doi.org/10.26434/chemrxiv.13176188.v2

Total Synthesis of Tiacumicin B: Study of the Challenging β-Selective Glycosylations

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Submitted date: 06/11/2020 • Posted date: 09/11/2020

Citation information: Tresse, cedric; François-Heude, Marc; Servajean, Vincent; Ravinder, Rubal; Lesieur, Clemence; Geiben, Lucie; et al. (2020): Total Synthesis of Tiacumicin B: Study of the Challenging β-Selective Glycosylations. ChemRxiv. Preprint. https://doi.org/10.26434/chemrxiv.13176188.v2

We report here a full account of the total synthesis of tiacumicin B (Tcn-B), a natural glycosylated macrolide with remarkable antibiotic properties. Our strategy is based on our experience with the synthesis of the tiacumicin B aglycone and on unique 1,2-cis-glycosylation steps. It features the conclusive use of sulfoxide anomeric leaving-groups in combination with a remote 3-O-picoloyl group on the donors allowing highly beta-selective rhamnosylation and noviosylation that rely on H-bond-mediated Aglycone Delivery (HAD). The rhamnosylated C1-C3 fragment was anchored to the C4-C19 aglycone fragment by a Suzuki-Miyaura cross-coupling. Ring-size selective Shiina macrolactonization provided a semi-glycosylated aglycone that was engaged directly in the noviosylation step with a virtually total beta-selectivity. Finally, a novel deprotection method was devised for the removal of a 2-naphthylmethylidene (Nap) ether on a phenol and efficient removal of all the protecting groups provided synthetic tiacumicin B.

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Total Synthesis of Tiacumicin B: Study of the Challenging β-Selective Glycosylations

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KEYWORDS: Antibiotics, Natural Products, Total Synthesis, 1,2-*Cis*-Glycosylation, Glycochemistry, Catalysis, Palladium Chemistry.

ABSTRACT: We report here a full account of the total synthesis of tiacumicin B (Tcn-B), a natural glycosylated macrolide with remarkable antibiotic properties. Our strategy is based on our experience with the synthesis of the tiacumicin B aglycone and on unique 1,2-*cis*-glycosylation steps. It features the conclusive use of sulfoxide anomeric leaving-groups in combination with a remote 3-*O*-picoloyl group on the donors allowing highly β-selective rhamnosylation and noviosylation that rely on H-bond-mediated Aglycone Delivery (HAD). The rhamnosylated C1-C3 fragment was anchored to the C4-C19 aglycone fragment by a Suzuki-Miyaura cross-coupling. Ring-size selective Shiina macrolactonization provided a semi-glycosylated aglycone that was engaged directly in the noviolysation step with a virtually total β-selectivity. Finally, a novel deprotection method was devised for the removal of a 2-naphthylmethylidene (Nap) ether on a phenol and efficient removal of all the protecting groups provided synthetic tiacumicin B.

Nowadays antibiotic resistance is one of the most serious threats to global health, food security and development, degrading the quality of life and heavily impacting the economy with longer hospital stays, higher medical expenses and higher mortality. This is a natural phenomenon whose process is accelerated by the excessive use or misuse of these drugs in humans and animals. An increasing number of infections, such as pneumonia, tuberculosis or salmonellosis, are becoming more and more difficult to treat because of the lack of effectiveness of the antibiotics used. To circumvent this resistance, one of the tracks consists in developing new antibiotics with new biological targets. Tiacumicin B (Tcn-B) meets these criteria and, received marketing authorization in 2011 in the United States for the treatment of *Clostridium difficile* intestinal infections, which are often of nosocomial origin and had previously been fatal in 25% of the cases.[1] Tcn-B interacts with bacterial RNA polymerase (RNAP)[2] blocking RNA synthesis, a strategy already used in broad-spectrum antibacterial therapy. Since Tcn-B inhibits bacterial RNAP by binding a site that does not overlap with other antibiotic binding sites, there is no known cross-resistance with the other antibiotics in use. There is no cross-resistance with rifamycin,[3] so Tcn-B is active on resistant strains of *mycobacterium tuberculosis*, which opens up new therapeutic possibilities.[4] In this context, designing reliable total syntheses of Tcn-B that could also lead to analogues proves particularly relevant.

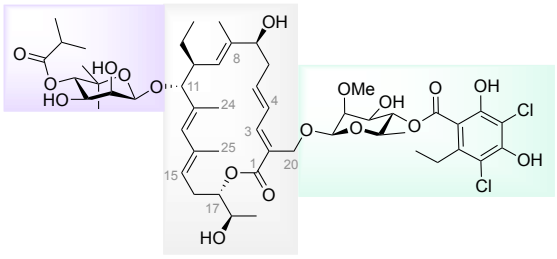


Figure 1. Tiacumicin B (Tcn-B)

Tcn-B is representative of a new class of antibiotic macrolides and is also known as clostomicin B1, fidaxomicin or lipiarmycin A3 (Figure 1).[5] This natural product was first isolated in the 70's from an actinobacterium, *Actinoplanes deccanensis*, found in the soil in India.[6] Its

structure was partially elucidated between 1983 and 1987 by Martinelli,[7] Arnone and Nasini[8] and recently its biosynthesis could be resolved by the team of Zhang.[9] Tcn-B is among the most complex and heavier macrolide and its structure can be divided into three main parts: 1) a central core composed of an eighteen-membered macrolactone displaying two (*E*),(*E*)-conjugated dienes, a trisubstituted (*E*)-alkene and featuring five stereogenic centers; 2) an eastern part with 2-*O*-methyl-D-rhamnose, linked as the β-anomer and esterified at the 4-position by an homodichloro-orsellinic acid; and 3) a western part consisting in a rare sugar, D-noviose, also linked as the β-anomer and esterified at the 4-position by isobutyric acid.

In 2015, aglycone's syntheses of Tcn-B were achieved by the Gadmann[10] and Altmann[11] groups while the Zhu[12] group synthesized the macrolactonic core of a diastereomer of Tcn-B (OH on the C-18). In 2017, we also reported our own syntheses of the aglycone by designing two closely related pathways.[13] The development of our strategy led us to discover a Kumada-Corriu reaction of vinyl sulfides catalyzed by Pd-nanoparticles.[14] We also reexplored the Grigg's allene/alkyne cross-coupling and proposed an unprecedented mechanism.[15] Until 2020, only the Gademann's team managed to complete the total synthesis of Tcn-B, providing solutions to the challenging problem of the 1,2-*cis*-glycosylations but there was still room for innovation and improvement of selectivity.[16] For the noviosylation step, the cyclic aglycone was found to show low reactivity toward a variety of different glycosyl donors or led exclusively to the α-glycosylated adduct. The mercury(II) Helferich's protocol[17] was then used for the glycosylation of an acyclic triene fragment with a noviosyl bromide giving the corresponding product in 63% yield (α/β: 1/3). After assembly and cyclization of the aglycone, the rhamnosylation was carried out on the macrolide with an acetimidate glycosyl donor delivering the fully protected Tcn-B (α/β: 1/4, 62%). Note that recently De Brabander used similar glycosylation strategies for the synthesis of the northern and southern glycosylated fragments of Tcn-B.[18] The total syntheses of tiacumicin A[19], mangrolide A[20] and D,[21] three congeners of tiacumicin B with a slightly simplified aglycone structure were also achieved.

In this article we wish to report with more details on our total synthesis of Tcn-B,[22] highlighting the original glycochemistry that we had to develop to achieve this goal. Displaying axial C-O bonds at C2, D-rhamnose and D-noviose can both be related to D-mannose derivatives, in which the methylhydroxyl group in the C5-position has been replaced by a methyl or a gem-dimethyl group, respectively. For this series, the glycosylation reactions leading to 1,2-cis derivatives are particularly challenging since the α-compound is favored for steric and thermodynamic (anomeric effect) reasons and its C-2 configuration precludes the application of conventional neighboring group participation effects.[23]

Our total synthesis of Tcn-B relies on our syntheses of the Tcn-B aglycone,[13] that are based on original and selective assembly of the three main regions of the molecule. We had originally imagined to sequentially glycosylate the aglycone, but finally opted for two more convergent retrosynthetic plans. In these scenarios, Tcn-B was disconnected into fragments **A1**, **B1**, and **C** or into fragments **A2**, **B2**, and **C** (Figure 2).[13] Connection of fragment **A1** together with fragment **B1** would first be achieved using ruthenium-catalyzed cross metathesis while a Suzuki coupling would allow the assembly of vinylbromide **B2** with the boronic ester **A2**. In both cases, following these steps, a ring-size selective macrolactonization would deliver a monoglycosylated aglycone having an unprotected OH at C-11 ready for the noviosylation step with fragment **C**. Knowing that the macrolactone has been described as a reluctant glycosyl acceptor, this challenging late β-glycosylation carried a high risk of failure.[11]

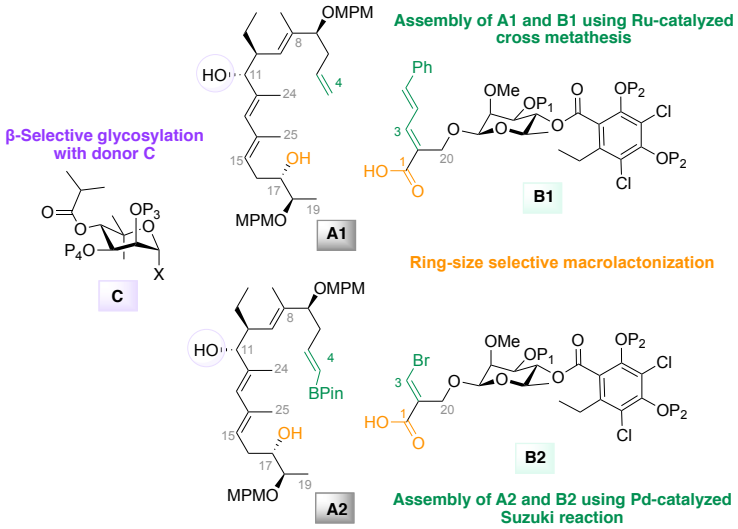
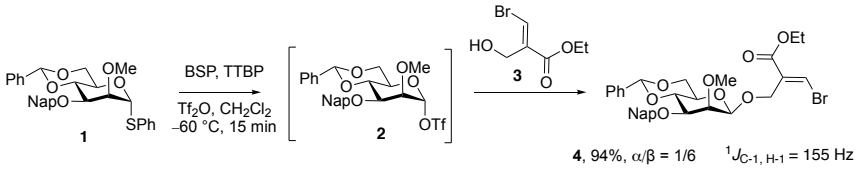


Figure 2. Pathways to tiacumicin B (Tcn-B).

Preparation of the eastern part with 2-*O*-methyl-D-rhamnose.

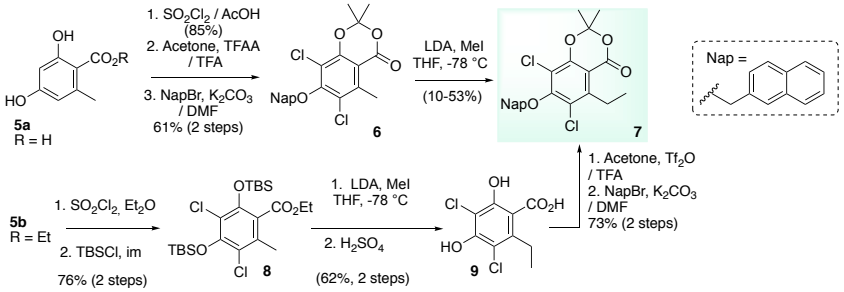
For the preparation of the rhamnose fragments **B1** or **B2**, we initially considered using the mannose β-glycosylation method described by Kahne[24] and Crich.[25] The activation of a mannosyl donor having a 4,6-benzylidene and an anomeric sulfoxide or a thioaryl leaving group

would allow the selective formation of the β-mannoside compound through S_N2 displacement of the corresponding α-anomeric triflate. The obtained glycoside would therefore be later functionalized into a rhamnoside derivative.



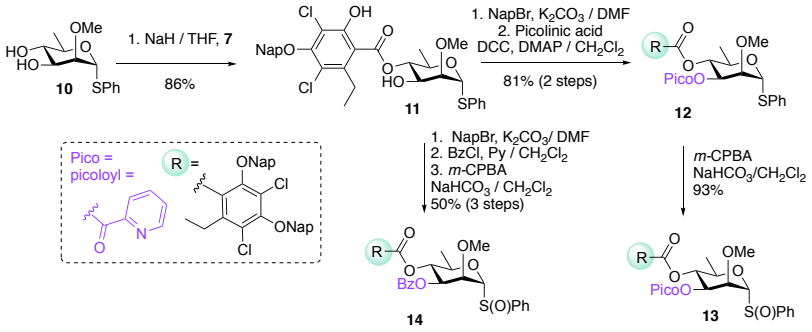
Scheme 1. Synthesis of β-mannoside **4**. BSP: 1-benzenesulfinyl piperidine, TTBP: 2,4,6-tri-tert-butylpyrimidine.

To this aim, thioglycosyl donor **1** was prepared[26] and submitted to Crich glycosylation conditions using pre-activation at –60 °C by 1-benzenesulfinyl piperidine (BSP) in the presence of 2,4,6-tri-tert-butylpyrimidine (TTBP) and Tf_2O (Scheme 1).[27] The intermediate triflate was then allowed to react with the acceptor **3**[13b] leading to the desired glycosylation product in a good 94% yield and a good selectivity of 1/6 in favor of the β-adduct. The stereochemistry was determined by measuring the C-1/H-1 coupling constant ($^1J_{C\text{-}1,\ H\text{-}1} \approx 160$ Hz if H-1 is axial and $^1J_{C\text{-}1,\ H\text{-}1} \approx 170$ Hz if H-1 is equatorial) derived from its ^{1}H-coupled heteronuclear single quantum correlation spectrum. Unfortunately, we did not succeed in further functionalizing this compound into the desired rhamnoside. We then turned to a glycosylation using the phenylthiorhamnosyl donor **12** comprising the homodichloroorsellinate ester at the 4-position and a picoloyl group (Pico) at *O*-3 (Scheme 3, Table 1)). This glycosylation strategy, developed by Demchenko, involves intermolecular H-bonding between the nitrogen of the picoloyl group and the acceptor, directing the selective facial attack on the glycosyl donor on the same side as the Pico group.[28] We started with the synthesis of orsellinate derivative **7** needed for the esterification at the 4-position of *S*-Phenyl-2-*O*-methyl-1-thio-α-D-rhamnopyranoside **10**.[22] This compound can be synthesized in a straightforward manner from commercially available carboxylic acid **5a** (Scheme 2). After dichlorination in acetic acid[29] and formation of the cyclic ester using acetone and trifluoracetic anhydride in trifluoroacetic acid,[30] the resulting phenol was protected as a 2-naphthylmethylidene ether (Nap) **6**. This protecting group was chosen as it could be removed using the same conditions (DDQ) as for 4-methoxybenzyl (MPM) ethers, already present on the aglycone. Lithiation of the benzylic methyl group of **6** with LDA at –78 °C followed by trapping the corresponding anion with methyl iodide allowed the formation of the targeted **7**. Unfortunately, this reaction proved unreproducible giving yields ranging from 53 to 10% on a larger scale. For this reason, we chose a longer but reliable sequence starting from commercially available ethyl orsellinate **5b**. The latter was chlorinated and both phenols protected as *tert*-butyldimethylsilyl ethers provided **8**.[22] With this compound, the sequence of the deprotonation of the benzylic methyl group/methylation proceeded in an almost quantitative yield to furnish reproducibly the homologated compound. After acidic hydrolysis with concentrated sulfuric acid to the deprotected carboxylic acid **9**, treatment with acetone and triflic anhydride in trifluoroacetic acid furnished the cyclic ester. Note that no reaction took place using trifluoracetic anhydride instead of Tf_2O. The remaining free phenol was finally protected, supplying Nap ether **7**.



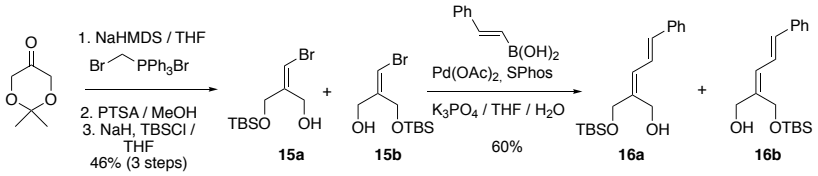
Scheme 2. Synthesis of orsellinate derivative **7**. TFA: trifluoroacetic acid, TFAA: trifluoroacetic anhydride, NapBr: 2-naphthalene-methyl bromide, LDA: Lithium di-*iso*-propylamide

The synthesis of donor **12** was performed from diol **10** obtained in a few steps from phenyl-2,3,4,6-tetra-*O*-acetyl-1-thio-β-D-mannopyranoside (Scheme 3).[22] Esterification of this diol using homodichloroorsellinate ester **7** and NaH in THF led to compound **11**. As observed by Gademann et *al.*,[19] the *O*-3 position is first esterified and the desired adduct is formed after ester migration on a prolongated reaction time. The liberated phenol was then protected as 2-Nap ether and the *O*-3 position of the rhamnoside was esterified with picolinic acid to give the desired donor **12**.



Scheme 3. Synthesis of rhamnopyranosyl donors **12-14**. DCC: dicyclohexylcarbodiimide, DMAP: 4-dimethylaminopyridine, *m*-CPBA: 3-Chloroperoxybenzoic acid.

Rhamnosyl donor **12** was first engaged in a glycosylation reaction with the monoprotected diol **16a** as the acceptor (Table 1, entry 1). This compound was prepared from 2,2-dimethyl-1,3-dioxan-5-one[31] after a Wittig reaction with bromotrimethylphenylphosphonium bromide in the presence of sodium bis(trimethylsilyl)amide (NaHMDS) in THF (Scheme 4). This was followed by deprotection of the acetonide and monoprotection of the resulting diol as TBS-ethers **15a** and **15b**.[32] A Suzuki cross coupling of a mixture of **15a,b** with phenylvinylboronic acid using catalytic $Pd(OAc)_2$ combined with 2-dicyclohexylphosphino-2′,6′-dimethoxybiphenyl (Sphos) as ligand and potassium phosphate in THF/water at room temperature was then carried out giving **16a** and **16b** that could be separated using preparative HPLC.



Scheme 4. Synthesis of acceptors **15a** and **16a**. NaHMDS: sodium bis(trimethylsilyl)amide, PTSA: *para*-toluene sulfonic acid, SPhos: 2-dicyclohexylphosphino-2′,6′-dimethoxybiphenyl.

The glycosylation reaction of **16a** was carried out in 1,2-dichloroethane (DCE) with dimethyl(methylthio)sulfonium triflate (DMTST), a classical promoter used in H-bond-mediated Aglycone Delivery (HAD). However, no glycosylation adduct was obtained with donor **12**, **16a** proving very unstable under these conditions. Acceptor **15a** was then used and with DMTST (2 eq.) in DCE at room temperature, we were pleased to obtain the glycosylation product **18** in 85% yield (Table 1, entry 2). A good α/β selectivity of 1/6.5 was also achieved suggesting that HAD might have worked to mediate a β-selective glycosylation through an intermediate such as **21**. Recrystallization allowed us to separate both anomers and to unambiguously determine the configuration of the major one through X-ray crystal diffraction analysis (Figure 3).[33] The reaction was also carried out in dichloromethane using *N*-iodosuccinimide (NIS, 1.2 eq.) and a catalytic amount of triflic acid (TfOH, 0.24 eq.), which gave a good yield (86%) but with a slightly lower stereoselectivity (α/β = 1:4) (Table 1, entry 3).

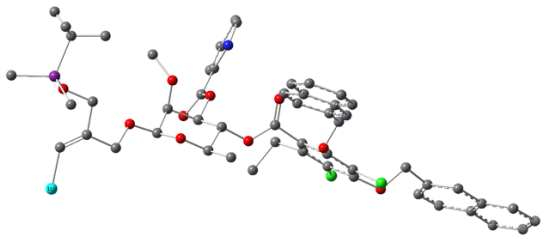
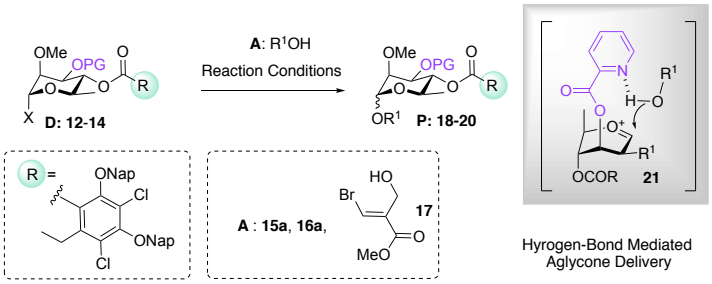


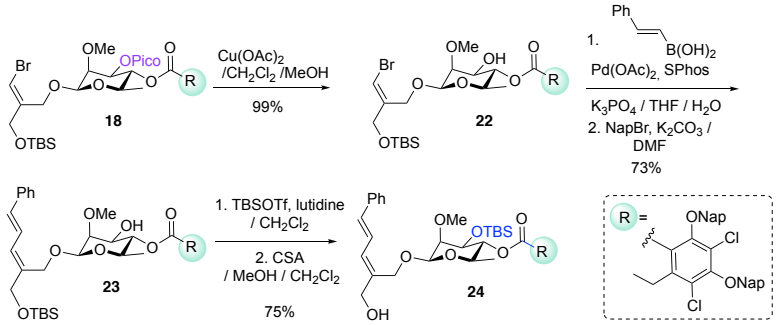
Figure 3. X-ray crystal structure of **18**.

Table 1. Rhamnosylation conditions of different acceptors with donors **12-14.**



Entry	**D** (eq.)	**A**	Conditions[a]	**P**, yield (%)[b]	α/β[c]
1	**12** (1.3)	**16a**	DMTST[d]	-	-
2	**12** (1.3)	**15a**	DMTST[d]	**18**, 85	1/6.5
3	**12** (1.3)	**15a**	NIS, cat. TfOH[e]	**18**, 86	1/4
4	**12** (1.3)	**17**	DMTST[d]	-	-
5	**12** (1.3)	**17**	NIS, TfOH cat.[e]	-	-
6	**12** (1.3)	**17**	BSP, TTBP, Tf_2O, –60 °C[f]	-	-
7	**12** (1.3)	**17**	NIS, TfOH[g]	**19**, 75-86	1/3-1/4
8	**13** (1.3)	**17**	Tf_2O, –50 °C[h]	**19**, 52	1/12
9	**13** (1.3)	**17**	Tf_2O, –70 °C[h]	**19**, 48	1/16
10	**13** (1.7)	**17**	Tf_2O, –70 °C[h]	**19**, 64	1/20
11	**13** (2.1)	**17**	Tf_2O, –70 °C[h]	**19**, 70	1/20
12	**13** (1.3)	**17**	Tf_2O, –70 °C[i]	**19**, 20	1/2
13	**14** (1.7)	**17**	Tf_2O,–70 °C[h]	**20**, 95	20/1

[a] Reaction performed in CH_2Cl_2 (*c* 0.01M) with 4Å MS unless otherwise stated. [b] After chromatography on silica gel. [c] Ratio and stereochemistry determined by ^1H NMR analysis of the crude mixture and by measuring $^1J_{C1,H1}$ coupling respectively. [d] With 2.6 eq. of the promotor in DCE as solvent from 0 °C to r.t. [e]. With 1.2 eq. of NIS and 0.24 eq. of TfOH from –40 °C to r.t. [f] With 1.3 eq. of BSP, 2.5 eq. of TTBP and 1.4 eq. of Tf_2O. [g] With 1.2 eq. of NIS and 1 eq. of TfOH from –40 °C to r.t. [h] With 1.3-1.9 eq. of Tf_2O, 3.5-4.6 eq. of DTBMP and 4.2-6 eq. of ADMB. [i] Preactivation protocol.



Scheme 5. Functionalization of **18**. CSA: camphor sulfonic acid.

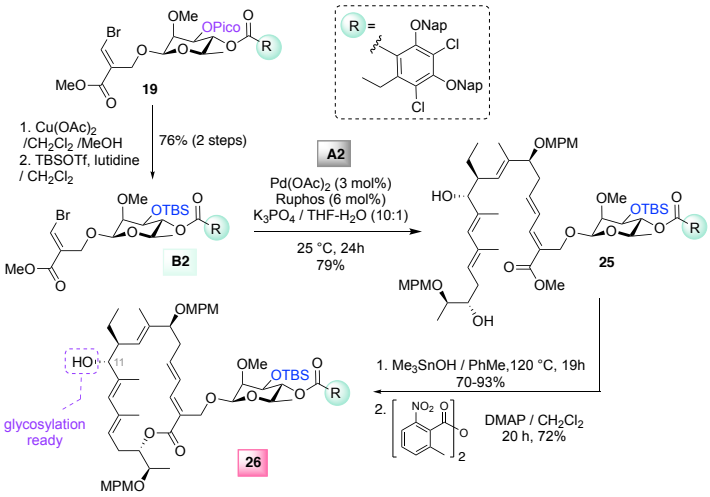
Before optimizing this glycosylation step, we chose to test the synthetic sequence leading to the key building block **B1** necessitating a terminal carboxylic acid group. Thus, the Pico group in **18** was smoothly and selectively removed with $Cu(OAc)_2$ in dichloromethane/methanol (Scheme 5). This was followed by a Pd-catalyzed Suzuki reaction with phenylvinylboronic acid using catalytic $Pd(OAc)_2$/Sphos and K_3PO_4 in THF/water at room temperature for 18 hours. Following these mild conditions, we noticed the presence of

about 20% of products displaying deprotected phenols on the orsellinate moiety. Direct treatment of the crude reaction mixture with NapBr in the presence of K_2CO_3 in DMF allowed us to reinstall the protective groups and obtain the targeted diene compound **23** in 73% yield. The 3-OH on the rhamnoside moiety was then protected as a TBS-ether and the primary alcohol was deprotected using camphor sulfonic acid in methanol/CH_2Cl_2, providing **24** in a 75% yield. Unfortunately, we did not succeed in oxidizing this compound into the corresponding carboxylic acid prior to the next Ru-catalyzed cross metathesis with fragment **A1**.

We then turned our attention toward the glycosylation of the alternative acceptor **17** already bearing the carboxylic function. Contrary to previous results with **15a**, activation of **12** with DMTST or NIS/cat. TfOH were disappointingly unsuccessful since no glycosylation adduct was observed (Table 1, entries 4 and 5). Activation with the BSP/Tf_2O method at –60 °C in the presence of TTBP was also tried without success leading to the degradation of the acceptor (Table 1, entry 6). However, by increasing the amount of TfOH (0.92 eq./donor)[34] used in combination with *N*-iodosuccinimide (1 eq./donor) in CH_2Cl_2 at –40 °C to r.t. produced **19** in a 76% yield as a mixture of anomers (α/β : 1/4) (Table 1, entry 7), that could be separated by preparative HPLC. Note that in this particular case, the excess of TfOH could disrupt the HAD pathway and the glycosylation would follow a different mechanism, probably involving the protonation of the nitrogen on the picoloyl and formation of a glycosyl triflate.[35] By changing parameters such as temperature, promoter or donor amount, dilution, etc., we were not able to obtain a better selectivity. Seeking for higher *β*-selectivity, we decided to explore the reaction with sulfoxide **13**, a type of anomeric leaving group never before used in combination with a directing picoloyl group. Following *m*-CPBA oxidation of sulfide **12**, the activation of donor **13** (1.3 eq.) was first examined in CH_2Cl_2 at –50 °C using Tf_2O in the presence of the acceptor **17**, 2,6-di-terbutyl-4-methylpiridine (DTBMP) as acid scavenger, and 4-allyl-1,2-dimethoxybenzene (ADMB) (Table 1, entry 8).[36,37] We were pleased to find that under these conditions the desired glycosylated compound **19** with an upgraded facial selectivity (α/β : 1/12) and a yield of 52%. Higher yield (70%) and selectivity (α/β : 1/20) could be further attained by increasing the donor amount (2.1 eq.) and by lowering the temperature of the activation at –70 °C (see Table 1, entries 8 to 11 for comparison). To verify the influence of the remote picoloyl group in stereodirecting the nucleophilic attack on the *β*-face by H-bonding, we carried out two control experiments. The first consisted in performing the reaction by pre-activating the donor using Tf_2O at –70 °C for 15 minutes followed by the addition of the acceptor (Table 1, entry 12). These conditions led to the formation of the expected glycoside **19** in only 20% yield and poor selectivity (α/β: 1/2). The second control experiment was achieved with donor **14** having a benzoyl group in place of the picoloyl (Table 1, entry 13). This reaction led to pure α-glycosylation product **20**, indicating that the HAD mechanism may effectively take place only with the picoloyl group. The picoloyl of **19** was then removed with $Cu(OAc)_2$ in CH_2Cl_2/MeOH, and replaced by a TBS group to lead to fragment **B2**.

Assemblage of A2 and B2 and macrolactonization

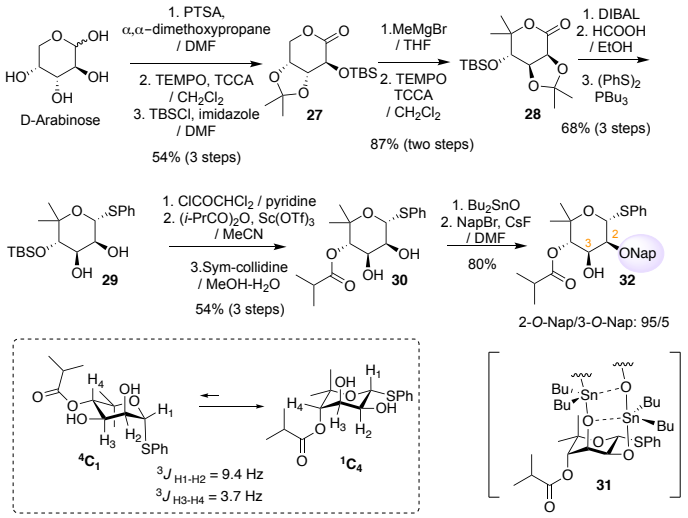
We could easily scale up our synthesis of the aglycone fragment **A2**. The convergent step of Pd-catalyzed cross-coupling of boronic ester **A2** with rhamnoside **B2** proceeded cleanly with catalytic $Pd(OAc)_2$ /Ruphos and potassium phosphate in a mixture of THF/water at r.t., furnishing ester **25** in 79% yield (Scheme 6). As reported by Nicolaou *et al.*,[38] the use of Me_3SnOH allowed us to hydrolyze selectively the methyl ester in the presence of the orsellinate on the rhamnoside moiety. Performed in toluene at 120 °C, the reaction led cleanly to seco-acid in 70 to 93% yields. With the latter in hand, we then focused on a ring-size selective macrolactonization using Yamaguchi conditions as described for the synthesis of our aglycone.[13] However, the transposition of these conditions on this substrate led to the desired hemi-glycosylated tiacumicin B **26** in a low 23% yield. With the Boden-Keck's protocol,[39] the yield reached 58% yield, but **26** proved to be a mixture of two products resulting from the isomerization of the C4-C5 alkene. Finally, a far cleaner and reproducible macrolactonization was achieved using the Shiina's conditions[40] with 2-methyl-6-nitrobenzoic anhydride furnishing **26** in 72% yield, and an isomerization minimized at 15%. This selective strategy allowed us to keep the free OH at C-11 so that **26** could be directly engaged in the next glycosylation step.



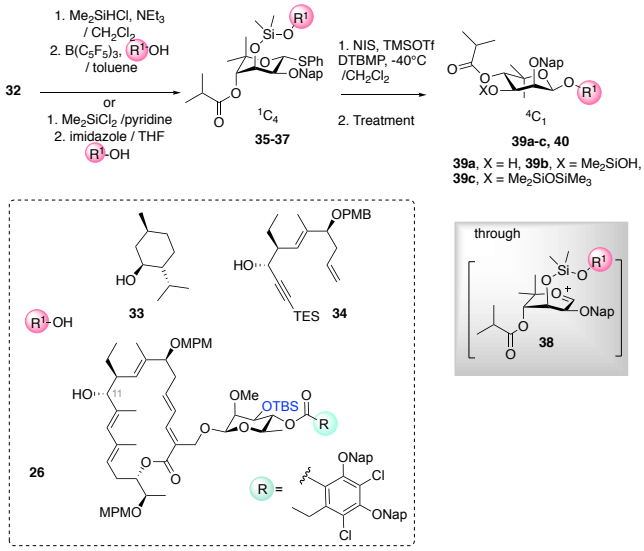
Scheme 6. Assemblage of **A2** and **B2** and macrolactonization to monoglycosylated **26**. Ruphos : 2-dicyclohexylphosphino-2′,6′-diisopropoxybiphenyl.

Preparation of the western part with D-niovose and noviosylation step.

For the noviosylation, we had first programmed Intramolecular Aglycone Delivery (IAD) using a silicon tether anchoring **26** to the 2-*O* position of the noviosyl moiety.[41] The axial configuration of the 2-hydroxyl group of the donor being favorable, this approach would *a priori* provide a 1,2-cis glycosidic linkage with complete β-stereocontrol. For the preparation of the required noviosyl donor, we started from D-arabinose (Scheme 7). Selective acetonide protection of the *cis*-diol, oxidation of the hemiacetal with trichloroisocyanuric acid (TCCA) and catalytic TEMPO followed by silylation of the remaining 2-OH group provided lactone **27**. Introduction of the gem-dimethyl groups was achieved using the reaction of **27** with the methyl Grignard reagent and the corresponding diol was re-oxidized to lactone **28**. Dibal-H reduction led to the lactol and a mild acidic treatment with formic acid allowed the selective removal of the acetonide protection, prior to the introduction of a thiophenyl group at the anomeric position. The resulting diol **29** was protected as dichloroacetyl esters, which upon treatment by $(i\text{PrCO})_2\text{O}$ in MeCN with a catalytic amount of $Sc(OTf)_3$ allowed the direct replacement of the TBS group by an isobutyrate.[42] The two dichloroacetates in the obtained compound were then selectively removed with *sym*-collidine in MeOH giving diol **30**. The latter was then selectively mono-alkylated (NapBr, CsF) after the prior formation of the stannylene **31** giving predominantly the compound **32** with 2-naphthylmethylidene ether at *O*-2 position (2-*O*-Nap/3-*O*-Nap = 95/5) in 80% yield.



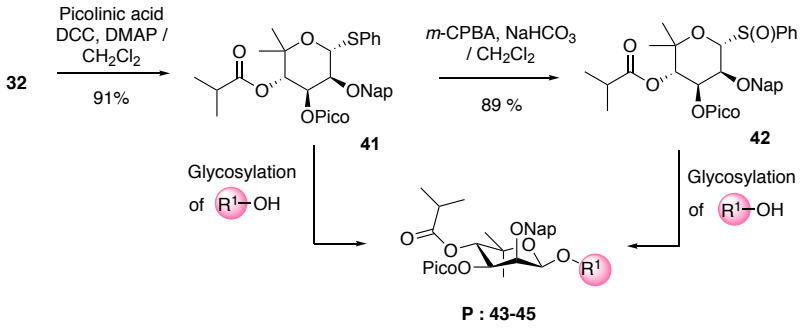
Scheme 7. Preparation of the noviosyl thioglycoside **32** from D-arabinose, conformational preference of diol **30** and likely structure of stannylene **31** with an equatorial C2-O2 bond. TEMPO: 2,2,6,6-tetramethyl-1-piperidinyloxy, TCCA: trichloroisocyanuric acid.



Scheme 8. Preparation of the silaketals **35-37** and glycosylation. NIS : N-iodosuccinimide; DTBMP: 2,6-Di-tert-butyl-4-methylpyridine.

This unexpected selectivity can be rationalized by the preferred conformation of the starting diol **30**, which is not the conventional $^4C_1$ chair but the $^1C_4$ chair, certainly imposed by the presence of the gem-dimethyl group. This was confirmed by the $^3J_{1,2}$ coupling constant of 9.5 Hz in the ^{1}H NMR spectrum of diol **30** indicating a H-1/H-2 *trans* diaxial orientation. The equatorial OH bond being more accessible, this accounts for the selectivity of this protection.

We chose to investigate IAD approach with **32**, although to our knowledge, no other example has been described with a glycosyl acceptor linked to the 3-*O* position of the donor (Scheme 8). Starting our study with (–)-menthol **33** as a model, the corresponding silaketal **35** could be easily synthesized with the recently reported method of Montgomery.[41c] After treatment of noviosyl adduct **32** with dimethylchlorosilane, the corresponding alkoxysilane reacted with (–)-menthol **33** in the presence of $B(C_6F_5)_3$ as catalyst. As indicated by the ^{1}H NMR spectrum, the silylated compound **35** also adopts exclusively a $^1C_4$ chair conformation. Considering that intermediate oxonium **38**, resulting from **35**, must display a half-chair conformation (Scheme 8), the alcohol to be transferred must then occupy a position favorable for the formation of the desired β-derivative. Optimized glycosylation conditions on **35** were obtained when the reaction was carried out with NIS (1.3 eq.) and TMSOTf (1.8 eq.) in CH_2Cl_2 in the presence of DTBMP (3 eq.) at –40 °C for 1 h. Treatment of the reaction mixture with a solution of TBAF in THF led to the desired glycosylation product **39a** (X = H) in 55% yield and as a single β-anomer. In this case, the obtained compound **39a** adopted a $^4C_1$ conformation with a measured $^1J_{C\text{-}1,H\text{-}1}$ of 159 Hz confirming the β-configuration. The moderate yield obtained here is likely due to the presence of the TBAF reagent that can cleave the *i*-butyrate ester. However, without TBAF treatment, we isolated, after silica gel chromatography, two stable glycosylation adducts bearing various silyl groups (**39b**, X= Me_2SiOH,[43] and **39c**, X = $Me_2SiOTMS$[44]) at the 3-*O* position of the novioside. To avoid their formation, an anhydrous HCl solution in methanol was added after completion of the glycosylation which delivered targeted product **39a** in a 81% yield with complete β-stereocontrol. The reaction was also carried out with the more complex alcohol **34**, a synthetic precursor of the aglycone fragment **A2**. The formation of the silaketal was performed as with (–)-menthol which produced **36** exclusively in a $^1C_4$ chair conformation and a good 76% yield. Using the glycosylation conditions described previously and acid treatment, the corresponding adduct **40** was obtained in 41% yield also as a single β-anomer. As for **39**, the obtained glycosylated compound **40** adopted a $^4C_1$ conformation with a measured $^1J_{C\text{-}1,H\text{-}1}$ of 159 Hz. Despite this unsatisfactory result, we decided to attempt the reaction with the semi-glycosylated tiacumicin B **26**. In this case we failed at preparing the silaketal using Montgomery's conditions but good results were obtained with the preliminary formation of the chloroalkoxysilane[41a] that reacted with **26** providing the corresponding dialkoxysilane **37** in 73% yield. Unfortunately, glycosylation using NIS and TMSOTf in DCM at –40 °C followed by an HCl treatment led to degradation of the compound without evidence of the formation of the targeted glycosylated adduct.



Scheme 9. Preparation of the noviosyl donors **D** (**41-42)** and glycosylation (structure of R^1OH in Scheme 8).

We then shifted to another strategy based this time on an H-bond-mediated Aglycone Delivery (HAD) approach involving the use of noviosyl donor **41** bearing a Pico group at the 3-position (Scheme 9). Following esterification of **32** with picolinic acid, the corresponding sulfide **41** was engaged in a glycosylation reaction with (–)-menthol as the acceptor (Table 2, entry 1). The reaction was carried out with DMTST as the promoter and led predominantly to the β-compound **43** (α/β: 1/5) in 83 % yield. With elaborated unsaturated alcohol **34**, this approach led to poor yields (11 to 21%) either with DMTST (Table 2, entry 2) or NIS/TfOH (Table 2, entry 3) and unfortunately turned out unsuccessful with macrolactonic acceptor **26** since no glycosylated adduct was detected.

