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

Pratik Pal, Nandan Jana and Samik Nanda*

Department of Chemistry, Indian Institute of Technology, Kharagpur, 721302, India

snanda@chem.iitkgp.ernet.in

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´; 3*S*,7*R*,8*R*,9*S*) 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 sterochemically pure methyl substituent at the C_{10}'-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.

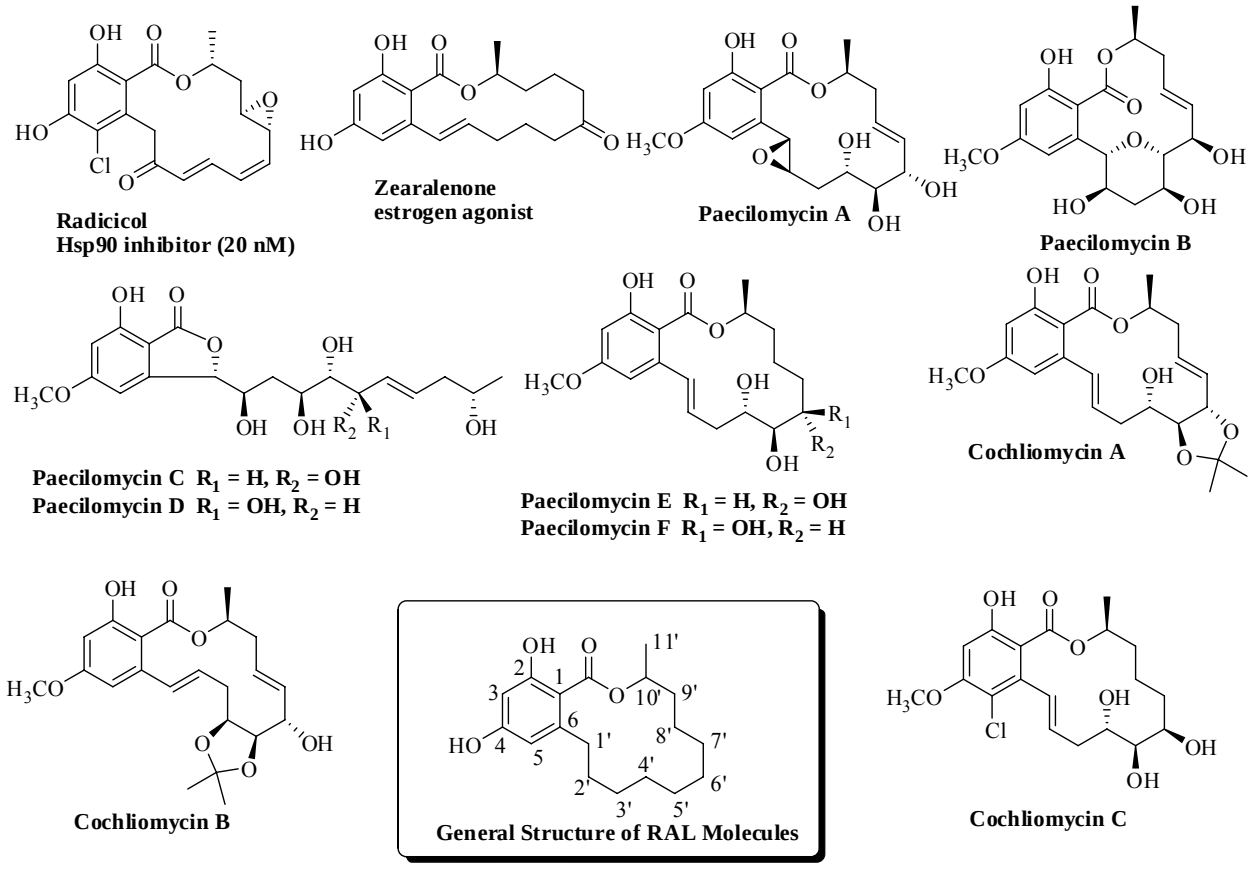


Figure 1: General structural feature of RALs with newly isolated paecilomycins and cochliomycins (uncorrected).

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*,

and antifouling activity was detected for the first time in this type of metabolites. Very recently two new brominated RALs (5-bromozeaenol and 3,5-dibromozeaenol) 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).

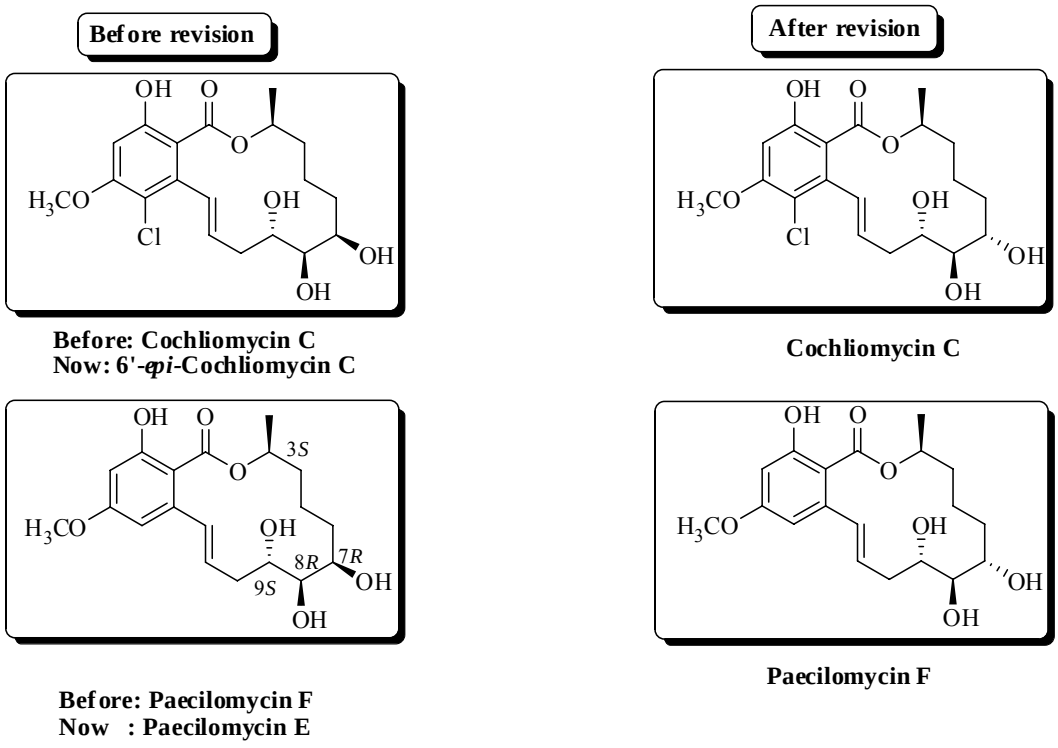


Figure 2: Structural revision of paecilomycin E and F and cochliomycin C.

