 Hz, 2H), 4.11 (d, J = 6.8 Hz, 1H), 4.56-4.52 (m, 1H), 3.9 (s, 1H), 3.89 (s, 3H), 3.80 (s, 3H), 3.71-3.64 (m, 1H), 2.49 (s, H), 1.37 (s, 3H), 1.32 (comp. 3H), 1.29 (s, 3H), 1.19-1.11 (m, 3H), 1.06 (comp. 3H), 1.03 (s, 9H), 0.87 (s, 9H), 0.02 (s, 6H).

13C NMR of compound 30 (50 MHz, CDCl₃): δ: 160.2, 159.3, 139.5, 136.2, 134.0, 133.7, 130.2, 130.0, 129.6, 127.8, 119.2, 107.8, 102.5, 97.6, 80.0, 78.1, 71.9, 68.8, 55.8, 55.4, 39.9, 38.7, 30.5, 29.4, 27.2, 26.1, 23.8, 22.9, 22.3, 19.6, 18.3, 14.3, -4.2, -4.5.

[a]<sup>28</sup> = 31.0 (c = 0.1, CHCl₃).

HRMS (ESI) for C₄₅H₆₈O₇Si₂Na [M + Na]<sup>+</sup>, calculated: 799.4401, found: 799.4393.

2-((S,E)-4-((4R,5R)-5-((S)-4-((tert-butyldimethylsilyloxy)pentyl)-2,2-dimethyl-1,3-dioxolan-4-yl)-4-((tert-butyldiphenylsilyloxy)but-1-enyl)-4,6-dimethoxybenzaldehyde (31)

To a stirring solution of compound 30 (700 mg, 0.90 mmol) in anhydrous CH₂Cl₂ (7 mL) was added activated MnO₂ (1.95g, 22.5 mmol) at room temperature and stirred for 48 h. The mixture was then filtered through celite and the residue was washed with 100 mL of CH₂Cl₂. The organic solvent was dried over anhydrous MgSO₄ and concentrated in *vacuo*. The crude product was then purified by flash column chromatography (EtOAc/hexane = 1:18) to furnish the aldehyde 31 (640 mg, 0.83 mmol) as colorless oil in 92% yield.

R<sub>f</sub> = 0.25 (EtOAc/hexane, 1:10).

1H NMR of compound 31 (400 MHz, CDCl₃): δ: 10.41(s, 1H), 7.71-7.62 (m, 4H), 7.42-7.33 (m, 6H), 7.23 (d, J = 14 Hz, 1H), 6.45 (s, 1H), 6.34 (s, 1H), 6.16 (td, J = 15.2, 6.8, 1H), 4.12-4.09 (m, 1H), 4.05-4.03 (m, 1H), 3.93-3.91 (m, 1H), 3.87 (s, 1H), 3.82 (s, 1H), 3.66-3.65 (m, 1H), 2.56-2.52 (m,2H), 1.36 (s, 3H), 1.33 (s, 2H), 1.27 (s, 3H), 1.25-1.21 (m, 4H), 1.09 (s, 3H), 1.08 (s, H), 0.87 (s, 9H), 0.01 (s, 6H).

13C NMR of compound 31 (50 MHz, CDCl₃): δ: 190.1, 164.6, 164.4, 143.4, 136.0, 133.7, 130.9, 129.8, 127.7, 115.9, 107.7, 103.9, 96.8, 96.2, 79.9, 77.9, 71.9, 68.6, 55.8, 55.4, 39.7,38.5, 30.3, 29.7, 28.2, 27.1, 26.0, 23.7, 22.19, 19.48, 18.20, -4.3, -4.5.
$[\alpha]_{D}^{28} = 31.0$ (c = 0.1, CHCl₃).

HRMS (ESI) for C₄₅H₆₆O₈Si₂Na [M + Na]⁺, calculated: 797.4244, found: 797.4249.

2-((S,E)-4-((4R,5R)-5-((S)-4-(tert-butyldiphenylsilyloxy)pentyl)-2,2-dimethyl-1,3-dioxolan-4-yl)-4-(tert-butyldiphenylsilyloxy)but-1-enyl)-4,6-dimethoxybenzoic acid (32)

The aldehyde 31 (640 mg, 0.83 mmol) was dissolved in tBuOH (2 mL) and 2.0 M solution of 2-methyl-2-butene (5.4 mL, 10.8 mmol) in THF was added to it. To this mixture was added a solution of NaClO₂ (80% purity, 747 mg, 10 mmol) and Na₂HPO₄ (691 mg, 7 mmol) in H₂O (2 mL). After two hours the yellow biphasic reaction mixture was poured onto H₂O (15 mL) and EtOAc (60 mL). The organic layer was separated and the aqueous part was washed with EtOAc (2×50 mL). The combined organic part was washed with brine solution (40 mL) and dried over anhydrous MgSO₄ and concentrated under reduced pressure to afford the crude acid. The crude material was purified by flash column chromatography (EtOAc/hexane = 1:7) to afford acid 32 (524 mg, 0.66 mmol) in 80% yield as colorless oil.

