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ORIGINAL ARTICLE

Total synthesis of avermectin B_{1a} revisited

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Avermectins were isolated as compounds possessing anthelmintic activity from the culture broth *of Streptomycesavermitilis* by Ōmura and co-workers. Owing to their potent anthelmintic and insecticidal activities, as well as their unique pentacyclic architecture, the avermectin family attracted keen interest from synthetic organic chemists. We have recently completed a more efficient and straightforward total synthesis of avermectin B_{1a}, as compared with previous syntheses.
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INTRODUCTION

In the 1970s, Ōmura's group at the Kitasato Institute and researchers of Merck Sharp and Dohme Research Laboratories discovered potent antiparasitic agents, the avermectins, from the culture broth *of Streptomyces avermitilis* (*S. avermectinius*).[1,2] Among this family, avermectin B_{1a} (**1**, Scheme 1) is the most potent anthelmintic congener. Ivermectin, a mixture of 22,23-dihydro-avermectins B_{1a} and B_{1b}, has been used as an important anthelmintic in veterinary fields and for the control of onchocerciasis and lymphatic filariasis in more than 200 million people worldwide.[3–5]

Avermectins are 16-membered macrolactones that consist of a 6,6-spiroacetal north segment attached to the disaccharide oleandrosyl-oleandrosyl, and a unique, highly sensitive hexahydrobenzofuran south segment. Avermectins and structurally related milbemycins[6] attracted keen interest from synthetic organic chemists. After some difficulties, total syntheses for avermectin B_{1a} (**1**),[7–9] A_{1a},[10] ivermectin (aglycon)[11] and milbemycin D[12] and G[13] were achieved. These successful syntheses used some indirect strategies to control the position of the C3–C4 double bond and C2 stereochemistry.[7–10,12–14] Construction of the hexahydrobenzofuran and the *E*,*E*-diene, however, was less than satisfactory in terms of control of stereo- and regiochemistries. Previously, we developed a straightforward route to the hexahydrobenzofuran segment,[15] which allowed us to complete a total synthesis of milbemycin α_1.[16] We describe herein an improved and efficient approach to the north[17,18] and south segments, as well as a stereocontrolled total synthesis of avermectin B_{1a} (**1**).

RESULTS AND DISCUSSION

Synthesis plan

Our renewed plan for the synthesis of avermectin B_{1a} (**1**) is shown in Scheme 1. The challenges of the present synthesis are: (1) stereoselective construction of the hexahydrobenzofuran and spiroacetal segments, as well as the C8–C11 *E*,*E*-diene; and (2) macrolactone cyclization without disturbing the readily epimerizable C2 stereogenic center and the C3–C4 double bond, which is prone to migrate to the C2 position. Straightforward retrosynthesis of **1** is summarized in Scheme 1. Based on our successful synthesis of milbemycin α_1,[16] seco acid **2** should be generated from oxetane acetal **4**, which could be assembled through Julia or Wittig coupling of the north segment **5** and the south segment **6**. Oxetane acetal **6** would be prepared from bis-carbonyl compound **7** via an intramolecular aldol reaction. It is noteworthy that the oxetane acetal group is a masked form of the labile β-hydroxy aldehyde, which can maintain the C2 stereochemistry and C3–C4 double bond during construction of **4** and is readily convertible to carboxylic acid **2**.

Synthesis of the south segment began with readily available D-sorbitol **8** (Scheme 2). Acid-promoted cyclization,[19] followed by formation of acetonide, afforded tetrahydrofuran **9**. Sequential protection of the remaining diol of **9** with *t*-butyldiphenylchlorosilane (TBDPSCl) and 2-naphtylmethyl (NAP) bromide gave fully protected **10**. Selective hydrolysis and oxidative cleavage of the resultant diol furnished aldehyde **11**, which was directly used in the next vinylogous Mukaiyama aldol reaction without purification. Treatment of **11** with 2-(trimethylsiloxy)furan **12** in the presence of $BF_3{\cdot}OEt_2$ in CH_2Cl_2 at −78 °C afforded the desired adduct **13** as a 5:1 C4-diastereomeric mixture.[20] The stereochemical outcome was assumed by the non-chelate Felkin–Anh model.[21] Hydrogenation of the double bond of **13** by $NiCl_2$ and $NaBH_4$, followed by *t*-butyldimethylsilyl (TBS) protection of the hydroxyl group gave lactone **14** in 90% overall yield. After diisobutylaluminum hydride (DIBAL) reduction of **14**, the resultant diol was protected as a bis-triethylsilyl (TES) ether, and then the NAP group was removed by treatment with DDQ (2,3-dichloro-5,6-dicyano-*p*-benzoquinone) to give **15**.[22] Oxidation of **15** by Dess–Martin periodinane (DMP)[23] in the presence of pyridine

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This article is dedicated to Professor Satoshi Ōmura on the occasion of his 80th birthday in sincere appreciation for his great achievements in the discovery of new microbial drugs.
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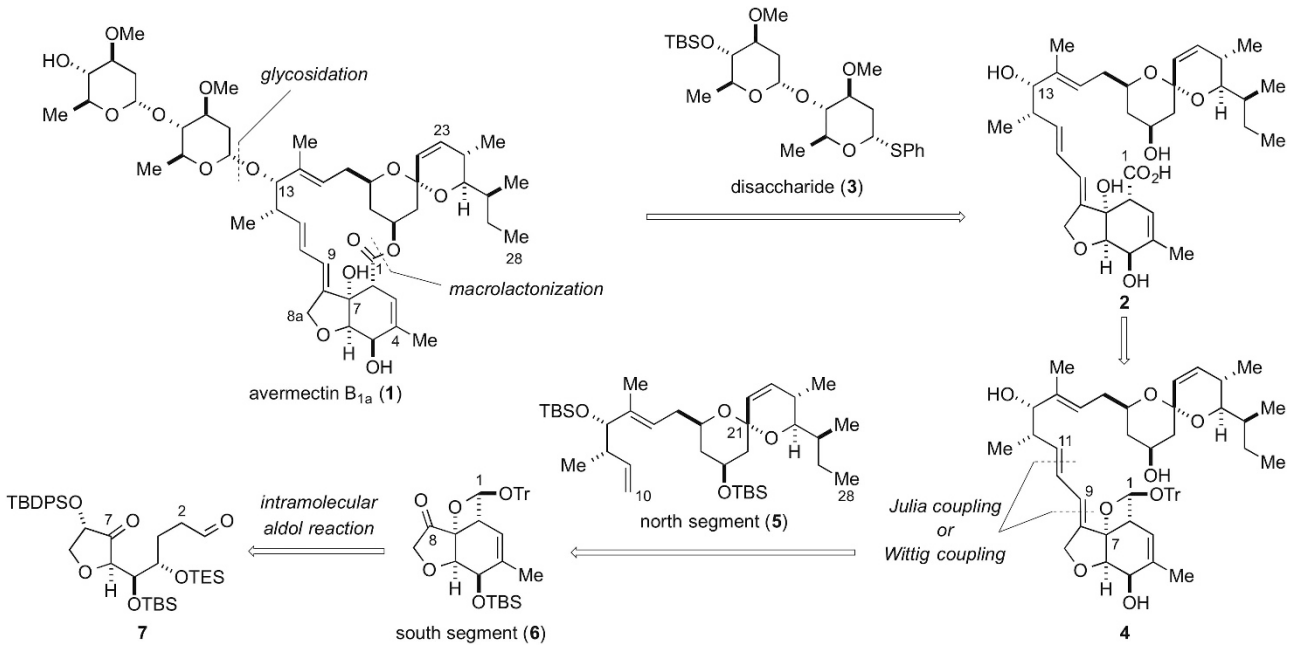


Scheme 1 Structure and synthesis plan for avermectin B_{1a} (**1**).

afforded bis-carbonyl compound **7** directly as a major product together with ketone **16**, which was converted to **7** through conventional hydrolysis and oxidation.

With the requisite **7** in hand, we examined the intramolecular aldol reaction. Upon treatment of **7** with Et_3N in 1,2-dichloroethane, no reaction occurred, even at high temperatures (entry 1; Scheme 2). Treatment with either lithium diisopropylamide or piperidine gave unfruitful results (entries 2 and 3). However, when **7** was reacted with 1,8-diazabicyclo[5.4.0]undec-7-ene in CH_2Cl_2 at 0 °C, cyclized product **17** was formed as a 3.9:1 mixture of C2-diastereomers (entry 4). Owing to the instability of **17** on silica gel, the crude product was used without purification in the next reaction.

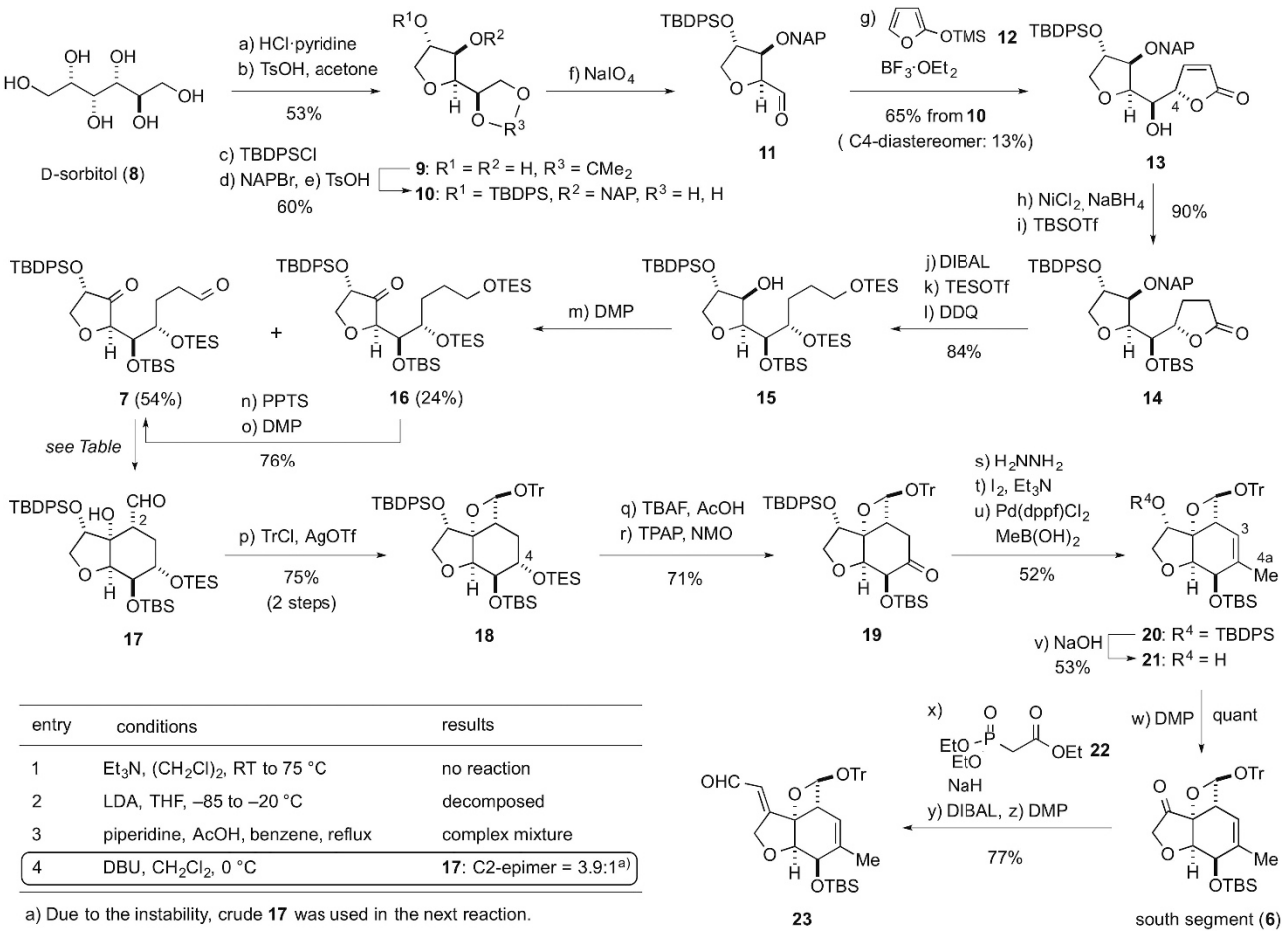
Based on our previous results,[16] β-hydroxy aldehyde **17** was applied to an oxetane acetal formation (Scheme 2). Crude **17** was treated at 50 °C with trityl trifluoromethanesulfonate, prepared *in situ* from trityl chloride and silver trifluoromethanesulfonate (AgOTf),[16,24] to successfully produce trityl oxetane acetal **18** as a single isomer in 75% overall yield (2 steps from **7**). Selective cleavage of the C4 TES ether of **18** by the action of AcOH-buffered TBAF (tetrabutylammonium fluoride), followed by TPAP (tetrapropylammonium perruthenate oxidation) afforded ketone **19** in 71% yield. The C4a methyl group and the C3–C4 double bond were then installed by the following three steps: (1) hydrazone formation; (2) iodination with iodine in the presence of Et_3N;[25] (3) Suzuki–Miyaura coupling with methylboronic acid,[26] which led to **20** in 94% yield. The structure of **20** was unambiguously confirmed by X-ray crystallography of the corresponding bis-TBS ether, as shown in Figure 1. Selective removal of the TBDPS group by NaOH[27] in the presence of the TBS group gave rise to secondary alcohol **21**. Dess–Martin oxidation of **21** afforded the south segment (**6**). Two carbon elongated south segment **23** was also synthesized from **6** (77% overall yield) in three steps: Horner–Wadsworth–Emmons olefination of **6** with **22**, DIBAL reduction, and subsequent Dess–Martin oxidation.

Next, we synthesized the C22–C28 unit **29** of the north segment (Scheme 3). Enantioselective reduction of ynone **24** was achieved by an asymmetric hydrogen transfer using Noyori catalyst **25** (ref. 28) to give a chiral secondary alcohol (98% ee), which was converted to the corresponding mesylate **26** in 84% overall yield. Diastereoselective coupling between **26** and aldehyde **27** was realized using Et_2Zn in the presence of a catalytic amount of $Pd(OAc)_2$ and PPh_3 according to the Marshall method.[29] Homopropargylic alcohol **28** was obtained in good diastereoselectivity (dr = 14:1). Removal of the trimethylsilyl (TMS) group of terminal alkyne **28** with K_2CO_3 in MeOH, followed by TMS protection of the secondary alcohol afforded the C22–C28 unit **29** in 87% yield.

The C15–C21 unit **36** was synthesized from propanediol monobenzyl ether **30** (ref. 30) (Scheme 3). TEMPO (2,2,6,6-tetramethylpiperidine 1-oxyl) oxidation of **30** in the presence of $PhI(OAc)_2$ gave aldehyde **31**, which was used directly in the next aldol reaction developed by Oguni *et al.*[31] Treatment of **31** with diketene **32** and Ti(O*i*-Pr)$_4$ in the presence of a catalytic amount of chiral Schiff base **33** afforded δ-hydroxy-β-ketoester **34** in 76% yield. Antiselective Evans reduction[32] of ketone **34** and acid catalyzed lactonization, followed by TBS protection of alcohol **35**, gave the C15–C21 unit **36** in 51% overall yield.

Carefully lithiated terminal alkyne **29** with *n*–BuLi was coupled with lactone **36** to give ynone in 64% yield (Scheme 3). Treatment of the ynone with citric acid in methanol caused selective cleavage of TMS ether and formation of methyl acetal **37**. Acetal **37** was converted to spiroacetal **38** via Lindler reduction,[33] acid treatment and Birch reduction in 59% overall yield. At this stage, the undesired minor diastereomer, which was derived from the antipode of **36**, was separable by silica gel column chromatography. The side chain of **38** was elongated via five steps following Danishefsky's procedure to give the north segment **4**.[10]

Having both segments, we in turn attempted Julia coupling between C10 and C11 (Scheme 3). The requisite sulfones **43a** and **43b** were prepared from **4**. Selective dihydroxylation of the terminal olefin, oxidative cleavage of the resultant diol, $NaBH_4$ reduction, Mitsunobu reaction with 1-phenyl-1*H*-tetrazole-5-thiol or benzothiazole-2-thiol, followed by Mo-catalyzed oxidation of sulfide[34] afforded sulfones **43a** and **43b**. Treatment of the PT sulfone **43a**[35] with either potassium



entry	conditions	results
1	Et_3N, $(CH_2Cl)_2$, RT to 75 °C	no reaction
2	LDA, THF, –85 to –20 °C	decomposed
3	piperidine, AcOH, benzene, reflux	complex mixture
4	DBU, CH_2Cl_2, 0 °C	**17**: C2-epimer = 3.9:1[a)]

a) Due to the instability, crude **17** was used in the next reaction.

Scheme 2 Synthesis of south segment. Reagents and conditions: (**a**) HCl·pyridine, 140 °C; (**b**) TsOH·H_2O, acetone, room temperature (rt), 53% (2 steps); (**c**) *t*-butyldiphenylchlorosilane (TBDPSCl), imidazole, dimethylformamide (DMF), 0 °C, 71%; (**d**) NAPBr, NaH, THF, rt; (**e**) TsOH·H_2O, THF, H_2O, reflux, 85% (2 steps); (**f**) $NaIO_4$, MeCN, H_2O, 0 °C; (**g**) **12** (1.3 eq), BF_3·OEt_2, CH_2Cl_2, –78 °C; citric acid, MeOH, rt, 65% (2 steps), **C4-epimer**: 13%; (**h**) $NiCl_2$·$6H_2O$, $NaBH_4$, MeOH, 0 °C, 93%; (**i**) *tert*-butyldimethylsilyl triflate (TBSOTf), 2,6-lutidine, CH_2Cl_2, rt, 97%; (**j**) diisobutylaluminum hydride (DIBAL), CH_2Cl_2, 0 °C, 96%; (**k**) TESOTf, 2,6-lutidine, CH_2Cl_2, rt, 97%; (**l**) DDQ (2,3-dichloro-5,6-dicyano-*p*-benzoquinone), CH_2Cl_2, pH 7, phosphate buffer, 0 °C, 90%; (**m**) Dess–Martin periodinane (DMP), pyridine, CH_2Cl_2, 0 °C to rt, **16**: 24%, **7**: 54%; (**n**) pyridinium *p*-toluenesulfonate (PPTS), MeOH, CH_2Cl_2, –50 to –20 °C, 91%; (**o**) DMP, $NaHCO_3$, CH_2Cl_2, 0 °C to rt, 84%; (**p**) trityl chloride (TrCl), silver trifluoromethanesulfonate (AgOTf), 2,6-lutidine, $(CH_2Cl)_2$, 50 °C, 75% (2 steps); (**q**) tetrabutylammonium fluoride (TBAF), AcOH, THF, 0 °C to rt; (**r**) tetrapropylammonium perruthenate (TPAP), NMO, 4 ÅMS, $(CH_2Cl)_2$, rt, 71% (2 steps); (**s**) H_2NNH_2·H_2O, Et_3N, EtOH, 60 °C; (**t**) I_2, Et_3N, THF, 0 °C, 55% (2 steps); (**u**) Pd(dppf)Cl_2, MeB$(OH)_2$, $CsCO_3$, DMF, toluene, H_2O, 60 °C, 94%; (**v**) NaOH, MeOH, 65 °C, 53%; (**w**) DMP, pyridine, CH_2Cl_2, 0 °C to rt, quant.; (**x**) **22**, NaH, THF, –90 °C to rt; (**y**) DIBAL, Et_2O, –78 °C, 81% (2 steps); (**z**) DMP, pyridine, CH_2Cl_2, 0 °C to rt, 95%.

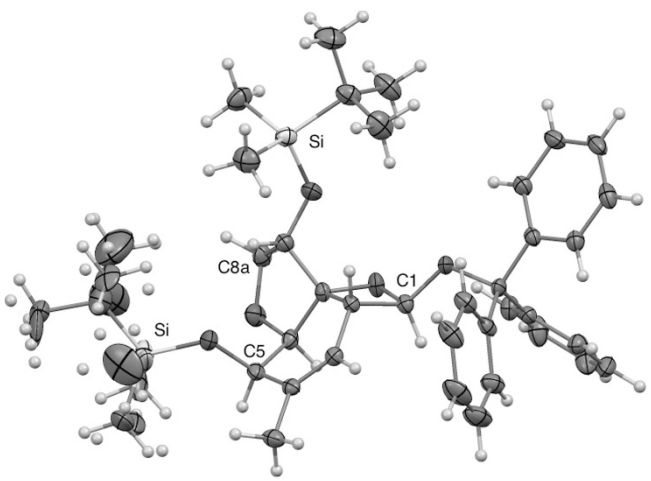
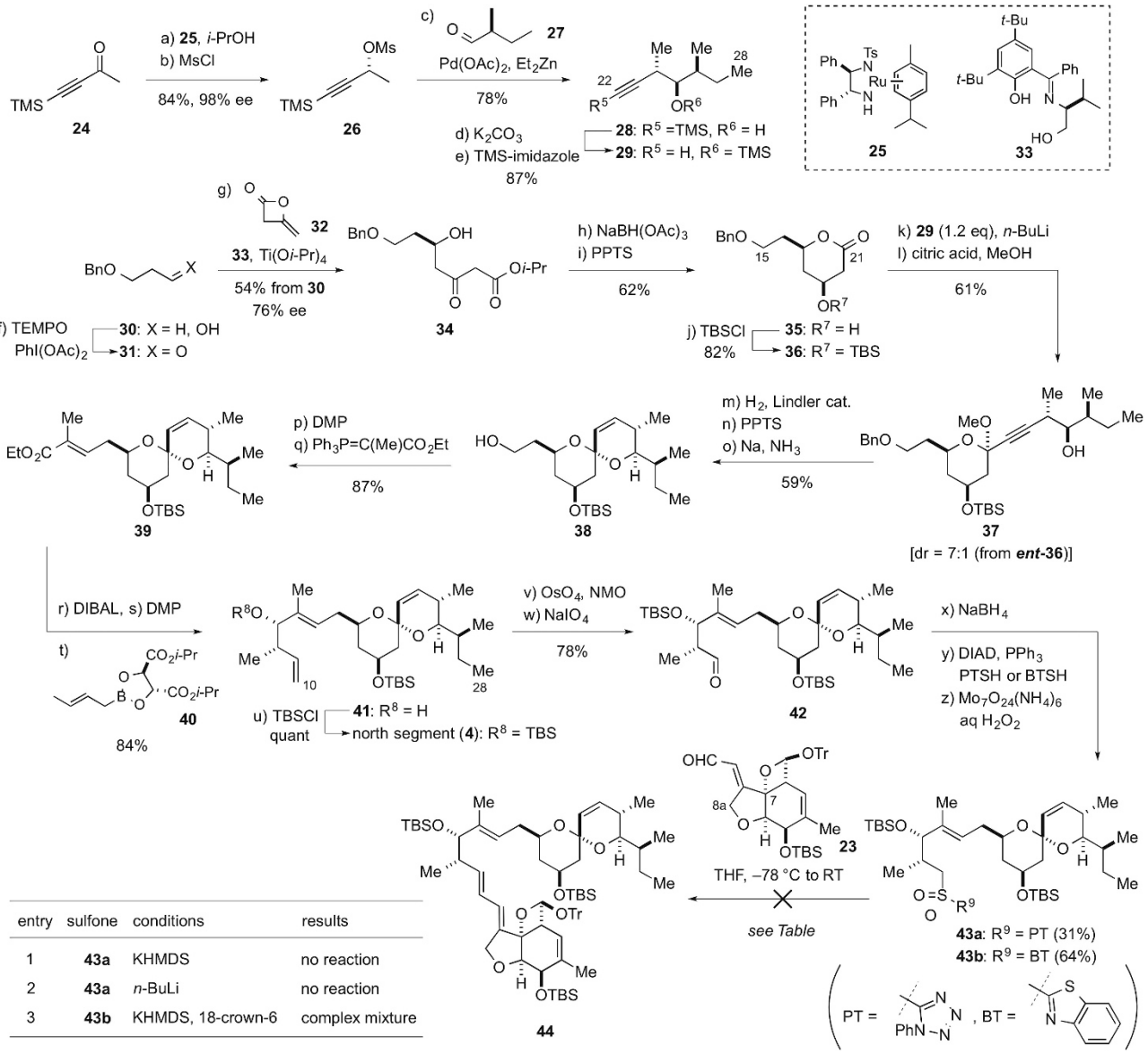


Figure 1 ORTEP drawing of bis-TBS ether of **20**.

hexamethyldisilazide or *n*-butyllithium in THF, followed by the addition of aldehyde **23** caused no reaction (entries 1 and 2; Scheme 3). When a smaller BT sulfone **43b** (ref. 36) was used, aldehyde **23** was consumed, but only a complex mixture was formed (entry 3). Thus, it is conceivable that the coupling reaction was prevented by deprotonation of the acidic C8a hydrogen of **23** to form the corresponding enolate. These results led us to abandon the Julia coupling route.