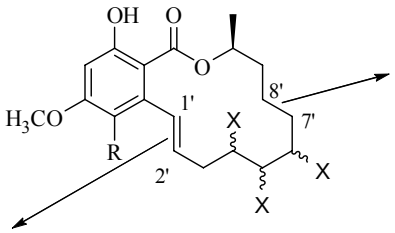
We have already reported the asymmetric total synthesis of several RALs such as cochliomycin A, zeaenol, [11] 5′-epi-cochliomycin C and F (uncorrected) [12] by successful exploration of several useful transformations e.g, ME-DKR (metal enzyme combined dynamic kinetic resolution), Keck asymmetric allylation, *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 ($C_{1'}$-$C_{11'}$), the notable difference being the substitution pattern in the aromatic ring in cochliomycin C (contains an extra "Cl" atom at C_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 $C_{1'}$-$C_{2'}$ 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 **3**. It was envisioned that as Julia-Kocienski (JK) olefination is known to be very efficient in generating *E*-alkene selectively, the internal "*E*" double bond between $C_{1'}$-$C_{2'}$ could be achieved by JK-olefination between sulfone **4** and aldehyde **5** to furnish compound **3**. Aldehyde **5** could be accessed from commercially available 3,5-dihydroxy benzoic acid (**7**). Wittig reaction or Z-selective JK-olefination between enantiopure aldehyde **10** and **9/8** should lead to olefinic compound **7** which upon substrate directed dihydroxylation and acetonide protection was thought to produce compound **4**. Compound **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 **8** and phosphonium salt **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)

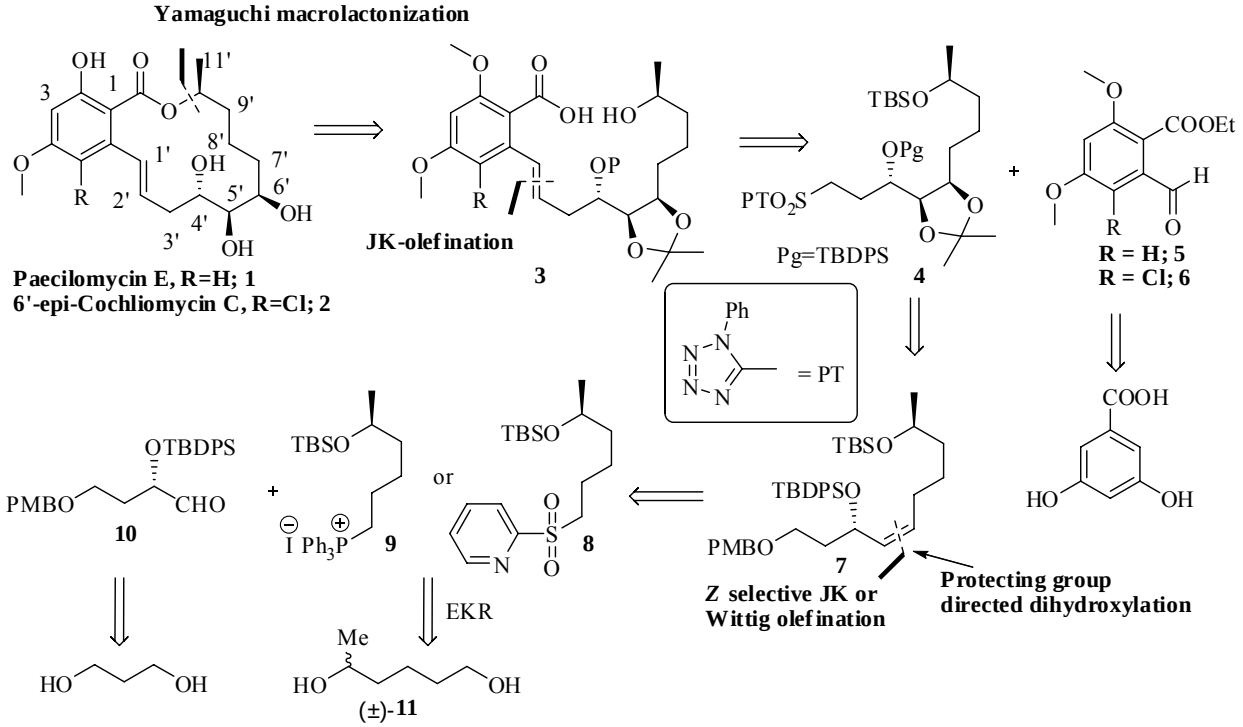


1. Julia-Kocienski or Cross metathesis for cochliomycin A (Ref: 11, 13c)
2. RCM for cochliomycin B (13b)

1.RCM for paecilomycin E and congeners (Ref: 12a-b; 13a)
2. RCM for cochliomycin A (Ref: 11)
3. Suzuki for cochliomycin B (Ref: 13b)
4. Stille for cochliomycin A (Ref: 13c)

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 ($C_{7'}$-$C_{8'}$) in case of cochliomycin A and B

Present work



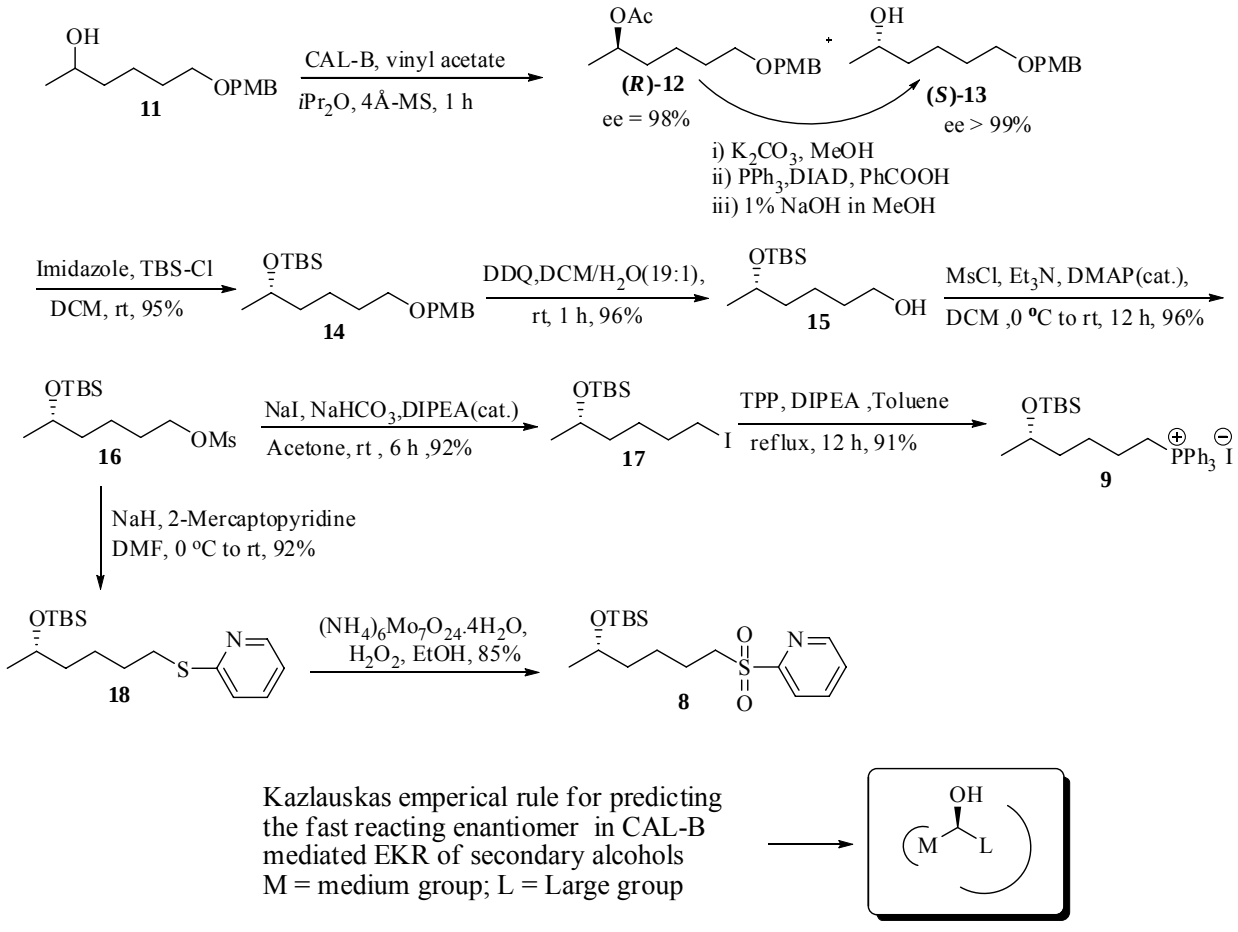
Scheme 1: Retrosynthetic analysis of Paecilomycin E and related RALs.

