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Stereocontrolled synthesis of the ABCDE ring moiety of ciguatoxin CTX3C

Shoji Kobayashi, Yusuke Takahashi, Kazuo Komano, Babak H. Alizadeh, Yuuya Kawada, Tohru Oishi,† Shin-ichiro Tanaka, Yoshihiro Ogasawara, Shin-ya Sasaki and Masahiro Hirama*

Department of Chemistry, Graduate School of Science, Tohoku University, Sendai 980-8578, Japan

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Abstract—The ABCDE ring moiety of ciguatoxin CTX3C, a major causative agent of ciguatera poisoning, was stereoselectively synthesized. The key transformations are a chiral auxiliary-based asymmetric alkylation and an asymmetric aldol condensation, which controlled the formation of the C11 and C21-stereocenters, respectively. A highly practical and efficient route to the ABCD ring fragment, a common precursor for the divergent synthesis of the left wings of ciguatoxins, was also established.

1. Introduction

Ciguatoxins (CTXs) produced by a marine dinoflagellate (*Gambierdiscus toxicus*) living on macroalgae, are transferred to and accumulated in a number of fish through the food chain, causing ciguatera seafood poisoning primarily in tropical and subtropical areas.[1] The complex structures of more than 20 CTX congeners such as CTX3C (**1**),[2] 51-hydroxyCTX3C (**2**),[3] CTX4B (**3**),[4] and CTX (**4**)[4] were elucidated on the basis of NMR and MS analyses. Biological studies have revealed that CTXs exert their toxicity through the activation of voltage-sensitive sodium channels (VSSCs).[5] To elucidate the interaction with VSSCs in more detail at the molecular level[5d] as well as to develop reliable immunochemical methods for detecting CTXs,[6] a practical supply of CTXs and their structural analogs has been required. However, the extremely low content of CTXs in fish has limited their supply from natural sources. Therefore, a number of synthetic efforts have been undertaken,[7] culminating in the first total synthesis of CTX3C (**1**) in our laboratory.[8] Our convergent strategy to synthesize **1** relied on the coupling of the left (ABCDE) wing and the right (HIJKLM) wing with the concomitant construction of the central FG ring system.[8,9] This strategy is expected to be applicable to all CTXs due to the common FG ring structure. Our recent research greatly improved the synthesis of the HIJKLM ring[10] in terms of number of synthetic steps, stereoselectivity, and overall yield.[11] On the other hand, preparation of the ABCDE ring moiety **5**[12] was yet to be optimized, especially with regard to stereocontrol. In the original synthesis of **5**, the stereoselectivity of the coupling between AB ring **9** and E ring **8** was unsatisfactory. Furthermore, E ring **8** was prepared from D-glucose via a non-stereocontrolled aldol condensation. Therefore, separation of undesired stereoisomers was required, followed by repeated epimerization processes, to supply a sufficient quantity of ring fragments for total synthesis. To overcome these stereochemical disadvantages, an alternative approach featuring chiral auxiliary-based stereoselective alkylation of **12** with **9** was developed to afford the ABCD ring fragment **11**.[13] The intermediate **11** was expected to be a common precursor for the divergent synthesis of the left wings of **1**, **2**, **3** and **4**. In our previous report,[14] the fully functionalized ABCDE ring moiety (**10**) of **4** was synthesized from **11** through installation of the dihydroxybutenyl substituent at C5 in the A ring and the tetrahydrooxepin E ring. In this publication, we have developed a stereocontrolled route to **5** from **11** using an asymmetric aldol condensation to regulate the C21-stereochemistry as a key transformation. A practical synthesis of the key intermediate **11** is also described herein. These developments are depicted in Scheme 1.

2. Results and discussion

2.1. Practical synthesis of the ABCD ring moiety

The AB ring unit **9** was synthesized from commercially

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* Corresponding author. Tel.: +81-22-217-6563; fax: +81-22-217-6566; e-mail: hirama@ykbsc.chem.tohoku.ac.jp
† Present address: Department of Chemistry, Graduate School of Science, Osaka University, Osaka 560-0043, Japan.

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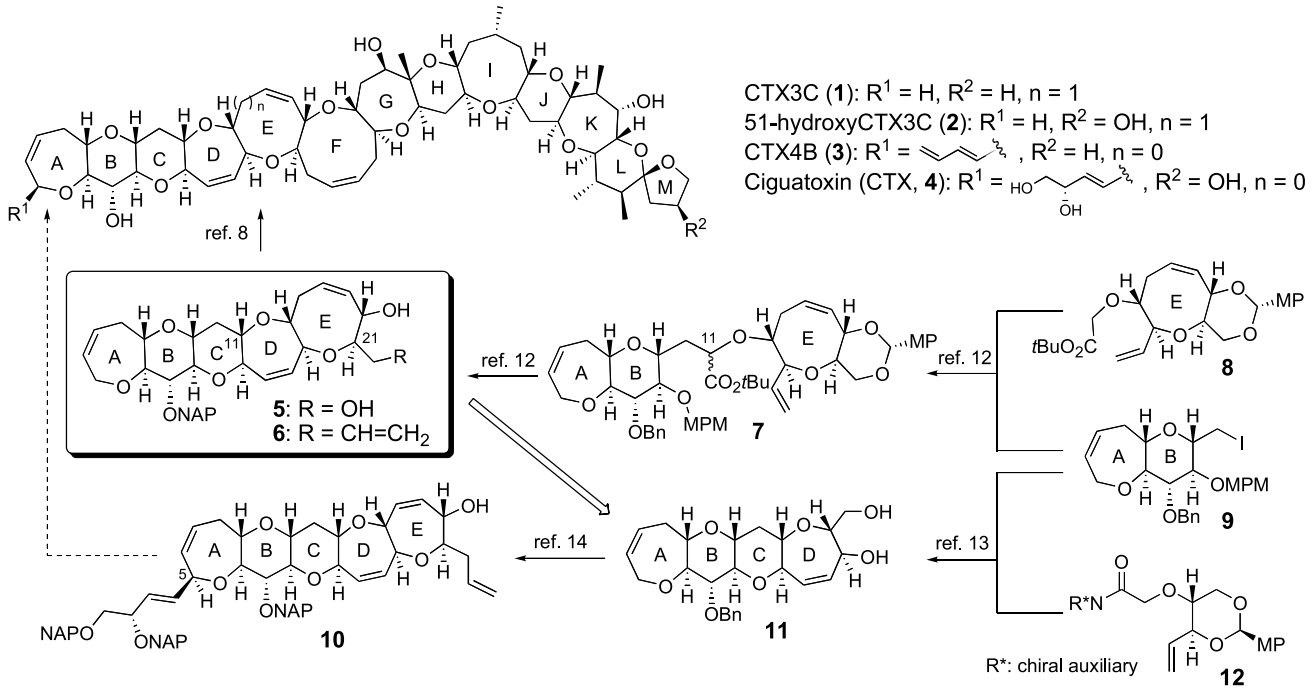
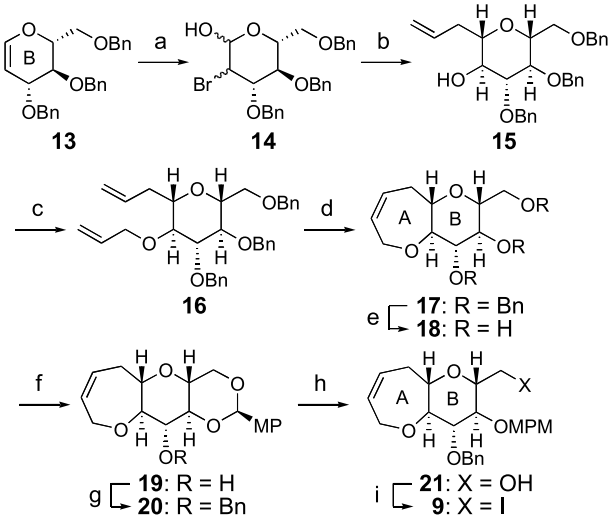


Scheme 1. Structures of ciguatoxins (CTXs) and synthetic strategy for the total synthesis of CTXs. Bn=benzyl; MP=*p*-methoxyphenyl; MPM=*p*-methoxybenzyl; NAP=2-naphthylmethyl.

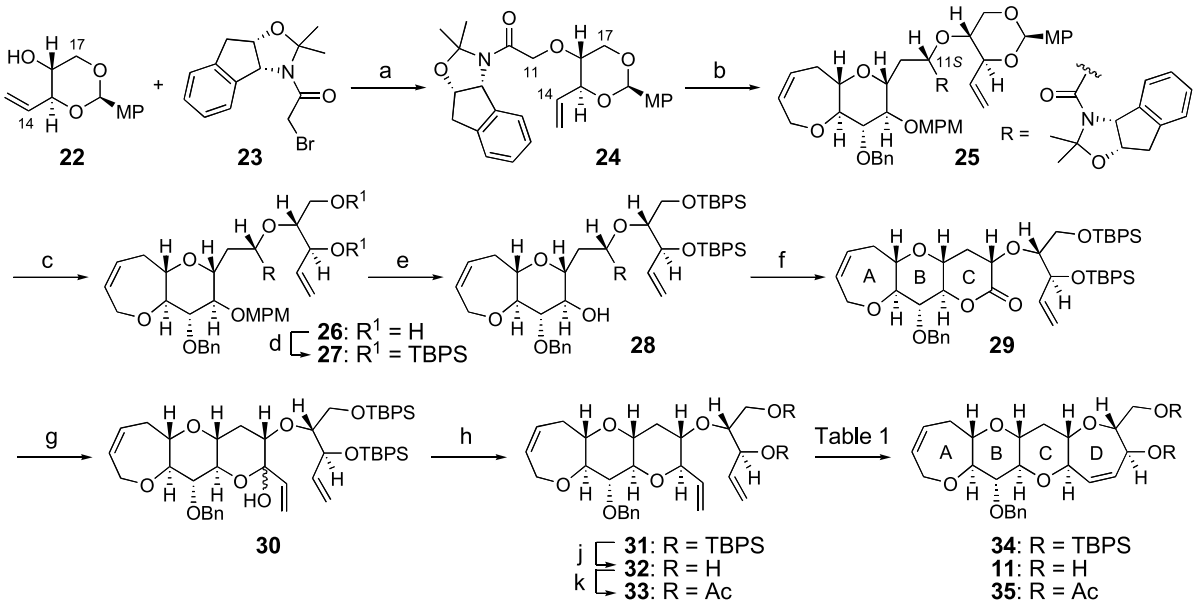
available tri-*O*-benzyl-D-glucal (**13**) using a slight modification of a previously reported procedure (Scheme 2),[12,15] as follows. Treatment of **13** with NBS in aqueous THF gave a diastereomeric mixture of bromohydrins **14**, which was converted to **15** using the Spilling method.[16] To obtain **15** with high stereoselectivity, it was critical to maintain strict temperature control at −78 °C during the treatment of **14**



Scheme 2. Reagents and conditions: (a) NBS, THF–H_2O (10:1), 0 °C, 1 h; (b) $KN(SiMe_3)_2$, 18-crown-6, toluene, −78 °C, 6 h, then allylmagnesium bromide, toluene–Et_2O, −68 °C to rt, 24 h, 45% (2 steps); (c) allyl bromide, NaH, THF–DMF (4:1), 0 °C to rt, 13 h, 99%; (d) $(PCy_3)_2Cl_2Ru$=CHPh (2 mol%), CH_2Cl_2, 4.5 h, 84%; (e) $TiCl_4$ (1.9 equiv.), $MeNO_2$, −5 °C, 30 min; (f) *p*$MeOC_6H_4CH(OMe)_2$, TsOH·H_2O, DMF, 0 °C to rt, 18 h, 91% (2 steps); (g) BnBr, NaH, THF–DMF (4:1), 0 °C to rt, 18 h; (h) DIBAL, CH_2Cl_2, −78 to −33 °C, 12 h, 97% (2 steps); (i) PPh_3, I_2, imidazole, toluene, 6 h, 96%. NBS=*N*-bromosuccinimide; Cy=cyclohexyl; DIBAL=diisobutylaluminum hydride; Ts=*p*-toluenesulfonyl.

with $KN(TMS)_2$. Alcohol **15** was then reacted with allyl bromide to give diene **16**, which was subjected to ring-closing metathesis (RCM)[17] to yield the AB ring **17**. Removal of the benzyl group of **17** under Birch conditions or with the use of lithium 4,4′-di-*tert*-butylbiphenyl resulted in the partial cleavage of the allylic ether linkage in the A ring.[8a,12] After considerable investigation, Lewis acid-mediated debenzylation using $TiCl_4$[18] was found to be optimal and selectively yielded triol **18**, which was easily converted to acetal **19** (91%, 2 steps). The secondary alcohol of **19** was protected as a benzyl ether, and the *p*-methoxybenzylidene acetal of **20** was selectively cleaved to give primary alcohol **21**. Finally, iodination of **21** afforded the AB ring moiety **9**.

The C14–C17 unit[19] was then assembled onto **9** (Scheme 3). After considerable experimentation,[20] we found that the protected (1*R*,2*S*)-1-amino-2-indanol derivative **24**[21] was suitable for diastereoselective alkylation. Amide **24** was readily prepared from alcohol **22**[12b] and bromide **23**. The key coupling reaction between iodide **9** and **24** (3.3 equiv.) was successfully performed using BuLi (3.3 equiv.) in the presence of DMPU (4.5 equiv.). The reaction reproducibly afforded the desired isomer **25** almost exclusively, even at the reaction scale of 17 g (33 mmol) of **9**, possibly through the transition state as shown in Figure 1, which shows attack of electrophile **9** from the less hindered C11-*si* face of the kinetically and thermodynamically favored *Z*-enolate of **24**.[21a,22] Selective removal of *p*-methoxybenzylidene acetal of **25** with PPTS and subsequent TBPS protection with TBPSOTf[23] in the presence of 2,6-lutidine afforded **27** in 74% overall yield from **9**. Oxidative MPM deprotection was then carefully performed at −5 °C to avoid Bn deprotection, yielding secondary alcohol **28**. Subsequent lactonization was not trivial. After extensive experimentation, it was found that addition of a catalytic amount of *p*-anisaldehyde



Scheme 3. Reagents and conditions: (a) NaH, THF–DMF (4:1), 13 h, 79%; (b) **9**, BuLi, DMPU, THF, −78 °C to rt, 19 h; (c) PPTS, PrOH, 16 h, 81% (2 steps); (d) TBPSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C, 2 h, 91%; (e) DDQ, CH_2Cl_2-H_2O (20:1), −5 °C, 2.5 h (three cycles), 86%; (f) CSA (3 equiv.), *p*-anisaldehyde (0.4 equiv.), toluene, 90 °C, 3 h; (g) tetravinyltin, MeLi, THF, −100 to −90 °C, 45 min, 77% (2 steps); (h) Et_3SiH, TMSOTf, CH_3CN, −40 to −20 °C, 40 min; (i) TBAF, THF, 44 h, 82% (2 steps); (j) Ac_2O, pyridine, DMAP, CH_2Cl_2, 3 h, 89%. DMPU=*N*,*N*′-dimethylpropyleneurea; PPTS=pyridinium *p*-toluenesulfonate; TBPS=*t*-butyldiphenylsilyl; DDQ=2,3-dichloro-5,6-dicyano-1,4-benzoquinone; CSA=(*1S*)-(+)-10-camphorsulfonic acid; TMS=trimethylsilyl; Tf=trifluoromethanesulfonyl; TBAF=tetrabutylammonium fluoride; Ac=acetyl; DMAP=4-(dimethylamino)pyridine.

to the reaction mixture of **28** and CSA (3 equiv.) in toluene at 90 °C reproducibly produced lactone **29** in good yield. This can be explained as follows: acid-catalyzed cleavage of the acetonide group on the chiral auxiliary can be expected to compete with the direct lactonization of tertiary amide **28**. The resultant secondary amide is likely to be less susceptible to lactonization. However, once it is converted in the presence of *p*-anisaldehyde to the corresponding *p*-methoxybenzylidene acetal, this tertiary amide would become reactive enough to form **29**. A vinyl group was then added to **29** at a temperature less than −90 °C to yield hemiacetal **30** as a mixture of diastereomers. Direct reduction of **30** was achieved with triethylsilane in the presence of TMSOTf in acetonitrile to afford a mixture of bis-TBPS ether **31**, diol **32**, and mono-TBPS ethers. The remaining TBPS groups were wholly removed by TBAF to yield **32** from **28** with an overall yield of 63%.

Subsequent RCM of the diene was highly dependent on the protective group and catalyst used, as shown in Table 1. The reaction of bis-TBPS ether **31** using catalyst **36**[17] or **37**[24] was very sluggish, presumably due to steric hindrance of the TBPS groups (entries 1 and 2). Although the reaction with the less hindered acetate **33** did proceed, more than 1 equiv. of catalyst and a long reaction time were required (entries 3 and 4). On the contrary, diol **32** smoothly underwent RCM (entries 5–7), and a catalytic amount of **37** was sufficient to yield **11** in 99% yield (entry 7). Thus, a reliable and stereoselective protocol for preparing the ABCD ring moiety **11** on a several-gram scale was developed.

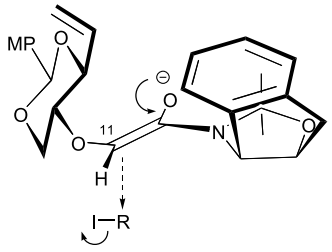


Figure 1. Proposed transition state of the alkylation of **24** with **9**. The energy-minimized structure of the *Z*-enolate of **24** was obtained using Macro Model ver. 6.0 with the MM2* force field.

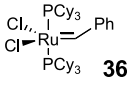
2.2. Attempts to construct the tetrahydrooxocin E ring using a chlorosulfide synthon

The tetrahydrooxocin E ring of **1** and **2** was constructed by adoption of the recently developed *O*,*S*-acetal forming reaction[9b,c,25] using the chlorosulfide synthon **41**[14] (Scheme 4). Since the 2-naphthylmethyl (NAP) group proved to be optimal for the global deprotection step in the last stage of the total synthesis of **1**,[8b] the benzyl group of **11** was replaced by the NAP group. Debenzylation was successfully performed under Lewis acidic conditions.[26] After sequential manipulation of the protective groups, primary alcohol **38** was converted to nitrile **39**. Reduction of the nitrile (**39**) with DIBAL and subsequent Wittig olefination followed by removal of the TBS group yielded alcohol **40**. This alcohol was successfully coupled with α-chlorosulfide **41** in the presence of AgOTf and 2,6-di-*tert*-butyl-4-methylpyridine to yield *O*,*S*-acetal **42** as a major diastereomer (6:1) in 84% yield.[27] RCM of the corresponding C20-alcohol **43** proceeded smoothly to afford **44** in 88% yield. After TBS protection, sulfide **45** was carefully oxidized to sulfone **46** by use of *m*CPBA at −15 °C. The stereochemistry of **46** was established by NOE experiments.

To insert the allyl group at C21, which is necessary for the construction of the nine-membered F ring via RCM in the

Table 1. RCM of the D ring

Entry	Substrate	Catalyst	mol% of Catalyst	Temperature	Time (h)	Yield (%)
1	**31**	**36**	Excess	Reflux	42	<10
2	**31**	**37**	50	Reflux	21	No reaction
3	**33**	**36**	120	Reflux	39	83
4	**33**	**37**	8	Reflux	3	No reaction
5	**32**	**36**	20	Reflux	5	Complex mixture
6	**32**	**37**	20	Reflux	0.5	48
7	**32**	**37**	2	rt	2.5	99



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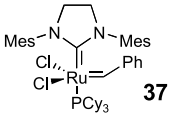

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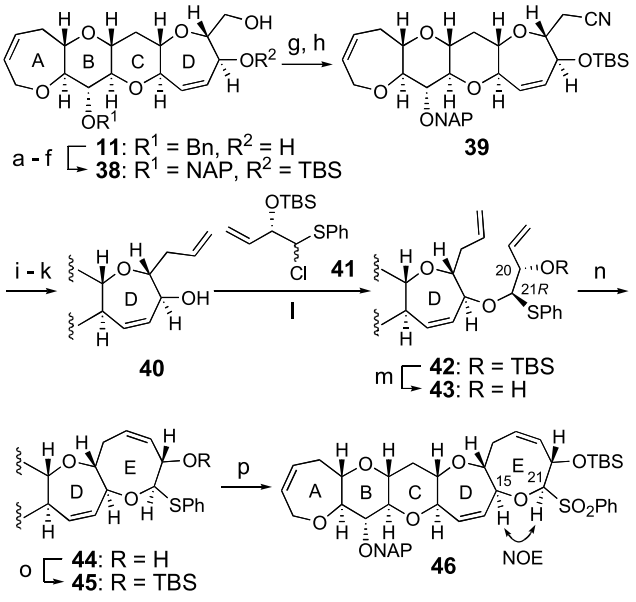
total synthesis of **1** and **2**,[8,9a,b] Lewis acid-mediated coupling of anomeric sulfone **46** with allyltrimethylsilane was attempted in the presence of $AlCl_3$ (Scheme 5).[14,28] However, ring-contraction products **51** and **52** were obtained in 50 and 20% yield, respectively, instead of the desired alkene **47**.[29] This can be explained as shown in Scheme 5. The rearrangement would be initiated via oxonium cation **48**. The resultant allylic cation **49** might form the less strained oxepin ring **50**, to which allylation could occur to produce **51** and **52**. To prevent this ring contraction, we planned insertion of the C22 carbon unit before the formation of the eight-membered ring. Acyclic sulfone **53**, which was prepared by the selective oxidation of **42** (*m*CPBA, CH_2Cl_2, −20 °C, 1 h, 31% yield), was treated with TMSCN and $EtAlCl_2$ (Scheme 6). In this case, the intramolecular cyclization product **56**[30] was mainly obtained instead of the desired **54**. Therefore, we abandoned the Lewis acid-mediated coupling strategy using anomeric sulfones, and investigated an alternative route, as described below.

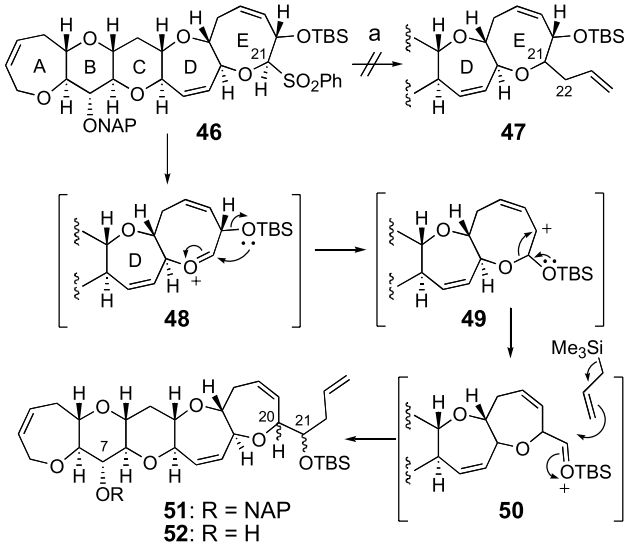


Scheme 4. Reagents and conditions: (a) $AlCl_3$ (3 equiv.), CH_2Cl_2–CH_3NO_2 (3:1), 0 °C, 20 min, 97%; (b) $Me_2C(OMe)_2$, PPTS, CH_2Cl_2–DMF (1:1), 13 h, 84%; (c) NAPBr, NaH, TBAI, THF–DMF (3:1), 40 °C, 30 min, 88%; (d) TsOH·H_2O, MeOH–THF (2:1), 27 h; (e) TBSOTf, 2,6-lutidine, CH_2Cl_2, 1 h, 98% (2 steps); (f) CSA, MeOH–THF (1:1), −15 °C, 14 h, 85%; (g) TsCl, pyridine, MS4A, 24 h, 96%; (h) NaCN, DMSO, 50 °C, 20 h, 94%; (i) DIBAL, CH_2Cl_2, −70 °C, 3 h; (j) Ph_3PCH_3Br, $NaN(SiMe_3)_2$, 0 °C, 1 h, 82% (2 steps); (k) TBAF, THF, 18 h, 91%; (l) **41** (3 equiv.), AgOTf (3.5 equiv.), 2,6-di-*tert*-butyl-4-methylpyridine (4.2 equiv.), MS4A, CH_2Cl_2, −40 to −20 °C, 1 h, 84% (21*R*/21*S*=6:1); (m) TBAF, THF, 1 h, 98%; (n) **37** (0.05 equiv.), CH_2Cl_2, 1 h, 88%; (o) TBSCl, imidazole, DMF, 24 h, 95%; (p) *m*CPBA, CH_2Cl_2, −15 °C, 4 h (three cycles), 98%. TBS=*tert*-butyldimethylsilyl; TBAI=tetrabutylammonium iodide; MS4A=molecular sieve 4 Å; *m*CPBA=*m*-chloroperbenzoic acid.