$R_f = 0.20$ (EtOAc/hexane, 1:5).

$^1$H NMR of compound 32 (400 MHz, CDCl₃): δ: 7.74-7.67 (m, 4H), 7.41-7.35 (m, 6H), 6.72 (d, $J$ = 15.6 Hz, 1H), 6.51 (s, 1H), 6.38 (s, 1H), 6.21-6.17 (m, 1H), 4.13-4.05 (m, 2H), 3.93-3.91 (m, 1H), 3.87 (s, 3H), 3.79 (s, 3H), 3.70-3.66 (m, 1H), 2.5 (s, 2H), 1.36-1.32 (m, 8H), 1.28-1.13 (m, 3H), 1.10 (d, $J$ = 6 Hz, 3H), 1.05 (s, 9H), 0.87 (s, 9H), 0.027 (s, 6H).

$^{13}$C NMR of compound 32 (50 MHz, CDCl₃, 77.23): δ: 169.93, 162.06, 158.90, 140.82, 136.15, 133.89, 133.80, 130.26, 129.95, 127.78, 113.21, 107.84, 103.27, 97.72, 96.30, 79.95, 78.03, 71.89, 68.83, 56.44, 55.53, 39.83, 38.54, 30.47, 29.85, 28.33, 27.20, 27.11, 23.79, 22.27, 19.57, 18.31, -4.20, -4.47.

$[\alpha]_{D}^{28} = 31.0$ (c = 0.1, CHCl₃).

HRMS (ESI) for C₄₅H₆₆O₈Si₂Na [M + Na]⁺, calculated: 813.4193, found: 813.4181.

2-((S,E)-4-(tert-butyldiphenylsilyloxy)-4-((4R,5R)-5-((S)-4-hydroxypentyl)-2,2-dimethyl-1,3-dioxolan-4-yl)but-1-enyl)-4,6-dimethoxybenzoic acid (3)

To a stirring solution of the acid 32 (524 mg, 0.66 mmol) in anhydrous acetonitrile (2 mL) and 2,2’ DMP (1.5 mL) was added pyridinium p-toluenesulfonate (2 g, 8 mmol) and stirred for 36 h at 45 °C. After completion of the reaction EtOAc (70 mL) and brine (30 mL) was added to the reaction mixture and the organic layer was separated. The aqueous part was then washed with EtOAc (2×50 mL). The combined organic part was washed with brine solution (30 mL) and
dried over anhydrous MgSO₄ and concentrated under reduced pressure. The crude material was purified by flash column chromatography (EtOAc/hexane = 1:1) to afford seco-acid 3 (379 mg, 0.56 mmol) in 85% yield as colorless oil. 

Rᵥ = 0.25 (EtOAc/hexane, 1:1).

1H NMR of compound 3 (400 MHz, CDCl₃): 7.72-7.67 (m, 4H), 7.38-7.34 (m, 6H), 6.69 (d, J = 15.6 Hz, 1H), 6.50 (s, 1H), 6.37 (s, 1H), 6.23-6.16 (m, 1H), 4.11-4.09 (m, 1H), 4.04-4.02 (m, 1H), 3.85 (s, 3H), 3.89-3.82 (m, 1H), 3.79 (s, 3H) 3.65-3.64 (m, 1H), 2.56-2.46 (m, 2H), 1.39 (s, 3H), 1.35-1.32 (m, 2H), 1.27 (s, 3H), 1.23 (s, 3H), 1.91 (s, 3H), 1.17-1.6 (m, 2H), 1.11 (d, J = 6 Hz, 3H), 1.04 (s, 9H).

13C NMR of compound 3 (100 MHz, CDCl₃): 176.2, 161.7, 158.5, 148.5, 137.8, 136.3, 136.1, 136.1, 133.8, 133.7, 130.1, 129.9, 129.9, 127.8, 127.8, 107.8, 102.5, 97.7, 79.9, 77.6, 72.2, 68.1, 56.3, 55.5, 38.9, 38.3, 30.1, 28.0, 27.3, 27.2, 27.1, 25.7, 23.3, 22.20, 19.5.