An alternative Wittig route through C8–C9 bond formation was thus examined, as depicted in Scheme 4. The phosphonate **46a**, triphenylphosphonium salt **46b** and trimethyl phosphonium salt **46c** were prepared from aldehyde **42** by conventional means. As the Horner–Wadsworth–Emmons reaction of ketone **6** with phosphonate **22** was successful, as shown in Scheme 2, phosphonate **46a** was first reacted with ketone **6** (entries 1 and 2, Scheme 4). Neither of these conditions, however, gave the desired product. When triphenylphosphonium salt **46b** was used, as in our previous study of the synthesis



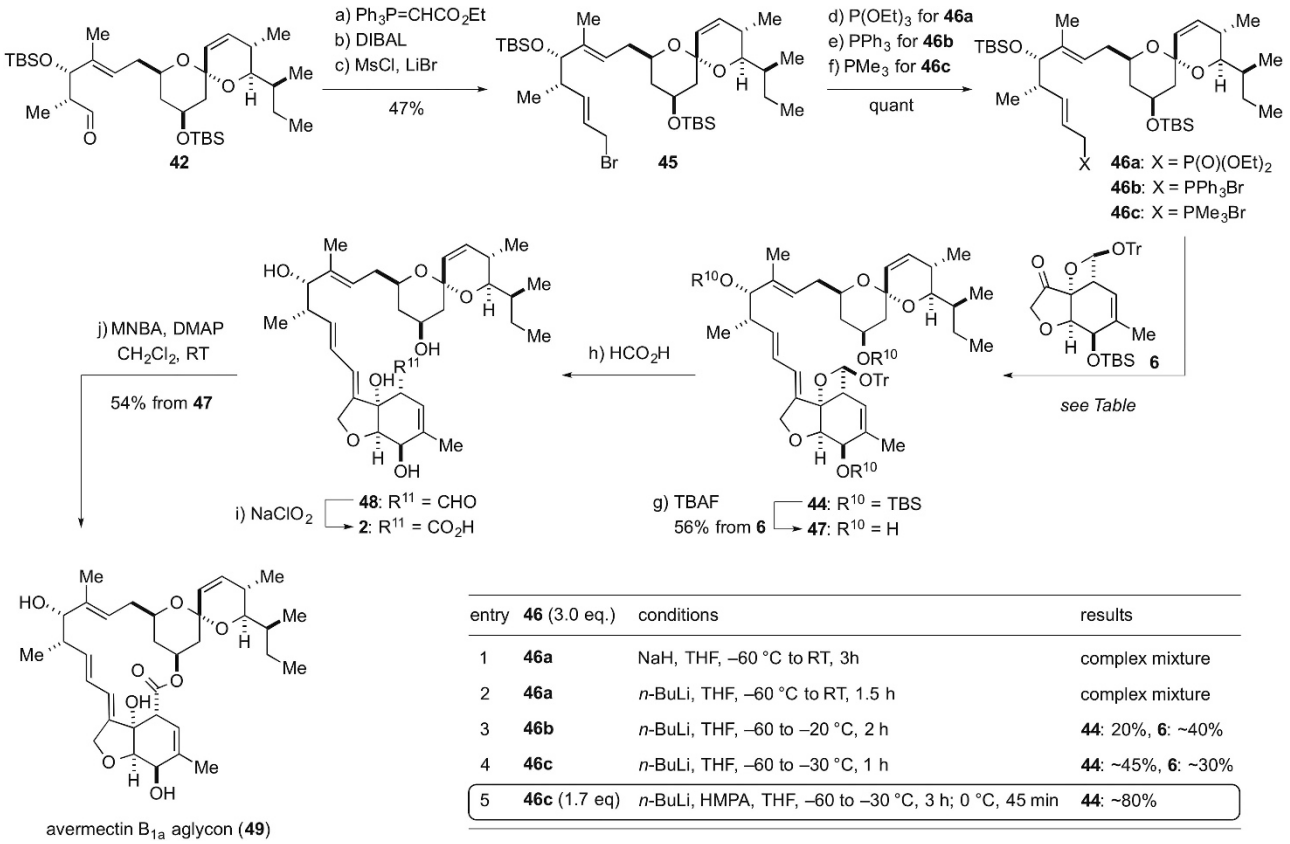
entry	sulfone	conditions	results
1	**43a**	KHMDS	no reaction
2	**43a**	*n*-BuLi	no reaction
3	**43b**	KHMDS, 18-crown-6	complex mixture

Scheme 3 Synthesis of north segment and attempted Julia coupling. Reagents and conditions: (**a**) **25**, *i*-PrOH, 40 °C, 88%; (**b**) MsCl, Et_3N, CH_2Cl_2, −85 °C, 96%; (**c**) **27**, $Pd(OAc)_2$, PPh_3, Et_2Zn, THF, −90 to 0 °C, 78% (dr = 14:1); (**d**) K_2CO_3, MeOH, rt; (**e**) trimethylsilyl (TMS)-imidazole, CH_2Cl_2, 0 °C to room temperature (rt), 87% (2 steps); (**f**) TEMPO (2,2,6,6-tetramethylpiperidine 1-oxyl), $PhI(OAc)_2$, CH_2Cl_2, rt; (**g**) diketene **32**, **33**, $Ti(Oi\text{-}Pr)_4$, CH_2Cl_2, −40 °C, 54% (2 steps, 76% ee); (**h**) $NaBH(OAc)_3$, acetic acid (AcOH), MeCN, −60 to 0 °C, 83%; (**i**) pyridinium *p*-toluenesulfonate (PPTS), CH_2Cl_2, reflux, 75%; (**j**) TBSCl, imidazole, DMF, 40 °C, 82%; (**k**) **29** (1.2 eq), *n*-BuLi, THF, −78 °C; **36**, 74% from **36** (dr = 7:1); (**l**) citric acid, MeOH, rt, 83% (dr = 7:1); (**m**) H_2, Lindler cat. MeOH, rt, 92% (dr = 7:1); (**n**) PPTS, Et_2O, rt, 86% (dr = 5:1); (**o**) Na, NH3, THF, −78 °C, 75%; (**p**) Dess–Martin periodinane (DMP), $NaHCO_3$, CH_2Cl_2, rt; (**q**) $Ph_3P{=}C(Me)CO_2Et$, THF, reflux, 87% (2 steps); (**r**) diisobutylaluminum hydride (DIBAL), CH_2Cl_2, −60 °C, 98%; (**s**) DMP, $NaHCO_3$, CH_2Cl_2, rt; (**t**) **40**, toluene, 4ÅMS, −80 to −30 °C, 86% (2 steps); (**u**) TBSCl, imidazole, DMF, rt, quant.; (**v**) OsO_4, NMO, *t*-BuOH, THF, H_2O, rt; (**w**) $NaIO_4$, MeOH, H_2O, rt, 78% (2 steps); (**x**) $NaBH_4$, MeOH, 0 °C, 95%; (**y**) DIAD, PPh_3, 1-phenyl-1*H*-tetrazole-5-thiol (PTSH) for **43a**, benzothiazole-2-thiol (BTSH) for **43b**, DMF, rt; (**z**) $Mo_7O_{24}(NH_4)_6{\cdot}4H_2O$, 30% aq. hydrogen peroxide (H_2O_2), EtOH, **43a**: 33% (2 steps), **43b**: 67% (2 steps).

of milbemycin,[16] the desired 8,9-*E*-adduct **44** was only formed at a low yield and 40% of **6** was recovered (entry 3). As steric repulsion between **46b** and **6** was likely to hinder the reaction, the smaller trimethylphosphonium salt **46c** was used.[37] As expected, *E*-adduct **44** was obtained in 45% yield. Furthermore, we found that addition of hexamethylphosphoric triamide improved the yield up to 80% (entry 5). Under these optimal conditions, 1.7 eq of **46c** was sufficient to complete the reaction. As **44** was unstable on silica gel, the reaction mixture was purified after removal of TBS groups by TBAF, giving rise to triol **47** in 56% overall yield.

Before further transformation of **47**, we examined the macrolactonization of seco acid **2**, which was degraded from natural avermectin B_{1a}.[38,39] Under Yonemitsu–Yamaguchi conditions,[40] the desired aglycon **49** was obtained in 36% yield. Furthermore, we found that Shiina macrolactonization of **2** using 2-methyl-6-nitrobenzoic anhydride[41] afforded **49** in 67% yield without serious side reactions.

Encouraged by our preliminary experiments, we then attempted a *de novo* synthesis of aglycon **49** from **47** (Scheme 4). As experienced in the synthesis of milbemycin,[16] removal of trityl group of **47** by formic acid[42] and subsequent Krause–Pinnick oxidation[43,44] must be carried



entry	**46** (3.0 eq.)	conditions	results
1	**46a**	NaH, THF, –60 °C to RT, 3h	complex mixture
2	**46a**	*n*-BuLi, THF, –60 °C to RT, 1.5 h	complex mixture
3	**46b**	*n*-BuLi, THF, –60 to –20 °C, 2 h	**44**: 20%, **6**: ~40%
4	**46c**	*n*-BuLi, THF, –60 to –30 °C, 1 h	**44**: ~45%, **6**: ~30%
5	**46c** (1.7 eq)	*n*-BuLi, HMPA, THF, –60 to –30 °C, 3 h; 0 °C, 45 min	**44**: ~80%

Scheme 4 Synthesis of avermectin aglycon **49**. Reagents and conditions: (**a**) $Ph_3P=CHCO_2Et$, toluene, room temperature (rt); (**b**) diisobutylaluminum hydride (DIBAL), Et_2O, –78 °C, 75% (2 steps); (**c**) MsCl, LiBr, Et_3N, THF, 0 °C to rt, 62%; (**d**) $P(OEt)_3$, KI, acetone, MeCN, 60 °C, quant.; (**e**) PPh_3, MeCN, 70 °C, quant.; (**f**) PMe_3, MeCN, rt, quant.; (**g**) TBAF, THF, 45 °C, 56% (2 steps); (**h**) HCO_2H, 2-Me-2-butene, *t*-BuOH; (**i**) $NaClO_2$, $NaHPO_4$, H_2O, rt; (**j**) 2-methyl-6-nitrobenzoic anhydride (MNBA), DMAP, CH_2Cl_2, rt, 54% (3 steps).

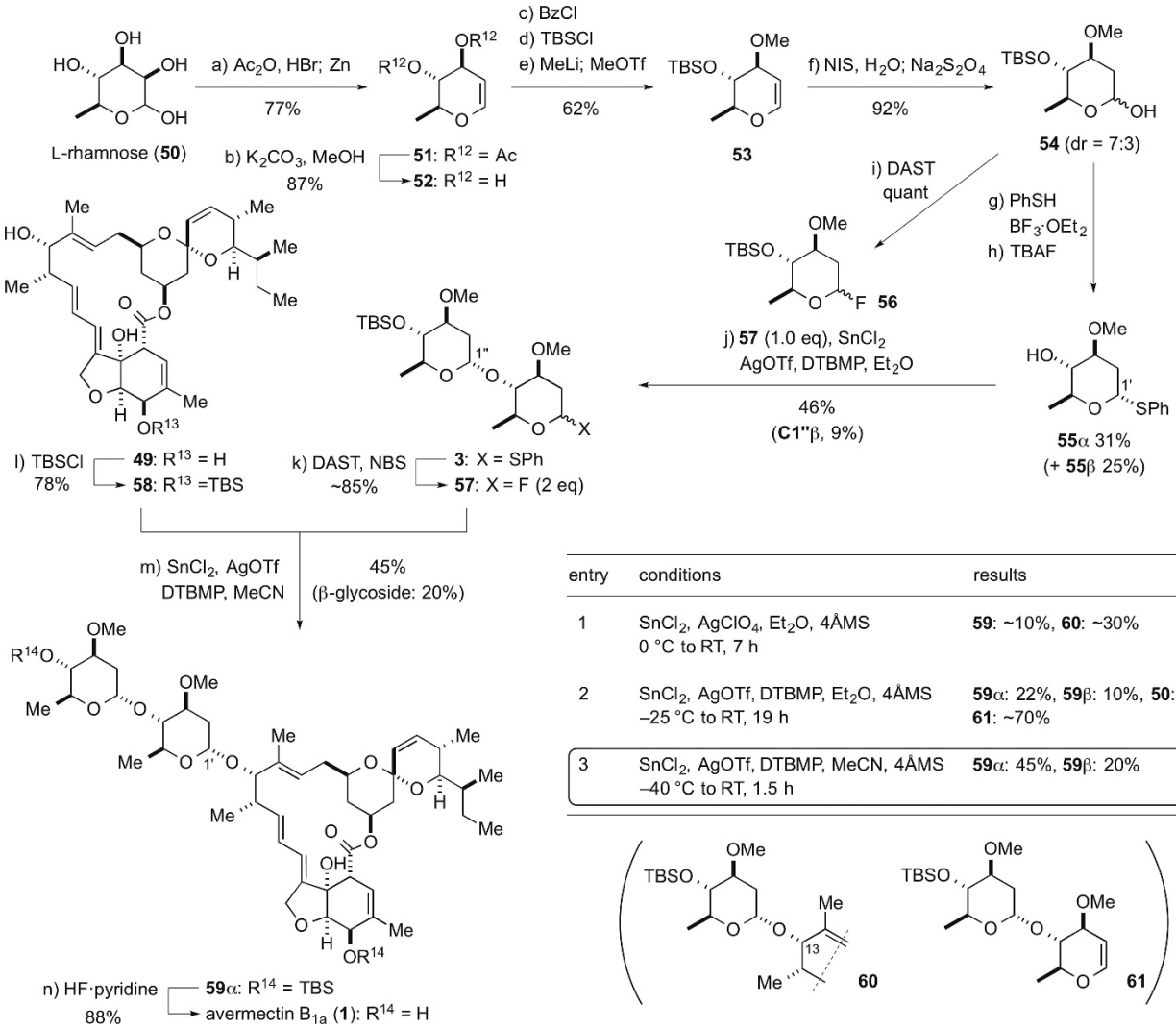
out under carefully degassed conditions using an argon atmosphere, as well as degassed reagents and solvents. Otherwise, we ended up with a complex mixture. Thus, the β,γ-unsaturated aldehyde **48** was very likely to be oxidized quickly by molecular oxygen and decomposed.[16] In practice, after **47** was treated with formic acid in degassed *t*-BuOH and 2-methyl-2-butene, the reaction mixture was directly added to a degassed aqueous solution of $NaClO_2$ and NaH_2PO_4 to give the seco acid **2**. Subsequent Shiinamacrolactonization of **2** produced the avermectin B_{1a} aglycon **49** in 54% overall yield.

As shown in Scheme 5, disaccharide **3** was prepared according to Nicolaou's procedure[39] with some modifications. L-rhamnal **52** was synthesized from L-rhamnose **50** by the modified Koreeda method.[45,46] Protection of diol **52** with benzoyl and TBS groups, respectively, followed by methyl ether formation gave **53**,[47] which was treated with NIS and then reduced to afford oleandrose **54**. Treatment of **54** with thiophenol in the presence of $BF_3{\cdot}OEt_2$, followed by TBAF deprotection, afforded a 1.2:1 anomeric mixture of thioglycosides (**55**α and **55**β). Fluoride **56** was also prepared by DAST. Treatment of **55**α and **56** under modified Mukaiyama conditions[39,48] ($SnCl_2$, AgOTf and 2,6-di-*t*-Bu-4-Me-pyridine (DTBMP) in Et_2O) gave C1″α-disaccharide **3** in 46% yield together with C1″ β-isomer (9%).

Glycosylation was tested using aglycon **58** derived from natural avermectin B_{1a}.[39] Aglycon **58** and fluoride **57**, prepared from thioglycoside **3** by DAST and *N*-bromosuccinimide (NBS), were treated with $SnCl_2$ and $AgClO_4$ in Et_2O (entry 1; Scheme 5). The desired disaccharide **59**, however, was obtained only as a minor product (~10%) along with hydrolyzed monosaccharide **60**. The addition of DTBMP as an acid scavenger improved the yield of **59**α to 22% in addition to C1′ β-isomer (10%), whereas a significant amount of glycal **61** was isolated. Thus, we assumed that generation of **61** is attributable to the short lifetime of the oxonium cation intermediate formed from **57**, and expected that MeCN as a solvent instead of ether might more effectively stabilize the intermediate. We found that MeCN gave **59**α in higher yield (45%; its β-isomer: 20%, entry 3).

Finally, the total synthesis of avermectin B_{1a} (**1**) was achieved as described in Scheme 5. The C5-hydroxy group of synthetic **49** was selectively protected, and the resultant **58** was coupled with glycosyl fluoride **57** by the action of $SnCl_2$ and AgOTf in the presence of DTBMP in MeCN to give the desired α-glycoside **59**α in 45% yield. Removal of TBS groups by buffered HF·pyridine in MeCN[9] gave avermectin B_{1a} (**1**) in 88% yield. Spectroscopic data of synthetic samples were consistent with those of the natural product.

In conclusion, we achieved an efficient and straightforward total synthesis of avermectin B_{1a} (**1**). The highlights of total synthesis include: (i) a vinylogous Mukaiyama aldol reaction to install the C1–C4 carbons (**11**+**12** → **13**); (ii) an intramolecular aldol reaction to form the octahydrobenzofuran (**7** → **17**) (iii) a formation of trityl oxetane acetal to protect a labile β-hydroxy aldehyde (**17** → **18**); (iv) a regioselective installation of C3–C4 double bond (**19** → **20**); (v) a highly diastereoselective construction of the north segment via coupling of the C22–C28 alkyne and the C15–C21 lactone (**29**+**36** → **4**); (vi) an *E*-selective Wittig reaction using trimethylphosphonium salt to connect the



entry	conditions	results
1	$SnCl_2$, $AgClO_4$, Et_2O, 4ÅMS 0 °C to RT, 7 h	**59**: ~10%, **60**: ~30%
2	$SnCl_2$, AgOTf, DTBMP, Et_2O, 4ÅMS –25 °C to RT, 19 h	**59**α: 22%, **59**β: 10%, **50**: ~30% **61**: ~70%
3	$SnCl_2$, AgOTf, DTBMP, MeCN, 4ÅMS –40 °C to RT, 1.5 h	**59**α: 45%, **59**β: 20%

Scheme 5 Total synthesis of avermectin B_{1a} (**1**). Reagents and conditions: (**a**) Ac_2O, HBr, AcOH, 0 °C to room temperature (rt); Zn, $CuSO_4$, NaOAc, H_2O, 77%; (**b**) K_2CO_3, MeOH, rt, 87%; (**c**) BzCl, pyridine, CH_2Cl_2, 0 °C; (**d**) TBSCl, imidazole, DMF, 40 °C, 73% (2 steps); (**e**) MeLi, THF, −80 °C; MeOTf, −90 to −55 °C, 85%; (**f**) NIS, MeCN, H_2O, 0 °C to rt; $Na_2S_2O_4$, $NaHCO_3$, DMF, H_2O, rt, 92% (α:β = 7:3); (**g**) PhSH, $BF_3{\cdot}OEt_2$, CH_2Cl_2, 0 °C; (**h**) TBAF, THF, 40 °C, **55**α: 31% (2 steps), **55**β: 25% (2 steps); (**i**) DAST, THF, −40 °C, quant.; (**j**) $SnCl_2$, AgOTf, 2,6-di-*t*-Bu-4-Me-pyridine (DTBMP), 4ÅMS, Et_2O, −30 °C to rt, **3**: 46%, **C1" β-isomer**: 9%; (**k**) DAST, NBS, CH_2Cl_2, −30 °C, ~85%; (**l**) TBSCl, imidazole, DMF, rt, 78%; (**m**) $SnCl_2$, AgOTf, DTBMP, 4ÅMS, MeCN, −40 °C to rt, **59**α: 45%, **59**β: 20%; (**n**) HF·pyridine, pyridine, MeCN, rt, 88%.

polyfunctionalized north and south segments (**6**+**46c** → **44**); (vii) an efficient Shiina macrolactonization using a genuine seco acid (**2** → **49**); (viii) a modified synthesis of the disaccharide and improved glycosylation to afford avermectin B_{1a} (**57**+**58** → **1**). In particular, we should emphasize that a unique and powerful 'trityl oxetane acetal' protecting group strategy worked well to prevent serious epimerization and double bond migration of the sensitive β-hydroxy carbonyl tetrahydrobenzofuran moiety of **1**.

EXPERIMENTAL PROCEDURE

All reactions sensitive to air or moisture were carried out under argon or nitrogen atmosphere in dry, freshly distilled solvents under anhydrous conditions, unless otherwise noted.

Analytical TLC was performed using E Merck Silica gel 60 F254 precoated plates (Merck, Frankfurt, Germany). Column chromatography was performed using 100–210 μm Silica Gel 60N (Kanto Chemical Co., Tokyo, Japan), and for flash column chromatography, 40–50 μm Silica Gel 60N (Kanto Chemical Co.) was used. ^{1}H- and ^{13}C NMR spectra were recorded on Agilent 400MR (400 and 100 MHz, respectively; Agilent, Santa Clara, CA, USA) or Bruker AVANCE III 700 (700 and 175 MHz, respectively; Bruker, Billerica, MA, USA) spectrometer. Chemical shifts are reported in terms of chemical shift relative to solvent signals (^{1}H NMR: $CHCl_3$ (7.26), C_6D_5H (7.16); ^{13}C NMR: $CDCl_3$ (77.16), C_6D_6 (128.06)). Signal patterns are indicated as: s = singlet; d = doublet; t = triplet; q = quartet; quint. = quintet; m = multiplet; br = broad peak. IR spectra were recorded on a Perkin-Elmer Spectrum BX FT-IR spectrometer (Perkin-Elmer, Waltham, MA, USA). High-resolution ESI-FT mass spectra were measured on Thermo Orbi-trap instrument (Thermo Scientific, Waltham, MA, USA). Melting points were measured on Yanaco MP-S3 micromelting point apparatus. The carbon numbering of compounds is corresponding with avermectin B_{1a}.

Diol 9

A mixture of D-sorbitol **8** (10.4 g, 57 mmol) and HCl·pyridine (10.4 g, 91 mmol) was heated to 140 °C. The reaction mixture was stirred at this temperature overnight, and then passed through a short pad of silica eluting with EtOAc/MeOH = 5/1. The solution was concentrated to provide tetraol **S1** (12.6 g, impure), which was used in the next reaction.

To a solution of tetraol **S1** (6.9 g, ca. 31 mmol) in acetone (62 ml) was added $TsOH{\cdot}H_2O$ (2.9 g, 15 mmol) at room temperature. The reaction mixture was stirred overnight, then quenched with EtOAc and saturated aqueous $NaHCO_3$. The phases were separated and the aqueous phase was extracted with EtOAc. The combined organic layer was dried over Na_2SO_4 and concentrated. The residue was purified by open column chromatography (EtOAc) to yield diol **9** (3.34 g, 53%, 2 steps) as a white solid. **9**: m.p. 72 °C; $[\alpha]_D^{28} = -11.1$ (*c* 0.41, $CHCl_3$); IR (KBr) *ν*: 3424, 2933, 1454, 1370, 1257 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 4.31 (1H, ddd, *J* = 6.3, 5.5, 5.5 Hz, H5), 4.30 (1H, dd, *J* = 7.8, 5.5 Hz, H6), 4.27 (1H, m, H8), 4.17 (1H, dd, *J* = 9.8, 3.9 Hz, H8a), 4.17 (1H, dd, *J* = 8.6, 6.3 Hz, H4), 3.99 (1H, dd, *J* = 7.8, 3.9 Hz, H7), 3.97 (1H, dd, *J* = 8.6, 5.5 Hz, H4), 3.75 (1H, dd, *J* = 9.8, 1.2 Hz, H8a), 2.54 (1H, d, *J* = 2.9 Hz, OH), 1.80 (1H, d, *J* = 3.9 Hz, OH), 1.44 (3H, s, acetonide), 1.36 (3H, s, acetonide); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 109.52 (C, acetonide), 81.35 (CH, C7), 77.77 (CH, C8), 77.58 (CH, C6), 73.87 (CH_2, C8a), 73.76 (CH, C5), 67.84 (CH_2, C4), 26.78 (CH_3, acetonide), 25.22 (CH_2, acetonide); HRMS (ESI) *m/z* calcd for $C_9H_{16}O_5Na$ $[(M+Na)]^+$ 227.0890, found 227.0890.

TBDPS ether S2

To a solution of diol **9** (8.3 g, 41 mmol) in DMF (40 ml) was added imidazole (6.9 g, 0.10 mol), followed by TBDPSCl (10.5 ml, 41 mmol) at 0 °C. The reaction mixture was stirred at this temperature for 5 h, and then added additional TBDPSCl (2.5 ml, 9.6 mmol). The reaction mixture was stirred at this temperature for 2 h, then quenched with saturated aqueous $NaHCO_3$. The phases were separated and the aqueous phase was extracted with hexane/EtOAc = 1/1. The combined organic layer was washed with brine, dried over Na_2SO_4 and concentrated. The residue was purified by open column chromatography (hexane/EtOAc = 5/1–4/1) to yield TBDPS ether **S2** (12.69 g, 71%) as a white solid. **S2**: m.p. 83 °C; $[\alpha]_D^{23} = -12.5$ (*c* 0.96, $CHCl_3$); IR (film) *ν*: 3447, 2932, 2858, 1589, 1472, 1427, 1219 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.65 (2H, m, TBDPS), 7.62 (2H, m, TBDPS), 7.47–7.36 (6H, m, TBDPS), 4.29 (1H, ddd, *J* = 7.6, 6.3, 5.5 Hz, H5), 4.22 (1H, ddd, *J* = 3.9, 1.4, 1.4 Hz, H8), 4.18 (1H, m, H7), 4.14 (1H, dd, *J* = 8.4, 6.3 Hz, H4), 4.07 (1H, dd, *J* = 7.6, 3.3 Hz, H6), 3.99 (1H, dd, *J* = 8.4, 5.5 Hz, H4), 3.96 (1H, dd, *J* = 9.4, 3.9 Hz, H8a), 3.71 (1H, dd, *J* = 9.4, 1.4 Hz, H8a), 2.19 (1H, d, *J* = 3.1 Hz, OH), 1.45 (3H, s, acetonide), 1.35 (3H, s, acetonide), 1.07 (9H, s, TBDPS); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 135.64 (CH, TBDPS), 129.94 (CH, TBDPS), 127.82 (CH, TBDPS), 127.79 (C, TBDPS), 109.33 (C, acetonide), 81.26 (CH, C6), 78.97 (CH, C8), 77.75 (CH, C7), 74.33 (CH_2, C8a), 73.86 (CH, C5), 67.65 (CH_2, C4), 26.84 (CH_3, TBDPS), 26.80 CH_3, acetonide), 25.21 (CH_3, acetonide), 19.08 (C, TBDPS); HRMS (ESI) *m/z* calcd for $C_{25}H_{34}O_5SiNa$ $[(M+Na)]^+$ 465.2068, found 465.2068.

Diol 10

To a solution of **S2** (4.0 g, 9.1 mmol) in THF (30 ml) was added NaH (0.73 g, 60% in oil, 18 mmol) at room temperature. The reaction mixture was stirred for 15 min and then added NAPBr (2.2 g, 10 mmol). The reaction mixture was stirred overnight and quenched with saturated aqueous NH_4Cl. The phases were separated and the aqueous phase was extracted with EtOAc. The combined organic layer was washed with brine, dried over Na_2SO_4 and concentrated to provide NAP ether **S3**, which was used in the next reaction.

To a solution of NAP ether **S3** in THF-H_2O (4:1, 30 ml) was added $TsOH{\cdot}H_2O$ (0.53 g, 2.8 mmol). The reaction mixture was stirred for 3 h under reflux conditions and then quenched with saturated aqueous $NaHCO_3$. The phases were separated and the aqueous phase was extracted with EtOAc. The combined organic layer was washed with brine, dried over Na_2SO_4 and concentrated. The residue was purified by open column chromatography (hexane/EtOAc = 1/1) to yield diol **10** (4.22 g, 85%, 2 steps) as a white amorphous. **10**: $[\alpha]_D^{21} = -52.0$ (*c* 0.98, $CHCl_3$); IR (film) *ν*: 3421, 2930, 2857, 1588, 1508, 1458, 1426 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.82–7.73 (3H, m, NAP), 7.71 (2H, m, TBDPS), 7.64 (2H, m, TBDPS), 7.51–7.38 (9H, m, TBDPS, NAP), 7.20 (1H, dd, *J* = 8.4, 1.6 Hz, NAP), 4.38 (1H, d, *J* = 3.7 Hz, H8), 4.25 (1H, d, *J* = 11.9 Hz, NAP), 4.12 (1H, dd, *J* = 8.0, 3.9 Hz, H6), 4.09 (1H, d, *J* = 11.9 Hz, NAP), 4.00 (1H, dd, *J* = 9.4, 3.7 Hz, H8a), 3.99 (1H, m, H5), 3.96 (1H, d, *J* = 3.9 Hz, H7), 3.83 (1H, m, H4), 3.82 (1H, d, *J* = 9.4 Hz, H8a), 3.71 (1H, ddd, *J* = 11.4, 5.7, 5.7 Hz, H4), 2.41 (1H, d, *J* = 5.7 Hz, OH), 2.07 (1H, m, OH), 1.07 (9H, s, TBDPS); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 135.89 (CH, TBDPS), 135.76 (CH, TBDPS), 134.85 (C), 133.27 (C), 133.08 (C), 132.93 (C), 130.17 (CH), 130.06 (CH), 128.44 (CH), 127.97 (CH, TBDPS), 127.91 (CH, TBDPS), 127.84 (CH), 127.70 (CH), 126.31 (CH), 126.27 (CH), 126.11 (CH), 125.19 (CH), 84.92 (CH, C7), 80.47 (CH, C6), 75.71 (CH, C8), 74.39 (CH_2, C8a), 71.69 (CH_2, NAP), 69.82 (CH, C5), 64.88 (CH_2, C4), 26.87 (CH_3, TBDPS), 19.05 (C, TBDPS); HRMS (ESI) *m/z* calcd for $C_{33}H_{38}O_5SiNa$ $[(M+Na)]^+$ 565.2381, found 565.2387.

