이학박사학위논문

Synthetic Studies of Madeirolide A: Visible-Light-Induced Radical Cyclization Approach

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가시광에 의한 라디칼 고리화 방법

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Abstract

In this thesis, our synthetic efforts toward marine natural product mardeirolide A are described. Madeirolide A is a biologically active polyketide that belongs to a group of macrolides. Madeirolide A have three bicyclic ether units embedded within a stereochemically decorated macrolactone scaffold. The bioactivity and structural complexity make madeirolide A an attractive target for total synthesis. Our approach for the synthesis of madeirolide A is based on the assembly of four fragments – C1-C10 fragment (A ring), C13-C19 fragment (B ring), C20-C27 fragment (C ring), and cinerulose fragment. Constructions of three oxacycles have been carried out through radical cyclization using a visible-light-induced transformation rapidly developed area in the past decade.

Chapter 1 contains the background about madeirolide A, biological activity and structure features. Also, presented briefly are all published synthetic studies.

Chapter 2 discusses all of the efforts that have been carried out in the laboratory towards a total synthesis of madeirolde A.

Key words: Madeirolide A, Natural products, Radical cyclization, Photoredox, Total synthesis

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Table of Contents

List of Tables

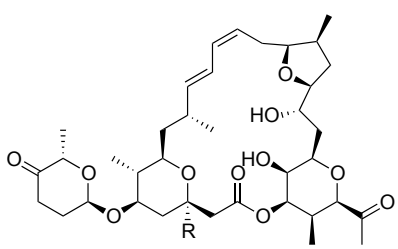
List of Figures

List of Schemes

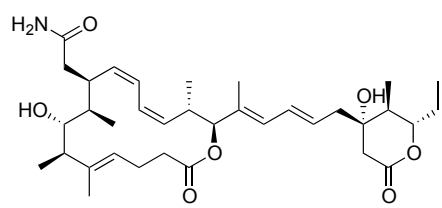
Chapter 1: Marine Macrolide Madeirolide A

1.1 Isolation, structure and biological activity

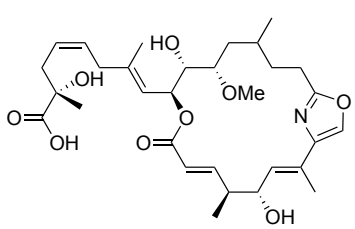
Various natural products found in sponges have been frequently studied as precursors of marketed drugs due to their valuable biological activities such as antibiotic and anticancer potency.[1] As these noble compounds, three marine natural product families, leiodelides, leiodermatolides and madeirolides have been newly reported since the mid 2000's from the sponges of genus *Leiodermatium* which have been less studied due to their deep water habitat. Leiodelide A was shown to have a significant cytotoxicity against HL-60 leukemia and OVCAR-3 ovarian cancer cells with a GI_{50} value of 250 nM.[2] Leiodermatolide A was found to exhibit potent antimitotic activity (IC_{50} <10 nM) against a range of human cancer cell lines and the total synthesis was also reported by Paterson's group.[3]



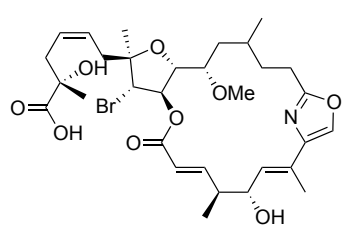
R= H, Madeirolide A (1.1)
R= OH, Madeirolide B (1.2)



Leiodermatolide



Proposed Leiodelide A



Proposed Leiodelide B

Figure 1.1 Marine natural products from *Leiodermatium* sp

Madeirolides were extracted from a *Leiodermatium* sp. by Wright and Winder in 2009 as a part of their program to discover bioactive marine natural products. Madeirolide A (**1.1**) and B (**1.2**) were shown to be effective inhibitors against the fungal pathogen *Candida albicans* (fungicidal MIC = 12.5 μg/mL, **1.1**/ 25 μg/mL, **1.2**).[4] When tested for anticancer effects against the PANC-1 pancreatic cancer cell line, 44% inhibition of proliferation was observed at 10 μg / mL. Structurally, **1.1** is a macrolide consisting of a cinerulose monosaccharide and a 24-membered macrolactone core featuring stereochemically decorated three bicyclic ether units, two 2,6-*cis*-tetrahydropyrans and one 2,5-*cis*-tetrahydrofuran.

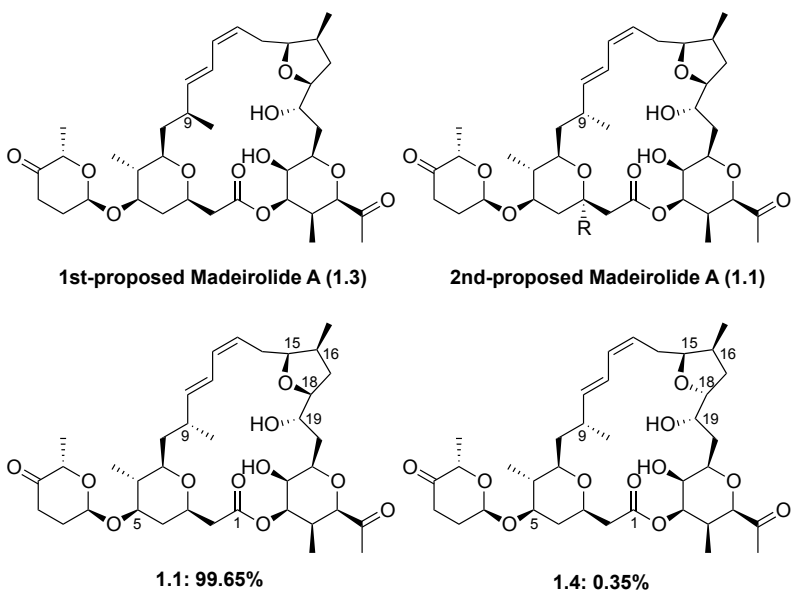


Figure 1.2 Highest probability structures as determined by the DP4 method

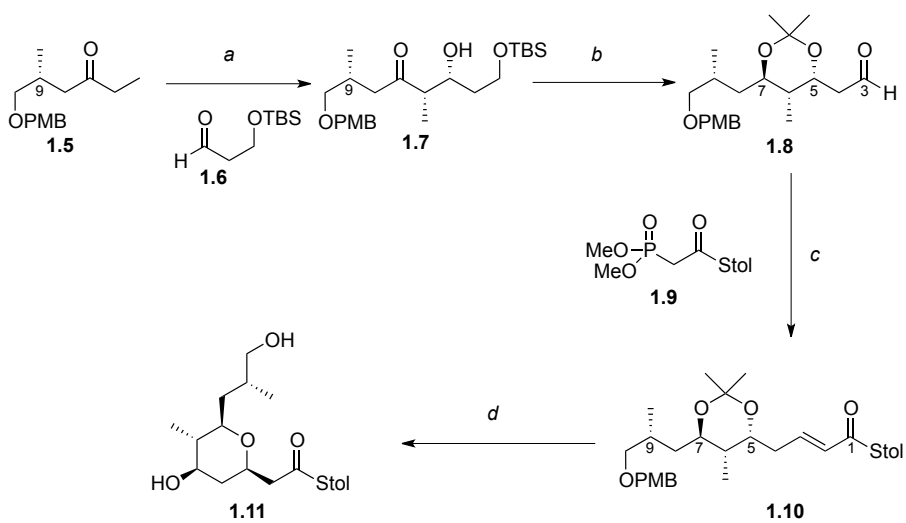
In the original isolation paper, the structure of madeirolide A was proposed as **1.3** that has (*S*)-configuration at C9 using detailed NMR spectroscopic analysis. After that, the proposed structure was revised by the Paterson group using Goodman's DP4 computational NMR method.[5] When they considering which

centers to vary, each tetrahydropyrans were considered as a single variable, and each stereocenters of C15-C18 tetrahydrofuran were handled as a variable, as were C9 and C19 centers. With these eight variables, DP4 calculation concluded that 9-*epi*-diastereomer **1.1** was shown to have the highest probability 99.65%, and second probable structure was 9-18-bis-*epi*-diastereomer **1.4** at 0.35%.

1.2 Synthesis of C1-C10 subunit of madeirolide A

Thus far, three partial syntheses of C1-C10 subunit, including our own, have been published. Both the Paterson[6] and the Carter[7] group were able to construct the 2,6-*cis*-THP-ring using the diastereoselective addition reaction of a hydroxyl group to the pi-bonding orbital. In the following section, all published results will be presented briefly.

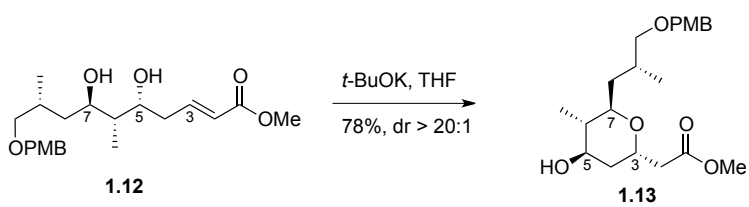
1.2.1 Paterson's Approach



(a) (-)-$(ipc)_2BOTf$, iPr_2NEt, DCM, then, **1.6**, 93%, dr > 95:5 (b) (i) SmI_2, EtCHO, THF (ii) K_2CO_3, MeOH (iii) $(MeO)_2CMe_2$, PPTS (iv) TBAF, THF (v) DMP, $NaHCO_3$, DCM, 82% over 5 steps (c) **1.9**, LiCl, TEA, THF, 95% (d) (i) TsOH, DCM (ii) DDQ, DCM pH 7 buff, 61% over 2 steps

Scheme 1.1 Paterson's approach to madeirolide A

The Paterson group reported the first fragment synthesis of madeirolide A in 2013 (Scheme 1.1). The synthetic route toward fragment **1.11** began with commercially available Roche ester having the appropriate stereochemistry at C9. The *syn*-adduct **1.7** possessing suitable C5 and C6 stereocenters was obtained by the asymmetric aldol reaction from ketone **1.5** and aldehyde **1.6** using (-)-$(ipc)_2BOTf$, a chiral boron reagent. After stereocontrolled reduction of *syn*-aldol product **1.7** under Evans-Tishchenko condition, resulting diol was subjected to sequential manipulations to give aldehyde **1.8** having requisite stereochemistry at C7. Condensation of aldehyde **1.8** and phosphonate **1.9** through a HWE reaction generated Michael acceptor **1.10** which was then cyclized under acid catalyzed acetonide deprotection conditions to give 2,6-*cis*-THP **1.11** with high diastereoselectivity. Interestingly, subjection of methyl ester **1.12** to a basic condition provided exclusively 2,6-*trans*-THP **1.13** (scheme 1.2). Computational investigations about this selectivity revealed that intramolecular-hydrogen bonding of the C5 hydroxyl group with C7 alkoxide group stabilized the boat-like transition state under basic condition, which led to the 2,6-*trans*-THP product.[7]

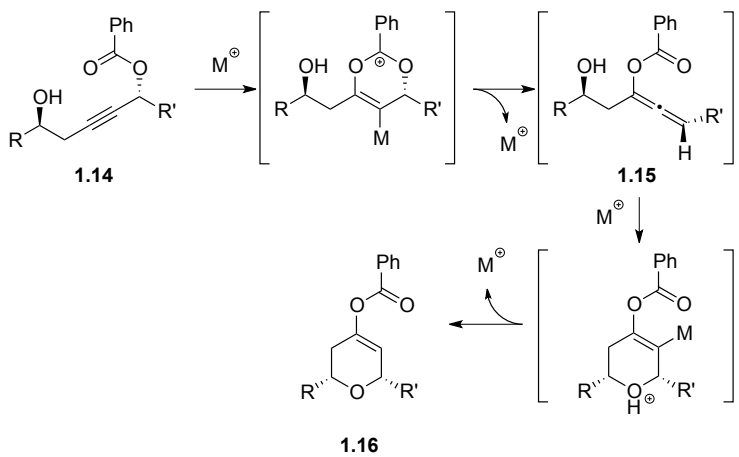


1.12 **1.13**

Scheme 1.2 Unexpected trans-cyclization of enoate 1.12

1.2.2 Carter's Approach

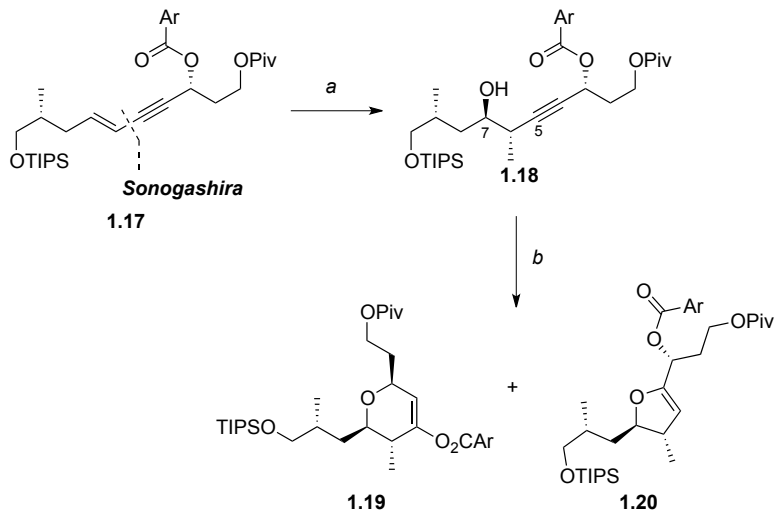
The Carter Group has been steadily conducting research on the synthesis of related natural products through the dihydrofuran construction via the silver catalyzed cyclization (AgCC) developed by the group. As an extension of this synthetic strategy, the same protocol was applied to the synthesis of 2,6-*cis*-dihydropyran, to produce the core structure of C1-C10 fragment of madeirolide A. In the mechanism (scheme 1.3), allene **1.15** was derived from ester **1.14**, which has a stereocenter at the propargylic position, by stereospecific rearrangement using the silver catalyst as alkyne activator. Then, 2,6-*cis*-dihydropyran **1.16** is formed by addition of the hydroxy group to the allene activated by silver.



Scheme 1.3 Metal catalyzed THP synthesis from propargyl benzoate

Two building blocks, already known in the literature, were coupled by a Sonogashira reaction to give enyne **1.17** (scheme 1.4). Subsequently, the requisite hydroxyl group and methyl group at C6-C7 were introduced through Shi epoxidation and regio-selective epoxide opening reaction from **1.17** in a stereocontrolled fashion. When alcohol **1.18** was subjected to Ag-catalyzed

cyclization, 2,6-*cis*-dihydropyran **1.19** was generated as major product along with dihydrofuran **1.20** in a 1.4:1 ratio. The generation of the undesired DHF **1.20** might be ascribed to slow rearrangement of the propargyl benzoate due to steric congestion at C6.



(a) (i) Shi epoxidation (ii) $LiAlMe_4$, BF_3OEt_2, DCM, 72% over 2 steps
(b) $AgBF_4$(20 mol_2%), toluene, 74%, **1.19** : **1.20** = 1.4 : 1

Scheme 1.4 Carter's approach to madeirolide A

1.3 Reference

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4. Winder, P. L. Ph.D. Thesis, Florida Atlantic University, **2009**.

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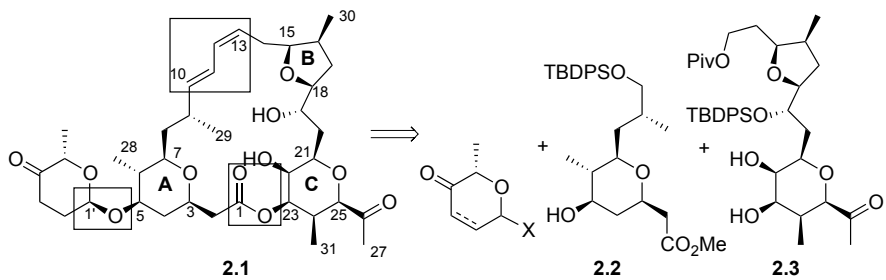
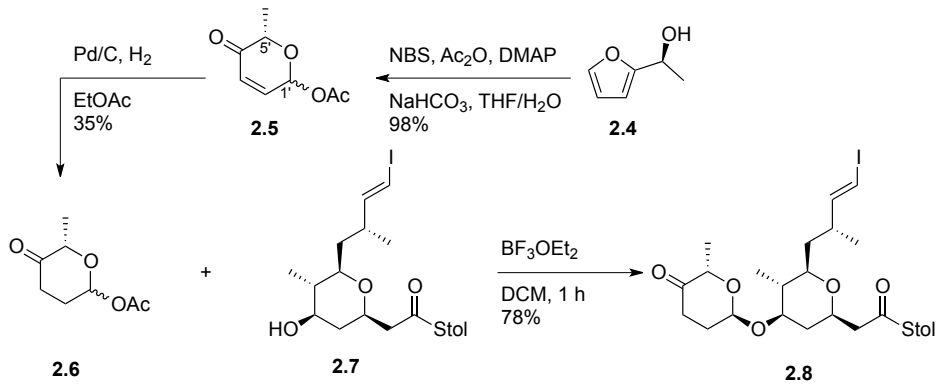
Chapter 2. Synthetic Studies Toward Madeirolide A

2.1 Synthetic plan



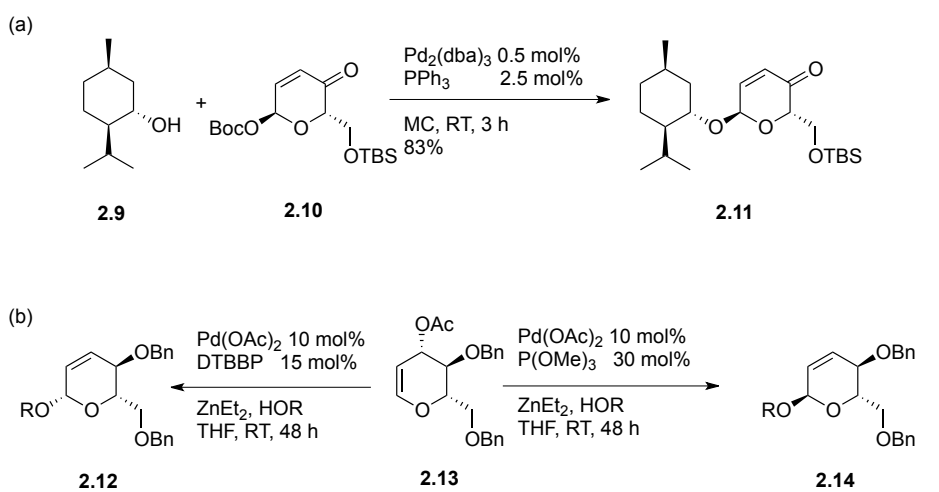
Scheme 2.1 Retrosynthetic analysis of madeirolide A, I

The most important point of consideration in designing the synthetic plan for madeirolide A is the efficient access to stereogenic centers of the A, B and C rings. As shown in the case of mandelalides where the stereochemistry was incorrectly predicted based on transannular-nOe analysis[1], the stereochemical assignment of macrolides also has the risk of being incorrect. Being mindful of the possibility that the relative domanial stereochemistry of madeirolides might have been wrongly assigned, we propose construction of madeiorlide A through fragment-assembly of absolutely stereo-controlled A-C subunits, thus maximizing stereochemical flexibility. In this respect, it is reasonable that we use the C10-C13 diene and C1 lactone linkage as ideal points for fragment union (Scheme 2.1). It has already been reported that the C10-C13 diene can be introduced via methods such as Suzuki, RCAM, Heck and Wittig reactions.[1] The α-cinerulose 5,1′-glycosidic linkage would be easily established with control of anomeric configuration.



Scheme 2.2 Glycosylation of Paterson group

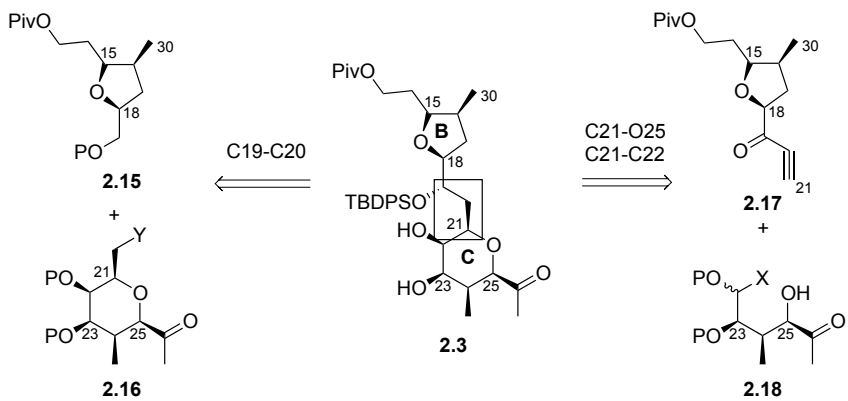
The Paterson group[2] found that acidic reaction of alcohol **2.7** and cinerulose derivative **2.6**, formed through Achmatowicz rearrangement of (*S*)-2-furyl ethanol **2.4**, resulted in the formation of α -glycoside **2.8** (Scheme 2.2).



Scheme 2.3 Palladium catalyzed glycosylation

In the process of preparing **2.6**, the yield of Pd-catalyzed reduction was poor because there were two reactive functional groups, alkene and allylic acetate. The

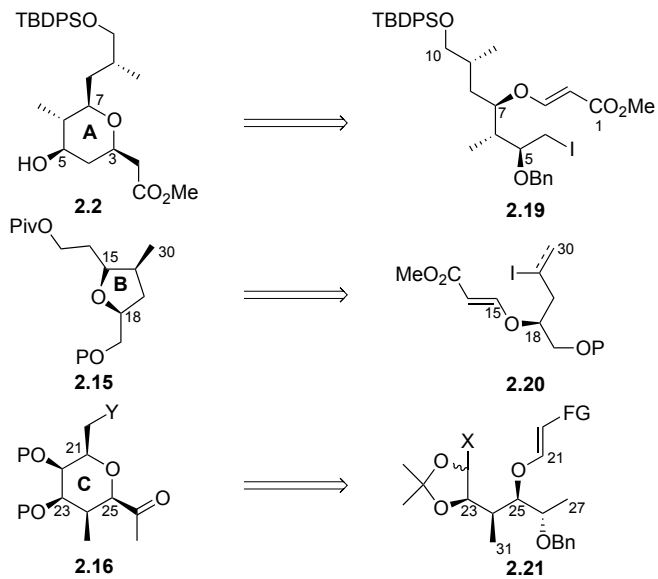
groups of O'Doherty and Lee independently reported palladium-catalyzed glycosylation methods using reactive allylic acetate derivatives. In the O'Doherty method,[3] Boc-pyranone **2.10** was used as a substrate and the anomeric stereochemistry was controlled by stereochemistry of substrate (Scheme 2.3a). On the other hand, in the process developed by the Lee group,[4] the stereochemistry of glycosylation of glycal **2.13** was controlled by choice of the catalyst (Scheme 2.3b). Therefore, we envisioned that α-cinerulose 5,1′-glycosidic linkage would be built through the Pd-catalyzed glycosylation and subsequent hydrogenation of the C2'-C3 'alkene.



Scheme 2.4 Retrosynthetic analysis of madeirolide A, II

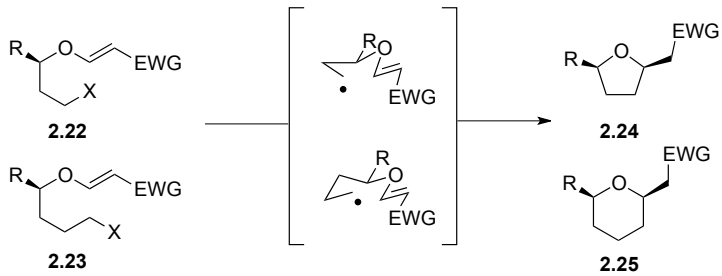
As illustrated in Scheme 2.4, there are two disconnection pathways toward **2.3**. First, we speculated about the feasibility of forming the C21-O25 bond as a key union step. The conjugate addition of alcohols to the activated triple bond of a propiolate is a well-known reaction that leads to valuable β-alkoxyacrylates,[5] excellent radical acceptors.[6a] If ynone **2.17** displays a similar reactivity toward alcohols as Michael acceptor, it will be the most concise route. As a second

strategy toward **2.3**, the C19-C20 bond formation reaction is considered as a key union step. Although the coupling of C19 and C20 is a challenging task, it is synthetically advantageous that a construction of complex all-*cis*-THP skeleton of C ring could be performed in early stages. More details will be discussed in the later part of the chapter, section 2.5.



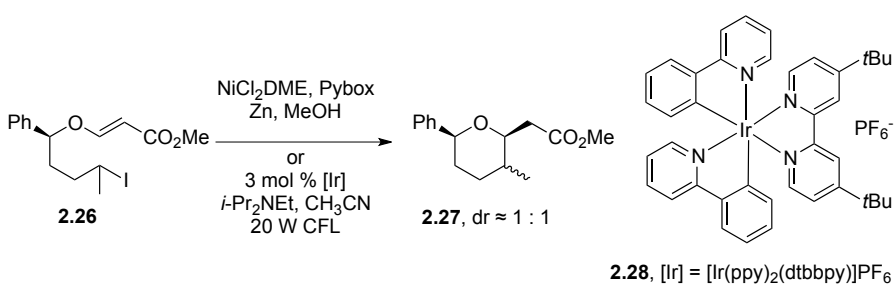
Scheme 2.5 Retrosynthetic analysis of madeirolide A, III

The next key question is how to prepare the proposed subunits **2.2**, **2.15** and **2.16** with control of both enantio- and diastereoselectivity. All three subunits have *cis*-oxacyclic structures, 2,6-*cis*-THP and 2,5-*cis*-THF. For the construction of this class of oxacyclic skeletons, the radical cyclization method developed by Lee[6a] is known to be highly useful.



Scheme 2.6 Diastereoselectivity of radical cyclization

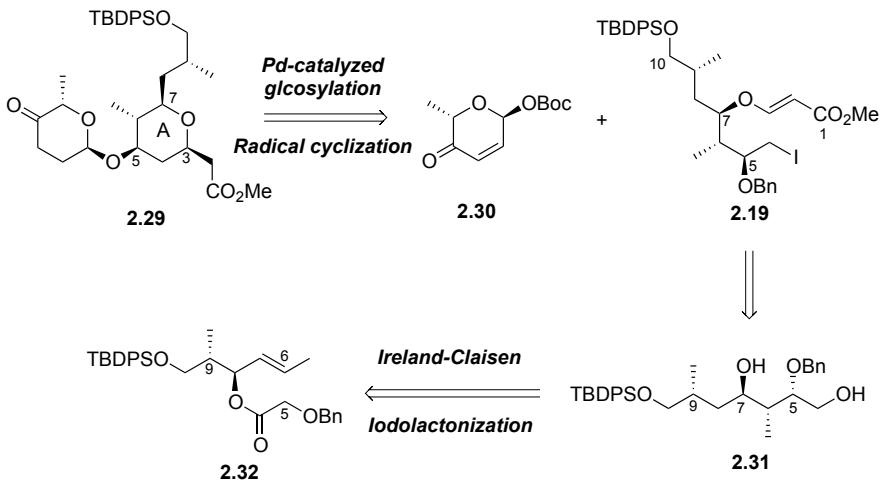
The radical cyclization of β-alkoxyacrylates can be achieved efficiently with high diastereoselectivity, which has been applied in a great number of natural product syntheses (Scheme 2.6).[6b] In this synthesis we plan to utilize visible-light-induced transformation for radical generation, an approach rapidly developed in the past decade.[7] Since poor 2,3-stereoselectivity was found in photo-induced free radical cyclization in our group[8] (Scheme 2.7), we need a solution to the additional diastereoselectivity issue encountered in the B and C rings. More details will be discussed in sections 2.3 and 2.4 of the chapter.



Scheme 2.7 Reductive cyclization of organohalide in Lee group

2.2 Synthesis of C1-C10 subunit, A ring

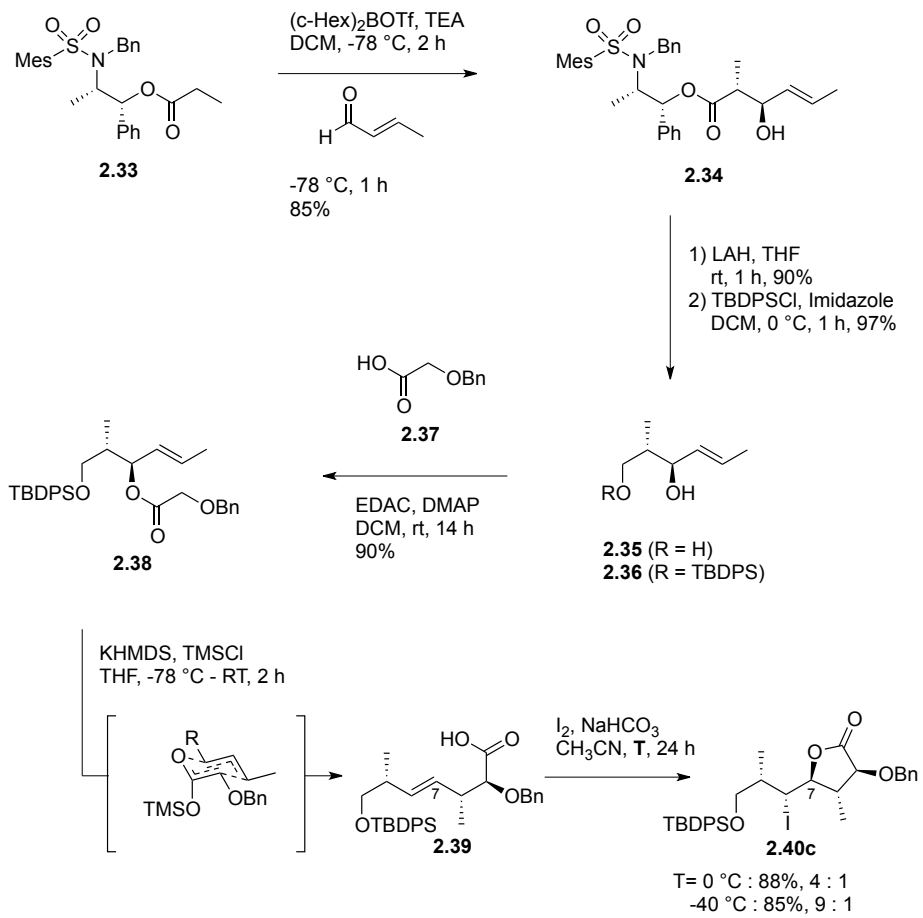
2.2.1 Retrosynthetic analysis



Scheme 2.8 Retrosynthetic analysis of C1-C10 subunit, A-ring

We proposed that the 2,6-*cis*-THP skeleton of **2.29** would be constructed through free radical cyclization of iodide **2.19** under visible-light-induced photoredox condition (scheme 2.8). After cyclization, the α-cinerulose 5,1′-glycosidic linkage would be built via palladium-catalyzed glycosylation with pyranone **2.30**. For the preparation of **2.19**, acrylation on secondary alcohol of diol **2.31** followed by iodination on primary alcohol is a straightforward as well as the most plausible route. Three stereogenic centers, C5-C7, would be established through a sequence of stereospecific Ireland-Claisen rearrangement and diastereoselective iodolactonization from aldol product **2.32**.

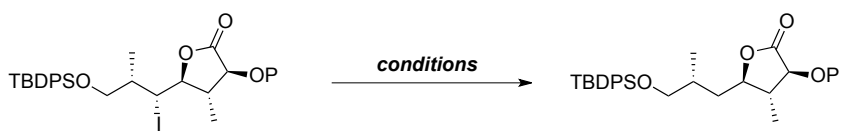
2.2.2 Construction of stereogenic centers of 2.31



Scheme 2.9 Construction of stereogenic centers

In the forward direction, the synthesis of allylic glycolate **2.38** began with norephedrine-derived chiral auxiliary **2.33**, which was subjected to anti-selective aldol reaction with crotonaldehyde.[9] After reductive removal of chiral auxiliary from anti-aldol **2.34**, the resulting diol **2.35** was silylated selectively to give mono-protected alcohol **2.36**. For the Ireland-Claisen substrate **2.38**, alcohol **2.36** was esterified with acid **2.37,** which was generated from bromoacetic acid and benzyl alcohol. With allylic glycolate **2.38** possessing two-stereogenic centers, the

Ireland-Claisen rearrangement occurred smoothly to give rise to two carbon-elongated acid **2.39** having three-stereogenic centers with excellent stereoselectivity[10]. In order to introduce stereo-controlled C7-hydroxy group, acid **2.39** was subjected to iodolactonization at various conditions. In the literature review, halolactonization of γ, δ-unsaturated acid with α or/and β substituents was known to have high π-facial selectivity[11]. After considerable experiments, we were able to obtain iodide **2.40c** with excellent yield (85% over two steps) and diastereoselectivity (dr = 9:1) through performing the reaction at – 40 °C using acetonitrile as solvent. When this reaction was carried out at high temperature or using other solvent such as, THF, DCM and toluene, we could only observe low diastereoselectivity (scheme 2.9).



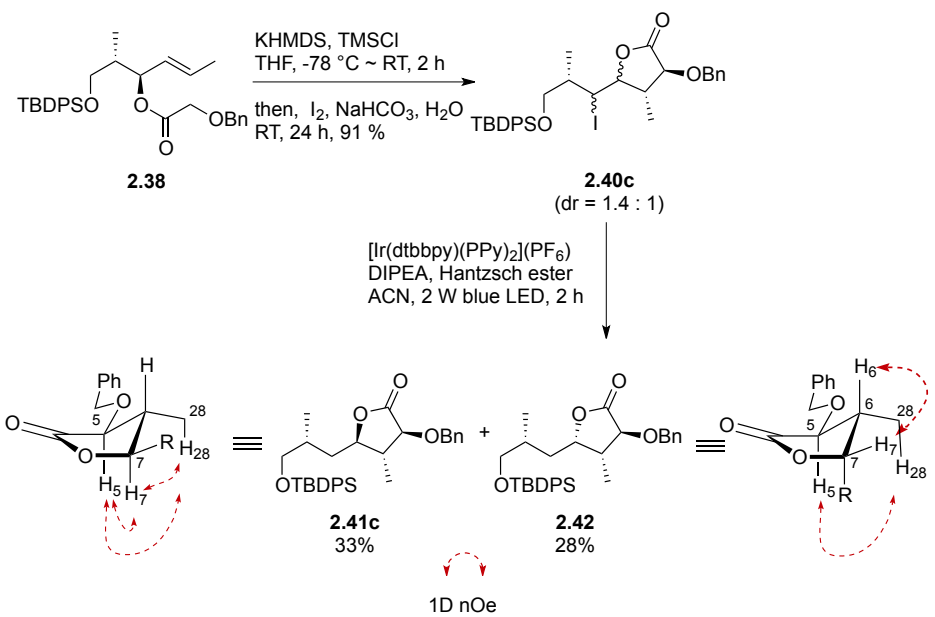
2.40a (P = PMB)
2.40b (P = TBDPS)
2.40c (P = Bn)

2.41a (P = PMB)
2.41b (P = TBDPS)
2.41c (P = Bn)

Entry	SM	Conditions	Yield [%]
1	**2.40a**	TTMSS, AIBN, 80 °C	54
2	**2.40a**	$[Ir(PPy)_2(dtbbpy)]PF_6$, DIPEA, 2 W blue led	complex mixture
3	**2.40b**	$[Ir(PPy)_2(dtbbpy)]PF_6$, DIPEA, 2 W blue led	20 (SM, 62%)
4	**2.40c**	TTMSS, AIBN, 80 °C	55
5	**2.40c**	$Ir(PPy)_3$, NBu_3, Hantzsch ester, 2 W blue led	71
6	**2.40c**	*fac*-Ir(*m*PPy)$_3$, DIPEA, *p*-toluenethiol, 2 W blue led	69
7	**2.40c**	$[Ir(PPy)_2(dtbbpy)]PF_6$, DIPEA, Hantzsch ester, 2 W blue led	81

Table 2.1 Reductive-deiodination reactions

With iodides **2.40a-c**, varying protection on C5-hydroxy group, in hand, radical-mediated hydrodeiodination was performed under various conditions (Table 1). Interestingly, PMB-iodide **2.40a** was observed to be particularly unstable compared to TBDPS-iodide **2.40b** under visible-light-induced photoredox condition by our group, probably due to the presence of a methoxy-aryl group that could participate in the redox process (entry 2, entry 3). In the reductive deiodination reaction with Bn-iodide **2.40c** that was more stable for redox-problem photocatalytic conditions gave higher yields of lactone **2.41c** than traditional organosilane based condition (entry 4, entry 5-7). After considerable experiments, lactone **2.41c** was obtained in 81% yield when the reaction was performed using the combination of $[Ir(ppy)_2(dtbbpy)]PF_6$ catalyst and both DIPEA and Hantzsch ester as the reductants.

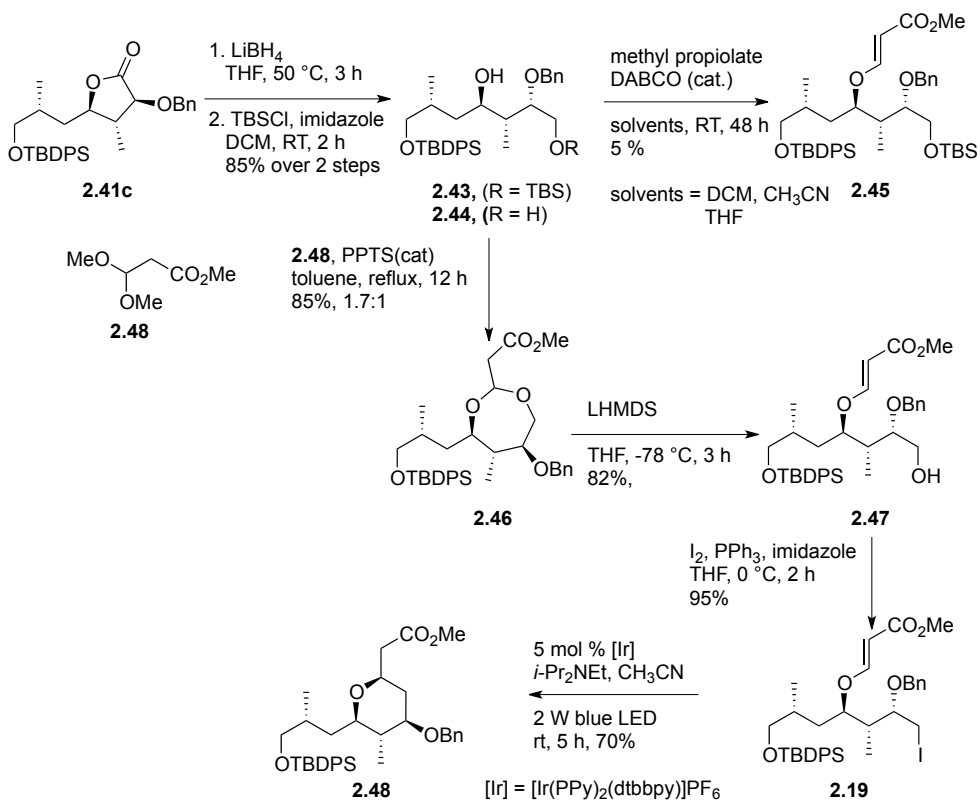


Scheme 2.10 Determination of relative C7 stereochemistry

After establishing the sequence involving Ireland-Claisen, iodolactonization and hydrodeiodination, the synthesis of minor lactone **2.42** commenced with slightly modified condition to ensure the structure of major lactone **2.41c**. Starting from acid **2.38**, γ, δ-unsaturated acid **2.39** was prepared and further reacted with iodine in situ in the presence of H_2O and $NaHCO_3$ at room temperature to provide inseparable mixture of iodide **2.40c** (1.4 : 1), which was converted to major lactone **2.41c** and minor lactone **2.42** by radical mediated transformation (Scheme 2.10). With two isomers **2.41c** and **2.42** in hand, determination of the relative C7 stereochemistry was realized through nOe analysis. Irradiation of H7 in **2.41c** showed nOe enhancements to H5 (2%) and H28 (2%) and irradiation of H7 in **2.42** showed nOe enhancements to H6 (4%) (Scheme 2.10). Based on this analysis, we concluded that major lactone **2.41c** has (*R*)-C7-configuration.

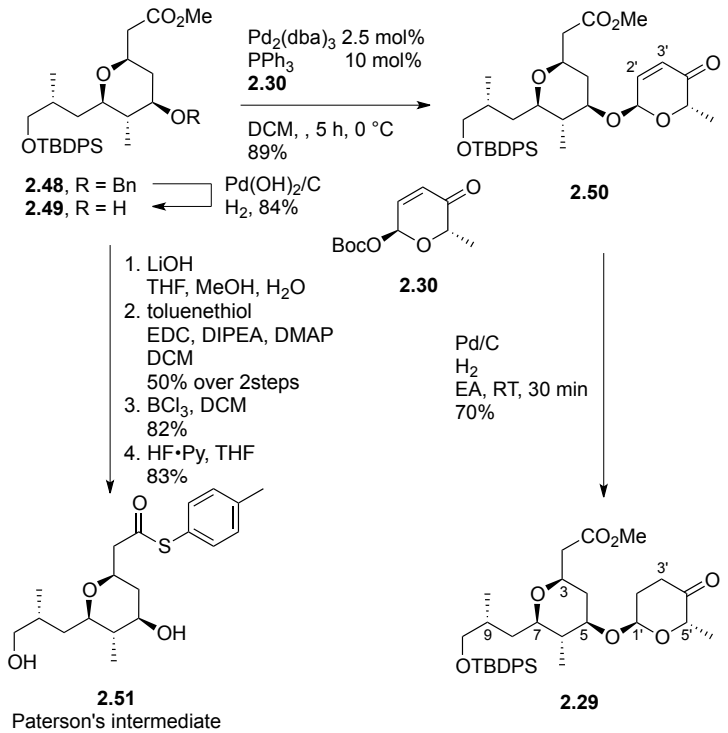
2.2.3 Completion of C1-C10 subunit, A ring

After the construction of C4-C10 subunit **2.41c** possessing four stereocenters, we turned our attention into β-alkoxyacrylate **2.19** for the radical cyclization (scheme 2.11). Following reduction of lactone **2.41**, the resulting diol **2.44** was silylated selectively at the primary hydroxyl group to give TBS ether **2.43**, which was then subjected to well-established protocols for the Michael reaction with propiolates. However, the Michael reaction of alcohol **2.40** at various conditions met with failure, producing the β-alkoxyacrylate **2.45** product in low yields (<5%), probably due to steric congestion around the C7 alcohol. To overcome this problem, we attempted to introduce cyclic acetal **2.46** that could generate β-alkoxyacrylate **2.47**, using the reactive primary alcohol of **2.44**.



Scheme 2.11 Synthesis of C1-C10 aglycon

As planned, transacetalization between diol **2.44** and acetal **2.48** gave a good yield of cyclic acetal **2.46**, which was then converted to **2.47** by selective β-elimination of lithium enolate.[12] By producing iodide **2.19** with an Appel reaction, we were ready for radical mediated cyclization. In the presence of the iridium catalyst in conjunction with DIPEA, irradiation of **2.19** with a 2 W blue LED (λ_{max} = 454 nm) strip led to clean reductive cyclization giving rise to the targeted tetrahydropyran **2.48** in 70% yield with complete 2,6-*cis*-selectivity.



Scheme 2.12 Completion of C1-C10 glycoside 2.29

Having C1-C10 aglycon **2.48** in hand, our attention was turned to stereoselective formation of an α-glycosidic linkage (Scheme 2.12). Following reductive removal of benzyl group from **2.48**, the resulting alcohol **2.49** was subjected to palladium-catalyzed glycosylation with pyranone **2.30**[13] to generate α-glycoside **2.50** as single anomer. Finally, hydrogenation of C2'-C3' alkene in the cinerulose furnished desired glycoside **2.29** in good yield with small amount (15%) of deglycosidic alcohol **2.49**.

After the construction of glycoside, we conducted detailed NMR comparisons of the C1-C10 glycoside **2.29** with the corresponding natural product data (Figure 2.1).[14] While there are some deviations in C9-C10 alcohol termini, a high degree of homology was noted in the all NMR signals from the C1−C7 as well as the C1′−C6′

regions. In addition, chemical correlation was also conducted by converting methyl ester **2.48** to thioester **2.51**[2] (Scheme 2.12), a key intermediate in the related synthesis reported by the Paterson group. All spectroscopic data of thioester **2.51** corresponded to the reported values in all aspects, indicating the identity of the structure.

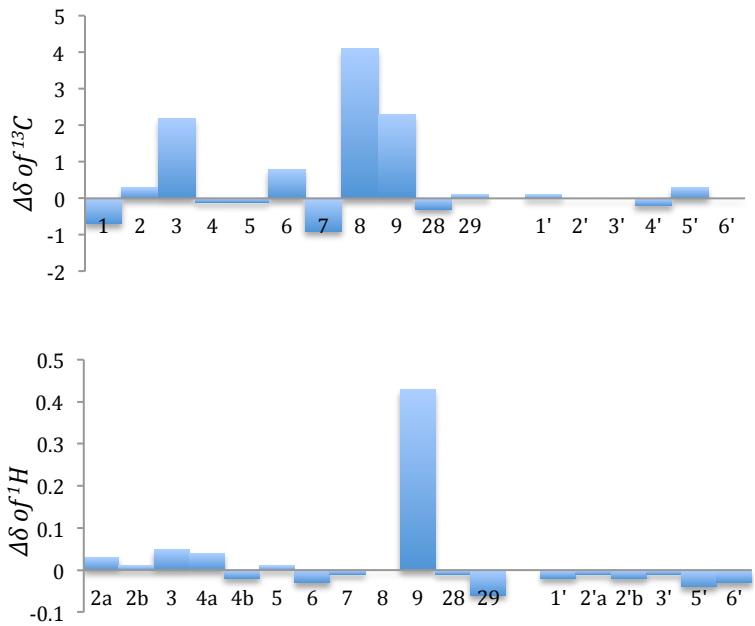
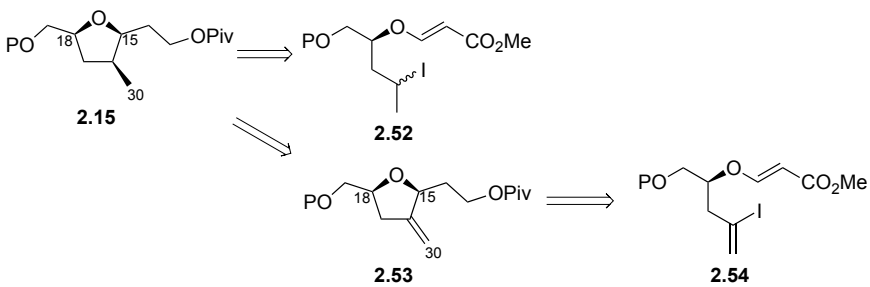


Figure 2.1 NMR comparison of the C1-C10 glycoside 2.29 with madeirolide A (2.1)

2.3 Synthesis of C13-C19 subunit, B ring

2.3.1 Synthetic plan

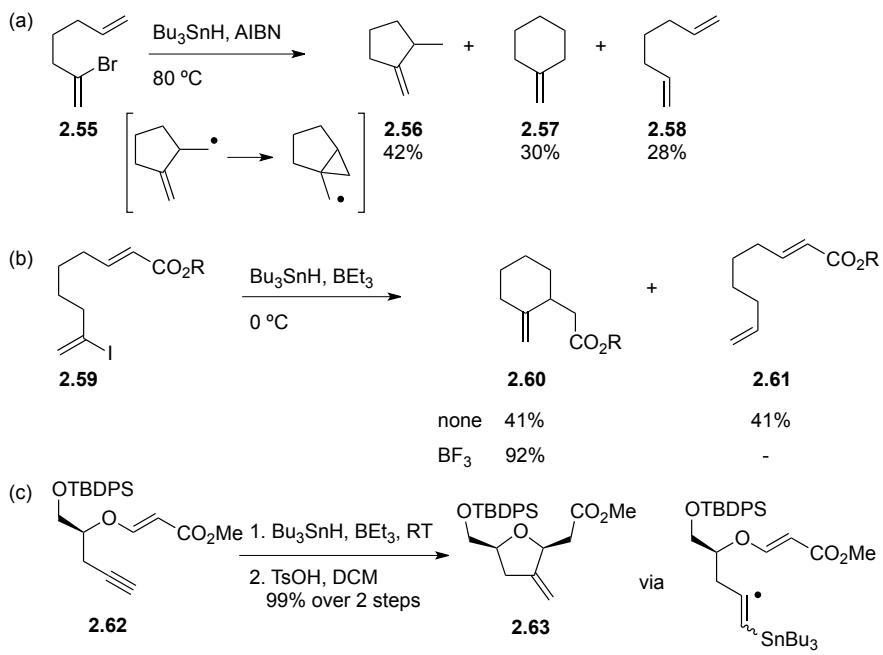


Scheme 2.13 Retrosynthetic analysis of C13-C19 subunit, B ring

Because of the aforementioned poor 2,3-stereoselectivity of radical cyclization from alkyl iodide **2.52**, we proposed *exo*-methylene-THF **2.53** as an alternative target which did not have stereochemical issue on C16. In mandelalide A syntheses, Smith's group[1g] and Carter's group[1f] found that 3-*exo*-methylene tetrahydrofuran skeleton of **2.53** was hydrogenated by Rh/H_2 condition in a stereocontrolled fashion, possessing the requisite stereochemistry at C16. We assumed that *exo*-methylene **2.53** would be obtained by free radical cyclization of vinyl iodide **2.54** under visible-light-induced photoredox condition (Scheme 2.13).

In the classical tin-mediated cyclization of vinyl radical, interesting features have been reported. Radical cyclization of simple bromide **2.55** gave cyclopentane **2.56**, cyclohexane **2.57** and alkene **2.58** in a 1.5:1.1:1 ratio.[15a] The generation of cyclohexane **2.57** was caused by radical rearrangement via α-cyclopropyl radical intermediate. When the radical cyclization was carried out at low temperature with iodide **2.59** having an ester moiety to stabilize the cyclized radical, rearrangement product was not observed. In addition, without the Lewis acid, the production of

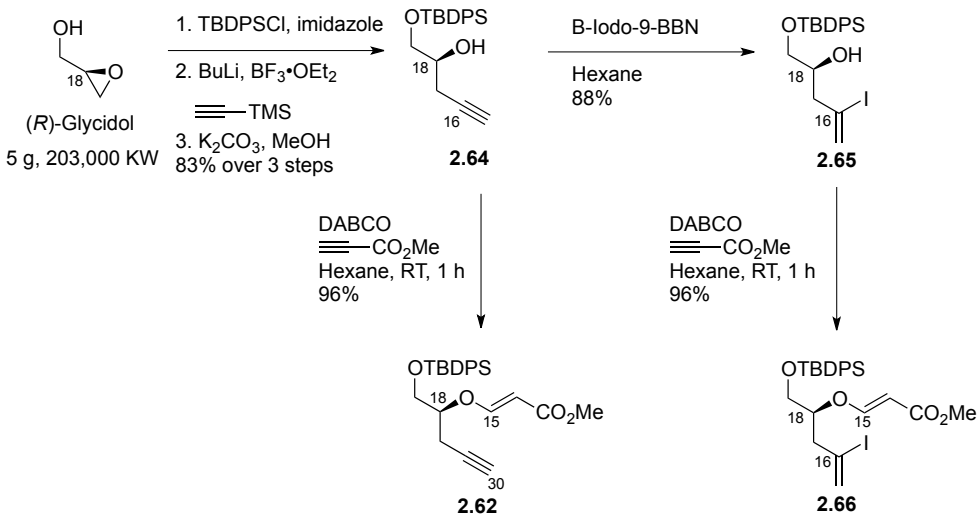
alkene **2.61** could not be prevented.[15b] In total synthesis of (-)-amphidinolide K, Lee's group reported that alkyne **2.62** was subjected to triethylborane-initiated radical cyclization condition to produce *exo*-methylene THF **2.63** via stannylated vinyl radical (scheme 2.14).[15c] Based on these results, visible-light-induced photoredox condition would be explored in an effort toward *exo*-methylene THF skeleton of **2.53** from vinyl iodide and/or alkyne moieties.



Scheme 2.14 Tin-mediated cyclization of vinyl radical

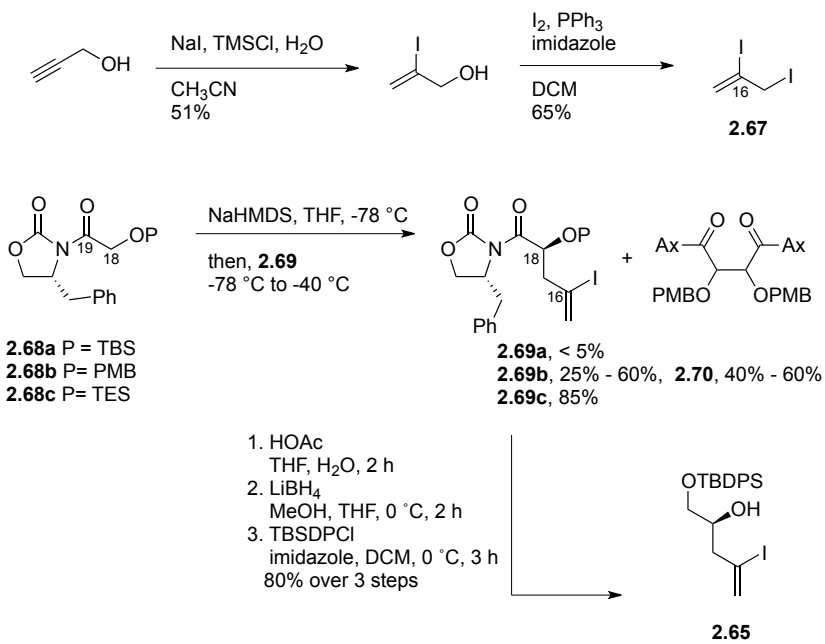
2.3.2 Substrate synthesis

Enyne **2.62** was prepared by the reported route[15c] starting with the commercially available (*R*)-glycidol possessing appropriate configuration at C18 (Scheme 2.15). After protection with TBDPSCl, epoxide opening, followed by selective deprotection of TMS-acetylide furnished homo-propargylic alcohol **2.64** in 85% yield.



Scheme 2.15 Substrate synthesis for radical cyclization, I

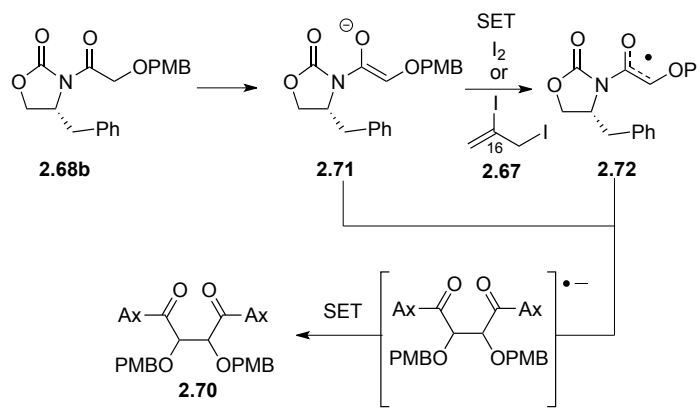
The conjugate addition of alcohol **2.64** to the activated triple bond of methyl propiolate was carried out under standard base-catalyzed conditions[5] to produce β-alkoxyacrylate **2.62**. Careful treatment of B-iodo-9-BBN[16] in nonpolar medium was used to convert alkyne **2.64** to the corresponding vinyl iodide **2.65** through a sequence involving regioselective iodoborylation and acid mediated deborylation. Resulting alcohol **2.65** was also transformed to β-alkoxyacrylate **2.66** under the standard condition.



Scheme 2.16 Substrate synthesis for radical cyclization, II

After following the Lee group route, we endeavored to construct our own synthetic route toward vinyl iodide **2.65**. In order to introduce C18 alcohol with stereocontrol, we attempted a diastereoselective allylation of chiral auxiliary-bearing glycolate[17] **2.68** with allylic iodide **2.67** (Scheme 2.16). Active iodide **2.67** was obtained by a simple sequence of hydroiodination[18] and Appel type iodination from propargyl alcohol. When we investigated the allyation with glycolate **2.68a-c**, varying protection group on C18-hydroxy group, TES-glycolate **2.68c** converted to corresponding vinyl idodie **2.69c** in good yield. On the other hand, the sodium enolate, generated from TBS-glycolate **2.68a**, was observed lack of reactivity due to steric bulkiness of TBS-protecting group. Interestingly, the allylation of PMB-glycolate **2.68b** gave corresponding vinyliodide **2.69b** in moderate yield with dimerization product **2.69** as a major product. A plausible mechanism for the isolation of dimer-product is outlined in Scheme 2.17. Electron-rich enolate **2.71**

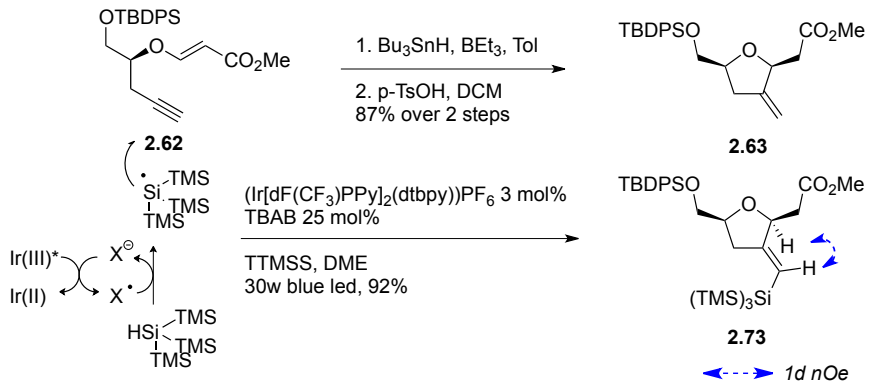
may participate in single electron transfer to I_2 which was produced by uncontrollable pathway from reactive iodide **2.67** or itself. The resulting radical **2.72** and enolate **2.71** might get coupled via radical addition to furnish anionic radical intermediate, which was then oxidized via single electron transfer to generate dimer **2.70**. Finally, after a sequence involving deprotection of the TES-ether and a reductive removal of the auxiliary, resulting diol was silylated selectively to give mono-protected alcohol **2.65**.



Scheme 2.17 Proposed mechanism for the generation of dimer 2.70

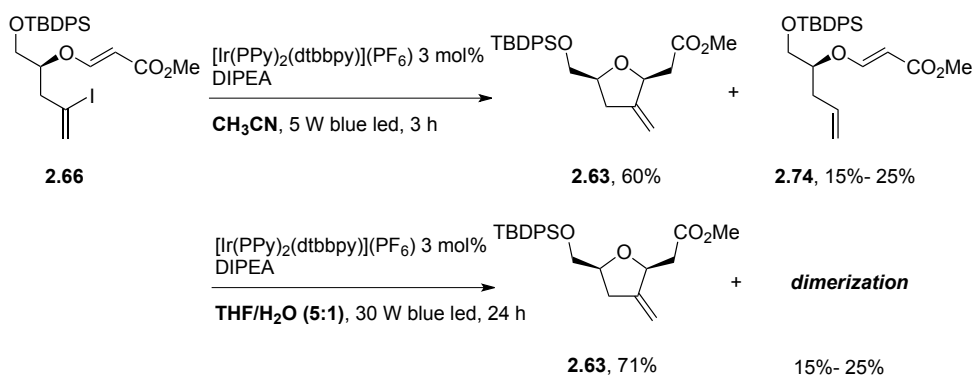
2.3.3 Visible-Light-Induced radical cyclization of B-ring

Having alkyne **2.62** and vinyl iodide **2.66** in hand, our attention was turned to visible-light-induced radical cyclization. In the classical tin-mediated reaction, the addition of stannyl radical to the alkyne could produce the β-stannylated vinyl radical[6a,19] that was a reliable intermediate in terms of radical cyclization. To reproduce this type of reaction in a photoredox condition, we attempted to utilize tirs(trimethylsilyl)silane as a precursor of assistant radical such as stannane.



Scheme 2.18 Radical cyclization of B ring, I

In the photoredox reaction using Ir[dF(CF_3)ppy]$_2$(dtbbpy)PF_6 as catalyst, MacMillan's group reported that single-electron oxidation of a bromide anion by a photoexcited catalyst produced electrophilic bromine radical which could then abstract hydrogen atoms from Si-H bond to generate the stable silyl radical intermediate of TTMSS.[20] Following this protocol, the reaction was performed with the combination of Ir[dF(CF_3)ppy]$_2$(dtbbpy)PF_6 catalyst (3 mol%), tetrabutyl-ammonium bromide (25 mol%) and TTMSS (1.5 equiv) to obtain oxolane **2.73** in 92% yield (Scheme 2.18).

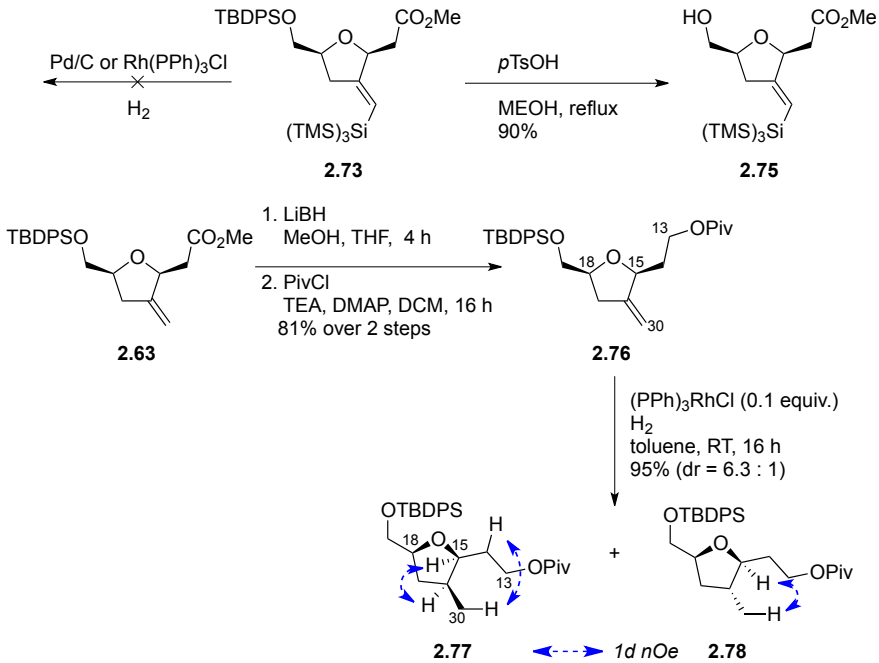


Scheme 2.19 Radical cyclization of B ring, II

With the success of the cyclization of alkyne **2.62**, photo-induced transformation of vinyl iodide **2.66** was next investigated (Scheme 2.19). Using the condition developed by our group ($[Ir(ppy)_2(dtbbpy)]PF_6$, DIPEA, acetonitrile and 5 W blue LED), vinyl iodide **2.66** was reductively cyclized giving rise to the targeted *exo*-methylene THF **2.63** in 60% yield with simple alkene **2.74** as a minor product. This observation indicated that rapid hydrogen abstraction due to the reactivity of vinyl radicals was a challenging problem. A brief survey of literature suggested that photoinduced transformation using THF as solvent would suppress the generation of simple reduction products from organohalides.[21] When the radical cyclization was carried out through standard condition with THF/H_2O as solvent, we observed a slight increase in yield of *exo*-methylene THF **2.63** without the generation of simple alkene **2.74.**

2.3.4 Completion of C13-C19 subunit and conclusion

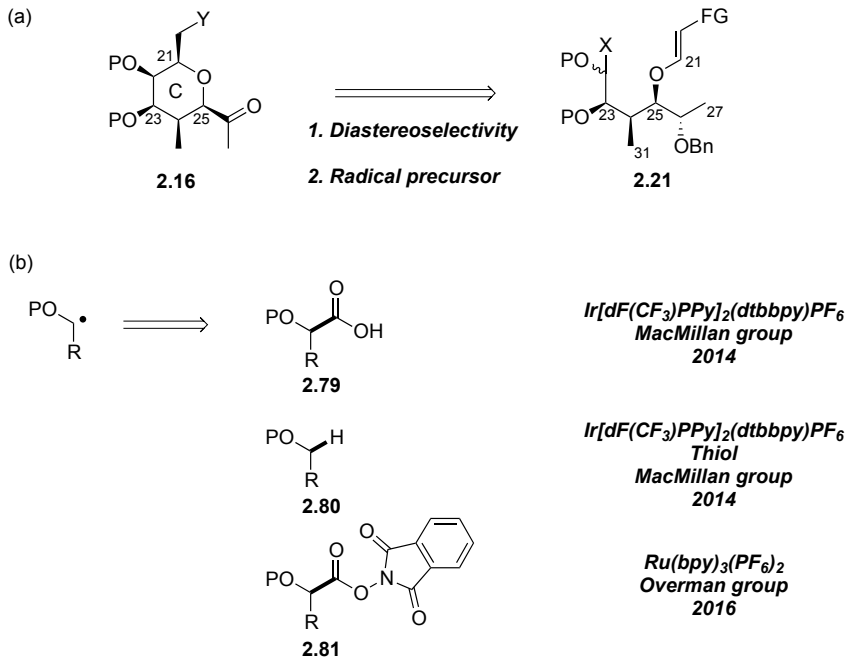
In an effort to include **2.73** in the synthetic route, the reactions aimed at the vinyl TTMS group of **2.73** such as hydrodemetallation and hydrogenation all failed. Therefore, we concluded that the cyclization strategy from alkyne **2.62** using an assistant radical should be practiced with an easily detachable group. With *exo*-methylene **2.63** in hand, the synthesis of C13-C19 subunit entered the final stage in which the construction of 2,3,5-*cis*-tetrahydrofuran-skeleton was carried out through the stereocontrolled hydrogenation on C16-C30 alkene (Scheme 2.20). Reduction of the ester, followed by protection of the resulting alcohol, furnished alkene **2.76** in 81% yield. Finally, the rhodium-catalyzed hydrogenation of C16-C30 alkene cleanly generated the fully elaborated C13-C19 fragment **2.77** in 83% yield with small amount of minor isomer **2.78**.