[α]D²⁸ = 21.7 (c = 0.1, CHCl₃).


(3aR,7R,17S,17aR,E)-17-(tert-butyldiphenylsilyloxy)-10,12-dimethoxy-2,2,7-trimethyl-4,5,6,7,17,17a-hexahydro-3aH-benzo[c][1,3]dioxolo[4,5-i][1]oxacyclotetradecin-9(16H)-one (33)

To a solution of TPP (294 mg, 1.12 mmol) and DIAD (0.22 mL, 1.12 mmol) in 75 mL toluene under N₂ atmosphere at -10 °C was added a solution of seco-acid 3 (95 mg, 0.14 mmol) in 50 mL toluene via syringe pump over 1 h. The resulting mixture was then slowly allowed to attain room temperature. After disappearance of starting material as indicated by TLC, the reaction mixture was concentrated in vacuo and the crude material was purified by flash chromatography (EtOAc/hexane = 1:7) to furnish the macrolactone 33 (59 mg, 0.09 mmol) in 65% yield.

Rᵥ = 0.40 (EtOAc/hexane, 1:5).

1H NMR of compound 33 (400 MHz, CDCl₃): δ: 7.65-7.63 (m, 4H), 7.39-7.28 (m, 6H), 6.33 (d, J = 2 Hz, 1H), 6.29 (d, J = 2 Hz, 1H), 6.18 (s, 2H), 5.04-5.01 (m, 1H), 4.11 (d, J = 7.2 Hz, 1H), 3.91-3.88 (m, 1H), 3.78 (s, 3H), 3.75 (s, 3H), 3.75-3.74 (m, 1H), 2.54-2.49 (m, 1H), 2.35-2.31 (m, 1H), 1.48-1.47 (m, 4H), 1.27 (s, 3H), 1.25 (s, 3H), 1.23 (s, 2H), 1.13 (s, 2H), 1.07 (s, 9H).

13C NMR of compound 33 (100 MHz, CDCl₃): δ: 167.8, 161.2, 157.5, 137.3, 136.1, 135.9, 133.8, 133.5, 131.8, 129.7, 129.6, 127.6, 127.6, 116.3, 107.6, 100.5, 97.7, 82.5, 76.9, 74.4, 72.2, 55.9, 55.4, 38.4, 35.9, 30.0, 27.1, 26.7, 24.7, 20.9, 20.5, 19.3.
$[\alpha]_D^{28} = 11.7$ (c = 0.1, CHCl$_3$).

HRMS (ESI) for C$_{39}$H$_{50}$O$_7$SiNa [M + Na]$^+$, calculated: 681.3223, found: 681.3218.

(3R,7R,8R,9S,E)-9-(tert-butyldiphenylsilyloxy)-7,8-dihydroxy-14,16-dimethoxy-3-methyl-3,4,5,6,7,8,9,10-octahydro-1H-benzo[c][1]oxacyclotetradecin-1-one (34)

To a stirring solution of macrolide 33 (59 mg, 0.09 mmol) in anhydrous CH$_2$Cl$_2$ (2 mL) was added p-toluenesulfonic acid mono hydrate (34 mg, 0.18 mmol) at room temperature and stirred for 2 h. After completion of the reaction 20 mg solid NaHCO$_3$ was added to the reaction mixture and the solvent was evaporated in vacuo. The residue was then purified by flash column chromatography (EtOAc/hexane = 1:3) to afford compound 34 (50 mg, 0.08 mmol) in 90% yield.

$R_f = 0.30$ (EtOAc/hexane, 1:3).

$^1$H NMR of compound 34 (400 MHz, CDCl$_3$): $\delta$: 7.70-7.67 (m, 4H), 7.47-7.37 (m, 6H), 6.47 (d, $J = 15.5$ Hz, 1H), 6.36 (s, 1H), 6.33 (d, $J = 1.2$ Hz, 1H), 5.71 (ddd, $J = 15.6$, 11.2, 4 Hz, 1H), 5.31-5.28 (m, 1H), 4.10 (dd, $J = 6.8$, 3.6 Hz, 1H), 3.89-3.86 (m,1H), 3.76 (s, 6H), 3.62-3.00 (m, 1H), 2.90-2.81 (m, 1H), 2.30-2.26 (m, 1H), 2.16-2.08 (m, 1H), 1.93-1.81 (m, 2H), 1.79-1.70 (m, 4H), 1.09 (d, $J = 6.4$ Hz, 3H), 1.08 (s, 9H).

