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Structural Revision of Baulamycin A and Structure-Activity Relationships of Baulamycin A Derivatives

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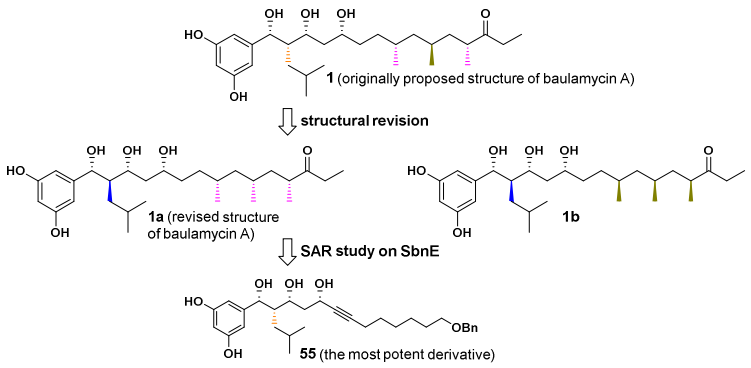


ABSTRACT: Total synthesis of the proposed structure of baulamycin A was performed. The spectral properties of the synthetic compound differ from those reported for the natural product. On the basis of comprehensive NMR study, we proposed two other possible structures for natural baulamycin A. Total syntheses of these two substances were performed, which enabled assignment of the correct structure of baulamycin A. Key features of the convergent and fully stereo-controlled route include Evans Aldol and Brown allylation reactions to construct the left fragment, a prolinol amide-derived alkylation/desymmetrization to install the methyl substituted centers in the right fragment, and finally a Carreira alkynylation to join both fragments. In

addition, we have determined the inhibitory activities of novel baulamycin A derivatives against the enzyme SbnE. This SAR study provides useful insight into the design of novel SbnE inhibitors that overcome the drug resistance of pathogens, which cause life-threatening infections.

Introduction

Bacteria secrete low molecular weight and high-affinity iron chelators called siderophores to acquire iron needed for their virulence.[1] The biosynthetic pathways employed to generate these siderophores, such as staphyloferrin B of *Staphylococcus aureus*[2] and petrobactin of *Bacillus anthracis*,[3] involve NRPS-independent siderophore (NIS) synthetases, which includes SbnE in staphyloferrin B and AsbA in petrobactin. Sherman *et al*[4] recently isolated baulamycin A (BmcA) and baulamycin B (BmcB) from marine microbial-derived extracts (NPEs) from *Streptomyces tempisquensis* and showed that these substances serve as novel inhibitors of SbnE and AsbA. BmcA is an invaluable substance as it provides a promising starting-point for designing substances that are effective against drug-resistant pathogens such as MRSA and *Bacillus anthracis*.

As a part of an ongoing program devoted to total synthesis of biologically active natural products,[5] we performed a total synthesis of Sherman's proposed[4] stereostructure of BmcA (**1**). A comparison of the spectroscopic properties of the synthetic and natural materials demonstrated that the earlier proposed stereostructure of the natural product is incorrect. In the effort described below, we established the correct stereostructure of this natural product by utilizing comprehensive NMR studies and three total syntheses. It should be noted that, during the preparation of this manuscript, Goswami *et.al*[6a] and Chandrasekhar *et.al*[6b] reported a synthesis of

Sherman's originally proposed stereostructure of BmcA by employing a strategy that differs from ours. Aggarwal *et.al*[6c] reported the correct structure of BmcA while our manuscript was under review. The reported stereostructure of BmcA has the following relative configurations at its seven stereogenic centers: 4*R**, 6*S**, 8*R**, 11*R**, 13*R**, 14*S**, and 1'*R** while the absolute configurations of these centers were arbitrarily represented by stereostructure **1** (Figure 1).[4]

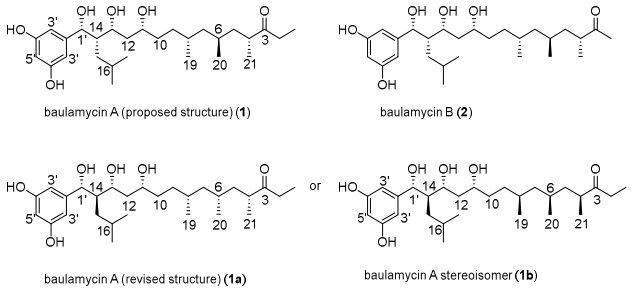
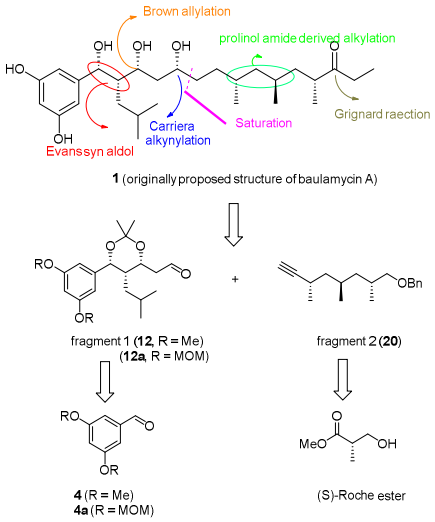


Figure 1. Structures of BmcA and BmcB.

Results and discussion

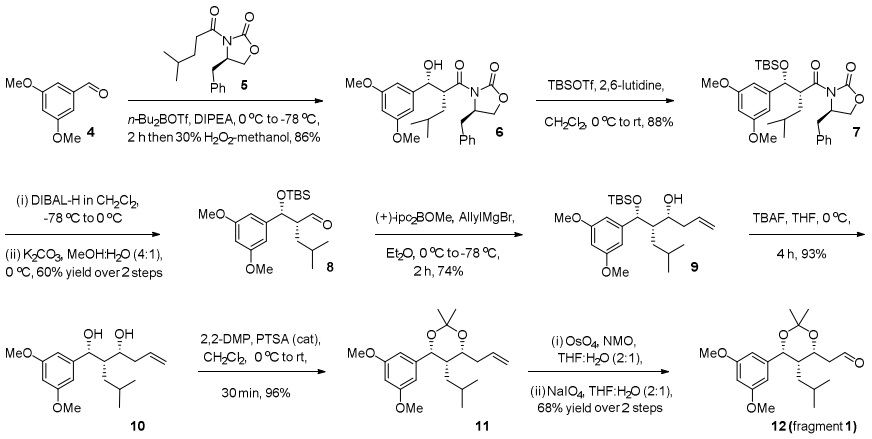
As depicted retrosynthetically in Scheme 1, our strategy for the synthesis of **1** involved joining fragments **1** and **2** by using the Carreira alkynylation process. In the plan, fragment **1** (**12** or **12a**) would be derived from a protected form (**4** or **4a**) of 3,5-dihydroxybenzaldehyde and fragment **2** (**20**) would be generated from (*S*)-Roche ester.

Scheme 1. Retrosynthetic analysis for the synthesis of 1



The synthetic pathway began with an Evans *syn* aldol reaction[7] between 3,5-dimethoxy benzaldehyde **4** and auxiliary **5**, which produced hydroxyamide **6** (86%, *dr* = 96:4 by NMR) and protection as its TBS ether **7** (88%) followed by reductive cleavage promoted by treatment with DIBAL-H generate aldehyde **8** (60%, 2 steps).[8] Brown allylation[9] of aldehyde **8** produced the homoallylic alcohol **9** (74%, *dr* = 92:8 by NMR).[10] Removal of the TBS group in **9** formed 1,3-diol **10** which upon reaction with 2,2-DMP, PTSA formed acetonide **11** (89%, 2 steps). The olefin group in **11** was cleaved by dihydroxylation followed by oxidative cleavage to afford aldehyde **12** (fragment **1**) (68%, 2 steps) (Scheme 2).

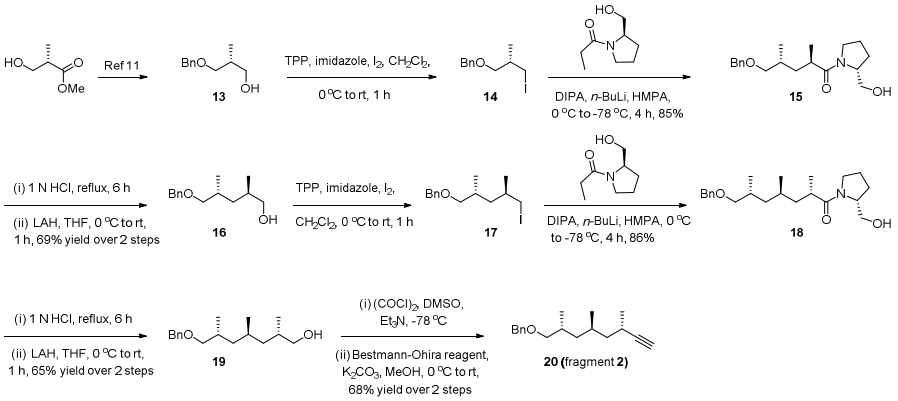
Scheme 2. Synthesis of fragment 1 (*syn* configuration)



The synthesis of fragment **2** was depicted in Scheme 3. Primary alcohol group in **13**[11] was converted to the corresponding iodide **14** by using TPP/Iodine. The lithium enolate, produced from L-prolinol *N*-propionamide by using *n*-BuLi, was coupled with iodide **14** to form 1,3-*anti* dimethyl[12] substituted amide **15** (85%, *dr* = 98:2 by NMR). Acid hydrolysis of **15**, followed by reduction formed primary alcohol **16** (69%, 2 steps), which was transformed to the iodide **17**. The lithium enolate derived from D-prolinol *N*-propionamide was coupled with iodide **17** to form 1,3,5-*anti*-trimethyl substituted amide **18** (86%, *dr* = 97:3 by NMR). Acid hydrolysis

of **18**, followed by reduction generated primary alcohol **19** (65%, 2 steps). Swern oxidation[13] of **19** followed by Bestmann-Ohira[14] reaction then produced the required alkyne **20** (68%, 2 steps).

Scheme 3. Synthesis of fragment 2 (*anti* configuration)



The crucial coupling reaction joining **12** and **20** was conducted by using Carreira alkynylation conditions (Scheme 4).[15] This process formed propargylic alcohol **21** (72%, *dr* = 95:5 by NMR), whose absolute configuration at the newly formed hydroxyl substituted center was confirmed as being '*S*' by utilizing the modified Mosher's ester method[16] (Figure 2). The hydroxyl group in **21** was protected to form TBS ether **22** (87%), which was subjected to complete reduction by using Pd/C promoted hydrogenation to produce saturated alcohol **23** (75%). Primary alcohol **23** was then oxidized to form a crude aldehyde which was subsequently reacted with EtMgBr to generate **24** (87%, 2 steps) which was a diastereomeric mixture (1:1 by NMR). Oxidation of the secondary alcohol group in **24** afforded ketone **25** (92%), which upon removal of both the acetonide and TBS groups using PTSA in methanol generated the BmcA precursor **26** (90%). Removal of methoxy groups in **26** under several conditions[17] proved to be fruitless except when aluminium iodide was employed, in which case BmcA (22%) was obtained but only after difficult purification.[18]

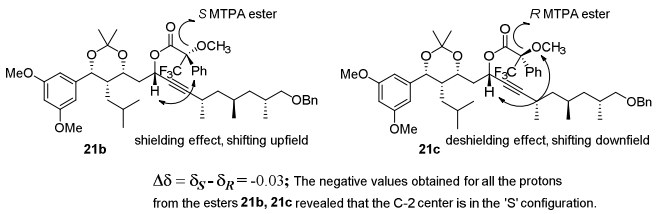
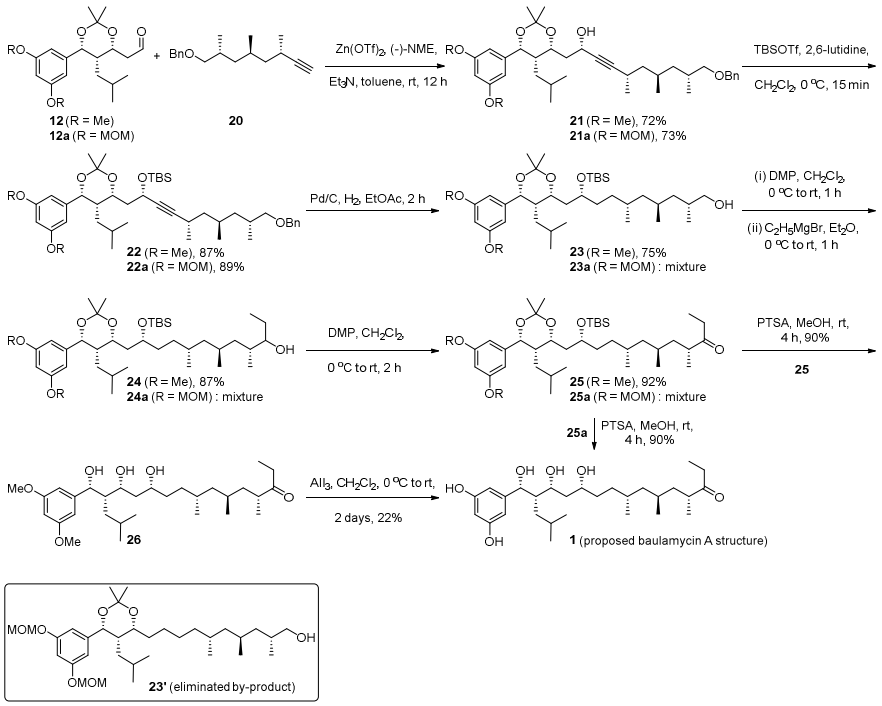


Figure 2. Modified Mosher's ester analysis.

Owing to the difficulty encountered with removal of the methoxy groups, the protection strategy was altered. Accordingly, the synthetic route was repeated using MOM protection of the phenolic hydroxy groups to produce aldehyde **12a**. Carreira alkynylation[15] between **12a** and **20** was conducted to deliver propargylic alcohol **21a** (73%, *dr* = 96:4 by NMR) which was protected as its TBS-ether **22a** (89%). The MOM protected intermediate **22a** was then subjected to hydrogenation by using Pd/C to produce an inseparable mixture of the saturated alcohol **23a** and TBS-ether elimination product **23'** in a 8:2 ratio (confirmed by ^{1}H NMR analysis). After several unsuccessful attempts to separate **23a**, the mixture was used in the next step. Contrary to expectations, purification was not successful until the final step in the sequence involving global removal of the MOM, acetonide and TBS groups in **25a** by using PTSA in methanol to form **1** (90%).

Scheme 4. Synthesis of the proposed stereostructure of BmcA



The absolute configurations at the stereogenic centers in **1**, prepared by using the route described above, were firmly established by using the modified Mosher's method and HSQC NMR analysis of the corresponding acetonide derivative (acetonide **A** and **B**, Figure 3). The NMR data for synthetic **1** clearly differed from those reported previously.[4] For instance, the ^{1}H and ^{13}C NMR chemical shifts for C/H-1' (δ_C 76.4; δ_H 4.84), C/H-14 (δ_C 49.1; δ_H 1.70) and C/H-6 (δ_C 28.8; δ_H 1.52) were observed for the synthetic material whereas C/H-1' (δ_C 76.5; δ_H 4.47), C/H-14 (δ_C 48.5; δ_H 1.88), and C/H-6 (δ_C 29.1; δ_H 1.42) were reported for natural BmcA.[4] These differences demonstrate that the proposed[4] stereostructure of the natural product is incorrect. The H-14 and C-14 chemical shift discrepancies and the results of a ROESY NMR study (Figure S137) with the acetonide derivative of **1** (Figure 3-a) suggest that the configurations at the three consecutive 1,3-hydroxy substituted centers and *iso*-butyl substituted carbon are 11*R**, 13*R**, 14*R** and 1'*R** rather than the originally proposed 11*R**, 13*R**, 14*S** and 1'*R**.

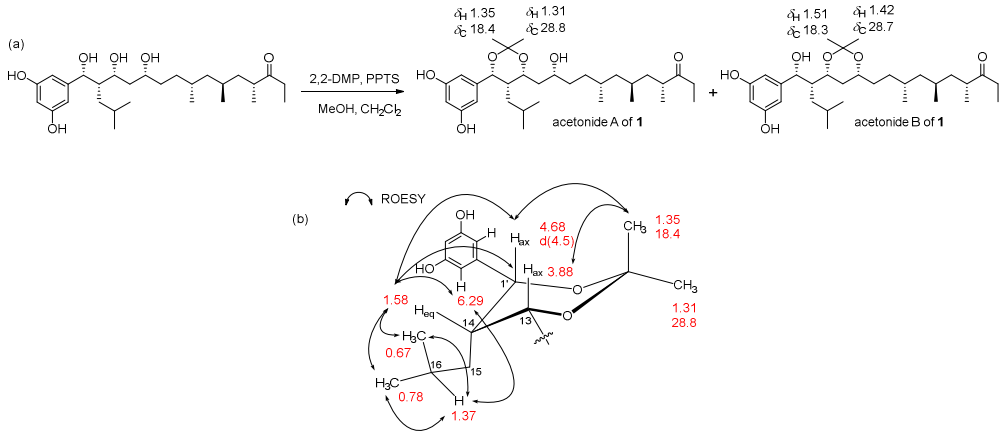


Figure 3. (a) Acetonide derivatization of **1**. ^{1}H and ^{13}C NMR chemical shifts indicating a *syn* relationship of the both acetonides. (b) The key ROESY correlations of the acetonide A of **1** showing the relative configuration of the *iso*-butyl group.

In order to address the C-6 and H-6 chemical shift discrepancies, NMR spectroscopic analysis was carried out on the trimethylheptanol derivatives **19**, **38** and **42** (Figure 4) to gain insight into the correct configurations of C-4, C-6 and C-8 in the natural product. The results show that the H-5 and H-7 ^{1}H chemical shifts of the protons in the two enantiomeric *syn*-*syn*-trimethylhepatanol fragments **42** and **38**, and the *anti*-*anti*-trimethylheptanol fragment **19** are remarkably different (Figure 4).

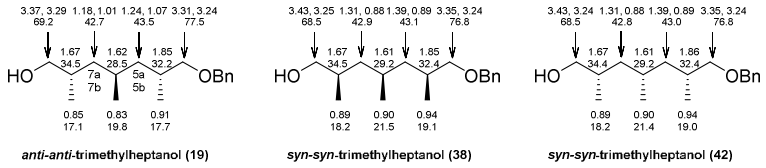


Figure 4. ^{1}H and ^{13}C chemical shifts of trimethylheptanol fragments.

The H-5 and H-7 methylene protons in the two enantiomeric *syn*-*syn*-trimethylhepatanol fragments, **38** and **42**, display ^{1}H NMR patterns that are consistent with those of the corresponding methylene protons in natural BmcA (eg., H-5a (δ_H 1.39)/H-5b (δ_H 0.89) and H-7a (δ_H 1.31)/H_2-7b (δ_H 0.88)). It was reported[4] that H-5a (δ_H 1.73) and H-7a (δ_H 1.22) in the

spectrum of natural BmcA are remarkably more deshielded than are H-5b (δ_H 0.98) and H-7b (δ_H 0.95), respectively. In contrast, in the spectrum of the *anti-anti*-trimethylheptanol fragment **19**, the chemical shifts of H-5a (δ_H 1.24)/H-5b (δ_H 1.07) and H-7a (δ_H 1.18)/H-7b (δ_H 1.01) are not that much different. The detailed ^{1}H NMR analysis of fragments **19**, **38** and **42**, led us to the conclusion that *syn-syn* relative configuration of the three methyl groups is more plausible for natural BmcA than the proposed *anti-anti* relative stereochemistry. A combination of the findings outlined above led us to propose the two plausible alternative stereostructures, **1a** and **1b**, (Figure 5) for natural BmcA.

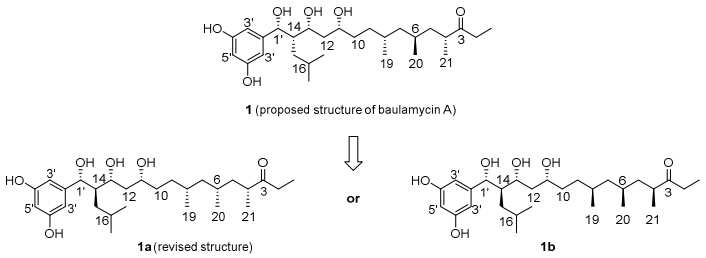
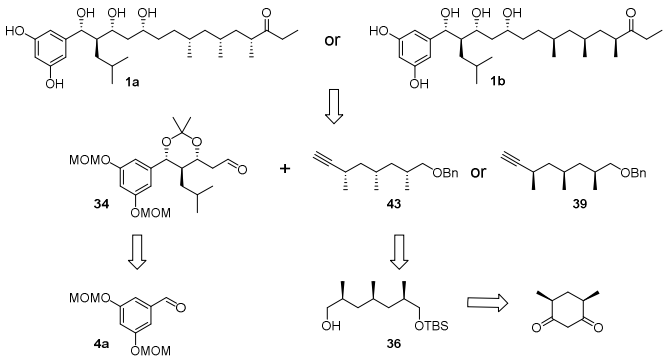


Figure 5. Proposed and revised structure of BmcA.

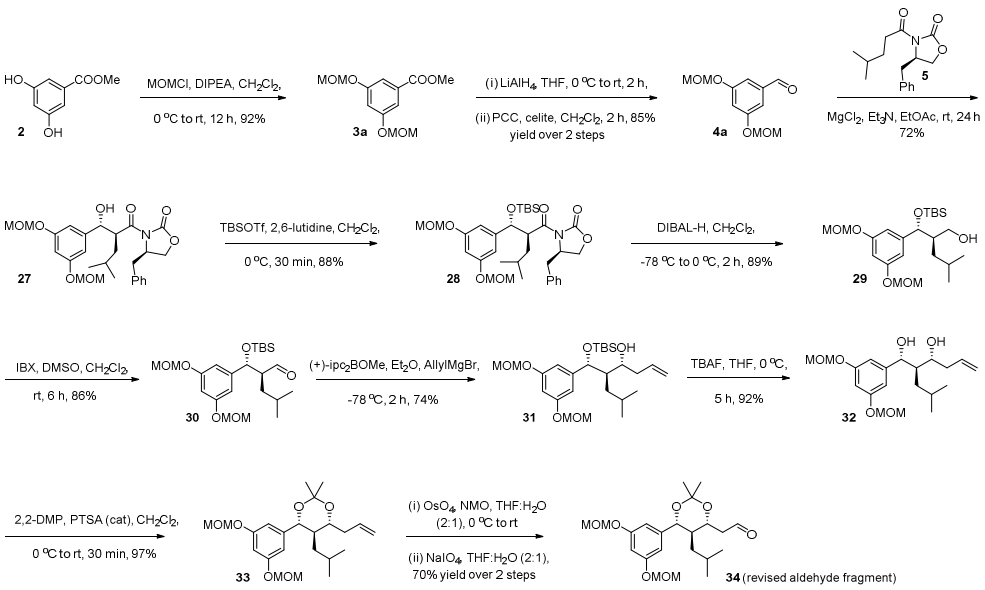
To resolve this issue and, consequently, assign the correct stereostructure to natural BmcA, we conducted total syntheses of both **1a** and **1b**. As depicted retrosynthetically in Scheme 5, the plan for these syntheses involved joining **39** and **43** with aldehyde **34** using the Carreira alkynylation protocol.[15] Fragment **34** was prepared from 3,5-bis(methoxymethoxy)benzaldehyde (**4a**) by employing a route similar to the one used to generate **12**. The redesigned alkyne fragments, **39** and **43** were synthesized starting with the common chiral precursor **36** which in turn was stereoselectively prepared from commercially available *cis*-4,6-dimethylcyclohexan-1,3-dione by employing an approach that uses enzymatic desymmetrization, Wittig olefination and Evans asymmetric alkylation.