The success of the above-mentioned rhamnosylation led us to consider that sulfoxide **42** derived from sulfide **41** could be a far more reactive donor. A first trial with (–)-menthol as acceptor under Tf_2O activation at –70 °C revealed the potency of this method, as the β-anomer **43** was obtained as the only adduct in 66% yield (Table 2, entry 4). With alcohol **34**, the use of the sulfoxide approach proved to be more efficient as well providing β-glycosylation product **44** in a 62% yield (Table 2, entry 5). Moreover, these reaction conditions applied to the hemi-glycosylated tiacumicin B **26** delightfully furnished the desired noviosylated product **45** in 68% yield, with high facial selectivity (Table 2, entry 6, $\alpha/\beta > 1/20$).

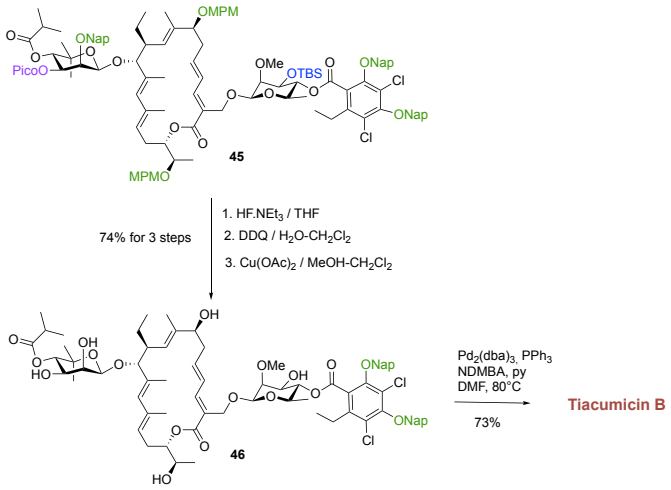
Table 2. Glycosylation conditions of donors D (41-42) with different acceptors.

Entry	**D** (eq.)	**R^1-OH**	Conditions[a]	**P**, yield (%)[b]	α/β[c]
1	**41** (1.3)	**33**	DMTST[d]	**43**, 83	1/5
2	**41** (1.3)	**34**	DMTST[d]	**44**, 11	nd
3	**41** (1.3)	**34**	NIS, TfOH[e]	**44**, 21	nd
4	**42** (1.3)	**33**	Tf_2O, –70 °C [f]	**43**, 66	>1/20
5	**42** (2.1)	**34**	Tf_2O, –70 °C [g]	**44**, 62	1/20
6	**42** (2.1)	**26**	Tf_2O, –70 °C[g]	**45**, 68	>1/20

[a] Reaction performed in CH_2Cl_2 (*c* 0.01M) with 4Å MS unless otherwise stated. [b]After chromatography on silica gel. [c] Ratio and stereochemistry determined by ^{1}H NMR analysis of the crude mixture and by measuring $^1J_{C1,H1}$ coupling. [d] With 2.3 eq. of the promotor in DCE (0.02M) from 0 °C to r.t. [e] With 1.4 eq. of NIS and 1.8 eq. of TfOH from –40 °C to r.t. [f] With 1.5 eq. of Tf_2O and 3 eq. of DTBMP. [g] With 1.9 eq. of Tf_2O, 4.7 eq. of DTBMP and 4.2 eq. of ADMB.

Final deprotection stages

The last steps consisting in the removal of all protective groups (2 MPM, 3 Nap, 1 Pico and 1 TBS) from compound **45** proved unpleasantly more difficult than expected (Scheme 10). Using HF.NEt_3 in THF allowed us to remove first the TBS group located on the rhamnosyl moiety giving the corresponding alcohol. The 2 MPM as well as the Nap located on the novioside were then oxidized with DDQ in CH_2Cl_2/H_2O. At this stage, the two Nap groups protecting the phenol functions of the rhamnosyl moiety resisted these conditions at 0 °C, and a longer reaction time at 20 °C led to an intractable mixture of products. The removal of the picoloyl was then cleanly carried out using $Cu(OAc)_2$ in CH_2Cl_2/MeOH at 0 °C to produce **46**. This deprotection sequence order was important as the Pico group had to be removed after its neighboring Nap group to avoid the DDQ-promoted formation of a 2,3-*O*-naphthylmethylidene on the novioside. These three operations were performed with no intermediate purifications providing an overall yield of 74% of **46**. However, the unexpected problem of cleavage of the two Nap groups located on the two phenol functions remained to be addressed. Lewis acid-mediated treatment of the Nap led only to the degradation of the molecule. Pd-catalyzed hydrogenation (Pd/C, cyclohexene) allowed the phenol deprotection but along with the reduction of the C4-C5 alkene.[45] As above mentioned, we observed a partial loss of the Nap groups located on the phenol moiety during the Pd-catalyzed Suzuki reaction of **23** with phenyl vinylboronic acid (see Scheme 5 and text). Exploiting this observation, we finally discover a new and selective method of deprotection of Nap ether on phenol. After a few optimizations, we found that using $Pd_2(dba)_3$ as a catalyst in combination with 4 PPh_3 along with 1,3-dimethylbarbituric acid (NDMBA) as methyl naphthyl scavenger and pyridine in DMF at 80 °C provided selective and smooth deprotection conditions. This ultimate step supplied the target compound tiacumicin B in 73% yield, with chemical data identical to those of the naturally occurring compound.[6b]



Scheme 10. Final deprotection steps. DDQ: 2,3-dichloro-5,6-dicyano-1,4-benzoquinone. NDMBA: 1,3-dimethylbarbituric acid

In conclusion we have achieved a convergent total synthesis of tiacumicin B, by assembling the three main regions of the molecule. A highly β-selective rhamnosylation of the C1-C3 fragment followed by a Suzuki cross-coupling allowed assembling the rhamnoside **19** with the C4-C19 aglycone fragment **A2**. A ring-size selective macrolactonization using Shiina conditions was carried out followed by a final highly selective β-noviosylation of the cyclic aglycone and removal of all the protecting groups. During our glycosylation studies, we discovered a novel variant of the Demchenko procedure thanks to the conjoint use of a phenylsulfoxide leaving-group and a remote 3-*O*-picoloyl group on the donor. This combination allowed us to solve the problem of 1,2-*cis* glycosylation with a sensitive and complex aglycone and to reach a remarkable facial selectivity relying on an H–bond-directed effect. This new procedure will certainly prove useful in addressing the biological relevance of the tiacumicin B carbohydrate sugars or for the preparation of a set of glycosylated analogues. We also found a new and effective method for the removal of a 2-naphthylmethylidene (Nap) ether protecting group on a phenol through the use of palladium catalysis.

ASSOCIATED CONTENT

Supporting Information

Crystallographic data for structure **18**, preparation of all of the compounds, ^{1}H and ^{13}C NMR spectra for new compounds **4**, **6**, **15-16**, **18**, **22-24**, **39-40**, **43-44**, ^{1}H and ^{13}C NMR spectra of the synthetic and natural Tcn-B

ACKNOWLEDGMENT

We gratefully acknowledge financial supports from the French Agence Nationale pour la Recherche (ANR-14-CE16-0019-02, SYNTIA project), the CNRS, and the Université de Paris. We thank Karim Hammad and Jean-François Gallard for NMR support and Rosemary Green Beau for her editing of the manuscript.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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Total Synthesis of Tiacumicin B: Study of the Challenging β-Selective Glycosylations

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Supplementary Information

X-ray Crystal Structure **18**

Methods for Crystal Growth

Compound **18** was recrystallized by slow evaporation of a mixture of EtOAc/Heptane (6/4). The best we could obtain was fragile thin platelets that could diffract enough to provide a reasonable crystal structure characterization.

Experimental.

The single crystal isolated in a Paratone drop under a binocular was mounted upon a nylon loop, and frozen directly in the LN_2 coldstream at -60°C for XRD analysis. The data collection was carried out on a Rigaku mm007 copper Cu Kα rotating anode equipped with CMF mirrors and coupled to a Rapid II curved Imaging plate detector that allows $2\theta \leq 130°$ measurements. Data reduction and scaling including semi-empirical absorption correction were performed by *Fs_Process*[1] as implemented within *CrystalClear 2.0* suite[2] that pilots the diffractometer. The structure of (??) was readily solved by intrinsic phasing methods (*SHELXT*)[3] in the monoclinic space group, P 2_1, despite poor Rint value >> 10% due to weakly scattering sample, slightly split, and some icing. Since no useful signal could be detected beyond atomic resolution limit despite reasonably long exposure, cut-off to a 1.1Å resolution limit was applied to the dataset in order to provide a model with acceptable geometry. The structure was refined by full-matrix least-squares methods on F^2 using *SHELX-L*.[4] To compensate the poor data over parameters ratio, the non-hydrogen atoms were refined anisotropically, with application of enhanced rigid-bond restraints [5] throughout the whole structure, and hydrogen atoms were riding on their carrier atom with U_{iso} set to xU_{eq} of the carbon atom (x= 1.5 for methyl carbons and 1.2 for all others). Nevertheless, the diffraction benefitted from the presence of strong anomalous scatterers (one Br and two Cl atoms within the molecule), confirming the absolute configuration of the compound via the significant value of the Flack parameter[5] or the post-refinement Bijvoet analysis [6] (see **Table S1**).

Crystallographic data structure **18** have been deposited in the Cambridge. Crystallographic Data Centre database (deposition number CCDC 2027426). Copies of the data can be obtained free of charge from the CCDC at www.ccdc.cam.ac.uk.

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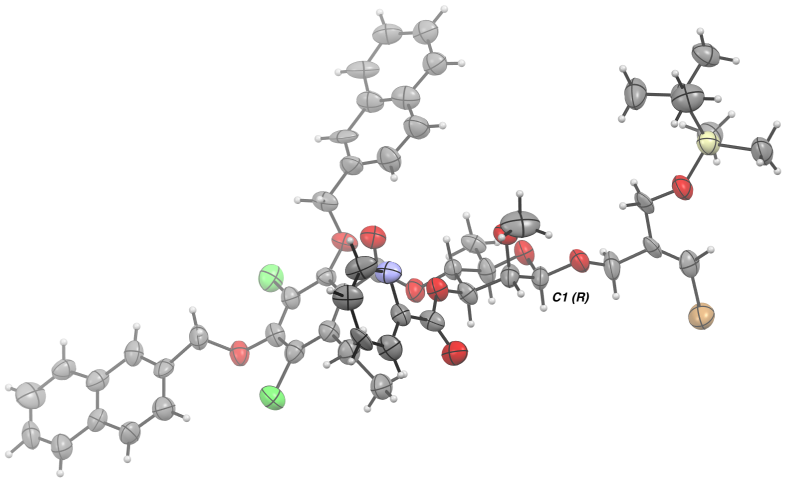


Figure S1 Ortep view of compound **18** with thermal ellipsoids drawn at 30% probability.

Table S1. Crystal data and structure refinement for compound **18**.

Empirical formula	$C_{54}H_{58}BrCl_2NO_{10}Si$	
Formula weight	1059.91	
Temperature	213(2) K	
Wavelength	1.54187 Å	
Crystal system	Monoclinic	
Space group	$P2_1$	
Unit cell dimensions	a = 16.1266(6) Å	α= 90°.
	b = 9.6924(3) Å	β= 95.044(7)°.
	c = 16.9284(11) Å	γ = 90°.
Volume	2635.8(2) $Å^3$	
Z	2	
Density (calculated)	1.335 Mg/m^3	
Absorption coefficient	2.683 mm^{-1}	
F(000)	1104	
Crystal size	0.25 x 0.24 x 0.02 mm^3	
Theta range for data collection	6.9 to 44.5°.	
Index ranges	$-14 \le h \le 14$, $-8 \le k \le 8$, $-15 \le l \le 15$	
Reflections collected	16578	
Independent reflections	4081 [R(int) = 0.1395]	
Completeness to θ max	99.2 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	1.000 and 0.567	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	4078 / 535 / 629	
Goodness-of-fit on F^2	1.093	
Final R indices [I>2σ(I)]	R1 = 0.0738, wR2 = 0.1163	
R indices (all data)	R1 = 0.1660, wR2 = 0.1601	
Absolute structure parameters:		
Flack parameter using 547 quotients	0.01(3)	
Hooft parameter using 1847 Bijvoet pairs	0.005(19)	
P2(true), P3(true), P3(rac-twin), P3(false)	*1.000, 1.000, $0.2.10^{-124}$, 0.000*	
Largest diff. peak and hole	0.278 and -0.323 $e.Å^{-3}$	

Experimental details

General

All reactions were performed in oven-dried round-bottomed flasks using anhydrous solvents and under an argon atmosphere unless otherwise stated. Anhydrous solvents (DMF, MeOH, MeCN, CH_2Cl_2, PhH) and reagents were obtained from commercial suppliers and used without further purification. Reactions were monitored with analytical thin-layer chromatography (TLC) on silica gel 60 F_{254} plates and visualized under UV (254 nm) and/or by staining with $KMnO_4$ or vanillin. Silica gel SDS 60 ACC 35-70 mm was used for column chromatography. Preparative TLC was done using Merck 60 F_{254} 0.5 mm. NMR spectra were recorded with AM 300, AVANCE 300 and AVANCE 500 Brüker spectrometers. Chemical shifts are given in parts per million, referenced to the solvent peak of $CDCl_3$, defined at 77.23 ppm (^{13}C NMR) and 7.26 ppm (^{1}H NMR). Melting points (uncorrected) were determined with the aid of a Büchi B-540 apparatus. IR spectra were recorded on a Perkin-Elmer Spectrum BX instrument with an FT-IR system. Optical rotations were measured on an Anton Paar MCP300 polarimeter using a cell of 1 dm-length path. All the reagent grade chemicals obtained from commercial sources were used as received.

Preparation of the eastern part with 2-*O*-methyl-D-rhamnose

(*E*)-ethyl 3-bromo-2-((((2*R*,4a*R*,6*R*,7*S*,8*S*,8a*R*)-7-methoxy-8-(naphthalen-2-ylmethoxy)-2-phenylhexahydropyrano[3,2-*d*][1,3]dioxin-6-yl)oxy)methyl)acrylate 4. A solution of donor **1** (600 mg, 1.16 mmol, 1 eq.) in anhydrous CH_2Cl_2 (23 mL) was stirred for 30 min in the presence of activated molecular sieves 4Å (1 g) at r.t. The solution was cooled at –60 °C followed by the addition of TTBP (432 mg, 1.74 mmol, 1.5 eq.) and BSP (268 mg, 1.28 mmol, 1.1 eq.). After 5 min at –60 °C, Tf_2O (0.23 mL, 1.39 mmol, 1.2 eq.) was added dropwise and the reaction mixture was stirred for 10 min at –60 °C. A solution of acceptor **3** (364 mg, 1.74 mmol, 1.5 eq.) in anhydrous CH_2Cl_2 (12 mL) was added dropwise at –60° C. After stirring for 1 h at –60 °C, the reaction was quenched with Et_3N (2 mL). The reaction mixture was diluted in DCM, washed with H_2O (2x 20 mL), brine (20 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (SiO_2, Hept/EtOAc : 95/5 to 70/30) to give the expected product **4** (669 mg, 1.09 mmol, 94%, α/β = 1/6) as a white amorphous solid: For the β-anomer $[\alpha]^{22}_D$ +105.7 (*c* 0.55, $CHCl_3$); FT-IR (neat) ν max 2981, 1714, 1230, 1091 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.84-7.69 (m, 5H), 7.54-7.33 (m, 8H), 5.61 (s, 1H), 4.99 (d, 1H, *J* =13.0 Hz), 4.89 (d, 1H, *J* =13.0 Hz), 4.70 (d, 1H, *J* =11.5Hz), 4.52 (d, 1H, *J* =11.5 Hz), 4.50 (s, 1H), 4.29 (dd, 1H, *J* = 10.0, 5.0 Hz), 4.21 (q, 2H, *J* = 7.0 Hz), 4.22-4.09 (m, 1H), 3.92 (t, 1H, *J* = 10.0 Hz), 3.66 (s, 3H), 3.67-3.55 (m, 2H), 3.32 (td, 1H, *J* = 10.0, 5.0 Hz), 1.28 (t, 3H, *J* = 7.0 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 164.0, 137.6, 135.8, 134.5, 133.2, 133.0, 128.9, 128.2, 128.1, 127.9, 127.7, 126.5, 126.1, 125.9, 125.7, 101.5, 101.4 (C1), 79.7, 78.7, 77.5, 72.6, 68.5, 67.5, 65.0, 62.2, 61.5, 14.1; $^1J_{C1\text{-}H1}$ = 155.0 Hz; ESIHRMS *m/z* = 635.1249 $[M+Na]^+$. $C_{31}H_{33}O_8Br$ requires 635.1256.

6,8-dichloro-2,2,5-trimethyl-7-(naphthalen-2-ylmethoxy)-4*H*-benzo[*d*][1,3]dioxin-4-one 6. To a stirred solution of 2,4-dihydroxy-6-methyl benzoic acid hydrate (632 mg, 3.76 mmol, 1 eq.) in acetic acid (3.8 mL) under argon atmosphere at room temperature is added sulfuryl chloride (0.6 mL, 7.5 mmol, 2 eq.). After stirring for 4 h 30 at room temperature, H_2O (10 ml) was added and the mixture was co-evaporated with toluene (3x 20 mL) under reduced pressure. The product was purified by recrystallisation from $CHCl_3$ to afford the targeted dichlorinated compound (760 mg, 3.2 mmol, 85%) as a brownish solid. FT-IR (neat) ν max 2988, 2901, 1731, 1260, 1200, 940 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 12.21-9.94 (bs, 3H), 2.46 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 171.0, 155.0, 152.2, 135.4, 113.8, 109.8, 107.0, 18.4; ESIHRMS *m/z* = 236.9732 $[M+H]^+$. $C_8H_7O_4Cl_2$ requires 236.9721. To a stirred solution of 3,5-dichloro-2,4-dihydroxy-6-methyl benzoic acid (480 mg, 1.91 mmol) in TFA (3 mL) under argon atmosphere at 0°C were added TFAA (1.7 mL) and anhydrous acetone (350 µL, 4.77 mmol, 2.5 eq.). After stirring for 18 h at room temperature, the reaction mixture was concentrated under reduced pressure and the residue was treated with aq. saturated $NaHCO_3$ (20 mL). The aqueous layer was extracted with EtOAc (3x 20 mL) and the organic layer was washed with water (20 mL), brine (20 mL) and

dried over Na_2SO_4. After filtration and concentration under reduced pressure, the crude product brown residue was used in the subsequent step without further purification (411 mg, 78% yield). To a stirred solution of the previously obtained phenol (0.410 mg, 1.48 mmol) and NapBr (0.982 g, 4.44 mmol, 3 eq.) in anhydrous DMF (4.5 mL), under argon atmosphere, was added at r.t. K_2CO_3 (0.6 g, 4.44 mmol, 3 eq.). After stirring for 6 h, the resulting mixture was quenched with H_2O (20 mL) and diluted with AcOEt (20 mL). The organic layer was separated, washed with H_2O (2x 20 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (Hept/EtOAc 100/0 to 90/10) to give **6** (483 mg, 0.78 mmol, 78%) as white solid. FT-IR (neat) ν max 3003, 2936, 1731, 1261, 1109 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 8.03-7.98 (bs, 1H), 7.96-7.87 (m, 3H), 7.75-7.69 (m, 2H), 7.57-7.48 (m, 2H), 5.30 (s, 2H), 2.83 (s, 3H), 1.79 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 159.0, 156.6, 152.6, 140.6, 133.4, 133.2, 128.4, 128.1, 127.8, 127.6, 126.4, 126.3, 126.0, 115.9, 110.7, 106.1, 75.3, 25.6, 18.1; ESIHRMS *m/z* = 635.1249 $[M+Na]^+$. $C_{31}H_{33}O_8Br$ requires 635.1256.

Ethyl 2,4-bis((*tert*-butyldimethylsilyl)oxy)-3,5-dichloro-6-methylbenzoate 8. To a stirred solution of **5b** (5g, 25.5 mmol, 1 eq.) in anhydrous Et_2O (300 mL) was added dropwise at 0 °C for 1 h SO_2Cl_2 (13.6 mL, 168 mmol, 6.6 eq.). The reaction mixture was diluted with EtOAc (200 mL) and washed with water (5x 200 mL) and brine (200 mL), dried over $Na_2S_2O_4$, filtered and concentrated under reduced pressure. The product was purified by recrystallization from a 8/2 mixture of heptane/AcOEt to afford the dichloro compound (5.3 g, 20 mmol, 78%) as a white solid.[7] To a stirred solution of the latter (5.3 g, 20 mmol, 1 eq.) in anhydrous DMF (50 mL) was added imidazole (4 g, 60 mmol, 3 eq.) and TBSCl (9 g, 60 mmol, 3 eq.). The reaction mixture was stirred at r.t. for 12h and diluted with EtOAc (200 mL) and aq. $CuSO_4$ (5%, 100 mL). The layers were separated and the organic one was washed with water (3 x 100 mL), dried over $Na_2S_2O_4$, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (SiO_2, Hept/EtOAc :95/5) to give **8** (9.7 g, 19.7 mmol, 98%) as colorless oil. FT-IR (neat) ν max 2955, 2930, 1724, 1403, 1254, 1127, 1100, 837, 823 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 4.31 (q, J = 7.0, 2H), 2.27(s, 3H), 1.35 (t, J = 7.0, 3H), 1.02 (s, 9H), 0.98 (s, 9H), 0.25 (s, 3H), 0.16 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 167.1, 150.0, 147.9, 132.9, 122.2, 120.5, 116.6, 61.5, 26.0, 25.9, 18.9, 18.7, 17.9, 14.1, -3.0, -3.5.; ESIHRMS *m/z* = 1007.3266 $[2M+Na]^+$. $C_{44}H_{76}O_8NaSi_4Cl_4$ requires 1007.3269.

3,5-dichloro-2-ethyl-4,6-dihydroxybenzoic acid 9. To a stirred solution of **8** (3.5 g, 7.1 mmol, 1 equiv.) in anhydrous THF (50 mL) was added at -78 °C, LDA (2.0 M in THF/heptane/ethylbenzene, 21.6 mmol, 3.05 eq.) with a syringe pump at a rate of 31 mL/h. The reaction mixture was stirred for 5 min at –78 °C, then MeI (1.3 mL, 21.6 mmol, 3 eq.) was added. After 5 min at -78 °C, the resulting mixture was stirred for 45 min at 0 °C and aq. saturated NH_4Cl (50 mL) was added. The reaction mixture was diluted with EtOAc (50 mL) and the aqueous phase was extracted with EtOAc (2x 50 mL). After drying over $Na_2S_2O_4$, the organic layer was filtered and concentrated under reduced pressure to afford the titled compound (3.6 g, 7.1 mmol, quant.). The crude obtained compound (3.5 g, 6.9 mmol) in concentrated H_2SO_4 (98%, 9 mL) was stirred at r.t. for 12 h. The reaction mixture was poured into ice (100 g) and was extracted with EtOAc (3x 100 mL). After drying over $Na_2S_2O_4$, the organic layer was filtered and concentrated under reduced pressure. The product was purified by recrystallisation from $CHCl_3$ to afford the titled compound **9** (1.07 g, 4.26 mmol, 62%) as a brownish solid.[8]

6,8-dichloro-5-ethyl-2,2-dimethyl-7-(naphthalen-2-ylmethoxy)-4*H*-benzo[*d*][1,3]dioxin-4-one 7. Under argon, to a solution of **9** (1.1 g, 4.38 mmol, 1 eq.) in TFA (6.4 mL) and Tf_2O (3 mL) at 0 °C was added anhydrous acetone (0.8 mL, 11.4 mmol, 2.6 equiv.) and the reaction mixture was stirred at r.t. overnight. The reaction mixture was poured into ice (50 g) and aq. saturated $NaHCO_3$ (50 mL) and the aqueous phase was extracted with EtOAc (3x 50 mL). After drying over $Na_2S_2O_4$, the organic layer was filtered and concentrated under reduced pressure. To a solution of the crude obtained (1.3 g, 4.46 mmol, 1 eq.) in DMF (19 mL) was added NapBr (1.48 g, 7.7 mmol, 1.5 equiv.) and K_2CO_3 (0.92 g, 7.7 mmol, 1.5 equiv.) and the reaction mixture was stirred at r.t. for 12 h. Water (30 mL) and AcOEt (30 mL) were added. The layers were separated and the organic one was washed with water (2x 30 mL), dried over $Na_2S_2O_4$, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (SiO_2, Hept/EtOAc : 100/0 to 90/10) to give **7** (1.4 g, 3.2 mmol, 73%) as white solid. FT-IR (neat) ν max 3448, 3058, 2934, 1732, 1574, 1554, 1403, 1276, 1232, 1200, 1050, 789 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.98-7.93 (m, 1H), 7.91-7.81 (m, 3H), 7.67 (dd, J = 1.5 and 8.5 Hz, 1H), 7.53-7.44 (m, 2H), 5.27 (s, 2H), 3.31 (q, J = 7.5 Hz, 2H), 1.74 (s, 3H), 1.21 (t, J = 7.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 166.6, 158.5, 156.7, 152.7, 146.3, 133.4, 133.2, 128.3, 128.1, 127.7, 127.6, 126.4, 126.3,

[7] The spectroscopic data agree with those reported in the literature: Gros, E. G.; Gruneiro, E. M., *J. Org. Chem.* **1971,** *36* (8), 1166-1169.
[8] The spectroscopic data agree with those reported in the literature: Alexy, M.; Scharf, H. D., *Liebigs Ann. Chem.* **1991,** *1991* (12), 1363-1364.

126.0, 125.0, 116.1, 110.1, 106.0, 75.3, 25.6, 24.5, 13.4; ESIHRMS *m/z* = 431.0854 $[M+H]^+$. $C_{23}H_{21}O_4Cl_2$ requires 431.0817.

(2*R*,3*S*,4*S*,5*S*,6*R*)-4-hydroxy-5-methoxy-2-methyl-6-(phenylthio)tetrahydro-2*H*-pyran-3-yl 3,5-dichloro-2-ethyl-6-hydroxy-4-(naphthalen-2-ylmethoxy)benzoate 11. To a stirred solution of **10** (0.76 g, 2.8 mmol) and orsellinate **7** (1.28 g, 2.98 mmol, 1.06 eq.) in anhydrous THF (28 mL, 0.1 M), under argon atmosphere, was slowly added at 0 °C NaH (60% dispersion in oil, 0.56 g, 14 mmol, 5 eq.). The resulting mixture was allowed to reach r.t. and stirred for 30 h. The reaction mixture was quenched with aq. saturated NH_4Cl (50 mL) and diluted with an excess of EtOAc (50 mL). The aqueous layer was extracted with EtOAc (2x 50 mL) and the organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography (SiO_2, Hept/AcOEt : 95/5 to 80/20) to afford **11** (1.56 g, 2.42 mmol, 86%) as a white amorphous solid. $[\alpha]^{22}_D$ +105.7 (*c* 0.55, $CHCl_3$); FT-IR (neat) ν max3445, 3057, 2981, 2935, 2877, 1733, 1661, 1582, 1389, 1310, 1242, 1221, 1098, 997, 729 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 10.46-10.29 (bs, 1H), 8.05-8.01 (m, 1H), 7.95-7.87 (m, 3H), 7.75 (d, *J* = 8.0 Hz, 1H), 7.55-7.49 (m, 4H), 7.40-7.29 (m, 3H), 5.71 (ap. s, 1H), 5.31 (d, *J* = 10.0 Hz, 1H), 5.29-5.25 (m, 2H), 4.46-4.37 (m, 1H), 4.06-3.99 (m, 1H), 3.90-3.87 (m, 1H), 3.54 (s, 3H), 3.14-3.06 (m, 2H), 2.65-2.48 (bs, 1H), 1.37-1.29 (m, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 169.1, 155.5, 155.3, 142.6, 133.9, 133.6, 133.4, 133.2, 131.2, 129.2, 128.3, 128.1, 127.7, 127.6, 127.5, 126.3, 126.2, 126.1, 121.7, 115.8, 112.8, 83.8, 81.6, 76.9, 75.0, 70.0, 66.9, 58.0, 26.0, 17.5, 21.6. ESIHRMS *m/z* = 665.1140 $[M+Na]^+$. $C_{33}H_{32}O_7NaSCl_2$ requires 665.1144.

(2*R*,3*R*,4*S*,5*S*,6*R*)-3-((3,5-dichloro-2-ethyl-4,6-bis(naphthalen-2-ylmethoxy)benzoyl)oxy)-5-methoxy-2-methyl-6-(phenylthio)tetrahydro-2*H*-pyran-4-yl picolinate 12. To a stirred solution of previously described **11** (0.600 g, 0.93 mmol) and NapBr (0.247 g, 1.12 mmol, 1.2 eq.) in anhydrous DMF (7 mL, 0.195 M), under argon atmosphere, was added at r.t. K_2CO_3 (0.155 g, 1.12 mmol, 1.2 eq.). After stirring for 3 h, the resulting mixture was quenched with H_2O (20 mL) and diluted with AcOEt (20 mL). The organic layer was separated, washed with H_2O (2 * 20 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. To the crude obtained product (0.73 g, 0.93 mmol) in DCM (12 mL, 0.08M), was added picolinic acid (0.156 g, 1.27 mmol, 1.36 eq.), DCC (0.269 g, 1.3 mmol, 1.4 eq.) and DMAP (23 mg, 0.186 mmol, 0.2 eq.). The resulting mixture was stirred under argon for 2 h at room temperature. The reaction mixture was diluted with DCM (20 mL) and the solid was filtered off. The filtrate was washed with sat. aq. $NaHCO_3$ (20 mL) and the organic phase was separated, dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by flash chromatography (DCM/EtOAc 100/0 to 95/5) to give **12** (0.67 g, 0.75 mmol, 81%) as an amorphous white solid. $\mathbf{[\alpha]^{22}_D}$ −79.6 (*c* 0.5, $CHCl_3$); FT-IR (neat) ν max 3055, 2936, 1739, 1661, 1571, 1304, 1241, 1098, 741 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 8.86-8.82 (m, 1H), 8.21 (d, *J* = 7.5 Hz, 1H), 8.03-7.79 (m, 9H), 7.72 (dd, *J* = 1.5 and 8.5 Hz, 1H), 7.66 (dd, *J* = 1.5 and 8.5 Hz, 1H), 7.56-7.42 (m, 6H), 7.32-7.26 (m, 4H), 5.70 (t, *J* = 10.0 Hz, 1H), 5.59 (d, *J* = 1.5 Hz, 1H), 5.48 (dd, *J* = 3.0 and 10.0 Hz, 1H), 5.35 (d, *J* = 10.5 Hz, 1H), 5.21 (s, 2H), 5.16 (d, *J* = 10.5 Hz, 1H), 4.41-4.28 (m, 1H), 4.25-4.19 (m, 1H), 3.44 (s, 3H), 2.51-2.39 (m, 2H), 1.06 (d, *J* = 6.0 Hz, 3H), 0.89 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 165.7, 163.9, 151.1, 150.3, 147.2, 138.9, 137.0, 133.8, 133.6, 133.4, 133.3, 133.2, 133.1, 131.4, 129.1, 128.3, 128.2, 128.1, 127.7, 127.6, 127.6, 127.5, 127.4, 127.2, 126.3, 126.2, 126.1, 126.0, 125.5, 84.4, 80.0, 76.9, 75.1, 73.2, 72.8, 67.6, 58.8, 25.3, 17.4, 13.8; ESIHRMS *m/z* = 888.2152 $[M+H]^+$. $C_{50}H_{44}NO_8SCl_2$ requires 888.2165.

(*E*) and (*Z*)-3-bromo-2-(((*tert*-butyldimethylsilyl)oxy)methyl)prop-2-en-1-ol 15a and 15b. To a solution of bromomethyltriphenylphosphoniumbromide (18 g, 42.25 mmol, 1.2 eq.) in anhydrous THF (100 mL) at –70 °C, was added dropwise NaHMDS (1M/THF, 42.3 mL, 42.3 mmol, 1.2 eq.). After stirring for 1 h, 2,2-Dimethyl-1,3-dioxan-5-one (4.6 g, 35.21 mmol, 1 eq.) in anhydrous THF (24 mL) was added slowly and the reaction was allowed to warm to r.t. overnight. Pentane (200 mL) was then added and the reaction mixture was filtered through a pad of celite®. After concentration under reduced pressure, the crude residue was purified by distillation under reduced pressure to led to the desired compound (5.3 g, 73% Bp = 80 °C at 2.3 mmHg) as a colorless oil.[9] To a solution of 5-bromomethylene-2,2-dimethyl-1,3-dioxane (2.5 g, 12.07 mmol, 1 eq.) in MeOH (40 mL) was added PTSA.H_2O (0.276 g, 1.45 mmol, 0.12 eq.). After stirring for 1 h at r.t., NEt_3 (0.2 mL, 1.45 mmol, 0.12 eq.) was added and the reaction mixture was concentrated under reduced pressure. The crude residue was purified by flash chromatography (SiO_2, Hept/EtOAc 70/30 to 50/50) to give the corresponding diol (1.65 g, 9.9 mmol, 82%) as colorless oil.[10] To a solution of 2-(bromomethylene)propane-

[9] The spectroscopic data agree with those reported in the literature: Riehs, G.; Urban, E.; Völlenkle, H., *Tetrahedron* **1996,** *52* (26), 8725-8732.

[10] The spectroscopic data agree with those reported in the literature: Burns, D. J.; Best, D.; Wieczysty, M. D.; Lam, H. W., *Angew. Chem., Int. Ed.* **2015,** *54* (34), 9958-9962.

1,3-diol (1.5 g, 9 mmol, 1 eq.) in THF (25 mL) was added NaH (50% dispersion in oil, 431 mg, 9 mmol, 1 eq.) at 0 °C. The resulting suspension was stirred at 0 °C for 1 h before addition of TBSCl (1.35 g, 9 mmol, 1 eq.). After stirring for 24 h at r.t., aq. saturated NH_4Cl (50 mL) was added and the mixture was diluted with EtOAc (50 mL). The reaction layers were separated, the aqueous layer was extracted with EtOAc (2x 50 mL) and the combined organic extracts were filtered and concentrated under reduced pressure. The crude residue was purified by flash chromatography (SiO_2, Hept/EtOAc 90/10) to give the corresponding monoprotected ethers **15a** and **15b** (1.95 g, 6.9 mmol, 77%) as a colorless oil. Both isomers can be further separated using preparative HPLC with Upti-prep® 100Å silica, 5 µm, Hept/EtOAc : 90/10) furnishing first **15a** (0.89 g) followed by **15b** (0.85 g). **15a:** FT-IR (neat) ν max 3302, 2925, 2874, 1631, 1297, 1007 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 6.26-6.22 (m, 1H), 4.33 (s, 2H), 4.27 (d, J = 1.5 Hz, 2H), 2.15 (bs, 1H), 0.89 (s, 9H), 0.07 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 104.9, 65.3, 61.9, 25.8, 18.2, -5.4; ESIHRMS *m/z* = 583.0840 $[2M+Na]^+$. $C_{20}H_{42}O_4NaSi_2Br_2$ requires 583.0886. **15b:** FT-IR (neat) ν max 3302, 2925, 2874, 1631, 1297, 1007 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 6.24-6.19 (m, 1H), 4.45 (d, J = 1.5 Hz, 2H), 4.19 (s, 2H), 2.62 (bs, 1H), 0.89 (s, 9H), 0.09 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 104.3, 65.0, 63.7, 25.8, 18.2, -5.4; ESIHRMS *m/z* = 583.0840 $[2M+Na]^+$. $C_{20}H_{42}O_4NaSi_2Br_2$ requires 583.0886.

(2*E*,4*E*)- and (2*Z*,4*E*)-2-(((*tert*-butyldimethylsilyl)oxy)methyl)-5-phenylpenta-2,4-dien-1-ol 16a and 16b. In a Schlenk tube were introduced phenyl vinyl boronic acid (286 mg, 1.94 mmol, 1.5 eq.), vinyl bromide derivative **15a** and **15b** (363 mg, 1.29 mmol, 1 eq.), $Pd(OAc)_2$ (29 mg, 0.129 mmol, 0.1 eq.), Sphos (106 mg, 0.26 mmol, 0.2 eq.) and K_3PO_4 (822 mg, 3.87 mmol, 3 eq.). Three vacuum/argon cycles were done, then THF (28 ml) and H_2O (7 ml) were added, the Schlenck tube was then sealed. After 18 h at r.t., the reaction medium was poured in a separatory funnel containing brine (25 mL), and EtOAc was used to extract organics molecules (3 x 30 mL). After drying over anhydrous Na_2SO_4, filtration, and removal of the solvent under vacuum, the crude residue was purified by flash chromatography (SiO_2, Hept/EtOAc 90/10 to 80/20) to give **16a** and **16b** (234 mg, 0.77 mmol, 60%) as a colorless oil. Both isomers can be further separated using preparative HPLC with Upti-prep® 100Å silica, 5 µm, Hept/EtOAc : 90/10) furnishing first **16a** (112 mg) followed by **16b** (106 mg). These compounds were found to be unstable. **16a :** FT-IR (neat) ν max 3420, 3028, 2953, 2928, 2856, 1675 cm^{-1}; ^1H NMR (CD_3CN, 300 MHz) δ 7.52-7.43 (m, 2H), 7.37-7.31 (m, 2H), 7.29-7.17 (m, 2H), 6.61 (d, J = 15.5 Hz, 1H), 6.31 (d, J = 11.3 Hz, 1H), 4.34-4.22 (m, 4H), 2.80 (t, J = 5.5 Hz, 1H), 0.94 (s, 9H), 0.11 (s, 6H); ^{13}C NMR (CD_3CN, 75 MHz) δ 141.0, 137.1, 137.3, 132.5, 128.3, 127.2, 126.0, 125.5, 123.9, 64.7, 57.3, 25.0, 17.7, -6.4; **16b :** FT-IR (neat) ν max 3420, 3028, 2953, 2928, 2856, 1675 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.42-7.36 (m, 2H), 7.34-7.27 (m, 2H), 7.25-7.19 (m, 1H), 6.94 (dd, J = 11.0 and 15.5 Hz, 1H), 6.57 (d, J = 15.5 Hz, 1H), 6.23 (d, J = 11.0 Hz, 1H), 4.54 (m, 2H), 4.25 (s, 2H), 2.38 (m, 1H), 0.92 (s, 9H), 0.13 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 139.1, 137.2, 134.2, 128.7, 128.8, 127.5, 126.5, 123.3, 66.8, 61.2, 25.9, 18.3, -5.3.