$^{13}$C NMR of compound 34 (50 MHz, CDCl$_3$): $\delta$: 167.8, 161.4, 157.8, 136.7, 136.1, 136.1, 133.5, 132.4, 130.4, 130.3, 129.9, 128.2, 128.1, 116.9, 101.5, 98.1, 77.7, 74.0, 73.5, 71.9, 56.2, 55.6, 38.5, 32.6, 27.3, 19.8, 19.5, 19.1.

$[\alpha]_D^{28} = 15.7$ (c = 0.06, CHCl$_3$).

HRMS (ESI) for C$_{36}$H$_{46}$O$_7$SiNa [M + Na]$^+$, calculated: 641.291, found: 641.283.

(3R,7R,8R,9S,E)-9-(tert-butyldiphenylsilyloxy)-7,8,16-trihydroxy-14-methoxy-3-methyl-3,4,5,6,7,8,9,10-octahydro-1H-benzo[c][1]oxacyclotetradecin-1-one (35)

Compound 34 (30 mg, 0.04 mmol) was dissolved in anhydrous CH$_2$Cl$_2$ (1.5 mL) and BBr$_3$ (0.08 mL, 1M, 0.08 mmol, dissolved in 1 mL anhydrous CH$_2$Cl$_2$) was added during 5 minute at 0$^\circ$ C under N$_2$ atmosphere. The reaction mixture was then stirred for 4 h at 0$^\circ$ C. After that water (10 mL) and CH$_2$Cl$_2$ (20 mL) was added and the organic layer was separated. The aqueous phase was extracted with additional CH$_2$Cl$_2$ (2x20 ml). The combined organic extracts were dried over anhydrous MgSO$_4$ and evaporated to dryness in vacuo. The crude material was then purified by flash column chromatography (EtOAc/hexane = 1:5) to afford compound 35 (20 mg, 0.034 mmol) in 85% yield.
R_f = 0.40 (EtOAc/hexane, 1:3).

1H NMR of compound 35 (400 MHz, CDCl_3): \( \delta \): 11.47 (s, 1H), 7.71-7.67 (m, 4H), 7.48-7.40 (m, 6H), 6.77 (d, \( J = 15.2 \) Hz, 1H), 6.36 (s, 1H), 6.75 (s, 1H), 5.80 (td, \( J = 15.2, 6.4 \) Hz, 1H), 5.08-5.06 (m, 1H), 4.20-4.19 (m, 1H), 3.79 (s, 3H), 3.76 (comp. 1H), 3.68-3.67 (m, 1H), 2.63-2.57 (m, 2H), 2.50-2.48 (m, 1H), 2.41-2.39 (m, 1H), 1.97-1.93 (m, 2H), 1.73-1.70 (m, 2H), 1.33 (d, \( J = 6 \) Hz, 3H), 1.21 (s, 9H).

13C NMR of compound 35 (100 MHz, CDCl_3): \( \delta \): 171.3, 164.7, 163.9, 142.2, 136.1, 136.1, 133.5, 133.1, 132.8, 130.4, 130.3, 128.1, 125.0, 127.5, 108.1, 105.1, 100.1, 73.8, 73.7, 73.7, 73.7, 55.6, 38.2, 34.8, 34.01, 27.3, 19.8, 19.5, 19.3.

\([\alpha]_{D^{28}} = 16.9 \) (c = 0.03, CHCl_3).

HRMS (ESI) for C_{35}H_{44}O_{7}SiNa [M + Na]^+, calculated:627.2753, found:627.2747.

4,11,12,13-Tetrahydroxy-2-methoxy-7-methyl-7,8,9,10,11,12,13,14-octahydro-6-oxa-benzocyclotetradecen-5-one (10'-epi-Paecilomycin E)

Compound 35 (20 mg, 0.034 mmol) was dissolved in 1 mL anhydrous THF in a polyethylene vessel and 200 micro liter of HF-Py was added to it at 0 ºC. The mixture was then stirred for 10 h at room temperature followed by addition of 15 mL of EtOAc and 5 mL of brine solution. The organic layer was separated and the aqueous layer was washed with (2×10 mL) of EtOAc. The combined organic part was washed with brine (5 mL) and the solution was dried over anhydrous MgSO_4 and then concentrated in vacuo. The crude material was then purified by flash column chromatography (EtOAc/hexane = 1:1) to afford 10'-epi-Paecilomycin E (9 mg, 0.027 mmol) in 80% yield.