2(*5H*)-furanone S4 (ref. 49)

To a solution of furfural (41 ml, 0.50 mol) in CH_2Cl_2 (200 ml) were added Na_2SO_4 (20 g) and *N*,*N*-dimethylethanolamine (17 ml, 0.17 mol), followed by formic acid (38 ml, 1.0 mol) at room temperature. Then, 35% hydrogen peroxide (78 ml, 0.8 mol) was added dropwise. The reaction mixture was stirred overnight. The phases were separated and the aqueous phase was extracted with CH_2Cl_2. The combined organic layer was washed with saturated aqueous $Na_2S_2O_3$, dried over $MgSO_4$ and concentrated. The residue was distilled under reduced pressure at 75–95 °C to yield 2(*5H*)-furanone **S4** (18.6 g, 44%) as pail yellow oil. **S4**: IR (film) *ν*: 3567, 3100, 1943, 1777, 1742, 1599, 1447 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.57 (1H, dt, *J* = 5.6, 1.6 Hz, H3), 6.17 (1H, dt, *J* = 5.6, 2.4 Hz, H2), 4.91 (2H, dd, *J* = 2.4, 1.6 Hz, H4); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 173.65 (C, C1), 152.70 (CH, C3), 121.61 (CH, C2), 72.08 (CH_2, C4).

Furan 12

To a solution of 2(*5H*)-furanone **S4** (5.8 g, 69 mmol) in CH_2Cl_2 (50 ml) was added Et_3N (12 ml, 83 mmol) at 0 °C. Then, TMSOTf (13 ml, 72 mmol) was added dropwise. The reaction mixture was gradually warmed to room temperature, stirred overnight and then diluted with pentane (100 ml). The phases were separated and the organic layer was washed with pH 7.0 phosphate buffer, 0.5 M $CuSO_4$ aq. and brine. The layer was dried over $MgSO_4$ and concentrated. The residue was distilled under reduced pressure at 50–60 °C to yield furan **12** (7.10 g, 65%) as a colorless oil. **12**: IR (film) *ν*: 2963, 1618, 1523, 1382, 1256 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 6.82 (1H, dd, *J* = 2.4, 1.2 Hz, H4), 6.21 (1H, dd, *J* = 3.2, 2.4 Hz, H3), 5.10 (1H, dd, *J* = 3.2, 1.2 Hz, H2), 0.30 (9H, s, TMS); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 156.66 (C, C1), 132.37 (CH, C4), 110.97 (CH, C3), 83.21 (CH, C2), −0.27 (CH_3, TMS).

Butenolide 13

To a solution of diol **10** (22.4 g, 41 mmol) in MeCN-H_2O (4:1, 206 ml) was added $NaIO_4$ (13.3 g, 62 mmol) at 0 °C. The reaction mixture was stirred at this temperature for 2.5 h, and quenched with H_2O. The phases were separated and the aqueous phase was extracted with EtOAc. The combined organic layer was washed with brine, dried over Na_2SO_4 and concentrated to provide aldehyde **11**, which was used in the next reaction.

To a solution of aldehyde **11** in CH_2Cl_2 (370 ml) was added $BF_3{\cdot}OEt_2$ (11 ml, 62 mmol) at −78 °C. The reaction mixture was stirred at this temperature for 15 min, and then added furan **12** (8.4 g, 54 mmol) in CH_2Cl_2 (40 ml). The reaction mixture was stirred at this temperature for 3 h, then quenched with EtOAc and saturated aqueous $NaHCO_3$. The phases were separated and the aqueous phase was extracted with CH_2Cl_2. The combined organic layer was washed with brine, dried over Na_2SO_4 and concentrated. To this residue in MeOH (200 ml) was added citric acid (10 g) at room temperature. The reaction mixture was stirred for 2 h, then quenched with EtOAc and saturated aqueous $NaHCO_3$. The phases were separated and the aqueous phase was extracted with EtOAc. The combined organic layer was washed with brine, dried over Na_2SO_4 and concentrated. The residue was purified by flash column chromatography (hexane/EtOAc = 3/1) to yield butenolide **13** (16.08 g, 65%, 2 steps) and its diastereomer (3.2 g, 13%) as a white amorphous. **13**: $[\alpha]_D^{23} = -85.9$ (*c* 1.01, $CHCl_3$); IR (film) *ν*: 3443, 3052, 2931, 2250, 1746, 1602, 1509, 1470, 1427 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.89 (1H, m, NAP), 7.75–7.71 (2H, m, NAP), 7.68 (2H, m, TBDPS), 7.62 (2H, m, TBDPS), 7.53 (1H, dd, *J* = 5.9, 1.6 Hz, H3), 7.50–7.38 (9H, m, TBDPS, NAP), 7.18 (1H, dd, *J* = 8.4, 1.8 Hz, NAP), 6.14 (1H, dd, *J* = 5.9, 2.0 Hz, H2), 5.27 (1H, ddd, *J* = 3.7, 2.0, 1.6 Hz, H4), 4.36 (1H, d, *J* = 3.7 Hz, H8), 4.28 (1H, dd, *J* = 8.0, 3.5 Hz, H6), 4.23 (1H, d, *J* = 11.6 Hz, NAP), 4.16 (1H, d, *J* = 11.6 Hz, NAP), 4.09 (1H, m, H5), 4.02

(1H, d, J=3.5 Hz, H7), 4.01 (1H, dd, J=9.8, 3.7 Hz, H8a), 3.84 (1H, d, J=9.8 Hz, H8a), 2.50 (1H, d, J=6.9 Hz, OH), 1.08 (9H, s, TBDPS); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 173.07 (C, C1), 154.52 (CH, C3), 135.84 (CH, TBDPS), 135.72 (CH, TBDPS), 134.72 (C), 133.09 (C), 133.03 (C), 132.95 (C), 130.18 (CH, NAP), 130.05 (C, NAP), 128.31 (CH), 127.98 (CH, TBDPS), 127.90 (CH, TBDPS), 127.85 (CH), 127.65 (CH), 126.50 (CH), 126.20 (CH), 126.07 (CH), 125.45 (CH, NAP), 122.09 (CH, C2), 84.92 (CH, C7), 84.42 (CH, C4), 79.93 (CH, C6), 75.79 (CH, C8), 74.64 (CH_2, C8a), 72.14 (CH_2, NAP), 69.61 (CH, C5), 26.86 (CH_3, TBDPS), 19.03 (C, TBDPS); HRMS (ESI) *m/z* calcd for $C_{36}H_{38}O_6SiNa$ $[(M+Na)]^+$ 617.2330, found 617.2331.

Lactone S5

To a solution of butenolide **13** (1.1 g, 1.9 mmol) in MeOH (19 ml) was added $NiCl_2{\cdot}6H_2O$ (0.26 g, 0.95 mmol), followed by $NaBH_4$ (0.14 g, 3.8 mmol) at 0 °C. The reaction mixture was stirred at this temperature for 55 min, then quenched with EtOAc and saturated aqueous NH_4Cl. The phases were separated and the aqueous phase was extracted with EtOAc. The combined organic layer was washed with brine, dried over Na_2SO_4 and concentrated. The residue was purified by open column chromatography (hexane/EtOAc=2/1) to yield lactone **S5** (1.06 g, 93%) as a white amorphous. **S5**: $[\alpha]_D^{22}=-31.3$ (c 0.90, $CHCl_3$); IR (film) ν: 3437, 3052, 2931, 2249, 1769, 1589, 1509, 1471 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.79 (1H, m, NAP), 7.76–7.72 (2H, m, NAP), 7.69 (2H, dt, J=6.5, 1.6 Hz, TBDPS), 7.62 (2H, dt, J=6.5, 1.6 Hz, TBDPS), 7.52–7.37 (9H, m, TBDPS, NAP), 7.18 (1H, dd, J=8.4, 1.6 Hz, NAP), 4.76 (1H, ddd, J=8.0, 6.3, 1.8 Hz, H4), 4.36 (1H, d, J=3.9 Hz, H8), 4.24 (1H, dd, J=7.2, 3.5 Hz, H6), 4.24 (1H, d, J=11.7 Hz, NAP), 4.14 (1H, d, J=11.7 Hz, NAP), 4.05 (1H, d, J=3.5 Hz, H7), 4.01 (1H, dd, J=9.6, 3.9 Hz, H8a), 3.91 (1H, ddd, J=7.2, 7.2, 1.8 Hz, H5), 3.82 (1H, d, J=9.6 Hz, H8a), 2.72 (1H, d, J=7.2 Hz, OH), 2.64 (1H, ddd, J=17.6, 9.6, 6.5 Hz, H2), 2.48 (1H, ddd, J=17.6, 10.2, 7.4 Hz, H2), 2.37–2.23 (2H, m, H3x2), 1.08 (9H, s, TBDPS); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 177.66 (C, C1), 135.86 (CH, TBDPS), 135.72 (CH, TBDPS), 134.73 (C), 133.12 (C), 133.10 (C), 133.05 (C), 130.17 (CH), 130.03 (CH), 128.31 (CH), 127.97 (CH, TBDPS), 127.89 (CH, TBDPS), 127.65 (CH), 126.54 (CH), 126.20 (CH), 126.08 (CH), 125.44 (CH, NAP), 85.52 (CH, C7), 80.11 (CH, C4), 79.62 (CH, C6), 75.87 (CH, C8), 74.38 (CH_2, C8a), 71.96 (CH_2, NAP), 71.58 (CH, C5), 28.53 (CH_2, C2), 26.86 (CH_3, TBDPS), 23.98 (CH_2, C3), 19.03 (C, TBDPS); HRMS (ESI) *m/z* calcd for $C_{36}H_{40}O_6SiNa$ $[(M+Na)]^+$ 619.2486, found 619.2486.

TBS ether 14

To a solution of lactone **S5** (2.7 g, 4.5 mmol) in CH_2Cl_2 (23 ml) was added 2,6-lutidine (1.6 ml, 14 mmol), followed by *tert*-butyldimethylsilyltriflate (TBSOTf; 1.6 ml, 6.8 mmol) at room temperature. The reaction mixture was stirred for 1.5 h and then quenched with saturated aqueous NH_4Cl. The phases were separated and the aqueous phase was extracted with EtOAc. The combined organic layer was washed with brine, dried over Na_2SO_4 and concentrated. The residue was purified by open column chromatography (hexane/EtOAc=5/1) to yield TBS ether **14** (3.12 g, 97%) as a white amorphous. **14**: $[\alpha]_D^{22}=-16.8$ (c 1.07, $CHCl_3$); IR (film) ν: 3052, 2929, 2252, 1777, 1589, 1471 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.78 (1H, m, NAP), 7.73 (2H, dt, J=6.5, 1.6 Hz, TBDPS), 7.72–7.69 (2H, m, NAP), 7.60 (2H, dt, J=6.5, 1.6 Hz, TBDPS), 7.53–7.36 (9H, m, TBDPS, NAP), 7.11 (1H, dd, J=8.4, 1.6 Hz, NAP), 4.80 (1H, ddd, J=7.4, 7.4, 3.5 Hz, H4), 4.38 (1H, d, J=4.1 Hz, H8), 4.18 (1H, dd, J=8.4, 2.5 Hz, H6), 4.12 (1H, dd, J=8.4, 3.5 Hz, H5), 4.03 (1H, dd, J=9.6, 4.1 Hz, H8a), 3.98–3.90 (2H, m, NAP), 3.84 (1H, d, J=9.6 Hz, H8a), 3.79 (1H, d, J=2.5 Hz, H7), 2.58–2.44 (2H, m, H2x2), 2.30–2.14 (2H, m, H3x2), 1.10 (9H, s, TBDPS), 0.88 (9H, s, TBS), 0.05 (3H, s, TBS), −0.04 (3H, s, TBS); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 177.38 (C, C1), 136.03 (CH, TBDPS), 135.69 (CH, TBDPS), 135.47 (C), 133.41 (C), 133.07 (C), 133.01 (C), 132.72 (C), 130.17 (CH), 129.99 (CH), 128.00 (CH, TBDPS), 127.88 (CH, TBDPS), 127.72 (CH), 127.62 (CH), 126.08 (CH), 125.79 (CH), 125.30 (CH), 124.89 (CH, NAP), 83.93 (CH, C7), 81.55 (CH, C6), 81.45 (CH, C4), 74.32 (CH_2, C8a), 74.09 (CH, C8), 70.05 (CH_2, NAP), 69.86 (CH, C5), 28.68 (CH_2, C2), 26.87 (CH_3, TBDPS), 25.95 (CH_3, TBS), 23.42 (CH_2, C3), 19.00 (C, TBDPS), 18.27 (C, TBS), −4.14 (CH_3, TBS), −4.49 (CH_3, TBS); HRMS (ESI) *m/z* calcd for $C_{42}H_{54}O_6Si_2Na$ $[(M+Na)]^+$ 733.3351, found 733.3345.

Diol S6

To a solution of **14** (0.59 g, 0.80 mmol) in CH_2Cl_2 (23 ml) was added DIBAL (4.7 ml, 1.02 M in toluene, 4.8 mmol) at 0 °C. The reaction mixture was stirred at this temperature for 30 min and then quenched with saturated aqueous Rochelle salt. After being stirred for 6 h, the phases were separated and the aqueous phase was extracted with EtOAc. The combined organic layer was washed with brine, dried over Na_2SO_4 and concentrated. The residue was purified by open column chromatography (hexane/EtOAc=5/1–2/1) to yield diol **S6** (548 mg, 96%) as a white amorphous. **S6**: $[\alpha]_D^{23}=-31.2$ (c 0.99, $CHCl_3$); IR (film) ν: 3478, 3053, 2928, 2246, 1589, 1510, 1470 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.78 (1H, m, NAP), 7.75–7.69 (4H, m, TBDPS, NAP), 7.60 (2H, m, TBDPS), 7.53–7.36 (9H, m, TBDPS, NAP), 7.12 (1H, dd, J=8.4, 1.6 Hz, NAP), 4.32 (1H, d, J=3.9 Hz, H8), 4.24–4.16 (2H, m, H5, H6), 4.04 (1H, dd, J=9.4, 3.9 Hz, H8a), 4.00 (1H, d, J=12.1 Hz, NAP), 3.93 (1H, d, J=12.1 Hz, NAP), 3.86 (1H, d, J=9.4 Hz, H8a), 3.79–3.64 (4H, m, H7, H1x2, H4), 3.48 (1H, d, J=10.0 Hz, OH), 2.94 (1H, brs, OH), 1.96 (1H, m, H2), 1.86–1.75 (2H, m, H3x2), 1.55 (1H, ddt, J=14.1, 10.6, 7.0 Hz, H2), 1.10 (9H, s, TBDPS), 0.87 (9H, s, TBS), 0.01 (3H, s, TBS), −0.08 (3H, s, TBS); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 135.99 (CH, TBDPS), 135.66 (CH, TBDPS), 135.47 (C), 133.35 (C), 133.07 (C), 132.97 (C), 132.70 (C), 130.19 (CH), 130.02 (CH), 127.99 (CH, TBDPS), 127.89 (CH, TBDPS), 127.86 (CH), 127.75 (CH), 127.61 (CH), 126.06 (CH), 125.75 (CH), 125.11 (CH), 124.76 (CH, NAP), 84.26 (CH, C7), 81.94 (CH, C6), 74.82 (CH, C4), 74.60 (CH_2, C8a), 73.94 (CH, C8), 70.47 (CH_2, NAP), 68.96 (CH, C5), 63.17 (CH_2, C1), 30.78 (CH_2, C3), 29.30 (CH_2, C2), 26.88 (CH_3, TBDPS), 25.82 (CH_3, TBS), 19.00 (C, TBDPS), 17.98 (C, TBS), −4.29 (CH_3, TBS), −4.97 (CH_2, TBS); HRMS (ESI) *m/z* calcd for $C_{42}H_{58}O_6Si_2Na$ $[(M+Na)]^+$ 737.3664, found 737.3663.

Bis-TES ether S7

To a solution of diol **S6** (5.6 g, 7.8 mmol) in CH_2Cl_2 (39 ml) was added 2,6-lutidine (4.5 ml, 39 mmol), followed by TESOTf (5.3 ml, 23 mmol) at room temperature. The reaction mixture was stirred for 1 h and then quenched with saturated aqueous NH_4Cl. The phases were separated and the aqueous phase was extracted with hexane/EtOAc=2/1. The combined organic layer was washed with brine, dried over Na_2SO_4 and concentrated. The residue was purified by open column chromatography (hexane/EtOAc=100/1) to yield **S7** (7.15 g, 97%) as a colorless oil. **S7**: $[\alpha]_D^{22}=-23.6$ (c 1.09, $CHCl_3$); IR (film) ν: 3052, 2930, 1589, 1509, 1462, 1311 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.76 (1H, m, NAP), 7.73 (2H, m, TBDPS), 7.71–7.66 (2H, m, NAP), 7.60 (2H, m, TBDPS), 7.51–7.35 (9H, m, TBDPS, NAP), 7.14 (1H, dd, J=8.6, 1.8 Hz, NAP), 4.32 (1H, d, J=4.1 Hz, H8), 4.17 (1H, dd, J=9.4, 2.6 Hz, H6), 4.07 (1H, dd, J=9.4, 1.8 Hz, H5), 4.03 (1H, dd, J=9.6, 4.1 Hz, H8a), 4.03 (1H, d, J=12.3 Hz, NAP), 3.96 (1H, d, J=12.3 Hz, NAP), 3.86 (1H, m, H4), 3.82 (1H, d, J=9.6 Hz, H8a), 3.78 (1H, d, J=2.6 Hz, H7), 3.68–3.57 (2H, m, H1x2), 1.76 (1H, m, H3), 1.67 (1H, m, H2), 1.61–1.46 (2H, m, H2, H3), 1.11 (9H, s, TBDPS), 1.00 (9H, t, J=7.8 Hz, TES), 0.94 (9H, t, J=7.8 Hz, TES), 0.89 (9H, s, TBS), 0.67 (6H, q, J=7.8 Hz, TES), 0.59 (6H, q, J=7.8 Hz, TES), 0.08 (3H, s, TBS), 0.00 (3H, s, TBS); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 136.11 (C), 136.04 (CH, TBDPS), 135.73 (CH, TBDPS), 133.57 (C), 133.24 (C), 133.14 (C), 132.66 (C), 130.05 (CH), 129.86 (CH), 127.91 (CH, TBDPS), 127.80 (CH, TBDPS), 127.73 (CH), 127.66 (CH), 127.58 (CH), 125.89 (CH), 125.54 (CH), 125.00 (CH), 124.85 (CH, NAP), 84.57 (CH, C7), 80.00 (CH, C6), 74.42 (CH, C8), 74.32 (CH_2, C8a), 73.60 (CH, C4), 71.14 (CH, C5), 70.24 (CH_2, NAP), 63.13 (CH_2, C1), 30.10 (CH_2, C2), 29.56 (CH_2, C3), 26.81 (CH_3, TBDPS), 26.07 (CH_3, TBS), 18.97 (C, TBDPS), 18.49 (C, TBS), 7.02 (CH_3, TES), 6.80 (CH_3, TES), 5.19 (CH_2, TES), 4.43 (CH_2, TES), −3.22 (CH_3, TBS), −3.65 (CH_3, TBS); HRMS (ESI) *m/z* calcd for $C_{54}H_{86}O_6Si_4Na$ $[(M+Na)]^+$ 965.5394, found 965.5390.

Alcohol 15

To a solution of **S7** (730 mg, 0.77 mmol) in CH_2Cl_2-pH 7 phosphate buffer (10:1, 7.7 ml) was added DDQ (209 mg, 0.92 mmol) at 0 °C. The reaction mixture was stirred at this temperature for 1.5 h, then quenched with saturated aqueous $NaHCO_3$ and saturated aqueous $Na_2S_2O_3$. The phases were separated and the aqueous phase was extracted with EtOAc. The combined organic layer was washed with brine, dried over Na_2SO_4 and concentrated. To this residue in

MeOH (8 ml) was added $NaBH_4$ (58 mg, 1.5 mmol) at room temperature. The reaction mixture was stirred for 10 min and then quenched with saturated aqueous $NaHCO_3$. The phases were separated and the aqueous phase was extracted with hexane/EtOAc = 2/1. The combined organic layer was washed with brine, dried over Na_2SO_4 and concentrated. The residue was purified by open column chromatography (hexane/EtOAc = 100/1–50/1) to yield alcohol **15** (553 mg, 90%) as a colorless oil. **15**: $[\alpha]_D^{22} = -20.0$ (*c* 0.98, $CHCl_3$); IR (film) ν: 3469, 3071, 2929, 1589, 1461, 1427 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.64 (4H, m, TBDPS), 7.44–7.33 (6H, m, TBDPS), 4.73 (1H, d, *J* = 1.2 Hz, OH), 4.31 (1H, dd, *J* = 4.7, 2.0 Hz, H5), 4.26 (1H, dd, *J* = 2.0, 2.0 Hz, H6), 4.22 (1H, d, *J* = 3.5 Hz, H8), 4.21 (1H, m, H7), 3.94 (1H, dd, *J* = 9.4, 3.5 Hz, H8a), 3.74 (1H, m, H4), 3.68–3.57 (3H, m, H8a, H1x2), 1.89 (1H, m, H3), 1.74 (1H, m, H2), 1.49 (1H, m, H2), 1.46 (1H, m, H3), 1.06 (9H, s, TBDPS), 0.99 (9H, t, *J* = 7.8 Hz, TES), 0.96 (9H, t, *J* = 7.8 Hz, TES), 0.85 (9H, s, TBS), 0.64 (6H, q, *J* = 7.8 Hz, TES), 0.60 (6H, q, *J* = 7.8 Hz, TES), 0.11 (3H, s, TBS), 0.10 (3H, s, TBS); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 135.67 (CH, TBDPS), 133.62 (C, TBDPS), 129.72 (CH, TBDPS), 127.69 (CH, TBDPS), 79.71 (CH, C7), 79.06 (CH, C8), 77.08 (CH, C6), 76.94 (CH, C5), 74.15 (CH, C4), 72.94 (CH_2, C8a) 62.90 (CH_2, C1), 30.52 (CH_2, C2), 28.03 (CH_2, C3), 26.81 (CH_3, TBDPS), 25.63 (CH_3, TBS), 19.07 (C, TBDPS), 17.90 (C, TBS), 6.92 (CH_3, TES), 6.79 (CH_3, TES), 5.18 (CH_2, TES), 4.43 (CH_2, TES), −4.90 (CH_3, TBS), −5.17 (CH_3, TBS); HRMS (ESI) *m/z* calcd for $C_{43}H_{78}O_6Si_4Na$ $[(M+Na)]^+$ 825.4768, found 825.4755.

Ketone 16 and bis-carbonyl compound 7

To a solution of alcohol **15** (920 mg, 1.1 mmol) in CH_2Cl_2 (11 ml) was added pyridine (1.7 ml, 21 mmol), followed by DMP (2.9 g, 6.9 mmol) at 0 °C. The reaction mixture was allowed to warm to room temperature, stirred for 3.5 h, then quenched with saturated aqueous $NaHCO_3$ and saturated aqueous $Na_2S_2O_3$. The phases were separated and the aqueous phase was extracted with hexane/EtOAc = 5/1. The combined organic layer was washed with brine, dried over Na_2SO_4 and concentrated. The residue was purified by open column chromatography (hexane/EtOAc = **16**: 150/1, **7**: 5/1) to yield ketone **16** (220 mg, 24%) as a colorless oil and bis-carbonyl compound **7** (424 mg, 54%) as a colorless oil. **16**: $[\alpha]_D^{21} = -12.4$ (*c* 1.32, $CHCl_3$); IR (film) ν: 3072, 2930, 1778, 1589, 1461, 1427, 1389 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.75 (2H, dt, *J* = 6.5, 1.4 Hz, TBDPS), 7.62 (2H, dt, *J* = 6.5, 1.4 Hz, TBDPS), 7.46–7.34 (6H, m, TBDPS), 4.22 (1H, dd, *J* = 10.0, 8.6 Hz, H8), 4.14 (1H, d, *J* = 1.0 Hz, H6), 3.90 (1H, dd, *J* = 9.0, 8.6 Hz, H8a), 3.79 (1H, dd, *J* = 5.7, 1.0 Hz, H5), 3.64–3.56 (3H, m, H1x2, H4), 3.55 (1H, dd, *J* = 10.0, 9.0 Hz, H8a), 1.78 (1H, m, H3), 1.68 (1H, m, H2), 1.54–1.37 (2H, m, H3, H2), 1.08 (9H, s, TBDPS), 0.97 (9H, t, *J* = 7.8 Hz, TES), 0.91 (9H, t, *J* = 7.8 Hz, TES), 0.68 (9H, s, TBS), 0.60 (6H, q, *J* = 7.8 Hz, TES), 0.54 (6H, q, *J* = 7.8 Hz, TES), −0.05 (3H, s, TBS), −0.19 (3H, s, TBS); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 210.51 (C, C7), 135.80 (CH, TBDPS), 135.57 (CH, TBDPS), 133.49 (C, TBDPS), 132.31 (C, TBDPS), 130.00 (CH, TBDPS), 129.88 (CH, TBDPS), 127.78 (CH, TBDPS), 79.94 (CH, C6), 76.79 (CH, C5), 74.24 (CH, C4), 73.66 (CH, C8), 68.97 (CH_2, C8a) 63.28 (CH_2, C1), 30.53 (CH_2, C_2), 28.48 (CH_2, C3), 26.70 (CH_3, TBDPS), 25.64 (CH_3, TBS), 19.19 (C, TBDPS), 17.77 (C, TBS), 6.84 (CH_3, TES), 6.80 (CH_3, TES), 4.96 (CH_2, TES), 4.43 (CH_2, TES), −4.80 (CH_3, TBS), −4.94 (CH_3, TBS); HRMS (ESI) *m/z* calcd for $C_{43}H_{76}O_6Si_4Na$ $[(M+Na)]^+$ 823.4611, found 823.4611. **7**: $[\alpha]_D^{22} = -18.3$ (*c* 1.26, $CHCl_3$); IR (film) ν: 2930, 1777, 1712, 1589, 1471, 1428 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 9.74 (1H, dd, *J* = 2.0, 2.0 Hz, H1), 7.75 (2H, dt, *J* = 6.5, 1.6 Hz, TBDPS), 7.63 (2H, dt, *J* = 6.5, 1.6 Hz, TBDPS), 7.46–7.34 (6H, m, TBDPS), 4.22 (1H, dd, *J* = 10.0, 8.6 Hz, H8), 4.17 (1H, d, *J* = 1.0 Hz, H6), 3.93 (1H, dd, *J* = 8.8, 8.6 Hz, H8a), 3.84 (1H, dd, *J* = 5.5, 1.0 Hz, H5), 3.60 (1H, m, H4), 3.58 (1H, dd, *J* = 10.0, 8.8 Hz, H8a), 2.48 (1H, m, H2), 2.42 (1H, m, H2), 2.13 (1H, m, H3), 1.93 (1H, m, H3), 1.08 (9H, s, TBDPS), 0.91 (9H, t, *J* = 7.8 Hz, TES), 0.69 (9H, s, TBS), 0.54 (6H, q, *J* = 7.8 Hz, TES), −0.04 (3H, s, TBS), −0.18 (3H, s, TBS); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 210.75 (C, C7), 203.06 (C, C1), 135.78 (CH, TBDPS), 135.56 (CH, TBDPS), 133.38 (C, TBDPS), 132.20 (C, TBDPS), 130.05 (CH, TBDPS), 129.94 (CH, TBDPS), 127.80 (CH, TBDPS), 79.80 (CH, C6), 77.00 (CH, C5), 73.71 (CH, C8), 73.11 (CH, C4), 68.94 (CH_2, C8a), 40.89 (CH_2, C2), 26.69 (CH_3, TBDPS), 25.61 (CH_3, TBS), 25.27 (CH_2, C3), 19.18 (C, TBDPS), 17.74 (C, TBS), 6.78 (CH_3, TES), 4.85 (CH_2, TES), −4.88 (CH_3, TBS), −4.97 (CH_3, TBS); HRMS (ESI) *m/z* calcd for $C_{37}H_{60}O_6Si_3Na$ $[(M+Na)]^+$ 707.3590, found 707.3590.

