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Iron-catalyzed cross-coupling between *C*-bromo mannopyranoside derivatives and a vinyl Grignard reagent: toward the synthesis of the C31–C52 fragment of amphidinol 3

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ABSTRACT

A chemo- and diastereoselective iron-catalyzed cross-coupling between *C*-bromo mannopyranoside derivatives and 2-methyl-1-propenylmagnesium bromide was developed. This method was used as the key step for the synthesis of the mirror image of the C31–C40 and C43–C52 fragments of amphidinol 3 (AM3). These syntheses were achieved from a common *trans*-tetrahydropyran derived from D-mannose.

1. Introduction

Marine dinoflagellates are a rich source of natural products such as polyketides, amphidinolides, or cyclic polyethers.[1,2] Among dinoflagellates, the genus *Amphidinium klebsii* has been recognized as a source of bioactive secondary metabolites such as amphidinol 3 (AM3), which was isolated from a growth culture of *A. klebsii* in 1996.[3] Amphidinol 3 displays antifungal and hemolytic activities, and was revealed to be a stronger hemolytic agent against human erythrocytes than other well-known antibiotics such as amphotericin B and filipin III. Biological assays have indicated that amphidinol 3 exhibits different mechanisms than for amphotericin B and filipin III as pores or lesions in biomembranes are formed depending on dosage concentrations.[4] The structure of AM3 is characterized by a skipped polyenic chain, a long irregular polyhydroxy chain both connected by a fragment containing two tetrahydropyran rings (Scheme 1). The absolute configuration of the stereogenic centers was first established in 1996[5] but, in 2008, the C2-stereocenter was revised to be (*S*),[6] and more recently, the isolation of karlotoxins has entailed some doubts concerning the absolute configuration of the tetrahydropyran moieties. Indeed, the structure of karlotoxin 2 has been reported to incorporate a C39–C50 fragment similar to the C42–C52 fragment of AM3, but with opposite configurations (Scheme 1).[7] Even if a recent report from Murata et al. seems to support the initially proposed configurations for the C42–C52 fragment of AM3,[8] the stereochemistry of AM3 is not yet unambiguously established.

Owing to its interesting structural features as well as its potential antifungal and hemolytic activities related to its membrane-permeabilizing abilities, AM3 has stimulated the work of several organic synthetic chemists involved in total synthesis and an array of fragments has been prepared, but the total synthesis of AM3 has not been completed yet.[9]

Since 2002, our group has embarked on the synthesis of AM3.[10–14] In our retrosynthetic approach, we decided to disconnect AM3 at the C29–C30 bond, which would be built through a Suzuki-type cross-coupling reaction between a vinylic iodide and a *B*-alkyl boronate, and the C52–C53 bond would be installed through a Julia olefination between an aldehyde at C52 and a polyenic sulfone (Scheme 1). We have already reported the synthesis of various polyol fragments such as the C1–C14,[10] C18–C30,[11] and C17–C30[12] fragments. On the other hand, the C53–C67 polyenic fragment has also been synthesized.[13] Herein, we would like to report our synthetic effort toward the synthesis of the bis-tetrahydropyranic fragment C31–C52 using as the key step an iron-catalyzed cross-