Scheme 5. Retrosynthetic analysis of two possible structures (1a and 1b) of BmcA



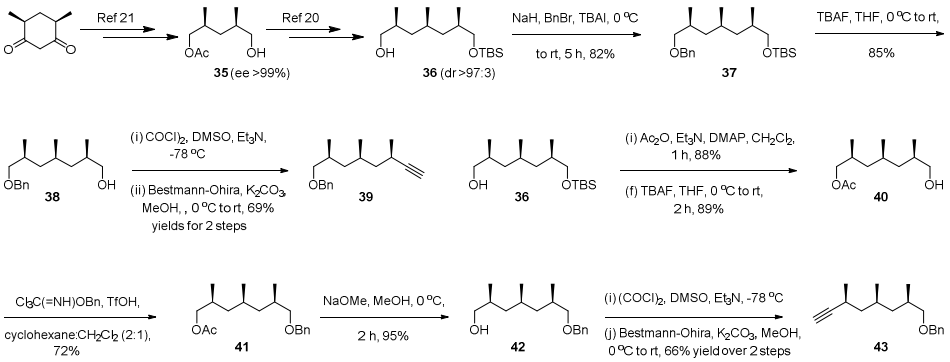
Synthesis of **34** commenced with preparation of MOM-protected aldehyde **4a** from **2** (78%, 3 steps). A*nti* aldol reaction[19] between amide **5** and MOM-protected aldehyde **4a** in presence of magnesium chloride produced hydroxyamide **27** (72%, *dr* = 97:3 by NMR). The *anti* aldol product **27** was then used in a reaction sequence that mimics the one used to prepare **12** to provide revised aldehyde fragment **34**. Accordingly, *anti* aldol product **27** was protected as its TBS ether **28** (88%). Amide group in **28** was reduced by DIBAL-H to get alcohol **29** which was subsequently oxidized to aldehyde **30** using IBX (76%, 2 steps). Brown allylation[9] of aldehyde **30** afforded homoallylic alcohol **31** (74%, *dr* = 90:10 by NMR).[10] It is noteworthy to mention that the diastereomeric mixture was separated in the next stage of the reaction. Deprotection of TBS group in **31** afforded 1,3-diol **32** followed by acetonide protection to provide **33** (89%, 2 steps). Dihydroxylation followed by oxidative cleavage of olefin **33** provided revised aldehyde fragment **34** (70%, 2 steps) (Scheme 6).

Scheme 6. Synthesis of revised aldehyde fragment 34 (*anti* configuration)



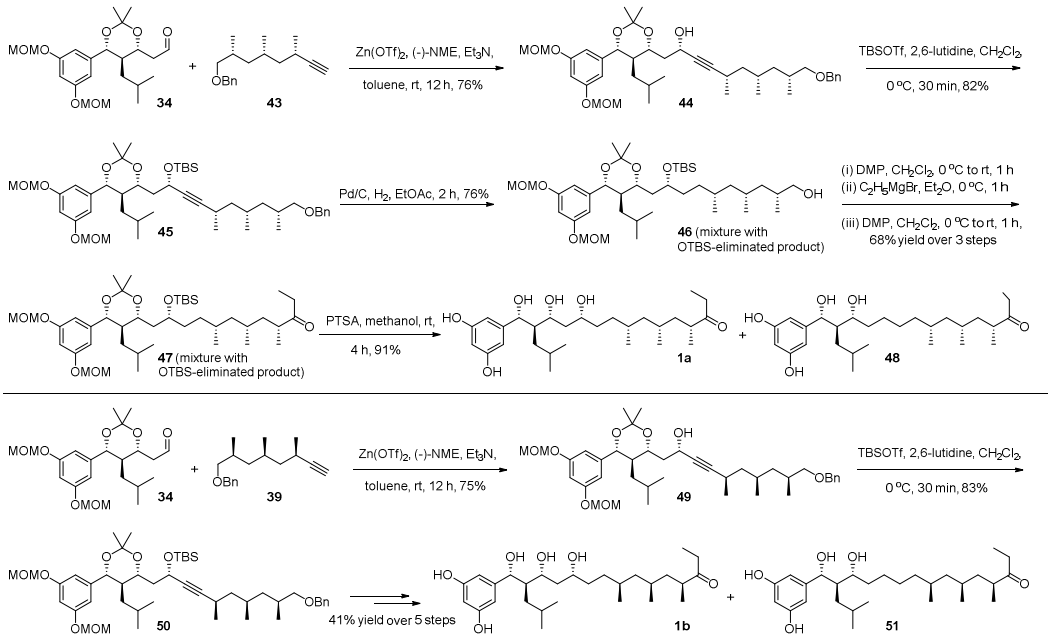
Both the revised alkyne fragments (**39** and **43**) derived from a known precursor **36** which was synthesized from **35** by following a reported protocol.[20] Fragment **35**, synthesized by using a known four step protocol starting with *cis*-4,6-dimethylcyclohexan-1,3-dione,[21] was transformed to alcohol **36**. Benzyl protection of hydroxyl group in **36** was carried out to afford **37** (82%). TBS group of **37** was deprotected to get primary alcohol **38** (85%) which was then subsequently oxidized under Swern condition[13] followed by Bestmann-Ohira reaction[14] to generate alkyne fragment **39** with all *syn* configuration (69%, 2 steps). On the other hand, acetyl protection of **36**, followed by deprotection of TBS ether delivered primary alcohol **40** (78%, 2 steps). Benzyl protection of hydroxyl group in **40** was done to afford **41** (72%), which was hydrolyzed under basic condition to afford primary alcohol **42** (95%). Primary alcohol **42** underwent Swern oxidation[13] followed by Bestmann-Ohira reaction[14] to generate alkyne fragment **43** with all *syn* configuration (66%, 2 steps) (Scheme 7).

Scheme 7. Synthesis of revised alkyne 39 and 43



Carreira alkynylation[15] of **34** and **43** occurred to form propargylic alcohol **44** (76%, *dr* = 95:5 by NMR). Protection of the hydroxyl group in **44** formed TBS ether **45** (82%), which was then subjected to hydrogenation to produce a mixture (76%) of saturated alcohol **46** and its TBS ether elimination product (8:2, confirmed by ^{1}H NMR analysis) which was inseparable. The mixture of **46** and its TBS ether elimination product was oxidized to generate a crude aldehyde, which was reacted with EtMgBr to produce a secondary alcohol which upon oxidation formed a mixture (68%, 3 steps) of ketone **47** and its TBS ether elimination product which was inseparable. Finally, global deprotection of the mixture was achieved by using PTSA to produce **1a** and 11-deoxy derivative **48** (91%, combined yield) which was separable. Similarly, the BmcA isomer **1b** was synthesized by condensing aldehyde **34** with alkyne **39**.[15] The formed propargylic alcohol **49** (75%, *dr* = 96:4 by NMR) was converted to its TBS ether **50** (83%), which when subjected to a similar reaction sequence utilized to form **1a** gave BmcA isomer **1b** along with 11-deoxy derivative **51** (41%, 5 steps) (Scheme 8). Comprehensive NMR analysis data (COSY, HSQC, HMBC, ^{1}H-^{1}H decoupling, and HETLOC) for **1a** are available in supporting information.

Scheme 8. Synthesis of 1a and 1b



The absolute configurations of the chiral centers on the left part of **1a** were confirmed by using NMR analysis of its acetonide derivatives (acetonide A and B, Figure 6). The ^{13}C chemical shifts of the *gem*-dimethyl groups in acetonide A are 20.1 and 30.6 ppm, indicating the existence of a *syn*-relationship between 13-OH and 1'-OH groups. The *gem*-dimethyl groups in acetonide B have ^{13}C chemical shifts of 20.3 and 30.7, indicating that 11-OH and 13-OH also have a *syn*-relationship (Figure 6).

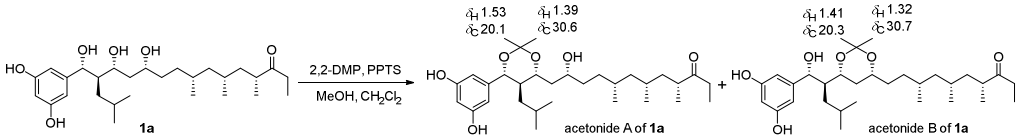


Figure 6. Acetonide derivatization of **1a**. Chemical shifts indicate a *syn* relationship of the both acetonides.

In addition, analysis of ^{1}H and 2D NMR spectra of acetonide A, which contains an isobutyl group in the 1,3-dioxane ring, shows that the H-14/H-1' coupling constant is 10.5 Hz. This large coupling shows that an axial-axial and thus *anti*-relationship exists between H-14 and H-1' (Figure 7). As depicted in Figure 7, H-1' (δ_H 4.35) and H-13 (δ_H 3.79) exhibit ROESY

correlations commonly associated with an axially oriented acetonide methyl group (δ_H 1.53). Moreover, H-1'/H_2-15 (δ_H 1.20 and 0.99) and H-13/H_2-15 ROESY correlations establish that the isobutyl group exists in an equatorial position, thus showing that a *syn*-relationship exists between H-1' and H-13. ROESY coupling between and H-16 (δ_H 0.95) and H-1' also support the assignment of the relative configuration in the 1,3-dioxane, thus confirming the 11*R**, 13*R**, 14*R**, and 1'*R** configuration of **1a**. Based on the absolute configuration of C-11 in this acetonide, established by using the modified Mosher's method, the absolute stereochemistry was unequivocally confirmed to be 11*R*, 13*R*, 14*R*, and 1'*R*.

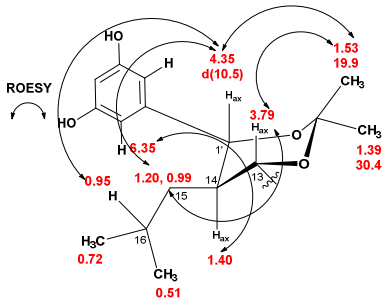


Figure 7. The key ROESY correlations of the acetonide A of **1a** showing the relative configuration of the *iso*-butyl group.

Importantly, the ^{1}H and ^{13}C NMR spectra of **1a**, having 4*R*, 6*R*, 8*R*, 11*R*, 13*R*, 14*R*, and 1'*R* configurations, were virtually identical to those of natural BmcA even though the reported[4] NMR spectra of natural BmcA include unidentified impurities (Figure S163). In contrast, the NMR data of **1b**, possessing 4*S*, 6*S*, 8*S*, 11*R*, 13*R*, 14*R*, and 1'*R* configurations, do not match those for natural BmcA. These observations strongly suggest that the relative configurations of BmcA need to be revised to be 4*R**, 6*R**, 8*R**, 11*R**, 13*R**, 14*R**, and 1'*R**. The optical rotation of synthetic **1a** is +10.0 (c 0.40, MeOH) whereas that of isolated natural BmcA $[\alpha]^{20}_{D}$ is -12.0 (c 0.20, MeOH). The magnitude of the two optical rotation values (**1a** and natural BmcA) was very similar but the sign was opposite, which suggests that synthetic **1a** would be enantiomer of the

natural product. However, because the ^{1}H NMR spectrum (Figure S163)[4] of natural BmcA shows that it contains many unidentified impurities the reported optical rotation is questionable. As previously mentioned, the absolute configuration of natural BmcA was arbitrarily assigned in the original report. Owing to the impurities in natural BmcA and the uncertainty of the reported optical rotation value, the absolute stereochemistry of BmcA was unclear to us. Aggarwal *et. al*.[6c] reported that synthetic **1a** is enantiomer of the natural product while our manuscript was under review. In the effort described above, we achieved the first total synthesis of correct enantiomer (**1a**) of BmcA. By using ^{1}H, ^{1}H-^{1}H decoupling, and HETLOC NMR experiments performed with a 900 MHz spectrometer, we have performed *J*-based configuration analysis (Figure 8) for **1a** and clarified the misinterpreted *J*-based configuration analysis in the previous report, which was possibly a result of overlapped ^{1}H signals in a lower field region of the ^{1}H NMR caused by using a 700 MHz instrument.

In order to revise the reported[4] configurations at stereocenters of natural baulamycin A, we focused to clarify what caused misinterpretation in *J*-based configuration analysis in the previous[4] report. The ^{1}H, ^{1}H-^{1}H decoupling, and HETLOC NMR experiments of **1a** performed in 900 MHz NMR spectrometer enabled us to obtain accurate $^{3}J_{HH}$, $^{3}J_{CH}$, and $^{2}J_{CH}$ values and compare them with those[4] in literature (Figure 8). Based on our careful measurement of $^{3}J_{HH}$, $^{3}J_{CH}$, and $^{2}J_{CH}$ values and *J*-based configuration analysis, we identified critical errors in the previous[4] report. Besides minor errors like alleged typos, wrong interpretation of *J* based configuration analysis of the stereogenic centers around C-6 and C-14 resulted in wrong assignments for the configurations of C-6 and C-14. First, we corrected $^{3}J_{H14,H13}$ value from 7.7 Hz to 4.0 Hz based on the ^{1}H-^{1}H decoupling experiment at H-15, which was not performed in the previous[4] report. Furthermore, $^{2}J_{C13H14}$ value was revised from 7.0 Hz to 2.0 Hz, establishing the

rotamer in Figure 8-b. Additional decoupling experiments were performed at H-10, H-11, H-12, and H-13 to correct the $^{3}J_{H13,H12a}$ (7.2 Hz to 3.5 Hz), $^{3}J_{H13,H12b}$ (3.1 Hz to 9.5 Hz), $^{3}J_{H11,H12a}$ (8.0 Hz to 4.5 Hz), and $^{3}J_{H11,H12b}$ (3.2 Hz to 8.5 Hz) values. Careful analysis of HETLOC data enabled to identify $^{2}J_{C13,H12a}$, $^{2}J_{C13,H12b}$, and $^{2}J_{C11,H12a}$ as 1.0, 4.5, and 1.5 Hz, which were misassigned as 6.2, 1.8, and 6.8 Hz respectively in the previous[4] report. The *anti*-relationship between H-13 and H-12b and large value of $^{2}J_{C13,H12b}$ constructed the revised rotamer depicted in Figure 8-c. The H-11/H-13, H-12a/H-13, H-12a/H-14, and H-12b/H-14 ROESY correlations supported this revised rotamer. The small coupling constant (4.5 Hz) of H-11/H-12a and the large coupling constant (8.5 Hz) of H-11/H-12b, which were previously reported in the opposite way [large (8.0 Hz) for $^{3}J_{H11,H12a}$ and small (3.2 Hz) for $^{3}J_{H11,H12b}$] were key evidence for the construction of the revised rotamer in Figure 8-d. Furthermore, several critical errors of coupling constants in the previous[4] report were found in C-7-C-6 (Figure 8-i) and C-5-C-4 (Figure 8-k) rotamers. For the extraction of accurate coupling constants, a suite of ^{1}H-^{1}H decoupling NMR experiments were performed for H_2-7, H-6, H_2-5, and H-4. Based on the newly measured $^{3}J_{HH}$ values, $^{3}J_{H7a,H6}$ (3.2 Hz) and $^{3}J_{H7b,H6}$ (3.0 Hz) were revised to 8.5 and 6.6 Hz, respectively. $^{3}J_{C5H7b}$ and $^{3}J_{C20H7b}$ values (6.0 Hz and 3.5 Hz), which were not reported in the previous[4] report, were also clearly measured in our HETLOC NMR data. Thus, *anti*-relationships between H-7a/H-6 and C-5/H-7b were established in Figure 8-i. The *gauche* relationships of H-7b/H-6, C-8/H-6, C-5/H-7a, C-20/H-7a, and C-20/H-7b were also identified by the coupling constants, completing the rotamer depicted in Figure 8-i. Additional proton decoupling experiments for H-4, H-5a, H-5b, H_3-19 revealed that reported[4] $^{3}J_{H5a,H4}$ (3.2 Hz) and $^{3}J_{H5b,H4}$ (8.0 Hz) values had to be revised to 8.5 and 5.0 Hz, respectively. Careful analysis of HETLOC data resulted in the correction of $^{3}J_{C21,H5a}$ (11.0 Hz) to 4.0 Hz. Thus, the *anti*-relationship between H-5a and H-4 was established

in Figure 8-k. The relationships between H-5b/H-4, C-6/H-4, C21/H-5a, and C-21/H-5b were determined as *gauche*, completing the rotamer depicted in Figure 8-k. Consequently, our comprehensive *J*-based configuration analysis utilizing ^{1}H, ^{1}H-^{1}H decoupling and HETLOC NMR experiments at high fields (800/900 MHz) allowed for the revision of J_{HH} and J_{CH}, thus confirming the configurations of synthetic baulamycin A (**1a**). In the previous[4] report of natural baulamycin A, the coupling constants were measured at lower magnetic field without performing ^{1}H-^{1}H decoupling experiments. This may have caused the mismeasurement of the coupling constants and thus resulted in the confusion for establishing the relative configurations because of highly overlapped ^{1}H signals in baulamycin A. Errors in coupling constant measurement in the previous report[4] are comprehensively noted in Figure S164.

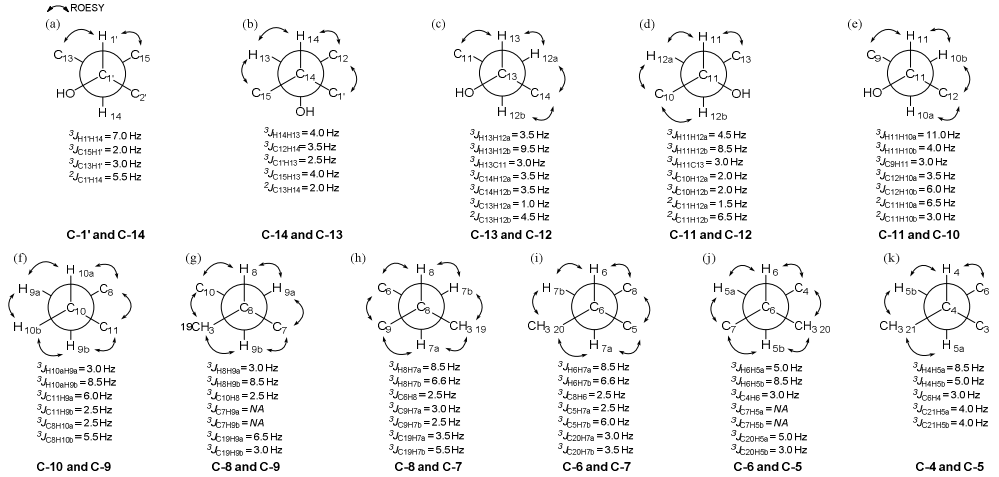
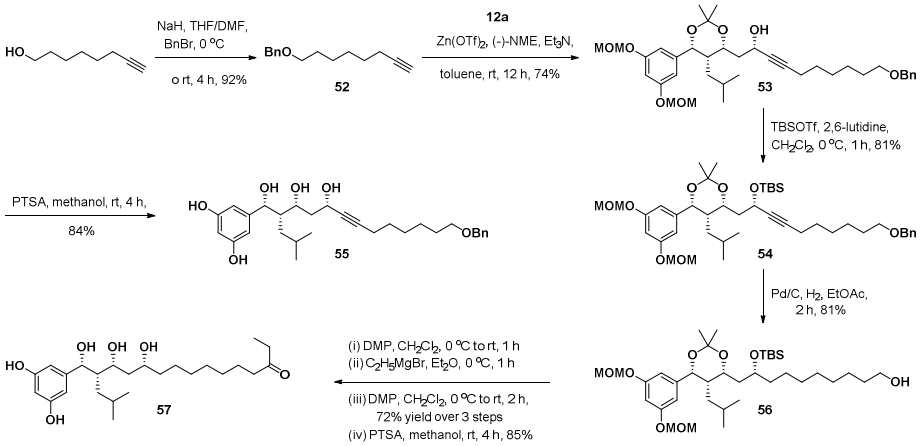


Figure 8. *J*-based configuration analysis of **1a**. Arrows represents ROESY correlations.

As part of these studies, twelve BmcA derivatives, including enantiomer of BmcA (**1a**), were subjected to SAR analysis to assess inhibitory activities against SbnE.[22] Synthesis of baulamycin A derivatives **55** and **57** is depicted in Scheme 9. Carreira alkynylation[15] between aldehyde fragment **12a** and benzyl-protected alkyne fragment **52** derived from 7-octyne-1-ol was achieved to deliver propargylic alcohol **53** (74%, *dr* = 96:4 by NMR). MOM and acetonide group in **53** was deprotected by using PTSA to afford polyhydroxy compound **55** (84%).

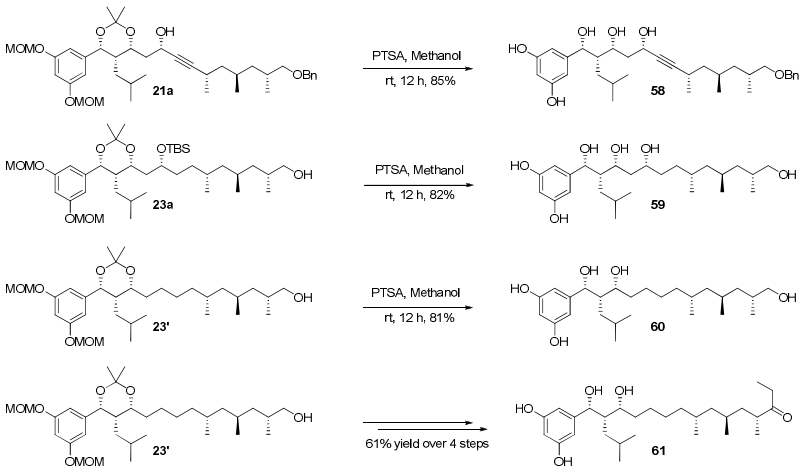
Propargylic hydroxyl group in **53** was protected as its TBS ether **54** (81%). Hydrogenation of **54** using Pd/C was carried out to provide saturated primary alcohol **56** (81%).[23] A similar sequence of reactions like baulamycin A preparation was adopted to deliver **57,** a derivative of baulamycin A (61%, 4 steps). Baulamycin A derivatives **55** and **57** were submitted for SAR study (Table 1).

Scheme 9. Synthesis of baulamycin A derivatives 55 and 57



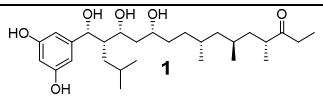
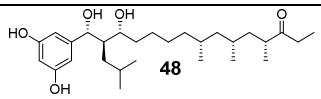
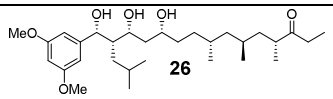
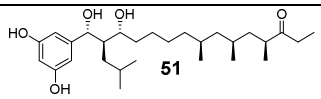
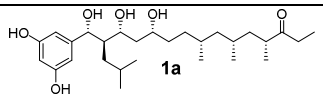
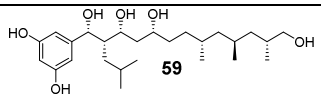
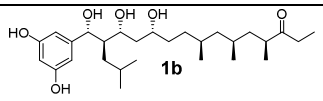
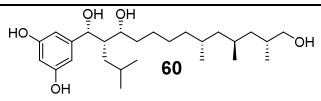
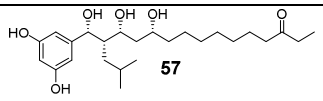
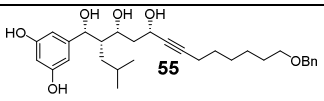
Synthesis of other baulamycin A derivatives **58**, **59**, **60** and **61** are outlined in Scheme 10. All of protecting groups (MOM, acetonide, and TBS) in **21a, 23a** and **23'** were deprotected to afford compound **58, 59** and **60** respectively and similar sequence of reactions (oxidation, Grignard reaction, oxidation, deprotection) like baulamycin A synthesis were applied on **23'** to provide **61** as a baulamycin A derivative (60%, 4 steps) (Scheme 10).

