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First total synthesis of the proposed structure of pandangolide 1

Krishanu Show,[a] Rajesh G. Gonnade,[b] and Pradeep Kumar*[a]

Abstract: The first total synthesis of proposed structure of pandangolide 1 is reported via both organocatalytic as well as chiral pool approach. The required stereochemistry at C-3 and C-5 was installed by using organocatalytic aldol reaction and stereoselective keto reduction. The construction of the 12-membered core was achieved via MNBA-mediated Shiina lactonization method. The structure of target molecule was confirmed unambiguously by the single crystal X-ray analysis, though the optical rotation and NMR data of synthesized pandangolide 1 were found to be inconsistent with the proposed structure.

Introduction

Marine fungi, which have already proved to be a significant source of structurally novel and biologically active secondary metabolites are attracting increased attention as a potential source of new pharmaceuticals and pharmaceutical leads.[1] Among the isolated secondary metabolites, 12-membered macrolides are of special interest due to their exceptional biological activities and hence have been subject to chemical modifications for the determination of structure-activity relationship. The Gross structure of pandangolide 1 (**1**) and its isolation was first reported by Ireland *et al.*[2] Later, in 2004 Kobayashi *et al*. not only reported the isolation[3] of pandangolide 1 (**1**) and sporiolide A (**3**) and B (**4**) from cultured broth of *Cladosporium sp.* separated from Okinawan marine brown algae *Actinotrichia fragilis* and the Red Sea sponge *Niphates rowi* but also proposed the chemical structure of sporiolide A (**3**) and B (**4**).[4]

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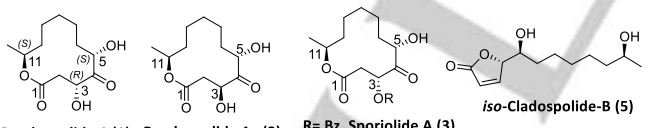

Figure 1. Structures of macrolides isolated from marine fungi *Cladosporium sp*.

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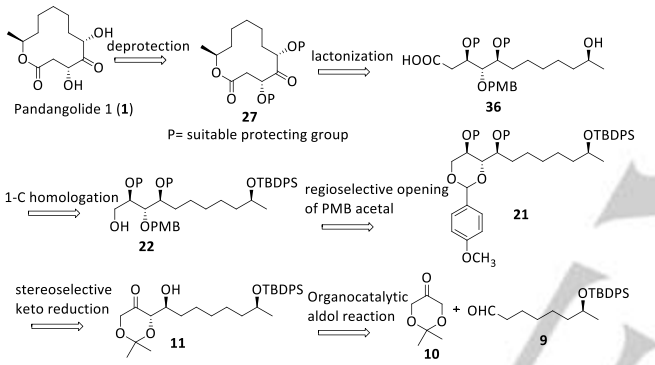
Supporting information for this article is given via a link at the end of the document.

But the absolute configuration of pandangolide 1(**1**) was not known until 2005, when Carmeli and co-workers reported the isolation as well as determination of complete stereostructure (by 1D and 2D NMR techniques and mass spectrometric data) of new hexaketide lactone pandangolide 1a (**2**), along with its known diastereomers pandangolide 1 (**1**) and *iso*-cladospolide B (**5**) from ethyl acetate extract of the same *Cladosporium sp.,* isolated from the Red Sea sponge *Niphates rowi*.[5a] The absolute configuration of the stereocentres was determined using Rigurera's method and circular dichroism. Later, Hartanti *et al.*[5b] and W.C. Tayone[5c] also reported the isolation of pandangolide 1 (**1**) from the culture broth of *Cladosporium oxysporum* and *L. brunneola fungus* respectively.

As a part of a research program directed towards the synthesis of biologically important natural products containing the lactone ring,[6] we became interested in the 12-membered natural macrolide not only for their diverse range of physiological activities (such as sporiolide A (**3**) and B (**4**) exhibit excellent cytotoxicity against murine lymphoma L1210 cell line with IC50 values of 0.13 and 0.81 µg /mL, respectively as well as very promising antifungal and antibacterial activity)[7] but also due to their unique molecular structure. If we scrutinize the structure of pandangolide 1 (**1**) and 1a (**2**), we can assume that presence of α-hydroxy keto stereocenters at 3- and 5-positions which are prone to epimerization, can lead to both the compounds from the same bio-precursor. Even a viable epimerization path can generate other possible stereoisomers at both 3- and 5-center, which might have different bioactivities. Apart from this, it is interesting to note that both pandangolide 1 (**1**) and 1a (**2**) and sporiolide A (**3**) and B (**4**), isolated from the same natural source have identical structures with substituent variation only at 3-position. However, to date neither a synthetic study nor a biological evaluation of pandangolide has been reported, although the structurally similar both sporiolide A (**3**) and B (**4**) have already been synthesized.[7] So, intrigued by all these observations, pandangolide 1 (**1**) was selected as the initial synthetic target anticipating its potential and unique bioactivity. Herein we describe the first total synthesis of proposed structure of pandangolide 1 (**1**) using organocatalytic aldol reaction and intramolecular lactonization as the key steps.

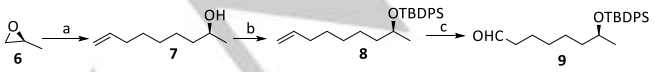
Results and Discussion

While devising a retrosynthetic route to the target pandangolide **1** (**1**), the choice of suitable protecting group for 3-hydroxy functionalities would be a necessary requirement. Keeping this in mind, we expected that the target molecule could be obtained from the final stage simultaneous double deprotection of suitably functionalized lactone **27** (P, indicates required protecting group) while lactone **27** could be prepared via intramolecular lactonization of seco-acid **36** (Scheme 1). The seco-acid **36** in turn could be obtained either from cyanation or one carbon homologation of compound **22**. The protected diol **22**, could be accessed by regioselective opening of PMB acetal **21**. The acetal compound that contains two of the required stereocenters of pandangolide **1** (**1**) could be obtained from stereoselective keto reduction of **11** whereas the hydroxy ketone **11** could be obtained from L-proline catalyzed aldol reaction between dioxanone **10** and aldehyde **9.**



Scheme 1. Retrosynthetic analysis of Pandangolide 1

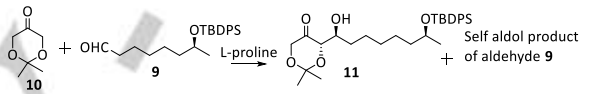
The synthesis of pandangolide 1 (**1**) began with the preparation of aldol partner dioxanone **10** and of aldehyde **9**. For the synthesis of aldehyde, the chiral *(S)*-propylene oxide **6** was regioselectively opened with Grignard reagent hex-5-enylmagnesium bromide (*in situ* prepared from 6-bromohex-1-ene and magnesium in THF) in the presence of CuI to afford secondary alcohol **7** in good yield, which was protected as its TBDPS ether **8** in 91% yield. The spectral and analytical data of **7** and **8** were in full accordance with the reported data.[8] Oxidative cleavage of **8** furnished the TBDPS-protected aldehyde **9** in 90% yield (Scheme 2). Meanwhile, dioxanone **10** was prepared from tris(hydroxymethyl)aminomethane hydrochloride in two steps following a literature procedure.[9]



Scheme 2. Reagents and conditions: (a) 6-bromohex-1-ene, Mg, THF, CuI, -30 °C, 4 h, 65%; (b) TBDPSCl, Imidazole, CH_2Cl_2, r.t., 5 h, 91%; (c) OsO_4, $NaIO_4$, dioxane-H_2O (3:1), 12 h, r.t., 90%.

With substantial amount of **9** and **10** in hand, efforts were focused on the crucial L-proline catalyzed diastereo- and enantioselective aldol reaction (Scheme 3).[10] All initial efforts using reported general conditions (such as stirring the reaction mixture using DMSO, DMF, $CHCl_3$ as solvent with different ratio of ketone and aldehyde) provided the desired hydroxy ketone **11** in low yield (Table 1, entries **1–7**). This is probably due to the unwanted self-aldol reaction of the reactive aldehyde. NMR analysis and HRMS data of the reaction mixture clearly indicated the formation of self-aldol product. After extensive experimentation, we observed that using 5 equiv. of ketone (with respect to aldehyde) and storing the reaction mixture (without stirring, using DMF as a solvent) at 4 °C for 3 days, the expected hydroxy ketone **11** could be successfully obtained in 65% yield with excellent diastereo- and enantiomeric excesses (de > 95% by NMR, ee = 97% by HPLC).

Table 1: Optimization for aldol reaction between 10 and 9

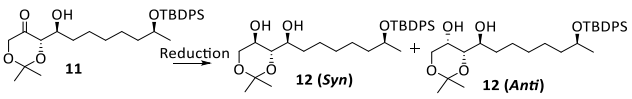


No.	Solvent	Ratio of 10 : 9	Temperature	Time: stirring(A)	Time: without stirring(B)	% yield of 11: A*	% yield of 11: B*
1.	DMF	2 : 1	0 °C	24 h	84 h	48	53
2.	DMF	3 : 1	0 °C	18 h	80 h	51	58
3.	DMF	5 : 1	0 °C	14 h	78 h	55	62
4.	DMF	6 : 1	0 °C	14 h	72 h	44	51
5.	DMF	5 : 1	4 °C	12 h	72 h	61	65
6.	DMSO	5 : 1	4 °C	12 h	70 h	50	52
7.	$CHCl_3$	5 : 1	4 °C	24 h	80 h	35	38

A* = yield of 11 (stirring condition)
B* = Yield of 11 (without stirring condition)

We then examined the diastereoselective reduction of hydroxy ketone **11** to afford *syn* diol **12**. After screening several reaction conditions (Table 2, entries **1–10**), reduction using L-selectride afforded the major *syn* diol **12** in 80% yield.