Scheme 2.20 Completion of C13-C19 subunit

2.4 Synthesis of C19-C27 subunit, C-ring

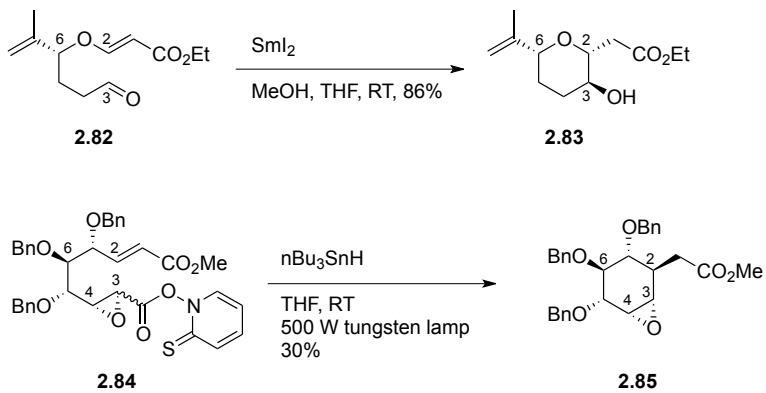
2.4.1 Synthetic plan



Scheme 2.21 (a) Synthetic issue of all-*cis*-THP 2.16 (b) Radical precursors

The C19-C27 fragment **2.16** has a complex and unusual all-*cis*-substituted tetrahydropyran core, a rare structure in natural products. From the viewpoint of the construction of oxacycles through visible-light-induced radical cyclization, some considerations should be made in terms of the diastereoselectivity issue and substrate structure as radical precursor (Scheme 2.21a). More specifically, it is challenging whether the THP core possessing requisite stereochemistry at C21-C22 could be established by the cyclization of radical precursor **2.21** having an appropriate functional group (X). In the literature study on suitable precursors, three α-oxyradical precursors were reported by the MacMillan group[22a,22b] and the Overman group[22c] in visible-light-induced photoredox-reaction. The photoredox-

reactions using the acid **2.79** or the active-ester **2.81** as a radical precursor had reliable chemoselectivity. However, in the case of ether **2.80**, which was converted into radicals through hydrogen abstraction by a thiol-radical, chemoselectivity could not be assured in the presence of C-H bonds having similar reactivity, and thus ether **2.80** was excluded as a precursor (Scheme 2.21b).

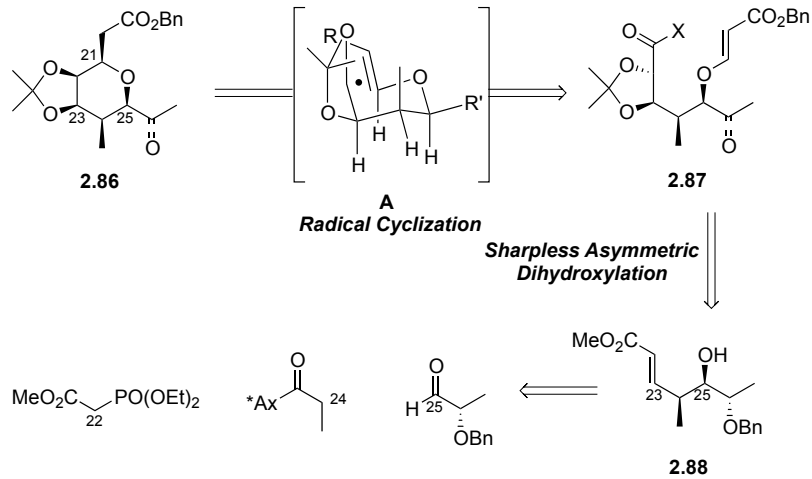


2.82 **2.83**

2.84 **2.85**

Scheme 2.22 Stereoselectivity of radical cyclization

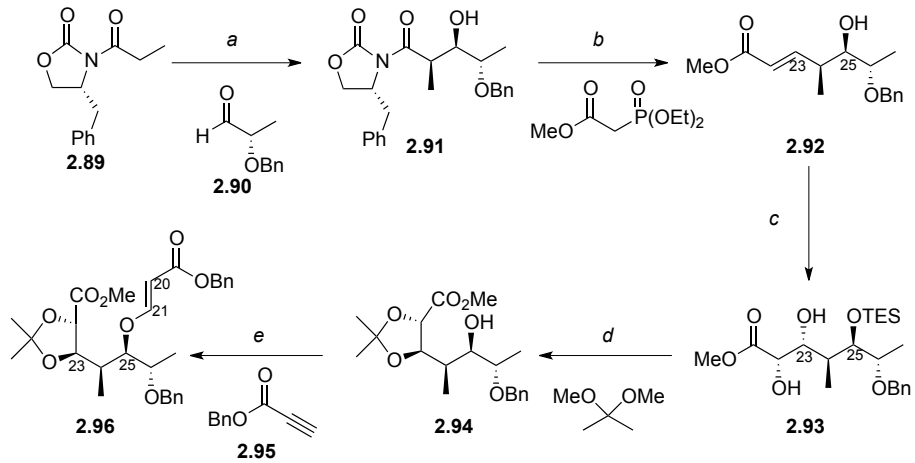
Diastereoselectivity, which was generally found high in the cyclization of α-oxyradicals, was next surveyed in literature (Scheme 2.22). When aldehyde **2.82** was exposed to SmI_2 to generate the α-hydroxy radical, the radical cyclization proceeded by way of 6-membered transition state with all-equatorial substituents, which led to furnish 2,3-*anti*-THP **2.83**.[23a] Thus, such α-hydroxy radicals are not suitable for the generation of 21,22-*cis*-THP **2.16** in a stereocontrolled fashion. In another example, the cyclization reaction was carried out using active ester **2.84**, from which α-oxyradical was generated at a rigid oxirane, to give *cis*-fused bicycle **2.85** with excellent selectivity.[23b] This encouraging result seemed to hold promise for the construction of the *cis*-diol at C22-C23.



Scheme 2.23 Retrosynthetic analysis of C19-C27 subunit

In light of the aforementioned reports, we proposed that the all-*cis*-THP skeleton of **2.86** would be constructed through free radical cyclization of ester derivative **2.87** under visible-light-induced photoredox condition. The requisite stereochemistry of THP **2.86** would be installed by way of transition state **A**, where rigidity of dioxolane structure may play a prominent role for *cis*-configuration at C22-C23. For the preparation of **2.87**, Sharpless asymmetric dihydroxylation from enoate **2.88** would generate a diol product with appropriate C23 stereocenter. Two stereogenic centers, C24-C25, of enoate **2.88** would be established through the Evans aldol reaction.

2.4.2 Substrate synthesis

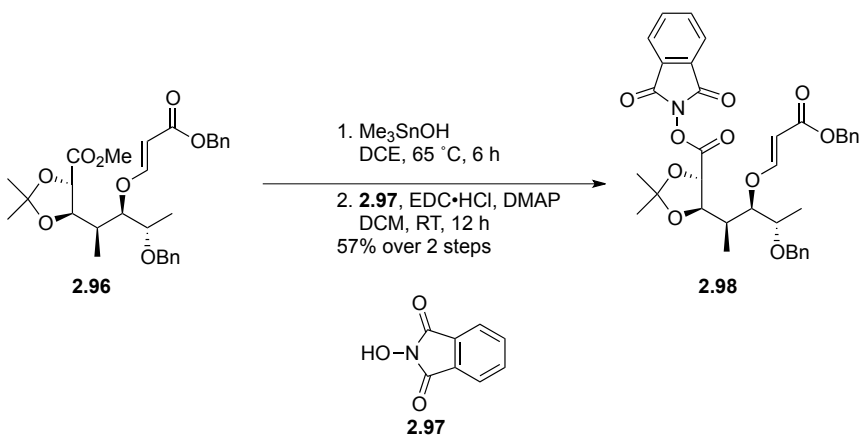


(a) Et_2BOTf, TEA, DCM, -78 ˚C, then, **2.90**, 2 h, 90% (b) (i) Dibal, THF, -78 °C, 5 h (ii) LiBr, TEA THF, rt, 16 h, 85% over 2 steps (c) (i) TESOTf, 2,6-Lutidine (ii) AD-mix-ß, $MeSO_2NH_2$, *t*-BuOH/H_2O, 0 ˚C, 48 h, 91% over 2 steps (d) TsOH(cat), DCM, rt, 60 h, 92 % (e) **2.95**, DABCO (20 mol%), Hexane, rt, 2 h, 92%

Scheme 2.24 Substrate synthesis of C19-C27 subunit, I

In the forward direction, the synthesis of ester **2.96** began with chiral auxiliary-bearing imide **2.89** which was subjected to a *syn*-aldol reaction with readily available aldehyde **2.90** to provide alcohol **2.91** with excellent diastereoselectiviy. After reductive removal of chiral auxiliary using DIBAL, the resulting aldehyde was exposed to Hornor-Wadsworth-Emmons conditions to give rise to two carbon-elongated enoate **2.92** in 85% yield over two steps. When the Sharpless asymmetric dihydroxylation reaction was conducted without protection of the hydroxy group at C25, the resulting triol transformed to a six-membered lactone or was hydrolyzed to form a free acid. Thus, protection of enoate **2.92** with TESCl and subsequent Sharpless asymmetric dihydroxylation gave diol **2.93** having suitable stereochemistry at C23-C25 in good yield. Resulting diol **2.93** was subjected to transacetalization and desilylation simultaneously under mildly acidic

condition in the presence of dimethoxypropane to produce 5-membered acetonide **2.94** as a major product. The conjugate addition of alcohol **2.94** to the activated triple bond of **2.95** was carried out under standard base-catalyzed condition[5] to furnish β-alkoxyacrylate **2.96**. For the synthesis of active ester **2.98**, acrylate **2.96** was subjected to selective methyl ester hydrolysis under various conditions. After failure to obtain the monoacid product under basic conditions using LiOH or KOTMS, the use of Me_3SnOH led to successful mono hydrolysis. The resulting acid was condensed with **2.97** to give active ester **2.98** in moderate yield due to its instability to silica gel chromatography.

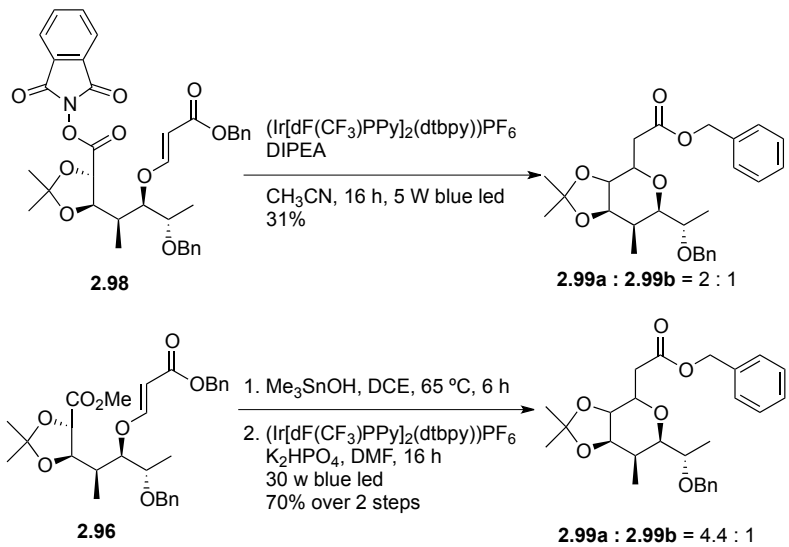


Scheme 2.25 Substrate synthesis of C19-C27 subunit, II

2.4.3 Visible-Light-Induced radical cyclization of C-ring

Having active ester **2.98** in hand, our attention was turned to visible-light-induced radical cyclization (Scheme 2.26). In the standard condition of our group ($[Ir(ppy)_2(dtbbpy)]PF_6$, DIPEA, acetonitrile and 5 W blue LED), the reductive cyclization of active ester **2.98** gave THP **2.99** in 31% yield as a 2:1 mixture of

diastereomers along with complex byproducts. Only two of the four theoretically possible diastereomers were observed, albeit with low diastereoselectivity.



Scheme 2.26 Radical cyclization of C19-C27 subunit

Photo-induced oxidation of carboxylic acids for generation of α-oxy radicals was also employed to perform the radical cyclization. Hydrolysis of ester **2.96** was performed using Me_3SnOH, then the resulting carboxylic acid was irradiated with 30 W blue LED in the presence of the iridium catalyst in conjunction with K_2HPO_4 to produce THP **2.99** in 70% yield as a 4.4:1 mixture of diastereomers. In order to correctly analyze these results, it was important to find out the structure of the two diastereoisomers. Two diastereomers could be purified by repeated column chromatography. Fortunately, X-ray crystallographic analysis revealed that the major diastereomer **2.99a** had an all-*cis*-substituted THP structure (Figure 2.2).

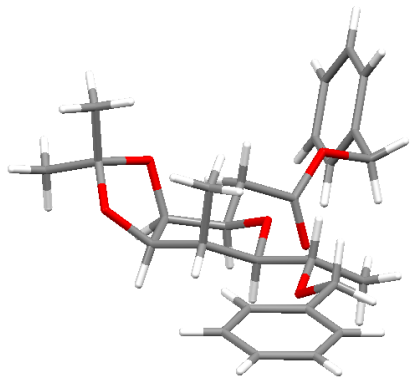


Figure 2.2 X-ray crystallography of 2.99a

After identifying the exact structure of THP **2.99a**, 1-D nOe analysis was conducted to elucidate the structure of the minor THP **2.99b** (figure 2.3). Irradiation of H21 in **2.99a** showed nOe enhancements at H23 and H25, whereas irradiation of H21 in **2.99b** showed nOe enhancements at H26 (Figure 2.3). Based on this analysis, we concluded that the minor THP **2.99b** has (*S*)-C21-configuration.

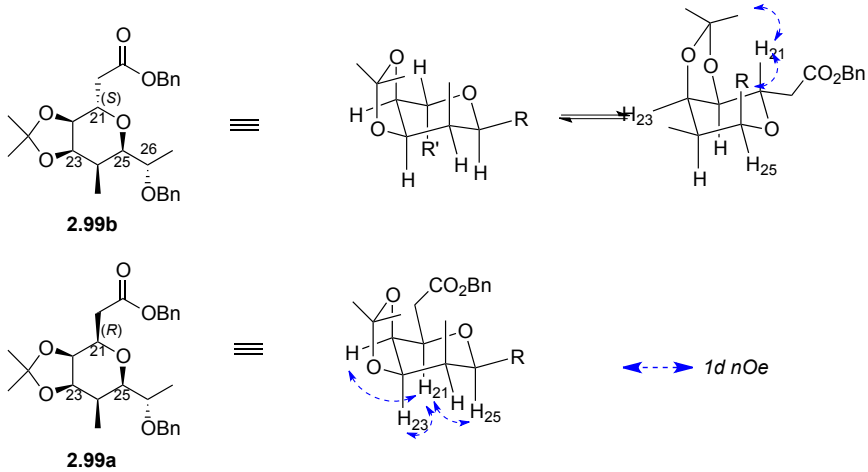
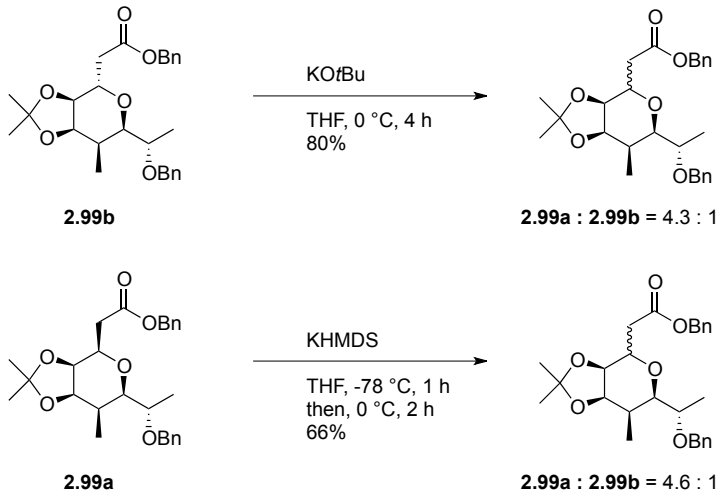


Figure 2.3 1D-nOe correlation of 2.99a and 2.99b

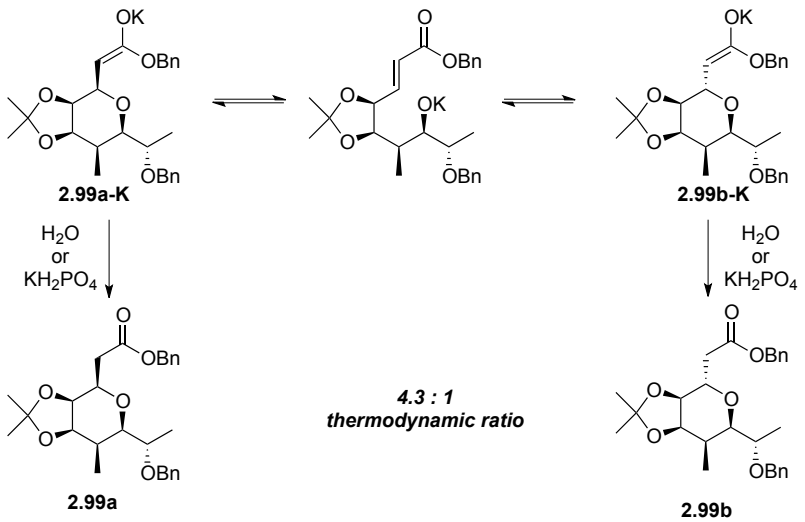


2.99b **2.99a : 2.99b** = 4.3 : 1

2.99a **2.99a : 2.99b** = 4.6 : 1

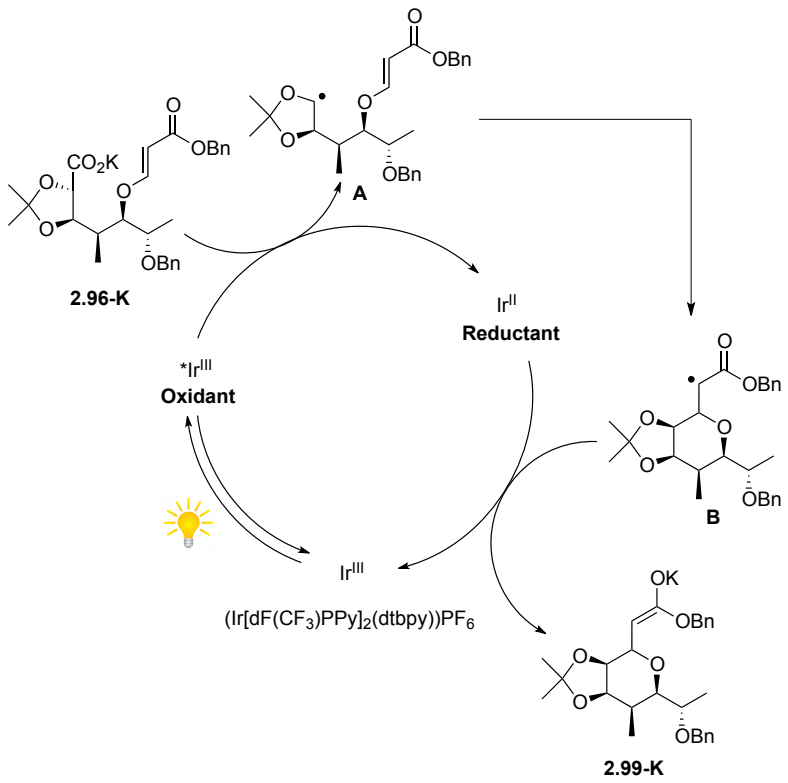
Scheme 2.27 Epimerization process of THP 2.99, I

After determining the exact structure of each isomer, epimerizations of **2.99a** and **2.99b** were carried out for further understanding the stereoselectivity of the photoredox induced radical cyclization (Scheme 2.27). The minor THP **2.99b**, when enolized under basic conditions of KO*t*Bu at 0 °C, provided THP **2.99a** as the major product in a 4.3:1 ratio. In the meanwhile, epimerization of **2.99a** also gave similar results. Two diastereomers of THP **2.99** could reach thermodynamic equilibrium through an elimination-addition process under basic conditions (Scheme 2.28). Based on these results, we could estimate the thermodynamic ratio of the two isomers to be around 4.3: 1.



Scheme 2.28 Epimerization process of THP 2.99, II

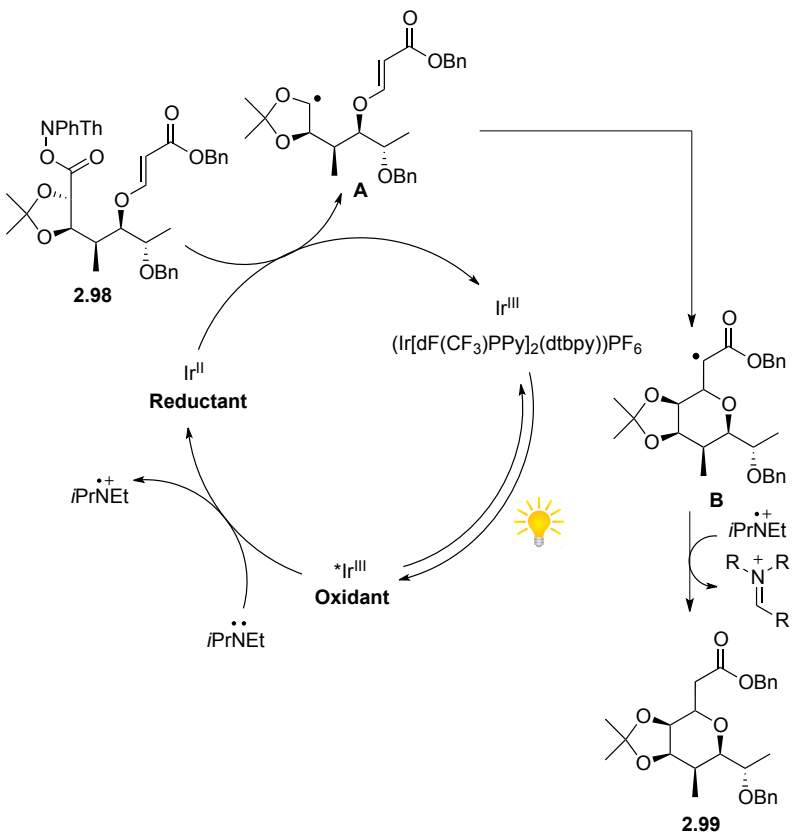
Before determining whether the selectivity of the two radical cyclizations was due to thermodynamic or kinetic preference, we would need to consider the mechanism of each reaction. In the carboxylate oxidation approach (Scheme 2.29), carboxylate potassium salt **2.96-K**, produced from ester **2.96**, is subjected to single electron oxidation by the visible-light excited photocatalyst $^{*}\mathbf{Ir^{III}}$ to generate the carboxyl radical species which immediately release CO_2 give α-oxy radical **A**. The cyclization of α-oxy radical **A**, subsequent SET reduction of resulting α-acyl radical **B** by $\mathbf{Ir^{II}}$, which was reduced by carboxylate **2.96-K**, finally produce potassium enolate **2.99-K**. If the lifetime of enolate **2.99-K** is long enough due to the slow rate of proton transfer between enolate **2.99-K** and KH_2PO_4, THP **2.99** is able to reach thermodynamic equilibrium according to the process in Scheme 2.28.



Scheme 2.29 Proposed mechanism of decarboxylative radical cyclization, free acid

The reductive cyclization of active ester **2.98** may follow a slightly different mechanism (Scheme 2.30). Following the SET reduction of active ester **2.98** by $\mathbf{Ir^{II}}$, which was generated by the redox process between excited photocatalyst $^{*}\mathbf{Ir^{III}}$ and DIPEA, homolytic fragmentation and decarboxylation of the resulting radical anion releases phthalimide, CO_2 and α-oxy radical **A**. Subsequently, after the cyclization to α-acyl radical **B**, unlike the above case where radical **B** was converted into enolate **2.99-K** through a reductive quenching process, neutral THP **2.99** is directly generated through the hydrogen abstraction with the aminyl radical. Based on this, the selectivity of the reaction with active ester **2.98** could arise from the kinetic preference of the ring closure event. However, unlike the theoretical predictions, experimental results suggest that the quenching process of the final α-

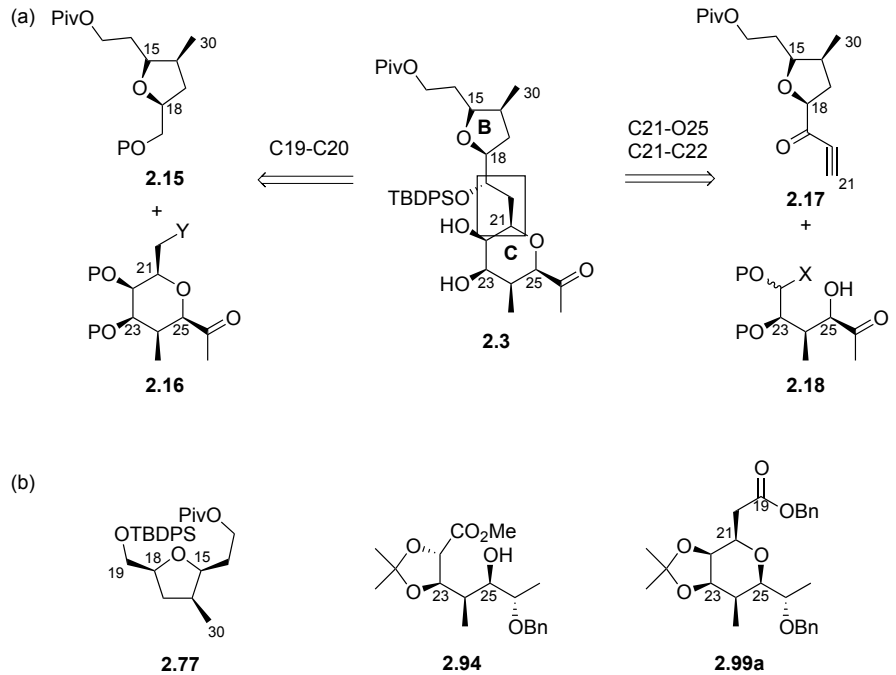
acyl radical **B** in the reductive radical cyclization can be carried out in two different ways depending on the conditions, the hydrogen abstraction process and the reduction process.[25] Thus, in order to measure the definite kinetic ratio, additional experimentation would be required under conditions that would exclude the SET reduction process, such as classic Barton decarboxylation. In conclusion, the desired all-*cis*-terahydropyran **2.99a** could be effectively synthesized in good yield and selectivity through visible-light induced radical cyclization of ester **2.96**.



Scheme 2.30 Proposed mechanism of decarboxylative radical cyclization, active ester

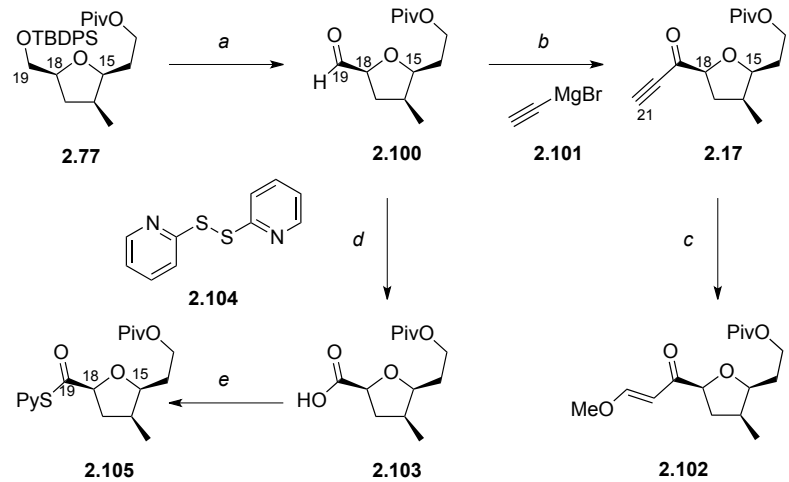
2.5 Synthesis of C13-C27 subunit

2.5.1 Substrate synthesis



Scheme 2.31 [a] Synthetic plan of C13-C27 subunit [b] Materials in our hand

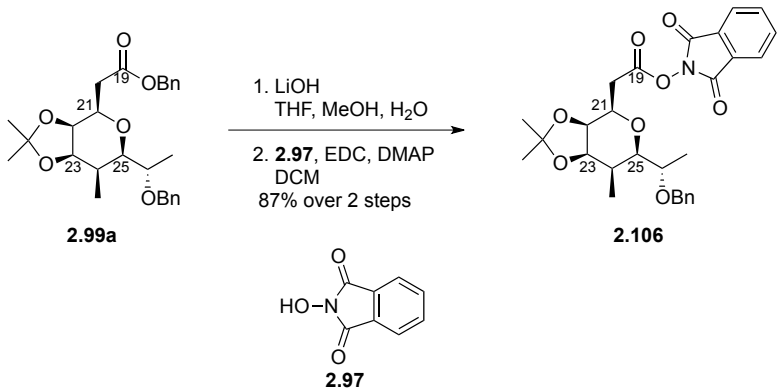
After the construction of B-C ring core structures, we combined the C13-C19 subunit **2.77** and C19-C27 subunit **2.99a**. We attempted to utilize the carbon skeleton of C19-C22 to combine the two subunits as discussed (Scheme 2.31). Furthermore, Michael reaction and decarboxylative transformation were applied, respectively, for the union of B and C ring domains. The Michael donor, alcohol **2.94**, was ready to be used, but we had to prepare the Michael acceptor ynone **2.17** from THF **2.77**. Another approach for the C13-C27 subunits **2.3** was to be explored by converting the ester group of THP **2.99a** to an active ester and conducting functional group manipulations of THF **2.77** for decarboxylative coupling.



(a) (i) TBAF, THF, RT, 3 h (ii) SO_3•Py, DIPEA, DCM, DMSO, 0 °C, 10 h, 98% over 2 steps (b) (i) **2.101**, THF, -20°C, 4 h (ii) DMP, DCM, RT, 3 h, 79% over 2 steps (c) NMM (cat.), MeOH, RT, 30 min, 90% (d) $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, tBuOH, H_2O, RT, 2 h, 84% (e) **2.104**, PPh_3, DCM, RT, 6 h, 88%

Scheme 2.32 Substrate preparation for C13-C27 subunit

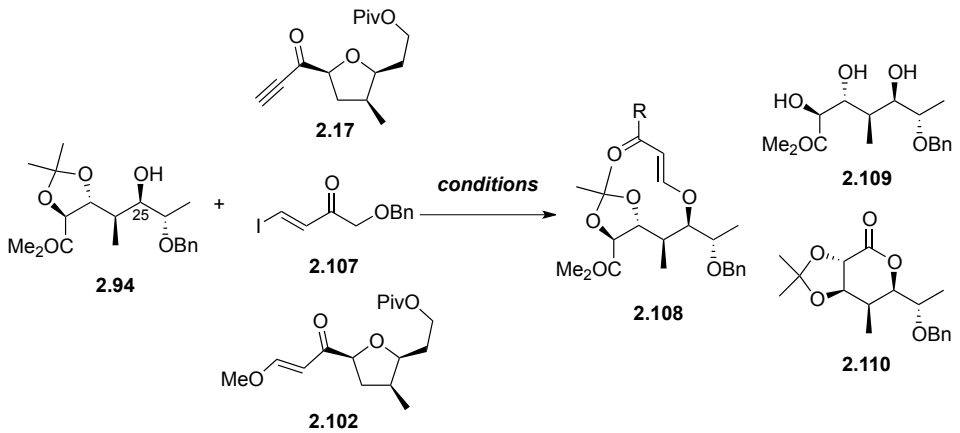
The synthetic sequence for preparation of the required precursors is outlined in Scheme 2.32. After desilylating THF **2.77**, subsequent Parikh-Doering oxidation produced aldehyde **2.100**. Following a Grignard reaction with acetylide **2.101**, the resulting alcohol was then oxidized with DMP to produce ynone **2.17** in 79% yield over two steps. In addition, enone **2.102**, which could be used as a precursor for forming β-alkoxyenone via condensation, was also prepared through methanol addition using a nucleophilic catalyst. To prepare the precursor for the decarboxylative coupling reaction, a Pinnick oxidation was conducted on aldehyde **2.100** to furnish acid **2.103**, which was then subjected to condensation under Corey-Nicolaou macrolactonization conditions (disulfide **2.104**, PPh_3) to generate thioester **2.105**.



Scheme 2.33 Substrate preparation for C13-C27 subunit, II

After functional group manipulations of THF **2.77**, the active ester was prepared for the decarboxylation coupling reaction. Hydrolysis of THP **2.99a** using LiOH, followed by the condensation of the resulting acid with **2.97**, then furnished active ester **2.106** in 87% yield over 2 steps.

2.5.2 Michael reaction approach



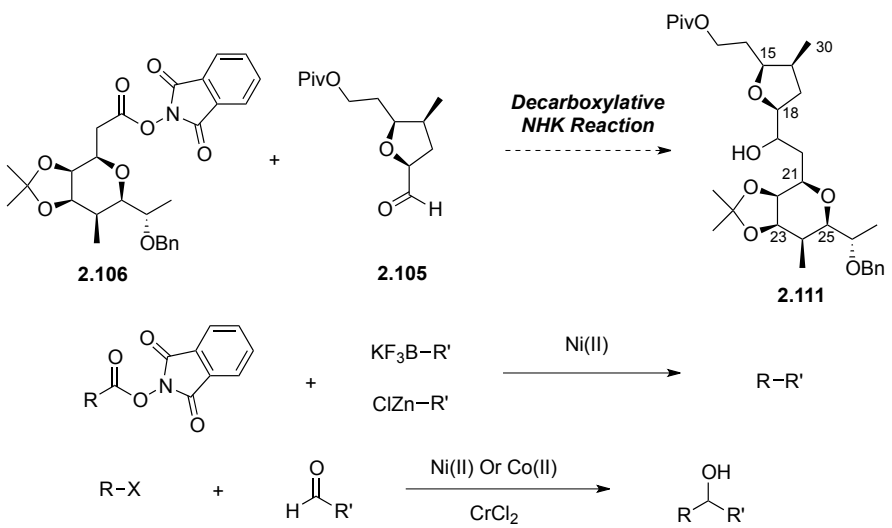
Entry	Acceptor	Conditions	Results
1	**2.17**	DABCO (0.1 equiv.), Hexane, RT, 1 h	**2.108**, 25%
2	**2.17**	PPh_3AuCl, AgOTf, DCM, 0 °C, 1 h, then, RT	**2.109**, 40%
3	**2.17**	PPh_3AuNTf_2, DCM, RT, 24 h	No reaction
4	**2.17**	CSA, DCM, RT, 24 h	No reaction
5	**2.107**	NaH, THF, then, **2.107**	**2.110**, 50%
6	**2.102**	PPTS (cat.), benzene, 20 mbar, 50 h	**2.108**, 20%

Table 2.2 Results of Michael reaction approach

The overall results for the Michael reaction of alcohol **2.94** and electrophiles are shown in Table 2.2. An attempted conjugate addition reaction of alcohol **2.94** with ynone **2.17** led to low conversion to the desired β-alkoxyenone **2.108** under standard base-catalyzed conditions[5] (entry 1). The problem with the reaction yield might be attributed to the greatly diminished reactivity of the hydroxyl group of **2.94** as Michael donor due to steric congestion around O25. In addition, the base-catalyzed reaction met with difficulty due to rapid formation of inseparable dimeric byproducts from ynone **2.17**. Consequently, Michael reactions using either π-acid[26] or Brønsted acid catalysts led to little or no consumption of both starting materials over prolonged reaction times with inconsistent triol **2.109** formation (entry 2-4).

When a sodium alkoxide was employed in order to overcome the low reactivity of alcohol **2.94**, only lactone **2.110** was obtained through intramolecular condensation (entry 5). Finally, condensation under acidic conditions with enone **2.102** led to conversion about 20% along with the formation of dimeric byproducts from **2.102** (entry 6). Based on these results, we concluded that the Michael reaction approach using alcohol **2.94** was deemed unsuitable for the fragment union.

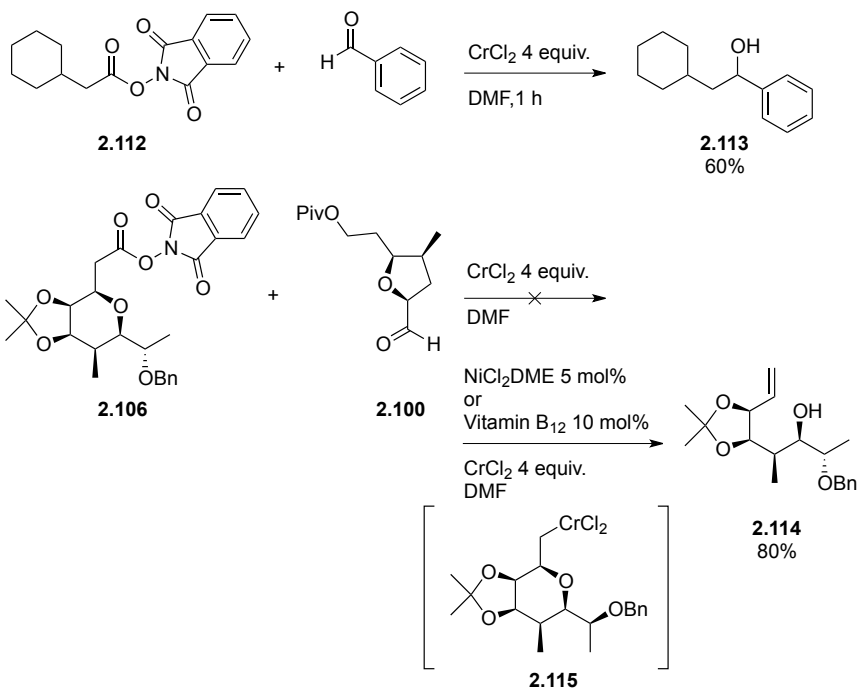
2.5.3 Decarboxylative NHK approach



Scheme 2.34 Decarboxylative union strategy, I

A first attempt of decarboxylative coupling was a Nozaki-Hiyama-Kishi reaction[27] (Scheme 2.34). The NHK reaction is a nickel/chromium-mediated coupling reaction that forms an alcohol from the reaction of an aldehyde with an organohalide. Recently, the Baran group reported that alkyl esters activated by N-hydroxy-phthalimide could engage in cross-couplings with organozinc or organoboron reagents under nickel mediated catalysis[28]. In light of these two

reactions, we proposed that the decarboxylative NHK reaction could be accomplished by a mechanistic sequence involving the oxidative addition of nickel into the active ester, transmetallation of nickel with chromium, and nucleophilic addition of organochromium with aldehyde. We expected that this method could not only unite active ester **2.106** and aldehyde **2.100**, but also introduce requisite stereochemistry at C19 under asymmetric NHK reaction conditions[29].

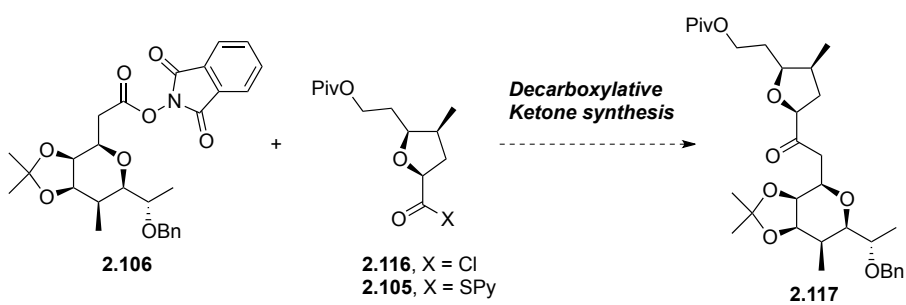


Scheme 2.35 Decarboxylative NHK approach

Prior to applying this approach to madeirolide A at the C19-C20 bond, we performed screening experiments with model active ester **2.112**. These studies confirmed that the decarboxylative NHK reaction was successfully accomplished with 4 equivalents of $CrCl_2$ to produce alcohol **2.113** with an acceptable yield. This reaction was found to be possible without nickel and cobalt, which were commonly

used to activate organohalides. On the other hand, the reaction was inefficient under chromium-catalyzed conditions using zinc or manganese as a reducing agent. Based on these basic results, the coupling reaction of active ester **2.106** with aldehyde **2.100** was carried out. While the reaction under already established conditions did not proceed, the same conditions using Ni(II) or Co(II) as an additional catalyst led to the complete consumption of active ester **2.106** with exclusive formation of alkene **2.114**. The generation of alkene **2.114** might be attributed to the β-alkoxy-elimination process from intermediate **2.115**, which was obtained through the sequence involving oxidative addition and transmetallation. A similar transformation from organozinc intermediates has been reported as a standard reaction to a pyran-ring opening strategy.[30] In conclusion, although the decarboxylative NHK reaction was found to be possible under simple reaction conditions, it could not be applied to active ester **2.106** due to the strong nucleophilicity of carbone-chromium bonds.

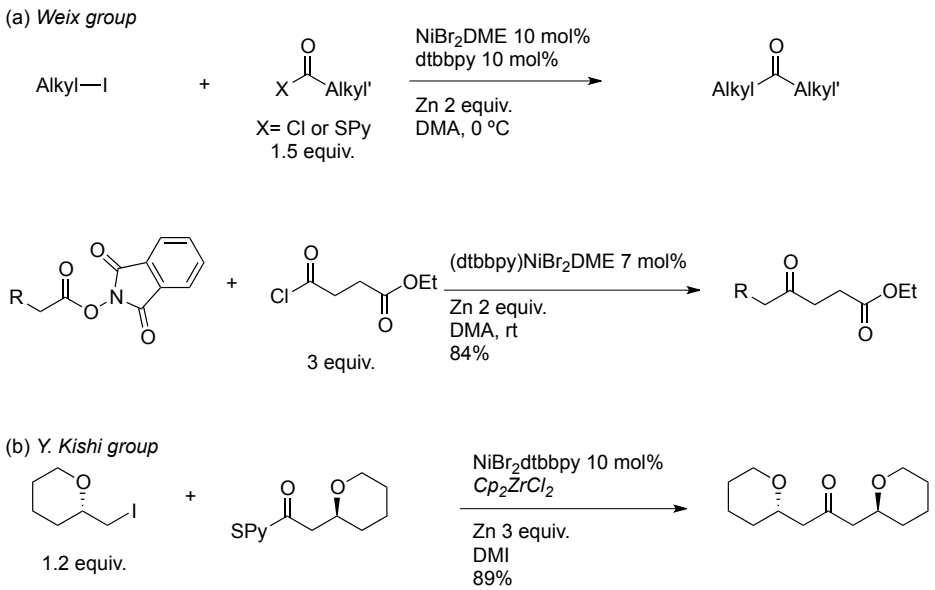
2.5.4 Reductive cross coupling: decarboxylative ketone synthesis



Scheme 2.36 Decarboxylative union strategy, II

After a series of failure to assemble the two fragments, we turned out attention to a decarboxylative ketone synthesis (Scheme 2.36). From previous work, we

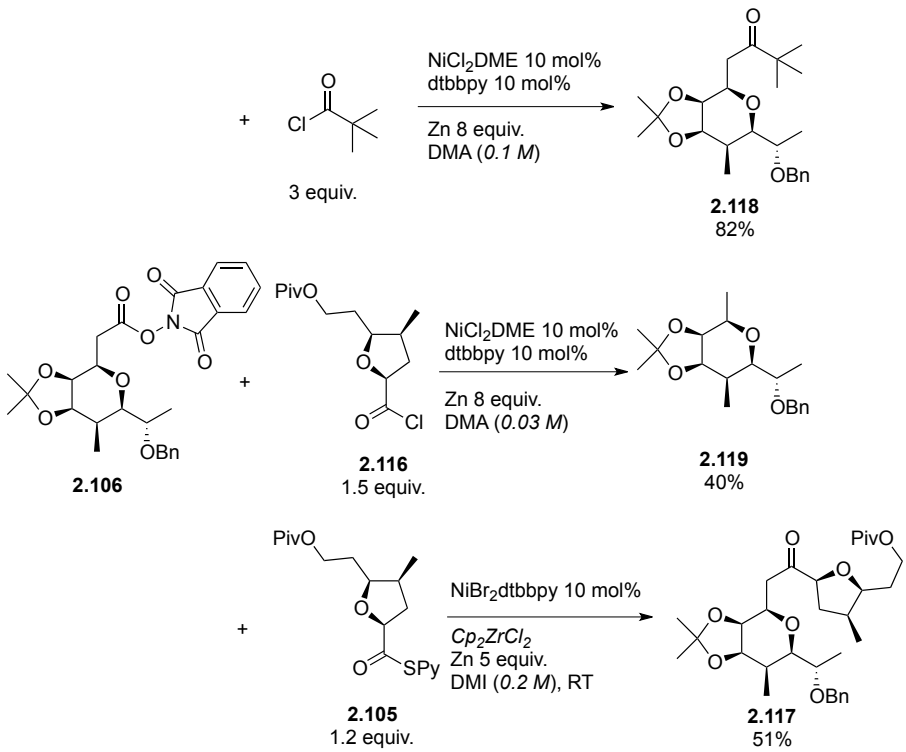
were cognizant of the reactivity of **2.106** under nickel-mediated catalysis. A brief literature review revealed that nickel intermediates might not cause a ring opening process unlike with the chromium intermediate.[31] Thus, we continued to focus on nickel catalyzed cross coupling of active ester **2.106** for the fragment assembly.



Scheme 2.37 Selected examples of Ni-catalyzed ketone synthesis

The Weix group reported that a nickel catalyzed reductive cross coupling of organohalides with acyl electrophiles like carboxylic acid chlorides and (2-pyridyl)thioesters produces dialkyl ketones with good yield.[32a] In subsequent studies, a similar transformation was reproduced using the esters activated by *N*-hydroxyphthalimide instead of organohalides[32b] (Scheme 2.37a). From the vantage point of natural product synthesis, the Kishi group dramatically improved the coupling of more complex substrates in the presence of Cp_2ZrCl_2 (Scheme 2.37b).

Consequently, the decarboxylative ketone synthesis strategy was performed based on these two results.

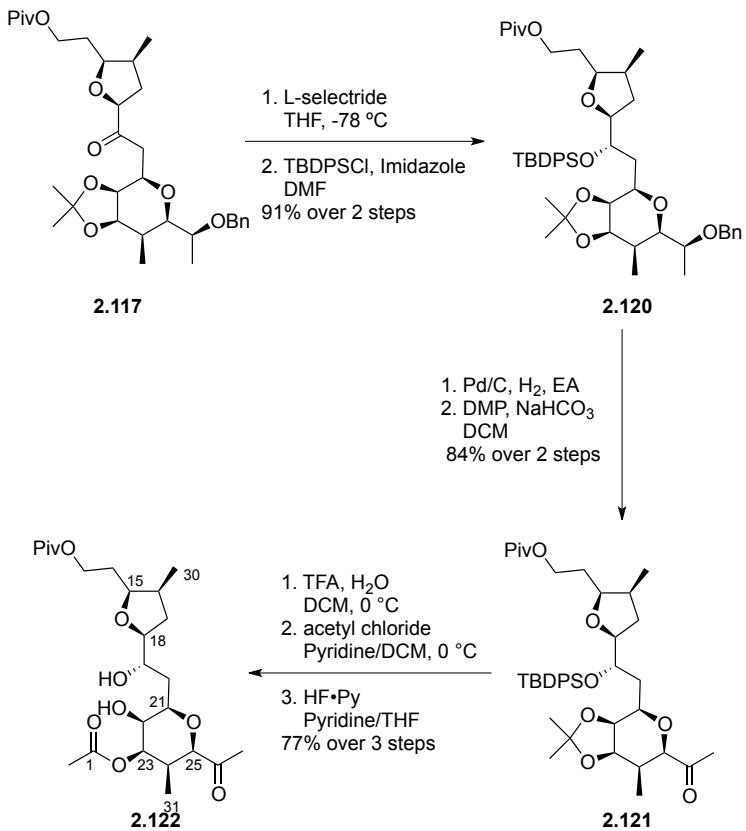


Scheme 2.38 Decarboxylative ketone synthesis approach

In a test reaction, active ester **2.106** was subjected to the nickel-catalyzed cross coupling with pivaloyl chloride under the Weix condition to produce ketone **2.118** in good yield. On the other hand, when the same condition was applied to the coupling of ester **2.106** with acyl chloride **2.116**, only the hydrodecarboxylation product **2.119** was obtained. This failure was attributed to the low concentration of the reaction due to a careful handling of chloride **2.116**. Finally, cross-coupling was carried out using a more stable electrophile, thioester **2.105**, as an alternative to **2.116** under Kishi's group conditions to produce ketone **2.117** at 51% yield. In

conclusion, it was possible to successfully assemble the two fragments by connecting the C19 of the B ring and the C20 of the C ring through the nickel-catalyzed decarboxylative cross-coupling.

2.5.4 Completion of C13-C27 subunit



Scheme 2.39 Completion of C13-C27 subunit

The synthesis of the eastern fragment **2.122** began with ketone **2.117** where all of the C13-C27 carbon skeletons were already in place. Subsequent to a Felkin-Anh selective L-selectride addition to ketone **2.117**, the resulting alcohol was directly silylated to give TBDPS ether **2.120** as a single diastereomer. The reductive detachment of the benzyl group and DMP oxidation furnished ketone

2.121 in good yield. After acidic deprotection of the acetonide group, the resulting diol was acylated with acetyl chloride selectively at the equatorial hydroxyl group to afford a mono-acylation product, thus suggesting this esterification reactivity might lend itself to the strategic step in the final stage of the total synthesis. Finally, desilylation with HF/pyridine synthesized the C13-C27 subunit **2.122.**

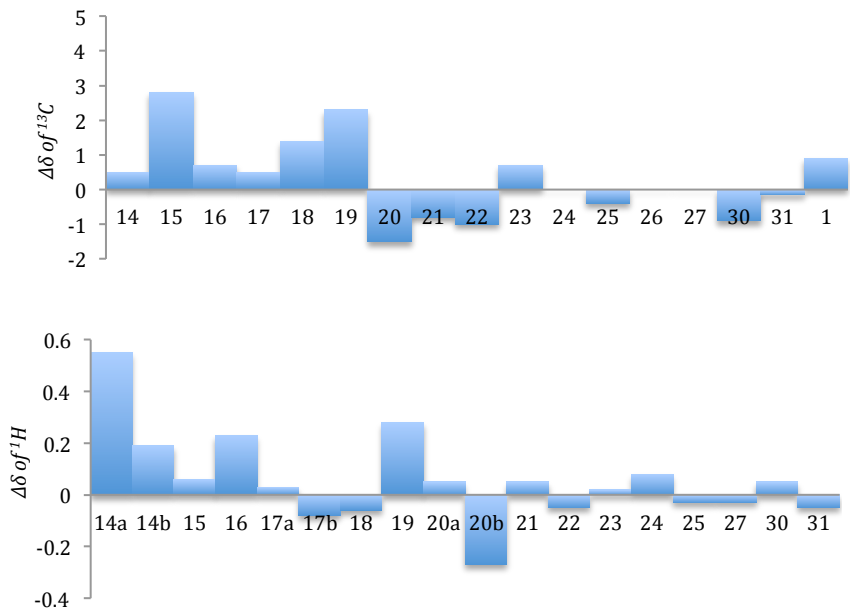
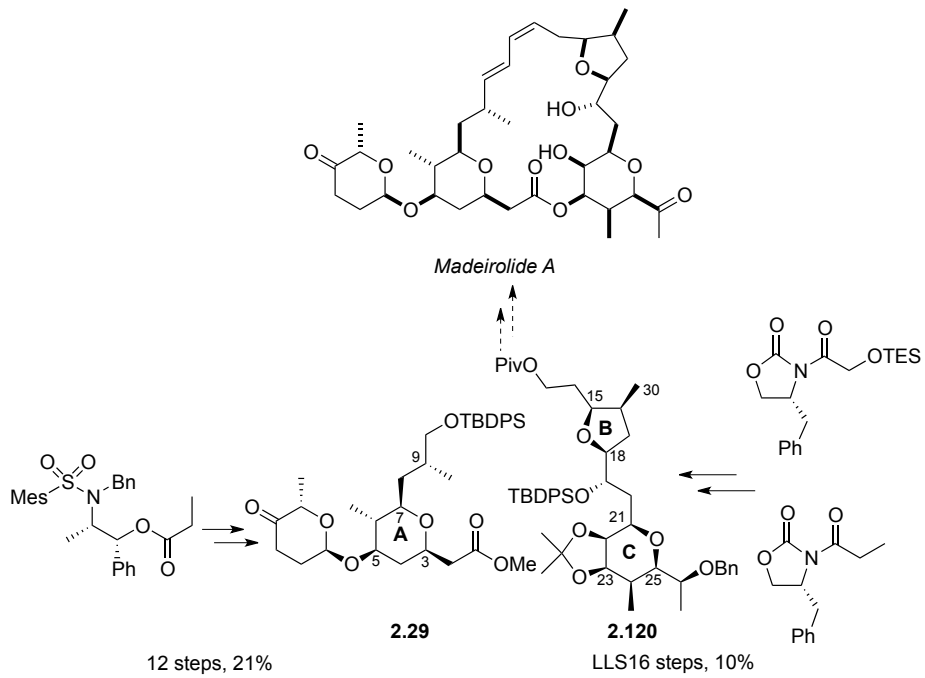


Figure 2.4 NMR comparison of the C13-C27 subunit 2.122 with madeirolide A (2.1)

Detailed NMR comparisons of C13-C27 fragment **2.122** with madeirolide A are summarized in Figure 2.4. While there are some deviations observed in the C13-C15/C19-C20 regions, which differed from the madeirolide A regions in terms of conformational freedom, a high degree of homology was noted in all NMR signals from the C21−C27 region.

2.6 Conclusion



Scheme 2.40 Summary

In summary, the syntheses of C1-C10 fragment **2.29** and C13-C27 fragment **2.120** have been successfully achieved for the total synthesis of madeirolide A (Scheme 2.32). Utilizing readily available starting materials bearing chiral auxiliary, our concise routes provided three distinct cyclic domains through the diastereo- and enantio-selective processes that included Abiko-Masamune anti aldol reaction, Ireland-Claisen reaction, iodolactonization, Evans alkylation, Evans aldol reaction, Sharpless asymmetric dihydroxylation, and radical cyclizations. Notably, three oxacycles were constructed by iridium catalyzed photo-induced radical cyclization with stereospecificity. In attempts to assemble the B ring and C ring, we investigated Michael addition and decarboxylative coupling reactions. The

nickel-catalyzed decarboxylative ketone synthesis, formulated from Weix and Kishi reactions, allowed the successful construction of the C13-C27 subunit **2.120**.

2.7 Reference

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2.8 Experimental section

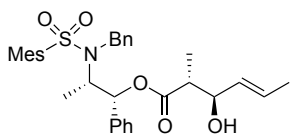
2.8.1 General information

NMR spectra were obtained on a Bruker DPX-300 (300 MHz), an Agilent 400-MR DD2 Magnetic Resonance System (400 MHz) and a Varian/Oxford As-500 (500 MHz) spectrophotometer. Chemical shift values were recorded as parts per million (δ) relative to tetramethylsilane as an internal standard unless otherwise indicated, and coupling constants in Hertz (Hz). The following abbreviations (or combinations thereof) were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, b = broad. IR spectra were measured on a Thermo Scientific Nicolet 6700 spectrometer. High resolution mass spectra were recorded from the Organic Chemistry Research Center (Seoul) on a Bruker Compact using electrospray ionization (ESI) method.

The progress of the reaction was checked on thin layer chromatography (TLC) plates (Merck 5554 Kiesel gel 60 F254), and the spots were visualized under 254 nm UV light and/or charring after dipping the TLC plate into a vanillin solution

(15.0 g of vanillin and 2.5 mL of concentrated sulfuric acid in 250 mL of ethanol), a $KMnO_4$ solution (3.0 g of $KMnO_4$, 20.0 g of K_2CO_3, and 5.0 mL of 5% NaOH solution in 300 mL of water), a ceric ammonium molybdate solution (0.5 g of Ceric ammonium sulfate, 12 g of ammonium molybdate and 15 mL of concentrated H_2SO_4 in 235 mL of H_2O) or a phosphomolybdic acid solution (250 mg phosphomolybdic acid in 50 mL ethanol). Column chromatography was performed on silica gel (Merck 9385 Kiesel gel 60). All solvents were obtained by passing through activated alumina columns of solvent purification systems from Glass Contour. Commercially available reagents were obtained from Sigma-Aldrich, Strem, TCI, Acros, or Alfa Aesar.

2.8.2 Experimental procedures and compound characterization

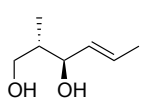


2.34

Into a flame-dried round-bottom flask were placed ester **2.33**[1] (1.30 g, 2.7 mmol), NEt_3 (0.75 mL, 6.5 mmol) and CH_2Cl_2 (13.5 mL) under nitrogen. The solution was cooled to -78 °C and a solution of dicyclohexylboron triflate (0.9 M in hexane, 6 mL, 5.4 mmol) was added dropwise. The resulting mixture was stirred at -78 °C for 2 h, after which crotonaldehyde (0.28 mL, 3.3 mmol) was slowly added over 1 h. After stirred at -78 °C for 1 h, warmed to room temperature over 1 h, the reaction mixture was quenched by addition of pH 7 buffer solution (10 mL) and hydrogen peroxide (34.5% aqueous solution, 4 mL), and was diluted with methanol

[1] Inoue, T.; Liu, J. F.; Buske, D. C.; Abiko, A. *J. Org. Chem.* **2002**, *67*, 5250.

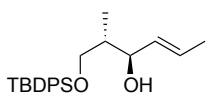
(25 mL). The whole mixture was stirred overnight and concentrated. The residue was partitioned between water and dichloromethane, and the aqueous layer was extracted with dichloromethane 3 times. The combined organic layers were washed with water and brine, and dried over with sodium sulfate. The filtered organic solution was concentrated. Flash chromatography (Hexane-EtOAc 20:1) gave aldol **2.34** (1.22 g, 2.2 mmol, 83%), and 160 mg (0.33 mmol) of starting material was recovered. $[\alpha]_d^{20}$ = 28.0 (*c* 1.25, $CHCl_3$); IR (neat) 3519, 3028, 2981, 2938, 1738, 1604, 1454, 1496, 1379, 1321, 1206, 1152, 1055, 1013, 967, 929, 858, 758, 730, 699, 661 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.36 – 7.13 (m, 8H), 6.89 (s, 2H), 6.83 (d, *J* = 7.9 Hz, 2H), 5.81 (d, *J* = 4.0 Hz, 1H), 5.78 – 5.65 (m, 1H), 5.42 (ddd, *J* = 15.2, 7.5, 1.2 Hz, 1H), 4.80 (d, *J* = 16.6 Hz, 1H), 4.57 (d, *J* = 16.6 Hz, 1H), 4.16 – 4.02 (m, 2H), 2.51 (s, 6H), 2.49 – 2.44 (m, 1H), 2.29 (s, 3H), 1.69 (d, *J* = 6.5 Hz, 3H), 1.15 (d, *J* = 7.0 Hz, 3H), 1.07 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.4, 142.7, 140.4, 138.8, 138.4, 133.6, 132.3, 131.1, 129.6, 128.5, 128.5, 128.0, 127.7, 127.3, 126.0, 78.4, 75.0, 56.9, 48.4, 45.8, 23.1, 21.0, 17.9, 14.2, 13.5; HRMS (ESI) *m/z* calc. for $[C_{32}H_{39}NO_5S+Na]$: 572.2447, found: 572.2441.



2.35

LAH (70 mg, 1.8 mmol) and THF (10 mL) were added to a dry round-bottom flask equipped with a magnetic stirring bar. The mixture was cooled to 0 °C and stirred for 10 min. To this suspension was added dropwise a THF solution (5 mL) of aldol **2.34** (830 mg, 1.5 mmol). After stirring was continued at room temperature for 1 h,

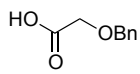
the reaction mixture was quenched with aqueous solution of Rochelle salt (saturated, 60 mL) and stirred overnight. The resulting slurry was partitioned between water and Et_2O, and the aqueous layer was extracted 5 times with Et_2O. The combined organics were dried over Na_2SO_4, filtered and concentrated. Purification by flash column chromatography (SiO_2) provided diol **2.35** (176 mg, 90%) as a colorless liquid. R_f 0.06 (hexane-EtOAc, 2:1); $[\alpha]_d^{20}$ = +9.27 (c 1.0, $CHCl_3$); IR (neat, v_{max}) 3355, 2961, 2881, 1672, 1450, 1378, 1333, 1261, 1082, 1007, 967, 927, 759 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.66 (dt, *J* = 15.6, 6.3 Hz, 1H), 5.47 (dd, *J* = 15.2, 7.7 Hz, 1H), 3.91 (td, *J* = 7.9, 2.3 Hz, 1H), 3.70 (dd, *J* = 10.8, 3.4 Hz, 1H), 3.58 (dd, *J* = 11.0, 7.6 Hz, 1H), 3.31 (br s, 1H), 3.08 (br s, 1H), 1.83 – 1.72 (m, 1H), 1.69 (d, *J* = 6.4 Hz, 3H), 0.78 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 132.8, 128.3, 79.0, 67.6, 40.1, 17.7, 13.5; HRMS (ESI) *m/z* calc. for [$C_7H_{14}O_2$+Na]: 153.0891, found: 153.0886.