1H NMR of 10'-epi-Paecilomycin E (400 MHz, CDCl_3): \( \delta \): 11.54 (s, 1H), 6.94 (d, \( J = 16 \) Hz, 1H), 6.46 (s, 1H), 6.40 (s, 1H), 6.11-6.00 (m, 1H), 5.22-5.18 (m, 1H), 4.2 (s, 1H), 3.97-3.74 (m, 1H), 3.81 (s, 3H), 3.75-3.74 (m, 1H), 2.80-2.70 (m, 2H), 2.04-1.98 (m, 2H), 1.81-1.80 (m, 2H), 1.78-1.70 (m, 2H), 1.36 (d, \( J = 6 \) Hz, 3H).

13C NMR of 10'-epi-Paecilomycin E (100 MHz, CDCl_3): \( \delta \): 171.1, 165.0, 164.2, 142.1, 134.2, 127.1, 108.4, 105.0, 100.4, 75.9, 75.7, 73.7, 73.5, 55.7, 38.7, 34.8, 34.5, 19.9, 19.8.

\([\alpha]_{D^{26}} = 19.9 \) (c = 0.01, CHCl_3).

HRMS (ESI) for C_{19}H_{26}O_{7}Na [M + Na]^+, calculated:389.1576, found: 389.1572.
(3aR,7S,17S,17aR,E)-17-(tert-butyldiphenylsilyloxy)-10,12-dimethoxy-2,2,7-trimethyl-4,5,6,7,17,17a-hexahydro-3aH-beno[c][1,3]dioxolo[4,5-i][1]oxacyclotetradecin-9(16H)-one (53)

Seco-acid 51 was cyclized to compound 53 via mitsunobu macrolactoni zation in 68% yield as presented earlier.

1H NMR of compound 53 (400 MHz, CDCl3): δ: 7.70-7.62 (m, 4H), 7.45-7.37 (m, 6H), 6.34-6.32 (m, 2H), 6.20 (d, J = 16.0 Hz, 1H), 6.04-5.97 (m, 1H), 4.96-4.92 (m, 1H), 4.15 (dd, J = 6.8, 3.2 Hz, 1H), 3.94-3.93 (m, 2H), 3.78 (s, 6H), 2.59-2.51 (m, 2H), 1.42 (s, 3H), 1.29 (comp. 2H), 1.25 (s, 3H), 1.24 (d, J = 6.4 Hz, 3H), 1.21-1.16 (comp.4H), 1.04 (s, 9H).

13C NMR of compound 53 (100 MHz, CDCl3): δ: 166.9, 161.4, 158.3, 138.8, 136.1, 136.1, 133.7, 133.8, 131.6, 130.1, 130.0, 129.5, 128.0, 115.8, 107.7, 102.7, 97.7, 82.6, 77.2, 72.4, 72.1, 56.2, 55.6, 37.1, 34.9, 30.8, 27.2, 26.9, 24.9, 20.1, 19.4.

[α]D28 = -11.7 (c = 0.01, CHCl3).


(3S,7R,8R,9S,E)-9-(tert-butyldiphenylsilyloxy)-7,8-dihydroxy-14,16-dimethoxy-3-methyl-3,4,5,6,7,8,9,10-octahydro-1H-benzo[c][1]oxacyclotetradecin-1-one (55)

Compound 53 was converted to 55 in 92% yield by PTSA in CH2Cl2 as described previously.

1H NMR of compound 55 (400 MHz, CDCl3): δ: 7.71-7.69 (m, 4H), 7.46-7.39 (m, 6H), 6.46 (d, J = 15.6 Hz, 1H), 6.37 d, J = 2.0 Hz, 1H), 6.34 (d, J = 2.0 Hz, 1H), 6.02-5.94 (m, 1H), 5.19-5.15 (m, 1H), 4.16-4.12 (m, 1H), 3.79 (s, 3H), 3.75 (s, 3H), 3.79-3.75 (comp. 1H), 3.64-3.62 (m, 1H), 2.59-2.52 (m, 1H), 2.38-2.33 (m, 1H), 1.76-1.56 (m, 4H), 1.51-1.56 (m, 2H), 1.30 (d, J = 6.4 Hz, 3H), 1.10 (s, 9H).