Table 2: Optimization for stereoselective keto reduction of aldol adduct 11

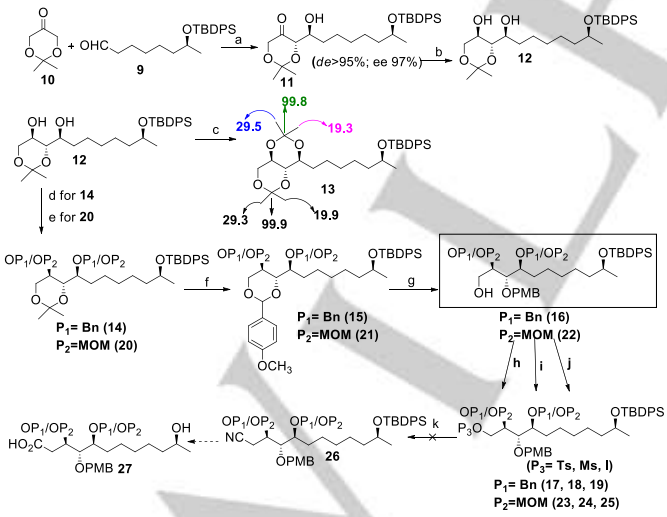


No.	Reagent	Condition	Ratio *syn* : *anti*[a]	(% yield)
1.	K-Selectride[b]	- 78 °C , THF	9 : 1	78
2.	LS-Selectride[b]	- 78 °C, THF	7.1 : 1	82
3.	L-Selectride[b]	- 78 °C, THF	19 : 1	80
4.	K-Selectride[c]/$LiBEt_3H$[d]	- 78 °C, THF	4 : 1	82
5.	$LiBH_4$	- 60 °C, THF	5 : 1	79
6.	$NaBH_4/CeCl_3.7H_2O$	-78 °C, MeOH	1.8 : 1	60
7.	$NaBH_4$[b]/$LiBEt_3H$[e]	- 78 °C, THF	2.5 : 1	78
8.	DIBAL-H	- 78 °C, THF	3.7 : 1	58
9.	$NaBH(OAc)_3$	- 20 °C, CH_2Cl_2, AcOH	11.5 : 1	65
10.	$Me_4NBH(OAc)_3$	- 40 °C, CH_3CN, AcOH	2 : 3	45

(a) determined by ^1H NMR
(b) -78 °C for 2 h. (c) -78 °C for 1 h (d) 0 °C for 1 h (e) r.t. for 1 h

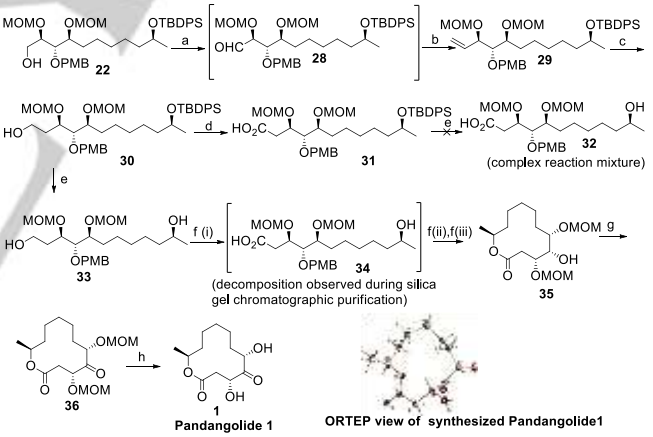
Meanwhile, to establish the *syn* relative configuration of the newly generated hydroxyl centre in **12,** we followed the Rychnovsky method.[11] Accordingly, the diol was protected with 2, 2-DMP in the presence of PPTS to give acetonide **13**. Analysis of the ^{13}C NMR spectrum of **13** revealed chemical shift of 19.3 and 29.5 ppm for the two methyl group and 99.8 ppm for the quaternary carbon, which correspond to *syn* acetonide (see supporting information page S-6).

The two free hydroxy groups in **12** represent the C-3 and C-5 functionalities in the target molecule, therefore their protection/deprotection can have an impact in successful synthesis as discussed earlier. So, having established the stereochemistry of newly generated centres, we further proceeded by protecting both the hydroxyl group of **12** as benzyl ether with benzyl bromide in the presence of NaH to give compound **14** in 79% yield. Acetonide cleavage of **14** using PPTS in methanol, followed by immediate protection of the diol as PMP-acetal using anisaldehyde dimethylacetal provided compound **15** in 71% yield. Regioselective opening of PMP-acetal **15** using DIBAL-H gave primary alcohol **16** in 70% yield. Next, we planned to substitute the activated hydroxy group of **16** to the required cyano group via S_N2 substitution. However, the reaction of corresponding tosylate (**17**), mesylate (**18**) and iodide (**19**) with different cyanating agents under various reaction conditions proved to be futile. This could probably be attributed to the steric hindrance around the leaving group caused by the adjacent bulky benzyl group which prevented the substitution reaction of activated hydroxy group with the cyanide ion.



Scheme 3. Reagents and conditions: (a) L-proline (30 mol %), DMF, 3 days, 4 °C, 65%; (b) L-Selectride, THF, 2 h, -78 °C, 80%; (c) 2,2-DMP, PPTS, CH_2Cl_2, r.t., 4 h, 88%; (d) BnBr, NaH, cat. TBAI, THF, r.t., 12 h, 79%; (e) MOMCl, DIPEA, CH_2Cl_2, 12 h, 85%; (f) (i) PPTS, MeOH, 12 h, r.t.; (ii) Anisaldehyde dimethylacetal, PPTS, CH_2Cl_2, 24 h, r.t., 71% for **15** and 82% for **21** (after 2 steps); (g) DIBAL-H, CH_2Cl_2, -78 °C, 3 h, 70% for **16** and 78% for **22**; (h) TsCl, NEt_3, CH_2Cl_2, 4 h, r.t., 85%; (i) MsCl, NEt_3, CH_2Cl_2, 1 h, r.t., 80%; (j) Ph_3P, I_2, Imidazole, toluene, 88%; (k) (i) KCN, DMF, r.t., 24 h; (ii) KCN, DMF, 100 °C, 24 h; (iii) KCN, DMSO, r.t., 48 h; (iv) KCN, DMSO,100 °C, 24 h; (v) KCN, 18-crown-6, toluene, 110 °C, 24 h; (vi) Bu_4NCN, toluene, 100 °C, 24 h; (vii) Bu_4NCN, DMF, 100 °C, 12 h.

To circumvent the above problem, we then decided to carry out one carbon homologation by olefination of the aldehyde **28** (*in situ* prepared by oxidation of primary alcohol **22**) as outlined in Scheme 4. Thus, oxidation of primary alcohol **22** using Dess-Martin periodinane gave aldehyde **28** which was immediately subjected to Tebbe olefintion to provide the terminal olefin **29** albeit in low yield (10%).[12] However, Wittig reaction using methylenetriphenylphosphorane (prepared from methyltriphenylphosphonium bromide and n-butyllithium) furnished **29** in 46% yield but with partial racemization. To our delight, the addition of aldehyde **28** to the rhodium catalyzed "salt free'' phosphorus ylide using Lebel protocol[13] (*in situ* generated from $TMSCHN_2$, 2-propanol, PPh_3 and $RhCl(PPh_3)_3$) produced the terminal olefin **29** in 66% yield without any racemization. Hydroboration-oxidation of **29** furnished the primary alcohol **30** in 70% yield. The alcohol obtained was oxidized using TEMPO/BAIB to the silyl protected seco-acid **31**. However, desilylation of compound **31** using TBAF (1.0 M in THF) gave only a complex reaction mixture under the basic reaction medium.



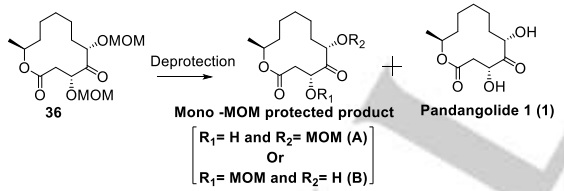
Scheme 4. Reagents and conditions: (a) Dess-Martin periodinane, CH_2Cl_2, r.t., 3 h; (b) $RhCl(Ph_3P)_3$,Ph_3P, 2-Propanol, $TMSCHN_2$, THF, 3 h, r.t., 66% (2 steps); (c) (i) 9-BBN, THF, 0°C to r.t., 4 h; (ii) H_2O_2/ NaOH, 0°C to r.t., 6 h, 70% (2 steps); (d) TEMPO, BAIB, CH_3CN/ H_2O (3:1), r.t., 6 h, 62%; (e) TBAF, THF, 4 h, r.t.; 85% for **33**; (f) (i) TEMPO, NaBr, nBu_4NBr, NaOCl, $NaHCO_3$, $NaClO_2$, 2-methyl-2-butene, r.t., 2 h; (f) (ii) MNBA, DMAP, CH_2Cl_2, r.t., 12 h; (f) (iii) DDQ, CH_2Cl_2/ H_2O (18:1), r.t., 45 min, 16% (3 steps); (g) Dess-Martin periodinane, CH_2Cl_2, r.t., 3 h; 88%; (h) 6 (M) HCl in THF, r.t., 24 h, 52%.

Therefore, we decided to reverse the order by carrying out the desilylation reaction first followed by selective oxidation of primary alcohol to acid to avoid exposure of seco-acid to the moderately basic TBAF conditions. Towards this end, desilylation of **30** using TBAF furnished the compound **33** in good yield. Selective oxidation of primary alcohol **33** employing Huang protocol[14] gave seco-acid **34** but it was

found to decompose during chromatographic purification using silica gel. So, we decided to use the crude seco-acid **34** directly for the next lactonization. We tried several lactonization protocols to find the best one. Eventually, after screening different reaction conditions (such as Yamaguchi mixed-anhydride method[15] or S-pyridyl ester lactonization method[16]), MNBA-mediated Shiina lactonization[17] protocol furnished the desired lactone along with unidentified impurities from which the required product could not be separated even after repeated chromatographic purification. However, this impurity did not interfere in the subsequent PMB deprotection with DDQ, affording compound **35** in 16% yield (over three steps). Oxidation of **35** with Dess-Martin periodinane gave ketone **36** in 85% yield.

Finally, the stage was set to deprotect both the MOM groups simultaneously. We studied its deprotection under several sets of reaction conditions (Table 3, entries **1–9**). We initially attempted at the TMSOTf-2,2'-Bipyridyl method,[18] which is one of the best deprotection methods known under mild conditions. However it gave only the mono-MOM deprotected lactone. Similar results were obtained when we treated the lactone **36** with TMSCl in MeOH and PPTS in ^{t}BuOH. Next, the deprotection with routine TFA in DCM and $BF_3.OEt_2$ in Me_2S method resulted into decomposition of starting material. Eventually the deprotection with HCl in dioxane produced the desired product only in 10% yield. Then the yield was improved to 23% by changing solvent from dioxane to 3 M HCl in THF. Finally increasing the concentration of HCl solution from 3M to 6 M afforded the target pandangolide 1 (**1**) as a white solid in 52% yield.