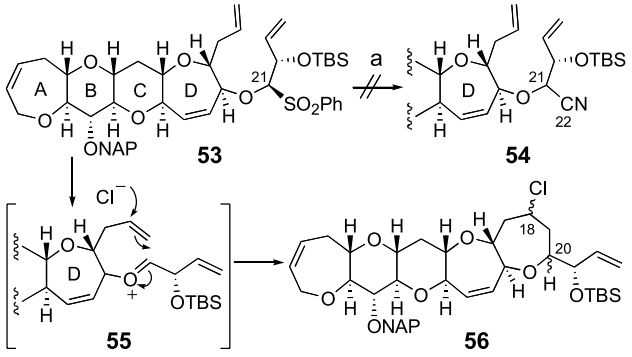
2.3. Stereocontrolled synthesis of the ABCDE ring moiety featuring an asymmetric aldol reaction and RCM

An alternative synthesis plan for the ABCDE ring moiety is outlined in Scheme 7. The key transformation is a chiral auxiliary-based asymmetric aldol reaction[31,32] of *O*-alkylated glycolic amide **57**. Since Crimmins and co-workers have recently succeeded in carrying out a 1,2-*anti*-selective aldol reaction by use of titanium enolates of *N*-glycolyloxazolidinethiones,[33,34] model experiments were first performed using chiral amides **59**–**61** (Table 2).

Under the Crimmins conditions,[33a] however, 20,21-*syn* aldol products (**63**, **64**) predominated (entry 1),[35] which implied that the 20,21-*syn*/*anti* selectivity is highly dependent on the structure of the *O*-alkyl group. Further investigation revealed that this selectivity was greatly



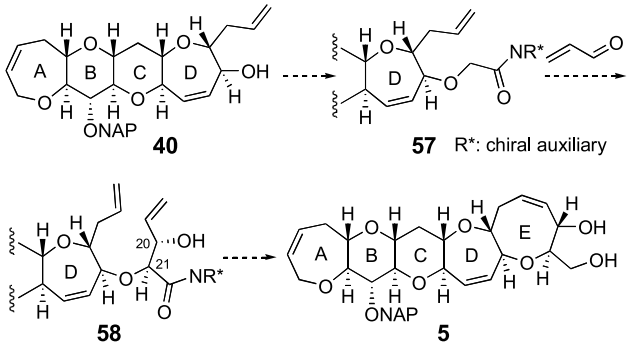
Scheme 5. Reagents and conditions: (a) allyltrimethylsilane, $AlCl_3$, CH_2Cl_2, −60 °C, 30 min, **51** (50%, 2:1 stereoisomers), **52** (20%, 2:1 stereoisomers).



Scheme 6. Reagents and conditions: (a) TMSCN, $EtAlCl_2$, CH_2Cl_2, −50 to −30 °C, 1 h, **56** (35%, 2:1 stereoisomers).

affected by the amines used. A remarkable preference of 20,21-*syn* isomer **64** with the undesired C21-configuration (21*R*) was observed when *i*Pr_2NEt or Et_3N was used (entries 3 and 4). Since the stereochemistry at C20 can be readily inverted through the Mitsunobu reaction,[36,37] we decided to change the chiral auxiliary from (*R*)-4-benzyl-2-oxazolidinethione to its enantiomer to reverse the C21-stereochemistry. As expected, the titanium enolate of **60** produced by $TiCl_4$ and *i*Pr_2NEt afforded a 5:95 mixture of 20,21-*anti* **62** and 20,21-*syn* isomer **63**, both of which possessed the desired C21-configuration (21*S*) (entry 5). The use of Et_3N accelerated the reaction and increased the proportion of 20,21-*anti* isomer **62** (entry 6). A similar result was obtained with (*S*)-4-benzyl-2-oxazolidinone **61**, although the undesired 15,21-*anti* isomer **64** was also produced (entry 7). The observed 20,21-*syn* selectivity can be explained by the Evans-type six-membered chair-like transition state as shown in Figure 2.[32–34]

Based on these model experiments, either the (*S*)-4-benzyl-2-oxazolidinethione or the (*S*)-4-benzyl-2-oxazolidinone auxiliary was introduced into the ABCD ring moiety **40** (Scheme 8). Since the direct *O*-alkylation of **40** with *N*-bromoacetyl-(*S*)-4-benzyl-2-oxazolidinone[38] in the presence of NaH was unsuccessful, the auxiliary was installed onto **40** in a stepwise manner. First, alkylation of **40** with *t*-butyl bromoacetate gave ester **65**, which was hydrolyzed by 10 M HCl. The resulting carboxylic acid **66** was converted to amide **70** or **71** via pivaloyl anhydride **67**, in preparation for the key asymmetric aldol reaction. When oxazolidinethione **70** was used, the desired 20,21-*anti*-15,21-*syn* isomer **72** and 20,21-*syn*-15,21-*syn* isomer **73**[39] were



Scheme 7. Synthesis plan of the ABCDE ring moiety featuring an asymmetric aldol reaction and RCM.

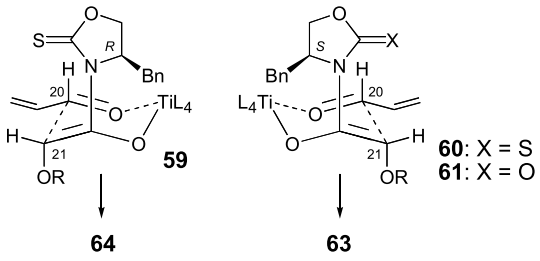


Figure 2. Proposed transition states involved in the formation of 20,21-*syn* products **64** and **63**.

obtained in 15 and 61% yield, respectively. Importantly, the use of Et_3N was essential and no reaction proceeded with *i*Pr_2NEt. The minor isomer **72** was directly converted to the ABCDE ring moiety **5**[12] by removal of the chiral auxiliary and constructing the tetrahydrooxocin E ring. On the other hand, the aldol reaction using oxazolidinone **71** gave rise to 20,21-*syn*-15,21-*syn* isomer **74** selectively in 72% yield along with a small amount of the corresponding 20,21-*syn*-15,21-*anti* product (12%). Chiral auxiliaries of the major products **73** and **74** were removed and the resulting diol **75** was subjected to RCM, yielding the C20-epimer **76** of **5**. Exposure of the mono-TBS ether **77** to standard Mitsunobu conditions[36,37] afforded benzoate **78** with complete inversion of the C20-stereochemistry. Finally, removal of the protective groups of **78** except NAP afforded **5** from **78** with an overall yield of 85%.

3. Conclusion

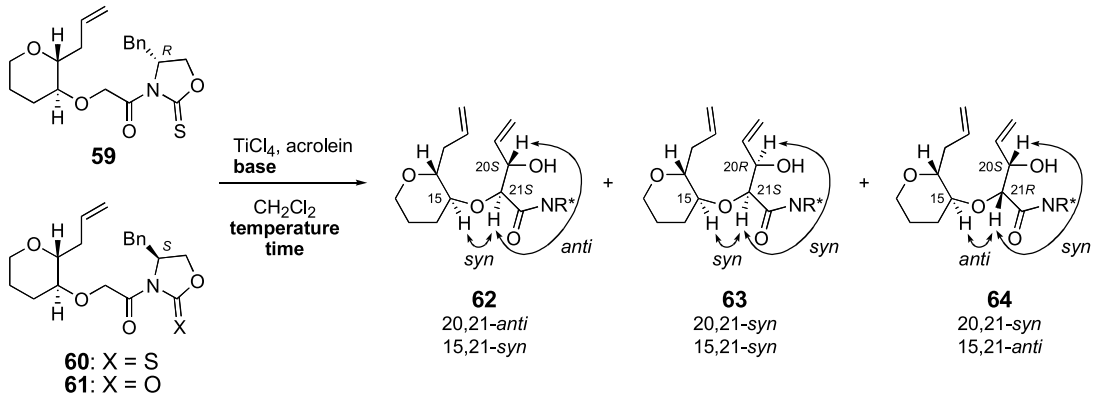
The left wing (**5**) of CTX3C (**1**) and 51-hydroxyCTX3C (**2**) was synthesized in a stereocontrolled manner from commercially available tri-*O*-benzyl-D-glucal (**13**). The key features of the present synthesis involve the highly practical and stereoselective preparation of the valuable ABCD ring intermediate **11**, as well as asymmetric construction of the tetrahydrooxocin E ring system. This synthesis avoids the repeated separation of undesired isomers and subsequent epimerization processes. The high reliability of the synthesis established here will enable a practical supply of the left wing not only for the total syntheses of CTXs but also for biomedical applications. Further investigations along this line are currently underway in our laboratory.

4. Experimental

4.1. General methods

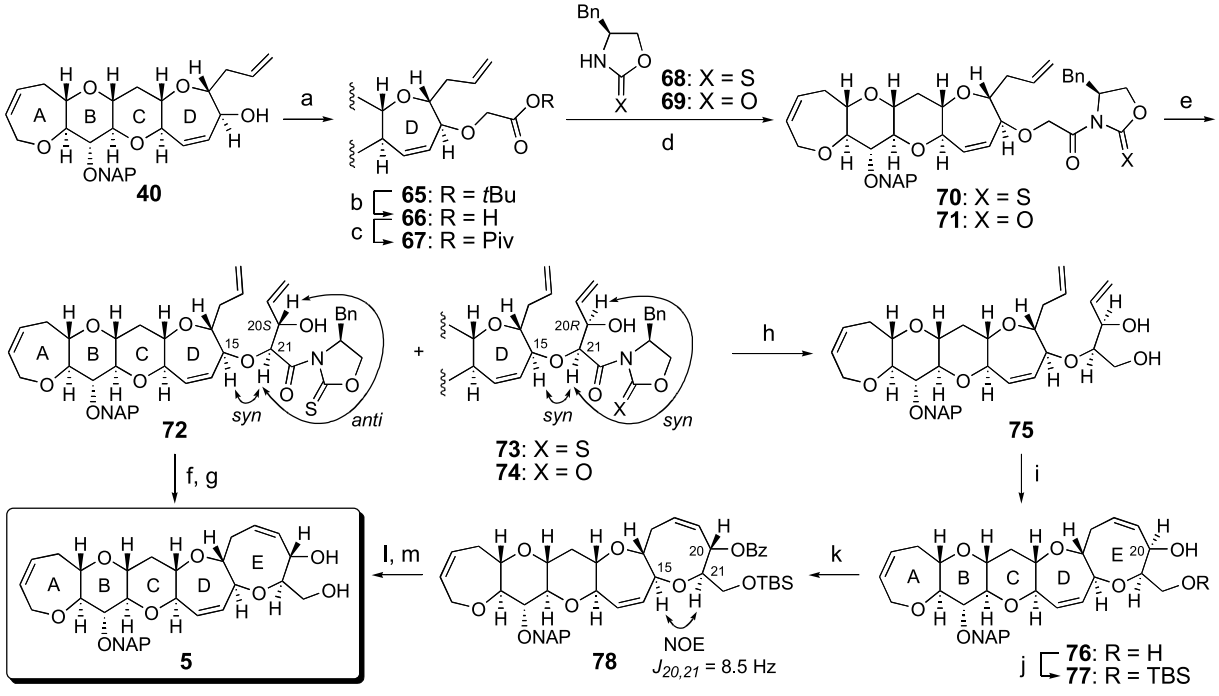
^1H and ^{13}C NMR spectra were recorded on a Varian Mercury 200 (200 MHz) or a Varian INOVA-500 (500 MHz) spectrometer. IR spectra were recorded on a Perkin–Elmer Spectrum BX FT-IR spectrometer. Matrix assisted laser desorption ionization time-of-flight mass spectra (MALDI-TOF MS) were recorded on an Applied Biosystems Voyager DE STR SI-3 instrument using α-cyano-4-hydroxy cinnamic acid as a matrix. Electron spray ionization time-of flight mass spectra (ESI-TOF MS) were recorded on an Applied Biosystems Mariner instrument. Optical rotations were recorded on a JASCO DIP-370

Table 2. Asymmetric aldol condensations in a model system[a]



Entry	Substrate	Amine	Temperature (°C)	Time (h)	Yield (%)[b]	Ratio (**62**:**63**:**64**)[c,d]	Recovery of s.m. (%)[b]
1[e]	**59**	(−)-Sparteine	−78	1	55	13:63:24	<10
2	**59**	TMEDA	−78 to −40	5	34	25:50:25	44
3	**59**	*i*Pt$_2$NEt	−78 to −50	4	58	2:5:93	20
4	**59**	Et$_3$N	−70	0.5	69	6:13:81	9
5	**60**	*i*Pt$_2$NEt	−78 to −50	4	67	5:95:0	23
6	**60**	Et$_3$N	−78	1	71	25:75:0	6
7	**61**	Et$_3$N	−78	0.5	72	3:72:25	2

[a] Performed with 4–6 equiv. of $TiCl_4$, 10 equiv. of amine, and 10 equiv. of acrolein except entry 1.
[b] Isolated yield.
[c] Determined by HPLC.
[d] Corresponding *anti*,*anti* isomer was not detected in each case.
[e] Since Crimmins' original method using 1.2 equiv. of (−)-sparteine and 1.2+4 equiv. of $TiCl_4$[33a] gave aldol products in low yield, excess (−)-sparteine (3 equiv.) and *N*-methyl-2-pyrrolidinone (3 equiv.)[33] were used along with 1.5+4 equiv. of $TiCl_4$.



Scheme 8. Reagents and conditions: (a) $BrCH_2CO_2tBu$, NaH, THF–DMF (4:1), 0 °C to rt, 10 h, 92%; (b) 10M HCl–THF (1:2), 30 °C, 23 h, 81%; (c) PivCl, Et_3N, CH_2Cl_2, −78 °C to rt, 40 min; (d) **68** or **69**, *n*BuLi, THF, −78 to 0 °C, 0.5–1 h, 51% for **70**, 96% for **71** (2 steps); (e) $TiCl_4$ (10 equiv.), Et_3N (20 equiv.), acrolein (20 equiv.), CH_2Cl_2, −78 °C, 20 min, **72** (15% from **70**), **73** (58% from **70**), **74** (72% from **71**); (f) $NaBH_4$, THF–H_2O (4:1), 10 min, 85%; (g) **37**, (0.1 equiv.), CH_2Cl_2, 30 min, 82%; (h) $NaBH_4$, THF–H_2O (4:1), 10–20 min, 79% from **73**, 99% from **74**; (i) **37**, (0.1 equiv.), CH_2Cl_2, 1 h, 92%; (j) TBSCl, imidazole, CH_2Cl_2, 0.5 h, 83%; (k) PPh_3, DEAD, BzOH, toluene, 20 min, 100%; (l) TBAF, THF, 3 h, 92%; (m) K_2CO_3, MeOH–THF (2:1), 1.5 h, 92%. Piv = pivaloyl; Bz = benzoyl; DEAD = diethyl azodicarboxylate.

digital polarimeter. Melting points were measured on a Yanaco MP-S3 micro melting point apparatus. Open column chromatography was performed using 100–210 μm Silica Gel 60 N (Kanto Chemical Co., Inc.), and for flash column chromatography 40–50 μm Silica Gel 60N (Kanto Chemical Co., Inc.) was used. All reactions sensitive to air or moisture were carried out under argon or nitrogen atmosphere in dry, freshly distilled solvents under anhydrous conditions. Dry solvents purchased from Kanto Chem. Co. were also used.

4.2. Synthesis of the ABCD ring fragment

4.2.1. Alcohol 15. To a solution of benzyl ether **13** (30.0 g, 72.0 mmol) in THF (160 ml) and H_2O (16 ml) was added NBS (14.1 g, 79.2 mmol) at 0 °C. The mixture was stirred for 1 h at 0 °C and quenched with water. Aqueous phase was extracted with Et_2O, and the combined organic phase was washed with saturated $Na_2S_2O_3$ solution, brine and dried over anhydrous $MgSO_4$. Concentration of the solution gave bromide **14** (45.3 g) as a diastereomeric mixture.

To a 2 l three-necked round-bottom flask equipped with mechanical stirrer and dropping funnel was added a solution of **14** (45.3 g) and 18-crown-6 (32.0 g, 121 mmol) in toluene (180 ml). The solution was cooled to −78 °C, and $KN(TMS)_2$ (1.2 M solution in toluene, 120 ml, 144 mmol) was slowly added over 1 h. The resulting mixture was stirred for 6 h at −78 °C and then warmed to −68 °C. Allylmagnesium bromide (0.8 M solution in ether, 180 ml, 144 mmol) was added over 1 h, and the resulting mixture was gradually warmed to room temperature over 24 h with stirring. The mixture was quenched with saturated NH_4Cl solution and neutralized with conc. HCl. Aqueous phase was extracted with hexane–EtOAc, and the organic phase was concentrated. The residue was purified by flash column chromatography (silica gel, hexane/EtOAc = 10–5) to give alcohol **15** (15.5 g, 32.6 mmol, 45%) as yellow oil. All spectroscopic data are identical to those reported in the literature.[12]

4.2.2. Diene 16. To a solution of alcohol **15** (12.6 g, 26.6 mmol) in THF (64 ml) and DMF (16 ml) was added NaH (60% dispersion in mineral oil, 2.55 g, 63.8 mmol) at 0 °C. The mixture was stirred for 30 min at 0 °C followed by the addition of allyl bromide (3.45 ml, 39.9 mmol). The resulting mixture was further stirred for 13 h at room temperature. The mixture was quenched with saturated NH_4Cl solution and the aqueous phase was extracted with hexane–EtOAc. The organic phase was washed with brine and dried over anhydrous $MgSO_4$. After concentration, the residue was purified by flash column chromatography (silica gel, hexane/EtOAc = 8) to give diene **16** (13.6 g, 26.5 mmol, 99%) as yellow oil. All spectroscopic data are identical to those reported in the literature.[12]

4.2.3. AB ring 17. To a solution of diene **16** (13.6 g, 26.5 mmol) in CH_2Cl_2 (530 ml) was added Grubbs catalyst **36** (536 mg, 0.650 mmol). The mixture was stirred for 4.5 h at ambient temperature and quenched with Et_3N (900 μl, 6.50 mmol). After concentration, the residue was purified by flash column chromatography (silica gel, hexane/EtOAc = 7.5) to give AB ring **17** (10.9 g, 22.4 mmol, 84%). All spectroscopic data are identical to those reported in the literature.[12]

4.2.4. Alcohol 19. To a solution of AB ring **17** (10.1 g, 20.7 mmol) in CH_3NO_2 (103 ml) was slowly added a solution of $TiCl_4$ (5.47 ml, 39.4 mmol) in CH_3NO_2 (103 ml) at −5 °C. The mixture was stirred for 30 min at −5 °C and quenched by the slow addition of MeOH. The resulting dark purple suspension was concentrated, and the residue was diluted with MeOH and filtered through a pad of Celite. The filter cake was washed with MeOH sufficiently and the combined filtrate was concentrated. The residue was purified by flash column chromatography (silica gel, EtOAc/MeOH = 10) to give triol **18** (5.59 g).

To a solution of triol **18** (5.59 g) in DMF (120 ml) were added anisaldehyde dimethyl acetal (9.58 ml, 51.7 mmol) and $TsOH \cdot H_2O$ (418 mg, 2.20 mmol) at 0 °C. The mixture was stirred for 18 h at ambient temperature and quenched with saturated $NaHCO_3$ solution. Aqueous phase was extracted with EtOAc and the organic phase was concentrated at 70 °C (to remove DMF). Et_2O was added to the residue, and the resulting precipitate was collected by filtration to yield acetal **19** (6.27 g, 18.8 mmol, 91% in 2 steps) as colorless powder. All spectroscopic data are identical to those reported in the literature.[12]

4.2.5. Alcohol 21. To a solution of alcohol **19** (13.0 g, 38.9 mmol) in THF (160 ml) and DMF (40 ml) was added NaH (60% dispersion in mineral oil, 1.70 g, 42.8 mmol) at 0 °C. The mixture was stirred for 30 min at 0 °C. BnBr (5.09 ml, 42.8 mmol) was added and the resulting mixture was stirred for 18 h at room temperature. The mixture was quenched with H_2O at 0 °C and the aqueous phase was extracted with EtOAc. The combined organic phase was washed with brine and dried over anhydrous $MgSO_4$. Concentration of the solution gave benzyl ether **20**.

A 1 l three-necked round-bottom flask equipped with mechanical stirrer and dropping funnel was charged with DIBAL (0.93 M in hexane, 335 ml, 311 mmol). The solution was cooled to −78 °C and a solution of **20** in CH_2Cl_2 (78 ml) was slowly added over 1.5 h. The mixture was gradually warmed to −33 °C over 12 h with stirring and re-cooled to −78 °C. EtOAc (100 ml) and Rochelle salt solution (60 ml) were added at −78 °C and the resulting mixture was vigorously stirred for 6 h at room temperature. The mixture was filtered through a pad of Celite and the filter cake was washed with EtOAc. The filtrate was concentrated and the residue was purified by flash column chromatography (silica gel, hexane/EtOAc = 2) to give alcohol **21** (16.1 g, 37.7 mmol, 97% in 2 steps). All spectroscopic data are identical to those reported in the literature.[12]

4.2.6. Iodide 9. To a solution of alcohol **21** (12.1 g, 28.3 mmol) in toluene (142 ml) were added PPh_3 (14.9 g, 56.7 mmol), imidazole (5.79 g, 75.1 mmol) and iodide (10.8 g, 42.6 mmol) in this order. The mixture was stirred for 6 h and quenched with saturated $Na_2S_2O_3$ solution. Organic phase was separated and the aqueous phase was extracted with EtOAc. The combined organic phase was washed with brine and dried over anhydrous $MgSO_4$. After

concentration, the residue was purified by flash column chromatography (silica gel, hexane/EtOAc = 50–7.9–3.0) to give iodide **9** (14.6 g, 27.2 mmol, 96%). All spectroscopic data are identical to those reported in the literature.[12]

4.2.7. Amide 23. To a solution of (1*R*,2*S*)-1-amino-2-indanol (20.0 g, 134 mmol) in THF (500 ml) were added Et_3N (20.6 ml, 148 mmol) and bromoacetyl bromide (12.9 ml, 148 mmol) at 0 °C. The mixture was stirred for 2 h at room temperature and cooled to 0 °C. CSA (12.5 g, 53.8 mmol) and 2-methoxypropene (25.7 ml, 268 mmol) were added and the resulting mixture was stirred for 2 h at room temperature. The reaction mixture was cooled to 0 °C, diluted with hexane (250 ml) and quenched with saturated $NaHCO_3$ solution (250 ml). Aqueous phase was extracted with EtOAc and the combined organic phase was washed with brine and dried over anhydrous $MgSO_4$. After concentration, the residue was recrystallized from AcOEt to give amide **23** (14.2 g, 45.9 mmol, 34%). The filtrate was concentrated and the residue was purified by flash column chromatography to give **23** (17.6 g, 56.7 mmol, 42%). **23**: colorless plate; mp 134–136 °C (hexane–EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.37 (s, 3H, auxiliary), 1.62 (s, 3H, auxiliary), 3.15 (d, 1H, J=1.0 Hz, auxiliary), 3.16 (d, 1H, J=4.0 Hz, auxiliary), 4.03 (d, 1H, J=10.0 Hz, H11), 4.23 (d, 1H, J=10.0 Hz, H11), 4.95 (dt, 1H, J=4.0, 1.0 Hz, auxiliary), 5.39 (d, 1H, J=4.0 Hz, auxiliary), 7.24–7.34 (m, 4H, auxiliary); ^{13}C NMR (50 MHz, $CDCl_3$) δ 22.95, 26.32, 29.23, 36.16, 66.16, 78.89, 96.84, 123.68, 125.97, 127.21, 128.65, 139.83, 140.74, 163.04; FT-IR (KBr) ν 3038, 2984, 2933, 1654, 1458, 1373, 1312, 1221, 1168, 1116, 1049, 1024, 983, 952, 907, 823 cm^{-1}; ESI-TOF MS $[M+H]^+$ calcd for $C_{14}H_{17}BrNO_2$ 310.0443, found 310.0424; $[\alpha]_D^{28.0}$ −165° (*c* 1.00, $CHCl_3$).