(2R,3S,4S,5R,6R)-2-(((E)-3-bromo-2-(((tert-butyldimethylsilyl)oxy)methyl)allyl)oxy)-5-((3,5-dichloro-2-ethyl-4,6-bis(naphthalen-2-ylmethoxy)benzoyl)oxy)-3-methoxy-6-methyltetrahydro-2H-pyran-4-yl picolinate 18. A mixture of the glycosyl donor **12** (452 mg, 0.51 mmol, 1.3 eq.), acceptor **15a** (110 mg, 0.391 mmol, 1 eq.) and freshly activated 4Å MS (1.5 g) in DCE (35 mL) were stirred at r.t. for 1 h. The mixture was then cooled to 0 °C before adding DMTST (202 mg, 0.782 mmol, 2 eq.). After stirring for 20 min at 0 °C, the reaction mixture was allowed to warm to r.t. and stirred for 18 h. After quenching with NEt_3 (0.2 mL), aq. saturated $NaHCO_3$ (30 mL) and CH_2Cl_2 (20 mL) were added. The two phases were separated and the organic layer was washed with water (20 mL) then dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (SiO_2, Hept/EtOAc 50/50) to give **18** (406 mg, 0.38 mmol, 85%, α/β = 1/6.5) as white solid. The pure β-anomer can be obtained by recrystallization a mixture of Hept/EtOAc 40/60 (MP= 180-182°C). $[\alpha]^{22}_D$ −71.3 (*c* 0.92, $CHCl_3$); FT-IR (neat) ν max 2976, 2935, 1737, 1715, 1308, 1243, 1075, 754 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 8.81-8.76 (m, 1H), 8.18 (d, J = 7.5 Hz, 1H), 7.96 (s, 1H), 7.91 (m, 1H), 7.89-7.80 (m, 5H), 7.77 (dd, J = 2.0 and 8.0 Hz, 1H), 7.67 (dd, J = 2.0 and 7.0 Hz, 1H), 7.61 (dd, J = 1.5 and 7.5 Hz, 1H), 7.53-7.42 (m, 6H), 6.35 (s, 1H), 5.61 (t, J = 9.5 Hz, 1H), 5.42 (dd, J = 3.5 and 10.0 Hz, 1H), 5.31 (d, J = 10.0 Hz, 1H), 5.18-5.14 (bs, 2H), 5.08 (d, J = 10.0 Hz, 1H), 4.87 (d, J = 1.5 Hz, 1H), 4.32 (d, J = 12.0 Hz, 1H), 4.22-4.18 (m, 2H), 4.15 (d, J = 12.0 Hz, 1H), 3.93-3.80 (m, 2H), 3.43 (s, 3H), 2.36 (q, J = 7.5 Hz, 2H), 1.04 (d, J = 6.0 Hz, 3H), 0.86 (s, 9H), 0.82 (t, J = 7.5 Hz, 3H), 0.04 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 165.8, 163.8, 153.2, 151.1, 150.4, 147.3, 140.3, 138.7, 137.1, 133.6, 133.4, 133.3, 133.2, 128.4, 128.3, 128.2, 128.1, 127.8, 127.7, 127.2, 126.4, 126.1, 125.5, 122.0, 106.7, 96.8, 77.7, 77.1, 75.1, 73.6, 72.8, 66.6, 64.8, 64.1, 59.7, 25.9, 25.4, 18.3, 17.6, 13.7, -5.4; ESIHRMS *m/z* = 1080.2244 $[M+Na]^+$. $C_{54}H_{58}NO_{10}NaSiCl_2Br$ requires 1080.2288.

(2*R*,3*S*,4*S*,5*S*,6*R*)-6-(((*E*)-3-bromo-2-(((*tert*-butyldimethylsilyl)oxy)methyl)allyl)oxy)-4-hydroxy-5-methoxy-2-methyltetrahydro-2*H*-pyran-3-yl 3,5-dichloro-2-ethyl-4,6-bis(naphthalen-2-ylmethoxy)benzoate 22. A solution of

18 (162 mg, 0.153 mmol, 1 eq.) and $Cu(OAc)_2$ (28 mg, 0.153 mmol, 1 eq.) in CH_2Cl_2 /MeOH (95/5 v/v, 2 mL) was stirred at r.t. for 2 h 30. The reaction mixture was quenched with saturated aqueous NH_4Cl (5 mL) and diluted with AcOEt (15 mL). The organic layer was washed with 1N aqueous HCl solution (5 mL x 2) and brine (5 mL), dried over Na_2SO_4, and concentrated. The residue was purified by flash chromatography (SiO_2, Hept/EtOAc 90/10 to 80/20) to give **22** (145 mg, 0.151 mmol, 99%) as white amorphous solid. $[\alpha]^{22}_D$ −46.4 (*c* 1.07, $CHCl_3$); FT-IR (neat) ν max 2976, 2935, 1737, 1715, 1308, 1243, 1075, 754 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 8.01-7.98 (m, 1H), 7.93-7.80 (m, 7H), 7.71 (dd, *J* = 1.5 and 8.5 Hz, 1H), 7.60 (dd, *J* = 1.5 and 8.5 Hz, 1H), 7.53-7.44 (m, 4H), 6.35 (s, 1H), 5.30 (d, *J* = 10.0 Hz, 1H), 5.21 (s, 2H), 5.10 (d, *J* = 10.0 Hz, 1H), 5.02 (t, *J* = 10.0 Hz, 1H), 5.45-4.36 (m, 2H), 4.33 (d, *J* = 12.0 Hz, 1H), 4.27-4.14 (m, 2H), 3.62 (s, 3H), 3.57-3.49 (m, *2*H), 3.33-3.22 (m, *2*H), 2.96-2.80 (m, 2H), 2.53 (d, *J* = 11.0 Hz, 1H), 1.28-1.17 (m, 3H), 1.06 (d, *J* = 6.0 Hz, 3H), 0.89 (s, 9H), 0.05 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ166.6, 155.3, 151.2, 140.6, 139.6, 133.8, 133.7, 133.6, 133.5, 133.4, 128.5, 128.3, 128.1, 127.9, 127.7, 126.6, 126.4, 126.3, 126.0, 122.0, 106.5, 100.6, 80.6, 76.5, 75.3, 72.2, 70.4, 66.9, 64.3, 62.3, 36.1, 25.4, 17.4, 14.3, -5.2; ESIHRMS *m/z* = 975.2094 $[M+Na]^+$. $C_{48}H_{55}NO_9NaSiCl_2Br$ requires 975.2073.

(2*R*,3*S*,4*S*,5*S*,6*R*)-6-(((2*E*,4*E*)-2-(((*tert*-butyldimethylsilyl)oxy)methyl)-5-phenylpenta-2,4-dien-1-yl)oxy)-4-hydroxy-5-methoxy-2-methyltetrahydro-2*H*-pyran-3-yl 3,5-dichloro-2-ethyl-4,6-bis(naphthalen-2-ylmethoxy)benzoate 23. In a Schlenk tube were introduced phenyl vinyl boronic acid (16 mg, 0.110 mmol, 1.5 eq.), **22** (70 mg, 0.073 mmol, 1 eq.), $Pd(OAc)_2$ (2 mg, 0.011 mmol, 0.15 eq.), Sphos (8 mg, 0.018 mmol, 0.25 eq.) and K_3PO_4 (47 mg, 0.220 mmol, 3 eq.). Three vacuum/argon cycles were done, then THF (2 ml) and H_2O (0.5 ml) were added, the Schlenck tube was then sealed. After 18 h at r.t., the reaction medium was poured in a separatory funnel containing brine (5 mL), and EtOAc was used to extract organics molecules (3 x 10 mL). The organic layers were dried over anhydrous Na_2SO_4, filtrated, and concentrated under vacuum. To a stirred solution of the crude obtained residue and NapBr (19 mg, 0.088 mmol, 1.2 eq.) in anhydrous DMF (0.5 mL), under argon atmosphere, was added at r.t. K_2CO_3 (12 mg, 0.088 mmol, 1.2 eq.). After stirring for 6 h, the resulting mixture was quenched with H_2O (10 mL) and diluted with AcOEt (10 mL). The organic layer was separated, washed with H_2O (2x 10 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (Hept/EtOAc 70/30) to give **23** (52 mg, 0.053 mmol, 73%) as white amorphous solid. $[\alpha]^{22}_D$ −42.8 (*c* 0.5, $CHCl_3$); FT-IR (neat) ν max 2928, 1733, 1367, 1248, 1063, 851, 815, 746 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.91 (bs, 1H), 7.86-7.68 (m, 6H), 7.63 (d, *J* = 8.5 Hz, 1H), 7.51 (d, *J* = 8.5 Hz, 1H), 7.46-7.34 (m, 4H), 7.29-7.31 (m, 2H), 7.18-7.03 (m, 2H), 6.95 (dd, *J* = 11.0 and 15.5 Hz, 1H), 6.47 (d, *J* = 15.5 Hz, 1H), 6.37 (d, *J* = 11.0 Hz, 1H), 5.21 (d, *J* = 11.5 Hz, 1H), 5.11 (s, 2H), 5.05-4.91 (m, 2H), 4.43-4.25 (m, 3H), 4.15 (s, 2H), 3.55 (s, 3H), 3.50-3.38 (m, *2*H), 3.21-3.09 (m, *1*H), 2.86-2.68 (m, 2H), 2.44 (d, *J* = 11.0 Hz, 1H), 1.12 (t, *J* = 6.5 Hz, 3H), 1.00 (d, *J* = 6.0 Hz, 3H), 0.84 (s, 9H), 0.00 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 166.4, 155.1, 151.0, 139.4, 137.1, 135.8, 133.6, 133.5, 133.3, 133.2, 129.3, 128.7, 128.6, 128.3, 128.2, 128.1, 128.0, 127.9, 127.7, 127.6, 127.4, 126.4, 126.3, 126.2, 126.1, 125.9, 123.3, 121.8, 106.5, 99.2, 80.6, 77.0, 76.3, 75.1, 72.1, 70.0, 65.0, 63.7, 62.1, 25.9, 25.2, 18.5, 17.3, 14.0, -5.3; ESIHRMS *m/z* = 999.3448 $[M+Na]^+$. $C_{56}H_{62}O_9NaSiCl_2$ requires 999.3438.

(2*R*,3*R*,4*S*,5*S*,6*R*)-4-((*tert*-butyldimethylsilyl)oxy)-6-(((2*Z*,4*E*)-2-(hydroxymethyl)-5-phenylpenta-2,4-dien-1-yl)oxy)-5-methoxy-2-methyltetrahydro-2*H*-pyran-3-yl 3,5-dichloro-2-ethyl-4,6-bis(naphthalen-2-ylmethoxy)benzoate 24. 2,6-Lutidine (0.143 mL, 1.23 mmol, 3 eq.) was added to a solution of **23** (400 mg, 0.409 mmol, 1 eq.) in anhydrous DCM (4 mL), followed by slow addition of TBSOTf (0.21 mL, 0.94 mmol, 2.3 eq.) at room temperature. After the mixture had been stirred overnight, the reaction was quenched with Et_3N (0.1 mL). The mixture was poured into water (15 mL), the organic layer was washed with aq. $Cu(SO_4)_2$ (15%, 3 mL), brine (3 mL), and dried over Na_2SO_4. After concentration under reduced pressure, the residue was diluted in MeOH/CH_2Cl_2 (4/1 v/v, 15 mL) and cooled to 0 °C before addition of CSA (19 mg, 0.082 mmol, 0.2 eq.). After stirring for 4 h at 0 °C, the resulting mixture was quenched with NEt_3 (20 µL) and concentrated under reduced pressure. The residue was purified by flash chromatography (Hept/EtOAc 80/20 to 60/40) then preparative HPLC with Upti-prep® 100Å silica, 5 µm, Hept/EtOAc : 75/25 to 70/30) furnishing **24** (300 mg, 0.306 mmol, 75%) as white amorphous solid. $[\alpha]^{22}_D$ −29.8 (*c* 0.5, $CHCl_3$); FT-IR (neat) ν max 3464, 3057, 2930, 2857, 1734, 1247, 1104, 907, 729 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.98 (bs, 1H), 7.92-7.80 (m, 7H), 7.70 (d, *J* = 8.5 Hz, 1H), 7.58 (d, *J* = 8.5 Hz, 1H), 7.53-7.45 (m, 4H), 7.42-7.35 (m, 2H), 7.33-7.19 (m, 3H), 6.97 (dd, *J* = 11.0 and 15.5 Hz, 1H), 6.58 (d, *J* = 15.5 Hz, 1H), 6.33 (d, *J* = 11.0 Hz, 1H), 5.30 (d, *J* = 11.0 Hz, 1H), 5.24 (s, 2H), 5.21-5.07 (m, 2H), 4.48 (d, *J* = 12.0 Hz, 1H), 4.38 (d, *J* = 12.0 Hz, 1H), 4.29 (m, 1H), 4.24-4.15 (m, 2H), 3.72 (dd, *J* = 2.5 and 8.5 Hz, 1H), 3.53(s, 3H), 3.46-3.41 (m, *1*H), 3.14-3.00 (m, 1H), 2.90-2.76 (m, 1H), 2.68-2.51 (m, 1H), 2.33-2.23 (m, 1H), 1.27 (d, *J* = 6.0 Hz, 3H), 1.21 (t, *J* = 6.0 Hz, 3H), 0.82 (s, 9H), 0.00 (s, 3H), -0.11 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 165.5, 153.3, 151.8, 139.9, 137.0, 136.3, 134.8, 133.9, 133.5, 133.3, 133.2, 133.1, 129.9, 128.7, 128.3, 128.1, 128.0, 127.9, 127.7, 127.5, 126.9, 126.8, 126.5, 126.3, 126.2, 126.1, 125.8, 125.6, 123.3,

122.0, 106.5, 99.3, 80.4, 76.5, 76.1, 75.1, 72.2, 71.1, 66.1, 65.5, 61.1, 26.3, 25.8, 18.7, 18.1, 14.1, -4.5, -4.6; ESIHRMS *m/z* = 999.3411 $[M+Na]^+$. $C_{56}H_{62}O_9NaSiCl_2$ requires 999.3438.

(2*R*,3*R*,4*S*,5*S*,6*R*)-3-((3,5-dichloro-2-ethyl-4,6-bis(naphthalen-2-ylmethoxy)benzoyl)oxy)-5-methoxy-2-methyl-6-(phenylsulfinyl)tetrahydro-2*H*-pyran-4-yl picolinate 13. To a stirred solution of **12** (0.640 g, 0.72 mmol) and $NaHCO_3$ (73 mg, 0.86 mmol, 1.2 eq.) in DCM (15 mL, 0.05 M), was added at –78 °C *m*-CPBA (75%, 0.174 g, 0.76 mmol, 1.05 eq.). After stirring for 2 h at –78 °C, the temperature of mixture was slowly raised to –30 °C over 2 h and quenched with a mixture of aq. saturated $NaHCO_3$ and aq. saturated $Na_2S_2O_3$ (1/1 v/v, 20 mL). The organic layer was separated, the aqueous phase was extracted with DCM (2 x15 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (SiO_2, Hept/EtOAc : 50/50 to 40/60) to give the expected product **13** (0.63 g, 0.696 mmol, 93%) as an amorphous white solid as only one diastereomer. $[\alpha]^{22}_D$ −124.4 (*c* 0.5, $CHCl_3$); FT-IR (neat) ν max 3320, 3058, 2929, 1732, 1309, 1242, 1119, 1100, 744 cm-1; ^{1}H NMR ($CDCl_3$, 300 MHz) *δ* 8.81 (d, *J* = 4.5 Hz, 1H), 8.18 (d, *J* = 8.0 Hz, 1H), 8.03-7.79 (m, 9H), 7.75-7.63 (m, 2H), 7.62-7.45 (m, 10H), 5.87 (dd, *J* = 9.5 and 3.5 Hz, 1H), 5.67 (t, *J* = 9.5 Hz, 1H), 5.34 (d, *J* = 10.5 Hz, 1H), 5.26-5.16 (m, 3H), 4.50 (bs, 1H), 4.39-4.33 (m, 1H), 4.32-4.18 (m, 1H), 3.18 (s, 3H), 2.55-2.40 (m, 2H), 1.07 (d, *J* = 6.0 Hz, 3H), 0.92 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) *δ* 165.6, 163.8, 151.1, 153.4, 151.3, 150.3, 147.0, 140.2, 139.2, 137.0, 133.6, 133.3, 133.2, 133.1, 131.5, 131.5, 129.4, 128.3, 128.2, 128.1, 127.7, 127.5, 127.3, 127.2, 126.2, 126.1, 126.0, 125.5, 124.3, 95.3, 76.6, 75.1, 73.9, 73.0, 72.0, 58.7, 25.3, 17.9, 13.8; ESIHRMS *m/z* = 904.2148 $[M+H]^+$. $C_{50}H_{44}NO_9SCl_2$ requires 888.2165.

(2*R*,3*S*,4*S*,5*R*,6*R*)-2-(((*E*)-3-bromo-2-(methoxycarbonyl)allyl)oxy)-5-((3,5-dichloro-2-ethyl-4,6-bis(naphthalen-2-ylmethoxy)benzoyl)oxy)-3-methoxy-6-methyltetrahydro-2*H*-pyran-4-yl picolinate 19. A mixture of the glycosyl donor **13** (118 mg, 0.131 mmol, 1.7 eq.), acceptor **17** (6 mg, 0.031 mmol, 1 eq.), 2,6-di-terbutyl-4-methylpiridine (30 mg, 0.145 mmol, 4.7 equiv.), 4-allyl-1,2-dimethoxybenzene (22 µL, 0.129 mmol, 4.2 eq.) and freshly activated 4Å MS (230 mg) in DCM (3 mL) was stirred at r.t. for 1 h. A solution of Tf_2O (10 µL, 0.058 mmol, 1.9 eq.) in DCM (0.3 mL) was then added dropwise at –70 °C and the reaction mixture was stirred for 2 h. The temperature was slowly raised to –60 °C over 1 h and quenched with NEt_3 (20 µL) and aq. saturated $NaHCO_3$ (15 mL). After filtration on Celite®, the aqueous phase was extracted with DCM (2*15 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (SiO_2, Hept/EtOAc : 70/30 to 60/40) to give the expected product **19** (21 mg, 0.022 mmol, 70%) as an amorphous white solid (α/β : 1/20[11]). $[\alpha]^{22}_D$ −92.0 (*c* 0.4, $CHCl_3$); FT-IR (neat) ν max 3056, 2981, 1721, 1306, 1237, 1119, 1071, 733 cm^{-1}; ^{1}H NMR (CD_3CN, 300 MHz) *δ* 8.76-8.71 (m, 1H), 8.10 (d, *J* = 7.5 Hz, 1H), 7.97-7.83 (m, 9H), 7.75 (s, 1H), 7.66 (dd, *J* = 1.5 and 8.5 Hz, 1H), 7.61-7.47 (m, 6H), 5.33 (t, *J* = 9.5 Hz, 1H), 5.26-5.17 (m, 2H), 5.17-5.13 (bs, 2H), 5.06 (d, *J* = 10.5 Hz, 1H), 4.65 (bs, 1H), 4.55 (d, *J* = 11.5 Hz, 1H), 4.44 (d, *J* = 11.5 Hz, 1H), 3.86 (d, *J* = 3.0 Hz, 1H), 3.68 (s, 3H), 3.48-3.37 (m, 4H), 2.30 (q, *J* = 7.5 Hz, 2H), 0.94 (d, *J* = 6.0 Hz, 3H), 0.78 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (CD_3CN, 75 MHz) *δ* 166.9, 165.7, 163.5, 154.5, 152.4, 151.4, 148.7, 140.2, 138.6, 136.0, 135.2, 134.6, 134.5, 129.5, 129.4, 129.3, 129.1, 129.0, 128.9, 128.8, 127.9, 127.8, 126.7, 101.6, 79.4, 78.2, 76.4, 75.6, 74.1, 71.3, 66.4, 62.3, 53.4, 26.4, 18.4, 14.5; $^1J_{C1\text{-}H1}$ = 157 Hz; ESIHRMS *m/z* = 972.1567 $[M+H]^+$. $C_{49}H_{45}NO_{11}Cl_2Br$ requires 972.1553.

(2*R*,3*R*,4*S*,5*S*,6*R*)-4-(benzoyloxy)-5-methoxy-2-methyl-6-(phenylthio)tetrahydro-2*H*-pyran-3-yl 3,5-dichloro-2-ethyl-4,6-bis(naphthalen-2-ylmethoxy)benzoate 14. To a stirred solution of previously described **11** (0.215 g, 0.33 mmol) and NapBr (89 mg, 0.401 mmol, 1.2 eq.) in anhydrous DMF (2 mL, 0.167 M), under argon atmosphere, was added at r.t. K_2CO_3 (55 mg, 0.401 mmol, 1.2 eq.). After stirring for 3 h, the resulting mixture was quenched with H_2O (10 mL) and diluted with AcOEt (10 mL). The organic layer was separated, washed with H_2O (2x 10 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. To the crude obtained product (0.26 g, 0.33 mmol) in DCM (4 mL, 0.083M), was added benzoic acid (0.057 g, 0.46 mmol, 1.4 eq.), DCC (0.103 g, 0.5 mmol, 1.5 eq.) and DMAP (8 mg, 0.09 mmol, 0.2 eq.). The resulting mixture was stirred under argon for 2 h at room temperature. The reaction mixture was diluted with DCM (10 mL) and the solid was filtered off. The filtrate was washed with sat. aq. $NaHCO_3$ (10 mL) and the organic phase was separated, dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by flash chromatography (SiO_2, Hept/EtOAc : 90/0 to 80/20) to give the benzoylated adduct (0.216 g, 0.24 mmol, 73%) as an amorphous white solid. $[\alpha]^{22}_D$ −7.3 (*c* 0.44, $CHCl_3$); FT-IR (neat) ν max 3058, 2936, 2979, 1722, 1270, 1242, 1098, 735 cm-1; ^{1}H NMR ($CDCl_3$, 300 MHz) *δ* 8.24-8.15 (m, 2H), 8.06-7.82 (m, 8H), 7.77-7.62 (m, 3H), 7.58-7.42 (m, 8H), 7.35-7.26 (m, 3H), 5.71 (t, *J* = 10.0 Hz, 1H), 5.59 (d, *J* = 1.5 Hz, 1H), 5.43 (dd, *J* = 3.0 and 10.0 Hz, 1H), 5.37 (d,

[11] Determined according to the ^{1}H NMR spectrum of the crude NMR

J = 10.0 Hz, 1H), 5.23 (s, 2H), 5.18 (d, *J* = 10.0 Hz, 1H), 4.44-4.32 (m, 1H), 4.22-4.16 (m, 1H), 3.46 (s, 3H), 2.48-2.43 (m, 2H), 1.08 (d, *J* = 6.0 Hz, 3H), 0.88 (t, *J* = 7.5 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 165.8, 165.7, 153.2, 151.2, 138.9, 134.0, 133.6, 133.5, 133.4, 133.3, 133.2, 133.1, 131.4, 130.0, 129.1, 128.5, 128.3, 128.2, 128.1, 127.8, 127.7, 127.6, 127.5, 127.4, 126.2, 126.1, 126.0, 84.9, 79.4, 76.9, 75.1, 72.7, 72.8, 67.6, 59.1, 24.1, 17.3, 13.8; ESIHRMS *m/z* = 909.2044 $[M+Na]^+$.$C_{51}H_{44}O_8SCl_2Na$ requires 909.2032. To a stirred solution of previously the described compound (0.105 g, 0.118 mmol) and $NaHCO_3$ (12 mg, 0.142 mmol, 1.2 eq.) in DCM (2 mL, 0.059 M), was added at –78 °C *m*CPBA (75%, 0.029 g, 0.124 mmol, 1.05 eq.). After stirring for 2 h at –78 °C, the temperature of mixture was slowly raised to –10 °C over 2 h and quenched with a mixture of aq. saturated $NaHCO_3$ and aq. saturated $Na_2S_2O_3$ (1/1 v/v, 10 mL). The organic layer was separated, the aqueous phase was extracted with DCM (2*10 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (SiO_2, Hept/EtOAc 90/10 to 70/30) to give **14** (73 mg, 0.696 mmol, 68%) as an amorphous white solid as only one diastereomer. $[\alpha]^{22}_D$ −112.3 (*c* 0.48, $CHCl_3$); FT-IR (neat) ν max 3057, 2978, 2936, 1723, 1309, 1269, 1242, 1101, 736 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.16 (d, *J* = 7.5 Hz, 1H), 8.03-7.85 (m, 8H), 7.75-7.55 (m, 5H), 7.55-7.47 (m, 9H), 5.79 (dd, *J* = 10.0 and 3.5 Hz, 1H), 5.67 (t, *J* = 10.0 Hz, 1H), 5.35 (d, *J* = 10.5 Hz, 1H), 5.23 (s, 2H), 5.18 (d, *J* = 10.5 Hz, 1H), 4.50 (bs, 1H), 4.40-4.36 (m, 1H), 4.22-4.14 (m, 1H), 3.25 (s, 3H), 2.48-2.37 (m, 2H), 1.04 (d, *J* = 6.0 Hz, 3H), 0.89 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 163.8, 163.5, 151.5, 149.3, 139.4, 137.2, 131.7, 131.5, 131.4, 131.3, 129.7, 128.1, 127.5, 126.7, 126.5, 126.3, 125.9, 125.6, 124.4, 124.2, 122.5, 95.9, 75.0, 73.3, 72.3, 71.0, 70.2, 70.1, 51.2, 23.5, 15.9, 11.8; ESIHRMS *m/z* = 925.2004 $[M+Na]^+$. $C_{51}H_{44}O_9NSCl_2$ requires 925.1981.

((2*R*,3*R*,4*S*,5*S*,6*S*)-4-(benzoyloxy)-6-(((*E*)-3-bromo-2-(methoxycarbonyl)allyl)oxy)-5-methoxy-2-methyltetrahydro-2*H*-pyran-3-yl 3,5-dichloro-2-ethyl-4,6-bis(naphthalen-2-ylmethoxy)benzoate 20. A mixture of the glycosyl donor **14** (58 mg, 0.065 mmol, 1.7 eq.), acceptor **17** (7 mg, 0.038 mmol, 1 eq.), 2,6-di-terbutyl-4-methylpiridine (32 mg, 0.156 mmol, 4.14 equiv.), 4-allyl-1,2-dimethoxybenzene (26 µL, 0.152 mmol, 4 eq.) and freshly activated 4Å MS (200 mg) in DCM (3.7 mL) was stirred at r.t. for 1h. A solution of Tf_2O (10 µL, 0.061 mmol, 1.6 eq.) in DCM (0.1 mL) was then added dropwise at –70 °C and the reaction mixture was stirred for 2h. The temperature was slowly raised to –60 °C over 1h and quenched with NEt_3 (50 µL) and aq. saturated $NaHCO_3$ (10 mL). After filtration on Celite®, the aqueous phase was extracted with DCM (2 x15 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by preparative TLC (SiO_2, Hept/EtOAc : 80/20) to give the expected product **20** (33 mg, 0.034 mmol, 89%) as an amorphous white solid (α/β > 20/1)[11]. $[\alpha]^{22}_D$ −52.7 (*c* 0.66, $CHCl_3$); FT-IR (neat) ν max 2932, 1739, 1704, 1512, 1244, 1065, 816, 744 cm-1; ^{1}H NMR (CD_3CN, 300 MHz) δ 8.15-8.08 (m, 2H), 7.97-7.79 (m, 7H), 7.71 (s, 1H), 7.70-7.54 (m, 3H), 7.52-7.39 (m, 7H), 5.59 (t, *J* = 10.0 Hz, 1H), 5.36 (dd, *J* = 3 and 10.0 Hz, 1H), 5.31 (d, *J* = 10.0 Hz, 1H), 5.19-5.13 (bs, 2H), 5.09 (d, *J* = 10.0 Hz, 1H), 4.65 (d, *J* = 1.5 Hz, 1H), 4.54 (d, *J* = 11.0 Hz, 1H), 4.31 (d, *J* = 11.0 Hz, 1H), 3.99-3.82 (m, *2* 1H), 3.73 (s, 3H), 3.42 (m, 3H), 2.30 (q, *J* = 7.5 Hz, 2H), 1.04 (d, *J* = 6.0 Hz, 3H), 0.78 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (CD_3CN, 75 MHz) δ 165.8, 165.7, 164.2, 153.1, 151.1, 138.8, 134.1, 133.6, 133.5, 133.4, 133.3, 133.2, 133.1, 129.9, 129.4, 128.6, 128.3, 128.2, 128.1, 128.0, 127.8, 127.7, 127.4, 127.8, 126.4, 126.4, 126.3, 126.2, 126.1, 97.9, 77.9, 77.0, 75.1, 72.7, 66.7, 63.7, 59.9, 52.5, 25.4, 17.4, 13.5; $^1J_{C1\text{-}H1}$ = 171 Hz; ESIHRMS *m/z* = 993.1143 $[M+Na]^+$. $C_{50}H_{45}O_{11}NaCl_2Br$ requires 993.1120.

(2*R*,3*R*,4*S*,5*S*,6*R*)-6-(((*E*)-3-bromo-2-(methoxycarbonyl)allyl)oxy)-4-((*tert*-butyldimethylsilyl)oxy)-5-methoxy-2-methyltetrahydro-2*H*-pyran-3-yl 3,5-dichloro-2-ethyl-4,6-bis(naphthalen-2-ylmethoxy)benzoate B2. A mixture of the compound **19** (232 mg, 0.238 mmol, 1 eq.) and $Cu(OAc)_2$ (43 mg, 0.238 mmol, 1 eq.) in DCM/MeOH (95/5 v/v, 2 mL) was stirred at r.t. for 2 h 30. The reaction mixture was quenched with aq. saturated NH_4Cl (10 mL) and diluted with EtOAc (20 mL). The organic layer was washed with aq. HCl solution (1N, 5 mL) and brine (5 mL), then it was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (SiO_2, Hept/EtOAc : 80/30 to 60/40) to give the corresponding adduct (180 mg, 0.207 mmol, 89%) as an amorphous white solid. $[\alpha]^{22}_D$ −65.3 (*c* 0.6, $CHCl_3$); FT-IR (neat) ν max 3546, 3056, 2976, 1721, 1238, 1065, 732 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.02-7.98 (m, 1H), 7.93-7.80 (m, 7H), 7.74-7.68 (m, 2H), 7.60 (dd, *J* = 1.5 and 8.5 Hz), 7.53-7.45 (m, 4H), 5.32 (d, *J* = 10.0 Hz, 1H), 5.24-5.19 (m, 2H), 5.10 (d, *J* = 10.0 Hz, 1H), 5.04 (t, *J* = 9.5 Hz, 1H), 4.66 (d, *J* = 12.0 Hz, 1H), 4.51-4.45 (m, 2H), 3.73 (s, 3H), 3.61 (s, 3H), 3.58-3.51 (m, 2H), 3.36-3.20 (m, 1H), 2.96-2.76 (m, 2H), 2.54 (d, *J* = 11.0 Hz, 1H), 1.22 (t, *J* = 7.5 Hz, 3H), 1.05 (d, *J* = 6.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 166.3, 164.4, 153.1, 151.0, 139.5, 134.4, 133.7, 133.5, 133.4, 133.3, 133.2, 133.1, 128.3, 128.2, 128.1, 127.9, 127.8, 127.7, 127.6, 127.5, 126.4, 126.3, 126.2, 126.1, 101.2, 80.3, 77.0, 76.3, 75.1, 71.9, 70.1, 65.0, 62.1, 52.4, 25.2, 17.2, 14.1; $^1J_{\mathbf{C1\text{-}H1}}$ = 155 Hz; ESIHRMS *m/z* = 889.1191 $[M+Na]^+$. $C_{43}H_{41}O_{10}Cl_2BrNa$ requires 889.1158. To a stirred solution of the previously obtained compound (0.28 g, 0.322 mmol, 1 eq.) and 2,6-lutidine (113 µL, 0.97 mmol, 3 eq.) in DCM (3.5 mL) was

added at 0 °C, TBSOTf (170 µL, 0.74 mmol, 2.3 eq.). The reaction was stirred at r.t. for 4 h, then was quenched with aq. $Cu(SO_4)_2$ (15%, 10 mL) and diluted with EtOAc (20 mL). The organic layer was washed with brine (20 mL), then it was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (SiO_2, Hept/EtOAc : 95/5 to 85/15) to give **B2** (0.27 g, 0.275 mmol, 85%) as an amorphous white solid. $[\alpha]^{22}_D$ −55.5 (*c* 0.4, $CHCl_3$); FT-IR (neat) ν max 3056, 2931, 1722, 1313, 1239, 1102, 1065, 816 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 8.01-7.95 (m, 1H), 7.94-7.80 (m, 7H), 7.72-7.63 (m, 2H), 7.60-7.54 (m, 1H), 7.53-7.43 (m, 4H), 5.31-5.24 (m, 3H), 5.19 (d, *J* = 11.0 Hz, 1H), 5.13 (t, *J* = 9.0 Hz, 1H), 4.58 (d, *J* = 12.0 Hz, 1H), 4.38 (d, *J* = 12.0 Hz, 1H), 4.30 (s, 1H), 3.73-3.64 (m, 4H), 3.55 (s, 3H), 3.45-3.38 (m, 1H), 3.13-2.99 (m, 1H), 2.96-2.80 (m, 1H), 2.71-2.53 (m, 1H), 1.31-1.13 (m, 6H), 0.82 (s, 9H), 0.00 (s, 3H), -0.11 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 165.5, 164.5, 153.2, 151.7, 139.9, 134.5, 133.9, 133.6, 133.3, 133.2, 133.1, 128.3, 128.2, 128.1, 127.7, 127.6, 127.5, 127.0, 126.5, 126.3, 126.1, 125.4, 100.7, 80.9, 76.6, 76.2, 75.1, 72.9, 71.2, 64.8, 61.4, 52.3, 26.5, 25.9, 18.4, 18.2, 14.1, -4.4, -4. 5; $^1J_{C1\text{-}H1}$ = 155 Hz; ESIHRMS *m/z* = 1003.2050 $[M+Na]^+$. $C_{49}H_{55}O_{10}NaSiCl_2Br$ requires 1003.2023.

Assemblage of A2 and B2 and macrolactonization

(2*R*,3*R*,4*S*,5*S*,6*R*)-4-((*tert*-butyldimethylsilyl)oxy)-6-(((2*E*,4*E*,7*S*,8*E*,10*S*,11*R*,12*E*,14*E*,17*S*,18*R*)-10-ethyl-11,17-dihydroxy-7,18-bis((4-methoxybenzyl)oxy)-2-(methoxycarbonyl)-8,12,14-trimethylnonadeca-2,4,8,12,14-pentaen-1-yl)oxy)-5-methoxy-2-methyltetrahydro-2*H*-pyran-3-yl 3,5-dichloro-2-ethyl-4,6-bis(naphthalen-2-ylmethoxy)benzoate 25. In a Schlenk tube are introduced: boronic ester **A2** (145.4 mg, 0.1925 mmol), vinyl bromide derivative **B2** (189.2 mg, 0.1925 mmol), $Pd(OAc)_2$ (1.3 mg, 5.8 µmol), Ruphos (5.4 mg, 11.6 µmol), and K_3PO_4 (122.6 mg, 0.5775 mmol). Three vacuum/argon cycles were done, then THF (1.9 ml) and H_2O (190 µml) were added, the Schlenck tube was then sealed, and plunged in an oil bath at 45 °C. After 22 h of agitation, the reaction medium was poured in a separatory funnel contained brine, and EtOAc was used to extract organics molecules. After drying over anhydrous Na_2SO_4, filtration, and removal of the solvent under vacuum, HPLC purification on Eurospher 100-5 Si from Knauer^{Gmbh} (heptane/EtOAc : 1/1) gave seco-ester **22** as colorless foam (228.5 mg, 79.4 %). $[\alpha]_D^{20}$ – 57.0 (*c* 0.99, CH_2Cl_2); FT-IR (neat) ν max 3466, 2952, 2931, 2859, 1734, 1709, 1513, 1247 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ (ppm) 7.9 (s, 1H), 7.83-7.91 (m, 7H), 7.7 (dd, *J*= 1.5, 8.5 Hz, 1H), 7.59 (d, *J*= 8.5 Hz, 1H), 7.47-7.51 (m, 4H), 7.24 (d, *J*= 11.0 Hz, 1H), 7.22 (d, *J*= 8.5 Hz, 2H), 7.15 (d, *J*= 8.5 Hz, 2H), 6.86 (d, *J*= 8.5 Hz, 2H), 6.83 (d, *J*= 8.5 Hz, 2H), 6.51 (dd, *J*= 11.5, 15.5 Hz, 1H), 6.00 (td, *J* = 7.5, 15.5 Hz, 1H), 5.84 (s, 1H), 5.33 (dd, *J* = 7.0, 6.5 Hz, 1H), 5.20-5.29 (m, 4H), 5.14 (t, *J*= 9.5 Hz, 1H), 5.02 (d, *J*= 10.5 Hz, 1H), 5.53 (d, *J*= 11.5 Hz, 1H), 4.47 (d, *J*= 11.5 Hz, 1H), 4.36 (d, *J*= 11.5 Hz, 1H), 4.29 (s, 1H), 4.29 (d, *J*= 9.5 Hz, 1H), 4.26 (d, *J*= 11.5 Hz, 1H), 4.00 (d, *J*= 11.5 Hz, 1H), 3.83 (d, *J*= 8.5 Hz, 1H), 3.79 (s, 3H), 3.75 (s, 3H), 3.71 (s, 3H), 3.69 (dd, *J*= 9.5 Hz, 2.8 Hz, 1H), 3.65 (dd, *J*= 7.0 Hz, 1H), 3.60 (ddd, *J*= 8.0, 5.0, 3.5 Hz, 1H), 3.55 (s, 3H), 3.41 (m, 2H), 3.04 (qd, *J*= 6.5, 9.5 Hz, 1H), 2.88 (qd, *J* = 7.5, 13.5 Hz, 1H), 2.63 (m, 1H), 2.51 (m, 2H), 2.30 (m, *J*= 7.5 Hz, 1H), 2.14 (m, 2H), 1.87 (m, 1H), 1.77 (s, 3H), 1.68 (s, 3H), 1.61 (s, 3H), 1.24 (t, *J*= 7.0 Hz, 3H), 1.21 (m, 3H), 1.09 (d, *J*= 6.5 Hz, 3H), 0.82 (s, 9H), 0.80 (t, *J*= 7.0 Hz, 3H), 0.00 (s, 3H), -0.12 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) □ (ppm) 168.1, 165.6, 159.3, 159.2, 153.3, 151.9, 144.0, 142.5, 140.0, 136.7, 135.0, 134.2, 134.0, 133.7, 133.4, 133.3, 133.3, 133.3, 131.5, 130.9, 130.7, 129.6, 129.3, 128.4, 128.2, 127.9, 127.8, 127.6, 127.2, 127.1, 127.1, 126.8, 126.4, 126.4, 126.3, 126.2, 126.2, 125.9, 125.7, 125.0, 122.2, 113.9, 113.9, 100.5, 84.3, 82.3, 81.2, 76.6, 76.4, 75.2, 73.2, 73.1, 71.1, 70.5, 69.4, 62.9, 61.6, 55.4, 55.4, 52.0, 43.6, 38.1, 31.3, 26.6, 26.3, 26.0, 24.6, 24.0, 23.4, 21.2, 18.5, 18.3, 17.4, 14.8, 14.3, 13.8, 13.4, 11.6, 11.3, 0.1, –4.3, –4.4; HRMS calculated for $C_{86}H_{106}Cl_2O_{16}NaSi$ ($[M+Na]^+$) : 1515.652489, found 1515.63753.[12]

(2*R*,3*R*,4*S*,5*S*,6*R*)-4-((*tert*-butyldimethylsilyl)oxy)-6-(((3*E*,5*E*,8*S*,9*E*,11*S*,12*R*,13*E*,15*E*,18*S*)-11-ethyl-12-hydroxy-8-((4-methoxybenzyl)oxy)-18-((*R*)-1-((4-methoxybenzyl)oxy)ethyl)-9,13,15-trimethyl-2-oxooxacyclooctadeca-3,5,9,13,15-pentaen-3-yl)methoxy)-5-methoxy-2-methyltetrahydro-2*H*-pyran-3-yl 3,5-dichloro-2-ethyl-4,6-bis(naphthalen-2-ylmethoxy)benzoate 26. To a toluene solution (3.1 ml, dried over 4Å sieves) of ester **25** (228.5 mg, 0.1529 mmol) in a Schlenk tube under argon was added Me_3SnOH (276.4 mg, 1.53 mmol). The tube was sealed and