13C NMR of compound 55 (100 MHz, CDCl3): δ: 167.8, 161.4, 158.2, 138.1, 136.1, 136.6, 133.0, 130.9, 130.3, 130.2, 129.9, 128.1, 128.0, 116.2, 103.0, 97.8, 76.4, 75.7, 72.7, 71.7, 56.2, 55.4, 37.1, 35.1, 33.5, 27.3, 20.3, 20.1, 19.5.

[α]D28 = -15.7 (c = 0.06, CHCl3).


(3S,7R,8R,9S,E)-9-(tert-butyldiphenylsilyl)-7,8,16-trihydroxy-14-methoxy-3-methyl-3,4,5,6,7,8,9,10-octahydro-1H-benzo[c][1]oxacyclotetradecin-1-one (57)

Compound 55 was reacted with BBr3 to afford compound 57 as described earlier in 82% yield.
$^1$H NMR of compound 57 (400 MHz, CDCl$_3$): $\delta$: 12.19 (s, 1H), 7.71-7.69 (m, 4H), 7.48-7.38 (m, 6H), 7.08 (d, $J = 15.2$ Hz, 1H), 6.36 (d, $J = 2.8$ Hz, 1H), 6.21 (d, $J = 2.8$ Hz, 1H), 5.47-5.40 (m, 1H), 5.29-4.99 (m, 1H), 4.18-4.14 (m, 1H), 3.89 (s, 1H), 3.78 (s, 3H), 3.70-3.68 (m, 1H), 2.84-2.76 (m, 2H), 2.37-2.17 (m, 2H), 1.84-1.71 (m, 2H), 1.70-1.62 (m, 2H), 1.38 (d, $J = 6.0$ Hz, 3H), 1.11 (s, 9H).

$^{13}$C NMR of compound 57 (100 MHz, CDCl$_3$): $\delta$: 171.8, 165.9, 164.1, 143.0, 136.1, 136.1, 134.0, 133.5, 132.7, 130.4, 130.3, 129.2, 128.1, 128.0, 108.5, 103.9, 100.3, 77.9, 74.6, 73.3, 73.1, 55.6, 38.6, 35.7, 32.7, 27.3, 20.8, 20.6, 19.5.

$[\alpha]_D^{28} = -36.9$ (c = 0.03, CHCl$_3$).

HRMS (ESI) for C$_{35}$H$_{44}$O$_7$SiNa $[M + Na]^+$, calculated: 627.2753, found: 627.2747.

($3S,7R,8R,9S,E$)-7,8,9,16-tetrahydroxy-14-methoxy-3-methyl-3,4,5,6,7,8,9,10-octahydro-1$^H$-benzo[c][1]oxacyclotetradecin-1-one (Paecilomycin E)

The TBDPS group in compound 57 was done with HF-Py in THF as stated earlier to furnish natural Paecilomycin E in 80% yield.

$^1$H NMR of Paecilomycin E (400 MHz, CDCl$_3$): $\delta$: 12.00 (s, 1H), 7.19 (dd, $J = 15.2$, 1.2 Hz, 1H), 6.37 (s, 1H), 6.37 (s, 1H), 5.27 (s, 1H), 4.97 (s, 1H), 4.16 (s, 1H), 3.92 (s, 1H), 3.78 (s, 1H), 3.67 (s, 2H), 2.72 (s, 1H), 2.64 (s, 1H), 1.77-1.73 (m, 6H), 1.40 (s, 3H).

$^1$H NMR of Paecilomycin E (600 MHz, Acetone-d$_6$, 2.09): $\delta$: 12.10 (s, 1H), 7.24 (dd, $J = 15.6$, 1.2 Hz, 1H), 6.51 (d, $J = 2.4$ Hz, 1H), 6.43 (d, $J = 2.4$ Hz, 1H), 5.99 (ddd, $J = 15.0$, 10.8, 3.6 Hz, 1H), 5.09-5.06 (m, 1H), 4.40 (s, 1H), 4.12-4.11 (m, 1H), 3.97 (s, 1H), 3.89 (s, 3H), 3.77 (s, 1H), 3.74 (s, 1H), 2.85-2.84 (m, 1H), 2.53-2.50 (m, 1H), 2.08-2.00 (m, 1H), 1.85-1.79 (m, 2H), 1.79 (m, 2H), 1.71-1.67 (m, 1H), 1.44 (d, $J = 6.0$ Hz, 3H).