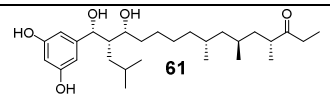
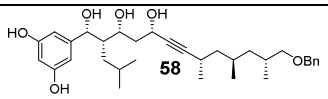
Scheme 10. Synthesis of baulamycin A derivatives 58, 59, 60 and 61



SbnE inhibition assay results, obtained by employing a malachite green-based method[24] are outlined in Table 1. In contrast to Sherman and co-workers report that natural BmcA has an IC_{50} value of 4.8 μM,[4] **1** possessing the originally proposed stereostructure of this substance has virtually no activity (IC_{50} >50 μM). In contrast, **1a**, whose stereostructure is now known to be that of enantiomer of natural BmcA, has an IC_{50} value of 14.4 μM.

Table 1: IC_{50} values of BmcA derivatives against SbnE.

Compound	IC_{50} (uM)	Compound	IC_{50} (uM)
 **1**	>50	 **48**	20.98
 **26**	>50	 **51**	25.73
 **1a**	14.40	 **59**	>50
 **1b**	47.27	 **60**	27.77
 **57**	>50	 **55**	7.16

 **61**	10.16	 **58**	11.07

The results of the SAR study show that the existence of branched methyl groups on the hydrocarbon tail (C-1 through C-10) has little to no effect on inhibitory activity. Based on a comparison of the IC_{50} values of **1**, **26**, **57** and **59** with those of **1a** and **1b**, the (*R*)-configuration at C-14 seems to be required for inhibitory activity for BmcA derivatives having three hydroxyl groups at C-11, C-13 and C-1' positions and saturated hydrocarbon tails (C-1 through C-10). However, BmcA derivatives **48**, **51**, **60** and **61** that do not contain the C-11 hydroxyl group possess inhibitory activities regardless of the stereochemistry at C-14. Interestingly, the acetylene derivatives **55** and **58** exhibit appreciable potencies despite having the (*S*)-configuration at C-14 and three hydroxyl groups at C-11, C-13 and C-1'. These compounds contain a chain-rigidifying modification caused by incorporation of a triple bond between C-9 and C-10, which may contribute to control of the hydrocarbon tail orientation for optimal interaction in the active site of SbnE. It should be noted that **55** has the highest potency among all of the tested derivatives. A more comprehensive SAR study probing the consequences of specific stereochemical and structural changes is underway and will be discussed in due course.

Conclusions

In summary, we have accomplished a synthesis of the earlier reported stereostructure of BmcA and found that discrepancies exist in the spectroscopic properties between the synthetic material and the natural BmcA. Two possibly correct stereostructures for BmcA, identified on the basis of comprehensive NMR analysis, were prepared by total synthesis. The synthetic pathways employ stereoselective Evans Aldol, Brown allylation and Carreira alkynylation reactions, and a prolinol

amide derived alkylation/desymmetrization protocol for installing three chiral centers at C-4, C-6 and C-8. Comprehensive NMR studies with these two synthetic materials (**1** and **1a**) enabled the assignment of the correct enantiomer (**1a**) of BmcA. Moreover, inhibitory activities of novel BmcA derivatives against SbnE were determined. The SAR data provide insight about how the configuration of C-14, the existence of OH-11 and chain-rigidifying group affect inhibitory activities against SbnE. It is worth noting that the propargylic alcohol **55**, having 14*S* configuration, exhibits the highest SbnE inhibitory activity even though it lacks three methyl groups at C-4, C-6 and C-8 and a ketone group, suggesting that the presence of a chain-rigidifying triple bond contributes to the inhibitory activity of members of this class of substances. This structural revision with efficient synthetic strategy and SAR study lay the groundwork for discovering new BmcA derivatives that overcome drug resistant pathogens that cause life-threatening infections.

Experimental Section

General Experimental Methods: All reactions were carried out under an inert atmosphere of argon or nitrogen using standard syringe, septa, and cannula techniques unless otherwise mentioned. Reactions were monitored by using TLC with 0.25 mm E. Merck precoated silica gel plates (60 F_{254}). Reaction progress was monitored by using TLC with a UV lamp, ninhydrin, or *p*-anisaldehyde stain for detection purposes. Commercially available reagents were used without further purification. All solvents were purified by using standard techniques. Purification of products was carried out by using silica gel column chromatography using Kieselgel 60 Art. 9385 (230-400 mesh). The purity of all compounds was determined to be over 95% by using a Waters LCMS system (Waters 2998 Photodiode Array Detector, Waters 3100 Mass Detector,

Waters SFO System Fluidics Organizer, Water 2545 Binary Gradient Module, Waters Reagent Manager, Waters 2767 Sample Manager) using SunFireTM C18 column (4.6 x 50 mm, 5 μm particle size): solvent gradient = 60% (or 95%) A at 0 min, 1% A at 5 min. Solvent A = 0.035% TFA in H_2O; Solvent B = 0.035% TFA in MeOH; flow rate: 3.0 (or 2.5) mL/min. ^1H and ^{13}C NMR spectra were obtained using a Bruker 400 MHz FT-NMR (400 MHz for ^1H and 100 MHz for ^{13}C) spectrometer. ^1H, ^{13}C, and 2D nuclear magnetic resonance (NMR) spectra were also recorded on Bruker Avance 600-MHz spectrometers at the National Center for Inter-university Research Facilities at Seoul National University (NCIRF) and on a Bruker Avance II 900-MHz NMR spectrometer at the Korea Basic Science Institute (KBSI) at Ochang. Standard abbreviations are used for denoting the signal multiplicities. Infrared spectra were measured on FT-IR Nicolet iS10 spectrometer. Samples were recorded under neat or as KBr optics. High-resolution mass spectra (HRMS) were recorded on a QTOF mass spectrometer. Optical rotations were measured by a JASCO P-200 polarimeter with a 1 cm cell. UV spectra were acquired with a Perkin Elmer Lambda 35 UV/VIS spectrometer. Electrospray ionization (ESI) low–resolution LC/MS data were acquired on an Agilent Technologies 6130 quadrupole mass spectrometer coupled with an Agilent Technologies 1200–series HPLC. Semi-preparative HPLC separations were performed with an HPLC system composed of a Gilson 305 pump and a Gilson UV/VIS-155 detector.

Methyl 3,5-Bis(methoxymethoxy)benzoate (3a). To a solution of methyl 3,5-dihydroxybenzoate **2** (10 g, 59.4 mmol) in anhydrous CH_2Cl_2 (200 mL) was added diisopropylethylamine (41.8 mL, 240 mmol), followed by MOMCl (10.6 mL, 120 mmol) dropwise at 0 ^oC. The mixture was warmed to room temperature and stirred for 12 h. The mixture was then quenched with water (30 mL) and diluted with CH_2Cl_2 (50 mL). The organic

layer was separated and washed with saturated $NaHCO_3$ solution (30 mL) and extracted with CH_2Cl_2 (3 x 100 mL). The combined organic layer was washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The resulting residue was subjected to silica gel column chromatography to afford compound **3a** (13.9 g, 92%) as colorless oil. [Known literature method][25]; R_f = 0.8 (30% EtOAc/hexane).[25] ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35 (d, J = 2.3 Hz, 2H), 6.90 (t, J = 2.3 Hz, 1H), 5.18 (s, 4H), 3.88 (s, 3H), 3.47 (s, 6H); LCMS (ESI): 257 (M + H)$^+$.

3,5-Bis(methoxymethoxy)benzaldehyde (4a). To a stirred solution of methyl 3,5-bis(methoxymethoxy)benzoate **3a** (12 g, 46.4 mmol) in anhydrous THF (120 mL) was added dropwise a solution of lithium aluminium hydride (56 mL of a 1.0 M solution in THF, 55.7 mmol). The mixture was stirred at ambient temperature for 4 h and treated dropwise sequentially with water (1 mL), 15% aqueous NaOH (1 mL) and water (3 mL). The mixture was stirred for additional 1 h and filtered and the resulting solid was washed with THF. The filtrate was concentrated to provide 3,5-bis(methoxymethoxy)benzyl alcohol as a colorless liquid which was directly used in the next step without further purification.

To a solution of PCC (13.1 g, 61.2 mmol) and sodium acetate (17.3 g, 21.4 mmol) in CH_2Cl_2 (100 mL) was added a solution of 3,5-bis(methoxymethoxy)benzyl alcohol (7 g, 30.6 mmol) in CH_2Cl_2 (8 mL). The mixture was stirred under nitrogen for 2 h and treated with ether (300 mL). The brown mixture was filtered through filter paper over Celite. The filtrate was concentrated to provide brown oil which was subjected to silica gel column chromatography to afford compound **4a** (8.9 g, 85% over two steps) as a colorless oil. [known literature method][25]; R_f = 0.4 (20% EtOAc/hexane); ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.89 (s, 1H), 7.19 (d, J = 2.3 Hz, 2H), 6.96 (t, J

= 2.3 Hz, 1H), 5.19 (s, 4H), 3.47 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 191.5, 158.7, 138.4, 111.1, 110.3, 94.4, 77.3, 77.0, 76.6, 56.1; LCMS (ESI): 227 $(M + H)^+$.

(*R*)-4-Benzyl-3-(4-methylpentanoyl)oxazolidin-2-one (5). To a stirred solution of 4-methylvaleric acid (4 g, 34.4 mmol) in anhydrous THF (100 mL) at -20 ^{o}C was added Et_3N (12 mL, 86.1 mmol) followed by pivaloyl chloride (4.2 mL, 34.4 mmol). The mixture was stirred for 1 h at -20 ^{o}C and treated sequentially with LiCl (2.2 g, 51.6 mmol) and (*R*)-4-benzyloxazolidin-2-one (6.7 g, 37.8 mmol) at same temperature. The mixture was stirred for 1 h at -20 ^{o}C and for 2 h at 0 ^{o}C and quenched with saturated NH_4Cl solution (30 mL). The mixture was diluted with EtOAc (50 mL) and extracted with EtOAc (3 x 50 mL). The combined organic layer was washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was subjected to silica gel column chromatography to afford **5** (8.5 g, 90%) as a yellow liquid. R_f = 0.3 (30% EtOAc/hexane); $[\alpha]_D^{24}$ = +45.4 (*c* 0.55, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35-7.31 (m, 2H), 7.29-7.25 (m, 1H), 7.22-7.19 (m, 2H), 4.69-4.64 (m, 1H), 4.21-4.09 (m, 2H), 3.28 (dd, *J* = 13.4, 3.3 Hz, 1H), 3.02-2.86 (m, 2H), 2.76 (dd, *J* = 13.4, 9.6 Hz, 1H), 1.70-1.52 (m, 3H), 0.93 (d, J = 6.4 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.6, 153.4, 135.3, 129.4, 128.9, 127.3, 66.1, 55.1, 37.9, 33.6, 33.1, 27.6, 22.3(2); HRMS (ESI): calcd. for $C_{16}H_{21}O_3NNa$ $[M + Na]^+$ 298.1419; found 298.1415.

(*R*)-4-Benzyl-3-((*R*)-2-((*R*)-(3,5-dimethoxyphenyl)(hydroxy)methyl)-4-methylpentanoyl)oxazolidin-2-one (6). To a 0.2-0.5 M solution of **5** (9.0 g, 32.7 mmol) in anhydrous CH_2Cl_2 (100 mL) under argon at 0 ^{o}C was added dibutylboron triflate (39.2 mL of a 1.0 M solution in CH_2Cl_2, 39.2 mmol), followed by diisopropylethylamine (7.4 mL, 42.5 mmol) dropwise. After stirred for 30 min at 0 ^{o}C, the mixture was cooled to -78 ^{o}C and treated with benzaldehyde **4** (6 g, 36 mmol). The mixture was then stirred for 30 min at -78 ^{o}C and for 1.5 h

at room temperature. The boron complex was quenched with phosphate buffer (pH~7, 50 mL) and oxidized with a mixture of 30% H_2O_2 and methanol (100 mL of a 2:1 solution) for 1 h at 0 ^oC. The mixture was stirred for 1 h at room temperature and the resulting mixture was concentrated to slurry. The residue was extracted with ether (3 x 100 mL) and the combined organic extracts were washed with 5% aqueous $NaHCO_3$ solution (30 mL), brine (30 mL), and then dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was subjected to silica gel column chromatography to afford **6** (13.7 g, 86%) as a colorless liquid. R_f = 0.2 (20% EtOAc/hexane); $[\alpha]_D^{24}$ = −206.6 (*c* 1.08, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 7.34-7.27 (m, 3H), 7.19-7.17 (m, 2H), 6.56 (d, *J* = 2.1 Hz, 2H), 6.35 (t, *J* = 2.3 Hz, 1H), 4.76 (q, *J* = 3.1 Hz, 1H), 4.49-4.45 (m, 1H), 4.43-4.36 (m, 1H), 4.01 (dd, *J* = 9.0, 2.2 Hz, 1H), 3.77 (s, 6H), 3.22 (dd, *J* = 13.4, 3.4 Hz, 1H), 2.68 (dd, *J* = 13.4, 9.8 Hz, 1H), 2.35 (d, *J* = 3.3 Hz, 1H), 2.04-1.94 (m, 1H), 1.58-1.49 (m, 3H), 0.91 (d, *J* = 2.6 Hz, 3H), 0.89 (d, *J* = 2.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 174.6, 160.4, 152.9, 144.1, 135.0, 129.2, 128.7, 127.1, 103.7, 100.1, 75.7, 65.7, 55.5, 55.1, 48.4, 37.7, 36.7, 26.5, 23.5, 21.7; HRMS (ESI): calcd. for $C_{25}H_{31}O_6NNa$ $[M + Na]^+$ 464.2049; found 464.2044.

(*R*)-4-Benzyl-3-((*R*)-2-((*R*)-((*tert*-butyldimethylsilyl)oxy)(3,5-dimethoxyphenyl)methyl)-4-methylpentanoyl)oxazolidin-2-one (7). To a solution of **6** (8 g, 18.1 mmol) in anhydrous CH_2Cl_2 (50 mL) was added 2,6-lutidine (8.4 mL, 72.4 mmol), followed by TBSOTf (8.3 mL, 36.2 mmol) slowly at 0 ^oC. The mixture was stirred for 1 h at 0 ^oC and quenched with water (15 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 x 50 mL). The combined organic layer was washed with saturated $NaHCO_3$ solution (30 mL) and dried over $MgSO_4$, concentrated under reduced pressure to give crude residue which was subjected to silica gel column chromatography to afford **7** (8.8 g, 88%) as a yellow liquid. R_f = 0.3 (30%

EtOAc/hexane); $[\alpha]_D^{24}$ = +218.5 (*c* 1.09, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.32-7.23 (m, 3H), 7.19-7.14 (m, 2H), 6.49 (d, *J* = 2.6 Hz, 2H), 6.30 (t, *J* = 2.2 Hz, 1H), 4.54 (d, *J* = 7.8 Hz, 1H), 4.36-4.31 (m, 1H), 4.17-4.12 (m, 1H), 3.88 (dd, *J* = 8.9, 1.6 Hz, 1H), 3.74 (s, 6H), 3.48 (t, *J* = 8.1 Hz, 1H), 3.11 (dd, *J* = 13.3, 3.2 Hz, 1H), 2.67 (dd, *J* = 13.3, 9.5 Hz, 1H), 1.99-1.91 (m, 1H), 1.68-1.59 (m, 1H), 0.93 (d, *J* = 6.4 Hz, 6H), 0.91-0.89 (m, 1H), 0.88 (s, 9H), 0.03 (s, 3H), -0.18 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 174.3, 160.3, 152.8, 145.1, 135.4, 129.4, 128.8, 127.2, 104.2, 100.2, 77.8, 65.7, 55.9, 55.4, 50.2, 38.1, 37.9, 26.8, 25.7, 23.7, 21.9, 18.1, -4.6, -5.2; HRMS (ESI): calcd. for $C_{31}H_{45}O_6NSiNa$ $[M + Na]^+$ 578.2914; found 578.2918.

(*R*)-2-((*R*)-((*tert*-Butyldimethylsilyl)oxy)(3,5-dimethoxyphenyl)methyl)-4-methylpentanal (8). To a solution of **7** (8 g, 14.4 mmol) in anhydrous CH_2Cl_2 (100 mL) was added DIBAL-H (25.6 mL, 36 mmol, 20% solution in toluene) slowly for 15 min at -78 ^{o}C. The mixture was stirred for 30 min at -78 ^{o}C before being quenched with methanol (10 mL) and aqueous saturated sodium potassium tartrate solution (50 mL). The mixture was passed through a small pad of Celite and then extracted with CH_2Cl_2 (3 x 50 mL). The combined organic layer was dried over $MgSO_4$, concentrated under reduced pressure to get crude residue which was used for next step without further purification.

In the next step, to a solution of crude residue in MeOH: H_2O (4:1, 40 mL) was added solid K_2CO_3 (8 g, 58 mmol) at 0 ^{o}C and the mixture was stirred for 1 h at the same temperature. The mixture was filtered through a pad of Celite and the filter cake was washed with CH_2Cl_2 (20 mL). The filtrate was washed with water (10 mL) and brine (10 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The residue was subjected to silica gel column chromatography to give compound **8** (3.3 g, 60% over two steps) as a colorless liquid. R_f = 0.8 (20% EtOAc/hexane); $[\alpha]_D^{24}$ = +51.8 (*c* 0.89, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.67 (d, *J*

= 2.8 Hz, 1H), 6.43 (d, *J* = 2.1 Hz, 2H), 6.34 (t, *J* = 2.2 Hz, 1H), 4.93 (d, *J* = 4.7 Hz, 1H), 3.77 (s, 6H), 2.59-2.52 (m, 1H), 1.74-1.66 (m, 1H), 1.49-1.38 (m, 1H), 1.33-1.25 (m, 1H), 0.90 (s, 9H), 0.83 (d, *J* = 6.5 Hz, 3H), 0.74 (d, *J* = 6.5 Hz, 3H), 0.03 (s, 3H), -0.13 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 205.0, 160.6, 144.7, 104.3, 99.3, 74.8, 58.2, 55.3, 33.0, 25.7, 23.3, 21.7, 18.1, -4.6, -5.3; HRMS (ESI): calcd. for $C_{21}H_{36}O_4SiNa$ $[M + Na]^+$ 403.2281; found 403.2272.

(4*R*,5*S*)-5-((*R*)-((*tert*-Butyldimethylsilyl)oxy)(3,5-dimethoxyphenyl)methyl)-7-methyloct-1-en-4-ol (9). To a stirred solution of (+)-ipc$_2$BOMe (3.3 g, 10.4 mmol) in anhydrous Et_2O (20 mL) was added allylmagnesium bromide (7.9 mL of 1.0 M solution in ether, 7.89 mmol,) at 0 ^{o}C. The mixture was stirred at room temperature for 1 h before being cooled to -78 ^{o}C. The mixture was treated dropwise with aldehyde **8** (2.0 g, 5.26 mmol) at -78 ^{o}C and stirred for 1 h at same temperature and allowed to warm to room temperature. The mixture was treated with an aqueous solution of NaOH (2 M in H_2O, 10 mL) and 30% H_2O_2 solution (5 mL) at 0 ^{o}C. The biphasic solution was separated and the aqueous layer was extracted with Et_2O (3 x 30 mL). The combined organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was subjected to silica gel column chromatography to give compound **9** (3.2 g, 74%) as a colorless liquid. R_f = 0.2 (10% EtOAc/hexane); $[\alpha]_D^{24}$= + 29.1 (*c* 0.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.48 (d, *J* = 2.1 Hz, 2H), 6.33 (t, *J* = 2.2 Hz,1H), 5.84-5.73 (m, 1H), 5.12-5.06 (m, 2H), 4.78 (d, *J* = 4.4 Hz, 1H), 3.88 (t, *J* = 7.5 Hz, 1H), 3.78 (s, 6H), 2.31-2.22 (m,1H), 2.18-2.11 (m, 1H), 1.67-1.63 (m, 1H), 1.56 (brs, 1H), 1.46-1.38 (m, 1H), 1.29-1.19 (m, 2H), 0.92 (s, 9H), 0.78 (d, *J* = 6.2 Hz, 3H), 0.72 (d, *J* = 6.2 Hz, 3H), 0.07 (s, 3H), -0.17 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.5, 146.2, 135.6, 117.2, 104.3, 99.1, 77.8, 72.4, 55.2, 48.0, 39.6, 32.3, 27.0, 25.8, 23.2, 22.4, 18.0, -4.5, -5.1; HRMS (ESI): calcd. for $C_{24}H_{42}O_4SiNa$ $[M + Na]^+$ 445.2750; found 445.2745.

(1*R*,2*S*,3*R*)-1-(3,5-Dimethoxyphenyl)-2-isobutylhex-5-ene-1,3-diol (10). To a stirred solution of silyl compound **9** (3 g, 7.10 mmol) in anhydrous THF (20 mL) was added TBAF (12.8 mL of 1 M solution in THF, 12.79 mmol) at 0 °C. The mixture was stirred for 4 h at room temperature, diluted with saturated $NaHCO_3$ solution (5 mL). Organic layer was separated and washed with brine (5 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The residue was subjected to silica gel column chromatography to give compound **10** (2.0 g, 93%) as a colorless liquid. R_f = 0.15 (20% EtOAc/hexane); $[\alpha]_D^{24}$ = +1.9 (*c* 0.69, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.51 (d, *J* = 2.2 Hz, 2H), 6.33 (t, *J* = 2.2 Hz, 1H), 5.87-5.77 (m, 1H), 5.18-5.14 (m, 2H), 4.97 (brs, 1H), 4.04-4.01 (m, 1H), 3.78 (s, 6H), 3.25 (d, *J* = 1.7 Hz, 1H), 2.56 (d, *J* = 2.2 Hz, 1H), 2.32-2.21 (m, 2H), 1.74-1.70 (m, 1H), 1.44-1.35 (m, 1H), 1.28-1.21 (m, 1H), 1.01-0.93 (m, 1H), 0.72 (d, *J* = 6.6 Hz, 3H), 0.52 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.6, 146.0, 135.0, 118.2, 103.7, 99.1, 78.1, 75.5, 55.3, 47.0, 39.9, 30.2, 27.3, 22.6, 22.5; HRMS (ESI): calcd. for $C_{18}H_{28}O_4Na$ $[M + Na]^+$ 331.1885; found 331.1885.

(4*R*,5*S*,6*R*)-4-Allyl-6-(3,5-dimethoxyphenyl)-5-isobutyl-2,2-dimethyl-1,3-dioxane (11). To a stirred solution of **10** (2.0 g, 6.49 mmol) in CH_2Cl_2 (20 mL) was added 2,2-dimethoxy propane (4 mL, 30 mmol) followed by PTSA (cat.) at 0 ^{o}C. The mixture was allowed to warm to room temperature and stirred for 30 min before being quenched with water (10 mL). The organic layer was extracted with CH_2Cl_2 (3 x 10 mL) and the combined organic layer was washed with brine (5 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The residue was subjected to silica gel column chromatography to afford **11** (2.2 g, 96%) as a colorless liquid. R_f = 0.8 (20% EtOAc/hexane); $[\alpha]_D^{24}$ = +49.4 (*c* 0.75, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.50 (dd, *J* = 2.4, 0.6 Hz, 2H), 6.33 (t, *J* = 2.2 Hz, 1H), 5.91-5.80 (m, 1H), 5.15-5.05 (m, 2H), 4.99 (d, *J* = 1.8 Hz, 1H), 4.10 (dt, *J* = 7.8, 2.1 Hz, 1H), 3.79 (s, 6H), 2.40-2.29 (m, 1H), 2.22-2.14 (m, 1H),

1.50-1.49 (m, 1H), 1.50 (s, 3H), 1.49 (s, 3H), 1.25-1.14 (m, 2H), 0.88-0.78 (m, 1H), 0.69 (d, J = 6.5 Hz, 3H), 0.45 (d, J = 6.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.6, 143.7, 135.1, 116.7, 103.9, 99.3, 98.8, 75.2, 74.2, 55.3, 40.9, 37.5, 30.2, 29.9, 27.2, 22.8, 22.5, 19.5; HRMS (ESI): calcd. for $C_{21}H_{32}O_4Na$ $[M + Na]^+$ 371.2198; found 371.2181.