Alcohol S8

To a solution of ketone **16** (63 mg, 78 μmol) in MeOH-CH_2Cl_2 (2:1, 1.5 ml) was added pyridinium *p*-toluenesulfonate(PPTS; 20 mg, 78 μmol) at −50 °C. The reaction mixture was gradually warmed to −20 °C over 1.5 h and then quenched with saturated aqueous $NaHCO_3$. The phases were separated and the aqueous phase was extracted with EtOAc. The combined organic layer was washed with brine, dried over Na_2SO_4 and concentrated. The residue was purified by open column chromatography (hexane/EtOAc = 20/1–10/1) to yield alcohol **S8** (48.8 mg, 91%) as a colorless oil. **S8**: $[\alpha]_D^{20} = -16.4$ (*c* 0.92, $CHCl_3$); IR (film) ν: 3541, 3072, 2929, 1777, 1590, 1471 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.75 (2H, m, TBDPS), 7.62 (2H, m, TBDPS), 7.46–7.34 (6H, m, TBDPS), 4.22 (1H, dd, *J* = 10.0, 8.8 Hz, H8), 4.14 (1H, d, *J* = 1.0 Hz, H6), 3.91 (1H, dd, *J* = 9.0, 8.8 Hz, H8a), 3.82 (1H, dd, *J* = 5.5, 1.0 Hz, H5), 3.68–3.63 (2H, m, H1x2), 3.60 (1H, m, H4), 3.56 (1H, dd, *J* = 10.0, 9.0 Hz, H8a), 1.85 (1H, m, H3), 1.70 (1H, m, H2), 1.58–1.45 (2H, m, H3, H2), 1.08 (9H, s, TBDPS), 0.92 (9H, t, *J* = 7.8 Hz, TES), 0.69 (9H, s, TBS), 0.54 (6H, q, *J* = 7.8 Hz, TES), −0.04 (3H, s, TBS), −0.18 (3H, s, TBS); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 210.77 (C, C7), 135.78 (CH, TBDPS), 135.56 (CH, TBDPS), 133.40 (C, TBDPS), 132.25 (C, TBDPS), 130.03 (CH, TBDPS), 129.91 (CH, TBDPS), 127.80 (CH, TBDPS), 79.89 (CH, C6), 76.78 (CH, C5), 73.95 (CH, C4), 73.72 (CH, C8), 68.92 (CH_2, C8a) 63.21 (CH_2, C1), 30.03 (CH_2, C2), 28.66 (CH_2, C3), 26.70 (CH_3, TBDPS), 25.63 (CH_3, TBS), 19.18 (C, TBDPS), 17.76 (C, TBS), 6.83 (CH_3, TES), 4.95 (CH_2, TES), −4.81 (CH_3, TBS), −4.90 (CH_3, TBS); HRMS (ESI) *m/z* calcd for $C_{37}H_{62}O_6Si_3Na$ $[(M+Na)]^+$ 709.3746, found 709.3751.

Bis-carbonyl compound 7

To a solution of alcohol **S8** (49 mg, 71 μmol) in CH_2Cl_2 (1.5 ml) was added $NaHCO_3$ (60 mg, 0.71 mmol), followed by DMP (90 mg, 0.21 mmol) at 0 °C. The reaction mixture was allowed to warm to room temperature, stirred for 1.5 h, then quenched with saturated aqueous $NaHCO_3$ and saturated aqueous $Na_2S_2O_3$. The phases were separated and the aqueous phase was extracted with EtOAc. The combined organic layer was washed with brine, dried over Na_2SO_4 and concentrated. The residue was purified by open column chromatography (hexane/EtOAc = 10/1) to yield dicarbonyl compound **7** (40.7 mg, 84%) as a colorless oil.

Oxetane acetal 18

To a solution of bis-carbonyl compound **7** (2.2 g, 3.2 mmol) in CH_2Cl_2 (64 ml) was added 1,8-diazabicyclo[5.4.0]undec-7-ene (0.96 ml, 6.4 mmol) at 0 °C. The reaction mixture was stirred at this temperature for 3 h and then quenched with saturated aqueous NH_4Cl. The phases were separated and the aqueous phase was extracted with EtOAc. The combined organic layer was washed with brine, dried over Na_2SO_4 and concentrated to provide aldehyde **17** (dr = 3.9:1), which was used in the next reaction.

To a solution of aldehyde **17** in $(CH_2Cl)_2$ (32 ml) was added 2,6-lutidine (2.2 ml, 19 mmol), followed by AgOTf (2.5 g, 9.6 mmol) and trityl chloride (2.7 mg, 9.6 mmol). After being stirred for 3.5 h at 50 °C, the mixture was filtered through filter paper and quenched with saturated aqueous $NaHCO_3$. The phases were separated and the aqueous phase was extracted with EtOAc. The combined organic layer was washed with brine, dried over Na_2SO_4 and concentrated. The residue was purified by flash column chromatography (hexane/EtOAc = 100/1, 1% Et_3N) to yield oxetane acetal **18** (2.23 g, 75%, 2 steps) as a white amorphous. **18**: $[\alpha]_D^{22} = -27.5$ (*c* 0.90, $CHCl_3$); IR (film) ν: 3057, 2930, 1732, 1597, 1492, 1470 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.84–7.79 (2H, m, TBDPS), 7.76–7.72 (2H, m, TBDPS), 7.46–7.16 (21H, m, TBDPS, Tr), 5.55 (1H, d, *J* = 4.9 Hz, H1), 4.26 (1H, d, *J* = 3.3 Hz, H6), 3.89 (1H, dd, *J* = 9.8, 7.4 Hz, H8), 3.67–3.60 (2H, m, H5, H4), 3.50–3.40 (2H, m, H8ax2), 2.76 (1H, dd, *J* = 8.4, 4.9 Hz, H2), 1.22 (1H, m, H3), 1.17 (9H, s, TBDPS), 0.74 (9H, t, *J* = 8.0 Hz, TES), 0.68 (9H, s, TBS), 0.34 (6H, m, TES), 0.29 (1H, m, H3), −0.13 (3H, s, TBS), −0.28 (3H, s, TBS); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 144.93 (C, Tr), 136.10 (CH, TBDPS), 136.02 (CH, TBDPS), 134.11 (C, TBDPS), 133.98 (C, TBDPS), 129.62 (CH, TBDPS), 129.59 (CH, TBDPS), 128.70 (CH, Tr), 127.72 (CH, Tr), 127.63 (CH), 127.54 (CH), 126.78

(CH), 101.19 (CH, C1), 87.32 (C, Tr), 82.08 (CH, C6), 80.39 (C, C7), 75.26 (CH, C8), 70.60 (CH, C4), 69.79 (CH, C5), 68.62 (CH_2, C8a), 42.72 (CH, C2), 27.13 (CH_3, TBDPS), 25.64 (CH_3, TBS), 23.35 (CH_2, C3), 19.61 (C, TBDPS), 17.86 (C, TBS), 6.73 (CH_3, TES), 4.61 (CH_2, TES), −4.93 (CH_3, TBS), −5.56 (CH_3, TBS); HRMS (ESI) *m/z* calcd for $C_{56}H_{74}O_6Si_3Na$ $[(M+Na)]^+$ 949.4685, found 949.4667.

Ketone 19

To a solution of oxetane acetal **18** (20.3 mg, 0.022 mmol) in THF (0.44 ml) were added TBAF (0.33 ml, 1.0 M in THF, 0.33 mmol) and AcOH (0.16 ml, 1.0 M in THF, 0.16 mmol) at 0 °C. The reaction mixture was allowed to warm to room temperature, stirred for 1 h and then passed through a short pad of silica, eluting with CH_2Cl_2. The solution was concentrated to provide a mixture of alcohol **S9** and oxetane acetal **18**, which was used in the next reaction.

To a solution of alcohol **S9** and oxetane acetal **18** mixture in $(CH_2Cl)_2$ (1.1 ml) was added MS4A, followed by NMO (7.7 mg, 0.066 mmol) and TPAP (1.5 mg, 4.4 μmol) at room temperature. The reaction mixture was stirred for 1 h and then filtered through a short pad of silica eluting with CH_2Cl_2 and concentrated. The residue was purified by flash column chromatography (hexane/EtOAc = **18**: 100/1, **19**: 50/1–10/1, 1% Et_3N) to yield ketone **19** (12.7 mg, 71%, 2 steps) as a white amorphous along with oxetane acetal **18** (~3 mg). **19**: $[\alpha]_D^{20} = -13.9$ (*c* 1.23, $CHCl_3$); IR (film) *ν*: 3068, 2929, 1731, 1589, 1471, 1427 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.89–7.86 (2H, m, TBDPS), 7.76–7.71 (2H, m, TBDPS), 7.46–7.22 (21H, m, TBDPS, Tr), 5.19 (1H, d, *J* = 5.1 Hz, H1), 4.33 (1H, d, *J* = 2.5 Hz, H6), 4.24 (1H, t, *J* = 4.7 Hz, H8), 4.06 (1H, d, *J* = 2.5 Hz, H5), 3.63 (2H, m, H8ax2), 2.72 (1H, dd, *J* = 9.2, 5.1 Hz, H2), 2.04 (1H, dd, *J* = 18.4, 9.2 Hz, H3), 1.17 (9H, s, TBDPS), 0.98 (1H, d, *J* = 18.4 Hz, H3), 0.81 (9H, s, TBS), 0.01 (3H, s, TBS), −0.09 (3H, s, TBS); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 207.09 (C, C4), 144.10 (C, Tr), 136.17 (CH, TBDPS), 135.86 (CH, TBDPS), 133.84 (C, TBDPS), 133.27 (C, TBDPS), 129.82 (CH, TBDPS), 129.76 (CH, TBDPS), 128.45 (CH, Tr), 128.07 (CH, Tr), 127.74 (CH), 127.72 (CH), 127.44 (CH), 100.37 (CH, C1), 88.78 (C, Tr), 82.81 (CH, C6), 81.79 (C, C7), 75.99 (CH, C8), 75.71 (CH, C5), 72.36 (CH_2, C8a), 44.56 (CH, C2), 33.75 (CH_2, C3), 26.96 (CH_3, TBDPS), 25.76 (CH_3, TBS), 19.49 (C, TBDPS), 18.34 (C, TBS), −4.86 (CH_3, TBS), −5.35 (CH_3, TBS); HRMS (ESI) *m/z* calcd for $C_{50}H_{58}O_6Si_2Na$ $[(M+Na)]^+$ 833.3664, found 833.3678.

Vinyl iodide S11

To a solution of ketone **19** (73 mg, 89 μmol) in EtOH (1.8 ml) was added Et_3N (62 μl, 0.45 mmol), followed by $H_2NNH_2{\cdot}H_2O$ (43 μl, 0.89 mmol) at 60 °C. The reaction mixture was stirred at this temperature for 3 h and then quenched with H_2O. The phases were separated and the aqueous phase was extracted with EtOAc. The combined organic layer was washed with brine, dried over Na_2SO_4 and concentrated to hydrazone **S10**, which was used in the next reaction.

To a solution of hydrazone **S10** in THF (1.8 ml) was added Et_3N (124 μl, 0.89 mmol), followed by I_2 (357 μl, 1.0 M in THF, 0.36 mmol) at 0 °C. The reaction mixture was stirred at this temperature for 1 h and then quenched with H_2O. The phases were separated and the aqueous phase was extracted with EtOAc. The combined organic layer was washed with brine, dried over Na_2SO_4 and concentrated. The residue was purified by flash column chromatography (hexane/EtOAc = 100/1, 1% Et_3N) to yield vinyl iodide **S11** (45.6 mg, 55%, 2 steps) as a white amorphous. **S11**: $[\alpha]_D^{19} = -21.9$ (*c* 1.27, $CHCl_3$); IR (film) *ν*: 3069, 2929, 2857, 1724, 1647, 1597, 1471 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.86–7.82 (2H, m, TBDPS), 7.79–7.75 (2H, m, TBDPS), 7.48–7.23 (21H, m, TBDPS, Tr), 5.10 (1H, d, *J* = 4.1 Hz, H1), 4.64 (1H, d, *J* = 4.1 Hz, H3), 4.29 (1H, dd, *J* = 6.4, 6.4 Hz, H8), 4.18 (1H, d, *J* = 4.3 Hz, H6), 4.15 (1H, d, *J* = 4.3 Hz, H5), 3.60 (1H, dd, *J* = 8.4, 6.4 Hz, H8a), 3.58 (1H, dd, *J* = 8.4, 6.4 Hz, H8a), 2.69 (1H, dd, *J* = 4.1, 4.1 Hz, H2), 1.19 (9H, s, TBDPS), 0.78 (9H, s, TBS), 0.10 (3H, s, TBS), −0.09 (3H, s, TBS); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 144.09 (C, Tr), 136.07 (CH, TBDPS), 135.97 (CH, TBDPS), 135.47 (CH, C3), 133.92 (C, TBDPS), 133.71 (C, TBDPS), 129.75 (CH), 128,46 (CH, Tr), 128.05 (CH, Tr), 127.71 (CH), 127.63 (CH), 127.22 (CH), 100.92 (CH, C1), 99.05 (C, C4), 87.92 (C, Tr), 81.58 (CH, C6), 80.97 (C, C7), 74.89 (CH, C8), 74.62 (CH, C5), 70.23 (CH_2, C8a), 49.68 (CH, C2), 27.11 (CH_3, TBDPS), 25.94 (CH_3, TBS), 19.59 (C, TBDPS), 18.04 (C, TBS), −4.46 (CH_3, TBS), −4.72 (CH_3, TBS); HRMS (ESI) *m/z* calcd for $C_{50}H_{57}IO_5Si_2Na$ $[(M+Na)]^+$ 943.2681, found 943.2681.

Hexahydrobenzofuran 20

To a solution of vinyl iodide **S11** (87 mg, 95 μmol) in DMF-toluene-H_2O (2:1:1, 4.8 ml) were added Cs_2CO_3 (618 mg, 1.9 mmol) and $MeB(OH)_2$ (57 mg, 0.95 mmol), followed by Pd(dppf)Cl_2 (16 mg, 19 μmol) at 60 °C. The reaction mixture was stirred at this temperature overnight and then quenched with H_2O. The phases were separated and the aqueous phase was extracted with hexane/EtOAc = 5/1. The combined organic layer was washed with brine, dried over Na_2SO_4 and concentrated. The residue was purified by flash column chromatography (hexane/EtOAc = 100/1, 1% Et_3N) to yield hexahydrobenzofuran **20** (72.1 mg, 94%) as a white amorphous. **20**: $[\alpha]_D^{18} = -40.3$ (*c* 0.98, $CHCl_3$); IR (film) *ν*: 3057, 2929, 2856, 1726, 1597, 1471, 1427 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.87–7.83 (2H, m, TBDPS), 7.79–7.76 (2H, m, TBDPS), 7.46–7.20 (21H, m, TBDPS, Tr), 5.00 (1H, d, *J* = 3.5 Hz, H1), 4.29 (1H, dd, *J* = 5.5, 5.5 Hz, H8), 4.13 (1H, d, *J* = 4.1 Hz, H6), 4.07 (1H, d, *J* = 4.5 Hz, H3), 3.98 (1H, d, *J* = 4.1 Hz, H5), 3.55 (1H, dd, *J* = 9.0, 5.5 Hz, H8a), 3.49 (1H, dd, *J* = 9.0, 5.5 Hz, H8a), 2.70 (1H, m, H2), 1.54 (3H, s, Me4a), 1.17 (9H, s, TBDPS), 0.79 (9H, s, TBS), 0.00 (3H, s, TBS), −0.06 (3H, s, TBS); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 144.39 (C, Tr), 136.99 (C, C4), 136.12 (CH, TBDPS), 135.96 (CH, TBDPS), 134.26 (C, TBDPS), 133.80 (C, TBDPS), 129.62 (CH), 128.59 (CH, Tr), 127.92 (CH, Tr), 127.65 (CH), 127.59 (CH), 127.08 (CH), 118.79 (CH, C3), 102.72 (CH, C1), 87.96 (C, Tr), 82.43 (C, C7), 80.03 (CH, C6), 75.93 (CH, C8), 70.88 (CH_2, C8a), 69.81 (CH, C5), 46.56 (CH, C2), 27.10 (CH_3, TBDPS), 25.83 (CH_3, TBS), 20.89 (CH_3, C4a), 19.61 (C, TBDPS), 18.12 (C, TBS), −4.43 (CH_3, TBS), −5.11 (CH_3, TBS); HRMS (ESI) *m/z* calcd for $C_{51}H_{60}O_5Si_2Na$ $[(M+Na)]^+$ 831.3871, found 831.3871.

Diol S12

To a solution of vinyl hexahydrobenzofuran **20** (49 mg, 61 μmol) in THF (1.2 ml) was added TBAF (1.2 ml, 1.0 M in THF, 1.2 mmol) at 40 °C. The reaction mixture was stirred at this temperature for 6 h and then quenched with H_2O. The phases were separated and the aqueous phase was extracted with EtOAc. The combined organic layer was washed with brine, dried over Na_2SO_4 and concentrated. The residue was purified by flash column chromatography (hexane/EtOAc = 3/1–1/1, 1% Et_3N) to yield diol **S12** (18.7 mg, 67%) as a white amorphous. **S12**: $[\alpha]_D^{19} = -82.4$ (*c* 0.94, $CHCl_3$); IR (film) *ν*: 3435, 3059, 2929, 1718, 1597, 1491, 1448 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.45–7.41 (6H, m, Tr), 7.35–7.24 (9H, m, Tr), 5.16 (1H d, *J* = 3.5 Hz,, H1), 4.68 (1H, dd, *J* = 3.1, 1.8 Hz, H3), 4.11 (1H, dd, *J* = 8.6, 8.6 Hz, H8a), 4.07 (1H, ddd, *J* = 8.8, 8.6, 8.6 Hz, H8), 4.02 (1H, d, *J* = 4.5 Hz, H6), 3.98 (1H, dd, *J* = 4.5, 2.2 Hz, H5), 3.49 (1H, dd, *J* = 8.6, 8.6 Hz, H8a), 3.26 (1H, ddd, *J* = 3.5, 3.1, 1.8 Hz, H2), 3.22 (1H, d, *J* = 8.8 Hz, OH), 2.31 (1H, d, *J* = 2.2 Hz, OH), 1.76 (3H, dd, *J* = 1.8, 1.8 Hz, Me4a); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 143.88 (C, Tr), 135.62 (C, C4), 128.39 (CH, Tr), 128.11 (CH, Tr), 127.43 (CH, Tr), 121.46 (CH, C3), 101.95 (CH, C1), 88.30 (C, Tr), 82.55 (C, C7), 82.40 (CH, C6), 74.03 (CH, C8), 70.71 (CH_2, C8a), 67.84 (CH, C5), 46.75 (CH, C2), 21.92 (CH_3, C4a); HRMS (ESI) *m/z* calcd for $C_{29}H_{28}O_5$ $[(M+Na)]^+$ 479.1829, found 479.1829.

Bis-TBS ether S13

To a solution of diol **S12** (15.4 mg, 34 μmol) in DMF (0.84 ml) were added imidazole (46 mg, 0.67 mmol) followed by TBSCl (51 mg, 0.34 mmol) at 40 °C. The reaction mixture was stirred at this temperature for 3.5 h and then quenched with saturated aqueous $NaHCO_3$. The phases were separated and the aqueous phase was extracted with hexane/EtOAc = 5/1. The combined organic layer was washed with brine, dried over Na_2SO_4 and concentrated. The residue was purified by flash column chromatography (hexane/EtOAc = 100/1, 1% Et_3N) to yield bis-TBS ether **S13** (17.2 mg, 75%) as a white solid. A single crystal for X-ray analysis was prepared by recrystallization from hexane and EtOAc. **S13**: m.p. = 154 °C; $[\alpha]_D^{19} = -61.5$ (*c* 0.90, $CHCl_3$); IR (film) *ν*: 2928, 2856, 1731, 1621, 1471, 1448 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ:7.50–7.44 (6H, m, Tr), 7.34–7.21 (9H, m, Tr), 5.00 (1H, d, *J* = 3.5 Hz, H1), 4.29 (1H, dd, *J* = 5.5, 5.5 Hz, H8), 4.28 (1H, d, *J* = 5.5 Hz, H3), 4.05 (1H, d, *J* = 4.1 Hz, H6), 4.03 (1H, d, *J* = 4.1 Hz, H5), 3.85 (1H, dd, *J* = 8.8, 5.5 Hz, H8a), 3.65 (1H, dd, *J* = 8.8, 5.5 Hz, H8a), 2.79 (1H, m, H2), 1.58 (3H, s, Me4a), 0.98 (9H, s, TBS),

0.86 (9H, s, TBS), 0.22 (3H, s, TBS), 0.18 (3H, s, TBS), 0.07 (3H, s, TBS), 0.05 (3H, s, TBS); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 144.35 (C, Tr), 137.17 (C, C4), 128.57 (CH, Tr), 127.92 (CH, Tr), 127.12 (CH, Tr), 118.65 (CH, C3), 102.65 (CH, C1), 87.88 (C, Tr), 82.30 (C, C7), 79.54 (CH, C6), 75.66 (CH, C8), 71.33 (CH_2, C8a), 69.75 (CH, C5), 46.66 (CH, C2), 26.02 (CH_3, TBS), 25.86 (CH_3, TBS), 20.88 (CH_3, C4a), 18.45 (C, TBS), 18.18 (C, TBS), −4.23 (CH_3, TBS), −4.28 (CH_3, TBS), −4.60 (CH_3, TBS), −5.08 (CH_3, TBS); HRMS (ESI) *m/z* calcd for $C_{41}H_{56}O_5Si_2Na$ $[(M+Na)]^+$ 707.3558, found 707.3558.

Alcohol 21

To a solution of TBDPS ether **20** (92.5 mg, 0.114 mmol) in THF (1.5 ml) was added 10% solution of NaOH in MeOH (11.4 ml) at room temperature. The reaction mixture was heated to 65 °C, stirred for 3 h at this temperature and then EtOAc and H_2O were added. The phases were separated and aqueous phase was extracted with EtOAc. The combined organic layer was washed with H2O, brine, dried over Na_2SO_4 and concentrated. The residue was purified by flash column chromatography (hexane/EtOAc = 200/1–100/1) to yield alcohol **21** (34.6 mg, 53%) as a white amorphous. **21**: $[\alpha]_D^{20}$ −82.4 (*c* 0.73, $CHCl_3$); IR (film) *ν*: 3528, 2928, 1734, 1560, 1449, 1388 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.46–7.40 (m, 6H, Tr), 7.36–7.23 (m, 9H, Tr), 5.16 (d, *J* = 3.3 Hz, 1H, H1), 4.64 (dd, *J* = 2.7, 1.8 Hz, 1H, H3), 4.16 (ddd, *J* = 9.4, 8.4, 8.4 Hz, 1H, H8), 4.07 (dd, *J* = 8.4, 8.4 Hz, 1H, H8a), 3.93 (d, *J* = 3.7 Hz, 1H, H6), 3.89 (d, *J* = 3.7 Hz, 1H, H5), 3.43 (dd, *J* = 8.4, 8.4 Hz, 1H, H8a), 3.31 (ddd, *J* = 3.3, 2.7, 1.8 Hz, 1H, H2), 3.20 (d, *J* = 9.4 Hz, 1H, OH), 1.68 (dd, *J* = 1.8, 1.8 Hz, 3H, H4a), 0.82 (s, 9H, TBS), 0.04 (s, 3H, TBS), 0.02 (s, 3H, TBS); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 144.04 (C, Tr), 137.27 (C, C4), 128.43 (CH, Tr), 128.07 (CH, Tr), 127.39 (CH, Tr), 120.70 (CH, C3), 101.91 (CH, C1), 88.40 (C, Tr), 83.64 (C, C7), 82.29 (CH, C6), 73.71 (CH, C8), 71.02 (CH_2, C8a), 69.85 (CH, C5), 46.88 (CH, C2), 25.76 (CH_3, TBS), 21.70 (CH_3, C4a), 18.04 (C, TBS), −4.44 (CH_3, TBS), −5.11 (CH_3, TBS); HRMS (ESI) *m/z* calcd for $C_{35}H_{42}O_5S$-iNa $[(M+Na)]^+$ 593.2694, found 593.2691.

The south segment ketone 6

To a solution of alcohol **21** (7.8 mg, 14 μmol) in CH_2Cl_2-pyridine (1:1, 1.4 ml) was added DMP (17 mg, 41 mmol) at 0 °C. The reaction mixture was allowed to warm to room temperature, stirred for 3 h, then quenched with saturated aqueous $NaHCO_3$ and saturated aqueous $Na_2S_2O_3$. The phases were separated and the aqueous phase was extracted with hexane/EtOAc = 5/1. The combined organic layer was washed with brine, dried over Na_2SO_4 and concentrated *in vacuo* to give the crude products. The residue was filtered through a florisil short column to give ketone **6**, which was used in next reaction without further purification. **6**: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.49–7.45 (m, 6H, Tr), 7.35–7.24 (m, 9H, Tr), 5.08 (d, *J* = 3.7 Hz, 1H, H1), 4.61 (dd, *J* = 3.7, 1.6 Hz, 1H, H3), 4.20 (d, *J* = 3.5 Hz, 1H, H6), 4.19 (d, *J* = 17.6 Hz, 1H, H8a), 4.18 (d, *J* = 3.5 Hz, 1H, H5), 4.12 (dd, *J* = 17.6 Hz, 1H, H8a), 3.34 (ddd, *J* = 3.7, 2.7, 2.0 Hz, 1H, H2), 1.68 (dd, *J* = 2.0, 1.6 Hz, 3H, H4a), 0.81 (s, 9H, TBS), 0.06 (s, 3H, TBS), 0.02 (s, 3H, TBS); HRMS (ESI) *m/z* calcd for $C_{35}H_{40}O_5SiNa$ $[(M+Na)]^+$ 591.2537, found 591.2537.

Alcohol S14

To a solution of 4-trimethylsilyl-3-butyn-2-one **24** (6.60 ml, 40 mmol) in degassed 2-propanol (400 ml) at 35 °C was added Ru[(1*R*,2*R*)-*p*-TsNCH(C_6H_5)CH(C_6H_5)NH](η^6-*p*-cymene) **25** (240 mg, 0.40 mmol). The reaction mixture was stirred overnight and then the solvent was removed *in vacuo*. The residue was distilled under reduce pressure at 80–90 °C to yield alcohol **S14** (5.01 g, 88%) as a colorless oil. **S14**: $[\alpha]_D^{24}$ = 28.6 (*c* 2.96, $CHCl_3$) (***ent*-S14**: lit. $[\alpha]_D^{23}$ = −27.6 (*c* 2.97, $CHCl_3$), 98% ee (*S*)[28]); IR (film) *ν*: 3338, 2961, 2899, 2175, 1406, 1327, 1250, 1119, 1046 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 4.51 (1H, qd, *J* = 6.7, 5.2 Hz, H24), 1.80 (1H, d, *J* = 5.2 Hz, OH), 1.45 (3H, d, *J* = 6.7 Hz, Me24a), 0.17 (9H, s, TMS); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 107.61 (C, C23), 88.41 (C, C22), 58.76 (CH, C24), 24.23 (CH_3, C24a), −0.17 (CH_3, TMS); HRMS (ESI) *m/z* calcd for $C_7H_{14}OSiNa$ $[M+Na]^+$ 165.0706, found 165.0703.