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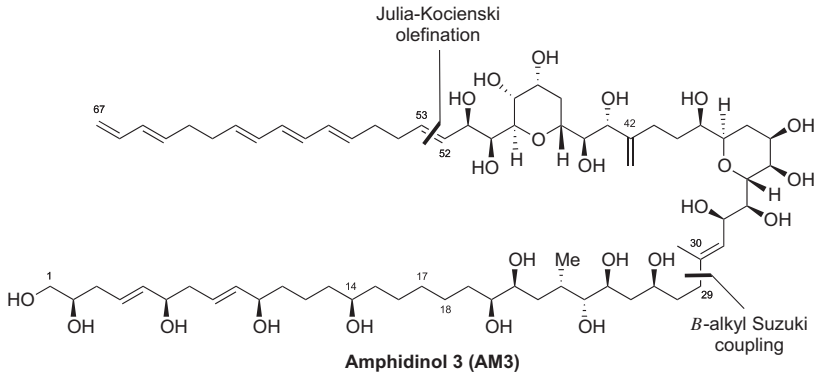
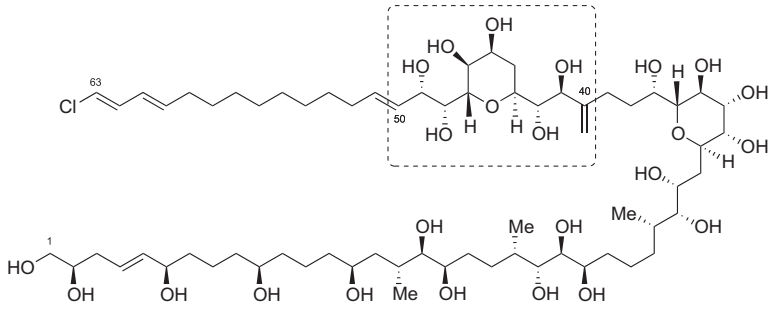
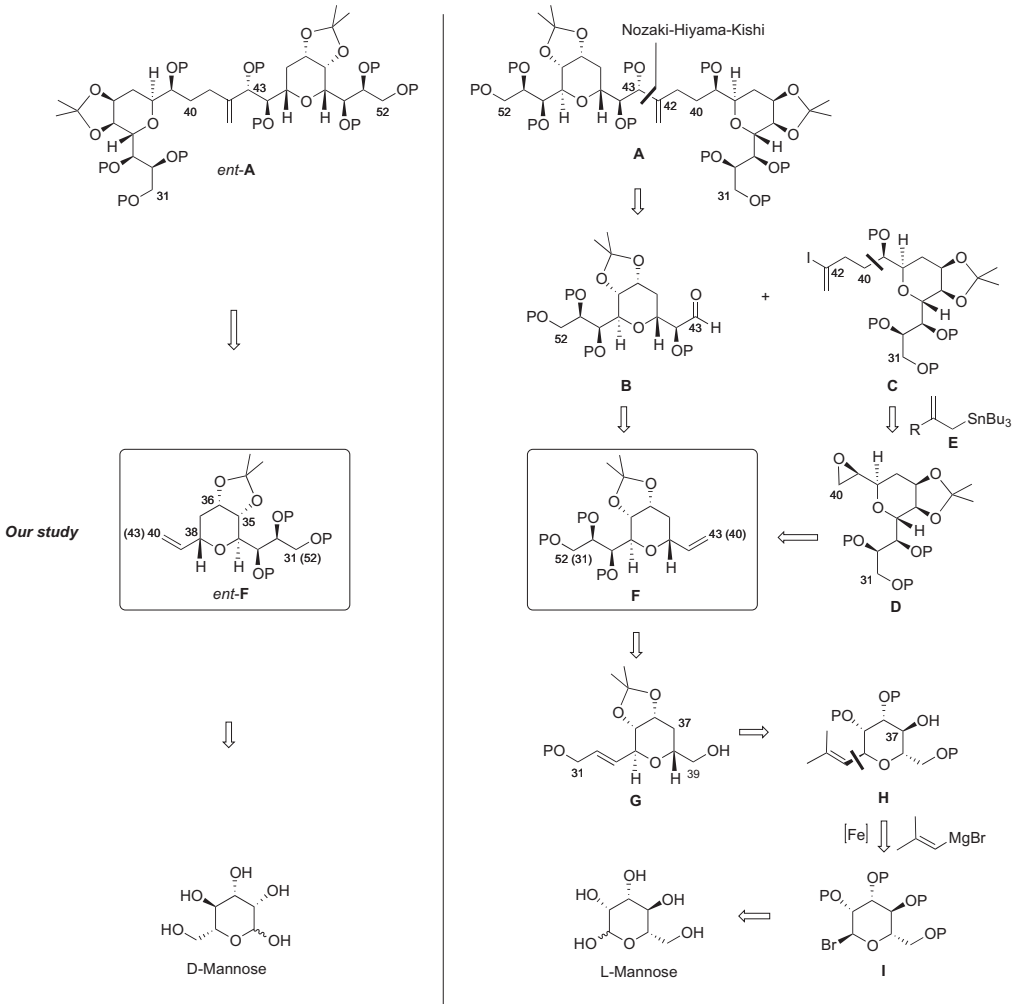


Amphidinol 3 (AM3)



Karlotoxin 2

Scheme 1.