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**).[12a] 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

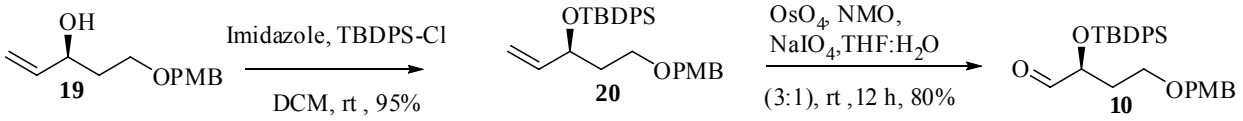
12 (yield = 48%, ee = 98%) and (*S*)-alcohol **13** (yield = 48% , ee > 99%) according to Kazlauskas empirical rule.[14] The unwanted acetate **12** was then hydrolysed with 1% NaOH in MeOH and the resulting alcohol was inverted by applying Mitsunobu inversion strategy to give desired compound (*S*)-**13** (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 [15] furnished the primary alcohol **15** which is then subsequently converted to its corresponding methanesulfonate **16**, by treatment with Ms-Cl (methanesulfonyl chloride) and Et_3N. 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). [16]



Scheme 2: Synthesis of the sulphone **8** and phosphonium salt **9**.

The iodo compound **17** was then refluxed with Ph_3P in toluene along with Hunig's base (DIPEA) to furnish the Wittig salt **9** in 91% yield. [17] 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 S_N2 reaction and subsequent Mo(IV)-catalyzed oxidation [18] 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**.[19] TBDPS protection of this alcohol with TBDPS-Cl and imidazole afforded compound **20** in 95% yield. Dihydroxylation and oxidative cleavage of olefin under Lemiux-Johnson condition of compound **20** afforded the aldehyde **10** in a single pot operation with 80% yield (Scheme 3). [20]



Scheme 3: Synthesis of aldehyde **10** .

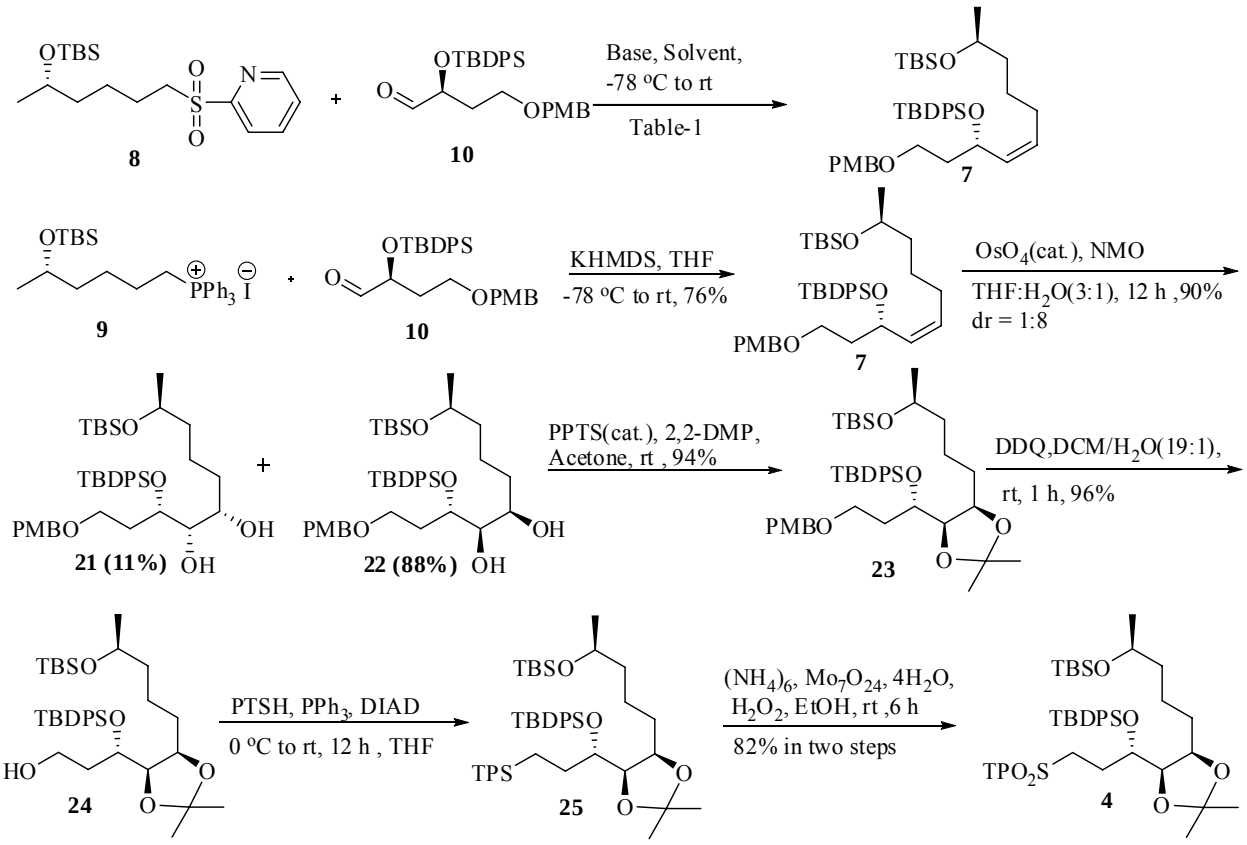
Synthesis of the sulfone 4: For the "*Z*"-selective JK-olefination reaction,[21] initially 2-pyridylsulfone **8** was reacted with aldehyde **10** under different reaction conditions (different solvent and different bases) but to our utter disappointment the desired "*Z*" olefinic compound **21** was 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. [22] 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 $A^{1,3}$-strain as a deciding factor. [23] 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-1*H*-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**