Mesylate 26

To a solution of alcohol **S14** (5.01 g, 35 mmol) in CH_2Cl_2 (70 ml) at −90 °C was added Et_3N (9.8 ml, 70 mmol), followed by MsCl (4.1 ml, 53 mmol). After being stirred for 3 h at the same temperature, the reaction mixture was gradually warmed to −20 °C and then quenched with saturated aqueous $NaHCO_3$. The phases were separated and the aqueous phase was extracted with Et_2O. The combined organic layer was washed with brine, dried over Na_2SO_4 and concentrated. The residue was purified by open column chromatography (hexane/EtOAc = 15/1) to yield mesylate **26** (7.43 g, 96%) as yellowish oil. **26**: $[\alpha]_D^{25}$ = 116.1 (*c* 2.32, $CHCl_3$); IR (film) *ν*: 2961, 2177, 1363, 1252, 1718, 1126, 1091, 1024 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.26 (1H, q, *J* = 6.8 Hz, H24), 3.12 (3H, s, Ms), 1.63 (3H, d, *J* = 6.8 Hz, Me24a), 0.19 (9H, s, TMS); ^{13}C NMR (100 MHz, $CDCl_3$) δ:101.21 (C, C23), 93.66 (C, C22), 68.58 (CH, C24), 39.10 (CH_3, Ms), 22.46 (CH_3, C24a), −0.49 (CH_3, TMS); HRMS (ESI) *m/z* calcd for $C_8H_{16}O_3SSiNa$ $[M+Na]^+$ 243.0482, found 243.0484.

Aldehyde 27

To a solution of (*S*)-(-)-2-methyl-1-butanol (7.6 ml, 70 mmol) in CH_2Cl_2 (70 ml) at 0 °C was added TEMPO (1.1 g, 7.0 mmol), followed by $PhI(OAc)_2$ (24.8 g, 77 mmol). After being stirred for 3 h at room temperature, the reaction mixture was quenched with saturated aqueous $Na_2S_2O_3$. The phases were separated and the aqueous phase was extracted with CH_2Cl_2. The combined organic layer was washed with saturated aqueous $NaHCO_3$ and brine, dried over $MgSO_4$ and concentrated to provide aldehyde **27**, which was used in the next reaction without further purification.

Homopropargyl alcohol 28

To a solution of $Pd(OAc)_2$ (337 mg, 1.5 mmol) in THF (300 ml) was added PPh_3 (393 mg, 1.5 mmol) at −90 °C. Then, aldehyde **27** (~70 mmol), mesylate **26** (6.6 g, 30 mmol) and Et_2Zn (90 ml, 1 M in hexane, 90 mmol) were added sequentially. The reaction mixture was allowed to warm to −20 °C and stirred overnight. After being stirred for 4 h at 0 °C, the reaction mixture was quenched with saturated aqueous NH_4Cl. The phases were separated and the aqueous phase was extracted with Et_2O. The combined organic layer was washed with brine and H2O, dried over $MgSO_4$ and concentrated. The residue was purified by open column chromatography (hexane/EtOAc = 100/1–50/1) to yield alcohol **28** (5.00 g, 78%, dr = 14:1) as a yellow oil. **28**: $[\alpha]_D^{25}$ −1.8 (*c* 1.02, $CHCl_3$); IR (film) *ν*: 3568, 2961, 2935, 2876, 2164, 1458, 1376, 1249 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.22 (1H, ddd, *J* = 6.1, 6.1, 4.7 Hz, H25), 2.68 (1H, qd, *J* = 6.9, 6.1 Hz, H24), 1.86 (1H, d, *J* = 6.1 Hz, OH), 1.55–1.41 (2H, m, H26, H27), 1.27 (1H, dqd, *J* = 14.9, 7.3, 1.8 Hz, H27), 1.17 (3H, d, *J* = 6.9 Hz, Me24a), 0.90 (3H, d, *J* = 6.9 Hz, Me26a), 0.90 (3H, t, *J* = 7.3 Hz, Me28), 0.15 (9H, s, TMS); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 108.19 (C, C22), 87.46 (C, C23), 77.11 (CH, C25), 37.55 (CH, C26), 31.88 (CH, C24), 26.58 (CH_2, C27), 17.69 (CH_3, C24a), 13.12 (CH_3, C26a), 11.62 (CH_3, C28), 0.12 (CH_3, TMS); HRMS (ESI) *m/z* calcd for $C_{12}H_{24}OSiNa$ $[M+Na]^+$ 235.1489, found 235.1489.

TMS ether 29

To a solution of alcohol **28** (5.00 g, 24 mmol) in MeOH (17 ml) was added K_2CO_3 (4.90 g, 35 mmol) at room temperature. After being stirred for 1.5 h, the reaction mixture was quenched with Et_2O and H_2O. The phases were separated and the aqueous phase was extracted with Et_2O. The combined organic layer was dried over $MgSO_4$ and concentrated. The residue was filtered through a short pad of silica gel (hexane/Et_2O = 1/1) to yield terminal alkyne **S15**, which was used in the next reaction.

To a solution of **S15** (<24 mmol) in CH_2Cl_2 (235 ml) was added TMS-imidazole (5.2 ml, 35 mmol) at 0 °C. After being stirred for 5 h at room temperature, the reaction mixture was quenched with Et_2O and H_2O. The phases were separated and the aqueous phase was extracted with Et_2O. The combined organic layer was dried over $MgSO_4$ and concentrated. The residue was purified by open column chromatography (hexane) to yield TMS ether **29** (4.35 g, 87%, 2 steps) as a colorless oil. **29**: $[\alpha]_D^{26}$ 4.9 (*c* 1.03, $CHCl_3$); IR (film) *ν*: 3306, 3018, 2964, 2399, 1250, 1215, 1055 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.43 (1H, dd, *J* = 6.3, 4.7 Hz, H25), 2.62 (1H, qdd, *J* = 7.0, 6.3, 2.5 Hz, H24), 2.04 (1H, d, *J* = 2.5 Hz, H22), 1.55 (1H, m, H26), 1.41 (1H, dqd, *J* = 12.9, 7.4, 2.3 Hz, H27), 1.19 (1H, dq, *J* = 12.9, 7.4 Hz, H27), 1.15 (3H, d, *J* = 7.0 Hz, Me24a), 0.90 (3H, t, *J* = 7.4 Hz, Me28), 0.85 (3H, d, *J* = 6.7 Hz, Me26a), 0.15 (9H, s, TMS); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 87.77 (C, C23), 78.96 (CH, C25), 69.39 (CH, C22), 37.81 (CH, C26), 30.96 (CH, C24), 26.84 (CH_2, C27),

17.95 (CH_3, C24a), 13.60 (CH_3, C26a), 11.75 (CH_3, C28), 0.89 (CH_3, TMS); HRMS (ESI) *m/z* calcd for $C_{12}H_{24}OSiNa$ $[M+Na]^+$ 235.1489, found 235.1492.

Benzyl ether 30

To a solution of 1,3-propanediol (21.0 ml, 0.30 mol) in THF (100 ml) was added NaH (6.00 g, 60% in oil, 0.15 mol) at 0 °C. The reaction mixture was stirred at this temperature for 1 h and then BnBr (12 ml, 0.10 mol) was added. The reaction mixture was gradually warmed to room temperature, stirred overnight, and then quenched with saturated aqueous NH_4Cl. The phases were separated and the aqueous phase was extracted with EtOAc. The combined organic layer was washed with brine, dried over Na_2SO_4 and concentrated. The residue was purified by open column chromatography (hexane/EtOAc = 4/1–2/1) to yield mono-benzyl ether **30** (17.0 g, 100%) as a colorless oil. **30**: IR (film) *ν*: 3391, 3030, 2944, 2866, 1718, 1453, 1364, 1275, 1074 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ: 7.37–7.27 (5H, m, Bn), 4.53 (2H, s, Bn), 3.79 (2H, td, *J* = 5.6, 5.6 Hz, H17), 3.67 (2H, t, *J* = 5.6 Hz, H15), 2.26 (1H, m, OH), 1.87 (2H, tt, *J* = 5.6, 5.6 Hz, H16); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 138.02 (C, Bn), 128.44 (CH, Bn), 127.71 (CH, Bn), 127.64 (CH, Bn), 73,27 (CH_2, Bn), 69.42 (CH_2, C15), 61.95 (CH_2, C17), 32.05 (CH_2, C16); HRMS (ESI) *m/z* calcd for $C_{10}H_{14}O_2Na$ $[M+Na]^+$ 189.0886, found 189.0886.

β-Ketoester 34

To a solution of **30** (3.00 g, 18 mmol) in CH_2Cl_2 (18 ml) was added TEMPO (0.28 g, 1.8 mmol), followed by $PhI(OAc)_2$ (6.4 g, 20 mmol) at 0 °C. The reaction mixture was allowed to warm to room temperature, stirred for 1.5 h and then quenched with saturated aqueous $Na_2S_2O_3$. The phases were separated and the aqueous phase was extracted with CH_2Cl_2. The combined organic layer was washed with saturated aqueous $NaHCO_3$ and brine, dried over $MgSO_4$ and concentrated to provide aldehyde **31**, which was used directly.

To a solution of Schiff base **33** (1.4 g, 3.6 mmol) in CH_2Cl_2 (18 ml) was added Ti(Oi-Pr)$_4$ (5.3 mmol, 18 mmol) at room temperature. The reaction mixture was stirred for 1 h and then cooled to −40 °C. To the reaction mixture were added aldehyde **31** (<18 mmol) and diketene **32** (2.8 ml, 36 mmol), stirred at this temperature for 48 h and then quenched with EtOAc and 1 N HCl. After being stirred for 2 h at room temperature, the phases were separated and the aqueous phase was extracted with EtOAc. The combined organic layer was dried over Na_2SO_4 and concentrated. The residue was purified by open column chromatography (hexane/EtOAc = 5/1–4/1) to yield β-ketoester **34** (2.98 g, 54%, 2 steps) as a yellow oil. **34**: $[\alpha]_D^{30} = -13.4$ (*c* 1.00, $CHCl_3$). The ee was determined to be 76% by HPLC analysis (Chiralpak AD, 5% ethanol and 0.01% trifluoroacetic acid in hexane, 1.0 ml min^{-1}, $\lambda = 254$ nm, *S* isomer 15.3 min, *R* isomer 19.2 min); IR (film) *ν*: 3503, 2981, 2935, 2868, 1735, 1717, 1313, 1105 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.37–7.27 (5H, m, Bn), 5.05 (1H, sept, *J* = 6.2 Hz, *i*Pr), 4.51 (2H, s, Bn), 4.30 (1H, m, H17), 3.69–3.58 (2H, m, H15x2), 3.44 (2H, s, H20), 3.29 (1H, brs, OH), 2.75–2.65 (2H, m, H18x2), 1.83–1.69 (2H, m, H16x2), 1.25 (6H, d, *J* = 6.2 Hz, *i*Pr); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 202.98 (C, C19), 166.47 (C, C21), 137.89 (C, Bn), 128.36 (CH, Bn), 127.65 (CH, Bn), 127.60 (CH, Bn), 73,19 (CH_2, Bn), 68.98 (CH, *i*Pr), 67.93 (CH_2, C15), 66.57 (CH, C17), 50.16 (CH_2, C20), 49.69 (CH_2, C18), 35.94 (CH_2, C16), 21.60 (CH_3, *i*Pr); HRMS (ESI) *m/z* calcd for $C_{17}H_{24}O_5Na$ $[M+Na]^+$ 331.1516, found 331.1521.

Diol S16

To a solution of $NaBH(OAc)_3$ (4.10 g, 19 mmol) in MeCN (96 ml) were added AcOH (3.30 ml, 58 mmol) and β-ketoester **34** (2.98 g, 9.6 mmol) at −60 °C. The reaction mixture was gradually warmed to 0 °C, stirred overnight and then quenched with K_2CO_3 and H_2O. The phases were separated and the aqueous phase was extracted with EtOAc. The combined organic layer was washed with saturated aqueous $NaHCO_3$ and brine, dried over Na_2SO_4 and concentrated. The residue was purified by open column chromatography (hexane/EtOAc = 2/1–1/1) to yield diol **S16** (2.48 g, 83%) as a yellowish oil. **S16**: $[\alpha]_D^{27} = -0.97$ (*c* 1.07, $CHCl_3$, 76% ee); IR (film) *ν*: 3447, 2979, 2937, 2866, 1734, 1718, 1707, 1375, 1281, 1107 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.37–7.27 (5H, m, Bn), 5.04 (1H, sept, *J* = 6.3 Hz, *i*Pr), 4.52 (2H, s, Bn), 4.32 (1H, m, H19), 4.15 (1H, m, H17), 3.76–3.61 (2H, m, H15x2), 3.57 (1H, d, *J* = 3.9 Hz, C19-OH), 3.45 (1H, d, *J* = 2.9 Hz, C17-OH), 2.52–2.38 (2H, m, H20), 1.87 (1H, m, H16), 1.73 (1H, m, H16), 1.66–1.57 (2H, m, H18), 1.24 (6H, d, *J* = 6.3 Hz, *i*Pr); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 172.24 (C, C21), 137.82 (C, Bn), 128.46 (CH, Bn), 127.77 (CH, Bn), 127.68 (CH, Bn), 73.37 (CH_2, Bn), 69.16 (CH_2, C15), 68.68 (CH, C17), 68.11 (CH, *i*Pr), 65.61 (CH, C19), 42.39 (CH_2, C18), 41.79 (CH_2, C20), 36.49 (CH_2, C16), 21.79 (CH_3, *i*Pr); HRMS (ESI) *m/z* calcd for $C_{17}H_{26}O_5Na$ $[M+Na]^+$ 333.1672, found 333.1676.

Lactone 35

To a solution of diol **S16** (2.48 g, 8.0 mmol) in $(CH_2Cl)_2$ (40 ml) was added PPTS (100 mg, 0.40 mmol). The reaction mixture was stirred for 5 h under reflux conditions and then introduced additional PPTS (100 mg, 0.40 mmol). The reaction mixture was stirred at this temperature for 1.5 h and then quenched with saturated aqueous $NaHCO_3$. The phases were separated and the aqueous phase was extracted with EtOAc. The combined organic layer was washed with brine and dried over Na_2SO_4 and concentrated. The residue was purified by open column chromatography (hexane/EtOAc = 1/2–0/1) to yield lactone **35** (1.65 g, purity 92%, 75%) as a colorless oil. **35**: $[\alpha]_D^{24} = 40.4$ (*c* 1.01, $CHCl_3$, 76% ee); IR (film) *ν*: 3435, 2926, 1732, 1455, 1364, 1252, 1096 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.37–7.27 (5H, m, Bn), 4.52 (1H, d, *J* = 11.8 Hz, Bn), 4.48 (1H, d, *J* = 11.8 Hz, Bn), 4.41 (1H, dddd, *J* = 11.7, 7.8, 4.5, 3.1 Hz, H17), 4.22 (1H, dddd, *J* = 9.0, 7.5, 5.9, 5.7 Hz, H19), 3.68 (1H, dt, *J* = 9.6, 4.5 Hz, H15), 3.61 (1H, dt, *J* = 9.6, 5.3 Hz, H15), 2.86 (1H, ddd, *J* = 17.0, 5.9, 1.4 Hz, H20), 2.44 (1H, dd, *J* = 17.0, 7.5 Hz, H20), 2.37 (1H, brs, OH), 2.24 (1H, dddd, *J* = 13.7, 5.7, 3.1, 1.4 Hz, H18), 2.03–1.88 (2H, m, H16), 1.59 (1H, ddd, *J* = 13.7, 11.7, 9.0 Hz, H18); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 170.65 (C, C21), 138.04 (C, Bn), 128.42 (CH, Bn), 127.73 (CH, Bn), 74.31 (CH, C17), 73.20 (CH_2, Bn), 65.58 (CH_2, C15), 63.75 (CH, C19), 39.41 (CH_2, C20), 37.85 (CH_2, C18), 35.76 (CH_2, C16); HRMS (ESI) *m/z* calcd for $C_{14}H_{18}O_4Na$ $[M+Na]^+$ 273.1097, found 273.1104.

TBS ether 36

To a solution of alcohol **35** (1.65 g, 6.6 mmol) in DMF (6.6 ml) was added imidazole (0.67 g, 9.9 mmol), followed by TBSCl (1.19 g, 7.9 mmol) at 40 °C. The reaction mixture was stirred at this temperature overnight, then quenched with EtOAc and saturated aqueous $NaHCO_3$. The phases were separated and the aqueous phase was extracted with hexane/EtOAc = 1/1. The combined organic layer was washed with brine, dried over Na_2SO_4 and concentrated. The residue was purified by open column chromatography (hexane/EtOAc = 5/1) to yield TBS ether **36** (1.97 g, 82%) as a colorless oil. **36**: $[\alpha]_D^{26}$ 21.1 (*c* 1.02, $CHCl_3$, 76% ee); IR (film) *ν*: 2954, 2929, 2857, 1740, 1458, 1388, 1362, 1252, 1101 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.37–7.27 (5H, m, Bn), 4.53 (1H, d, *J* = 11.7 Hz, Bn), 4.48 (1H, d, *J* = 11.7 Hz, Bn), 4.41 (1H, dddd, *J* = 11.7, 7.6, 4.3, 3.1 Hz, H17), 4.15 (1H, dddd, *J* = 9.2, 7.8, 5.7, 5.7 Hz, H19), 3.69 (1H, dt, *J* = 8.4, 4.9 Hz, H15), 3.61 (1H, dt, *J* = 8.4, 5.3 Hz, H15), 2.81 (1H, ddd, *J* = 17.2, 5.7, 1.4 Hz, H20), 2.42 (1H, dd, *J* = 17.2, 7.8 Hz, H20), 2.14 (1H, dddd, *J* = 13.7, 5.7, 3.1, 1.4 Hz, H18), 2.02–1.86 (2H, m, H16), 1.60 (1H, ddd, *J* = 13.7, 11.7, 9.2 Hz, H18), 0.87 (9H, s, TBS), 0.07 (6H, s, TBS); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 170.64 (C, C21), 138.01 (C, Bn), 128.42 (CH, Bn), 127.74 (CH, Bn), 127.72 (CH, Bn), 74.11 (CH, C17), 73.23 (CH_2, Bn), 65.64 (CH_2, C15), 64.50 (CH, C19), 40.16 (CH_2, C20), 38.72 (CH_2, C18), 35.96 (CH_2, C16), 25.65 (CH_3, TBS), 17.92 (C, TBS), −4.77 (CH_3, TBS); HRMS (ESI) *m/z* calcd for $C_{20}H_{32}O_4SiNa$ $[M+Na]^+$ 387.1962, found 387.1959.

Ynone S17

To a solution of alkyne **29** (102 mg, 0.48 mmol) in THF (8 ml) was added *n*-BuLi (0.31 ml, 1.56 M in hexane, 0.48 mmol) at −78 °C. After the reaction mixture was stirred at this temperature for 20 min, lactone **36** (144 mg, 0.40 mmol) was added dropwise. The reaction mixture was stirred at this temperature for 1 h and then quenched with saturated aqueous NH_4Cl. The phases were separated and the aqueous phase was extracted with EtOAc. The combined organic layer was washed with brine, dried over Na_2SO_4 and concentrated. The residue was purified by open column chromatography (hexane/EtOAc = 20/1–15/1) to yield ynone **S17** (175 mg, purity 97%, 74%) as an inseparable mixture with hemiacetal. **S17**: yellowish oil; $[\alpha]_D^{27} = 5.8$ (*c* 1.12, $CHCl_3$); IR (film) *ν*: 3528, 29257, 2857, 2210, 1671, 1458, 1362, 1251, 1076 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.36–7.27 (5H, m, Bn), 4.55 (1H, m,

H19), 4.52 (1H, d, J=12.0 Hz, Bn), 4.49 (1H, d, J=12.0 Hz, Bn), 4.04 (1H, m, H17), 3.66 (1H, ddd, J=9.4, 6.5, 5.5 Hz, H15), 3.62 (1H, ddd, J=9.4, 6.5, 5.5 Hz, H15), 3.48 (1H, dd, J=5.9, 4.3 Hz, H25), 3.33 (1H, brs, OH), 2.86 (1H, dd, J=15.7, 6.1 Hz, H20), 2.80–2.73 (1H, m, H24), 2.77 (1H, dd, J=15.7, 6.6 Hz, H20), 1.80–1.66 (3H, m, H16x2, H18), 1.61 (1H, m, H18), 1.54 (1H, m, H26), 1.41 (1H, m, H27), 1.22 (1H, m, H27), 1.19 (3H, d, J=7.2 Hz, Me24a), 0.90 (3H, t, J=7.0 Hz, Me28), 0.88 (9H, s, TBS), 0.86 (3H, d, J=6.7 Hz, Me26a), 0.14 (9H, s, TMS), 0.12 (3H, s, TBS), 0.09 (3H, s, TBS); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 185.49 (C, C21), 138.21 (C, Bn), 128.39 (CH, Bn), 127.65 (CH, Bn), 127.60 (CH, Bn), 97.92 (C, C22), 82.42 (C, C23), 78.49 (CH, C25), 73.19 (CH_2, Bn), 68.07 (CH_2, C15), 67.21 (CH, C19), 66.83 (CH, C17), 52.83 (CH_2, C20), 43.38 (CH_2, C18), 38.13 (CH, C26), 37.44 (CH_2, C16), 31.66 (CH, C24), 26.67 (CH_2, C27), 25.80 (CH_3, TBS), 17.93 (C, TBS), 17.18 (CH_3, C24a), 13.59 (CH_3, C26a), 11.80 (CH_3, C28), 0.80 (CH_3, TMS), −4.75 (CH_3, TBS), −4.78 (CH_3, TBS); HRMS (ESI) *m/z* calcd for $C_{32}H_{56}O_5Si_2Na$ $[M+Na]^+$ 599.3558, found 599.3557.

Methyl acetal 37

To a solution of ketone **S17** (2.46 g, 4.3 mmol) in MeOH (85 ml) was added citric acid (1.23 g, 6.4 mmol) at room temperature. The reaction mixture was stirred overnight and then quenched with saturated aqueous $NaHCO_3$. The phases were separated and the aqueous phase was extracted with EtOAc. The combined organic layer was washed with brine, dried over Na_2SO_4 and concentrated. The residue was purified by open column chromatography (hexane/EtOAc=15/1) to yield methyl acetal **37** (1.84 g, 83%, dr=7:1) as a colorless oil. **37**: $[\alpha]_D^{27}$ 26.7 (*c* 0.98, $CHCl_3$); IR (film) ν: 3503, 2956, 2856, 2239, 1458, 1381, 1255, 1186, 1147, 1115 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.36–7.27 (5H, m, Bn), 4.49 (2H, s, Bn), 4.03 (1H, dddd, J=10.9, 10.9, 4.8, 4.8 Hz, H19), 3.76 (1H, dddd, J=12.2, 8.6, 3.9, 1.8 Hz, H17), 3.66 (1H, ddd, J=9.2, 9.2, 5.1 Hz, H15), 3.57 (1H, dt, J=9.2, 5.1 Hz, H15), 3.48 (1H, s, OH), 3.32–3.22 (4H, m, H25, OMe), 2.74 (1H, dq, J=7.0, 6.8 Hz, H24), 2.20 (1H, ddd, J=12.9, 4.8, 1.6 Hz, H20), 1.88–1.73 (3H, m, H16x2, H18), 1.69 (1H, dd, J=12.9, 10.9 Hz, H20), 1.57–1.43 (2H, m, H26, H27), 1.32–1.23 (2H, m, H27, H18), 1.21 (3H, d, J=6.8 Hz, H24a), 0.92 (3H, d, J=6.7 Hz, Me26a), 0.91 (3H, t, J=7.4 Hz, Me28), 0.87 (9H, s, TBS), 0.05 (3H, s, TBS), 0.04 (3H, s, TBS); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 138.35 (C, Bn), 128.36 (CH, Bn), 127.73 (CH, Bn), 127.58 (CH, Bn), 95.91 (C, C21), 85.33 (C, C22), 81.06 (C, C23), 77.32 (CH, C25), 73.11 (CH_2, Bn), 66.57 (CH_2, C15), 65.99 (CH, C17), 64.63 (CH, C19), 49.99 (CH_3, OMe), 45.82 (CH_2, C20), 40.85 (CH_2, C18), 37.65 (CH, C26), 35.69 (CH_2, C16), 30.74 (CH, C24), 26.45 (CH_2, C27), 25.81 (CH_3, TBS), 18.04 (C, TBS), 17.56 (CH_3, C24a), 13.20 (CH_3, C26a), 11.57 (CH_3, C28), −4.63 (CH_3, TBS); HRMS (ESI) *m/z* calcd for $C_{30}H_{50}O_5SiNa$ $[M+Na]^+$ 541.3320, found 541.3320.

Cis-olefin S18

To a solution of methyl acetal **37** (419 mg, 0.83 mmol) in MeOH (17 ml) was added Lindlar catalyst (166 mg) at room temperature. The reaction mixture was stirred under H_2 atmosphere for 3 h and then filtered through Celite and concentrated. The residue was purified by open column chromatography (hexane/EtOAc=30/1–25/1) to yield *cis*-olefin **S18** (0.43 g, purity 92%, 92%, dr=7:1) as a colorless oil. **S18**: $[\alpha]_D^{24}$ 44.2 (*c* 1.34, $CHCl_3$); IR (film) ν: 3567, 3032, 2957, 2856, 1654, 1461, 1382, 1255, 1076 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.35–7.30 (5H, m, Bn), 5.70 (1H, dd, J=9.8, 1.8 Hz H23), 5.55 (1H, dd, J=9.8, 2.5 Hz, H22), 4.50 (1H, d, J=11.7 Hz, Bn), 4.47 (1H, d, J=11.7 Hz, Bn), 4.12 (1H, dddd, J=11.0, 11.0, 4.5, 4.5 Hz, H19), 3.91 (1H, dddd, J=11.5, 7.8, 4.5, 2.0 Hz, H17), 3.63–3.52 (2H, m, H15x2), 3.48 (3H, s, OMe), 3.33 (1H, dd, J=9.8, 1.8 Hz, H25), 2.22 (1H, dqdd, J=9.8, 7.2, 2.5, 1.8 Hz, H24), 1.90–1.71 (4H, m, H16x2, H18, H20), 1.52 (1H, m, H26), 1.46–1.30 (3H, m, H20, H27x2), 1.29–1.18 (1H, m, H18), 0.91 (3H, d, J=7.2 Hz, Me24a), 0.88 (9H, s, TBS), 0.88 (3H, m, Me28), 0.85 (3H, d, J=7.2 Hz, Me26a), 0.06 (3H, s, TBS), 0.05 (3H, s, TBS); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 138.48 (C, Bn), 135.05 (CH, C23), 128.58 (CH, C22), 128.29 (CH, Bn), 127.66 (CH, Bn), 127.45 (CH, Bn), 95.38 (C, C21), 75.71 (CH, C25), 73.03 (CH_2, Bn), 67.21 (CH_2, C15), 66.43 (CH, C17), 65.46 (CH, C19), 50.85 (CH_3, OMe), 44.72 (CH_2, C20), 41.32 (CH_2, C18), 36.13 (CH_2, C16), 35.49 (CH, C26), 30.55 (CH, C24), 27.90 (CH_2, C27), 25.89 (CH_3, TBS), 18.21 (C, TBS), 16.69 (CH_3, C24a), 12.38 (CH_3, C28), 12.23 (CH_3, C26a), −4.68 (CH_3, TBS); HRMS (ESI) *m/z* calcd for $C_{30}H_{52}O_5SiNa$ $[M+Na]^+$ 543.3476, found 543.3472.