Table 3: Optimization for simultaneous double MOM deprotection of Lactone 36



No.	Reagent	Condition	Mono MOM (A/B)[b]	Pandangolide 1
1.	TMSOTf-2,2'-Bipyridyl in CH_2Cl_2[a]	0 °C , 0.5 h	55%	—
2.	$CeCl_3.7H_2O$ in CH_3CN/MeOH[a]	reflux, 4 h	30%	—
3.	TMSCl in MeOH	40 °C, 6 h	30%	—
4.	PPTS in ^{t}BuOH.	80 °C, 6 h	30%	—
5.	TFA in CH_2Cl_2	0 °C to r.t, 4 h	Starting material decomposed	
6.	$BF_3.OEt_2$ in Me_2S	-10 °C to r.t., 1 h	Starting material decomposed	
7.	HCl in dioxane	0 °C to r.t, 24 h	—	10%
8.	3 M HCl in THF	0 °C to r.t, 24 h	—	23%
9.	6 M HCl in THF	0 °C to r.t, 24 h	—	52%

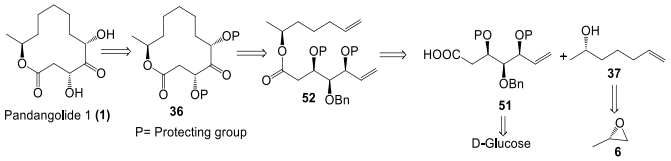
(a) Even excess use of reagent failed to deprotect both MOM groups.
(b) Mono -MOM deprotection was characterized by NMR, HRMS (but at this stage the exact regioisomer could not be determined)

Unfortunately, the optical rotation value and NMR spectra of synthetic pandangolide 1 (**1**) differ significantly from the data reported for isolated sample.[5a] For example, for the synthetic compound, the CH_2 of C-2 appeared at δ 2.82ppm (dd, *J*=10.7, 15.1 Hz, 1H) and 2.72 ppm (dd, *J*=3.6, 15.1Hz, 1H) respectively while the same methylene protons appeared at δ 3.15 ppm (dd, *J*=5.1, 19.2 Hz, 1H) and 3.30 ppm (dd, *J*=3.5, 19.2 Hz, 1H) for the isolated one. Furthermore, the chemical shift observed for CH of C-3 and CH of C-5 in synthetic compound are δ 4.76 (dd, *J*=3.5, 10.6 Hz, 1H), 4.90 (dd, *J*= 2.2, 6.7) whereas the same protons for natural compound were reported at δ 4.42 (dd, *J*=3.3, 5.1 Hz), 4.10 (dd, *J*=2.8, 7.8 Hz). Likewise, in the ^{13}C NMR spectrum of synthetic 1, carbon signals due to C-1, C-2, C-3, C-4, C-5 and C-11 appeared at δ 171.0, 38.9, 69.2, 210.5, 73.9, 72.5 ppm respectively, while the corresponding carbons for the natural sample were resonated at δ 175.3, 43.9, 66.9, 213.0, 77.4, 74.6 ppm respectively (for detailed comparison see supporting information, page S-20). In order to confirm the framework of our synthesized product, COSY, NOESY, HSQC and HMBC were carried out which clearly indicated the structure of macrocycle core moiety.

We feared the acidic deprotection condition might lead to the epimerization of one or both α-centers to ketone. As the final compound is solid, we chose to crystallize for single crystal X-ray analysis for unambiguous structure determination rather than Riguera's method employed by the isolation group.[5a] It is likely that following Riguera's method, the compound could undergo epimerization due to the addition of $Ba(ClO_4)_2$ salt (which may act as a Lewis acid also) during the NMR experiment itself. The good quality single crystal of synthesized pandangolide 1 (**1**) was obtained from the crystallization from methanol. The single crystal X-ray diffraction data collection was carried out with Cu (Cu Kα = 1.54178 Å) radiation which unambiguously determined the absolute configuration of Pandangolide 1 (**1**) and clearly established that our synthesized compound has (3*R*, 5*S*, 11*S*) configuration which exactly matched with proposed structure (Figure 2).[5a] The absolute configuration was established by anomalous dispersion effect (Flack parameter, 0.09(5)) in X-ray diffraction measurements (for details see supporting information; **CCDC No: 1506724**).

Figure 2. ORTEP view of synthesized pandangolide 1 drawn with 50% probability displacement ellipsoid and H-atoms are shown as small spheres of arbitrary radii.

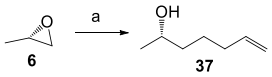
As the crucial macrolactonization step provided unsatisfactory yield, we decided to explore an alternate strategy for 1 (**1**). As outlined in Scheme **5,** we envisioned that the common penultimate lactone **36** could be prepared via ring closing metathesis (RCM) of diene ester **52** which in turn could be assembled from esterification of acid fragment **51** and alcohol fragment **37**. For the acid fragment **33** (protected at C-3 and C-5 position) D-glucose was identified as a suitable chiral precursor whereas the alcohol fragment **37** could be synthesized from chiral *(S)*-propylene oxide **6**.



Scheme 5. Retrosynthetic analysis for pandangolide 1 (**1**)

Synthesis of alcohol fragment 37:

For synthesis of the alcohol fragment, the chiral *(S)*-propylene oxide **6** was regioselectively opened with 3-butenyl magnesium bromide to afford the alcohol fragment **37** in 75% yield. The spectral and analytical data of **37** was in complete accordance with the reported data (Scheme 6).[19]

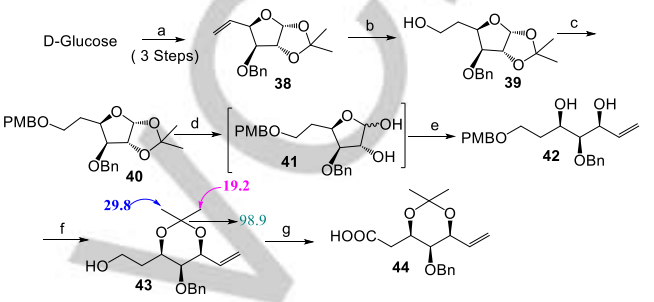


Scheme 6. Reagents and conditions: (a) butenyl bromide, Mg, CuI, -20 ^{o}C, 6 h, 75%.

Synthesis of acid fragment 44 (Route 1, Scheme 7):

The journey for synthesis of the acid fragment commenced from known olefin **38,** which was prepared from D-glucose diacetonide in 3 steps (Scheme 7).[20] Hydroboration-oxidation of olefin **38** using 9-BBN furnished the primary alcohol **39** in 76% yield. The primary hydroxyl group of **39** was protected as p-anisyl ether in the presence of NaH, PMBCl, and cat. TBAI to give compound **40** in 88% yield. Acidic hydrolysis of isopropylidene acetal **40** with acetic acid-water (3:2) gave an anomeric mixture of the hemiacetal **41**, which was immediately subjected to one carbon Wittig homologation using CH_2=PPh_3 (in situ generated from treatment of Ph_3PCH_3Br with n-BuLi) produced hydroxyl olefin **42** in 65% yield.

Relative *syn* stereochemistry of the newly generated stereogenic hydroxyl group at C-3 and C-5 position of compound **42** was determined by Rychnovsky method.[11] Accordingly, the diol was protected as its acetonide derivative, followed by simultaneous deprotection of PMB group to give compound **43**. Analysis of the ^{13}C NMR spectrum of **43** revealed chemical shift of 19.2 and 29.8 ppm for the two methyl groups and 98.9 ppm for the quaternary carbon, which correspond to *syn* acetonide (see supporting information S-31).

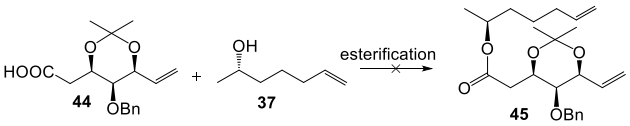


Scheme 7. Reagents and conditions: (a) Ref.20; (b) (i) 9-BBN, THF, 6 h, r.t.; (ii) NaOH-H_2O_2, 4 h, 76%; (c) PMBCl, NaH, TBAI, 6 h, r.t., 88%; (d) 60% AcOH-H_2O, r.t., 50 ^{o}C, 12 h; (e) PPh_3Br, nBuLi, 0^{o}C to r.t., 4 h, 65% (2 steps); (f) (i) 2,2-DMP, PPTS, CH_2Cl_2, r.t., 4 h, (ii) DDQ, CH_2Cl_2-H_2O (18:1); 0.5 h, r.t.63% (after 2 steps) (g) TEMPO/BAIB, CH_3CN-H_2O (3:1), 7 h, r.t., 69%.

Attempted esterification through coupling of acid fragment 44 and alcohol fragment 37 (Route 1, Scheme 8):

Apart from determination of relative stereochemistry of both the hydroxyl group at C-3 and C-5 position (which is *syn*), we wanted to take the advantage of this acetonide protection to complete the synthesis of acid fragment. Towards this end, compound **43** was subjected to one pot oxidation using 2,2,6,6-tetramethylpipridine-1-oxyl (TEMPO) and bis(acetoxy)iodobenzene (BAIB) in CH_3CN/H_2O (3:1) to furnish acid **44** in 69% yield.

But to our surprise, attempted esterification of acid **44** with alcohol **37** under known conditions (like Yamaguchi, Shiina, Steglich) was fruitless.



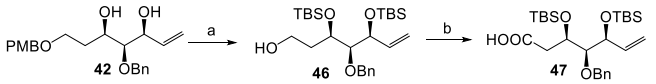
Scheme 8. Reagents and conditions: (a) 2,4,6-trichlorobenzoyl chloride, NEt_3, DMAP, CH_2Cl_2; (b) DCC, DMAP, CH_2Cl_2; (c) MNBA, NEt_3, DMAP, CH_2Cl_2.

The failure of this reaction could probably be attributed to the restricted mobility of acid moiety due to the presence of acetonide group.

Synthesis of acid fragment 47 (Route 2, Scheme 9):

In an alternative route to the esterification reaction, we considered revising the synthetic plan by protecting both the hydroxyl group as TBS ether. It was hoped that by

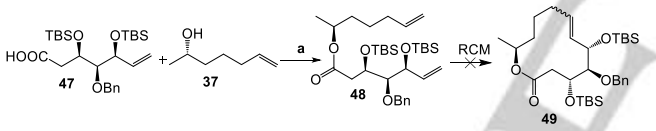
changing the cyclic acetonide to acyclic TBS ether, the rigidity of the acid moiety would diminish in order to perform the esterification reaction smoothly as well as at the final stage it could be deprotected easily. Thus, the protection of both hydroxyl groups as TBS ether followed by cleavage of PMB group with DDQ gave alcohol **46,** which was oxidized with TEMPO and BAIB to give acid **47** in 65% yield



Scheme 9. Reagents and conditions: (a) (i) TBSCl, Imidazole, CH_2Cl_2, 8 h; (ii) DDQ, CH_2Cl_2-H_2O (18:1); 0.5 h, r.t., 53% (after 2 steps) (b) TEMPO/BAIB, CH_3CN-H_2O (3:1), 7 h, r.t., 65%.