2-((4*R*,5*S*,6*R*)-6-(3,5-Dimethoxyphenyl)-5-isobutyl-2,2-dimethyl-1,3-dioxan-4-yl)acetaldehyde (12). To a stirred solution of compound **11** (2 g, 5.75 mmol) in THF:H_2O (3:1, 20 mL) was added NMO (1.2 g, 10.35 mmol) followed by osmium tetroxide (600 µL, 0.06 mmol) at 25 ^{o}C. The mixture was stirred at the same temperature for 2 h and quenched with aqueous $Na_2S_2O_4$ solution (5 mL). The mixture was extracted with EtOAc (3 x 10 mL) and the combined organic layer was washed with brine (5 mL), dried over $MgSO_4$ and concentrated under reduced pressure to get crude diol which was directly used for next step without further purification.

To a stirred solution of crude diol in THF:H_2O (2:1, 20 mL) was added $NaIO_4$ (1.9 g, 9.2 mmol) portion wise at 0 ^{o}C. The mixture was stirred for 2 h at room temperature and then diluted with saturated $NaHCO_3$ solution (5 mL). The layers were separated and the organic layer was washed with brine (5 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The residue was subjected to silica gel column chromatography to give compound **12** (1.37 g, 68% over two steps) as a colorless liquid. R_f = 0.4 (20% EtOAc/hexane); $[\alpha]_D^{24}$ = +172.1 (*c* 3.47, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.79 (t, J = 1.7 Hz, 1H), 6.49 (d, J = 1.7 Hz, 2H), 6.34 (t, J = 2.2 Hz, 1H), 5.07 (d, J = 2.0 Hz, 1H), 4.71-4.67 (m, 1H), 3.78 (s, 6H), 2.71 (ddd, J = 16.8, 8.8, 1.8 Hz, 1H), 2.45 (ddd, J = 16.9, 4.5, 1.5 Hz, 1H), 1.59-1.55 (m, 1H), 1.52 (s, 3H), 1.47 (s, 3H), 1.22-1.17 (m, 2H), 0.83-0.71 (m, 1H), 0.66 (d, J = 6.4 Hz, 3H), 0.45 (d, J = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 200.9, 160.6, 143.1, 103.8, 99.6, 98.9, 74.8, 69.0, 55.3, 47.1, 40.8, 30.4,

29.7, 27.4, 22.7, 22.3, 19.4; HRMS (ESI): calcd. for $C_{20}H_{30}O_5Na$ $[M + Na]^+$ 373.1991; found 373.1981.

2-((4*R*,5*S*,6*R*)-6-(3,5-Bis(methoxymethoxy)phenyl)-5-isobutyl-2,2-dimethyl-1,3-dioxan-4-yl)acetaldehyde (12a). ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.79 (t, J = 1.7 Hz, 1H), 6.67 (dd, J = 2.2, 0.7 Hz, 2H), 6.60 (t, J = 2.2 Hz, 1H), 5.15 (s, 4H), 5.07 (d, J = 1.9 Hz, 1H), 4.68 (ddd, J = 8.9, 6.2, 1.9 Hz, 1H), 3.45 (s, 6H), 2.70 (ddd, J = 16.8, 8.9, 1.9 Hz, 1H), 2.44 (ddd, J = 16.8, 5.7, 1.5 Hz, 1H), 1.59-1.54 (m, 1H), 1.51 (s, 3H), 1.47 (s, 3H), 1.18 (dd, J = 6.9, 4.4 Hz, 2H), 0.84-0.74 (m, 1H), 0.68 (d, J = 6.4 Hz, 3H), 0.46 (d, J = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 200.9, 158.0, 143.2, 107.2, 103.2, 99.6, 94.4, 74.6, 69.0, 55.9, 47.1, 40.7, 30.3, 29.7, 27.4, 22.7, 22.1, 19.5; HRMS (ESI): calcd. for $C_{22}H_{34}O_7Na$ $[M + Na]^+$ 433.2202; found 433.2187.

(2*R*,4*R*)-5-(Benzyloxy)-1-((*R*)-2-(hydroxymethyl)pyrrolidin-1-yl)-2,4-dimethylpentan-1-one (15). To a solution of alcohol **13** (10 g, 55.5 mmol) in CH_2Cl_2 (150 mL) was added successively triphenylphosphine (17.5 g, 66.6 mmol) and imidazole (5.6 g, 83.2 mmol) followed by iodine (25 g, 99.9 mmol) at 0 ^{o}C. The mixture was stirred for 1 h at 0 ^{o}C and quenched with saturated $Na_2S_2O_3$ solution (50 mL). The organic layer was extracted with Et_2O (3 x 100 mL) and the combined extract was washed with brine (20 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure to afford the crude iodo compound **14** as a colorless liquid which was used for next step without further purification; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39-7.26 (m, 5H), 4.53 (s, 2H), 3.40 (dd, J = 9.3, 5.1 Hz, 1H), 3.38-3.28 (m, 3H), 1.85-1.74 (m, 1H), 1.00 (d, J = 6.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 138.3, 128.3, 127.6, 74.1, 73.2, 35.1, 17.6, 13.9; LCMS (ESI): 291 $(M + H)^+$.

To a stirred solution of LDA (83.3 mmol) in anhydrous THF (0.5 M) was added dropwise (*S*)-prolinol propionamide (4.8 g, 30.6 mmol) at 0 ^{o}C. The mixture was stirred for 30 min at room

temperature, followed by the addition of HMPA (13.4 mL, 83 mmol). The mixture was cooled to -78 ^{o}C and treated dropwise with iodide **14** (11.5, 39.6 mmol) in THF (60 mL) at a rate to maintain the temperature. The mixture was stirred for 1 h at -78 ^{o}C and for 3 h at room temperature and then quenched by dropwise addition of saturated NH_4Cl solution (30 mL). The layers were separated and the organic layer was washed with brine (20 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The residue was subjected to silica gel column chromatography to give compound **15** (10.7 g, 85%) as yellow liquid. R_f = 0.3 (30% EtOAc/hexane); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36-7.26 (m, 5H), 5.24 (dd, J = 7.6, 2.1 Hz, 1H), 4.46 (dd, J = 18.7, 12.0 Hz, 2H), 4.25-4.15 (m, 1H), 3.67-3.58 (m, 1H), 3.57-3.47 (m, 1H), 3.47-3.42 (m, 1H), 3.40-3.32 (m, 1H), 3.30-3.22 (m, 2H), 2.75-2.63 (m, 1H), 2.05-1.67 (m, 5H), 1.60-1.39 (m, 2H), 1.11 (d, J = 6.7 Hz, 3H), 0.93 (d, J = 6.7 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 178.1, 138.4, 128.2, 127.5, 127.4, 76.1, 73.0, 67.3, 60.8, 47.4, 37.9, 35.6, 31.3, 28.0 28.0, 24.2, 17.7, 17.4; HRMS (ESI): calcd. for $C_{19}H_{29}NO_3Na$ $[M + Na]^+$ 342.2045; found 342.2052.

(2*R*,4*R*)-5-(Benzyloxy)-2,4-dimethylpentan-1-ol (16). A solution of **15** (10 g, 31.3 mmol) in 1 N HCl (50 mL) was heated at reflux for 6 h, then cooled to 0 ^{o}C and treated with 15% NaOH solution for 10 min. The mixture was acidified to pH ~ 3 and extracted with ether (3 x 100 mL). The combined ether extracts were dried over $MgSO_4$ and concentrated under reduced pressure to give crude carboxylic acid which was directly used for next step without further purification.

To a stirred solution of the crude acid in anhydrous ether (100 mL) was added dropwise lithium aluminium hydride (56 mL of 1.0 M solution in THF, 55.7 mmol) at 0 ^{o}C. The mixture was stirred for 4 h at ambient temperature. To the reaction mixture, water (2 mL), 15% aqueous NaOH (2 mL) and water (5 mL) were added sequentially. After the final addition, stirring was

continued for 1 h, and the mixture was filtered. The solid was washed with THF, and the filtrate was evaporated to provide crude alcohol. The residue was subjected to silica gel column chromatography to give compound **16** (4.79 g, 69% over two steps) as a colorless liquid. R_f = 0.3 (20% EtOAc/hexane); $[\alpha]_D^{24}$ = +41.0 (*c* 2.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37-7.27 (m, 5H), 4.51 (s, 2H), 3.44 (dd, *J* = 9.0, 6.4 Hz, 2H), 3.29 (dd, *J* = 6.4, 3.6 Hz, 2H), 1.96-1.85 (m, 1H), 1.79-1.70 (m, 1H), 1.66 (brs, 1H), 1.29-1.15 (m, 2H), 0.93 (d, *J* = 6.7 Hz, 3H), 0.89 (d, *J* = 6.7 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 138.4, 128.2, 127.4, 127.4, 76.5, 72.9, 68.6, 37.1, 32.9, 30.5, 16.8, 16.2; HRMS (ESI): calcd. for $C_{14}H_{22}O_2Na$ $[M + Na]^+$ 245.1517; found 245.1517.

(2*S*,4*R*,6*R*)-7-(Benzyloxy)-1-((*R*)-2-(hydroxymethyl)pyrrolidin-1-yl)-2,4,6-trimethylheptan-1-one (18). To a solution of alcohol **16** (4.5 g, 24.7 mmol) in CH_2Cl_2 (100 mL) was added successively triphenylphosphine (7.8 g, 29.7 mmol) and imidazole (2.5 g, 37 mmol) followed by iodine (11.3 g, 44.6 mmol) at 0 ^{o}C. The reaction mixture was stirred for 1 h at 0 ^{o}C and quenched with saturated $Na_2S_2O_3$ solution (50 mL). The organic layer was extracted with ether (3 x 100 mL) and the combined extracts were washed with brine (20 mL). The organic extracts were dried over $MgSO_4$, filtered and concentrated under reduced pressure to afford the crude iodo compound **17** as a colorless liquid which was used for next step without further purification; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39-7.26 (m, 5H), 4.52 (s, 2H), 3.38-3.12 (m, 4H), 1.91-1.81 (m, 1H), 1.68-1.55 (m, 1H), 1.36-1.18 (m, 2H), 0.98 (d, *J* = 6.5 Hz, 3H), 0.94 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 138.6, 128.3, 127.4, 127.4, 76.1, 73.0, 40.7, 32.2, 31.0, 20.2, 18.3, 17.0; LCMS (ESI): 333 $(M + H)^+$.

To a stirred solution of LDA (23.3 mmol) in anhydrous THF (0.5 M) was added (*R*)-prolinol propionamide (1.5 g, 9.3 mmol) at 0 ^{o}C slowly dropwise. The resulting solution was stirred at

room temperature for 30 min, followed by the addition of of HMPA (4 mL, 22.3 mmol). The mixture was cooled to -78 ^{o}C and iodide **17** (3.7 g, 11.1 mmol) in THF (30 mL) added dropwise. The reaction mixture was stirred for 1 h at -78 ^{o}C and 3 h at room temperature and then quenched by dropwise addition of saturated NH_4Cl solution (10 mL). The layers were separated and the organic layer was washed with brine (20 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The residue was subjected to silica gel column chromatography to give compound **18** (3.44 g, 86%) as a yellow liquid. R_f = 0.35 (30% EtOAc/hexane); $[\alpha]_D^{24}$ = +132.0 (*c* 2.55, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36-7.26 (m, 5H), 4.48 (s, 2H), 4.25-4.19 (m, 1H), 3.67-3.44 (m, 4H), 3.30-3.20 (m, 2H), 2.68-2.59 (m, 2H), 2.03-1.77 (m, 4H), 1.60-1.44 (m, 3H), 1.37-1.29 (m, 1H), 1.25-1.16 (m, 1H), 1.11 (d, *J* = 6.6 Hz, 3H), 1.08-1.01 (m, 1H), 0.88 (d, *J* = 6.6 Hz, 3H), 0.85 (d, *J* =6.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 178.5, 138.7, 128.2, 127.4, 127.4, 76.4, 72.9, 67.8, 61.1, 47.7, 41.4, 41.2, 35.6, 30.7, 28.2, 27.7, 24.4, 19.2, 17.4, 16.8; HRMS (ESI): calcd. for $C_{22}H_{35}O_3NNa$ $[M + Na]^+$ 384.2514; found 384.2576.

(2*S*,4*S*,6*R*)-7-(Benzyloxy)-2,4,6-trimethylheptan-1-ol (19). A solution of **18** (3.44 g, 9.5 mmol) in 1 N HCl (30 mL) was heated at reflux for 6 h and cooled to 0 ^{o}C and then treated with 15% NaOH solution for 10 min. The reaction mixture was acidified to pH ~ 3 and extracted with ether (3 x 50 mL). The combined ether extracts were dried over $MgSO_4$ and concentrated under reduced pressure to give crude carboxylic acid which was directly used for next step without further purification.

To a stirred solution of crude acid in anhydrous ether (60 mL) at 0 ^{o}C was added dropwise lithium aluminium hydride (17 mL of 1.0 M solution in THF, 17.1 mmol). The mixture was stirred for 4 h at ambient temperature and treated dropwise sequentially water (1 mL), 15% aqueous NaOH (1 mL) and water (3 mL). The mixture was stirred for 1 h and filtered and the

resulting solid was washed with THF. The filtrate was concentrated to provide crude alcohol. The residue was subjected to silica gel column chromatography to give compound **19** (1.63 g, 65% over two steps) as a colorless liquid. R_f = 0.2 (20% EtOAc/hexane); $[\alpha]_D^{24}$ = −32.6 (*c* 0.85, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37-7.26 (m, 5H), 4.50 (s, 2H), 3.47 (dd, *J* = 10.4, 5.6 Hz, 1H), 3.38 (dd, *J* = 10.4, 6.6 Hz, 1H), 3.31 (dd, *J* = 9.0, 5.7, Hz, 1H), 3.22 (dd, *J* = 9.0, 6.9 Hz, 1H), 1.94-1.82 (m, 1H), 1.78-1.67 (m, 1H), 1.66-1.55 (m, 1H), 1.28-1.13 (m, 2H), 1.09-0.99 (m, 2H), 0.91 (d, *J* = 6.6 Hz, 3H), 0.87 (d, *J* = 6.6 Hz, 3H), 0.82 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 138.7, 128.2, 127.4, 127.3, 76.4, 72.8, 68.8, 41.9, 41.3, 33.0, 30.7, 27.0, 19.0, 17.0, 16.3; HRMS (ESI): calcd. for $C_{17}H_{28}O_2Na$ $[M + Na]^+$ 287.1987; found 287.1990.

((((2*R*,4*S*,6*S*)-2,4,6-Trimethyloct-7-yn-1-yl)oxy)methyl)benzene (20). To a solution of oxalyl chloride (0.8 mL, 9.25 mmol) in CH_2Cl_2 (10 mL) was added DMSO (0.78 mL, 11.1 mmol) at -78 ^{o}C. The mixture was stirred for 10 min at -78 ^{o}C and treated drop-wise with a solution of alcohol **20** (1.63 g, 6.17 mmol) in CH_2Cl_2 (20 mL). The mixture was stirred for 30 min at the same temperature and then treated dropwise with Et_3N (5.1 mL, 37 mmol). The mixture was stirred for 45 min at same temperature and treated with saturated NH_4Cl solution (15 mL). The organic layer was separated and washed with saturated $NaHCO_3$ solution (10 mL), dried over $MgSO_4$ and concentrated under reduce pressure to give the crude aldehyde, which was used in the next step without further purification.

To a stirred solution of crude aldehyde and Bestmnn-Ohira reagent (1.7 g, 9.2 mmol) in methanol (10 mL) K_2CO_3 (2.48 g, 18 mmol) was added at 0 ^{o}C. The mixture was stirred for 1 h at room temperature and passed through a small pad of Celite and then extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layer was washed with brine (10 mL), dried over $MgSO_4$, concentrated under reduced pressure. The residue was subjected to silica gel column

chromatography to give compound **20** (1.0 g, 68% over two steps) as a colorless liquid. R_f = 0.8 (10% EtOAc/hexane); $[\alpha]_D^{24}$ = +96.6 (*c* 0.88, $CHCl_3$); IR (KBr): 2964, 2927, 2871, 2848, 1453, 1378, 1098, 735, 676, 630 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.37-7.27 (m, 5H), 4.51 (s, 2H), 3.33-3.23 (m, 2H), 2.56-2.47 (m, 1H), 2.02 (d, *J* = 2.4 Hz, 1H), 1.95-1.82 (m, 1H), 1.82-1.71 (m, 1H), 1.47-1.36 (m, 1H), 1.34-1.23 (m, 1H), 1.18-1.13 (m, 2H), 1.16 (d, *J* = 6.9 Hz, 3H), 0.91 (d, *J* = 6.6 Hz, 3H), 0.87 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 138.7, 128.3, 127.5, 127.4, 89.3, 72.9, 68.0, 45.1, 40.1, 30.8, 27.8, 23.2, 21.1, 19.7, 16.6; HRMS (ESI): calcd. for $C_{18}H_{26}ONa$ $[M + Na]^+$ 281.1881; found 281.1876.

(2*S*,5*S*,7*S*,9*R*)-10-(Benzyloxy)-1-((4*R*,5*S*,6*R*)-6-(3,5-dimethoxyphenyl)-5-isobutyl-2,2-dimethyl-1,3-dioxan-4-yl)-5,7,9-trimethyldec-3-yn-2-ol (21). To a suspension of $Zn(OTf)_2$ (1 g, 2.70 mmol), which was dried under high vacuum at 60 to 80 °C for 20 min prior to use, and (-)-*N*-methylephedrine (516 mg, 2.80 mmol) in toluene (1 mL) was added triethylamine (400 µL, 2.80 mmol). The mixture was stirred for 3 h at room temperature and treated dropwise with a solution of alkyne **20** (485 mg, 1.88 mmol) in toluene (1 mL) via cannula. The mixture was stirred for 45 min and treated dropwise with a solution of aldehyde **12** (300 mg, 1.11 mmol) in toluene (1 mL + 500 µL × 2 rinse) via cannula. The mixture was stirred for 12 h at room temperature and then was quenched with saturated NH_4Cl solution (5 mL). The mixture was extracted with diethyl ether (3 x 10 mL) and the organic layer was washed with brine (5 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was subjected to silica gel column chromatography to afford compound **21** (485 mg, 72%) as a light yellow liquid. R_f = 0.4 (20% EtOAc/hexane); $[\alpha]_D^{24}$ = +62.7 (*c* 0.51, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 7.36-7.26 (m, 5H), 6.48 (d, *J* = 2.3 Hz, 2H), 6.34 (t, *J* = 2.3 Hz, 1H), 5.02 (brs, 1H), 4.62-4.56 (m, 1H), 4.50 (d , *J* = 1.1 Hz, 2H), 4.36 (d, *J* = 10.3 Hz, 1H), 3.78 (s, 6H), 3.33-3.21

(m, 2H), 2.71 (brs, 1H), 2.61-2.52 (m, 1H), 2.12-2.04 (m, 1H), 1.93-1.85 (m, 1H), 1.81-1.72 (m, 1H), 1.70-1.62 (m, 1H), 1.50 (s, 3H), 1.47 (s, 3H), 1.32-1.21 (m, 3H), 1.18-1.15 (m, 4H), 1.15 (d, J = 6.7 Hz, 3H), 0.94 (d, J = 6.6 Hz, 3H), 0.89-0.80 (m, 1H), 0.88 (d, J = 6.6 Hz, 3H), 0.70 (d, J = 6.5 Hz, 3H), 0.45 (d, J = 6.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.5, 143.2, 138.6, 128.2, 127.4, 127.3, 103.7, 99.3, 98.8, 89.9, 80.8, 76.5, 75.0, 73.1, 72.8, 61.5, 55.2, 45.2, 41.4, 40.0, 30.8, 30.4, 29.8, 27.9, 27.3, 23.4, 22.7, 22.2, 21.2, 19.7, 19.4, 16.6; HRMS (ESI): calcd. for $C_{38}H_{56}O_6Na$ $[M + Na]^+$ 631.3975; found 631.3979.

The procedure for preparation of **21a** was same as that for the preparation of **21**. **21a** was isolated (73%) as a light yellow liquid. R_f = 0.3 (20% EtOAc/hexane); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35-7.30 (m, 4H), 7.29-7.24 (m, 1H), 6.67 (d, J = 2.2 Hz, 2H), 6.59 (t, J = 2.2 Hz, 1H), 5.14 (s, 4H), 5.01 (brs, 1H), 4.60-4.57 (m, 1H), 4.50-4.49 (m, 2H), 4.34-4.30 (m, 1H), 3.44 (s, 6H), 3.35-3.22 (m, 2H), 2.76 (brs, 1H), 2.60-2.52 (m, 1H), 2.10-2.03 (m, 1H), 1.93-1.85 (m, 1H), 1.80-1.72 (m, 1H), 1.67-1.60 (m, 1H), 1.49-1.47 (m, 1 H), 1.49 (s, 3H), 1.46 (s, 3H), 1.46-1.36 (m, 1H), 1.32-1.27 (m, 1H), 1.18-1.08 (m, 3H), 1.15 (d, J = 6.6 Hz, 3H), 0.96-0.91 (m, 1H), 0.93 (d, J = 6.6 Hz, 3H), 0.89 (d, J = 6.6 Hz, 3H), 0.89-0.83 (m, 1H), 0.67 (d, J = 6.6 Hz, 3H), 0.44 (d, J = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 157.9, 143.3, 138.7, 128.2, 127.5, 127.4(2), 107.1, 103.2, 99.4, 94.3, 90.0, 80.7, 74.9, 73.2, 72.9, 61.6, 55.8, 45.3, 41.4(2), 41.3, 40.1, 30.8, 30.4, 29.8, 27.9, 27.3, 23.4, 22.7, 22.1, 21.2, 19.7, 19.5, 16.7; LCMS (ESI): 669 $(M + H)^+$.

To a solution of **21** (12 mg) in CH_2Cl_2 (1 mL) were added sequentially (*S*)-(-)-α-methoxy-α-(trifluoromethyl)phenylacetic acid (7 mg), *N*,*N*′-dicyclohexylcarbodiimide (5 mg) and 4-(dimethylamino)pyridine (0.01 mg). The mixture was stirred for 2 h at room temperature and filtered through a pad of Celite. The filtrate was washed with water (2 mL), brine (2 mL), dried

over $MgSO_4$, and concentrated under reduced pressure. The residue was subjected to silica gel column chromatography to give (*S*)-**21b**-MTPA ester (9.8 mg, 60% yield) as yellow oil. R_f = 0.4 (20% EtOAc/hexane); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.63-7.50 (m, 2H), 7.46-7.36 (m, 3H), 7.36-7.26 (m, 5H), 6.48 (d, *J* = 2.2 Hz, 2H), 6.34 (t, *J* = 2.2 Hz, 1H), 5.75-5.70 (m, 1H), 4.97 (s, 1H), 4.49 (s, 2H), 4.28 (d, *J* = 8.3 Hz, 1H), 3.78 (s, 6H), 3.60 (s, 3H), 3.34-3.18 (m, 2H), 2.64-2.52 (m, 1H), 2.06-1.97 (m, 1H), 1.92-1.82 (m, 1H), 1.78-1.68 (m, 3H), 1.47 (s, 3H), 1.44 (s, 3H), 1.41-1.25 (m, 3H), 1.22-1.14 (m, 4H), 1.16 (d, *J* = 6.8 Hz, 3H), 0.93 (d, *J* = 6.6 Hz, 3H), 0.88 (d, *J* = 6.6 Hz, 3H), 0.64 (d, *J* = 6.5 Hz, 3H), 0.45 (d, *J* = 6.5 Hz, 3H); LCMS (ESI): 825 $(M + H)^+$.