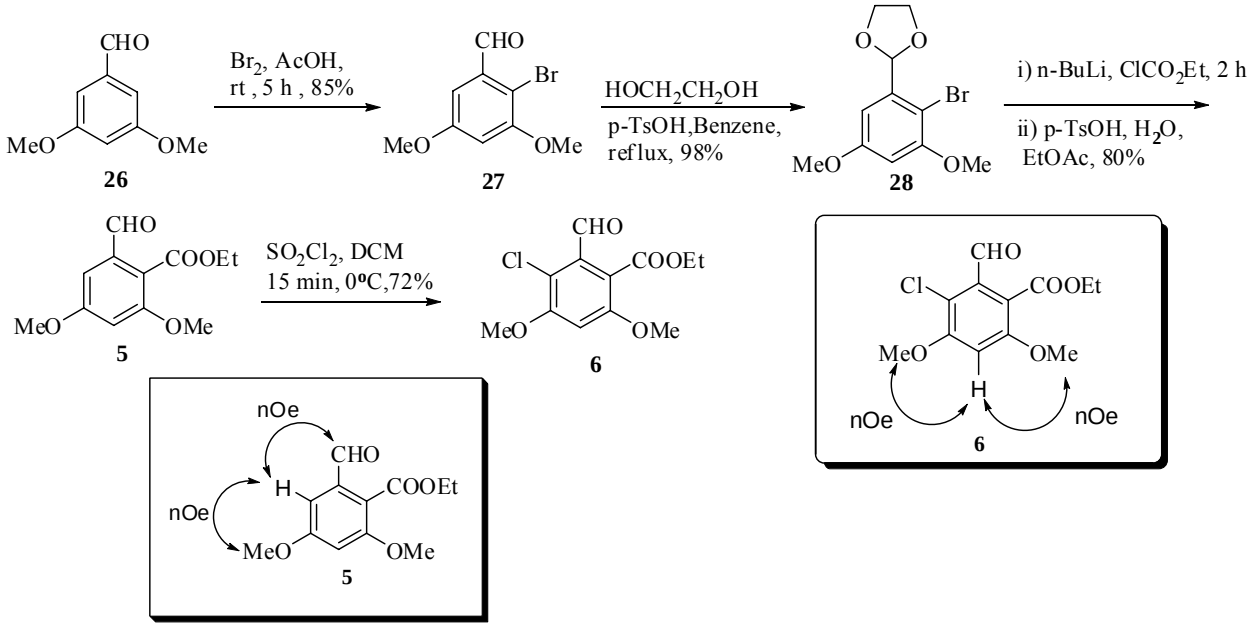
Entry	Sulfone	Aldehyde	Base	Temperature (^{o}C)	Solvent	Yield (%)
1	**8**	**10**	KHMDS	-78	Toluene	~5
2	**8**	**10**	KHMDS	0	THF	nr [a]
3	**8**	**10**	KHMDS	-78	THF	~8
4	**8**	**10**	KHMDS	-78	THF/HMPA [b]	~8
5	**8**	**10**	KHMDS	-78	THF/DMPU [c]	~5
6	**8**	**10**	NaHMDS	-78	Toluene	nr [a]
7	**8**	**10**	NaHMDS	-78	THF	nr [a]
8	**8**	**10**	LiHMDS	-78	Toluene	nr [a]
9	**8**	**10**	LiHMDS	-78	THF	nr [a]
10	**8**	**10**	nBuLi	-78	THF/HMPA [b]	~5

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.

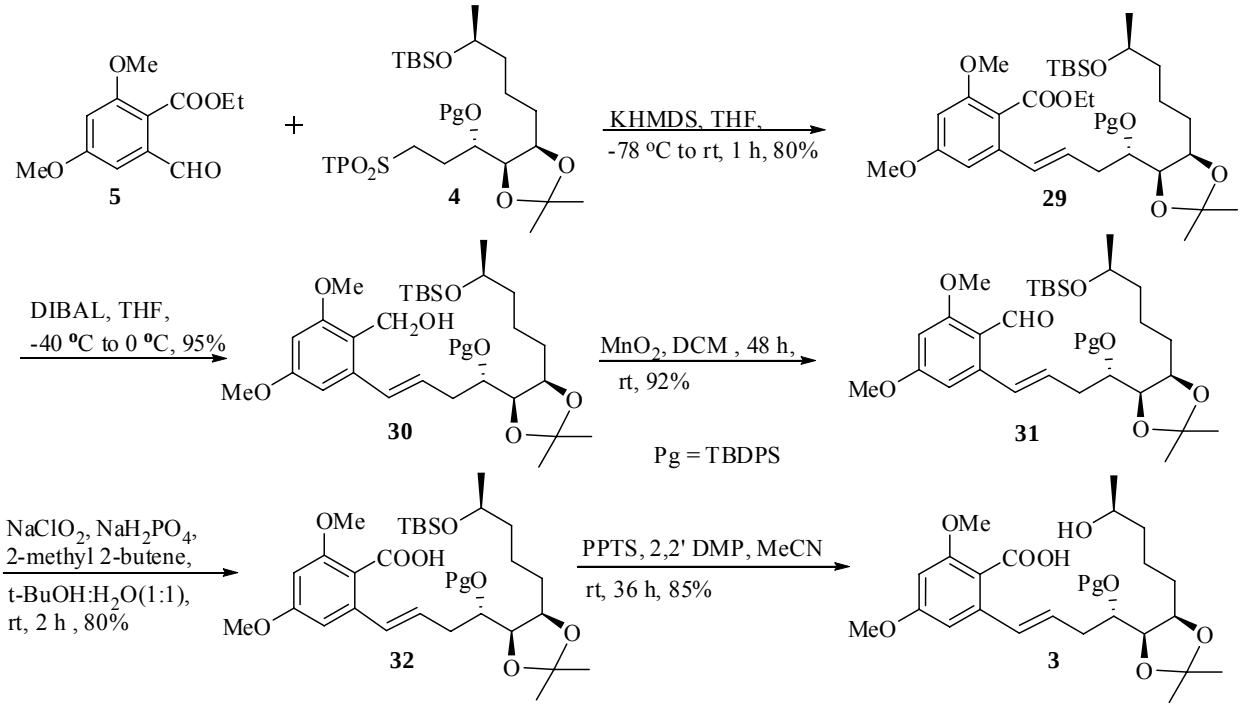
Synthesis of the highly functionalized aromatic aldehyde 5 and corresponding "Cl" derivative 6: The synthesis was initiated from known 3,5-dimethoxybenzaldehyde (**26**). Regioselective electrophilic bromoination of **26** was performed using Br_2 in AcOH to afford compound **27** in 85% yield as a sole 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 SO_2Cl_2 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 (^{1}H-NMR spectrum; see the supporting information).



Scheme 5: Synthesis of aldehyde **5** and **6**.