Attempted synthesis of pandangolide 1(1) by coupling of acid fragment (47) and alcohol fragment (37) through RCM (Scheme 10):

Esterification of acid **47** with alcohol **37** under Shiina's condition[17] gave diene ester **48** in only 30% yield (Yamaguchi and Steglich conditions gave only 10-15% yield). The diene ester was then subjected to the RCM reaction but unfortunately using variety of Grubbs' catalyst and different reaction condition (like using CH_2Cl_2, toluene, benzene solvent in different dilutions), we did not get our desired lactone **49**. Failure may be attributed to the steric hindrance of bulky TBS protecting groups and as per some

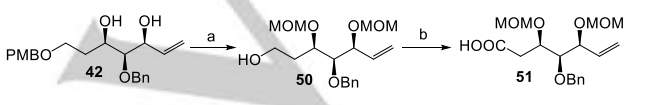


Scheme 10. Reagents and conditions: (a) 2-Methyl-6-nitrobenzoic anhydride, NEt_3, DMAP, CH_2Cl_2, 12 h, 30%.

literature precedences, the presence of bulky group in the vicinity of the RCM site might hinder the progress of the reaction thus disfavoring the RCM reaction. Moreover, replacement of TBS ether by relatively less bulky benzoate groups also failed to form the macrolide under same reaction conditions.

Synthesis of acid fragment 51 (Route 3, Scheme 11):

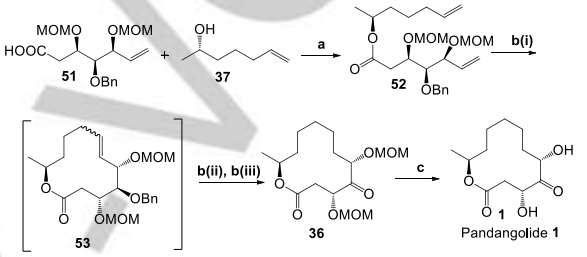
Finally, we decided to again protect the hydroxyl group of compound **42** as MOM ether. Towards this end, both the hydroxyl group of compound **42** was protected as MOM ether followed by deprotection of PMB group to give compound **50** in 80% yield. One- pot oxidation of **50** using TEMPO and BAIB afforded the desired acid **51** in 72% yield.



Scheme 11. (a) (i) MOMCl, DIPEA, 0 °C to r.t., 5 h, (ii) DDQ, CH_2Cl_2-H_2O (18:1), 0.5 h, r.t., 80% (2 steps); (b) TEMPO/BAIB, CH_3CN-H_2O (3:1), 7 h, r.t., 72%.

Completion of the synthesis of pandangolide 1 (1) by coupling of acid fragment (51) and alcohol fragment (37) through RCM (Scheme 12):

With both the cross coupling partners **51** and **37** in hand, the coupling of these two fragments using Shiina's esterification protocol provided diene ester **52** in 90% yield. Treating **52** with Grubb's II catalyst (10 mol%) in CH_2Cl_2 at reflux under high dilution (0.001M) led to crude lactone **53** (Scheme 12). The RCM reaction was little bit sluggish and also the separation of resulting lactone from the crude



Scheme 12. Reagents and conditions: (a) 2-Methyl-6-nitrobenzoic anhydride, NEt_3, DMAP, CH_2Cl_2, 12 h, 90%; (b) (i) Grubbs II catalyst (10 mol %), CH_2Cl_2, reflux, 24 h; (ii) H_2, Pd/C , MeOH, 8 h; (iii) Dess-Martin periodinane, CH_2Cl_2, 3 h, 57% (after 3 steps). (c) 6 M HCl in THF, r.t., 24 h, 52%.

reaction mixture was found to be difficult. Even after repeated chromatographic purification, it was always found to be contaminated with catalyst impurity. In this context, crude RCM reaction mixture **53** was directly subjected to hydrogenation. Thus hydrogenation of crude lactone **53** with Pd/C (10%) under H_2 atmosphere (with a balloon) reduced both benzyl and double bond, afforded the secondary alcohol accompanied by an unidentified impurity (both appears at same Rf). Oxidation of the secondary alcohol with Dess-Martin periodinane gave the ketone **36** in good yield (60% over 3 steps). Finally deprotection of lactone **36** under same condition (Table 3, entry **9**) provided the target pandangolide 1 (**1**) which was identical in every respect to the previous synthetic one (single crystal structure analysis also confirmed that the relative configuration at C-3 and C-5 are 3*R*, 5*S* with respect to the reference chiral center 11*S* at C-11, for details, see supporting information for details, see supporting information S23-S27).

After synthesizing proposed structure of pandangolide 1(**1**) by both strategies, we contacted the isolation group[5a] for the sample of natural product. The group expressed inability to provide the sample (due to unavailability of sample) and therefore we could not make the direct comparison of our synthesized compound with the isolated one. Since the NMR spectra of our synthetic material did not match with the spectra reported for the isolated one,

there is still a need to revisit the isolated natural product which could be a closely related isomer of pandngolide 1 (**1**).

Conclusions

In summary, we have efficiently synthesized the proposed structure of pandangolide 1 using both organocatalytic approah as well as chiral pool approach. The proposed structure of target molecule was unambiguously confirmed by single crystal X-ray analysis. Currently the screenings of various antifungal, antibacterial activity as well as cytotoxic activities against different cell lines using synthetic pandangolide 1 are under progress and will be reported in due course.

Experimental Section

General Experimental Methods:

All reactions were carried out under anhydrous conditions, using flame-dried glassware under a positive pressure of argon unless otherwise mentioned. CH_2Cl_2, Et_3N, and iPr_2NEt were distilled from CaH_2; Et_2O and THF was distilled from Na/benzophenone. Other reagents were obtained from commercial suppliers and used as received. Air sensitive reagents and solutions were transferred via syringe or cannula and were introduced to the apparatus via rubber septa. Reactions were monitored by thin layer chromatography (TLC) with 0.25 mm precoated silica gel plates (60 F254). Visualization was accomplished with either UV light, iodine adsorbed on silica gel, or by immersion in ethanolic solution of phosphomolybdic acid (PMA), p-anisaldehyde, or KMnO4 followed by heating with a heat gun for ~15 s. Flash chromatography was performed on silica gel (230−400 mesh). All ^{1}H NMR and ^{13}C NMR spectra were obtained using a 200, 400, or 500 MHz spectrometer in $CDCl_3$ or CD_3OD. Coupling constants were measured in Hertz. All chemical shifts were quoted in ppm, relative to TMS, using the residual solvent peak as a reference standard. The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, quin = quintet, m = multiplet, and br = broad. HRMS (ES+) were recorded on an ORBITRAP mass analyzer. Infrared (IR) spectra were recorded on a FT-IR spectrometer as thin films using NaCl plates, wave numbers are indicated in cm^{-1}. Optical rotations were measured using a polarimeter with a 1 dm path length. Chemical nomenclature was generated using Chem Bio Draw Ultra 14.0.

(*S*)-4-((1*S*,7*S*)-7-((tert-Butyldiphenylsilyl)oxy)-1-hydroxyoctyl)-2,2-dimethyl-1,3-dioxan-5-one (11):

To a stirred solution of dioxanone **10** (1.70 g, 13.08 mmol) and L-proline (0.09 g, 0.78 mmol) in DMF (10 mL) was added aldehyde **9** (1.00 g, 2.61 mmol) in one portion. The reaction mixture was stored at 4ºC under argon for 3 days. Progress of the reaction was monitored by TLC. To the reaction mixture cold water was added, extracted with Et_2O (3 × 20 mL) and the combined organic layers were washed with brine, dried over Na_2SO_4 and evaporated *in vacuo*. The crude product was purified by column chromatography (100-200 mesh silica gel, eluent: 30% EtOAc in pet ether) to give the aldol product **11** (0.871 g, 65%) as colourless liquid. (de> 98% by NMR, ee = 97% by HPLC, Chiralcel ODH, pet ether–iPrOH, 10: 90; major isomer 8.01 min, minor isomer 8.75 min). $[\alpha]_D^{25}$: –72.0 (c 2.0, $CHCl_3$); IR ($CHCl_3$, cm^{-1}) ν_{max}: 3545, 3029, 2934, 2860, 1732, 1323, 832, 756; ^{1}H NMR (500 MHz, $CDCl_3$):δ= 7.75 - 7.63 (m, 4 H), 7.47 - 7.30 (m, 6 H), 4.26 (d, J = 17.4 Hz, 1 H), 4.14 - 3.98 (m, 2 H), 3.85 (td, J = 5.7, 11.7 Hz, 2 H), 2.95 (br. s., 1 H), 1.64 - 1.57 (m, 2 H), 1.45 (s, 3 H), 1.48 (s, 3 H), 1.40 - 1.20 (m, 8 H), 1.06 (s, 12 H);^{13}C NMR (125 MHz, $CDCl_3$): δ = 211.2, 135.9, 135.6, 135.0, 134.6, 129.4, 129.3, 127.5, 127.4, 127.3, 100.9, 75.9, 70.5, 69.5, 66.7, 39.4, 32.1, 29.6, 27.0, 25.2, 24.9, 23.8, 23.5, 23.2, 19.3; HRMS (ESI) for $C_{30}H_{44}O_5NaSi$ $(M + Na)^+$ found 535.2855, calcd 535.2850.

(4*S*,5*R*)-4-((1*S*,7*S*)-7-((tert-Butyldiphenylsilyl)oxy)-1-hydroxyoctyl)-2,2-dimethyl-1,3-dioxan-5-ol (12):

To a stirred solution of **11** (0. 437 g, 0.85 mmol) in dry THF, L-selectride (1.02 mL, 1.0 M in THF, 1.02 mmol) was added dropwise at -78 °C and the reaction mixture was stirred for 2 h at same temperature. After completion of the reaction (TLC), reaction mixture was quenched with water, the organic layer was extracted with ether (4 × 20 mL) and dried over Na_2SO_4, then the solvent was removed under reduced pressure. The crude residue was purified by column chromatography (100-200 mesh silica gel, eluent: 45% EtOAc in pet ether) to give the product **12** (80% yield, 0.351 g) as colourless thick liquid. $[\alpha]_D^{25}$: –18.9 (c 5.8, $CHCl_3$); IR ($CHCl_3$, cm^{-1}) ν_{max}::3445, 3392, 3029, 2934, 2860, 1732, 1323, 832, 756; ^{1}H NMR (400 MHz, CDCl3): δ = 7.73 - 7.65 (m, 4 H), 7.47 - 7.33 (m, 6 H), 3.95 - 3.89 (m, 1 H), 3.87 - 3.76 (m, 2 H), 3.75 - 3.67 (m, 1 H), 3.63 (dd, J = 8.5, 11.3 Hz, 1 H), 3.49 - 3.41 (m, 1 H), 3.33 (br. s., 1 H), 2.24 (br. s., 1 H), 1.72 - 1.58 (m, 1 H), 1.55 - 1.48 (m, 1 H), 1.47 (s, 3 H), 1.45 - 1.39 (m, 2 H), 1.38 (s, 3 H), 1.35 - 1.16 (m, 6 H), 1.06 (s, 12 H);^{13}C NMR (100 MHz, CDCl3): δ= 135.9, 135.6, 134.9, 134.6, 129.5, 129.4, 129.3, 127.5, 127.4, 98.7, 75.6, 74.8, 69.5, 67.1, 64.1, 39.3, 33.3, 29.5, 28.2, 27.0, 26.9, 25.1, 24.8, 23.2, 19.6, 19.2; HRMS (ESI) for $C_{30}H_{46}O_5NaSi$ $(M + Na)^+$ found 537.3007, calcd 537.3005.