Similarly, the (*R*)-MTPA ester **21c** (9 mg, 58%) was obtained using (*R*)-(+)-*α*-methoxy-*α*-(trifluoromethyl) phenylacetic acid (MTPA). R_f = 0.4 (20% EtOAc/hexane); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.60-7.52 (m, 2H), 7.42-7.36 (m, 3H), 7.36-7.27 (m, 5H), 6.48 (d, *J* = 2.2 Hz, 2H), 6.34(t, *J* = 2.2 Hz, 1H), 5.74-5.68 (m, 1H), 5.00 (brs, 1H), 4.49 (s, 2H), 4.36 (d, *J* = 9.9 Hz, 1H), 3.78 (s, 6H), 3.57 (s, 3H), 3.32-3.18 (m, 2H), 2.61-2.48 (m, 1H), 2.13-1.99 (m, 2H), 1.92-1.65 (m, 3H), 1.48 (s, 6H), 1.22-1.14 (m, 5H), 1.13 (d, *J* = 6.8 Hz, 3H), 0.92 (d, *J* = 6.6 Hz, 3H), 0.89 (d, *J* = 6.6 Hz, 3H), 0.87-0.76 (m, 2H), 0.67 (d, *J* = 6.3 Hz, 3H), 0.46 (d, *J* = 6.3 Hz, 3H); LCMS (ESI): 825 $(M + H)^+$.

(2*R*,4*S*,6*R*,9*R*)-9-((*tert*-Butyldimethylsilyl)oxy)-10-((4*R*,5*S*,6*R*)-6-(3,5-dimethoxyphenyl)-5-isobutyl-2,2-dimethyl-1,3-dioxan-4-yl)-2,4,6-trimethyldecan-1-ol (23). To a solution of **21** (450 mg, 0.74 mmol) in anhydrous CH_2Cl_2 (5 mL) was added slowly 2,6-lutidine (0.2 mL, 1.85 mmol) followed by TBSOTf (0.3 mL, 1.33 mmol) at 0 ^oC. The mixture was stirred for 1 h at 0 ^oC and quenched with water (3 mL) and washed with saturated $NaHCO_3$ solution (5 mL). Organic layer was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layer was dried over $MgSO_4$, concentrated under reduced pressure. The residue was subjected to silica gel

column chromatography to give compound **22** (464 mg, 87%) as a colorless liquid. R_f = 0.5 (10% EtOAc/hexane); $[\alpha]_D^{24}$ = +72.6 (*c* 0.52, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36-7.26 (m, 5H), 6.49 (d, *J* = 2.2 Hz, 2H), 6.33 (t, *J* = 2.2 Hz, 1H), 4.99 (brs, 1H), 4.55-4.50 (m, 1H), 4.50 (s, 2H), 4.34 (d, *J* = 7.2 Hz, 1H), 3.78 (s, 6H), 3.34-3.20 (m, 2H), 2.61-2.47 (m, 1H), 1.98-1.74 (m, 3H), 1.70-1.62 (m, 2H), 1.47 (s, 6H), 1.21-1.13 (m, 4H), 1.15 (d, *J* = 6.7 Hz, 3H), 0.94 (d, *J* = 6.6 Hz, 3H), 0.92 (s, 9H), 0.92-0.90 (m, 3H), 0.89 (d, *J* = 6.6 Hz, 3H), 0.67 (d, *J* = 6.5 Hz, 3H), 0.47 (d, *J* = 6.5 Hz, 3H), 0.15 (d, *J* = 6.5 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.6, 143.7, 138.7, 128.3, 127.5, 127.4, 103.8, 99.2, 98.8, 89.7, 81.4, 75.2, 72.9, 71.1, 60.9, 55.3, 45.6, 42.4, 41.2, 40.1, 30.9, 30.6, 29.8, 28.1, 27.3, 25.9, 25.6, 23.5, 22.7, 22.4, 21.3, 19.8, 19.4, 18.2, 16.7, -4.3, -4.8; LCMS (ESI): 723 $(M + H)^+$.

The procedure for the preparation of **22a** was same as that for the preparation of **22**. **22a** was isolated (89%) as a colorless liquid. R_f = 0.4 (10% EtOAc/hexane); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.34-7.27 (m, 5H), 6.68 (d, *J* = 1.9 Hz, 2H), 6.59 (t, *J* = 2.3 Hz, 1H), 5.14 (s, 4H), 5.00 (brs, 1H), 4.55-4.52 (m, 1H), 4.50 (s, 2H), 4.31 (d, *J* = 7.7 Hz, 1H), 3.45 (s, 6H), 3.33-3.22 (m, 2H), 2.60-2.49 (m, 1H), 1.97-1.87 (m, 2H), 1.83-1.73 (m, 1 H), 1.67-1.61 (m, 1H), 1.49-1.47 (m, 1H), 1.47 (s, 3H), 1.46 (s, 3 H), 1.43-1.37 (m, 1H), 1.31-1.25 (m, 2H), 1.19 (d, *J* = 6.5 Hz, 3H), 1.61 (d, *J* = 6.8 Hz, 3H), 0.94 (d, *J* = 6.6 Hz, 3H), 0.92 (s, 9H), 0.91-0.89 (m, 1H), 0.90 (d, *J* = 6.6 Hz, 3H), 0.67 (d, *J* = 6.5 Hz, 3H), 0.47 (d, *J* = 6.5 Hz, 3H), 0.15 (d, *J* = 5.8 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 158.0, 143.8, 138.8, 128.3, 127.5, 107.2, 103.1, 99.2, 94.4, 89.7, 81.4, 75.1, 72.9, 71.1, 60.9, 55.9, 53.4, 45.6, 42.4, 41.1, 40.2, 30.9, 30.5, 29.8, 28.0, 27.3, 25.9, 25.6, 23.5, 22.7, 22.3, 21.3, 19.7, 19.4, 18.2, 16.7, -4.3, -4.8; LCMS (ESI): 783 $(M + H)^+$.

To a solution of **22** (450 mg, 0.62 mmol) in EtOAc (10 mL) under H_2 was added Pd/C (40 mg, 10 mol%). The mixture was stirred for 2 h at room temperature, filtered through a pad of Celite,

washed with EtOAc, and concentrated under reduced pressure. The residue was subjected to silica gel column chromatography to afford compound **23** (290 mg, 75%) as a colorless liquid. R_f = 0.3 (20% EtOAc/hexane); $[\alpha]_D^{24}$ = +70.7 (*c* 0.67, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.49 (d, *J* = 1.8 Hz, 2H), 6.33 (t, *J* = 1.8 Hz, 1H), 4.98 (brs, 1H), 4.32-4.26 (m, 1H), 3.78 (m, 1H), 3.78 (s, 6H), 3.56-3.36 (m, 2H), 1.78-1.65 (m, 2H), 1.64-1.54 (m, 4H), 1.48-1.37 (m, 4H), 1.48 (s, 6H), 1.37-1.25 (m, 3H), 1.20-1.11 (m, 3H), 1.11-1.00 (m, 4H), 0.93 (s, 9H), 0.89 (d, *J* = 6.4 Hz, 3H), 0.83 (d, *J* = 6.6 Hz, 3H), 0.68 (d, *J* = 6.2 Hz, 3H), 0.45 (d, *J* = 6.2 Hz, 3H), 0.08 (d, *J* = 9.8 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.5, 143.8, 103.8, 99.1, 98.8, 75.3, 70.7, 69.3, 69.0, 55.3, 45.7, 41.5, 41.2, 41.0, 40.2, 34.7, 33.2, 32.8, 30.4, 30.2, 29.9, 27.4, 27.2, 25.9, 22.8, 22.4, 19.5, 19.2, 18.1, 16.4, -4.2, -4.4; HRMS (ESI): calcd. for $C_{37}H_{68}O_6SiNa$ $[M + Na]^+$ 659.4683; found 659.4678.

(2*R*,4*S*,6*S*)-10-((4*R*,5*S*,6*R*)-6-(3,5-Bis(methoxymethoxy)phenyl)-5-isobutyl-2,2-dimethyl-1,3-dioxan-4-yl)-2,4,6-trimethyldec-7-yn-1-ol (23'). Compound **23'** was isolated as a colorless liquid. R_f = 0.3 (20% EtOAc/hexane); ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.68 (d, *J* = 2.2 Hz, 2H), 6.58 (t, *J* = 2.2 Hz, 1H), 5.14 (s, 4H), 4.98 (brs, 1H), 4.00-3.98 (m, 1H), 3.52-3.46 (m, 1H), 3.45 (s, 6H), 3.43-3.37 (m, 1H), 1.80-1.67 (m, 1H), 1.65-1.52 (m, 3H), 1.50-1.48 (m, 1H), 1.48 (s, 3H), 1.47 (s, 3H), 1.43-1.35 (m, 2H), 1.35-1.25 (m, 3H), 1.22-1.17 (m, 1H), 1.16-0.97 (m, 5H), 0.89 (d, *J* = 6.6 Hz, 3H), 0.86-0.79 (m, 6H), 0.68 (d, *J* = 6.4 Hz, 3H), 0.45 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 157.9, 144.0, 107.2, 103.1, 99.2, 94.3, 75.1, 74.3, 69.0, 55.9, 45.6, 41.4, 41.1, 37.6, 37.0, 33.1, 30.3, 29.9, 29.8, 27.2, 27.2, 26.9, 26.2, 22.8, 22.3, 20.0, 19.5, 19.2, 16.4; LCMS (ESI): 563 $(M + H)^+$.

(4*R*,6*S*,8*R*,11*R*)-11-((*tert*-Butyldimethylsilyl)oxy)-12-((4*R*,5*S*,6*R*)-6-(3,5-dimethoxyphenyl)-5-isobutyl-2,2-dimethyl-1,3-dioxan-4-yl)-4,6,8-trimethyldodecan-3-ol (24). To a solution of

23 (250 mg, 0.4 mmol) in CH_2Cl_2 (5 mL) were added $NaHCO_3$ (84 mg, 1 mmol) and Dess-Martin periodinane (320 mg, 0.72 mmol) at 0 °C. The mixture was stirred for 1 h at room temperature, diluted with CH_2Cl_2 (10 mL), and washed with saturated $NaHCO_3$ solution (5 mL). The organic layer was separated, dried over $MgSO_4$ and concentrated under reduced pressure. The crude aldehyde was directly used for the next step without further purification.

To a stirred solution of crude aldehyde in ether (10 mL) was added dropwise C_2H_5MgBr (1.6 mL of 1 M solution, 1.6 mmol) at 0 ^oC. The mixture was stirred for 1 h at the same temperature and quenched with saturated NH_4Cl solution (3 mL). Organic layer was extracted with EtOAc (3 x 10 mL). The combined organic layer was dried over $MgSO_4$, concentrated under reduced pressure. The residue was subjected to silica gel column chromatography to give compound **24** (230 mg, 87% over two steps) as a colorless liquid. R_f = 0.4 (20% EtOAc/hexane); $[\alpha]_D^{24}$ = +65.3 (*c* 0.85, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 6.48 (d, *J* = 2.1 Hz, 2H), 6.33 (t, *J* = 2.2 Hz, 1H), 4.98 (brs, 1H), 4.26 (brm, 1H), 3.82-3.78 (m, 1H), 3.78 (s, 6H), 3.42-3.28 (m, 1H), 1.79-1.48 (m, 11H), 1.48 (d, *J* = 4.0 Hz, 6H), 1.22-1.02 (m, 7H), 0.94 (d, *J* = 6.8 Hz, 3H), 0.93 (s, 9H), 0.89-0.84 (m, 4H), 0.85 (d, *J* = 6.6 Hz, 3H), 0.81 (d, *J* = 6.5 Hz, 3H), 0.68 (d, *J* = 6.3 Hz, 3H), 0.45 (d, *J* = 6.3 Hz, 3H), 0.09 (d, *J* = 9.5 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.5, 143.8, 103.8, 99.1, 98.7, 78.1, 77.2, 75.3, 70.7, 69.2, 55.3, 45.7 (2), 41.7, 41.0, 35.0, 32.9, 30.4, 30.1, 29.9, 27.4, 27.2, 25.9, 22.8, 22.4, 19.6, 19.5, 19.5, 19.1, 18.1, 13.4, 10.5, 10.5, -4.2, -4.4; HRMS (ESI): calcd. for $C_{39}H_{72}O_6SiNa$ $[M + Na]^+$ 687.4996; found 687.4928.

(4*R*,6*S*,8*R*,11*R*)-11-((*tert*-Butyldimethylsilyl)oxy)-12-((4*R*,5*S*,6*R*)-6-(3,5-dimethoxyphenyl)-5-isobutyl-2,2-dimethyl-1,3-dioxan-4-yl)-4,6,8-trimethyldodecan-3-one (25). To a solution of **24** (200 mg, 0.3 mmol) in CH_2Cl_2 (5 mL) were added $NaHCO_3$ (50 mg, 0.6 mmol) and Dess-Martin periodinane (230 mg, 0.54 mmol) at 0 °C. The mixture was stirred for 1 h at 0 °C and for

1 h at room temperature and then diluted with CH_2Cl_2 (10 mL), and washed with saturated $NaHCO_3$ solution (5 mL). The organic layer was washed with brine (5 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The residue was subjected to silica gel column chromatography to give compound **25** (180 mg, 92%) as a colorless liquid. R_f = 0.3 (10% EtOAc/hexane); $[\alpha]_D^{24}$ = +22.1 (*c* 0.67, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.48 (brs, 2H), 6.33 (brs, 1H), 4.98 (brs, 1H), 4.29-4.24 (m, 1H), 3.78 (m, 1H), 3.78 (s, 6H), 2.67-2.55 (m, 1H), 2.45 (q, *J* = 7.2 Hz, 2H), 1.81-1.66 (m, 1H), 1.64-1.47 (m, 5H), 1.47 (d, *J* = 3.6 Hz, 6H), 1.36-1.12 (m, 7H), 1.11-0.99 (m, 5H), 1.06 (d, *J* = 6.6 Hz, 3H), 0.93 (s, 9H), 0.89-0.84 (m, 1H), 0.84 (d, *J* = 6.4 Hz, 3H), 0.82 (d, *J* = 6.4 Hz, 3H), 0.68 (d, *J* = 6.1 Hz, 3H), 0.44 (d, *J* = 6.3 Hz, 3H), 0.08 (d, *J* = 10.1 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 215.5, 160.6, 143.8, 103.8, 99.1, 98.8, 77.2, 75.3, 70.7, 69.2, 55.3, 45.1, 43.7, 41.1, 41.0, 40.2, 34.4, 34.1, 32.9, 30.3, 30.1, 29.9, 28.0, 27.3, 25.9, 25.9, 22.8, 22.4, 19.5, 19.3, 19.3, 18.1, 16.5, 7.9, -0.02, -4.2, -4.4; HRMS (ESI): calcd. for $C_{39}H_{70}O_6SiNa$ $[M + Na]^+$ 685.4839; found 685.4833.

(4*R*,6*S*,8*R*,11*R*,13*R*,14*S*)-14-((*R*)-(3,5-dimethoxyphenyl)(hydroxy)methyl)-11,13-dihydroxy-4,6,8,16-tetramethylheptadecan-3-one (26). To a stirred solution of **25** (180 mg, 0.27 mmol) in MeOH (5 mL) was added PTSA (5 mg, 0.03 mmol) at room temperature. The mixture was stirred for 4 h at the same temperature and quenched with saturated $NaHCO_3$ solution (5 mL). The organic layer was extracted with CH_2Cl_2 (3 x 10 mL) and combined organic layer was washed with brine (2 mL), dried over $MgSO_4$, concentrated under reduced pressure. The residue was subjected to silica gel column chromatography to give compound **26** (120 mg, 90%) as a colorless liquid. R_f = 0.3 (30% EtOAc/hexane); $[\alpha]_D^{24}$ = +23.6 (*c* 1.2, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.51 (d, *J* = 2.3 Hz, 2H), 6.34 (t, *J* = 2.3 Hz, 1H), 5.04 (brs, 1H), 4.29 (d, *J* = 10.4 Hz, 1H), 3.92-3.78 (m, 1H), 3.78 (s, 6H), 3.15-2.92 (brs, 3H), 2.66-2.55 (m, 1H), 2.46 (q, *J*

= 7.3 Hz, 2H), 1.73-1.61 (m, 2H), 1.56-1.34 (m, 6H), 1.32-1.18 (m, 6H), 1.09-0.98 (m, 8H), 0.82 (d, *J* = 6.6 Hz, 3H), 0.81 (d, *J* = 6.6 Hz, 3H), 0.72 (d, *J* = 6.5 Hz, 3H), 0.53 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 215.7, 160.7, 146.0, 103.6, 99.1, 78.1, 77.8, 77.2, 73.8, 55.4, 48.2, 45.0, 43.7, 41.0, 35.7, 34.0, 33.2, 30.4, 30.0, 27.8, 27.3, 22.7, 22.4, 20.0, 19.3, 19.3, 16.4, 7.8; HRMS (ESI): calcd. for $C_{30}H_{52}O_6Na$ $[M + Na]^+$ 531.3662; found 531.3666.

(4*R*,6*S*,8*R*,11*R*,13*R*,14*S*)-14-((*R*)-(3,5-Dihydroxyphenyl)(hydroxy)methyl)-11,13-dihydroxy-4,6,8,16-tetramethylheptadecan-3-one (1). To a stirred solution of **26** (100 mg, 0.19 mmol) in CH_2Cl_2 (5 mL) AlI_3 (380 mg, 0.95 mmol) was added at one time under nitrogen atmosphere at 0 ^oC. The mixture was sealed with a stopper and stirred for 2 days at room temperature. After the completion of the reaction monitored by LCMS, the mixture was quenched with 1 N HCl (few drops) at 0 ^oC and stirred for additional 2 h. Organic layer was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layer was washed with brine (5 mL), dried over $MgSO_4$, concentrated under reduced pressure. The residue was subjected to silica gel column chromatography to give compound **1** (20 mg, 22%) as a white amorphous solid. R_f = 0.2 (5% MeOH/CH_2Cl_2); $[\alpha]_D^{24}$ = +20.6 (*c* 0.68, MeOH); [$_{lit}[\alpha]_D^{20}$ = -12.0 (*c* 0.20, MeOH)]; IR (KBr): 3346, 2925, 1699, 1605, 1458, 1378, 1339, 1102, 1004, 844, 668, 657, 613 cm^{-1}; ^{1}H NMR (600 MHz, CD_3OD): δ 6.33 (d, *J* = 2.2 Hz, 2H), 6.15 (t, *J* = 2.2 Hz, 1H), 4.84 (d, *J* = 4.0 Hz, 1H), 3.96 (m, 1H), 3.69 (m, 1H), 2.71 (m, 1H), 2.57-2.52 (m, 2H), 1.70 (m, 1H), 1.68-1.62 (m, 2H), 1.52-1.49 (m, 3H), 1.45-1.40 (m, 3H), 1.30-1.24 (m, 5H), 1.13-1.11 (m, 2H), 1.04 (d, *J* = 6.5 Hz, 3H), 1.01 (t, *J* = 7.5 Hz, 3H), 0.86 (d, *J* = 6.5 Hz, 3H), 0.85 (d, *J* = 6.5 Hz, 3H), 0.78 (d, *J* = 6.5 Hz, 3H), 0.64 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR (150 MHz, CD_3OD): δ 218.1, 158.9, 148.2, 105.3, 101.6, 76.4, 74.6, 71.8, 49.1, 45.9, 44.5, 42.0, 41.9, 35.5, 34.8, 34.1, 33.1, 31.0, 28.8, 28.0, 23.1,

22.6, 19.5, 19.5, 16.7 7.8; HRMS (ESI): calcd. for $C_{28}H_{48}O_6Na$ $[M + Na]^+$ 503.3349; found 503.3336.

(*R*)-4-Benzyl-3-((*S*)-2-((*R*)-(3,5-bis(methoxymethoxy)phenyl)(hydroxy)methyl)-4-methylpentanoyl)oxazolidin-2-one (27). To a stirred solution of **5** (9.5 g, 34.5 mmol) in EtOAc (50 mL) was added $MgCl_2$ (500 mg, 5.76 mmol), Et_3N (8 mL, 57.6 mmol) and di-MOM-protected aldehyde **4** (6.5 g, 28.8 mmol) at 23 ^oC. The mixture was stirred for 24 h, filtered through a pad of Celite, washed with EtOAc and concentrated under reduced pressure. The residue was subjected to silica gel column chromatography to afford compound **27** (10.4 g, 72%) as a yellow liquid. R_f = 0.3 (20% EtOAc/hexane); $[\alpha]_D^{24}$ = +13.0 (*c* 2.77, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 7.31-7.22 (m, 3H), 7.11 (d, *J* = 6.7 Hz, 2H), 6.78 (d, *J* = 2.2 Hz, 2H), 6.66 (t, *J* = 2.2 Hz, 1H), 5.13 (dd, *J* = 15.4, 6.7 Hz, 4H), 4.75 (d, *J* = 6.7 Hz, 1H), 4.65-4.56 (m, 2H), 4.14-4.06 (m, 2H), 3.42 (s, 6H), 3.29 (brs, 1H), 3.10 (dd, *J* = 13.6, 3.2 Hz, 1H), 2.45 (dd, *J* = 13.6, 9.6 Hz, 1H), 1.79-1.72 (m, 1H), 1.62-1.51 (m, 1H), 1.41-1.34 (m, 1H), 0.88 (t, *J* = 6.1 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 176.5, 158.4, 153.4, 145.1, 135.4, 129.3, 128.9, 127.2, 107.8, 104.1, 94.5, 75.9, 65.7, 56.0, 55.4, 46.6, 38.7, 37.3, 26.1, 22.8, 22.4; HRMS (ESI): calcd. for $C_{27}H_{35}NO_8Na$ $[M + Na]^+$ 524.2260; found 524.2312.

(*R*)-4-Benzyl-3-((*S*)-2-((*R*)-(3,5-bis(methoxymethoxy)phenyl)((*tert*-butyldimethylsilyl)oxy)methyl)-4-methylpentanoyl)oxazolidin-2-one (28). To a solution of **27** (10 g, 19.9 mmol) in anhydrous CH_2Cl_2 (60 mL) was added 2,6-lutidine (5.8 mL, 49.9 mmol), followed by TBSOTf (7.3 mL, 31.8 mmol) slowly at 0 ^oC. The mixture was stirred for 1 h at 0 ^oC and quenched with water (15 mL) and then washed with saturated $NaHCO_3$ solution (20 mL). Organic layer was extracted with CH_2Cl_2 (3 x 50 mL). The combined organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was subjected to silica gel

column chromatography to afford **28** (10.7 g, 88%) as a yellow liquid. R_f = 0.3 (20% EtOAc/hexane); $[\alpha]_D^{24}$ = +23.2 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36-7.33 (m, 2H), 7.28-7.26 (m, 3H), 6.76 (d, *J* = 2.2 Hz, 2H), 6.64 (t, *J* = 2.2 Hz, 1H), 5.15 (s, 4H), 4.75 (d, *J* = 8.5 Hz, 1H), 4.66-4.59 (m, 1H), 4.50 (t, *J* = 8.2 Hz, 1H), 4.13-4.09 (m, 2H), 3.56 (dd, *J* = 13.2, 3.0 Hz, 1H), 3.45 (s, 6H), 2.58 (dd, *J* = 13.1, 11.1 Hz, 1H), 1.71-1.53 (m, 2H), 1.34-1.25 (m, 1H), 0.83 (s, 9H), 0.77 (d, *J* = 6.6 Hz, 3H), 0.73 (d, *J* = 6.6 Hz, 3H), -0.03 (s, 3H), -0.26 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 175.7, 157.8, 153.0, 145.1, 136.0, 129.3, 128.9, 127.2, 109.2, 104.2, 94.5, 77.8, 65.8, 56.2, 55.9, 49.0, 38.4, 34.6, 31.5, 26.2, 25.8, 23.6, 22.6, 21.8, 20.6, 18.0, 14.1, -4.6, -5.0; HRMS (ESI): calcd. for $C_{33}H_{49}NO_8SiNa$ $[M + Na]^+$ 638.3125; found 638.3130.