2.36

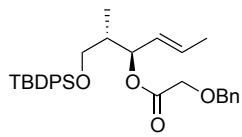
TBDPSCl (1.7 mL, 6.6 mmol) was added to a solution of **2.35** (783 mg, 6.0 mmol) and imidazole (531mg, 7.8 mmol) in CH_2Cl_2 (60 mL) at 0 °C. After stirring for 1 h, the reaction mixture was partitioned with H_2O and EtOAc. The organic phase was washed with brine, dried over Na_2SO_4, filtered, and concentrated. Purification by flash column chromatography (SiO_2) provided alcohol **2.36** (2.25 g, 98%) as a colorless liquid. R_f 0.44 (hexane-EtOAc, 5:1); $[\alpha]_d^{20}$ = +15.96 (*c* 1.0, $CHCl_3$); IR (neat, v_{max}) 3443, 3071, 2959, 2931, 2858, 1471, 1428, 1390, 1362, 1188, 1111, 1007, 967, 928, 863, 823, 741, 702, 613 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.88 –

7.61 (m, 4H), 7.56 – 7.31 (m, 6H), 5.73 (dq, *J* = 15.1, 6.4 Hz, 1H), 5.50 (dd, *J* = 15.3, 7.3 Hz, 1H), 4.06 (t, *J* = 7.2 Hz, 1H), 3.79 (dd, *J* = 10.2, 4.1 Hz, 1H), 3.63 (dd, *J* = 10.5, 7.1 Hz, 1H), 3.6 (s, 1H), 1.84 (ddd, *J* = 14.3, 7.2, 4.2 Hz, 1H), 1.73 (d, *J* = 6.5 Hz, 3H), 1.08 (s, 9H), 0.81 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 135.7, 135.7, 134.9, 133.0, 132.7, 129.9, 127.9, 127.8, 77.8, 68.7, 40.3, 26.9, 19.2, 17.9, 13.5; HRMS (ESI) *m/z* calc. for [$C_{23}H_{32}O_2Si$+Na]: 391.2069, found: 391.2064.



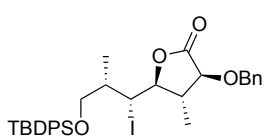
2.37

Benzyl alcohol (4.31 mL, 41.6 mmol) was added to a suspension of NaH (60% dispersion in mineral oil, 3.2 g, 80 mmol) in THF (80 mL) at 0 °C. After the gas evolution ceased (ca. 5 min), a solution of bromoacetic acid (2.89 g, 20.8 mmol) in THF (10 mL) was added dropwise and the resulting mixture was heated under reflux for overnight. The reaction mixture was cooled to room temperature, quenched with water, and partitioned with saturated $NaHCO_3$ solution and EtOAc. The aqueous layer was washed away with EtOAc (2 times), and 12 N HCl was added to acidify the aqueous phase (pH < 4). The aqueous layer was extracted with EtOAc (3 times) and the combined organics were dried over Na_2SO_4 and filtered. Concentration gave acid **2.37** (3.37g, 98% yield) as a yellow liquid. R_f 0.12 (hexane-EtOAc-AcOH, 80:20:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.74 (br s, 1H), 7.41-7.32 (m, 5H), 4.67 (s, 2H), 4.17 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 175.9, 136.6, 128.6, 128.2, 128.1, 73.4, 66.5.



2.38

A suspension of EDAC·HCl (1.07 g, 5.6 mmol) in CH_2Cl_2 (5 mL) was added to a mixture of alcohol **2.36** (1.48 g, 4.0 mmol), acid **2.37** (800 mg, 4.8 mmol), DMAP (48 mg, 0.4 mmol) and CH_2Cl_2 (20 mL) at 0 °C. The reaction mixture was stirred at room temperature for 13 h, poured into water and extracted with EtOAc. The organic layers were washed with saturated $NaHCO_3$ solution 3 times, saturated NH_4Cl solution 2 times, and brine once, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. Purification by flash column chromatography (SiO_2) provided ester **2.38** (1.98 g, 93%) as a colorless liquid. R_f 0.60 (hexane-EtOAc, 5:1); $[\alpha]_d^{20}$ = +3.52 (*c* 1.0, $CHCl_3$); IR (neat, ν_{max}) 3069, 2960, 2932, 2858, 1752, 1471, 1428, 1390, 1262, 1198, 1112, 1028, 967, 823, 741, 702, 615 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.66 – 7.62 (m, 4H), 7.43 – 7.29 (m, 11H), 5.83 – 5.72 (m, 1H), 5.46 – 5.32 (m, 2H), 4.58 (s, 2H), 3.99 (s, 2H), 3.53 (d, *J* = 5.6 Hz, 2H), 2.04 – 1.95 (m, 1H), 1.68 (dd, *J* = 6.5, 1.5 Hz, 3H), 1.06 (s, 9H), 0.92 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.4, 135.6, 131.2, 129.6, 128.4, 128.0, 127.6, 126.8, 77.3, 73.2, 67.3, 65.0, 39.5, 26.8, 19.2, 17.8, 12.6; HRMS (ESI) *m/z* calc. for [$C_{32}H_{40}O_4Si$+Na]: 539.2594, found: 539.2588.



2.40c

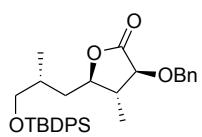
Freshly distilled TMSCl (0.29 mL, 2.3 mmol) was added to a solution of ester **2.38** (300 mg, 0.58 mmol) in THF (15 mL) at -78 °C. After stirring at -78 °C for 20 min,

KHMDS (0.5 M in toluene, 1.2 mL, 2.3 mmol) was added dropwise. After stirring at -78 °C for 30 min, the reaction mixture was allowed to warm up to room temperature and stirred for additional 2 h, after which it was poured into a 1:1 mixture of saturated aqueous NH_4Cl and 1 M HCl solutions. After extraction with EtOAc (3 times), the combined organic extracts were washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure to provide crude acid **2.39** (305 mg) as yellowish sticky oil. The crude acid was dissolved in CH_3CN (10 mL) and mixed with sat. aq. $NaHCO_3$ (487 mg, 5.8 mmol). To this solution cooled to -40 °C was added dropwise a solution (10 mL) of iodine (589 mg, 2.3 mmol) in CH_3CN (10 mL). After stirring at -40 °C for 24 h, the reaction mixture was diluted with Et_2O and quenched by addition of sat. aq. $Na_2S_2O_3$ solution. The mixture was extracted with Et_2O (3 times) and the combined organic extracts were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash column chromatography (SiO_2) provided an inseparable diastereomeric mixture (dr = 9:1) of iodide **2.40c** (321 mg, 85%) as a colorless liquid.

2.39 $[\alpha]_d^{20}$ = -10.34 (*c* 1.00, $CHCl_3$); IR (neat, ν_{max}) 3030, 2958, 2930, 2857, 1717, 1589, 1567, 1458, 1427, 1387, 1214, 1111, 1027, 1027, 972, 939, 823, 739, 702, 612 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.67 – 7.65 (m, 4H), 7.43 – 7.29 (m, 11H), 5.53 – 5.42 (m, 2H), 4.67 (d, *J* = 12.1 Hz, 1H), 4.45 (d, *J* = 12.1 Hz, 1H), 3.88 (d, *J* = 4 Hz, 1H), 3.54 (dd, *J* = 9.6, 6.4 Hz, 1H), 3.46 (dd, *J* = 9.6, 6.8 Hz, 1H), 2.72 – 2.64 (m, 1H), 2.41 – 2.31 (m, 1H), 1.07 (d, *J* = 7.2 Hz, 3H), 1.05 (s, 9H), 1.01 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.3, 137.0, 137.0, 135.8, 134.5, 134.4, 134.1, 130.5, 130.5, 129.7, 128.6, 128.3, 128.3, 128.2, 127.7, 82.1, 73.4,

68.8, 40.0, 39.3, 27.0, 19.5, 16.8, 15.1.; HRMS (ESI) *m/z* calc. for [$C_{32}H_{40}O_4Si$+Na]: 539.2594, found: 539.2589.

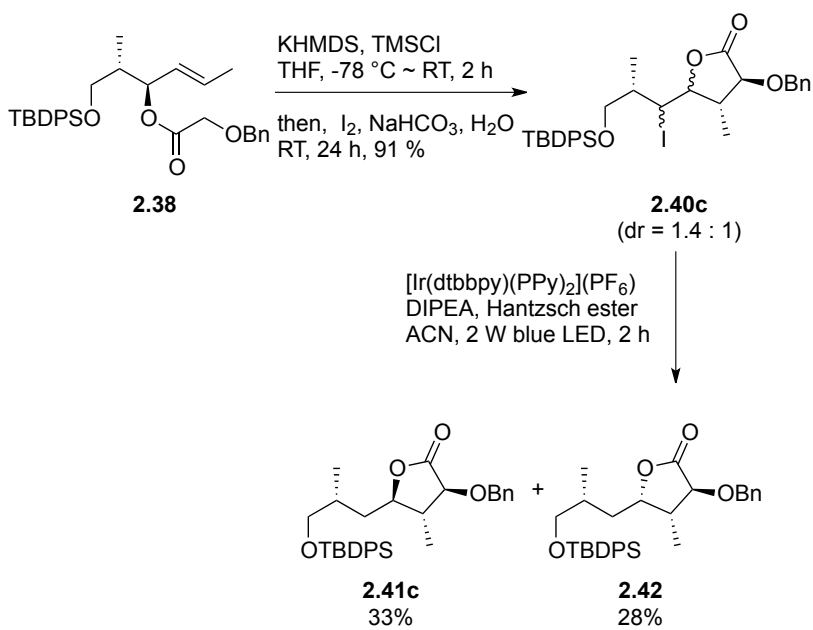
2.40c R_f 0.55 (hexane-EtOAc, 5:1); $[\alpha]_d^{20}$ = -35.57 (*c* 1.0, $CHCl_3$); IR (neat, ν_{max}) 3069, 2959, 2931, 2858, 1786, 1589, 1459, 1427, 1388, 1324, 1183, 1107, 979, 824, 807, 741, 700, 639, 613 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.80 – 7.58 (m, 4H), 7.58 – 7.27 (m, 11H), 4.94 (d, *J* = 12.1 Hz, 1H), 4.75 (d, *J* = 12.1 Hz, 1H), 4.36 (dd, *J* = 9.9, 4.5 Hz, 1H), 3.73 (d, *J* = 4.8 Hz, 1H), 3.51 (dd, *J* = 10.2, 5.3 Hz, 1H), 3.38 (t, *J* = 9.7 Hz, 1H), 2.71 – 2.36 (m, 1H), 1.84 – 1.50 (m, 1H), 1.25 (d, *J* = 7.2 Hz, 3H), 1.04 (s, 9H), 0.79 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.9, 136.9, 135.8, 135.6, 133.4(2), 129.9, 129.8, 128.7, 128.4, 128.3, 127.9, 127.8, 85.6, 79.3, 72.3, 68.1, 43.7, 42.5, 36.3, 26.9, 19.3, 17.9, 13.6; HRMS (ESI) *m/z* calc. for [$C_{32}H_{39}IO_4Si$+Na]: 665.1560, found: 665.1555.



2.41c

To a 10 mL round-bottom flask equipped with a magnetic stir bar were placed iodide **2.40c** (20 mg, 0.031 mmol), Hantzsch ester (16 mg, 0.062 mmol) and $[Ir(ppy)_2(dtbbpy)]PF_6$ (1 mg, 1 μmol). The flask was then flushed with a stream of argon before the addition of CH_3CN (1 mL) and DIPEA (10 μL, 0.062 mmol). The resulting yellow solution was placed in an irradiation apparatus equipped with a 2 W blue light-emitting diode (LED) strip, and stirred at room temperature for 2 h, at which point the TLC analysis indicated complete consumption of the starting iodide. The reaction mixture was passed through a bed of silica gel by elution with

ethyl acetate. The filtrate was concentrated and purified by flash column chromatography on silica gel to furnish lactone **2.41c** (13 mg, 81%) as a colorless liquid. R_f 0.26 (hexane-EtOAc, 10:1); $[\alpha]_d^{20}$ = -36.4 (*c* 1.0, $CHCl_3$); IR (neat, ν_{max}) 3069, 2960, 2932, 2858, 1781, 1460, 1428, 1390, 1226, 1183, 1111, 1029, 978, 824, 743, 703, 615 cm^{-1}; ^1H NMR (400 MHz, cdcl$_3$) δ 7.73 – 7.57 (m, 4H), 7.50 – 7.28 (m, 11H), 5.11 (d, *J* = 11.7 Hz, 1H), 4.79 (d, *J* = 11.7 Hz, 1H), 3.96 (ddd, *J* = 9.8, 9.8, 2.3 Hz, 1H), 3.81 (d, *J* = 10.6 Hz, 1H), 3.50 (d, *J* = 5.2 Hz, 2H), 2.22 – 2.08 (m, 1H), 2.08 – 1.94 (m, 1H), 1.76 (ddd, *J* = 14.2, 10.1, 3.8 Hz, 1H), 1.49 (ddd, *J* = 14.4, 9.9, 2.3 Hz, 1H), 1.09 (d, *J* = 6.6 Hz, 3H), 1.05 (s, 9H), 0.95 (d, *J* = 6.7 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.2, 137.4, 135.7, 135.7, 133.8, 133.8, 129.7, 128.6, 128.34 128.2, 127.8, 80.4, 79.6, 72.5, 68.9, 43.5, 37.3, 32.4, 27.0, 19.4, 16.2, 14.2; HRMS (ESI) *m/z* calc. for [$C_{32}H_{40}O_4Si$+Na]: 539.2594, found: 539.2588.

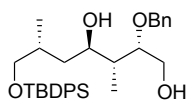


Following the previous procedure for the Ireland-Claisen rearrangement, ester **2.38** (400 mg, 0.77 mmol) in THF (15 mL) was reacted with TMSCl (0.4 mL, 3.1 mmol) and KHMDS (0.5 M in toluene, 6 mL, 3 mmol). After TLC monitoring indicated complete consumption of the starting ester, H_2O (0.14 mL, 7.7 mmol) and $NaHCO_3$ (647 mg, 7.7 mmol) were added to the reaction mixture. After 10 min, iodine (780 mg, 3.1 mmol) was added, and the stirring was continued at room temperature for 24 h. The reaction mixture was diluted with Et_2O and quenched by addition of saturated $Na_2S_2O_3$ solution. After extraction with ether (3 times), the combined organic extracts were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash column chromatography (SiO_2) provided iodide **2.40c** (450 mg, 91%, dr = 1.4:1, inseparable mixture) as a colorless liquid. R_f 0.55 (hexane-EtOAc, 5:1).

To a 10 mL round-bottom flask equipped with a magnetic stir bar were placed iodide **2.40c** (446 mg, 0.69 mmol), Hantzsch ester (350 mg, 1.38 mmol) and $[Ir(ppy)_2(dtbbpy)]PF_6$ (32 mg, 0.035 mmol). The flask was then flushed with a stream of argon before the addition of CH_3CN (50 mL) and DIPEA (0.24 mL, 1.38 mmol). The resulting yellow solution was placed in an irradiation apparatus equipped with a 2 W blue light-emitting diode (LED) strip, and stirred at room temperature for 2 h, at which point the TLC analysis indicated complete consumption of the starting iodide. The reaction mixture was passed through a pad of silica gel by elution with ethyl acetate. The filtrate was concentrated and purified by flash column chromatography on silica gel to furnish isomeric lactones **2.41c** (120 mg, 33%) and **2.42** (97 mg, 28%) both as colorless liquid.

2.42 R_f 0.29 (hexane-EtOAc, 10:1); $[\alpha]_d^{20}$ = -65.6 (*c* 1.0, $CHCl_3$); IR (neat, ν_{max}) 3070, 2959, 2931, 2858, 1775, 1459, 1427, 1389, 1341, 1203, 1110, 1026, 976,

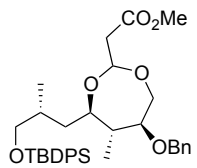
938, 823, 756, 703, 614 cm^{-1}; ^{1}H NMR (499 MHz, $CDCl_3$) δ 7.96 – 7.55 (m, 4H), 7.55 – 7.28 (m, 11H), 4.99 (d, *J* = 11.7 Hz, 1H), 4.72 (d, *J* = 11.7 Hz, 1H), 4.67 (ddd, *J* = 10.4, 6.5, 4.1 Hz, 1H), 3.78 (d, *J* = 6.3 Hz, 1H), 3.61 (dd, *J* = 10.1, 4.9 Hz, 1H), 3.51 (dd, *J* = 10.1, 5.7 Hz, 1H), 2.62 – 2.44 (m, 1H), 1.94 – 1.83 (m, 1H), 1.79 (ddd, *J* = 14.1, 7.3, 4.1 Hz, 1H), 1.32 (ddd, *J* = 14.1, 10.3, 6.1 Hz, 1H), 1.07 (s, 9H), 1.01 (d, *J* = 7.0 Hz, 3H), 0.99 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 174.9, 137.3, 135.7, 135.7, 133.8, 133.7, 129.8, 128.6, 128.3, 128.2, 127.8, 127.8, 127.8, 80.2, 79.5, 72.2, 67.7, 39.8, 33.8, 32.7, 27.0, 19.4, 17.9, 11.5; HRMS (ESI) *m/z* calc. for [$C_{32}H_{40}O_4Si$+Na]: 539.2594, found: 539.2588.



2.44

A solution of $LiBH_4$ (2 M in THF, 0.23 mL, 0.46 mmol) was added to a stirred solution of lactone **2.41c** (234 mg, 0.45 mmol) in THF (5 mL) at 0 °C. The reaction mixture was stirred at 50 °C for 3 h, cooled to 0 °C, quenched by sat. aq. NH_4Cl (10 mL), and extracted with EtOAc (3 x 10 mL). The combined organics were washed with brine, dried over sodium sulfate, filtered, and concentrated *in vacuo*. Purification of the residue by flash column chromatography (SiO_2) afforded diol **2.44** (220 mg, 95%) as a colorless liquid. R_f 0.21 (hexane-EtOAc, 2:1); $[\alpha]_d^{20}$ = +13.8 (*c* 1.0, $CHCl_3$); IR (neat, ν_{max}) 3433, 3069, 2931, 2858, 1470, 1389, 1361, 1216, 1110, 1028, 824, 756, 703, 615 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 – 7.66 (m, 4H), 7.51 – 7.28 (m, 11H), 4.80 – 4.63 (m, 2H), 3.80 (m, 2H), 3.76 – 3.72 (m, 1H), 3.72 – 3.64 (m, 1H), 3.55 (d, *J* = 6.0, 2H), 2.49 (s, 2H), 2.07 – 1.94 (m, 1H), 1.92 – 1.79 (m, 1H), 1.57 – 1.47 (m, 1H), 1.47 – 1.37 (m, 1H), 1.10 (s, 9H),

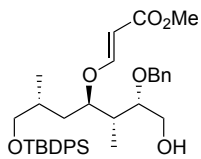
1.00 – 0.92 (m, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 138.3, 135.7, 133.7, 129.7, 128.6, 128.6, 128.0, 127.9, 127.7, 82.1, 72.7, 72.0, 70.1, 62.6, 40.5, 40.1, 33.0, 27.0, 19.4, 17.0, 12.7; HRMS (ESI) *m/z* calc. for [$C_{32}H_{44}O_4Si$+Na]: 543.2907, found: 543.2901.



2.46

To a solution of diol **2.44** (130 mg, 0.25 mmol) in toluene (5 mL) were added methyl 3,3-dimehoxypropionate (0.11 mL, 0.75 mmol) and pyridinium *p*-toluenesulfonate (3 mg, 0.013 mmol) at room temperature. After heated to reflux for 12 h, the reaction mixture was concentrated under reduced pressure. Purification of the residue by flash column chromatography (SiO_2) afforded acetal **2.46** (128 mg, 85%, inseparable diastereomeric mixture, dr = 1: 1.7) as a colorless liquid. R_f 0.17 (hexane-EtOAc, 10:1); $[\alpha]_d^{20}$ = -10.2 (*c* 1.0, $CHCl_3$); IR (neat, ν_{max}) 2933, 2860, 1744, 1429, 1388, 1259, 1255, 1194, 1130, 1102, 1069, 824, 751, 704 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 (d, *J* = 6.3 Hz, 4H), 7.48 – 7.27 (m, 11H), 5.24 (t, J= 6 Hz, 0.4H), 5.17 (t, *J* = 5.8 Hz, 0.6H), 4.71 – 4.59 (m, *J* = 11.5 Hz, 1H), 4.51 (d, *J* = 11.4 Hz, 1H), 4.04 (dd, *J* = 11.6, 4.0 Hz, 0.4H), 3.76 (m, 1.6H), 3.69 (s, 1.9H), 3.69 (s, 1.1H), 3.64 – 3.34 (m, 4H), 3.12 (m, 1H), 2.71 – 2.56 (m, 1.6H), 2.52 (dd, *J* = 14.9, 5.1 Hz, 0.4H), 1.99 – 1.83 (m, 0.6H), 1.83 – 1.69 (m, 0.4H), 1.67 – 1.57 (m, 1H), 1.57 – 1.47 (m, 1H), 1.42 – 1.31 (m, *J* = 10.7, 7.9, 2.4 Hz, 1H), 1.07 (s, 9H), 1.00 – 0.88 (m, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.2, 138.3, 135.8, 135.8, 135.7, 134.1, 134.0, 129.6, 128.5, 128.1, 128.1, 127.9, 127.7, 99.1,

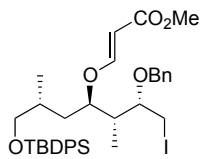
97.6, 83.5, 82.5, 77.6, 73.0, 72.6, 70.4, 69.8, 67.4, 61.5, 51.9, 51.8, 44.8, 44.7, 39.8, 39.6, 37.3, 36.9, 31.6, 31.5, 27.0, 19.5, 19.4, 16.5, 16.3, 15.4, 15.2; HRMS (ESI) *m/z* calc. for [$C_{36}H_{48}O_6Si$+Na]: 627.3118, found: 627.3112.



2.47

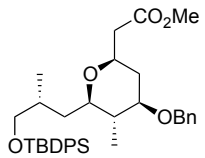
LHMDS (0.93 mL, 1 M in hexane) was added to a solution of acetal **2.46** (120 mg, 0.20 mmol) in THF (4 mL) at -78 °C. After stirring for 3 h at -78 °C, the reaction was quenched by addition of MeOH (1 mL) and saturated aqueous $NaHCO_3$ (3 mL). The quenched reaction mixture was warmed to room temperature and extracted with Et_2O (3 x 10 mL). The combined organics were washed with brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Purification of the residue by flash column chromatography (SiO_2) afforded alcohol **2.47** (100 mg, 82%) as a colorless liquid. R_f 0.33 (hexanes-EtOAc, 2:1); $[\alpha]_d^{20}$ = -19.6 (*c* 1.0, $CHCl_3$); IR (neat, ν_{max}) 3482, 3069, 2954, 2858, 1711, 1637, 1471, 1429, 1390, 1332, 1292, 1211, 1138, 1110, 1054, 825, 756, 703, 615 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.65 (dd, *J* = 7.8, 1.4 Hz, 4H), 7.48 (d, *J* = 12.3 Hz, 1H), 7.45 – 7.28 (m, 11H), 5.32 (d, *J* = 12.3 Hz, 1H), 4.63 (d, *J* = 11.5 Hz, 1H), 4.55 (d, *J* = 11.5 Hz, 1H), 4.06 (dd, *J* = 11.8, 4.5 Hz, 1H), 3.79 – 3.62 (m, 4H), 3.53 (dd, *J* = 9.3, 4.7 Hz, 1H), 3.50 – 3.42 (m, 2H), 2.13 – 1.98 (m, 1H), 1.91 – 1.73 (m, 2H), 1.44 (s, 1H), 1.35 – 1.19 (m, 1H), 1.06 (s, 9H), 0.96 (d, *J* = 7.0 Hz, 3H), 0.90 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.6, 163.0, 138.5, 135.7, 135.7, 133.9, 133.9, 129.7, 128.6, 127.9, 127.8, 127.8, 97.1, 83.4, 79.7, 72.8, 69.3, 62.8, 51.1, 39.0, 34.8, 32.0, 27.0,

19.4, 16.4, 10.5; HRMS (ESI) *m/z* calc. for [$C_{36}H_{48}O_6Si$+Na]: 627.3118, found: 627.3112.



2.19

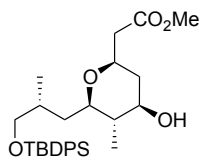
To a solution of alcohol **2.47** (75 mg, 0.12 mmol) in THF (5 mL) were added PPh_3 (130 mg, 0.5 mmol), imidazole (68 mg, 1 mmol), and I_2 (126 mg, 0.5 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 2 h, diluted with ether and quenched by addition of saturated aqueous $Na_2S_2O_3$ solution. After extraction with ether, the combined organic extracts were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. Purification by flash column chromatography (SiO_2) provided iodide **19** (84 mg, 95%) as a colorless liquid. R_f 0.33 (hexanes-EtOAc, 10:1); $[\alpha]_d^{20}$ = -0.7 (*c* 1.0, $CHCl_3$); IR (neat, ν_{max}) 3069, 2952, 2858, 1712, 1638, 1460, 1429, 1390, 1331, 1207, 1136, 1111, 1028, 961, 825, 756, 703, 615 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.71 – 7.60 (m, 4H), 7.38 – 7.28 (m, 12H), 5.31 (d, *J* = 12.3 Hz, 1H), 4.65 (d, *J* = 11.4 Hz, 1H), 4.43 (d, *J* = 11.4 Hz, 1H), 3.98 (t, *J* = 8.6 Hz, 1H), 3.80 – 3.64 (m, 4H), 3.46 (dd, *J* = 10.9, 6.3 Hz, 2H), 3.43 – 3.34 (m, 1H), 3.14 (t, *J* = 9.6 Hz, 1H), 2.37 – 2.19 (m, 1H), 1.92 – 1.73 (m, 2H), 1.41 – 1.30 (m, 1H), 1.06 (s, 9H), 0.89 (d, *J* = 6.9 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.5, 163.1, 138.1, 135.8, 135.7, 133.9, 129.7, 128.6, 128.0, 127.8, 127.8, 97.2, 84.2, 78.2, 72.2, 69.3, 51.1, 40.1, 35.5, 31.9, 27.0, 19.4, 16.5, 9.1, 5.1; HRMS (ESI) *m/z* calc. for [$C_{36}H_{47}IO_5Si$+Na]: 737.2135, found: 737.2130.



2.48

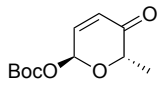
To a 10 mL round-bottom flask equipped with a magnetic stir bar were placed iodide **2.19** (80 mg, 0.11 mmol) and $[Ir(ppy)_2(dtbbpy)]PF_6$ (5 mg, 6 μmol). The flask was then flushed with a stream of argon before the addition of CH_3CN (1 mL) and DIPEA (0.2 mL, 1.1 mmol). The resulting yellow solution was placed in an irradiation apparatus equipped with a 2 W blue light-emitting diode (LED) strip. After stirred at room temperature for 5 h, at which point a TLC analysis indicated complete consumption of the starting iodide, the mixture was filtered through a bed of silica gel by eluting with ethyl acetate. The filtrate was concentrated and purified by flash column chromatography on silica gel to furnish THP **2.48** (45 mg, 70%) as colorless liquid. R_f 0.2 (hexanes-EtOAc, 10:1); $[\alpha]_d^{20}$ = -17.5 (*c* 1.0, $CHCl_3$); IR (neat, ν_{max}) 3070, 2953, 2857, 1741, 1470, 1429, 1389, 1360, 1264, 1207, 1153, 1110, 1087, 1009, 824, 756, 703, 614 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.78 – 7.62 (m, 4H), 7.45 – 7.27 (m, 11H), 4.67 (d, *J* = 11.5 Hz, 1H), 4.45 (d, *J* = 11.4 Hz, 1H), 3.82 – 3.70 (m, 1H), 3.68 (s, 3H), 3.55 (dd, *J* = 9.7, 5.3 Hz, 1H), 3.44 (dd, *J* = 9.6, 6.4 Hz, 1H), 3.17 (td, *J* = 10.5, 4.6 Hz, 1H), 3.05 (td, *J* = 9.6, 3.3 Hz, 1H), 2.59 (dd, *J* = 15.0, 8.3 Hz, 1H), 2.44 (dd, *J* = 14.9, 5.2 Hz, 1H), 2.21 (ddd, *J* = 12, 4.4, 1.2 Hz, 1H), 1.96 (m, 1H), 1.54 – 1.36 (m, 3H), 1.30 (ddd, *J* = 11.6, 11.6, 11.2 Hz, 1H), 1.06 (s, 9H), 0.95 (d, *J* = 6.6 Hz, 3H), 0.93 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.8, 138.6, 135.8, 135.7, 134.2, 134.2, 129.6, 128.5, 127.9, 127.7, 127.7, 80.4, 78.9, 72.2, 70.7, 69.8, 51.7, 42.4, 41.3,

36.9, 36.4, 32.0, 27.0, 19.5, 15.9, 13.2; HRMS (ESI) *m/z* calc. for [$C_{36}H_{48}O_5Si$+Na] 611.3169, found: 611.3163.



2.49

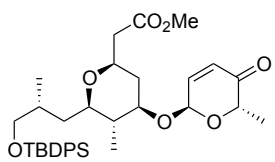
Palladium hydroxide on carbon (20% w/w, 7 mg, 0.01 mmol) was added to a solution of THP **2.48** (21 mg, 0.036 mmol) in EtOAc (1.5 mL). The reaction mixture was stirred with hydrogen balloon at room temperature. After 10 h, the reaction mixture was filtered with a pad of celite and eluted with EtOAc. After concentration of the filtrate, purification of the residue by flash column chromatography (SiO_2) provided alcohol **2.49** (16 mg, 91%) as colorless liquid. R_f 0.23 (hexanes-EtOAc, 2:1); $[\alpha]_d^{20}$ = +7.6 (*c* 1.0, $CHCl_3$); IR (neat, ν_{max}) 3428, 3071, 2933, 2857, 1740, 1471, 1429, 1374, 1389, 1318, 1262, 1212, 1146, 1110, 1009, 823, 759, 704, 614 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.74 – 7.62 (m, 4H), 7.49 – 7.31 (m, 6H), 3.84 – 3.71 (m, 1H), 3.66 (s, 3H), 3.53 (dd, *J* = 9.6, 5.3 Hz, 1H), 3.44 (dd, *J* = 9.6, 6.5 Hz, 1H), 3.38 (td, *J* = 10.5, 4.6 Hz, 1H), 3.03 (td, *J* = 9.6, 3.3 Hz, 1H), 2.55 (dd, *J* = 14.9, 8.4 Hz, 1H), 2.42 (dd, *J* = 14.9, 5.1 Hz, 1H), 2.02 (ddd, *J* = 12.1, 4.5, 1.4 Hz, 1H), 1.99 – 1.88 (m, 1H), 1.65 (s, 1H), 1.50 – 1.36 (m, 2H), 1.30 (ddd, *J* = 11.6, 11.6, 11.2 Hz, 1H), 1.25 – 1.13 (m, 1H), 1.05 (s, 9H), 0.94 (d, *J* = 6.6 Hz, 3H), 0.92 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.8, 135.8, 135.7, 134.2, 134.2, 129.6, 127.7, 78.6, 73.6, 72.2, 69.8, 51.7, 44.4, 41.2, 40.8, 36.3, 32.0, 27.0, 19.5, 15.9, 12.9; HRMS (ESI) *m/z* calc. for [$C_{29}H_{42}O_5Si$+Na]: 521.2699, found: 521.2694.



2.30

Pyranone **2.30** was prepared according to the procedure described in the reference literature.[2]

$[\alpha]_d^{20}$ = +99.0 (*c* 1.0, $CHCl_3$); IR (neat, ν_{max}) 2984, 1750, 1702, 1372, 1396, 1333, 1277, 1258, 1158, 1105, 1057, 1029, 944, 861, 841, 791, 758, 737 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.86 (dd, *J* = 10.2, 3.7 Hz, 7H), 6.32 (d, *J* = 3.6 Hz, 6H), 6.19 (d, *J* = 10.2 Hz, 6H), 4.63 (q, *J* = 6.7 Hz, 8H), 1.51 (s, 55H), 1.40 (d, *J* = 6.7 Hz, 17H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 195.9, 152.0, 141.1, 128.6, 89.3, 83.8, 72.3, 27.8, 15.4; HRMS (ESI) *m/z* calc. for [$C_{11}H_{16}O_5$+Na]: 251.0895, found: 251.0890.

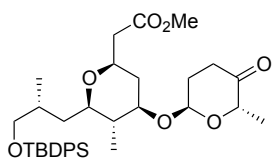


2.50

To a solution of alcohol **2.49** (25 mg, 0.05 mmol) and pyranone **2.30** (23 mg, 0.1 mmol) in CH_2Cl_2 (0.8 mL) was added a solution of $Pd_2(dba)_3$•$CHCl_3$ (1.3 mg, 1 μmol) and PPh_3 (1.3 mg, 5 μmol) in CH_2Cl_2 (0.2 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 5 h, quenched with saturated aqueous $NaHCO_3$ solution, extracted with Et_2O, dried (Na_2SO_4) and concentrated under reduced pressure. Purification by flash column chromatography (SiO_2) provided enone **2.50** (27 mg, 89%) as a colorless liquid. $[\alpha]_d^{20}$ = +24.8 (*c* 1.0, $CHCl_3$); IR (neat, ν_{max}) 2934, 2858,

[2] Wu, B.; Li, M.; O'Doherty, G. A. *Org. Lett.* **2010**, *12*, 5466.

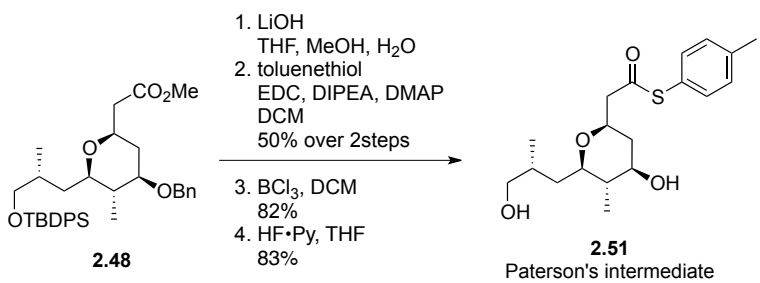
1740, 1701, 1470, 1429, 1391, 1374, 1233, 1210, 1156, 1108, 1082, 1025, 823, 808, 759, 704, 615 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.65 (dd, *J* = 6.5, 1.3 Hz, 4H), 7.53 – 7.31 (m, 5H), 6.76 (ddd, *J* = 10.2, 3.5, 0.8 Hz, 1H), 6.10 (d, *J* = 10.2 Hz, 1H), 5.34 (d, *J* = 3.4 Hz, 1H), 4.61 (qd, *J* = 6.8, 0.8 Hz, 1H), 3.83 – 3.71 (m, 1H), 3.67 (s, 3H), 3.60 (td, *J* = 10.3, 4.4 Hz, 1H), 3.53 (dd, *J* = 9.0, 5.4 Hz, 1H), 3.44 (dd, *J* = 9.3, 6.8 Hz, 1H), 3.09 (td, *J* = 9.6, 2.8 Hz, 1H), 2.59 (dd, *J* = 15.0, 7.9 Hz, 1H), 2.43 (dd, *J* = 15.0, 5.0 Hz, 1H), 2.17 (dd, *J* = 11.8, 4.3 Hz, 1H), 2.02 – 1.88 (m, 1H), 1.52 – 1.34 (m, 6H), 1.33 – 1.20 (m, 1H), 1.05 (s, 9H), 0.94 (d, *J* = 6.6 Hz, 3H), 0.92 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 197.0, 171.5, 143.8, 135.8, 135.7, 134.1, 134.1, 129.6, 127.7, 127.5, 89.3, 78.8, 77.9, 71.9, 70.6, 69.7, 51.8, 42.1, 41.2, 36.4, 36.4, 32.0, 27.0, 19.5, 16.0, 15.3, 13.3; HRMS (ESI) *m/z* calc. for [$C_{35}H_{48}O_7Si$+Na]: 631.3067, found:631.3062.

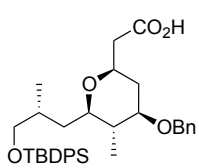


2.29

Palladium on activated carbon (10% w/w, 8 mg, 8 μmol) was added to a solution of enone **2.50** (24 mg, 0.04 mmol) in EtOAc (1 mL). The resulting suspension was stirred with hydrogen balloon at room temperature. After 30 min, the reaction mixture was filtered with a short pad of celite by eluting with ethyl acetate. After concentration of the filtrate, purification of the residue by flash column chromatography (SiO_2) provided glycoside **2.29** (17 mg, 70%) as colorless liquid and alcohol **2.49** (3 mg, 15 %). R_f 0.23 (hexane-EtOAc, 10:1); $[\alpha]_d^{20}$ = -112.2 (*c* 0.5, $CHCl_3$); IR (neat, ν_{max}) 2938, 2856, 1736, 1429, 1372, 1211, 1110, 1051, 1033,

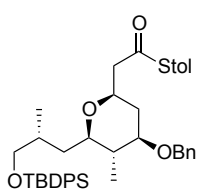
1008, 825, 759, 705, 616 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.75 – 7.59 (m, 4H), 7.47 – 7.31 (m, 6H), 5.17 (t, *J* = 5.2 Hz, 1H), 4.30 (q, *J* = 6.7 Hz, 1H), 3.81 – 3.70 (m, 1H), 3.66 (s, 3H), 3.59 – 3.49 (m, 2H), 3.43 (dd, *J* = 9.4, 6.6 Hz, 1H), 3.08 (td, *J* = 9.7, 2.8 Hz, 1H), 2.57 (dd, *J* = 14.9, 8.0 Hz, 1H), 2.53 – 2.37 (m, 3H), 2.35 – 2.23 (m, 1H), 2.15 (dd, *J* = 11.6, 3.9 Hz, 1H), 2.03 – 1.85 (m, 2H), 1.53 – 1.14 (m, 5H), 1.29 (d, *J* = 6.8 Hz, 3H), 1.04 (s, 9H), 0.91 (d, *J* = 6.5 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 211.2, 171.7, 135.8, 135.8, 134.2, 134.2, 129.6, 127.7, 92.5, 78.8, 76.0, 72.0, 71.2, 69.8, 51.8, 42.1, 41.3, 36.4, 36.3, 33.8, 32.0, 28.8, 27.0, 19.5, 16.0, 15.0, 13.3; HRMS (ESI) *m/z* calc. for $[C_{35}H_{50}O_7Si+Na]$: 633.3224, found: 633.3218. $CDCl_3$





LiOH (34 mg, 1.4 mmol) was added to a solution of THP methyl ester **2.48** (40 mg, 0.068 mmol) in THF/MeOH/H_2O (2:2:1, 5 mL). The mixture was stirred at room temperature overnight (ca. 10 h) and then washed away with EtOAc. The aqueous layer was acidified to pH 1-2 with 1 M aqueous HCl and extracted with EtOAc.

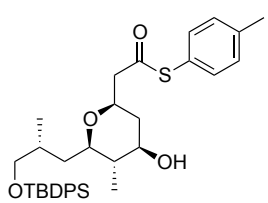
The combined organic phases were washed with brine, dried over $MgSO_4$, and concentrated to provide acid **S1** (38 mg, 97%) as a colorless liquid. $[\alpha]_d^{20}$ = -16.5 (*c* 1.0, $CHCl_3$); IR (neat, ν_{max}) 2962, 1712, 1453, 1427, 1392, 1217, 1156, 1109, 1074, 901, 824, 757, 702, 615 cm^{-1}; ^1H NMR (499 MHz, $CDCl_3$) δ 7.67 (d, *J* = 6.9 Hz, 4H), 7.51 – 7.27 (m, 11H), 4.67 (d, *J* = 11.5 Hz, 1H), 4.44 (d, *J* = 11.5 Hz, 1H), 3.80 – 3.65 (m, 1H), 3.53 (dd, *J* = 9.6, 5.6 Hz, 1H), 3.46 (dd, *J* = 9.6, 6.2 Hz, 1H), 3.17 (td, *J* = 10.4, 4.4 Hz, 1H), 3.09 (dd, *J* = 13.8, 5.6 Hz, 1H), 2.60 (dd, *J* = 15.7, 8.0 Hz, 1H), 2.49 (dd, *J* = 15.6, 4.9 Hz, 1H), 2.20 (dd, *J* = 11.8, 3.4 Hz, 1H), 2.02 – 1.89 (m, *J* = 5.8, 3.7 Hz, 1H), 1.58 – 1.21 (m, 4H), 1.06 (s, 9H), 0.94 (d, 6.5 Hz, 3H), 0.92 (d, 6.5 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 175.9, 138.5, 135.8, 135.8, 134.2, 134.1, 129.6, 128.5, 127.9, 127.8, 127.7, 80.1, 79.3, 71.8, 70.7, 69.7, 42.3, 41.0, 36.7, 36.5, 32.0, 27.0, 19.5, 16.0, 13.3; HRMS (ESI) *m/z* calc. for $[C_{35}H_{46}O_5Si+Na]$: 597.3012, found: 597.3007.



S2

EDC•HCl (18 mg, 0.096 mmol) was added to a solution of acid **S1** (137 mg, 0.064 mmol), DMAP (1 mg, 3 μmol), DIPEA (17 μL, 0.096 mmol), and toluenethiol (12 mg, 0.096 mmol) in CH_2Cl_2 (3 mL) at 0 °C. After stirred at room temperature for 18 h, the reaction mixture was diluted with EtOAc, washed successively with saturated aqueous NH_4Cl, $NaHCO_3$ and NaCl, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification of the residue by flash

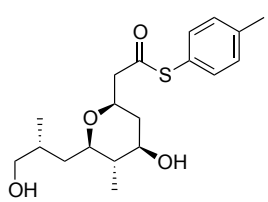
chromatography (SiO_2) gave thioester **S2** (22 mg, 50%) as a white solid. R_f 0.24 (hexanes-EtOAc, 10:1); $[\alpha]_d^{20}$ = -35.8 (*c* 0.5, $CHCl_3$); IR (neat, ν_{max}) 3028, 2934, 2855, 1703, 1494, 1469, 1427, 1360, 1215, 1110, 1010, 975, 807, 758, 702, 619 cm^{-1}; ^1H NMR (499 MHz, $CDCl_3$) δ 7.71 – 7.65 (m, 4H), 7.46 – 7.30 (m, 11H), 7.29 (d, *J* = 8.0 Hz , 2H), 7.20 (d, *J* = 8.0 Hz, 2H), 4.67 (d, *J* = 11.5 Hz, 1H), 4.44 (d, *J* = 11.5 Hz, 1H), 3.89 – 3.73 (m, *J* = 14.7, 8.5 Hz, 1H), 3.57 (dd, *J* = 9.7, 5.3 Hz, 1H), 3.46 (dd, *J* = 9.6, 6.7 Hz, 1H), 3.16 (td, *J* = 10.4, 4.5 Hz, 1H), 3.06 (td, *J* = 10.2, 2.3 Hz, 1H), 2.93 (dd, *J* = 14.6, 8.4 Hz, 1H), 2.68 (dd, *J* = 14.6, 4.6 Hz, 1H), 2.37 (s, 3H), 2.21 (dd, *J* = 11.6, 3.8 Hz, 1H), 2.17 – 2.04 (m, 1H), 1.54 – 1.23 (m, 4H), 1.07 (s, 9H), 0.94 (d, *J* = 6.7 Hz, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 196.0, 139.8, 138.6, 135.8, 135.8, 134.6, 134.2, 134.2, 130.2, 129.6, 128.5, 127.9, 127.8, 127.7, 124.4, 80.3, 78.9, 72.5, 70.7, 69.9, 49.9, 42.5, 36.9, 36.6, 32.0, 27.0, 21.5, 19.5, 16.1, 13.2; HRMS (ESI) *m/z* calc. for [$C_{42}H_{52}O_4SSi$+Na]: 703.3253, found: 703.3248.



S3

BCl_3 (0.14 mL, 1 M in CH_2Cl_2, 0.14 mmol) was added dropwise to a solution of thioester **Ss** (20 mg, 0.029 mmol) in CH_2Cl_2 (3 mL) at -78 °C. After stirring at -78 °C for 5 h, the reaction mixture was quenched by addition of saturated $NaHCO_3$ (3 mL) solution. The solution was warmed to room temperature and the aqueous layer extracted with Et_2O (3 times). The combined organics were washed with brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Purification of the

residue by flash column chromatography (SiO_2) afforded alcohol **S3** (14 mg, 82%) as a colorless liquid. R_f 0.29 (hexane-EtOAc, 2:1); $[\alpha]_d^{20}$ = -18.7 (*c* 0.5, $CHCl_3$); IR (neat, ν_{max}) 3490, 2930, 2856, 1703, 1493, 1469, 1427, 1389, 1330, 1216, 1110, 1015, 974, 904, 807, 758, 704, 616 cm^{-1}; ^1H NMR (499 MHz, $CDCl_3$) δ 7.67 (dt, *J* = 8.1, 1.6 Hz, 4H), 7.46 – 7.32 (m, 6H), 7.26 (d, *J* = 8.1 Hz, 2H), 7.17 (d, *J* = 8.1 Hz, 2H), 3.93 – 3.76 (m, 1H), 3.55 (dd, *J* = 9.7, 5.4 Hz, 1H), 3.45 (dd, *J* = 9.7, 6.6 Hz, 1H), 3.37 (td, *J* = 10.5, 4.7 Hz, 1H), 3.04 (td, *J* = 10.1, 2.6 Hz, 1H), 2.88 (dd, *J* = 14.6, 8.5 Hz, 1H), 2.65 (dd, *J* = 14.6, 4.6 Hz, 1H), 2.35 (s, 3H), 2.15 – 2.05 (m, *J* = 9.9, 6.0, 3.6 Hz, 1H), 2.02 (ddd, *J* = 12.1, 4.6, 1.5 Hz, 1H), 1.54 – 1.45 (m, 1H), 1.44 (s, 1H), 1.42 – 1.29 (m, 2H), 1.24 – 1.15 (m, 1H), 1.06 (s, 9H), 0.95 (d, 6.5 Hz, 3H), 0.93 (d, 6.5 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 195.9, 139.8, 135.8, 135.8, 134.5, 134.2, 134.2, 130.2, 129.6, 127.7, 124.3, 78.6, 73.5, 72.5, 69.9, 49.8, 44.5, 40.8, 36.5, 32.0, 27.1, 21.5, 19.5, 16.1, 12.9; HRMS (ESI) *m/z* calc. for $[C_{35}H_{46}O_4SSi+Na]$: 613.2784, found: 613.2778.



2.51
Paterson's intermediate

HF·pyridine (0.08 mL, HF 3 mmol, pyridine 0.33 mmol) was added to a solution of TBDPS ether **S3** (13 mg, 0.022 mmol) and pyridine (0.15 mL, 0.19 mmol) in THF (1 mL) at 0 °C. The resulting mixture was stirred at room temperature for 8 h, diluted with EtOAc, and neutralized with saturated aqueous $NaHCO_3$ solution. After extraction with EtOAc (2 times), the combined organic phases were washed

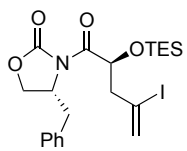
successively with saturated aqueous NH_4Cl, $NaHCO_3$ and NaCl, dried over Na_2SO_4, filtered, and concentrated. Purification by flash column chromatography (SiO_2) afforded diol **2.52,** the Paterson intermediate (7 mg, 90%) as a colorless liquid. R_f 0.13 (hexane-EtOAc, 1:1); $[\alpha]_d^{20}$ = -13.9 (*c* 0.33, $CHCl_3$); IR (neat, ν_{max}) 3380, 2924, 2870, 1701, 1493, 1462, 1374, 1260, 1215, 1148, 1072, 1027, 976, 807, 759, 666, 647, 624 cm^{-1}; ^1H NMR (499 MHz, $CDCl_3$) δ 7.29 (d, *J* = 8.2 Hz, 2H), 7.22 (d, *J* = 7.9 Hz, 2H), 3.89 (dddd, *J* = 11.4, 8.2, 4.7, 1.9 Hz, 1H), 3.52 (dd, *J* = 10.7, 5.3 Hz, 1H), 3.43 (dd, *J* = 10.7, 5.9 Hz, 1H), 3.37 (ddd, *J* = 10.9, 10.0, 4.7 Hz, 1H), 3.11 – 3.01 (m, 1H), 2.91 (dd, *J* = 14.9, 8.3 Hz, 1H), 2.70 (dd, *J* = 14.9, 4.7 Hz, 1H), 2.37 (s, 3H), 2.02 (ddd, *J* = 12.3, 4.7, 1.9 Hz, 1H), 1.88 (td, *J* = 12.6, 6.6 Hz, 1H), 1.50 (t, *J* = 6.7 Hz, 2H), 1.36 (ddd, *J* = 11.3, 11.3, 11.3 Hz, 1H), 1.31 – 1.17 (m, 1H), 0.98 (d, *J* = 6.5 Hz, 3H), 0.91 (d, *J* = 6.8 Hz, 3H).; ^{13}C NMR (126 MHz, $CDCl_3$) δ 195.6, 139.9, 134.6, 130.2, 124.2, 80.0, 73.3, 72.3, 68.5, 49.6, 44.2, 40.7, 36.9, 33.5, 21.5, 17.3, 13.2; HRMS (ESI) *m/z* calc. for $[C_{19}H_{28}O_4S+Na]$: 375.1606, found: 375.1600.

2.67

PPh_3 (8.66 g, 33 mmol), imidazole (2.25 g, 33 mmol), and I_2 (8.38 g, 33 mmol) were added to a stirred solution of 2-iodoprop-2-en-1-ol[3] (5.8g, 32 mmol) in THF (50 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 2 h, diluted with hexane (100ml) and filtered through a pad of silica gel. The filtrate was concentrated, diluted with hexane (100 ml) and filtered through a pad of silica gel

[3] Kamiya, N.; Chikami, Y.; Ishii, Y. *Synlett,* **1990**, 675.

to give iodide **2.67** (6.92 g, 73%) as a light brown oil that was used without further purification. R_f 0.85 (hexanes-EtOAc, 5:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.41 (dt, *J* = 2 Hz, 1 Hz, 1H), 5.76 (d, *J* = 2 Hz, 1H), 4.29 (d, *J* = 1 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 129.6, 105.4, 16.4.

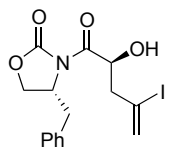


2.69c

A solution of LHMDS (6.84 mL, 1.0 M in THF, 6.84 mmol) was added dropwise to a stirred solution of (*R*)-4-benzyl-3-(triethylsilanoxyacetyl)-oxazolidin-2-one[4] (1.84 g, 5.26 mmol) in THF (30 mL) at -78 °C and the mixture was stirred for 30 min. Then, a solution of iodide **2.67** (4 g, 2.6 mmol) in THF (10 mL + 5 mL × 2 to rinse) was added to the enolate solution and the resulting mixture was stirred for 8 h with warming to -45 °C. The reaction mixture was quenched with sat. aq. $NaHCO_3$ and extracted with Et_2O (3 times). The combined organic extracts were dried ($MgSO_4$), filterd, concentrated *in vacuo* and purified by flash column chromatography to give imide **2.69c** (2.30 g, 4.47 mmol, 85%) as a colorless oil. R_f 0.44 (hexane-EtOAc, 5:1); $[\alpha]_d^{20}$ = -43.6 (*c* 1.0, $CHCl_3$); IR (neat, ν_{max}) 2956, 2914, 2878, 1784, 1714, 1391, 1350, 1286, 1243, 1214, 1139, 1108, 1014, 982, 747, 703 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 (m, 3H), 7.29 (d, *J* = 6.8 Hz, 1H), 7.20 (d, *J* = 7.9 Hz, 2H), 6.25 (s, 1H), 5.88 (s, 1H), 5.59 (dd, *J* = 8.7, 3.6 Hz, 1H), 4.77 – 4.68 (m, 1H), 4.29 (t, *J* = 8.6 Hz, 1H), 4.22 (dd, *J* = 9.2, 3.5 Hz, 1H), 3.27 (dd, *J* = 13.4, 3.4 Hz, 1H), 2.93 (dd, *J* = 14.0, 3.7 Hz, 1H), 2.80 – 2.60 (m, 2H), 0.97 (t, *J* =

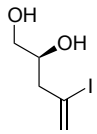
[4] Lee, C. B.; Wu, Z.; Zhang, F.; Chappell, M. D.; Stachel, S. J.; Chou, T.-C.; Guan, Y.; Danishefsky, S. J. *Am. Chem. Soc* **2001**, *123*, 5249.

7.9 Hz, 9H), 0.66 (q, *J* = 7.9 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.1, 153.1, 134.9, 130.1, 129.5, 129.1, 127.6, 103.9, 69.6, 66.9, 55.2, 50.0, 38.0, 6.9, 4.9; HRMS (ESI) *m/z* calc. for [$C_{21}H_{30}INO_4Si$+Na]: 538.0886, found: 538.0883.



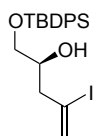
S4

AcOH (9 mL) was added to a stirred solution of imide **2.69c** (410 mg, 0.8 mmol) in THF/H_2O (1:1, 6 mL) and the reaction mixture was stirred at room temperature for 2 h. The reaction mixture was diluted with EtOAc (100 mL), washed with sat. aq. NH_4Cl (70 mL × 3) and the organic extract was dried ($MgSO_4$), filtered, concentrated *in vacuo* and purified by flash column chromatography to give alcohol **S4** (319 mg, 0.77 mmol, 97%) as a colorless oil. R_f 0.21 (hexane-EtOAc, 2:1); $[\alpha]_d^{20}$ = -41.4 (*c* 1.00, $CHCl_3$); IR (neat, ν_{max}) 3485, 1783, 1696, 1614, 1497, 1479, 1454, 1391, 1354, 1294, 1214, 1118, 1052, 1012, 977, 904, 762, 702 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 (t, *J* = 7.2 Hz, 2H), 7.30 (t, *J* = 7.0 Hz, 1H), 7.20 (d, *J* = 7.3 Hz, 2H), 6.27 (s, 1H), 5.93 (s, 1H), 5.22 (td, *J* = 8.4, 3.5 Hz, 1H), 4.83 – 4.68 (m, 1H), 4.34 (t, *J* = 8.6 Hz, 1H), 4.27 (dd, *J* = 9.2, 3.4 Hz, 1H), 3.51 (d, *J* = 8.2 Hz, 1H, OH), 3.32 (dd, *J* = 13.5, 3.5 Hz, 1H), 3.04 (dd, *J* = 14.8, 3.5 Hz, 1H), 2.82 (dd, *J* = 13.5, 9.5 Hz, 1H), 2.70 (dd, *J* = 14.8, 8.6 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.3, 153.4, 134.7, 129.7, 129.5, 129.2, 127.7, 103.5, 70.0, 67.5, 55.3, 48.8, 38.1; HRMS (ESI) *m/z* calc. for [$C_{15}H1_6INO_4$+Na]: 424.0022, found: 424.0037.



S5

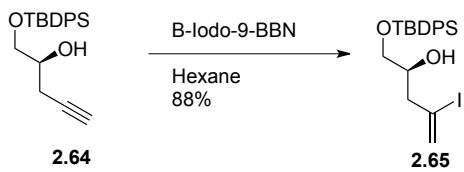
A solution of $LiBH_4$ (0.83 mL , 2.0 M in THF, 1.65 mmol) was added to a stirred solution of alcohol **S4** (330 mg, 0.82 mmol) and MeOH (0.07 mL, 1.65 mmol) in THF (8 mL) at 0 °C. After 2 h, the reaction mixture was then quenched with sat. aq NH_4Cl (10 mL) and extracted with Et_2O (3 times). The combined organic extracts were dried ($MgSO_4$), filtered, concentrated *in vacuo* to give crude diol **13** with Evans auxiliary. Crude **S5** was used without further purification. R_f 0.11 (hexane-EtOAc, 1:1); $[\alpha]_d^{20}$ = -2.3 (*c* 1.00, $CHCl_3$); IR (neat, ν_{max}) 3374, 2927, 1618, 1417, 1344, 1199, 1123, 1090, 1030, 899, 862, 677 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.20 (s, 1H), 5.87 (s, 1H), 4.08 – 3.93 (m, 1H), 3.73 (ddd, *J* = 11.3, 6.2, 3.3 Hz, 1H), 3.55 (dt, *J* = 11.5, 6.1 Hz, 1H), 2.57 (d, *J* = 6.4 Hz, 2H), 2.10 (d, *J* = 3.9 Hz, 1H, OH), 1.85 (t, *J* = 6.0 Hz, 1H, OH); ^{13}C NMR (101 MHz, $CDCl_3$) δ 129.0, 106.6, 70.6, 65.5, 48.8; HRMS (ESI) *m/z* calc. for [$C_5H_9IO_2$+Na]: 250.9545, found: 250.9541.



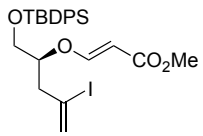
2.65

TBDPSCl (0.21 mL, 0.82 mmol) was added to a stirred solution of crude diol **S5** and imidazole (110 mg, 1.65 mmol) in CH_2Cl_2 (6 mL) at 0 °C. After 3 h, the reaction mixture was then quenched with sat. aq. NH_4Cl (10 mL) and extracted with Hexane (3 times). The combined organic extracts were dried ($MgSO_4$),

filtered, concentrated *in vacuo* and purified by flash column chromatography to give alcohol **2.65** (325 mg, 0.70 mmol, 85% over 2 steps) as a colorless oil. R_f 0.34 (hexane-EtOAc, 10:1); $[\alpha]_d^{20}$ = -1.6 (*c* 1.00, $CHCl_3$); IR (neat, ν_{max}) 3448, 2930, 2956, 2892, 2857, 1617, 1470, 1427, 1390, 1361, 1263, 1196, 1111, 898, 823, 799, 740, 702 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.68 (d, *J* = 7.1 Hz, 4H), 7.48 – 7.36 (m, 5H), 6.12 (s, 1H), 5.79 (s, 1H), 4.07 – 3.94 (m, 1H), 3.72 (dd, *J* = 10.2, 4.0 Hz, 1H), 3.60 (dd, *J* = 10.2, 6.3 Hz, 1H), 2.56 (d, *J* = 6.4 Hz, 2H), 2.43 (d, *J* = 4.4 Hz, 1H, OH), 1.09 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 135.7, 134.9, 133.1, 133.1, 130.0, 128.4, 128.0, 127.8, 106.7, 70.5, 66.6, 48.8, 27.0, 19.4; HRMS (ESI) *m/z* calc. for [$C_{21}H_{27}IO_2Si$+Na]: 489.0723, found: 489.0718.

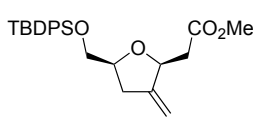


A solution of Iodo-9-BBN (4.5 mL, 1 M in hexane, 4.5 mmol) was added to a stirred solution of alkyne **2.62** (760 mg, 2.24 mmol) in hexane (20 mL) at -25 °C and the reaction mixture was stirred at -10 °C for 6 h. AcOH was added and the mixture was stirred at 0 °C for 2 h. The reaction mixture was then quenched with aq. $Na_2S_2O_3/Na_2CO_3$ (1:1, 40 mL) and the mixture was stirred vigorously for 30 min, while warming to room temperature. The mixture was then extracted with EtOAc (3 times) and the combined organic extracts were dried ($MgSO_4$), filtered, concentrated *in vacuo* and purified by flash column chromatography to give alcohol **S8** (897 mg, 1.97 mmol, 88%) as a colorless oil.



2.66

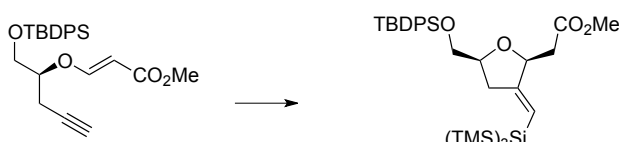
A solution of methyl propiolate (5 mL, 0.32 M in hexane, 1.6 mmol) was added dropwise via syringe pump over 1 h to a stirred solution of alcohol **2.65** (713 mg, 1.53 mmol) and DABCO (17 mg, 0.15 mmol) in hexane (10 mL) at room temperature. The reaction mixture was stirred for additional 1 h, then concentrated *in vacuo* and the resulting crude mixture was purified by flash column chromatography to give acrylate **2.66** (800 mg, 1.45 mmol, 95%) as a colorless oil. R_f 0.41 (hexane-EtOAc, 10:1); $[\alpha]_d^{20}$ = -22.6 (*c* 1.00, $CHCl_3$); IR (neat, ν_{max}) 2950, 2930, 2858, 1713, 1641, 1621, 1471, 1429, 1363, 1329, 1290, 1201, 1130, 1113, 949, 901, 824, 799, 741, 703 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.73 – 7.60 (m, 4H), 7.56 (d, *J* = 12.3 Hz, 1H), 7.49 – 7.33 (m, 6H), 6.11 (s, 1H), 5.79 (s, 1H), 5.28 (d, *J* = 12.3 Hz, 1H), 4.29 – 4.16 (m, 1H), 3.71 (d, *J* = 4.9 Hz, 2H), 3.69 (s, 3H), 2.78 – 2.56 (m, 2H), 1.05 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ168.3, 163.1, 135.7, 132.9, 130.0, 129.5, 128.0, 104.6, 97.5, 97.5, 82.6, 64.7, 51.2, 51.1, 46.5, 26.8, 19.3; HRMS (ESI) *m/z* calc. for [$C_{25}H_{31}IO_4Si$+Na]: 573.0934, found: 573.0931.



2.63

A 50 mL round-bottom flask was charged with acrylate **2.66** (70 mg, 0.13 mmol), $[Ir(ppy)_2(dtbbpy)]PF_6$ (4 mg, 4 μmol) and a magnetic stir bar. The flask was then flushed with a stream of argon before the addition of THF/H_2O (7:1, 13 mL,

degassed by 3 times freeze-pump-thaw) and DIPEA (0.22 mL, 1.3 mmol). The reaction mixture was irradiated with 30 W blue led (at approximately 2 cm away from the light source) at room temperature for 24 h. The reaction mixture was concentrated *in vacuo*, diluted with sat. aq. NH_4Cl (10 mL) and EtOAc (10 mL) and the phases separated. The aqueous phase was further extracted with EtOAc (2 times). The combined organic extracts were dried ($MgSO_4$), filtered, concentrated *in vacuo* and purified by flash column chromatography to give oxolane **2.63** (39 mg, 0.092 mmol, 72%) as a colorless oil. R_f 0.36 (hexane-EtOAc, 10:1); $[\alpha]_d^{20}$ = -23.0 (*c* 1.00, $CHCl_3$); IR (neat, ν_{max}) 2953, 2929, 2892, 2857, 1740, 1667, 1471, 1428, 1389, 1361, 1307, 1266, 1164, 1133, 1110, 1051, 988, 959, 890, 823, 796, 741, 703 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.76 – 7.63 (m, 4H), 7.48 – 7.32 (m, 6H), 5.03 (s, 1H), 4.88 (s, 1H), 4.77 (br t, *J* = 6.8 Hz, 1H), 4.18 – 4.00 (m, 1H), 3.79 – 3.59 (m, 5H), 2.67 – 2.56 (m, 4H), 1.06 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.7, 150.4, 135.8, 135.7, 134.9, 133.7, 133.6, 129.8, 129.7, 127.8, 105.5, 78.9, 77.4, 65.8, 51.8, 41.1, 35.1, 26.9, 19.4; HRMS (ESI) *m/z* calc. for [$C_{25}H_{32}O_4Si$+Na]: 447.1968, found: 447.1964.