[12] The analysis was realized using a LTQ-Orbitrap XL mass spectrometer (Thermo Scientific (Bremen), Bremen, Germany). The analysis was performed in positive-ion mode. The optimized ESI parameters were set as follows: capillary temperature of 250 ◦C; sheath gas (nitrogen) flow of 30 arb.; auxiliary gas (nitrogen) flow of 10 arb.; source voltage of 4.25 kV; capillary voltage of 25 V; tube lens voltage of 110 V. The resolution of the Orbitrap mass analyzer was set at 60,000. The isolation width was 15 amu, and the normalized collision energy (CE) was set from 10 to 50. Collision-induced dissociation (CID) was conducted in LTQ with an activation q value of 0.25 and activation time of 30 ms. All instruments were controlled by the Xcalibur data system, and the data acquisition was carried out by analyst software Xcalibur (version 2.1) (Waltham, MA, USA) from Thermo Electron Corp.

placed in an oil bath heated at 120 °C during 24 h. Then the solvent was removed under vacuum and the residue was taken by 5 ml of a heptane/EtOAc (1/1) + 0.5% of AcOH solution and injected in the HPLC column (Eurospher 100-5 Si from Knauer^{Gmbh}). After elution with heptane/EtOAc (1/1) + 0.5% of AcOH, the corresponding seco-acid was obtained as a white foam (159.3 mg, 70%). $[\alpha]_D^{20}$ – 52.0 (*c* 1.09, CH_2Cl_2); FT-IR (neat) ν max 3450, 2933, 1736, 1513, 1248 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ (ppm) 7.99, (s, 1H), 7.84-7.90 (m, 7H), 7.70 (dd, *J*= 2.0, 8.5 Hz, 1H), 7.59 (dd, *J* = 2.0, 8.5 Hz, 1H), 7.45-7.52 (m, 4H), 7.35 (d, *J* = 11.5 Hz, 1H), 7.22 (d, *J*= 8.5 Hz, 2H), 7.16 (d, *J*= 8.5 Hz, 2H), 6.86 (d, *J*= 8.5 Hz, 2H), 6.83 (d, *J*= 8.5 Hz, 2H), 6.53 (dd, *J*= 12.0, 15.0 Hz, 1H), 6.05 (td, *J*= 7.0, 15.0 Hz, 1H), 5.84 (s, 1H), 5.31 (m, 2H), 5.25 (d, *J*= 3.5 Hz, 2H), 5.11-5.20 (m, 2H), 5.02 (dd, *J*= 2.0, 10.5 Hz, 1H), 4.53 (d, *J*= 12.0 Hz, 1H), 4.47 (d, *J*= 11.5 Hz, 1H), 4.36 (d, *J*= 11.5 Hz, 1H), 4.25 (m, 2H), 4.01 (d, *J*= 11.3 Hz, 1H), 3.83 (d, *J*= 8.5 Hz, 1H), 3.78 (s, 3H), 3.75 (s, 3H), 3.59-3.70 (m, 3H), 3.54 (s, 3H), 3.38-3.44 (m, 2H), 2.99 (tdd, *J*= 6.0, 7.0, 9.5 Hz, 1H), 2.88 (tdd, *J*= 7.0, 8.0, 13.5 Hz, 1H), 2.63 (qd, *J*= 7.5, 13.5 Hz, 1H), 2.47-2.55 (m, 2H), 2.31 (ddd, *J*= 7.0, 8.5, 14.0 Hz, 1H), 2.12-2.19 (m, 2H), 2.09 (s, 3H), 1.88 (m, 1H), 1.76 (s, 3H), 1.68 (s, 3H), 1.62 (d, J= 1.0 Hz, 3H), 1.20-1.26 (m, 6H), 1.09 (d, *J*= 6.5 Hz, 3H), 0.82 (s, 9H), 0.78 (t, *J*= 7.5 Hz, 3H), 0.01 (s, 3H), – 0.11 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ (ppm) 177.0, 172.5, 165.6, 159.3, 159.2, 153.3, 151.9, 146.0, 143.9, 140.0, 136.6, 134.9, 134.9, 134.2, 134.0, 133.7, 133.4, 133.3, 133.3, 131.5, 130.9, 130.6, 129.6, 129.3, 128.4, 128.2, 128.2, 127.9, 127.8, 127.6, 127.2, 127.0, 126.9, 126.4, 126.3, 126.3, 126.2, 125.9, 125.7, 124.2, 122.2, 113.9, 113.9, 100.5, 84.1, 82.3, 81.0, 76.6, 76.3, 75.2, 73.1, 72.9, 71.1, 70.4, 69.4, 62.6, 61.6, 55.4, 55.3, 43.5, 38.1, 31.3, 26.5, 26.0, 24.6, 18.6, 18.2, 17.4, 14.3, 14.2, 13.8, 13.4, 11.6, 11.3, –4.3, –4.4; HRMS TOF MS ES-, calculated for $C_{85}H_{103}Cl_2O_{16}Si$ ($[M-H]^-$): 1477.6379, found 1477.6392. A CH_2Cl_2 solution (7.6 ml) of the seco-acid (172.5 mg, 0.1165 mmol) was added *via* a syringe-pump over 20 h to a CH_2Cl_2 solution (43.7 ml) of 2-methyl-6-nitrobenzoic anhydride (60.2 mg, 0.1748 mmol) and 4-DMAP (71.2 mg, 0.5825 mmol). The reaction was allowed to run for 3 more hours after the end of the addition in order to consume totally the remaining seco-acid (tlc). The reaction medium was then poured into a separatory funnel containing water and the organic phase was then dried over anhydrous Na_2SO_4 and evaporated under vacuum. Purification by HPLC (heptane/EtOAc : 2/1) afforded macrolactone **25** (122.2 mg, 72%) as a white foam which is contaminated with around 15% of what seems to be a C5-C4 *Z* isomer. $[\alpha]_D^{20}$ – 50.3 (*c* 0.87, CH_2Cl_2); FT-IR (neat) ν max 3513, 2958, 2931, 2859, 1734, 1703, 1513, 1248; ^1H NMR (600 MHz, $CDCl_3$) δ (ppm) 7.99 (s, 1H), 7.92 (s, 1H), 7.83-7.89 (m, 6H), 7.71 (d, J= 8.4Hz, 1H), 7.59 (dd, *J*= 1.5, 8.5 Hz, 1H), 7.47-7.51 (m, 4H), 7.25 (d, *J*= 8.5 Hz, 2H), 7.18 (d, *J*= 8.0 Hz, 2H), 6.99 (d, *J*= 11.5 Hz, 1H), 6.87 (d, *J*= 8.0 Hz, 2H), 6.83 (d, *J*= 8.0 Hz, 2H), 6.42 (dd, *J*= 11.5, 14.5 Hz,1H), 5.82 (ddd, *J*= 14.0, 8.0, 6.5 Hz, 1H), 5.80 (s, 1H), 5.30 (d, *J*= 11.2 Hz, 1H), 5.25 (d, *J*= 4.5 Hz, 1H), 5.19 (d, *J*= 11.0 Hz, 1H), 5.12 (t, *J*= 9.0 Hz, 1H), 4.94 (dd, *J*= 7.5, 9.0 Hz, 1H), 4.77 (dt, *J*= 4.5, 6.0 Hz, 1H), 4.57 (d, *J*= 11.5 Hz, 1H), 4.51 (d, *J*= 11.5 Hz, 1H), 4.48 (d, *J*= 11.5 Hz, 1H), 4.41 (d, *J*= 11.5 Hz, 1H), 4.31 (d, *J*= 12.0 Hz, 1H), 4.29 (s, 1H), 4.18 (d, *J*= 12.0 Hz, 1H), 3.83 (d, *J*= 9.5 Hz, 1H), 3.79 (m,1H), 3.79 (s, 3H), 3.77 (s, 3H), 3.67 (dq, *J*= 3.0, 9.5 Hz, 1H), 3.50 (s, 3H), 3.41 (d, *J* = 3.0 Hz, 1H), 3.01 (m, *J*= 6.5, 9.5 Hz, 1H), 2.88 (qd, *J*= 7.5, 13.5 Hz, 1H), 2.68 (ddd, *J*= 7.5, 6.5, 13.5 Hz, 1H), 2.62 (m , *J*= 7.0 Hz, 1H), 2.56 (ddd, *J*= 19.0, 9.5, 3.0 Hz, 1H), 2.45 (m, 2H), 2.32 (ddd, *J*= 14.0, 8.5, 4.5 Hz, 1H), 1.98 (m, 1H), 1.68 (s, 6H), 1.57 (s, 3H), 1.24 (t, J= 7.5 Hz, 3H), 1.21 (d, 3H, *J*= 6.0 Hz), 1.18 (d, *J*= 6.0 Hz, 3H), 0.91 (t, *J*= 7.5 Hz, 3H), 0.82 (s, 9H), – 0.01 (s, 3H), –0.12 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ (ppm) 167.8, 165.7, 159.2, 159.1, 153.3, 151.9, 144.0, 141.7, 140.0, 136.6, 135.4, 134.0, 133.7, 133.4, 133.3, 133.3, 133.3, 133.1, 132.2, 131.0, 130.7, 129.9, 128.8, 128.4, 128.2, 127.9, 127.8, 127.6, 127.2, 127.1, 126.9, 126.4, 126.4, 126.3, 126.2, 125.9, 125.7, 125.1, 124.9, 122.1, 114.1, 114.0, 113.9, 113.8, 101.4, 83.0, 81.2, 79.1, 76.6, 76.4, 76.3, 75.2, 73.1, 73.0, 71.1, 71.0, 70.0, 63.5, 61.6, 55.5, 55.4, 53.6, 42.5, 34.6, 27.5, 26.6, 26.0, 25.9, 24.0, 18.6, 18.3, 17.1, 16.7, 15.4, 14.3, 12.3, 11.2, –4.3, –4,4. HRMS TOF MS ES-, calculated for $C_{85}H_{101}Cl_2O_{15}Si$ ($[M-H]^-$) : 1459.6287, found 1459.6256.

Preparation of the western part with D-niovose and noviosylation step

2-*O*-*tert*-Butyldimethylsilyl-3,4-*O*-isopropylidene-*D*-arabinono-1,5-lactone 27. To a stirred solution of commercially available *D*-arabinose (10 g, 66.7 mmol) in dry DMF (80 mL), under argon atmosphere, were successively added CSA (310 mg, 1.3 mmol, 0.02 eq.) and 2,2-dimethoxypropane (12.2 mL, 100 mmol, 1.5 eq.). The resulting mixture was stirred at r.t. for 4 h, then Et_3N was added at 0 °C and DMF was removed under reduced pressure. The crude product was purified by flash chromatography (5% to 30% MeOH in CH_2Cl_2) to afford the desired product (10.5 g, 55.4 mmol, 83%, α/β = 37:63) as a colorless oil.[13] To a stirred solution of previously described compound (4.5 g 23.6 mmol) in anhydrous CH_2Cl_2 (110 mL, 0.2 M, stab. EtOH), under argon atmosphere, were added at 0 °C trichloroisocyanuric acid (5.8 g, 24.8

[13] The spectroscopic data agree with those reported in the literature: Yamaguchi T., Kawada Y., Obika S., Imanishi T., Miyashita K., *Tetrahedron* **2010**, *66*, 8181.

mmol, 1.05 eq.), and TEMPO (370 mg, 2.4 mmol, 10 mol%). The reaction mixture was allowed to reach r.t. and stirred overnight, then filtered through a pad of Celite® which was washed with an excess of EtOAc (200 mL). The organic filtrate was washed with aq. 1 M HCl (100 mL), aq. saturated $NaHCO_3$ (100 mL), brine (100 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. To a stirred solution of the obtained crude product (3.34 g, 17.7 mmol) in anhydrous DMF (30 mL, 0.6 M), under argon atmosphere, were added at 0 °C imidazole (3.02 g, 44.4 mmol, 2.5 eq.) and TBSCl (5.35 g, 35.6 mmol, 2 eq.). The ice-bath was removed and the resulting mixture was stirred at r.t. overnight. The reaction mixture was diluted with 5% $CuSO_{4(aq.)}$ (70 mL) and extracted with EtOAc (3x 150 mL)). The combined organic extracts were washed with H_2O (3 x 100 mL), brine (100 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography (SiO_2, Hept/EtOAc : 80/20) to afford **26** (4.67 g, 15.4 mmol, 65%) as a white solid. [14]

(3a*S*,7*S*,7a*R*)-7-((*tert*-Butyldimethylsilyl)oxy)-2,2,6,6-tetramethyltetrahydro-4H-[1,3]dioxolo[4,5-c]pyran-4-one 28. To a stirred solution of previously described **26** (5 g, 16.5 mmol) in anhydrous THF (100 mL, 0.2 M), under argon atmosphere, was added at 0 °C methylmagnesium bromide (13.8 mL, 41.3 mmol, 2.5 eq., 3 M in Et_2O). The ice-bath was removed, the reaction mixture was stirred at r.t. for 90 min before being diluted with EtOAc (100 mL) and quenched with aq. saturated NH_4Cl (150 mL). The layers were separated and the aqueous layer was extracted with EtOAc (2 x 100 mL). The combined organic layers were washed with aq. saturated NH_4Cl (150 mL), brine (100 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure to afford the desired product as a white solid which was used in the subsequent step without further purification. To a stirred solution of the previously obtained compound (5.88 g, 17.6 mmol) in anhydrous CH_2Cl_2 (88 mL, 0.2 M, stab. EtOH), under argon atmosphere, were added at 0 °C trichloroisocyanuric acid (8.58 g, 36.9 mmol, 2.1 eq.), and TEMPO (137 mg, 0.88 mmol, 5 mol%). The reaction mixture was allowed to reach r.t. and stirred for 2 h, then filtered through a pad of Celite® which was washed with an excess of EtOAc (150 mL). The organic filtrate was washed with aq. 1 M HCl (100 mL), aq. saturated $NaHCO_3$ (100 mL)), brine (100 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography (SiO_2, Hept/EtOAc : 95/5 to 70/30) to afford **27** (4.8 g, 14.4 mmol, 87%) as colorless needles. $[\alpha]^{22}_D$ +14.9 (*c* 1.2, $CHCl_3$); FT-IR (neat) ν max 2991, 2955, 2931, 2859, 1754, 1472, 1464, 1373, 1252, 1211 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 4.72 (d, J = 8.5 Hz, 1H), 4.37 (dd, J = 8.5, 6.5 Hz, 1H), 3.64 (d, J = 6.5 Hz, 1H), 1.50 (s, 3H), 1.42 (s, 3H), 1.39 (s, 3H), 1.37 (s, 3H), 0.92 (s, 9H), 0.17 (s, 3H), 0.13 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 169.0, 111.0, 83.0, 78.2, 77.1, 71.6, 27.5, 26.6, 25.7, 24.7, 21.7, 17.9, −4.2, −5.3; ESIHRMS *m/z* = 331.1941$[M+H]^+$. $C_{16}H_{31}O_5Si$ requires 331.1963.

(2*R*,4*R*,5*S*)-5-((*tert*-Butyldimethylsilyl)oxy)-6,6-dimethyl-2-(phenylthio)tetrahydro-2*H*-pyran-3,4-diol 29. To a stirred solution of previously described **26** (5.02 g, 15.2 mmol) in anhydrous CH_2Cl_2 (150 mL, 0.1 M), under argon atmosphere, was added dropwise at −78 °C Dibal-H (18.2 mL, 18.2 mmol, 1.2 eq., 1 M in CH_2Cl_2). The reaction mixture was stirred at −78 °C for 30 min, then quenched with MeOH (15 mL) followed by aq. 1M HCl (100 mL) at this temperature. The cooling-bath was removed and the reaction mixture was allowed to reach r.t., then extracted with CH_2Cl_2 (3x 100 mL). The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure to afford the desired product (5.03 g, 15.2 mmol, quant., mixture α/β : 65:35) as a colorless oil that was used in the subsequent step without further purification. A round-bottom flask was charged with a stirring bar and previously obtained compound (5.03 g, 15.2 mmol). To this was added a solution of formic acid (22.8 mL, 605.0 mmol, 40 eq.) in EtOH (95%, 22.8 mL). The resulting mixture was stirred at r.t. overnight. The reaction mixture was cooled down to 0 °C, quenched with Et_3N (42 mL, 302.5 mmol, 20 eq.) and concentrated under reduced pressure. The crude product was purified by flash chromatography (SiO_2, Hept/EtOAc : 85/15 to 30/70) to afford the unreacted starting material (750 mg, 2.25 mmol) and the titled compound (2.92 g, 10.0 mmol, mixture 93:7 α/β, 78% over two steps) as a colorless oil. $[\alpha]^{22}_D$ −31.0 (*c* 1.09, $CHCl_3$); FT-IR (neat) ν max 3411, 2954, 2930, 2895, 2858, 1472, 1382, 1368, 1251, 1120, 1074, 1022, 947, 874, 837, 777 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz, α-anomer) δ 4.97 (ap. dd, J = 8.5, 1.5 Hz, 1H), 3.98 (dd, J = 3.0 and 1.5 Hz, 1H), 3.83 (d, J = 8.5 Hz, 1H), 3.66 (dd, J = 9.5 and 3.0 Hz, 1H), 3.57 (d, J = 9.5 Hz, 1H), 2.77 (brs, 1H), 2.29 (brs, 1H), 1.30 (s, 3H), 1.19 (s, 3H), 0.91 (s, 9H), 0.16 (s, 3H), 0.12 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz, α-anomer) δ 89.5, 75.6, 75.4, 71.6, 71.4, 28.6, 25.9, 18.2, 17.9 ($C(CH_3)_2$), -3.7, -4.7. To a stirred solution of previously described compound (1.38 g, 4.72 mmol) in anhydrous CH_2Cl_2 (23.6 mL, 0.2 M), under argon atmosphere, were added diphenyl disulfide (1.13 g, 5.19 mmol, 1.1 eq.) and tributylphosphine (2.33 mL, 9.44 mmol, 2 eq.) at 0 °C. The cooling bath was removed and the reaction mixture was slowly warmed-up to r.t. and stirred overnight.

[14] The spectroscopic data are in agreement with those reported in the literature: Jones N. A., Jenkinson S. F., Soengas R., Fanefjord M., Wormald M. R., Dwek R. A., Kiran G. P., Devendar R., Takata G., Morimoto K., Izumori K., Fleet G. W. J., *Tetrahedron: Asymmetry* **2007**, *18*, 774.

The reaction mixture was quenched with aq. NaOH (1M, 30 mL) at 0 °C and the layers were separated. The organic layer was washed with aq. NaOH (1M, 2x 30 mL), then with brine (50 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography (SiO_2, Hept/EtOAc : 100/0 to 80/20) to give the desired product **29** (1.59 g, 4.13 mmol, 88%, mixture α/β > 95:5) as a colorless oil. $[\alpha]^{22}_D$ +46.1 (*c* 0.90, $CHCl_3$); FT-IR (neat) ν max 3455, 2955, 2930, 2886, 2857, 1473, 1440, 1388, 1364, 1251, 1156, 1082, 1027, 998, 915, 881, 861, 836, 775, 745, 691 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.61-7.57 (m, 2H), 7.32-7.28 (m, 3H), 5.03 (d, *J* = 9.5 Hz, 1H), 4.04 (dd, *J* = 3.5 an 3.5 Hz, 1H), 3.75 (dd, *J* = 9.5 and 3.5 Hz, 1H), 3.60 (d, *J* = 3.5 Hz, 1H), 2.49 (brs, 2H), 1.49 (s, 3H), 1.27 (s, 3H), 0.85 (s, 9H), 0.06 (s, 3H), 0.05 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 133.3, 132.4, 128.8, 127.7, 80.9, 77.9, 73.8, 71.9, 66.2, 27.2, 25.7, 23.0, 17.9, -4.8, -5.0; ESIHRMS *m/z* = 791.3475 $[2M+Na]^+$. $C_{38}H_{64}O_8NaSi_2S_2$ requires 791.3479.

(3*S*,4*R*,6*R*)-4,5-Dihydroxy-2,2-dimethyl-6-(phenylthio)tetrahydro-2*H*-pyran-3-yl isobutyrate 30. To a stirred solution of **29** (1.4 g, 3.64 mmol) in anhydrous CH_2Cl_2 (36.4 mL, 0.1 M), under argon atmosphere, were added at 0 °C pyridine (1.76 mL, 21.8 mmol, 6 eq.) and dichloroacetyl chloride (1.05 mL, 10.9 mmol, 3 eq.). The reaction mixture was stirred at 0 °C for 1.5 h, then quenched with water (100 mL). The layers were separated, the aqueous layer was extracted with CH_2Cl_2 (2 x 100 mL), and the combined organic extracts were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography (SiO_2, Hept/EtOAc : 100/0 to 90/10) to deliver the diacylated compound (2 g, 3.30 mmol, 91%) as a pale yellow oil. $[\alpha]^{22}_D$ +40.1 (*c* 0.97, $CHCl_3$); FT-IR (neat) ν max 2956, 2931, 2885, 2858, 1773, 1764, 1473, 1440, 1389, 1367, 1264, 1160, 1107, 1045, 1026, 924, 878, 838, 816, 778, 748, 692cm-1; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.57-7.54 (m, 2H), 7.33-7.30 (m, 3H), 5.99 (s, 1H), 5.92 (s, 1H), 5.31 (dd, *J* = 4.0 and 3.5 Hz, 1H), 5.21 (d, *J* = 9.5 Hz, 1H), 5.10 (dd, *J* = 9.5 and 3.5 Hz, 1H), 3.61 (d, *J* = 4.0 Hz, 1H), 1.48 (s, 3H), 1.32 (s, 3H), 0.85 (s, 9H), 0.12 (s, 3H), 0.07 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 163.5, 158.2, 134.0, 129.2, 128.9, 128.5, 77.9, 76.8, 73.6, 72.1, 68.9, 63.9, 63.8, 26.7, 25.6, 22.8, 17.8, -4.9, -5.1; ESIHRMS *m/z* = 1231.0767 $[2M+Na]^+$. $C_{46}H_{64}O_{12}NaSi_2S_2Cl_8$ requires 1231.0784. To a stirred solution of the diacylated compound (1.49 g, 2.46 mmol) in anhydrous acetonitrile (12.3 mL, 0.2 M), under argon atmosphere, were added at 0 °C isobutyric anhydride (0.81 mL, 4.91 mmol, 2 eq.) and scandium(III) triflate (121 mg, 0.25 mmol, 10 mol%). The reaction mixture was allowed to reach r.t. and stirred for 1.5 h. The solvent was evaporated under reduced pressure and the residue was purified by flash chromatography (SiO_2, Hept/EtOAc : 100/0 to 90/10) to afford the desired compound (1.24 g, 2.20 mmol, 89%) as a pale yellow oil. $[\alpha]^{22}_D$ +34.5° (*c* 0.20, $CHCl_3$); FT-IR (neat) ν max 2979, 1760, 1471, 1440, 1390, 1372, 1268, 1241, 1147, 1046, 925, 815, 749, 692 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.58-7.54 (m, 2H), 7.37-7.32 (m, 3H), 5.98 (s, 1H), 5.93 (s, 1H), 5.42 (dd, *J* = 5.0 and 3.5 Hz, 1H), 5.28 (d, *J* = 8.5 Hz, 1H), 5.13 (dd, *J* = 8.5 and 3.5 Hz, 1H), 5.03 (d, *J* = 5.0 Hz, 1H), 2.59 (septet, *J* = 7.0 Hz, 1H), 1.53 (s, 3H), 1.35 (s, 3H), 1.16 (d, *J* = 7.0 Hz, 3H), 1.15 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 175.2, 163.0,162.9, 133.6, 131.0, 129.0, 128.6, 78.4, 76.9, 71.1, 70.4, 70.1, 63.8, 63.7, 34.0, 25.4, 23.9, 18.7. ESIHRMS *m/z* = 582.9903 $[M+Na]^+$. $C_{21}H_{24}O_7NaSCl_4$ requires 582.9895. To a stirred solution of previously described compound (1.02 g, 1.81 mmol) in a mixture of MeOH (180 mL, 0.01 M) and water (13 mL), was added sym-collidine (0.50 mL, 3.81 mmol, 2.1 eq.). The reaction mixture was stirred at r.t. for 5 h. At the end of the reaction, the solvent was evaporated under reduced pressure and the aqueous residue was diluted with aq. citric acid (10%, 50 mL) and EtOAc (100 mL). The layers were separated, the aqueous layer was extracted with EtOAc (2x 50 mL)) and the combined organic extracts were washed with brine (50 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography (SiO_2, Hept/EtOAc : 90/10 to 70/30 10%) to give **30** (415 mg, 1.22 mmol, 67%) as a colorless oil. $[\alpha]^{22}_D$ +80.4 (*c* 0.97, $CHCl_3$); FT-IR (neat) ν max 3449, 2977, 2935, 1735, 1472, 1440, 1387, 1368, 1197, 1158, 1041, 984, 922, 882, 746, 692 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.61-7.58 (m, 2H), 7.35-7.30 (m, 3H), 5.11 (d, *J* = 9.5 Hz, 1H), 4.93 (d, *J* = 3.5 Hz, 1H), 4.03 (dd, *J* = 3.5 and 3.5 Hz, 1H), 3.65 (dd, *J* = 9.5 and 3.5 Hz, 1H), 2.69 (brs, 1H), 2.57 (brs, 1H), 2.55 (septet, *J* = 7.0 Hz, 1H), 1.55 (s, 3H), 1.25 (s, 3H), 1.15 (d, *J* = 7.0 Hz, 3H), 1.14 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 175.8, 132.4, 132.1, 128.9, 127.9, 81.2, 76.3, 73.6, 69.4, 66.8, 34.1, 26.3, 23.1, 18.9. ESIHRMS *m/z* = 363.1234 $[M+Na]^+$. $C_{17}H_{24}O_5NaS$ requires 363.1242.

(3*S*,4*S*,6*R*)-4-Hydroxy-2,2-dimethyl-5-(naphthalen-2-ylmethoxy)-6-(phenylthio)tetrahydro-2*H*-pyran-3-yl isobutyrate 32. To a stirred solution of **30** (394 mg, 1.16 mmol) in anhydrous toluene (11.6 mL, 0.1 M), under argon atmosphere, was added dibutyltin oxide (317 mg, 1.27 mmol, 1.1 eq.). The resulting suspension was heated to reflux and stirred for 4 h (the suspension progressively turned into solution). The reaction mixture was then cooled down to r.t., the solvent was removed under reduced pressure and the residue was immediately placed under inert atmosphere. Anhydrous DMF (5.8 mL, 0.2 M) was then added, followed by cesium fluoride (351 mg, 2.31 mmol, 2 eq.) and 2-(bromomethyl)naphthalene (384 mg, 1.74 mmol, 1.5 eq.) and the resulting mixture was stirred at r.t. overnight. The

reaction mixture was diluted with a large amount of CH_2Cl_2 (50 mL), filtered through a Celite® pad and the filtrate was washed with water (3x 50 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography (SiO_2, Hept/EtOAc : 100/0 to 80/20) to afford **32** (445 mg, 0.92 mmol, inseparable mixture of regioisomers, 80%) as a colorless oil. Both isomers can be separated using preparative HPLC with Uptiprep® *100Å silica, 5* µm, Hept/EtOAc : 90/10 to 85/15). $[\alpha]^{22}_D$ +17.7 (*c* 1.24, $CHCl_3$); FT-IR (neat) ν max 3481, 3057, 2976, 2933, 1735, 1584, 1509, 1470, 1439, 1387, 1368, 1255, 1192, 1155, 1101, 1072, 1042, 1025, 984, 921, 858, 820, 746, 692 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.84-7.75 (m, 3H), 7.61-7.56 (m, 3H), 7.51-7.46 (m, 3H), 7.32-7.28 (m, 3H), 5.29 (d, *J* = 8.0 Hz, 1H), 4.95 (d, *J* = 5.0 Hz, 1H), 4.87 (d, *J* = 11.5 Hz, 1H), 4.70 (d, *J* = 11.5 Hz, 1H), 3.86 (dd, *J* = 5.0 and 3.5 Hz, 1H), 3.72 (dd, *J* = 8.0 and 3.5 Hz, 1H), 2.44 (septet, *J* = 7.0 Hz, 1H), 1.46 (s, 3H), 1.27 (s, 3H), 1.02 (d, *J* = 7.0 Hz, 3H), 0.99 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 175.8, 134.5, 134.3, 133.1, 132.5, 131.7, 128.9, 128.5, 127.9, 127.7, 127.4, 127.3, 126.3, 126.2, 126.0, 80.3, 76.3, 74.6, 73.6, 72.9, 68.6, 34.0, 25.5, 24.2, 18.7; ESIHRMS *m/z* = 503.1867 $[M+Na]^+$. $C_{28}H_{32}O_5NaS$ requires 503.1868.

(3*S*,4*S*,6*R*)-4-(((((1*R*,2*S*,5*R*)-2-Isopropyl-5-methylcyclohexyl)oxy)dimethylsilyl)oxy)-2,2-dimethyl-5-(naphthalen-2-ylmethoxy)-6-(phenylthio)tetrahydro-2*H*-pyran-3-yl isobutyrate 35. To a stirred solution of alcohol **32** (60 mg, 0.125 mmol, 1 eq.) in anhydrous CH_2Cl_2 (0.65 mL), under argon atmosphere, was added NEt_3 (34 µL, 0.25 mmol, 2 eq.) at 0 °C. After 5 min, dimethylchlorosilane (21 µL, 0.19 mmol, 1.5 eq.) was added and the resulting mixture was allowed to reach r.t. and stirred for 4 h. Volatiles were evaporated under reduced pressure and a solution iced aqueous sat. $NaHCO_3$ (5 mL) was added. The aqueous layer was extracted with CH_2Cl_2 (3 x 10 mL), the combined organic extracts were dried over Na_2SO_4, filtered and concentrated under reduced pressure. A solution of menthol **33** (12 mg, 0.074 mmol, 0.67 eq.) and 4Å molecular sieves (50 mg) in anhydrous toluene (0.25 mL) was stirred at r.t. under argon atmosphere for 45 min. Tris(pentafluorophenyl)borane (2 mg, 0.004 mmol, 0.03 eq.) was added followed by dropwise addition of a solution of the previously prepared alkoxysilane in toluene (0.75 mL). After 3h, the reaction mixture was concentrated under reduced pressure. The crude product was purified by preparative TLC (heptane/EtOAc 7:3) to afford the desired product **35** (61 mg, 0.088 mmol, 70%) as a colorless oil. $[\alpha]^{20}_D$ +13.0 (*c* 0.7, $CHCl_3$); FT-IR (neat) ν max 3058, 2955, 2923, 2871, 1736, 1255, 1104 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.83-7.75 (m, 3H), 7.63-7.58 (m, 3H), 7.53-7.45 (m, 3H), 7.31-7.25 (m, 3H), 5.38 (d, *J* = 9.0 Hz, 1H), 4.84-4.75 (m, *3*H), 4.13-4.06 (m, 1H), 3.62 (dd, *J* = 9.0 and 3.0 Hz, 1H), 3.54 (td, *J* = 10.3, 4.3 Hz), 2.41-2.28 (m, 1H), 2.23-2.10 (m, 1H), 1.95-1.84 (m, 1H), 1.60-1.54 (m, 2H), 1.52 (s, 3H), 1.31-1.24 (m, 1H), 1.20 (s, 3H), 1.18-1.10 (m, 1H), 0.98 (d, *J* = 7.0 Hz, 3H), 0.91 (d, *J* = 7.0 Hz, 3H), 0.87 (d, *J* = 7.0 Hz, 3H), 0.80 (d, *J* = 6.4 Hz, 3H), 0.72 (d, *J* = 7.0 Hz, 3H), 0.18 (s, 3H), 0.17 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 175.5, 135.2, 134.7, 133.1, 133.0, 131.3, 128.7, 128.0, 127.9, 127.6, 127.2, 126.9, 126.3, 126.0, 125.9, 80.0, 76.0, 75.0, 73.5, 72.6, 72.3, 69.4, 49.8, 45.3, 34.4, 34.0 31.6, 26.4, 25.4, 23.7, 22.9, 22.2, 21.2, 18.7, 15.9, 1.0, 1.3; ESIHRMS *m/z* = 715.3461 $[M+Na]^+$. $C_{40}H_{56}O_6NaSiS$ requires 715.3465.

(3*S*,4*S*,5*S*,6*R*)-4-Hydroxy-6-(((1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyl)oxy)-2,2-dimethyl-5-(naphthalen-2-ylmethoxy)tetrahydro-2*H*-pyran-3-yl isobutyrate 39. To a stirred solution of previously described **35** (33 mg, 0.048 mmol) in anhydrous CH_2Cl_2 (2.4 mL, 0.02 M), under argon atmosphere, were added *N*-iodosuccinimide (13.9 mg, 0.062 mmol, 1.3 eq.) and 2,6-di-tert-butyl-4-methylpyridine (29.3 mg, 0.143 mmol, 3 eq.) at −40 °C. After stirring for 5 min, trimethylsilyl trifluoromethanesulfonate (15.5 µL, 0.086 mmol, 1.8 eq.) was added and the reaction mixture was stirred for an additional hour, then quenched with a mixture of aqueous sat. NH_4Cl and aqueous sat. $Na_2S_2O_3$ (1:1 v/v, 10 mL) at −40 °C. The mixture was allowed to reach r.t. and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (2 x 10 mL), the combined organic extracts were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was placed under argon atmosphere, dissolved in anhydrous MeOH (2.4 mL, 0.02 M), cooled down to -10 °C and a solution of HCl/MeOH (1.25 M in MeOH, 0.15 mL, 0.190 mmol, 4 eq.) was added. After stirring for 10 min at -10 °C, the reaction mixture was quenched with aqueous sat. $NaHCO_3$ until reaching pH ≈ 7 and concentrated under reduced pressure. The aqueous residue was diluted was extracted with CH_2Cl_2 (3 x 15 mL)) and the combined organic extracts were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by preparative TLC (heptane/EtOAc 8:2) to give exclusively the β-compound **39** (20.5 mg, 0.039 mmol, 81%) as a colorless oil. $[\alpha]^{22}_D$ −120.8 (*c* 1.06, $CHCl_3$); FT-IR (neat) ν max 3547, 2952, 2924, 2870, 1738, 1468, 1385, 1368, 1257, 1198, 1153, 1097, 1073, 1037, 953, 922, 854, 819, 794, 749 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.85-7.82 (m, 3H), 7.79 (br s, 1H), 7.53-7.46 (m, 3H), 5.20 (d, *J* = 12.0 Hz, 1H), 5.04 (d, *J* = 10.0 Hz, 1H), 4.82 (d, *J* = 12.0 Hz, 1H), 4.78 (d, *J* = 0.5 Hz, 1H), 3.80 (dd, *J* = 0.5 and 3.5 Hz, 1H), 3.64 (ddd, *J* = 11.5, 10.0 and 3.5 Hz, 1H), 3.45 (td, *J* = 10.5, 4.0 Hz), 2.59 (septet, *J* = 7.0 Hz, 1H), 2.44-2.32 (m, 1H), 2.33 (d, *J* = 11.5 Hz, 1H), 2.03-1.90 (m, 1H), 1.73-1.64 (m, 2H), 1.47-1.26 (m, 2H), 1.24 (s, 3H), 1.22 (s, 3H), 1.19 (d, *J* = 7.0 Hz, 3H), 1.17 (d, *J* = 7.0 Hz, 3H), 1.10-0.99 (m, 1H), 0.95 (d, *J* = 6.5 Hz, 3H), 0.93-0.90 (m, 1H), 0.89 (d, *J* = 7.0 Hz, 3H), 0.87-0.83 (m, 1H), 0.80 (d, *J* = 7.0 Hz, 3H).

^{13}C NMR ($CDCl_3$, 75 MHz) δ 177.0, 135.8, 133.2, 133.0, 128.2, 127.9, 127.7, 127.1, 126.3, 126.0, 125.8, 93.9, 78.6, 77.2, 75.3, 74.8, 73.0, 69.6, 48.2, 41.0, 34.4, 34.1, 31.5, 28.1, 25.1, 22.9, 22.4, 21.1, 19.1, 18.9, 18.8, 15.7; $^1J_{C\text{-}1,H\text{-}1}$ of 159 Hz; ESIHRMS *m/z* = 1075.6494 $[2M+Na]^+$. $C_{64}H_{92}O_{12}Na$ requires 1075.6486.

(3*S*,4*S*,6*R*)-4-(((((3*R*,4*S*,7*S*,*E*)-4-Ethyl-7-((4-methoxybenzyl)oxy)-6-methyl-1-(triethylsilyl)deca-5,9-dien-1-yn-3-yl)oxy)dimethylsilyl)oxy)-2,2-dimethyl-5-(naphthalen-2-ylmethoxy)-6-(phenylthio)tetrahydro-2H-pyran-3-yl isobutyrate 36. To a stirred solution of alcohol **32** (122 mg, 0.254 mmol, 1 eq.) in anhydrous CH_2Cl_2 (1.25 mL), under argon atmosphere, was added NEt_3 (69 µL, 0.51 mmol, 2 eq.) at 0 °C. After 5 min, dimethylchlorosilane (42 µL, 0.38 mmol, 1.5 eq.) was added and the resulting mixture was allowed to reach r.t. and stirred for 4 h. Volatiles were evaporated under reduced pressure and a solution iced aqueous sat. $NaHCO_3$ (5 mL) was added. The aqueous layer was extracted with CH_2Cl_2 (3 x 10 mL), the combined organic extracts were dried over Na_2SO_4, filtered and concentrated under reduced pressure. A solution of **34** (75 mg, 0.169 mmol, 0.67 eq.) and 4Å molecular sieves (80 mg) in anhydrous toluene (0.2 mL) was stirred at r.t. under argon atmosphere for 45 min. Tris(pentafluorophenyl)borane (9 mg, 0.017 mmol, 0.07 eq.) was added followed by dropwise addition of a solution of the previously prepared silane in toluene (1.8 mL) over 45 min. After 1h, the reaction mixture was concentrated under reduced pressure. The crude product was purified by flash chromatography (SiO2, Hept/EtOAc 95:5 to 8:2) to afford the desired product **36** (126 mg, 0.128 mmol, 76%) as a colorless oil. $[\alpha]^{22}_D$ +43.5 (*c* 1.04, $CHCl_3$); FT-IR (neat) ν max 2958, 2875, 1737, 1613, 1513, 1466, 1367, 1249, 1076, 1039, 957, 854, 801, 740 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.83-7.72 (m, 3H), 7.64-7.57 (m, 3H), 7.50-7.45 (m, 3H), 7.32-7.28 (m, 3H), 7.25 (d, *J* = 8.5 Hz, 2H), 6.86 (d, *J* = 8.5 Hz, 2H), 5.74-5.59 (m, 1H), 5.39 (d, *J* = 9.0 Hz, 1H), 5.21 (dd, *J* = 10.0 and 1.0 Hz, 1H), 5.06-4.94 (m, 2H), 4.80 (d, *J* = 4.0 Hz, 1H), 4.78 (s, 2H), 4.52 (d, *J* = 6.0, 1H), 4.44 (d, *J* = 11.5 Hz, 1H), 4.17 (d, *J* = 11.5 Hz, 1H), 4.08 (dd, *J* = 4.0 and 3.0 Hz, 1H), 3.80 (s, 3H), 3.68 (t, *J* = 7.0 Hz, 1H), 3.63 (dd, *J* = 9.0 and 3.0 Hz, 1H), 2.62-2.43 (m, 1H), 2.44-2.22 (m, 3H), 1.60 (d, *J* = 1.0 Hz, 3H), 1.54 (s, 3H), 1.21 (s, 3H,), 0.99-0.89 (17 H), 0.73 (t, *J* = 7.5 Hz, 3H), 0.57 (q, *J* = 7.5 Hz, 6H), 0.27 (s, 3H), 0.20 (s, 3H).^{13}C NMR ($CDCl_3$, 75 MHz): δ 175.5, 158.9, 136.6, 135.2, 135.1, 134.6, 133.1, 133.0, 131.3, 131.0, 129.8, 129.5, 128.7, 128.1, 127.8, 127.6, 127.2, 126.9, 126.2, 126.1, 125.9, 116.0, 113.6, 107.0, 87.2, 84.1, 79.8, 76.0, 75.0, 73.3, 72.5, 69.7, 68.8, 66.3, 55.2, 46.2, 38.3, 33.9, 26.4, 24.2, 23.7, 18.6, 11.5, 11.3, 7.4, 4.3, -1.3, -1.8. ESIHRMS *m/z* = 1001.4847 $[M+Na]^+$. $C_{57}H_{78}O_8Si_2SNa$ requires 1001.4854.