(5S,11S)-5-((4S,5R)-5-(Methoxymethoxy)-2,2-dimethyl-1,3-dioxan-4-yl)-11,14,14-trimethyl-13,13-diphenyl-2,4,12-trioxa-13-silapentadecane (20) :

To the precooled solution of **12** (0.140 g, 0.27 mmol) and DIPEA (0.38 mL, 2.18 mmol) in DCM (10 mL) at 0 ºC, MOMCl (0.08 mL, 1.08 mmol) was added slowly and the reaction mixture allowed to attain room temperature. The reaction mixture was stirred at room temperature for another 12 h at which time TLC showed the consumption of starting material. Then the solution was diluted with saturated NH_4Cl and extracted with DCM (4 x 10 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated *in vacuo* to furnish an crude oil, which was purified by column chromatography (100-200 mesh silica gel, eluent: 10% EtOAc in pet ether) to give the product **20** as a pale yellow liquid (0.139 g , 85%). $[\alpha]_D^{25}$: – 25.2 (c 1.2, $CHCl_3$); IR ($CHCl_3$, cm^{-1}) ν_{max}: 3031, 2909, 2245, 1523, 716; ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.74 - 7.63 (m, 4 H), 7.47 - 7.31 (m, 6 H), 4.85 - 4.76 (m, 1 H), 4.70 - 4.60 (m, 3 H), 4.02 - 3.78 (m, 3 H), 3.77 - 3.60 (m, 3 H), 3.40 (s, 3 H), 3.36 (s, 3 H), 1.66 - 1.48 (m, 4 H), 1.47 (s, 3 H), 1.39 (s, 3 H), 1.36 - 1.14 (m, 6 H), 1.11 - 0.99 (m, 12 H).^{13}C NMR (50 MHz, $CDCl_3$): δ = 135.8, 135.5, 134.9, 134.5, 129.4, 129.3, 127.5, 127.4, 127.3, 98.8, 96.33, 96.31, 77.6, 74.1, 71.1, 69.5, 63.1, 55.7, 39.4, 29.9, 29.6, 27.7, 27.0, 26.8, 26.2, 25.2, 23.2, 19.9, 19.2. HRMS (ESI) for $C_{34}H_{54}O_7NaSi$ $(M + Na)^+$ found 625.3532, calcd 625.3531.

(5S,11S)-5-((4S,5R)-5-(Methoxymethoxy)-2-(4-methoxyphenyl)-1,3-dioxan-4-yl)-11,14,14-trimethyl-13,13-diphenyl-2,4,12-trioxa-13-silapentadecane (21):

To a stirred solution of **20** (0.493 g, 0.82 mmol) in MeOH (10 mL) was added PPTS (0.021g, 0.08 mmol) and then stirred at room temperature

for 12h. After completion of the reaction, a saturated aq.$NaHCO_3$ solution (10 mL) was added to the reaction mixture and then concentrated under reduced pressure and extracted with CH_2Cl_2 (4 x 15 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. The crude diol was used for next step without purification.

To the solution of crude diol (0.410 g, 0.73 mmol) in dry CH_2Cl_2 (10 mL), anisaldehyde dimethylacetal (0.19 mL, 1.09 mmol) and PPTS (0.018 g, 0.07 mmol) was added and the reaction mixture was stirred at room temperature for 24 h. After completion of reaction the mixture was diluted with saturated aq.$NaHCO_3$ solution (10mL) and extracted with CH_2Cl_2 (3 x 15 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. The crude acetal was purified by column chromatography (100-200 mesh silica gel, eluent: 5% EtOAc in pet ether) to give the product **21** as colourless liquid (0.457 g , 82%). $[\alpha]_D^{25}$: –20.3 (c 1.0, $CHCl_3$); IR ($CHCl_3$, cm^{-1}) ν_{max}: 3130, 2869, 2245, 1603, 816; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.72 - 7.64 (m, 4 H), 7.45 - 7.33 (m, 8 H), 6.88 (d, J = 8.9 Hz, 2 H), 5.43 (s, 1 H), 4.84 (d, J = 6.7 Hz, 1 H), 4.69 (dd, J = 3.7, 6.7 Hz, 2 H), 4.67 - 4.62 (m, 1 H), 4.40 (dd, J = 5.0, 10.5 Hz, 1 H), 3.86-3.84 (m, 3 H), 3.80 (s, 3 H), 3.78 - 3.73 (m, 1 H), 3.68 - 3.60 (m, 1 H), 3.41 (s, 3 H), 3.38 (s, 3 H), 1.58 - 1.20 (m, 10 H), 1.06 (s, 12 H);^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.9, 135.8, 135.6, 134.9, 134.6, 130.3, 129.43, 129.4, 129.3, 127.5, 127.45, 127.4, 127.3, 113.5, 101.0, 96.7, 96.3, 81.9, 77.5, 70.0, 69.5, 68.7, 55.7, 55.6, 55.2, 39.4, 30.5, 29.6, 27.0, 26.8, 26.5, 25.2, 23.2, 19.2;HRMS (ESI) for $C_{39}H_{56}O_8NaSi$ $(M + Na)^+$ found 703.3637, calcd 703.3637.

(2R,3S,4S,10S)-10-((tert-Butyldiphenylsilyl)oxy)-3-((4-methoxybenzyl)oxy)-2,4-bis(methoxymethoxy)undecan-1-ol (22):

To a stirred solution of **21** (0.450 g, 0.66 mmol) in dry CH_2Cl_2 at -78 ºC, DIBAL-H (1 mL, 0.99 mmol, 1 M in Toluene) was added drop wise and the reaction mixture was stirred at same temperature for another 3 h. After completion of the reaction aqueous solution of sodium potassium tartrate (20 mL) was added to it and stirred for 2 h followed by extraction with CH_2Cl_2 (4 x 25 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. The crude residue was purified by column chromatography (100-200 mesh silica gel, eluent: 15% EtOAc in pet ether) to give the product **22** as colourless liquid (0.350 g, 78%). $[\alpha]_D^{25}$: – 4.5 (c 1.8, $CHCl_3$);IR ($CHCl_3$, cm^{-1}) ν_{max}: 3489, 2315, 1985, 1563, 761; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.74 - 7.59 (m, 4 H), 7.44 - 7.32 (m, 6 H), 7.26 (d, J = 8.2 Hz, 2 H), 6.86 (d, J = 8.5 Hz, 2 H), 4.73 (t, J = 6.7 Hz, 2 H), 4.69 - 4.60 (m, 3 H), 4.57 (d, J = 11.0 Hz, 1 H), 3.86 - 3.75 (m, 6 H), 3.74 - 3.62 (m, 3 H), 3.40 (s, 3 H), 3.38 (s, 3 H), 3.06 (br. s., 1 H), 1.71 - 1.57 (m, 3 H), 1.56 - 1.44 (m, 2 H), 1.41 - 1.24 (m, 5 H), 1.04 (s, 12 H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 159.2, 135.8, 135.6, 134.9, 134.6, 130.3, 129.5, 129.4, 129.3, 127.5, 127.4, 127.3, 113.8, 96.7, 96.2, 80.5, 79.9, 77.8, 73.2, 69.5, 62.7, 55.9, 55.8, 55.2, 39.4, 30.4, 29.8, 27.0, 26.9, 25.8, 25.2, 23.2, 19.2. HRMS (ESI) for $C_{39}H_{58}O_8NaSi$ $(M + Na)^+$ found 705.3793, calcd 705.3793.

(5R,6S,7S,13S)-6-((4-Methoxybenzyl)oxy)-7-(methoxymethoxy)-13,16,16-trimethyl-15,15-diphenyl-5-vinyl-2,4,14-trioxa-15-silaheptadecane (29):

The alcohol **22** (0.350 g, 0.51mmol) was dissolved in dry CH_2Cl_2 followed by addition of Dess Martin Periodinane (0.324 g, 0.76 mmol). The reaction mixture was stirred for 3 h at r.t.and monitored by TLC. After completion of the reaction, saturated Na_2SO_3 was added to it and extracted with CH_2Cl_2 (3 x 10 mL). The organic layer was washed with brine, dried over Na_2SO_4 and concentrated. The crude unstable aldehyde was immediately used for methylenation without further purification.

To the red coloured stirred solution of PPh_3 (0.135 g, 0.51 mmol) and $RhCl(PPh_3)_3$ (0.005 g, 0.006 mmol) in THF, 2-propanol was added followed by crude aldehyde (0.320 g, 0.47 mmol). After stirring for another 5 minute at room temperature, $TMSCHN_2$ (0.4 ml, 0.66 mmol) was added to the reaction mixture. The reaction mixture was stirred at room temperature for another 3 h. After completion of the reaction, the reaction mixture was diluted with water and extracted with EtOAc. The combined organic layer was washed with brine, dried and concentrated *in vacuo*. The resulting crude olefin was purified by column chromatography (100-200 mesh silica gel, eluent: 10% EtOAc in pet ether) to give olefin **29** as colourless liquid (0.230 g, 66%). $[\alpha]_D^{25}$: – 38.8 (c 1.2, $CHCl_3$); IR ($CHCl_3$, cm^{-1}) ν_{max}: 3089, 2035, 1498, 1163, 761; ^{1}H NMR (500 MHz, $CDCl_3$): δ= 7.61-7. 58 (m, 4 H), 7.36 - 7.25 (m, 6 H), 7.19 (d, J = 8.2 Hz, 2 H), 6.77 (d, J = 8.5 Hz, 2 H), 5.81 - 5.70 (m, 1 H), 5.27 - 5.19 (m, 2 H), 4.64 - 4.57 (m, 3 H), 4.56 - 4.46 (m, 3 H), 4.18 - 4.06 (m, 1 H), 3.79 - 3.72 (m, 1 H), 3.71 (s, 3 H), 3.65 - 3.57 (m, 1 H), 3.53-3.51 (m, 1 H), 3.31 (s, 3 H), 3.29 (s, 3 H), 1.58 - 1.50 (m, 3 H), 1.44 - 1.36 (m, 1 H), 1.33-1.26 (m, 2 H), 1.18-1.13 (m, 4 H), 0.99 - 0.94 (m, 12 H);^{13}C NMR (125 MHz, $CDCl_3$): δ = 159.1, 135.8, 135.2, 134.9, 134.6, 130.8, 129.5, 129.4, 129.3, 127.5, 127.4, 127.3, 119.1, 113.6, 96.3, 93.7, 81.8, 78.2, 77.6, 73.4, 69.6, 55.9, 55.6, 55.2, 39.5, 30.1, 30.0, 29.7, 27.0, 25.4, 25.3, 23.2, 19.2.HRMS (ESI) for $C_{40}H_{58}O_7NaSi$ $(M + Na)^+$ found 701.3842, calcd 701.3844.