$^{13}$C NMR of Paecilomycin E (100 MHz, CDCl$_3$, 77.00): $\delta$: 171.34, 165.57, 164.03, 142.97, 134.53, 128.33, 108.60, 103.88, 100.18, 77.30, 75.99, 74.07, 71.37, 55.42, 53.40, 38.96, 35.40, 33.80, 21.19, 20.46.

$[\alpha]_D^{26} = -83.97$ (c = 0.08, CHCl$_3$).

HRMS (ESI) for C$_{19}$H$_{26}$O$_7$Na $[M + H]^+$, calculated:367.1757, found: 367.1743.

($3aR,7S,17S,17aR,E$)-17-$(tert$-butyldiphenylsilyloxy)$-13$-$(chloro$-10,12$-dimethoxy$-2,2,7$-trimethyl$-4,5,6,7,17,17a$-hexahydro$-3aH$-benzo[c][1,3]dioxolo[4,5-i][1]oxacyclotetradecin$-9(16H)$-one (54)
Seco-acid 52 was converted to 54 via Mitsunobu macrolactonization in 65% yield as stated earlier.

$^1$H NMR of compound 54 (400 MHz, CDCl$_3$): $\delta$: 7.76-7.70 (m, 4H), 7.43-7.41 (m, 6H), 6.41 (s, 1H), 6.30 (d, $J = 16.0$ Hz, 1H), 5.99-5.91 (m, 1H), 4.67-4.64 (m, 1H), 4.14 (dd, $J = 7.2$, 2 Hz, 1H), 3.90 (s, 3H), 3.82 (s, 3H), 3.82 (comp. 1H), 3.71 (s, 1H), 2.76-2.69 (m, 1H), 2.58-2.52 (m, 1H), 1.49 (s, 3H), 1.50-1.41 (m, 3H), 1.37-1.33 (m, 3H), 1.31 (s, 3H), 1.21 (d, $J = 6.4$ Hz, 3H), 1.04 (s, 9H).

$^{13}$C NMR of compound 54 (50 MHz, CDCl$_3$): $\delta$: 166.9, 156.4, 155.9, 136.4, 136.1, 135.3, 134.6, 133.6, 129.9, 129.7, 128.2, 127.8, 127.2, 118.2, 113.7, 107.7, 95.5, 82.6, 77.8, 73.2, 72.9, 56.6, 56.5, 38.7, 34.8, 29.7, 27.3, 26.7, 24.9, 22.3, 21.3, 19.5.

$[\alpha]_D^{28} = -11.7$ (c = 0.01, CHCl$_3$).

HRMS (ESI) for C$_{39}$H$_{49}$ClO$_7$SiNa [M + Na]$^+$, calculated: 715.2833, found: 715.2825.

$(3S,7R,8R,9S,E)-9$-($\text{-tert}$-\text{butyldiphenylsilyloxy})$-13$-chloro$-7,8$-dihydroxy$-14,16$-dimethoxy$-3$-methyl$-3,4,5,6,7,8,9,10$-octahydro$-1$H$-$benzo[c][1]$\text{oxacyclotetradecin}$-1$-$one (56)

Deprotection of acetonide group in compound 54 was performed as stated earlier to furnish compound 56 in 95% yield.

$^1$H NMR of compound 56 (400 MHz, CDCl$_3$): $\delta$: 7.70-7.69 (m, 4H), 7.44-7.38 (m, 6H), 6.40 (s, 1H), 6.30 (d, $J = 16.0$ Hz, 1H), 5.82-5.75 (m, 1H), 5.07-5.02 (m, 1H), 4.03 (d, $J = 9.2$ Hz, 1H), 3.93 (s, 3H), 3.86-3.84 (m, 1H), 3.80 (s, 3H), 3.60-3.59 (m, 1H), 2.80-2.75 (m, 2H), 2.35-2.25 (m, 1H), 1.54-1.52 (m, 2H), 1.49-1.43 (m, 3H), 1.27 (d, $J = 6.0$ Hz, 3H), 1.04 (s, 9H).

$^{13}$C NMR of compound 56 (100 MHz, CDCl$_3$): $\delta$: 167.6, 156.2, 155.8, 136.3, 135.8, 135.8, 134.1, 133.3, 132.9, 129.9, 128.4, 127.8, 127.8, 127.2, 117.6, 113.5, 110.2, 95.2, 75.9, 72.2, 70.8, 70.8, 6.4, 56.4, 37.9, 34.7, 30.4, 27.1, 20.7, 19.3, 19.2.

$[\alpha]_D^{28} = -17.7$ (c = 0.05, CHCl$_3$).