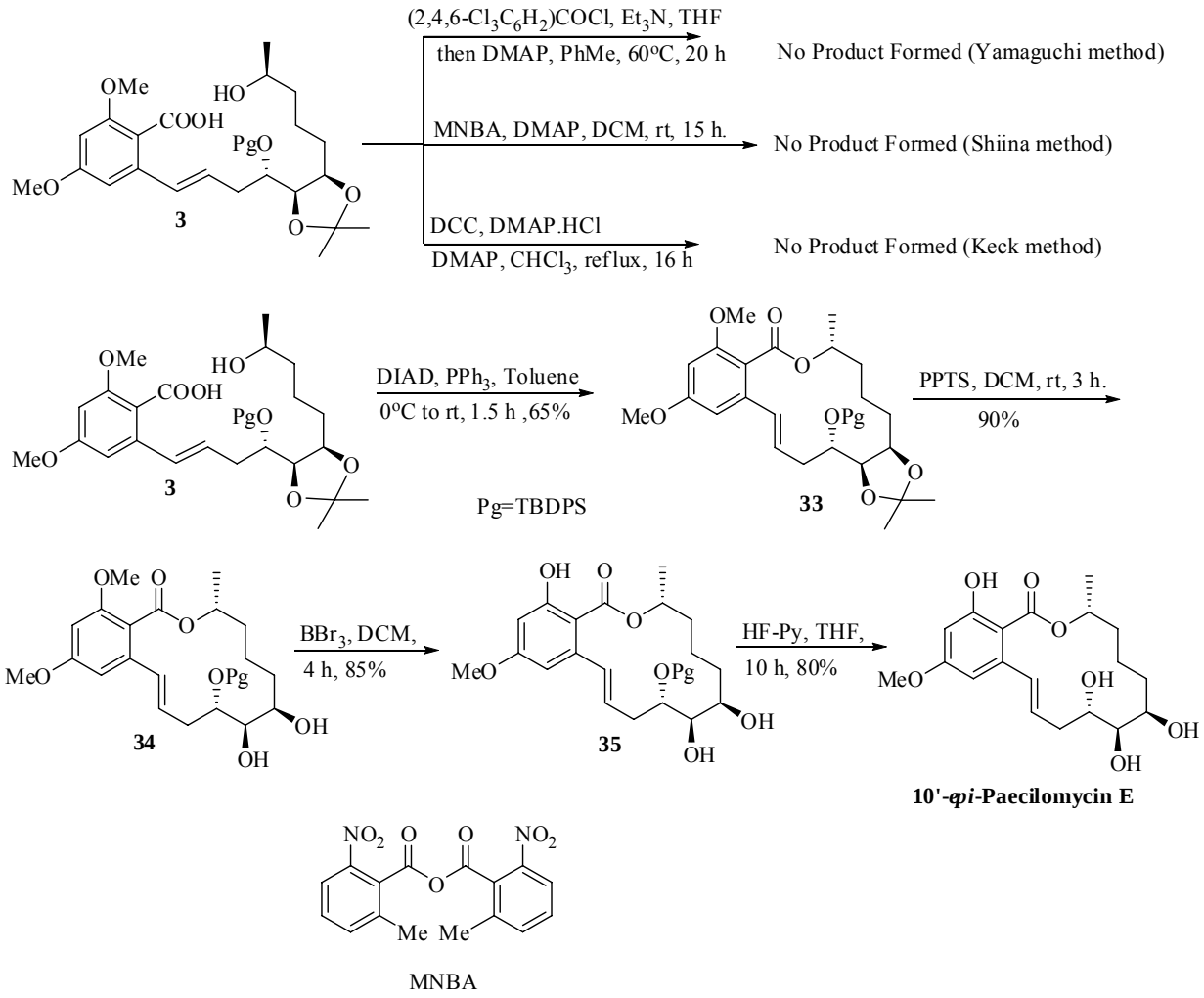
Fragment assembly for the synthesis of the seco-acid 3: The sulfone (**4**) was now reacted with the aromatic aldehyde **5** in presence KHMDS at -78^{o}C to afford the *trans* olefin **29** exclusively in 80% yield. Attempted hydrolysis of the ester functionality in compound **29** was a bit problematic 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 ^{t}BuOK in THF as an alternate reagent only removes the TBDPS group in 2h without affecting the CO_2Et functionality (Scheme 7). We assume that due to presence of two -OMe groups in the aromatic ring (*o* and *p* to -CO_2Et 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 MnO_2 [26] 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).



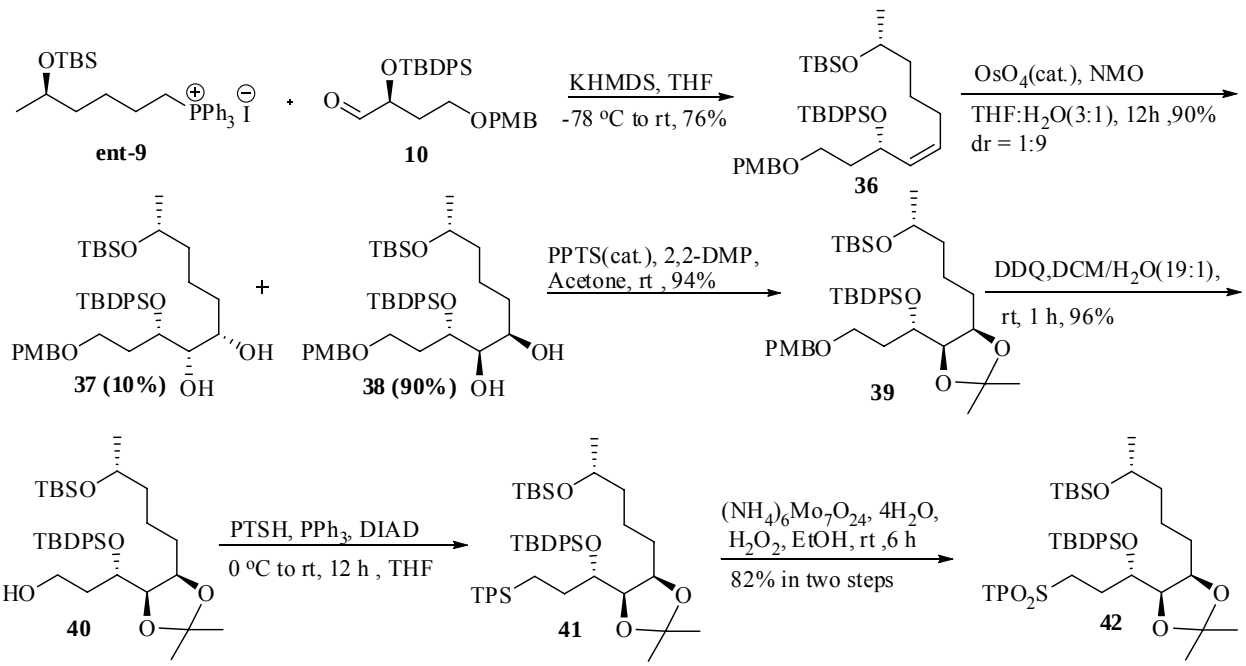
Scheme 6: Synthesis of the seco-acid 3.

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,[28] Shiina macrolactonization,[29] Keck macrolactonization [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). [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_3 [32] afforded compound **35** in 85% yield. Compound **35** was then treated with HF-Pyridine [33] in THF for 10 h to furnish the 10′-*epi*-paecilomycin E in 80% yield (Scheme 7; overall yield is 3.5% from 1,5 hexane diol and 13.5% from compound **19**).