(3*S*,4*S*,5*S*,6*R*)-6-(((3*R*,4*S*,7*S*,*E*)-4-Ethyl-7-((4-methoxybenzyl)oxy)-6-methyl-1-(triethylsilyl)deca-5,9-dien-1-yn-3-yl)oxy)-4-hydroxy-2,2-dimethyl-5-(naphthalen-2-ylmethoxy)tetrahydro-2H-pyran-3-yl isobutyrate 40. A solution of **36** (43 mg, 0.044 mmol, 1 eq.), 2,6-di-tert-butyl-4-methylpyridine (26 mg, 0.127 mmol, 2.9 eq.) and 4Å molecular sieves (87 mg) in anhydrous CH_2Cl_2 (2.2 mL) was stirred at r.t. under argon atmosphere for 45 min. *N*-iodosuccinimide (12 mg, 0.053 mmol, 1.2 eq.) was then added at −40 °C followed by trimethylsilyl trifluoromethanesulfonate (18 µL, 0.101 mmol, 2.3 eq.). The reaction mixture was stirred for 30 min at −40 °C, then warmed up to 0°C and stirred for 3 h 30 min. The reaction was quenched with a mixture of aqueous sat. NH_4Cl and aqueous sat. $Na_2S_2O_3$ (1:1 v/v, 10 mL) at 0 °C and the aqueous layer was extracted with CH_2Cl_2 (2 x 10 mL), the combined organic extracts were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was placed under argon atmosphere, dissolved in anhydrous MeOH (1.5 mL, 0.02 M), cooled down to 0 °C and a solution of HCl/MeOH (1.25 M in MeOH, 0.11 mL,) was added. After stirring for 10 min at 0 °C, the reaction mixture was quenched with aqueous sat. $NaHCO_3$ until reaching pH ≈ 7 and concentrated under reduced pressure. The aqueous residue was diluted was extracted with CH_2Cl_2 (3 x 15 mL)) and the combined organic extracts were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by preparative TLC (heptane/EtOAc 8:2) to give exclusively the β-compound **40** (15 mg, 0.018 mmol, 41%) as a colorless oil. $[\alpha]^{22}_D$ − 40.4 (*c* 0.25, $CHCl_3$); FT-IR (neat) ν max 3520, 2957, 2934, 2874, 2175, 1739, 1613, 1513, 1465, 1385, 1369, 1247, 1171, 1149, 1072, 1038, 912, 855, 819, 739, 728 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.83-7.77 (m, 3H), 7.73 (ap. s, 1H), 7.50-7.44 (m, 3H), 7.23 (d, *J* = 8.5 Hz, 2H), 6.82 (d, *J* = 8.5 Hz, 2H), 5.77-5.59 (m, 1H), 5.28 (dd, *J* = 10.0, 1.0 Hz, 1H), 5.16 (d, *J* = 12.0 Hz, 1H), 5.08 (d, *J* = 1.0 Hz, 1H), 5.08-4.91 (m, 3H), 4.75 (d, *J* = 12.0 Hz, 1H), 4.44 (d, *J* = 11.5 Hz, 1H), 4.40 (d, *J* = 7.0, 1H), 4.18 (d, *J* = 11.5 Hz, 1H), 3.85 (dd, *J* = 3.5 and 1.0 Hz, 1H), 3.76 (s, 3H), 3.71-3.59 (m, 2H), 2.81-2.68 (m, 1H), 2.59-2.33 (m, 3H), 2.30-2.16 (m, 1H), 1.89-1.71 (m, 1H), 1.64 (s, 3H), 1.31 (s, 3H), 1.25 (s, 3H), 1.22 (m, 1H), 1.16 (d, *J* = 7.0 Hz, 3H), 1.14 (d, *J* = 7.0 Hz, 3H), 0.97 (t, *J* = 8.0 Hz, 9H), 0.85 (t, *J* = 7.0 Hz, 3H), 0.58 (q, *J* = 8.0 Hz, 6H).^{13}C NMR ($CDCl_3$, 75 MHz): δ 176.8 , 155.7, 136.8, 135.6, 135.1, 134.3, 133.7, 130.7, 129.4, 129.3, 128.3, 127.9, 127.7, 126.9, 126.0, 125.9, 116.3, 113.6, 105.8, 95.7, 89.2, 83.7, 77.5, 75.0, 74.4, 73.7, 73.3, 69.4, 69.0, 55.2, 44.3, 38.4, 34.1, 28.2, 24.4, 19.9, 19.0, 18.8, 11.6, 7.5, 4.3;$^1J_{C\text{-}1,H\text{-}1}$ of 159 Hz; ESIHRMS *m/z* = 835.4585 $[M+Na]^+$. $C_{49}H_{68}O_8SiNa$ requires 835.4581.

(2R,3R,4S,5S,6R)-4-((tert-butyldimethylsilyl)oxy)-6-(((3E,5E,8S,9E,11S,12R,13E,15E,18S)-11-ethyl-12-(((((3S,4S,5S,6R)-3-(isobutyryloxy)-2,2-dimethyl-5-(naphthalen-2-ylmethoxy)-6-(phenylthio)tetrahydro-2H-pyran-4-yl)oxy)dimethylsilyl)oxy)-8-((4-methoxybenzyl)oxy)-18-((R)-1-((4-methoxybenzyl)oxy)ethyl)-9,13,15-trimethyl-2-oxooxacyclooctadeca-3,5,9,13,15-pentaen-3-yl)methoxy)-5-methoxy-2-methyltetrahydro-2H-pyran-3-yl 3,5-dichloro-2-ethyl-4,6-bis(naphthalen-2-ylmethoxy)benzoate 37. To a solution of dimethyldichlorosilane (0.085 mL, 0.71 mmol, 20 eq.) in anhydrous pyridine (0.5 mL) was added dropwise at r.t a solution of **32** (17 mg, 0.035 mmol, 1 eq.) in pyridine (0.2 mL). After stirring for 2 h, the volatiles were evaporated under reduced pressure and a solution of **26** (16 mg, 0.011 mmol, 0.3 eq.) and imidazole (3 mg, 0.042 mmol, 1.2 eq.) in anhydrous THF (0.8 mL) was added. The resulting mixture was stirred at r.t. for 1 h 30 min, then filtrated on a pad of celite® and concentrated under reduced pressure. The crude product was purified by preparative TLC (heptane/EtOAc 6:4) to afford the desired product **37** (16 mg, 0.008 mmol, 73%) as a colorless oil. $[\alpha]^{22}_{D}$ − 18.3 (*c* 0.65, $CHCl_3$); FT-IR (neat) ν max 3055, 2962, 2932, 2855, 1735, 1702, 1368, 1246, 1104, 1067, 1037, 796, 739 cm^{-1}; ^1H NMR (CD_3CN, 500 MHz) δ 8.02-7.87 (m, 7H), 7.85-7.75 (m, 3H), 7.70 (d, *J* = 8.5 Hz, 1H), 7.66-7.59 (m, 2H), 7.57-7.46 (m, 7), 7.33-7.24 (m, 3H), 7.23-7.15 (m, 3H), 7.02 (d, *J* = 11.5 Hz, 1H), 6.86-6.79 (m, 3H), 6.42 (dd, *J* = 11.5 and 14.5 Hz, 1H), 5.87 (ddd, *J* = 5.0, 9.5 and 14.5 Hz, 1H), 5.82 (s, 1H), 5.42-5.36 (m, 1H), 5.34 (d, *J* = 8.5 Hz, 1H), 5.32-5.24 (m, 3H), 5.18 (d, *J* = 11.0 Hz, 1H), 5.06 (d, *J* = 10.5 Hz, 1H), 4.86 (t, *J* = 9.5 Hz, 1H), 4.82 (d, *J* = 4.6 Hz, 1H), 4.77-4.62 (m, 3H, 2 x C*H*$_2$), 4.49 (d, *J* = 11.0 Hz, 1H), 4.38 (d, *J* = 11.0 Hz, 1H), 4.36-4.25 (m, 3H, 2 x C*H*$_2$), 4.28 (d, *J* = 11.5 Hz, 1H), 4.22 (d, *J* = 11.5 Hz, 1H), 4.19-4.14 (m, 1H), 3.99 (d, *J* = 9.5 Hz, 1H), 3.90-3.80 (m, 2H), 3.77 (dd, *J* = 3.0 and 10.0 Hz, 1H), 3.73 (s, 3H), 3.71 (m, 3H), 3.63 (dd, *J* = 3.0 and 8.5 Hz, 1H), 3.42-3.36 (m, 4H), 3.11-3.03 (m, 1H), 2.93-2.83 (m, 1H), 2.93-2.83 (m, 1H), 2.71-2.62 (m, 1H), 2.59-2.22 (m, 6H), 1.98-1.91 (m, 2H, *H22*), 1.73 (s, 3H), 1.70 (s, 3H), 1.56 (s, 3H), 1.44 (s, 3H), 1.20 (t, *J* = 7.5 Hz, 3H), 1.17-1.11 (m, 6H), 1.07 (t, *J* = 6.0 Hz, 3H), 1.00 (t, *J* = 7.0 Hz, 3H), 0.94 (t, *J* = 7.0 Hz, 3H), 0.80 (s, 9H), 0.08 (s, 3H), 0.07 (s, 3H), -0.00 (s, 3H), -0.15 (s, 3H); ^{13}C NMR (CD_3CN, 125 MHz): δ 175.0, 166.9, 165.4, 158.9, 158.8, 143.5, 142.1, 139.5, 135.7, 135.5, 135.3, 134.4, 133.9, 133.4, 133.0, 132.8, 132.7, 132.5 , 132.4, 130.8, 130.6, 130.5, 128.9, 128.7, 128.6, 127.8, 127.7, 127.6, 127.5, 127.4, 127.3, 127.2, 126.7, 126.5, 126.4, 126.3, 126.2, 126.1, 126.0, 125.9, 125.8, 125.7, 125.5, 124.6, 124.0, 113.3, 113.2, 100.3, 83.1, 80.9, 79.7, 79.3, 76.1, 75.9, 74.8, 74.4, 74.3, 71.9, 71.7, 70.8, 69.9, 69.6, 68.7, 62.3, 60.4, 54.6, 40.0, 33.9, 33.5, 26.8, 26.1, 26.3, 25.1, 25.0, 23.3, 17.8, 17.7, 16.2, 15.8, 14.4, 13.2, 11.8, 10.3, -2.2, -2.5, -5.5, -5.6; ESIHRMS *m/z* = 2019.8322 $[M+Na]^+$. $C_{115}H_{138}O_{20}NaSi_2SCl_2$ requires 2019.8383.

(3*S*,4*S*,6*R*)-3-(Isobutyryloxy)-2,2-dimethyl-5-(naphthalen-2-ylmethoxy)-6-(phenylthio)tetrahydro-2H-pyran-4-yl picolinate 41. To a stirred solution of previously described **32** (230 mg, 0.48 mmol) in anhydrous CH_2Cl_2 (5 mL, 0.095 M), under argon atmosphere, were successively added at r.t. picolinic acid (80 mg, 0.65 mmol, 1.36 eq.), DCC (148 mg, 0.72 mmol, 1.5 eq.) and DMAP (12 mg, 0.096 mmol, 0.2 eq.). After 24h at r.t., the reaction mixture was diluted with CH_2Cl_2 (10 mL) and the solid was filtered off. The filtrate was washed with aq. $NaHCO_3$ (15 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography (SiO_2, Hept/EtOAc : 80/20 to 60/40) to afford **41** (240 mg, 0.41 mmol, 86%) as an amorphous solid. $[\alpha]^{22}_{D}$ +34.8 (*c* 2.40, $CHCl_3$); FT-IR (neat) ν max 2978, 2935, 2876, 1739, 1584, 1469, 1439, 1388, 1369, 1303, 1290, 1242, 1151, 1125, 1088, 1044, 993, 945, 922, 857, 820, 745, 701 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 8.77 (d, *J* = 4.0 Hz, 1H), 8.01 (d, *J* = 7.5 Hz, 1H), 7.83-7.71 (m, 2H), 7.68-7.62 (m, 2H), 7.60-7.57 (m, 2H), 7.52 (ap. s, 1H), 7.49-7.36 (m, 4H), 7.30-7.27 (m, 3H), 5.64 (dd, *J* = 6.0 and 3.5 Hz, 1H), 5.44 (d, *J* = 7.0 Hz, 1H), 5.28 (d, *J* = 6.0 Hz, 1H), 4.68 (s, 2H), 3.97 (dd, *J* = 7.0 and 3.5, 1H), 2.44 (septet, *J* = 7.0 Hz, 1H), 1.55 (s, 3H), 1.37 (s, 3H), 1.04 (d, *J* = 7.0 Hz, 3H), 0.98 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 175.5, 167.7, 149.9, 147.1, 137.1, 134.5, 133.7, 133.0, 132.4, 128.9, 128.1, 127.9, 127.6, 127.5, 127.3, 127.0, 126.2, 126.0, 125.9, 125.2, 81.5, 76.9, 73.4, 72.5, 71.9, 69.7, 34.0, 25.1, 25.0, 18.7; ESIHRMS *m/z* = 586.2267 $[M+H]^+$. $C_{34}H_{36}O_6NS$ requires 586.2263.

(3*S*,4*S*,5*S*,6*R*)-3-(isobutyryloxy)-2,2-dimethyl-5-(naphthalen-2-ylmethoxy)-6-(phenylsulfinyl)tetrahydro-2*H*-pyran-4-yl picolinate 42. To a stirred solution of previously the described **41** (0.278 g, 0.475 mmol) and $NaHCO_3$ (48 mg, 0.57 mmol, 1.2 eq.) in DCM (10 mL, 0.05 M), was added at -78 °C *m*-CPBA (75%, 0.119 g, 0.52 mmol, 1.05 eq.). After stirring for 3 h at -78 °C, the reaction mixture was quenched with a 1/1 (v/v) mixture of aq. saturated $NaHCO_3$ and aq. saturated $Na_2S_2O_3$ (10 mL). The organic layer was separated, the aqueous phase was extracted with DCM (2*15 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (SiO_2, Hept/EtOAc : 70/30 to 50/50) to give the expected product **42** (0.255 g, 0.42 mmol, 89%) as an amorphous white solid (3/7 mixture of diastereomers). Minor diastereomer : $[\alpha]^{22}_{D}$ +99.4 (*c* 5.2, $CHCl_3$); FT-IR (neat) ν max 3059, 2975, 2933, 2876, 1736, 1585, 1469, 1447, 1370, 1304, 1242, 1148, 1123, 1072, 1045, 993, 858, 820, 746 cm-1; ^1H NMR ($CDCl_3$, 300 MHz) δ 8.72-8,67 (m, 1H), 7.98 (d, *J* = 7.5 Hz), 7.76 (td, *J* = 2.0 and 7.5 Hz, 1H), 7.72-

7.62 (m, 4H), 7.61-7.55 (m, 2H), 7.46-7.32 (m, 7H), 5.48 (dd, *J* = 3.5, 6.0 Hz, 1H), 5.20 (d, *J* = 6.0 Hz, 1H), 4.73 (d, 1H, *J* = 11.5 Hz), 4.68 (d, 1H, *J* = 11.5 Hz), 4.61 (d, *J* = 7.0 Hz, 1H), 4.20 (dd, *J* = 3.5 and 7.0 Hz, 1H), 2.49 (septet, *J* = 7.0 Hz, 1H), 1.33 (s, 3H), 1.21 (s, 3H), 1.08 (d, *J* = 7.0 Hz, 3H), 1.08 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 175.7, 163.7, 150.1, 147.2, 140.4, 136.8, 134.0, 133.1, 133.0, 131.2, 128.8, 128.2, 127.9, 127.6, 127.0, 126.2, 126.0, 125.4, 125.2, 89.9, 77.6, 72.6, 71.6, 70.1, 70.0, 33.9, 24.6, 24.2, 18.9, 18.8; ESIHRMS *m/z* = 602.2190 $[M+H]^+$. $C_{34}H_{36}O_7NS$ requires 602.2212. Major diastereomer : $[\alpha]^{22}_D$ −15.5 (*c* 6, $CHCl_3$); FT-IR (neat) ν max 3059, 2975, 2933, 2876, 1736, 1585, 1469, 1447, 1370, 1304, 1242, 1148, 1123, 1072, 1045, 993, 858, 820, 746 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz,) δ 8.76 (d, *J* = 4.0 Hz, 1H), 8.01 (d, *J* = 7.5 Hz, 1H), 7.80-7.73 (m, 2H), 7.69-7.60 (m, 2H), 7.59-7.50 (m, 2H), 7.52 (ap. s, 1H), 7.49-7.38 (m, 4H), 7.37-7.30 (m, 3H), 5.74 (dd, *J* = 7.5, 3.5 Hz, 1H), 5.38 (d, *J* = 7.5 Hz, 1H), 4.88 (d, *J* = 5.0 Hz, 1H), 4.63 (d, 1H, *J* = 12.0 Hz), 4.59 (d, 1H, *J* = 12.0 Hz), 4.31-4.24 (m, 1H), 2.44 (septet, *J* = 7.0 Hz, 1H), 1.51 (s, 3H), 1.39 (s, 3H), 1.07 (d, *J* = 7.0 Hz, 3H), 1.02 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 175.6 (*C*O), 163.6, 150.1, 147.3, 140.7, 136.8, 134.5, 133.0, 132.9, 131.2, 128.8, 128.1, 127.9, 127.6, 127.0, 126.9, 126.0, 125.9, 125.4, 125.2, 93.2, 78.0, 71.9, 71.4, 70.9, 69.4, 34.0, 25.6, 24.3, 18.8, 18.7; ESIHRMS: *m/z* = 602.2190 $[M+H]^+$. $C_{34}H_{36}O_7NS$ requires 602.2212.

(3*S*,4*S*,5*S*,6*R*)-4-hydroxy-6-(((1*S*,2*S*,5*S*)-2-isopropyl-5-methylcyclohexyl)oxy)-2,2-dimethyl-5-(naphthalen-2-ylmethoxy)tetrahydro-2*H*-pyran-3-yl isobutyrate-methane 43. A mixture of the glycosyl donor **42** (50 mg, 0.083 mmol, 1.3 eq.), acceptor **33** (10 mg, 0.064 mmol, 1 eq.), 2,6-di-terbutyl-4-methylpiridine (40 mg, 0.192 mmol, 3 eq.) and freshly activated 4Å MS (150 mg) in CH_2Cl_2 (6.4 mL) were stirred at r.t. for 1 h. The mixture was then cooled to at -70°C before adding Tf_2O (16 µL, 0.096 mmol, 1.5 eq.). After stirring for 20 min at −70°C, the reaction mixture was allowed to warm to -60°C and was quenched with NEt_3 (27 µL). An aq. saturated $NaHCO_3$ (10 mL) and CH_2Cl_2 (10 mL) were added. After filtration on Celite®, the aqueous phase was extracted with CH_2Cl_2 (2x15 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by preparative TLC (SiO_2, Hept/EtOAc : 55/45) to give the expected product **43** (27 mg, 0.042 mmol, 66%, β-anomer) as an amorphous white solid. $[\alpha]^{22}_D$ = −4.4 (*c* 0.34, $CHCl_3$); FT-IR (neat) ν max 2957, 2923, 1740, 1060 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.68-8.65 (m, 1H), 7.81 (d, *J* = 8.0 Hz, 1H), 7.69 (s, 1H), 7.67-7.58 (m, 3H), 7.49 (d, *J* = 8.0 Hz, 1H), 7.44-7.33 (m, 5H), 5.64 (d, *J* = 10.5 Hz, 1H), 5.24 (dd, *J* = 3.0 and 10.5 Hz, 1H), 5.08 (d, *J* = 13.0 Hz, 1H), 4.92 (bs, 1H), 4.74 (d, *J* = 13.0 Hz, 1H), 4.15-4.11 (m, 1H), 3.49 (td, *J* = 4.5 and 10.5 Hz), 2.50-2.37 (m, 2H), 2.08-1.97 (m, 1H), 1.74-1.64 (m, 3H), 1.34 (s, 3H), 1.30 (s, 3H), 1.04 (d, *J* = 7.0 Hz, 3H), 0.99-0.90 (m, 10H), 0.83 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 176.0, 163.7, 150.0, 146.9, 136.8, 136.1, 133.1 132.7, 127.8, 127.6, 127.5, 126.9, 126.8, 126.4, 125.7, 125.4, 125.3, 93.4, 77.5, 77.2, 75.0, 72.7, 71.6, 48.1, 40.0, 34.4, 34.0, 31.5, 28.1, 25.1, 23.0, 22.3, 21.1, 19.1, 18.9, 18.8, 15.8; $^1J_{C\text{-}1,H\text{-}1}$ of 155 Hz; ESIHRMS *m/z* = 632.3482 $[M+H]^+$. $C_{38}H_{50}NO_7$ requires 632.3487.

(3*S*,4*S*,5*S*,6*R*)-6-(((3*R*,4*S*,7*S*,*E*)-4-Ethyl-7-((4-methoxybenzyl)oxy)-6-methyl-1-(triethylsilyl)deca-5,9-dien-1-yn-3-yl)oxy)-3-(isobutyryloxy)-2,2-dimethyl-5-(naphthalen-2-ylmethoxy)tetrahydro-2H-pyran-4-yl picolinate 44 A mixture of the glycosyl donor **42** (51 mg, 0.085 mmol, 2.1 eq.) and acceptor **34** (18 mg, 0.041 mmol, 1 eq.) were co-evaporated with anhydrous toluene (3 x 1 mL). 2,6-di-terbutyl-4-methylpiridine (39 mg, 0.191 mmol, 4.7 equiv.), 4-allyl-1,2-dimethoxybenzene (29 µL, 0.171 mmol, 4.2 eq.), freshly activated 4Å MS (300 mg) and CH_2Cl_2 (4 mL) were added and the mixture was stirred at r.t. for 1 h. The mixture was then cooled to at -70°C before adding Tf_2O (13 µL, 0.096 mmol, 1.9 eq.) in CH_2Cl_2 (0.5 mL). After stirring for 2 h at -70°C, the reaction mixture was allowed to warm to -60°C for 1 h and was quenched with NEt_3 (30 µL). An aq. saturated $NaHCO_3$ (10 mL) and CH_2Cl_2 (10 mL) were added. After filtration on Celite®, the aqueous phase was extracted with CH_2Cl_2 (2x15 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by preparative TLC (SiO_2, Hept/EtOAc : 55/45) to give the expected product **44** (23 mg, 0.025 mmol, 62%, β-anomer) as a colorless oil. : $[\alpha]^{22}_D$ = −49.8 (*c* 0.62, $CHCl_3$); FT-IR (neat) ν max 2957, 2933, 2167, 1742, 1242, 1065, 729 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.64 (d, *J* = 4.0 Hz, 1H), 7.73 (d, *J* = 7.7 Hz, 1H), 7.63-7.58 (m, 3H), 7.54 (dd, *J* = 7.9, 1.4 Hz, 1H), 7.49 (d, *J* = 8.5 Hz, 1H), 7.40-7.30 (m, 4H), 7.24 (d, *J* = 8.5 Hz, 2H), 6.81 (d, *J* = 8.5 Hz, 2H), 5.76-5.59 (m, 1H), 5.61 (d, *J* = 10.5 Hz, 1H), 5.29-5.21 (m, 2H), 5.20 (ap. s, 1H), 5.09 (d, *J* = 12.6 Hz, 1H), 5.07-4.96 (m, 2H), 4.66 (d, *J* = 12.6 Hz, 1H), 4.47 (d, *J* = 11.7 Hz, 1H), 4.37 (d, *J* = 7.0 Hz, 1H), 4.23-4.19 (m, 2H), 3.75 (s, 3H), 3.71 (t, *J* = 7.1 Hz, 1H), 2.78 (m, 1H), 2.50-2.36 (m, 2H), 2.30-2.16 (m, 1H), 1.90-1.82 (m, 1H), 1.70 (d, *J* = 0.7 Hz, 3H), 1.38 (s, 3H), 1.33 (s, 3H), 1.29-1.21 (m, 1H), 1.03 (d, *J* = 7.0 Hz, 3H), 1.00 (t, *J* = 7.9 Hz, 9H), 0.95 (d, *J* = 7.0 Hz, 3H), 0.85 (t, *J* = 7.4 Hz, 3H), 0.6 (q, *J* = 7.9 Hz, 6H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 176.0, 158.9, 149.7, 148.2, 137.0, 136.9, 135.9, 135.1, 133.0, 132.7, 130.8, 129.5, 129.2, 127.9, 127.8, 127.5, 126.9, 126.7, 126.2, 125.7, 125.5, 125.3, 116.2, 113.6, 104.2, 94.9, 89.3, 83.7, 76.9, 75.2, 73.9, 73.3, 72.5, 71.4, 69.1,

55.2, 44.6, 38.4, 34.1, 28.1, 24.4, 19.1, 18.9, 18.7, 11.7, 11.5, 7.5, 4.3; $^{1}J_{C\text{-}1,H\text{-}1}$ of 154 Hz; ESIHRMS *m/z* = 918.4912 $[M+H]^+$. $C_{55}H_{72}NSiO_9$ requires 918.4976.

(3*S*,4*S*,5*S*,6*R*)-6-(((2*S*,4*E*,6*E*,8*R*,9*S*,10*E*,12*S*,14*E*,16*E*)-17-((((2*R*,3*S*,4*S*,5*R*,6*R*)-4-((*tert*-butyldimethylsilyl)oxy)-5-((3,5-dichloro-2-ethyl-4,6-bis(naphthalen-2-ylmethoxy)benzoyl)oxy)-3-methoxy-6-methyltetrahydro-2*H*-pyran-2-yl)oxy)methyl)-9-ethyl-12-((4-methoxybenzyl)oxy)-2-((*R*)-1-((4-methoxybenzyl)oxy)ethyl)-5,7,11-trimethyl-18-oxooxacyclooctadeca-4,6,10,14,16-pentaen-8-yl)oxy)-3-(isobutyryloxy)-2,2-dimethyl-5-(naphthalen-1-ylmethoxy)tetrahydro-2*H*-pyran-4-yl picolinate 45. A mixture of the glycosyl donor **35** (41 mg, 0.069 mmol, 2.1 eq.) and acceptor **26** (48 mg, 0.033 mmol, 1 eq.) were co-evaporated with anhydrous toluene (3 x 1 mL). 2,6-di-terbutyl-4-methylpiridine (32 mg, 0.154 mmol, 4.7 equiv.), 4-allyl-1,2-dimethoxybenzene (24 µL, 0.138 mmol, 4.2 eq.), freshly activated 4Å MS (440 mg) and DCM (2.5 mL) were added and the mixture was stirred at r.t. for 1 h. A solution of Tf_2O (10 µL, 0.154 mmol, 1.9 eq.) in DCM (0.1 mL) was then slowly added at −70 °C and the reaction mixture was stirred for 2 h. The temperature was slowly raised to -60 °C vover 1 h and quenched with NEt_3 (50 µL) and $NaHCO_3$ (10 mL). After filtration on Celite®, the aqueous phase was extracted with DCM (2x15 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by preparative TLC (SiO_2, Hept/EtOAc : 55/45) to give the expected product (43 mg, 0.022 mmol, 68%) as an amorphous white solid, which is contaminated with around 15% of what seems to be a C5-C4 *Z* isomer. $[\alpha]^{22}_D$ −24.5 (*c* 0.6, $CHCl_3$); FT-IR (neat) ν max 2932, 1739, 1704, 1512, 1244, 1124, 1105, 1065, 1036, 816 cm-1; ^{1}H NMR (CD_3CN, 500 MHz) δ 8.71-8.66 (m, 1H), 8.02-7.39 (m, 24H), 7.24-7.16 (m, 4H), 7.11 (d, *J* = 11.5 Hz, 1H), 6.85 (d, *J* = 8.0 Hz, 4H), 6.46 (dd, *J* = 11.5 and 14.5 Hz, 1H), 5.92 (ddd, *J* = 5.0, 9.5 and 14.5 Hz, 1H), 5.82 (s, 1H), 5.59-5.53 (m, 1H), 5.32-5.24 (m, 5H), 5.18 (d, *J* = 11.0 Hz, 1H), 5.12 (d, *J* = 10.0 Hz, 1H), 5.00 (d, *J* = 12.0 Hz, 1H), 4.94-4.83 (m, 3H), 4.78-4.70 (m, 1H), 4.54 (d, *J* = 11.0 Hz, 1H), 4.43-4.29 (m, 5H), 4.24 (d, *J* = 11.0 Hz, 1H), 4.13 (bs, 1H), 3.93-3.84 (m, 2H), 3.78 (dd, *J* = 3.0 and 10.0 Hz, 1H), 3.76-3.63 (m, 7H), 3.44-3.36 (m, 4H), 3.13-3.02 (m, 1H), 2.93-2.84 (m, 1H), 2.79-2.68 (m, 2H), 2.60-2.44 (m, 3H), 2.44-2.36 (m, 2H), 1.98-1.91 (m, 1H), 1.81 (s, 3H), 1.75 (s, 3H), 1.62 (s, 3H), 1.40-1.31 (m, 1H), 1.20 (t, *J* = 7.5 Hz, 3H), 1.18-1.13 (m, 6H), 1.11-1.05 (m, 6H), 0.96 (t, *J* = 7.0 Hz, 3H), 0.90-0.85 (m, 6H), 0.80 (s, 9H), 0.00 (s, 3H), -0.14 (s, 3H); ^{13}C NMR (CD_3CN, 125 MHz) δ 175.6, 166.8, 164.5, 163.6, 158.8, 152.9, 151.5, 149.7, 147.1, 143.7, 142.2, 139.5, 136.8, 136.1, 135.4, 134.1, 133.9, 133.4, 133.3, 133.0, 132.8, 132.7, 132.5 , 130.8, 130.7 (*Cq*), 128.7, 128.6, 127.8, 127.7, 127.6, 127.5, 127.4, 127.3, 127.2, 126.9, 126.6, 126.5, 126.3, 126.2, 126.1, 126.0, 125.7, 125.5, 125.4, 124.8, 124.5, 113.3, 113.2, 100.3, 96.0, 92.3, 80.9, 79.3, 77.0, 76.1 (CH_2), 75.9, 75.7, 74.8, 74.4, 74.3, 72.8, 72.0, 71.8, 71.3, 70.7, 69.9, 69.6, 62.3, 60.4, 54.6, 54.5, 40.9, 33.9, 33.5, 27.4, 26.8, 26.1, 25.5, 25.4, 17.8, 17.4, 16.3, 15.8, 14.3, 13.2, 12.7, 9.9, -5.5, -5.6; $^{1}J_{C1'\text{-}H1'\ (noviose)}$ = 155.8 Hz, $^{1}J_{C1''\text{-}H1''(rhamnose)}$ = 155.8 Hz; ESIHRMS *m/z* = 1958.8280 $[M+Na]^+$. $C_{113}H_{131}NO_{21}SiCl_2Na$ requires 1958.8258.

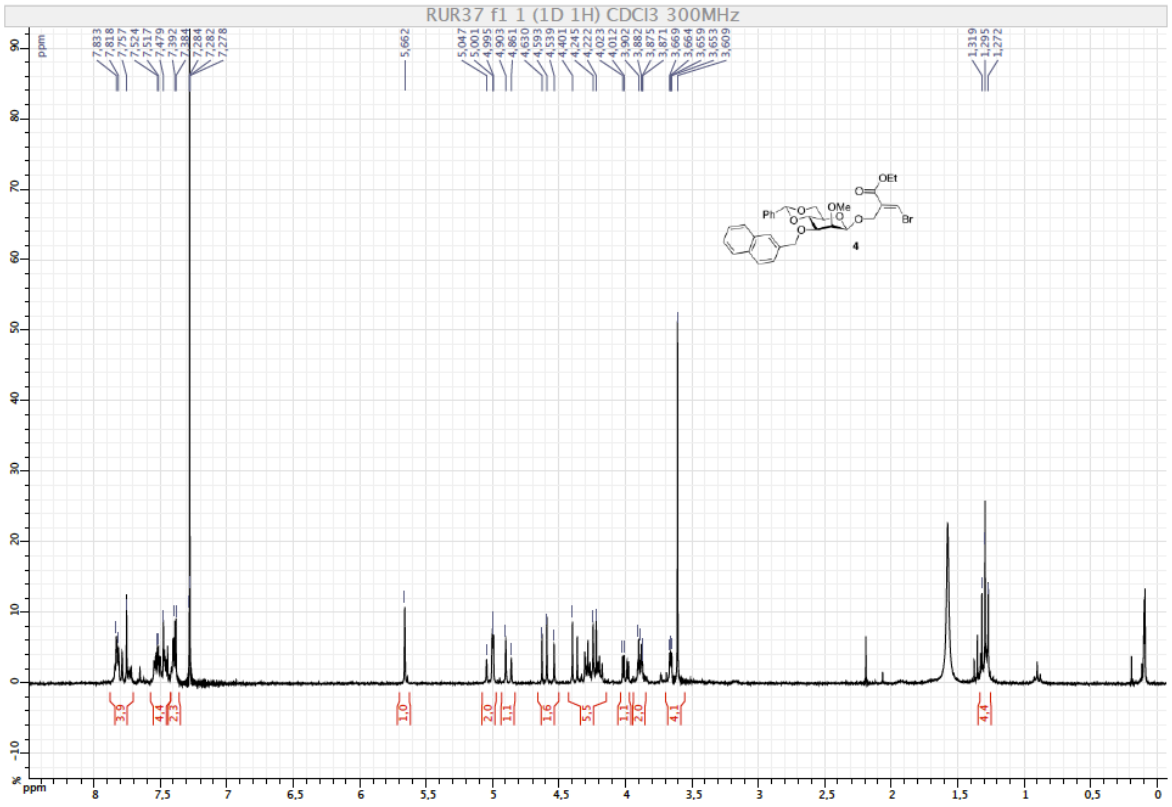
Final deprotection stages

(2*R*,3*S*,4*S*,5*S*,6*R*)-6-(((3*E*,5*E*,8*S*,9*E*,11*S*,12*R*,13*E*,15*E*,18*S*)-12-(((2*R*,3*S*,4*R*,5*S*)-3,4-dihydroxy-5-(isobutyryloxy)-6,6-dimethyltetrahydro-2*H*-pyran-2-yl)oxy)-11-ethyl-8-hydroxy-18-((*R*)-1-hydroxyethyl)-9,13,15-trimethyl-2-oxooxacyclooctadeca-3,5,9,13,15-pentaen-3-yl)methoxy)-4-hydroxy-5-methoxy-2-methyltetrahydro-2*H*-pyran-3-yl 3,5-dichloro-2-ethyl-4,6-bis(naphthalen-2-ylmethoxy)benzoate 46. To a stirred solution of previously described **45** (30 mg, 0.015 mmol) in anhydrous THF (1.5 mL, 0.01 M), under argon atmosphere, was added at $HF.NEt_3$ (0.25 mL, 1.5 mmol) and the reaction mixture was heated at 50 °C. After 24 h, $NaHCO_3$ (2 mL) was added and the reaction mixture was diluted with EtOAc (5 mL). The organic layer was separated, the aqueous phase was extracted with EtOAc (2x 5 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. To the crude residue in a 20/1 mixture of CH_2Cl_2/water (1 mL) was added at 0 °C, DDQ (24 mg, 0.107 mmol, 7 eq.). The reaction was stirred for 1 h at 0 °C then at r.t. 1 h 30. Saturated aq. $Na_2S_2O_3$ (2 mL) was added and the reaction mixture was diluted with CH_2Cl_2 (5 mL). The organic layer was separated and the aqueous phase was extracted with CH_2Cl_2 (2*5 mL). The combined organic extracts were washed with brine (2 mL) then dried over Na_2SO_4, filtered and concentrated under reduced pressure. To the crude residue in a 95/5 mixture of CH_2Cl_2/MeOH (2.2 mL) was added at 0 °C, $Cu(OAc)_2$ (3 mg, 0.1015 mmol, 1 eq.). The reaction was stirred for 30 min at 0 °C then at r.t. for 1 h. water (2 mL) was added and the reaction mixture was diluted with CH_2Cl_2 (2 mL). The organic layer was separated and the aqueous phase was extracted with CH_2Cl_2 (2 x 2 mL). The combined organic dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by preparative TLC (SiO_2, heptane/EtOAc : 30/70) to afford the desired product (15 mg, 0.011 mmol, 74%) as an amorphous solid, which is contaminated with around 15% of what seems to be a C5-C4 *Z* isomer. Both isomers can be separated using preparative HPLC with Luna *C18 5* µm *(250 x 21.2) 100Å,* AXIA packed, AcCN/water : 88/12 to 100/0

). $[\alpha]^{22}_{D}$ −53.7 (c 0.3, $CHCl_3$); FT-IR (neat) ν max 3476, 2974, 2934 1731, 1641, 1369, 1245, 1105, 1065, 1022 cm-1; ^{1}H NMR (CD_3CN, 500 MHz) δ 8.05 (m, 1H), 8.01-7.91 (m, 7H), 7.76 (dd, J = 1.0 and 7.5 Hz, 1H), 7.76 (dd, J = 1.0 and 8.5 Hz, 1H), 7.60-7.55 (m, 4H), 7.16 (d, J = 11.5 Hz, 1H), 6.50 (dd, J = 12.0 and 14.5 Hz, 1H), 5.88 (ddd, J = 4.5, 10.0 and 14.5 Hz, 1H), 5.79 (s, 1H), 5.53 (t, J = 8.0 Hz, 1H), 5.30 (d, J = 10.5 Hz, 1H), 5.27 (s, 2H), 5.16 (d, J = 10.5 Hz, 1H), 5.03 (d, J = 10.5 Hz, 1H), 4.90 (t, J = 10.0 Hz, 1H), 4.87 (d, J = 10.0 Hz, 1H), 4.70-4.66 (m, 1H), 4.65 (s, 1H), 4.48 (s, 1H), 4.47 (d, J = 11.5 Hz, 1H), 4.34 (d, J = 11.5 Hz, 1H), 4.16 (bs, 1H), 3.96 (h, J = 6.0 Hz, 1H), 3.89-3.84 (m, 1H), 3.69-3.63 (m, 2H), 3.78 (td, J = 3.0 and 10.0 Hz, 1H), 3.52 (s, 3H), 3.49 (d, J = 3.0 Hz, 1H), 3.38-3.30 (m, 1H), 3.19 (d, J = 10.0 Hz, 1H), 3.15 (d, J = 5.5 Hz, 1H), 3.19 (d, J = 3.5 Hz, 1H), 2.96-2.81 (m, 3H), 2.71 (d, J = 4.5 Hz, 1H), 2.70-2.55 (m, 4H), 2.40-2.31 (m, 3H), 1.98-1.91 (m, 1H), 1.77 (s, 3H), 1.73 (s, 3H), 1.63 (s, 3H), 1.29-1.20 (m, 1H), 1.22 (t, J = 7.5 Hz, 3H), 1.17 (d, J = 6.5 Hz, 3H), 1.17 (d, J = 6.5 Hz), 1.16 (d, J = 6.5 Hz, 3H), 1.13 (d, J = 6.5 Hz, 3H), 1.10 (s, 3H), 1.08 (s, 3H), 1.02 (d, J = 6.0 Hz, 3H), 0.87 (t, J = 7.5 Hz, 6H); **^{13}C NMR (CD_3CN, 125 MHz** δ 176.2, 167.0, 165.6, 163.6, 152.7, 150.7, 144.1, 142.2, 139.2, 135.9 135.1, 134.6, 133.6, 133.5, 133.0, 132.9, 132.8, 127.9, 127.7, 127.6, 127.4, 127.3, 127.0, 126.2, 126.1, 126.0, 125.7, 125.3, 124.3, 122.6, 121.5, 100.3, 96.0, 92.3, 80.5, 72.2, 76.5, 76.2, 74.8, 74.3, 72.6, 71.7, 71.3, 71.1, 69.2, 68.7, 66.8, 62.1, 60.7, 40.9, 36.0, 33.7, 27.3, 26.9, 25.2, 24.5, 18.8, 18.0, 17.8, 17.3, 16.8, 16.2, 14.0, 13.2, 12.6. $^1J_{C1'\text{-}H1'(noviose)}$ = 156.6 Hz, $^1J_{C1''\text{-}H1''(rhamnose)}$ = 156.6 Hz; **ESIHRMS** *m/z* = 1359.5396 $[M+Na]^+$. $C_{74}H_{90}O_{18}Cl_2Na$ requires 1359.5402.