HRMS (ESI) for C$_{36}$H$_{45}$ClO$_7$SiNa [M + Na]$^+$, calculated: 675.2520, found: 675.2527.

$(3S,7R,8R,9S,E)-9$-($\text{-tert}$-\text{butyldiphenylsilyloxy})$-13$-chloro$-7,8,16$-trihydroxy$-14$-methoxy$-3$-methyl$-3,4,5,6,7,8,9,10$-octahydro$-1$H$-$benzo[c][1]$\text{oxacyclotetradecin}$-1$-$one (58)

Selective demethylation of compound 56 was performed as stated earlier to afford compound 58 in 85% yield.

$^1$H NMR of compound 58 (400 MHz, CDCl$_3$): $\delta$: 11.99 (s, 1H), 7.69-7.68 (m, 4H), 7.45-7.38 (m, 6H), 6.52 (d, $J = 17.6$ Hz, 1H), 6.43 (s, 1H), 5.34-5.27 (m, 1H), 5.07 (s, 1H), 4.11-4.08 (m, 1H),
3.89 (s, 3H), 3.89 (comp. 1H), 3.59-3.58 (m, 1H), 2.73-2.69 (m, 1H), 2.60-2.58 (m, 1H), 2.46-2.42 (m, 1H), 1.70-1.68 (m, 1H), 1.57-1.55 (m, 3H), 1.32 (d, J = 6.0 Hz, 3H), 1.31-1.29 (m, 1H), 1.10 (s, 9H).

$^{13}$C NMR of compound 58 (100 MHz, CDCl$_3$): δ: 171.1, 163.5, 160.2, 140.1, 136.1, 136.0, 133.3, 132.7, 132.6, 130.4, 130.3, 128.3, 128.1, 128.0, 114.3, 105.9, 99.8, 79.1, 79.1, 74.6, 72.4, 56.6, 37.9, 35.8, 33.4, 27.3, 21.2, 20.8, 19.5.

$\left[\alpha\right]_{D}^{28} = -36.9$ (c = 0.03, CHCl$_3$).

HRMS (ESI) for C$_{35}$H$_{43}$ClO$_7$SiNa [M + Na]$^+$, calculated: 661.2364, found: 661.2363.

(3S,7R,8R,9S,E)-13-chloro-7,8,9,16-tetrahydroxy-14-methoxy-3-methyl-3,4,5,6,7,8,9,10-octahydro-1H-benzo[c][1]oxacyclotetradecin-1-one (6'-epi-cochliomycin C)

Removal of TBDPS group was achieved when compound 58 was reacted with HF-Py to form 6'-epi-cochliomycin C in 82% yield as described earlier.

$^1$H NMR of 6'-epi-cochliomycin C (400 MHz, CDCl$_3$): δ: 11.72 (s, 1H), 6.72 (d, J = 14.0 Hz, 1H), 6.47 (s, 1H), 5.62 (s, 1H), 5.10 (s, 1H), 4.09-4.03 (m, 1H), 3.91 (s, 3H), 3.78-3.64 (m, 2H), 2.76 (m, 2H), 1.69-1.67 (comp. 6H), 1.36 (d, J = 5.2 Hz, 3H).

$^1$H NMR of 6'-epi-cochliomycin C (600 MHz, Acetone-d$_6$): δ: 11.38 (s, 1H), 6.72 (d, J = 16.2 Hz, 1H), 6.63 (s, 1H), 5.85-5.80 (m, 1H), 5.21-5.16 (m, 1H), 4.40 (s, 1H), 3.97 (s, 3H), 3.97 (comp. 1H), 3.80-3.90 (m, 1H), 3.71 (s, 1H), 2.81 (m, 1H), 2.63 (m, 1H), 1.86-1.85 (m, 2H), 1.75-1.72 (m, 2H), 1.68-1.65 (m, 2H), 1.39 (d, J = 6.0 Hz, 3H).

$^{13}$C NMR of 6'-epi-cochliomycin C (100 MHz, CDCl$_3$): δ: 170.8, 163.1, 160.3, 140.3, 129.3, 114.5, 106.2, 99.9, 77.5, 77.2, 76.9, 74.3, 56.6, 38.4, 36.1, 32.1, 21.5, 20.8.

$\left[\alpha\right]_{D}^{26} = -30.5$ (c = 0.02, CHCl$_3$).

HRMS (ESI) for C$_{19}$H$_{25}$ClO$_7$Na [M + H]$^+$, calculated: 401.1367, found: 401.1360.

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References