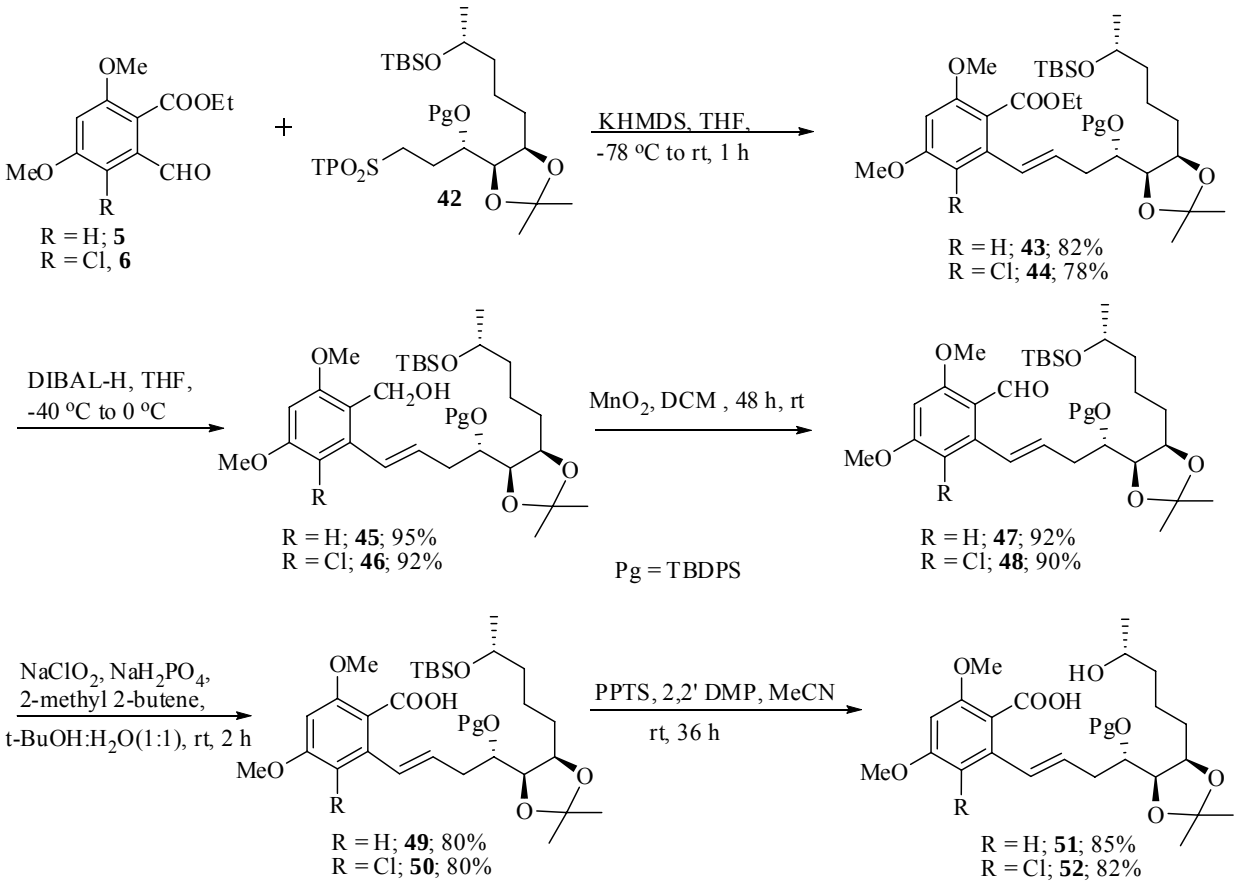
Scheme 7: Synthesis of 10´-epi-paecilomycin E.

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 $-CO_2Et$ functionality with DIBAL-H afforded the benzyl alcohols **45** and **46**, and subsequent oxidation with activated MnO_2 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).

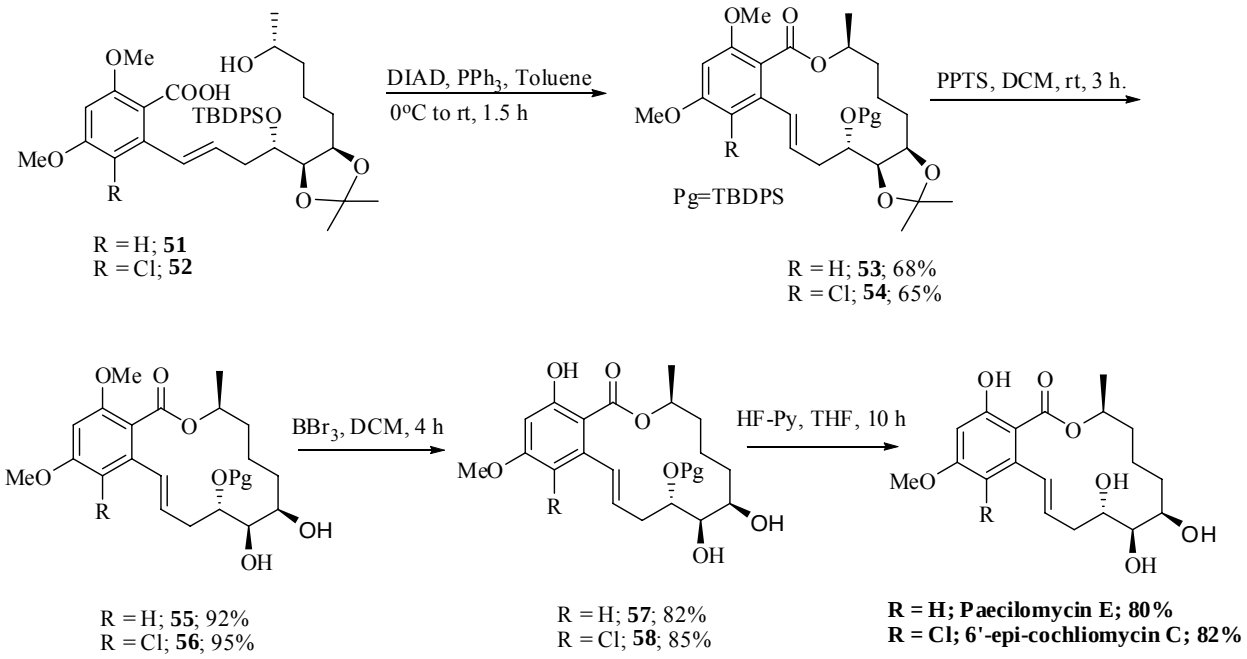


Scheme 9: Synthesis of the seco-acids **51** and **52**.

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. Acetonide deprotection and selective demethylation with BBr_3 furnished the compounds **57** and **58**, which on desylilation 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 $CDCl_3$ solvent. We have also recorded the ^{1}H-NMR spectrum of paecilomycin E and 6′-epi-cochliomycin C in acetone (d_6) as a solvent, and we observe sharp resolution in the corresponding spectrum (see the supporting information) when compared to the spectrum obtained in $CDCl_3$.

Table 2: Comparison of ^{1}H and ^{13}C NMR data for Paecilomycin E

	^{1}H NMR (δ and *J* in Hz)			^{13}C NMR (δ)	
Position	Natural (400 MHz in $CDCl_3$)	Synthetic (400 MHz in $CDCl_3$)	Synthetic (600 MHz in Acetone-d_6)	Natural (100 MHz in $CDCl_3$)	Synthetic (100 MHz in $CDCl_3$)
1				103.9	103.9
2				164.0	164.0
3	6.38 s	6.37 s	6.51 d (2.4)	100.2	100.1
4				165.9	165.6
5	6.38 s	6.37 s	6.43 d (2.4)	108.6	108.6
6				143.0	142.9
7				171.3	171.3
1′	7.20 dd (15.4, 1.6)	7.19 dd (15.2, 1.2)	7.24 dd (15.6, 1.2)	128.3	128.3
2′	5.75 ddd (15.4, 10.6, 3.0)	5.27 s	5.99 ddd (15, 10.8, 3.6)	134.5	134.5
3′	2.75 dt (14.6, 10.8), 2.63 m	2.72 s , 2.64 s	2.85-2.84 m, 2.53-2.50 m	39.0	38.9
4′	4.17 m	4.16 s	4.12 s	77.3	77.3
5′	3.67 br d (3.5)	3.67 br s	3.74 s	71.3	71.3
6′	3.93 dd (10.7, 6.4)	3.92 s	3.97 s	76.0	75.9
7′	1.71-1.86 m	1.77-1.73 m	1.79 m	33.8	33.8
8′	1.66 m, 1.42 m		1.67-1.71 m	21.1	21.1
9′	1.71-1.86 m		1.79-1.85 m	35.8	35.8
10′	5.00 m	4.99 s	5.09-5.06 m	74.1	74.1
11′	1.40 d (6.1)	1.40 s	1.44 d (6)	20.5	20.4
4-OMe	3.79 s	3.78	3.98	55.4	55.4
2-OH	12.00 br s	12.00 br s	12.10 br s		