Spiroacetal S19

To a solution of *cis*-alkene **S18** (0.34 g, 0.65 mmol) in Et_2O (22 ml) was added PPTS (16.3 mg, 65 μmol) at room temperature. The reaction mixture was stirred for 3 h and then quenched with saturated aqueous $NaHCO_3$. The phases were separated and the aqueous phase was extracted with EtOAc. The combined organic layer was washed with brine, dried over Na_2SO_4 and concentrated. The residue was purified by open column chromatography (hexane/EtOAc=50/1) to yield spiroacetal **S19** (0.27 g, 86%, dr=5:1) as a colorless oil. **S19**: $[\alpha]_D^{24}$=62.6 (*c* 0.98, $CHCl_3$); IR (film) ν: 3032, 2957, 2928, 2856, 1654, 1460, 1381, 1255, 1117, 1076 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.36–7.27 (5H, m, Bn), 5.70 (1H, dd, J=9.8, 2.5 Hz, H23), 5.55 (1H, dd, J=9.8, 2.5 Hz, H22), 4.50 (1H, d, J=11.9 Hz, Bn), 4.46 (1H, d, J=11.9 Hz, Bn), 4.12 (1H, dddd, J=11.2, 11.2, 4.7, 4.7 Hz, H19), 3.92 (1H, dddd, J=11.9, 7.8, 4.5, 2.0 Hz, H17), 3.59 (1H, dd, J=6.3, 3.1 Hz, H15), 3.58 (1H, dd, J=6.3, 2.2 Hz, H15), 3.34 (1H, dd, J=10.0, 1.8 Hz, H25), 2.23 (1H, dqdd, J=10.0, 7.0, 2.5, 2.5 Hz, H24), 1.91–1.71 (4H, m, H16x2, H18, H20), 1.55 (1H, m, H26), 1.46–1.29 (2H, m, H27x2), 1.41 (1H, dd, J=12.3, 11.2 Hz, H20), 1.23 (1H, ddd, J=11.9, 11.9, 11.2 Hz, H18), 0.91 (3H, d, J=7.0 Hz, Me24a), 0.88 (9H, s, TBS), 0.88 (3H, m, H28), 0.85 (3H, d, J=7.4 Hz, Me26a), 0.06 (3H, s, TBS), 0.05 (3H, s, TBS); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 138.51 (C, Bn), 135.06 (CH, C23), 128.59 (CH, C22), 128.30 (CH, Bn), 127.67 (CH, Bn), 127.46 (CH, Bn), 95.38 (C, C21), 75.72 (CH, C25), 73.04 (CH_2, Bn), 67.22 (CH_2, C15), 66.44 (CH, C17), 65.46 (CH, C19), 44.74 (CH_2, C20), 41.34 (CH_2, C18), 36.15 (CH_2, C16), 35.50 (CH, C26), 30.57 (CH, C24), 27.92 (CH_2, C27), 25.90 (CH_3, TBS), 18.23 (C, TBS), 16.70 (CH_3, C24a), 12.40 (CH_3, C28), 12.24 (CH_3, C26a), −4.67 (CH_3, TBS), −4.65 (CH_3, TBS); HRMS (ESI) *m/z* calcd for $C_{29}H_{48}O_4SiNa$ $[M+Na]^+$ 511.3214, found 511.3214.

Alcohol 38

To a solution of spiroacetal **S19** (761 mg, 1.6 mmol) in THF (60 ml) and NH_3 (ca. 60 ml) was added sodium in small pieces at −60 °C. The reaction mixture was stirred at this temperature for 30 min and then quenched with THF and NH_4Cl. After excess NH_3 was removed at room temperature over 3 h, H_2O was added. The phases were separated and the aqueous phase was extracted with EtOAc. The combined organic layer was washed with brine, dried over Na_2SO_4 and concentrated. The residue was purified by flash column chromatography (hexane/EtOAc=20/1) to yield alcohol **38** (505 mg, purity 93%, 75%) as a yellowish oil. **38**: $[\alpha]_D^{24}$ 85.8 (*c* 0.91, $CHCl_3$); IR (film) ν: 3467, 2959, 1654, 1459, 1382, 1255, 1117, 1076 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.69 (1H, dd, J=9.5, 1.5 Hz, H23), 5.53 (1H, dd, J=9.5, 2.5 Hz, H22), 4.13 (1H, dddd, J=11.3, 11.3, 4.5, 4.5 Hz, H19), 4.00 (1H, dddd, J=11.3, 9.2, 2.6, 2.6 Hz, H17), 3.80–3.74 (2H, m, H15x2), 3.34 (1H, dd, J=10.0, 1.8 Hz, H25), 2.85 (1H, brs, OH), 2.23 (1H, dqdd, J=10.0, 7.0, 2.5, 1.5 Hz, H24), 1.88 (1H, ddd, J=12.3, 4.5, 2.0 Hz, H20), 1.84–1.75 (2H, m, H16, H18), 1.70 (1H, m, H16), 1.57 (1H, m, H26), 1.49–1.38 (2H, m, H27x2), 1.42 (1H, dd, J=12.3, 11.3 Hz, H20), 1.33 (1H, ddd, J=11.3, 11.3, 11.3 Hz, H18), 0.96 (3H, t, J=7.0 Hz, Me28), 0.90 (3H, d, J=7.0 Hz, Me24a), 0.88 (9H, s, TBS), 0.87 (3H, d, J=7.0 Hz, Me26a), 0.06 (3H, s, TBS), 0.06 (3H, s, TBS); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 135.30 (CH, C23), 128.21 (CH, C22), 95.68 (C, C21), 75.96 (CH, C25), 70.32 (CH, C17), 65.08 (CH, C19), 61.92 (CH_2, C15), 44.59 (CH_2, C20), 41.25 (CH_2, C18), 37.64 (CH_2, C16), 35.43 (CH, C26), 30.49 (CH, C24), 28.07 (CH_2, C27), 25.88 (CH_3, TBS), 18.20 (C, TBS), 16.63 (CH_3, C24a), 12.38 (CH_3, C26a, C28), −4.67 (CH_3, TBS); HRMS (ESI) *m/z* calcd for $C_{22}H_{42}O_4SiNa$ $[M+Na]^+$ 421.2745, found 421.2748.

Ester 39

To a solution of alcohol **38** (913 mg, 2.3 mmol) in CH_2Cl_2 (46 ml) was added $NaHCO_3$ (1.93 g, 23 mmol), followed by DMP (2.86 g, 6.9 mmol) at 0 °C. The reaction mixture was stirred at this temperature for 30 min and then allowed to warm to room temperature. After being stirred for 1.5 h, the mixture was quenched with saturated aqueous $Na_2S_2O_3$. The phases were separated and the aqueous phase was extracted with CH_2Cl_2. The combined organic layer was

washed with brine, dried over Na_2SO_4 and concentrated to provide aldehyde **S20**, which was used in the next reaction.

To a solution of aldehyde **S20** in THF (46 ml) was added $Ph_3P=C(Me)CO_2Et$ (1.67 g, 4.6 mmol). The reaction mixture was stirred overnight under reflux conditions and then quenched with saturated aqueous NH_4Cl. The phases were separated and the aqueous phase was extracted with hexane/EtOAc = 5/1. The combined organic layer was washed with brine, dried over Na_2SO_4 and concentrated. The residue was purified by open column chromatography (hexane/EtOAc = 200/1–10/1) to yield ester **39** (965 mg, 87%, 2 steps) as a colorless oil. **39**: $[\alpha]_D^{23} = 43.6$ (*c* 0.91, $CHCl_3$); IR (film) ν: 2958, 1712, 1654, 1459, 1381, 1256, 1076 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 6.82 (1H, td, *J* = 7.0, 1.2 Hz, H15), 5.71 (1H, dd, *J* = 10.0, 1.8 Hz, H23), 5.55 (1H, dd, *J* = 10.0, 2.7 Hz, H22), 4.17 (2H, q, *J* = 7.1 Hz, Et), 4.12 (1H, dddd, *J* = 11.0, 11.0, 4.5, 4.5 Hz, H19), 3.84 (1H, m, H17), 3.39 (1H, dd, *J* = 10.0, 1.7 Hz, H25), 2.40 (1H, ddd, *J* = 15.5, 7.0, 7.0 Hz, H16), 2.33 (1H, ddd, *J* = 15.5, 7.0, 7.0 Hz, H16), 2.23 (1H, dqdd, *J* = 10.0, 7.1, 2.7, 1.8 Hz, H24), 1.88 (1H, ddd, *J* = 12.5, 4.5, 1.8 Hz, H20), 1.82 (3H, d, *J* = 1.2 Hz, Me14a), 1.81 (1H, m, H18), 1.58 (1H, m, H26), 1.46–1.30 (3H, m, H20, H27x2), 1.27 (3H, t, *J* = 7.1 Hz, Et), 1.28 (1H, m, H18), 0.92 (3H, t, *J* = 7.4 Hz, Me28), 0.91 (3H, d, *J* = 7.1 Hz, Me24a), 0.88 (9H, s, TBS), 0.87 (3H, d, *J* = 6.9 Hz, Me26a), 0.06 (3H, s, TBS), 0.06 (3H, s, TBS); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 168.01 (C, C13), 138.10 (CH, C15), 135.28 (CH, C23), 129.24 (C, C14), 128.42 (CH, C22), 95.62 (C, C21), 75.16 (CH, C25), 68.29 (CH, C17), 65.37 (CH, C19), 60.34 (CH_2, Et), 44.63 (CH_2, C20), 40.81 (CH_2, C18), 35.41 (CH, C26), 35.11 (CH_2, C16), 30.55 (CH, C24), 27.81 (CH_2, C27), 25.88 (CH_3, TBS), 18.18 (C, TBS), 16.59 (CH_3, C24a), 14.25 (CH_3, Et), 12.67 (CH_3, C28), 12.59 (CH_3, C14a), 12.24 (CH_3, C26a), −4.65 (CH_3, TBS); HRMS (ESI) *m/z* calcd for $C_{27}H_{48}O_5SiNa$ $[M+Na]^+$ 503.3163, found 503.3159.

Alcohol S21

To a solution of ester **39** (965 mg, 1.8 mmol) in CH_2Cl_2 (90 ml) was added DIBAL (14.3 ml, 1.01 M in toluene, 14.4 mmol) at −60 °C. The reaction mixture was stirred at this temperature for 5 min and then quenched with saturated aqueous Rochelle salt. After being stirred for 2 h, the phases were separated and the aqueous phase was extracted with EtOAc. The combined organic layer was washed with brine, dried over Na_2SO_4 and concentrated. The residue was purified by open column chromatography (hexane/EtOAc = 20/1–5/1) to yield alcohol **S21** (867 mg, 98%) as a colorless oil. **S21**: $[\alpha]_D^{22}$ 62.4 (*c* 1.11, $CHCl_3$); IR (film) ν: 3434, 2928, 2857, 1734, 1654, 1461, 1381, 1255, 1117, 1071 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 5.70 (1H, dd, *J* = 10.0, 1.8 Hz, H23), 5.55 (1H, dd, *J* = 10.0, 2.6 Hz, H22), 5.46 (1H, t, *J* = 7.0 Hz, H15), 4.10 (1H, dddd, *J* = 11.7, 11.7, 4.5, 4.5 Hz, H19), 4.00 (2H, brs, H13), 3.76 (1H, m, H17), 3.54 (1H, d, *J* = 5.1 Hz, OH), 3.39 (1H, dd, *J* = 9.8, 1.6 Hz, H25), 2.29 (1H, ddd, *J* = 14.7, 7.0, 7.0 Hz, H16), 2.25–2.15 (2H, m, H16, H24), 1.87 (1H, ddd, *J* = 12.3, 4.5, 1.8 Hz, H20), 1.81 (1H, dddd, *J* = 11.7, 4.5, 1.8, 1.8 Hz, H18), 1.66 (3H, s, Me14a), 1.55 (1H, qtd, *J* = 6.9, 6.9, 1.6 Hz, H26), 1.47–1.23 (3H, m, H20, H27x2), 1.20 (1H, ddd, *J* = 11.7, 11.7, 11.7 Hz, H18), 0.91 (3H, t, *J* = 7.4 Hz, Me28), 0.90 (3H, d, *J* = 7.2 Hz, Me24a), 0.88 (9H, s, TBS), 0.85 (3H, d, *J* = 6.9 Hz, Me26a), 0.06 (3H, s, TBS), 0.05 (3H, s, TBS); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 136.62 (C, C14), 135.22 (CH, C23), 128.56 (CH, C22), 121.84 (CH, C15), 95.57 (C, C21), 74.92 (CH, C25), 68.98 (CH, C17), 68.87 (CH_2, C13), 65.49 (CH, C19), 44.73 (CH_2, C20), 40.61 (CH_2, C18), 35.33 (CH, C26), 34.11 (CH_2, C16), 30.55 (CH, C24), 27.74 (CH_2, C27), 25.88 (CH_3, TBS), 18.17 (C, TBS), 16.54 (CH_3, C24a), 13.87 (CH_3, C14a), 12.70 (CH_3, C26a), 12.22 (CH_3, C28), −4.64 (CH_3, TBS); HRMS (ESI) *m/z* calcd for $C_{25}H_{46}O_4SiNa$ $[M+Na]^+$ 461.3058, found 461.3065.

Allylic alcohol 41

To a solution of alcohol **S21** (865 mg, 2.0 mmol) in CH_2Cl_2 (20 ml) was added $NaHCO_3$ (1.70 g, 20 mmol), followed by DMP (2.50 g, 5.9 mmol) at 0 °C. The reaction mixture was stirred at this temperature for 30 min and then allowed to warm to room temperature. After being stirred for 2.5 h, the mixture was quenched with saturated aqueous $Na_2S_2O_3$. The phases were separated and the aqueous phase was extracted with CH_2Cl_2. The combined organic layer was washed with brine, dried over Na_2SO_4 and concentrated to provide aldehyde **S22**, which was used in the next reaction.

To a solution of aldehyde **S22** in toluene (99 ml) was added MS4A (2 g), followed by (*E*)-crotyl boronate **40** (6.6 ml, 0.9 M in toluene, 5.9 mmol) at −80 °C. The reaction mixture was stirred this temperature for 1 h and then (*E*)-crotyl boronate **40** (2.2 ml, 0.9 M in toluene, 2.0 mmol) was added. The reaction mixture was stirred at this temperature for 30 min and then quenched with 2 N NaOH. After being stirred for 1 h, the phases were separated and the aqueous phase was extracted with EtOAc. The combined organic layer was washed with brine, dried over Na_2SO_4 and concentrated. The residue was purified by open column chromatography (hexane/EtOAc = 40/1–10/1) to yield allylic alcohol **41** (839 mg, 86%, 2 steps) as a colorless oil. **41**: $[\alpha]_D^{23} = 39.6$ (*c* 0.89, $CHCl_3$); IR (film) ν: 3462, 2958, 2857, 1733, 1636, 1458, 1380, 1255, 1117, 1074 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 5.74 (1H, ddd, *J* = 17.2, 10.2, 8.3 Hz, H11), 5.68 (1H, dd, *J* = 10.0, 1.8 Hz, H23), 5.55 (1H, dd, *J* = 10.0, 2.5 Hz, H22), 5.43 (1H, t, *J* = 6.7 Hz, H15), 5.15 (1H, ddd, *J* = 17.2, 1.9, 1.0 Hz, H10), 5.13 (1H, ddd, *J* = 10.2, 1.9, 0.6 Hz, H10), 4.11 (1H, dddd, *J* = 11.4, 11.4, 4.5, 4.5 Hz, H19), 3.76 (1H, dddd, *J* = 11.4, 6.5, 6.5, 1.0 Hz, H17), 3.67 (1H, d, *J* = 8.4 Hz, H13), 3.39 (1H, dd, *J* = 10.0, 1.8 Hz, H25), 2.38–2.27 (2H, m, H12, H16), 2.25–2.13 (2H, m, H16, H24), 1.86 (1H, ddd, *J* = 12.8, 4.5, 1.8 Hz, H20), 1.83 (1H, dddd, *J* = 11.4, 6.5, 4.5, 1.8 Hz, H18), 1.62 (3H, s, Me14a), 1.56 (1H, m, H26), 1.49–1.29 (2H, m, H27x2), 1.41 (1H, dd, *J* = 12.8, 11.4 Hz, H20), 1.20 (1H, ddd, *J* = 11.4, 11.4, 11.4 Hz, H18), 0.94 (3H, t, *J* = 7.2 Hz, Me28), 0.90 (3H, d, *J* = 8.6 Hz, Me24a), 0.88 (3H, d, *J* = 8.4 Hz, Me12a), 0.88 (9H, s, TBS), 0.86 (3H, d, *J* = 8.4 Hz, Me26a), 0.06 (3H, s, TBS), 0.05 (3H, s, TBS); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 141.25 (C, C14), 136.84 (CH, C11), 135.07 (CH, C23), 128.59 (CH, C22), 124.62 (CH, C15), 116.37 (CH_2, C10), 95.58 (C, C21), 81.36 (CH, C13), 75.01 (CH, C25), 68.95 (CH, C17), 65.52 (CH, C19), 44.76 (CH_2, C20), 42.15 (CH, C12), 40.81 (CH_2, C18), 35.35 (CH, C26), 34.24 (CH_2, C16), 30.55 (CH, C24), 27.84 (CH_2, C27), 25.89 (CH_3, TBS), 18.22 (C, TBS), 16.90 (CH_3, C12a), 16.52 (CH_3, C24a), 12.61 (CH_3, C26a), 12.31 (CH_3, C28), 11.22 (CH_3, C14a), −4.66 (CH_3, TBS); HRMS (ESI) *m/z* calcd for $C_{29}H_{52}O_4SiNa$ $[M+Na]^+$ 515.3527, found 515.3522.

The north segment 4

To a solution of alcohol **41** (0.206 g, 0.418 mmol) in DMF (4.2 ml) were added imidazole (0.171 g, 2.51 mmol) and TBSCl (0.189 g, 1.25 mmol) at room temperature. The reaction mixture was heated to 60 °C, stirred for 2 h at this temperature and then quenched with saturated aqueous $NaHCO_3$. The phases were separated and aqueous phase was extracted with hexane/EtOAc = 2/1. The combined organic layer was washed with brine, dried over Na_2SO_4 and concentrated. The residue was purified by open column chromatography (hexane/EtOAc = 100/1) to yield the north segment **4** (0.254 g, quant.) as a colorless oil. **4**: $[\alpha]_D^{25} = 48.0$ (*c* 0.96, $CHCl_3$); IR (film) ν: 2958, 2928, 2856, 1458, 1254, 1066, 997, 873, 835, 774 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 5.84 (1H, ddd, *J* = 17.5, 10.5, 7.4 Hz, H11), 5.70 (1H, dd, *J* = 10.0, 1.7 Hz, H23), 5.56 (1H, dd, *J* = 10.0, 2.6 Hz, H22), 5.26 (1H, t, *J* = 7.1 Hz, H15), 4.95–4.99 (2H, m, H10x2), 4.10 (1H, dddd, *J* = 11.1, 11.1, 4.6, 4.6 Hz, H19), 3.75 (1H, m, H17), 3.66 (1H, d, *J* = 7.7 Hz, H13), 3.41 (1H, dd, *J* = 9.7, 1.4 Hz, H25), 2.12–2.36 (4H, m, H12, H16x2, H24), 1.84–1.89 (2H, m, H18, H20), 1.55 (4H, m, H26, Me14a), 1.33–1.47 (3H, m, H20, H27x2), 1.16 (1H, ddd, *J* = 11.7, 11.7, 11.1 Hz, H18), 0.93 (3H, t, *J* = 7.4 Hz, Me28), 0.90 (3H, d, *J* = 7.2 Hz, Me24a), 0.88 (9H, s, TBS), 0.87 (9H, s, TBS), 0.86 (3H, d, *J* = 6.9 Hz, Me12a), 0.83 (3H, d, *J* = 7.1 Hz, Me26a), 0.05 (6H, s, TBS), 0.00 (3H, s, TBS), −0.06 (3H, s, TBS); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 142.30 (CH, C11), 138.56 (C, C14), 135.23 (CH, C23), 128.73 (CH, C22), 122.51 (CH, C15), 113.79 (CH_2, C10), 95.73 (C, C21), 82.99 (CH, C13), 75.12 (CH, C25), 69.19 (CH, C17), 65.70 (CH, C19), 44.89 (CH_2, C20), 42.25 (CH, C12), 40.84 (CH_2, C18), 35.47 (CH, C26), 34.32 (CH_2, C16), 30.71 (CH, C24), 27.99 (CH_2, C27), 26.05 (CH_3, TBS), 26.02 (CH_3, TBS), 18.39 (C × 2, TBS), 16.83 (CH_3, C12a), 16.67 (CH_3, C24a), 12.74 (CH_3, C26a), 12.48 (CH_3, C28), 11.80 (CH_3, C14a), −4.30 (CH_3, TBS), −4.50 (CH_3, TBS), −4.54 (CH_3, TBS), −4.83 (CH_3, TBS); HRMS (ESI) *m/z* calcd for $C_{35}H_{66}O_4Si_2Na$ $[M+Na]^+$ 629.4392, found 629.4397.

Aldehyde 42

To a solution of **4** (227 mg, 375 μmol) in *t*-BuOH (5.4 ml)/THF (1.6 ml)/H_2O (0.54 ml) were added NMO (65.8 mg, 562 μmol) and OsO_4 (0.37 ml, 50 mM in H2O, 18.7 μmol) at room temperature. After being stirred for 2 h at this

temperature, the reaction mixture was quenched with saturated aqueous $Na_2S_2O_3$. The phases were separated and aqueous phase was extracted with ethyl acetate. The combined organic layer was washed with brine, dried over Na_2SO_4 and concentrated. The residue was purified by open column chromatography (hexane/EtOAc = 10/1) to yield diol **S23** (192 mg, 88%, dr = 7: 3) as a white amorphous.

To a solution of diol **S23** (190 g, 299 μmol) in MeOH (9.6 ml)/H_2O (2.4 ml) were added KH_2PO_4 (1.20 g, 8.82 mmol) and $NaIO_4$ (192 mg, 896 μmol) at room temperature. The reaction mixture was stirred for 3 h at this temperature and then quenched with water. The phases were separated and aqueous phase was extracted with ethyl acetate. The combined organic layer was washed with brine, dried over Na_2SO_4 and concentrated. The residue was purified by open column chromatography (hexane/EtOAc = 100/1) to yield aldehyde **42** (162 mg, 89%) as a colorless oil: $[\alpha]_D^{24} = 36.6$ (*c* 1.00, $CHCl_3$); IR (film) *ν*: 2957, 2929, 2856, 1731, 1462, 1381, 1252, 1066, 997, 836, 775 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 9.57 (1H, d, *J* = 2.9 Hz, H11), 5.69 (1H, dd, *J* = 10.0, 1.7 Hz, H23), 5.54 (1H, dd, *J* = 10.0, 2.6 Hz, H22), 5.38 (1H, t, *J* = 7.0 Hz, H15), 4.11 (1H, dddd, *J* = 11.7, 11.1, 4.6, 4.6 Hz, H19), 4.09 (1H, d, *J* = 8.6 Hz, H13), 3.77 (1H, dddd, *J* = 11.7, 7.0, 7.0, 2.3 Hz, H17), 3.38 (1H, dd, *J* = 10.3, 2.0 Hz, H25), 2.55 (1H, dqd, *J* = 8.6, 6.0, 2.9 Hz, H12), 2.33 (1H, ddd, *J* = 14.0, 7.0, 7.0 Hz, H16), 2.15–2.25 (2H, m, H16, H24), 1.80–1.89 (2H, m, H18eq, H20eq), 1.58 (4H, m, H26, H14a), 1.33–1.46 (3H, m, H20ax, H27x2), 1.18 (1H, ddd, *J* = 11.7, 11.7, 11.7 Hz, H18ax), 0.93 (3H, t, *J* = 7.1 Hz, H28), 0.89 (3H, d, *J* = 7.4 Hz, H24a), 0.85–0.88 (24H, m, TBS × 2(0.88, 0.85), H12a, H26a), 0.052 (3H, s, TBS), 0.049 (3H, s, TBS), 0.02 (3H, s, TBS), −0.03 (3H, s, TBS); ^{13}C NMR (100 MHz, $CDCl_3$) δ:205.54 (CH, C11), 136.63 (C, C14), 135.20 (CH, C23), 128.61 (CH, C22), 124.64 (CH, C15), 95.74 (C, C21), 80.55 (CH, C13), 75.25 (CH, C25), 68.85 (CH, C17), 65.56 (CH, C19), 50.32 (CH, C12), 44.85 (CH_2, C20), 40.94 (CH_2, C18), 35.44 (CH, C26), 34.36 (CH_2, C16), 30.66 (CH, C24), 28.03 (CH_2, C27), 26.02 (CH_3, TBS), 25.83 (CH_3, TBS), 18.36 (C × 2, TBS), 18.18 (CH_3, C12a), 16.65 (CH_3, C24a), 12.66 (CH_3, C26a), 12.48 (CH_3, C28), 11.29 (CH_3, C14a), −4.27 (CH_3, TBS), −4.53 (CH_3, TBS), −4.57 (CH_3, TBS), −5.19 (CH_3, TBS); HRMS (ESI) *m/z* calcd for $C_{34}H_{64}O_5Si_2Na$ $[M+Na]^+$ 631.4184, found 631.4190.

Allylic alcohol S24

To a solution of aldehyde **42** (136 mg, 222 μmol) in THF (4.5 ml) was added ethyl (triphenylphosphoranylidene)acetate (233 mg, 669 μmol) at room temperature. After being stirred for 12 h at this temperature, the reaction mixture quenched with water. The phases were separated and aqueous phase was extracted with ethyl acetate. The combined organic layer was washed with brine, dried over Na_2SO_4 and concentrated.