4.2.8. Amide 24. To a solution of alcohol **22**[12] (26.6 g, 113 mmol) and bromide **23** (42.0 g, 135 mmol) in THF (320 ml) and DMF (80 ml) was added NaH (60% dispersion in mineral oil, 5.4 g, 135 mmol) at 0 °C. The mixture was stirred for 5 h at room temperature and quenched with water at 0 °C. Aqueous phase was extracted with hexane, and the combined organic phase was washed with brine and dried over anhydrous $MgSO_4$. After concentration, the residue was purified by flash column chromatography to give amide **24** (51.6 g, 110 mmol, 98%). **24**: colorless amorphous; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.34 (s, 3H, auxiliary), 1.64 (s, 3H, auxiliary), 3.13 (s, 2H, auxiliary), 3.54 (dt, 1H, J=10.0, 5.0 Hz, H16), 3.76 (t, 1H, J=10.0 Hz, H17), 3.80 (s, 3H, OMe), 4.18 (dd, 1H, J=10.0, 6.0 Hz, H15), 4.45 (d, 1H, J=14.0 Hz, H11), 4.57 (d, 1H, J=14.0 Hz, H11), 4.60 (dd, 1H, J=10.0, 5.0 Hz, H17), 4.87 (dt, 1H, J=4.5, 2.5 Hz, auxiliary), 5.31 (d, 1H, J=4.5 Hz, auxiliary), 5.33 (d, 1H, J=11.0 Hz, *CH*$_2$=CH–), 5.51 (d, 1H, J=17.0 Hz, *CH*$_2$=CH–), 5.51 (s, 1H, *CH*MP), 6.09 (ddd, 1H, J=17.0, 11.0, 6.0 Hz, H14), 6.88 (d, 2H, J=8.0 Hz, MP), 7.23–7.33 (m, 4H, auxiliary), 7.43 (d, 2H, J=8.0 Hz, MP); ^{13}C NMR (50 MHz, $CDCl_3$) δ 24.10, 26.44, 36.25, 55.19, 64.65, 69.14, 70.65, 74.37, 79.30, 81.12, 96.98, 100.69, 113.51, 118.48, 124.19, 125.94, 127.20, 127.42, 128.61, 130.02, 135.01, 140.32, 140.76, 159.96, 165.14; FT-IR (film) ν 2935, 1661, 1615, 1518, 1426, 1376, 1249, 1172, 1142, 1103, 1032, 933, 904, 830 cm^{-1}; MALDI-TOF MS $[M+Na]^+$ calcd for $C_{27}H_{31}NNaO_6$ 488.2049, found 488.2003; $[\alpha]_D^{29.0}$ −121° (*c* 1.00, $CHCl_3$).

4.2.9. Diol 26. To a solution of amide **24** (51.2 g, 110 mmol) in THF (170 ml) was slowly added *n*BuLi (1.56 M solution in hexane, 70.5 ml, 110 mmol) over 30 min at −78 °C. The mixture was stirred for 20 min at −78 °C, and a solution of iodide **9** (17.9 g, 33.3 mmol) and DMPU (18.1 ml, 150 mmol) in THF (50 ml) was slowly added over 20 min at −78 °C. The resulting mixture was gradually warmed to room temperature over 3 h and the stirring was continued for an additional 15 h at room temperature. The reaction mixture was quenched with saturated NH_4Cl solution and the aqueous phase was extracted with EtOAc. The combined organic phase was concentrated and the residue was roughly purified by open column chromatography (silica gel, hexane/EtOAc = 6–3–2) to give amide **25** (47.4 g).

To a solution of **25** (47.4 g) in *n*PrOH (362 ml) was added PPTS (3.64 g, 14.5 mmol). The mixture was stirred for 16 h at room temperature and quenched with Et_3N (35 ml). After concentration, the residue was purified by flash column chromatography (silica gel, hexane/EtOAc = 8–3–1) to give diol **26** (21.0 g, 27.8 mmol, 76% in 2 steps) and recovery of **25** (8.47 g). The recovered **25** (8.47 g) was subjected to the same reaction and purification conditions to yield **26** (1.08 g, 1.43 mmol, 5% in 2 steps). **26**: colorless amorphous; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.37 (s, 3H, auxiliary), 1.59 (s, 3H, auxiliary), 1.72 (brs, 2H, OH), 2.08–2.18 (m, 2H, H4, H10), 2.25 (ddd, 1H, J=15.5, 8.5, 4.5 Hz, H10), 2.44 (ddd, 1H, J=16.0, 8.5, 4.0 Hz, H4), 2.99 (dd, 1H, J=17.0, 4.0 Hz, auxiliary), 3.09 (d, 1H, J=17.0 Hz, auxiliary), 3.24 (dt, 1H, J=9.5, 4.0 Hz, H5), 3.36 (t, 1H, J=9.5 Hz, H6), 3.50 (dt, 1H, J=9.5, 4.5 Hz, H9), 3.54–3.61 (m, 2H, H7, H8), 3.74 (d, 1H, J=9.0 Hz, H17), 3.78–3.87 (m, 2H, H16, H17), 3.80 (s, 3H, OMe), 3.98 (dq, 1H, J=16.0, 3.0 Hz, H1), 4.12 (brs, 1H, H15), 4.25 (dd, 1H, J=16.0, 6.0 Hz, H1), 4.61 (t, 1H, J=4.0 Hz, auxiliary), 4.68 (d, 1H, J=10.0 Hz, *CH*$_2$Ph), 4.81 (d, 1H, J=11.0 Hz, *CH*$_2$Ph), 4.86 (d, 1H, J=10.0 Hz, *CH*$_2$Ph), 4.94 (d, 1H, J=11.0 Hz, *CH*$_2$Ph), 5.00 (dd, 1H, J=8.5, 2.0 Hz, H11), 5.16 (d, 1H, J=10.5 Hz, *CH*$_2$=CH–), 5.27 (d, 1H, J=4.0 Hz, auxiliary), 5.32 (d, 1H, J=17.0 Hz, *CH*$_2$=CH–), 5.66 (ddt, 1H, J=11.5, 8.5, 3.0 Hz, H3), 5.83 (ddt, 1H, J=11.5, 6.0, 3.0 Hz, H2), 5.96 (ddd, 1H, J=17.0, 10.5, 6.0 Hz, H14), 6.85 (d, 2H, J=8.5 Hz, MPM), 7.21 (d, 2H, J=8.5 Hz, MPM), 7.24–7.39 (m, 8H, auxiliary, Bn), 7.51 (d, 1H, J=7.5 Hz, auxiliary); ^{13}C NMR (50 MHz, $CDCl_3$) δ 23.67, 26.54, 33.92, 34.63, 36.17, 55.21, 63.04, 64.22, 67.78, 72.09, 74.74, 75.58, 75.90, 76.07, 76.67, 79.15, 79.84, 83.74, 85.52, 87.52, 97.15, 113.81, 116.57, 124.13, 125.89, 126.58, 127.39, 127.55, 127.85, 128.29, 128.64, 129.47, 130.40, 131.37, 136.34, 138.71, 139.69, 140.62, 159.25, 171.01; FT-IR (KBr) ν 3379, 2933, 1638, 1513, 1431, 1363, 1247, 1192, 927, 822 cm^{-1}; ESI-TOF MS $[M+H]^+$ calcd for $C_{44}H_{54}NO_{10}$ 756.3748, found 756.3651; $[\alpha]_D^{28.0}$ −109° (*c* 1.00, $CHCl_3$).

4.2.10. TBPS ether 27. To a solution of diol **26** (30.5 g, 40.4 mmol) and 2,6-lutidine (37.6 ml, 323 mmol) in CH_2Cl_2 (202 ml) was added TBPSOTf (46.0 g, 118 mmol) at 0 °C. The mixture was stirred for 2 h at 0 °C and quenched with

saturated $NaHCO_3$ solution. Aqueous phase was extracted with hexane–EtOAc, and the combined organic phase was washed with 1M HCl and dried over anhydrous $MgSO_4$. After concentration, the residue was purified by flash column chromatography (silica gel, hexane/EtOAc=10–5–4) to give bis-TBPS ether **27** (45.2 g, 36.7 mmol, 91%). **27**: colorless amorphous; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.94 (s, 9H, *t*-Bu), 1.00 (s, 9H, *t*-Bu), 1.24 (s, 3H, auxiliary), 1.58 (s, 3H, auxiliary), 1.98 (ddd, 1H, J=13.0, 9.5, 5.0 Hz, H10), 2.08 (ddq, 1H, J=16.0, 9.0, 3.0 Hz, H4), 2.16 (ddd, 1H, J=16.0, 8.0, 4.0 Hz, H4), 2.35 (ddd, 1H, J=13.0, 9.0, 2.5 Hz, H10), 2.97 (dd, 1H, J=17.0, 4.0 Hz, auxiliary), 3.09 (dt, 1H, J=9.0, 4.0 Hz, H8), 3.09 (d, 1H, J=17.0 Hz, auxiliary), 3.16 (t, 1H, J=9.0 Hz, H8), 3.28 (t, 1H, J=9.0 Hz, H6), 3.31 (ddd, 1H, J=9.5, 9.0, 2.5 Hz, H9), 3.52 (t, 1H, J=9.0 Hz, H7), 3.70–3.76 (m, 2H, H17, H17), 3.74 (s, 3H, OMe), 3.94 (dq, 1H, J=15.0, 3.0 Hz, H1), 3.97 (td, 1H, J=7.0, 2.0 Hz, H16), 4.24 (dq, 1H, J=15.0, 6.0 Hz, H1), 4.45 (d, 1H, J=10.5 Hz, CH_2Ph), 4.64–4.69 (m, 1H, H15), 4.65 (d, 1H, J=10.5 Hz, CH_2Ph), 4.66 (dd, 1H, J=4.5, 4.0 Hz, auxiliary), 4.74 (d, 1H, J=11.0 Hz, CH_2Ph), 4.83 (d, 1H, J=17.5 Hz, CH_2=CH–), 4.88 (d, 1H, J=11.0 Hz, CH_2Ph), 4.90 (d, 1H, J=10.0 Hz, CH_2=CH–), 4.99 (dd, 1H, J=9.0, 5.0 Hz, H11), 5.59 (ddd, 1H, J=12.0, 8.0, 3.0 Hz, H3), 5.63 (d, 1H, J=4.5 Hz, auxiliary), 5.84 (ddt, 1H, J=12.0, 6.0, 3.0 Hz, H2), 5.90 (ddd, 1H, J=17.5, 10.0, 7.0 Hz, H14), 6.75 (d, 2H, J=8.5 Hz, MPM), 7.10 (d, 2H, J=8.5 Hz, MPM), 7.16–7.38 (m, 21H, Ph), 7.52–7.58 (m, 4H, Ph), 7.60–7.65 (m, 4H, Ph); ^{13}C NMR (50 MHz, $CDCl_3$) δ 19.08, 19.42, 24.50, 26.71, 26.90, 27.08, 34.55, 35.58, 36.45, 55.20, 63.55, 65.06, 67.86, 74.64, 75.63, 75.80, 75.85, 76.05, 76.38, 76.62, 79.41, 81.40, 85.31, 87.96, 97.09, 113.67, 116.51, 125.42, 126.63, 127.26, 127.33, 127.46, 127.62, 127.83, 128.28, 129.40, 129.53, 129.59, 130.43, 131.60, 133.18, 133.25, 133.94, 134.03, 135.53, 136.17, 137.06, 139.12, 140.18, 141.01, 159.07, 168.48; FT-IR (film) ν 2930, 2856, 1654, 1513, 1459, 1427, 1361, 1247, 1111, 923, 823 cm^{-1}; MALDI-TOF MS $[M+Na]^+$ calcd for $C_{76}H_{89}NaNO_{10}Si_2$ 1254.5917, found 1254.5856; $[\alpha]_D^{29.0}$ −26.0° (*c* 1.00, $CHCl_3$).

4.2.11. Alcohol 28. To a solution of MPM ether **27** (46.2 g, 37.5 mmol) in CH_2Cl_2 (357 ml) and water (17.8 ml) was added 2.41 g (10.7 mmol) each of DDQ in four portions at intervals of 30 min at −5 °C. The mixture was totally stirred for 2.5 h at −5 °C, and quenched with saturated $Na_2S_2O_3$ solution and then saturated $NaHCO_3$ solution. The resulting suspension was filtered though a pad of Celite and the filtrate was extracted with hexane–EtOAc. The combined organic phase was dried over anhydrous $MgSO_4$. After concentration, the residue was purified by flash column chromatography (silica gel, hexane/EtOAc=10–8–6–2.9, twice) to give alcohol **28** (29.0 g, 26.1 mmol, 70%) and recovery of **27** (13.2 g, 10.7 mmol, 29%). The recovered **27** (13.2 g) was subjected to the same reaction and purification conditions another twice to give **28** (6.85 g, 6.16 mmol, 16%). **28**: colorless amorphous; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.96 (s, 9H, *t*-Bu), 1.03 (s, 9H, *t*-Bu), 1.24 (s, 3H, auxiliary), 1.59 (s, 3H, auxiliary), 2.03 (dt, 1H, J=12.5, 7.0 Hz, H10), 2.14 (ddq, 1H, J=15.0, 9.0, 3.0 Hz, H4), 2.24–2.32 (m, 2H, H4, H10), 2.41 (d, 1H, J=1.5 Hz, OH), 3.03 (dd, 1H, J=17.0, 3.0 Hz, auxiliary), 3.10 (d, 1H, J=17.0 Hz, auxiliary), 3.12 (td, 1H, J=9.0, 4.0 Hz, H5), 3.26–3.30 (m, 4H, H6, H7, H8, H9), 3.71 (dd, 1H, J=10.5, 7.0 Hz, H17), 3.76 (dd, 1H, J=10.5, 6.0 Hz, H17), 3.89–3.97 (m, 1H, H1), 3.93 (dd, 1H, J=7.0, 6.0 Hz, H16), 4.24 (dq, 1H, J=15.5, 6.0 Hz, H1), 4.71 (d, 1H, J=11.0 Hz, CH_2Ph), 4.72 (t, 1H, J=4.0 Hz, auxiliary), 4.75 (d, 1H, J=7.0 Hz, H15), 4.85 (d, 1H, J=17.5 Hz, CH_2=CH–), 4.90 (d, 1H, J=10.5 Hz, CH_2=CH–), 4.92 (d, 1H, J=11.0 Hz, CH_2Ph), 5.03 (dd, 1H, J=7.0 Hz, H11), 5.63 (d, 1H, J=4.0 Hz, auxiliary), 5.61–5.68 (m, 1H, H3), 5.80–5.89 (m, 1H, H2), 5.84 (ddd, 1H, J=17.5, 10.0, 7.0 Hz, H14), 7.04 (t, 1H, J=7.5 Hz, Ph), 7.20–7.39 (m, 19H, Ph), 7.53–7.58 (m, 5H, Ph), 7.62–7.66 (m, 4H, Ph); ^{13}C NMR (125 MHz, $CDCl_3$) δ 19.14, 19.43, 24.34, 26.72, 26.94, 27.11, 34.57, 35.99, 36.46, 63.44, 65.06, 67.87, 73.94, 75.22, 75.80, 75.95, 76.09, 76.34, 76.59, 79.38, 81.54, 84.84, 87.48, 97.10, 116.59, 125.31, 125.43, 126.81, 127.27, 127.37, 127.61, 127.74, 128.19, 128.42, 129.44, 129.53, 131.51, 133.24, 133.31, 133.94, 134.06, 135.56, 136.18, 136.93, 139.11, 140.16, 140.93, 168.61; FT-IR (KBr) ν 3427, 3069, 3045, 2930, 2890, 2856, 1660, 1650, 1471, 1461, 1427, 1330, 1241, 1111, 1090, 934, 822 cm^{-1}; MALDI-TOF MS $[M+Na]^+$ calcd for $C_{68}H_{81}NNaO_9Si_2$ 1134.5342, found 1134.5345; $[\alpha]_D^{29.0}$ −28.9° (*c* 1.00, $CHCl_3$).

4.2.12. Hemiacetal 30. A solution of alcohol **28** (2.00 g, 1.80 mmol) and *p*-anisaldehyde (43.8 µl, 0.360 mmol) in toluene (18 ml) was warmed to 90 °C. CSA (836 mg, 3.60 mmol) was added and the mixture was stirred for 1 h at 90 °C. *p*-Anisaldehyde (43.8 µl, 0.360 mmol) and CSA (418 mg, 1.80 mmol) were further added to the mixture, and the stirring was continued for an additional 1 h at 90 °C. The reaction mixture was cooled to 0 °C, and diluted with hexane (35 ml) and quenched with saturated $NaHCO_3$ solution. Aqueous phase was extracted with EtOAc, and the combined organic phase was dried over anhydrous $MgSO_4$. After concentration, the residue was roughly purified by open column chromatography (FLORISIL® =10 g, hexane/EtOAc=5) to give lactone **29** (1.58 g). Analytical sample was obtained by further purification using silica gel column chromatography. **29**: colorless syrup; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.94 (s, 9H, *t*-Bu), 1.01 (s, 9H, *t*-Bu), 1.86 (ddd, 1H, J=14.0, 9.5, 5.0 Hz, H10), 2.26–2.36 (m, 1H, H4), 2.46 (dt, 1H, J=14.0, 7.0 Hz, H10), 2.63 (ddd, 1H, J=17.0, 8.0, 4.0 Hz, H4), 3.25 (td, 1H, J=9.0, 4.0 Hz, H5), 3.28 (t, 1H, J=9.0 Hz, H6), 3.34 (td, 1H, J=9.5, 7.0 Hz, H9), 3.52 (dd, 1H, J=9.5, 9.0 Hz, H7), 3.68 (dd, 1H, J=12.0, 9.0 Hz, H17), 3.89 (dt, 1H, J=9.0, 4.5 Hz, H16), 3.89 (dd, 1H, J=12.0, 4.5 Hz, H17), 3.98 (dd, 1H, J=16.0, 3.0 Hz, H1), 4.21 (dd, 1H, J=7.0, 4.5 Hz, H15), 4.24 (dd, 1H, J=16.0, 10.0 Hz, H1), 4.26 (t, 1H, J=9.5 Hz, H8), 4.46 (dd, 1H, J=7.0, 5.0 Hz, H11), 4.79 (d, 1H, J=11.5 Hz, CH_2Ph), 4.80 (d, 1H, J=18.0 Hz, CH_2=CH–), 4.88 (d, 1H, J=11.5 Hz, CH_2Ph), 4.89 (d, 1H, J=10.5 Hz, CH_2=CH–), 5.72 (ddd, 1H, J=18.0, 10.5, 7.0 Hz, H14), 5.72–5.77 (m, 1H, H3), 5.85 (ddt, 1H, J=12.0, 6.0, 3.0 Hz, H2), 7.22–7.45 (m, 17H, Ph), 7.53 (d, 2H, J=7.5 Hz, Ph), 7.56 (d, 2H, J=7.5 Hz, Ph), 7.61 (d, 4H, J=8.0 Hz, Ph); ^{13}C NMR (50 MHz, $CDCl_3$) δ 19.29, 26.84, 26.97, 33.30, 34.36, 64.96, 68.38, 71.07, 74.31, 75.19, 75.84, 76.84, 79.44, 81.90, 83.56, 86.65, 117.95, 126.31, 127.22, 127.37, 127.43, 127.74, 128.16, 129.40, 129.49, 129.65, 129.72, 131.30, 133.07, 133.24, 133.55, 133.75, 135.53, 136.03, 136.08, 136.91, 138.79, 169.01; FT-IR (film) ν 3071, 2931, 2890, 2858,

1757, 1471, 1427, 1361, 1113, 935, 823 cm^{-1}; MALDI-TOF MS $[M+Na]^+$ calcd for $C_{56}H_{66}NaO_8Si_2$ 945.4188, found 945.4189; $[\alpha]_D^{29.0}$ −47.8° (*c* 1.00, $CHCl_3$).

To a solution of tetravinyltin (249 μl, 1.37 mmol) in THF (13 ml) was added MeLi (0.92 M solution in Et_2O, 5.58 ml, 5.13 mmol) at −78 °C. The mixture was stirred for 30 min at −78 °C and then cooled to −100 °C. A solution of lactone **29** (1.58 g) in THF (16 ml) was slowly added over 30 min and the resulting mixture was stirred for 15 min at −100 °C to −90 °C. The reaction mixture was quenched with saturated NH_4Cl solution and the aqueous phase was extracted with hexane–EtOAc. The combined organic phase was washed with brine and dried over anhydrous $MgSO_4$. After concentration, the residue was purified by flash column chromatography (silica gel, hexane/EtOAc=5) to give hemiacetal **30** (1.31 g, 1.38 mmol, 77% in 2 steps). **30**: colorless amorphous; ^1H NMR (500 MHz, $CDCl_3$) δ 0.95 (s, 9H), 1.02 (s, 9H), 1.56 (ketoalcohol, q, 1H, J=12.0 Hz), 1.81 (ketoalcohol, ddt, 1H, J=16.0, 9.0, 4.5 Hz), 2.05–2.19 (m), 2.28–2.42 (m), 2.38 (ketoalcohol, ddd, 1H, J=16.0, 8.0, 4.0 Hz), 2.51 (hemiacetal, brs, 1H), 2.64 (hemiacetal, ddd, 1H, J=16.0, 8.0, 3.0 Hz), 2.96 (hemiacetal, ddd, 1H, J=12.0, 10.0, 4.0 Hz), 3.02 (ketoalcohol, td, 1H, J=9.5, 4.0 Hz), 3.18–3.29 (m), 3.32 (hemiacetal, t, 1H, J=9.0 Hz), 3.37 (hemiacetal, s, 1H), 3.45 (hemiacetal, t, 1H, J=9.0 Hz), 3.49–3.80 (m), 3.91 (ketoalcohol, dq, 1H, J=15.0, 3.0 Hz), 3.98 (hemiacetal, t, 1H, J=9.5 Hz), 4.00 (hemiacetal, dq, 1H, J=15.5, 3.0 Hz), 4.22 (ketoalcohol, dd, 1H, J=15.0, 6.0 Hz), 4.28 (hemiacetal, dd, 1H, J=15.5, 6.0 Hz), 4.40 (hemiacetal, d, 1H, J=8.0 Hz), 4.46 (ketoalcohol, d, 1H, J=7.0 Hz), 4.47 (hemiacetal, m, 1H), 4.53 (ketoalcohol, dd, 1H, J=8.0, 4.0 Hz), 4.58–4.99 (m), 5.20 (hemiacetal, dd, 1H, J=10.5, 1.5 Hz), 5.46 (hemiacetal, dd, 1H, J=17.0, 1.5 Hz), 5.56 (ketoalcohol, dd, 1H, J=11.0, 2.0 Hz), 5.69 (ddt, 1H, J=12.0, 8.0, 3.0 Hz), 5.76 (ddd, 1H, J=18.0, 10.5, 7.0 Hz), 5.81–5.89 (m), 5.84 (ketoalcohol, ddt, 1H, J=12.0, 6.0, 3.0 Hz), 6.08 (hemiacetal, dd, 1H, J=17.0, 10.5 Hz), 6.28 (ketoalcohol, dd, 1H, J=17.5, 2.0 Hz), 6.81 (ketoalcohol, dd, 1H, J=17.5, 11.0 Hz), 7.22–7.44 (m, 17H), 7.50–7.66 (m, 8H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 19.05, 19.30, 26.77, 27.08, 31.11, 34.02, 34.69, 34.86, 63.46, 63.92, 67.70, 68.40, 72.96, 73.00, 73.37, 74.32, 74.55, 75.04, 75.71, 75.83, 76.49, 76.71, 77.19, 81.24, 81.44, 81.66, 83.03, 84.94, 87.30, 87.86, 94.71, 115.97, 117.12, 126.60, 127.27, 127.45, 127.55, 127.64, 127.77, 127.86, 128.06, 128.33, 128.49, 129.47, 129.57, 129.63, 131.28, 131.39, 132.42, 133.15, 133.21, 133.67, 133.84, 135.51, 136.03, 136.29, 139.04, 139.10, 139.40, 200.32; FT-IR (film) ν 3470, 3071, 2931, 2857, 2360, 1702, 1611, 1589, 1471, 1427, 1361, 1112, 998, 935, 823 cm^{-1}; MALDI-TOF MS $[M+Na]^+$ calcd for $C_{58}H_{70}NaO_7Si_2$ 973.4501, found 973.4455; $[\alpha]_D^{28.0}$ −13.1° (*c* 1.50, $CHCl_3$).

4.2.13. Diol 32. To a solution of hemiacetal **30** (3.02 g, 3.17 mmol) and Et_3SiH (5.06 ml, 31.7 mmol) in CH_3CN (14 ml) was added TMSOTf (500 μl, 2.76 mmol) at −40 °C. The mixture was gradually warmed to −20 °C over 40 min with stirring and quenched with saturated $NaHCO_3$ solution. Aqueous phase was extracted with EtOAc, and the combined organic phase was dried over anhydrous $MgSO_4$. After concentration, the residue was purified by flash column chromatography (silica gel, hexane/EtOAc=50–20–15–7–5–2–0.5) to give bis-TBPS ether **31** (789 mg, 0.844 mmol, 27%), C15-mono-TBPS ether (378 mg, 0.542 mmol, 17%), C17-mono-TBPS ether (277 mg, 0.397 mmol, 13%), and diol **32** (370 mg, 0.810 mmol, 24%).