Tiacumicin B. A stirred solution of **45** (19 mg, 0.014 mmol), *N*,*N*-dimethylbarbituric acid (18 mg, 0.114 mmol, 8 eq.), $Pd_2(dba)_3$ (5 mg, 0.006 mmol, 0.4 eq.), PPh_3 (6 mg, 0.023 mmol, 1.6 eq.) and pyridine (18 µl, 0.227 mmol, 16 eq.) in anhydrous DMF (1.4 mL, 0.01 M), under argon atmosphere was heated at 80 °C. After 2 h, aq. saturated NH_4Cl (1 mL) and EtOAc (2 mL) were added and the organic layer was separated. The organic phase was washed with water (1 x 2 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by preparative TLC (SiO_2, heptane/EtOAc : 20/80) and then by preparative HPLC with Upti-prep® *100Å silica, 5* µm, Hept/EtOAc : 30/70 to 20/80 to afford the desired product (11 mg, 0.010 mmol, 73%).

NMR Spectra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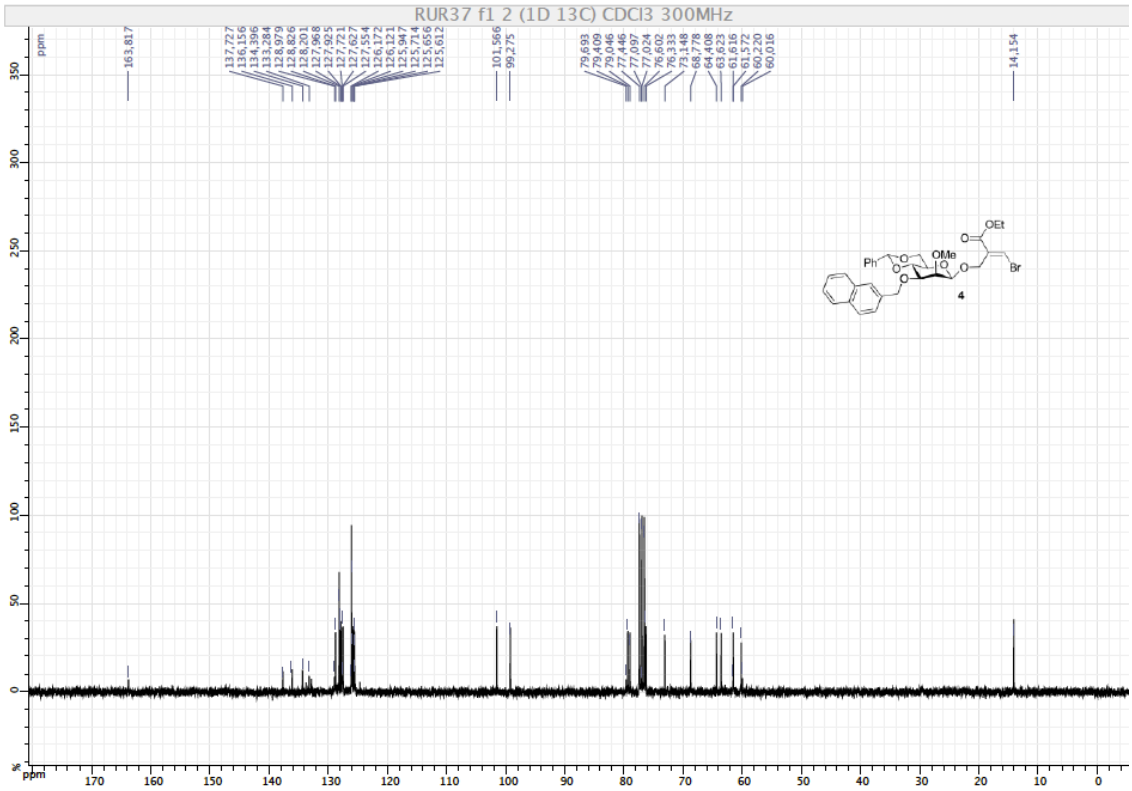
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OMe
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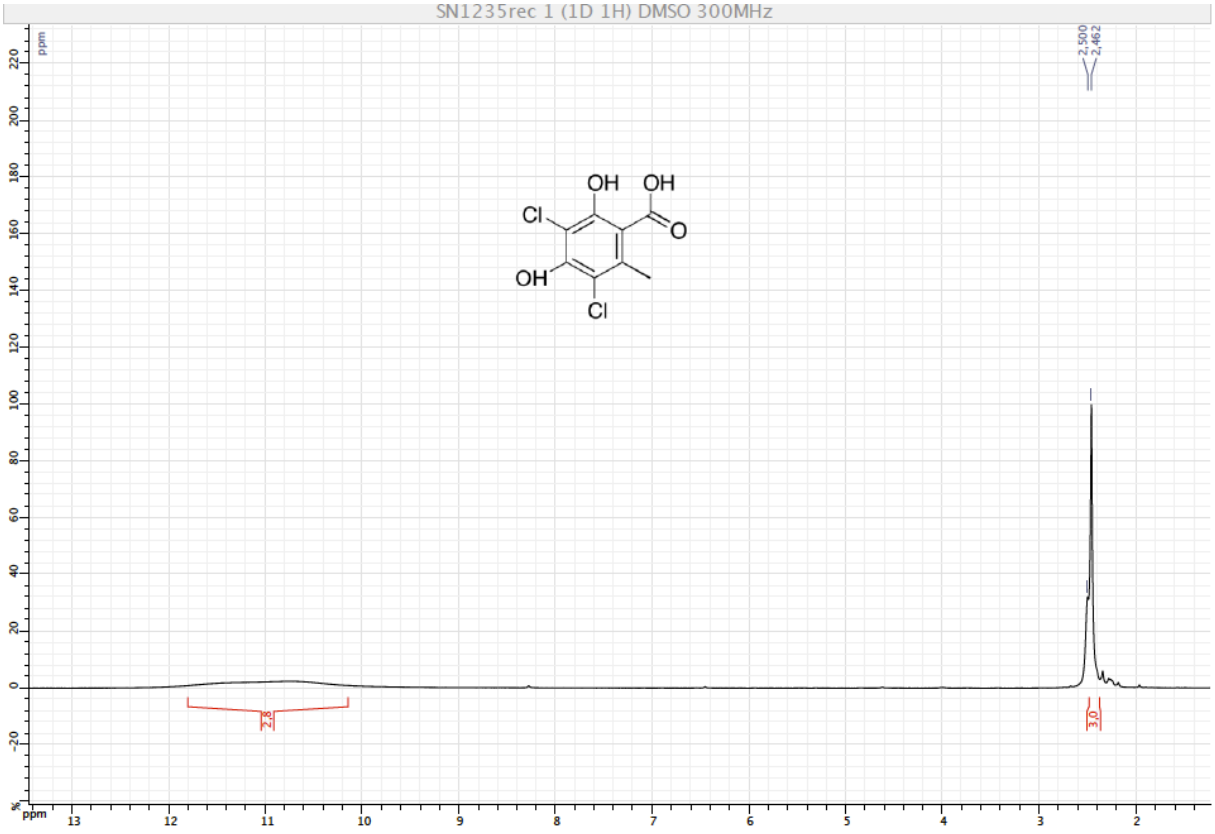
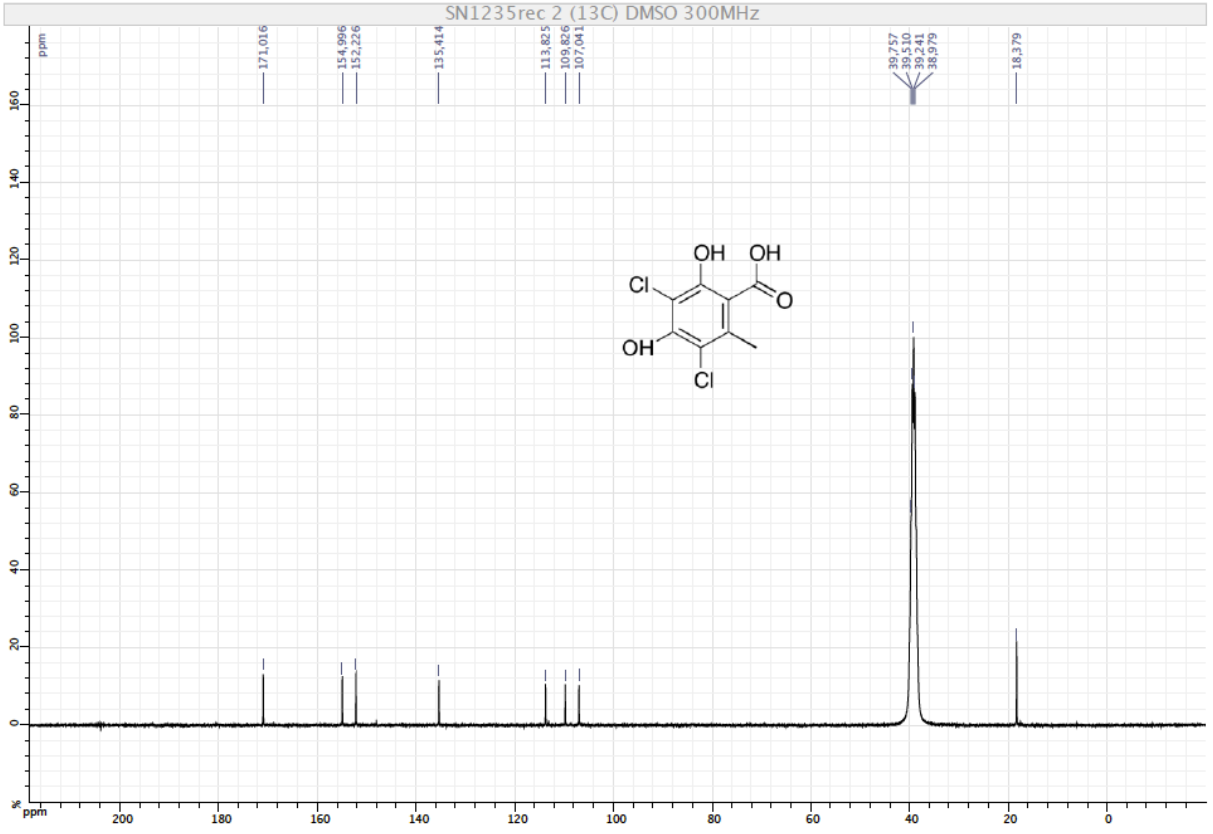
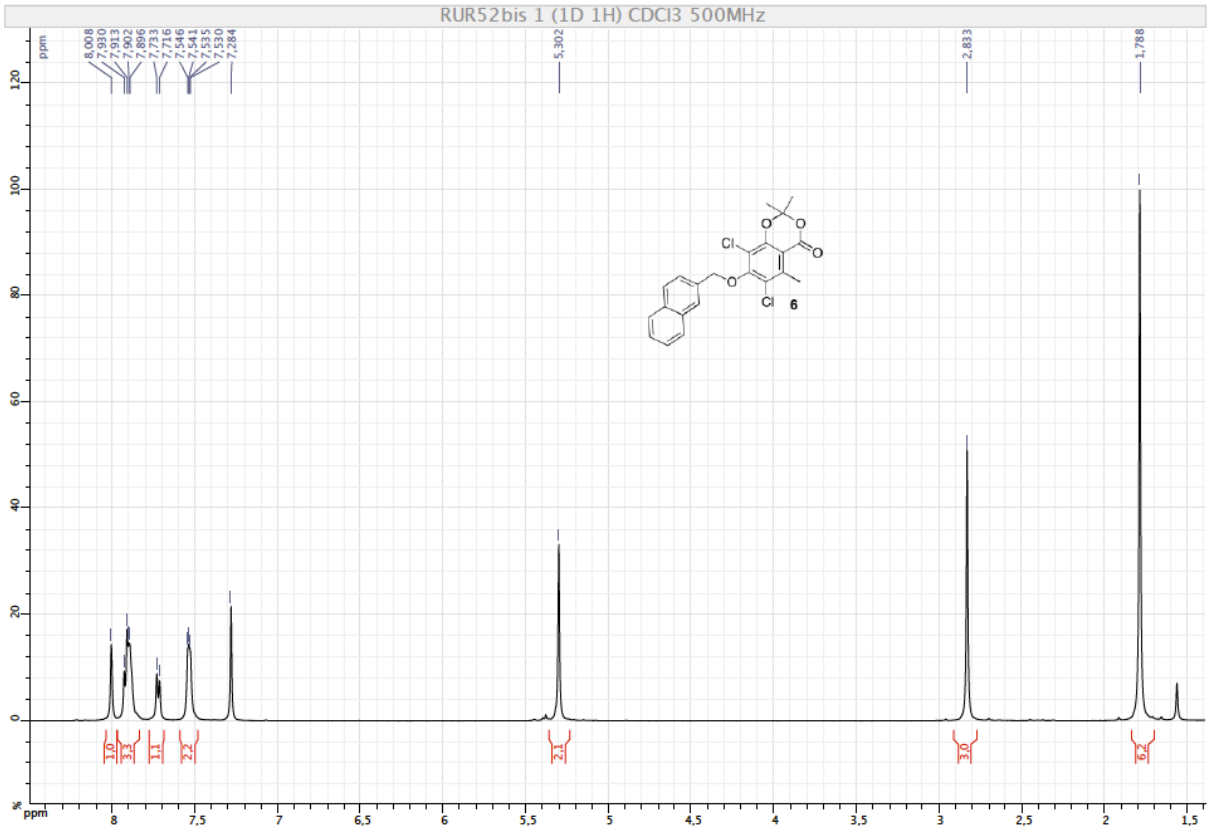
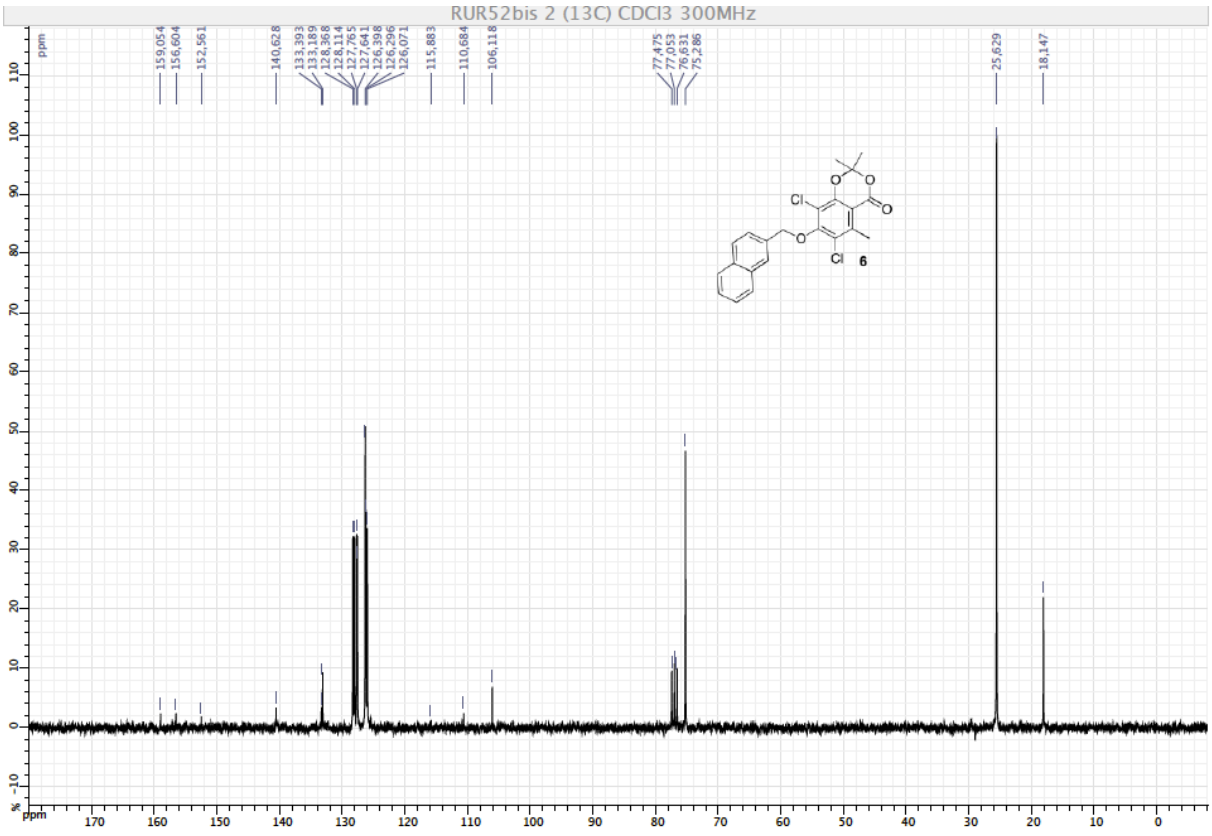
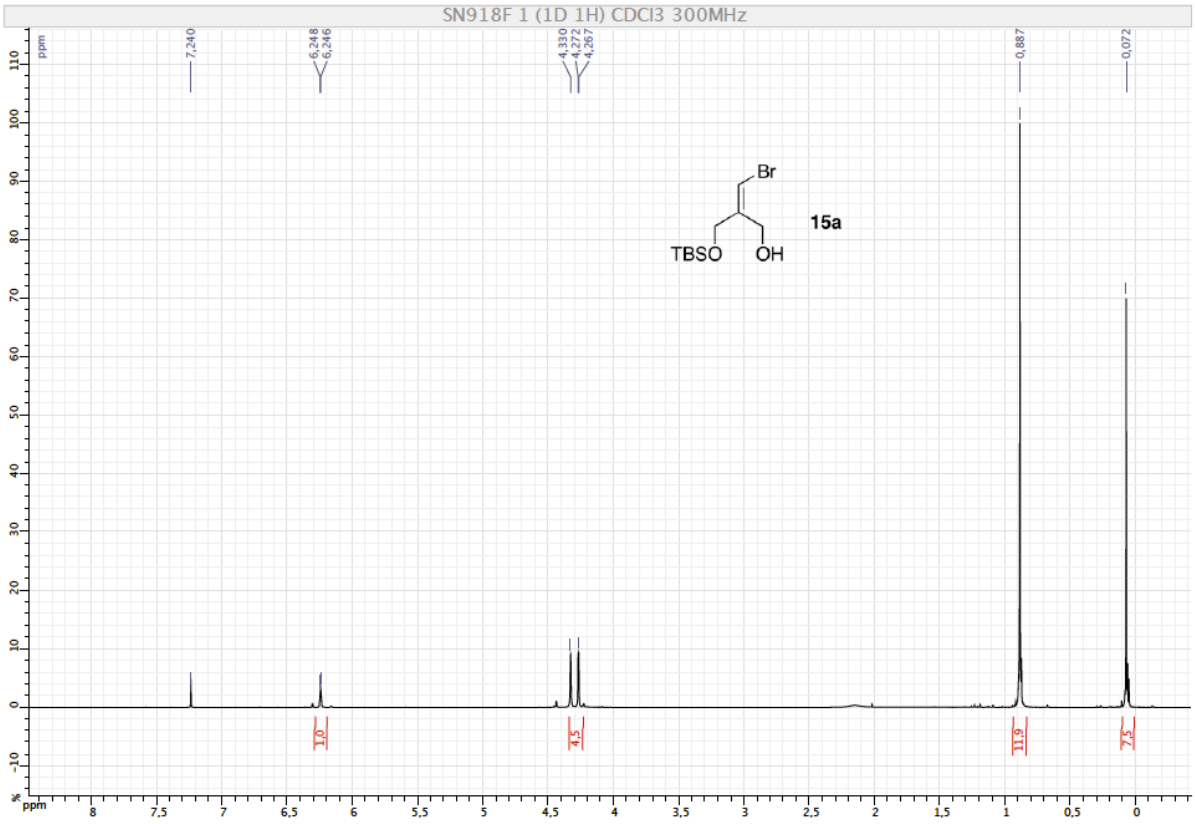
Br
4

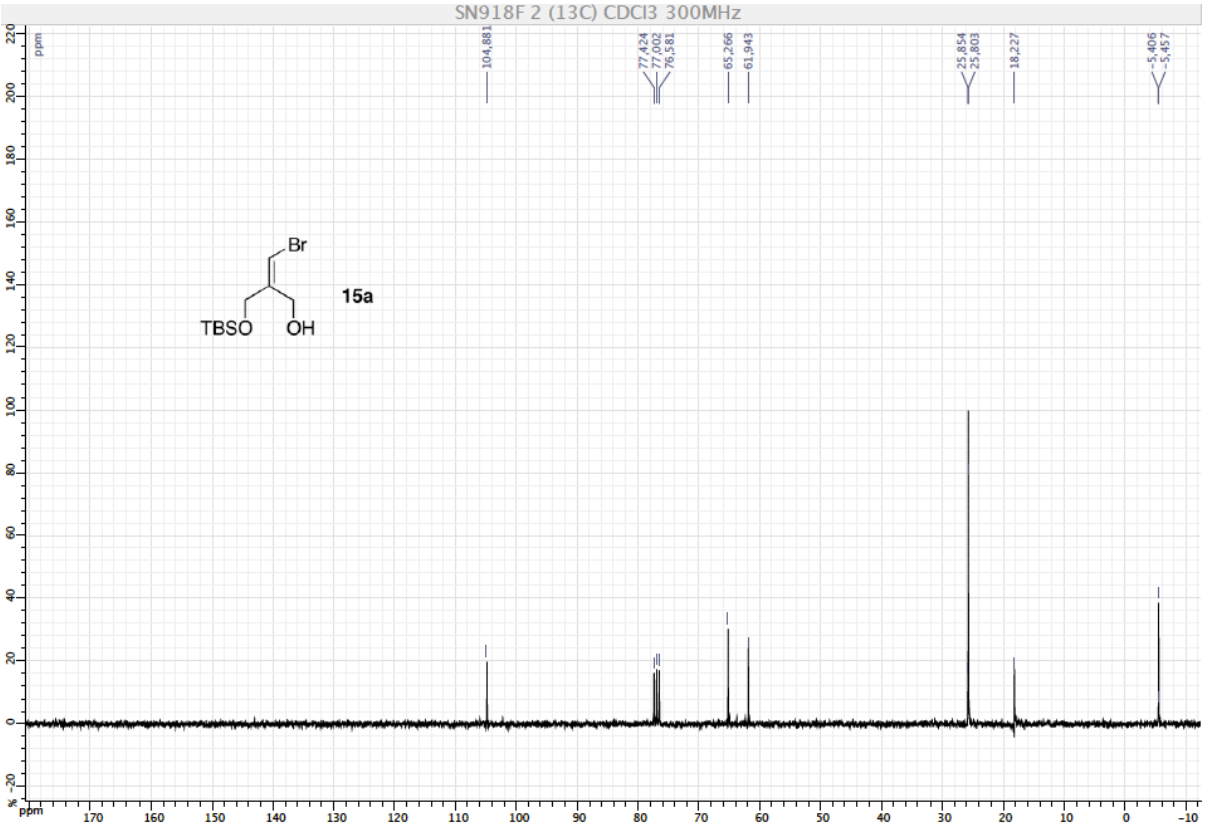

SN1235rec 1 (1D 1H) DMSO 300MHz
ppm
2,500
2,462
OH
OH
Cl
O
OH
Cl
2,8
3,0
13
12
11
10
9
8
7
6
5
4
3
2

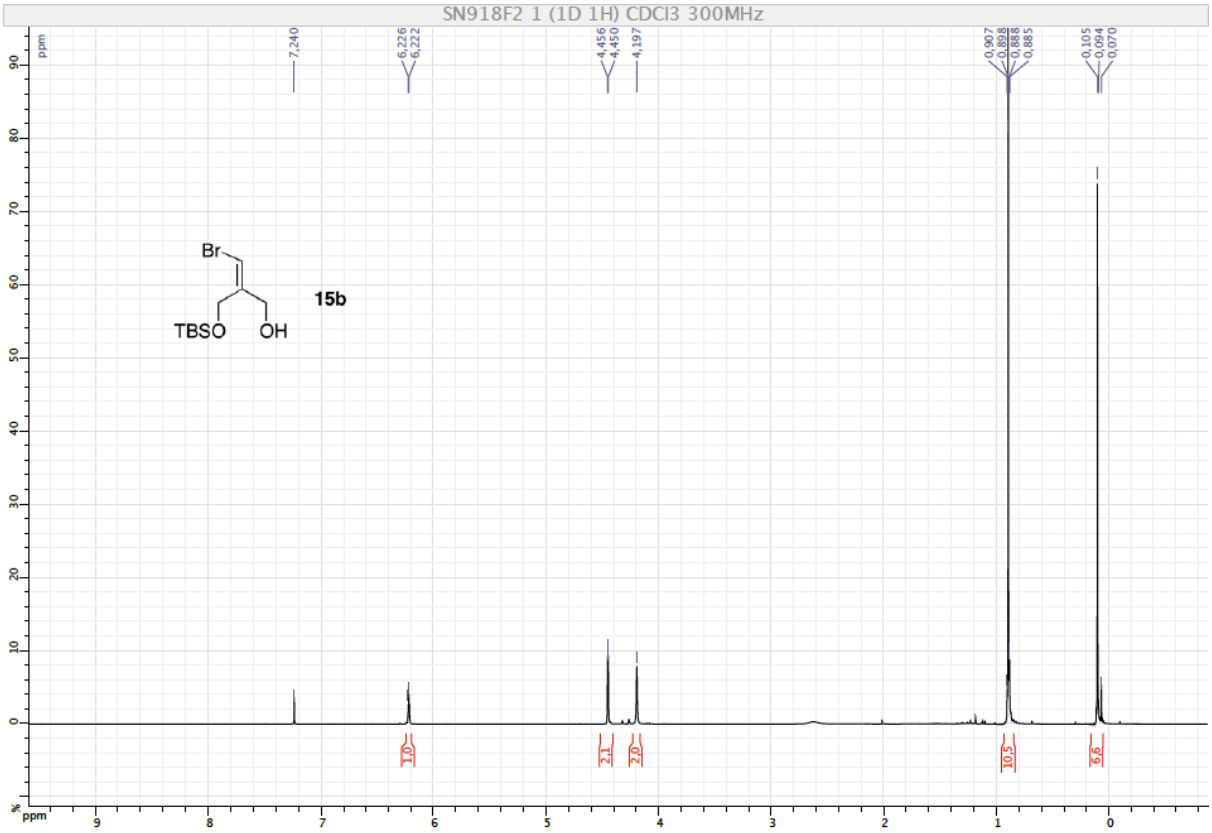

SN1235rec 2 (13C) DMSO 300MHz
ppm
171,016
154,996
152,226
135,414
113,825
109,826
107,041
39,757
39,510
39,341
38,879
18,379
OH
OH
Cl
O
OH
Cl
200
180
160
140
120
100
80
60
40
20
0

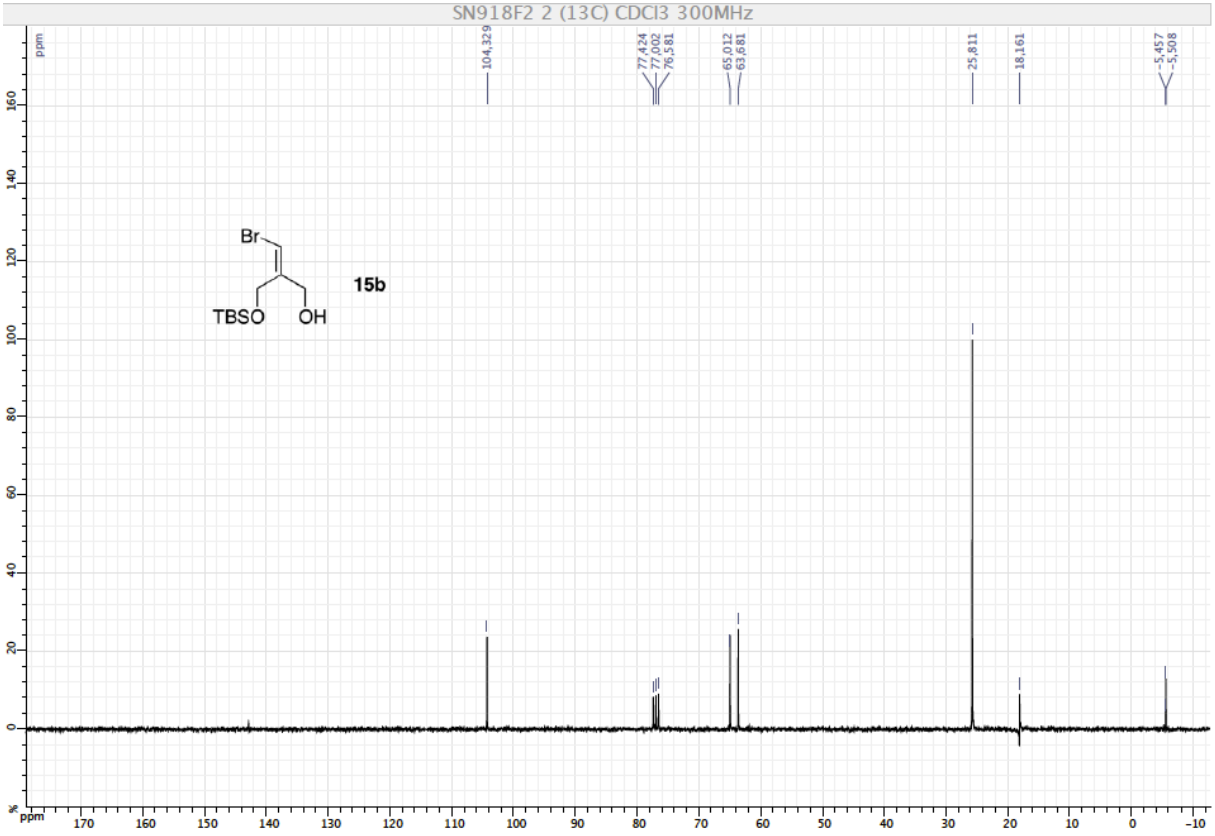

RUR52bis 1 (1D 1H) CDCl3 500MHz
8,008
7,930
7,913
7,902
7,896
7,733
7,716
7,546
7,541
7,535
7,530
7,284
5,302
2,833
1,788
1,0
3,3
1,1
2,2
2,1
3,0
6,2
6

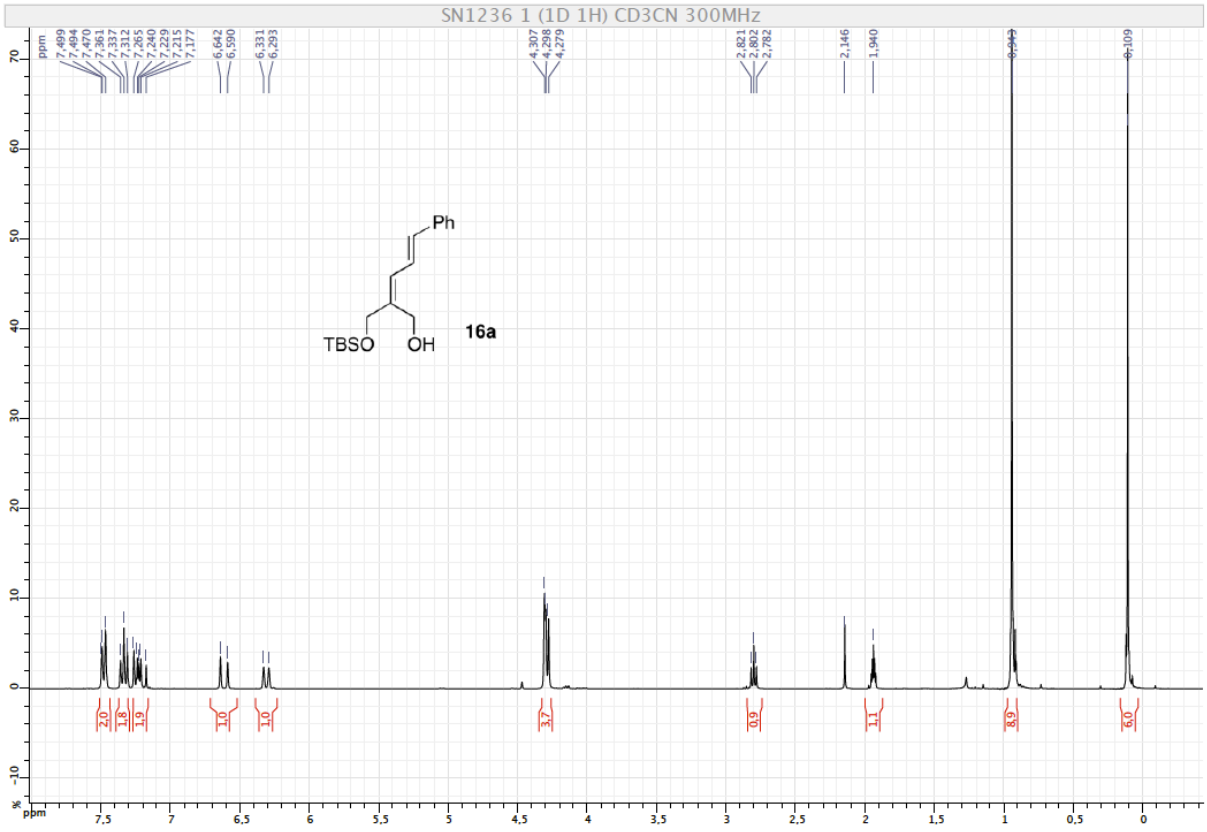

RUR52bis 2 (13C) CDCl3 300MHz
159,054
156,604
152,561
140,628
133,393
133,189
128,368
128,114
127,765
127,641
126,398
126,296
126,071
115,883
110,684
106,118
77,475
77,053
76,631
75,286
25,629
18,147
6

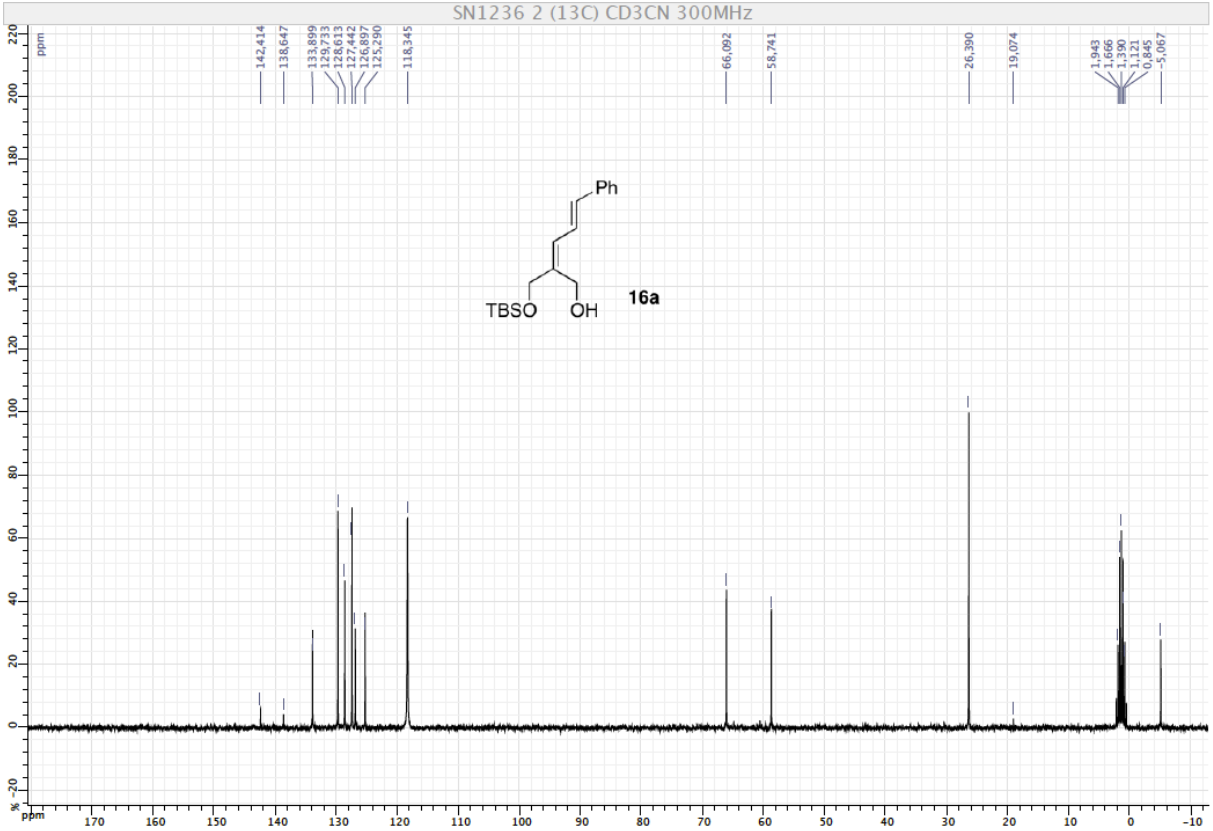

SN918F 1 (1D 1H) CDCl3 300MHz
7,240
6,248
6,246
4,330
4,272
4,267
0,887
0,072
Br
TBSO
OH
15a
1,0
4,5
11,9
7,5
ppm