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*-stereoseletive 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_2Cl_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, δ), downfield from

tetramethylsilane (TMS, δ = 0.00 ppm), and are referenced to residual solvent ($CDCl_3$, δ = 7.26 ppm (^1H), 77.16 ppm (^{13}C) and CD_3COCD_3, 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)

(5*S*,11*S*,*Z*)-5-(2-(4-methoxybenzyloxy)ethyl)-2,2,11,13,13,14,14-heptamethyl-3,3-diphenyl-4,12-dioxa-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. NH_4Cl 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 $MgSO_4$ and concentrated under reduced pressure. Purification by means of flash column chromatography (EtOAc/hexane = 1:40) furnished the *Z*-alkene **7** as colorless oil (2.71 g, 4.1 mmol) in 76% yield.

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

^1H NMR (200 MHz, $CDCl_3$): 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).

^{13}C NMR (50 MHz, $CDCl_3$): 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.

$[\alpha]_D^{28}$ = 12.16 (c = 1.16, $CHCl_3$).

HRMS (ESI) for $C_{40}H_{60}O_4Si_2Na$ $[M + Na]^+$, calculated: 683.3927, found: 683.3920.

(5*S*,6*R*,7*R*,11*S*)-5-(2-(4-methoxybenzyloxy)ethyl)-2,2,11,13,13,14,14-heptamethyl-3,3-diphenyl-4,12-dioxa-3,13-disilapentadecane-6,7-diol (22) and (5*S*,6*S*,7*S*,11*S*)-5-(2-(4-methoxybenzyloxy)ethyl)-2,2,11,13,13,14,14-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 ºC. To this solution NMO (1.4 g, 12.3 mmol) and 0.05 M solution of OsO_4 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. Na_2SO_3 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 $MgSO_4$ 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.

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

^{1}H NMR of compound **22** (400 MHz, $CDCl_3$): 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).

^{13}C NMR of compound 22 (50 MHz, $CDCl_3$): 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.

$[\alpha]_D^{28}$ = 11.1 (c = 0.8, $CHCl_3$).

HRMS (ESI) for $C_{40}H_{62}O_6Si_2Na$ $[M + Na]^+$, calculated: 717.3982, found: 717.3973.

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

^{1}H NMR of compound **21** (400 MHz, $CDCl_3$): δ: 7.71-7.66 (m, 4H), 7.46-7.36 (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, $CDCl_3$): δ: 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 $C_{40}H_{62}O_6Si_2Na$ $[M + Na]^+$, calculated: 717.3982, found: 717.3988.

tert-butyl((*S*)-1-((4*R*,5*R*)-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, $CDCl_3$): δ: 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, $CDCl_3$): δ: 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 $C_{43}H_{66}O_6Si_2Na$ $[M + Na]^+$, calculated: 757.4295, found: 757.4283.

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

Compound **23** (4.47 g, 6.1 mmol) was dissolved in 24 mL of CH_2Cl_2/ phosphate buffer (pH = 7; 19:1) and the solution was cooled to 0 ºC. 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_2Cl_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 $C_{35}H_{58}O_5Si_2Na$ $[M + Na]^+$, calculated: 637.3720, found: 637.3711.

5-((*S*)-3-((4*R*,5*R*)-5-((*S*)-4-(*tert*-butyldimethylsilyloxy)pentyl)-2,2-dimethyl-1,3-dioxolan-4-yl)-3-(*tert*-butyldiphenylsilyloxy)propylthio)-1-phenyl-1*H*-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, 8.37mmol) 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, $CDCl_3$): δ: 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, $CDCl_3$): δ: 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 $C_{42}H_{62}N_4O_4SSi_2Na$ $[M + Na]^+$, calculated: 797.3927, found: 797.3935.

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

To a stirring solution of sulfide **25** (4.3 g, 5.55 mmol) in ethanol (60 mL) was added a mixture of $(NH_4)_6Mo_7O_{24}.4H_2O$ (1.236 g, 1.0 mmol) and 30% H_2O_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% $Na_2S_2O_3$ 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, $CDCl_3$): δ: 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, $CDCl_3$): δ: 153.5, 136.1, 135.9, 133.3, 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 $C_{42}H_{62}N_4O_6SSi_2Na$ $[M + Na]^+$, calculated: 829.3826, found: 829.3815.

Ethyl 2-((*S*,*E*)-4-((4*R*,5*R*)-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 NH_4Cl and extracted with diethyl ether (150 mL). The organic layer was washed with brine solution and dried with anhydrous $MgSO_4$ 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, 1:10).

^{1}H NMR of compound **29** (400 MHz, $CDCl_3$): 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 (copm. 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).

^{13}C NMR of compound **29** (50 MHz, $CDCl_3$): 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.

$[\alpha]_D^{28}$ = 25.3 (c = 0.1, $CHCl_3$).

HRMS (ESI) for $C_{47}H_{70}O_8Si_2Na$ $[M + Na]^+$, calculated: 841.4506, found: 841.4495.

(2-((*S*,*E*)-4-((4*R*,5*R*)-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

$MgSO_4$ 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_f = 0.20 (EtOAc/hexane, 1:10).

^{1}H NMR of compound **30** (400 MHz, $CDCl_3$): 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 (m, 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).

^{13}C NMR of compound **30** (50 MHz, $CDCl_3$): 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, 29.9, 28.4, 27.2, 26.1, 23.8, 22.9, 22.3, 19.6, 18.3, 14.3, -4.2, -4.5.

$[\alpha]_D^{28}$ = 31.0 (c = 0.1, $CHCl_3$).

HRMS (ESI) for $C_{45}H_{68}O_7Si_2Na$ $[M + Na]^+$, calculated: 799.4401, found: 799.4393.

2-((*S*,*E*)-4-((4*R*,5*R*)-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 CH_2Cl_2 (7 mL) was added activated MnO_2 (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 CH_2Cl_2. The organic solvent was dried over anhydrous $MgSO_4$ 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_f = 0.25 (EtOAc/hexane, 1:10).

^{1}H NMR of compound **31** (400 MHz, $CDCl_3$): δ: 10.41(s, 1H), 7.71-7.62 (m, 4H), 7.40-7.33 (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).

^{13}C NMR of compound **31** (50 MHz, $CDCl_3$): 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, $CHCl_3$).

HRMS (ESI) for $C_{45}H_{66}O_7Si_2Na$ $[M + Na]^+$, calculated: 797.4244, found: 797.4249.