(*R*)-2-((*R*)-(3,5-bis(Methoxymethoxy)phenyl)((*tert*-butyldimethylsilyl)oxy)methyl)-4-methylpentan-1-ol (29). To a stirred solution of **28** (10 g, 16.2 mmol) in anhydrous CH_2Cl_2 (100 mL) was added slowly DIBAL-H (28.9 mL, 40 mmol, 20% solution in toluene) for 15 min at -78 ^{o}C. The mixture was stirred for 30 min at -78 ^{o}C and for 0 ^{o}C for 1 h and then quenched with methanol (10 mL) and aqueous saturated sodium potassium tartarate solution (50 mL). The mixture was passed through a small pad of Celite and extracted with CH_2Cl_2 (3 x 60 mL). The combined organic layer was dried over $MgSO_4$, concentrated under reduced pressure. The residue was subjected to silica gel column chromatography to afford **29** (6.4 g, 89%) as a colorless liquid. R_f = 0.2 (20% EtOAc/hexane); $[\alpha]_D^{24}$ = +30.0 (*c* 0.36, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.60 (d, *J* = 2.1 Hz, 2H), 6.55 (t, *J* = 2.1 Hz, 1H), 5.07 (dd, *J* = 10.3, 6.7 Hz, 4H), 4.61 (d, *J* = 4.6 Hz, 1H), 3.68 (dd, *J* = 11.0, 2.1 Hz, 1H), 3.45-3.38 (m, 1H), 3.38 (s, 6H), 2.96 (brs, 1H), 1.68-1.63 (m, 1H), 1.63-1.53 (m, 1H), 1.32-1.25 (m, 1H), 1.14-1.07 (m, 1H), 0.85 (s, 9H), 0.83 (d, *J* = 6.6 Hz, 3H), 0.75 (d, *J* = 6.5 Hz, 3H), 0.01 (s, 3H), -0.21 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 157.8, 146.0, 107.8, 103.4, 94.2, 78.9, 62.8, 55.6, 45.1, 37.3, 25.6, 25.1,

23.1, 22.0, 17.8, -4.8, -5.4; HRMS (ESI): calcd. for $C_{23}H_{42}O_6SiNa$ $[M + Na]^+$ 465.2648; found 465.2646.

(1*R*,2*R*,3*R*)-1-(3,5-Bis(methoxymethoxy)phenyl)-2-isobutylhex-5-ene-1,3-diol (32). To a stirred solution of IBX (7.3 g, 26.1 mmol) in DMSO (20 mL) was added dropwise a solution of alcohol **29** (6.4 g, 14.5 mmol) in CH_2Cl_2 (60 mL) at 25 °C. The mixture was stirred at 25 °C for 6 h and then filtered. The resulting solid was washed with diethyl ether. The filtrate was washed with saturated $NaHCO_3$ solution (15 mL), water (10 mL) and brine (15 mL), dried over $MgSO_4$, concentrated under reduced pressure to furnish crude aldehyde **30** (5.5 g, 86%) as a colorless liquid. R_f = 0.7 (20% EtOAc/hexane); ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.69 (d, J = 3.9 Hz, 1H), 6.64 (d, J = 2.1 Hz, 2H), 6.62 (t, J = 2.1 Hz, 1H), 5.13 (s, 4H), 4.71 (d, J = 6.8 Hz, 1H), 3.45 (s, 6H), 2.65-2.58 (m, 1H), 1.59-1.50 (m, 1H), 1.50-1.37 (m, 1H), 1.09-1.00 (m, 1H), 0.84 (s, 9H), 0.82 (d, J = 6.6 Hz, 3H), 0.76 (d, J = 6.6 Hz, 3H), 0.01 (s, 3H), -0.21 (s, 3H); LCMS (ESI): 441 $(M + H)^+$.

To a stirred solution of (+)-ipc$_2$BOMe (6.5 g, 20.4 mmol) in anhydrous Et_2O (30 mL) was added allylmagnesium bromide (17 mL, 17.1 mmol, 1.0 M in ether) at 0 ^{o}C. The mixture was stirred for 1 h at room temperature before being cooled to -78 ^{o}C. The mixture was treated dropwise with aldehyde **30** (5 g, 11.4 mmol) at -78 ^{o}C, stirred for 1 h at -78 ^{o}C, and then warmed slowly to room temperature. An aqueous solution of NaOH (2 M in H_2O) (20 mL) was added, followed by slow addition of 30% H_2O_2 solution (10 mL) at 0 ^{o}C. The biphasic solution was separated and the aqueous layer was extracted with Et_2O (3 x 50 mL). The combined organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was subjected to silica gel column chromatography to give compound **31** along with diastereomeric mixture (*dr* = 90:10)

(4.1 g, 74%) as a colorless liquid. R_f = 0.5 (30% EtOAc/hexane) which could not be separated at this stage and was purified in the next step; LCMS (ESI): 483 $(M + H)^+$, 505 $(M + Na)^+$.

To a stirred solution of **31** (4 g, 8.3 mmol) in dry THF (30 mL) was added TBAF (12.4 mL of 1 M solution in THF, 12.4 mmol,) at 0 °C. The mixture was stirred for 5 h at room temperature, diluted with saturated $NaHCO_3$ solution (10 mL). Organic layer was separated, washed with brine (10 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The residue was subjected to silica gel column chromatography to afford pure **32** (2.81 g, 92%) as a colorless liquid. R_f = 0.2 (30% EtOAc/hexane); $[\alpha]_D^{24}$ = +2.8 (*c* 13.6, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.69-6.58 (m, 3H), 5.82-5.71 (m, 1H), 5.13-4.99 (m, 6H), 4.57 (d, *J* = 7.1 Hz, 1H), 3.71-3.67 (m, 1H), 3.42 (s, 6H), 2.42-2.29 (m, 1H), 2.23-2.13 (m, 1H), 1.82 (t, *J* = 6.1 Hz, 1H), 1.29-1.22 (m, 1H), 1.14-1.00 (m, 2H), 0.93-0.83 (m, 2H), 0.77 (d, *J* = 6.6 Hz, 3H), 0.65 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 157.9, 146.5, 135.4, 117.8, 108.2, 103.7, 94.2, 77.5, 74.4, 55.8, 46.4, 40.3, 38.2, 25.8, 22.5, 22.4; HRMS (ESI): calcd. for $C_{20}H_{32}O_6Na$ $[M + Na]^+$ 391.2097; found 391.2088.

(4*R*,5*R*,6*R*)-4-Allyl-6-(3,5-bis(methoxymethoxy)phenyl)-5-isobutyl-2,2-dimethyl-1,3-dioxane (33). To a stirred solution of **32** (2.8 g, 7.61 mmol) in CH_2Cl_2 (20 mL) was added 2,2-dimethoxy propane (4 mL, 30 mmol) followed by PTSA (cat.) at 0 ^{o}C. The mixture was warmed to room temperature and stirred for 30 min and then quenched with water (10 mL). The organic layer was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layer was washed with brine (5 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The residue was subjected to silica gel column chromatography to afford **33** (3.01 g, 97%) as a colorless liquid. R_f = 0.7 (20% EtOAc/hexane); $[\alpha]_D^{24}$ = +34.4 (*c* 0.77, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.74 (d, *J* = 2.3 Hz, 2H), 6.63 (t, *J* = 6.63 Hz, 1H), 5.99-5.89 (m, 1H), 5.15 (dd, *J* = 10.8, 6.7 Hz, 4H), 5.12-5.04

(m, 2H), 4.37 (d, J = 10.3 Hz, 1H), 3.68-3.62 (m, 1H), 3.45 (s, 6H), 2.46-2.40 (m, 1H), 2.22-2.15 (m, 1H), 1.51 (s, 3H), 1.51-1.47 (m, 1H), 1.46 (s, 3H), 0.97-0.86 (m, 3H), 0.68 (d, J = 6.1 Hz, 3H), 0.48 (d, J = 6.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 158.0, 143.0, 135.3, 116.2, 109.4, 104.5, 98.4, 94.3, 78.4, 74.1, 55.8, 43.1, 37.4, 36.7, 30.1, 26.7, 22.7, 22.5, 19.6; HRMS (ESI): calcd. for $C_{23}H_{36}O_6Na$ $[M + Na]^+$ 431.2410; found 431.2428.

2-((4*R*,5*R*,6*R*)-6-(3,5-Bis(methoxymethoxy)phenyl)-5-isobutyl-2,2-dimethyl-1,3-dioxan-4-yl)acetaldehyde (34). To a stirred solution of compound **33** (3 g, 7.35 mmol) in THF:H_2O (3:1, 20 mL) was added NMO (1.7 g, 14.7 mmol) followed by osmium tetroxide (0.2 mL, 0.24 mmol) at 25 ^{o}C. The mixture was stirred at the same temperature for 1 h and quenched with aqueous $Na_2S_2O_4$ solution (10 mL). The organic layer was extracted with EtOAc (3 x 10 mL) and the combined organic layer was washed with brine (5 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The crude residue was used for next step without further purification.

To a stirred solution of crude diol in THF:H_2O (2:1, 20 mL) was added portion wise $NaIO_4$ (3.14 g, 14.7 mmol) at 0 ^{o}C. The mixture was stirred for 3 h at room temperature and then diluted with saturated $NaHCO_3$ solution (5 mL). The organic layer was washed with brine (5 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The residue was subjected to silica gel column chromatography to give compound **34** (2.11 g, 70% over two steps) as a colorless liquid. R_f = 0.5 (20% EtOAc/hexane); $[\alpha]_D^{24}$ = +39.8 (c 0.77, $CHCl_3$); IR (KBr): 2992, 2955, 2868, 2827, 1728, 1599, 1467, 1400, 1381, 1203, 1144, 1034, 925, 852 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.80 (m, 1H), 6.73 (d, J = 2.2 Hz, 2H), 6.64 (t, J = 2.2 Hz, 1H), 5.13 (dd, J = 11.8, 6.7 Hz, 4H), 4.42 (d, J = 10.1 Hz, 1H), 4.21-4.15 (m, 1H), 3.45 (s, 6H), 2.64-2.48 (m, 2H), 1.58-1.54 (m, 1H), 1.54 (s, 3H), 1.42 (s, 3H), 1.05-0.98 (m, 1H), 0.88-0.77 (m, 2H), 0.66 (d, J = 6.1 Hz, 3H), 0.48 (d, J = 6.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 201.5, 158.1, 142.4, 109.2, 104.6, 98.7, 94.3, 78.2,

70.4, 55.8, 47.0, 43.2, 36.4, 29.8, 26.7, 22.5, 22.4, 19.5; HRMS (ESI): calcd. for $C_{22}H_{34}O_7Na$ [M + Na]$^+$ 433.2202; found 433.2187.

(((2*R*,4*R*,6*S*)-7-(Benzyloxy)-2,4,6-trimethylheptyl)oxy)(*tert*-butyl)dimethylsilane (37). To a stirred solution of NaH (208 mg, 5.21 mmol) in anhydrous THF (10 mL) was added alcohol **36** (1 g, 3.47 mmol) in THF (10 mL) at 0 ^{o}C. The mixture was stirred for 30 min at room temperature and cooled to 0 ^{o}C. The mixture was treated with TBAI (110 mg, 0.3 mmol), followed by BnBr (0.4 mL, 3.82 mmol). The mixture was stirred for 5 h at room temperature and quenched with water (10 mL). The organic layer was extracted with EtOAc (3 x 10 mL) and the combined organic layer was washed with brine (5 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The residue was subjected to silica gel column chromatography to afford **37** (1.07 g, 82%) as a colorless oil. R_f = 0.6 (10% EtOAc/hexane); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40-7.27 (m, 5H), 4.54 (dd, *J* = 15.0, 12.1 Hz, 2H), 3.50 (dd, *J* = 9.6, 5.0 Hz, 1H), 3.42-3.36 (m, 2H), 3.25 (dd, *J* = 8.9, 7.1 Hz, 1H), 1.99-1.87 (m, 1H), 1.79-1.69 (m, 1H), 1.69-1.58 (m, 1H), 1.43-1.32 (m, 2H), 0.99 (d, *J* = 6.7 Hz, 3H), 0.95 (s, 9H), 0.94 (d, *J* = 6.6 Hz, 3H), 0.93 (d, *J* = 6.6 Hz, 3H), 0.93-0.84 (m, 2H), 0.09 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 138.8, 128.2, 127.4, 127.3, 75.9, 72.9, 68.0, 41.7, 41.1, 33.1, 30.9, 27.7, 25.9, 21.0, 18.3, 18.3, 17.9, -5.4; HRMS (ESI): calcd. for $C_{23}H_{42}O_2SiNa$ [M + Na]$^+$ 401.2852; found 401.2879.

(2*R*,4*S*,6*S*)-7-(Benzyloxy)-2,4,6-trimethylheptan-1-ol (38). To a stirred solution of **37** (1 g, 2.64 mmol) in anhydrous THF (20 mL) was added TBAF (4.7 mL of 1 M solution in THF, 4.76 mmol,) at 0 °C. The mixture was stirred for 6 h at room temperature and quenched with saturated $NaHCO_3$ solution (5 mL). Organic layer was separated, extracted with EtOAc (3 x 10 mL), washed with brine (5 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The residue was subjected to silica gel column chromatography to give compound **38** (590 mg, 85%)

as a colorless liquid. R_f = 0.2 (20% EtOAc/hexane); $[\alpha]_D^{24}$ = +7.2 (*c* 0.4, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37-7.26 (m, 5H), 4.49 (dd, *J* = 15.7, 12.1 Hz, 2H), 3.49 (dd, *J* = 10.5, 5.0 Hz, 1H), 3.35 (dd, *J* = 10.5, 5.1 Hz, 2H), 3.22 (dd, *J* = 9.0, 6.8 Hz, 1H), 1.91-1.82 (m, 1H), 1.75-1.67 (m, 1H), 1.65-1.53 (m, 2H), 1.39-1.24 (m, 3H), 0.96 (d, *J* = 6.6 Hz, 3H), 0.91 (d, *J* = 6.6 Hz, 3H), 0.91 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 138.7, 128.2, 127.4, 127.3, 75.7, 72.9, 68.0, 41.5, 41.1, 33.0, 30.9, 27.6, 20.9, 18.3, 17.5; LCMS (ESI): 265 $(M + H)^+$.

((((2*S*,4*S*,6*R*)-2,4,6-Trimethyloct-7-yn-1-yl)oxy)methyl)benzene (39). To a solution of oxalyl chloride (0.2 mL, 2.84 mmol) in CH_2Cl_2 (3 mL) was added DMSO (0.24 mL, 3.40 mmol) at -78 ^{o}C. The mixture was stirred for 10 min at -78 ^{o}C and treated dropwise with a solution of alcohol **38** (500 mg, 1.89 mmol) in CH_2Cl_2 (6 mL). The mixture was stirred for 30 min at -78 ^{o}C and then treated dropwise with Et_3N (1.6 mL, 11.3 mmol). The mixture was stirred for 45 min at -78 ^{o}C and then treated with the saturated NH_4Cl solution (5 mL). The organic layer was separated and washed with saturated $NaHCO_3$ solution (5 mL), dried over $MgSO_4$ and concentrated under reduce pressure to afford crude aldehyde, which was used in the next step without further purification.

To a stirred solution of crude aldehyde and Bestmnn-Ohira reagent (544 mg, 2.83 mmol) in MeOH (10 mL) was added K_2CO_3 (780 mg, 5.67 mmol) at 0 ^{o}C. The mixture was stirred for 1 h at room temperature and passed through a small pad of Celite. The filtrate was extracted with CH_2Cl_2 (3 x 10 mL) and the combined organic layer was washed with brine (10 mL) dried over $MgSO_4$, concentrated under reduced pressure. The residue was subjected to silica gel column chromatography to give compound **39** (336 mg, 69% over two steps) as a colorless liquid. R_f = 0.8 (10% EtOAc/hexane); $[\alpha]_D^{24}$ = -12.2 (*c* 1.1, $CHCl_3$); IR (KBr): 2965, 2927, 2871, 1453, 1378, 1099, 735, 676, 630 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38-7.26 (m, 5H), 4.53 (dd, *J* = 14.4,

12.1 Hz, 2H), 3.43-3.35 (m, 1H), 3.32-3.23 (m, 1H), 2.59-2.49 (m, 1H), 2.04 (d, J = 2.4 Hz, 1H), 1.99-1.79 (m, 2H), 1.58-1.52 (m, 1H), 1.44-1.33 (m, 1H), 1.22 (d, J = 6.8 Hz, 3H), 1.09-1.01 (m, 2H), 0.99 (d, J = 6.7 Hz, 3H), 0.94 (d, J = 6.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 138.8, 128.2, 127.4, 127.3, 88.8, 76.1, 72.9, 68.2, 43.7, 41.8, 30.7, 28.1, 23.5, 21.7, 20.0, 17.6; HRMS (ESI): calcd. for $C_{18}H_{26}ONa$ $[M + Na]^+$ 281.1881; found 281.1882.

(2*S*,4*S*,6*R*)-7-Hydroxy-2,4,6-trimethylheptyl acetate (40). To a stirred solution of **36** (1 g, 3.47 mmol) in CH_2Cl_2 (10 mL), Et_3N (0.9 mL, 6.94 mmol) was added followed by Ac_2O (0.5 mL, 5.20 mmol) and DMAP (cat.) at 0 ^oC and stirred for 30 min. The reaction mixture was quenched with water (5 mL) and extracted with CH_2Cl_2 (3 x 10 mL).The combined organic layer was washed with brine (5 mL) dried over $MgSO_4$, concentrated under reduced pressure to get crude reaction mixture and used for next step without further purification.

To a stirred solution of crude reaction mixture in dry THF (15 mL) was added TBAF (5.5 mL of 1 M solution in THF, 5.55 mmol,) at 0 °C. The mixture was stirred for 2 h at room temperature, diluted with saturated $NaHCO_3$ solution (5 mL). Organic layer was separated, washed with brine (5 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The residue was subjected to silica gel column chromatography to give compound **40** (584 mg, 78% over two steps) as a colorless liquid. R_f = 0.2 (10% EtOAc/hexane); ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.88 (dd, J = 10.7, 5.0 Hz, 1H), 3.77 (dd, J = 10.7, 6.8 Hz, 1H), 3.43 (dd, J = 10.5, 5.1 Hz, 1H), 3.28 (dd, J = 10.4, 6.7 Hz, 1H), 2.19 (brs, 1H), 1.98 (s, 3H), 1.88-1.74 (m, 1H), 1.68-1.57 (m, 1H), 1.57-1.45 (m, 1H), 1.31-1.15 (m, 2H), 0.89-0.85 (m, 2H), 0.86 (d, J = 6.7 Hz, 3H), 0.84 (d, J = 6.6 Hz, 3H), 0.84 (d, J = 6.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 69.0, 67.7, 41.0, 40.9, 32.8, 29.7, 27.4, 20.7, 20.6, 17.9, 17.3; LCMS (ESI): 217 $(M + H)^+$.

(2*S*,4*S*,6*R*)-7-(Benzyloxy)-2,4,6-trimethylheptyl acetate (41). To a stirred solution of **40** (580 mg, 2.69 mmol) and $Cl_3C(=NH)OBn$ (1.2 g, 4.84 mmol) in cyclohexane:CH_2Cl_2 (2:1, 20 mL) was added dropwise TfOH (20 μL, 0.27 mmol) at 0 ^oC. The mixture was stirred for 1 h at 0 ^oC and for 3 h at room temperature and quenched with saturated $NaHCO_3$ solution (10 mL). Organic layer was separated, extracted with EtOAc (3 x 10 mL), washed with brine (5 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The residue was subjected to silica gel column chromatography to give compound **41** (592 mg, 72%) as a colorless liquid. R_f = 0.6 (10% EtOAc/hexane); $[\alpha]_D^{24}$ = -1.4 (*c* 1.38, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.34-7.26 (m, 5H), 4.49 (dd, *J* = 15.0, 12.1 Hz, 2H), 3.96 (dd, *J* = 10.7, 5.1 Hz, 1H), 3.81 (dd, *J* = 10.7, 7.1 Hz, 1H), 3.33 (dd, *J* = 8.9, 5.1 Hz, 1H), 3.21 (dd, *J* = 9.0, 6.9 Hz, 1H), 2.04 (s, 3H), 1.94-1.82 (m, 2H), 1.63-1.53 (m, 1H), 1.37-1.24 (m, 4H), 0.93 (d, *J* = 6.6 Hz, 3H), 0.92 (d, *J* = 6.7 Hz, 3H), 0.88 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.2, 138.7, 128.3, 127.4, 127.4, 75.8, 73.0, 69.2, 41.5, 41.1, 30.8, 29.8, 27.5, 20.9, 20.7, 18.1, 17.9; LCMS (ESI): 307 $(M + H)^+$.

(2*S*,4*R*,6*R*)-7-(Benzyloxy)-2,4,6-trimethylheptan-1-ol (42). To a stirred solution of **41** (590 mg, 1.93 mmol) in methanol (6 mL) was added portion wise solid NaOMe (415 mg, 7.72 mmol) at 0 ^oC. The mixture was stirred for 2 h at room temperature, diluted with CH_2Cl_2 (10 mL), and quenched with saturated NH_4Cl solution (5 mL). Organic layer was separated, extracted with CH_2Cl_2 (3 x 10 mL), washed with brine (5 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The residue was subjected to silica gel column chromatography to give compound **42** (592 mg, 95%) as a colorless liquid. R_f = 0.2 (20% EtOAc/hexane); $[\alpha]_D^{24}$ = -6.1 (*c* 1.4, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36-7.24 (m, 5H), 4.50 (dd, *J* = 15.7, 12.1 Hz, 2H), 3.49 (dd, *J* = 10.4, 5.0 Hz, 1H), 3.37-3.29 (m, 2H), 3.21 (dd, *J* = 9.0, 6.9 Hz, 1H), 1.94-1.80 (m, 1H), 1.77-1.63 (m, 1H), 1.63-1.47 (m, 2H), 1.39-1.23 (m, 2H), 0.95-0.90 (m, 2H), 0.95 (d, *J* =

6.7 Hz, 3H), 0.91 (d, *J* = 6.5 Hz, 3H), 0.90 (d, *J* = 6.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 138.7, 128.2, 127.4, 127.3, 75.7, 72.9, 68.0, 41.5, 41.1, 33.0, 30.9, 27.7, 20.9, 18.3, 17.5; HRMS (ESI): calcd. for $C_{17}H_{28}O_2Na$ $[M + Na]^+$ 287.1987; found 287.1991.

((((2*R*,4*R*,6*S*)-2,4,6-Trimethyloct-7-yn-1-yl)oxy)methyl)benzene (43). To a solution of oxalyl chloride (0.27 mL, 3.12 mmol) in CH_2Cl_2 (4 mL) was added DMSO (0.26 mL, 3.74 mmol) at -78 ^{o}C. The mixture was stirred for 10 min at -78 ^{o}C and treated dropwise with a solution of alcohol **42** (550 mg, 2.08 mmol) in CH_2Cl_2 (6 mL). The mixture was stirred for 30 min at -78 ^{o}C and then treated dropwise with Et_3N (1.7 mL, 12.48 mmol). The mixture was stirred for 45 min -78 ^{o}C and treated with saturated NH_4Cl solution (5 mL). The organic layer was separated, washed with saturated $NaHCO_3$ solution (5 mL), dried over $MgSO_4$ and concentrated under reduce pressure, which was used in the next step without further purification.