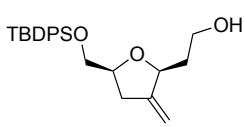


2.62 **2.73**

A 25 mL round-bottom flask was charged with alkyne **2.62**[5] (50 mg, 12 mmol), $Ir[dF(CF_3)ppy]_2(dtbbpy)PF_6$ (3 mg, 3 μmol), tetrabutylammonium bromide (10 mg, 30 μmol), $(SiMe_3)_3SiH$ (0.06 mL, 0.19 mmol) and a magnetic stir bar. The flask

[5] Ko, H. M. *et. al. Angew. Chem., Int. Ed.* **2009**, *121*, 2400.

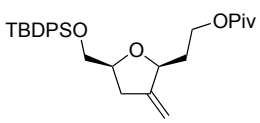
was then purged with 3 cycles of argon/vacuum before the addition of DME (5 mL). The reaction mixture was irradiated with 30 W blue led (at approximately 2 cm away from the light source) at room temperature for 24 h. The reaction mixture was concentrated *in vacuo*, diluted with H_2O (10 mL) and Et_2O (10 mL) and the phases separated. The aqueous phase was further extracted with Et_2O (2 times). The combined organic extracts were dried ($MgSO_4$), filtered, concentrated *in vacuo* and purified by flash column chromatography to give oxolane **2.73** (73 mg, 0.1 mmol, 91%) as a colorless oil. R_f 0.57 (hexane-EtOAc, 10:1); $[\alpha]_d^{20}$ = +1.0 (*c* 1.00, $CHCl_3$); IR (neat, ν_{max}) 2951, 2894, 2859, 1744, 1472, 1429, 1392, 1361, 1306, 1245, 1164, 1112, 834, 740, 703, 688cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 – 7.58 (m, 4H), 7.47 – 7.30 (m, 6H), 5.37 (d, *J* = 2.2 Hz, 1H), 4.74 (t, *J* = 6.5 Hz, 1H), 4.16 – 4.00 (m, 1H), 3.79 (dd, *J* = 10.4, 4.1 Hz, 1H), 3.73 – 3.62 (m, 1H), 3.67 (S, 3H), 2.66 – 2.49 (m, 4H), 1.04 (s, 9H), 0.20 (s, 27H).; ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.7, 159.1, 135.8, 135.7, 133.6, 133.6, 129.8, 129.7, 127.8, 127.8, 111.5, 79.9, 79.4, 65.8, 51.8, 41.9, 37.2, 26.9, 19.4, 1.3.; HRMS (ESI) *m/z* calc. for [$C_{34}H_{58}O_4Si_5$+Na]: 693.3079, found: 693.3072.



S6

A solution of $LiBH_4$ (4.7 mL, 2.0 M in THF, 9.4 mmol) was added to a stirred solution of oxolane **2.63** (2 g, 4.7 mmol) and MeOH (0.38 mL, 9.4 mmol) in THF (50 mL) at 0 °C. The reaction mixture was stirred at room temperature for 4 h, then quenched with sat. aq. NH_4Cl (70 mL) and extracted with Et_2O (3 times). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo*

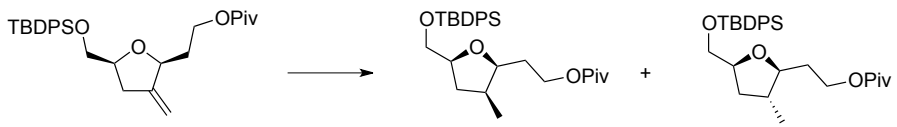
to give crude alcohol **S6** (1.57 g, 3.9 mmol, 84%) as a colorless oil. R_f 0.33 (hexane-EtOAc, 5:1); $[\alpha]_d^{20}$ = -37.4 (*c* 1.00, $CHCl_3$); IR (neat, ν_{max}) 3444, 3072, 2931, 2859, 1472, 1428, 1390, 1361, 1186, 1112, 1060, 977, 887, 824, 741, 703 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.68 (d, *J* = 6.8 Hz, 4H), 7.51 – 7.32 (m, 6H), 5.01 (br s, 1H), 4.84 (br s, 1H), 4.52 (br d, *J* = 7.9 Hz, 1H), 4.12 – 3.99 (m, 1H), 3.90 – 3.77 (m, 2H), 3.77 – 3.61 (m, 2H), 2.74 (br t, *J* = 5.7 Hz, 1H, OH), 2.67 – 2.47 (m, 2H), 2.08 – 1.95 (m, 1H), 1.85 – 1.72 (m, 1H), 1.06 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 150.8, 135.7, 133.5, 133.5, 129.8, 127.8, 105.1, 81.2, 79.0, 65.6, 61.0, 37.0, 35.2, 26.9, 19.4; HRMS (ESI) *m/z* calc. for [$C_{24}H_{32}O_3Si$+Na]: 419.2018, found: 419.2015.



2.76

Trimethylacetyl chloride (0.56 mL, 4.5 mmol) was added to a stirred solution of alcohol **S6** (1.5 g, 3.8 mmol), triethylamine (1.59 mL, 11.4 mmol) and DMAP (50 mg, 0.38 mmol) in CH_2Cl_2 (40 mL) at room temperature. The reaction mixture was stirred at room temperature for 16 h, then quenched with sat. aq. NH_4Cl (40 mL) and extracted with Et_2O (3 times). The combined organic extracts were dried ($MgSO_4$), filtered, concentrated *in vacuo* and purified by flash column chromatography to give pivalate **2.76** (1.78 g, 3.7 mmol, 97%) as a colorless oil. R_f 0.75 (hexane-EtOAc, 5:1); $[\alpha]_d^{20}$ = -28.6 (*c* 1.00, $CHCl_3$); IR (neat, ν_{max}) 2960, 2932, 2859, 1729, 1477, 1429, 1284, 1157, 1112, 977, 889, 824, 741, 704 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.77 – 7.59 (m, 4H), 7.52 – 7.30 (m, 6H), 5.01 (q, *J* = 2.3 Hz, 1H), 4.87 (q, *J* = 2.3 Hz, 1H), 4.41 (br d, *J* = 8.7 Hz, 1H), 4.31 – 4.13 (m,

2H), 4.13 – 3.99 (m, 1H), 3.79 – 3.68 (m, 2H), 2.68 – 2.49 (m, 2H), 2.07 – 1.93 (m, 1H), 1.91 – 1.76 (m, 1H), 1.20 (s, 9H), 1.06 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 178.6, 151.0, 135.7, 133.7, 133.6, 129.8, 127.8, 105.0, 78.8, 77.9, 65.9, 61.5, 38.8, 35.3, 34.9, 27.3, 26.9, 19.4; HRMS (ESI) *m/z* calc. for [$C_{29}H_{40}O_4Si$+Na]: 503.2594, found: 503.2589.



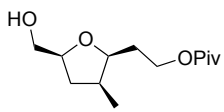
2.76 **2.77** **2.78**

Wilkinson's catalyst (340 mg, 0.37mmol) was added to a stirred solution of pivalate **2.76** (1.78 g, 3.7 mmol) in toluene (40 mL) at room temperature and the flask was purged with 3 cycles of H_2/vacuum. The reaction mixture was stirred under H_2 atmosphere (balloon) at room temperature. After stirring for 16 h, the reaction mixture was concentrated *in vacuo* and purified by flash column chromatography, eluting with 9% Et_2O/Hexane to give oxolane **2.77** (1.47 g, 3.0 mmol, 82%) as a colorless oil and oxolane **2.78** (230 mg, 0.47 mmol, 13%) as a colorless oil.

2.77 R_f 0.27 (hexane-Et_2O, 10:1, 3 times); $[\alpha]_d^{20}$ = -24.2 (*c* 1.00, $CHCl_3$); IR (neat, ν_{max}) 2961, 2932, 2859, 1728, 1476, 1428, 1391, 1363, 1284, 1155, 1110, 1032, 998, 937, 823, 803, 740, 703 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 – 7.64 (m, 4H), 7.47 – 7.31 (m, 6H), 4.27 – 4.10 (m, 2H), 4.05 – 3.96 (m, 1H), 3.93 (q, *J* = 6.8 Hz, 1H), 3.73 – 3.61 (m, 2H), 2.43 – 2.22 (m, 1H), 2.08 (dt, *J* = 12.5, 7.3 Hz, 1H), 1.70 (q, *J* = 6.9 Hz, 2H), 1.49 (dt, *J* = 12.4, 8.1 Hz, 1H), 1.19 (s, 8H), 1.05 (s, 9H), 0.93 (d, *J* = 7.0 Hz, 3H).; ^{13}C NMR (101 MHz, $CDCl_3$) δ 178.7, 135.8, 135.7, 133.8, 133.7, 129.7, 127.8, 79.1, 78.4, 66.7, 62.5, 38.8, 36.0, 35.8, 30.4, 27.4, 27.0,

19.4, 15.1.; HRMS (ESI) *m/z* calc. for [$C_{29}H_{42}O_4Si$+Na]: 505.2750, found: 505.2746.

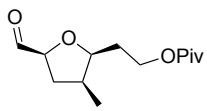
2.78 R_f 0.31 (hexane-Et_2O, 10:1, 3 times); $[\alpha]_d^{20}$ = -12.8 (*c* 1.00, $CHCl_3$); IR (neat, ν_{max}) 2960, 2932, 2859, 1729, 1477, 1461, 1428, 1392, 1363, 1157, 1111, 1032, 938, 823, 741, 703 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.75 – 7.60 (m, 4H), 7.46 – 7.33 (m, 6H), 4.29 – 4.20 (m, 1H), 4.20 – 4.14 (m, 1H), 4.13 – 4.05 (m, 1H), 3.67 – 3.56 (m, 2H), 3.46 (td, *J* = 8.3, 3.4 Hz, 1H), 2.14 – 2.04 (m, 1H), 1.95 – 1.82 (m, 2H), 1.79 – 1.67 (m, 1H), 1.65 – 1.56 (m, 1H), 1.19 (s, 9H), 1.06 (s, 9H), 1.01 (d, *J* = 6.6 Hz, 3H).; ^{13}C NMR (101 MHz, $CDCl_3$) δ 178.6, 135.8, 133.8, 129.7, 129.7, 127.8, 83.1, 78.4, 66.7, 62.1, 38.8, 38.5, 36.5, 33.8, 27.3, 27.0, 19.4, 17.1.; HRMS (ESI) *m/z* calc. for [$C_{29}H_{42}O_4Si$+Na]: 505.2750, found: 505.2747.



S7

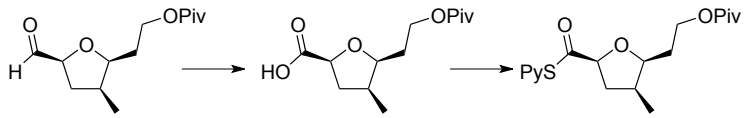
A solution of TBAF (4.6 mL, 1.0 M in THF, 4.6 mmol) was added to a stirred solution of oxolane **2.77** (1.47 g, 3.0 mmol) in THF (30 mL) at 0 °C. The reaction mixture was stirred at room temperature for 3 h, then quenched with sat. aq. NH_4Cl (30 mL) and extracted with Et_2O (3 times). The combined organic extracts were dried ($MgSO_4$), filtered, concentrated *in vacuo* and purified by flash column chromatography to give alcohol **S7** (730 mg, 2.98 mmol, 98%) as a colorless oil. R_f 0.28 (hexane-EtOAc, 2:1); $[\alpha]_d^{20}$ = -42.8 (*c* 1.00, $CHCl_3$); IR (neat, ν_{max}) 3442, 2963, 2934, 2875, 1727, 1480, 1460, 1397, 1366, 1285, 1228, 1157, 1097, 1032, 941, 923, 859, 772 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.29 (ddd, *J* = 10.8, 7.4, 5.5 Hz, 1H), 4.10 (dt, *J* = 10.9, 7.4 Hz, 1H), 4.03 – 3.95 (m, 1H), 3.92 (ddd, *J* = 9.0,

6.7, 4.7 Hz, 1H), 3.74 (ddd, *J* = 11.7, 6.2, 3.1 Hz, 1H), 3.49 (dt, *J* = 11.8, 6.0 Hz, 1H), 2.47 – 2.29 (m, 1H), 2.12 – 2.00 (m, 2H), 1.81 – 1.61 (m, 2H), 1.41 (dt, *J* = 12.5, 8.2 Hz, 1H), 1.19 (s, 9H), 0.96 (d, *J* = 7.0 Hz, 3H).; ^{13}C NMR (101 MHz, $CDCl_3$) δ 178.8, 79.1, 78.6, 65.2, 62.4, 38.8, 36.1, 35.0, 30.4, 27.3, 15.1.; HRMS (ESI) *m/z* calc. for [$C_{13}H_{24}O_4$ +Na]: 267.1572, found: 267.1568.



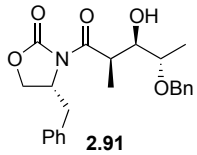
2.100

A solution of SO_3•Py (8 mL, 0.88 M in DMSO, 7.1 mmol) was added to a stirred solution of alcohol **S7** (575 mg, 2.35 mmol) and DIPEA (2.5 ml, 14.1 mmol) in CH_2Cl_2 (40 mL) at 0 °C. The reaction mixture was stirred for 3 h at 0 °C before being quenched with sat. aq. NH_4Cl (40 mL) and the phases separated. The aqueous phase was further extracted with Et_2O (3 times) and the combined organic extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo* to give crude aldehyde **2.100** as a pale yellow oil that was used without further purification. A sample was further purified by flash column chromatography for characterization. R_f 0.55 (hexane-EtOAc, 2:1); $[\alpha]_d^{20}$ = -84.5 (*c* 1.00, $CHCl_3$); IR (neat, ν_{max}) 2970, 2934, 2908, 2879, 1729, 1481, 1460, 1422, 1397, 1368, 1286, 1230, 1159, 1093, 1062, 1034, 938 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.69 (s, 1H), 4.33 – 4.10 (m, 3H), 4.06 (dt, *J* = 9.6, 5.2 Hz, 1H), 2.45 – 2.28 (m, 2H), 1.78 (dq, *J* = 8.5, 6.2, 5.5 Hz, 2H), 1.74 – 1.63 (m, 1H), 1.20 (s, 9H), 0.89 (d, *J* = 6.7 Hz, 3H).; ^{13}C NMR (101 MHz, $CDCl_3$) δ 203.3, 178.6, 82.0, 80.0, 62.0, 38.8, 36.2, 35.5, 30.0, 27.3, 14.4.; HRMS (ESI) *m/z* calc. for [$C_{13}H_{22}O_4$+Na]: 265.1416, found: 265.1412.



2.100 **2.103** **2.105**

To a stirred solution of crude aldehyde **2.100** (as prepared above) in THF/H_2O (5:2, 21 mL) were added NaH_2PO_4•$2H_2O$ (1.83 g, 11.8 mmol), 2-methyl-2-butene (1.2 mL, 11.8 mmol) and $NaClO_2$ (850 mg, 9.4 mmol) at room temperature. After stirring for 2 h, the reaction mixture was then quenched with sat. aq. Na_2SO_3 (20 mL) and extracted with EtOAc (4 times). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo* to give crude acid **2.103** as a pale yellow oil that was used without further purification. PPh_3 (904 mg, 3.45 mmol) and dipyridyl disulfide (760 mg, 3.45 mmol) were added to a stirred solution of crude acid **2.103** in CH_2Cl_2 (24 mL) at room temperature. After stirring for 6 h, the reaction mixture was concentrated *in vacuo* and purified by flash column chromatography to give thioester **2.105** (607 mg, 1.73 mmol, 74% over 3 steps) as a pale yellow oil. R_f 0.11 (hexane-EtOAc, 5:1); $[\alpha]_d^{20}$ = -127.5 (*c* 1.00, $CHCl_3$); IR (neat, ν_{max}) 2967, 2932, 2876, 1748, 1725, 1617, 1570, 1560, 1479, 1447, 1417, 1396, 1368, 1284, 1200, 1159, 1141, 1066, 1033, 986, 759 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.63 (dd, *J* = 4.9, 1.8 Hz, 1H), 7.72 (td, *J* = 7.7, 1.9 Hz, 1H), 7.56 (d, *J* = 7.9 Hz, 1H), 7.27 (dd, *J* = 7.1, 4.7 Hz, 1H), 4.53 (t, *J* = 7.5 Hz, 1H), 4.43 – 4.26 (m, 2H), 4.20 (ddd, *J* = 10.0, 6.3, 3.7 Hz, 1H), 2.55 – 2.31 (m, 2H), 2.10 – 1.65 (m, 3H), 1.20 (s, 9H), 1.03 (d, *J* = 6.9 Hz, 3H).; ^{13}C NMR (101 MHz, $CDCl_3$) δ 201.5, 178.6, 151.7, 150.6, 137.1, 130.7, 123.5, 83.2, 80.7, 62.0, 38.9, 38.5, 35.9, 30.3, 27.3, 14.6.; HRMS (ESI) *m/z* calc. for [$C_{18}H_{25}NO_4S$+Na]: 374.1402, found: 374.1399.

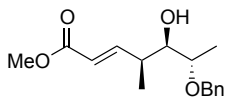


2.91

TfOH (0.65 mL, 7.3 mmol) was added to a stirred solution of BEt_3 (7 mL, 1 M, 7 mmol) in hexane at 0 °C. After stirring at 40 °C for 1 h, the reaction mixture was diluted with CH_2Cl_2 (24 mL) at -78 °C. A solution of imide **2.89** (1.48 g, 6.3 mmol) in CH_2Cl_2 (4mL + 2 mL × 2 to rinse) and NEt_3 (1.33 mL, 9.6 mmol) were added to the stirred solution of Et_2BOTf at -78 °C. The resulting mixture was allowed to warm to 0 °C and stirred for 0.5 h. A solution of aldehyde **2.90**[6] (1.15 g, 7 mmol) in CH_2Cl_2 (4mL + 2 mL × 2 to rinse) was added slowly to the enolate solution at -78 °C. After stirring at -78 °C for a further 2 h, the reaction mixture was allowed to warm to 0 °C and stirred for additional 1 h. The reaction mixture was then quenched with pH 7 phosphate buffer (20 mL). MeOH/30% aq. H_2O_2 solution (2:1, 18 mL) was added slowly, and the mixture was stirred vigorously for 1 h, while warming to room temperature. The mixture was then extracted with Et_2O (3 times) and the combined organic extracts were dried ($MgSO_4$), filtered, concentrated *in vacuo* and purified by flash column chromatography to give aldol **2.91** (2.25 g, 5.7 mmol, 90%) as a white solid. R_f 0.41 (hexane-EtOAc, 2:1); $[\alpha]_d^{20}$ = -36.7 (*c* 1.00, $CHCl_3$); IR (neat, ν_{max}) 3492, 3029, 2974, 2931, 1778, 1693, 1497, 1454, 1384, 1351, 1210, 1105, 1072, 1029, 972, 746, 699, 507, 460 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.36 – 7.24 (m, 8H), 7.18 (d, *J* = 7.2 Hz, 2H), 4.65 (d, *J* = 11.5 Hz, 1H), 4.58 – 4.48 (m, 1H), 4.41 (d, *J* = 11.4 Hz, 1H), 4.16 – 4.02 (m, 2H), 3.95 – 3.87 (m, 2H), 3.50 (p, *J* = 6.3 Hz, 1H), 3.20 (dd, *J* = 13.4, 3.4 Hz, 1H), 2.82 (d, *J* = 3.7 Hz, 1H), 2.74 (dd, *J* = 13.4, 9.5 Hz, 1H), 1.32 (d, *J* = 6.1 Hz, 3H), 1.23 (d, *J* = 7.0 Hz,

[6] Enders, D.; Berg, S. von; Jandeleit, B. *Org. Synth.* **2002**, *78*, 177.

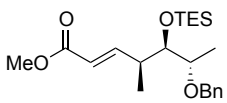
3H).; ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.5, 152.9, 138.4, 135.2, 129.5, 129.0, 128.5, 127.9, 127.7, 127.5, , 75.5, 74.6, 70.8, 66.0, 55.0, 39.4, 37.9, 16.1, 12.2.; HRMS (ESI) *m/z* calc. for [$C_{23}H_{27}NO_5$ +Na]: 420.1487, found: 420.1782.



2.92

A solution of DIBAL-H (19.3 mL, 1 M in hexane, 19.3 mmol) was added to a stirred solution of aldol **2.91** (2.95 g, 7.4 mmol) in THF (120 mL) at -78 °C and the resulting mixture was stirred for 5 h. The reaction mixture was then quenched with sat. aq. Rochelle's salt (70 mL), diluted with Et_2O (120 mL) and stirred vigorously for 2 h with warming to room temperature. The phases separated and the aqueous phase was extracted with Et_2O (3 times). The combined organic extracts were dried ($MgSO_4$), filtered and concentrated *in vacuo* to give crude aldehyde as a pale yellow oil that was immediately used without further purification. A 250 mL round-bottom flask was charged with LiBr (2.57 g, 29.6 mmol) and a magnetic stir bar. The flask was then dried by heating with a hairdryer under vacuum for 3 min before the addition of THF (110 mL) and methyl diethylphosphonoacetate (1.63 mL, 8.9 mmol). The reaction mixture was stirred at room temperature for 30 min and NEt_3 was added to the mixture. After stirring for 30 min, a solution of the crude aldehyde in THF (5mL + 2 mL × 2 to rinse) was added to the stirred solution and the resulting mixture was stirred at room temperature for 16 h. The reaction mixture was quenched with sat. aq. NH_4Cl (70 mL) and extracted with Et_2O (3 times). The combined organic extracts were dried ($MgSO_4$), filtered, concentrated *in vacuo* and purified by flash column chromatography to give enoate **2.92** (1.76 g,

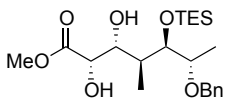
6.3 mmol, 85% over 2 steps) as a colorless oil. R_f 0.25 (hexane-EtOAc, 5:1); $[\alpha]_d^{20}$ = +0.9 (*c* 1.00, $CHCl_3$); IR (neat, ν_{max}) 3478, 2971, 2876, 1721, 1653, 1454, 1435, 1276, 1195, 1178, 1150, 1094, 1062, 1028, 988, 863, 736, 698, 607, 420 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.39 – 7.26 (m, 4H), 6.86 (dd, *J* = 15.7, 8.7 Hz, 1H), 5.85 (d, *J* = 15.7 Hz, 1H), 4.58 (d, *J* = 11.5 Hz, 1H), 4.46 (d, *J* = 11.5 Hz, 1H), 3.73 (s, 3H), 3.65 (dt, *J* = 7.3, 3.4 Hz, 1H), 3.54 – 3.44 (m, 1H), 2.60 – 2.42 (m, 1H), 2.25 (br s, 1H), 1.19 (d, *J* = 6.2 Hz, 3H), 1.14 (d, *J* = 6.7 Hz, 3H).; ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.0, 150.7, 138.3, 128.6, 127.9, 127.8, 121.2, 76.1, 75.6, 70.8, 51.7, 39.1, 15.8, 13.3.; HRMS (ESI) *m/z* calc. for [$C_{16}H_{22}O_4$+Na]: 301.1416, found: 301.1412.



S8

TESCl (0.55 mL, 2.44 mmol) was added to a stirred solution of enoate **2.92** (340 mg, 1.22 mmol) and 2,6-lutidine (0.57 ml, 4.88 mmol) in CH_2Cl_2 (12 mL) at 0 °C. After stirring at 0 °C for 1 h, the reaction mixture was then quenched with sat. aq. $NaHCO_3$ (10 mL) and extracted with Et_2O (3 times). The combined organic extracts were dried ($MgSO_4$), filtered, concentrated *in vacuo* and purified by flash column chromatography to give TES ether **S8** (463 mg, 1.18 mmol, 97%) as a colorless oil. R_f 0.52 (hexane-EtOAc, 10:1); $[\alpha]_d^{20}$ = +5.8 (*c* 1.00, $CHCl_3$); IR (neat, ν_{max}) 2955, 2910, 2878, 1726, 1658, 1455, 1435, 1383, 1336, 1273, 1235, 1193, 1176, 1156, 1107, 1063, 1012, 801, 736, 697 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.40 – 7.26 (m, 5H), 6.93 (dd, *J* = 15.8, 8.1 Hz, 1H), 5.80 (d, *J* = 15.7 Hz, 1H), 4.55 (d, *J* = 11.6 Hz, 1H), 4.41 (d, *J* = 11.6 Hz, 1H), 3.73 (s, 3H), 3.67 (t, *J* = 5.2

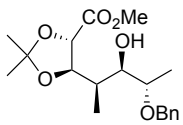
Hz, 1H), 3.46 – 3.36 (m, 1H), 2.63 – 2.49 (m, 1H), 1.16 (d, *J* = 6.2 Hz, 3H), 1.05 (d, *J* = 6.8 Hz, 3H), 0.94 (t, *J* = 7.9 Hz, 9H), 0.61 (q, *J* = 7.9 Hz, 6H).; ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.1, 152.4, 138.7, 128.4, 127.8, 127.6, 120.6, 78.3, 76.5, 70.8, 51.6, 51.5, 40.4, 15.0, 14.6, 7.1, 5.4.; HRMS (ESI) *m/z* calc. for [$C_{16}H_{22}O_4$+Na]: 415.2281, found: 415.2278.



2.93

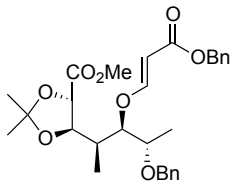
$MeSO_2NH_2$ (333 mg, 3.51 mmol) was added to a stirred solution of K_2OsO_4•$2H_2O$ (9 mg, 24 μmol), $(DHQD)_2PHAL$ (73 mg, 94 μmol), K_2CO_3 (485 mg, 3.51 mmol) and $K_3Fe(CN)_6$ (1.16 g, 3.51 mmol) in H_2O/*t*BuOH (2:1, 12 mL) at room temperature. After stirring for 30 min, a solution of TES ether **S8** (460 mg, 1.17 mmol) in *t*BuOH (2mL + 1 mL × 2 to rinse) was added to the resulting mixture at 0 °C and the reaction was further stirred at 0 °C for 16 h. The reaction mixture was quenched with Na_2SO_3 (1.7 g), then stirred for 1 h with warming to room temperature, diluted with H_2O (10 mL) and extracted with Et_2O (3 times). The combined organic extracts were dried ($MgSO_4$), filtered, concentrated *in vacuo* and purified by flash column chromatography to give diol **2.93** (470 mg, 1.1 mmol, 94%) as a colorless oil. R_f 0.12 (hexane-EtOAc, 5:1); $[\alpha]_d^{20}$ = +17.5 (*c* 1.00, $CHCl_3$); IR (neat, ν_{max}) 3469, 2954, 2911, 2876, 1742, 1454, 1274, 1238, 1160, 1098, 1035, 1009, 737, 697 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 – 7.27 (m, 5H), 4.59 (d, *J* = 11.6 Hz, 1H), 4.45 (d, *J* = 11.6 Hz, 1H), 4.17 (d, *J* = 7.8 Hz, 1H), 3.93 (dd, *J* = 5.9, 2.6 Hz, 1H), 3.88 (dd, *J* = 10.4, 4.8 Hz, 1H), 3.82 (s, 3H), 3.72 (d, *J* = 5.0 Hz, 1H), 3.66 (p, *J* = 6.1 Hz, 1H), 2.96 (d, *J* = 7.8 Hz, 1H), 2.29 – 2.11 (m,

1H), 1.28 (d, *J* = 6.1 Hz, 3H), 0.97 (t, *J* = 7.9 Hz, 9H), 0.92 (d, *J* = 7.1 Hz, 3H), 0.66 (q, *J* = 7.9 Hz, 6H).; ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.4, 138.5, 128.4, 127.9, 127.6, 78.4, 75.9, 75.0, 71.6, 70.8, 52.7, 38.5, 16.8, 12.8, 7.0, 5.1.; HRMS (ESI) *m/z* calc. for [$C_{22}H_{38}O_6Si$+Na]: 449.2332, found:449.2335.



2.94

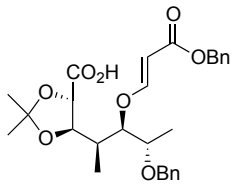
TsOH•H_2O (21 mg, 0.11 mmol) was added to a stirred solution of diol **2.93** (470mg, 1.1 mmol) and dimethoxypropane (1.35 ml, 11 mmol) in CH_2Cl_2 (11 mL) at room temperature. After stirring for 60 h, the reaction mixture was then quenched with sat. aq. $NaHCO_3$ (10 mL) and extracted with Et_2O (3 times). The combined organic extracts were dried ($MgSO_4$), filtered, concentrated *in vacuo* and purified by flash column chromatography to give acetonide **2.94** (352 mg, 1.0 mmol, 91%) as a colorless oil. R_f 0.12 (hexane-EtOAc, 5:1); $[\alpha]_d^{20}$ = +35.6 (*c* 1.00, $CHCl_3$); IR (neat, ν_{max}) 3516, 2985, 2936, 1754, 1454, 1438, 1382, 1372, 1259, 1208, 1168, 1096, 1027, 988, 869, 739, 698, 472, 442, 427 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 – 7.21 (m, 5H), 4.66 (d, *J* = 11.6 Hz, 1H), 4.42 (d, *J* = 9.3 Hz, 1H), 4.39 (d, *J* = 4.9 Hz, 1H), 4.27 (dd, *J* = 7.1, 4.8 Hz, 1H), 3.78 (s, 3H), 3.78 – 3.73 (m, 1H) 3.54 (p, *J* = 6.1 Hz, 1H), 2.65 (d, *J* = 4.3 Hz, 1H), 2.36 (q, *J* = 6.9 Hz, 1H), 1.48 (s, 3H), 1.41 (s, 3H), 1.31 (d, *J* = 6.0 Hz, 3H), 0.96 (d, *J* = 7.1 Hz, 3H).; ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.4, 138.6, 128.5, 127.8, 127.7, 110.9, 82.9, 76.8, 75.2, 73.9, 70.8, 52.6, 36.2, 27.1, 25.4, 16.3, 9.8.; HRMS (ESI) *m/z* calc. for [$C_{19}H_{28}O_6$+Na]: 375.1784, found: 375.1780.



2.96

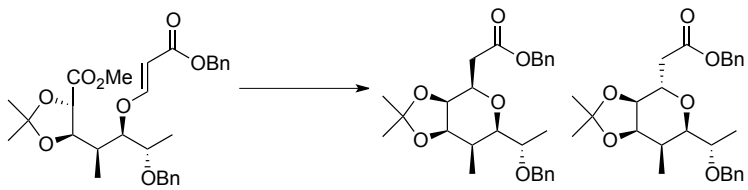
A solution of benzyl propiolate[7] (5 mL, 1.08 M in hexane, 5.4 mmol) was added dropwise via syringe pump over 1 h to a stirred solution of acetonide **2.94** (953mg, 2.7 mmol) and DABCO (30 mg, 0.27 mmol) in hexane (22 mL) at room temperature. The reaction mixture was stirred for additional 1 h, then concentrated *in vacuo* and the resulting crude mixture was purified by flash column chromatography to give acrylate **2.96** (1.26 g, 2.5 mmol, 91%) as a colorless oil. R_f 0.35 (hexane-EtOAc, 5:1); $[\alpha]_d^{20}$ = +7.5 (*c* 1.00, $CHCl_3$); IR (neat, ν_{max}) 3032, 2984, 2938, 2886, 1754, 1707, 1638, 1496, 1454, 1438, 1374, 1325, 1276, 1203, 1165, 1120, 1023, 956, 916, 871, 833, 740, 697 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.59 (d, *J* = 12.2 Hz, 1H), 7.42 – 7.27 (m, 10H), 5.39 (dd, *J* = 12.1, 1.1 Hz, 1H), 5.18 (d, *J* = 12.5 Hz, 1H), 5.12 (d, *J* = 12.4 Hz, 1H), 4.65 (d, *J* = 11.6 Hz, 1H), 4.42 (d, *J* = 11.6 Hz, 1H), 4.22 (d, *J* = 6.4 Hz, 1H), 4.13 (dd, *J* = 8.1, 2.1 Hz, 1H), 4.03 (dd, *J* = 9.3, 6.4 Hz, 1H), 3.76 (s, 3H), 3.69 – 3.59 (m, 1H), 2.37 – 2.17 (m, 1H), 1.44 (s, 3H), 1.37 (s, 3H), 1.24 (d, *J* = 6.1 Hz, 3H), 0.86 (d, *J* = 6.9 Hz, 3H).; ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.8, 167.9, 164.6, 138.0, 136.6, 128.6, 128.5, 128.2, 128.1, 127.9, 111.4, 97.5, 86.8, 80.2, 78.7, 73.1, 70.8, 65.6, 52.6, 38.1, 27.3, 25.7, 16.4, 9.4.; HRMS (ESI) *m/z* calc. for [$C_{29}H_{36}O_8$+Na]: 535.2308, found: 535.2302.

[7] Fan, Y. C.; Kwon, O. *Org. Lett.* **2012**, *14*, 3264.



S9

Me_3SnOH (2.25 g, 12.4 mmol) was added to a stirred solution of acrylate **2.96** (1.26 g, 2.5 mmol) in 1,2-dichloroethane (50 mL) at room temperature and the reaction mixture was stirred at 65 °C for 5 h. The reaction mixture was cooled to room temperature, concentrated *in vacuo* and diluted with EtOAc (100 mL). The organic layer was washed with aq. $KHSO_4$ (0.01 N, 100 mL × 3), dried ($MgSO_4$), filtered, concentrated *in vacuo* to give crude acid S**9** (1.26 g, 2.5 mmol, 91%) as a colorless oil that was immediately used without further purification. R_f 0.5 ($CHCl_3$-MeOH, 10:1); $[\alpha]_d^{20}$ = +9.8 (*c* 1.00, $CHCl_3$); IR (neat, ν_{max}) 3064, 3032, 2983, 2937, 1708, 1679, 1636, 1496, 1454, 1382, 1327, 1277, 1206, 1121, 1025, 955, 914, 871, 833, 738, 697 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 10.31 (s, 1H), 7.60 (d, *J* = 12.1 Hz, 1H), 7.42 – 7.26 (m, 10H), 5.40 (d, *J* = 12.1 Hz, 1H), 5.18 (d, *J* = 12.5 Hz, 1H), 5.12 (d, *J* = 12.4 Hz, 1H), 4.65 (d, *J* = 11.6 Hz, 1H), 4.42 (d, *J* = 11.6 Hz, 1H), 4.26 (d, *J* = 6.2 Hz, 1H), 4.14 (dd, *J* = 8.1, 2.1 Hz, 1H), 4.04 (dd, *J* = 9.3, 6.3 Hz, 1H), 3.71 – 3.57 (m, 1H), 2.42 – 2.21 (m, 1H), 1.45 (s, 3H), 1.38 (s, 3H), 1.25 (d, *J* = 6.0 Hz, 3H), 0.91 (d, *J* = 6.9 Hz, 3H).; ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.9, 168.1, 164.7, 138.0, 136.5, 128.6, 128.6, 128.2, 128.2, 128.0, 128.0, 111.8, 97.5, 86.7, 80.2, 78.3, 73.1, 70.8, 65.8, 38.4, 27.3, 25.6, 16.4, 9.5.; HRMS (ESI) *m/z* calc. for [$C_{28}H_{34}O_8$ +Na]: 521.2151, found: 521.2144.

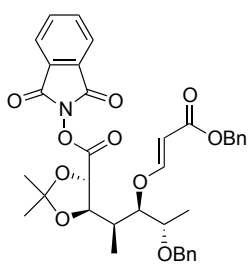


A 1 L round-bottom flask was charged with crude acid **S9** (as prepared above, < 2.5 mmol), $Ir[dF(CF_3)ppy]_2(dtbbpy)PF_6$ (140 mg, 0.13 mmol), K_2HPO_4 (871 mg, 5 mmol) and a magnetic stir bar. The flask was then purged with 3 cycles of argon/vacuum before the addition of DMF (500 mL) The reaction mixture was irradiated with 30 W blue led (at approximately 2 cm away from the light source) at room temperature for 24 h. The reaction mixture was concentrated *in vacuo*, diluted with sat. aq. NH_4Cl (250 mL) and Et_2O (250 mL) and the phases separated. The aqueous phase was further extracted with Et_2O (2 times). The combined organic extracts were dried ($MgSO_4$), filtered, concentrated *in vacuo* and purified by flash column chromatography to give oxane **2.99a** (630 mg, 1.4 mmol, 56% over 2 steps) as a white solid and oxane **2.99b** (162 mg, 0.36 mmol, 14% over 2 steps) as a colorless oil.

2.99a R_f 0.34 (hexane-EtOAc, 5:1); $[\alpha]_d^{20}$ = +44.4 (*c* 1.00, $CHCl_3$); IR (neat, ν_{max}) 2961, 2932, 2859, 1728, 1476, 1428, 1391, 1363, 1284, 1155, 1110, 1032, 998, 937, 823, 803, 740, 703 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.45 – 7.08 (m, 10H), 5.15 (s, 2H), 4.61 (d, *J* = 11.3 Hz, 1H), 4.35 (d, *J* = 11.3 Hz, 1H), 4.29 (t, *J* = 6.6 Hz, 1H), 4.18 (ddd, *J* = 8.5, 5.0, 3.4 Hz, 1H), 4.05 (dd, *J* = 6.2, 3.4 Hz, 1H), 3.61 – 3.47 (m, 1H), 3.06 (dd, *J* = 8.9, 2.2 Hz, 1H), 2.84 (dd, *J* = 16.2, 8.5 Hz, 1H), 2.72 (dd, *J* = 16.2, 5.1 Hz, 1H), 2.41 – 2.28 (m, 1H), 1.49 (s, 3H), 1.28 (s, 3H), 1.23 (d, *J* = 5.9 Hz, 3H), 0.89 (d, *J* = 7.2 Hz, 3H).; ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.1, 138.4, 136.0, 128.6, 128.5, 128.3, 128.3, 128.0, 127.8, 108.5, 80.8, 75.3, 73.6, 73.4,

72.8, 70.8, 66.4, 36.6, 31.7, 25.6, 25.6, 17.0, 10.1.; HRMS (ESI) *m/z* calc. for [$C_{27}H_{34}O_6$+Na]: 477.2253, found: 477.2249.

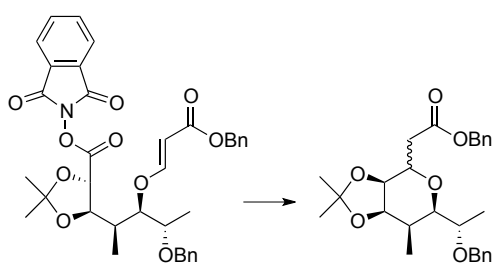
2.99b R_f 0.38 (hexane-EtOAc, 5:1); $[\alpha]_d^{20}$ = -9.1 (*c* 1.00, $CHCl_3$); IR (neat, ν_{max}) 2960, 2932, 2859, 1729, 1477, 1461, 1428, 1392, 1363, 1284, 1157, 1111, 1032, 938, 822, 741, 703 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.49 – 7.17 (m, 10H), 5.14 (s, 2H), 4.58 (d, *J* = 11.1 Hz, 1H), 4.39 (d, *J* = 11.0 Hz, 1H), 4.26 (t, *J* = 5.3 Hz, 1H), 4.08 – 3.93 (m, 1H), 3.87 (td, *J* = 8.7, 3.3 Hz, 1H), 3.80 (dd, *J* = 8.6, 5.7 Hz, 1H), 3.42 (dd, *J* = 9.2, 4.7 Hz, 1H), 2.71 (dd, *J* = 14.8, 3.4 Hz, 1H), 2.52 – 2.36 (m, 2H), 1.49 (s, 3H), 1.35 (s, 3H), 1.21 (d, *J* = 6.0 Hz, 3H), 1.14 (d, *J* = 7.5 Hz, 3H).; ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.1, 138.5, 136.0, 128.6, 128.4, 128.4, 128.3, 128.0, 127.6, 109.5, 77.5, 77.2, 76.9, 76.8, 75.7, 75.4, 74.5, 70.7, 69.3, 66.5, 39.3, 33.2, 27.9, 25.8, 16.7, 13.2.; HRMS (ESI) *m/z* calc. for [$C_{27}H_{34}O_6$+Na]: 477.2253, found: 477.2250.



2.98

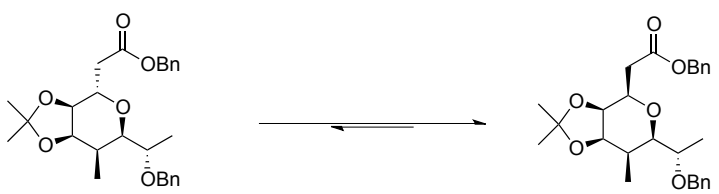
Me_3SnOH (530 mg, 2.9 mmol) was added to a stirred solution of acrylate **2.96** (300 mg, 0.59 mmol) in 1,2-dichloroethane (12 mL) at room temperature and the reaction mixture was stirred at 65 °C for 5 h. The reaction mixture was cooled to room temperature, concentrated *in vacuo* and diluted with EtOAc (20 mL). The organic layer was washed with aq. $KHSO_4$ (0.01 N, 15 mL × 3), dried ($MgSO_4$), filtered, concentrated *in vacuo* to give crude acid **S9** as a colorless oil that was

immediately used without further purification. EDC•HCl (170 mg, 0.89 mmol) was added to a stirred solution of crude acid (as prepared above, < 0.59 mmol), N-hydroxyphthalimide (144 mg, 0.89) and DMAP (7 mg, 0.06 mmol) in CH_2Cl_2 (6 mL) at room temperature. After stirring for 3 h, the reaction mixture was concentrated *in vacuo* and purified by flash column chromatography to give active ester **2.98** (217 mg, 0.34 mmol, 57% over 2 steps) as a white solid. R_f 0.43 (hexane-EtOAc, 2:1); $[\alpha]_d^{20}$ = -11.6 (*c* 1.00, $CHCl_3$); IR (neat, ν_{max}) 3032, 2984, 2937, 1815, 1789, 1736, 1708, 1639, 1496, 1466, 1455, 1374, 1325, 1277, 1206, 1186, 1123, 1079, 1025, 964, 913, 876, 785, 742, 696 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.88 (dd, *J* = 5.4, 3.1 Hz, 2H), 7.79 (dd, *J* = 5.6, 3.1 Hz, 2H), 7.61 (d, *J* = 12.2 Hz, 1H), 7.42 – 7.27 (m, 10H), 5.42 (d, *J* = 12.2 Hz, 1H), 5.18 (d, *J* = 12.5 Hz, 1H), 5.12 (d, *J* = 12.5 Hz, 1H), 4.66 (d, *J* = 11.6 Hz, 1H), 4.57 (d, *J* = 6.3 Hz, 1H), 4.43 (d, *J* = 11.6 Hz, 1H), 4.28 (dd, *J* = 9.1, 6.3 Hz, 1H), 4.15 (dd, *J* = 8.1, 2.1 Hz, 1H), 3.73 – 3.60 (m, 1H), 2.48 – 2.29 (m, 1H), 1.49 (s, 3H), 1.44 (s, 3H), 1.27 (d, *J* = 6.0 Hz, 3H), 0.99 (d, *J* = 7.0 Hz, 3H).; ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.3, 167.9, 164.5, 161.5, 138.0, 136.6, 135.0, 128.9, 128.6, 128.2, 128.1, 128.0, 127.9, 124.2, 112.5, 97.7, 97.7, 86.6, 80.8, 76.8, 73.1, 70.9, 65.6, 38.2, 27.1, 25.2, 16.4, 9.7.; HRMS (ESI) *m/z* calc. for [$C_{36}H_{37}NO_{10}$+Na]: 666.2309, found: 666.2315.



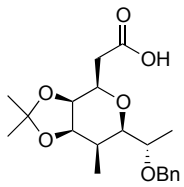
2.98 **2.99**

A 25 mL round-bottom flask was charged with active ester **2.98** (80 mg, 0.12 mmol), $[Ir(ppy)_2(dtbbpy)]PF_6$ (4 mg, 4 μmol) and a magnetic stir bar. The flask was then flushed with a stream of argon before the addition of CH_3CN (4 mL, degassed by 3 times freeze-pump-thaw) and DIPEA (0.22 mL, 1.3 mmol). The reaction mixture was irradiated with 6 W blue led (at approximately 2 cm away from the light source) at room temperature for 12 h. The reaction mixture was concentrated *in vacuo*, diluted with sat. aq. NH_4Cl (10 mL) and EtOAc (10 mL) and the phases separated. The aqueous phase was further extracted with EtOAc (2 times). The combined organic extracts were dried ($MgSO_4$), filtered, concentrated *in vacuo* and purified by flash column chromatography to give oxane **2.99** (17 mg, 0.037 mmol) in 31% yield as a 2:1 mixture of diastereomers along with complex byproducts.



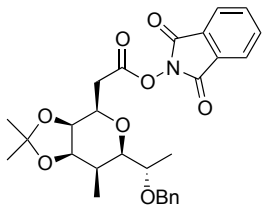
2.99b **2.99a**

KO*t*Bu (40 mg, 0.36 mmol) was added to a stirred solution of oxane **2.99b** (150 mg, 0.33 mmol) in THF (4 mL) at 0 °C and the reaction mixture was stirred at 0 °C for 4 h. The reaction mixture was then quenched with sat. aq. NH_4Cl (6 mL) and extracted with Et_2O (3 times). The combined organic extracts were dried ($MgSO_4$), filtered, concentrated *in vacuo* and purified by flash column chromatography to give oxane **2.99b** (24 mg, 0.052 mmol, 16%) as a colorless oil and oxane **2.99a** (96 mg, 0.21 mmol, 64%) as a white solid.



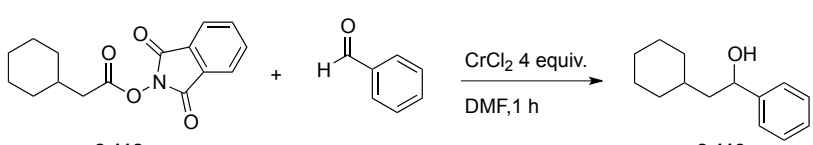
S10

$LiOH•2H_2O$ (180 mg, 4.3 mmol) was added to a stirred solution of oxane **2.99a** (490 mg, 1.08 mmol) in $THF/H_2O/MeOH$ (2:1:1, 20 mL) at 0 °C and the reaction mixture was stirred at room temperature for 3 h. The reaction mixture was then quenched with pH 6 phosphate buffer (120 mL) and extracted with EtOAc (4 times). The combined organic extracts were dried ($MgSO_4$), filtered, concentrated *in vacuo* to give crude acid **S10** as a pale yellow oil that was used without further purification. A sample was further purified by flash column chromatography for characterization. R_f 0.5 ($CHCl_3$-MeOH, 10:1); $[\alpha]_d^{20}$ = +53.1 (*c* 1.00, $CHCl_3$); IR (neat, ν_{max}) 2980, 2926, 2885, 1711, 1453, 1380, 1309, 1285, 1244, 1208, 1150, 1137, 1095, 1061, 1025, 1007, 991, 971, 941, 911, 871, 829, 738, 697 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.42 – 7.22 (m, 5H), 4.63 (d, *J* = 11.3 Hz, 1H), 4.37 (d, *J* = 11.3 Hz, 1H), 4.32 (t, *J* = 6.6 Hz, 1H), 4.15 (ddd, *J* = 8.3, 5.0, 3.4 Hz, 1H), 4.08 (dd, *J* = 6.3, 3.4 Hz, 1H), 3.65 – 3.51 (m, 1H), 3.11 (dd, *J* = 8.8, 2.4 Hz, 1H), 2.83 (dd, *J* = 16.5, 8.3 Hz, 1H), 2.73 (dd, *J* = 16.4, 5.0 Hz, 1H), 2.46 – 2.26 (m, 1H), 1.51 (s, 3H), 1.33 (s, 3H), 1.28 (d, *J* = 5.9 Hz, 3H), 0.91 (d, *J* = 7.2 Hz, 3H).; ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.7, 138.3, 128.5, 128.0, 127.8, 108.6, 80.8, 75.3, 73.5, 73.3, 72.8, 70.8, 36.4, 31.6, 25.6, 25.6, 17.0, 10.2.; HRMS (ESI) *m/z* calc. for $[C_{20}H_{28}O_6+Na]$: 387.1784, found: 387.1780.



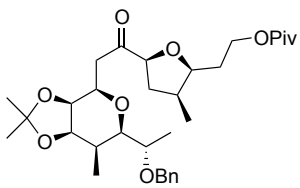
2.106

EDC•HCl (263 mg, 1.6 mmol) was added to a stirred solution of crude acid **S10** (as prepared above, < 1.08 mmol), N-hydroxyphthalimide and DMAP (26 mg, 0.21 mmol) in CH_2Cl_2 (11 mL) at room temperature. After stirring for 3 h, the reaction mixture was concentrated *in vacuo* and purified by flash column chromatography to give active ester **2.106** (474 mg, 0.93 mmol, 87% over 2 steps) as a white solid. R_f 0.49 (hexane-EtOAc, 2:1); $[\alpha]_d^{20}$ = +44.2 (*c* 1.00, $CHCl_3$); IR (neat, ν_{max}) 2983, 2928, 1817, 1789, 1745, 1466, 1454, 1379, 1310, 1244, 1209, 1186, 1146, 1082, 1062, 1009, 988, 969, 876, 746, 721, 697cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 (dd, *J* = 5.5, 3.1 Hz, 2H), 7.79 (dd, *J* = 5.5, 3.1 Hz, 2H), 7.39 – 7.26 (m, 5H), 4.64 (d, *J* = 11.3 Hz, 1H), 4.38 (d, *J* = 11.2 Hz, 1H), 4.34 (t, *J* = 6.6 Hz, 1H), 4.27 (ddd, *J* = 8.4, 5.1, 3.4 Hz, 1H), 4.14 (dd, *J* = 6.2, 3.4 Hz, 1H), 3.68 – 3.54 (m, 1H), 3.20 – 3.09 (m, 2H), 3.04 (dd, *J* = 16.4, 5.1 Hz, 1H), 2.45 – 2.31 (m, 1H), 1.53 (s, 3H), 1.35 (s, 3H), 1.33 (d, *J* = 5.9 Hz, 3H), 0.93 (d, *J* = 7.2 Hz, 3H).; ^{13}C NMR (101 MHz, $CDCl_3$) δ 167.5, 161.8, 138.4, 134.9, 129.0, 128.5, 128.0, 127.8, 124.1, 108.8, 81.0, 75.2, 73.5, 73.0, 72.4, 70.8, 33.7, 31.6, 25.6, 17.0, 10.1.; HRMS (ESI) *m/z* calc. for [$C_{28}H_{31}NO_8$+Na]: 532.1947, found: 532.1944.



2.112 **2.113**

To a stirred solution of active ester **2.112** (50 mg, 0.17 mmol) and benzaldehyde (33 mg, 0.31 mmol) in DMF (2 mL) was added $CrCl_2$ (84 mg, 0.68 mmol) at room temperature and the reaction mixture was stirred at room temperature for 1 h. The reaction mixture was then quenched with 1 M potassium serinate solution (1 g of serine and 1g of $KHCO_3$ in 10 mL of H_2O), diluted with EtOAc (10 mL) and the mixture was stirred vigorously for 1 h. The mixture was then extracted with EtOAc (3 times) and the combined organic extracts were dried ($MgSO_4$), filtered, concentrated *in vacuo* and purified by flash column chromatography to give alcohol **2.113** (21 mg, 0.10 mmol, 60%) as a colorless oil. R_f 0.26 (hexane-EtOAc, 10:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 – 7.22 (m, 5H), 4.79 (dd, J = 8.7, 5.1 Hz, 1H), 1.86 – 1.56 (m, 6H), 1.57 – 1.48 (m, 1H), 1.48 – 1.36 (m, 1H), 1.31 – 1.08 (m, 3H), 1.04 – 0.80 (m, 2H).

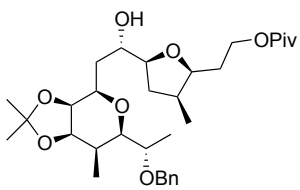


2.117

$NiBr_2$•dtbbpy[8] (11 mg, 23 μmol), Zn dust (80 mg, 1.2 mmol) and $CpZrCl_2$ (117 mg, 0.4 mmol) were added to a stirred solution of active ester **2.106** (76 mg, 150 μmol) and thioester **2.105** (66 mg, 190 μmol) in DMI (0.5 mL, degassed by 3 times freeze-pump-thaw, pre-stirred with 3 Å M.S. for 1 h) at room temperature. After stirring for 2 h, the reaction mixture was filtered through a pad of silica gel (hexane-EtOAc, 2:1, 500 mL), concentrated *in vacuo* and purified by flash column chromatography to give ketone **2.117** (43 mg, 77 μmol, 51)) as a colorless oil. R_f

[8] Ai, Y.; Ye, N.; Wang, Q.; Yahata, K.; Kishi, Y.; *Angew. Chem. Int. Ed.* **2017**, *56*, 10791.

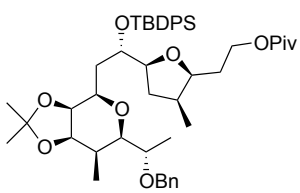
0.52 (hexane-acetone, 5:1); $[\alpha]_d^{20}$ = -4.2 (*c* 1.00, $CHCl_3$); IR (neat, ν_{max}) 2970, 2930, 2876, 1725, 1479, 1455, 1417, 1380, 1366, 1308, 1284, 1244, 1209, 1154, 1095, 1062, 1005, 971, 883, 869, 737, 698 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.38 – 7.27 (m, 5H), 4.61 (d, *J* = 11.4 Hz, 1H), 4.35 (d, *J* = 11.1 Hz, 1H), 4.33 – 4.18 (m, 4H), 4.08 (dd, *J* = 6.3, 3.4 Hz, 1H), 4.02 (q, *J* = 6.0 Hz, 1H), 3.57 – 3.47 (m, 1H), 3.11 – 2.99 (m, 2H), 2.85 (dd, *J* = 17.3, 6.0 Hz, 1H), 2.42 – 2.26 (m, 3H), 1.77 (q, *J* = 6.7 Hz, 2H), 1.74 – 1.65 (m, 1H), 1.49 (s, 3H), 1.29 (s, 3H), 1.25 (d, *J* = 5.8 Hz, 3H), 1.20 (d, *J* = 1.0 Hz, 9H), 0.95 – 0.85 (m, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ δ 209.1, 178.6, 138.4, 128.5, 128.0, 127.8, 108.3, 82.8, 80.7, 79.8, 75.2, 73.6, 72.8, 72.7, 70.8, 62.2, 40.0, 38.9, 36.7, 35.6, 31.7, 30.1, 27.3, 25.7, 25.6, 17.1, 14.6, 10.1.; HRMS (ESI) *m/z* calc. for $[C_{32}H_{48}O_8+Na]$: 583.3247, found: 583.3244.



S11

A solution of L-selectride (0.19 mL , 1.0 M in THF, 0.19 mmol) was added to a stirred solution of ketone **2.117** (35 mg, 62 μmol) in THF (3 mL) at -78 °C and the reaction mixture was stirred at -78 °C for 4 h. The reaction mixture was then quenched with 2 N NaOH/30% aq. H_2O_2 solution (1:1, 6 mL) and the mixture was stirred vigorously for 1 h, while warming to room temperature. The mixture was then extracted with Et_2O (3 times) and the combined organic extracts were dried ($MgSO_4$), filtered, concentrated *in vacuo* and purified by flash column chromatography to give alcohol **S11** (33 mg, 59 μmol, 93%) as a colorless oil. R_f 0.12 (hexane-acetone, 7:1); $[\alpha]_d^{20}$ = -0.9 (*c* 1.00, $CHCl_3$); IR (neat, ν_{max}) 3513, 2967,

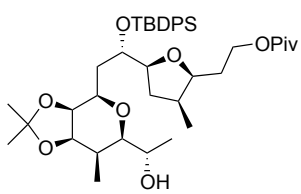
2930, 2876, 1726, 1495, 1479, 1455, 1380, 1366, 1285, 1254, 1244, 1209, 1154, 1101, 1066, 1029, 1005, 985, 889, 864, 829, 792, 772, 736, 699 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.35 – 7.26 (m, 5H), 4.62 (d, *J* = 11.2 Hz, 1H), 4.36 (d, *J* = 11.3 Hz, 1H), 4.28 (t, *J* = 6.5 Hz, 1H), 4.24 (t, *J* = 6.1 Hz, 1H), 4.13 (dt, *J* = 10.9, 7.4 Hz, 1H), 4.07 (dd, *J* = 6.2, 3.3 Hz, 1H), 3.98 (td, *J* = 6.8, 3.1 Hz, 1H), 3.95 – 3.88 (m, 1H), 3.78 (q, *J* = 7.3 Hz, 1H), 3.70 – 3.62 (m, 1H), 3.62 – 3.54 (m, 1H), 3.10 (dd, *J* = 8.8, 2.4 Hz, 1H), 2.89 (s, 1H), 2.45 – 2.28 (m, 2H), 2.09 (dt, *J* = 12.5, 7.3 Hz, 1H), 1.94 – 1.81 (m, 2H), 1.78 – 1.62 (m, 2H), 1.50 (s, 3H), 1.40 – 1.29 (m, 1H), 1.32 (s, 3H), 1.29 (d, *J* = 6.0 Hz, 3H), 1.19 (s, 9H), 0.95 (d, *J* = 6.9 Hz, 3H), 0.91 (d, *J* = 7.2 Hz, 3H).; ^{13}C NMR (101 MHz, $CDCl_3$) δ 178.7, 138.4, 128.5, 128.0, 127.8, 108.3, 81.8, 81.0, 78.5, 75.3, 75.1, 73.5, 73.0, 72.7, 70.9, 62.4, 38.8, 36.1, 35.7, 34.6, 31.9, 30.4, 27.3, 25.7, 25.7, 17.3, 15.2, 10.2.; HRMS (ESI) *m/z* calc. for [$C_{32}H_{50}O_8$+Na]: 584.3403, found: 585.3399.



2.120

TBDPSCl (24 μL, 87 μmol) was added to a stirred solution of alcohol **S11** (30 mg, 53 μmol) and imidazole (36 mg, 0.54 mmol) in DMF (0.5 mL) at room temperature. After stirring for 24 h, additional TBDPSCl (24 μL, 87 μmol) was added at room temperature. After stirring for a further 24 h, the reaction mixture was then quenched with sat. aq. NH_4Cl (10 mL) and extracted with Et_2O (3 times). The combined organic extracts were dried ($MgSO_4$), filtered, concentrated *in vacuo* and purified by flash column chromatography to give TBDPS ether **2.120** (42 mg,

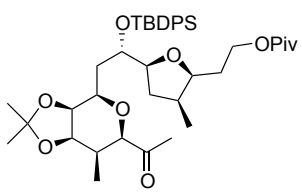
51 μmol, 98%) as a colorless oil. R_f 0.13 (hexane-EtOAc, 10:1); $[\alpha]_d^{20}$ = +10.7 (*c* 1.00, $CHCl_3$); IR (neat, ν_{max}) 2961, 2930, 2897, 2857, 1727, 1474, 1456, 1427, 1380, 1364, 1284, 1254, 1244, 1208, 1153, 1105, 1030, 1004, 938, 871, 822, 740, 701 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.76 – 7.65 (m, 4H), 7.45 – 7.26 (m, 11H), 4.61 (d, *J* = 11.3 Hz, 1H), 4.35 (d, *J* = 11.2 Hz, 1H), 4.10 – 3.88 (m, 4H), 3.87 – 3.79 (m, 1H), 3.79 – 3.67 (m, 2H), 3.53 – 3.41 (m, 1H), 3.08 (dd, *J* = 6.3, 3.3 Hz, 1H), 2.77 (dd, *J* = 8.9, 2.1 Hz, 1H), 2.32 – 2.16 (m, 2H), 2.06 (dt, *J* = 12.6, 7.3 Hz, 1H), 1.93 – 1.82 (m, 1H), 1.82 – 1.72 (m, 1H), 1.67 – 1.55 (m, 2H), 1.38 (s, 3H), 1.32 – 1.26 (m, 1H), 1.23 (d, *J* = 5.9 Hz, 3H), 1.20 (s, 6H), 1.06 (s, 6H), 1.04 (s, 2H), 0.82 (d, *J* = 7.0 Hz, 2H), 0.79 (d, *J* = 7.1 Hz, 2H).; ^{13}C NMR (101 MHz, $CDCl_3$) δ 178.6, 138.4, 136.3, 136.1, 134.6, 134.0, 129.7, 129.6, 128.5, 128.0, 127.8, 127.7, 127.5, 107.8, 81.6, 80.8, 78.1, 75.1, 73.5, 73.5, 73.4, 72.2, 70.9, 62.5, 38.8, 35.9, 35.7, 35.3, 31.7, 30.4, 27.4, 27.1, 25.6, 25.4, 19.8, 17.3, 15.4, 10.0.; HRMS (ESI) *m/z* calc. for [$C_{48}H_{68}O_8Si$+Na]: 823.4581, found: 823.4579.



S13

Palladium on activated carbon (10 mg, 10% w/w, 9 μmol) was added to a stirred solution of ether **2.120** (40 mg, 50 μmol) in EtOAc (2 mL) at room temperature and the flask was purged with 3 cycles of H_2/vacuum. The reaction mixture was stirred under H_2 atmosphere (balloon) at room temperature. After stirring for 36 h, the reaction mixture was filtered through a pad of celite (eluting with EtOAc) and concentrated *in vacuo*, The crude mixture was purified by flash column

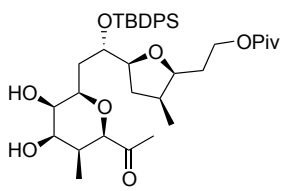
chromatography to give alcohol **S12** (32 mg, 45 μmol, 90%) as a colorless. R_f 0.4 (hexane-EtOAc, 2:1); $[\alpha]_d^{20}$ = -15.6 (*c* 1.00, $CHCl_3$); IR (neat, ν_{max}) 3444, 2961, 2930, 2856, 1727, 1474, 1459, 1427, 1381, 1363, 1285, 1253, 1208, 1155, 1106, 1086, 1063, 1011, 938, 871, 822, 793, 772, 740, 703, 688 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.76 – 7.64 (m, 4H), 7.45 – 7.29 (m, 6H), 4.00 (dddd, *J* = 28.4, 15.2, 9.9, 6.2 Hz, 4H), 3.84 – 3.73 (m, 3H), 3.70 (td, *J* = 6.7, 3.0 Hz, 1H), 3.20 (dd, *J* = 6.5, 3.1 Hz, 1H), 2.79 (dd, *J* = 7.5, 3.0 Hz, 1H), 2.31 – 2.18 (m, 1H), 2.13 – 2.00 (m, 2H), 1.85 (ddd, *J* = 11.1, 7.2, 3.5 Hz, 1H), 1.80 – 1.71 (m, 2H), 1.64 – 1.56 (m, 2H), 1.38 (s, 3H), 1.35 – 1.23 (m, 1H), 1.20 (d, *J* = 6.1 Hz, 3H), 1.19 (s, 9H), 1.08 (s, 3H), 1.06 (s, 9H), 0.93 (d, *J* = 7.2 Hz, 3H), 0.81 (d, *J* = 7.0 Hz, 3H).; ^{13}C NMR (101 MHz, $CDCl_3$) δ 178.6, 136.3, 136.1, 134.6, 134.0, 129.7, 129.6, 127.6, 127.5, 108.0, 81.5, 81.3, 78.1, 75.3, 73.4, 72.9, 72.7, 67.3, 62.5, 38.8, 35.9, 35.7, 35.1, 31.6, 30.4, 27.4, 27.1, 25.6, 25.4, 21.2, 19.8, 15.3, 10.7.; HRMS (ESI) *m/z* calc. for [$C_{41}H_{62}O_8Si$ Si+Na]: 733.4112, found: 733.4106.