2-((*S*,*E*)-4-((4*R*,5*R*)-5-((*S*)-4-(*tert*-butyldimethylsilyloxy)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 *t*BuOH (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 $NaClO_2$ (80% purity, 747 mg, 10 mmol) and NaH_2PO_4 (691 mg, 7 mmol) in H_2O (2 mL). After two hours the yellow biphasic reaction mixture was poured onto H_2O (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 $MgSO_4$ 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, $CDCl_3$): 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, $CDCl_3$, 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 .

$[\alpha]_D^{28}$ = 29.7 (c = 0.1, $CHCl_3$).

HRMS (ESI) for $C_{45}H_{66}O_8Si_2Na$ $[M + Na]^+$, calculated:813.4193, found: 813.4181.

2-((*S*,*E*)-4-(*tert*-butyldiphenylsilyloxy)-4-((4*R*,5*R*)-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 ºC. 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 $MgSO_4$ 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.

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

^{1}H NMR of compound **3** (400 MHz, $CDCl_3$): 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).

^{13}C NMR of compound **3** (100 MHz, $CDCl_3$): δ: 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 .

$[\alpha]_D^{28}$ = 21.7 (c = 0.1, $CHCl_3$).

HRMS (ESI) for $C_{39}H_{52}O_8SiNa$ $[M + Na]^+$, calculated: 699.3328, found: 699.3319.

(3a*R*,7*R*,17*S*,17a*R*,*E*)-17-(*tert*-butyldiphenylsilyloxy)-10,12-dimethoxy-2,2,7-trimethyl-4,5,6,7,17,17a-hexahydro-3a*H*-benzo[c][1,3]dioxolo[4,5-i][1]oxacyclotetradecin-9(16*H*)-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 N_2 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.

R_f = 0.40 (EtOAc/hexane, 1:5).

^{1}H NMR of compound **33** (400 MHz, $CDCl_3$): 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).

^{13}C NMR of compound **33** (100 MHz, $CDCl_3$): 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 $C_{39}H_{50}O_7SiNa$ $[M + Na]^+$, calculated:681.3223, found: 681.3218.

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

To a stirring solution of macrolide **33** (59 mg, 0.09 mmol) in anhydrous CH_2Cl_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, $CDCl_3$): δ: 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, $CDCl_3$): δ: 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 $C_{36}H_{46}O_7SiNa$ $[M + Na]^+$, calculated:641.291, found: 641.283.

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

Compound **34** (30 mg, 0.04 mmol) was dissolved in anhydrous CH_2Cl_2 (1.5 mL) and BBr_3 (0.08 mL, 1M, 0.08 mmol, dissolved in 1 mL anhydrous CH_2Cl_2) was added during 5 minute at 0º C under N_2 atmosphere. The reaction mixture was then stirred for 4 h at 0º C. After that water (10 mL) and CH_2Cl_2 (20 mL) was added and the organic layer was separated. The aqueous phase was extracted with additional CH_2Cl_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).

^{1}H NMR of compound **35** (400 MHz, $CDCl_3$): δ: 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).

^{13}C NMR of compound **35** (100 MHz, $CDCl_3$): δ: 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 $C_{35}H_{44}O_7SiNa$ $[M + Na]^+$, 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.

^{1}H NMR of **10'-*epi*-Paecilomycin E** (400 MHz, $CDCl_3$): δ: 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).

^{13}C NMR of **10'-*epi*-Paecilomycin E** (100 MHz, $CDCl_3$): δ: 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 $C_{19}H_{26}O_7Na$ $[M + Na]^+$, calculated:389.1576, found: 389.1572.

(3a*R*,7*S*,17*S*,17a*R*,*E*)-17-(*tert*-butyldiphenylsilyloxy)-10,12-dimethoxy-2,2,7-trimethyl-4,5,6,7,17,17a-hexahydro-3a*H*-benzo[c][1,3]dioxolo[4,5-i][1]oxacyclotetradecin-9(16*H*)-one (53)

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

^{1}H NMR of compound **53** (400 MHz, $CDCl_3$): 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).

^{13}C NMR of compound **53** (100 MHz, $CDCl_3$): 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.

$[\alpha]_D^{28}$ = -11.7 (c = 0.01, $CHCl_3$).

HRMS (ESI) for $C_{39}H_{50}O_7SiNa$ $[M + Na]^+$, calculated:681.3223, found: 681.3215.

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

Compound **53** was converted to **55** in 92% yield by PTSA in CH_2Cl_2 as described previously.

^{1}H NMR of compound **55** (400 MHz, $CDCl_3$): 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).

^{13}C NMR of compound **55** (100 MHz, $CDCl_3$): δ: 167.8, 161.4, 158.2, 138.1, 136.6, 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.

$[\alpha]_D^{28}$ = -15.7 (c = 0.06, $CHCl_3$).

HRMS (ESI) for $C_{36}H_{46}O_7SiNa$ $[M + Na]^+$, calculated:641.291, found: 641.288.

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

Compound **55** was reacted with BBr_3 to afford compound **57** as described earlier in 82% yield.

^{1}H NMR of compound **57** (400 MHz, $CDCl_3$): δ: 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, $CDCl_3$): δ: 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 $C_{35}H_{44}O_7SiNa$ $[M + Na]^+$, calculated: 627.2753, found: 627.2747.

(3*S*,7*R*,8*R*,9*S*,*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, $CDCl_3$): δ: 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): δ: 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): δ: 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 $C_{19}H_{26}O_7Na$ $[M + H]^+$, calculated:367.1757, found: 367.1743.

(3a*R*,7*S*,17*S*,17a*R*,*E*)-17-(*tert*-butyldiphenylsilyloxy)-13-chloro-10,12-dimethoxy-2,2,7-trimethyl-4,5,6,7,17,17a-hexahydro-3a*H*-benzo[c][1,3]dioxolo[4,5-i][1]oxacyclotetradecin-9(16*H*)-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, $CDCl_3$): δ: 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, $CDCl_3$): δ: 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 $C_{39}H_{49}ClO_7SiNa$ $[M + Na]^+$, calculated:715.2833, found: 715.2825.

(3*S*,7*R*,8*R*,9*S*,*E*)-9-(*tert*-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]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, $CDCl_3$): δ: 7.70-7.69 (m, 4H), 7.44-7.38 (m, 6H), 6.40 (s,1H), 6.30m (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), 1.49-143 (m, 3H), 1.27 (d, *J* = 6.0 Hz, 3H), 1.04 (s, 9H).

^{13}C NMR of compound **56** (100 MHz, $CDCl_3$): δ: 167.4, 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 $C_{36}H_{45}ClO_7SiNa$ $[M + Na]^+$, calculated:675.2520, found: 675.2527.

(3*S*,7*R*,8*R*,9*S*,*E*)-9-(*tert*-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]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, $CDCl_3$): δ: 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.

$[\alpha]_D^{28}$ = -36.9 (c = 0.03, $CHCl_3$).

HRMS (ESI) for $C_{35}H_{43}ClO_7SiNa$ $[M + Na]^+$, calculated:661.2364, found:661.2363.

(3*S*,7*R*,8*R*,9*S*,*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.

$[\alpha]_D^{26}$ = -30.5 (c = 0.02, $CHCl_3$).

HRMS (ESI) for $C_{19}H_{25}ClO_7Na$ $[M + H]^+$, calculated:401.1367, found: 401.1360.

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