The crude product was dissolved in ether (4.5 ml) and added DIBAL (1.8 ml, 1.0 M in toluene, 1.78 mmol) at −78 °C. The reaction mixture was stirred for 20 min at this temperature, then quenched with MeOH and saturated aqueous Rochelle salt. After being stirred for 2 h, the phases were separated and aqueous phase was extracted with EtOAc. The combined organic layer was washed with brine, dried over Na_2SO_4 and concentrated *in vacuo* to give the crude products. The residue was purified by open column chromatography (hexane/EtOAc = 15/1) to yield allylic alcohol **S24** (106 mg, 75%) as a colorless oil. **S24**: $[\alpha]_D^{28}$ 41.3 (*c* 1.22, $CHCl_3$); IR (film) *ν*: 3415, 2957, 2929, 2857, 1462, 1380, 1254, 1064, 998, 873, 835, 774 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 5.70 (1H, dd, *J* = 10.0, 1.7 Hz, H23), 5.68 (1H, dd, *J* = 15.1, 7.1 Hz, H11), 5.60 (1H, dt, *J* = 15.1, 5.4 Hz, H10), 5.55 (1H, dd, *J* = 10.0, 2.6 Hz, H22), 5.25 (1H, t, *J* = 7.1 Hz, H15), 4.09 (3H, m, H9x2, H19), 3.75 (1H, dddd, *J* = 12.0, 7.1, 7.1, 1.7 Hz, H17), 3.64 (1H, d, *J* = 8.3 Hz, H13), 3.40 (1H, dd, *J* = 10.3, 2.3 Hz, H25), 2.25–2.35 (2H, m, H12, H16), 2.23 (1H, dqdd, *J* = 10.3, 7.1, 2.6, 1.7 Hz, H24), 2.15 (1H, ddd, *J* = 14.2, 7.1, 7.1 Hz, H16), 1.81–1.88 (2H, m, H18, H20), 1.54 (4H, m, H26, Me14a), 1.35–1.45 (3H, m, H20, H27x2), 1.17 (1H, ddd, *J* = 12.0, 12.0, 12.0 Hz, H18), 0.93 (3H, t, :*J* = 7.4 Hz, Me28), 0.90 (3H, d, *J* = 7.1 Hz, Me24a), 0.88–0.86 (21H, m, TBS × 2 (0.88, 0.86), Me12a), 0.83 (3H, d, *J* = 6.9 Hz, Me26a), 0.053(3H, s, TBS), 0.049 (3H, s, TBS), −0.01 (3H, s, TBS), −0.06 (3H, s, TBS); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 138.40 (C, C14), 136.85 (CH, C11), 135.23 (CH, C23), 128.70 (CH, C22), 128.52 (CH, C10), 122.82 (CH, C15), 95.72 (C, C21), 83.10 (CH, C13), 75.12 (CH, C25), 69.10 (CH, C17), 65.70 (CH, C19), 64.21 (CH_2, C9), 44.86 (CH_2, C20), 40.98 (CH, C12), 40.78 (CH_2, C18), 35.45 (CH, C26), 34.23 (CH_2, C16), 30.68 (CH, C24), 27.99 (CH_2, C27), 26.03 (CH_3, TBS), 25.95 (CH_3, TBS), 18.37 (C, TBS),18.33 (C, TBS), 17.01 (CH_3, C12a), 16.65 (CH_3, C24a), 12.72 (CH_3, C26a), 12.46 (CH_3, C28), 11.64 (CH_3, C14a), −4.33 (CH_3, TBS), −4.54 (CH_3 × 2, TBS), −4.86 (CH_3, TBS); HRMS (ESI) *m/z* calcd for $C_{36}H_{68}O_5Si_2Na$ $[M+Na]^+$ 659.4497, found 659.4503.

Allyl bromide 45

To a solution of allylic alcohol **S24** (88.2 mg, 138 μmol) in THF (3.5 ml) was added LiBr (180 mg, 2.08 mmol), Et_3N (77.2 μl, 554 μmol) and MsCl (21.4 μl, 277 μmol) at 0 °C. After being stirred for stirred for 5 h at room temperature, the reaction mixture was quenched with saturated aqueous $NaHCO_3$. The phases were separated and aqueous phase was extracted with ethyl acetate. The combined organic layer was washed with brine, dried over Na_2SO_4 and concentrated. The residue was purified by open column chromatography (hexane/EtOAc = 50/1) to yield allyl bromide **45** (59.9 mg, 62%) as a colorless oil. **45**: $[\alpha]_D^{25} = 34.7$ (*c* 0.90, $CHCl_3$); IR (film) *ν*: 2957, 2928, 2856, 2363, 1458, 1380, 1253, 1067, 997, 872, 835, 774 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 5.78 (1H, dd, *J* = 15.4, 7.4 Hz, H11), 5.69 (1H, dd, *J* = 10.0, 1.7 Hz, H23), 5.64 (1H, dt, *J* = 15.4, 7.7 Hz, H10), 5.55 (1H, dd, *J* = 10.0, 2.6 Hz, H22), 5.26 (1H, t, *J* = 7.0 Hz, H15), 4.10 (1H, dddd, *J* = 11.7, 11.7, 4.3, 4.3 Hz, H19), 3.96 (1H, dd, *J* = 12.0, 7.7 Hz, H9), 3.94 (1H, dd, *J* = 12.0, 7.7 Hz, H9), 3.75 (1H, dddd, *J* = 11.7, 7.0, 7.0, 1.7 Hz, H17), 3.64 (1H, d, *J* = 8.3 Hz, H13), 3.40 (1H, dd, *J* = 9.7, 1.7 Hz, H25), 2.35–2.27 (2H, m, H12, H16), 2.23 (1H, dqdd, *J* = 9.7, 7.1, 2.6, 1.7 Hz, H24), 2.16 (1H, ddd, *J* = 14.0, 7.0, 7.0 Hz, H16), 1.88–1.81 (2H, m, H18, H20), 1.59–1.54 (4H, m, H26, Me14a), 1.47–1.35 (3H, m, H20, H27x2), 1.17 (1H, ddd, *J* = 11.7, 11.7, 11.7 Hz, H18), 0.93 (3H, t, *J* = 7.1 Hz, Me28), 0.90 (3H, d, *J* = 7.1 Hz, Me24a), 0.88 (9H, s, TBS), 0.86 (9H, s, TBS), 0.86 (3H, d, *J* = 6.6 Hz, Me12a), 0.83 (3H, d, *J* = 6.9 Hz, Me26a), 0.052 (3H, s, TBS), 0.048 (3H, s, TBS), 0.00 (3H, s, TBS), −0.06 (3H, s, TBS); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 140.01 (CH, C11), 138.27 (C, C14), 135.22 (CH, C23), 128.71 (CH, C22), 125.70 (CH, C10), 123.02 (CH, C15), 95.73 (C, C21), 82.99 (CH, C13), 75.15 (CH, C25), 69.08 (CH, C17), 65.65 (CH, C19), 44.88 (CH_2, C20), 40.92 (CH, C12), 40.86 (CH_2, C18), 35.47 (CH, C26), 34.31 (CH_2, C16), 33.99 (CH_2, C9), 30.69 (CH, C24), 27.99 (CH_2, C27), 26.04 (CH_3, TBS), 26.00 (CH_3, TBS), 18.37 (C, TBS),18.33 (C, TBS), 16.77 (CH_3, C12a), 16.67 (CH_3, C24a), 12.72 (CH_3, C26a), 12.48 (CH_3, C28), 11.64 (CH_3, C14a), −4.32 (CH_3, TBS), −4.49 (CH_3, TBS), −4.54 (CH_3, TBS), −4.85 (CH_3, TBS); HRMS (ESI) *m/z* calcd for $C_{36}H_{67}BrO_4Si_2Na$ $[M+Na]^+$ 721.3653, found 721.3657.

Phosphonium salt 46c

To a solution of bromide **45** (45.8 mg, 65.4 μmol) in MeCN (1.3 ml) was added PMe_3 (13 μl, 1.0 M in toluene, 131 μmol) at room temperature. The reaction mixture was stirred for 1 h at this temperature, and then concentrated *in vacuo* to give the phosphonium salt **46c** (50.7 mg, quant.) as a colorless solid. **46c**: $[\alpha]_D^{25}$ 29.3 (*c* 1.15, $CHCl_3$); IR (film) *ν*: 2928, 2958, 2856, 1462, 1253, 1071, 985, 873, 835, 774 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ:5.82 (1H, ddd, *J* = 15.1, 7.5, 7.5 Hz, H11), 5.67 (1H, dd, *J* = 10.0, 1.7 Hz, H23), 5.51 (1H, dd, *J* = 10.0, 2.3 Hz, H22), 5.30–5.21 (2H, m, H10, H15), 4.08 (1H, dddd, *J* = 12.0, 12.0, 4.6, 4.6 Hz, H19), 3.74 (1H, dddd, *J* = 12.0, 7.1, 7.1, 2.0 Hz, H17), 3.68 (1H, d, *J* = 7.4 Hz, H13), 3.38 (1H, ddd, *J* = 15.1, 15.1, 7.5 Hz, H9), 3.36 (1H, brd, *J* = 8.6 Hz, H25), 3.17 (1H, ddd, *J* = 15.1, 15.1, 7.5 Hz, H9), 2.33–2.27 (2H, m, H12, H16), 2.23–2.06 (2H, m, H16, H24), 2.15 (9H, m, PMe_3), 1.86–1.78 (2H, m, H18, H20), 1.57–1.50 (4H, m, H26, Me14a), 1.42–1.33 (3H, m, H20, H27x2), 1.16 (1H, ddd, *J* = 12.0, 12.0, 12.0 Hz, H18), 0.90 (3H, t, *J* = 7.4 Hz, Me28), 0.86–0.83 (9H, m, Me12a, Me24a, Me26a), 0.85 (9H, s, TBS), 0.83 (9H, s, TBS), 0.03 (6H, s, TBS × 2), −0.03 (3H, s, TBS), −0.07 (3H, s, TBS); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 144.42 (CH, d, J_{c-p} = 13.0 Hz, C11), 137.93 (C, C14), 135.21 (CH, C23), 128.62 (CH, C22), 122.78 (CH, C15), 114.03 (CH, d, J_{c-p} = 10.7 Hz, C10), 95.69 (C, C21), 82.16 (CH, C13), 75.15 (CH, C25), 68.84 (CH, C17), 65.50 (CH, C19), 44.88 (CH_2, C20), 41.50 (CH, C12), 40.76 (CH_2, C18), 35.38 (CH, C26), 34.21 (CH_2, C16), 30.62 (CH, C24), 28.27 (CH_2, d, J_{c-p} = 51.1 Hz, C9), 27.94 (CH_2, C27), 25.99 (CH_3 × 2, TBS), 18.29 (C × 2, TBS), 17.55 (CH_3, C12a), 16.67 (CH_3, C24a), 12.65 (CH_3, C26a), 12.45 (CH_3, C28), 12.11 ($_{CH3}$, C14a), 8.48 (CH_3x3, d, J_{c-p} = 54.9 Hz, PMe_3), −4.29

(CH_3, TBS), −4.53 (CH_3, TBS), −4.58 (CH_3, TBS), −4.77 (CH_3, TBS); HRMS (ESI) *m/z* calcd for $C_{39}H_{76}O_4PSi_2$ $[M\text{-Br}]^+$ 695.5014, found 695.5014.

Triol 47

To a solution of phosphonium salt **46c** (19.1 mg, 24.6 μmol) in hexamethylphosphoric triamide (15.0 μl)/THF (0.2 ml) was slowly added *n*-BuLi (15.8 μl, 1.56 N in hexane, 24.6 μmol) at −78 °C. The reaction mixture was stirred for 15 min and gradually warmed to −60 °C. Later, a THF solution of ketone **6** (8.16 mg, 14.4 μmol) was added dropwise and the mixture was stirred for 3 h at −60 to −40 °C and 45 min at 0 °C. Afterwards, the mixture was quenched with saturated aqueous $NaHCO_3$. The phases were separated and aqueous phase was extracted with EtOAc. The combined organic layer was washed with brine, dried over Na_2SO_4 and concentrated. The residue was filtered through a florisil short column, and the resulting coupling product **44** was used in next reaction without further purification.

To a solution of crude product **44** in THF (0.83 ml) was added TBAF (0.33 ml, 1.0 M in THF, 0.33 mmol) at room temperature. The reaction mixture was heated to 45 °C and stirred for 4 h at this temperature. In this term, further TBAF (0.15 × 3 ml) was added every 1 h. Then the mixture was quenched with pH 7 phosphate buffer. The phases were separated and aqueous phase was extracted with ethyl acetate. The combined organic layer was washed with brine, dried over Na_2SO_4 and concentrated. The residue was purified by flash column chromatography (hexane/EtOAc = 1/2, 1% Et_3N) to yield triol **47** (6.5 mg, 56%) as a colorless solid. **47**: $[\alpha]_D^{26} = 19.8$ (*c* 0.38, CH_2Cl_2); IR (film) *ν*: 3416, 2960, 2926, 1651, 1448, 1378, 1072, 983, 735, 702 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.47–7.45 (6H, m, Tr), 7.34–7.24 (9H, m, Tr), 6.71 (1H, dt, *J* = 11.4, 2.3 Hz, H9), 6.04 (1H, dd, *J* = 15.0, 11.4 Hz, H10), 5.80 (1H, dd, *J* = 15.0, 8.9 Hz, H11), 5.72 (1H, dd, *J* = 10.0, 1.7 Hz, H23), 5.56 (1H, dd, *J* = 10.0, 2.3 Hz, H22), 5.45 (1H, t, *J* = 7.1 Hz, H15), 5.03 (1H, d, *J* = 3.4 Hz, H1), 4.59 (2H, d, *J* = 2.3 Hz, H8ax2), 4.43 (1H, dd, *J* = 5.1, 1.4 Hz, H3), 4.15–4.09 (2H, m, H5, H19), 4.07 (1H, d, *J* = 5.4 Hz, H6), 3.78 (1H, m, H17), 3.75 (1H, d, *J* = 8.6 Hz, H13), 3.41 (1H, dd, *J* = 8.3, 1.7 Hz, H25), 3.01 (1H, brs, H2), 2.45–2.34 (2H, m, H12, H16), 2.26–2.19 (2H, m, H16, H24), 2.00–1.97 (2H, m, H18, H20), 1.68 (3H, brs, Me4a), 1.63 (3H, s, Me14a), 1.61–1.55 (1H, m, H26), 1.45–1.35 (3H, m, H20, H27x2), 1.13 (1H, ddd, *J* = 12.0, 12.0, 12.0 Hz, H18), 0.93 (3H, t, *J* = 7.4 Hz, Me28), 0.91–0.86 (9H, m, Me12a, Me24a, Me26a); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 144.33 (C, Tr), 141.74 (C, C8), 139.53 (CH, C11), 137.19 (C, C14), 136.67 (C, C4), 135.65 (CH, C23), 128.63 (CH, Tr), 128.50 (CH, C22), 128.19 (CH, Tr), 128.14 (CH, C10), 127.45 (CH, Tr), 124.65 (CH, C15), 123.34 (CH, C9), 118.87 (CH, C3), 102.09 (CH, C1), 95.75 (C, C21), 88.15 (CH, C13), 81.64 (C, C7), 81.42 (CH, C6), 75.26 (CH, C25), 69.13 (CH_2, C8a), 68.84 (CH × 2, C5, C17), 64.97 (CH, C19), 50.61 (CH, C2), 44.39 (CH_2, C20), 41.65 (CH, C12), 40.25 (CH_2, C18), 35.40 (CH, C26), 34.34 (CH_2, C16), 30.70 (CH, C24), 27.83 (CH_2, C27), 20.26 (CH_3, C4a), 17.61 (CH_3, C12a), 16.62 (CH_3, C24a), 12.85 (CH_3, C26a), 12.42 (CH_3, C28), 11.45 (CH_3, C14a); HRMS (ESI) *m/z* calcd for $C_{53}H_{64}O_8Na$ $[M+Na]^+$ 851.4493, found 851.4499.

Avermectin aglycon 49

To a degassed solution of **47** (6.5 mg, 7.84 μmol) in 2-methyl-2-butene (0.35 ml) and *t*-BuOH (0.35 ml) was added HCOOH (35.5 μl, 0.941 mmol) under argon at room temperature. After being stirred for 45 min, the reaction mixture was slowly added to a degassed aqueous solution of $NaClO_2$ (28.3 mg, 0.313 mmol) and $NaH_2PO_4 \cdot 2H_2O$ (48.8 mg, 0.313 mmol) at room temperature. After being stirred for 1 h, the mixture was diluted with brine and extracted with Et_2O and dried over Na_2SO_4. Toluene (1 ml) was added and the mixture was concentrated *in vacuo*. After this procedure was repeated again, the volatiles were removed completely *in vacuo* to give yellow residue. To a solution of 2-methyl-6-nitrobenzoic anhydride (8.1 mg, 23.5 μmol) and DMAP (5.7 mg, 47.0 μmol) in CH_2Cl_2 (5.2 ml) at room temperature was added a solution of crude seco acid **2** in dry CH_2Cl_2 (2.6 ml) over 15 min. After being stirred for 1 h, the mixture was cooled to 0 °C and then quenched with saturated aqueous $NaHCO_3$. The phases were separated and aqueous phase was extracted with EtOAc. The combined organic layer was washed with brine, dried over Na_2SO_4 and concentrated. The residue was purified by flash column chromatography (hexane/EtOAc = 2/1) to yield avermectin aglycon **49** (2.5 mg, 54%) as a colorless solid: $[\alpha]_D^{28}$ 61.9 (*c* 0.20, $CHCl_3$), (lit. $[\alpha]_D = 65.5$ (*c* 0.595, $CHCl_3$)[38]); IR (film) *ν*: 3466, 2961, 2929, 1718, 1458, 1376, 1159, 1117, 1035, 994 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 5.83 (1H, dt, *J* = 11.1, 2.3 Hz, H9), 5.80–5.68 (3H, m, H10, H11, H23), 5.54 (1H, dd, *J* = 10.0, 2.9 Hz, H22), 5.42 (1H, brs, H3), 5.40–5.31 (2H, m, H15, H19), 4.71 (1H, dd, *J* = 14.3, 2.3 Hz, H8a), 4.66 (1H, dd, *J* = 14.3, 2.3 Hz, H8a), 4.29 (1H, dd, *J* = 6.3, 6.3 Hz, H5), 4.01 (1H, brs, H13), 3.98 (1H, s, OH), 3.97 (1H, d, *J* = 6.3 Hz, H6), 3.87 (1H, m, H17), 3.46 (1H, dd, *J* = 10.0, 1.7 Hz, H25), 3.27 (1H, q, *J* = 2.3 Hz, H2), 2.53 (1H, m, H12), 2.34–2.24 (4H, m, H16x2, H24, OH), 2.01 (1H, ddd, *J* = 12.0, 4.8, 2.0 Hz, H20), 1.87 (3H, t, *J* = 2.3 Hz, Me4a), 1.77 (1H, dddd, *J* = 12.0, 4.6, 2.0, 2.0 Hz, H18), 1.61–1.57 (1H, m, H26), 1.52 (3H, s, Me14a), 1.51–1.44 (3H, m, H20, H27x2), 1.18 (3H, d, *J* = 6.9 Hz, Me12a), 0.96 (3H, t, *J* = 7.4 Hz, Me28), 0.92 (6H, m, Me24a, Me26a), 0.87 (1H, ddd, *J* = 12.0, 12.0, 12.0 Hz, H18); ^{13}C NMR (175 MHz, $CDCl_3$) δ: 173.64 (C, C1), 139.95 (C, C8), 138.82 (C, C14), 137.97 (C, C4), 137.16 (CH, C11), 136.40 (CH, C23), 127.96 (CH, C22), 124.95 (CH, C10), 120.53 (CH, C9), 118.27 (CH, C3), 117.28 (CH, C15), 95.87 (C, C21), 80.41 (C, C7) 79.28 (CH, C6), 77.77 (CH, C13), 75.37 (CH, C25), 68.63 (C17 or C8a or C19), 68.51 (C17 or C8a or C19), 68.42 (C17 or C8a or C19), 67.87 (CH, C5), 45.84 (CH, C2), 40.77 (CH_2, C20), 40.25 (CH, C12), 36.66 (CH_2, C18), 35.40 (CH, C26), 34.56 (CH_2, C16), 30.72 (CH, C24), 27.76 (CH_2, C27), 20.10 (CH_3, C4a), 19.30 (CH_3, C12a), 16.55 (CH_3, C24a), 14.75 (CH_3, C14a), 12.97 (CH_3, C26a), 12.30 (CH_3, C28); HRMS (ESI) *m/z* calcd for $C_{34}H_{48}O_8Na$ $[M+Na]^+$ 607.3241, found 607.3245.

Bis-acetate 51

To a suspension of L-rhamnose monohydrate **50** (10.0 g, 54.9 mmol) in acetic anhydride (31 ml, 329 mmol) was added HBr (1 ml, 33% in AcOH, 5.5 mmol) at 0 °C. After being stirred for 1 h at room temperature, the additional HBr (51 ml, 33% in AcOH, 281mmol) was added and the reaction mixture was stirred 2 h. Anhydrous sodium acetate (25 g) was then added to neutralized the excess HBr, and the reaction mixture was poured into a suspension of pulverized $CuSO_4 \cdot 5H_2O$ (2.5 g) and zinc powder (100 g) in a solution of water (100 ml) and acetic acid (50 ml) containing sodium acetate (75 g) at 0 °C. The reaction mixture was stirred vigorously at room temperature for 2 h. The mixture was filtered and the collected solid was washed with ethyl acetate and water. The filtered phases were separated and the aqueous phase was extracted with EtOAc. The combined organic layer was washed with water, saturated aqueous $NaHCO_3$ and brine, dried over Na_2SO_4 and concentrated. The residue was purified by open column chromatography (hexane/EtOAc = 7/1–5/1) to yield rhamnal **51** (9.04 g, 77%) as a colorless oil. **51**: $[\alpha]_D^{23} = 52.4$ (*c* 1.10, $CHCl_3$); IR (film) *ν*: 2987, 1738, 1648, 1375, 1225, 1051 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 6.43 (1H, dd, *J* = 6.1, 1.4 Hz, H1′), 5.33 (1H, dddd, *J* = 6.1, 2.9, 1.4, 0.6 Hz, H3′), 5.02 (1H, dd, *J* = 8.2, 6.1 Hz, H4′), 4.77 (1H, dd, *J* = 6.1, 2.9 Hz, H2′), 4.10 (1H, dq, *J* = 8.2, 6.5 Hz, H5′), 2.08 (3H, s, Ac), 2.04 (3H, s, Ac), 1.31 (3H, d, *J* = 6.5 Hz, H6′); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 170.69 (C, Ac), 169.94 (C, Ac), 145.96 (CH, C1′), 98.73 (CH, C2′), 72.48 (CH, C5′), 71.79 (CH, C4′), 68.28 (CH, C3′), 21.07 (CH_3, Ac), 20.89 (CH_3, Ac), 16.52 (CH_3, C6′); HRMS (ESI) *m/z* calcd for $C_{10}H_{14}O_5Na$ $[M+Na]^+$ 237.0733, found 237.0733.

Rhamnal 52

To a solution of bis-acetate **51** (9.04 g, 42 mmol) in MeOH (48 ml) was added K_2CO_3 (2.9 g, 21 mmol) at room temperature. The reaction mixture was stirred overnight and then quenched with EtOAc and H_2O. The phases were separated and the aqueous phase was extracted with EtOAc. The combined organic layer was dried over Na_2SO_4 and concentrated. The residue was purified by recrystallization (hexane) to yield diol **52** (4.79 g, 87%) as a white solid. **52**: m.p. = 69 °C; $[\alpha]_D^{23} = 23.8$ (*c* 1.13, $CHCl_3$); IR (film) *ν*: 3270, 2931, 1645, 1448, 1227, 1149, 1046 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 6.31 (1H, dd, *J* = 6.0, 1.6 Hz, H1′), 4.70 (1H, dd, *J* = 6.0, 2.2 Hz, H2′), 4.21 (1H, m, H3′), 3.85 (1H, dq, *J* = 9.6, 6.5 Hz, H5′), 3.51–3.37 (2H, m, OH, H4′), 2.94 (1H, m, OH), 1.38 (3H, d, *J* = 6.5 Hz, Me6′); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 144.82 (CH, C1′), 102.66 (CH, C2′), 75.34 (CH, C4′), 74.46 (CH, C5′), 70.32 (CH, C3′), 17.17 (CH_3, C6′); HRMS (ESI) *m/z* calcd for $C_6H_{10}O_3Na$ $[M+Na]^+$ 153.0522, found 153.0522.

TBS ether S26

To a solution of rhamnal **52** (4.79 g, 37 mmol) in CH_2Cl_2 (60 ml) was added pyridine (8.9 ml, 110 mmol), followed by BzCl (4.3 ml, 37 mmol) at 0 °C. The reaction mixture was stirred for 1 h and then quenched with saturated aqueous $NaHCO_3$. The phases were separated and the aqueous phase was extracted with EtOAc. The combined organic layer was washed with brine, dried over Na_2SO_4 and concentrated to give benzoate **S25**, which was used directly in the next reaction.

To a solution of crude benzoate **S25** in DMF (37 ml) was added imidazole (5.0 g, 74 mmol), followed by TBSCl (8.3 g, 55 mmol) at 40 °C. The reaction mixture was stirred at this temperature overnight, then quenched with EtOAc and saturated aqueous $NaHCO_3$. The phases were separated and the aqueous phase was extracted with hexane/EtOAc = 3/1. The combined organic layer was washed with brine, dried over Na_2SO_4 and concentrated. The residue was purified by open column chromatography (hexane/EtOAc = 50/1) to yield TBS ether **S26** (9.34 g, 73%, 2 steps) as a colorless oil. **S26**: $[\alpha]_D^{24} = 166.2$ (*c* 0.99, $CHCl_3$); IR (film) ν: 2930, 2857, 1719, 1648, 1451, 1272, 1105 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.07–8.03 (2H, m, Bz), 7.57 (1H, m, Bz), 7.48–7.42 (2H, m, Bz), 6.42 (1H, dd, *J* = 6.0, 1.4 Hz, H1′), 5.50 (1H, ddd, *J* = 6.5, 2.5, 1.4 Hz, H3′), 4.80 (1H, dd, *J* = 6.0, 2.5 Hz, H2′), 3.96 (1H, dq, *J* = 9.0, 6.3 Hz, H5′), 3.88 (1H, dd, *J* = 9.0, 6.5 Hz, H4′), 1.40 (3H, d, *J* = 6.3 Hz, Me6′), 0.82 (9H, s, TBS), 0.12 (3H, s, TBS), −0.02 (3H, s, TBS); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 166.30 (C, Bz), 146.07 (CH, C1′), 133.00 (C, Bz), 130.26 (C, Bz), 129.66 (CH, Bz), 128.34 (CH, Bz), 99.59 (CH, C2′), 75.51 (CH, C5′), 73.76 (CH, C3′), 72.43 (CH, C4′), 25.69 (CH_3, TBS), 18.00 (C, TBS), 17.76 (CH_3, C6′), −4.15 (CH_3, TBS), −4.56 (CH_3, TBS); HRMS (ESI) *m/z* calcd for $C_{19}H_{28}O_4SiNa$ $[M+Na]^+$ 371.1649, found 371.1651.

Methyl ether 53

To a solution of **S26** (1.00 g, 2.9 mmol) in THF (30 ml) was added MeLi (9.0 ml, 1.06 M in Et_2O, 8.5 mmol) at −80 °C. The reaction mixture was stirred for 30 min and then MeOTf (830 μl, 7.3 mmol) was added at −90 °C. The reaction mixture gradually warmed to −55 °C, stirred 1 h and then added with *i*Pr_2NH (3 ml). The reaction mixture was gradually warmed to room temperature, stirred overnight and quenched with saturated aqueous $NaHCO_3$. The phases were separated and the aqueous phase was extracted with hexane/EtOAc = 10/1. The combined organic layer was washed with brine, dried over Na_2SO_4 and concentrated. The residue was purified by open column chromatography (hexane/EtOAc = 50/1) to yield methyl ether **53** (636 mg, 85%) as a colorless oil. **53**: $[\alpha]_D^{23} = 22.7$ (*c* 1.06, $CHCl_3$); IR (film) ν: 2930, 2888, 2857, 1646, 1472, 1254, 1125 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 6.34 (1H, dd, *J* = 6.1, 1.4 Hz, H1′), 4.83 (1H, dd, *J* = 6.1, 2.2 Hz, H2′), 3.79 (1H, dq, *J* = 9.4, 6.3 Hz, H5′), 3.73 (1H, ddd, *J* = 6.9, 2.2, 1.4 Hz, H3′), 3.48 (1H, dd, *J* = 9.4, 6.9 Hz, H4′), 3.32 (3H, s, OMe), 1.32 (3H, d, *J* = 6.3 Hz, Me6′), 0.90 (9H, s, TBS), 0.12 (3H, s, TBS), 0.10 (3H, s, TBS); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 144.85 (CH, C1′), 99.33 (CH, C2′), 79.49 (CH, C3′), 75.38 (CH, C5′), 73.66 (CH, C4′), 55.54 (CH_3, Me), 25.91 (CH_3, TBS), 18.20 (C, TBS), 17.85 (CH_3, C6′), −4.14 (CH_3, TBS), −4.89 (CH_3, TBS); HRMS (ESI) *m/z* calcd for $C_{13}H_{26}O_3SiNa$ $[M+Na]^+$ 281.1543, found 281.1543.