2.121

Dess-Martin periodinane (36 mg, 84 μmol) was added to a cloudy solution of alcohol **S12** (30 mg, 42 μmol) and $NaHCO_3$ (35 mg, 420 μmol) in CH_2Cl_2 (1 mL) at room temperature and the reaction mixture was stirred for 1 h. The reaction mixture was then quenched with sat. aq. $NaHCO_3$ (10 mL) and extracted with Et_2O (3 times). The combined organic extracts were dried ($MgSO_4$), filtered, concentrated *in vacuo* and purified by flash column chromatography to give

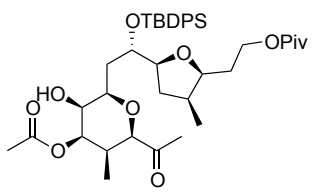
Ketone **2.121** (28 mg, 39 μmol, 93%) as a colorless oil. R_f 0.33 (hexane-EtOAc, 5:1); $[\alpha]_d^{20}$ = +22.3 (*c* 1.00, $CHCl_3$); IR (neat, ν_{max}) 2959, 2931, 2857, 1724, 1475, 1459, 1427, 1381, 1361, 1284, 1256, 1240, 1208, 1151, 1107, 1065, 1007, 937, 875, 822, 770, 740, 703 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.78 – 7.64 (m, 4H), 7.45 – 7.29 (m, 6H), 4.05 (q, *J* = 6.5 Hz, 2H), 4.01 – 3.92 (m, 2H), 3.83 (q, *J* = 9.1, 7.2 Hz, 2H), 3.72 (td, *J* = 6.5, 2.8 Hz, 1H), 3.46 (d, *J* = 4.1 Hz, 1H), 3.31 (dd, *J* = 6.6, 3.0 Hz, 1H), 2.34 – 2.21 (m, 1H), 2.19 – 2.12 (m, 1H), 2.14 (s, 3H), 2.07 (dd, *J* = 13.4, 6.5 Hz, 1H), 1.88 (q, *J* = 6.1, 5.3 Hz, 2H), 1.66 – 1.58 (m, 2H), 1.39 (s, 3H), 1.32 (dt, *J* = 12.6, 8.0 Hz, 1H), 1.19 (s, 9H), 1.11 (s, 3H), 1.06 (s, 9H), 0.83 (d, *J* = 7.3 Hz, 3H), 0.81 (d, *J* = 7.3 Hz, 3H).; ^{13}C NMR (101 MHz, $CDCl_3$) δ 210.2, 178.6, 136.3, 136.1, 134.6, 129.7, 129.7, 127.6, 127.5, 108.4, 82.9, 81.3, 78.1, 74.6, 73.2, 72.6, 62.5, 38.8, 35.9, 35.7, 34.9, 33.0, 30.4, 27.8, 27.4, 27.1, 25.6, 25.2, 19.8, 15.4, 11.4.; HRMS (ESI) *m/z* calc. for [$C_{41}H_{60}O_8Si$+Na]: 731.3955, found: 731.3953.



S13

CF_3CO_2H/H_2O (4:1, 100 μmol) was added to a stirred solution of ketone **2.121** (27 mg, 38 μmol) in CH_2Cl_2 (1 mL) at 0 °C and the reaction mixture was stirred at 0 °C for 2 h. The reaction mixture was then quenched with sat. aq. $NaHCO_3$ (10 mL) and extracted with Et_2O (3 times). The combined organic extracts were dried ($MgSO_4$), filtered, concentrated *in vacuo* and purified by flash column chromatography to give diol **S13** (24 mg, 36 μmol, 94%) as a colorless oil. R_f 0.1 (hexane-EtOAc, 2:1); $[\alpha]_d^{20}$ = -1.8 (*c* 1.00, $CHCl_3$); IR (neat, ν_{max}) 3443, 2960,

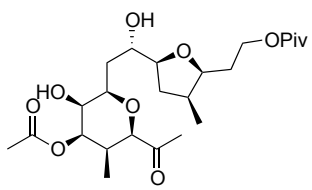
2930, 2856, 1716, 1460, 1427, 1390, 1355, 1285, 1228, 1156, 1104, 1037, 1003, 938, 917, 879, 857, 821, 775, 740, 702, 689 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.74 – 7.62 (m, 4H), 7.46 – 7.30 (m, 6H), 4.13 (dt, *J* = 10.9, 6.4 Hz, 1H), 4.02 – 3.92 (m, 2H), 3.88 (q, *J* = 5.8 Hz, 1H), 3.86 – 3.79 (m, 1H), 3.49 – 3.38 (m, 2H), 3.24 (t, *J* = 6.7 Hz, 1H), 3.16 (d, *J* = 3.3 Hz, 1H), 2.49 (s, 1H), 2.39 – 2.28 (m, 1H), 2.28 – 2.17 (m, 1H), 2.14 – 2.08 (m, 1H), 2.11 (s, 3H), 2.04 – 1.91 (m, 1H), 1.81 (dt, *J* = 14.2, 5.9 Hz, 1H), 1.67 – 1.60 (m, 2H), 1.48 – 1.36 (m, 1H), 1.18 (s, 9H), 1.05 (s, 9H), 0.90 (d, *J* = 7.0 Hz, 3H), 0.83 (d, *J* = 7.1 Hz, 3H).; ^{13}C NMR (101 MHz, $CDCl_3$) δ 209.2, 178.7, 136.1, 136.0, 134.4, 133.7, 129.9, 129.9, 127.7, 127.7, 84.5, 81.0, 78.3, 76.0, 71.8, 71.0, 69.6, 62.4, 38.8, 36.1, 35.6, 35.2, 34.3, 30.4, 27.7, 27.3, 27.1, 19.6, 15.4, 8.2.; HRMS (ESI) *m/z* calc. for [$C_{38}H_{56}O_8Si$ +Na] 691.3641, found: 691.3638.



S14

Acetyl chloride (11 μL, 165 μmol) was added to a stirred solution of diol **S13** (22 mg, 33 μmol) in pyridine/CH_2Cl_2 (1:4. 1 mL) at -20 °C and the reaction mixture was stirred at 0 °C for 2 h. The reaction mixture was then quenched with sat. aq. NH_4Cl (10 mL) and extracted with Et_2O (3 times). The combined organic extracts were dried ($MgSO_4$), filtered, concentrated *in vacuo* and purified by flash column chromatography to give ester **S14** (21 mg, 30 μmol, 90%) as a colorless oil. R_f 0.43 (hexane-EtOAc, 2:1); $[\alpha]_d^{20}$ = +3.8 (*c* 1.00, $CHCl_3$); IR (neat, ν_{max}) 3472, 2962, 2929, 2856, 1720, 1459, 1427, 1362, 1285, 1234, 1157, 1101, 1035, 997, 932, 881,

844, 821, 791, 769, 740, 703, 688 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ δ 7.77 – 7.61 (m, 4H), 7.45 – 7.29 (m, 6H), 4.57 (dd, *J* = 5.5, 3.3 Hz, 1H), 4.11 (dt, *J* = 11.9, 6.4 Hz, 1H), 3.97 (dt, *J* = 12.1, 7.7 Hz, 2H), 3.88 – 3.76 (m, 2H), 3.53 (d, *J* = 2.7 Hz, 1H), 3.41 (t, *J* = 6.6 Hz, 1H), 3.15 (s, 1H), 2.47 – 2.36 (m, 1H), 2.36 – 2.24 (m, 1H), 2.12 (s, 3H), 2.10 (s, 3H), 2.14 – 2.08 (m, 1H), 1.98 – 1.89 (m, 1H), 1.88 – 1.79 (m, 1H), 1.63 (q, *J* = 7.2 Hz, 2H), 1.36 (dt, *J* = 12.6, 8.4 Hz, 1H), 1.19 (s, 9H), 1.05 (s, 9H), 0.88 (d, *J* = 7.1 Hz, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 208.2, 178.7, 169.7, 136.2, 136.0, 134.4, 133.7, 129.8, 127.7, 127.7, 110.2, 84.2, 81.1, 78.1, 75.9, 73.8, 72.4, 67.9, 62.5, 38.8, 35.7, 35.5, 34.3, 33.5, 30.5, 27.6, 27.3, 27.1, 21.2, 19.7, 15.3, 9.0.; HRMS (ESI) *m/z* calc. for [$C_{40}H_{58}O_9Si$+Na]: 733.3748, found: 733.3744.



2.122

HF•Pyridine complex (1.8 mL, 70% HF) was added to a stirred solution of ester **S14** (20 mg, 28 μmol) in pyridine/THF (1:1. 3.6 mL) in polypropylene tube at 0 °C and the reaction mixture was stirred at room temperature for 48 h. The reaction mixture was slowly quenched with sat. aq. $NaHCO_3$ (30 mL) and extracted with Et_2O (3 times). The combined organic extracts were dried ($MgSO_4$), filtered, concentrated *in vacuo* and purified by flash column chromatography to give diol **2.122** (12 mg, 25 μmol, 91%) as a white solid. R_f 0.43 (hexane-acetone, 2:1); $[\alpha]_d^{20}$ = -18.5 (*c* 1.00, $CHCl_3$); IR (neat, ν_{max}) 3491, 2963, 2929, 2876, 1710, 1480, 1460, 1416, 1364, 1286, 1238, 1176, 1121, 1094, 1059, 1035, 926, 847, 793, 679 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.95 (dd, *J* = 5.5, 3.4 Hz, 1H), 4.26 (ddd, *J* = 10.9,

7.5, 5.1 Hz, 1H), 4.10 (dt, *J* = 10.8, 7.5 Hz, 1H), 4.00 – 3.85 (m, 3H), 3.84 – 3.71 (m, 2H), 3.71 – 3.61 (m, 1H), 2.58 – 2.47 (m, 1H), 2.40 (p, *J* = 7.1 Hz, 1H), 2.21 (s, 3H), 2.16 – 2.05 (m, 1H), 2.13 (s, 3H), 2.01 – 1.85 (m, 2H), 1.75 – 1.58 (m, 2H), 1.35 (dt, *J* = 12.6, 8.5 Hz, 1H), 1.19 (s, 9H), 1.02 (d, *J* = 7.1 Hz, 3H), 0.96 (d, *J* = 7.0 Hz, 3H).; ^{13}C NMR (101 MHz, $CDCl_3$) δ 208.0, 178.8, 169.9, 84.5, 81.8, 78.5, 77.4, 76.7, 73.9, 71.9, 68.1, 62.4, 38.9, 36.4, 35.7, 34.3, 33.8, 30.5, 27.6, 27.3, 21.2, 15.0, 9.1.; HRMS (ESI) *m/z* calc. for [$C_{24}H_{40}O_9$+Na]: 495.2570, found: 495.2566.

국문 초록

해양천연물 마데이롤라이드 에이의 합성을 위한 연구를 진행하였다. 마데이롤라이드 에이는 16 개의 입체중심과 세 개의 산소고리를 포함하는 21 각 마크로락톤고리와 단당류인 씨너룰로즈로 구성된 마크롤라이드의 하나로 생리활성적으로, 구조적으로 모두 매력적인 천연물 이다.

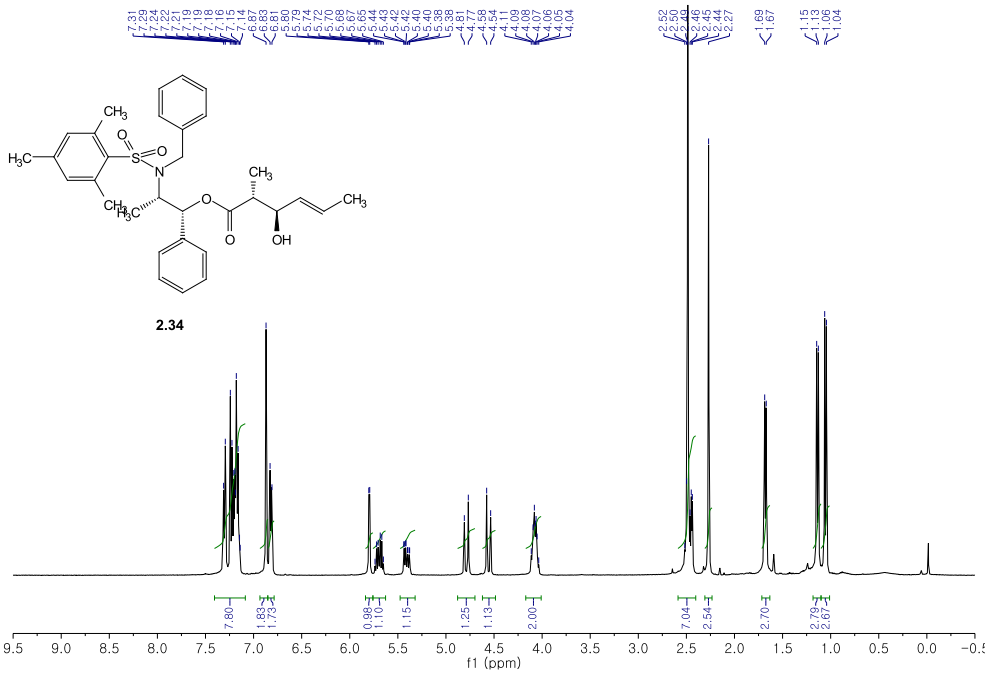
이미 알려진 간단한 시작 물질로 부터 입체특이적인 반응을 연속적으로 사용하여 마데이롤라이드 에이의 16 개의 입체중심을 효율적으로 도입하였다. 가시광선에 의해 유도된 광촉매 반응을 이용한 라디칼 고리화반응을 통해 세 개의 산소고리구조를 입체선택적으로 합성하였다. 마지막으로 전이금속을 이용한 교차짝지음 반응을 통해 부분구조의 결합에 대한 다양한 전략을 연구했다.

주제어: 마데이롤라이드 에이, 천연물, 라디칼 고리화 반응, 광산화환원, 전합성

학번: 2009-20318

Appendix

NMR Spectra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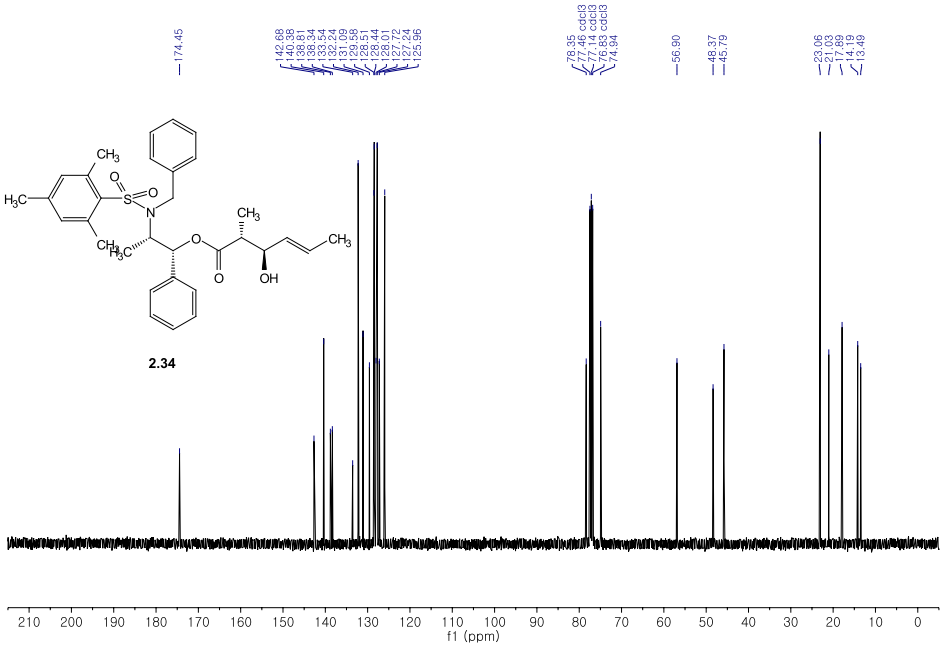
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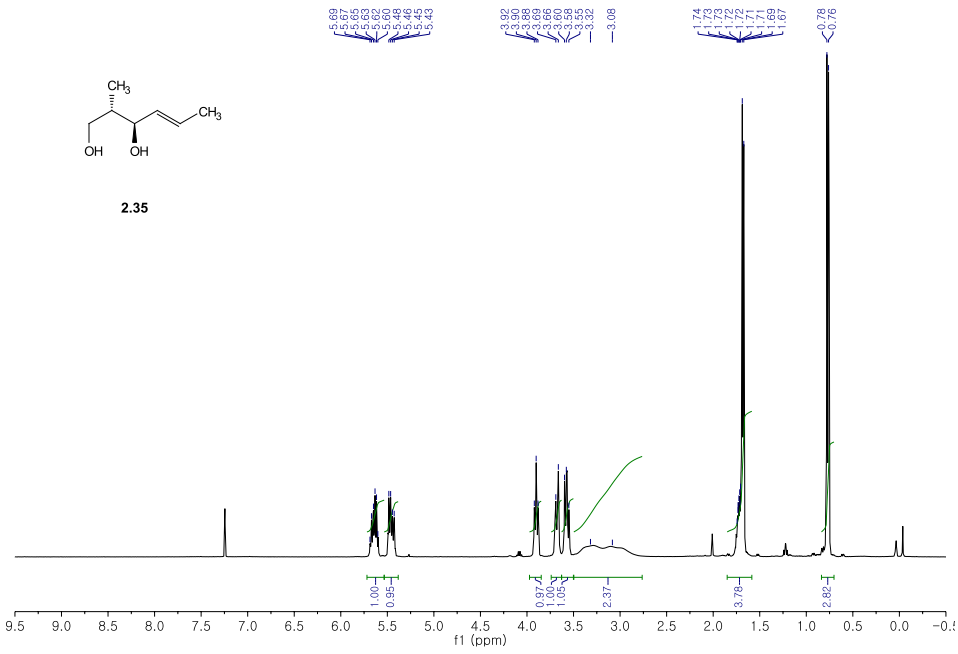
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3.58
3.55
3.32
3.08
1.74
1.73
1.73
1.72
1.72
1.71
1.71
1.69
1.67
0.78
0.76
CH3
CH3
OH
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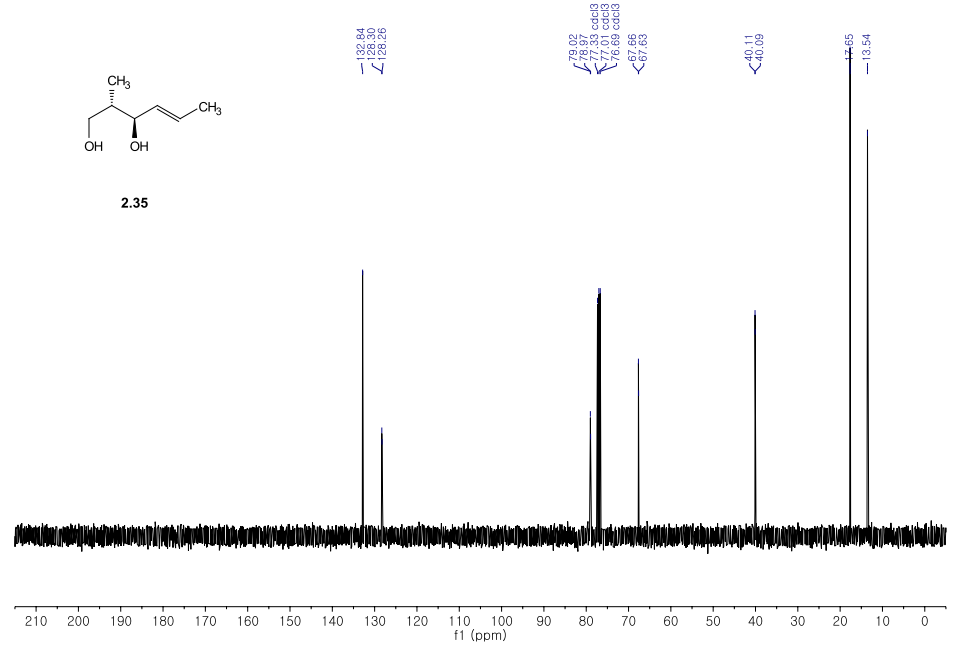
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CH3
CH3
OH
OH
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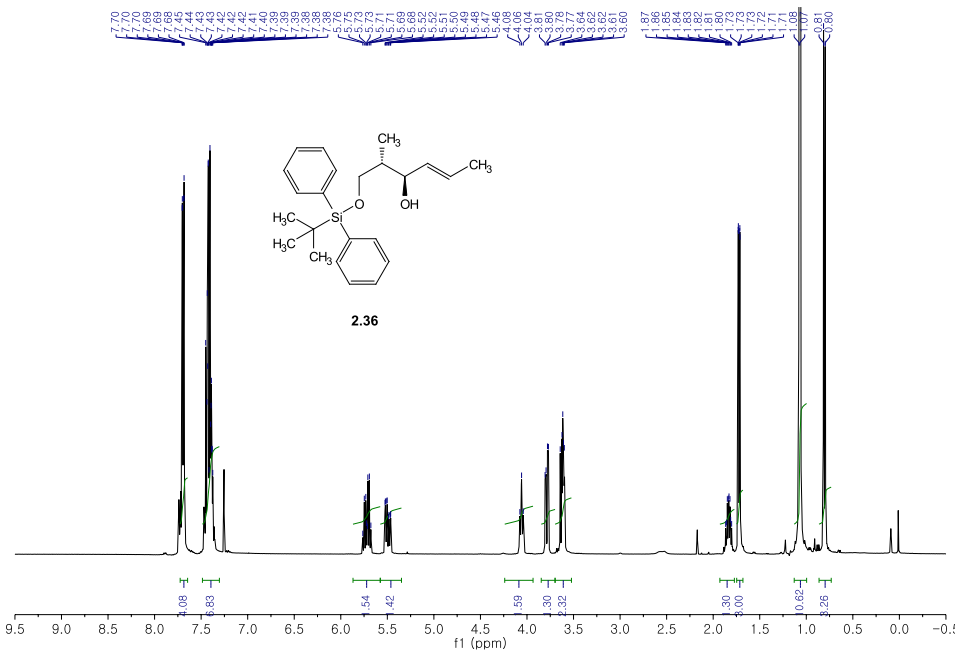
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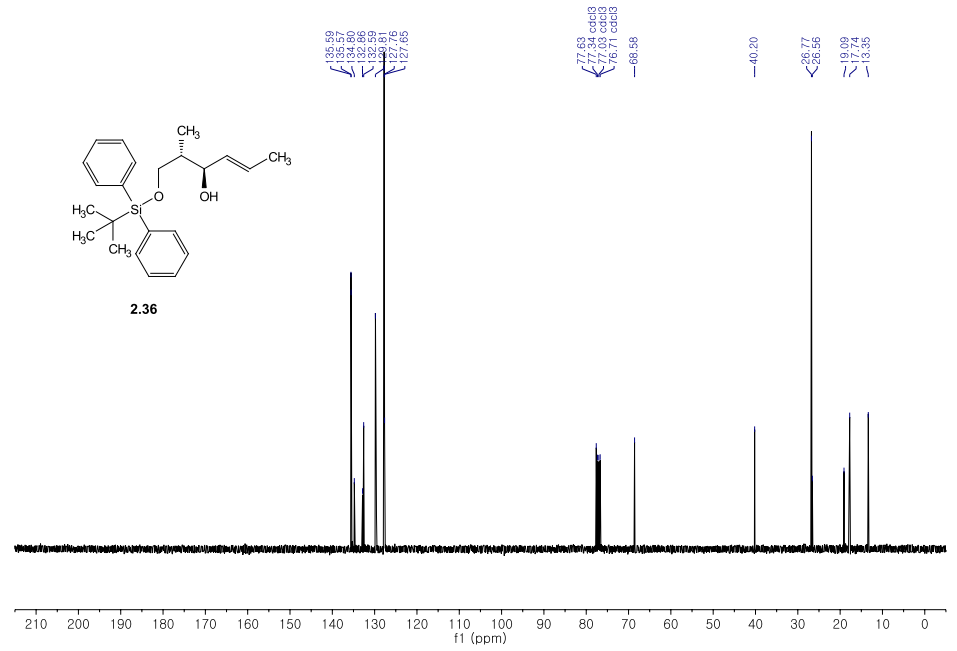
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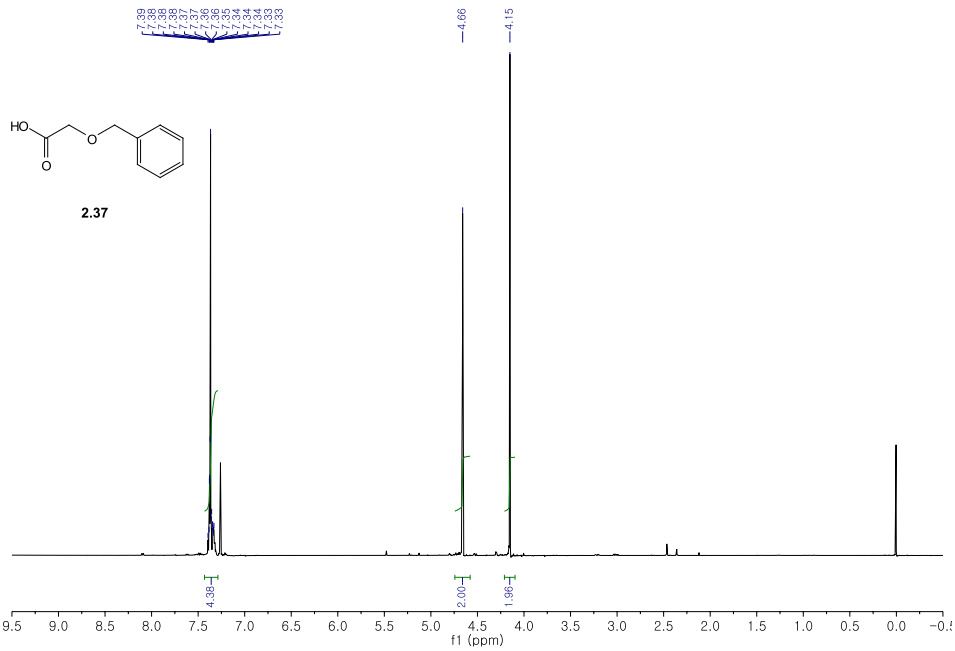
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4.15
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O
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4.38
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1.96
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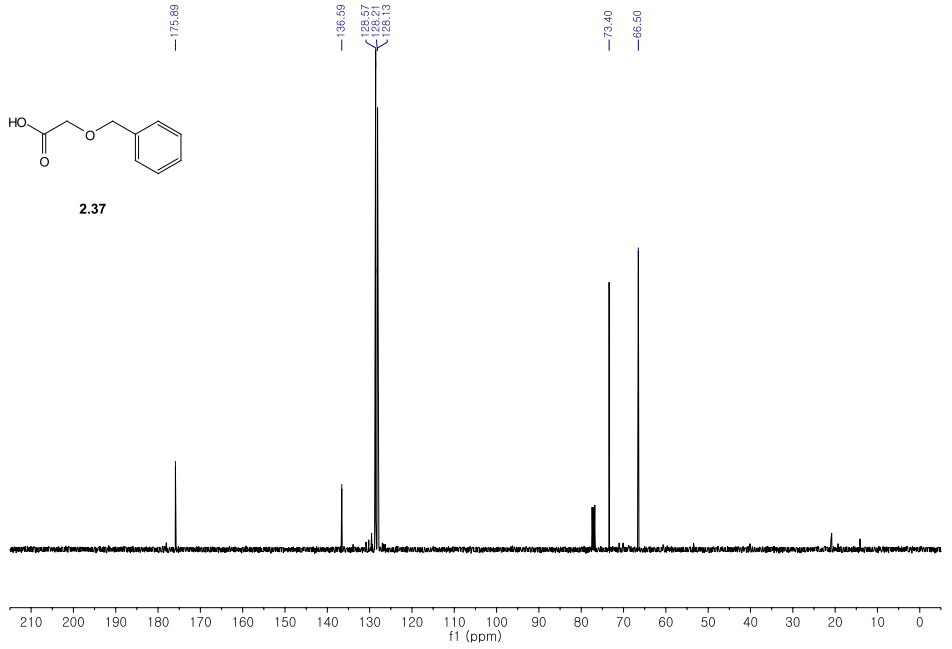
f1 (ppm)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O
O
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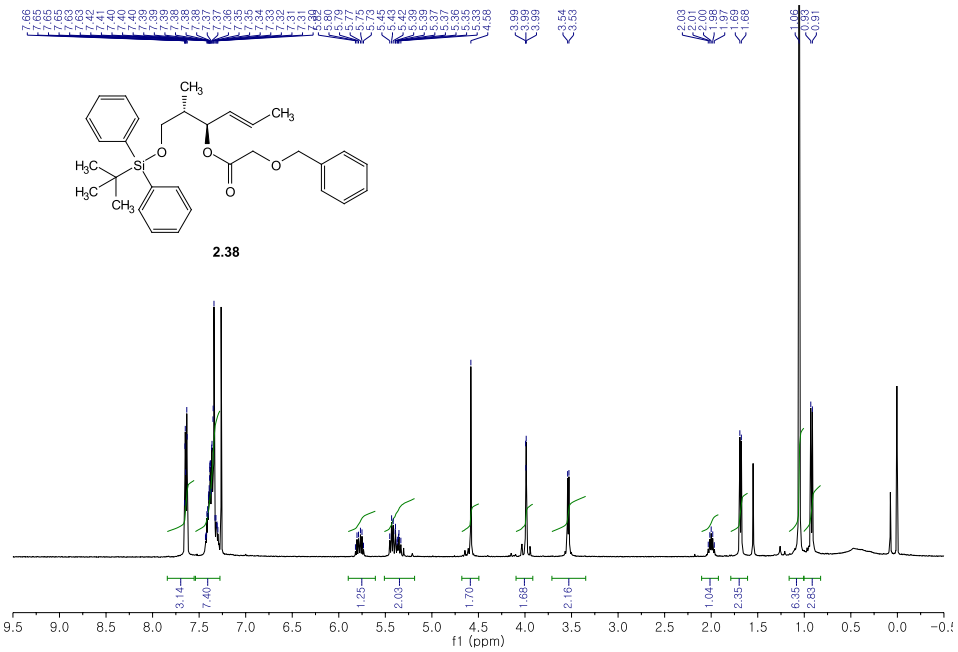
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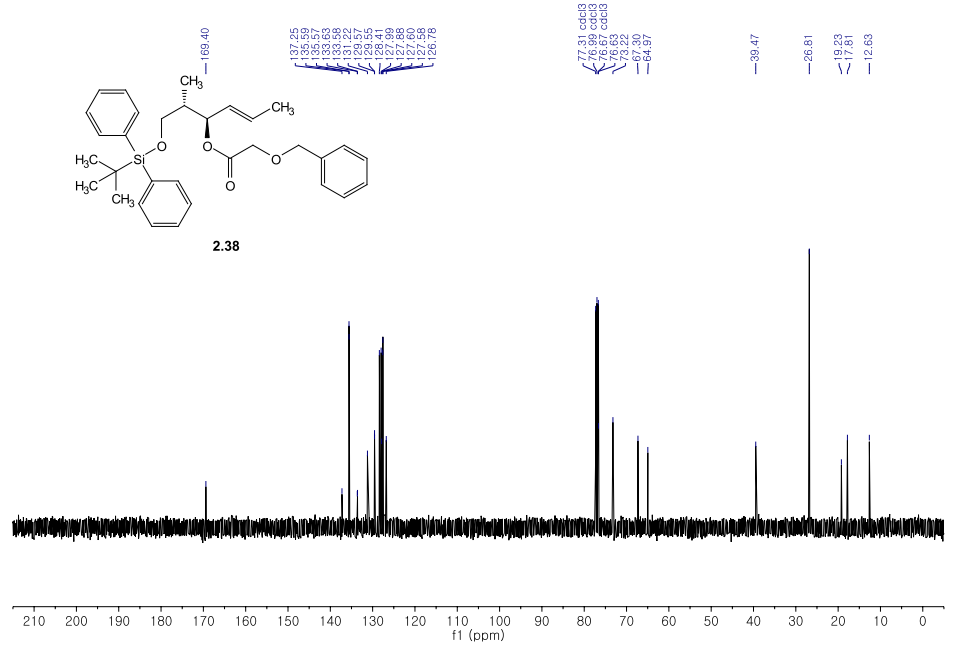
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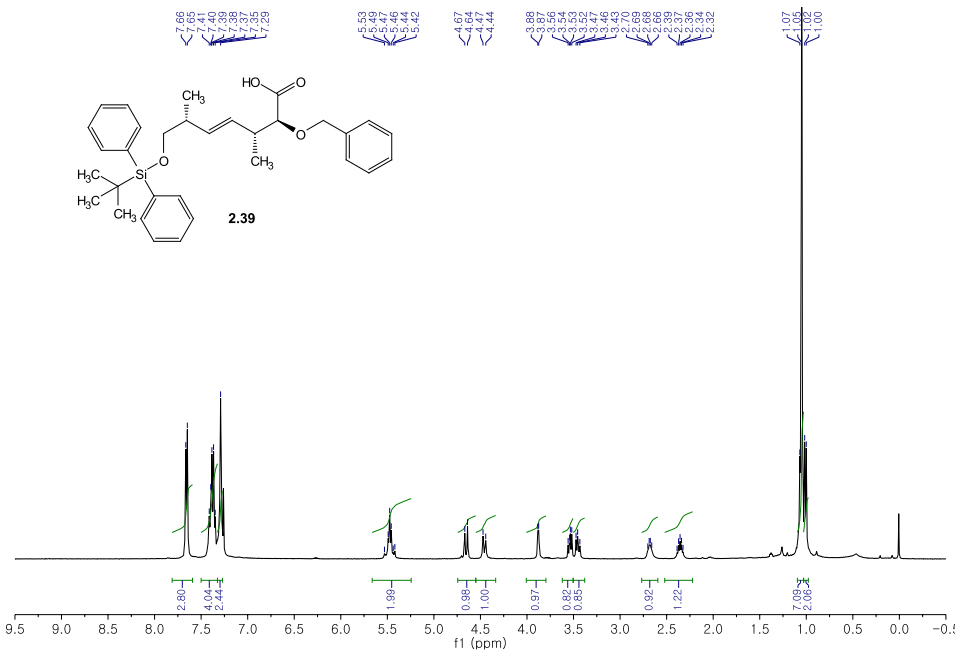
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H3C
CH3
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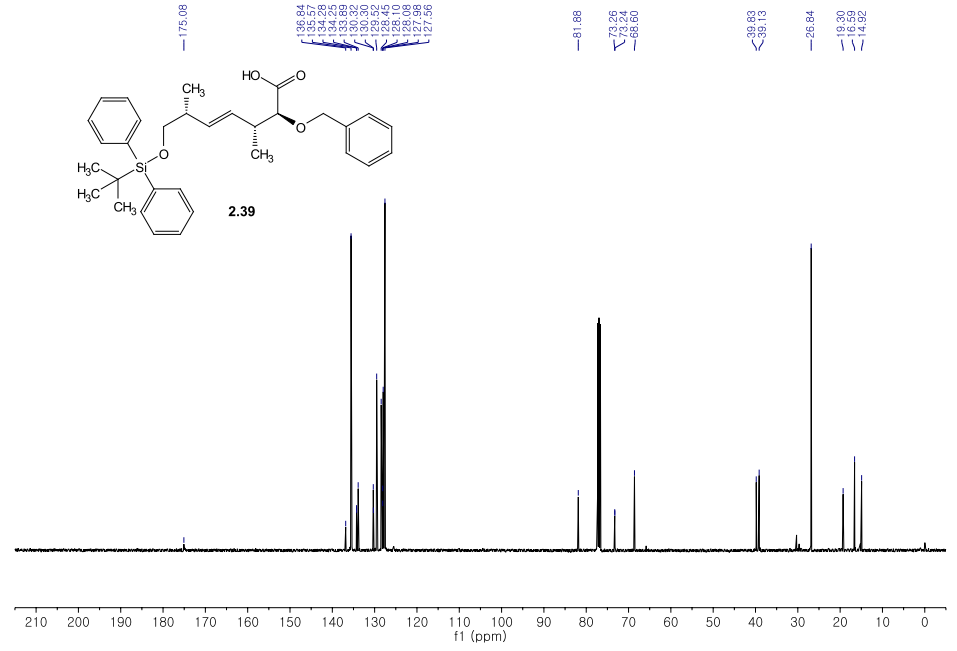
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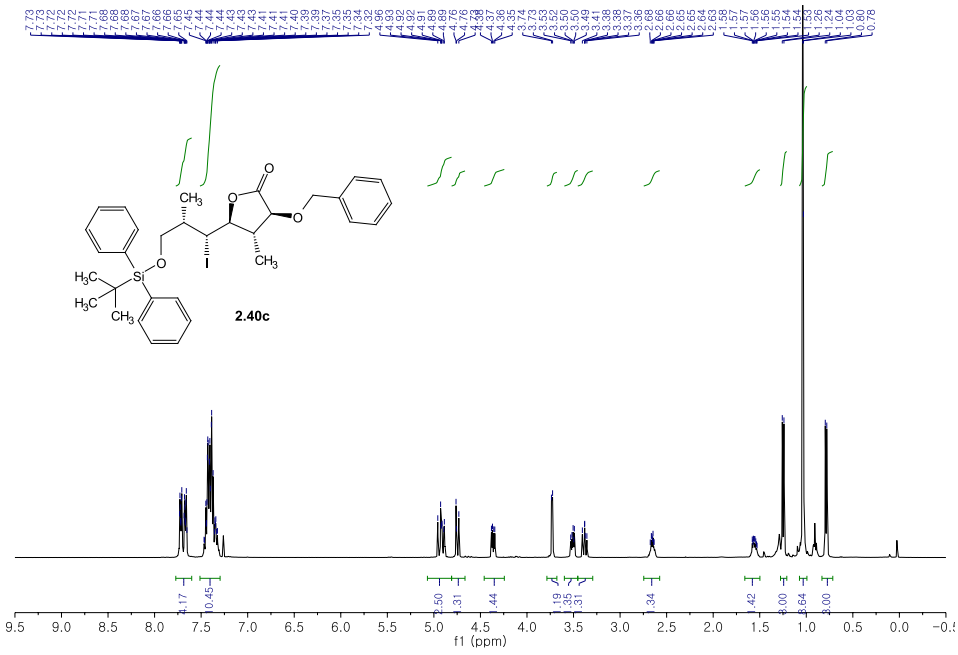
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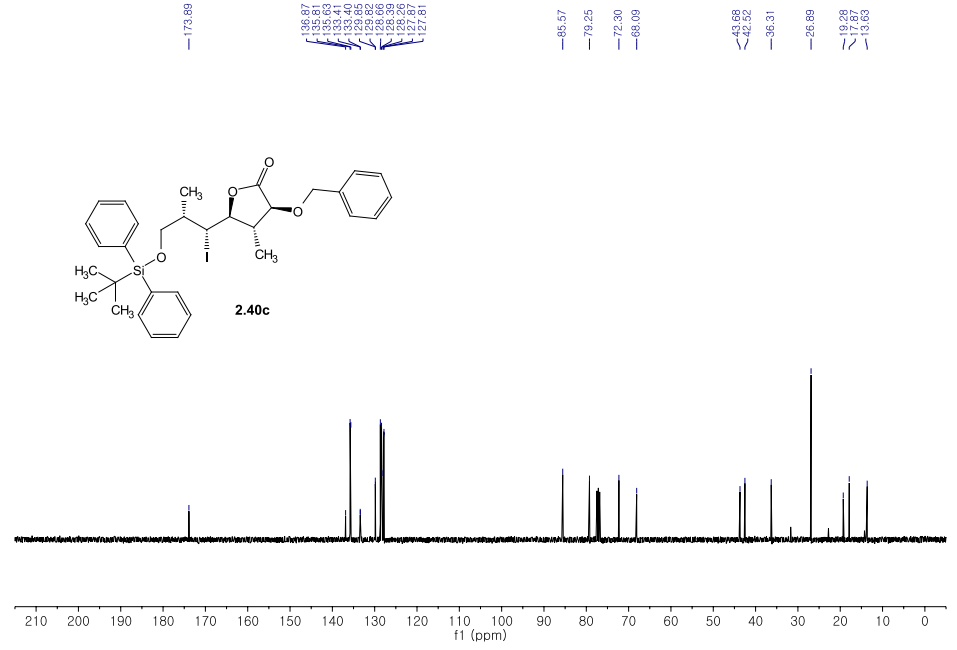
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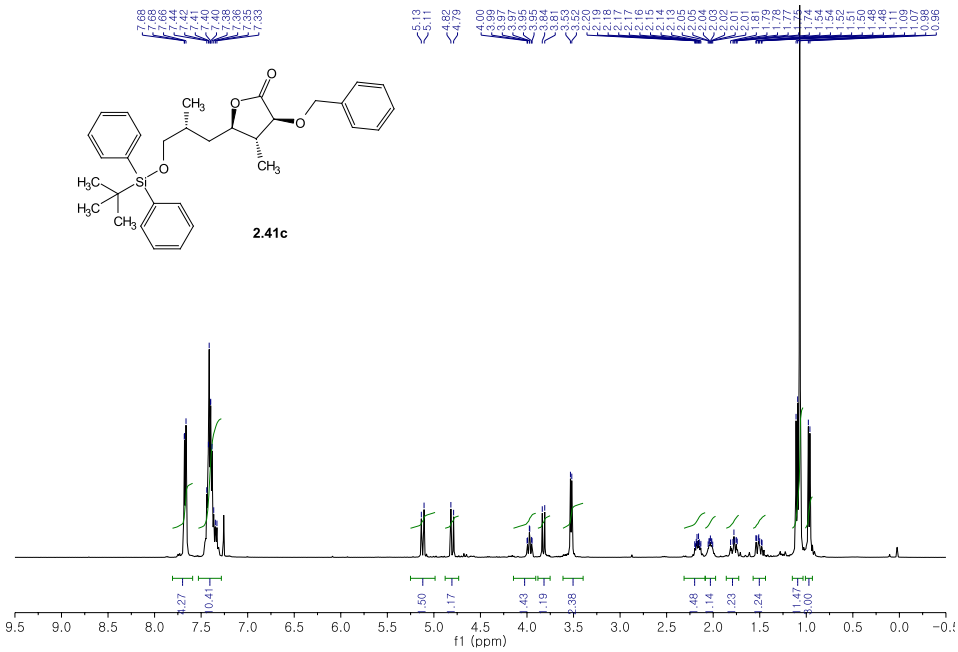
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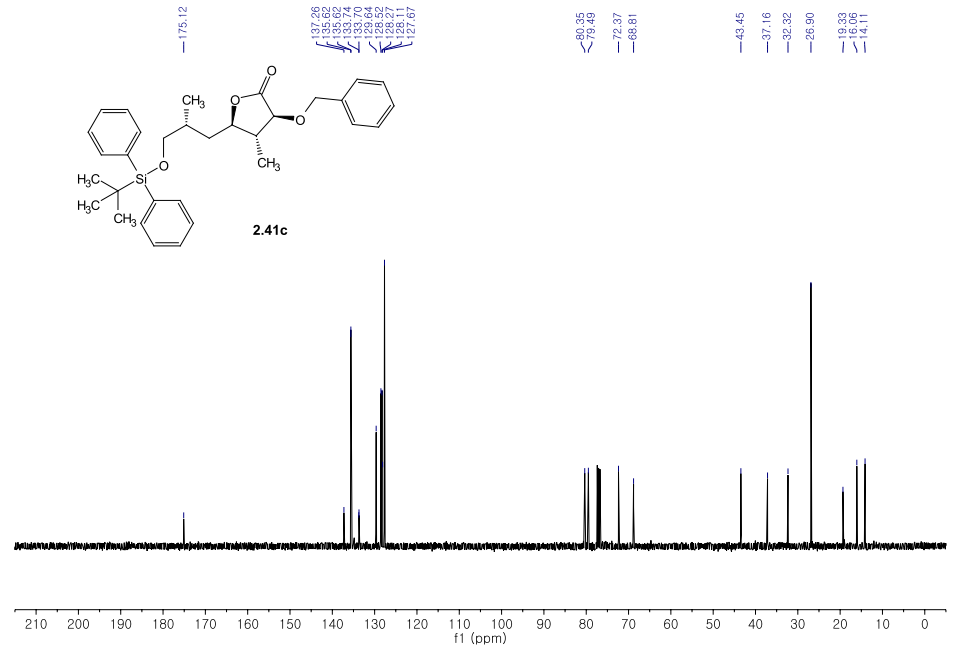
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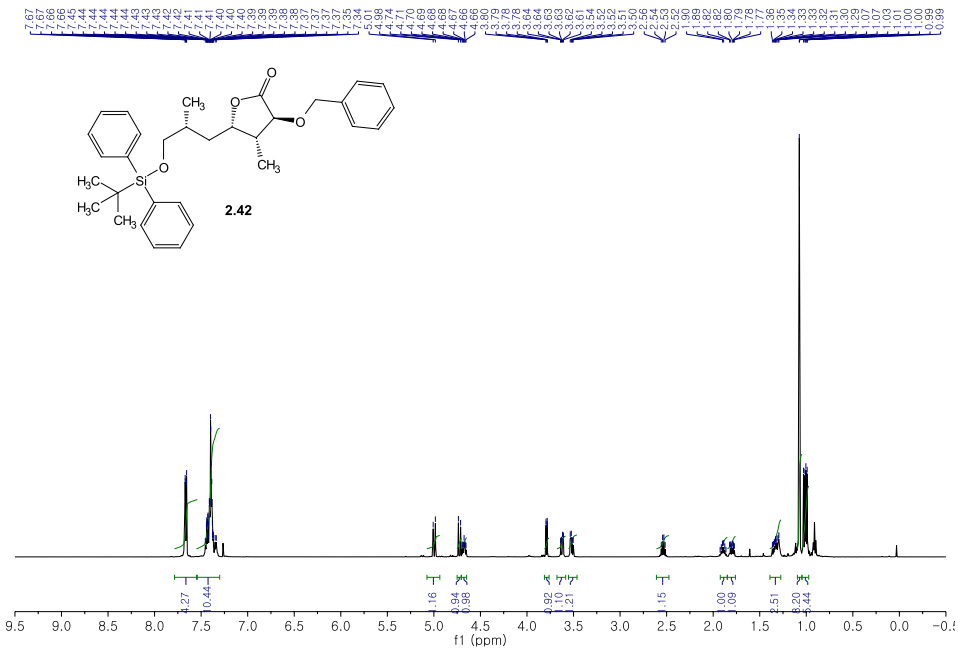
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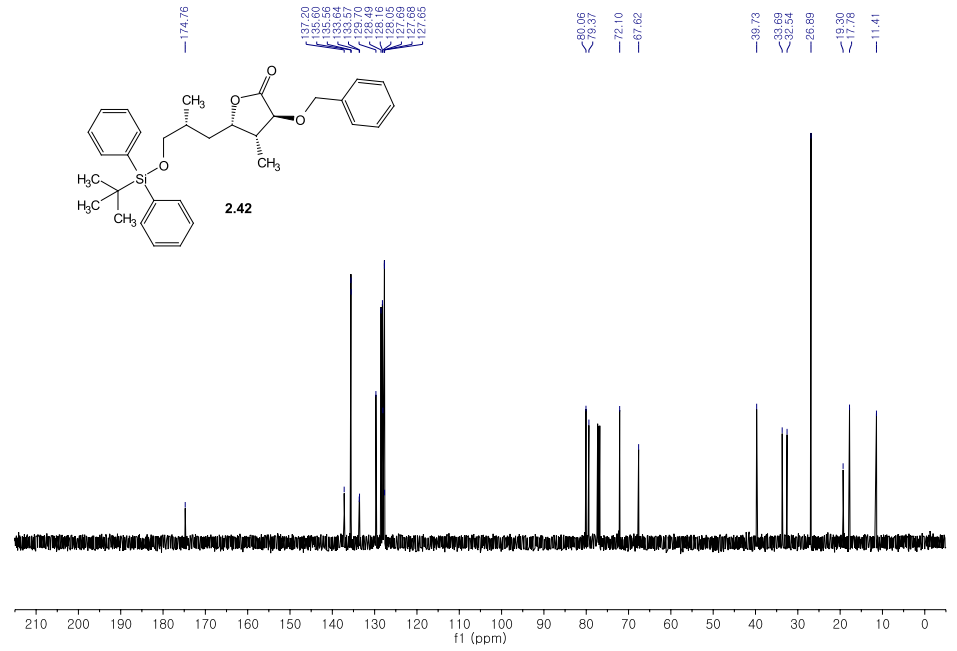
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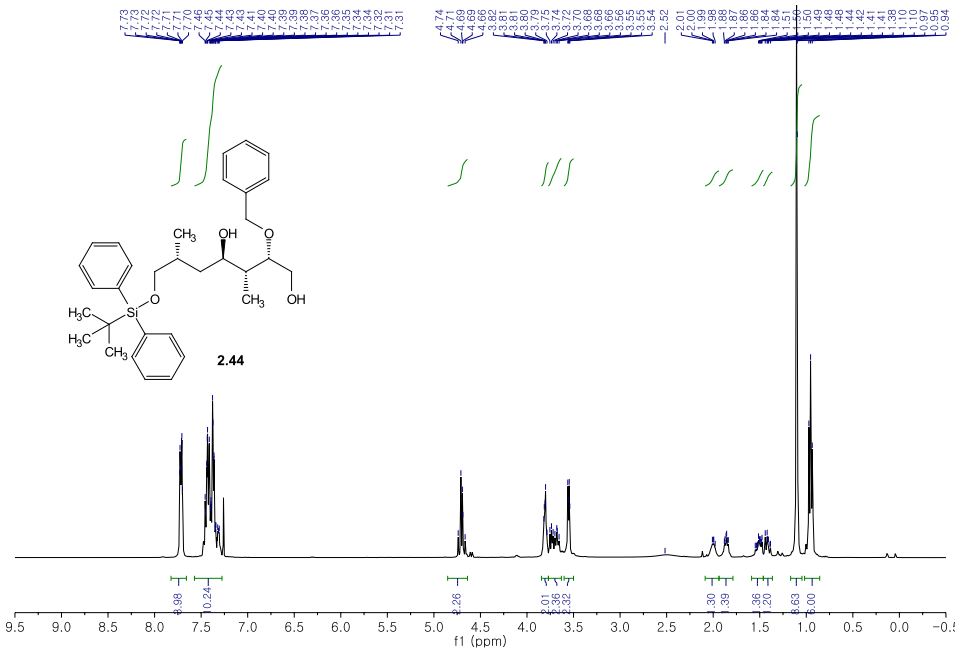
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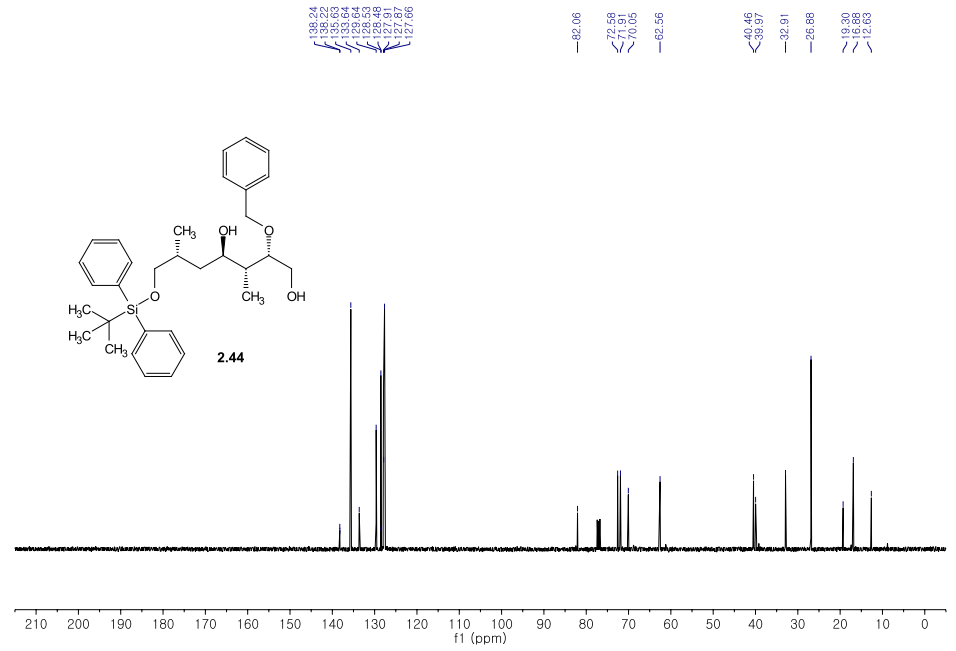
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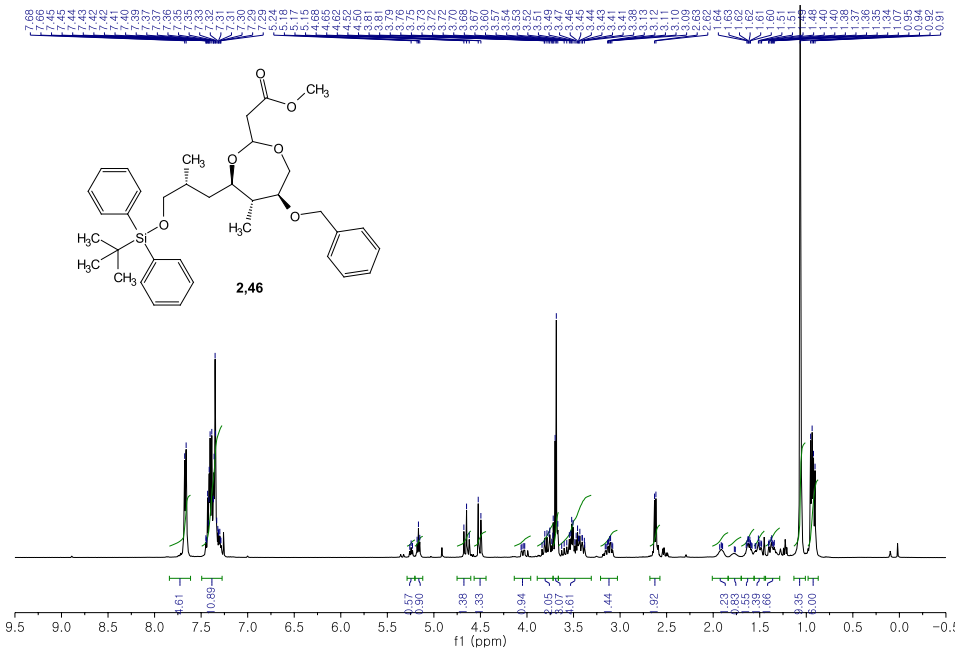
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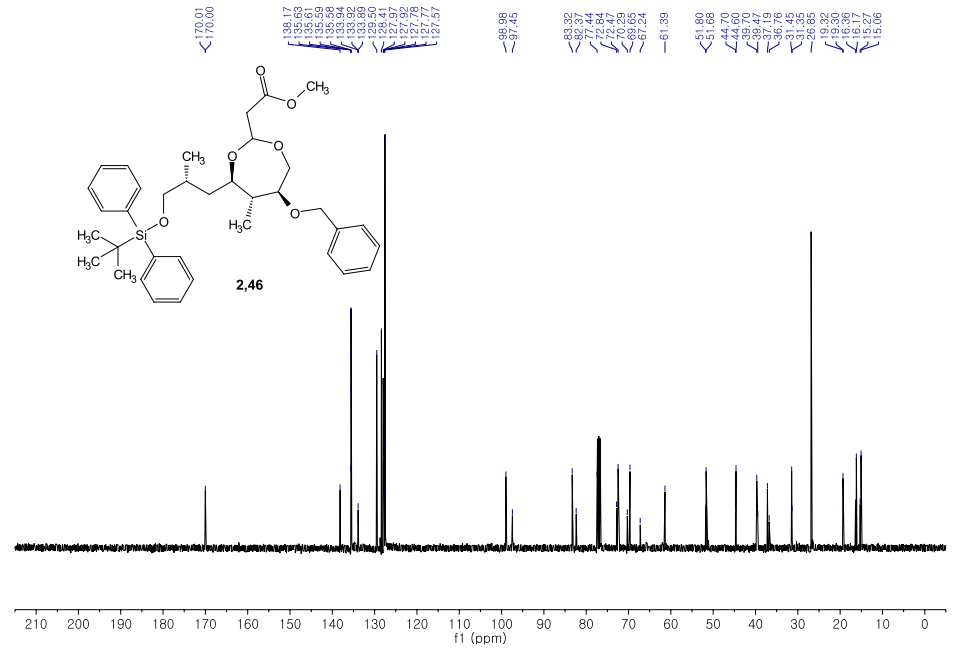
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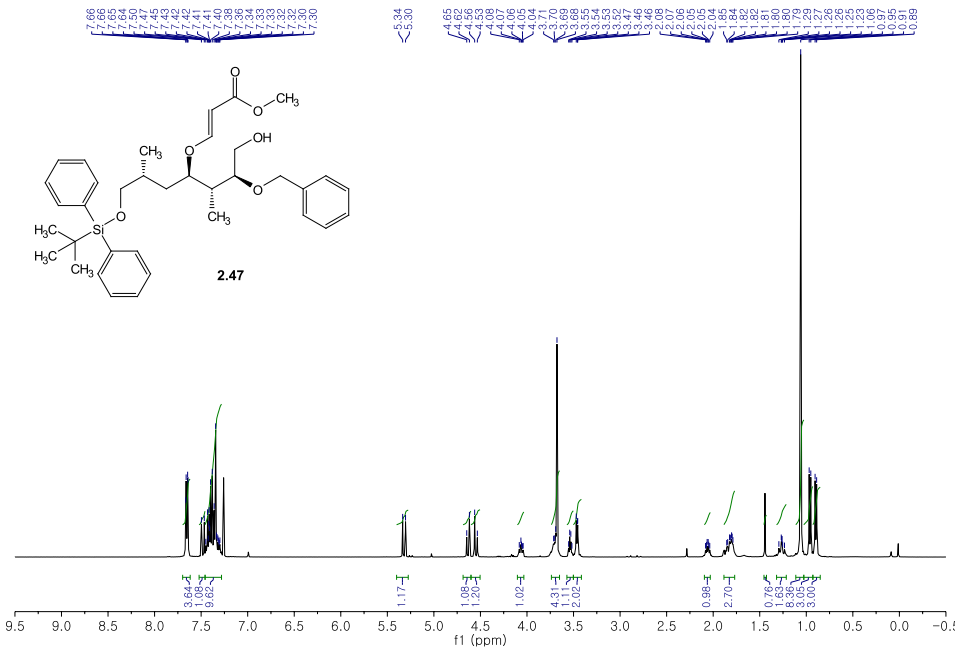
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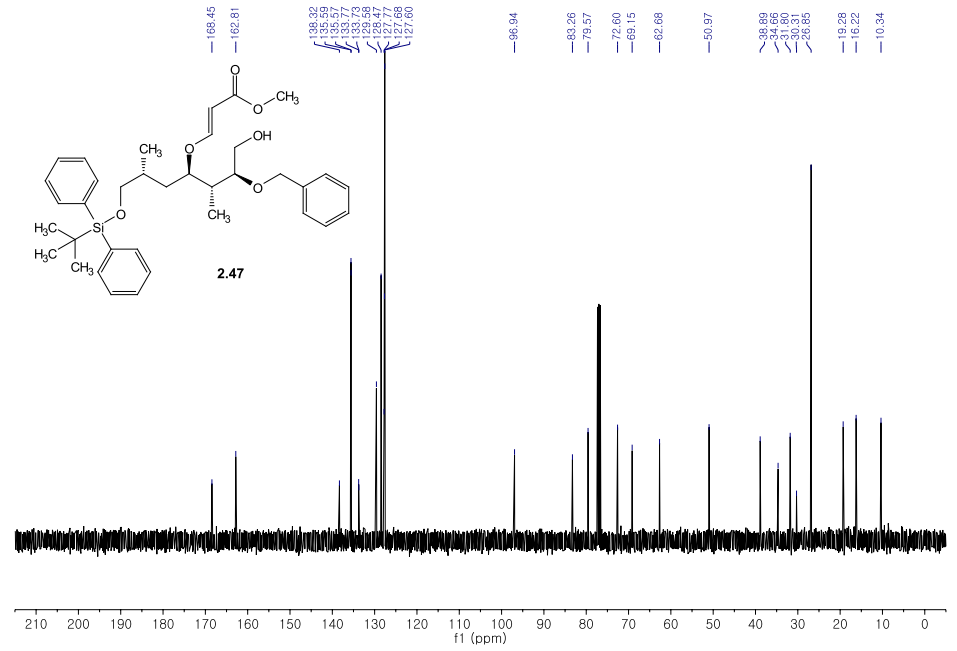
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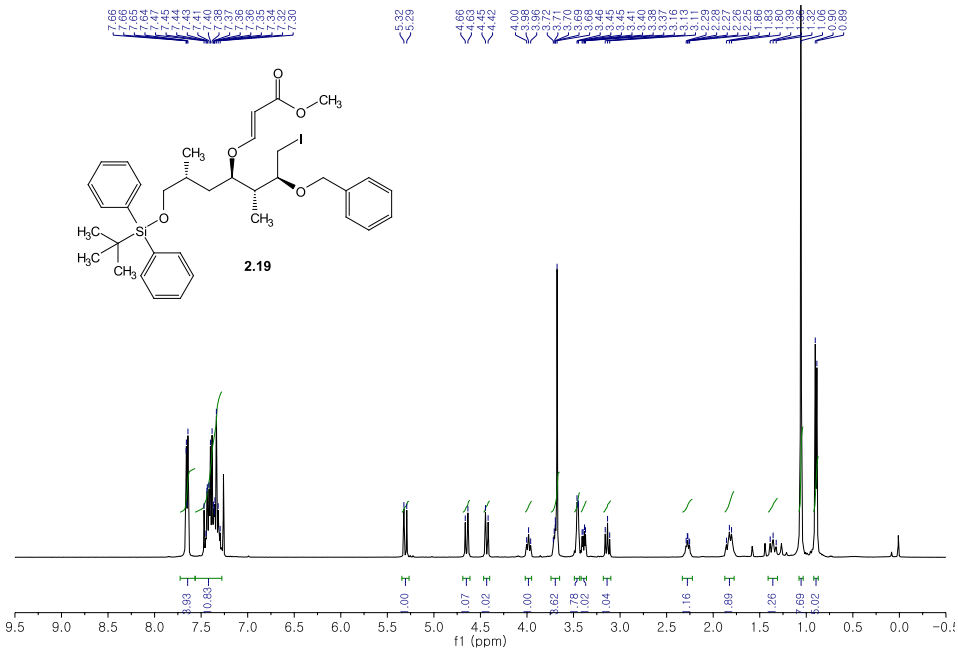
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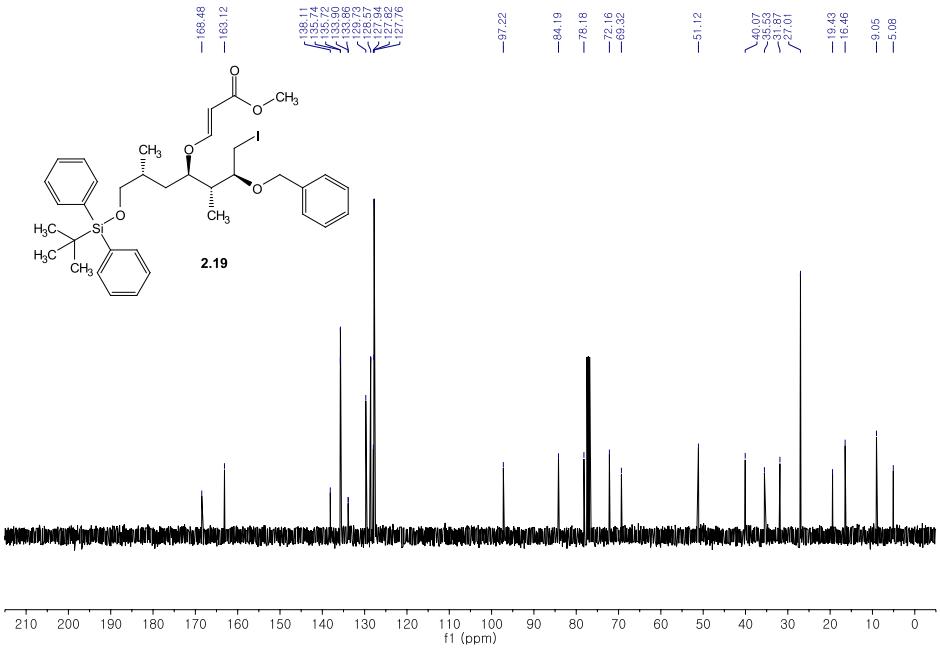
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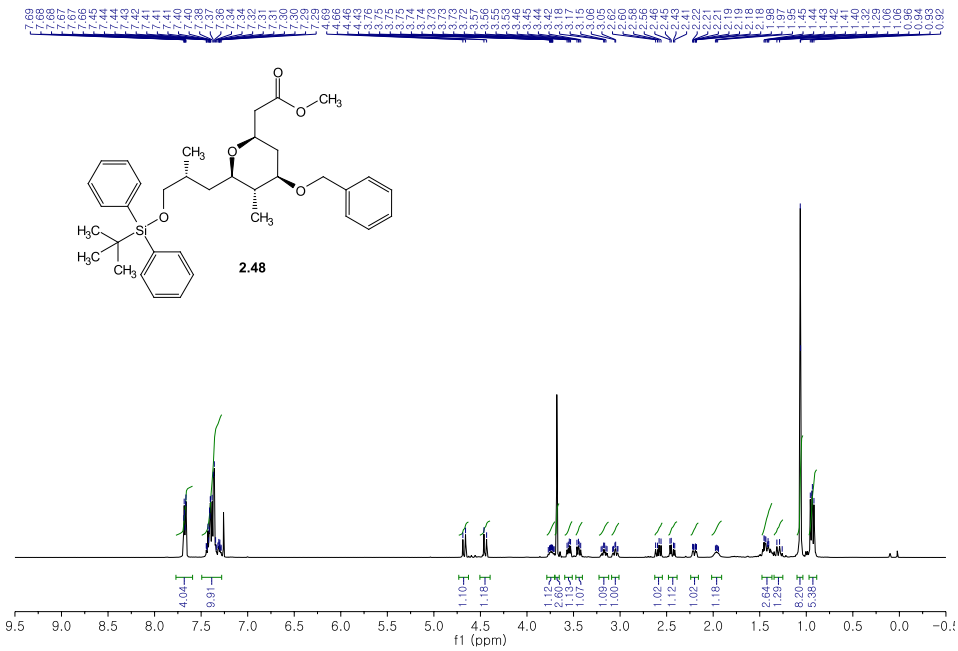
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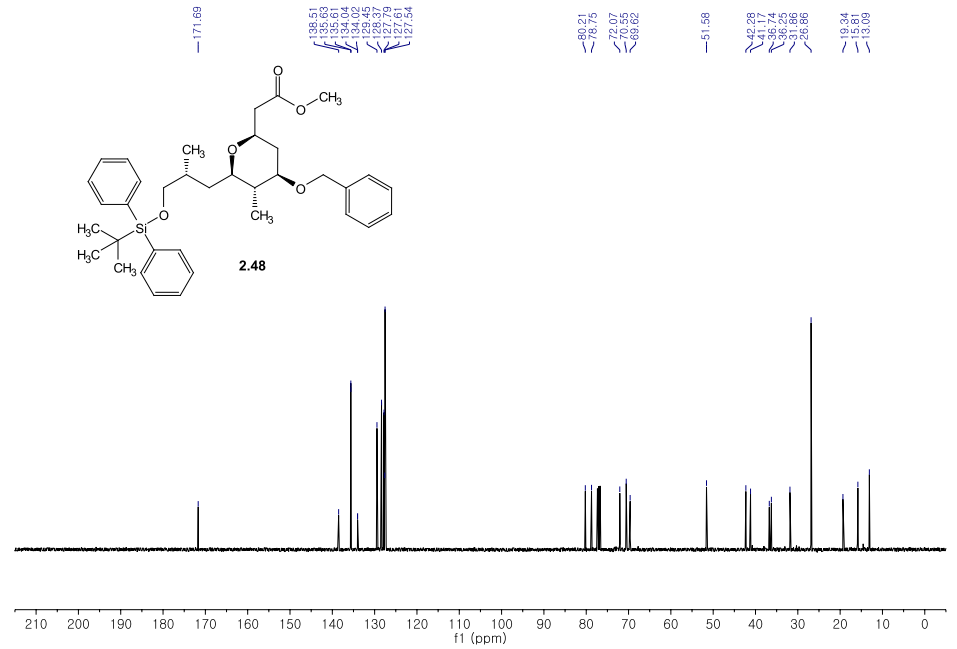
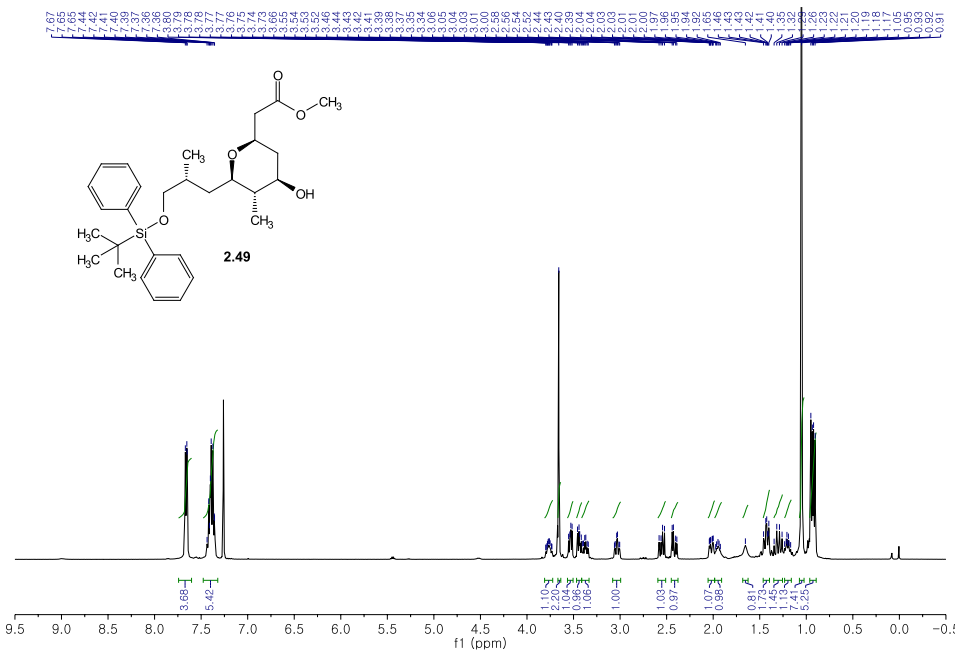