To a mixture of bis-TBPS ether **31** (789 mg, 0.844 mmol, 27%), C15-mono-TBPS ether (378 mg, 0.542 mmol, 17%), and C17-mono-TBPS ether (277 mg, 0.397 mmol, 13%) in THF (18 ml) was added TBAF (1.0 M solution in THF, 4.46 ml, 4.46 mmol). The mixture was stirred for 44 h at room temperature and concentrated. The residue was purified by flash column chromatography (silica gel, hexane/EtOAc=3–0.5, then hexane/EtOAc/MeOH=5:10:1) to give diol **32** (818 mg, 1.78 mmol, 58% in 2 steps). **32**: colorless powder; mp 159–160 °C (hexane–CH_2Cl_2); ^1H NMR (500 MHz, $CDCl_3$) δ 1.52 (q, 1H, J=11.5 Hz, H10), 1.90 (brs, 1H, OH), 2.33 (ddq, 1H, J=16.0, 9.0, 3.0 Hz, H4), 2.39 (brs, 1H, OH), 2.56 (dt, 1H, J=11.5, 4.5 Hz, H10), 2.63 (ddd, 1H, J=16.0, 8.0, 4.0 Hz, H4), 3.14 (ddd, 1H, J=11.5, 9.0, 4.5 Hz, H9), 3.20 (t, 1H, J=9.0 Hz, H8), 3.29 (td, 1H, J=9.0, 4.0 Hz, H5), 3.31–3.38 (m, 1H, H11), 3.34 (t, 1H, J=9.0 Hz, H6), 3.46–3.50 (m, 1H, H16), 3.49 (t, 1H, J=9.0 Hz, H7), 3.65 (brd, 1H, J=12.0 Hz, H17), 3.68–3.73 (m, 1H, H17), 3.73 (dd, 1H, J=9.5, 5.5 Hz, H12), 4.02 (dq, 1H, J=15.0, 3.0 Hz, H1), 4.29 (dd, 1H, J=15.0, 6.0 Hz, H1), 4.33 (brs, 1H, H15), 4.81 (d, 1H, J=11.0 Hz, CH_2Ph), 4.88 (d, 1H, J=11.0 Hz, CH_2Ph), 5.24 (dt, 1H, J=11.0, 1.5 Hz, CH_2=CH–), 5.35 (dq, 1H, J=10.0, 1.5 Hz, CH_2=CH–), 5.37 (dt, 1H, J=17.0, 1.5 Hz, CH_2=CH–), 5.46 (dt, 1H, J=17.0, 1.5 Hz, CH_2=CH–), 5.76 (ddt, 1H, J=11.0, 8.0, 3.0 Hz, H3), 5.84 (ddd, 1H, J=17.0, 11.0, 5.5 Hz, H14), 5.86 (ddt, 1H, J=11.0, 6.0, 3.0 Hz, H2), 6.00 (ddd, 1H, J=17.0, 10.0, 5.5 Hz, H13), 7.23–7.28 (m, 1H, Ph), 7.32 (t, 2H, J=8.0 Hz, Ph), 7.40 (d, 2H, J=8.0 Hz, Ph); ^{13}C NMR (50 MHz, $CDCl_3$) δ 34.58, 36.21, 61.55, 68.34, 72.84, 75.03, 76.04, 76.34, 76.79, 80.75, 81.01, 81.80, 87.18, 116.68, 118.25, 126.52, 127.33, 127.80, 128.10, 131.82, 135.78, 135.91, 138.99; FT-IR (film) ν 3446, 3028, 2930, 2874, 1455, 1361, 1263, 1096, 926, 738 cm^{-1}; ESI-TOF MS $[M+NH_4]^+$ calcd for $C_{26}H_{38}NO_7$ 476.2648, found 476.2623; $[\alpha]_D^{28.0}$ +23.1° (*c* 1.30, $CHCl_3$).

4.2.14. ABCD ring 11. A solution of diol **32** (500 mg, 1.09 mmol) and Grubbs catalyst **37** (18.5 mg, 0.0218 mmol) in CH_2Cl_2 (55 ml) was stirred for 2.5 h at room temperature. Et_3N (400 μl) was added and the mixture was concentrated. The residue was washed with hexane by decantation and the remaining precipitate was recrystallized from hexane–EtOAc to give ABCD ring **11** (463 mg, 1.08 mmol, 99%). **11**: colorless solid; mp 190 °C (hexane–AcOEt); ^1H NMR (500 MHz, $CDCl_3$) δ 1.55 (q, 1H, J=11.0 Hz, H10), 2.15 (t, 1H, J=6.5 Hz, OH), 2.19 (d, 1H, J=6.0 Hz, OH), 2.30–2.36 (m, 1H, H4, H10), 2.64 (ddd, 1H, J=16.5, 7.5, 4.0 Hz, H4), 3.08–3.16 (m, 2H, H8, H9), 3.28 (td, 1H, J=9.5, 4.0 Hz, H5), 3.32–3.37 (m, 1H, H11), 3.34 (t, 1H, J=8.5 Hz, H6), 3.44 (ddd, 1H, J=9.5, 6.0, 4.0 Hz, H16), 3.48 (t, 1H, J=8.5 Hz, H7), 3.73 (dt, 1H, J=12.0, 6.0 Hz, H17), 3.84–3.88 (m, 2H, H12, H17), 4.01 (brdt, 1H, J=15.5, 3.0 Hz, H1), 4.29 (dd, 1H, J=15.5, 6.0 Hz, H1), 4.29–4.38 (m, 1H, H15), 4.83 (d, 1H, J=11.5 Hz, CH_2Ph), 4.87 (d, 1H, J=11.5 Hz, CH_2Ph), 5.66–5.74 (m, 2H, H13, H14),

5.74–5.80 (m, 1H, H3), 5.84–5.89 (m, 1H, H2), 7.24–7.29 (m, 1H, Ph), 7.33 (t, 2H, J=8.0 Hz, Ph), 7.41 (d, 2H, J=8.0 Hz, Ph); ^{13}C NMR (50 MHz, $CDCl_3$) δ 34.75, 36.89, 64.35, 68.53, 71.76, 73.23, 75.33, 77.00, 78.51, 80.45, 81.12, 82.20, 84.01, 87.54, 126.85, 127.59, 127.90, 128.36, 131.30, 131.53, 134.37, 139.29; FT-IR (film) ν 3331, 3208, 3032, 2935, 2873, 2824, 1488, 1453, 1363, 1326, 1289, 1261, 1105, 1066, 1040, 978, 957 cm^{-1}; ESI-TOF MS $[M+NH_4]^+$ calcd for $C_{24}H_{34}NO_7$ 448.2335, found 448.2314; $[\alpha]_D^{19.2}$ −7.3° (c 0.670, $CHCl_3$).

4.3. Attempts to construct the tetrahydrooxocin E ring using a chlorosulfide synthon

4.3.1. Alcohol 38. To a solution of diol **11** (500 mg, 1.16 mmol) in CH_2Cl_2 (17 ml) was added a solution of $AlCl_3$ (465 mg, 3.48 mmol) in CH_3NO_2 (5 ml) at 0 °C. The mixture was stirred for 20 min at 0 °C and quenched by the slow addition of MeOH (8 ml). After concentration, the residue was purified by flash column chromatography (silica gel, hexane/EtOAc=5–3.5–0.5, then EtOAc/MeOH=20–10) to give a corresponding triol (384 mg, 1.13 mmol, 97%).

To a solution of the triol (384 mg, 1.13 mmol) in DMF (6 ml) and CH_2Cl_2 (6 ml) were added 2,2-dimethoxypropane (1.38 ml, 11.3 mmol) and PPTS (85.0 mg, 0.338 mmol). The mixture was stirred for 13 h at room temperature and quenched with saturated $NaHCO_3$ solution. Aqueous phase was extracted with Et_2O, and the combined organic phase was washed with brine and dried over anhydrous $MgSO_4$. After concentration, the residue was recrystallized from hexane–EtOAc to give a corresponding acetonide (360 mg, 0.946 mmol, 84%). colorless powder; mp 245–245 °C (hexane–AcOEt); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.39 (s, 3H, Me), 1.47 (s, 3H, Me), 1.52 (q, 1H, J=11.5 Hz, H10), 2.29 (dt, 1H, J=11.8, 4.4 Hz, H10), 2.34–2.40 (m, 1H, H4), 2.61 (brddd, 1H, J=16.0, 8.5, 2.8 Hz, H4), 3.04 (t, 1H, J=9.3 Hz, H8), 3.13 (ddd, 1H, J=11.8, 9.3, 4.5 Hz, H9), 3.21–3.28 (m, 2H, H5, H6), 3.30–3.38 (m, 2H, H11, H16), 3.60 (d, 1H, J=11.0 Hz, H17), 3.62–3.66 (m, 1H, H7), 3.82 (dd, 1H, J=11.5, 5.5 Hz, H17), 3.92 (brdq, 1H, J=9.3, 2.2 Hz, H12), 4.02 (brdq, 1H, J=15.0, 3.0 Hz, H1), 4.33 (dd, 1H, J=15.5, 6.0 Hz, H1), 4.35 (brdd, 1H, J=9.0, 2.0 Hz, H15), 5.64 (brdt, 1H, J=12.7, 2.4 Hz, H13), 5.74 (brdt, 1H, J=12.5, 2.1 Hz, H14), 5.80–5.86 (m, 1H, H3), 5.90–5.95 (m, 1H, H2); ^{13}C NMR (50 MHz, $CDCl_3$) δ 18.68, 28.75, 34.25, 36.47, 62.51, 68.16, 72.75, 72.96, 74.01, 75.21, 75.94, 76.79, 80.14, 80.59, 87.61, 98.33, 127.54, 131.29, 131.60, 132.46; FT-IR (film) ν 3446, 3028, 2930, 2874, 1455, 1361, 1263, 1096, 926, 738 cm^{-1}; $[\alpha]_D^{19.3}$ −9.3° (c 1.03, $CHCl_3$).

To a solution of the acetonide (2.75 g, 7.24 mmol) in THF (120 ml) and DMF (40 ml) were added NAPBr (4.80 g, 21.7 mmol) and NaH (60% dispersion in mineral oil, 1.45 g, 36.2 mmol) at room temperature. After stirring for 5 min, TBAI (2.67 g, 7.24 mmol) was added and the resulting mixture was stirred for 30 min at 40 °C. The reaction mixture was quenched with saturated NH_4Cl solution and the aqueous phase was extracted with EtOAc. The combined organic phase was washed with brine and dried over anhydrous $MgSO_4$. After concentration, the residue was purified by flash column chromatography (silica gel, hexane/EtOAc=30–1.5) to give a corresponding NAP–ether (3.31 g, 6.36 mmol, 88%). All spectroscopic data are identical to those reported in the literature.[14]

To a solution of the NAP–ether (1.14 g, 2.18 mmol) in MeOH (32 ml) and THF (16 ml) was added $TsOH\cdot H_2O$ (57.0 mg, 0.218 mmol). The mixture was stirred for 27 h at room temperature and quenched with Et_3N (1 ml). Concentration of the solution gave a corresponding diol (1.11 g). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.56 (q, 1H, J=11.5 Hz, H10), 2.31–2.37 (m, 2H, H4, H10), 2.64 (1H, ddd, J=16.0, 8.0, 4.0 Hz, H4), 3.10–3.16 (m, 2H, H8, H9), 3.29 (ddd, 1H, J=10.5, 10.5, 4.0 Hz, H5), 3.35 (ddd, 1H, J=11.5, 9.5, 5.0 Hz, H11), 3.38 (dd, 1H, J=9.0, 9.0 Hz, H6), 3.45 (ddd, 1H, J=9.0, 6.0, 4.0 Hz, H16), 3.53 (t, 1H, J=9.0 Hz, H7), 3.74 (dt, 1H, J=11.5, 5.5 Hz, H17), 3.86 (dd, 1H, J=7.0, 4.0 Hz, H17), 3.89 (brd, 1H, J=9.5 Hz, H12), 4.04 (ddd, 1H, J=15.5, 5.5, 2.5 Hz, H1), 4.31 (dd, 1H, J=15.5, 5.5 Hz, H1), 4.37 (brdd, 1H, J=9.0, 5.5 Hz, H15), 5.00 (d, 1H, J=12.0 Hz, NAP), 5.04 (d, 1H, J=12.0 Hz, NAP), 5.72 (s, 2H, H13, H14), 5.78 (ddt, 1H, J=11.5, 8.5, 3.0 Hz, H3), 5.88 (ddt, 1H, J=11.5, 6.0, 3.5 Hz, H2), 7.44–7.47 (m, 2H, NAP) 7.55 (dd, 1H, J=9.0, 2.0 Hz, NAP) 7.81–7.84 (m, 4H, NAP); ^{13}C NMR (125 MHz, $CDCl_3$) δ 30.79, 34.74, 36.87, 44.93, 49.95, 64.34, 68.53, 71.75, 73.21, 75.35, 78.47, 80.44, 81.09, 82.10, 83.98, 87.62, 125.81, 126.05, 126.22, 126.48, 126.91, 127.82, 128.02, 131.55, 134.36, 146.88; MALDI-TOF MS $[M+Na]^+$ calcd for $C_{28}H_{32}NaO_7$ 503.2046, found 503.2215.

To a solution of the diol (1.11 g) and 2,6-lutidine (763 μl, 6.55 mmol) in CH_2Cl_2 (44 ml) was added TBSOTf (1.5 ml, 6.55 mmol) at 0 °C. The mixture was stirred for 1 h at 0 °C and quenched with saturated $NaHCO_3$ solution. Aqueous phase was extracted with EtOAc and the combined organic phase was washed with 1M HCl, brine and dried over anhydrous Na_2SO_4. After concentration, the residue was purified by flash column chromatography (silica gel, hexane–hexane/AcOEt=10) to give a corresponding bis-TBS ether (1.52 g, 2.15 mmol, 98% in 2 steps). ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.04–0.10 (m, 12H, TBS), 0.88–0.92 (m, 18H, TBS) 1.56 (q, 1H, J=11.0 Hz, H10), 2.32–2.37 (m, 2H, H4, H10), 2.65 (ddd, 1H, J=16.0, 8.0, 4.0 Hz, H4), 3.11–3.18 (m, 2H, H8, H9), 3.27–3.34 (m, 2H, H5, H11), 3.36–3.40 (m, 2H, H6, H16), 3.53 (t, 1H, J=8.5 Hz, H7), 3.64 (dd, 1H, J=11.0, 6.0 Hz, H17), 3.82 (dd, 1H, J=10.5, 1.5 Hz, H17), 3.87 (d, 1H, J=8.5 Hz, H12), 4.04 (brdd, 1H, J=15.5, 3.0 Hz, H1), 4.26 (d, 1H, J=9.0 Hz, H15), 4.31 (dd, 1H, J=15.5, 5.5 Hz, H1), 4.99 (d, 1H, J=12.0 Hz, NAP), 5.04 (d, 1H, J=11.5 Hz, NAP), 5.65 (s, 2H, H13, H14), 5.78 (ddt, 1H, J=11.0, 7.5, 3.0 Hz, H3), 5.88 (ddd, 1H, J=12.5, 6.5, 3.5 Hz, H2), 7.43–7.48 (m, 2H, NAP), 7.55 (dd, 1H, J=8.5, 1.5 Hz, NAP), 7.81–7.84 (m, 4H, NAP); ^{13}C NMR (125 MHz, $CDCl_3$) δ −4.96, −4.87, −4.33, −3.43, 18.11, 18.66, 25.79, 25.85, 25.93, 26.14, 34.78, 36.95, 64.21, 68.51, 71.27, 73.42, 75.29, 78.27, 80.75. 81.12, 82.15, 85.74, 87.57, 104.90, 125.76, 126.00, 126.24, 126.44, 126.91, 127.80, 128.00, 128.04, 130.42, 131.58, 136.26, 136.84; FT-IR (film) ν 2953, 2930, 2857, 1469, 1362, 1254, 1091, 1007, 940, 869, 836 cm^{-1}; MALDI-TOF MS $[M+Na]^+$ calcd for $C_{40}H_{60}NaO_7Si_2$ 731.3775, found 731.3781.

To a solution of the bis-TBS ether (1.52 g, 2.15 mmol) in MeOH (22 ml) and THF (22 ml) was added CSA (50.0 mg, 0.215 mmol) at −15 °C. The mixture was stirred for 14 h at −15 °C, and quenched with Et_3N (218 μl) and then saturated $NaHCO_3$ solution. After concentration, the residue was purified by flash column chromatography (silica gel, hexane/AcOEt=3–1) to give alcohol **38** (1.09 g, 1.83 mmol, 85%), recovery of bis-TBS ether (130 mg, 0.183 mmol, 9%) and a corresponding diol (38.2 mg, 0.0795 mmol, 4%). **38**: colorless solid; mp: 160–161 °C (hexane/EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.08 (s, 3H, $SiMe_3$), 0.10 (s, 3H, $SiMe_3$), 0.90 (s, 9H, *t*Bu), 1.55 (dd, 1H, *J*=11.5 Hz, H10), 2.14–2.16 (m, 1H, H17), 2.32–2.37 (m, 2H, H4, H10), 2.65 (ddd, 1H, *J*=16.0, 8.0, 4.0 Hz, H4), 3.10–3.16 (m, 2H, H8, H9), 3.29 (td, 1H, *J*=9.0, 4.0 Hz, H5), 3.34 (ddd, 1H, *J*=13.5, 5.0, 2.5 Hz, H11), 3.38 (t, 1H, *J*=9.0 Hz, H6), 3.46–3.55 (m, 2H, H7, H16), 3.77–3.82 (m, 1H, H17), 3.90 (d, 1H, *J*=8.5 Hz, H12), 4.04 (brdd, 1H, *J*=12.5, 2.5 Hz, H1), 4.22 (brd, 1H, *J*=8.5 Hz, H15), 4.32 (dd, 1H, *J*=15.0, 5.5 Hz, H1), 4.99 (d, 1H, *J*=12.5 Hz, NAP), 5.04 (d, 1H, *J*=12.0 Hz, NAP), 5.68 (s, 2H, H13, H14), 5.78 (ddt, 1H, *J*=11.0, 8.5, 2.5 Hz, H3), 5.88 (ddd, 1H, *J*=12.0, 6.0, 3.0 Hz, H2), 7.43–7.48 (m, 2H, NAP), 7.55 (dd, 1H, *J*=8.5, 1.5 Hz, NAP), 7.81–7.84 (m, 4H, NAP); ^{13}C NMR (125 MHz, $CDCl_3$) δ −4.90, −4.32, 18.06, 25.87, 34.73, 36.82, 63.79, 68.51, 72.45, 73.14, 75.30, 78.07, 80.44. 81.01, 82.03, 84.42, 87.58, 125.78, 126.01, 126.23, 126.46, 126.92, 127.80, 128.01, 128.02, 130.77, 131.54, 133.11, 133.41, 136.13, 136.77; FT-IR (film) ν 2931, 2859, 2070, 1254, 1087, 864, 838 cm^{-1}; MALDI-TOF MS $[M+Na]^+$ calcd for $C_{34}H_{46}NaO_7Si$ 617.2910, found 617.2963; $[\alpha]_D^{22.0}$ +25.7°(*c* 0.780, $CHCl_3$).

4.3.2. Nitrile 39. To a suspension of alcohol **38** (1.05 g, 1.76 mmol) and MS4A (powder, activated) in pyridine (22 ml) was added TsCl (1.34 g, 7.03 mmol). The mixture was stirred for 24 h at room temperature, and diluted with EtOAc and quenched with saturated $NaHCO_3$ solution. Aqueous phase was extracted with EtOAc and the combined organic phase was washed with brine and dried over anhydrous $MgSO_4$. After concentration, the residue was purified by flash column chromatography (silica gel, hexane/AcOEt=10–5) to give a corresponding tosylate (1.26 g, 1.68 mmol, 96%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.06 (s, 3H, $SiMe_3$), 0.09 (s, 3H, $SiMe_3$), 0.88 (s, 9H, *t*Bu), 1.39 (dd, 1H, *J*=11.5 Hz, H10), 2.18 (dt, 1H, *J*=11.5, 4.5 Hz, H10), 2.33–2.39 (m, 1H, H4), 2.44 (s, 3H, Ts), 2.66 (ddd, 1H, *J*=16.0, 8.0, 4.0 Hz, H4), 3.04–3.12 (m, 2H, H8, H9), 3.20 (ddd, 1H, *J*=13.5, 5.0, 1.5 Hz, H11), 3.28 (td, 1H, *J*=9.5, 4.0 Hz, H5), 3.38 (t, 1H, *J*=9.0 Hz, H6), 3.53 (t, 1H, *J*=8.0 Hz, H7), 3.58 (ddd, 1H, *J*=8.5, 6.5, 2.0 Hz, H16), 3.83 (brdd, 1H, *J*=9.0, 2.0 Hz, H12), 4.02 (dd, 1H, *J*=10.5, 7.0 Hz, H17), 4.05 (brdd, 1H, *J*=15.5, 2.5 Hz, H1), 4.19 (brdd, 1H, *J*=9.5, 2.0 Hz, H15), 4.24 (dd, 1H, *J*=10.5, 2.5 Hz, H17), 4.32 (dd, 1H, *J*=15.5, 6.0 Hz, H1), 5.00 (d, 1H, *J*=12.0 Hz, NAP), 5.04 (d, 1H, *J*=12.5 Hz, NAP), 5.62 (dt, 1H, *J*=13.5, 2.0 Hz, H13), 5.67 (dt, 1H, *J*=13.0, 2.0 Hz, H14), 5.79 (ddt, 1H, *J*=11.0, 8.0, 2.5 Hz, H3), 5.88 (ddd, 1H, *J*=12.5, 6.5, 3.5 Hz, H2), 7.33 (d, 2H, J=8.0 Hz, Ts), 7.46 (dt, 2H, *J*=5.5, 2.0 Hz, NAP), 7.56 (dd, 1H, *J*=8.5, 1.5 Hz, NAP), 7.79–7.84 (m, 6H, NAP, Ts); ^{13}C NMR (125 MHz, $CDCl_3$) δ −4.95, −4.28, 17.95, 21.73, 25.81, 25.90, 34.75, 36.56, 68.51, 70.85, 71.36, 73.11, 75.25, 78.18, 80.33, 81.10, 82.07, 82.18, 87.58, 125.76, 126.00, 126.19, 126.40, 126.88, 127.78, 127.97, 128.00, 128.13, 129.86, 129.97, 131.31, 131.50, 133.10, 133.29, 133.41, 135.25, 136.81, 144.77; FT-IR (film) ν 3026, 2928, 1919, 1733, 1654, 1599, 1509, 1495, 1462, 1368, 1258, 1258, 1098, 838 cm^{-1}; MALDI-TOF MS $[M+Na]^+$ calcd for $C_{41}H_{52}NaO_9SSi$ 771.2999, found 771.2968; $[\alpha]_D^{18.0}$ +13.2° (*c* 0.874, $CHCl_3$).

To a solution of the tosylate (582 mg, 0.778 mmol) in DMSO (11 ml) was added NaCN (78.9 mg, 1.61 mmol). The mixture was stirred for 20 h at 50 °C and diluted with AcOEt. The organic phase was washed with water and brine, and dried over anhydrous $MgSO_4$. After concentration, the residue was purified by flash column chromatography (silica gel, hexane–hexane/AcOEt=10) to give nitrile **39** (443 mg, 0.733 mmol, 94%). **39**: colorless solid; mp 121–122 °C (hexane/EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.11 (s, 3H, $SiMe_3$), 0.12 (s, 3H, $SiMe_3$), 0.91 (s, 9H, *t*Bu), 1.58 (q, 1H, *J*=11.0 Hz, H10), 2.32–2.43 (m, 2H, H4, H10), 2.49 (dd, 1H, *J*=16.5, 8.0 Hz, H17), 2.64 (ddd, 1H, *J*=16.5, 8.5, 4.5 Hz, H4), 2.75 (dd, 1H, *J*=16.5, 3.5 Hz, H17), 3.09–3.16 (m, 2H, H8, H9), 3.28 (td, 1H, *J*=9.5, 4.0 Hz, H5), 3.34 (ddd, 1H, *J*=13.5, 4.0, 2.5 Hz, H11), 3.39 (t, 1H, *J*=9.5 Hz, H6), 3.53 (t, 1H, *J*=8.5 Hz, H7), 3.63 (td, 1H, *J*=7.5, 3.0 Hz, H16), 3.91 (brdd, 1H, *J*=9.0, 2.5 Hz, H17), 4.04 (brdd, 1H, *J*=15.5, 2.5 Hz, H1), 4.17 (brdd, 1H, *J*=9.0, 2.0 Hz, H15), 4.32 (dd, 1H, *J*=15.5, 5.5 Hz, H1), 5.00 (d, 1H, *J*=11.5 Hz, NAP), 5.03 (d, 1H, *J*=12.5 Hz, NAP), 5.66 (dt, 1H, *J*=13.5, 2.5 Hz, H13), 5.72 (dt, 1H, *J*=12.5, 2.5 Hz, H14), 5.78 (ddt, 1H, *J*=11.0, 8.0, 2.0 Hz, H3), 5.87 (ddd, 1H, *J*=12.0, 6.0, 3.0 Hz, H2), 7.44–7.48 (m, 2H, NAP), 7.55 (dd, 1H, *J*=9.0, 1.5 Hz, NAP), 7.82–7.84 (m, 4H, NAP); ^{13}C NMR (125 MHz, $CDCl_3$) δ −4.83, −4.16, 17.99, 22.80, 25.84, 34.71, 36.55, 68.50, 73.07, 73.56, 75.25, 78.49, 80.06, 80.27, 81.04, 82.04, 87.59, 117.84, 125.77, 126.00, 126.19, 126.42, 126.96, 127.78, 127.98, 128.00, 131.47, 131.97, 133.09, 133.39, 134.83, 136.78; FT-IR (film) ν 3023, 2954, 2858, 2359, 2252, 1509, 1467, 1365, 1302, 1258, 1094, 1009, 910, 861 cm^{-1}; MALDI-TOF MS $[M+Na]^+$ calcd for $C_{35}H_{45}NaNO_6Si$ 626.2914, found 626.2835; $[\alpha]_D^{26.8}$ +24.4° (*c* 1.01, $CHCl_3$).