To a stirred solution of crude aldehyde and Bestmnn-Ohira reagent (600 mg, 3.12 mmol) in MeOH (10 mL) was added K_2CO_3 (860 mg, 6.24 mmol) at 0 ^{o}C. The mixture was stirred for 1 h at room temperature, passed through a small pad of Celite, and extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layer was washed with brine (10 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The residue was subjected to silica gel column chromatography to give compound **43** (354 mg, 66% over two steps) as a colorless liquid. R_f = 0.8 (10% EtOAc/hexane); $[\alpha]_D^{24}$ = +2.8 (*c* 13.6, $CHCl_3$); IR (KBr): 2964, 2927, 2872, 2849, 1453, 1378, 1362, 1098, 1028, 735, 676, 630 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37-7.27 (m, 5H), 4.53 (d, *J* = 1.6 Hz, 2H), 3.42-3.33 (m, 1H), 3.30-3.22 (m, 1H), 2.58-2.52 (m, 1H), 2.05-2.02 (m, 1H), 1.97-1.81 (m, 2H), 1.58-1.51 (m, 1H), 1.43-1.30 (m, 1H), 1.20 (dd, *J* = 6.8, 1.3 Hz, 3H), 1.09-1.00 (m, 2H), 0.98 (dd, *J* = 6.7, 1.6 Hz, 3H), 0.93 (dd, *J* = 6.6, 1.3 Hz, 3H); ^{13}C NMR

(100 MHz, $CDCl_3$): δ 138.8, 128.2, 127.4, 127.3, 88.8, 76.1, 72.9, 68.2, 43.7, 41.8, 30.7, 28.1, 23.5, 21.7, 20.0, 17.6; HRMS (ESI): calcd. for $C_{18}H_{26}ONa$ $[M + Na]^+$ 281.1881; found 281.1882.

(2*S*,5*S*,7*R*,9*R*)-10-(Benzyloxy)-1-((4*R*,5*R*,6*R*)-6-(3,5-bis(methoxymethoxy)phenyl)-5-isobutyl-2,2-dimethyl-1,3-dioxan-4-yl)-5,7,9-trimethyldec-3-yn-2-ol (44). To a suspension of $Zn(OTf)_2$ (816 mg, 2.25 mmol), which was dried under high vacuum at 60-80 °C for 20 min prior to use, and (-)-*N*-methylephedrine (420 mg, 2.34 mmol) in toluene (1 mL) was added triethylamine (326 μL, 2.34 mmol). The mixture was stirred for 2.5 h at room temperature, and treated dropwise with a solution of alkyne **43** (350 mg, 1.35 mmol) in toluene (1 mL) via cannula. The mixture was stirred for 45 min, and treated dropwise with a solution of aldehyde **34** (370 mg, 0.9 mmol) in toluene (1 mL + 500 μL x 2 rinse) via cannula. The mixture was stirred for 12 h at room temperature, quenched with saturated aqueous NH_4Cl solution (5 mL), and extracted with diethyl ether (3 x 10 mL). The organic layer was washed with brine (5 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was subjected to silica gel column chromatography to give compound **44** (452 mg, 76%) as a colorless liquid. R_f = 0.4 (30% EtOAc/hexane); $[\alpha]_D^{24}$ = +6.6 (*c* 0.45, $CHCl_3$); IR (KBr): 2956, 2927, 1589, 1455, 1379, 1263, 1143, 1030, 925, 697 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.34-7.26 (m, 5H), 6.74 (d, *J* = 2.1 Hz, 2H), 6.65 (t, *J* = 2.1 Hz, 1H), 5.14 (dd, *J* = 10.9, 6.8 Hz, 4H), 4.61-4.59 (m, 1H), 4.50 (s, 2H), 4.37 (d, *J* = 10.3 Hz, 1H), 3.85 (t, *J* = 10.3 Hz, 1H), 3.44 (s, 6H), 3.38-3.19 (m, 2H), 2.89 (d, *J* = 2.5 Hz, 1H), 2.61-2.51 (m, 1H), 2.01-1.77 (m, 4H), 1.53 (s, 3H), 1.44 (s, 3H), 1.40-1.27 (m, 3H), 1.18 (d, *J* = 6.7 Hz, 3H), 1.06-0.96 (m, 2H), 0.96 (d, *J* = 6.7 Hz, 3H), 0.91 (d, *J* = 6.5 Hz, 3H), 0.89 (d, *J* = 6.3 Hz, 3H), 0.70 (d, *J* = 5.7 Hz, 3H), 0.47 (d, *J* = 5.7 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 158.0, 142.5, 138.7, 128.2, 127.4, 127.3, 109.3, 104.6, 98.5, 94.3, 89.5, 80.9, 78.3, 76.2, 73.8, 72.9, 61.6, 55.8, 43.5, 41.7, 41.4, 36.3, 31.5, 30.7, 30.0, 28.2, 26.7, 23.7, 22.6, 22.6,

22.4, 21.8, 20.3, 19.5, 17.5, 14.0; HRMS (ESI): calcd. for $C_{40}H_{60}O_8Na$ $[M + Na]^+$ 691.4186; found 691.4185.

(((2*S*,5*S*,7*R*,9*R*)-10-(Benzyloxy)-1-((4*R*,5*R*,6*R*)-6-(3,5-bis(methoxymethoxy)phenyl)-5-isobutyl-2,2-dimethyl-1,3-dioxan-4-yl)-5,7,9-trimethyldec-3-yn-2-yl)oxy)(*tert*-butyl)dimethylsilane (45). To a solution of **44** (450 mg, 0.67 mmol) in anhydrous CH_2Cl_2 (5 mL) was added 2,6-lutidine (0.2 mL, 1.68 mmol), followed by TBSOTf (0.23 mL, 1.00 mmol) dropwise at 0 ^oC. The mixture was stirred for 30 min at 0 ^oC, quenched with water (3 mL), and washed with saturated $NaHCO_3$ solution (5 mL). Organic layer was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layer was dried over $MgSO_4$, concentrated under reduced pressure. The residue was subjected to silica gel column chromatography to give compound **45** (430 mg, 82%) as a colorless liquid. R_f = 0.7 (10% EtOAc/hexane); $[\alpha]_D^{24}$ = +6.0 (*c* 0.45, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 7.35-7.26 (m, 5H), 6.76 (d, *J* = 2.2 Hz, 2H), 6.64 (t, *J* = 2.2 Hz, 1H), 5.14 (dd, *J* = 11.8, 6.7 Hz, 4H), 4.63 (ddd, *J* = 10.4, 4.3, 1.6 Hz, 1H), 4.51 (d, *J* = 2.7 Hz, 2H), 4.39 (d, *J* = 10.3 Hz, 1H), 3.81 (td, *J* = 10.3, 1.5 Hz, 1H), 3.45 (s, 6H), 3.41-3.31 (m, 1H), 3.27-3.20 (m, 1H), 2.64-2.49 (m, 1H), 1.99-1.80 (m, 3H), 1.77-1.69 (m, 1H), 1.51 (s, 3H), 1.44 (s, 3H), 1.38-1.27 (m, 2H), 1.18 (d, *J* = 6.8 Hz, 3H), 1.08-0.99 (m, 3H), 0.98 (d, *J* = 6.7 Hz, 3H), 0.96-0.89 (m, 15H), 0.69 (d, *J* = 5.7 Hz, 3H), 0.48 (d, *J* = 5.7 Hz, 3H), 0.14 (d, *J* = 4.5 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 158.0, 142.9, 138.7, 128.2, 127.4, 127.3, 109.4, 104.5, 98.3, 94.3, 89.2, 81.5, 78.5, 76.3, 75.9, 72.9, 71.7, 60.9, 55.8, 53.3, 43.7, 43.3, 42.5, 41.8, 36.2, 30.9, 30.8, 30.0, 28.1, 26.7, 25.8, 23.6, 22.7, 22.4, 21.9, 20.1, 19.5, 18.2, 17.6, -4.5, -4.9; HRMS (ESI): calcd. for $C_{46}H_{74}O_8SiNa$ $[M + Na]^+$ 805.5051; found 805.5067.

(2*R*,4*R*,6*R*,9*R*)-10-((4*R*,5*R*,6*R*)-6-(3,5-Bis(methoxymethoxy)phenyl)-5-isobutyl-2,2-dimethyl-1,3-dioxan-4-yl)-9-((*tert*-butyldimethylsilyl)oxy)-2,4,6-trimethyldecan-1-ol (46). To a

solution of **45** (430 mg, 0.55 mmol) in EtOAc (8 mL) was added Pd/C (25 mg, 10 mol%) under H_2. The mixture was stirred for 2 h at room temperature. The mixture was filtered through a pad of Celite, washed with EtOAc, and concentrated under reduced pressure. The residue was subjected to silica gel column chromatography to afford a mixture of compound **46** and TBS-ether eliminated product (290 mg, 76% combined yield) as a colorless liquid. R_f = 0.3 (20% EtOAc/hexane); ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.74 (d, J = 2.2 Hz, 2H), 6.62 (t, J = 2.2 Hz, 1H), 5.17-5.12 (m, 4H), 4.35 (d, J = 10.3 Hz, 1H), 3.89-3.86 (m, 1H), 3.63 (t, J = 8.4 Hz, 1H), 3.56-3.49 (m, 1H), 3.44 (s, 6H), 3.41-3.32 (m, 1H), 1.83-1.67 (m, 3H), 1.64-1.51 (m, 2H), 1.51-1.43 (m, 4H), 1.49 (s, 3H), 1.42 (s, 3H), 1.35-1.05 (m, 3H), 0.99 (d, J = 6.7 Hz, 3H), 0.93 (d, J = 6.6 Hz, 3H), 0.92-0.87 (m, 15H), 0.87 (d, J = 6.7 Hz, 3H), 0.68 (d, J = 5.9 Hz, 3H), 0.46 (d, J = 5.9 Hz, 3H), 0.06 (d, J = 3.5 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.2, 143.0, 109.4, 104.5, 98.2, 94.3, 78.8, 71.2, 69.5, 68.2, 55.8, 45.1, 43.8, 41.2, 40.6, 36.5, 33.0, 32.9, 31.6, 30.1, 27.9, 27.5, 26.8, 25.9, 25.9, 22.5, 20.9, 20.4, 19.5, 18.1, 17.6, 17.5, -4.3, -4.6; HRMS (ESI): calcd. for $C_{39}H_{72}O_8SiNa$ $[M + Na]^+$ 719.4894; found 719.4897.

(4*R*,6*R*,8*R*,11*R*)-12-((4*R*,5*R*,6*R*)-6-(3,5-Bis(methoxymethoxy)phenyl)-5-isobutyl-2,2-dimethyl-1,3-dioxan-4-yl)-11-((*tert*-butyldimethylsilyl)oxy)-4,6,8-trimethyldodecan-3-one (47). To a solution of **46** (290 mg, 0.42 mmol) in CH_2Cl_2 (5 mL) were added $NaHCO_3$ (70 mg, 0.83 mmol) and Dess-Martin periodinane (320 mg, 0.75 mmol) at 0 °C. The mixture was stirred for 1 h at room temperature, diluted with CH_2Cl_2 (10 mL), and washed with saturated $NaHCO_3$ solution (5 mL). The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The crude aldehyde was directly used for the next step.

To a stirred solution of crude aldehyde in Et_2O (10 mL) was added dropwise C_2H_5MgBr (1.7 mL of 1 M solution, 1.68 mmol) at 0 ^{o}C. The mixture was stirred for 1 h at 0 ^{o}C and quenched with

saturated NH_4Cl solution (5 mL). Organic layer was extracted with EtOAc (3 x 10 mL). The combined organic layer was dried over $MgSO_4$, concentrated under reduced pressure to give crude alcohol which was directly used for the next step without further purification.

To a stirred solution of crude alcohol in CH_2Cl_2 (5 mL) were added $NaHCO_3$ (70 mg, 0.84 mmol) and Dess-Martin periodinane (284 mg, 0.67 mmol) at 0 °C. The mixture was stirred for 1 h at room temperature and then diluted with CH_2Cl_2 (10 mL), and washed with saturated $NaHCO_3$ solution (5 mL). The organic layer was washed with brine (5 mL), dried over $MgSO_4$, and concentrated under reduced pressure. The residue was subjected to silica gel column chromatography to afford a mixture (200 mg, 68% over three steps) of compound **47** and TBS-ether eliminated by-product as a colorless liquid. R_f = 0.3 (10% EtOAc/hexane); ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.75 (d, *J* = 2.1 Hz, 2H), 6.62 (t, *J* = 2.1 Hz, 1H), 5.14 (dd, *J* = 11.1, 6.7 Hz, 4H), 4.64 (td, *J* = 16.5, 7.9, 3.3 Hz, 1H), 4.34 (d, *J* = 10.3 Hz, 1H), 3.56-3.46 (m, 1H), 3.45 (s, 6H), 2.69-2.59 (m, 1H), 2.56-2.36 (m, 2H), 1.86-1.58 (m, 3H), 1.55-1.40 (m, 8H), 1.50 (s, 3H), 1.44 (s, 3H), 1.08-1.00 (m, 8H), 0.95 (d, *J* = 6.6 Hz, 3H), 0.89-0.88 (m, 12H), 0.86 (d, *J* = 6.6 Hz, 3H), 0.67 (d, *J* = 6.1 Hz, 3H), 0.47 (d, *J* = 6.1 HZ, 3H), 0.09 (s, 3H), 0.07 (s, 3H); LCMS (ESI): 723 $(M + H)^+$.

(4*R*,6*R*,8*R*,11*R*,13*R*,14*R*)-14-((*R*)-(3,5-Dihydroxyphenyl)(hydroxy)methyl)-11,13-dihydroxy-4,6,8,16-tetramethylheptadecan-3-one (1a). To a stirred solution of **47** (100 mg, 0.14 mmol) in MeOH (5 mL) was added PTSA (5 mg, 0.04 mmol) at room temperature. The mixture was stirred for 4 h at the same temperature and quenched with saturated $NaHCO_3$ solution (4 mL). The organic layer was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layer was washed with brine (5 mL), dried over $MgSO_4$, concentrated under reduced pressure. The residue was subjected to silica gel column chromatography to separate compound **1a** (52 mg, 91%

combined yield) and **48** (8 mg) as a white solid. Spectroscopic data for compound **48** has given later. R_f = 0.4 (5% MeOH/CH_2Cl_2); $[\alpha]_D^{24}$ = +10.0 (*c* 0.40, MeOH); IR (KBr): 3346, 2925, 1699, 1605, 1458, 1378, 1339, 1102, 844, 668, 657, 613 cm^{-1}; ^1H NMR (900 MHz, CD_3OD): δ 6.33 (d, *J* = 2.2 Hz, 2H), 6.15 (t, *J* = 2.2 Hz, 1H), 4.47 (d, *J* = 4.0 Hz, 1H), 4.01 (ddd, *J* = 9.5, 4.0, 3.5 Hz, 1H), 3.69 (dddd, *J* = 11.0, 8.5, 4.5, 4.0 Hz, 1H), 2.76 (ddq, *J* = 8.5, 6.5, 5.0 Hz, 1H), 2.57-2.49 (m, 2H), 1.88 (ddq, *J* = 7.0, 6.5, 4.0 Hz, 1H), 1.79 (ddd, *J* = 11.0, 4.5, 3.5 Hz, 1H), 1.72 (ddd, *J* = 11.0, 8.5, 5.0 Hz, 1H), 1.55 (ddd, *J* = 11.0, 9.5, 8.5 Hz, 1H), 1.53 (ddddq, *J* = 8.5, 8.5, 6.6, 6.5, 3.0 Hz, 1H) 1.42 (dddqd, *J* = 8.5, 8.5, 6.6, 6.5, 5.0 Hz, 1H) 1.41 (dddd, *J* = 11.5, 11.0, 8.5, 5.0 Hz, 1H), 1.39 (dddd, *J* = 11.5, 5.0, 4.0, 3.0 Hz, 1H), 1.38 (m, 1H), 1.33 (dddd, *J* = 11.0, 5.0, 3.0, 3.0 Hz, 1H), 1.22 (ddd, *J* = 11.0, 8.5, 8.5 Hz, 1H), 1.21 (m, 2H), 1.19 (dddd, *J* = 11.0, 8.5, 5.0 3.0 Hz, 1H), 1.06 (d, *J* = 6.5 Hz, 3H), 1.02 (t, *J* = 7.5 Hz, 3H), 0.99 (ddd, *J* = 11.0, 8.5, 5.0 Hz, 1H), 0.95 (ddd, *J* = 11.0, 6.6, 6.6 Hz, 1H), 0.88 (d, *J* = 6.5 Hz, 3H), 0.86 (d, *J* = 6.5 Hz, 3H), 0.83 (d, *J* = 6.5 Hz, 3H), 0.77 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR (225 MHz, CD_3OD): δ 218.3, 159.1, 148.3, 105.9, 101.9, 76.5, 73.4, 72.5, 48.5, 46.3, 44.6, 41.7, 40.7, 37.3, 35.4, 35.1, 33.1, 30.9, 29.2, 26.6, 23.3, 22.5, 20.5, 20.3, 17.9, 7.8; HRMS (ESI): calcd. for $C_{28}H_{48}O_6Na$ $[M + Na]^+$ 503.3349; found 503.3336.

(4*R*,6*R*,8*R*,13*R*,14*R*)-14-((*R*)-(3,5-Dihydroxyphenyl)(hydroxy)methyl)-13-hydroxy-4,6,8,16-tetramethylheptadecan-3-one (48). R_f = 0.5 (5% MeOH/CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$): δ 6.39 (brs, 2H), 6.24 (brs, 1H), 4.52-4.46 (m, 1H), 3.67 (d, *J* = 3.8 Hz, 1H), 2.77-2.57 (m, 1H), 2.55-2.37 (m, 2H), 1.86-1.64 (m, 4H), 1.48-1.28 (m, 9H), 1.11-0.97 (m, 10H), 0.84 (d, *J* = 6.5 Hz, 3H), 0.83 (d, *J* = 6.5 Hz, 3H), 0.82 (d, *J* = 6.8 Hz, 3H), 0.78 (d, *J* = 6.6 Hz, 3H), 0.67 (t, *J* = 6.5 Hz, 3H); LCMS (ESI): 487 $(M + Na)^+$.

(2*S*,5*R*,7*S*,9*S*)-10-(Benzyloxy)-1-((4*R*,5*R*,6*R*)-6-(3,5-bis(methoxymethoxy)phenyl)-5-isobutyl-2,2-dimethyl-1,3-dioxan-4-yl)-5,7,9-trimethyldec-3-yn-2-ol (49). The procedure for the preparation of **49** was same as that for the preparation of **44**. Alkyne **39** (300 mg, 1.16 mmol) and aldehyde **34** (317 mg, 0.77 mmol) were used to afford compound **49** (380 mg, 75%) as a colorless liquid. R_f = 0.4 (30% EtOAc/hexane); IR (KBr): 2956, 2927, 1589, 1455, 1379, 1263, 1143, 1030, 925, 697 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.33-7.23 (m, 5H), 6.74 (d, J = 2.1 Hz, 2H), 6.64 (t, J = 2.1 Hz, 1H), 5.13 (dd, J = 10.1, 6.6 Hz, 4H), 4.61 (t, J = 6.1 Hz, 1H), 4.49 (s, 2H), 4.36 (d, J = 10.3 Hz, 1H), 3.85 (t, J = 10.1 Hz, 1H), 3.44 (s, 6H), 3.37-3.22 (m, 2H), 2.78 (brs, 1H), 2.63-2.48 (m, 1H), 1.99-1.76 (m, 4H), 1.52 (s, 3H), 1.44 (s, 3H), 1.44-1.28 (m, 3H), 1.16 (d, J = 6.8 Hz, 3H), 1.07-0.94 (m, 2H), 0.96 (d, J = 6.7 Hz, 3H), 0.95 (d, J = 6.6 Hz, 3H), 0.91 (d, J = 6.6 Hz, 3H), 0.68 (d, J = 5.7 Hz, 3H), 0.48 (d, J = 5.7 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 158.0, 142.6, 138.7, 128.2, 127.3, 127.3, 109.4, 104.6, 98.5, 94.3, 89.5, 81.0, 78.3, 76.2, 73.6, 72.9, 61.4, 55.7, 43.7, 43.5, 41.7, 41.5, 36.3, 30.8, 30.0, 28.3, 28.2, 26.7, 23.7, 22.6, 22.4, 21.8, 20.2, 19.5, 17.5; HRMS (ESI): calcd. for $C_{40}H_{60}O_8Na$ $[M + Na]^+$ 691.4186; found 691.4185.

(((2*S*,5*R*,7*S*,9*S*)-10-(Benzyloxy)-1-((4*R*,5*R*,6*R*)-6-(3,5-bis(methoxymethoxy)phenyl)-5-isobutyl-2,2-dimethyl-1,3-dioxan-4-yl)-5,7,9-trimethyldec-3-yn-2-yl)oxy)(*tert*-butyl)dimethylsilane (50). The procedure for the preparation of **50** was same as that for the preparation of **45**. Alcohol **49** (350 mg, 0.52 mmol) was used to deliver compound **50** (340 mg, 83%) as a colorless liquid. R_f = 0.7 (10% EtOAc/hexane); ^1H NMR (400 MHz, $CDCl_3$): δ 7.36-7.26 (m, 5H), 6.76 (d, J = 2.2 Hz, 2H), 6.63 (t, J = 2.2 Hz, 1H), 5.15 (dd, J = 12.2, 6.7 Hz, 4H), 4.67-4.61 (m, 1H), 4.50 (d, J = 3.3 Hz, 2H), 4.38 (dd, J = 10.3, 3.6 Hz, 1H), 3.82 (t, J = 10.3 Hz, 1H), 3.45 (s, 6H), 3.42-3.30 (m, 1H), 3.28-3.20 (m, 1H), 2.63-2.47 (m, 1H), 1.98-1.78 (m, 3H),

1.78-1.67 (m, 1H), 1.51 (s, 3H), 1.43 (s, 3H), 1.40-1.29 (m, 2H), 1.17 (d, J = 6.8 Hz, 3H), 1.09-0.98 (m, 3H), 0.98 (d, J = 6.6 Hz, 3H), 0.94-0.89 (m, 15H), 0.69 (d, J = 5.7 Hz, 3H), 0.47 (d, J = 5.7 Hz, 3H), 0.13 (d, J = 4.9 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 158.0, 142.9, 138.8, 128.3, 127.4, 127.3, 109.4, 104.6, 98.4, 94.3, 89.2, 81.5, 78.5, 76.3, 72.9, 71.7, 60.9, 55.8, 43.5, 43.3, 42.5, 41.8, 41.5, 36.3, 30.8, 30.0, 28.2, 26.7, 25.9, 23.6, 22.7, 22.4, 22.0, 21.1, 20.7, 20.1, 19.5, 18.3, 17.6, -4.5, -4.8; HRMS (ESI): calcd. for $C_{46}H_{74}O_8SiNa$ $[M + Na]^+$ 805.5051; found 805.5067.