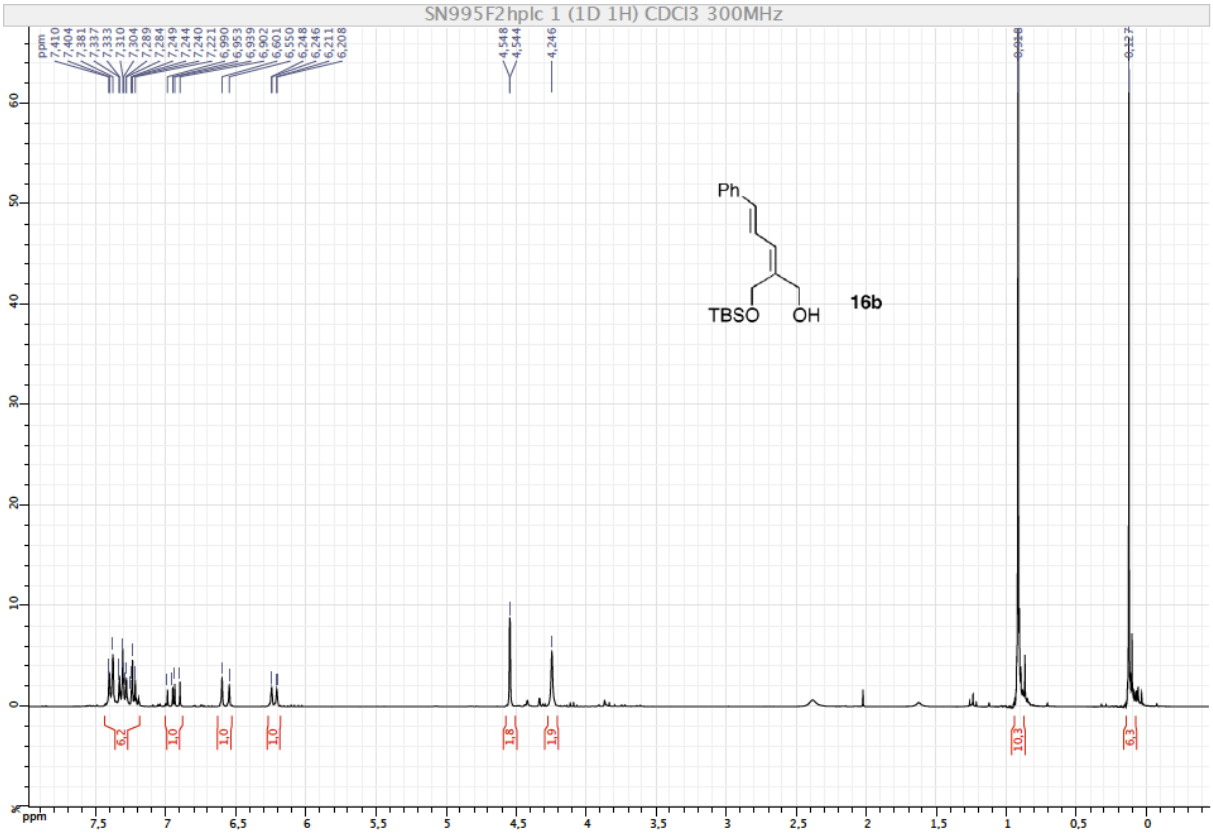

SN918F 2 (13C) CDCl3 300MHz
104,881
77,424
77,002
76,581
65,266
61,943
25,854
25,803
18,227
-5,406
-5,457
Br
TBSO
OH
15a
ppm

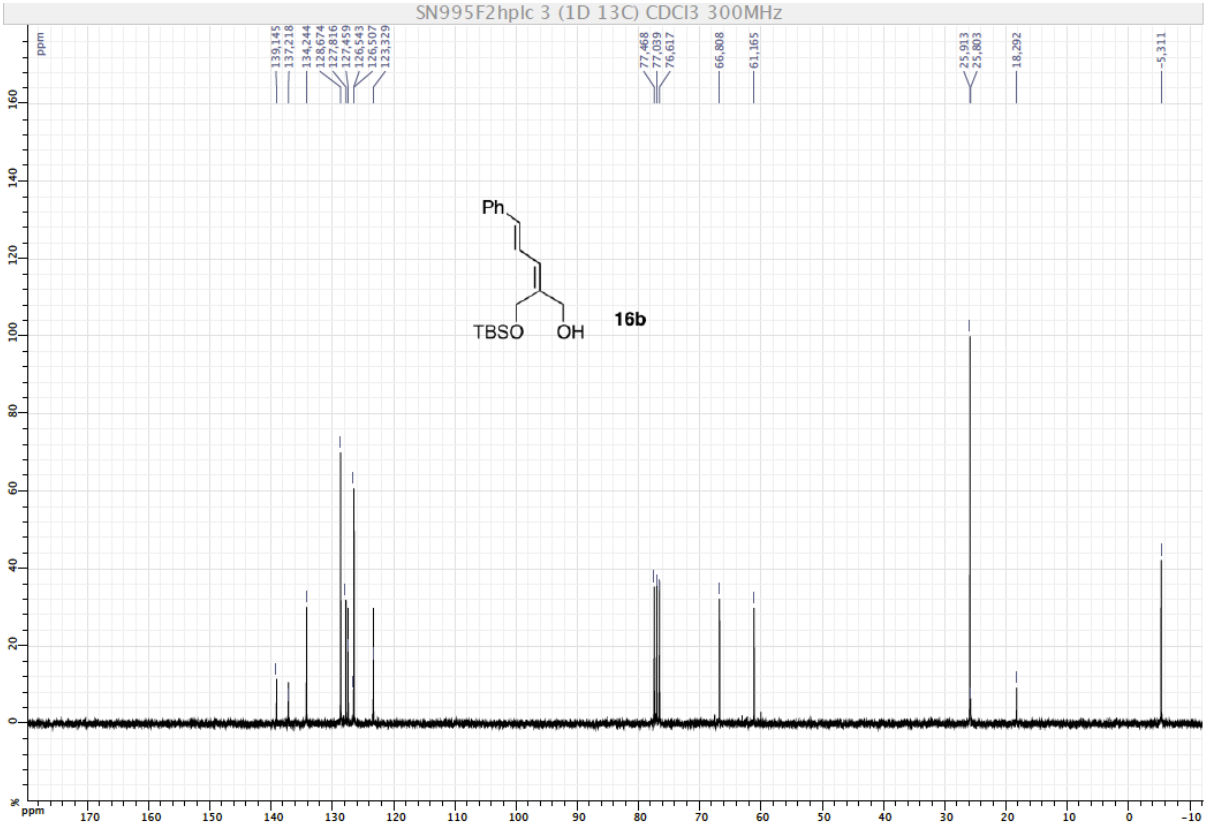

SN918F2 1 (1D 1H) CDCl3 300MHz
7,240
6,226
6,222
4,456
4,450
4,197
0,907
0,898
0,888
0,885
0,105
0,094
0,070
Br
TBSO
OH
15b
1,0
2,1
2,0
10,5
6,6
ppm

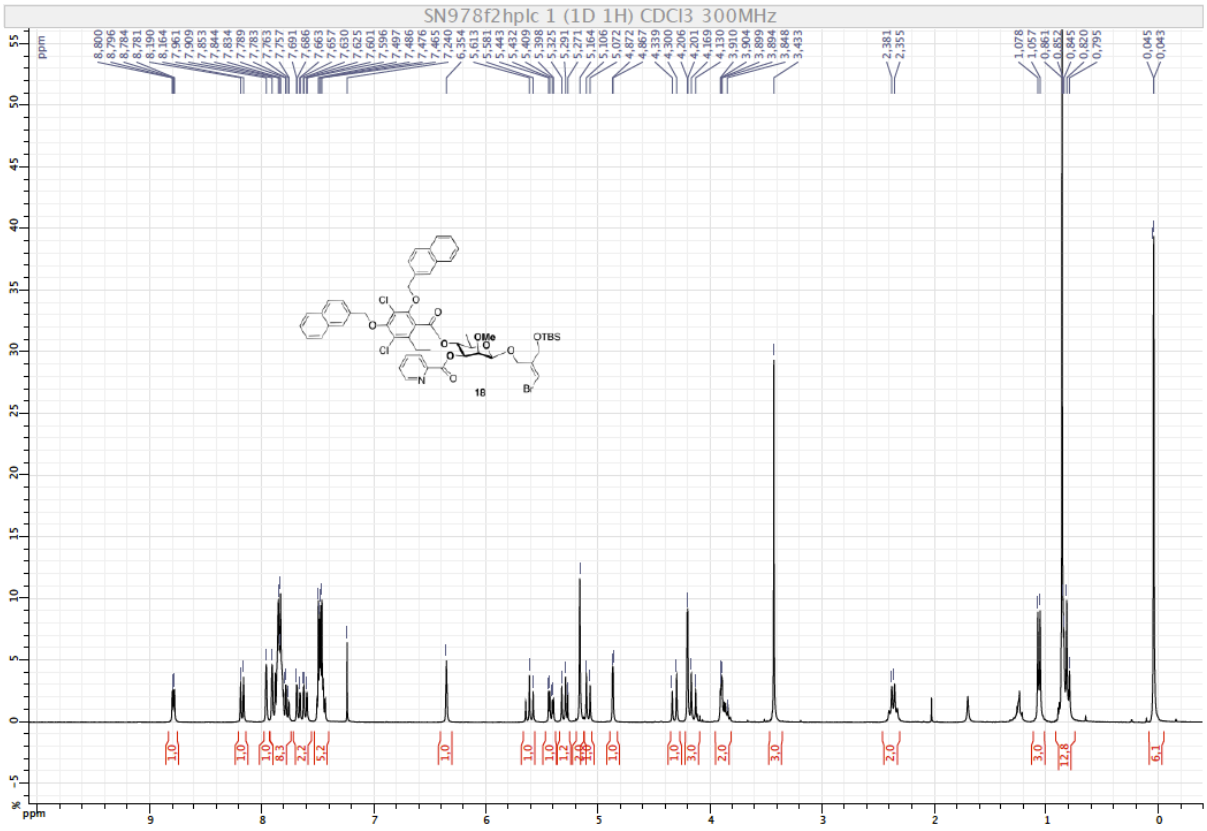

SN918F2 2 (13C) CDCl3 300MHz
104,329
77,424
77,002
76,581
65,012
63,681
25,811
18,161
-5,457
-5,908
Br
TBSO
OH
15b
ppm