(3R,4S,5S,11S)-11-((tert-Butyldiphenylsilyl)oxy)-4-((4-methoxybenzyl)oxy)-3,5-bis(methoxymethoxy)dodecan-1-ol (30):

Olefinic compound **29** (0.230 g, 0.34mmol) was taken in 15 mL dry THF and 9-BBN (1 mL, 0.51 mmol, 0.5 M in THF) was added to it drop wise for 1 h period at 0 ºC. The reaction mixture was stirred at same temperature for another 4 h. Then the reaction mixture was quenched with 2 mL of water at 0 ºC and stirred for 5 mins. A solution of 3 N NaOH (4 mL) followed by 30% H_2O_2 solution (4 mL) were added to the reaction mixture and stirred for 6 h at room temperature. The mixture was extracted with ethyl acetate for several times (3 x 50 mL). Combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. The crude residue was purified by column chromatography (100-200 mesh silica gel, eluent: 15% EtOAc in pet ether) to give alcohol **30** (0.165 g, 70%) as colourless liquid. $[\alpha]_D^{25}$: –12.3 (c 2.2, $CHCl_3$);IR ($CHCl_3$, cm^{-1}) ν_{max}: 3519, 2835, 1341,1236, 932, 845, 789; ^{1}H NMR (400 MHz, $CDCl_3$):δ = 7.71 - 7.65 (m, 4 H), 7.43 - 7.34 (m, 6 H), 7.27 (d, J = 8.7 Hz, 2 H), 6.86 (d, J = 8.7 Hz, 2 H), 4.83 (d, J = 6.4 Hz, 1 H), 4.70 - 4.57 (m, 5 H), 4.00 - 3.91 (m, 1 H), 3.85 - 3.79 (m, 3 H), 3.79 (s, 3 H), 3.74 - 3.66 (m, 1 H), 3.64 - 3.54 (m, 1H), 3.42 (s, 3 H), 3.38 (s, 3 H), 1.71 - 1.61 (m, 3 H), 1.43 - 1.31 (m, 4 H), 1.21 - 1.12 (m, 5 H), 1.07 - 1.03 (m, 12 H); ^{13}C NMR (100 MHz, $CDCl_3$):δ= 159.3, 135.8, 134.9, 134.6, 130.4, 130.0, 129.4, 129.3, 127.4, 127.3, 113.8, 113.7, 98.1, 96.4, 81.8, 77.4, 76.9, 74.2, 69.6, 59.2, 56.0, 55.2, 39.4, 33.9, 30.5, 29.8, 29.7, 27.0, 25.8, 25.2, 23.2, 19.2. HRMS (ESI) for $C_{40}H_{60}O_8NaSi$ $(M + Na)^+$ found 719.38.

(3R,4S,5S,11S)-4-((4-Methoxybenzyl)oxy)-3,5-bis(methoxymethoxy)dodecane-1,11-diol (33):

To a stirred soln. of **30** (0.160 g, 0.23 mmol) in dry THF (10 mL) was added 1M TBAF (0.4 mL, 0.34 mmol) in THF at room temperature, and the mixture was stirred for 4 h. The reaction was diluted with saturated aq NH_4Cl (2 x 10 mL), and the mixture was extracted with ethyl acetate (2 x 15 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. The crude product was purified by silica gel column chromatography (100-200 mesh, eluent: 25% EtOAc in pet ether) to give **33** (0.089 g, 85%)as a light yellow oil. $[\alpha]_D^{25}$: – 54.3 (c 3.2, $CHCl_3$); IR ($CHCl_3$, cm^{-1}) ν_{max}: 3639, 2903, 1457, 1376, 1236, 1086, 895, 759; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.29 (d, J = 8.6 Hz , 2 H), 6.88

(d, J = 8.6 Hz, 2 H), 4.84 (d, J = 6.6 Hz, 1 H), 4.73 - 4.58 (m, 5 H), 4.01 - 3.91 (m, 1 H), 3.89 - 3.73 (m, 6 H), 3.73 - 3.65 (m, 1 H), 3.65 - 3.57 (m, 1 H), 3.42 (s, 3 H), 3.39 (s, 3 H), 2.06 (br. s., 2 H), 1.95 (tdd, J = 4.6, 9.3, 14.1 Hz, 2 H), 1.74 - 1.53 (m, 3 H), 1.53 - 1.31 (m, 7 H), 1.19 (d, J = 6.1 Hz, 3 H);^{13}C NMR (100 MHz, $CDCl_3$): δ= 159.3, 130.3, 130.1, 113.7, 98.1, 96.4, 81.5, 77.2, 76.9, 74.1, 68.0, 59.1, 56.0, 55.3, 39.2, 33.9, 30.4, 29.6, 25.7, 23.5; HRMS (ESI) for $C_{24}H_{42}O_8Na$ $(M + Na)^+$ found 481.2772; calcd 481.2767.

(4R,5S,6S,12S)-5-Hydroxy-4,6-bis(methoxymethoxy)-12-methyloxacyclododecan-2-one (35):

An aqueous solution of NaBr (1 M, 0.2 mL), an aqueous solution of tetrabutylammonium bromide (1 M, 0.4 mL), TEMPO (0.016 g, 0.10 mmol) and a saturated aqueous solution of $NaHCO_3$ (1 mL) were added to a solution of alcohol **33** (0.154 g, 0.34 mmol) in CH_2Cl_2 (7 mL) and water (1.5 mL) in an ice–water bath. The resulted mixture was treated with an aqueous solution of NaOCl (1.1 mL) and continuously stirred for 1 hour as the temperature increased from 0 ºC to room temperature. To the reaction medium, ^{t}BuOH (5.0 mL), 2-methylbut-2-ene in THF (2 M, 10.5 mL) and a solution of $NaClO_2$ (0.370 g) and NaH_2PO_4 (0.300 g) in water (2 mL) were added. The reaction mixture was kept at room temperature for 2 h, diluted with saturated aqueous NaH_2PO_4 solution (20 mL), and extracted with EtOAc (5 x 10 mL). The organic layers were combined and dried over Na_2SO_4. After removal of the solvent, the desired seco-acid **34** was used for next lactonization step without purification.

To a solution of MNBA (0.08 g, 0.23 mmol) and DMAP (0.004 g, 0.03 mmol) in dichloromethane (40 mL) at room temperature was slowly added a solution of the seco-acid **34** (0.088 g, 0.19 mmol) in CH_2Cl_2 (20 mL) with a mechanically driven syringe over a 12 h period. After completion of reaction, the reaction mixture was diluted with water and extracted with dichloromethane (2 x 10 mL). The organic layer was washed with brine and water and dried over Na_2SO_4. After evaporation of the solvent, the crude product was purified by column chromatography. The product accompanied with some other impurities was used as such for the next reaction.

This semi purified lactone (0.030 g, 0.06 mmol) was dissolved in 10 mL of CH_2Cl_2-H_2O (18:1) and DDQ (0.027 g, 0.12 mmol) was added to it and the reaction mixture stirred for 45 minute. Completion of the reaction was monitored by TLC. The reaction mixture was diluted with 5% $NaHCO_3$ solution, water and brine and extracted with CH_2Cl_2 (3 x 20 ml). The organic layer was dried over Na_2SO_4 and concentrated *in vacuo*. The crude residue was purified by column chromatography (100-200 mesh silica gel, eluent: 15% EtOAc in pet ether) to give compound **35** (0.018 g, 16% after 3 steps) as a colourless liquid. $[\alpha]_D^{25}$: – 14.8 (c 0.8, $CHCl_3$); IR ($CHCl_3$, cm^{-1}) ν_{max}: 3511, 2883, 1689, 1422, 1131, 764, 623; ^{1}H NMR (500MHz, $CDCl_3$) δ = 5.20 - 5.09 (m, 1 H), 4.81 (d, J = 7.2 Hz, 1 H), 4.74 (dd, J = 7.1, 17.4 Hz, 2 H), 4.65 (d, J = 6.9 Hz, 1 H), 4.09 (td, J = 3.9, 8.2 Hz, 1 H), 3.94 (ddd, J = 2.7, 5.6, 8.1 Hz, 1 H), 3.77 (t, J = 5.1 Hz, 1 H), 3.44 (s, 3 H), 3.40 (s, 3 H), 2.83 (dd, J = 8.0, 13.7 Hz, 1 H), 2.75 (dd, J = 3.4, 13.7 Hz, 1 H), 1.95 - 1.90 (m, 1 H), 1.80 - 1.41 (m, 9 H), 1.22 (d, J = 6.5 Hz, 3 H);^{13}C NMR (125 MHz, $CDCl_3$): δ = 169.5, 96.1, 95.6, 75.8, 74.7, 71.1, 70.7, 56.0, 55.8, 37.2, 30.9, 26.6, 25.3, 20.8, 20.0, 18.3; HRMS (ESI) for $C_{16}H_{30}O_7Na$ $(M + Na)^+$ found 357.1878; calcd 357.1884.

(4R,6S,12S)-4,6-bis(Methoxymethoxy)-12-methyloxacyclododecane-2,5-dione (36):

Compound **35** (0.070 g, 0.21 mmol) was dissolved in dry CH_2Cl_2 followed by addition of Dess Martin Periodinane (0.135 g, 0.32 mmol). The reaction mixture was stirred for 3 h at r.t.and reaction monitored by TLC. After completion of the reaction, saturated $Na_2S_2O_3$ was added to it and extracted with CH_2Cl_2 (3 x 10 ml). The organic layer was washed with brine, dried over Na_2SO_4 and concentrated. The crude product was purified by column chromatography (100-200 mesh silica gel, eluent: 20% EtOAc in pet ether) to afford keto compound **36** (0.061 g, 88%) as a thick liquid. $[\alpha]_D^{25}$: + 41.1 (c 0.4, $CHCl_3$); IR ($CHCl_3$,cm^{-1}) ν_{max}: 2998, 2907,1721, 1698, 750.^{1}H NMR (500 MHz, $CDCl_3$)δ = 5.03 - 4.95 (m, 1 H), 4.79 - 4.73 (m, 2 H), 4.69 (dd, J = 2.7, 7.3 Hz, 1 H), 4.67- 4.61 (m, 2 H), 4.58 (d, J = 7.0 Hz, 1 H), 3.46 (s, 3 H), 3.36 (s, 3 H), 2.96 (dd, J = 10.4, 15.9 Hz, 1 H), 2.82 (dd, J = 3.1, 15.6 Hz, 1 H), 2.02 - 1.93 (m, 1 H), 1.93 - 1.84 (m, 1 H), 1.55 - 1.41 (m, 4 H), 1.34 - 1.24 (m, 4 H), 1.19 (d, J = 6.4 Hz, 3 H); ^{13}C NMR(125 MHz, $CDCl_3$) δ = 204.4, 168.6, 96.9, 95.4, 77.7, 74.1, 71.6, 56.3, 55.7, 35.4, 31.6, 28.1, 26.1, 19.5, 18.94, 18.9.HRMS (ESI) for $C_{16}H_{28}O_7Na$ $(M + Na)+$ found 355.1729, calcd 355.1727.