4.3.3. Alcohol 40. To a solution of nitrile **39** (854 mg, 1.41 mmol) in CH_2Cl_2 (60 ml) was added DIBAL (0.93 M solution in hexane, 3.00 ml, 2.83 mmol) at −70 °C. The mixture was stirred for 3 h at −70 °C and quenched with saturated Rochelle salt solution. The resulting mixture was stirred for 2 h at room temperature and the aqueous phase was extracted with EtOAc. The combined organic phase was washed with brine and dried over anhydrous $MgSO_4$. Concentration of the solution gave a corresponding aldehyde, which was subjected to the next reaction without purification.

To a suspension of methyltriphenylphosphonium bromide (3.03 g, 8.49 mmol) in THF (100 ml) was added $NaN(SiMe_3)_2$ (2.0 M solution in THF, 3.50 ml, 7.07 mmol) at 0 °C. The mixture was stirred for 30 min at 0 °C followed by the addition of the crude aldehyde in THF (40 ml). The resulting mixture was stirred for 1 h at 0 °C and quenched with saturated NH_4Cl solution. Aqueous phase

was extracted with AcOEt and the combined organic phase was washed with brine and dried over anhydrous $MgSO_4$. After concentration, the residue was purified by flash column chromatography (silica gel, hexane/AcOEt = 10) to give a corresponding alkene (246 mg, 0.407 mmol, 29% in 2 steps) and recovery of aldehyde (457 mg, 0.753 mmol, 53%). The recovered aldehyde (457 mg, 0.753 mmol) was subjected to the same reaction and purification conditions to give the alkene (481 mg, 0.795 mmol, 56% in 2 steps).

To a solution of the alkene (1.02 g, 1.68 mmol) in THF (60 ml) was added TBAF (1.0 M solution in THF, 3.80 ml, 3.80 mmol). The mixture was stirred for 18 h at room temperature and quenched with water. Aqueous phase was extracted with EtOAc and the combined organic phase was washed with brine and dried over anhydrous $MgSO_4$. After concentration, the residue was purified by flash column chromatography (silica gel, hexane/AcOEt = 30–10–3) to give alcohol **40** (749 mg, 1.53 mmol, 91%). **40**: colorless solid; mp 178–179 °C (hexane/EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.54 (dd, 1H, J = 11.0 Hz, H10), 1.79 (brs, 1H, OH), 2.26 (dt, 1H, J = 15.0, 7.5 Hz, H17), 2.31–2.37 (m, 2H, H4, H10), 2.53–2.58 (m, 1H, H17), 2.63 (ddd, 1H, J = 16.0, 8.0, 4.0 Hz, H4), 3.09–3.17 (m, 2H, H8, H9), 3.26–3.31 (m, 2H, H5, H11), 3.35–3.40 (m, 2H, H6, H16), 3.53 (t, 1H, J = 8.0 Hz, H7), 3.87 (d, 1H, J = 9.0 Hz, H12), 4.04 (brdd, 1H, J = 15.5, 2.5 Hz, H1), 4.15 (brd, 1H, J = 10.0 Hz, H15), 4.31 (dd, 1H, J = 16.0, 6.0 Hz, H1), 4.99 (d, 1H, J = 12.0 Hz, NAP), 5.04 (d, 1H, J = 12.0 Hz, NAP), 5.08 (d, 1H, J = 10.5 Hz, CH_2=CH–), 5.12 (d, 1H, J = 17.0 Hz, CH_2=CH–), 5.70 (dd, 2H, J = 16.5, 13.0 Hz, H13, H14), 5.77 (ddt, 1H, J = 11.5, 8.5, 2.5 Hz, H3), 5.85–5.97 (m, 2H, H2, H18), 7.43–7.47 (m, 2H, NAP), 7.55 (d, 1H, J = 8.5 Hz, NAP), 7.81–7.85 (m, 4H, NAP); ^{13}C NMR (125 MHz, $CDCl_3$) δ 34.76, 36.79, 37.71, 68.53, 73.36, 73.81, 75.34, 78.78, 80.54, 81.13, 82.21, 84.50, 87.60, 117.22, 125.78, 126.02, 126.21, 126.43, 126.91, 127.80, 128.00, 128.02, 131.35, 131.51, 133.11, 133.42, 134.29, 135.03, 136.80; FT-IR (KBr) ν 3327, 3021, 2881, 2351, 1842, 1638, 1505, 1438, 1353, 1099, 1008, 916, 854 cm^{-1}; MALDI-TOF MS $[M+Na]^+$ calcd for $C_{30}H_{34}NaO_6Si$ 513.2253, found 513.2307; $[\alpha]_D^{28.0}$ −5.93° (c 1.01, $CHCl_3$).

4.3.4. Alcohol 43. To a solution of (2*S*)-1-phenylthio-2-*tert*-butyldimethylsilyloxy-3-butene[14] (187 mg, 0.636 mmol) in CCl_4 (6 ml) was added NCS (98.0 mg, 0.734 mmol). The mixture was stirred for 2 h at room temperature and filtered. The filter cake was washed with CCl_4 and the filtrate was concentrated to give the α-chlorosulfide **41**. To a suspension of alcohol **40** (95.7 mg, 0.195 mmol) and MS4A (50 mg, powdered, activated) in CH_2Cl_2 (5 ml) were added AgOTf (151 mg, 0.683 mmol) and 2,6-di-*tert*-butyl-4-methylpyridine (168 mg, 0.819 mmol) at −40 °C. After stirring for 15 min at −40 °C, a solution of **41** in CH_2Cl_2 (5 ml) was added and the resulting mixture was gradually warmed to 0 °C over 1 h with stirring. The mixture was eluted through a short plug of silica gel (silica gel = 2.5 g, hexane/AcOEt = 0.5) to give yellow oil, which was further purified by flash column chromatography (silica gel, hexane/AcOEt = 10–5–2–1) to give TBS ether **42** (129 mg, 0.165 mmol, 84%) as a 6:1 diastereomeric mixture, and recovery of **40** (7.1 mg, 0.0145 mmol, 7%).

To a solution of the TBS ether **42** (129 mg, 0.165 mmol) in THF (3 ml) was added TBAF (1.0 M in THF solution, 329 μl, 0.329 mmol). The mixture was stirred for 1 h at room temperature and concentrated. The residue was purified by flash column chromatography (silica gel, hexane/AcOEt = 10–5–3) to give alcohol **43** (92.3 mg, 0.138 mmol, 84%) and a C21-epimer of **43** (15.4 mg, 0.0230 mmol, 14%). **43**: colorless solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.50 (q, 1H, J = 11.5 Hz, H10), 2.09 (dt, 1H, J = 15.0, 7.5 Hz, H17), 2.23–2.37 (m, 2H, H4, H10), 2.47–2.53 (m, 1H, H17), 2.57 (d, 1H, J = 4.5 Hz, OH), 2.63 (ddd, 1H, J = 14.0, 7.5, 3.5 Hz, H4), 3.07–3.15 (m, 2H, H8, H9), 3.25–3.31 (m, 2H, H5, H11), 3.38 (t, 1H, J = 9.0 Hz, H6), 3.49 (td, 1H, J = 9.0, 3.0 Hz, H16), 3.53 (t, 1H, J = 8.5 Hz, H7), 3.83 (brdd, 1H, J = 8.5, 2.0 Hz, H12), 4.04 (brdd, 1H, J = 15.5, 2.5 Hz, H1), 4.08 (brdd, 1H, J = 8.5, 2.0 Hz, H15), 4.27–4.33 (m, 2H, H1, H20), 4.80 (d, 1H, J = 5.5 Hz, H21), 4.99–5.06 (m, 4H, CH_2=CH-, NAP), 5.34 (brd, 1H, J = 10.0 Hz, CH_2=CH–), 5.47 (dt, 1H, J = 15.5, 1.5 Hz, CH_2=CH–), 5.73 (dt, 1H, J = 13.0, 2.5 Hz, H14), 5.76–5.83 (m, 2H, H3, H18), 5.87 (ddd, 1H, J = 12.0, 6.0, 3.0 Hz, H2), 5.98 (dt, 1H, J = 13.0, 2.5 Hz, H13), 6.04 (ddd, 1H, J = 17.0, 10.5, 5.5 Hz, H19), 7.31–7.34 (m, 3H, Ph), 7.45–7.48 (m, 2H, NAP), 7.50–7.52 (m, 2H, Ph), 7.56(dd, 1H, J = 8.5, 1.5 Hz, NAP), 7.82–7.86 (m, 4H, NAP); ^{13}C NMR (125 MHz, $CDCl_3$) δ 34.73, 36.65, 37.12, 68.49, 73.27, 74.17, 75.31, 78.61, 80.40, 81.05, 81.13, 82.15, 83.43, 87.60, 96.67, 117.23, 118.19, 125.77, 126.01, 126.18, 126.41, 126.86, 127.79, 127.99, 128.00, 128.30, 129.39, 131.46, 131.48, 132.79, 132.91, 133.09, 133.20, 133.41, 133.58, 134.83, 135.87, 136.79; FT-IR (film) ν 3466, 2877, 1737, 1439, 1368, 1260, 1098, 922, 855, 817 cm^{-1}; MALDI-TOF MS $[M+Na]^+$ calcd. for $C_{40}H_{44}NaO_7S$ 691.2705, found 691.2722.

4.3.5. TBS ether 45. A solution of alcohol **43** (106 mg, 0.158 mmol) and Grubbs catalyst **37** (4.0 mg, 4.7 μmol) in CH_2Cl_2 (16 ml) was stirred for 6 h at room temperature. Et_3N (100 μl) was added and the mixture was concentrated. The residue was purified by flash column chromatography (silica gel, hexane/AcOEt = 5–3–1–AcOEt only) to give alcohol **44** (91.2 mg, 0.142 mmol, 90%).

To a solution of the alcohol **44** (91.2 mg, 0.142 mmol) in DMF (7 ml) were added imidazole (194 mg, 2.85 mmol) and TBSCl (215 mg, 1.42 mmol). The mixture was stirred for 25 h at room temperature and diluted with AcOEt and quenched with saturated NH_4Cl solution. Aqueous phase was extracted with AcOEt and the combined organic phase was washed with brine and dried over anhydrous Na_2SO_4. After concentration, the residue was purified by flash column chromatography (silica gel, hexane/AcOEt = 20–5) to give TBS ether **45** (103 mg, 0.136 mmol, 95%). **45**: colorless solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.13 (s, 3H, $SiMe_3$), 0.16 (s, 3H, $SiMe_3$), 0.94 (s, 9H, *t*Bu), 1.47 (q, 1H, J = 12.5 Hz, H10), 2.22–2.25 (m, 2H, H10, H17), 2.29–2.34 (m, 1H, H4), 2.62 (ddd, 1H, J = 16.0, 7.5, 4.0 Hz, H4), 2.76 (ddd, 1H, J = 13.0, 9.0, 4.0 Hz, H17), 3.02–3.08 (m, 2H, H8, H9), 3.10–3.15 (m, 1H, H11), 3.25 (td, 1H, J = 9.0, 4.0 Hz, H5), 3.33 (t, 1H, J = 8.0 Hz, H6), 3.46 (t, 1H, J = 8.0 Hz, H7), 3.54 (dt, 1H, J = 8.5, 3.5 Hz, H16), 3.68 (brdd, 1H, J = 9.0, 2.0 Hz, H12), 3.90 (brdd, 1H, J = 9.0, 2.0 Hz, H15), 4.01 (brdd, 1H, J = 16.0, 3.0 Hz, H1), 4.29 (dd, 1H, J = 15.5,

6.5 Hz, H1), 4.46 (dd, 1H, J=8.5, 3.0 Hz, H20), 4.65 (dt, 1H, J=13.0, 3.0 Hz, H13), 4.93 (d, 1H, J=8.5 Hz, H21), 4.94 (d, 1H, J=12.5 Hz, NAP), 4.99 (d, 1H, J=12.5 Hz, NAP), 5.29 (dt, 1H, J=12.5, 2.0 Hz, H14), 5.73 (d, 2H, J=3.0 Hz, H18, H19), 5.73–5.78 (m, 1H, H3), 5.83–5.88 (m, 1H, H2), 7.29–7.54 (m, 8H, Ph, NAP), 7.79–7.83 (m, 4H, NAP); ^{13}C NMR (125 MHz, $CDCl_3$) δ −4.73, −4.24, 18.41, 25.78, 25.99, 32.61, 34.74, 36.90, 68.50, 72.94, 73.24, 75.22, 77.93, 80.51, 80.99, 82.13, 82.25, 84.22, 87.48, 97.05, 125.77, 126.00, 126.16, 126.38, 126.80, 126.88, 127.80, 127.86, 127.93, 127.99, 129.05, 129.13, 130.29, 130.64, 131.49, 133.08, 133.41, 133.70, 133.93, 134.13, 136.82, 137.21; FT-IR (film) ν 3009, 2931, 2858, 1735, 1648, 1602, 1584, 1509, 1472, 1440, 1391, 1363, 1302, 1256, 1216, 1087, 837 cm^{-1}; MALDI-TOF MS [M+Na]$^+$ calcd for $C_{44}H_{54}NaO_7SSi$ 777.3257, found 777.3306; $[\alpha]_D^{22.0}$ −27.5° (c 0.412, $CHCl_3$).

4.3.6. Sulfone 46. To a solution of sulfide **45** (103 mg, 0.136 mmol) in CH_2Cl_2 (30 ml) was added *m*-CPBA (180 mg, 0.679 mmol) at −15 °C. The mixture was stirred for 4 h at −15 °C and quenched with Et_3N and then saturated $NaHCO_3$ solution. Aqueous phase was extracted with AcOEt, and the combined organic phase was washed with brine and dried over anhydrous Na_2SO_4. After concentration, the residue was purified by flash column chromatography (silica gel, hexane/AcOEt=10–5–3–1) to give sulfone **46** (79.1 mg, 0.101 mmol, 74%) and a corresponding sulfoxide (29.8 mg). The sulfoxide (29.8 mg) was subjected to the same reaction and purification conditions another twice to give **46** (25.9 mg, 0.033 mmol, 24%). **46**: colorless solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.16 (s, 3H, $SiMe_3$), 0.22 (s, 3H, $SiMe_3$), 0.96 (s, 9H, *t*Bu), 1.43 (q, 1H, J=12.0 Hz, H10), 2.20–2.33 (m, 3H, H4, H10, H17), 2.61 (ddd, 1H, J=16.0, 8.0, 4.0 Hz, H4), 2.67 (ddd, 1H, J=12.5, 8.5, 3.5 Hz, H17), 3.00–3.03 (m, 2H, H8, H9), 3.07 (ddd, 1H, J=11.0, 9.0, 5.0 Hz, H11), 3.24 (td, 1H, J=9.5, 4.0 Hz, H5), 3.32 (t, 1H, J=9.0 Hz, H6), 3.44 (t, 1H, J=8.5 Hz, H7), 3.48 (dt, 1H, J=9.0, 2.5 Hz, H16), 3.62 (brdd, 1H, J=8.5, 2.0 Hz, H12), 3.83 (brdd, 1H, J=8.5, 2.5 Hz, H15), 3.87 (brd, 1H, J=12.5 Hz, H14), 4.00 (brdd, 1H, J=15.0, 3.0 Hz, H1), 4.28 (dd, 1H, J=16.0, 6.0 Hz, H1), 4.31 (d, 1H, J=8.5 Hz, H21), 4.92 (d, 1H, J=12.0 Hz, NAP), 4.93 (d, 1H, J=8.5 Hz, H20), 4.96 (d, 1H, J=12.0 Hz, NAP), 5.18 (dt, 1H, J=12.5, 2.5 Hz, H13), 5.71–5.77 (m, 3H, H3, H18, H19), 5.85 (ddd, 1H, J=7.5, 6.0, 3.0 Hz, H2), 7.42–8.08 (m, 12H, Ph, NAP); ^{13}C NMR (125 MHz, $CDCl_3$) δ −4.77, −4.36, 14.27, 18.33, 22.80, 25.96, 31.74, 32.59, 34.72, 36.79, 68.51, 69.92, 73.12, 75.22, 77.90, 80.31, 80.96, 82.14, 83.62, 84.10, 87.47, 97.59, 125.82, 126.03, 126.12, 126.34, 126.86, 127.82, 127.94, 127.96, 129.09, 129.60, 129.96, 131.24, 131.48, 131.55, 133.07, 133.40, 133.65, 133.81, 136.79, 138.79; FT-IR (film) ν 3026, 2931, 2858, 1726, 1446, 1328, 1257, 1153, 1089, 1006, 857, 839 cm^{-1}; MALDI-TOF MS [M+Na]$^+$ calcd for $C_{44}H_{54}NaO_9SSi$ 809.3155, found 809.2830; $[\alpha]_D^{20.0}$ −54.2° (c 1.12, $CHCl_3$).

4.3.7. Attempted allylation of 46 with allyltrimethylsilane in the presence of $AlCl_3$. Allyltrimethylsilane (95.3 μl, 0.600 mmol) was added to a suspention of $AlCl_3$ (40.0 mg, 0.300 mmol) in CH_2Cl_2 (3 ml) at −70 °C. The mixture was stirred for 30 min at −70 °C, followed by the addition of sulfone **46** (47.2 mg, 0.0600 mmol) in CH_2Cl_2 (3 ml), and the resulting mixture was stirred for 30 min at −60 °C. The reaction mixture was quenched with saturated $NaHCO_3$ solution and the aqueous phase was extracted with AcOEt. The combined organic phase was washed with brine and dried over anhydrous Na_2SO_4. After concentration, the residue was purified by flash column chromatography (silica gel, hexane/AcOEt=7–3–1) to give NAP ether **51** (20.8 mg, 30.3 μmol, 50%, 2:1 stereoisomers) and a corresponding C7-alcohol **52** (6.7 mg, 12.3 μmol, 20%, 2:1 stereoisomers).

To a solution of TBS ether **51** (29.2 mg, 0.0430 mmol, 2:1 stereoisomers) in THF (2 ml) was added TBAF (1.0 M solution in THF, 85 μl, 0.085 mmol). The mixture was stirred for 24 h at room temperature and concentrated. The residue was purified by flash column chromatography (silica gel, hexane/AcOEt=5–3–1) to give a corresponding C21-alcohol (24.7 mg, 0.043 mmol, 100%) as a 2:1 stereoisomers. The stereoisomers were separated by HPLC for spectral analyses. Major stereoisomer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.51–1.58 (m, 1H, H10), 2.26–2.31 (m, 3H, H4, H17, H22), 2.34–2.39 (m, 2H, H10, H22), 2.64 (ddd, 1H, J=16.0, 8.0, 4.0 Hz, H4), 2.77 (brdd, 1H, J=15.5, 6.5 Hz, H17), 3.09–3.15 (m, 2H, H8, H9), 3.28 (td, 2H, J=9.5, 4.0 Hz, H5, H11), 3.38 (t, 1H, J=9.0 Hz, H6), 3.51–3.56 (m, 2H, H7, H16), 3.67 (brs, 1H, H21), 3.89 (ddd, 1H, J=9.0, 4.5, 2.5 Hz, H12), 4.04 (brdd, 1H, J=15.0, 2.5 Hz, H1), 4.08 (td, 1H, J=4.0, 2.0 Hz, H20), 4.25 (brdd, 1H, J=8.0, 2.5 Hz, H15), 4.31 (dd, 1H, J=15.5, 6.0 Hz, H1), 4.99 (d, 1H, J=12.5 Hz, NAP), 5.04 (d, 1H, J=12.0 Hz, NAP), 5.11–5.16 (m, 2H, H24, H24), 5.66 (dd, 1H, J=12.5, 4.0 Hz, H19), 5.68 (dt, 1H, J=12.0, 2.5 Hz, H14), 5.79 (ddt, 1H, J=10.5, 8.5, 2.5 Hz, H3), 5.79–5.92 (m, 4H, H2, H13, H18, H23), 7.44–7.47 (m, 2H, NAP), 7.55 (dd, 1H, J=8.5, 1.5 Hz, NAP), 7.81–7.85 (m, 4H, NAP); ^{13}C NMR (125 MHz, $CDCl_3$) δ 33.24, 34.76, 37.02, 37.42, 68.52, 72.82, 73.33, 75.32, 78.06, 80.61, 81.05, 82.16, 82.33, 82.71, 82.74, 87.62, 117.82, 125.79, 126.03, 126.24, 126.47, 126.94, 127.82, 128.01, 128.04, 128.33, 128.38, 129.19, 130.85, 130.98, 131.54, 133.12, 133.44, 134.13, 134.55, 136.82; FT-IR (film) ν 3468, 3027, 2931, 2875, 1640, 1509, 1438, 1367, 1270, 1087, 1011, 915, 855, 817 cm^{-1}; MALDI-TOF MS [M+Na]$^+$ calcd for $C_{35}H_{40}NaO_7$ 595.2672, found 595.2608; $[\alpha]_D^{23.0}$ −34.3° (c 0.150, $CHCl_3$). Minor stereoisomer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.51–1.56 (m, 1H, H10), 2.00 (d, 1H, J=6.0 Hz, OH), 2.26–2.31 (m, 3H, H10, H17, H22), 2.33–2.39 (m, 2H, H4, H22), 2.64 (ddd, 1H, J=16.0, 8.0, 4.0 Hz, H4), 2.76–2.81 (m, 1H, H17), 3.08–3.14 (m, 2H, H8, H9), 3.28 (td, 2H, J=10.0, 4.0 Hz, H5, H11), 3.38 (t, 1H, J=9.0 Hz, H6), 3.52 (t, 1H, J=8.5 Hz, H7), 3.56 (dt, 1H, J=8.5, 5.0 Hz, H16), 3.78 (dtd, 1H, J=9.0, 8.5, 4.5 Hz, H21), 3.89 (ddd, 1H, J=9.0, 4.0, 2.0 Hz, H12), 4.04 (brdd, 1H, J=15.5, 3.0 Hz, H1), 4.18 (brs, 1H, H20), 4.24 (ddd, 1H, J=8.5, 5.0, 3.0 Hz, H15), 4.31 (dd, 1H, J=16.0, 6.0 Hz, H1), 4.99 (d, 1H, J=12.5 Hz, NAP), 5.04 (d, 1H, J=12.0 Hz, NAP), 5.12–5.17 (m, 2H, H24, H24), 5.67 (dt, 1H, J=12.5, 2.5 Hz, H14), 5.70 (brdd, 1H, J=11.5, 3.0 Hz, H19), 5.77 (ddt, 1H, J=11.5, 8.5, 3.0 Hz, H3), 5.83 (dt, 1H, J=13.0, 3.0 Hz, H13), 5.85–5.89 (m, 2H, H2, H23), 5.88–5.93 (m, 1H, H18), 7.44–7.47 (m, 2H, NAP), 7.55 (dd, 1H, J=9.0, 1.5 Hz, NAP), 7.81–7.85 (m, 4H, NAP); ^{13}C NMR (125 MHz, $CDCl_3$) δ

33.24, 34.78, 37.02, 37.12, 68.53, 73.17, 73.35, 75.32, 77.11, 78.02, 80.67, 81.06, 82.18, 83.13, 83.32, 87.62, 118.07, 125.78, 126.02, 126.24, 126.46, 126.94, 127.82, 128.00, 128.04, 128.16, 130.12, 130.73, 131.53, 133.14, 133.46, 134.41, 134.84, 136.85; FT-IR (film) ν 3481, 3025, 2875, 1734, 1643, 1508, 1454, 1367, 1261, 1087, 1011, 914, 855, 817 cm^{-1}; MALDI-TOF MS $[M+Na]^+$ calcd for $C_{35}H_{40}NaO_7$ 595.2672, found 595.2677.