2.48
f1 (ppm)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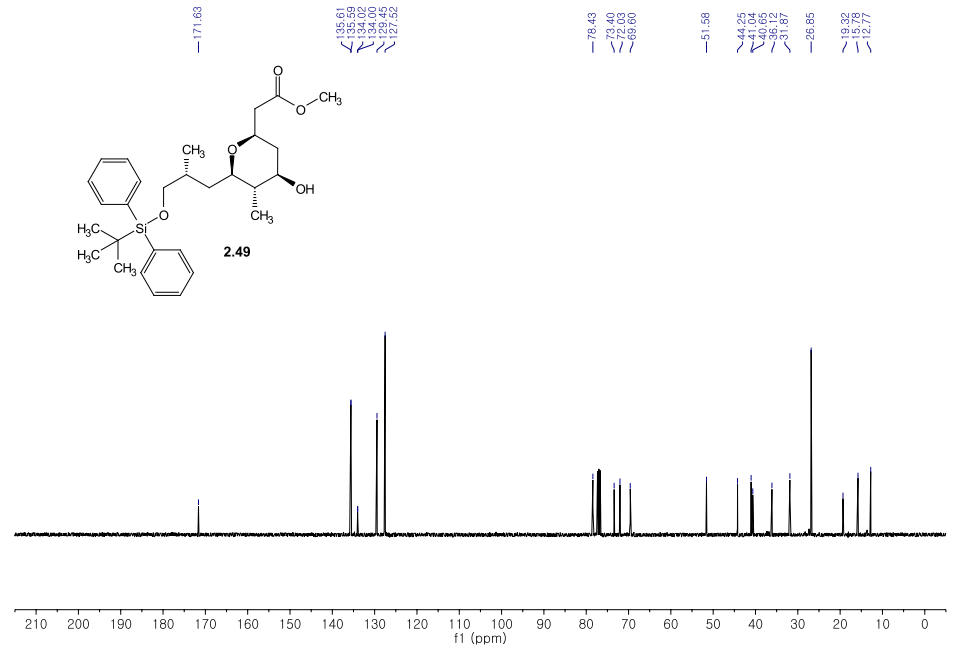
f1 (ppm)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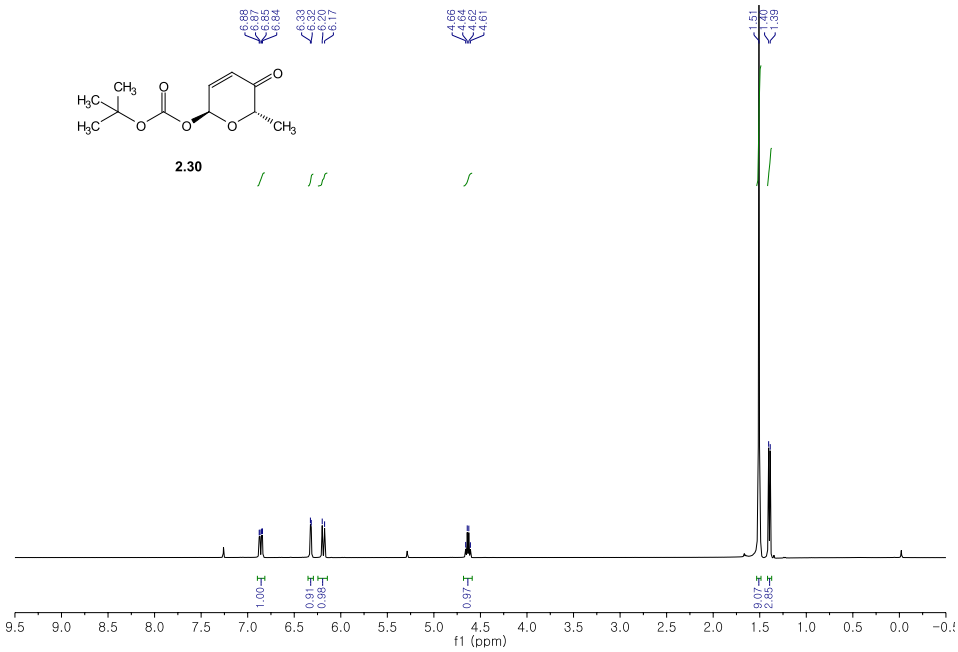
f1 (ppm)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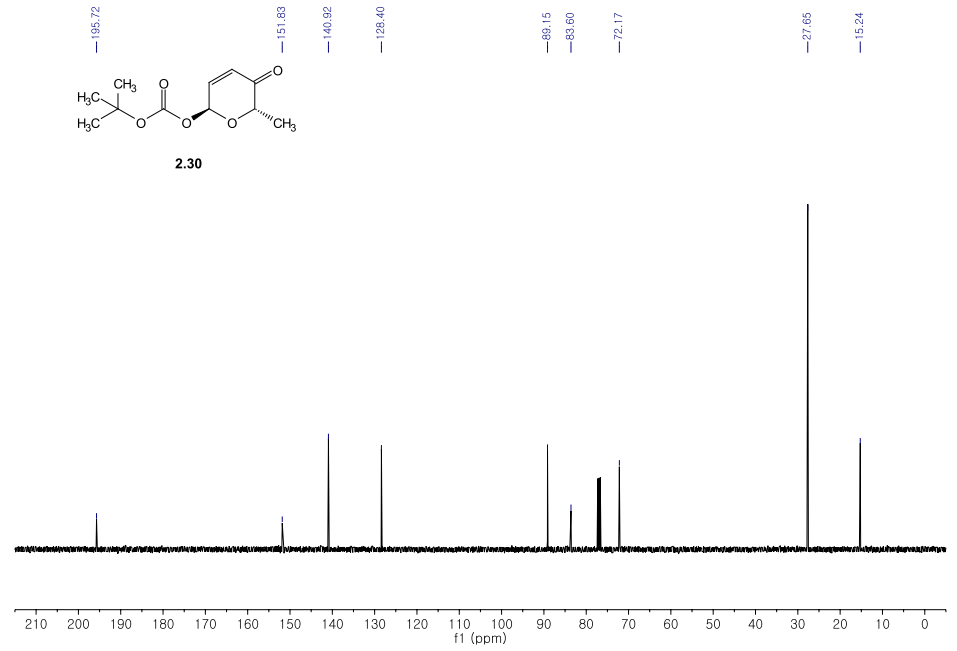
6.87
6.85
6.84
6.33
6.32
6.20
6.17
4.66
4.64
4.62
4.61
1.51
1.40
1.39
2.30
1.00
0.91
0.98
0.97
9.07
2.85
f1 (ppm)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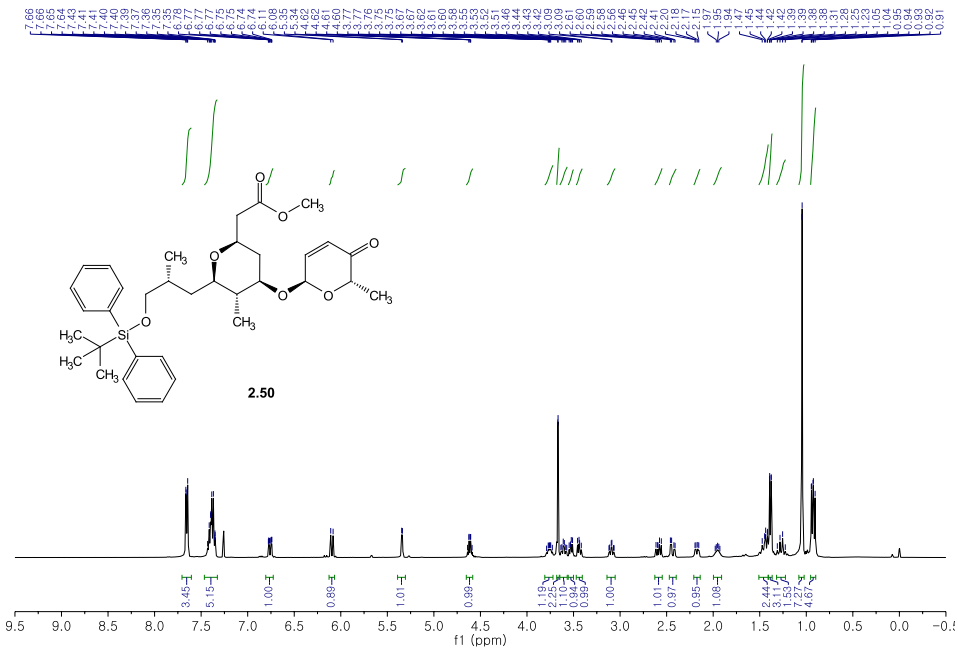
128.40
89.15
83.60
72.17
27.65
15.24
2.30
f1 (ppm)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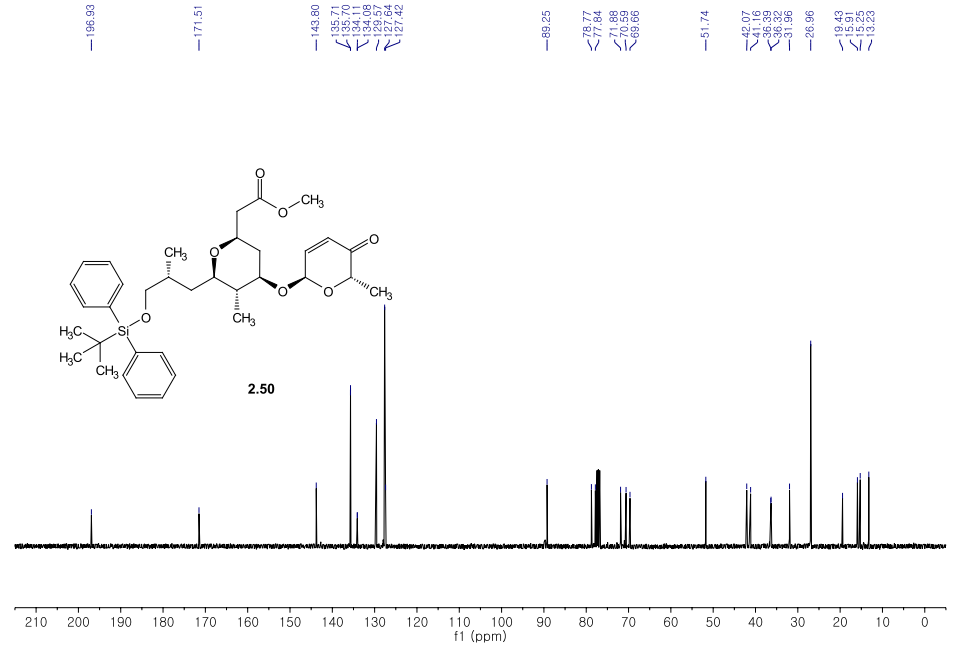
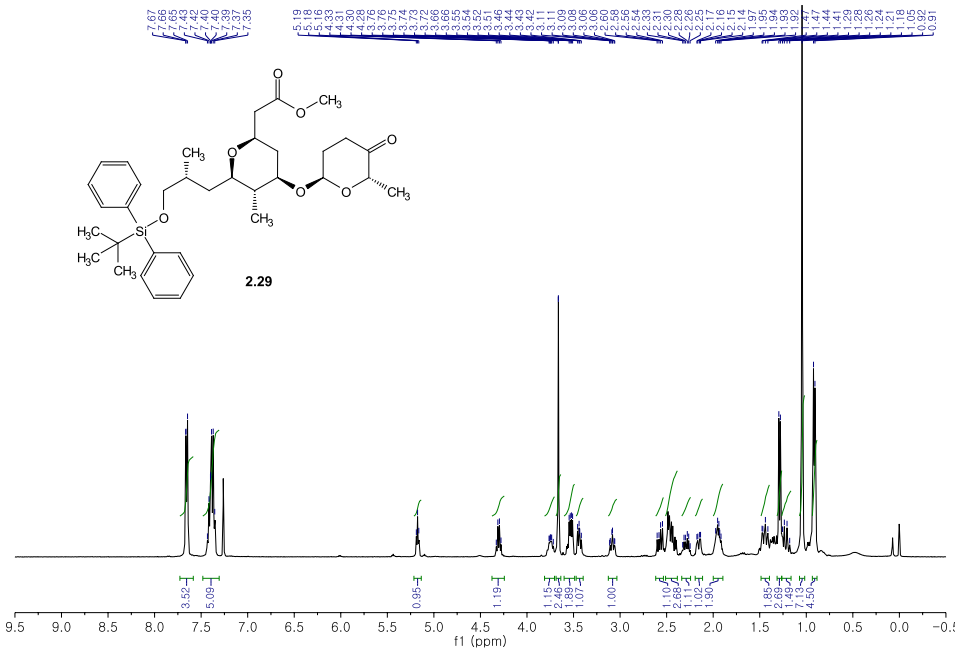
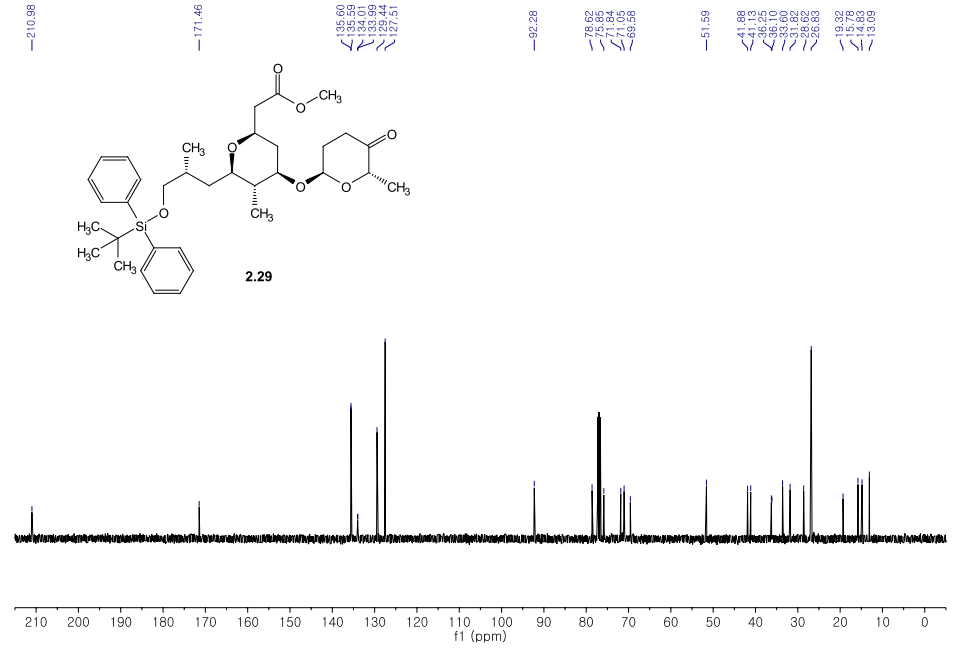
f1 (ppm)


2.50
f1 (ppm)


2.29
f1 (ppm)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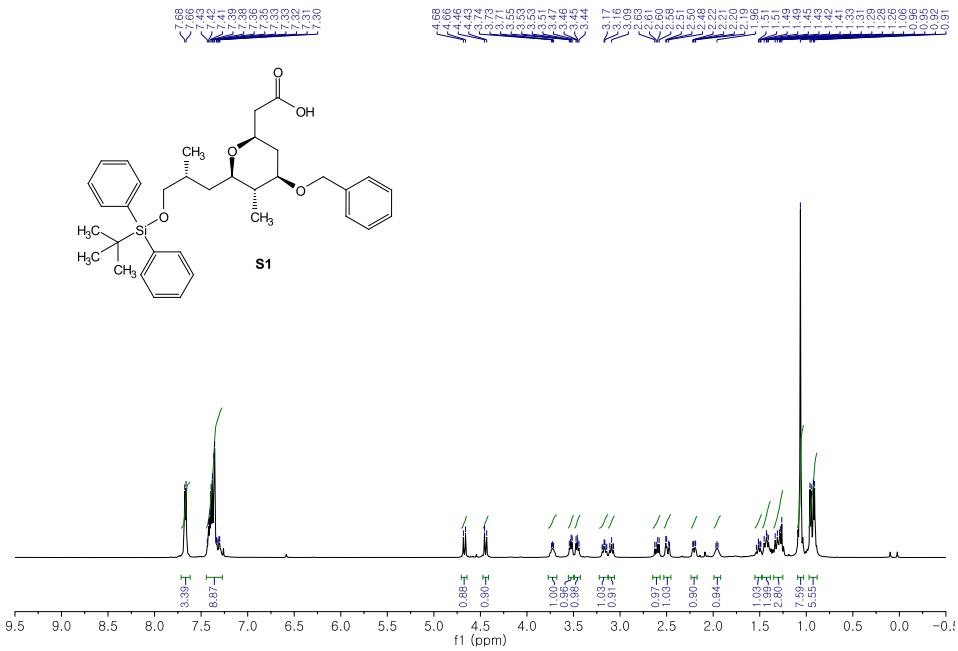
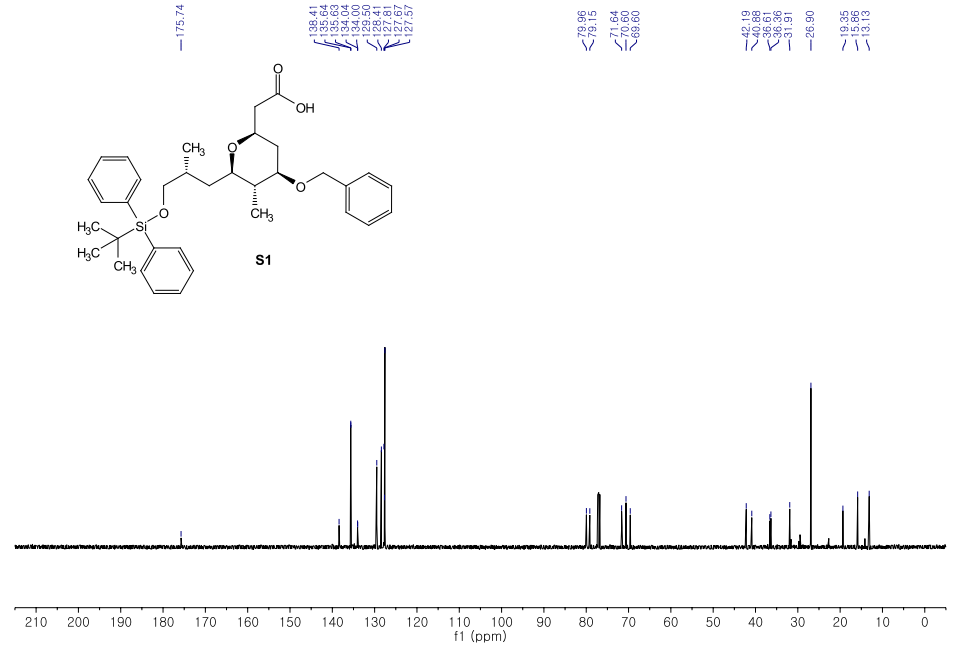
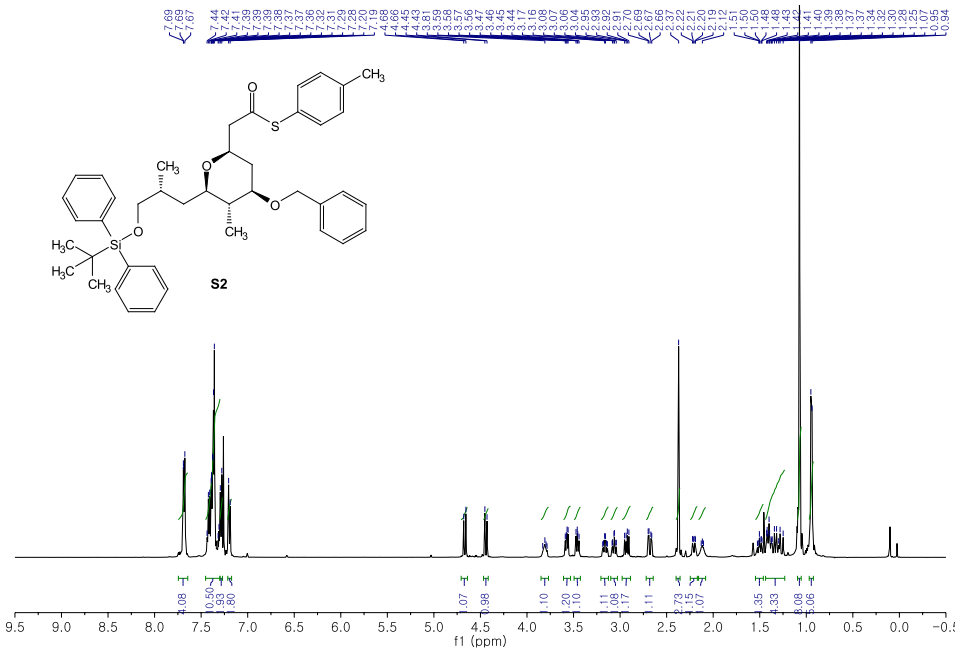
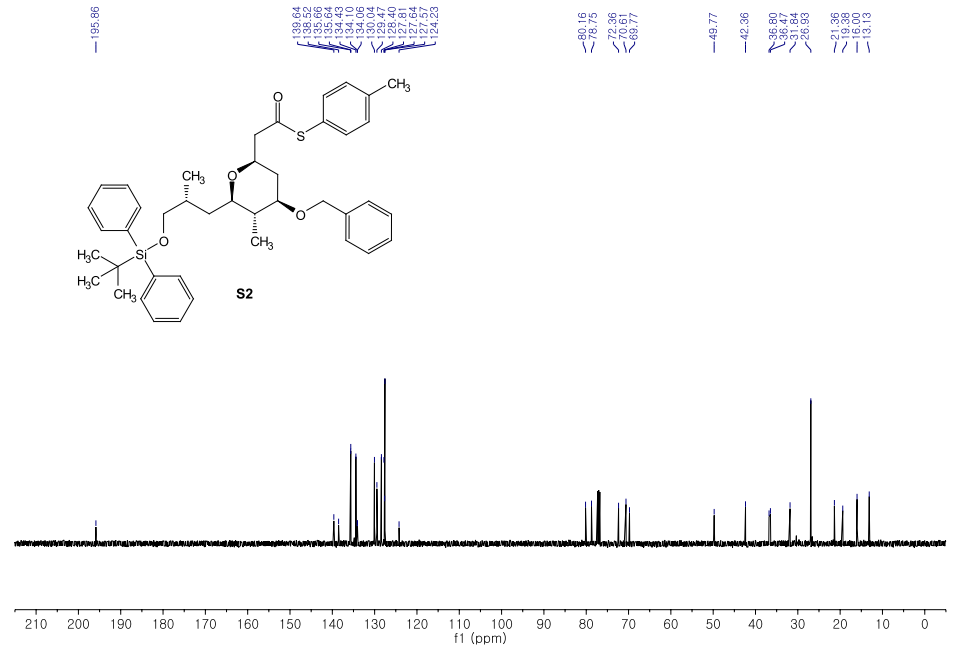
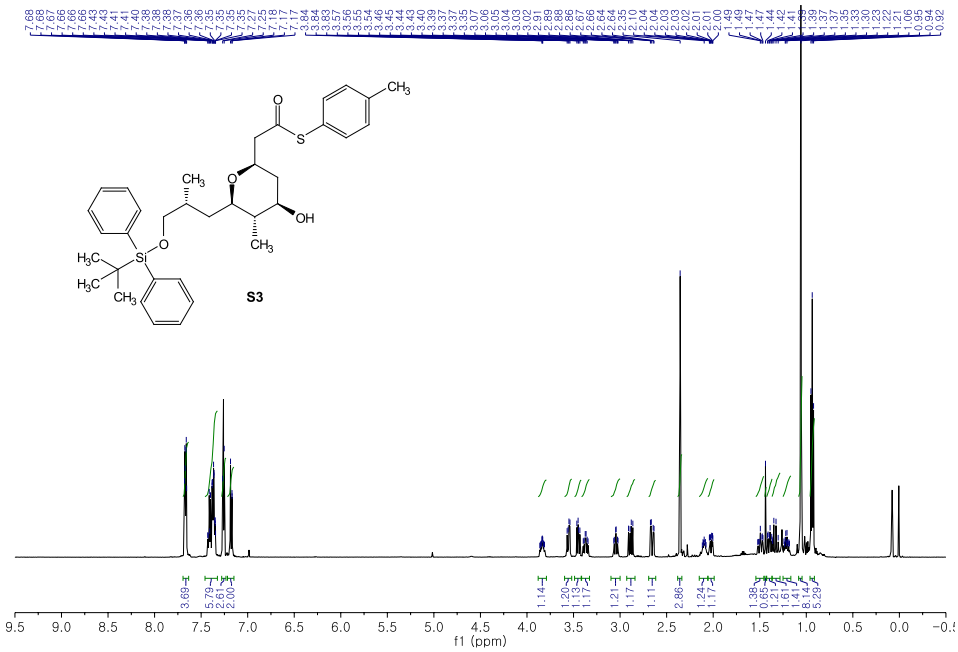
f1 (ppm)

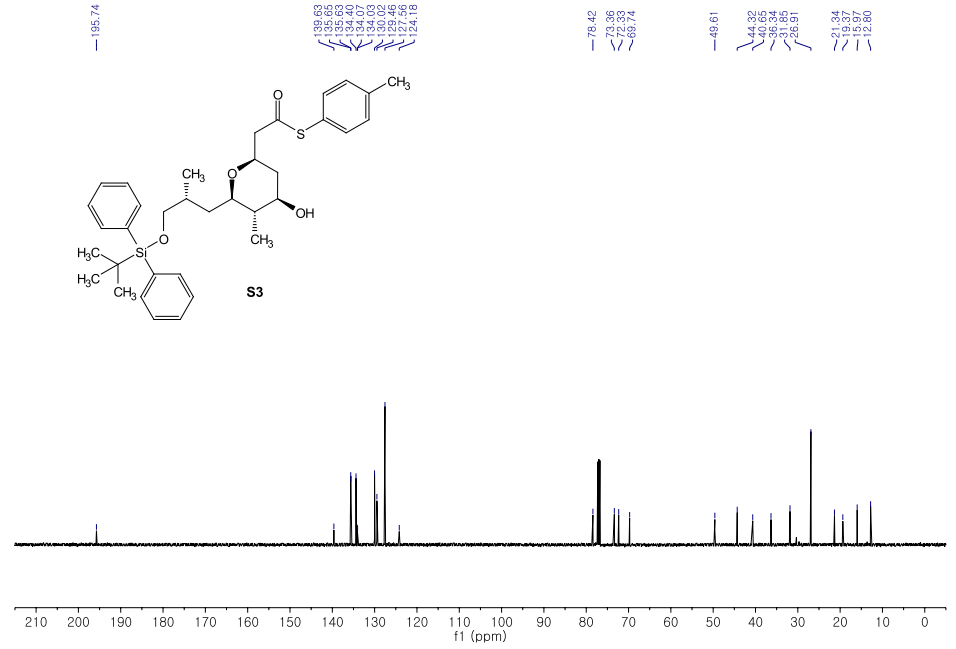

S1
f1 (ppm)

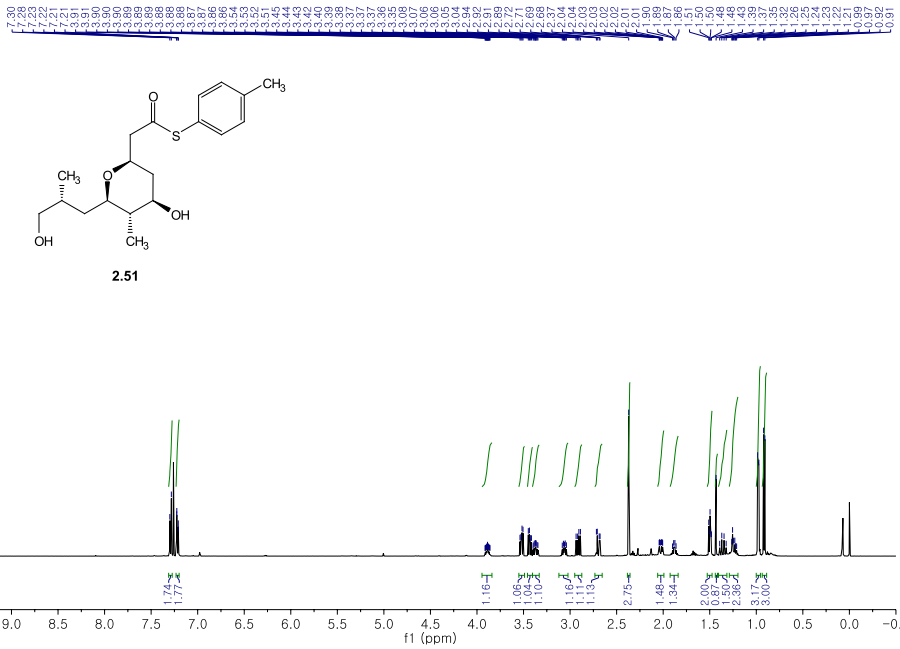

S1
f1 (ppm)

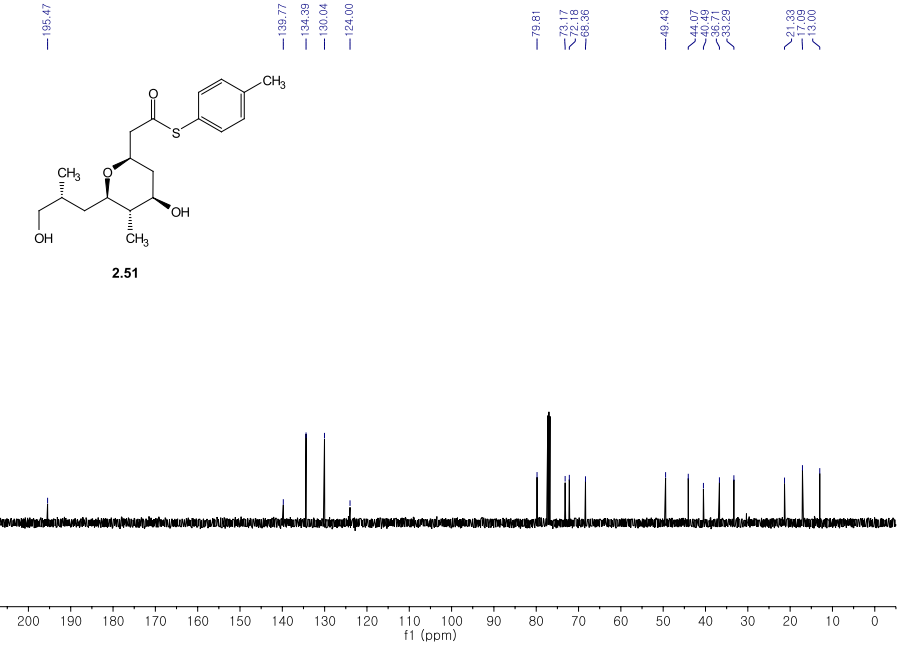

S2
f1 (ppm)

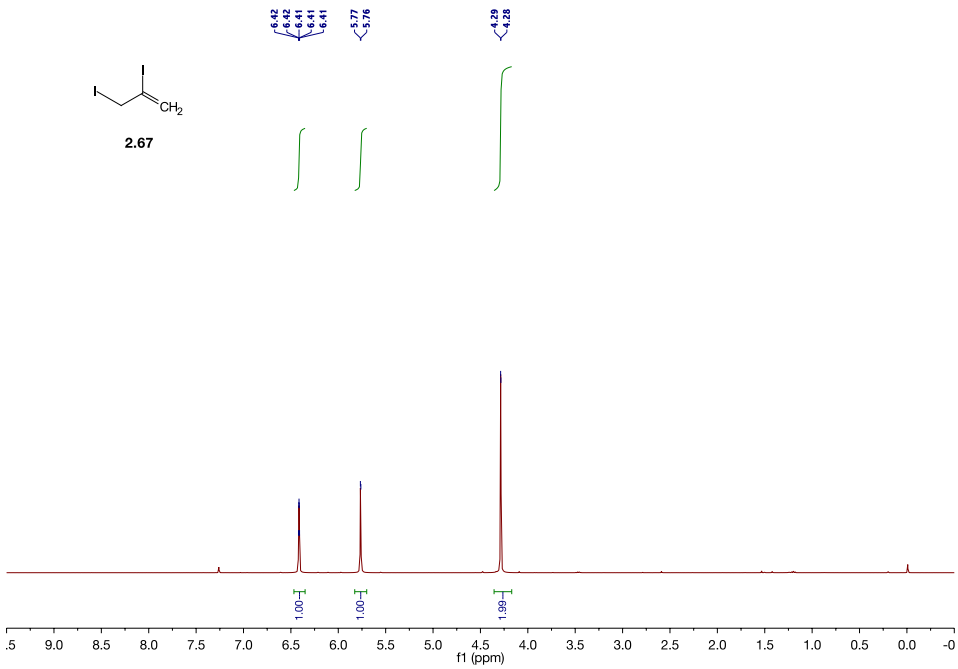

S2
f1 (ppm)

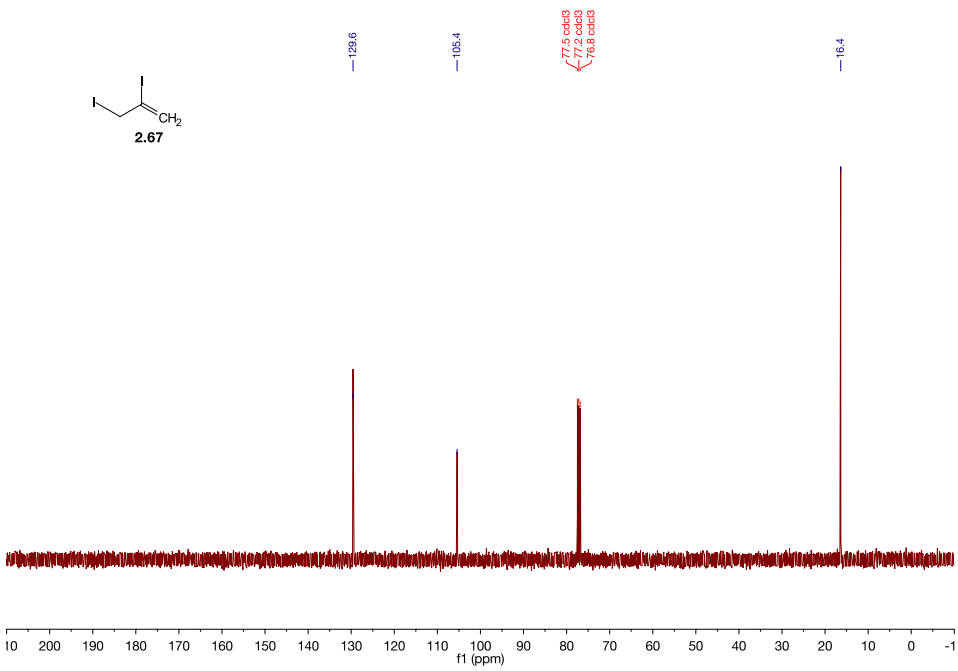

S3
f1 (ppm)

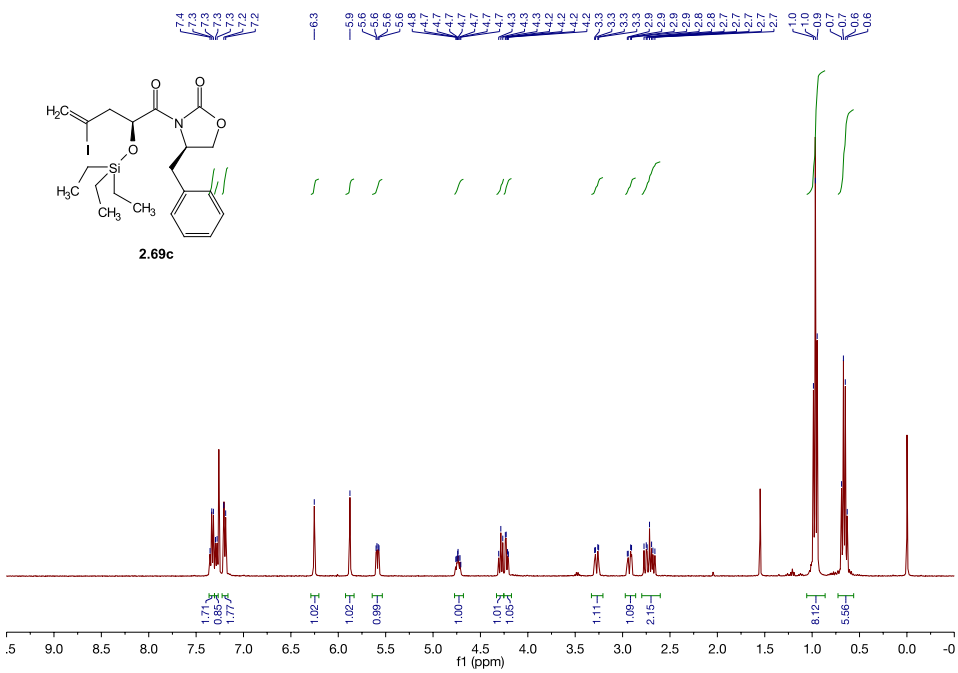

S3
f1 (ppm)

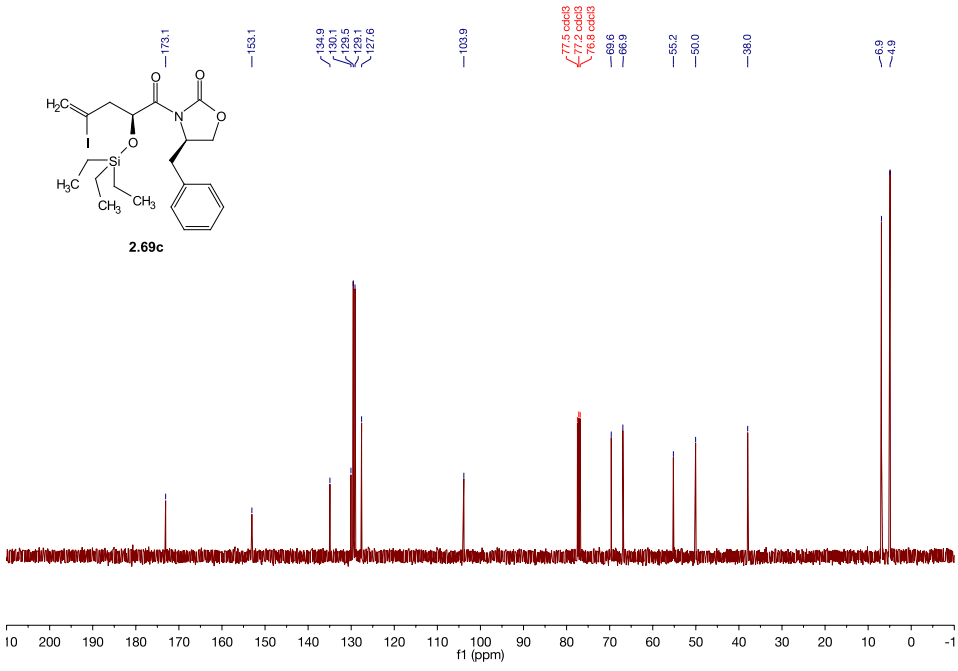

7.30 7.28 7.23 7.22 7.21 7.21 3.91 3.90 3.90 3.90 3.89 3.89 3.89 3.88 3.88 3.87 3.87 3.86 3.86 3.54 3.53 3.52 3.51 3.45 3.44 3.43 3.42 3.40 3.38 3.38 3.37 3.37 3.37 3.36 3.35 3.08 3.07 3.06 3.05 3.04 2.94 2.92 2.91 2.89 2.72 2.71 2.69 2.68 2.37 2.04 2.04 2.03 2.03 2.02 2.02 2.01 2.01 1.90 1.89 1.87 1.86 1.51 1.50 1.50 1.48 1.48 1.43 1.39 1.37 1.35 1.32 1.26 1.25 1.24 1.23 1.22 1.21 0.99 0.97 0.92 0.91
CH3
O
S
CH3
O
OH
OH
CH3
2.51
1.74
1.77
1.16
1.06
1.04
1.10
1.16
1.11
1.13
2.75
1.48
1.34
2.00
0.87
1.50
2.38
3.17
3.00
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)


195.47
139.77
134.39
130.04
124.00
79.81
73.17
72.18
68.36
49.43
44.07
40.49
36.71
33.29
21.33
17.09
13.00
CH3
O
S
CH3
O
OH
OH
CH3
2.51
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


6.42
6.42
6.41
6.41
6.41
5.77
5.76
4.29
4.28
I
I
CH2
2.67
1.00
1.00
1.99
f1 (ppm)


129.6
105.4
77.5 cdcl3
77.2 cdcl3
76.8 cdcl3
16.4
I
I
CH2
2.67
f1 (ppm)


2.69c
f1 (ppm)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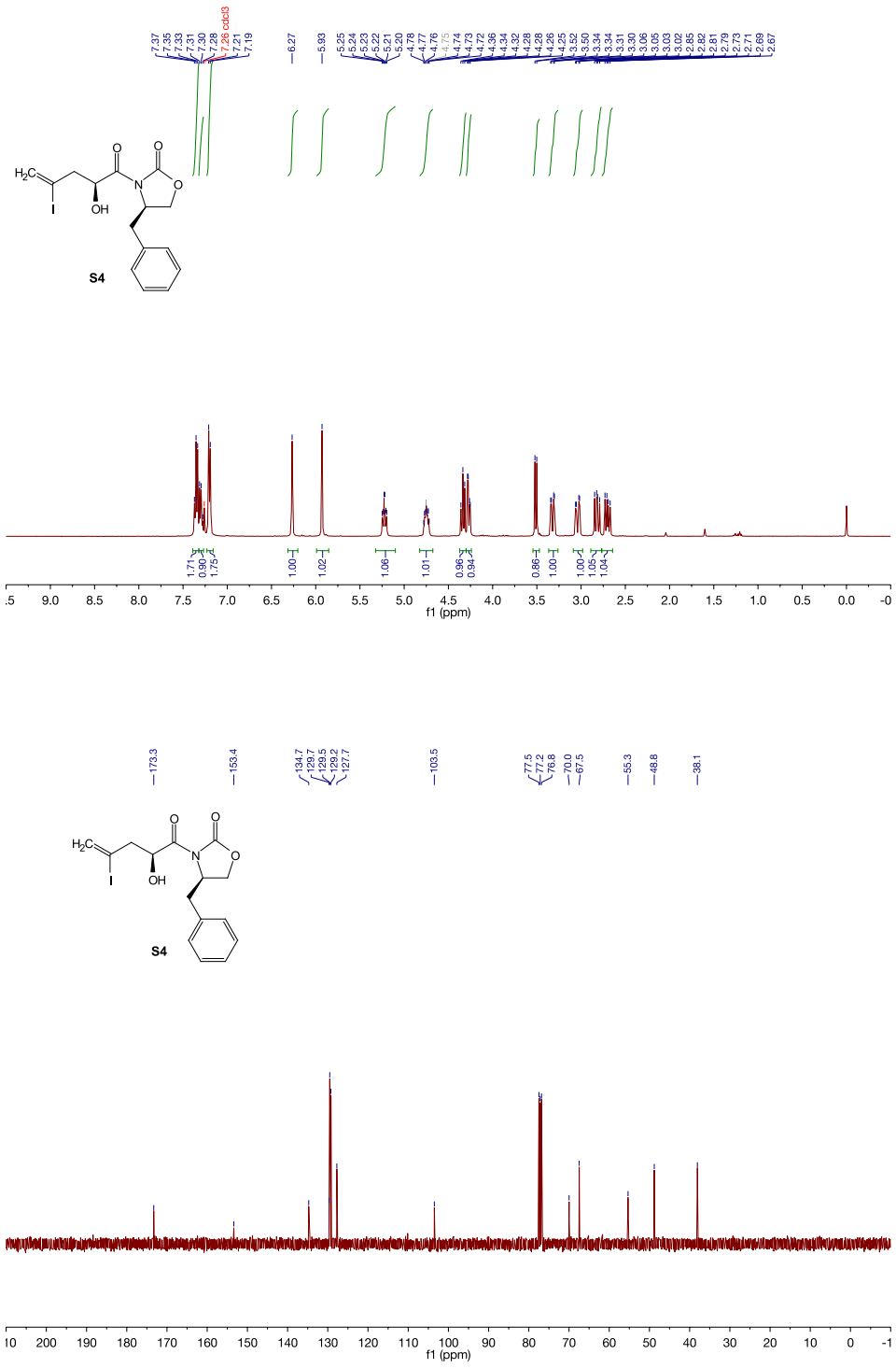
f1 (ppm)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7.33
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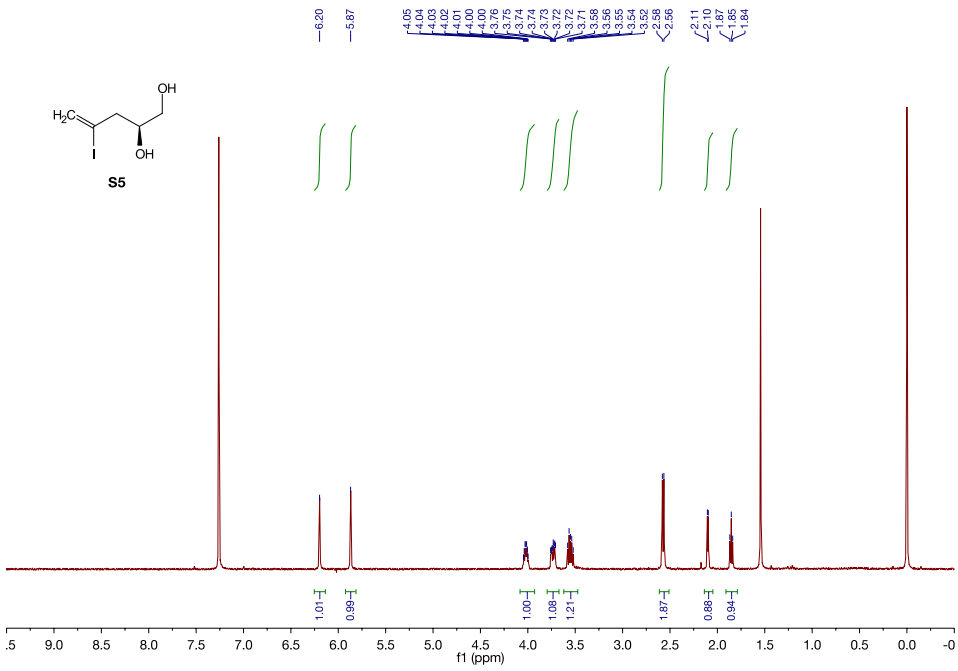
7.30
7.28
7.26 cdcl3
7.21
7.19
6.27
5.93
5.25
5.24
5.23
5.22
5.21
5.20
4.78
4.77
4.76
4.75
4.74
4.73
4.72
4.36
4.34
4.32
4.28
4.28
4.26
4.25
3.52
3.50
3.34
3.34
3.31
3.30
3.06
3.05
3.03
3.02
2.85
2.82
2.81
2.79
2.73
2.71
2.69
2.67
S4
1.71
0.90
1.75
1.00
1.02
1.06
1.01
0.96
0.94
0.86
1.00
1.00
1.05
1.04
f1 (ppm)
173.3
153.4
134.7
129.7
129.5
129.2
127.7
103.5
77.5
77.2
76.8
70.0
67.5
55.3
48.8
38.1
S4
f1 (ppm)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5.87
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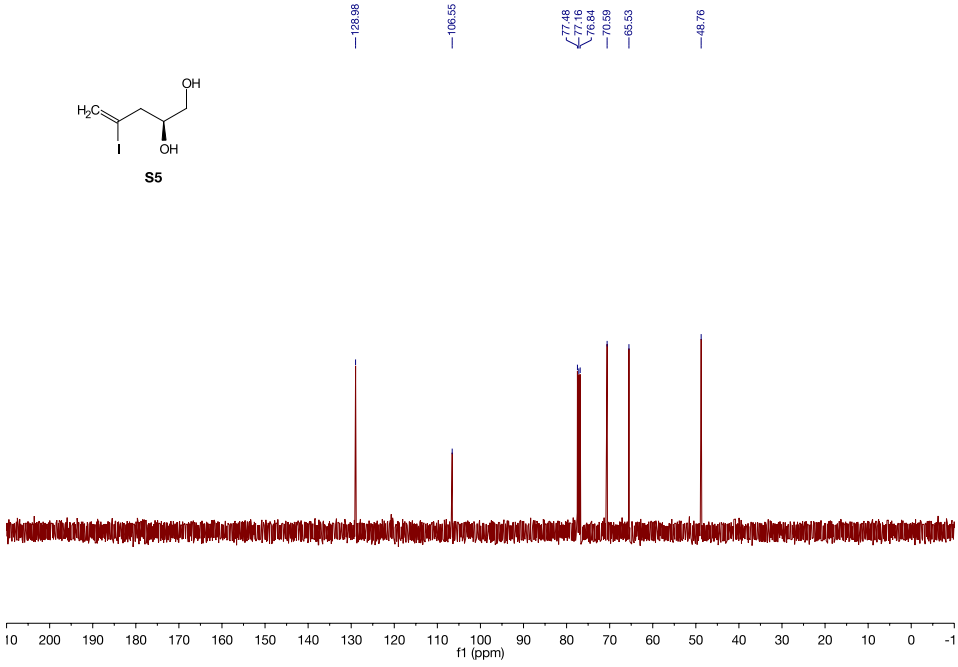
4.00
4.00
3.76
3.75
3.74
3.74
3.73
3.72
3.72
3.71
3.58
3.56
3.55
3.54
3.52
2.58
2.56
2.11
2.10
1.87
1.85
1.84
OH
H2C
I
OH
S5
1.01
0.99
1.00
1.08
1.21
1.87
0.88
0.94
f1 (ppm)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76.84
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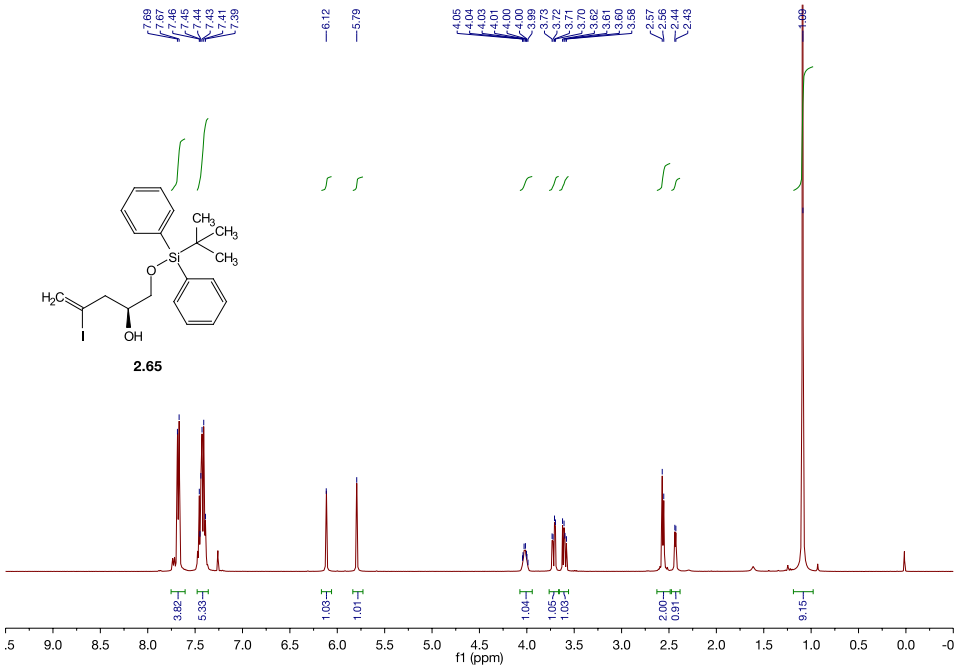
65.53
48.76
OH
H2C
I
OH
S5
f1 (ppm)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7.43
7.41
7.39
6.12
5.79
4.05
4.04
4.03
4.01
4.00
4.00
3.99
3.73
3.72
3.71
3.70
3.62
3.61
3.60
3.58
2.57
2.56
2.44
2.43
1.00
CH3
CH3
CH3
Si
O
H2C
I
OH
2.65
3.82
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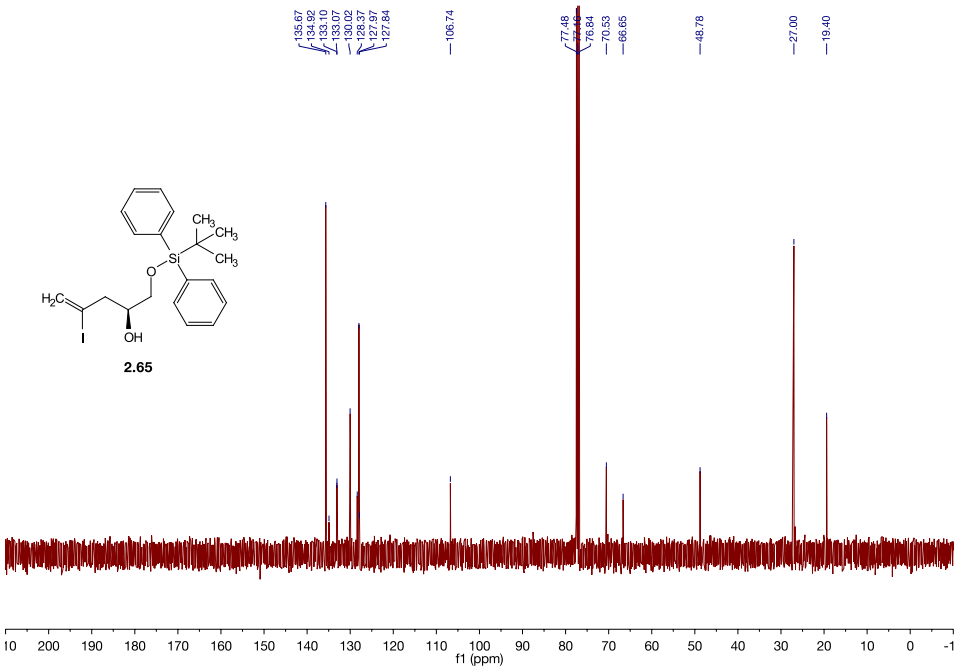
1.03
1.01
1.04
1.05
1.03
2.00
0.91
9.15
f1 (ppm)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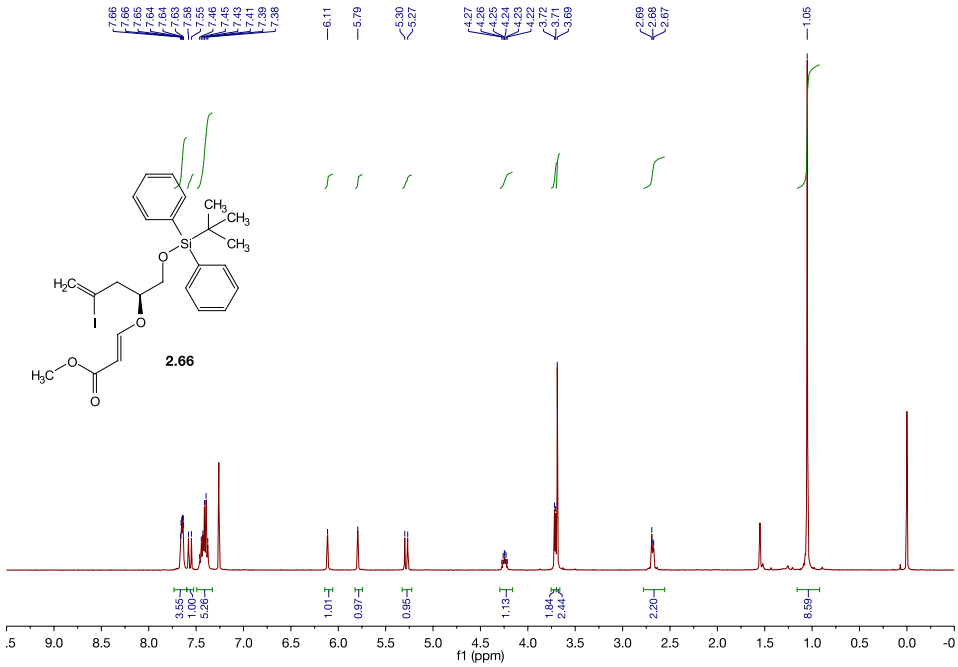
127.84
106.74
77.48
77.16
76.84
70.53
66.65
48.78
27.00
19.40
CH3
CH3
CH3
Si
O
H2C
I
OH
2.65
f1 (ppm)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7.66
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7.64
7.63
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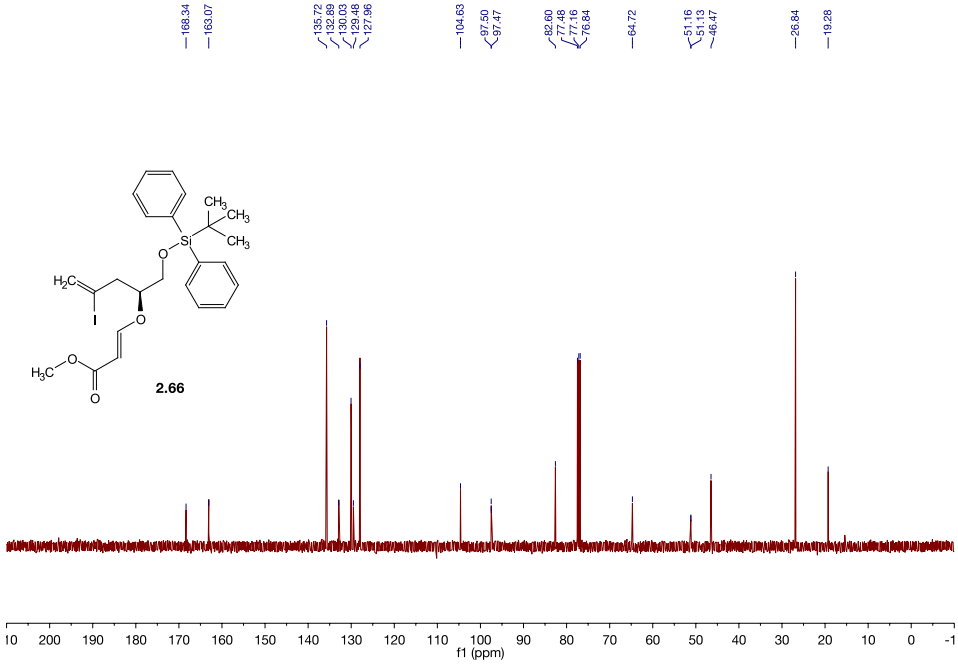
7.55
7.46
7.45
7.43
7.41
7.39
7.38
6.11
5.79
5.30
5.27
4.27
4.26
4.25
4.24
4.23
4.22
3.72
3.71
3.69
2.69
2.68
2.67
1.05
2.66
3.55
1.00
5.26
1.01
0.97
0.95
1.13
1.84
2.44
2.20
8.59
f1 (ppm)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135.72
132.89
130.03
129.48
127.96
104.63
97.50
97.47
82.60
77.48
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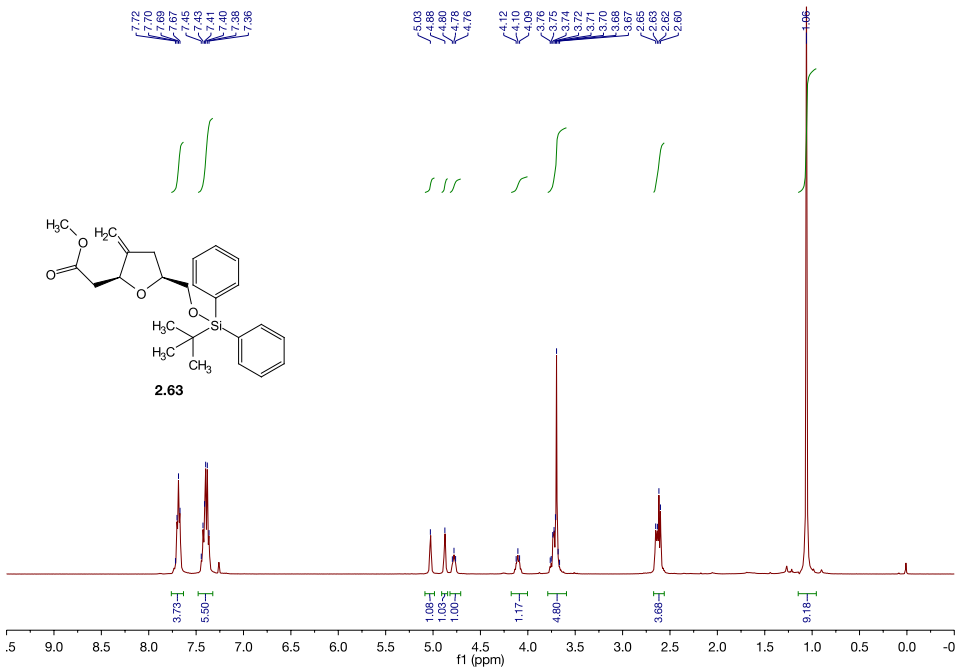
46.47
26.84
19.28
2.66
f1 (ppm)