Pandangolide 1 (1):

6 M HCl (3 mL) was added to a solution of **36** (0.020 g, 0.06 mmol) in THF (5 mL) and the resulting mixture stirred at r.t. for 24 h. After careful quenching with excess sat.$NaHCO_3$ (aq) solution the layers were separated. The aqueous layer was extracted with EtOAc (4 x 10 mL), the combined organic layers were dried over Na_2SO_4 and solvent evaporated *in vacuo*. The residue was purified by column chromatography (100-200 mesh silica gel, eluent: 35% EtOAc in pet ether) to give compound **1** as a white solid (0.007 g, 52%). $[\alpha]_D^{25}$: +102.6 (c 0.4, MeOH); lit[5a]$[\alpha]_D^{25}$: - 30.0 (c 2.3, MeOH); IR ($CHCl_3$, cm^{-1}) ν_{max} = 3379, 2927, 1725, 1701, 1264, 838. ^{1}H NMR (700 MHz, CD_3OD at 278 K) δ= 4.99 - 4.92 (m, 1 H), 4.90 (dd, J = 2.2, 6.7 Hz, 1 H), 4.76 (dd, J = 3.5, 10.6 Hz, 1 H), 2.82 (dd, J = 10.7, 15.1 Hz, 1 H), 2.72 (dd, J = 3.6, 15.1 Hz, 1 H), 2.00 - 1.94 (m, 1 H), 1.94 - 1.87 (m, 1 H), 1.57 - 1.49 (m, 3 H), 1.44 - 1.39 (m, 1 H), 1.37 - 1.33 (m, 1 H), 1.29 - 1.24 (m, 2 H), 1.19 (d, J = 6.4 Hz, 3 H), 1.18 - 1.15 (m, 1 H); ^{13}C NMR (175MHz, CD_3OD) δ = 210.5, 171.0, 73.9, 72.5, 69.2, 38.9, 32.7, 30.8, 27.1, 20.8, 20.0, 19.1. HRMS (ESI) for $C_{12}H_{20}O_5Na$ $(M + Na)^+$ found 267.1200, calcd 267.1203.

2-((3a*R*,5*R*,6*S*,6a*R*)-6-(Benzyloxy)-2,2-dimethyltetrahydrofuro[2,3-d][1,3]dioxol-5- yl)ethanol (39):

Olefinic compound **38** (2.5 g, 9.0 mmol) was taken in 30 mL dry THF and 9BBN (27 mL, 13.5 mmol, 0.5 M in THF) was added to it drop wise for 1 h period at 0 ºC. The reaction mixture was stirred at same temperature for 2 h more. Then the reaction mixture was quenched with 2 mL of water at 0 ºC and stirred for 5 min. Then, 3 N NaOH solution (16 mL) followed by 30% H_2O_2 solution (16 mL) were added to the reaction mixture and stirred for 3 h at room temperature. The whole mixture was then extracted with ethyl acetate (3 x 50 mL). The combined organic layer was dried over sodium sulphate and concentrated under vacuum. The crude residue was purified by column chromatography (100-200 mesh silica gel, eluent 15% EtOAc / pet ether) to obtain a yellowish thick liquid **39** (2.02 g, 76%). $[\alpha]_D^{25}$: –17.8 (c 2.0, $CHCl_3$); IR ($CHCl_3$, cm^{-1}) ν_{max}: 3502, 2953, 1638, 1453, 1100, 780. 1H NMR (400 MHz, $CDCl_3$): δ = 7.38 - 7.29 (m, 5 H), 5.93 (d, J = 4.1 Hz, 1 H), 4.72 (d, J = 12.4 Hz, 1 H), 4.63 (d, J = 4.1 Hz, 1 H), 4.50 (d, J = 11.9 Hz, 1 H), 4.37 - 4.30 (m, 1 H), 3.84 (d, J = 3.2 Hz, 1 H), 3.76 (t, J = 6.0 Hz, 2 H), 2.15 - 2.00 (m, 2 H), 1.88 - 1.83 (m, 1 H), 1.50 (s, 3 H), 1.33 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 137.4, 128.5, 128.0, 127.7, 111.4, 104.7, 82.5, 82.1, 78.6, 71.7, 60.4, 30.9, 26.6, 26.1.HRMS (ESI) for $C_{16}H_{22}O_5Na$ $(M + Na)^+$ found 317.1353, calcd 317.1359.

(3a*R*,5*R*,6*S*,6a*R*)-6-(Benzyloxy)-5-(2-((4-methoxybenzyl)oxy)ethyl)-2,2-dimethyltetrahydrofuro[2,3-d][1,3]dioxole (40):

To a stirred solution alcohol **39** (1.0 g, 3.40 mmol) in dry THF at 0 °C, NaH was added (0.2 g, 5.1 mmol, 60% in mineral oil) portion wise and stirred for 30 minutes. Then, PMBCl (0.6 mL, 4.08 mmol) followed by catalytic amount of TBAI was added to it and the reaction was monitored by TLC. After completion of the reaction, cold water was added to it and extracted with ethylacetate (4 x 10 mL). The organic layers were washed with brine, dried over sodium sulphate and concentrated under vacuum. The crude residue was purified by column chromatography (100-200 mesh silica gel, eluent 8% EtOAc / pet ether) to give compound **40** (1.23 g, 88%) as a colorless liquid. $[\alpha]_D^{25}$: –7.60 (c 1.2, $CHCl_3$), IR ($CHCl_3$, cm^{-1}) ν_{max}: 3012, 2853, 1253, 1090, 680. ^1H NMR (500 MHz, $CDCl_3$): δ = 7.37 - 7.29 (m, 5 H), 7.27 - 7.22 (d, J = 8.5 Hz, 2 H), 6.89 - 6.84 (d, J = 8.5 Hz, 2 H), 5.92 (d, J = 4.0 Hz, 1 H), 4.67 (d, J = 11.9 Hz, 1 H), 4.61 (d, J = 4.0 Hz, 1 H), 4.45 - 4.40 (m, 2 H), 4.33 (ddd, J = 3.1, 5.5, 7.9 Hz, 1 H), 3.81 (s, 3 H), 3.80 - 3.75 (m, 2 H), 3.54 (t, J = 6.6 Hz, 2 H), 2.13 - 2.04 (m, 1 H), 1.98 (qd, J = 6.8, 13.5 Hz, 1 H), 1.50 (s, 3 H), 1.33 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 159.1, 137.5, 130.5, 129.3, 128.4, 127.8, 127.7, 113.7, 111.3, 104.6, 82.3, 82.2, 77.7, 72.7, 71.6, 67.1, 55.2, 28.5, 26.7, 26.2. HRMS (ESI) for $C_{24}H_{30}O_6Na$ $(M + Na)^+$ found 437.1931, calcd 437.1935.

(3*S*,4*S*,5*R*)-4-(Benzyloxy)-7-((4-methoxybenzyl)oxy)hept-1-ene-3,5-diol (42):

PMB protected compound **40** (1.80 g, 4.81 mmol) was dissolved in 60% aqueous acetic acid solution and heated at 50 °C for 6 h. After completion of the reaction, the reaction mixture was evaporated in *vacuo* [for complete evaporation the residual part of reaction mixture was treated with toluene (3 x 50 mL) and removed as azeotrope mixture] to give lactol **41** which was directly used for next step without further purification.

Crude lactol **41 (**1.35 g, 3.6 mmol) was dissolved in dry THF and it was added to the already generated 1-carbon Wittig ylide [in situ generated by using triphenylphosphoniun iodide (14.5 g) and 1.6 M BuLi solution in n-hexane (9.7 mL) in 50 mL dry THF for 1 h] at 0 °C. After complete addition of the lactol, the temperature of the reaction was warmed to room temperature and stirred for another 4 h at same temperature. After completion of the reaction, saturated NH_4Cl was added to it and extracted with ethylacetate (4 x 10 mL). The organic layers were washed with brine, dried over Na_2SO_4 and concentrated under vacuum. The crude residue was purified by column chromatography (100-200 mesh silica gel, eluent 40% EtOAc / pet ether) to give diol compound **42** (1.04 g, 65% after two steps) as a colorless liquid. $[\alpha]_D^{25}$: - 16.1 (c 1.7, $CHCl_3$); IR ($CHCl_3$, cm^{-1}) ν_{max}: 3412, 3042, 3018, 2947, 2902, 1455, 1103, 799. ^1H NMR (200 MHz, $CDCl_3$): δ = 7.41 - 7.29 (m, 5 H), 7.24 (d, J = 6.9 Hz, 2 H), 6.88 (d, J = 8.7 Hz, 2 H), 5.96 (ddd, J = 5.6, 10.5, 17.2 Hz, 1 H), 5.40 (td, J = 1.6, 17.2 Hz, 1 H), 5.22 (td, J = 1.5, 10.5 Hz, 1 H), 4.79 - 4.59 (m, 2 H), 4.44 (s, 2 H), 4.36 (dd, J = 4.4, 5.4 Hz, 1 H), 4.02 - 3.89 (m, 1 H), 3.80 (s, 3 H), 3.67 - 3.55 (m, 2 H), 3.35 (t, J = 4.0 Hz, 1 H), 2.82 (br. s., 2 H), 2.01 - 1.75 (m, 2 H). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 159.2, 138.2, 137.9, 130.1, 129.3, 128.5, 128.0, 116.1, 113.8, 83.9, 75.1, 73.0, 72.9, 70.9, 67.8, 55.2, 33.6; HRMS (ESI) for $C_{22}H_{28}O_5Na$ $(M + Na)^+$ found 395.1827, calcd 395.1829.

(3*R*,4*S*,5*S*)-4-(Benzyloxy)-3,5-bis(methoxymethoxy)hept-6-en-1-ol (50):

To the pre-cooled solution of **42** (1.10 g, 2.95 mmol) and DIPEA (4.1 mL, 23.6 mmol) in CH_2Cl_2 (20 mL) at 0 °C, MOMCl (0.9 mL, 11.8 mmol) was added slowly and the reaction mixture allowed to attain room temperature. The reaction mixture was stirred at room temperature for another 12 h at which time TLC showed the complete consumption of starting material. Then the solution was diluted with saturated NH4Cl and extracted with CH_2Cl_2 (4x10 ml). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated *in vacuo* to furnish a crude oil, which was used for next step without purification.