4.3.8. Attempted cyanization of 53 with TMSCN in the presence of $EtAlCl_2$. To a solution of sulfide **42** (129 mg, 0.165 mmol) in CH_2Cl_2 (8 ml) was added *m*-CPBA (131 mg, 0.495 mmol) at −20 °C. After stirring for 1 h at −20 °C to −10 °C, the reaction mixture was quenched with saturated $NaHSO_3$ solution and then saturated $NaHCO_3$ solution. Aqueous phase was extracted with AcOEt, and the combined organic phase was washed with brine and dried over anhydrous Na_2SO_4. After concentration, the residue was purified by flash column chromatography (silica gel, hexane–hexane/AcOEt=10–5–2) to give sulfone **53** (41.7 mg, 0.0512 mmol, 31%).

Trimethylsilyl cyanide (29.9 μl, 0.238 mmol) was added to a suspension of $EtAlCl_2$ (132 μl, 0.119 mmol) in CH_2Cl_2 (1 ml) at −50 °C. The mixture was stirred for 10 min at −50 °C followed by the addition of the sulfone **53** (9.7 mg, 0.0119 mmol) in CH_2Cl_2 (1 ml). The resulting mixture was stirred for 2 h at −50 °C to −30 °C. The reaction mixture was quenched with saturated $NaHCO_3$ solution and then saturated Rochelle salt solution. Aqueous phase was extracted with AcOEt and the combined organic phase was washed with brine and dried over anhydrous Na_2SO_4. After concentration, the residue was purified by flash column chromatography (silica gel, hexane/AcOEt=7–3–1) to give chloride **56** (3.6 mg, 5.08 μmol, 35%) as a 2:1 stereoisomers. **56** (2:1 stereoisomers): ^1H NMR (500 MHz, $CDCl_3$) δ 0.04 (s, 3H, TBS major), 0.05 (s, 3H, TBS minor), 0.08 (s, 3H, TBS minor), 0.08 (s, 3H, TBS major), 0.90 (s, 9H, TBS major), 0.90 (s, 9H, TBS minor), 1.48–1.53 (m, 1H, H10), 1.82–1.89 (m, 1H, H19 minor), 1.91 (ddd, 1H, J=14.0, 9.5, 5.5 Hz, H19 major), 2.23–2.40 (m, 4H, H4, H10, H17, H19), 2.44 (dd, 1H, J=13.5, 4.0 Hz, H17), 2.64 (ddd, 1H, J=16.0, 8.0, 4.0 Hz, H4), 3.08–3.14 (m, 2H, H8, H9), 3.21–3.31 (m, 2H, H5, H11), 3.38 (t, 1H, J=9.0 Hz, H6), 3.44 (td, 1H, J=9.5, 4.5 Hz, H16), 3.52 (t, 1H, J=8.5 Hz, H7), 3.60 (ddd, 1H, J=10.0, 5.5, 5.0 Hz, H20), 3.85 (brdd, 1H, J=9.0, 2.0 Hz, H12), 3.95 (brdd, 1H, J=9.0, 2.0 Hz, H15), 4.02–4.08 (m, 2H, H1, H21), 4.11–4.20 (m, 1H, H18 major), 4.30 (dd, 1H, J=16.0, 6.0 Hz, H1), 4.41 (brdd, 1H, J=10.0, 7.5 Hz, H18 minor), 4.98 (d, 1H, J=12.0 Hz, NAP minor), 4.99 (d, 1H, J=12.0 Hz, NAP major), 5.03 (d, 1H, J=12.0 Hz, NAP minor), 5.04 (d, 1H, J=12.0 Hz, NAP major), 5.17–5.20 (m, 1H, H23), 5.27 (dt, 1H, J=17.0, 2.0 Hz, H23 minor), 5.29 (dt, 1H, J=17.0, 2.0 Hz, H23 major), 5.64 (ddd, 1H, J=12.0, 2.5 Hz, H14 minor), 5.67 (dt, 1H, J=12.5, 2.5 Hz, H14 major), 5.74–5.90 (m, 4H, H2, H3, H13, H22), 7.43–7.47 (m, 2H, NAP), 7.54 (dd, 1H, J=9.0, 2.0 Hz, NAP), 7.81–7.85 (m, 4H, NAP); FT-IR (film) ν 3024, 2955, 2929, 2857, 1645, 1603, 1509, 1471, 1462, 1455, 1361, 1338, 1257, 1091, 1032, 1007 cm^{-1}; MALDI-TOF MS $[M+Na]^+$ calcd for $C_{40}H_{53}NaClO_7Si$ 731.3147, found 731.3147.

4.4. General procedure of asymmetric aldol reaction in a model system

To a solution of amine (10 equiv.) in CH_2Cl_2 was added $TiCl_4$ (1.0 M solution in CH_2Cl_2, 4–6 equiv.) at −78 °C. The mixture was stirred for 30 min at −78 °C followed by the addition of amide **59**, **60**, or **61** (1 equiv.) and the stirring was continued for an additional 30 min at −78 °C. Freshly distilled acrolein (10 equiv.) was added and the resulting mixture was stirred for indicated times at indicated temperature as shown in Table 2. The reaction mixture was quenched with saturated NH_4Cl solution and the aqueous phase was extracted with AcOEt. The combined organic phase was washed with brine and dried over anhydrous Na_2SO_4. After concentration, the residue was purified by flash column chromatography to give a mixture of aldol products **62**, **63**, **64**, and recovery of amide **59**, **60**, or **61**. The aldol products were separated by HPLC for spectral analysis.

4.4.1. 20,21-*anti*-15,21-*syn* Aldol product of 59. Colorless oil; ^1H NMR (500 MHz, $CDCl_3$); δ 1.43 (ddd, 1H, J=23.0, 12.0, 5.5 Hz, H3) 1.58–1.64 (m, 2H, H2, H2) 1.99 (brdd, 1H, J=12.0, 3.0 Hz, H3), 2.29 (dt, 1H, J=15.0, 7.5 Hz, H6), 2.66–2.71 (m, 1H, H6), 2.72 (dd, 1H, J=13.5, 10.0 Hz, H13), 2.85 (d, 1H, J=9.0 Hz, OH), 3.21 (ddd, 1H, J=10.0, 8.5, 4.0 Hz, H4), 3.28–3.33 (m, 3H, H1, H5, H13), 3.87 (dt, 1H, J=11.0, 2.0 Hz, H1), 4.35–4.41 (m, 2H, H15, H15), 4.48 (dt, 1H, J=9.5, 6.0 Hz, H11), 5.01 (ddd, 1H, J=14.0, 7.0, 3.5 Hz, H14), 5.09 (d, 1H, J=9.5 Hz, H8), 5.14 (dd, 1H, J=17.0, 1.5 Hz, H8), 5.32 (dt, 1H, J=10.5, 1.0 Hz, H9), 5.42 (dt, 1H, J=17.5, 1.5 Hz, H9), 5.90 (dddd, 1H, J=17.5, 10.0, 8.0, 7.0 Hz, H7), 6.10 (ddd, 1H, J=17.5, 10.5, 6.0 Hz, H10), 6.30 (d, 1H, J=6.5 Hz, H12), 7.23–7.35 (m, 5H, Bn); ^{13}C NMR (125 MHz, $CDCl_3$) δ 25.45, 30.26, 36.70, 37.74, 60.63, 67.67, 71.28, 74.52, 78.11, 79.23, 79.86, 117.07, 117.81, 127.69, 129.23, 129.53, 135.09, 135.15, 136.29, 173.32, 186.21; FT-IR (film) ν 3481, 3073, 3028, 2930, 2855, 1711, 1642, 1497, 1454, 1369, 1326, 1285, 1197, 1161, 1098 1028, 963 cm^{-1}; MALDI-TOF MS $[M+Na]^+$ calcd for $C_{23}H_{29}NaNO_5S$ 454.1664, found 454.1661; $[\alpha]_D^{21.0}$ −112° (*c* 0.500, $CHCl_3$).

4.4.2. 20,21-*syn*-15,21-*syn* Aldol product of 59. Colorless oil; ^1H NMR (500 MHz, $CDCl_3$) δ 1.39 (tdd, 1H, J=13.0, 10.5, 5.0 Hz, H3), 1.66 (ddt, 1H, J=26.0, 13.5, 4.5 Hz, H2), 1.71–1.74 (m, 1H, H2), 2.27 (dt, 1H, J=15.0, 7.5 Hz, H6), 2.40 (brdd, 1H, J=12.0, 3.0 Hz, H3), 2.45 (d, 1H, J=7.0 Hz, OH), 2.82 (dd, 1H, J=13.0, 10.5 Hz, H13), 2.82–2.87 (m, 1H, H6), 3.21 (td, 1H, J=8.5, 4.0 Hz, H4), 3.25 (ddd, 1H, J=8.5, 3.0 Hz, H5), 3.35 (td, 1H, J=11.5, 2.5 Hz, H1), 3.37 (dd, 1H, J=13.0, 3.5 Hz, H13), 3.92 (ddt, 1H, J=11.0, 4.5, 1.5 Hz, H1), 4.26 (dd, 1H, J=9.0, 7.5 Hz, H15), 4.35 (dd, 1H, J=9.5, 2.0 Hz, H15), 4.44 (ddt, 1H, J=12.5, 5.5, 1.0 Hz, H11), 4.83 (dddd, 1H, J=10.0, 7.5, 4.0, 2.0 Hz, H14), 5.07 (ddt, 1H, J=10.5, 2.0, 1.0 Hz, H8), 5.16 (ddd, 1H, J=17.0, 4.0, 2.0 Hz, H8), 5.22 (dt, 1H, J=10.5, 1.5 Hz, H9), 5.36 (dt, 1H, J=17.5, 1.5 Hz, H9), 5.93 (ddt, 1H, J=17.5, 10.5, 7.5 Hz, H7), 6.01 (ddd, 1H, J=17.0, 11.0, 5.5 Hz, H10), 6.64 (d, 1H, J=5.5 Hz, H12), 7.22–7.36 (m, 5H, Bn); MALDI-TOF MS $[M+Na]^+$ calcd for $C_{23}H_{29}NaNO_5S$ 454.1664, found 454.1767.

4.4.3. 20,21-*syn*-15,21-*anti* Aldol product of 59. Colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.34 (tdd, 1H, J=12.5, 10.5, 4.5 Hz, H3), 1.64 (ddt, 1H, J=26.0, 12.5, 4.5 Hz, H2), 1.72 (brd, 1H, J=12.5 Hz, H2), 2.31 (dt, 2H, J=16.0, 8.0 Hz, H3, H6), 2.46 (d, 1H, J=8.5 Hz, OH), 2.84 (dd, 1H, J=13.0, 10.0 Hz, H13), 2.88 (dddt, 1H, J=14.5, 6.5, 2.5, 1.5 Hz, H6), 3.21 (td, 1H, J=8.5, 4.5 Hz, H4), 3.26 (td, 1H, J=8.5, 3.0 Hz, H5), 3.34 (td, 1H, J=11.5, 2.5 Hz, H1), 3.36 (dd, 1H, J=13.0, 3.5 Hz, H13), 3.91 (brdd, 1H, J=11.5, 5.0 Hz, H1), 4.30 (dd, 1H, J=9.5, 7.5 Hz, H15), 4.37 (dd, 1H, J=9.0, 2.0 Hz, H15) 4.50 (brs, 1H, H11), 4.87 (dddd, 1H, J=10.0, 7.5, 3.5, 2.0 Hz, H14), 5.08 (dd, 1H, J=10.5, 1.5 Hz, H8), 5.17 (dd, 1H, J=17.0, 1.5 Hz, H8), 5.24 (d, 1H, J=10.5 Hz, H9), 5.36 (d, 1H, J=17.0 Hz, H9), 5.90–5.99 (m, 2H, H7, H10), 6.43 (d, 1H, J=3.5 Hz, H12), 7.23–7.36 (m, 5H, Bn); ^{13}C NMR (125 MHz, $CDCl_3$) δ 25.22, 29.08, 36.71, 37.70, 61.02, 67.68, 71.13, 73.83, 76.03, 76.31, 80.15, 116.64, 117.24, 127.65, 129.16, 129.49, 135.07, 135.65, 136.51, 171.54, 185.60; FT-IR (film) ν 3431, 3073, 3028, 2938, 2854, 1714, 1641, 1604, 1497, 1454, 1364, 1327, 1285, 1196, 1098, 960 cm^{-1}; MALDI-TOF MS $[M+Na]^+$ calcd for $C_{23}H_{29}NaNO_5S$ 454.1664, found 454.1735; $[\alpha]_D^{22.0}$ +21.1° (c 2.04, $CHCl_3$).

4.4.4. 20,21-*anti*-15,21-*syn* Aldol product of 60. Colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.41–1.51 (m, 1H, H3), 1.64–1.69 (m, 2H, H2, H2), 2.16 (brd, 1H, J=12.5 Hz, H3), 2.32 (dt, 1H, J=14.5, 7.5 Hz, H6), 2.39 (d, 1H, J=7.0 Hz, OH), 2.68 (ddt, 1H, J=14.5, 6.5, 1.0 Hz, H6), 2.77 (dd, 1H, J=13.0, 10.5 Hz, H15), 3.30–3.39 (m, 4H, H1, H4, H5, H15), 3.89 (brdt, 1H, J=11.5, 2.0 Hz, H1), 4.27 (dd, 1H, J=9.5, 7.5 Hz, H13), 4.36 (dd, 1H, J=9.5, 2.0 Hz, H13), 4.44 (dd, 1H, J=13.0, 6.0 Hz, H11), 4.85 (dddd, 1H, J=11.0, 7.5, 3.5, 2.0 Hz, H14), 5.10 (dd, 1H, J=10.0, 1.0 Hz, H8), 5.14 (dd, 1H, J=17.5, 1.5 Hz, H8), 5.27 (d, 1H, J=10.5 Hz, H9), 5.39 (brd, 1H, J=17.0 Hz, H9), 5.92 (dddd, 1H, J=17.0, 10.0, 7.0, 6.0 Hz, H7), 6.02 (ddd, 1H, J=17.5, 11.0, 5.5 Hz, H10), 6.52 (d, 1H, J=5.5 Hz, H12), 7.23–7.36 (m, 5H, Bn); ^{13}C NMR (125 MHz, $CDCl_3$) δ 25.50, 30.47, 36.83, 37.76, 60.95, 67.73, 71.13, 74.09, 77.85, 79.16, 79.79, 116.99, 117.54, 127.71, 129.24, 129.56, 135.12, 135.22, 135.96, 173.19, 186.22; FT-IR (film) ν 3400, 3073, 3028, 2933, 2855, 1705, 1641, 1497, 1454, 1364, 1327, 1285, 1196, 1098, 961 cm^{-1}; MALDI-TOF MS $[M+Na]^+$ calcd for $C_{23}H_{29}NaNO_5S$ 454.1664, found 454.1757; $[\alpha]_D^{22.2}$ +37.7° (c 0.395, $CHCl_3$).

4.4.5. 20,21-*syn*-15,21-*syn* Aldol product of 60. Colorless oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.49 (ddd, 1H, J=23.0, 12.0, 5.5 Hz, H3), 1.60–1.70 (m, 2H, H2, H2), 2.16 (brdd, 1H, J=12.5, 3.0 Hz, H3), 2.29 (dt, 1H, J=14.5, 7.0 Hz, H6), 2.50 (brd, 1H, J=8.0 Hz, OH), 2.66 (dddt, 1H, J=14.5, 6.5, 3.5, 1.5 Hz, H6), 2.81 (dd, 1H, J=13.5, 10.0 Hz, H15), 3.26–3.31 (m, 1H, H4), 3.33–3.37 (m, 3H, H1, H5, H15), 3.89 (ddt, 1H, J=11.5, 4.0, 2.0 Hz, H1), 4.30 (dd, 1H, J=8.5, 7.5 Hz, H13), 4.37 (dd, 1H, J=9.0, 1.0 Hz, H13), 4.50 (brs, 1H, H11), 4.86 (dddd, 1H, J=10.5, 7.0, 3.0, 2.0 Hz, H14), 5.10 (d, 1H, J=10.5 Hz, H8), 5.14 (dd, 1H, J=17.5, 1.5 Hz, H8), 5.27 (d, 1H, J=11.0 Hz, H9), 5.39 (d, 1H, J=17.5 Hz, H9), 5.91 (ddt, 1H, J=17.0, 10.0, 7.0 Hz, H7), 6.00 (ddd, 1H, J=17.0, 10.0, 5.5 Hz, H10), 6.37 (d, 1H, J=3.5 Hz, H12), 7.23–7.36 (m, 5H, Bn); ^{13}C NMR (125 MHz, $CDCl_3$) δ 25.48, 30.25, 36.86, 37.62, 61.00, 67.67, 71.09, 74.13, 78.50, 79.59, 79.93, 116.99, 117.56, 127.70, 129.22, 129.55, 135.09, 135.15, 136.35, 172.38, 185.54; FT-IR (film) ν 3468, 3074, 3028, 2931, 2855, 1714, 1642, 1497, 1454, 1366, 1327, 1286, 1196, 1098, 958 cm^{-1}; MALDI-TOF MS $[M+Na]^+$ calcd for $C_{23}H_{29}NaO_5S$ 454.1664, found 454.1793; $[\alpha]_D^{23.0}$ +51.8° (c 1.10, $CHCl_3$).

4.4.6. 20,21-*anti*-15,21-*syn* Aldol product of 61. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.36 (brddd, 1H, J=23.0, 13.0, 5.0 Hz, H3), 1.57–1.72 (m, 2H, H2, H2), 2.11 (brdt, 1H, J=12.5, 3.0 Hz, H3), 2.30 (dt, 1H, J=14.5, 7.0 Hz, H6), 2.56 (d, 1H, J=7.5 Hz, OH), 2.65–2.70 (m, 1H, H6), 2.80 (dd, 1H, J=13.0, 10.0 Hz, H13), 3.25 (ddd, 1H, J=10.0, 8.5, 4.0 Hz, H4), 3.32–3.40 (m, 3H, H1, H5, H15), 3.89–3.92 (m, 1H, H1), 4.23–4.27 (m, 2H, H13), 4.37–4.40 (m, 1H, H11), 4.66–4.71 (m, 1H, H14), 5.11 (brd, 1H, J=10.5 Hz, H8), 5.15 (dt, 1H, J=17.0, 1.5 Hz, H8), 5.28 (dt, 1H, J=11.0, 1.5 Hz, H9), 5.30 (d, 1H, J=3.5 Hz, H12), 5.39 (dt, 1H, J=17.0, 1.5 Hz, H9), 5.88–5.94 (m, 1H, H7), 5.98 (ddd, 1H, J=17.0, 11.0, 6.0 Hz, H10), 7.24–7.38 (m, 5H, Bn); MALDI-TOF MS $[M+Na]^+$ calcd for $C_{23}H_{29}NNaO_6$ 438.1893, found 438.1861.

4.4.7. 20,21-*syn*-15,21-*syn* Aldol product of 61. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.51 (brddd, 1H, J=23.0, 12.0, 5.0 Hz, H3), 1.60–1.71 (m, 2H, H2, H2), 2.11 (brdt, 1H, J=12.5, 3.0 Hz, H3), 2.30 (dt, 1H, J=14.5, 7.0 Hz, H6), 2.56 (d, 1H, J=7.5 Hz, OH), 2.65–2.70 (m, 1H, H6), 2.80 (dd, 1H, J=13.0, 10.0 Hz, H13), 3.25 (ddd, 1H, J=10.0, 8.5, 4.0 Hz, H4), 3.32–3.40 (m, 3H, H1, H5, H15), 3.89–3.92 (m, 1H, H1), 4.23–4.27 (m, 2H, H13), 4.37–4.40 (m, 1H, H11), 4.66–4.71 (m, 1H, H14), 5.11 (brd, 1H, J=10.5 Hz, H8), 5.15 (dt, 1H, J=17.0, 1.5 Hz, H8), 5.28 (dt, 1H, J=11.0, 1.5 Hz, H9), 5.30 (d, 1H, J=3.5 Hz, H12), 5.39 (dt, 1H, J=17.0, 1.5 Hz, H9), 5.88–5.94 (m, 1H, H7), 5.98 (ddd, 1H, J=17.0, 11.0, 6.0 Hz, H10), 7.24–7.38 (m, 5H, Bn); ^{13}C NMR (125 MHz, $CDCl_3$) δ 25.46, 30.20, 36.81, 37.90, 55.71, 67.07, 67.65, 74.06, 79.06, 79.56, 79.88, 117.02, 117.49, 127.64, 129.16, 129.52, 135.05, 135.09, 136.49, 153.68, 171.21; FT-IR (film) ν 3480, 3074, 3029, 2933, 2855, 1770, 1713, 1642, 1604, 1496, 1481, 1454, 1392, 1350, 1211, 1097, 999, 920 cm^{-1}; MALDI-TOF MS $[M+Na]^+$ calcd for $C_{23}H_{29}NNaO_6$ 438.1893, found 438.1846; $[\alpha]_D^{22.6}$ +59.0° (c 1.85, $CHCl_3$).

4.4.8. 20,21-*syn*-15,21-*anti* Aldol product of 61. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.33 (brddd, 1H, J=23.5, 12.5, 4.5 Hz, H3), 1.56–1.72 (m, 2H, H2, H2), 2.24 (brdt, 1H, J=13.0, 3.5 Hz, H3), 2.30 (dt, 1H, J=15.0, 7.0 Hz, H6), 2.52 (d, 1H, J=8.0 Hz, OH), 2.81 (dd, 1H, J=13.5, 9.5 Hz, H13), 2.90–2.95 (m, 1H, H6), 3.12 (ddd, 1H, J=10.5, 8.5, 4.0 Hz, H4), 3.25–3.30 (m, 2H, H5, H13), 3.35 (td, 1H, J=12.0, 2.0 Hz, H1), 3.92 (brdd, 1H, J=11.0, 4.5 Hz, H1), 4.26 (dd, 1H, J=9.5, 3.5 Hz, H15), 4.32 (dd, 1H, J=9.0, 8.5 Hz, H15), 4.48–4.51 (m, 1H, H11), 4.78–4.83 (m, 1H, H14), 5.10 (brdd, 1H, J=10.0, 1.0 Hz, H8), 5.18 (brd, 1H, J=17.0, 1.5 Hz, H8), 5.28 (brd, 1H, J=11.5 Hz, H9), 5.35 (d, 1H, J=3.0 Hz, H12), 5.41 (brd, 1H, J=17.5 Hz, H9), 5.92–6.00 (m, 1H, H7), 5.99 (ddd, 1H, J=17.5, 11.0, 6.0 Hz, H10), 7.25–7.38 (m, 5H, Bn); FT-IR (film) ν 3525, 3073, 2938, 2855, 1775, 1715, 1640, 1497, 1454, 1393, 1352, 1275, 1215, 1099, 1052, 995 cm^{-1}; ^{13}C NMR (125 MHz, $CDCl_3$) δ 25.25, 28.97, 36.76, 37.79, 55.09,

66.99, 67.75, 73.68, 76.31, 76.46, 80.26, 116.58, 117.27, 127.61, 129.14, 129.64, 134.88, 135.83, 136.81, 153.76, 170.32; MALDI-TOF MS $[M+Na]^+$ calcd for $C_{23}H_{29}NNaO_6$ 438.1893, found 438.1879; $[\alpha]_D^{22.6}$ +115° (*c* 0.445, $CHCl_3$).