7.72
7.70
7.69
7.67
7.45
7.43
7.41
7.40
7.38
7.36
5.03
4.88
4.80
4.78
4.76
4.12
4.10
4.09
3.76
3.75
3.74
3.72
3.71
3.70
3.68
3.67
2.65
2.63
2.62
2.60
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3.73
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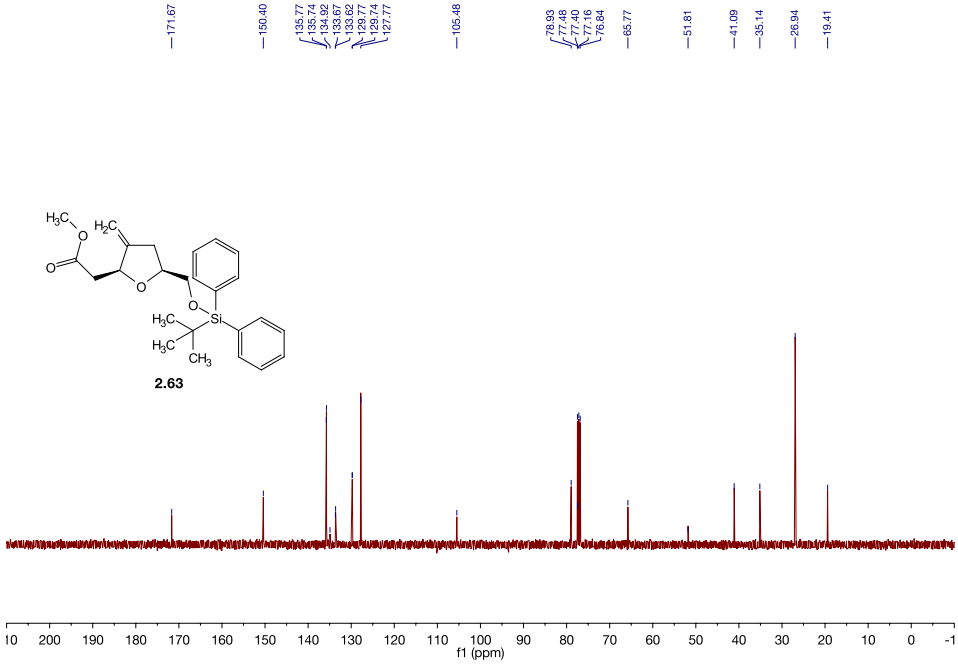
1.08
1.03
1.00
1.17
4.80
3.68
9.18
f1 (ppm)

2.63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127.77
105.48
78.93
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76.84
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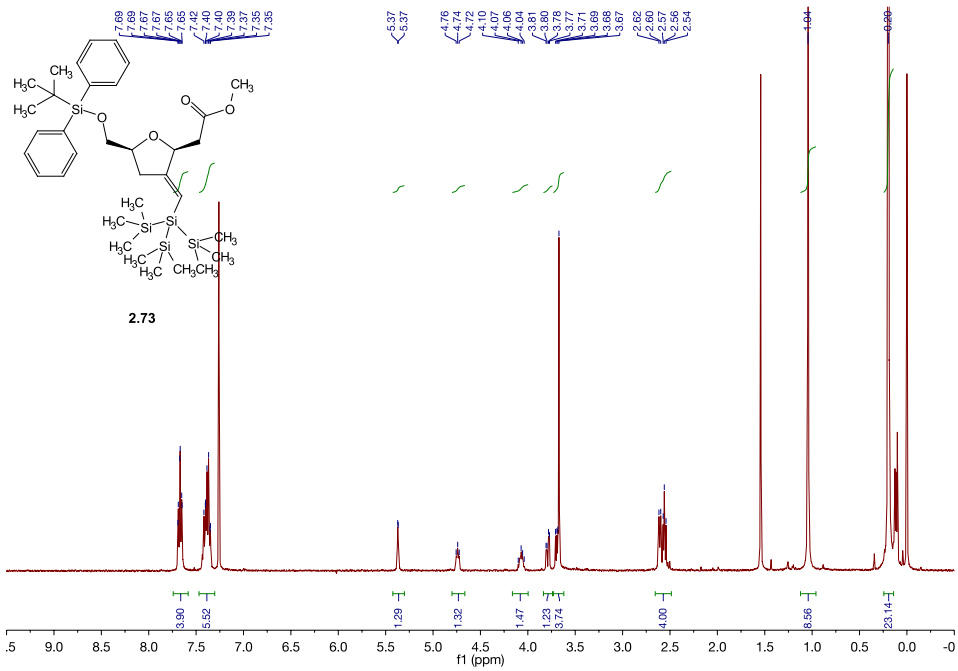
51.81
41.09
35.14
26.94
19.41
f1 (ppm)

2.63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7.67
7.65
7.42
7.40
7.39
7.37
7.35
5.37
4.76
4.74
4.72
4.10
4.07
4.06
4.04
3.81
3.80
3.78
3.77
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3.69
3.68
3.67
2.62
2.60
2.57
2.56
2.54
1.04
0.00
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3.90
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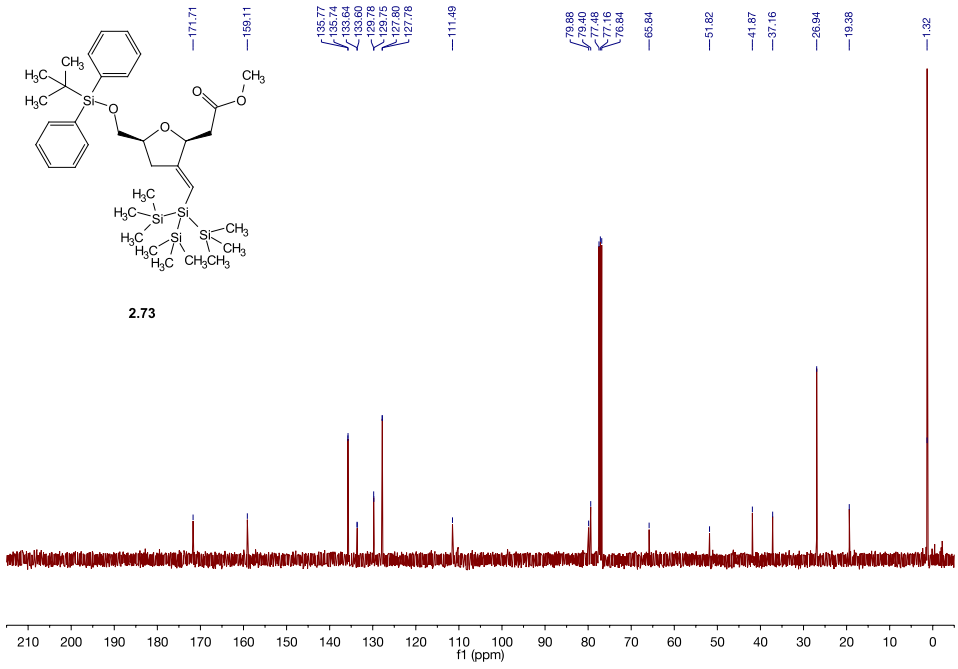
1.29
1.32
1.47
1.23
3.74
4.00
8.56
23.14
f1 (ppm)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133.60
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129.75
127.80
127.78
111.49
79.88
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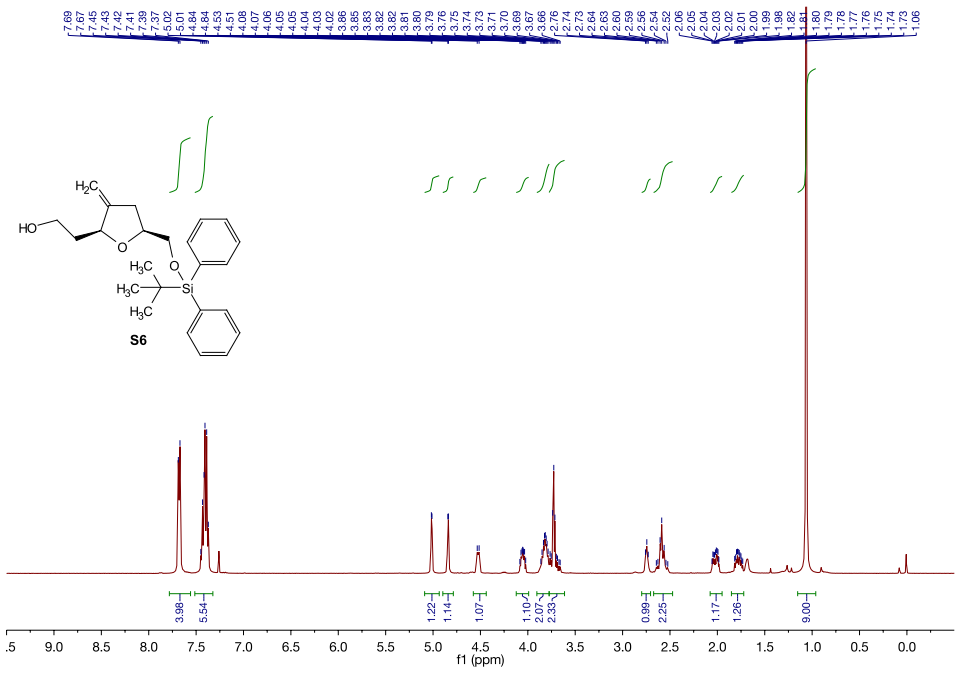
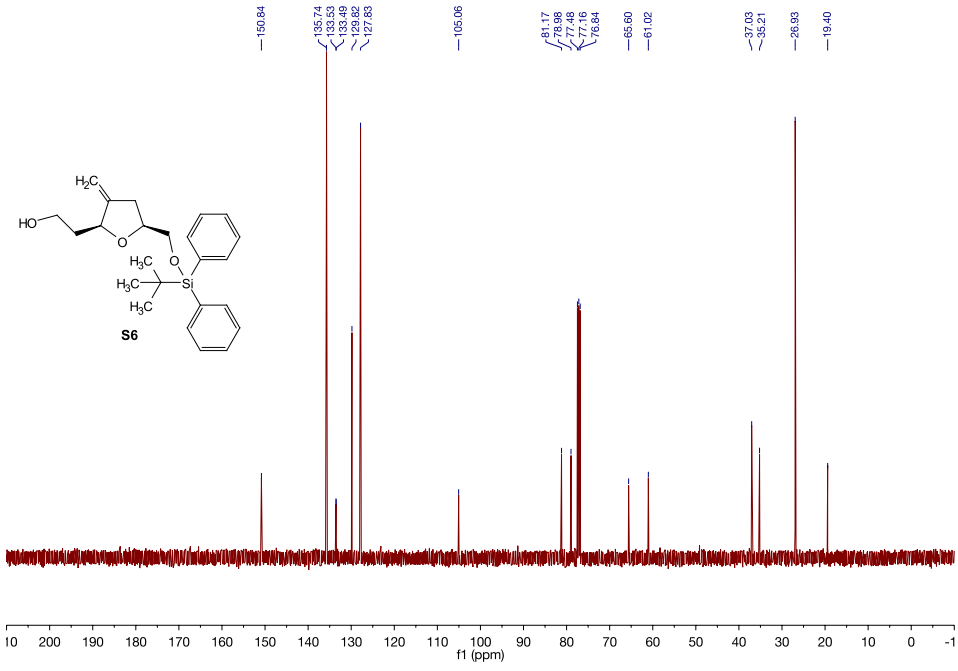
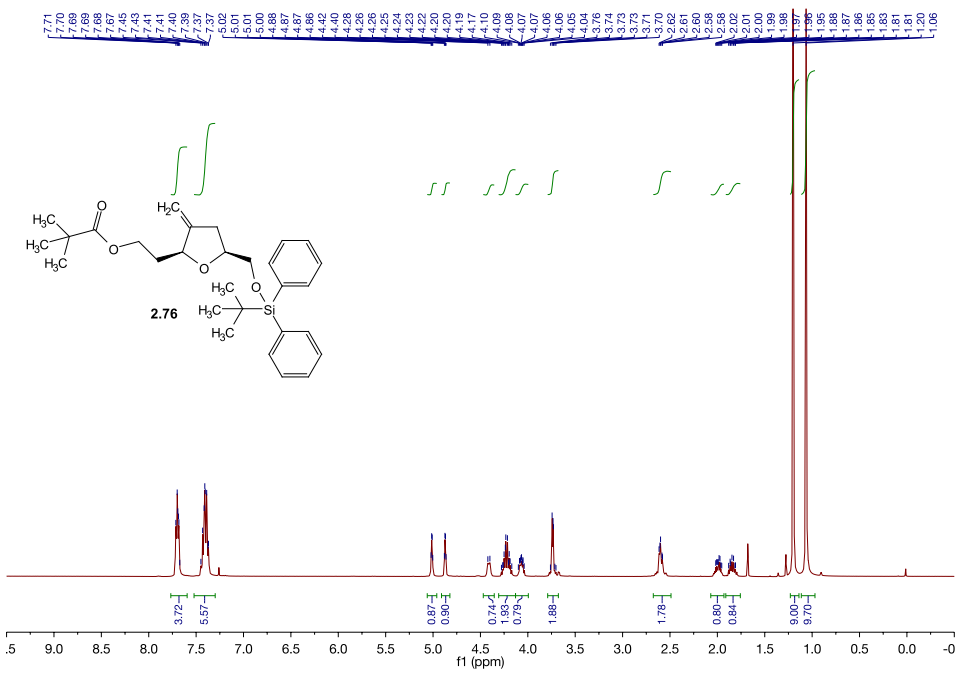
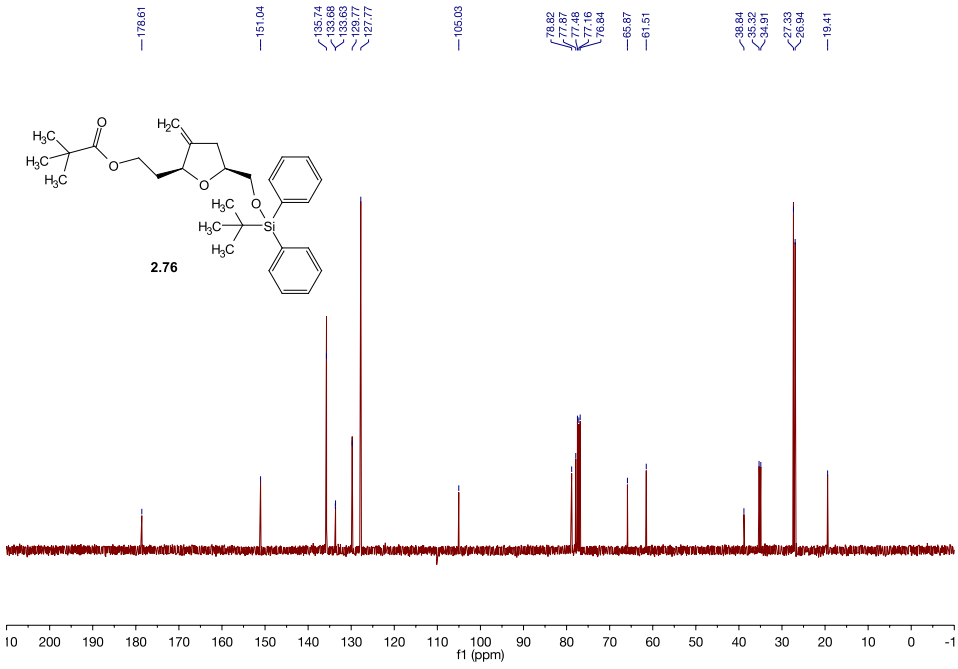
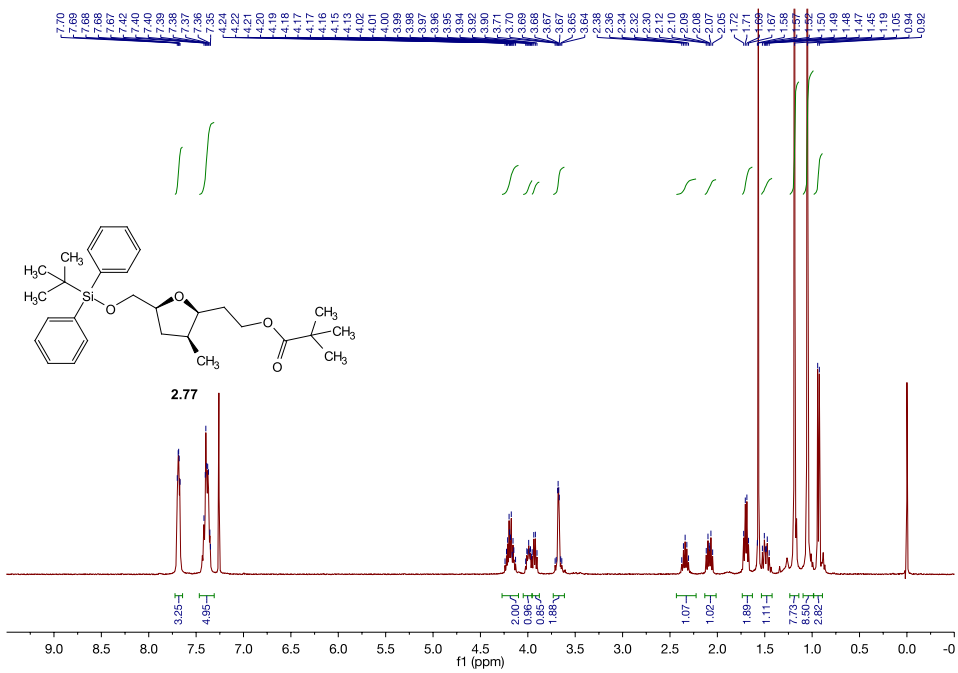
26.94
19.38
1.32
2.73
f1 (ppm)

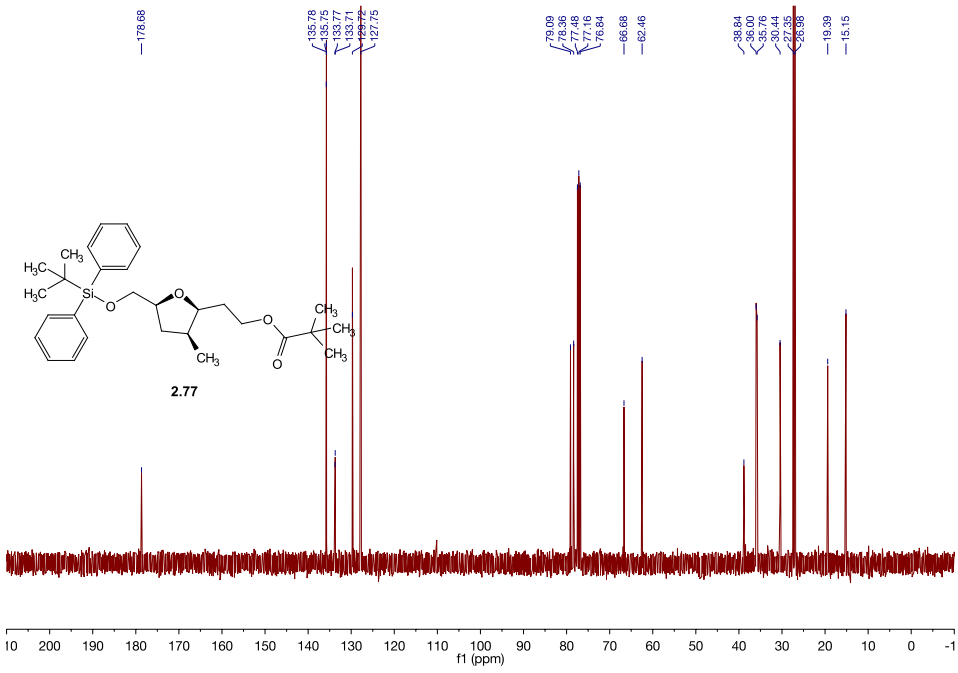

S6
f1 (ppm)

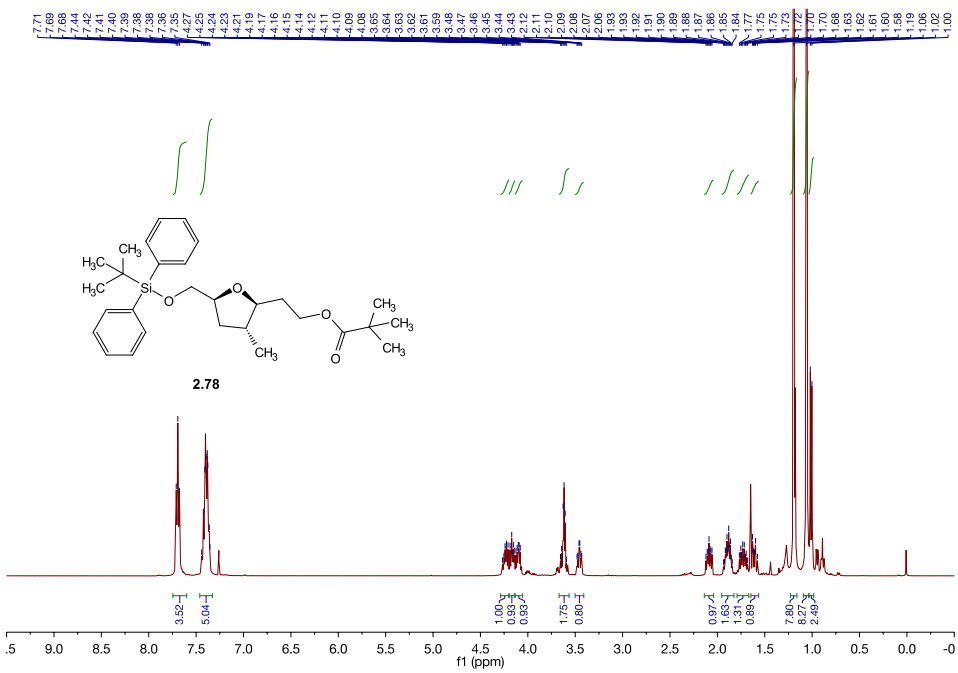

S6
f1 (ppm)


2.76
f1 (ppm)


2.76
f1 (ppm)


2.77
f1 (ppm)


2.77
f1 (ppm)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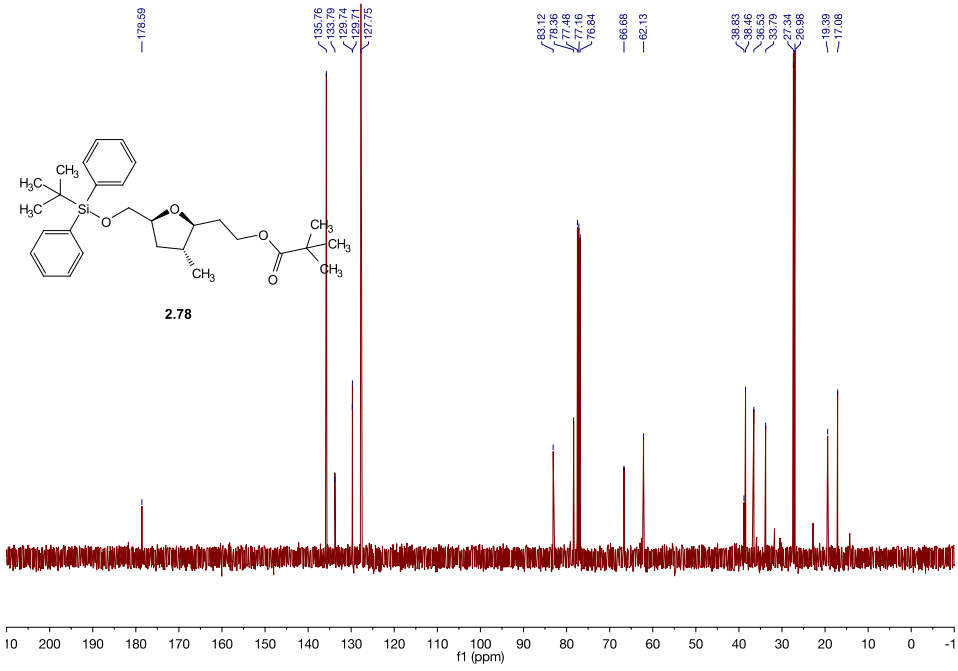
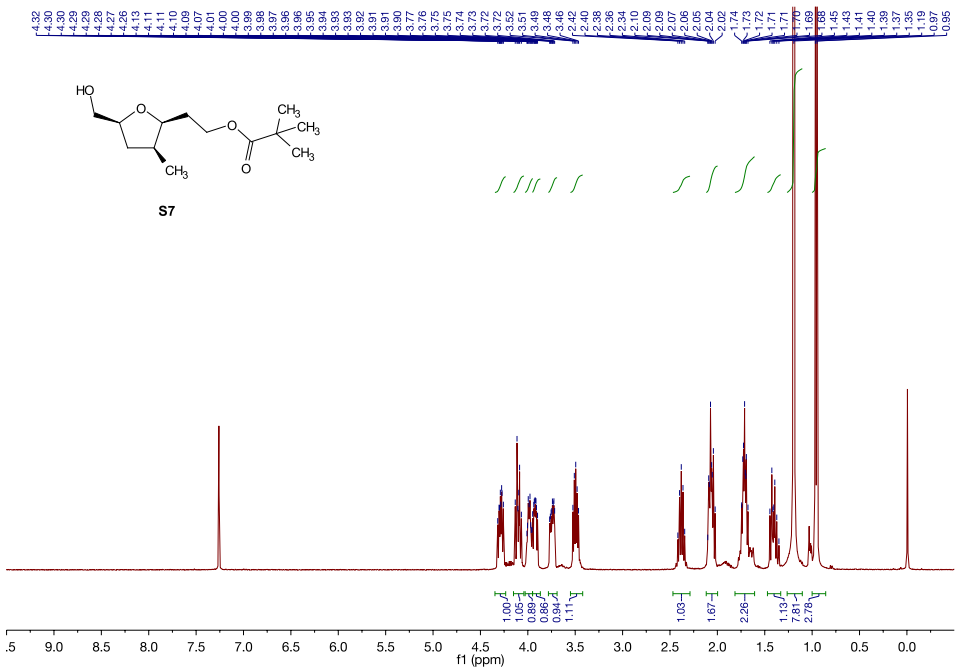
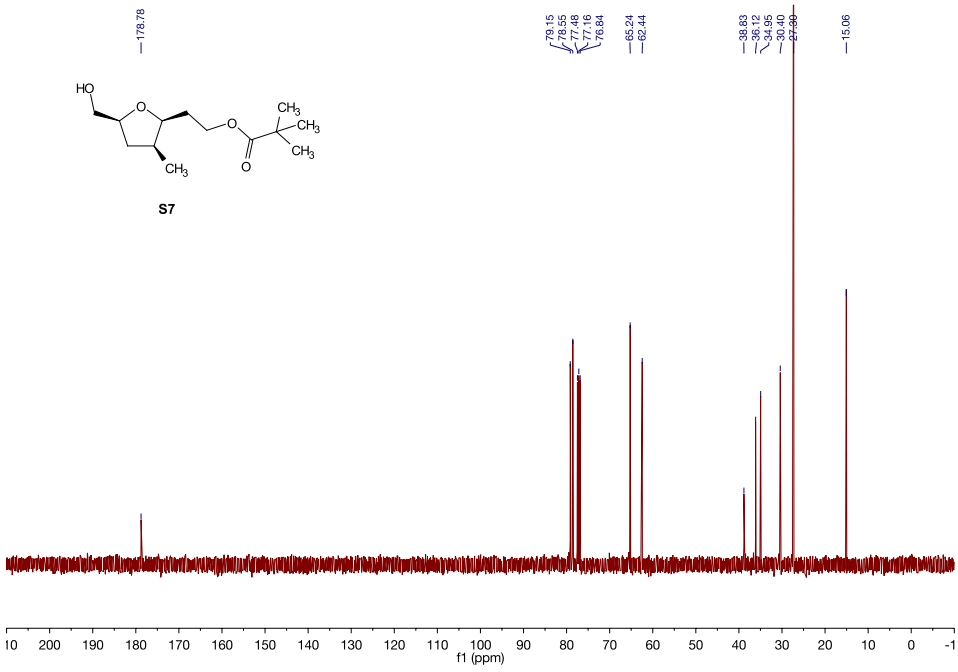
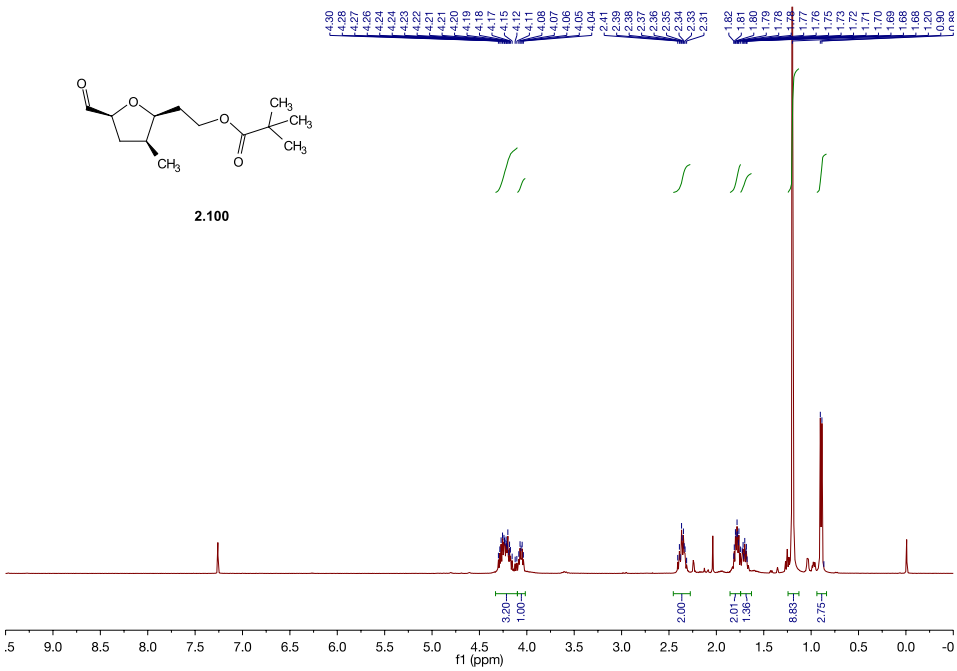
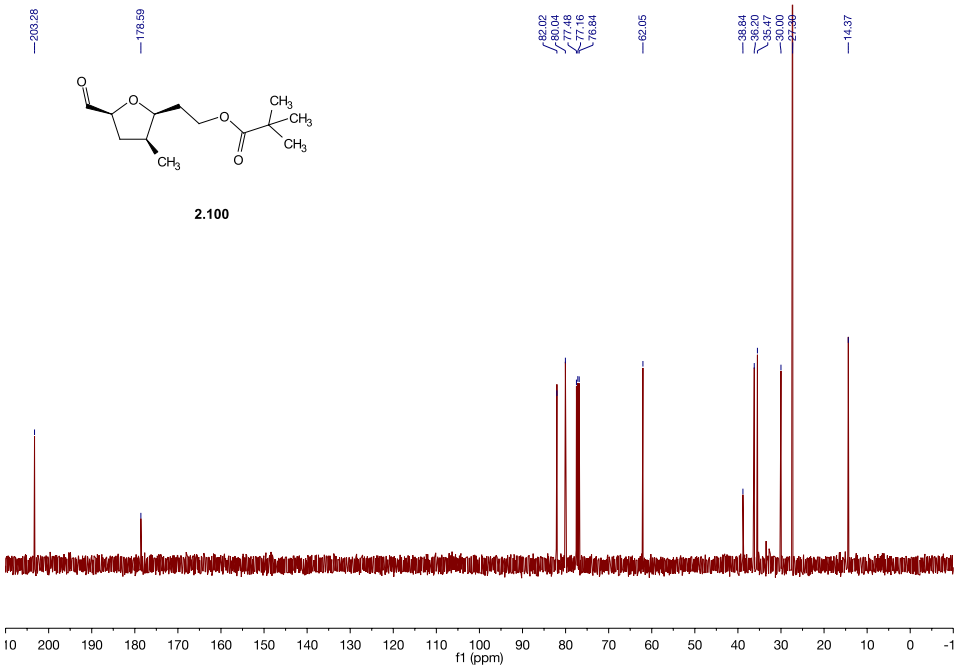
f1 (ppm)

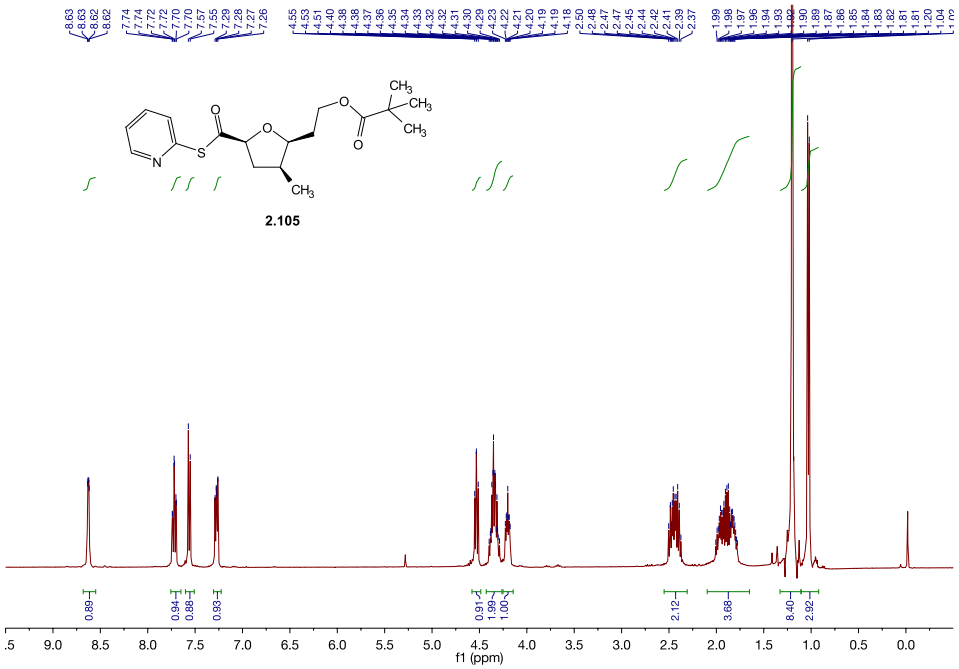

2.78
f1 (ppm)


HO
O
O
O
CH3
CH3
CH3
CH3
S7
f1 (ppm)


HO
O
O
O
CH3
CH3
CH3
CH3
S7
178.78
79.15
78.55
77.48
77.16
76.84
65.24
62.44
38.83
36.12
34.95
30.40
27.00
15.06
f1 (ppm)


4.30 4.28 4.27 4.26 4.24 4.24 4.23 4.22 4.21 4.21 4.20 4.19 4.18 4.17 4.15 4.12 4.11 4.08 4.07 4.06 4.05 4.04 2.41 2.39 2.38 2.37 2.36 2.35 2.34 2.33 2.31 1.82 1.81 1.80 1.79 1.78 1.78 1.77 1.76 1.75 1.73 1.72 1.71 1.70 1.69 1.68 1.68 1.20 0.90
O
O
O
O
CH3
CH3
CH3
CH3
2.100
3.20 1.00 2.00 2.01 1.36 8.83 2.75
.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0
f1 (ppm)


203.28
178.59
82.02
80.04
77.48
77.16
76.84
62.05
38.84
36.20
35.47
30.00
27.00
14.37
O
O
O
CH3
CH3
CH3
CH3
2.100
10 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -1
f1 (ppm)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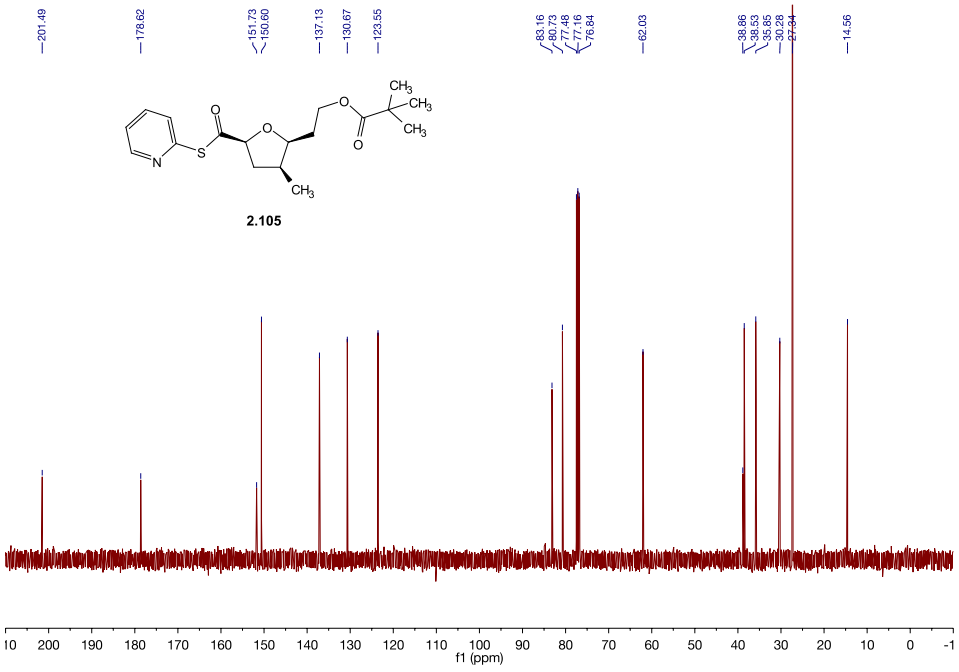
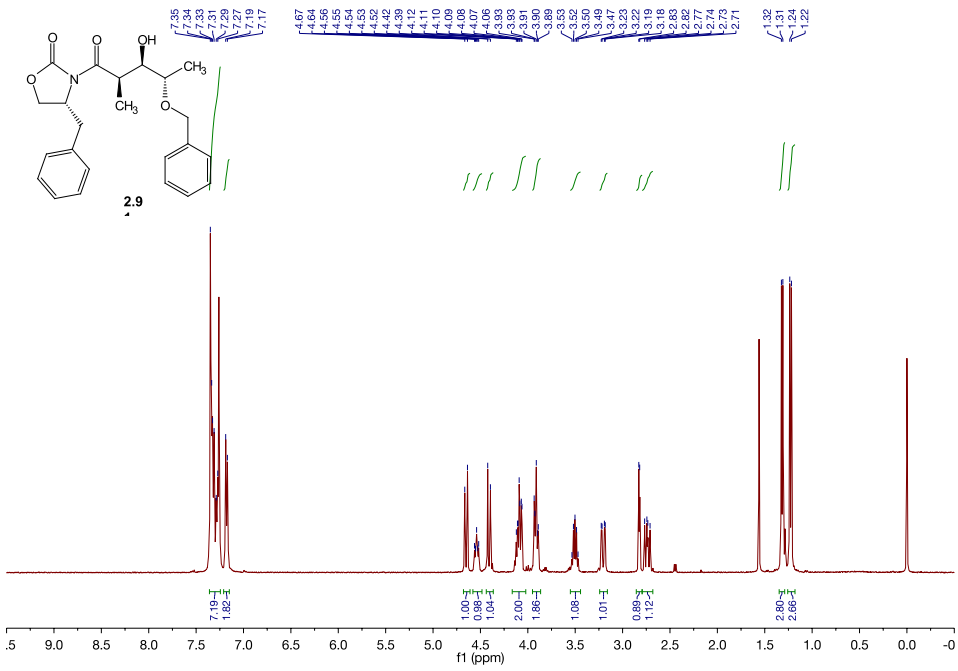
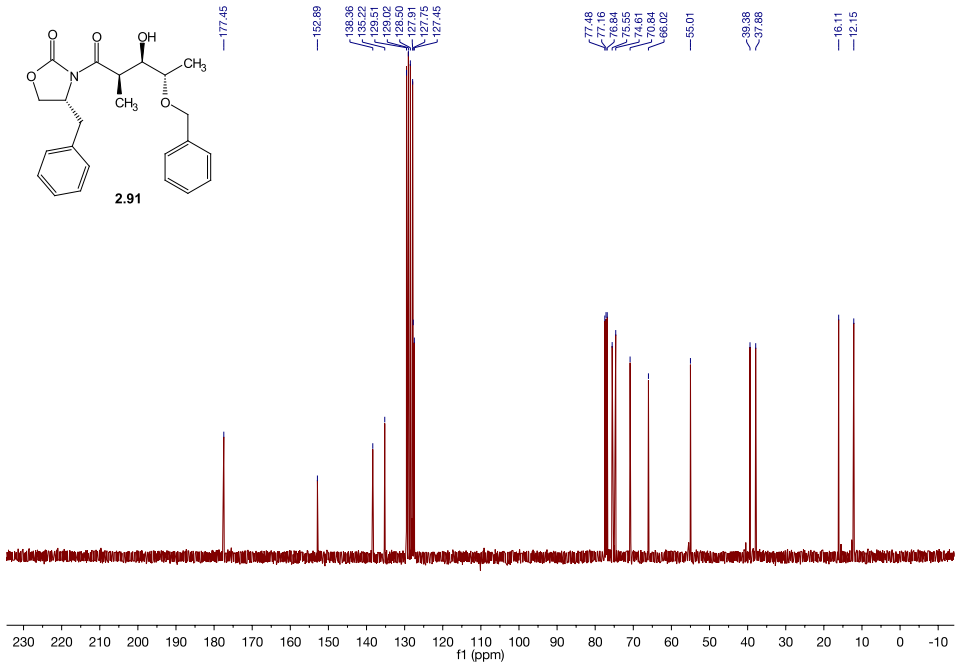
8.63
8.62
8.62
7.74
7.74
7.72
7.72
7.70
7.70
7.57
7.55
7.29
7.28
7.27
7.26
4.55
4.53
4.51
4.40
4.38
4.38
4.37
4.36
4.35
4.34
4.33
4.32
4.32
4.31
4.30
4.29
4.23
4.22
4.21
4.20
4.19
4.18
2.50
2.48
2.47
2.47
2.45
2.44
2.42
2.41
2.39
2.37
1.99
1.98
1.97
1.96
1.94
1.93
1.92
1.90
1.89
1.87
1.86
1.85
1.84
1.83
1.82
1.81
1.81
1.20
1.04
1.03
CH3
CH3
CH3
O
O
O
S
N
CH3
2.105
0.89
0.94
0.88
0.93
0.91
1.99
1.00
2.12
3.68
8.40
2.92
f1 (ppm)


201.49
178.62
151.73
150.60
137.13
130.67
123.55
83.16
80.73
77.48
77.16
76.84
62.03
38.86
38.53
35.85
30.28
27.34
14.56
CH3
CH3
CH3
O
O
O
S
N
CH3
2.105
f1 (ppm)


2.9
f1 (ppm)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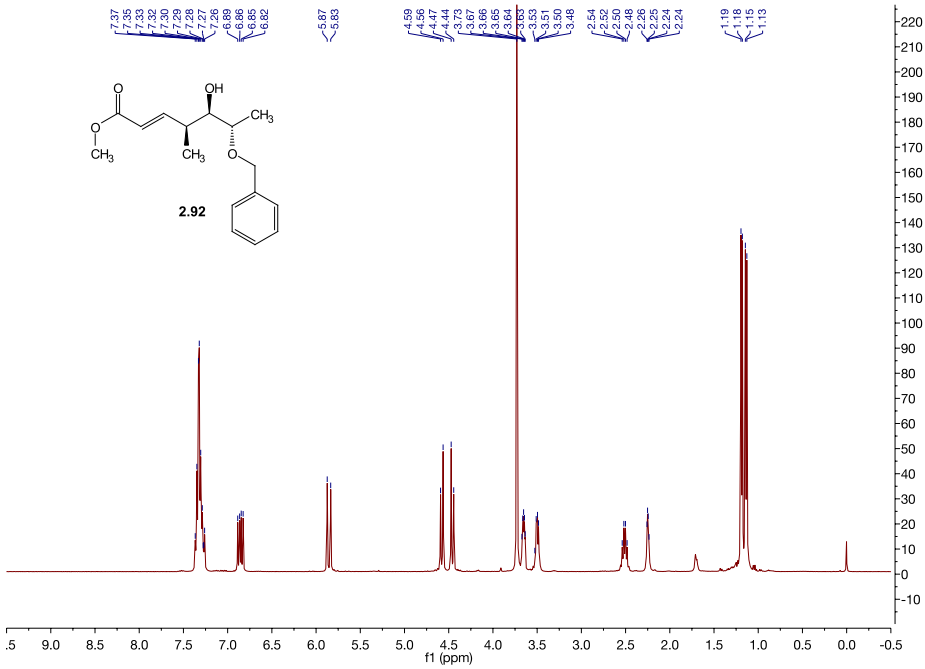
f1 (ppm)


7.37
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7.32
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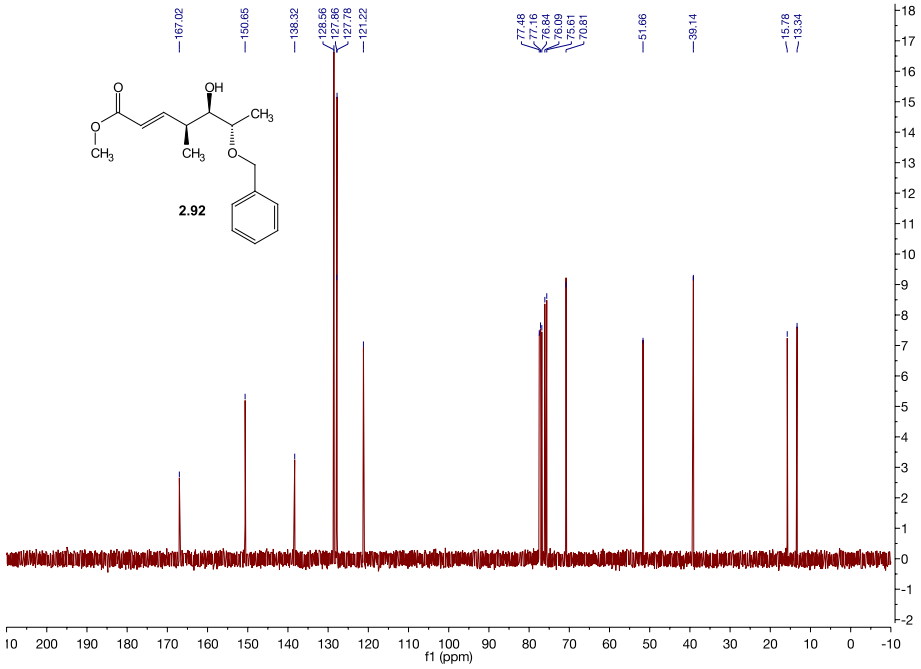
7.29
7.28
7.27
7.26
6.69
6.66
6.65
6.62
5.87
5.83
4.59
4.56
4.47
4.44
3.73
3.67
3.66
3.65
3.64
3.63
3.53
3.51
3.50
3.48
2.54
2.52
2.50
2.48
2.26
2.25
2.24
2.24
1.19
1.18
1.15
1.13
O
OH
CH3
O
CH3
CH3
O
2.92
f1 (ppm)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127.86
127.78
121.22
77.48
77.16
76.84
76.09
75.61
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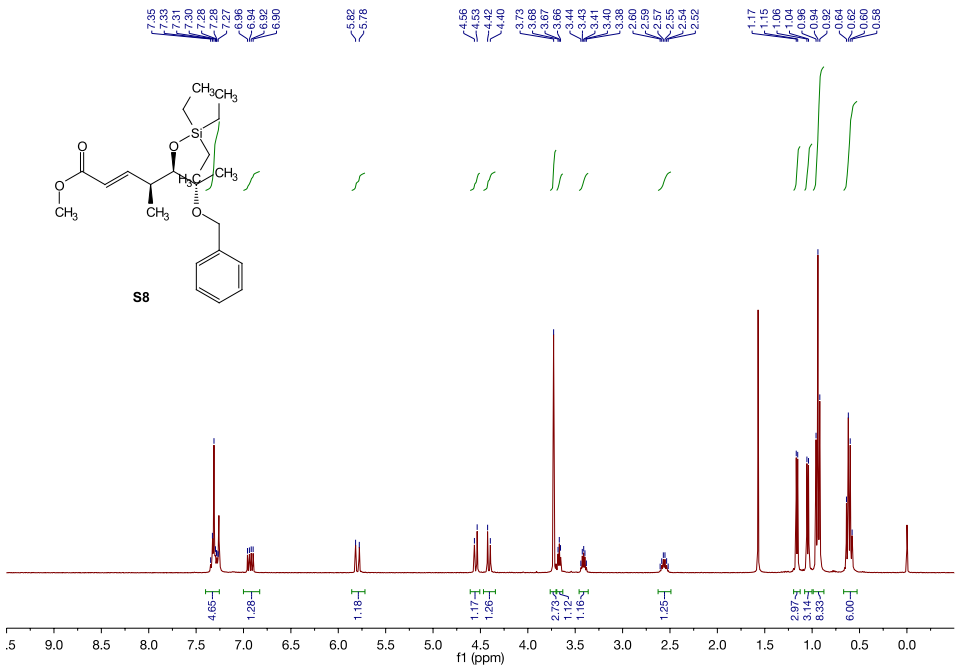
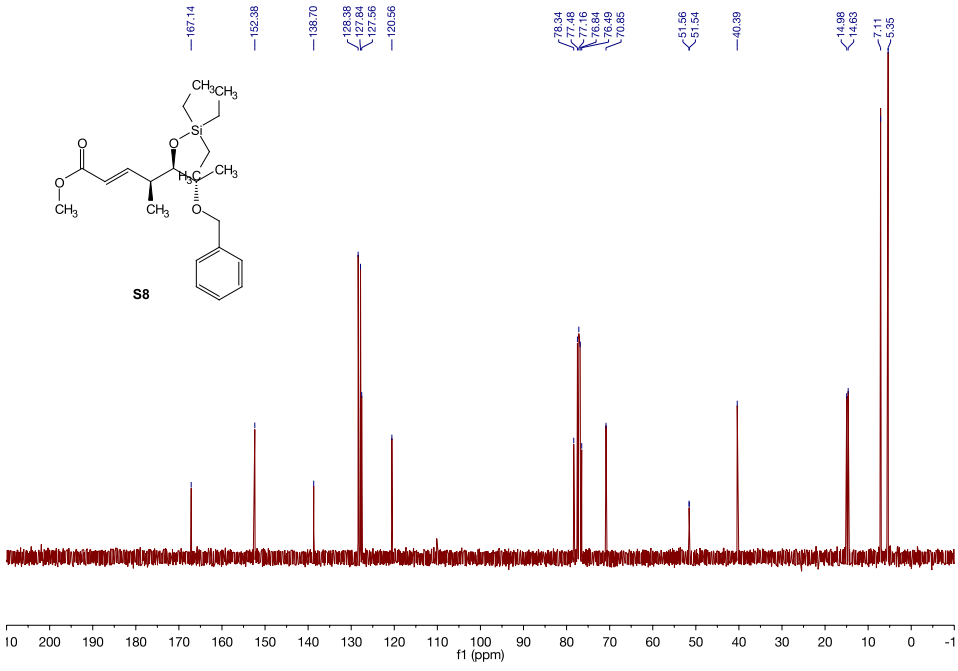
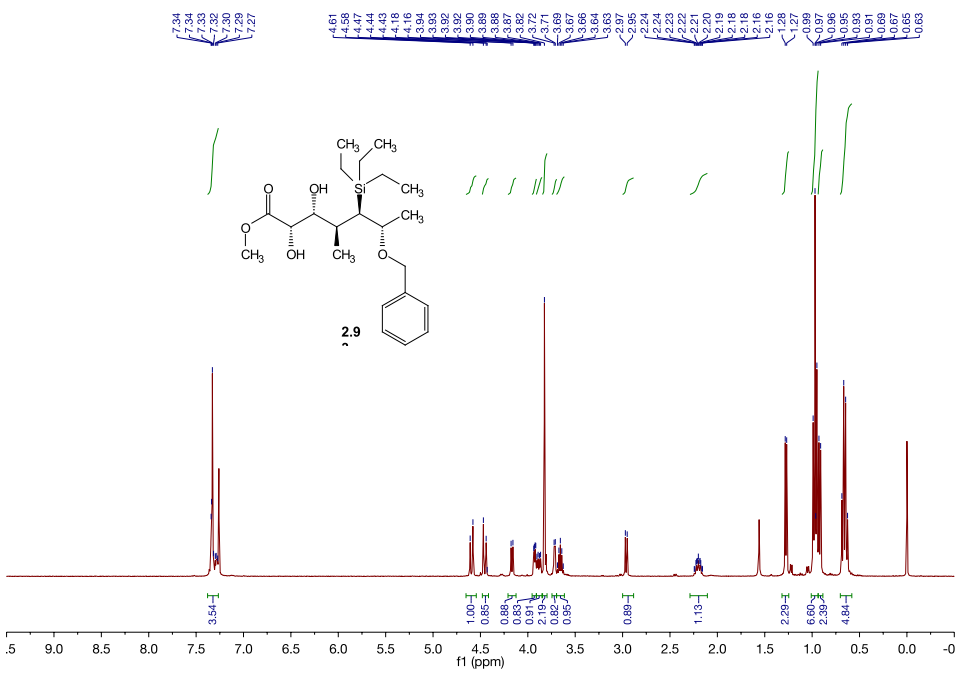
CH3
O
CH3
CH3
O
2.92
f1 (ppm)


S8
f1 (ppm)