Hemiacetal 54

To a solution of methyl ether **53** (3.6 g, 12 mmol) in MeCN-H_2O (95:5, 95 ml) was added *N*-iodosuccinimide (2.9 g, 13 mmol) at 0 °C. The reaction mixture was allowed to warm to room temperature and stirred for 25 min. The solvent was then removed *in vacuo*. The residue was dissolved in DMF (60 ml) and H_2O (119 ml). To the solution were added $NaHCO_3$ (10.0 g, 119 mmol) and $Na_2S_2O_4$ (8.3 g, 48 mmol) at room temperature. The reaction mixture was stirred for 4 h and then quenched with EtOAc and H_2O. The phases were separated and the aqueous phase was extracted with hexane/EtOAc = 1/1. The combined organic layer was washed with H_2O and brine, dried over Na_2SO_4 and concentrated. The residue was purified by open column chromatography (hexane/EtOAc = 7/1) to yield hemiacetal **54** (3.01 g, 92%, α/β = 7/3) as a colorless oil. **54**: IR (film) ν: 3400, 2930, 1463, 1252, 1109 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 5.34 (7/10H, m, H1′α), 4.80 (3/10H, ddd, *J* = 9.8, 6.7, 2.0 Hz, H1′β), 3.87 (7/10H, dq, *J* = 8.8, 6.3 Hz, H5′α), 3.45 (7/10H, ddd, *J* = 11.4, 8.8, 4.9 Hz, H3′α), 3.32 (3H, s, OMe), 3.31 (3/10H, m, H5′β), 3.20–3.12 (1H, m, H4′), 3.12 (3/10H, m, H3′β), 2.59 (7/10H, d, *J* = 2.2 Hz, OHα), 2.43 (3/10H, ddd, *J* = 12.2, 4.5, 2.0 Hz, H2′β), 2.30 (7/10H, ddd, *J* = 13.1, 4.9, 1.2 Hz, H2′α), 1.47 (7/10H, dddd, *J* = 13.1, 11.4, 3.5, 2.2 Hz, H2′α), 1.34 (3/10H, m, H2′β), 1.28 (9/10H, d, *J* = 6.3 Hz, Me6′β), 1.23 (21/10H, d, *J* = 6.3 Hz, Me6′α), 0.89 (63/10H, s, TBSα), 0.88 (27/10H, s, TBSβ), 0.09 (21/10H, s, TBSα), 0.09 (9/10H, s, TBSβ), 0.07 (3H, s, TBS); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 93.97 (CH, C1′β), 92.05 (CH, C1′α), 80.77 (CH, C3′β), 78.09 (CH, C3′α), 77.19 (CH, C4′α), 76.37 (CH, C4′β), 72.88 (CH, C5′β), 68.61 (CH, C5′α), 56.35 (CH_3, OMeα), 56.18 (CH_3, OMeβ), 37.06 (CH_2, C2′β), 34.35 (CH_2, C2′α), 25.99 (CH_3, TBS), 18.53 (CH_3, C6′α), 18.49 (CH_3, C6′β), 18.29 (C, TBSα), 18.27 (C, TBSβ), −3.98 (CH_3, TBS), −4.79 (CH_3, TBS); HRMS (ESI) *m/z* calcd for $C_{13}H_{28}O_4SiNa$ $[M+Na]^+$ 299.1649, found 299.1651.

Alcohol 55

To a solution of hemiacetal **54** (1.5 g, 5.4 mmol) in CH_2Cl_2 (54 ml) was added PhSH (463 μl, 5.4 mmol), followed by $BF_3{\cdot}Et_2O$ (0.48 ml, 2.7 mmol) at 0 °C. The reaction mixture was stirred for 10 min at this temperature and then additional $BF_3{\cdot}Et_2O$ (0.48 ml, 2.7 mmol) was added. The reaction mixture was stirred for 5 min and then quenched with saturated aqueous $NaHCO_3$. The phases were separated and the aqueous phase was extracted with EtOAc. The combined organic layer was washed with brine, dried over Na_2SO_4 and concentrated to provide thioglycoside **S27**, which was used directly in the next reaction.

To a solution of crude thioglycoside **S27** in THF (108 ml) was added TBAF (10.8 ml, 1.0 M in THF, 10.8 mmol) at 40 °C. The reaction mixture was stirred for overnight and then quenched with saturated aqueous NH_4Cl. The phases were separated and the aqueous phase was extracted with EtOAc. The combined organic layer was washed with brine, dried over Na_2SO_4 and concentrated. The residue was purified by flash column chromatography (hexane/EtOAc = α: 7/1–6/1; β: 6/1–5/1) to yield alcohol **55** (α: 418 mg; β: 362 mg, total 56%, 2 steps) as yellow oil. **55**α: $[\alpha]_D^{23} = 275.2$ (*c* 1.14, $CHCl_3$); IR (film) ν: 3447, 2931, 1582, 1478, 1438, 1082 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.48–7.44 (2H, m, SPh), 7.33–7.28 (2H, m, SPh), 7.25 (1H, m, SPh), 5.62 (1H, dd, *J* = 5.7, 1.0 Hz, H1′), 4.19 (1H, dq, *J* = 9.0, 6.3 Hz, H5′), 3.52 (1H, ddd, *J* = 11.7, 9.0, 4.7 Hz, H3′), 3.43 (3H, s, OMe), 3.20 (1H, dd, *J* = 9.0, 9.0 Hz, H4′), 2.56 (1H, s, OH), 2.49 (1H, ddd, *J* = 13.3, 4.7, 1.0 Hz, H2′), 1.93 (1H, ddd, *J* = 13.3, 11.7, 5.7 Hz, H2′), 1.31 (3H, d, *J* = 6.3 Hz, Me6′); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 135.11 (C, SPh), 131.14 (CH, SPh), 128,93 (CH, SPh), 127.09 (CH, SPh), 83.95 (CH, C1′), 78.86 (CH, C3′), 76.38 (CH, C4′), 68.50 (CH, C5′), 56.61 (CH_3, OMe), 34.84 (CH_2, C2′), 17.69 (CH_3, C6′); HRMS (ESI) calcd for $C_{13}H_{18}O_3SNa$ $(M+Na)^+$ 277.0869, found 277.0874. **55**β: $[\alpha]_D^{23} = 578.0$ (*c* 1.08, $CHCl_3$); IR (film) ν: 3436, 2932, 1584, 1479, 1439, 1292, 1078 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.51–7.48 (2H, m, SPh), 7.33–7.27 (3H, m, SPh), 4.78 (1H, dd, *J* = 11.7, 2.0 Hz, H1′), 3.40 (3H, s, OMe), 3.38 (1H, m, H5′), 3.27–3,14 (2H, m, H3′, H4′), 2.47 (1H, ddd, *J* = 12.5, 4.5, 2.0 Hz, H2′), 1.63 (1H, ddd, *J* = 12.5, 11.7, 10.8 Hz, H2′), 1.37 (3H, d, *J* = 6.3 Hz, Me6′); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 133.40 (C, SPh), 131.34 (CH, SPh), 128.84 (CH, SPh), 127.38 (CH, Ph), 81.96 (CH, C3′), 81.92 (CH, C1′), 75.79 (CH, C5′), 75.28 (CH, C4′), 56.48 (CH_3, OMe), 35.33 (CH_2, C2′), 18.16 (CH_3, C6′); HRMS (ESI) *m/z* calcd for $C_{13}H_{18}O_3SNa$ $[M+Na]^+$ 277.0869, found 277.0871.

Fluoroglycoside 56

To a solution of hemiacetal **54** (750 mg, 2.7 mmol) in THF (27 ml) was added DAST (538 μl, 4.1 mmol) at −40 °C. The reaction mixture was stirred at this temperature for 1 h and then quenched with saturated aqueous $NaHCO_3$. The phases were separated and the aqueous phase was extracted with CH_2Cl_2. The combined organic layer was washed with brine, dried over Na_2SO_4 and concentrated. The residue was purified by NH column chromatography (hexane/EtOAc = 50/1) to yield fluoride **56**, which was used in the next reaction without further purification.

Disaccharide 3

To a solution of fluoride **56** (10.5 mg, 0.038 mmol) in Et_2O (0.38 ml) and alcohol **55**α (9.6 mg, 0.038 mmol) was added MS4A (3.8 mg), followed by $SnCl_2$ (14 mg, 0.076 mmol) and AgOTf (19 mg, 0.076 mmol) at −30 °C. The

reaction mixture was allowed to warm to 0 °C and stirred for 3 h. The mixture was warmed to room temperature, stirred for 2.5 h and then quenched with saturated aqueous $NaHCO_3$. The phases were separated and the aqueous phase was extracted with EtOAc. The combined organic layer was washed with brine, dried over Na_2SO_4 and concentrated. The residue was purified by flash column chromatography (hexane/EtOAc = 30/1) to yield disaccharide **3** (8.7 mg, 46%) as a colorless oil and its β-glycoside (1.7 mg, 9%). **3**: $[\alpha]_D^{19}$ − 258.1 (*c* 0.29, $CHCl_3$); IR (film) *ν*: 3436, 2932, 1584, 1479, 1439, 1292, 1078 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.47–7.43 (2H, m, SPh), 7.32–7.22 (3H, m, SPh), 5.59 (1H, dd, *J* = 5.7, 1.6 Hz, H1′), 5.30 (1H, dd, *J* = 4.1, 1.4 Hz, H1″), 4.16 (1H, dq, *J* = 9.0, 6.3 Hz, H5′), 3.70 (1H, dq, *J* = 8.8, 6.3 Hz, H5″), 3.58 (1H, ddd, *J* = 11.7, 9.0, 4.9 Hz, H3′), 3.39 (3H, s, OMe), 3.34 (1H, m, H3″), 3.34 (3H, s, OMe), 3.25 (1H, dd, *J* = 9.0, 9.0 Hz, H4′), 3.14 (1H, dd, *J* = 8.8, 8.8 Hz, H4″), 2.45 (1H, ddd, *J* = 13.5, 4.9, 1.6 Hz, H2′), 2.31 (1H, ddd, *J* = 13.1, 4.9, 1.4 Hz, H2″), 1.95 (1H, ddd, *J* = 13.5, 11.7, 5.7 Hz, H2′), 1.50 (1H, ddd, *J* = 13.1, 11.3, 4.1 Hz, H2″), 1.30 (3H, d, *J* = 6.3 Hz, Me6′), 1.22 (3H, d, *J* = 6.3 Hz, Me6″), 0.90 (9H, s, TBS), 0.10 (3H, s, TBS), 0.08 (3H, s, TBS); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 135.12 (C, SPh), 131.18 (CH, SPh), 128.92 (CH, SPh), 127.08 (CH, SPh), 98.71 (CH, C1″), 83.70 (CH, C1′), 81.12 (CH, C4′), 79.78 (CH, C3′), 78.56 (CH, C3″), 77.07 (CH, C4″), 69.13 (CH, C5″), 67.82 (CH, C5′), 56.64 (CH_3, OMe), 56.35 (CH_3, OMe), 35.26 (CH_2, C2′), 34.69 (CH_2, C2″), 26.02 (CH_3, TBS), 18.35 (CH_3, C6′), 18.31 (C, TBS), 18.29 (CH_3, C6″), − 3.98 (CH_3, TBS), − 4.74 (CH_3, TBS); HRMS (ESI) *m/z* calcd for $C_{26}H_{44}O_6SSiNa$ $[M+Na]^+$ 535.2520, found 535.2526.

Fluoride 57

To a solution of thio glycoside **3** (40.0 mg, 78.0 μmol) in CH_2Cl_2 (1.56 ml) was added DAST (15.5 μl, 117 μmol) and NBS (18.0 mg, 101 μmol) at − 30 °C. The reaction mixture was stirred for 25 min at this temperature, and then poured into saturated aqueous $NaHCO_3$. The phases were separated and aqueous phase was extracted with Et_2O. The combined organic layer was washed with brine, dried over Na_2SO_4 and concentrated. The residue was purified by NH column chromatography (hexane/EtOAc = 100/1) to yield fluoride **57** (~28 mg, ca. 85%), which was used in the next reaction without further purification.

TBS ether 58

To a solution of alcohol **49** (3.3 mg, 5.64 μmol) in DMF (0.5 ml) were added imidazole (4.6 mg, 67.8 μmol) and TBSCl (5.2 mg, 33.8 μmol) at room temperature. After being stirred for 3.5 h, the reaction mixture was quenched with saturated aqueous $NaHCO_3$. The phases were separated and aqueous phase was extracted with EtOAc. The combined organic layer was washed with brine, dried over Na_2SO_4 and concentrated. The residue was purified by flash column chromatography (hexane/EtOAc = 5/1) to yield TBS ether **58** (3.1 mg, 78%) as a colorless solid: $[\alpha]_D^{26}$ 55.3 (*c* 0.15, $CHCl_3$); IR (film) *ν*: 3462, 2958, 2928, 2856, 1715, 1456, 1376, 1250, 1160, 1123, 1081, 995, 866, 836 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 5.81–5.65 (4H, m, H9, H10, H11, H23), 5.54 (1H, dd, *J* = 9.7, 2.6 Hz, H22), 5.36–5.28 (3H, m, H3, H15, H19), 4.68 (1H, d, *J* = 14.0 Hz, H8a), 4.58 (1H, d, *J* = 14.0 Hz, H8a), 4.43 (1H, m, H5), 4.01 (2H, m, H13, OH), 3.86 (1H, m, H17), 3.82 (1H, d, *J* = 5.7 Hz, H6),, 3.46 (1H, dd, *J* = 10.0, 1.1 Hz, H25), 3.36 (1H, q, *J* = 2.3 Hz, H2), 2.52 (1H, m, H12), 2.37–2.24 (3H, m, H16x2, H24), 2.03 (1H, ddd, *J* = 11.9, 4.9, 2.1 Hz, H20), 1.79 (3H, d, *J* = 2.3 Hz, Me4a), 1.76 (1H, m, H18), 1.65–1.43 (7H, m, Me14a, H20, H26, H27x2), 1.17 (3H, d, *J* = 7.1 Hz, Me12a), 0.93 (9H, s, TBS), 0.98–0.85 (10H, m, H18, Me24a, Me26a, Me28), 0.13 (6H, s, TBS); ^{13}C NMR (175 MHz, $CDCl_3$) δ: 173.90 (C, C1), 140.52 (C, C8), 138.90 (C, C14), 137.56 (C, C4), 136.63 (CH, C11), 136.33 (CH, C23), 128.00 (CH, C22), 125.03 (CH, C10), 119.47 (CH, C9), 117.49 (CH, C3), 117.25 (CH, C15), 95.88 (C, C21), 80.30 (CH, C6; C, C7), 77.81 (CH, C13), 75.35 (CH, C25), 69.60 (CH, C5), 68.53 (CH, C17; CH, C19), 68.10 (CH_2, C8a), 45.91 (CH, C2), 40.77 (CH_2, C20), 40.14 (CH, C12), 36.59 (CH_2, C18), 35.41 (CH, C26), 34.60 (CH_2, C16), 30.71 (CH, C24), 27.75 (CH_2, C27), 26.03 (CH_3, TBS), 20.18 (CH_3, C4a), 19.39 (CH_3, C12a), 18.59 (C, TBS), 16.56 (CH_3, C24a), 14.79 (CH_3, C14a), 12.96 (CH_3, C26a), 12.30 (CH_3, C28), − 4.50 (CH_3, TMS), − 4.83 (CH_3, TMS); HRMS (ESI) *m/z* calcd for $C_{40}H_{62}O_8SiNa$ $[M+Na]^+$ 721.4106, found 721.4111.

Glycoside 59α

To a mixture of alcohol **58** (5.7 mg, 8.11 μmol), MS4A (30 mg) in MeCN (0.3 ml) were added $SnCl_2$ (3.4 mg, 17.8 μmol) and AgOTf (4.6 mg, 17.8 μmol) at room temperature and stirred 5 min. After the mixture was cooled to − 40 °C, MeCN solution of DTBMP (12.0 mg, 48.6 μmol) and fluoride **57** (6.9 mg, 16.2 μmol) was added at this temperature. The reaction mixture was allowed to warm up to 0 °C over 1 h and then stirred for 30 min at room temperature. Later, the precipitates were filtered and the filtrate was extracted with ether. The combined organic layer was washed with saturated aqueous $NaHCO_3$ and brine, dried over Na_2SO_4 and concentrated. The residue was purified by flash column chromatography (hexane/EtOAc = 10/1) to yield **59** as a 2.3:1 mixture of α and β isomers. The mixture was purified by HPLC (YMC-Pack SIL-06, hexane/EtOAc = 9/1, 1.0 ml min^{-1}, R_t = 15 min (α isomer), 16.3 min (β isomer)) to yield **59**α (4.0 mg, 45%) as a colorless solid. **59**α: $[\alpha]_D^{26}$ 39.3 (*c* 0.33, $CHCl_3$); IR (film) *ν*: 2959, 2930, 2856, 1717, 1459, 1386, 1250, 1159, 1123, 1102, 987, 870, 836, 776 cm^{-1}; ^1H NMR (700 MHz, $CDCl_3$) δ: 5.82 (1H, m, H9), 5.76 (1H, dd, *J* = 9.9, 1.6 Hz, H23), 5.51–5.73 (2H, m, H10, H11), 5.55 (1H, dd, *J* = 9.9, 2.7 Hz, H22), 5.37 (1H, dddd, *J* = 11.5, 11.5, 4.8, 4.8 Hz, H19), 5.32 (2H, m, H3, H1″), 4.98 (1H, m, H15), 4.76 (1H, brd, *J* = 3.2 Hz, H1′), 4.68 (1H, dd, *J* = 14.4, 2.4 Hz, H8a), 4.59 (1H, d, *J* = 14.4, 2.4 Hz, H8a), 4.43 (1H, m, H5), 4.12 (1H, s, OH), 3.93 (1H, brs, H13), 3.88–3.82 (3H, m, H6, H17, H5′), 3.69 (1H, dq, *J* = 8.8, 6.4 Hz, H5″), 3.61 (1H, ddd, *J* = 11.2, 8.8, 4.8 Hz, H3′), 3.48 (1H, dd, *J* = 9.9, 1.6 Hz, H25), 3.44 (3H, s, OMe), 3.39 (1H, q, *J* = 2.1 Hz, H2), 3.35 (1H, m, H3″), 3.34 (3H, s, OMe), 3.21 (1H, dd, *J* = 8.8, 8.8 Hz, H4′), 3.14 (1H, dd, *J* = 8.8, 8.8 Hz, H4″), 2.51 (1H, m, H12), 2.33 (1H, ddd, *J* = 13.1, 4.8, 1.1 Hz, H2″), 2.30–2.25 (3H, m, H16x2, H24), 2.21 (1H, ddd, *J* = 12.8, 4.8, 1.0 Hz, H2′), 2.02 (1H, ddd, *J* = 12.0, 4.8, 1.9 Hz, H20), 1.79 (3H, s, Me4a), 1.76 (1H, m, H18), 1.62–1.45 (6H, m, H20, H26, H27x2, H2′, H2″), 1.50 (3H, s, Me14a), 1.26 (3H, d, *J* = 6.1 Hz, Me6′), 1.22 (3H, d, *J* = 6.4 Hz, Me6″), 1.16 (3H, d, *J* = 7.0 Hz, Me12a), 0.93 (9H, s, TBS), 0.89 (9H, s, TBS), 0.94–0.88 (10H, m, H18, Me24a, Me26a, Mr28), 0.13 (6H, s, TBS), 0.09 (3H, s, TBS), 0.08 (3H, s, TBS); ^{13}C NMR (175 MHz, $CDCl_3$) δ: 174.27, 140.38, 137.75, 137.73, 136.39, 135.37, 127.94, 124.96, 119.46, 118.42, 117.35, 98.77, 95.92, 95.13, 82.15, 80.98, 80.40, 80.19, 79.43, 78.71, 77.29, 75.01, 69.65, 69.20, 68.60, 68.50, 68.10, 67.47, 56.79, 56.51, 45.92, 40.60, 39.83, 36.72, 35.32, 34.81, 34.70, 34.45, 30.72, 27.67, 26.18, 26.04, 20.46, 20.21, 18.59, 18.53, 18.49, 18.45, 16.53, 15.30, 13.13, 12.20, − 3.81, − 4.43, − 4.59, − 4.71; HRMS (ESI) *m/z* calcd for $C_{60}H_{100}O_{14}Si_2Na$ $[M+Na]^+$ 1123.6544, found 1123.6550.

Avermectin B_{1a} (1)

To a solution of **59**α (3.0 mg, 2.72 μmol) in MeCN (0.15 ml)/pyridine (0.15 ml) was added pyridinium hydrofluoride (0.11 ml) at room temperature. After being stirred for 2 h, an additional pyridinium hydrofluoride (0.11 ml) was added to the reaction mixture. After being stirred for 12 h, an additional pyridinium hydrofluoride (0.05 ml) was introduced. After being stirred for further 1 h, the mixture was diluted with Et_2O and quenched with saturated aqueous $NaHCO_3$. The mixture was stirred for 30 min and the phases were separated. The aqueous phase was extracted with ether and the combined organic layer was washed with 5% HCl, saturated aqueous $NaHCO_3$, water and brine. The resultant organic layer was dried over Na_2SO_4 and concentrated *in vacuo* to give the crude products. The residue was purified by flash column chromatography (hexane/EtOAc = 1/2) to yield **1** (2.1 mg, 88%) as a colorless solid. **1**: $[\alpha]_D^{24}$ = 63.3 (*c* 0.22, $CHCl_3$), (lit. $[\alpha]_D^{27}$ 55.7 (*c* 1.06, $CHCl_3$);[2] lit. $[\alpha]_D^{20}$ = 63.7 (*c* 0.98, $CHCl_3$);[8] lit. $[\alpha]_D^{23}$ = 62.2 (*c* 0.78, $CHCl_3$)[9]); IR (film) *ν*: 3467, 2966, 2931, 1718, 1457, 1376, 1340, 1159, 1117, 1050, 985, 732 cm^{-1}; ^1H NMR (700 MHz, $CDCl_3$) δ: 5.86 (1H, ddd, *J* = 10.4, 2.4, 2.4 Hz, H9), 5.77 (1H, dd, *J* = 9.9, 1.6 Hz, H23), 5.75–5.72 (2H, m, H10, H11), 5.55 (1H, dd, *J* = 9.9, 2.7 Hz, H22), 5.42 (1H, brs, H3), 5.40 (1H, d, *J* = 4.0 Hz, H1″), 5.39 (1H, m, H19), 4.98 (1H, m, H15), 4.77 (1H, brd, *J* = 3.2 Hz, H1′), 4.70 (1H, dd, *J* = 14.2, 2.4 Hz, H8a), 4.67 (1H, d, *J* = 14.2, 2.4 Hz, H8a), 4.30 (1H, dd, *J* = 6.5, 6.5 Hz, H5), 4.04 (1H, s, OH), 3.97 (1H, d, *J* = 6.5 Hz, H6), 3.94 (1H, brs, H13), 3.87 (1H, m, H17), 3.84 (1H, dq, *J* = 9.1, 6.1 Hz, H5′), 3.77 (1H, dq, *J* = 9.1, 6.1 Hz, H5″), 3.63 (1H, ddd, *J* = 11.2, 9.1, 4.8 Hz, H3′), 3.50–3.47 (2H, m, H25, H3″), 3.44 (3H, s, OMe), 3.43 (3H, s, OMe), 3.30 (1H, dd, *J* = 4.5, 2.1 Hz, H2), 3.25 (1H, dd, *J* = 9.1, 9.1 Hz, H4′), 3.17 (1H, dd, *J* = 9.1, 9.1 Hz, H4″), 2.52 (1H, m, H12), 2.35–2.25 (4H, m, H16x2, H24, H2″), 2.22 (1H, ddd, *J* = 12.8, 4.8, 1.3 Hz, H2′), 2.01 (1H,

ddd, $J=12.0$, 4.8, 2.0 Hz, H20), 1.88 (3H, brs, Me4a), 1.78 (1H, dddd, $J=12.3$, 4.8, 2.0, 2.0 Hz, H18), 1.44–1.62 (6H, m, H20, H26, H27x2, H2′, H2″), 1.49 (3H, s, Me14a), 1.28 (3H, d, $J=6.1$ Hz, Me6′), 1.26 (3H, d, $J=6.1$ Hz, Me6″), 1.17 (3H, d, $J=7.2$ Hz, Me12a), 0.94 (3H, t, $J=7.5$ Hz, Me28), 0.92 (3H, d, $J=6.7$ Hz, Me24a), 0.92 (3H, d, $J=7.5$ Hz, Me26a), 0.88 (1H, ddd, $J=12.3$, 12.3, 12.3 Hz, H18); ^{13}C NMR (175 MHz, $CDCl_3$) δ: 173.98 (C, C1), 139.79 (C, C8), 138.24 (CH, C11), 138.19 (C, C4), 136.46 (CH, C22), 135.31 (C, C14), 127.90 (CH, C23), 124.89 (CH, C10), 120.56 (CH, C9), 118.43 (CH, C3), 118.17 (CH, C15), 98.67 (CH, C1″), 95.92 (CH_2, C21), 95.09 (CH, C1′), 82.06 (CH, C13), 80.54×2 (C, C7, CH, C4′), 79.52 (CH, C3′), 79.20 (CH, C6), 78.31 (CH, C3″), 76.27 (CH, C4″), 75.06 (CH, C25), 68.64 (C8a or C17 or C19 or C5″), 68.50×2 (C8a or C17 or C19 or C5″), 68.25 (C8a or C17 or C19 or C5″), 67.87 (CH, C5), 67.41 (CH, C5′), 56.69 (CH_3, OMe), 56.56 (CH_3, OMe), 45.88 (CH, C2), 40.61 (CH_2, C20), 39.92 (CH, C12), 36.80 (CH_2, C18), 35.32 (CH, C26), 34.65 (C16 or C2′ or C2″), 34.41 (C16 or C2′ or C2″), 34.32 (C16 or C2′ or C2″), 30.73 (CH, C24), 27.67 (CH_2, C27), 20.36 (CH_3, C12a), 20.14 (CH_3, C4a), 18.56 (CH_3, C6″), 17.83 (CH_3, C6′), 16.53 (CH_3, C24a), 15.28 (CH_3, C14a), 13.12 (CH_3, C26a), 12.20 (CH_3, C28); HRMS (ESI) *m/z* calcd for $C_{48}H_{72}O_{14}Na$ $[M+Na]^+$ 895.4814, found 895.4818.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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