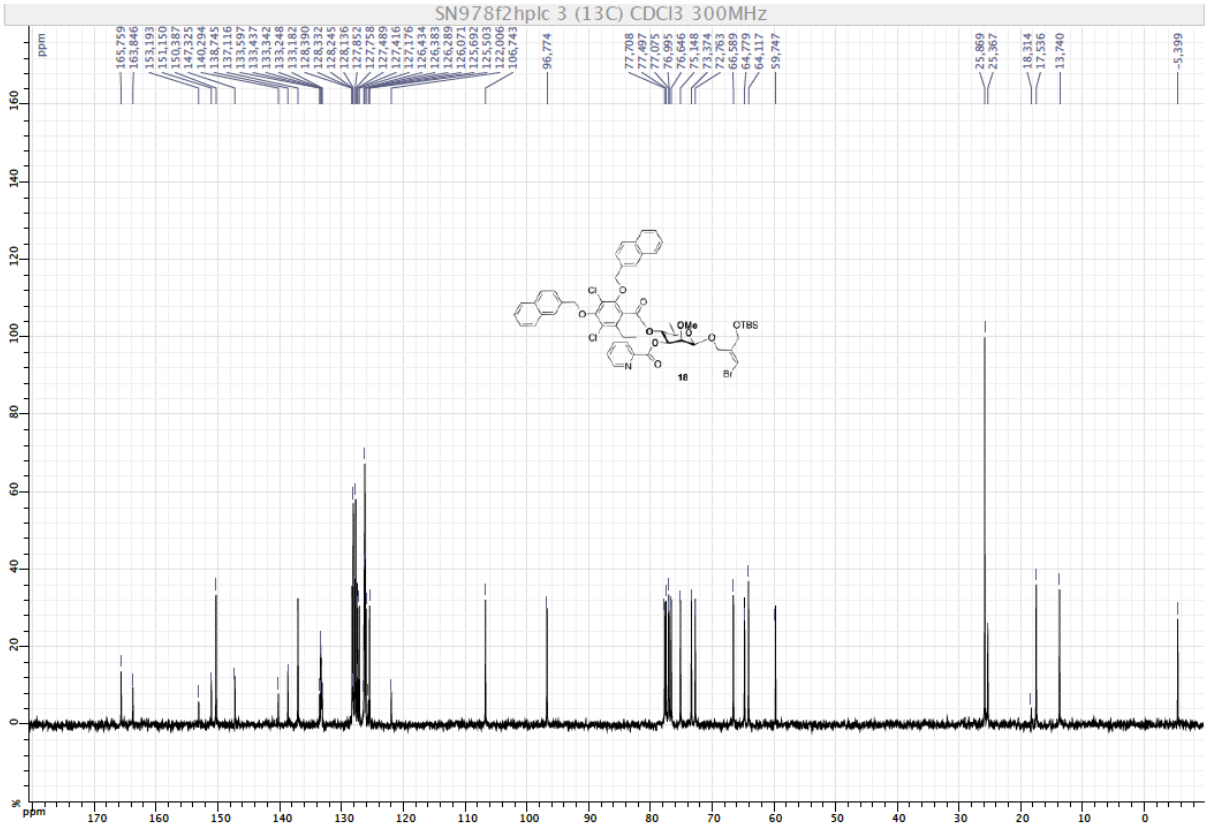

SN1236 1 (1D 1H) CD3CN 300MHz
Ph
TBSO
OH
16a

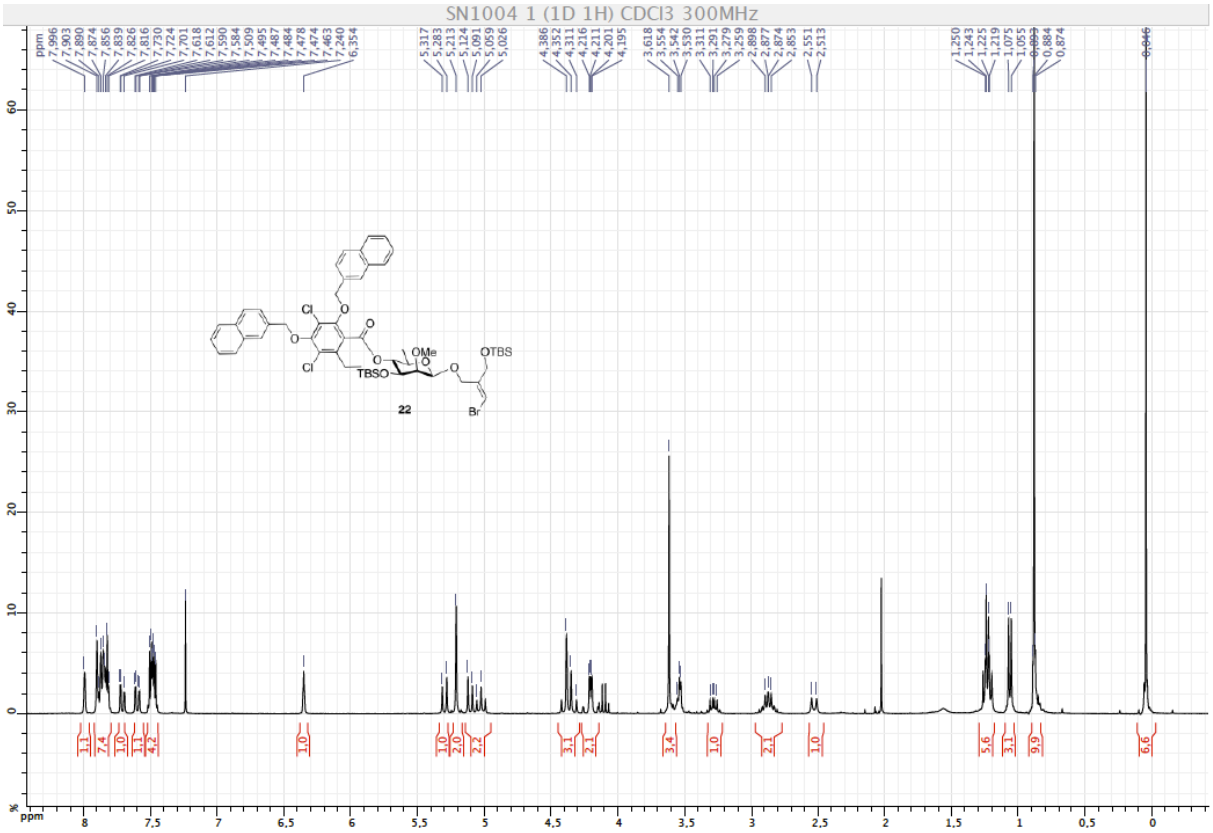

SN1236 2 (13C) CD3CN 300MHz
Ph
TBSO
OH
16a

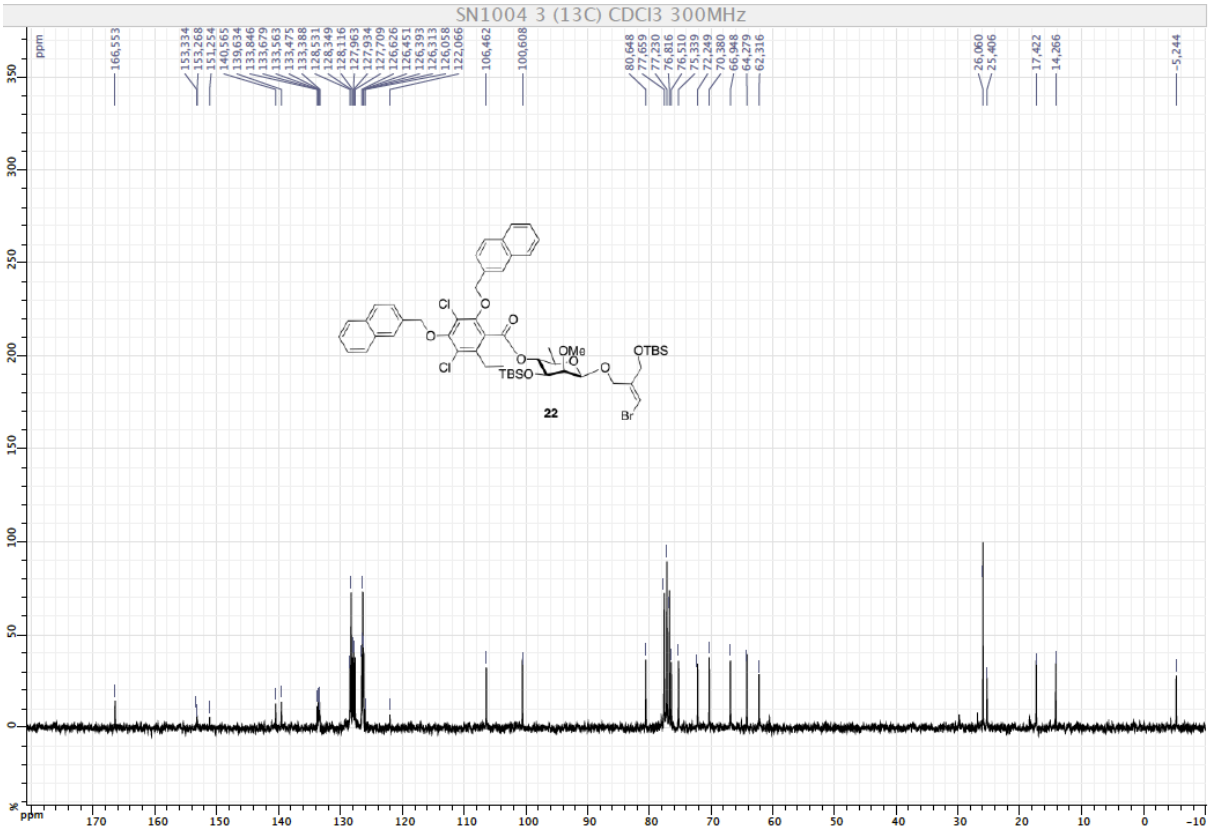

SN995F2hplc 1 (1D 1H) CDCl3 300MHz
Ph
TBSO
OH
16b

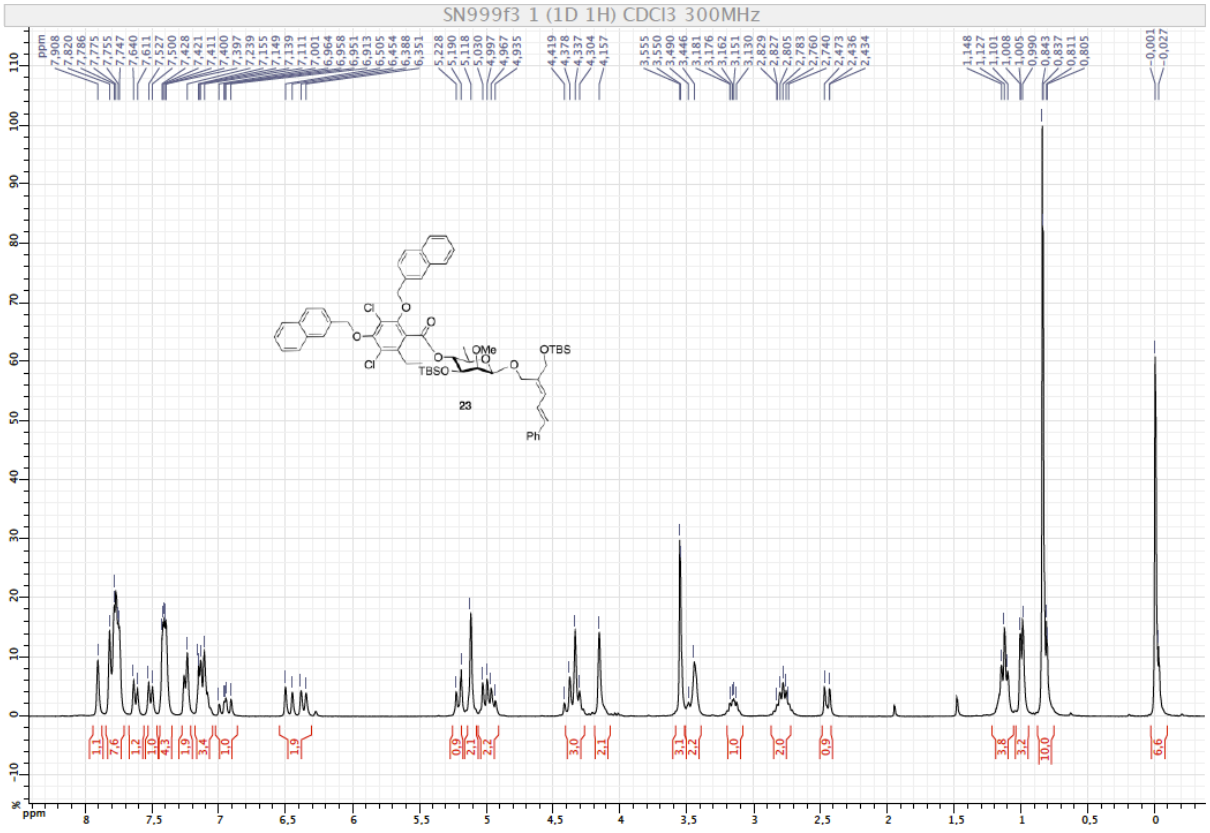

SN995F2hplc 3 (1D 13C) CDCl3 300MHz
Ph
TBSO
OH
16b

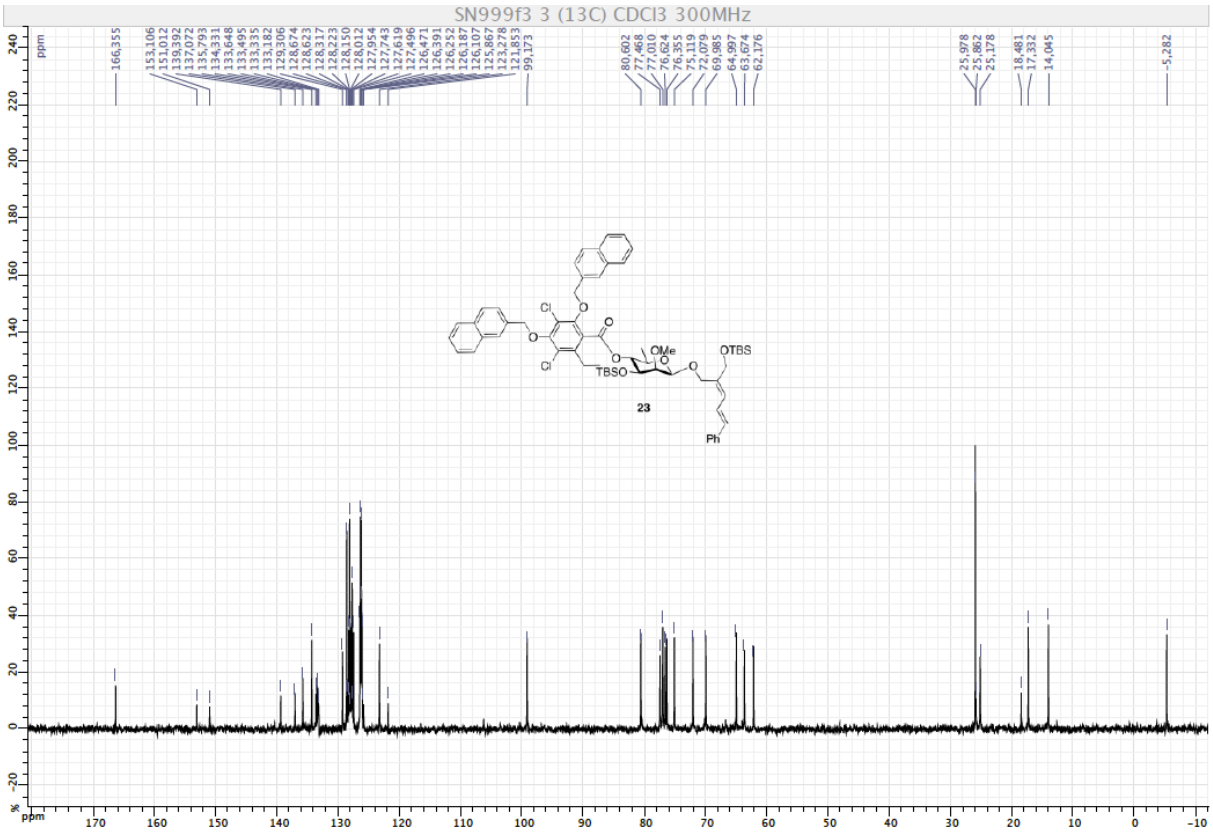

SN978f2hplc 1 (1D 1H) CDCl3 300MHz
ppm
OMe
OTBS
Br
18

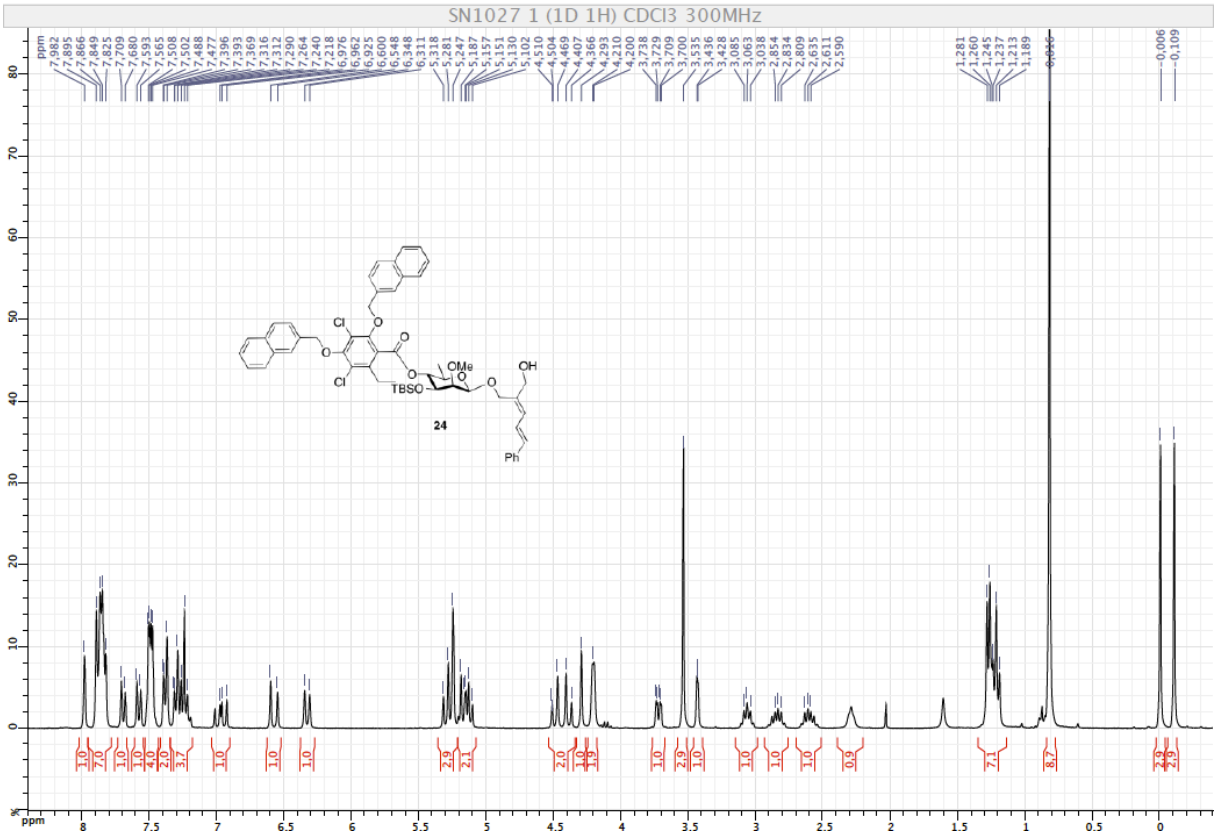

SN978f2hplc 3 (13C) CDCl3 300MHz
ppm
OMe
OTBS
Br
18

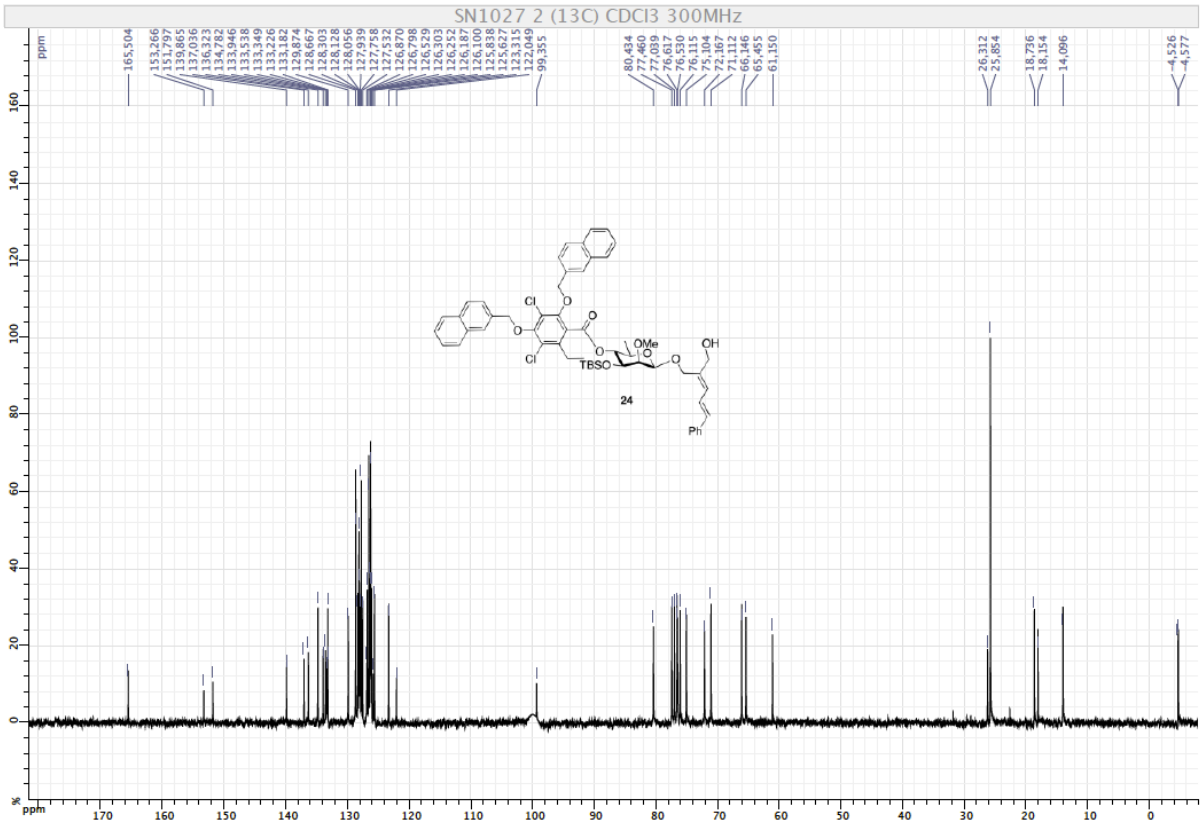

SN1004 1 (1D 1H) CDCl3 300MHz
22

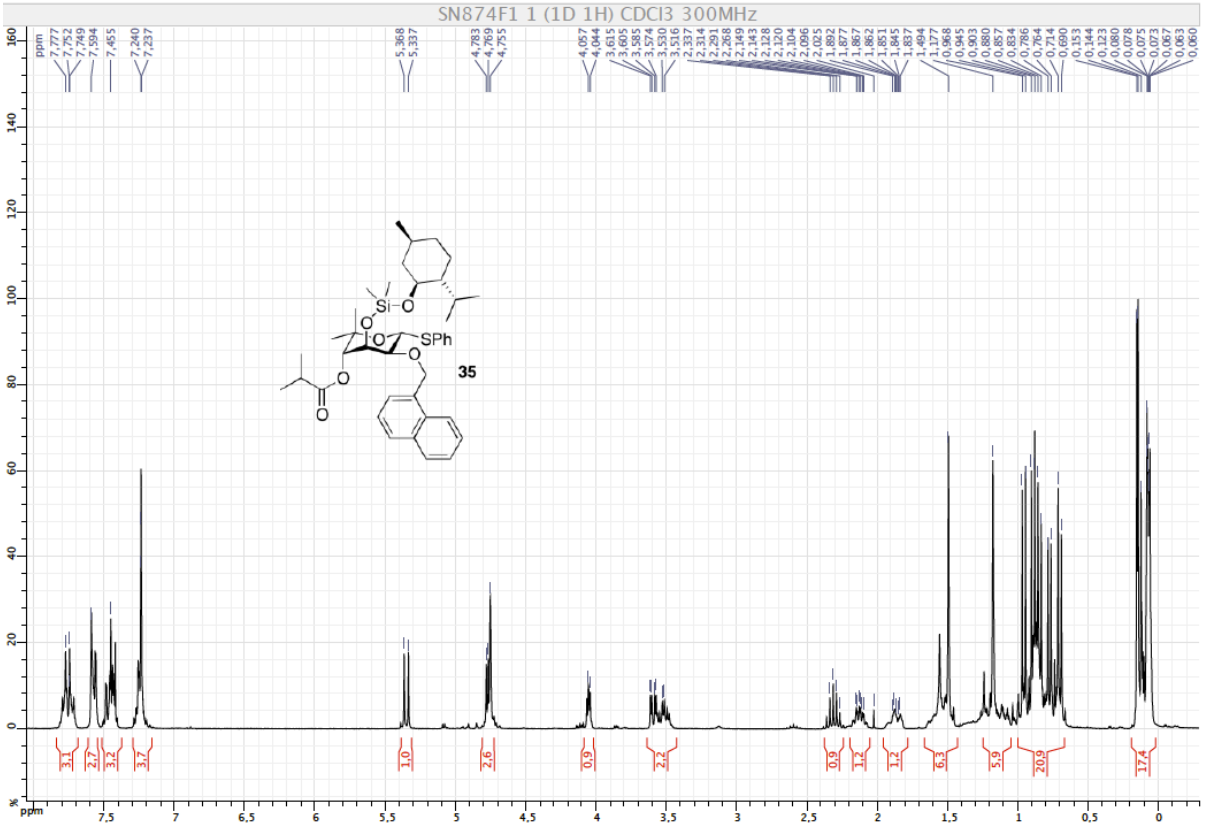

SN1004 3 (13C) CDCl3 300MHz
22

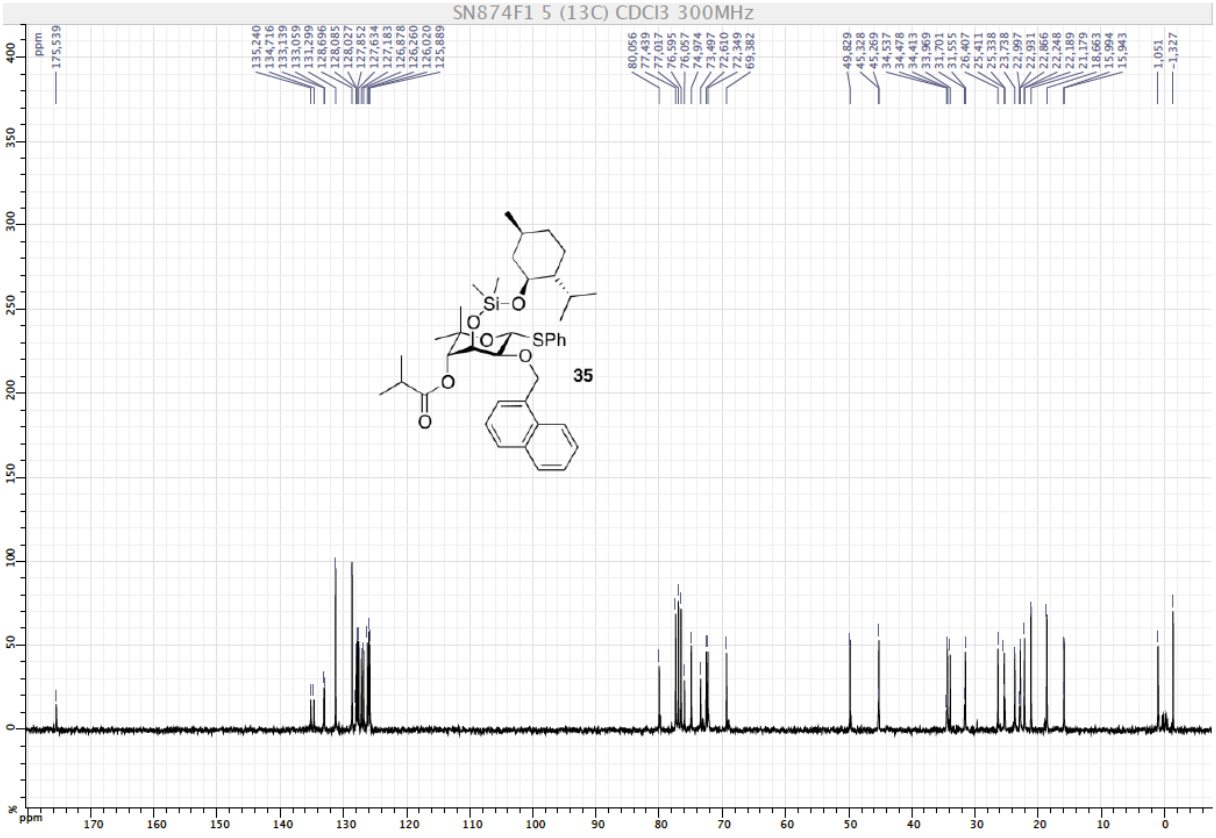

SN999f3 1 (1D 1H) CDCl3 300MHz
23

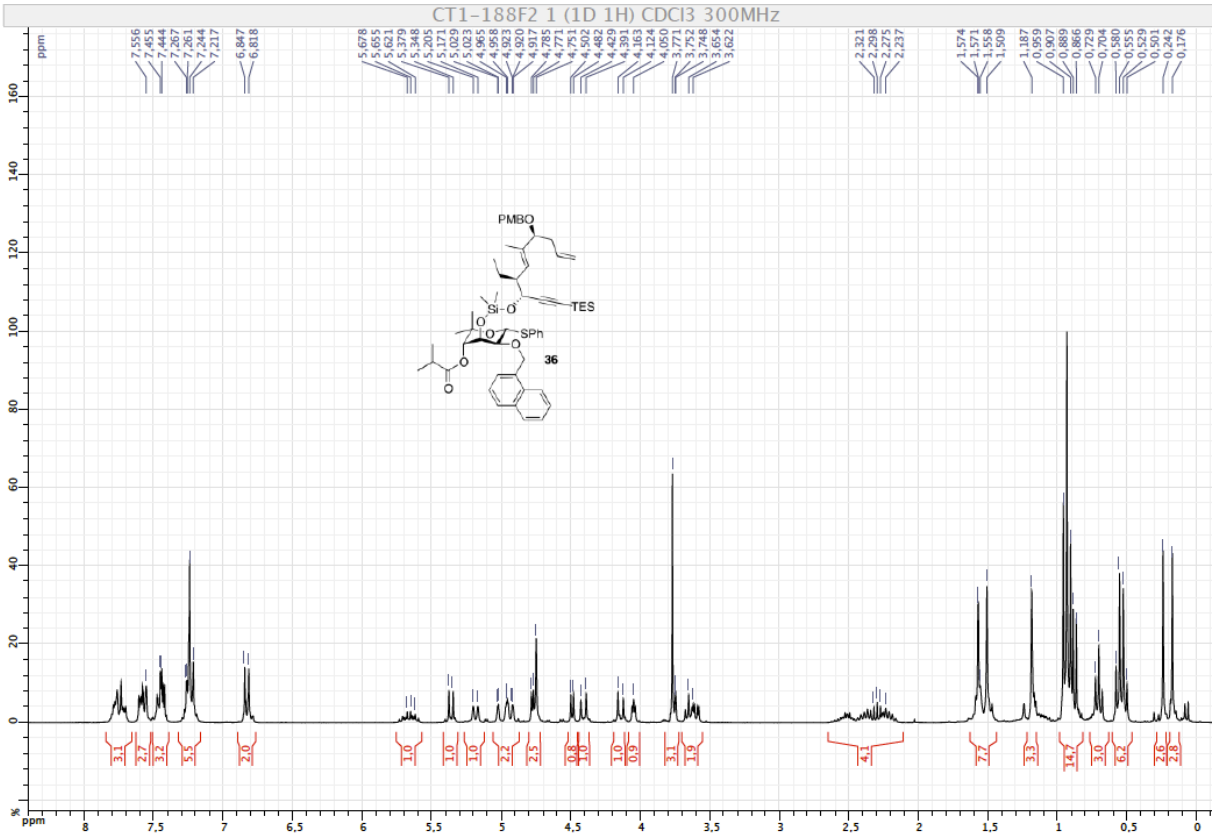

SN999f3 3 (13C) CDCl3 300MHz
23

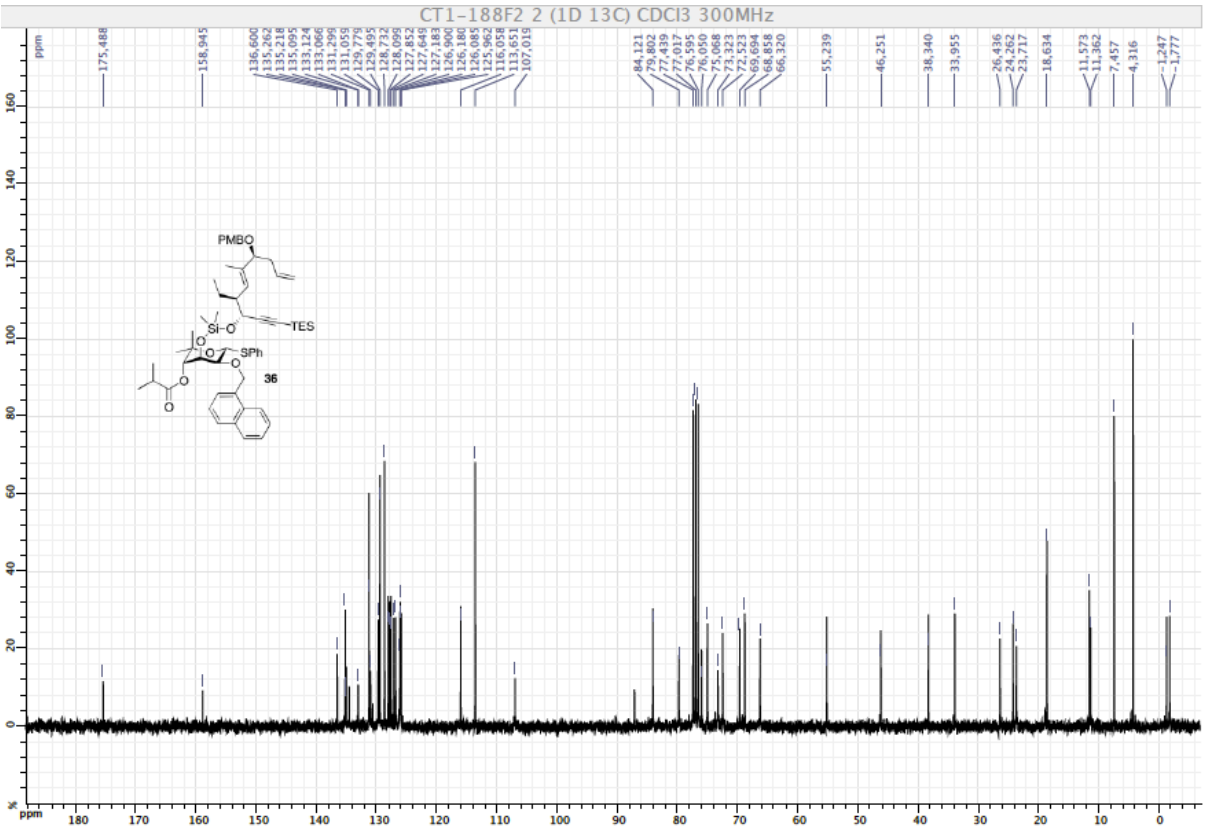

SN1027 1 (1D 1H) CDCl3 300MHz
24

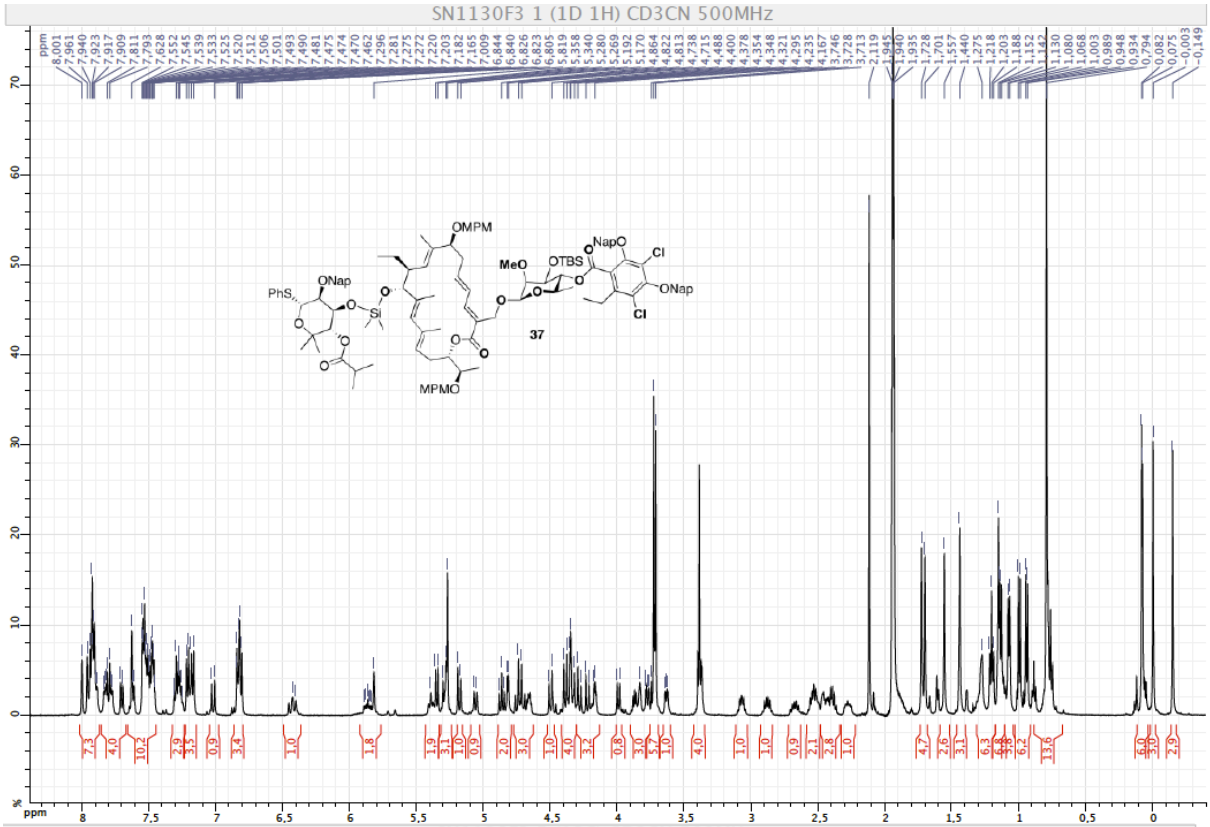

SN1027 2 (13C) CDCl3 300MHz
24

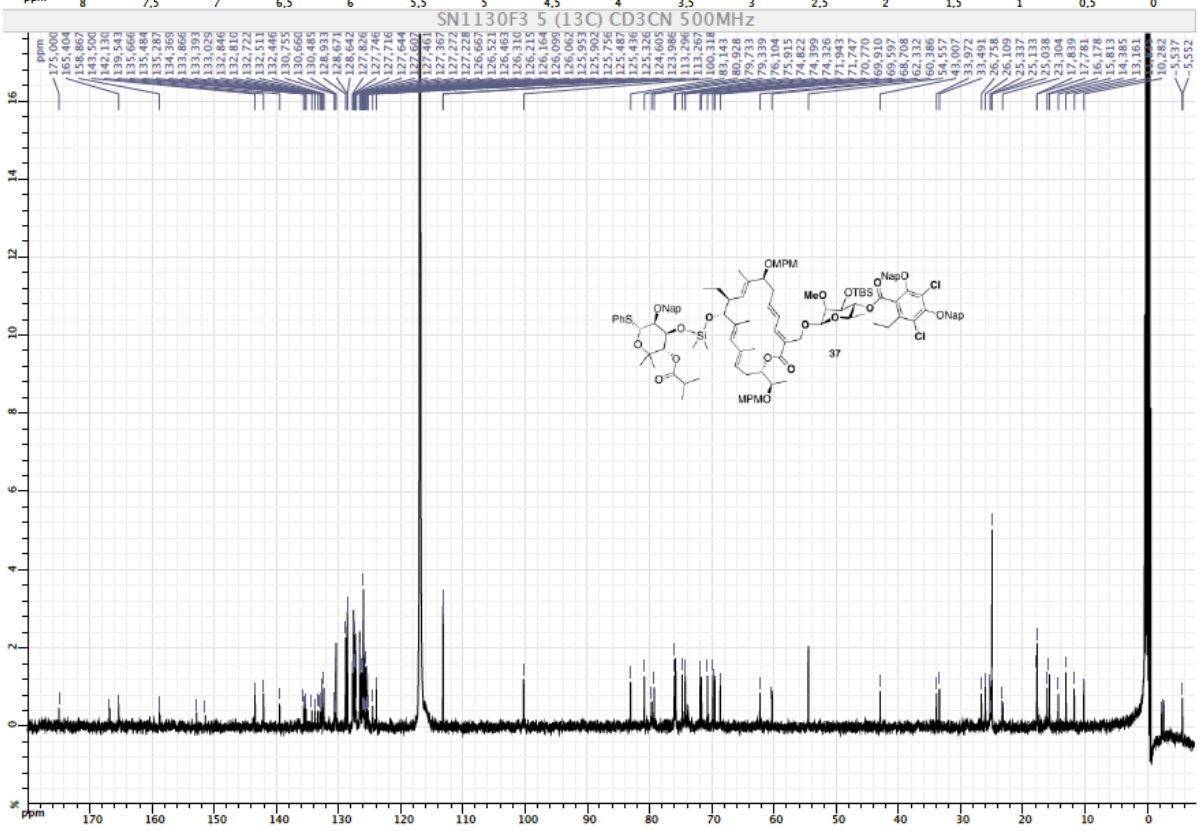

SN874F1 1 (1D 1H) CDCl3 300MHz
35

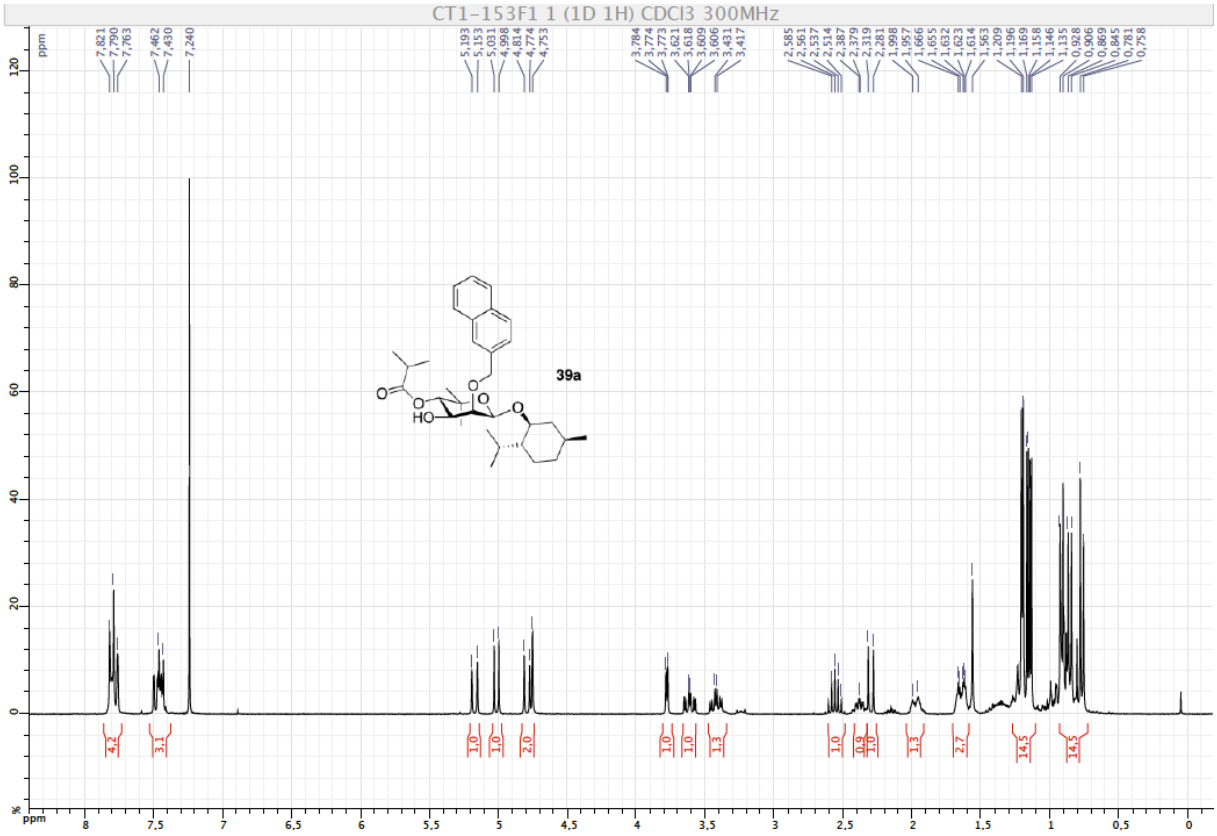

SN874F1 5 (13C) CDCl3 300MHz
35

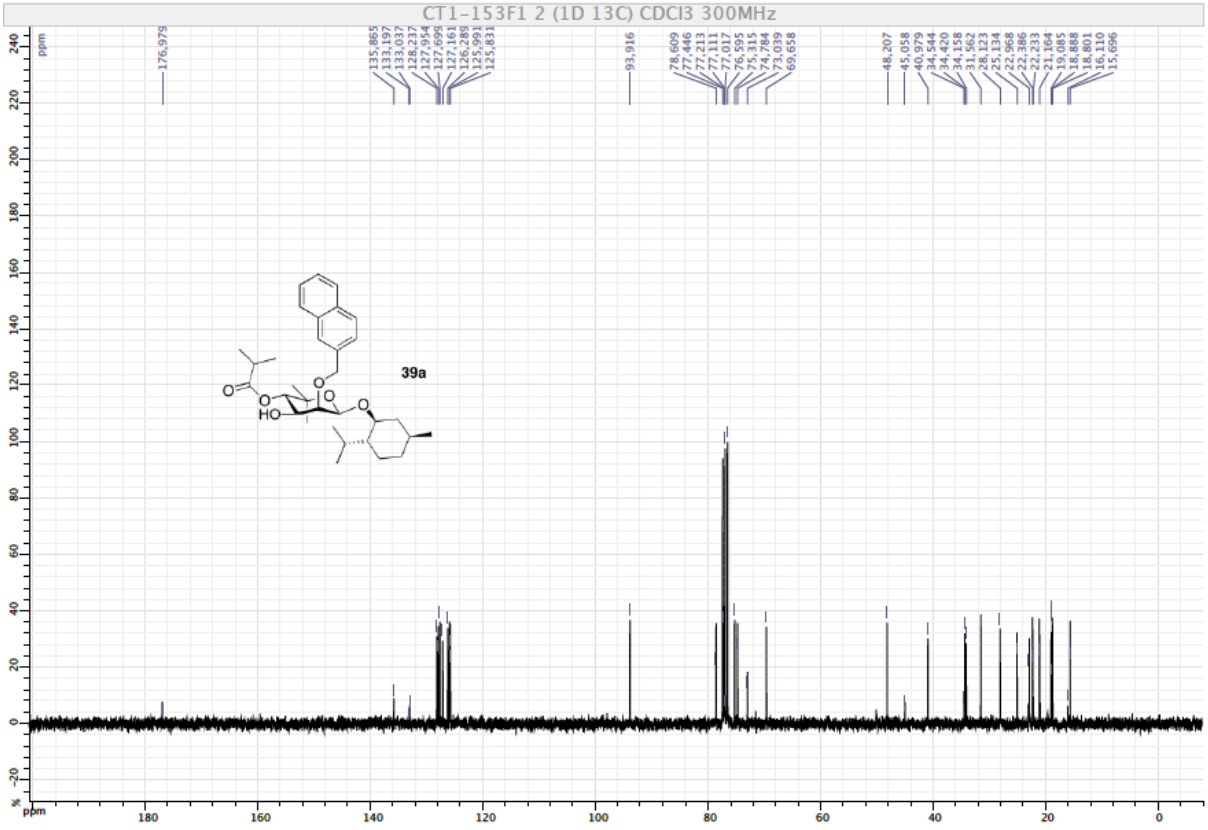

CT1-188F2 1 (1D 1H) CDCl3 300MHz
PMBO
TES
Si-O
SPh
36

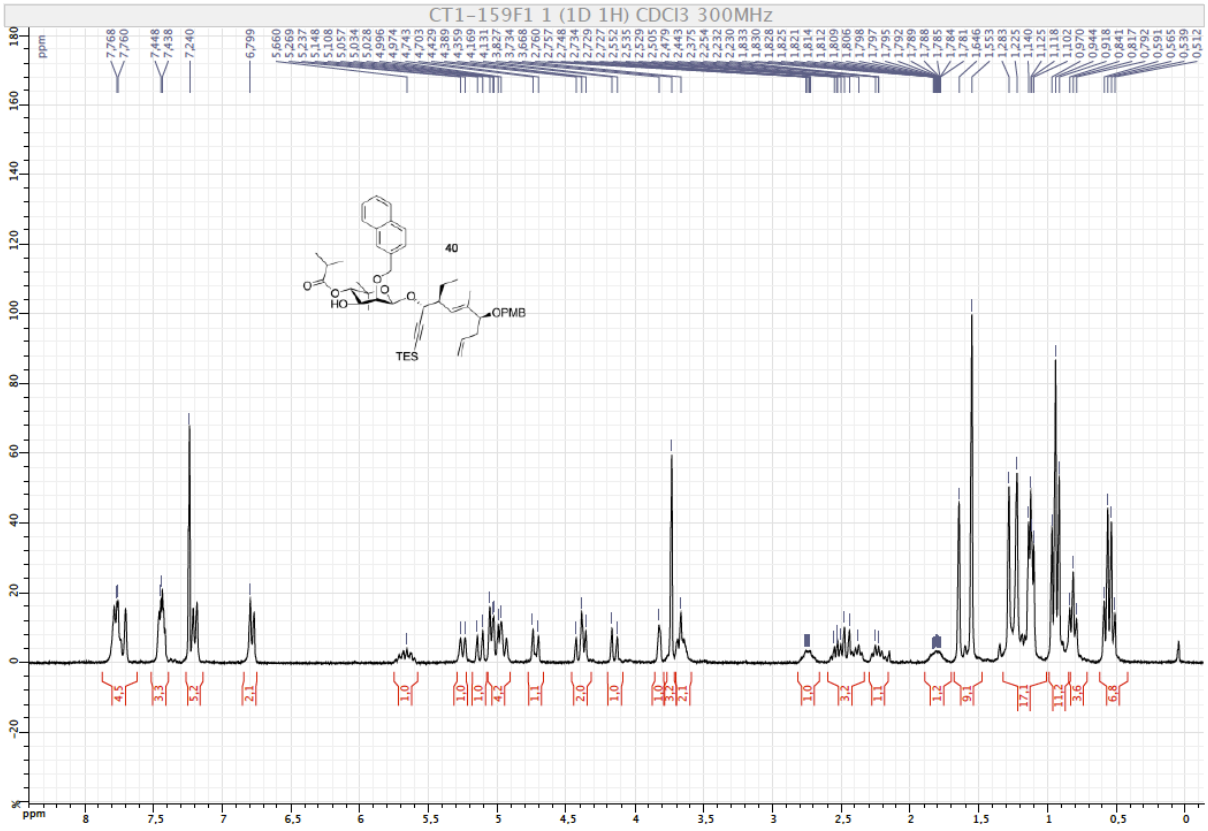

CT1-188F2 2 (1D 13C) CDCl3 300MHz
PMBO
TES
Si-O
SPh
36

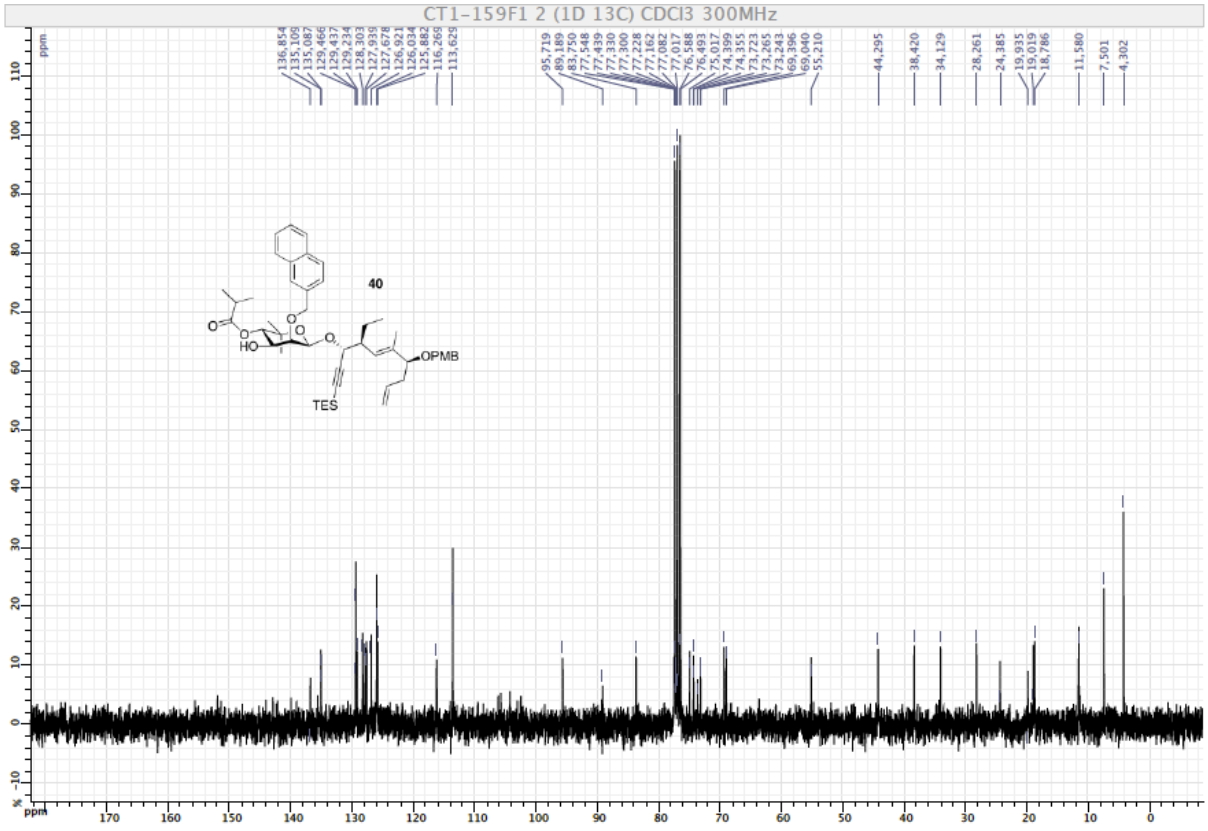

SN1130F3 1 (1D 1H) CD3CN 500MHz
OMPM
NapO
MeO
OTBS
Cl
ONap
PhS
ONap
Si
Cl
37
MPMO

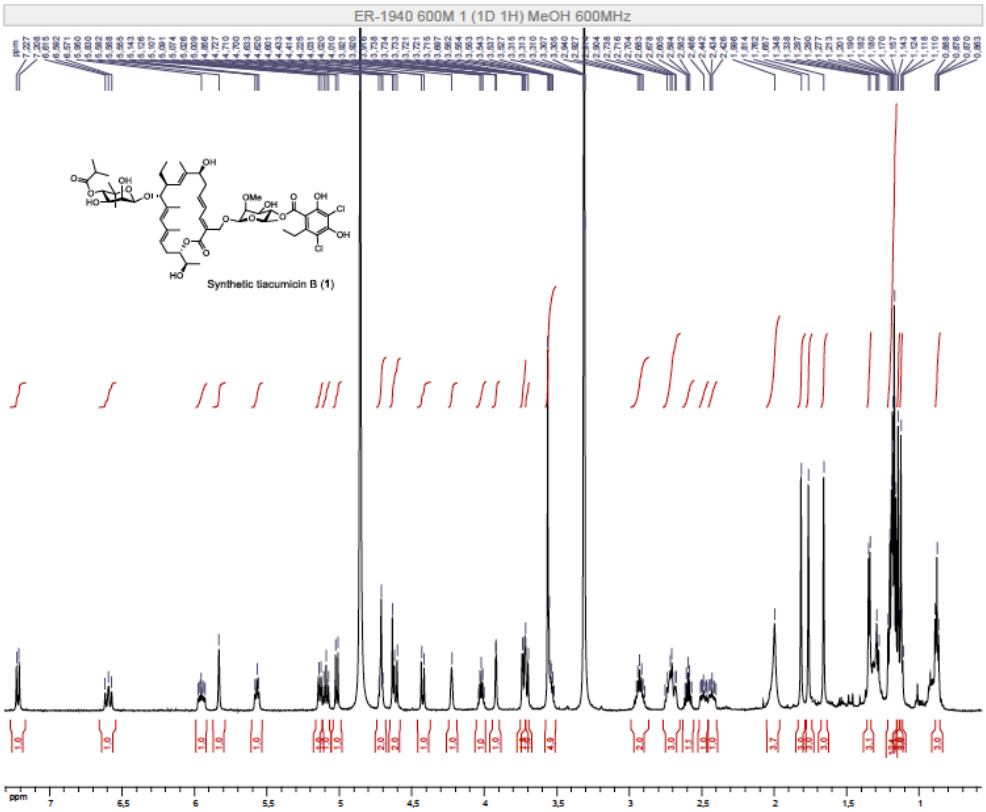

SN1130F3 5 (13C) CD3CN 500MHz
OMPM
NapO
MeO
OTBS
Cl
ONap
PhS
ONap
Si
Cl
37
MPMO

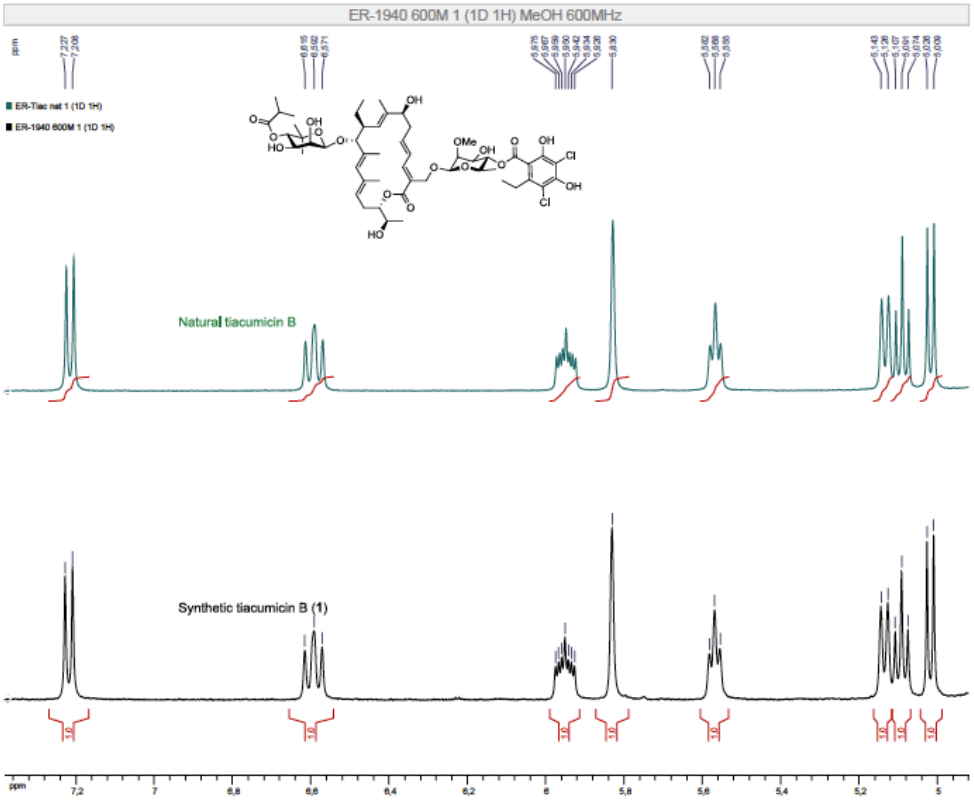

CT1-153F1 1 (1D 1H) CDCl3 300MHz
39a

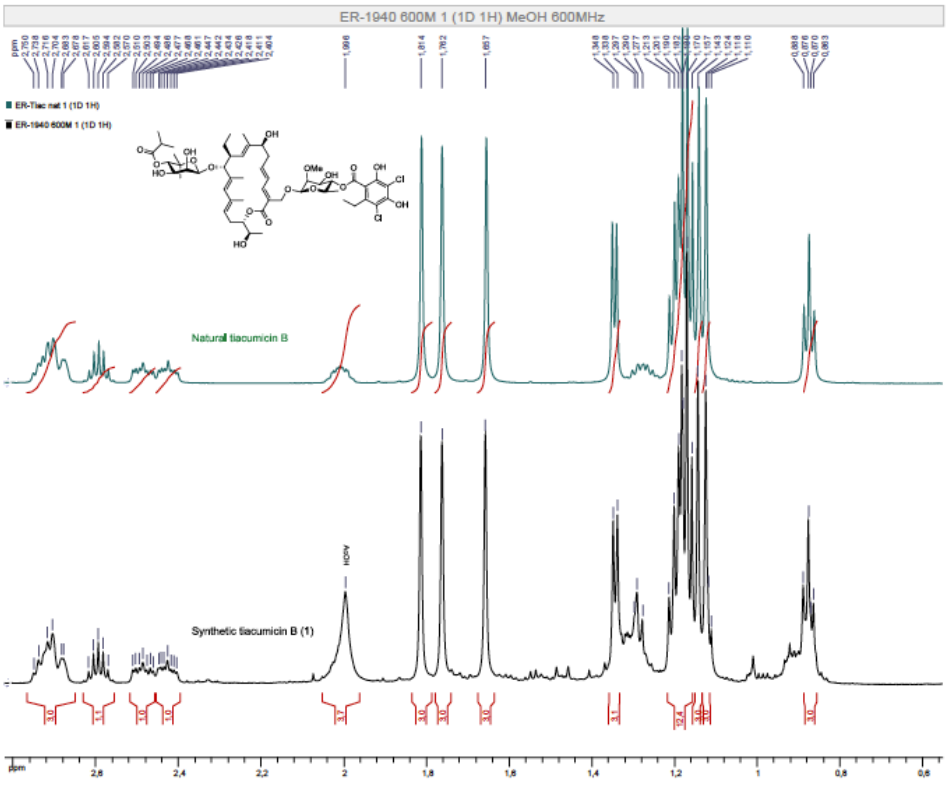

CT1-153F1 2 (1D 13C) CDCl3 300MHz
39a

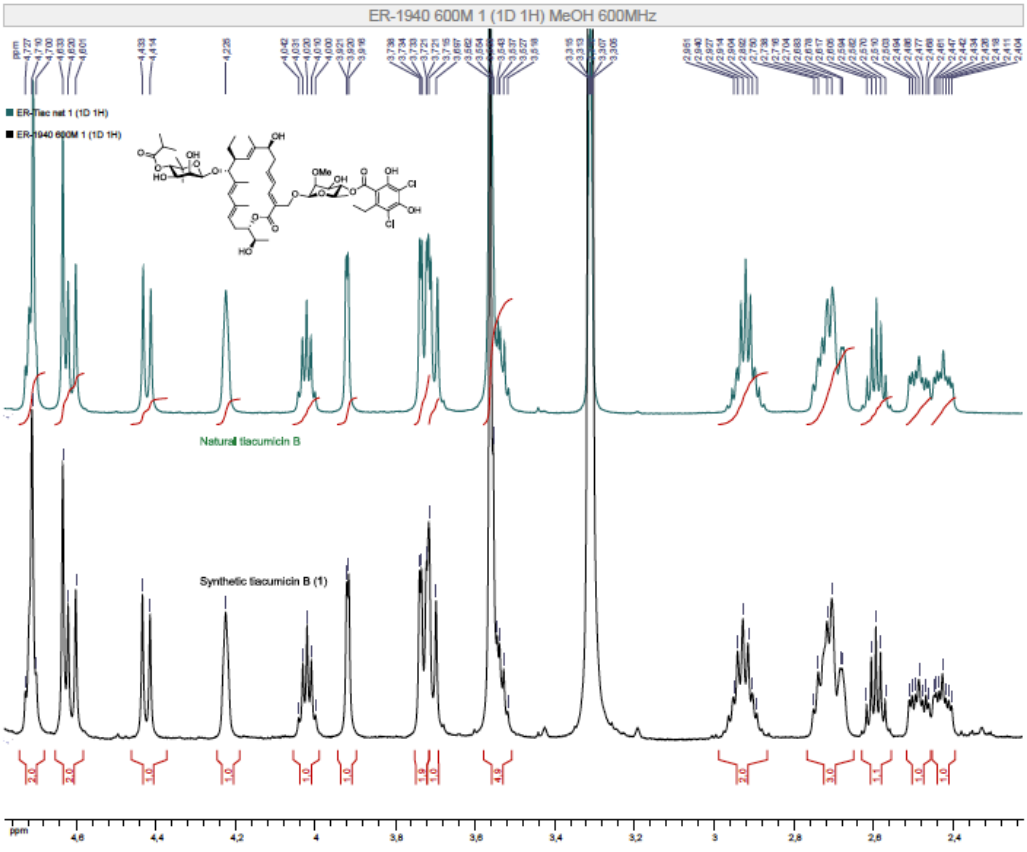

CT1-159F1 1 (1D 1H) CDCl3 300MHz
40
OPMB
TES
HO

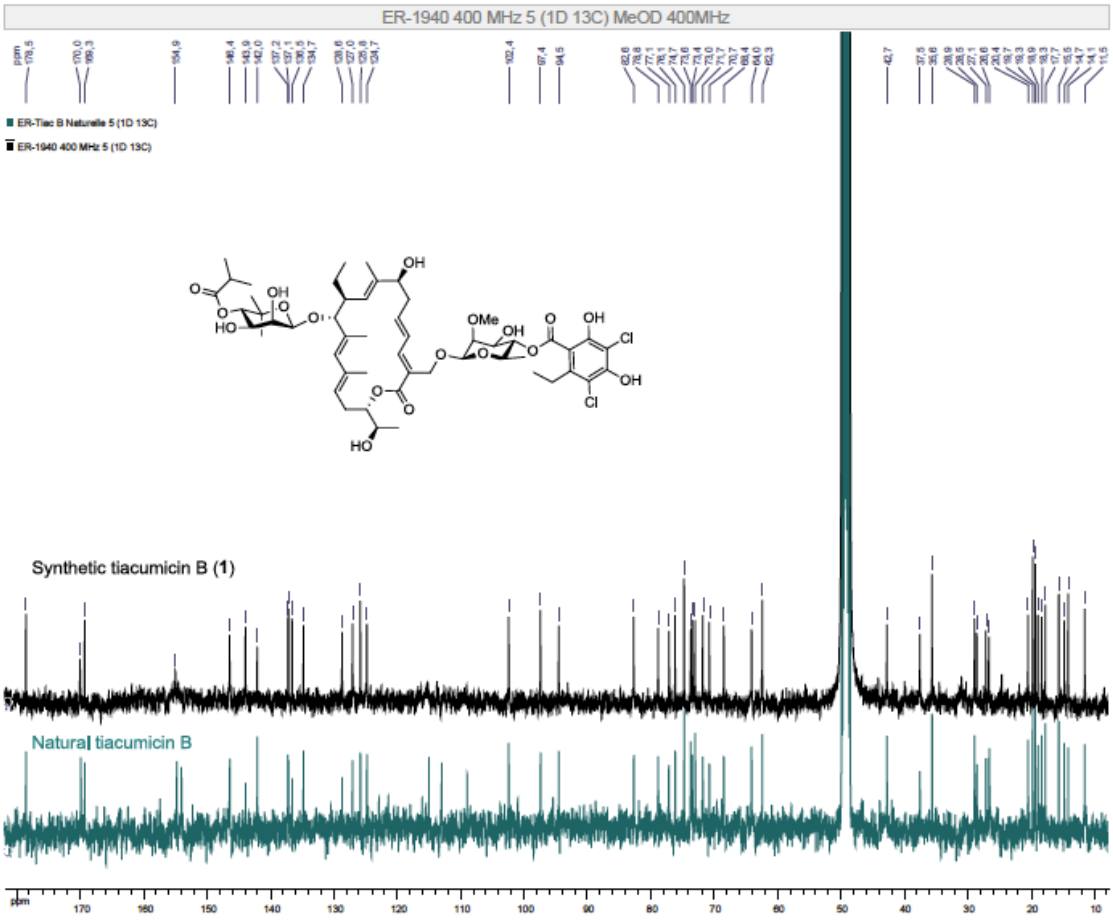

CT1-159F1 2 (1D 13C) CDCl3 300MHz
40
OPMB
TES
HO


ER-1940 600M 1 (1D 1H) MeOH 600MHz
Synthetic tiacumicin B (1)


ER-1940 600M 1 (1D 1H) MeOH 600MHz
ER-Tiac nat 1 (1D 1H)
ER-1940 600M 1 (1D 1H)
Natural tiacumicin B
Synthetic tiacumicin B (1)


ER-1940 600M 1 (1D 1H) MeOH 600MHz
ER-Tiac nat 1 (1D 1H)
ER-1940 600M 1 (1D 1H)
Natural tiacumicin B
Synthetic tiacumicin B (1)
HDIV


ER-1940 600M 1 (1D 1H) MeOH 600MHz
ER-Tiac nat 1 (1D 1H)
ER-1940 600M 1 (1D 1H)
Natural tiacumicin B
Synthetic tiacumicin B (1)


ER-1940 400 MHz 5 (1D 13C) MeOD 400MHz
ER-Tiac B Naturelle 5 (1D 13C)
ER-1940 400 MHz 5 (1D 13C)
Synthetic tiacumicin B (1)
Natural tiacumicin B
ppm