(4*S*,6*S*,8*S*,11*R*,13*R*,14*R*)-14-((*R*)-(3,5-Dihydroxyphenyl)(hydroxy)methyl)-11,13-dihydroxy-4,6,8,16-tetramethylheptadecan-3-one (1b). The procedure for the preparation of **1b** was same as that for the preparation of **1a** from **45**. Compound **50** (300 mg, 0.38 mmol) was used to synthesize compound **1b** (55 mg, 41% combined yield over five steps). Compound **51** was isolated (10 mg) as a white solid. Spectroscopic data for compound **51** has given later. R_f = 0.4 (5% MeOH/CH_2Cl_2); $[\alpha]_D^{24}$ = +27.2 (*c* 0.4, MeOH); IR (KBr): 3345, 2925, 1699, 1605, 1458, 1378, 1102, 844, 657, 613 cm^{-1}; ^{1}H NMR (600 MHz, CD_3OD): δ 6.33 (d, J = 2.2 Hz, 2H), 6.15 (t, J = 2.2 Hz, 1H), 4.47 (d, J = 4.0 Hz, 1H), 4.00 (m, 1H), 3.69 (m, 1H), 2.75 (m, 1H), 2.57-2.49 (m, 2H), 1.87 (m, 1H), 1.79 (m, 1H), 1.72 (ddd, J = 11.0, 8.5, 5.0 Hz, 1H), 1.52-1.50 (m, 2H), 1.47-1.46 (m, 2H), 1.41-1.33 (m, 3H), 1.23-1.21 (m, 3H), 1.05 (d, J = 6.5 Hz, 3H), 1.04 (m, 1H), 1.01 (t, J = 7.5 Hz, 3H), 0.98 (m, 1H), 0.93 (m, 1H), 0.87 (d, J = 6.5 Hz, 3H), 0.85 (d, J = 6.5 Hz, 3H), 0.82 (d, J = 6.5 Hz, 3H), 0.76 (d, J = 6.5 Hz, 3H); ^{13}C NMR (150 MHz, CD_3OD): δ 218.4, 159.2, 148.2, 106.1, 102.0, 76.6, 73.5, 72.9, 48.7, 46.3, 44.6, 41.6, 40.8, 37.4, 35.5, 35.3, 33.3, 31.2, 29.2, 26.7, 23.4, 22.6, 20.6, 20.0, 17.8, 7.8; HRMS (ESI): calcd. for $C_{28}H_{48}O_6Na$ $[M + Na]^+$ 503.3349; found 503.3336.

(4*S*,6*S*,8*S*,13*R*,14*R*)-14-((*R*)-(3,5-Dihydroxyphenyl)(hydroxy)methyl)-13-hydroxy-4,6,8,16-tetramethylheptadecan-3-one (51). R_f = 0.4 (5% MeOH/CH_2Cl_2); ^{1}H NMR (400 MHz, MeOD): δ 6.35 (d, J = 2.1 Hz, 2H), 6.17 (t, J = 2.1 Hz, 1H), 4.46 (d, J = 7.3 Hz, 1H), 3.78-3.76 (m, 1H), 2.82-2.65 (m, 1H), 2.63-2.44 (m, 2H), 1.89-1.82 (m, 1H), 1.78-1.68 (m, 1H), 1.68-1.47 (m, 3H), 1.47-1.19 (m, 10 H), 1.15 (t, J = 6.3 Hz, 3H), 1.11-1.00 (m, 8H), 0.89 (t, J = 6.3 Hz, 3H), 0.88 (t, J = 6.7 Hz, 3H), 0.84 (t, J = 6.5 Hz, 3H), 0.73 (d, J = 6.5 Hz, 3H); HRMS (ESI): calcd. for $C_{28}H_{48}O_5Na$ $[M + Na]^+$ 487.3399; found 487.3399.

((Oct-7-yn-1-yloxy)methyl)benzene (52). To a stirred solution of NaH (336 mg, 8.4 mmol) in THF:DMF (3:1, 20 mL) was added oct-7-yn-1-ol (890 mg, 7.0 mmol) in THF (20 mL) at 0 ^{o}C. The mixture was stirred for 1 h at room temperature and cooled to 0 ^{o}C. The mixture was treated dropwise with BnBr (0.99 mL, 8.4 mmol), stirred for 3 h at room temperature, and quenched with saturated NH_4Cl solution (10 mL). The organic layer was extracted with EtOAc (3 x 10 mL). The combined organic layer was washed with brine (5 mL), dried over $MgSO_4$, concentrated under reduced pressure. The residue was subjected to silica gel column chromatography to afford compound **52** (1.4 g, 92%) as a colorless liquid. R_f = 0.8 (10% EtOAc/hexane); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36-7.26 (m, 5H), 4.51 (s, 2H), 3.47 (t, J = 6.6 Hz, 2H), 2.19 (td, J = 7.0, 2.6 Hz, 2H), 1.94 (t, J = 2.6 Hz, 1H), 1.67-1.59 (m, 2H), 1.58-1.46 (m, 2H), 1.46-1.34 (m, 4H); LCMS (ESI): 217 $(M + H)^+$.

(*S*)-10-(Benzyloxy)-1-((4*R*,5*S*,6*R*)-6-(3,5-bis(methoxymethoxy)phenyl)-5-isobutyl-2,2-dimethyl-1,3-dioxan-4-yl)dec-3-yn-2-ol (53). The procedure for the preparation of **53** was same as that for the preparation of **44** and **21**. Alkyne **52** (210 mg, 0.97 mmol) and aldehyde **12a** (200 mg, 0.49 mmol) were used to afford compound **53** (226 mg, 74%) as a colorless liquid. R_f = 0.4 (20% EtOAc/hexane); $[\alpha]_D^{24}$ = +24.7 (c 0.49, $CHCl_3$); IR (KBr): 3446, 2934, 2864, 1653, 1598,

1457, 1381, 1264, 1143, 1084, 1030, 927, 697 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.36-7.31 (m, 4H), 7.31-7.26 (m, 1H), 6.66 (d, J = 2.2 Hz, 2H), 6.59 (t, J = 2.2 Hz, 1H), 5.14 (s, 4H), 5.03-5.02 (m, 1H), 4.63-4.57 (m, 1H), 4.49 (s, 2H), 4.36-4.29 (m, 1H), 3.46 (t, J = 6.4 Hz, 2H), 3.45 (s, 6H), 2.76-2.75 (m, 1H), 2.23 (dt, J = 7.0, 1.9 Hz, 2H), 2.11-2.04 (m, 1H), 1.68-1.59 (m, 4H), 1.57-1.49 (m, 3H), 1.49 (s, 3H), 1.46 (s, 3H), 1.41-1.37 (m, 3H), 1.17-1.06 (m, 1H), 0.92-0.82 (m, 1H), 0.70 (d, J = 6.4 Hz, 3H), 0.45 (d, J = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 158.0, 143.4, 138.6, 128.3, 127.6, 127.4, 107.1, 103.2, 99.4, 94.3, 85.5, 80.7, 74.9, 73.3, 72.8, 70.3, 61.8, 60.4, 55.9, 41.4, 41.3, 30.4, 29.8, 29.6, 28.7, 28.6, 27.4, 25.7, 22.8, 22.1, 19.5, 18.7, 14.2; HRMS (ESI): calcd. for $C_{37}H_{54}O_8Na$ $[M + Na]^+$ 649.3716; found 649.3734.

(((*S*)-10-(Benzyloxy)-1-((4*R*,5*S*,6*R*)-6-(3,5-bis(methoxymethoxy)phenyl)-5-isobutyl-2,2-dimethyl-1,3-dioxan-4-yl)dec-3-yn-2-yl)oxy)(*tert*-butyl)dimethylsilane (54). The procedure for the preparation of **54** was same as that for the preparation of **45** and **22**. Alcohol **53** (150 mg, 0.24 mmol) was used to afford compound **54** (140 mg, 81%) as a colorless liquid. R_f = 0.8 (10% EtOAc/hexane); ^1H NMR (400 MHz, $CDCl_3$): δ 7.36-7.26 (m, 5H), 6.68 (d, J = 2.1 Hz, 2H), 6.59 (t, J = 2.1 Hz, 1H), 5.15 (s, 4H), 5.01 (brs, 1H), 4.54-4.49 (m, 1H), 4.49 (s, 2H), 4.29 (d, J = 8.1 Hz, 1H), 3.48-3.45 (m, 2H), 3.45 (s, 6H), 2.23 (td, J = 6.9, 1.7 Hz, 2H), 1.96-1.89 (m, 1H), 1.67-1.57 (m, 2H), 1.56-1.47 (m, 4H), 1.46 (d, J = 1.9 Hz, 6H), 1.46-1.34 (m, 4H), 1.31-1.06 (m, 2H), 0.92 (s, 9H), 0.89-0.75 (m, 1H), 0.67 (d, J = 6.5 Hz, 3H), 0.45 (d, J = 6.5 Hz, 3H), 0.14 (d, J = 5.7 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 157.9, 143.8, 138.6, 128.3, 127.5, 127.4, 107.2, 103.1, 99.2, 94.3, 85.1, 81.3, 75.0, 72.8, 71.0, 70.3, 60.9, 55.8, 42.3, 41.1, 30.5, 29.8, 29.7, 28.7, 28.6, 27.3, 25.8, 25.7, 25.6, 22.7, 22.2, 19.4, 18.6, 18.2, -4.4, -4.9; LCMS (ESI): 741 $(M + H)^+$.

(*R*)-10-((4*R*,5*S*,6*R*)-6-(3,5-Bis(methoxymethoxy)phenyl)-5-isobutyl-2,2-dimethyl-1,3-dioxan-4-yl)-9-((*tert*-butyldimethylsilyl)oxy)decan-1-ol (56). The procedure for the preparation of **56**

was same as that for the preparation of **23**. Compound **54** (86 mg, 0.16 mmol) was used to afford compound **56** (140 mg, 81%) as a colorless liquid. R_f = 0.4 (20% EtOAc/hexane); ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.66 (d, J =1.9 Hz, 2H), 6.58 (t, J = 1.9 Hz, 1H), 5.14 (s, 4H), 4.97 (brs, 1H), 4.22 (t, J = 6.1 Hz, 1H), 3.79 (t, J = 5.7 Hz, 1H), 3.63 (t, J = 6.7 Hz, 2H), 3.45 (s, 6H), 1.77-1.62 (m, 1H), 1.62-1.46 (m, 5H), 1.46 (s, 6H), 1.34-1.21 (m, 12H), 1.18-1.11 (m, 2H), 0.92 (s, 9H), 0.83-0.72 (m, 1H), 0.67 (d, J = 6.3 Hz, 3H), 0.45 (d, J = 6.3 Hz, 3H), 0.10 (s, 3H), 0.07 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 157.9, 143.9, 107.3, 103.1, 99.1, 94.4, 75.1, 70.7, 69.0, 63.0, 55.9, 40.8, 40.3, 37.2, 37.8, 30.3, 29.9, 29.7, 29.5, 29.3, 27.3, 25.9, 25.7, 24.9, 22.8, 22.3, 19.5, 18.1, -4.2, -4.5; LCMS (ESI): 655 $(M + H)^+$.

(11*R*,13*R*,14*S*)-14-((*R*)-(3,5-Dihydroxyphenyl)(hydroxy)methyl)-11,13-dihydroxy-16-methylheptadecan-3-one (57). The procedure for the preparation of **57** was same as that for the preparation of **1a** from **46**. Compound **56** (120 mg, 0.18 mmol) was used to prepare compound **57** (48 mg, 61% over 4 steps). R_f = 0.3 (5% MeOH/CH_2Cl_2); $[\alpha]_D^{24}$ = +5.8 (*c* 0.26, $CHCl_3$); IR (KBr): 3346, 2924, 2852, 1701, 1602, 1461, 1261, 1153, 1031, 668 cm^{-1}; ^{1}H NMR (400 MHz, CD_3OD): δ 6.25 (d, J = 2.2 Hz, 2H), 6.05 (t, J = 2.2 Hz, 1H), 4.75 (d, J = 3.5 Hz, 1H), 3.92-3.88 (m, 1H), 3.68-3.61 (m, 1H), 2.41-2.35 (m, 4H), 1.63-1.52 (m, 3H), 1.52-1.36 (m, 3H), 1.39-1.27 (m, 5H), 1.27-1.11 (m, 9H), 0.93 (t, J = 7.3 Hz, 3H), 0.68 (d, J = 6.1 Hz, 3H), 0.56 (d, J = 6.1 Hz, 3H); ^{13}C NMR (100 MHz, CD_3OD): δ 214.8, 159.3, 148.6, 105.7, 102.0, 76.8, 75.1, 72.0, 49.3, 43.1, 42.3, 38.6, 36.6, 33.4, 30.7, 30.5, 30.3, 28.3, 26.4, 25.0, 23.4, 23.0, 8.1; HRMS (ESI): calcd. for $C_{25}H_{42}O_6Na$ $[M + Na]^+$ 461.2879; found 461.2866.

(1*R*,2*S*,3*R*,5*S*)-13-(Benzyloxy)-1-(3,5-dihydroxyphenyl)-2-isobutyltridec-6-yne-1,3,5-triol (55). To a stirred solution of **53** (50 mg, 0.08 mmol) in MeOH (2 mL) was added PTSA (cat.) at room temperature. The mixture was stirred for 4 h at room temperature and then quenched with

saturated $NaHCO_3$ solution (2 mL). The organic layer was extracted with CH_2Cl_2 (3 x 5 mL). The combined organic layer was washed with brine (2 mL), dried over $MgSO_4$, concentrated under reduced pressure. The residue was subjected to silica gel column chromatography to afford **55** (32 mg, 84%) as a colorless liquid. R_f = 0.6 (5% MeOH/CH_2Cl_2); $[\alpha]_D^{24}$ = +18.2 (*c* 1.5, $CHCl_3$); ^{1}H NMR (400 MHz, MeOD): δ 7.34-7.29 (m, 4H), 7.30-7.24 (m, 1H), 6.33 (d, *J* = 2.0 Hz, 2H), 6.14 (t, *J* = 2.0 Hz, 1H), 4.83 (d, *J* = 3.6 Hz, 1H), 4.49-4.45 (m, 3H), 4.01-3.98 (m, 1H), 3.48 (t, *J* = 6.4 Hz, 2H), 2.19 (td, *J* = 6.6, 1.7 Hz, 2H), 2.00-1.93 (m, 1H), 1.78-1.69 (m, 2H), 1.64-1.57 (m, 2H), 1.51-1.27 (m, 9H), 0.80 (d, *J* = 6.1 Hz, 3H), 0.67 (d, *J* = 6.1 Hz, 3H); ^{13}C NMR (100 MHz, MeOD): δ 157.8, 147.4, 138.4, 128.0, 127.5, 127.3, 104.3, 100.5, 84.6, 80.9, 74.7, 72.5, 71.6, 70.0, 60.5, 48.5, 42.8, 32.3, 29.3, 28.4, 28.3, 26.6, 25.4, 22.2, 21.4, 17.9; HRMS (ESI): calcd. for $C_{30}H_{42}O_6Na$ $[M + Na]^+$ 521.2879; found 521.2876.

(1*R*,2*S*,3*R*,5*S*,8*S*,10*S*,12*R*)-13-(Benzyloxy)-1-(3,5-dihydroxyphenyl)-2-isobutyl-8,10,12-trimethyltridec-6-yne-1,3,5-triol (58). The procedure for the preparation of **58** was same as that for the preparation of **55**. MOM-protected **21a** (20 mg, 0.03 mmol) was used to afford compound **58** (12 mg, 85%) as a colorless liquid. R_f = 0.5 (5% MeOH/CH_2Cl_2); ^{1}H NMR (400 MHz, MeOD): δ 7.33-7.32 (m, 4H); 7.28-7.22 (m, 1H), 6.34-6.32 (m, 2H), 6.17-6.14 (m, 1H), 4.90-4.87 (m, 1H), 4.51-4.44 (m, 3H), 4.04-4.01 (m, 1H), 3.35-3.21 (m, 2H), 2.60-2.46 (m, 1H), 2.06-1.93 (m, 1H), 1.92-1.72 (m, 4H), 1.45-1.22 (m, 5H), 1.17-1.14 (m, 2H), 1.11 (d, *J* = 6.8 Hz, 3H), 0.94 (d, *J* = 6.8 Hz, 3H), 0.90 (d, *J* = 6.4 Hz, 3H), 0.80 (d, *J* = 5.7 Hz, 3H), 0.65 (d, *J* = 5.7 Hz, 3H); ^{13}C NMR (100 MHz, MeOD): δ 159.2, 148.7, 139.8, 129.3, 128.8, 128.5, 105.6, 101.9, 90.5, 82.5, 77.6, 75.9, 73.9, 73.1, 61.8, 49.7, 49.6, 48.3, 46.6, 44.1, 41.4, 33.5, 32.0, 29.1, 27.9, 24.6, 23.6, 22.7, 21.7, 20.3, 17.3; HRMS (ESI): calcd. for $C_{33}H_{48}O_6Na$ $[M + Na]^+$ 563.3349; found 563.3363.

(1*R*,2*S*,3*R*,5*R*,8*R*,10*S*,12*R*)-1-(3,5-Dihydroxyphenyl)-2-isobutyl-8,10,12-trimethyltridecane-1,3,5,13-tetraol (59). The procedure for the preparation of **59** was same as that for the preparation of **55**. MOM-protected **23a** (20 mg, 0.03 mmol) was used to afford compound **59** (10.5 mg, 82%) as a white solid. R_f = 0.4 (10% MeOH/CH_2Cl_2); ^{1}H NMR (400 MHz, MeOD): δ 6.25 (d, J = 1.9 Hz, 2H), 6.04 (t, J = 1.9 Hz, 1H), 4.74 (d, J = 2.7 Hz, 1H), 3.90-3.88 (m, 1H), 3.63-3.59 (m, 1H), 3.38-3.22 (m, 2H), 1.67-1.48 (m, 6H), 1.48-1.24 (m, 6H), 1.24-0.88 (m, 7H), 0.79 (d, J = 6.7 Hz, 3H), 0.78 (d, J = 6.7 Hz, 3H), 0.76 (d, J = 6.6 Hz, 3H), 0.70 (d, J = 5.8 Hz, 3H), 0.56 (d, J = 5.8 Hz, 3H); ^{13}C NMR (100 MHz, MeOD): δ 159.8, 149.1, 106.2, 102.4, 77.3, 75.5, 72.8, 69.6, 49.7, 47.5, 43.2, 42.8, 42.3, 36.5, 34.8, 33.9, 31.8, 29.0, 28.8, 23.9, 23.4, 20.4, 20.2, 17.5; HRMS (ESI): calcd. for $C_{26}H_{46}O_6Na$ $[M + Na]^+$ 477.3192; found 477.3187.

(1*R*,2*S*,3*R*,8*R*,10*S*,12*R*)-1-(3,5-Dihydroxyphenyl)-2-isobutyl-8,10,12-trimethyltridecane-1,3,13-triol (60). The procedure for the preparation of **60** was same as that for the preparation of **55**. MOM-protected TBS-ether eliminated **23'** (20 mg, 0.03 mmol) was used to afford compound **60** (10.6 mg, 81%) as a viscous liquid. R_f = 0.4 (10% MeOH/CH_2Cl_2); ^{1}H NMR (400 MHz, MeOD): δ 6.33 (d, J = 2.2 Hz, 2H), 6.14 (t, J = 2.2 Hz, 1H), 4.78 (d, J = 3.7 Hz, 1H), 3.74-3.71 (m, 1H), 3.42-3.35 (m, 1H), 3.31-3.27 (m, 1H), 1.75-1.58 (m, 3H), 1.58-1.46 (m, 4H), 1.46-1.31 (m, 5H), 1.21-0.94 (m, 6H), 0.94-0.83 (m, 12H), 0.77 (d, J = 6.1 Hz, 3H), 0.64 (d, J = 6.1 Hz, 3H); ^{13}C NMR (100 MHz, CD_3OD): δ 159.2, 148.4, 105.7, 101.9, 77.7, 76.1, 69.0, 48.8, 42.7, 38.8, 36.0, 34.2, 33.3, 32.7, 31.1, 31.0, 28.5, 27.6, 23.6, 23.2, 23.0, 19.7, 17.0, 14.4; HRMS (ESI): calcd. for $C_{26}H_{46}O_5Na$ $[M + Na]^+$ 461.3243; found 461.3230.

(4*R*,6*S*,8*R*,13*R*,14*S*)-14-((*R*)-(3,5-Dihydroxyphenyl)(hydroxy)methyl)-13-hydroxy-4,6,8,16-tetramethylheptadecan-3-one (61). The procedure for the preparation of **61** was same as that for the preparation of **1a** from **46**. MOM-protected TBS-ether eliminated **23'** (20 mg, 0.04 mmol)

was used to afford compound **61** (11.3 mg, 61% over four steps) as a viscous liquid. R_f = 0.5 (5% MeOH/CH_2Cl_2); ^{1}H NMR (400 MHz, CD_3OD): δ 6.25 (d, J = 2.2 Hz, 2H), 6.06 (t, J = 2.2 Hz, 1H), 4.70 (d, J = 2.9 Hz, 1H), 3.67 (m, 1H), 2.73-2.55 (m, 1H), 2.52-2.35 (m, 2H), 1.62-1.42 (m, 1H), 1.42-1.28 (m, 8H), 1.27-1.09 (m, 8H), 1.03-0.97 (m, 3H), 0.97 (d, J = 6.8 Hz, 3H), 0.95 (d, J = 6.1 Hz, 3H), 0.78 (d, J = 6.6 Hz, 3H), 0.76 (t, J = 6.5 Hz, 3H), 0.70 (d, J = 5.8 Hz, 3H), 0.56 (d, J = 5.8 Hz, 3H); ^{13}C NMR (100 MHz, CD_3OD): δ 218.3, 159.2, 148.4, 105.7, 101.9, 77.7, 76.0, 48.8, 46.1, 44.9, 42.3, 38.9, 36.0, 35.1, 33.4, 31.1, 29.2, 28.5, 27.6, 23.3, 23.1, 19.8, 17.0, 8.1; HRMS (ESI): calcd. for $C_{28}H_{48}O_5Na$ $[M + Na]^+$ 487.3399; found 487.3397.

Isolation and purification of synthetic baulamycin A products (1, 1a, and 1b): The crude product including **1** was injected to a semi-preparative reversed-phase HPLC column (Kromasil C18: 250 × 10 mm, 5 μm) with a gradient solvent system (35% acetonitrile/water to 75% acetonitrile/water over 40 min, UV 280 nm detection, flow rate: 2 mL/min). The major peak at the retention time of 36.0 min was obtained as pure synthetic baulamycin A (proposed structure, **1**). Similarly, the crude product containing **1a** was subjected to a semi-preparative reversed-phase HPLC column (Kromasil C18: 250 × 10 mm, 5 μm) with a gradient solvent system (35% acetonitrile/water to 75% acetonitrile/water over 40 min, UV 280 nm detection, flow rate: 2 mL/min). An HPLC peak bearing **1a** eluted at the retention time of 36.5 min. To remove impurities, this compound was further purified under isocratic solvent conditions (35% acetonitrile/water, UV 280 nm detection, flow rate: 2 mL/min) using a chiral column (YMC cellulose-SC: 250 × 4.6 mm, 5 μm). **1a** eluted as pure compound at the retention time of 20.5 min. The purification of **1b** was performed in the same manner using the combination of C18 and chiral HPLC columns (retention time through the final chiral HPLC: 20.3 min).

Experimental procedure for assessing inhibitory-activities on SbnE.

For evaluation of the inhibitory-activities of baulamycin derivatives on SbnE, a modified malachite green assay was employed. To an Eppendorf tube containing 25 mM HEPES, 5 mM $MgCl_2$, 100 μM ATP, 100 μM sodium citrate, 100 μM L-2,3-diaminopropionic acid, and 0.001 U/μL inorganic pyrophosphatase (IPP) was added a synthesized baulamycin derivative dissolved in DMSO to a final concentration of 46 nM, 137 nM, 412 nM, 1.23 μM, 3.70 μM, 11.1 μM, 33.3 μM, or 100 μM (for negative control, a DMSO vehicle was used). Each reaction was then initiated by addition of SbnE (25 nM) at 37 ºC. The total reaction volume was 100 μL. The reaction mixture was incubated for 1 h before addition of 25 μL quenching solution composed of 50 parts of malachite green solution, 12.5 parts of 7.5% ammonium molybdate, and 1 part of 11% Tween-20 solution. After additional incubation for 15 min at 37 ºC, 100 μL aliquot of each mixture was loaded in a 96-well clear bottom plate and the absorbance at 630 nm was measured using a Hidex Sense microplate reader (Hidex, Finland). For positive control, a reaction containing all the same components except for SbnE was conducted. All data were collected in duplicates. The observed absorbance values were converted to the % inhibition, and then the resulting % inhibition vs log[compound] plots were fitted using GraphPad Prism version 7 to calculate the IC_{50} values (Figure S165).

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Supporting Information. Spectra for all compounds. This material is available free of charge via the Internet at ACS Publications website.

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