4.5. Stereocontrolled synthesis of the ABCDE ring moiety

4.5.1. Ester 65. To a solution of alcohol **40** (93.4 mg, 0.190 mmol) in THF (5 ml) and DMF (1.3 ml) was added NaH (60% dispersion in mineral oil, 15.2 mg, 0.381 mmol) at 0 °C. After stirring for 5 min, *t*-butyl bromoacetate (54.1 μl, 0.571 mmol) was added and the resulting mixture was stirred for 10 h at room temperature. The reaction mixture was quenched with saturated NH_4Cl solution and the aqueous phase was extracted with AcOEt. The combined organic phase was washed with brine and dried over anhydrous Na_2SO_4. After concentration, the residue was purified by flash column chromatography (silica gel, hexane–hexane/AcOEt=10–5–1) to give ester **65** (106 mg, 0.175 mmol, 92%). **65**: colorless solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.49 (s, 9H, *t*Bu), 1.49–1.60 (m, 1H, H10), 2.24 (dt, 1H, *J*=15.0, 8.0 Hz, H17), 2.32–2.37 (m, 2H, H4, H10), 2.61–2.67 (m, 2H, H4, H17), 3.09–3.16 (m, 2H, H8, H9), 3.26–3.32 (m, 2H, H5, H11), 3.37 (t, 1H, *J*=8.5 Hz, H6), 3.48 (td, 1H, *J*=9.5, 3.0 Hz, H16), 3.53 (t, 1H, *J*=8.5 Hz, H7), 3.87 (d, 2H, *J*=8.5 Hz, H12, H15), 4.00 (d, 1H, *J*=16.0 Hz, H21), 4.03 (brd, 1H, *J*=16.5 Hz, H1), 4.06 (d, 1H, *J*=16.5 Hz, H21), 4.31 (dd, 1H, *J*=15.5, 6.0 Hz, H1), 4.99 (d, 1H, *J*=12.0 Hz, NAP), 5.04 (d, 2H, *J*=11.5 Hz, CH_2=CH-, NAP), 5.09 (dd, 1H, *J*=17.5, 2.0 Hz, CH_2=CH–), 5.75–5.91 (m, 5H, H2, H3, H13, H14, H18), 7.43–7.48 (m, 2H, NAP), 7.55 (dd, 1H, *J*=8.5, 1.5 Hz, NAP), 7.81–7.85 (m, 4H, NAP); ^{13}C NMR (125 MHz, $CDCl_3$) δ 28.26, 34.76, 36.73, 37.27, 67.95, 68.52, 73.34, 75.32, 78.59, 80.56, 81.11, 81.91, 81.97, 82.24, 83.60, 87.62, 116.96, 125.76, 126.01, 126.21, 126.42, 126.91, 127.80, 127.98, 128.02, 131.50, 131.71, 132.37, 133.11, 133.44, 135.23, 136.85, 169.21; FT-IR (film) ν 2977, 2876, 1750, 1452, 1368, 1301, 1228, 1131, 1098, 1008, 956, 915, 851, 817 cm^{-1}; MALDI-TOF MS $[M+Na]^+$ calcd for $C_{36}H_{44}NaO_8$ 627.2934, found 627.2738; $[\alpha]_D^{24.5}$ +24.0° (*c* 0.460, $CHCl_3$).

4.5.2. Carboxylic acid 66. To a solution of ester **65** (66.1 mg, 0.109 mmol) in THF (3.3 ml) was added HCl (10 M, 1.64 ml, 16.4 mmol) at 0 °C. The mixture was warmed to 30 °C and stirred for 23 h. The reaction mixture was diluted with water and AcOEt. Aqueous phase was extracted with AcOEt and the combined organic phase was dried over anhydrous Na_2SO_4. After concentration, the residue was purified by flash column chromatography (silica gel, hexane/AcOEt=5–1) to give carboxylic acid **66** (48.4 mg, 88.2 μmol, 81%). **66**: colorless powder; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.54 (q, 1H, *J*=11.5 Hz, H10), 2.26 (dt, 1H, *J*=15.0, 7.5 Hz, H17), 2.31–2.38 (m, 2H, H4, H10), 2.55–2.60 (m, 1H, H17), 2.63 (ddd, 1H, *J*=16.5, 7.5, 4.0 Hz, H4), 3.09–3.16 (m, 2H, H8, H9), 3.26–3.33 (m, 2H, H5, H11), 3.39 (t, 1H, *J*=9.0 Hz, H6), 3.52 (td, 1H, *J*=9.0, 3.5 Hz, H16), 3.54 (t, 1H, *J*=8.5 Hz, H7), 3.87 (brdd, 1H, *J*=8.5, 2.0 Hz, H12), 3.95 (brdd, 1H, J=8.5, 2.0 Hz, H15), 4.04 (brdd, 1H, *J*=15.5, 2.5 Hz, H1), 4.15 (d, 1H, *J*=16.5 Hz, H21), 4.24 (d, 1H, *J*=16.5 Hz, H21), 4.31 (dd, 1H, *J*=16.0, 6.0 Hz, H1), 4.99 (d, 1H, *J*=12.0 Hz, NAP), 5.04 (d, 1H, *J*=12.0 Hz, NAP), 5.07 (brd, 1H, *J*=11.5 Hz, CH_2=CH–), 5.09 (brd, 1H, *J*=17.5 Hz, CH_2=CH–), 5.74–5.80 (m, 2H, H3, H13), 5.82–5.92 (m, 3H, H2, H14, H18), 7.44–7.47 (m, 2H, NAP), 7.54 (dd, 1H, *J*=9.0, 1.5 Hz, NAP), 7.81–7.84 (m, 4H, NAP); FT-IR (KBr) ν 3026, 2961, 2885, 1742, 1602, 1436, 1355, 1261, 1094, 1024, 806 cm^{-1}; MALDI-TOF MS $[M+Na]^+$ calcd for $C_{32}H_{36}NaO_8$ 571.2308, found 571.2390; $[\alpha]_D^{21.0}$ −1.1° (*c* 0.400, $CHCl_3$).

4.5.3. Amide 70. A solution of carboxylic acid **66** (48.4 mg, 88.2 μmol) and Et_3N (86.1 μl, 0.618 mmol) in CH_2Cl_2 (3 ml) was cooled to −78 °C. PivCl (109 μl, 0.882 mmol) was added and the mixture was stirred for 1 h at 0 °C to produce a mixed anhydride **67**. In another flask, to a solution of (*S*)-4-benzyl oxazolidinethione **68** (141 mg, 0.730 mmol) in THF (3 ml) was added *n*-BuLi (1.56 M solution in hexane, 340 μl, 0.529 mmol) at −78 °C. The solution was stirred for 15 min at −78 °C and transferred into the cooled solution of the mixed anhydride **67** *via* cannula at −78 °C. After stirring for 15 min at −78 °C, the mixture was warmed to 0 °C and the stirring was continued for an additional 1 h. The reaction mixture was quenched with saturated NH_4Cl solution and the aqueous phase was extracted with AcOEt. The combined organic phase was washed with brine and dried over anhydrous Na_2SO_4. After concentration, the residue was purified by flash column chromatography (silica gel, hexane–hexane/AcOEt=5–4–3) and then HPLC to give amide **70** (32.4 mg, 44.8 μmol, 51%). **70**: colorless solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.51–1.57 (m, 1H, H10), 2.27–2.36 (m, 3H, H4, H10, H17), 2.64 (ddd, 1H, *J*=16.5, 8.0, 4.0 Hz, H4), 2.65–2.71 (m, 1H, H17), 2.81 (dd, 1H, *J*=13.0, 9.5 Hz, auxiliary), 3.10–3.17 (m, 2H, H8, H9), 3.26–3.35 (m, 3H, H5, H11, auxiliary), 3.38 (t, 1H, *J*=8.0 Hz, H6), 3.54 (t, 1H, *J*=8.0 Hz, H7), 3.57 (td, 1H, *J*=8.0, 3.0 Hz, H16), 3.89 (brdd, 1H, *J*=9.0, 2.0 Hz, H12), 3.96 (brdd, 1H, *J*=9.0, 2.0 Hz, H15), 4.04 (brdd, 1H, *J*=16.0, 2.5 Hz, H1), 4.31 (dd, 1H, *J*=16.0, 6.0 Hz, H1), 4.37–4.42 (m, 2H, auxiliary), 4.95 (tt, 1H, *J*=10.0, 4.0 Hz, auxiliary), 4.99 (d, 1H, *J*=12.0 Hz, NAP), 5.04 (d, 1H, *J*=12.0 Hz, NAP), 5.04 (d, 1H, *J*=17.5 Hz, H21), 5.05–5.08 (m, 1H, CH_2=CH–), 5.11 (brdd, 1H, *J*=17.5, 2.0 Hz, CH_2=CH–), 5.21 (d, 1H, *J*=18.0 Hz, H21), 5.75–5.80 (m, 1H, H3), 5.82 (dt, 1H, *J*=13.0, 2.0 Hz, H4), 5.85–5.89 (m, 1H, H2), 5.89 (dt, 1H, *J*=12.5, 2.5 Hz, H13), 5.89–5.95 (m, 1H, H18), 7.22–7.36 (m, 5H, auxiliary), 7.43–7.47 (m, 2H, NAP), 7.55 (dd, 1H, *J*=8.5, 1.5 Hz, NAP), 7.81–7.84 (m, 4H, NAP); ^{13}C NMR (125 MHz, $CDCl_3$) δ 34.77, 36.76, 37.29, 37.68, 60.05, 68.53, 71.40, 71.60, 73.33, 75.34, 78.56, 80.57, 81.14, 81.88, 82.24, 83.50, 87.63, 117.12, 125.77, 126.02, 126.21, 126.42, 126.90, 127.70, 127.80, 128.00, 128.02, 129.25, 129.55, 131.49, 132.75, 133.12, 133.44, 135.08, 135.15, 136.84, 170.57, 184.84; FT-IR (film) ν 3027, 2878, 1714, 1367, 1330, 1207, 1167, 1096, 1011, 963, 911, 857, 818 cm^{-1}; MALDI-TOF MS $[M+Na]^+$ calcd for $C_{42}H_{45}NNaO_8S$ 746.2764, found 746.2737; $[\alpha]_D^{22.0}$ +66.3° (*c* 0.530, $CHCl_3$).

4.5.4. Amide 71. A solution of carboxylic acid **66** (70.2 mg, 0.128 mmol) and Et_3N (154 μl, 1.11 mmol) in CH_2Cl_2 (5 ml) was cooled to −78 °C. PivCl (195 μl, 1.58 mmol)

was added and the mixture was stirred for 1 h at 0 °C to produce a mixed anhydride **66**. In another flask, to a solution (*S*)-4-benzyl oxazolidinone **69** (168 mg, 0.948 mmol) in THF (5 ml) was added *n*-BuLi (1.56 M solution in hexane, 506 μl, 0.79 mmol) at −78 °C. The solution was stirred for 15 min at −78 °C and transferred into the cooled solution of the mixed anhydride **67** *via* cannula at −78 °C. After stirring for 15 min at −78 °C, the mixture was warmed to 0 °C and the stirring was continued for an additional 30 min. The reaction mixture was quenched with saturated NH_4Cl solution and the aqueous phase was extracted with AcOEt. The combined organic phase was washed with brine and dried over anhydrous Na_2SO_4. After concentration, the residue was purified by flash column chromatography (silica gel, hexane/AcOEt=10–5–1) to give amide **71** (87.4 mg, 0.123 μmol, 96%). **71**: colorless solid; mp 160 °C (hexane–EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.54 (dd, 1H, J=11.5 Hz, H10), 2.26–2.37 (m, 3H, H4, H10, H17), 2.64 (ddd, 1H, J=16.5, 8.0, 4.0 Hz, H4), 2.66–2.67 (m, 1H, H17), 2.82 (dd, 1H, J=13.5, 10.0 Hz, auxiliary), 3.10–3.17 (m, 2H, H8, H9), 3.28 (td, 1H, J=9.0, 4.0 Hz, H5), 3.29–3.33 (m, 1H, H11), 3.35 (dd, 1H, J=13.0, 3.5 Hz, auxiliary), 3.38 (t, 1H, J=9.0 Hz, H6), 3.53 (t, 1H, J=8.5 Hz, H7), 3.56 (td, 1H, J=8.5, 2.5 Hz, H16), 3.89 (brdd, 1H, J=9.5, 2.0 Hz, H12), 3.96 (brdd, 1H, J=9.0, 2.0 Hz, H15), 4.04 (brdd, 1H, J=15.5, 3.0 Hz, H1), 4.24 (dd, 1H, J=8.5, 3.0 Hz, auxiliary), 4.28–4.29 (m, 1H, auxiliary), 4.32 (dd, 1H, J=9.5, 6.0 Hz, H1), 4.67–4.72 (m, 1H, auxiliary), 4.71 (d, 1H, J=17.5 Hz, H21), 4.81 (d, 1H, J=18.0 Hz, H21), 4.99 (d, 1H, J=12.0 Hz, NAP), 5.04 (d, 1H, J=11.5 Hz, NAP), 5.05–5.07 (m, 1H, CH_2=*CH*–), 5.11 (brdd, 1H, J=18.0, 2.0 Hz, CH_2=*CH*–), 5.75–5.95 (m, 5H, H2, H3, H13, H14, H18), 7.21–7.36 (m, 5H, auxiliary), 7.43–7.85 (m, 8H, NAP); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.26, 22.79, 29.18, 30.07, 31.72, 34.77, 36.74, 37.28, 37.92, 45.03, 55.03, 62.22, 67.48, 68.52, 69.59, 73.34, 75.33, 76.94, 78.57, 80.56, 81.12, 81.96, 82.25, 83.49, 87.62, 117.06, 125.76, 126.01, 126.21, 126.43, 126.90, 127.65, 127.80, 127.99, 128.03, 129.19, 129.54, 131.47, 131.50, 132.67, 133.12, 133.44, 135.03, 135.17, 136.85, 153.54, 169.72; FT-IR (film) ν 3020, 2881, 1786, 1714, 1642, 1390, 1351, 1297, 1260, 1213, 1139, 1099, 1010, 976, 922, 858, 821, 755, 705 cm^{-1}; ESI-TOF MS $[M+NH_4]^+$ calcd for $C_{42}H_{49}N_2O_9$ 725.3438, found 725.3390; $[\alpha]^{22.0}_D$ +44.5° (*c* 1.03, $CHCl_3$).

4.5.5. Aldol reaction of 70. To a solution of Et_3N (102 μl, 0.732 mmol) in CH_2Cl_2 (2 ml) was added $TiCl_4$ (1.0 M solution in CH_2Cl_2, 366 μl, 0.366 mmol) at −78 °C. A solution of amide **70** (26.5 mg, 36.6 μmol) in CH_2Cl_2 (6 ml) was then added, and the resulting mixture was stirred for 30 min at −78 °C. To the resulting violet solution, freshly distilled acrolein (49.0 μl, 0.732 mmol) was added, and the stirring was continued for 20 min at −78 °C. The reaction mixture was quenched with saturated NH_4Cl solution and the aqueous phase was extracted with AcOEt. The combined organic phase was washed with brine and dried over anhydrous Na_2SO_4. After concentration, the residue was purified by flash column chromatography (silica gel, hexane/AcOEt=3–1) to give a mixture of aldol products **72** and **73** (21.7 mg, 27.8 μmol, 76%) and recovery of **70** (4.0 mg, 5.5 μmol, 15%). The aldol products were further separated by HPLC to give 20,21-*syn*-15,21-*syn* isomer **73** (16.5 mg, 21.1 μmol, 58%) and 20,21-*anti*-15,21-*syn* isomer **72** (4.2 mg, 5.39 μmol, 15%). **72**: colorless solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.53 (dd, 1H, J=11.0 Hz, H10), 2.24–2.31 (m, 1H, H17), 2.31–2.36 (m, 2H, H4, H10), 2.43 (d, 1H, J=6.5 Hz, OH), 2.60–2.66 (m, 2H, H4, H17), 2.81 (dd, 1H, J=13.0, 10.0 Hz, auxiliary), 3.09–3.16 (m, 2H, H8, H9), 3.27 (td, 1H, J=10.0, 4.0 Hz, H5), 3.32–3.35 (m, 1H, H11), 3.36 (t, 1H, J=9.0 Hz, H6), 3.35–3.40 (m, 1H, auxiliary), 3.51 (t, 1H, J=8.5 Hz, H7), 3.56 (td, 1H, J=8.0, 3.0 Hz, H16), 3.88 (brdd, 1H, J=9.5, 2.5 Hz, H12), 4.02 (brdd, 1H, J=15.5, 2.5 Hz, H1), 4.11–4.14 (m, 1H, H15), 4.26 (brt, 1H, J=8.0 Hz, auxiliary), 4.30 (dd, 1H, J=15.5, 6.0 Hz, H1), 4.36 (dd, 1H, J=9.5, 2.0 Hz, auxiliary), 4.50 (brdd, 1H, J=12.0, 6.0 Hz, H20), 4.85 (dddd, 1H, J=10.0, 7.0, 3.5, 2.0 Hz, auxiliary), 4.95 (d, 1H, J=12.5 Hz, NAP), 5.00 (d, 1H, J=12.0 Hz, NAP), 5.08 (dd, 1H, J=10.5, 2.0 Hz, CH_2=CH–), 5.12 (brdd, 1H, J=17.0, 2.0 Hz, CH_2=CH–), 5.27 (dt, 1H, J=11.0, 1.5 Hz, CH_2=CH–), 5.41 (dt, 1H, J=17.0, 1.5 Hz, CH_2=CH–), 5.76–5.79 (m, 2H, H3, H14), 5.84–5.93 (m, 3H, H2, H13, H18), 6.03 (ddd, 1H, J=17.0, 10.0, 5.0 Hz, H19), 6.70 (d, 1H, J=5.0 Hz, H21), 7.23–7.36 (m, 5H, auxiliary), 7.40–7.44 (m, 2H, NAP), 7.52 (dd, 1H, J=8.5, 2.0 Hz, NAP), 7.77–7.81 (m, 4H, NAP); ^{13}C NMR (125 MHz, $CDCl_3$) δ 34.78, 36.72, 37.28, 37.85, 61.00, 68.54, 71.15, 73.32, 75.29, 78.47, 79.30, 80.52, 81.21, 82.20, 82.39, 83.57, 87.58, 117.25, 117.70, 125.74, 126.00, 126.19, 126.39, 126.88, 127.75, 127.79, 127.97, 128.02, 129.27, 129.60, 131.51, 131.83, 132.67, 133.10, 134.99, 135.07, 135.64, 136.85, 172.47; FT-IR (film) ν 3452, 2876, 1707, 1366, 1327, 1197, 1160, 1097, 962, 856, 818 cm^{-1}; MALDI-TOF MS $[M+Na]^+$ calcd for $C_{45}H_{49}NaNO_9S$ 802.3026, found 802.3214. **73**: colorless solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.53 (dd, 1H, J=11.0 Hz, H10), 2.22 (brdt, 1H, J=15.0, 8.0 Hz, H17), 2.31–2.36 (m, 2H, H4, H10), 2.45 (d, 1H, J=8.5 Hz, OH), 2.58–2.64 (m, 1H, H17), 2.63 (ddd, 1H, J=16.5, 8.0, 4.0 Hz, H4), 2.84 (dd, 1H, J=13.0, 10.0 Hz, auxiliary), 3.09–3.16 (m, 2H, H8, H9), 3.28 (td, 1H, J=10.0, 4.0 Hz, H5), 3.33–3.40 (m, 3H, H6, H11, auxiliary), 3.52 (t, 1H, J=8.5 Hz, H7), 3.56 (td, 1H, J=9.0, 2.5 Hz, H16), 3.87 (ddt, 1H, J=9.0, 2.5, 2.0 Hz, H12), 4.01–4.05 (m, 2H, H1, H15), 4.30 (dd, 1H, J=15.5, 6.0 Hz, H1), 4.31 (dd, 1H, J=9.5, 8.0 Hz, auxiliary), 4.37 (dd, 1H, J=9.0, 2.0 Hz, auxiliary), 4.54–4.58 (m, 1H, H20), 4.89 (dddd, 1H, J=9.5, 7.5, 3.5, 2.0 Hz, auxiliary), 4.95 (d, 1H, J=12.5 Hz, NAP), 5.00 (d, 1H, J=12.0 Hz, NAP), 5.08 (dd, 1H, J=10.5, 2.0 Hz, CH_2=CH–), 5.11 (brdd, 1H, J=17.5, 1.5 Hz, CH_2=CH–), 5.29 (dt, 1H, J=10.0, 1.5 Hz, CH_2=CH–), 5.41 (dt, 1H, J=17.5, 1.5 Hz, CH_2=CH–), 5.74–5.81 (m, 2H, H3, H14), 5.84–5.92 (m, 2H, H2, H18), 5.98–6.01 (m, 1H, H13), 6.02 (ddd, 1H, J=18.0, 11.0, 6.0 Hz, H19), 6.52 (d, 1H, J=3.0 Hz, H21), 7.23–7.36 (m, 5H, auxiliary), 7.40–7.45 (m, 2H, NAP), 7.52 (dd, 1H, J=9.0, 1.5 Hz, NAP), 7.80 (brt, 4H, J=8.5 Hz, NAP); ^{13}C NMR (125 MHz, $CDCl_3$) δ 34.78, 36.71, 37.25, 37.70, 61.06, 68.53, 71.14, 73.31, 75.28, 78.40, 80.27, 80.49, 81.23, 82.18, 82.68, 83.75, 87.57, 117.28, 117.59, 125.74, 126.00, 126.19, 126.38, 126.87, 127.75, 127.79, 127.97, 128.02, 129.26, 129.60, 131.51, 131.90, 132.46, 133.09, 133.42, 134.92, 135.07, 136.39, 136.84, 171.86; FT-IR (film) ν 3462, 3027, 2876, 1710, 1452, 1366, 1328, 1197, 1160, 1097, 1013, 961, 912, 857, 819 cm^{-1}; MALDI-TOF MS $[M+Na]^+$ calcd for $C_{45}H_{49}NaNO_9S$ 802.3026, found 802.3301.

4.5.6. Synthesis of the ABCDE ring moiety (5) from 72. To a solution of amide **72** (4.2 mg, 5.4 μmol) in THF (1 ml) was added a solution of $NaBH_4$ (1.0 mg, 27 μmol) in water (0.25 ml). The mixture was stirred for 10 min at room temperature and quenched with saturated NH_4Cl solution. Aqueous phase was extracted with AcOEt and the combined organic phase was washed with brine and dried over anhydrous Na_2SO_4. After concentration, the residue was purified by flash column chromatography (silica gel, hexane/AcOEt=2–1–0.5) to give a corresponding diol (2.7 mg, 4.6 μmol, 85%).

A solution of the diol (2.7 mg, 4.6 μmol) in CH_2Cl_2 (1 ml) was added the Grubbs catalyst **37** (0.4 mg, 0.457 μmol). The mixture was stirred for 30 min at room temperature and concentrated. The residue was purified by flash column chromatography (silica gel, hexane/AcOEt=1–0.5–0.33) to give the ABCDE ring moiety **5** (2.1 mg, 3.7 μmol, 82%). **5**: colorless solid; mp 126–126.5 °C (hexane–AcOEt); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.52 (q, 1H, J=11.5 Hz, H10), 2.18–2.24 (brs, 2H, OH), 2.25–2.38 (m, 3H, H4, H10, H17), 2.63 (ddd, 1H, J=16.5, 8.0, 4.0 Hz, H4), 2.67 (ddd, 1H, J=13.0, 9.5, 3.5 Hz, H17), 3.09–3.12 (m, 2H, H8, H9), 3.24 (ddd, 1H, J=12.0, 9.5, 4.5 Hz, H11), 3.28 (td, 1H, J=9.5, 4.0 Hz, H5), 3.37 (t, 1H, J=8.5 Hz, H6), 3.41 (m, 1H, H21), 3.52 (t, 1H, J=8.5 Hz, H7), 3.61 (td, 1H, J=9.0, 3.0 Hz, H16), 3.77–3.83 (m, 3H, H12, H22, H22), 4.04 (brdd, 1H, J=15.5, 2.5 Hz, H1), 4.14 (brdd, 1H, J=8.5, 2.5 Hz, H15), 4.31 (dd, 1H, J=15.5, 6.0 Hz, H1), 4.46 (brd, 1H, J=6.5 Hz, H20), 4.98 (d, 1H, J=12.5 Hz, NAP), 5.02 (d, 1H, J=12.5 Hz, NAP), 5.64 (dt, 1H, J=13.0, 2.5 Hz, H14), 5.71–5.81 (m, 4H, H2, H3, H13, H18), 5.86 (ddd, 1H, J=11.5, 6.0, 3.5 Hz, H19), 7.43–7.48 (m, 2H, NAP), 7.56 (dd, 1H, J=8.5, 1.5 Hz, NAP), 7.79–7.85 (m, 4H, NAP); ^{13}C NMR (125 MHz, $CDCl_3$) δ 32.50, 34.59, 36.83, 64.48, 68.36, 70.20, 73.17, 75.15, 78.03, 80.47, 80.81, 81.09, 82.01, 84.70, 84.99, 87.46, 125.63, 125.87, 126.06, 126.30, 126.76, 126.84, 127.64, 127.84, 127.86, 130.89, 131.36, 132.96, 133.27, 134.89, 136.22, 136.62; FT-IR (film) ν 3399, 2875, 2360, 1367, 1260, 1093 cm^{-1}; MALDI-TOF MS $[M+Na]^+$ calcd for $C_{33}H_{38}NaO_8$ 585.2465, found 585.2457; $[\alpha]_D^{21.0}$ −61.1° (c 0.82, $CHCl_3$).