To the crude solution of di-MOM (1.22 g, 2.65 mmol) in 15 mL of CH_2Cl_2-H_2O (18:1), DDQ (0.90 g, 3.97 mmol) was added and the reaction mixture stirred for 45 minute. Completion of the reaction was monitored by TLC. The reaction mixture was diluted with 5% $NaHCO_3$ solution, water and brine and extracted with CH_2Cl_2 (3 x 20 mL). The organic layer was dried over Na_2SO_4 and concentrated *in vacuo*. The crude residue was purified by column chromatography (100-200 mesh silica gel, eluent 15% EtOAc / pet ether) to give alcohol compound **50** (0.80 g, 80% after two steps) as a colorless liquid. $[\alpha]_D^{25}$: + 89.2 (c 0.6, $CHCl_3$); IR ($CHCl_3$, cm^{-1}) ν_{max}: 3452, 3091, 2911, 1357, 1103, 812. ^1H NMR (200 MHz, $CDCl_3$): δ = 7.40 - 7.30 (m, 5 H), 5.98 - 5.73 (m, 1 H), 5.39 - 5.23 (m, 2 H), 4.80 (d, J = 6.6 Hz, 1 H), 4.73 - 4.53 (m, 5 H), 4.25 (dd, J = 4.4, 7.3 Hz, 1 H), 3.97 (ddd, J = 4.3, 6.3, 9.0 Hz, 1 H), 3.82 - 3.61 (m, 2 H), 3.47 (dd, J = 4.3, 6.3 Hz, 1 H), 3.40 (s, 3 H), 3.38 (s, 3 H), 2.70 (br. s., 1 H), 2.01 - 1.86 (m, 1 H), 1.77 - 1.65 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 138.0, 134.8, 128.4, 128.3, 127.8, 127.6, 118.7, 98.3, 94.0, 84.0, 76.9, 76.8, 75.2, 59.0, 56.0, 33.8, 26.5. HRMS (ESI) for $C_{18}H_{28}O_6Na$ $(M + Na)^+$ found 363.1778, calcd 363.1778.

(3R,4S,5S)-4-(Benzyloxy)-3,5-bis(methoxymethoxy)hept-6-enoic acid (51):

To a stirred solution of alcohol **50** (0.30 g, 0.9 mmol) in CH_3CN (3 mL) and H_2O (1 mL) were added TEMPO (0.029 g, 0.1 mmol) and BAIB (0.90 g, 2.8 mmol) at 0 °C and reaction monitored by TLC. The reaction mixture was stirred for 7 h, until TLC indicated the complete consumption of starting material. The reaction was diluted by the addition of saturated aqueous Na_2SO_3 (20 mL), and the aqueous layer was extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (eluent 35% EtOAc / pet ether) to give acid compound **51** (0.225 g, 72%) as a light yellow oil. $[\alpha]_D^{25}$: - 39.2 (c 1.1, $CHCl_3$); IR ($CHCl_3$, cm^{-1}) ν_{max}: 3112, 2911, 1706, 1410, 1320, 950. ^1H NMR (500 MHz, $CDCl_3$): δ = 7.39 - 7.25 (m, 5 H), 5.84 (ddd, J = 7.7, 10.3, 17.5 Hz, 1 H), 5.34 - 5.28 (m, 2 H), 4.81 - 4.75 (m, 1 H), 4.72 - 4.68 (m, 4H), 4.60 (d, J = 6.6 Hz, 1 H), 4.38 - 4.32 (m, 1 H), 4.17 - 4.09 (m, 1 H), 3.63 (t, J = 5.0 Hz, 1 H), 3.38 (s, 3 H), 3.34 (s, 3 H), 2.80 (dd, J = 5.1, 16.4 Hz, 1 H), 2.72 (dd, J = 7.0, 16.3 Hz, 1 H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 177.0, 137.9, 134.7, 128.4, 128.3, 127.8, 119.0, 97.8, 94.1, 81.8, 77.3, 75.2, 74.8, 55.92, 55.9, 36.7. HRMS (ESI) for $C_{18}H_{26}O_7Na$ $(M + Na)^+$ found 377.1569, calcd 377.1571.

(S)-Hept-6-en-2-yl-(3R,4R,5S)-4-(benzyloxy)-3,5-bis(methoxymethoxy)hept-6-enoate (52):

To a stirred solution of triethylamine (0.066 g, 0.653 mmol) in dry CH_2Cl_2 (5 mL) was added DMAP (0.003 g, 0.020 mmol) followed by MNBA (0.083 g, 0.241 mmol) and acid **51** (0.085 g, 0.242 mmol). The reaction mixture was stirred for another 45 minute, then hydroxy olefin **37** (0.023 g, 0.2 mmol) in dry CH_2Cl_2 was added to it and progress of the reaction was monitored by TLC. Then this reaction mixture was stirred for 12 h and quenched by addition of saturated aqueous NH_4Cl solution. The aqueous layer was extracted with CH_2Cl_2 (3 x 20 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (100-200 mesh silica gel, eluent 20% EtOAc /pet ether) to afford diene **52** (0.082 g, 90%) as a colorless

liquid. $[\alpha]_D^{25}$: + 46.3 (c 3.5, $CHCl_3$); IR ($CHCl_3$, cm^{-1}) ν_{max}: 2998, 2907, 1647, 1345, 750. ^1H NMR (500 MHz, $CDCl_3$): δ = 7.41 - 7.25 (m, 5 H), 5.92 - 5.71 (m, 2 H), 5.36 - 5.28 (m, 2 H), 5.08 - 4.86 (m, 3 H), 4.80 (d, J = 11.3 Hz, 1 H), 4.72 (d, J = 6.7 Hz, 1 H), 4.70 - 4.65 (m, 3 H), 4.61 (d, J = 6.7 Hz, 1 H), 4.38 - 4.34 (m, 1 H), 4.19 - 4.10 (m, 1 H), 3.63 (dd, J = 4.6, 5.5 Hz, 1 H), 3.38 (s, 3 H), 3.35 (s, 3 H), 2.77 (dd, J = 5.8, 16.2 Hz, 1 H), 2.69 (dd, J = 6.6, 16.0 Hz, 1 H), 2.13 - 1.98 (m, 2 H), 1.65-1.57 (m, 1 H), 1.54 - 1.31 (m, 3 H), 1.20 (d, J = 6.4 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 171.1, 138.3, 138.1, 134.9, 128.4, 128.3, 127.7, 119.0, 114.8, 97.7, 94.0, 82.2, 77.5, 75.4, 75.1, 71.0, 55.9, 55.8, 37.0, 35.3, 33.5, 24.6, 19.9. HRMS (ESI) for $C_{25}H_{38}O_7Na$ $(M + Na)^+$ found 473.2510, calcd 473.2510.

(4*R*,6*S*,12*S*)-4,6-bis(Methoxymethoxy)-12-methyloxacyclododecane-2,5-dione (36):

The diene **52** (0.16 g, 0.35 mmol) which was dissolved in 100 ml freshly distilled CH_2Cl_2 (degassed for 15 minute through bubbling of argon) was added drop wise (over 2 h) to the refluxing solution of already dissolved Grubbs' II catalyst (0.030 g, 10 mol%, in 1000 ml degassed dry CH_2Cl_2). The reaction mixture was further refluxed for another 24 h (completion of the reaction was checked by TLC). The solvent was removed *in vacuo* and the crude product was purified by silica gel column chromatography (100-200 mesh silica gel, eluent 25% EtOAc/pet ether) to give compound **53** (0.11 g) as a brownish oil contaminated with catalyst impurity.

The semi-purified lactone **53** (0.110 gm) was dissolved in methanol and 10% Pd/C (0.002 mg) was added to it. The reaction mixture was stirred under hydrogen atmosphere (balloon pressure) for 12 h. Completion of the reaction was monitored by TLC. The reaction mixture was filtered through a plug of celite and concentrated *in vacuo*. The resulting crude secondary alcohol product was then immediately subjected for next reaction without further purification.

The crude secondary alcohol (0.083 g, 0.25 mmol) was dissolved in dry CH_2Cl_2 followed by addition of Dess-Martin Periodinane (0.156 g, 0.37 mmol). The reaction mixture was stirred for 4 h at rt and reaction monitored by TLC. After completion of the reaction, saturated $Na_2S_2O_3$ was added to it and extracted with CH_2Cl_2 (3 x 10 mL). The organic layer was washed with brine, dried over Na_2SO_4 and concentrated. The crude product was purified by column chromatography (100-200 mesh silica gel, eluent 20% EtOAc / pet ether) to afford keto compound **36** (0.068 g, 57% over 3 steps) as a thick liquid. $[\alpha]_D^{25}$: + 38.5 (c 0.1, $CHCl_3$); IR ($CHCl_3$, cm^{-1}) ν_{max}: 2992, 2912, 1718, 1695, 751. ^1H NMR (500 MHz, $CDCl_3$) δ = 5.03 - 4.97 (m, 1 H), 4.79 - 4.76 (m, 2 H), 4.70 (dd, J = 2.7, 7.3 Hz, 1 H), 4.67- 4.61 (m, 2 H), 4.59 (d, J = 6.7 Hz, 1 H), 3.47 (s, 3 H), 3.37 (s, 3 H), 2.97 (dd, J = 10.4, 15.6 Hz, 1 H), 2.83 (dd, J = 3.1, 15.6 Hz, 1 H), 2.02 - 1.95 (m, 1 H), 1.93 - 1.87 (m, 1 H), 1.55 - 1.43 (m, 4 H), 1.37 - 1.27 (m, 4 H), 1.20 (d, J = 6.4 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ = 204.4, 168.6, 97.0, 95.5, 77.9, 74.2, 71.6, 56.4, 55.7, 35.4, 31.7, 28.2, 26.2, 19.7, 19.02, 19.01; HRMS (ESI) for $C_{16}H_{28}O_7Na$ $(M + Na)^+$ found 355.1720, calcd 355.1727.

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Keywords: Macrolide • Aldol reaction • Macrolactonization • Hydroboration-oxidation • Ring-closing metathesis

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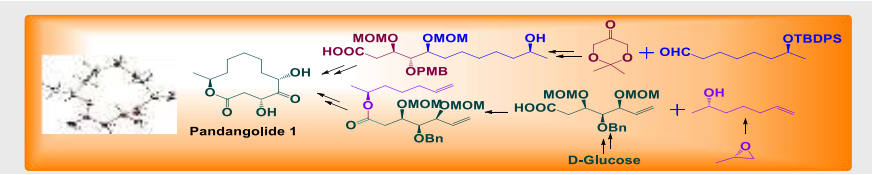

The first total synthesis of proposed structure of pandangolide 1 is reported. The construction of the 12 membered core was achieved via both via MNBA-mediated intramolecular Shiina lactonization and RCM protocol. The structure of target molecule was confirmed unambiguously by the single crystal X-ray analysis, though the optical rotation and NMR data of synthesized pandangolide 1 were found to be inconsistent with the proposed structure.

Key Topic* Total synthesis Macrolide • Aldol reaction • Macrolactonization • Hydroboration-oxidation • Ring-closing metathesis

*Krishanu Show(s), Rajesh. G. Gonnade(s) and Pradeep Kumar(s)**

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