S8
f1 (ppm)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7.27
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4.58
4.47
4.44
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4.18
4.16
4.14
3.93
3.92
3.92
3.90
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3.87
3.82
3.72
3.71
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3.67
3.66
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3.63
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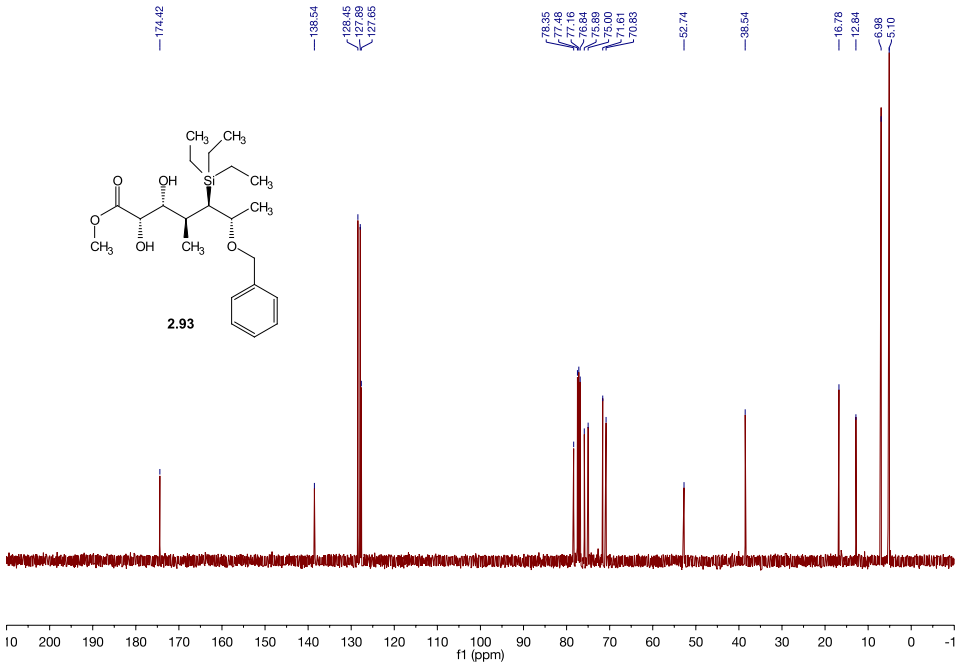
2.24
2.23
2.22
2.21
2.20
2.19
2.18
2.18
2.16
2.15
1.28
1.27
0.99
0.97
0.96
0.95
0.93
0.91
0.69
0.67
0.65
0.63
2.9
3.54
1.00
0.85
0.88
0.85
0.91
2.19
0.82
0.95
0.89
1.13
2.29
6.60
2.39
4.84
f1 (ppm)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79.35
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77.16
76.84
75.89
75.00
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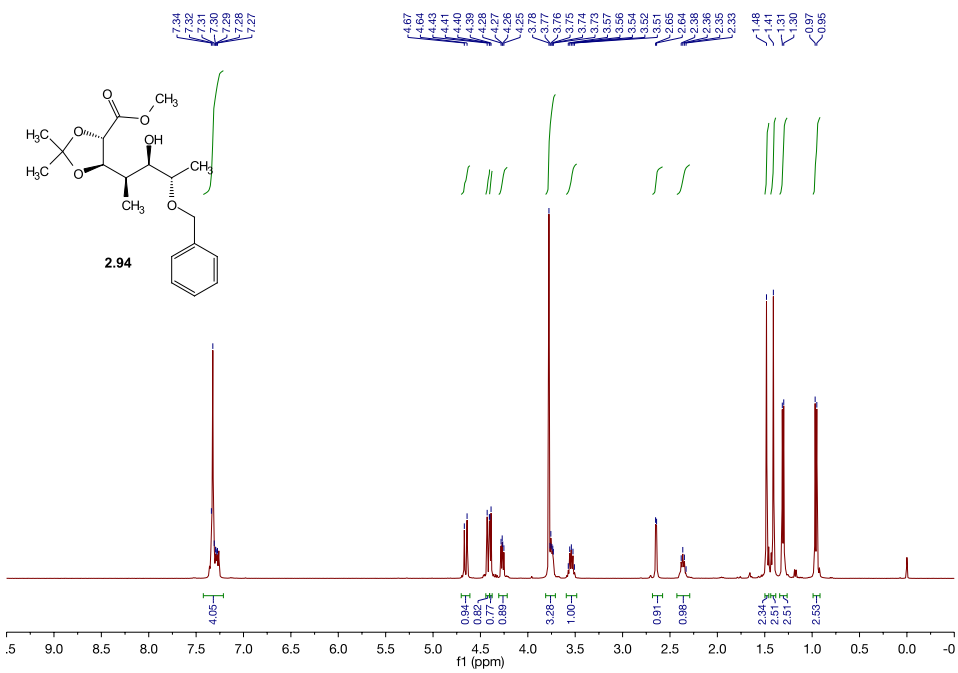
12.84
6.98
5.10
2.93
f1 (ppm)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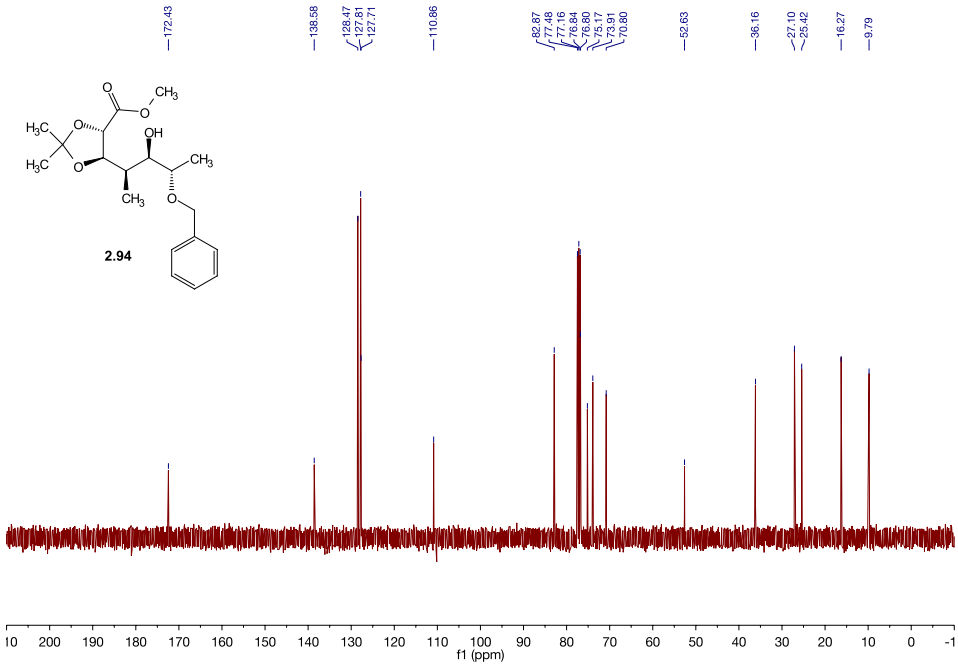
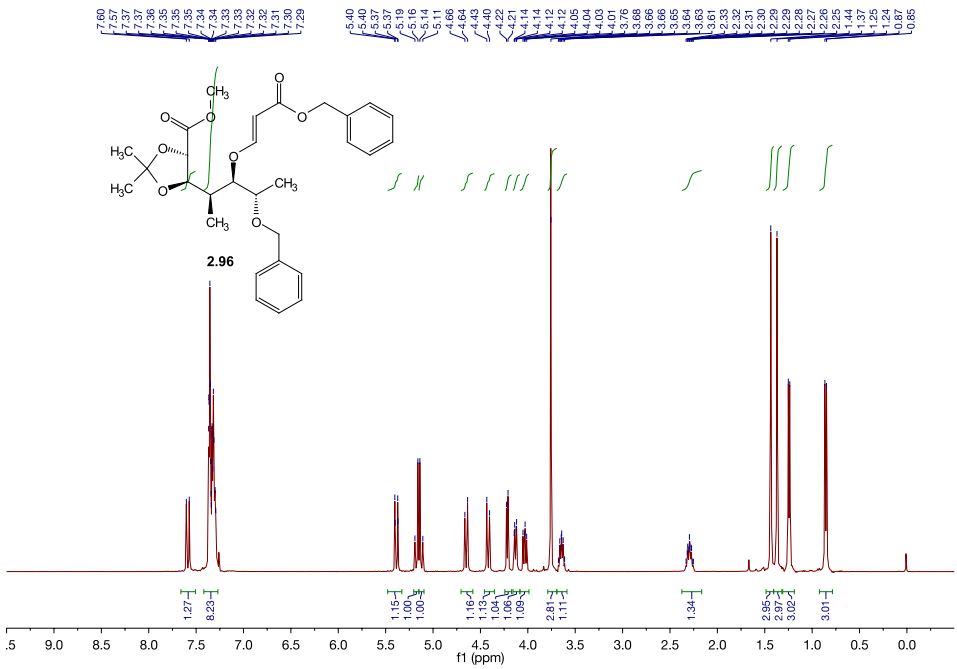
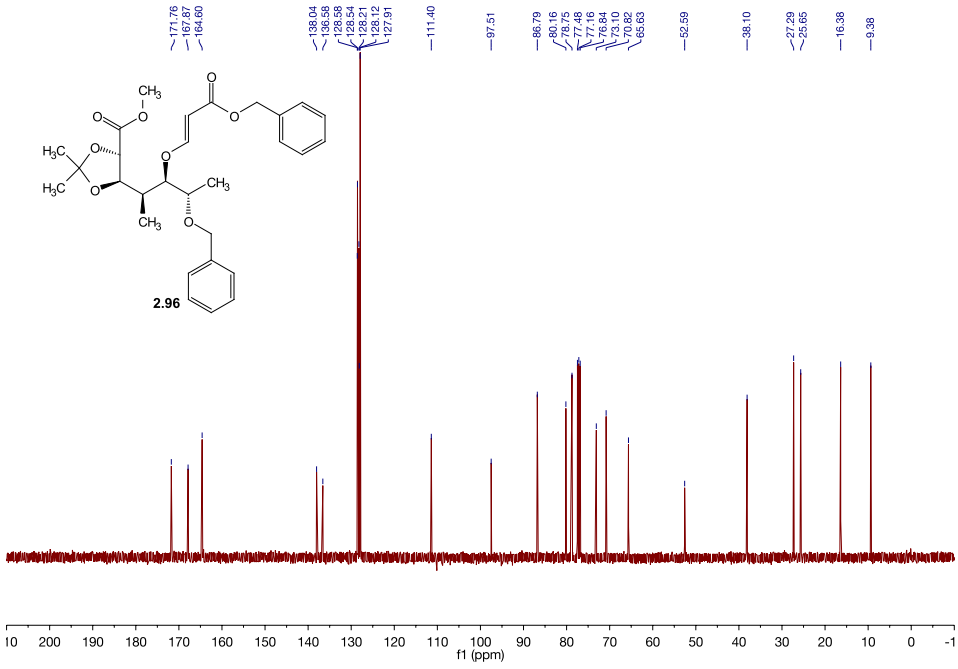
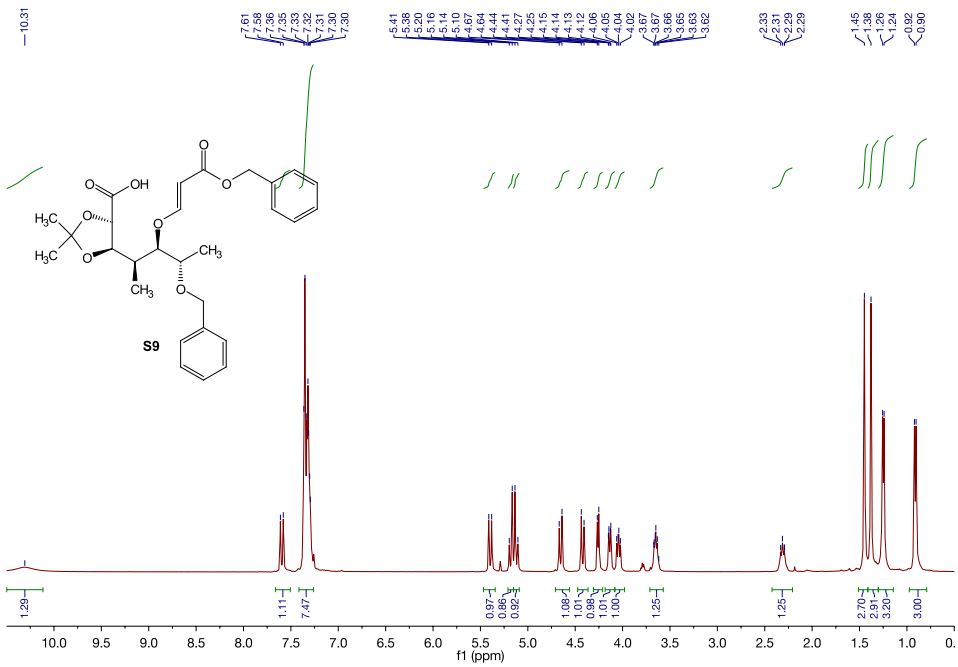
f1 (ppm)


2.94
f1 (ppm)


2.96
f1 (ppm)


2.96
f1 (ppm)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7.31
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7.30
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5.38
5.20
5.16
5.14
5.10
4.67
4.64
4.44
4.41
4.27
4.25
4.15
4.14
4.13
4.12
4.06
4.05
4.04
4.02
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3.66
3.65
3.63
3.62
2.33
2.31
2.29
2.29
1.45
1.38
1.26
1.24
0.92
0.90
S9
1.29
1.11
7.47
0.97
0.86
0.92
1.08
1.01
0.98
1.01
1.00
1.25
1.25
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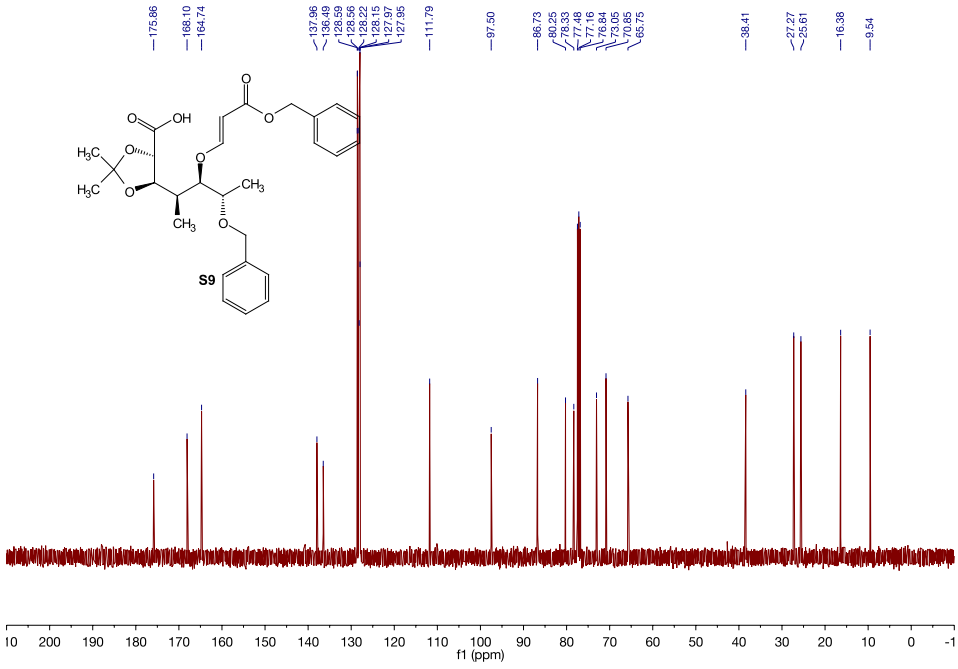
2.91
3.20
3.00
f1 (ppm)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127.97
127.95
111.79
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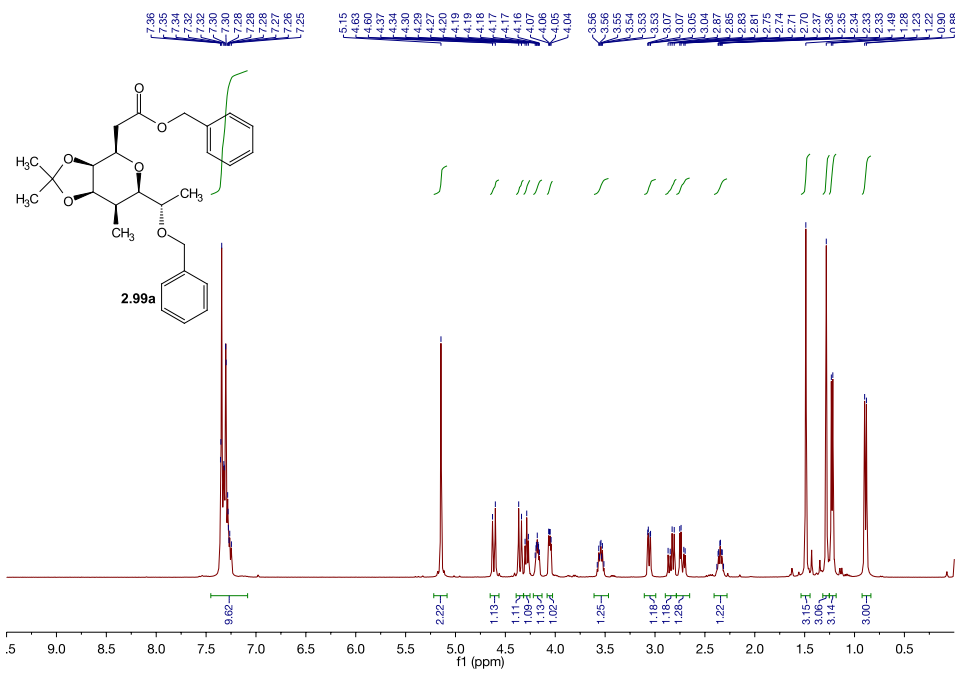
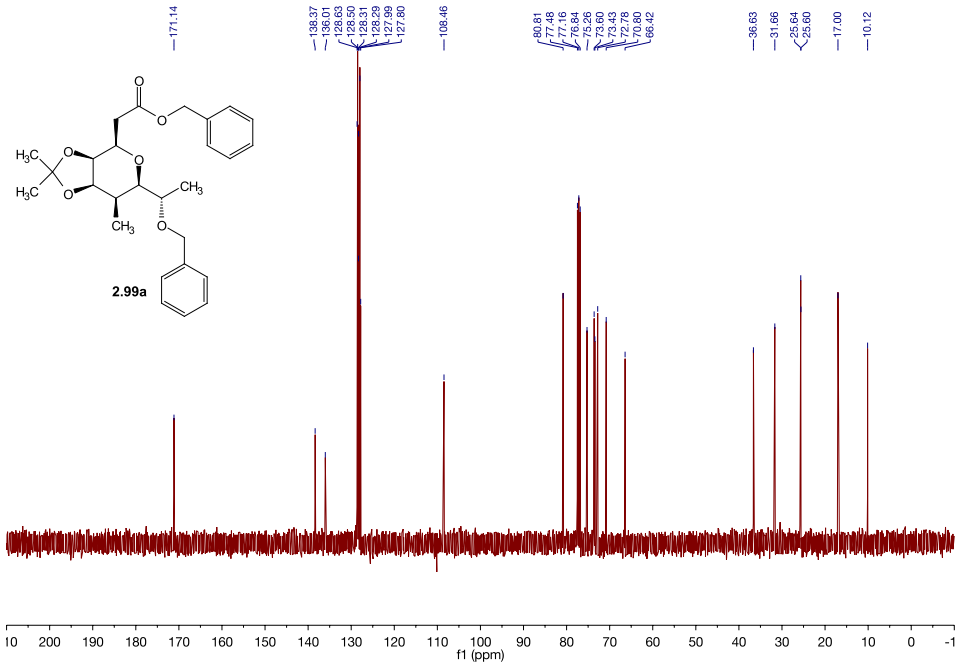
80.25
78.33
77.48
77.16
76.84
73.05
70.85
65.75
38.41
27.27
25.61
16.38
9.54
S9
f1 (ppm)


2.99a
f1 (ppm)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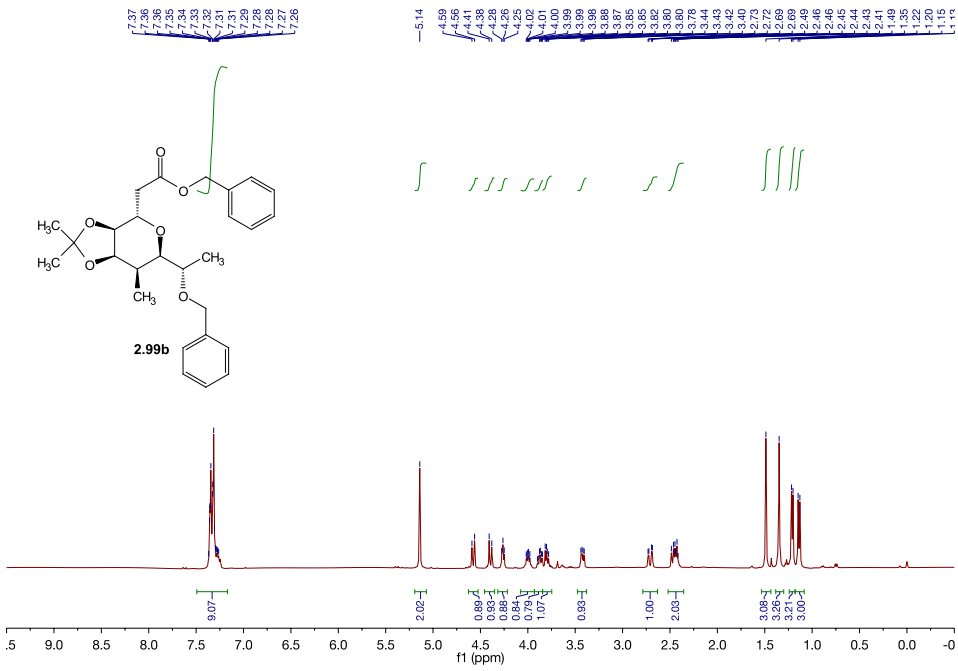
f1 (ppm)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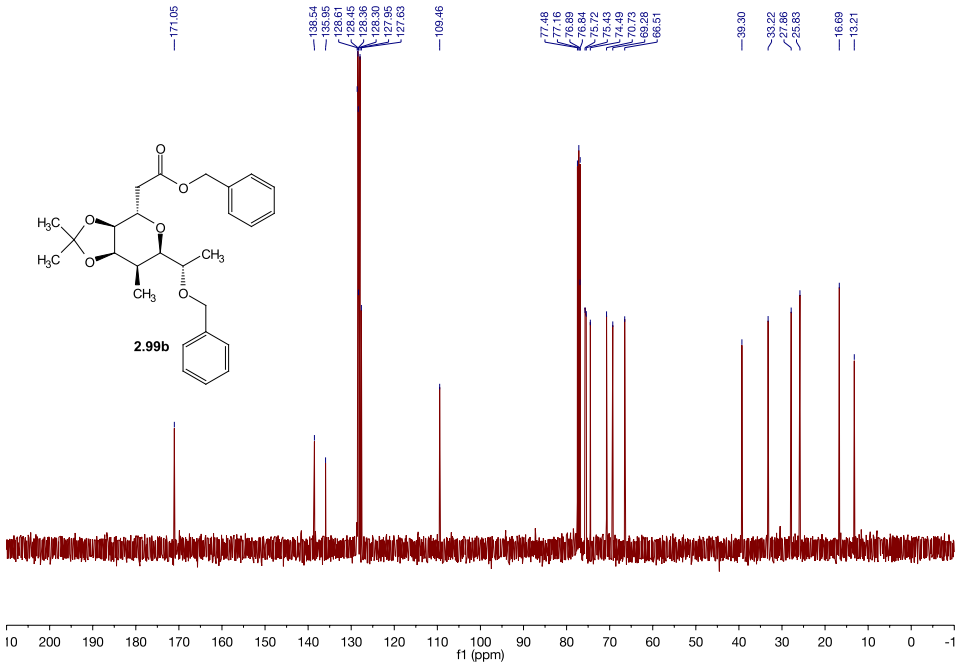
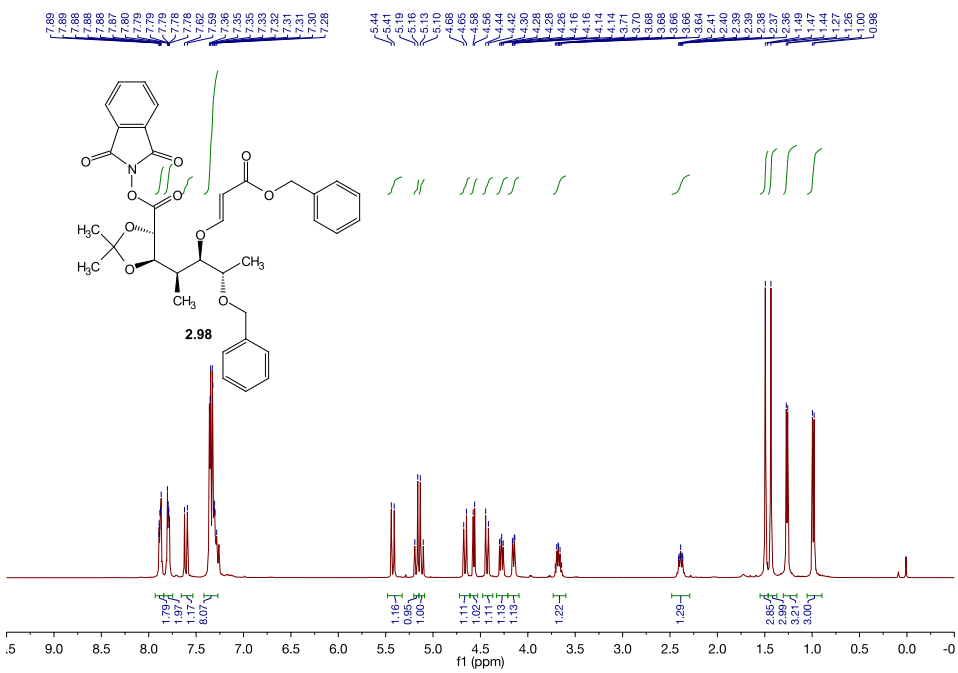
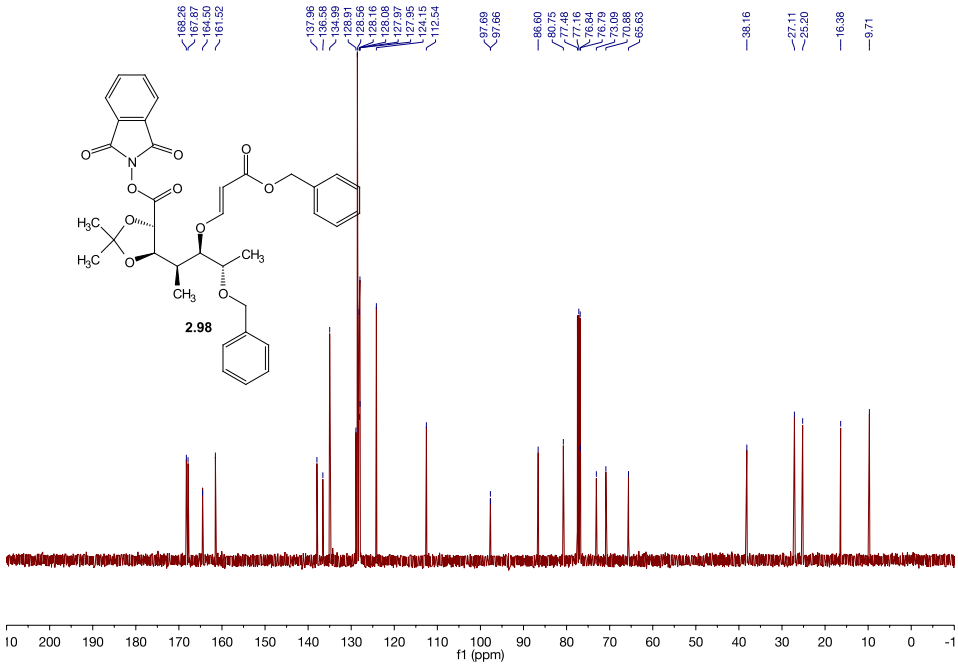
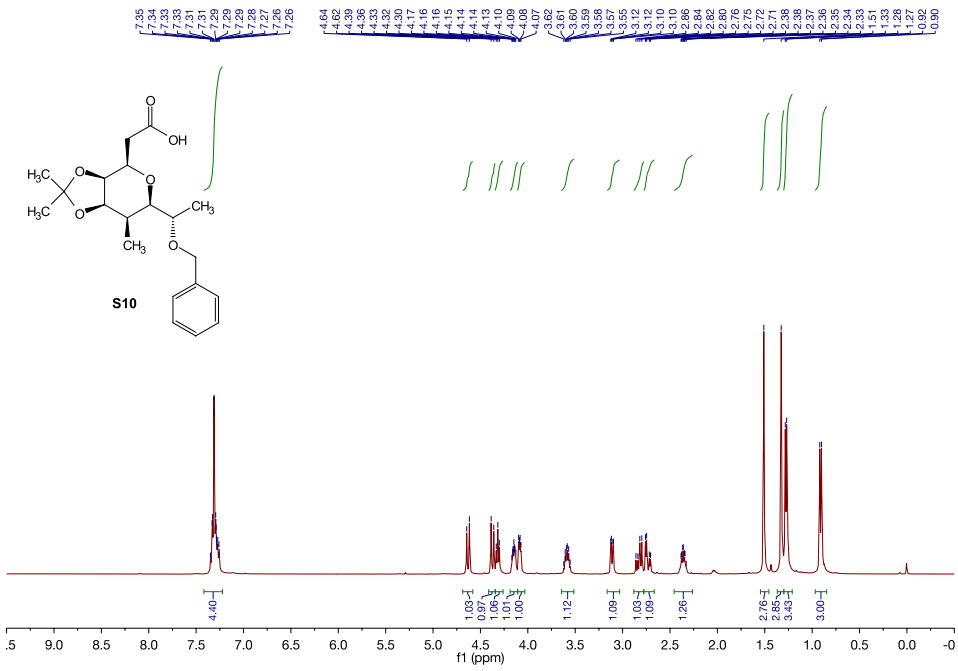
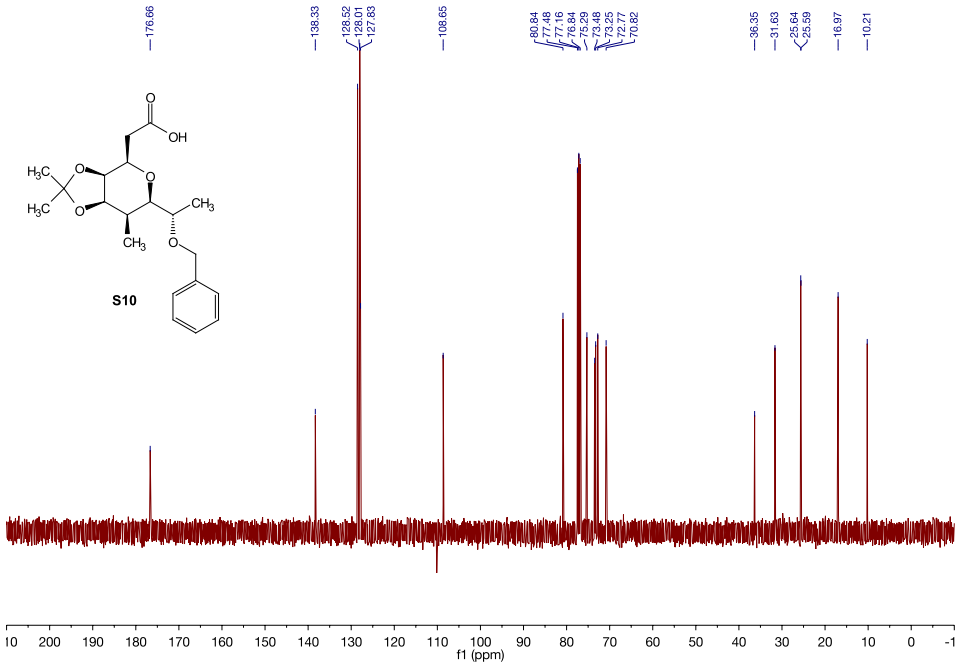
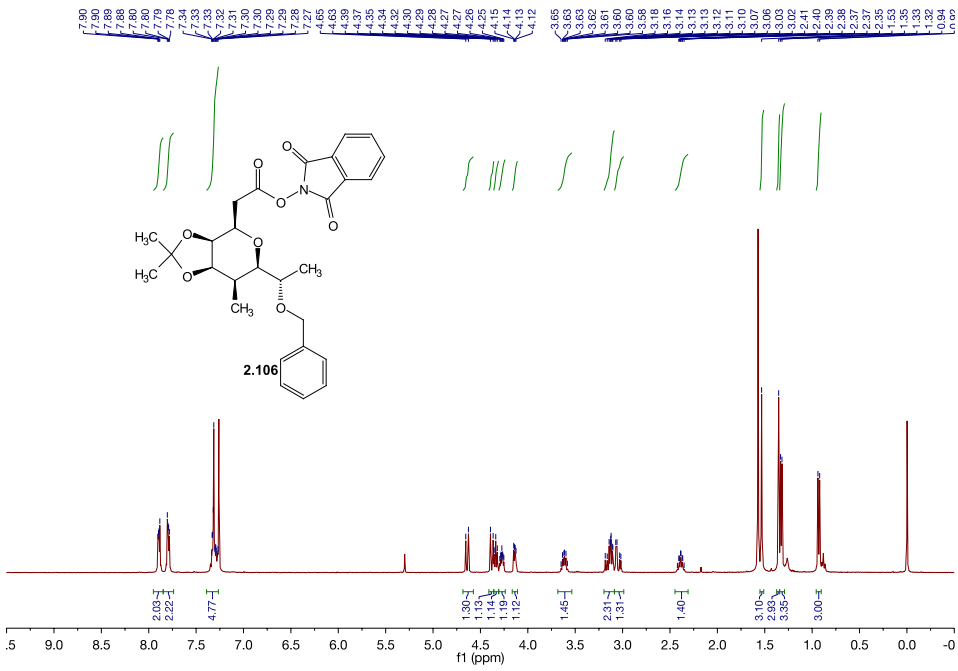

2.99b
f1 (ppm)


2.98
f1 (ppm)


2.98
f1 (ppm)


S10
f1 (ppm)


S10
f1 (ppm)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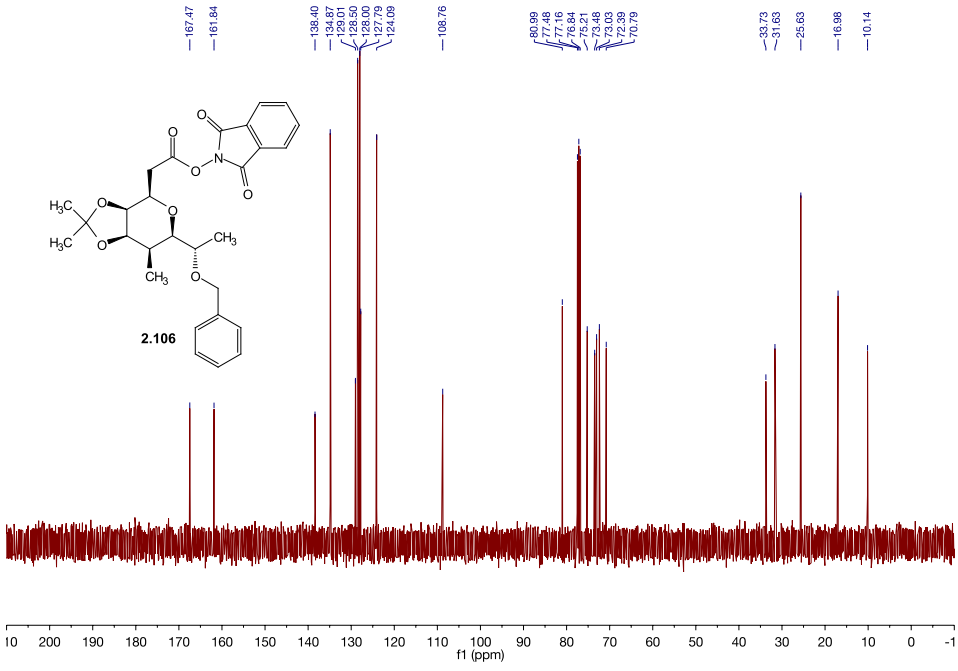
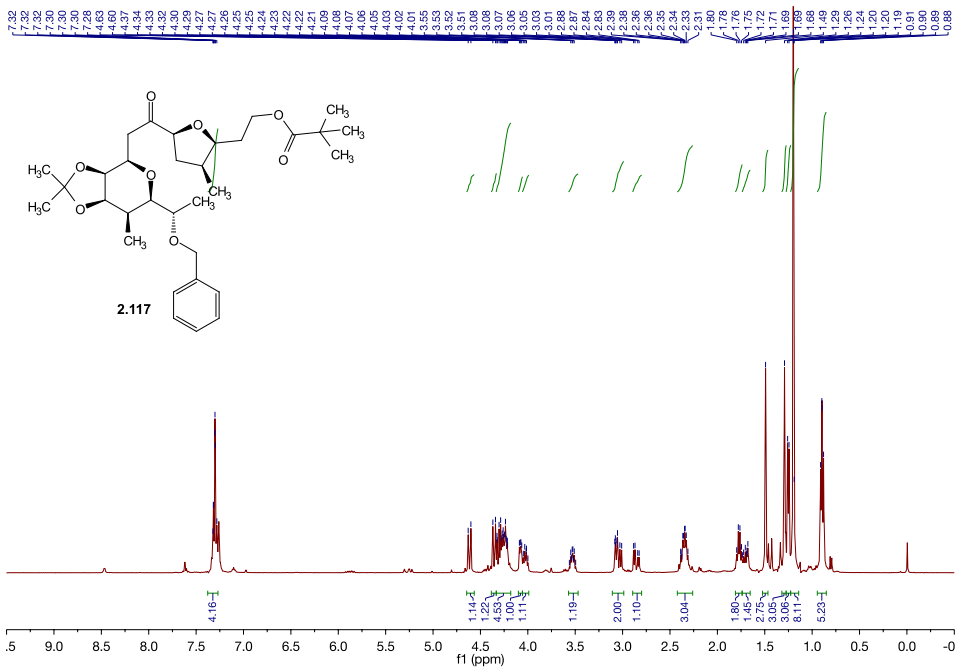
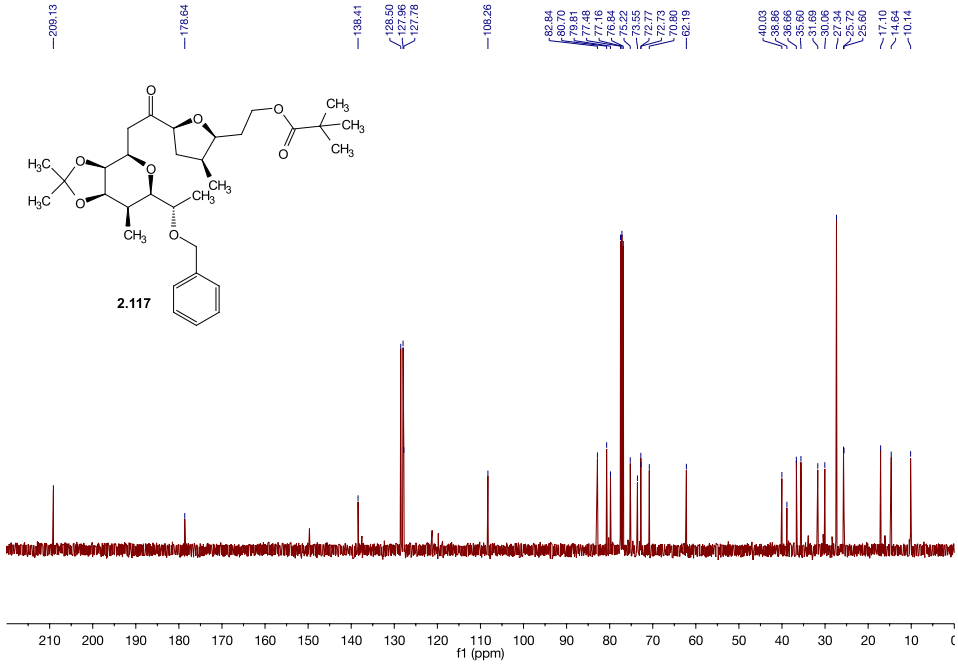
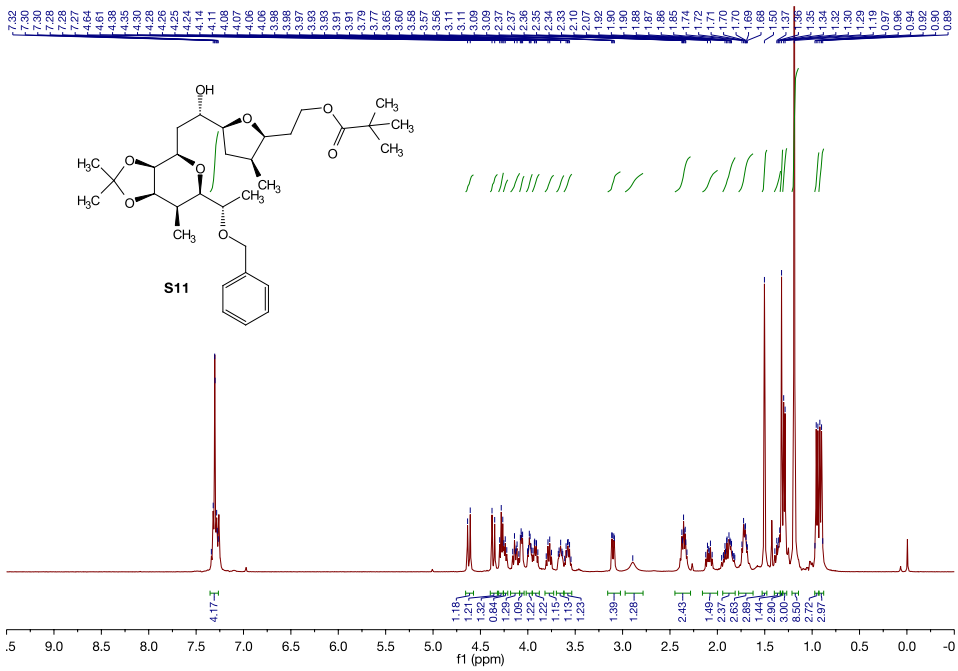
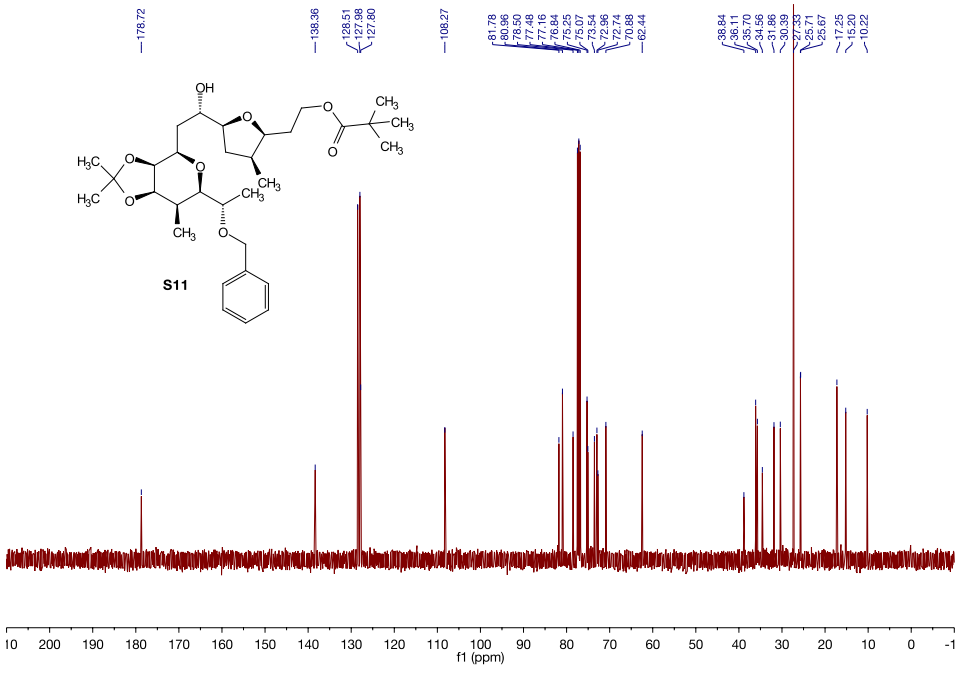
f1 (ppm)

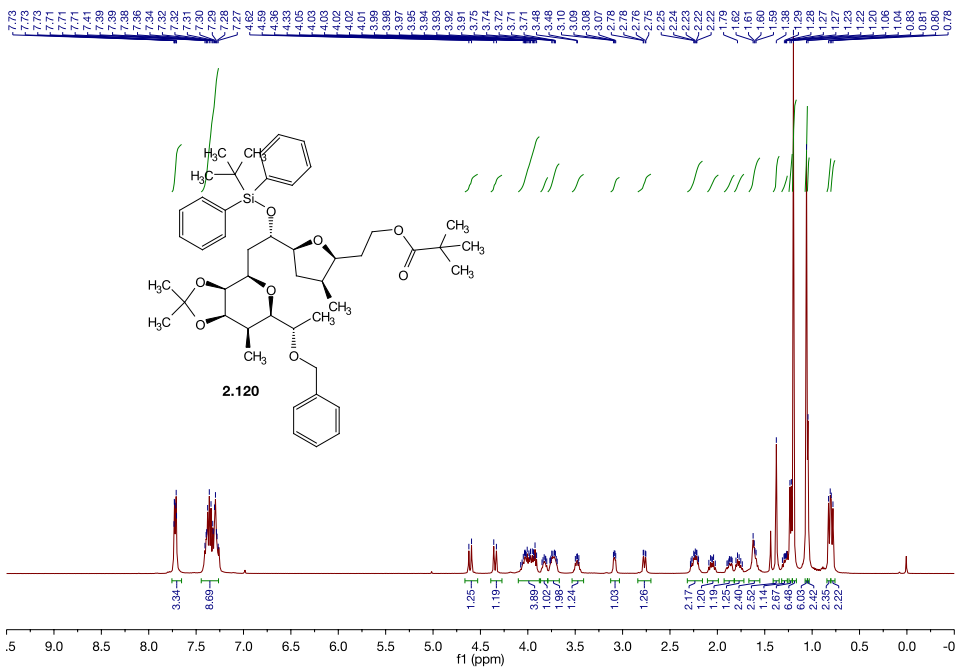

2.106
f1 (ppm)


2.117
f1 (ppm)


2.117
f1 (ppm)


S11
f1 (ppm)


S11
f1 (ppm)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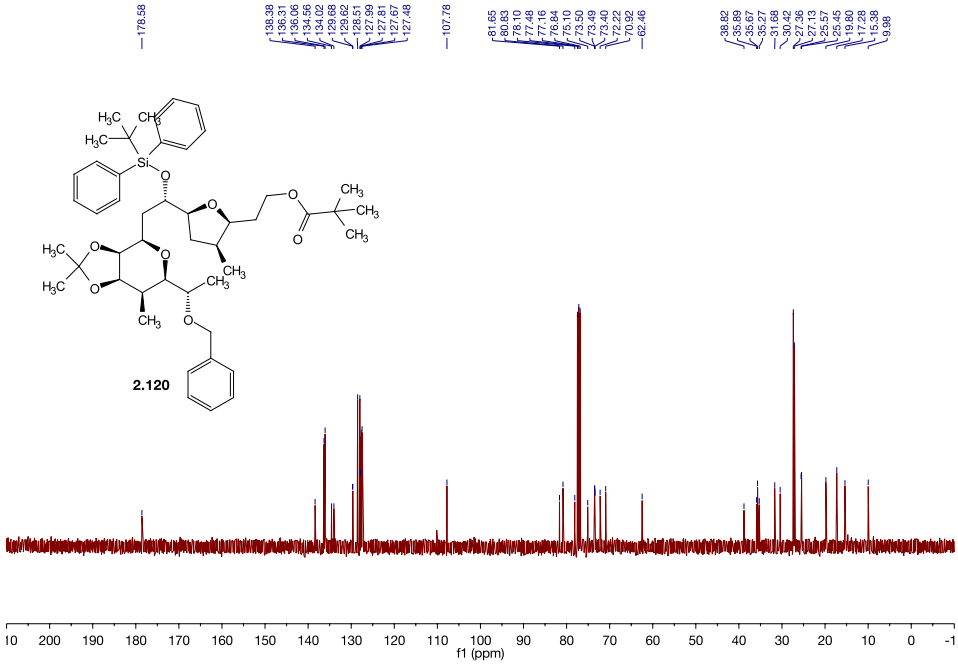
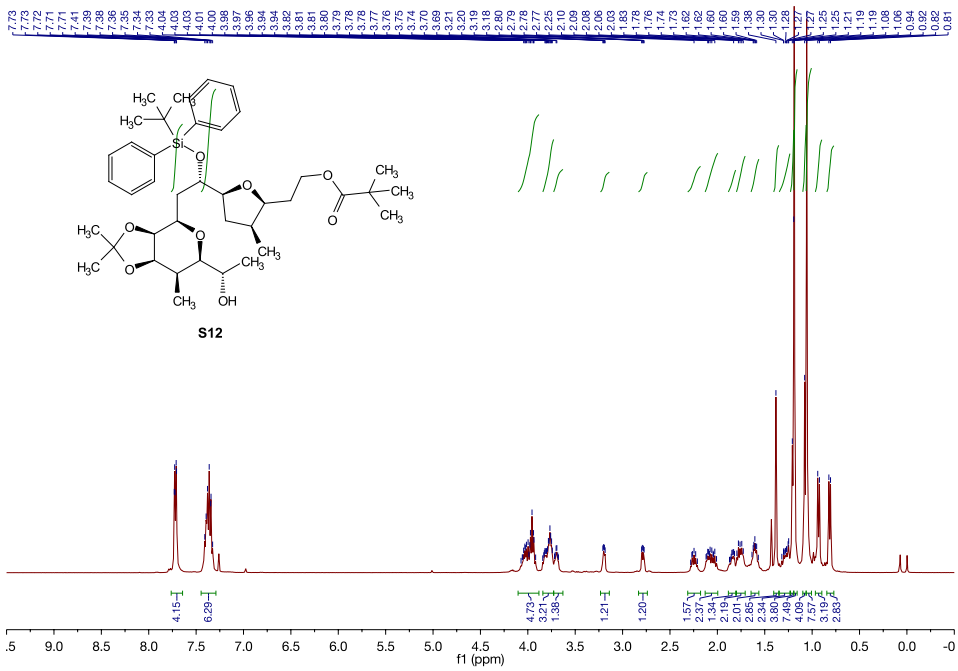
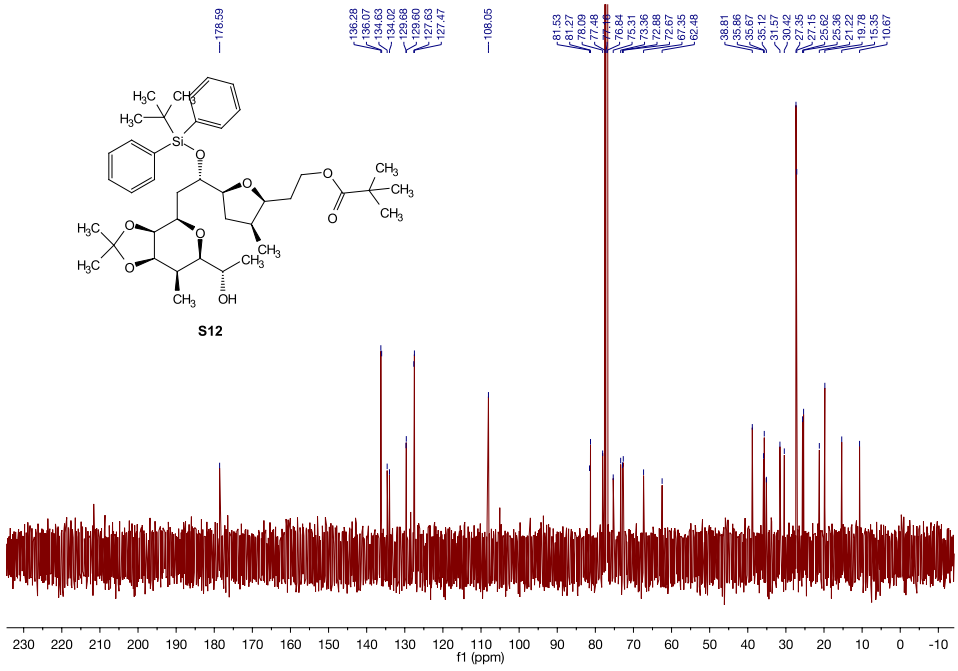
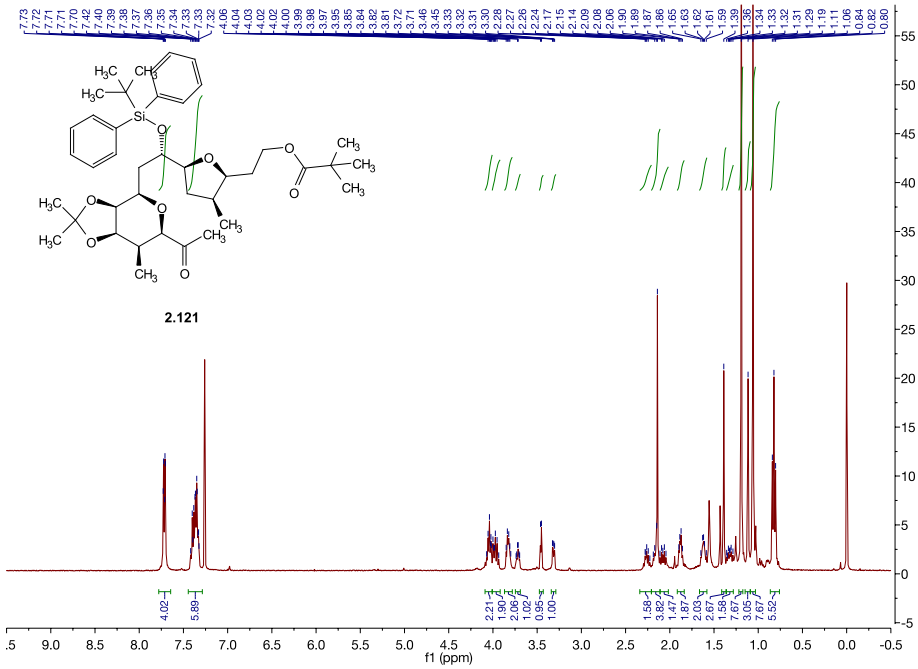
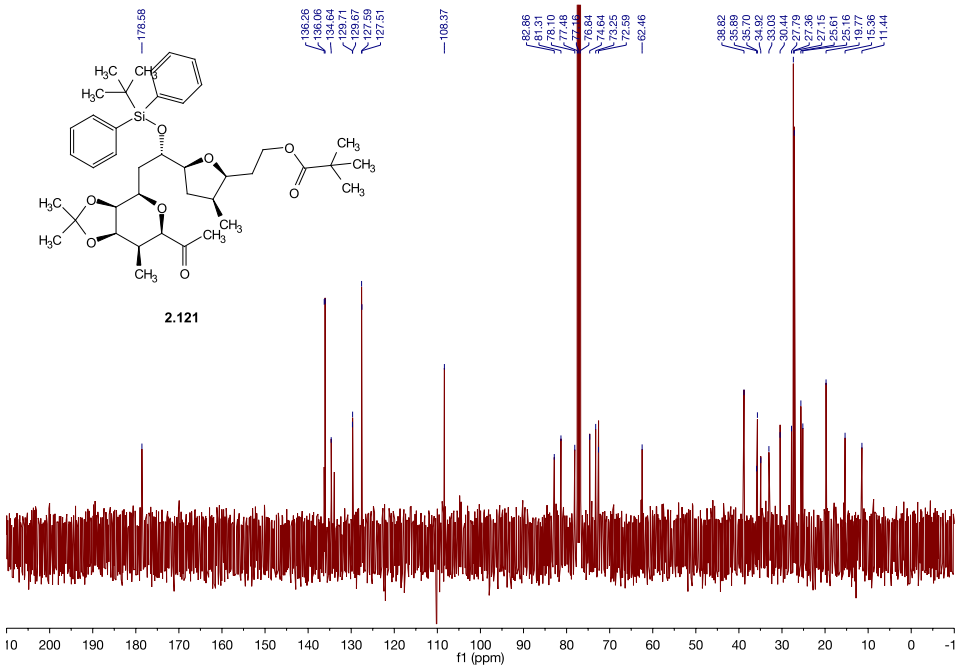
f1 (ppm)

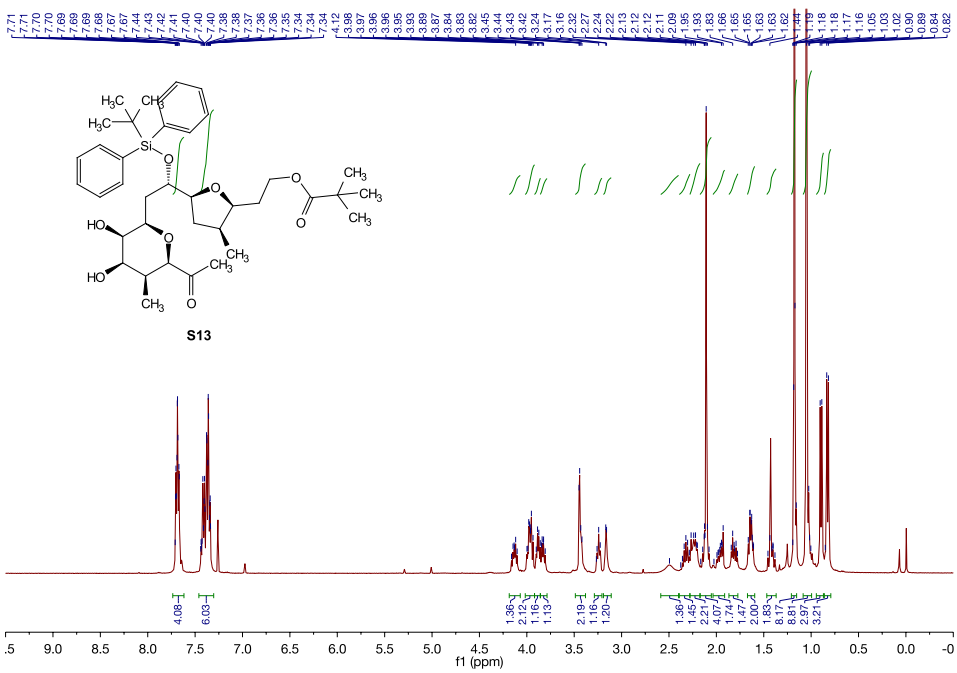

2.120
f1 (ppm)

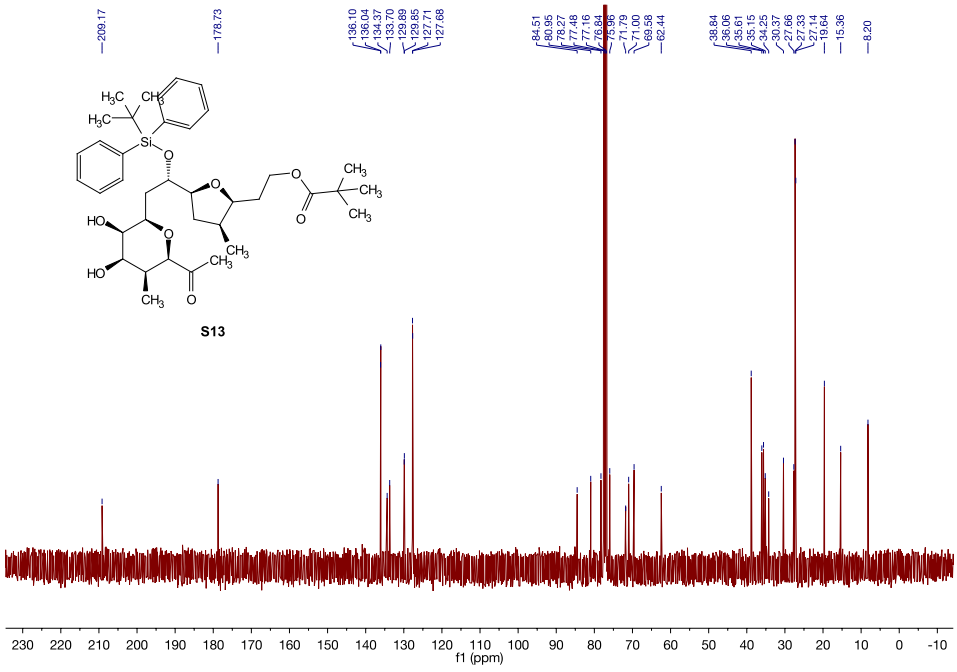

S12
f1 (ppm)

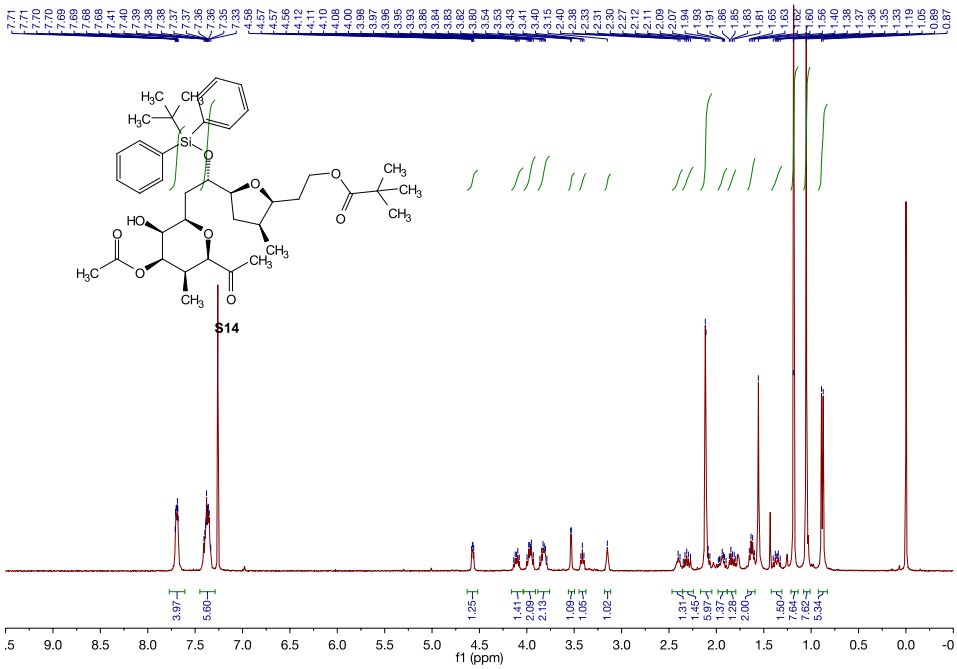

S12
f1 (ppm)

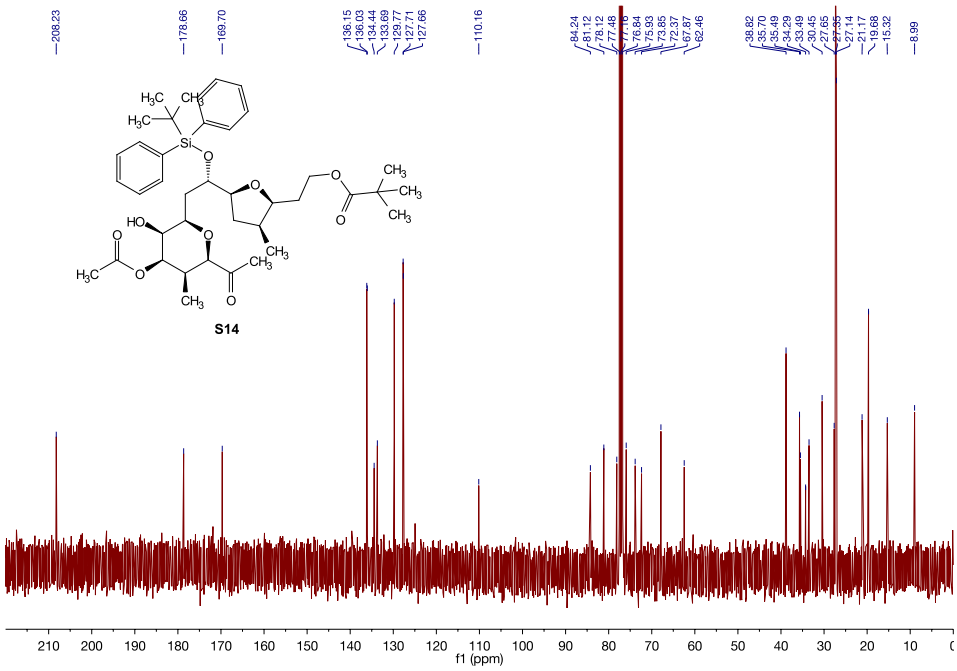

2.121
f1 (ppm)

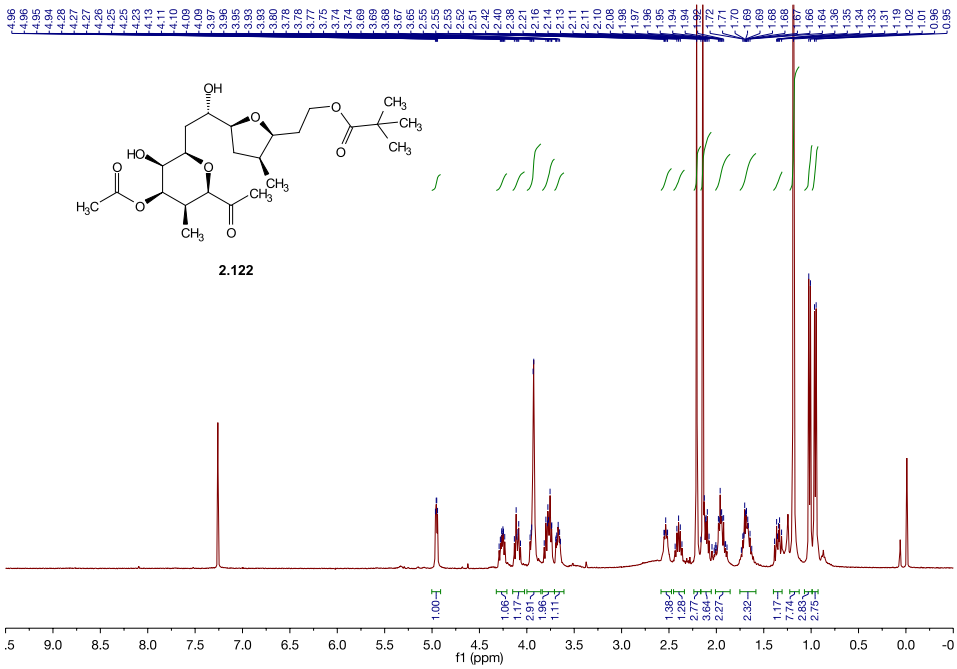

2.121
f1 (ppm)

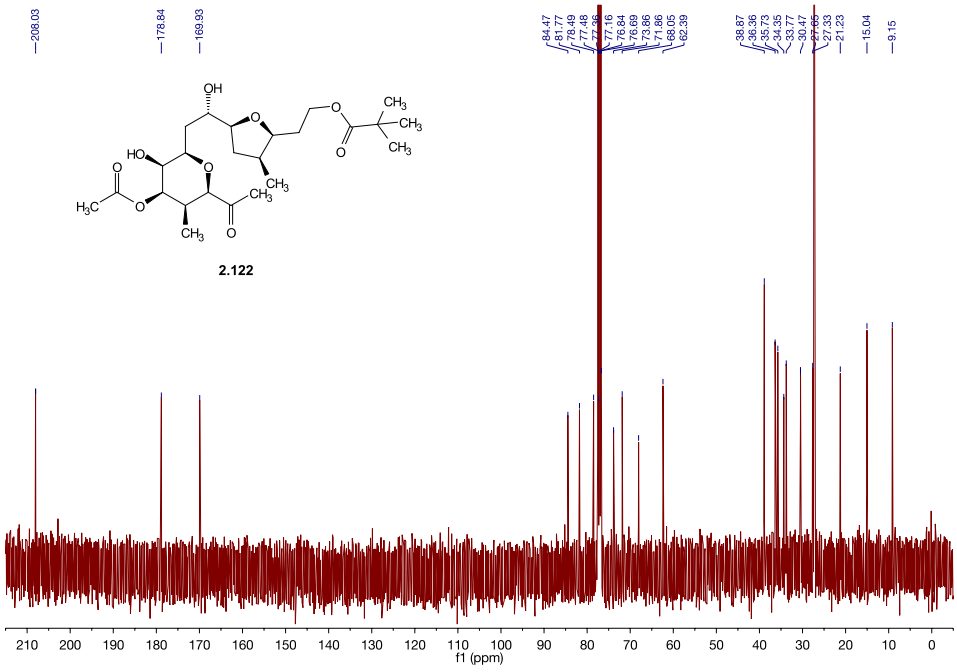

S13
f1 (ppm)


S13
f1 (ppm)


S14
f1 (ppm)


S14
f1 (ppm)


OH
HO
O
O
O
O
O
O
O
O
CH3
CH3
CH3
CH3
CH3
CH3
H3C
2.122
f1 (ppm)


208.03
178.84
169.93
OH
HO
O
O
O
O
O
O
O
O
CH3
CH3
CH3
CH3
CH3
CH3
H3C
2.122
f1 (ppm)