4.5.7. Aldol reaction of 71. To a solution of Et_3N (50.4 μl, 0.362 mmol) in CH_2Cl_2 (2 ml) was added $TiCl_4$ (1.0 M solution in CH_2Cl_2, 181 μl, 0.181 mmol) at −78 °C. A solution of amide **71** (12.8 mg, 18.1 μmol) in CH_2Cl_2 (5 ml) was then added, and the resulting mixture was stirred for 30 min at −78 °C. To the resulting violet solution, freshly distilled acrolein (24.2 μl, 0.362 mmol) was added and the stirring was continued for 20 min at −78 °C. The reaction mixture was quenched with saturated NH_4Cl solution and the aqueous phase was extracted with AcOEt. The combined organic phase was washed with brine and dried over anhydrous Na_2SO_4. After concentration, the residue was purified by flash column chromatography (silica gel, hexane/AcOEt=3–1) and then HPLC to give 20,21-*syn*-15,21-*syn* isomer **74** (9.9 mg, 13.0 μmol, 72%), a corresponding 20,21-*syn*-15,21-*anti* isomer (1.6 mg, 2.1 μmol, 12%), and recovery of **71** (1.3 mg, 1.9 μmol, 10%). **74**: colorless amorphous; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.53 (q, 1H, J=11.5 Hz, H10), 2.21 (brdt, 1H, J=15.5, 8.5 Hz, H17), 2.31–2.36 (m, 2H, H4, H10), 2.48 (d, 1H, J=7.5 Hz, OH), 2.59–2.63 (m, 1H, H17), 2.63 (ddd, 1H, J=16.0, 8.0, 4.0 Hz, H4), 2.83 (dd, 1H, J=13.5, 9.5 Hz, auxiliary), 3.09–3.16 (m, 2H, H8, H9), 3.28 (td, 1H, J=9.5, 4.0 Hz, H5), 3.32–3.39 (m, 3H, H6, H11, auxiliary), 3.51 (t, 1H, J=8.5 Hz, H7), 3.54–3.58 (m, 1H, H16), 3.87 (dq, 1H, J=8.5, 2.5 Hz, H12), 3.98 (dq, 1H, J=9.0, 2.5 Hz, H15), 4.02 (brdd, 1H, J=15.5, 3.0 Hz, H1), 4.23–4.25 (m, 2H, auxiliary), 4.30 (dd, 1H, J=15.0, 6.5 Hz, H1), 4.40–4.44 (m, 1H, H20), 4.68 (ddt, 1H, J=10.0, 7.0, 3.5 Hz, auxiliary), 4.95 (d, 1H, J=12.0 Hz, NAP), 5.00 (d, 1H, J=11.5 Hz, NAP), 5.07 (dd, 1H, J=10.5, 2.0 Hz, CH_2=CH–), 5.11 (dd, 1H, J=17.0, 2.0 Hz, CH_2=CH–), 5.28 (dt, 1H, J=11.0, 1.5 Hz, CH_2=CH–), 5.39 (dt, 1H, J=16.0, 1.5 Hz, CH_2=CH–), 5.41 (d, 1H, J=3.5 Hz, H21), 5.74–5.79 (m, 2H, H3, H14), 5.83–5.91 (m, 2H, H2. H18), 5.94–6.01 (m, 2H, H13, H19), 7.22–7.36 (m, 5H, auxiliary), 7.41–7.43 (m, 2H, NAP), 7.52 (dd, 1H, J=8.5, 1.5 Hz, NAP), 7.77–7.81 (m, 4H, NAP); ^{13}C NMR (125 MHz, $CDCl_3$) δ 34.73, 36.68, 37.23, 37.88, 55.73, 67.10, 68.49, 73.26, 73.88, 75.24, 76.91, 78.33, 80.44, 80.85, 81.16, 82.15, 82.81, 83.60, 87.53, 117.26, 117.55, 125.71, 125.96, 126.16, 126.35, 126.83, 127.67, 127.75, 127.93, 127.98, 129.17, 129.55, 131.46, 131.89, 132.52, 133.06, 133.38, 134.86, 134.97, 136.44, 136.80, 153.60, 170.74; FT-IR (film) ν 3437, 3059, 3027, 2930, 2876, 1779, 1711, 1642, 1603, 1497, 1479, 1454, 1392, 1350, 1261, 1212, 1099, 1009 cm^{-1}; MALDI-TOF MS $[M+Na]^+$ calcd for $C_{45}H_{49}NaNO_{10}$ 786.3254, found 786.3293; $[\alpha]_D^{20.5}$ +32.7° (c 0.800, $CHCl_3$). 20,21-*syn*-15,21-*anti* isomer: colorless amorphous; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.51 (q, 1H, J=11.5 Hz, H10), 2.28 (brdt, 1H, J=15.0, 8.0 Hz, H17), 2.30–2.37 (m, 2H, H4, H10), 2.47 (d, 1H, J=8.5 Hz, OH), 2.63 (ddd, 1H, J=16.0, 7.5, 4.0 Hz, H4), 2.79 (dd, 1H, J=14.0, 9.0 Hz, auxiliary), 2.83–2.88 (m, 1H, H17), 3.08–3.14 (m, 2H, H8, H9), 3.25–3.34 (m, 3H, H5, H11, auxiliary), 3.37 (t, 1H, J=8.5 Hz, H6), 3.49–3.54 (m, 1H, H7, H16), 3.83–3.88 (m, 2H, H12, H15), 4.04 (brdd, 1H, J=15.5, 3.0 Hz, H1), 4.24 (dd, 1H, J=8.5, 3.0 Hz, auxiliary), 4.30 (t, 1H, J=8.5 Hz, auxiliary), 4.31 (dd, 1H, J=15.5, 6.0 Hz, H1), 4.50–4.55 (m, 1H, H20), 4.74–4.79 (m, 1H, auxiliary), 4.98 (d, 1H, J=12.0 Hz, NAP), 5.02 (d, 1H, J=12.0 Hz, NAP), 5.06 (dd, 1H, J=10.5, 1.0 Hz, CH_2=CH–), 5.13 (dd, 1H, J=17.5, 2.0 Hz, CH_2=CH–), 5.30 (dt, 1H, J=10.5, 1.5 Hz, CH_2=CH–), 5.36 (d, 1H, J=3.5 Hz, H21), 5.42 (dt, 1H, J=17.5, 1.5 Hz, CH_2=CH–), 5.74 (dt, 1H, J=13.0, 2.5 Hz, H13), 5.75–5.80 (m, 1H, H3), 5.82 (dt, 1H, J=13.0, 2.5 Hz, H14), 5.85–5.94 (m, 2H, H2, H18), 6.01 (ddd, 1H, J=17.0, 11.0, 6.0 Hz, H19), 7.23–7.36 (m, 5H, auxiliary), 7.43–7.47 (m, 2H, NAP), 7.54 (d, 1H, J=8.0 Hz, NAP), 7.81–7.83 (m, 4H, NAP); ^{13}C NMR (125 MHz, $CDCl_3$) δ 34.77, 36.72, 37.31, 37.78, 55.16, 67.02, 68.53, 73.30, 73.69, 75.36, 77.73, 78.26, 80.20, 80.44, 81.12, 82.17, 83.47, 87.63, 116.63, 117.66, 125.79, 126.04, 126.25, 126.48, 126.89, 127.64, 127.82, 128.04, 129.16, 129.65, 130.67, 131.52, 133.14, 133.47, 134.87, 135.73, 136.63, 136.78, 153.68, 169.81; FT-IR (film) ν 3503, 3027, 2927, 2874, 1778, 1714, 1639, 1603, 1454, 1392, 1351, 1216, 1099, 1006, 923, 856 cm^{-1}; MALDI-TOF MS $[M+Na]^+$ calcd for $C_{45}H_{49}NaNO_{10}$ 786.3254, found 786.3272; $[\alpha]_D^{27.0}$ +62.6° (c 0.332, $CHCl_3$).

4.5.8. Diol 76. To a solution of amide **73** (18.0 mg, 23.1 μmol) in THF (2 ml) was added a solution of $NaBH_4$

(4.4 mg, 120 μmol) in water (0.5 ml). The mixture was stirred for 20 min at room temperature and quenched with saturated NH_4Cl solution. Aqueous phase was extracted with AcOEt and the combined organic phase was washed with brine and dried over anhydrous Na_2SO_4. After concentration, the residue was purified by flash column chromatography (silica gel, hexane/AcOEt=3–1–0.33) to give diol **75** (10.8 mg, 18.3 μmol, 79%).

A solution of the diol **75** (10.8 mg, 18.3 μmol) and Grubbs catalyst **37** (0.8 mg, 0.9 μmol) in CH_2Cl_2 (4 ml) was stirred for 1 h at room temperature. Et_3N was added and the mixture concentrated. The residue was purified by flash column chromatography (silica gel, hexane/AcOEt=1–0.5–0.33) to give diol **76** (9.5 mg, 17 μmol, 92%). **76**: colorless solid; mp 175–177 °C (CH_2Cl_2–AcOEt); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.52 (dd, 1H, J=11.5 Hz, H10), 2.13 (brs, 1H, 22-OH), 2.26 (brs, 1H, 20-OH), 2.27–2.37 (m, 3H, H4, H10, H17), 2.64 (ddd, 1H, J=16.0, 8.0, 4.0 Hz, H4), 3.09–3.18 (m, 3H, H8, H9, H17), 3.28 (td, 2H, J=10.0, 4.0 Hz, H5, H11), 3.37 (t, 1H, J=9.0 Hz, H6), 3.52 (brt, 1H, J=8.5 Hz, H7), 3.62–3.66 (m, 2H, H16, H21), 3.76–3.84 (m, 3H, H12, H22, H22), 4.03 (brdd, 1H, J=15.5, 2.5 Hz, H1), 4.11 (brdd, 1H, J=8.5, 2.5 Hz, H15), 4.31 (dd, 1H, J=15.5, 6.0 Hz, H1), 4.40 (brd, 1H, J=6.5 Hz, H20), 4.99 (d, 1H, J=12.5 Hz, NAP), 5.03 (d, 1H, J=12.5 Hz, NAP), 5.67 (dt, 1H, J=13.0, 2.5 Hz, H14), 5.75–5.81 (m, 1H, H3), 5.80 (dt, 1H, J=12.5, 2.5 Hz, H13), 5.85–5.97 (m, 3H, H2, H18, H19), 7.43–7.48 (m, 2H, NAP), 7.54 (dd, 1H, J=8.5, 1.5 Hz, NAP), 7.80–7.84 (m, 4H, NAP); ^{13}C NMR (125 MHz, $CDCl_3$) δ 33.47, 34.77, 37.05, 64.50, 68.52, 69.96, 73.35, 75.34, 78.39, 80.56, 81.03, 82.20, 82.71, 83.15, 84.92, 87.65, 125.79, 126.03, 126.22, 126.46, 126.92, 127.81, 128.00, 128.02, 128.05, 131.12, 131.52, 132.00, 132.03, 134.75, 134.76; FT-IR (film) ν 3415, 3025, 2879, 1450, 1366, 1264, 1092, 909, 857, 818, 733 cm^{-1}; MALDI-TOF MS $[M+Na]^+$ calcd for $C_{33}H_{38}NaO_8$ 585.2464, found 585.2494; $[\alpha]_D^{24.1}$ −43.4° (*c* 1.14, $CHCl_3$).

4.5.9. TBS ether 77. To a solution of diol **76** (14.8 mg, 26.3 μmol) in CH_2Cl_2 (4 ml) were added imidazole (17.9 mg, 263 μmol) and TBSCl (19.8 mg, 132 μmol). The mixture was stirred for 30 min at room temperature and quenched with saturated NH_4Cl solution. Aqueous phase was extracted with AcOEt and the combined organic phase was washed with brine and dried over anhydrous Na_2SO_4. After concentration, the residue was purified by flash column chromatography (silica gel, hexane/AcOEt=10–3–2) to give TBS ether **77** (14.8 mg, 21.9 μmol, 83%). **77**: colorless solid; mp 134–135 °C (hexane–AcOEt); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.10 (s, 6H, TBS), 0.92 (s, 9H, TBS), 1.52 (dd, 1H, J=11.5 Hz, H10), 2.28–2.34 (m, 3H, H4, H10, H17), 2.64 (ddd, 1H, J=16.0, 8.0, 4.0 Hz, H4), 2.70 (d, 1H, J=4.5 Hz, 20-OH), 3.10–3.13 (m, 3H, H8, H9, H17), 3.24–3.30 (m, 2H, H5, H11), 3.37 (t, 1H, J=9.5 Hz, H6), 3.52 (brt, 1H, J=9.0 Hz, H7), 3.58–3.61 (m, 2H, H16, H21), 3.79 (d, 2H, J=5.5 Hz, H22, H22), 3.80–3.84 (m, 1H, H12), 4.03 (brdd, 1H, J=15.5, 3.0 Hz, H1), 4.08 (brdd, 1H, J=8.5, 2.0 Hz, H15), 4.30 (dd, 1H, J=16.0, 6.0 Hz, H1), 4.40 (brd, 1H, J=4.5 Hz, H20), 4.98 (d, 1H, J=12.0 Hz, NAP), 5.04 (d, 1H, J=12.0 Hz, NAP), 5.64 (brd, 1H, J=12.5 Hz, H14), 5.75–5.84 (m, 2H, H3, H13), 5.84–5.91 (m, 3H, H2, H18, H19), 7.43–7.46 (m, 2H, NAP), 7.54 (brd, 1H, J=7.5 Hz, NAP), 7.80–7.85 (m, 4H, NAP); ^{13}C NMR (125 MHz, $CDCl_3$) δ −5.36, −5.29, 18.37, 25.98, 33.38, 34.75, 37.03, 64.87, 68.48, 69.29, 73.35, 75.27, 76.90, 78.30, 80.62, 81.01, 82.22, 82.86, 85.08, 87.59, 125.72, 125.97, 126.19, 126.40, 126.88, 127.77, 127.94, 128.00, 130.66, 131.48, 132.43, 133.10, 133.43, 135.36, 136.86; FT-IR (film) ν 3467, 3020, 2952, 2929, 2882, 2858, 1602, 1509, 1470, 1462, 1363, 1300, 1257, 1216, 1091, 1008 cm^{-1}; MALDI-TOF MS $[M+Na]^+$ calcd for $C_{39}H_{52}NaO_8Si$ 699.3329, found 699.3374; $[\alpha]_D^{24.5}$ −46.8° (*c* 1.02, $CHCl_3$).

4.5.10. Benzoate 78. To a solution of alcohol **77** (7.9 mg, 12 μmol) in toluene (2 ml) were added PPh_3 (15.3 mg, 58.4 μmol), BzOH (8.6 mg, 70 μmol) and DEAD (9.2 μl, 58 μmol). The mixture was stirred for 20 min at room temperature and quenched with water. Aqueous phase was extracted with AcOEt and the combined organic phase was washed with brine and dried over anhydrous Na_2SO_4. After concentration, the residue was purified by flash column chromatography (silica gel=1 g, hexane–hexane/AcOEt=10–5) to give benzoate **78** (9.2 mg, 12 μmol, 100%). **78**: colorless amorphous; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.02 (s, 3H, TBS), 0.04 (s, 3H, TBS), 0.88 (s, 9H, TBS), 1.53 (dd, 1H, J=11.0 Hz, H10), 2.28–2.37 (m, 3H, H4, H10, H17), 2.65 (ddd, 1H, J=16.5, 8.0, 4.0 Hz, H4), 2.88 (ddd, 1H, J=13.5, 10.0, 3.5 Hz, H17), 3.09–3.15 (m, 2H, H8, H9), 3.27 (td, 1H, J=9.5, 5.0 Hz, H11), 3.29 (td, 1H, J=9.0, 4.5 Hz, H5), 3.38 (t, 1H, J=9.0 Hz, H6), 3.53 (t, 1H, J=8.5 Hz, H7), 3.68–3.73 (m, 3H, H16, H21, H22), 3.82–3.86 (m, 2H, H12, H22), 4.04 (brdd, 1H, J=15.0, 3.0 Hz, H1), 4.18 (brdd, 1H, J=9.0, 2.5 Hz, H15), 4.31 (dd, 1H, J=16.0, 6.0 Hz, H1), 4.99 (d, 1H, J=12.5 Hz, NAP), 5.05 (d, 1H, J=11.5 Hz, NAP), 5.58 (ddd, 1H, J=8.5, 5.5, 1.5 Hz, H20), 5.64 (dt, 1H, J=12.5, 2.5 Hz, H14), 5.68 (dd, 1H, J=11.0, 5.5 Hz, H19), 5.78 (ddt, 1H, J=11.0, 8.0, 3.0 Hz, H3), 5.83–5.89 (m, 2H, H2, H18), 5.94 (dt, 1H, J=12.5, 3.0 Hz, H13), 7.43–7.64 (m, 4H, Bz, NAP), 7.81–7.86 (m, 4H, NAP), 8.02 (brd, 2H, J=7.5 Hz, Bz), 8.12 (dd, 2H, J=8.0, 1.0 Hz, Bz); ^{13}C NMR (125 MHz, $CDCl_3$) δ −5.15, −5.10, 18.46, 26.06, 32.86, 34.78, 37.01, 64.34, 68.52, 71.76, 73.38, 75.31, 78.21, 80.80, 81.04, 81.69, 82.25, 84.73, 85.19, 87.62, 125.77, 126.01, 126.24, 126.46, 126.96, 127.81, 127.94, 127.98, 128.04, 128.59, 128.64, 129.76, 130.35, 130.61, 131.50, 132.85, 133.13, 133.30, 133.91, 135.21, 136.87, 165.38; FT-IR (film) ν 3030, 2931, 2883, 1724, 1693, 1603, 1453, 1415, 1319, 1268, 1091, 1023, 977, 908, 837, 775, 712 cm^{-1}; MALDI-TOF MS $[M+Na]^+$ calcd for $C_{46}H_{56}NaO_9Si$ 803.3591, found 803.3536; $[\alpha]_D^{26.2}$ −35.4° (*c* 0.968, $CHCl_3$).

4.5.11. Synthesis of the ABCDE ring moiety 5 from 78. To a solution TBS ether **78** (16.9 mg, 21.6 μmol) in THF (2 ml) was added TBAF (1.0 M solution in THF, 65 μl, 65 μmol). After stirring for 1 h at room temperature, TBAF (65 μl, 65 μmol) was further added to the mixture and the stirring was continued for an additional 2 h. The reaction mixture was quenched with saturated NH_4Cl solution and the aqueous phase was extracted with AcOEt. The combined organic phase was washed with brine and dried over anhydrous Na_2SO_4. After concentration, the residue was purified by flash column chromatography (silica gel, hexane–hexane/AcOEt=5–2) to give a corresponding alcohol (13.3 mg, 19.9 μmol, 92%). colorless solid; mp

143–144 °C (hexane–AcOEt); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.52 (q, 1H, J=11.5 Hz, H10), 2.25–2.37 (m, 3H, H4, H10, H17), 2.64 (ddd, 1H, J=16.5, 8.0, 4.0 Hz, H4), 2.70 (ddd, 1H, J=13.0, 9.5, 3.5 Hz, H17), 3.08–3.12 (m, 2H, H8, H9), 3.23 (ddd, 1H, J=12.0, 9.5, 4.5 Hz, H11), 3.27 (td, 1H, J=9.5, 4.0 Hz, H5), 3.37 (t, 1H, J=8.5 Hz, H6), 3.51 (brt, 1H, J=9.0 Hz, H7), 3.61–3.66 (m, 2H, H16, H21), 3.81 (ddd, 1H, J=9.0, 5.0, 2.5 Hz, H12), 4.03 (brdd, 1H, J=15.5, 3.0 Hz, H1), 4.15 (brdd, 1H, J=9.0, 2.5 Hz, H15), 4.30 (dd, 1H, J=16.0, 6.0 Hz, H1), 4.39 (brdd, 1H, J=9.0, 4.5 Hz, H20), 4.59 (dd, 1H, J=11.5, 3.0 Hz, H22), 4.67 (dd, 1H, J=11.5, 6.0 Hz, H22), 4.97 (d, 1H, J=12.0 Hz, NAP), 5.03 (d, 1H, J=12.5 Hz, NAP), 5.59 (dt, 1H, J=12.5, 2.5 Hz, H14), 5.73–5.83 (m, 4H, H3, H13, H18, H19), 5.86 (ddt, 1H, J=12.0, 6.5, 3.0 Hz, H2), 7.43–7.49 (m, 4H, Bz, NAP), 7.54 (dd, 1H, J=8.0, 1.5 Hz, NAP), 7.58–7.61 (m, 1H, Bz), 7.80–7.84 (m, 4H, NAP), 8.09–8.11 (m, 2H, Bz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 32.67, 34.78, 36.99, 66.30, 68.52, 69.26, 73.32, 75.28, 78.10, 80.69, 81.01, 81.56, 82.18, 83.95, 84.70, 87.59, 125.77, 126.01, 126.22, 126.44, 126.92, 127.34, 127.80, 127.98, 128.02, 128.61, 129.94, 130.05, 130.30, 130.97, 131.51, 133.12, 133.38, 133.44, 135.17, 135.92, 136.83, 167.35; FT-IR (film) ν 3468, 3023, 2932, 2876, 1718, 1602, 1584, 1509, 1452, 1369, 1350, 1316, 1276, 1175, 1078, 1027 cm^{-1}; MALDI-TOF MS $[M+Na]^+$ calcd for $C_{40}H_{42}NaO_9$ 689.2727, found 689.2797; $[\alpha]_D^{26.4}$ −90.6° (c 1.00, $CHCl_3$).

To a solution of the alcohol (9.0 mg, 14 μmol) in MeOH (2 ml) and THF (1 ml) was added K_2CO_3 (9.3 mg, 68 μmol). The mixture was stirred for 1 h and quenched with saturated NH_4Cl solution. Aqueous phase was extracted with AcOEt and the combined organic phase was dried over anhydrous Na_2SO_4. After concentration, the residue was purified by flash column chromatography (silica gel, hexane/AcOEt=1–0.5–0.33) to give the ABCDE ring moiety **5** (7.0 mg, 12 μmol, 92%).

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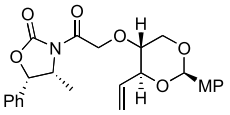
19. The numbering of carbon atoms in all compounds in this paper corresponds to that of CTX3C.
20. For instance, the corresponding oxazolidinone **A** did not give any coupling products, and instead decomposition of **A** occurred under various coupling conditions.



A

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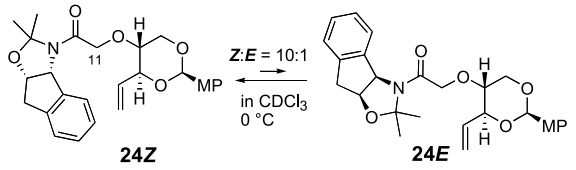
22. ^{1}H NMR of **24** suggested that **24** existed as a 10:1 equilibrium of amide rotamers (**24Z**:**24E**) in $CDCl_3$ at 0 °C because the major isomer showed NOE between the C11-methylene and indane aromatic proton. We assumed that this geometry was maintained in the enolate form.



24Z **24E**

23. TBPSOTf was prepared by treatment of TBPSCl and AgOTf in CH_2Cl_2 at 30 °C for 48 h and was used without distillation
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27. A minor diastereomer was separated after removal of the TBS group.
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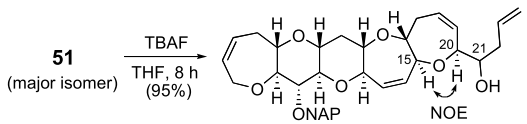
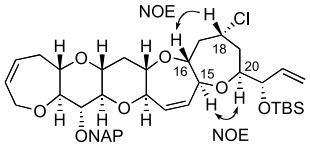
29. The C20-stereochemistry of the major isomer of **51** was identified by NOE experiments after removal of the TBS group.



30. The stereochemistry of the major isomer of **56** was assigned by NOE experiments.



56 (major isomer)

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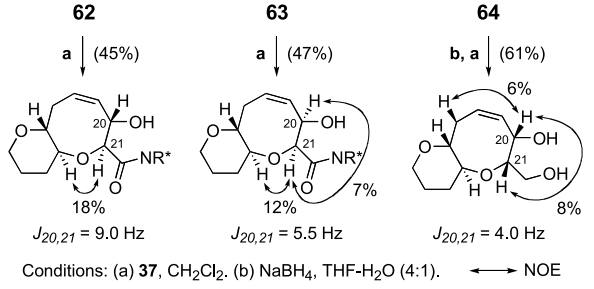

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39. The C20- and C21-stereochemistries of **73** were confirmed by NMR after RCM.