Scheme 2.

coupling of a *C*-bromo mannopyranoside with a vinyl Grignard reagent to form the C33–C34 and C49–C50 bonds of the tetrahydropyrans.

In our approach, the C31–C52 fragment **A** would be the result of a Nozaki–Hiyama–Kishi coupling between aldehyde **B** and vinyl iodide **C** (Scheme 2). Vinyl iodide **C** would be obtained through the regioselective opening of epoxide **D** with allylstannane **E**. As fragments **B** and **D** feature seven stereocenters with identical configurations, they should be both prepared from the same tetrahydropyran **F**. Vinyl tetrahydropyran **F** would be obtained from **G** after aldehyde methylenation and diastereoselective dihydroxylation of the C32–C33 double bond, and **G** would be obtained after functional modifications of the trisubstituted olefin, deoxygenation at C37, and deprotection/oxidation of the alcohol at C39 in **H**. In contrast to the strategies developed by other groups, in the synthesis of the tetrahydropyran moieties, by forming either the tetrahydropyranyl C38–O or C34–O bond or the C35–C36 bond through a ring-closing metathesis, the construction of the tetrahydropyranyl core has been envisaged through a challenging iron-catalyzed cross-coupling between a vinyl Grignard and a *C*-halogeno mannopyranoside **I** derived from L-mannose, installing the C33–C34 bond as well as the C49–C50 bond (Scheme 2). Considering the high cost of L-mannose and the controversy about the absolute configuration of the C42–C52 fragment of AM3 compared to karlotoxin 2,[7,8] we decided to focus on the synthesis of *ent*-**A**, which would be accessible from *ent*-**F** starting from D-mannose (Scheme 2).

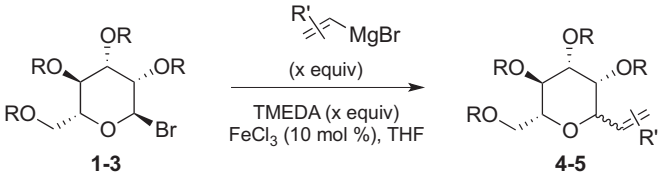
2. Results and discussion

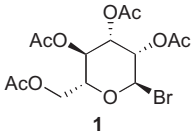
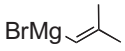
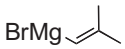
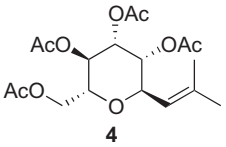
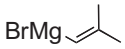
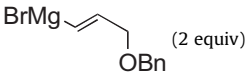
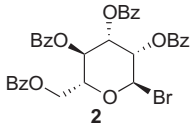
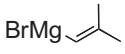
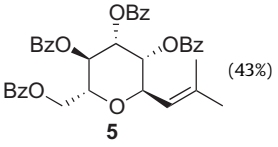
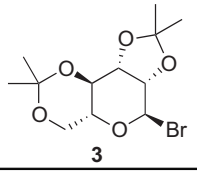
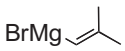
2.1. Iron-catalyzed cross-coupling

In 2007, we have reported an iron-catalyzed cross-coupling of primary and secondary alkyl halides with alkenyl Grignard reagents.[14,15] This cross-coupling, using $FeCl_3$ (5 mol %) and TMEDA (1.9 equiv) in THF, is chemoselective as it tolerates ethers, carbamates, and esters, and displays low level of β-H elimination.

In order to extend this method to the synthesis of *ent*-**H** from *ent*-**I** using Grignard reagents, we first prepared *C*-bromo mannopyranose derivatives **1**–**3**.[16] The optimization of the conditions of this cross-coupling is reported in Table 1. When the acetyl protected *C*-bromo mannopyranoside **1** in the presence of $FeCl_3$ (10 mol %), in

Table 1
Optimization of the iron-catalyzed cross-coupling of *C*-bromo sugars **1**–**3** and vinyl Grignard reagents



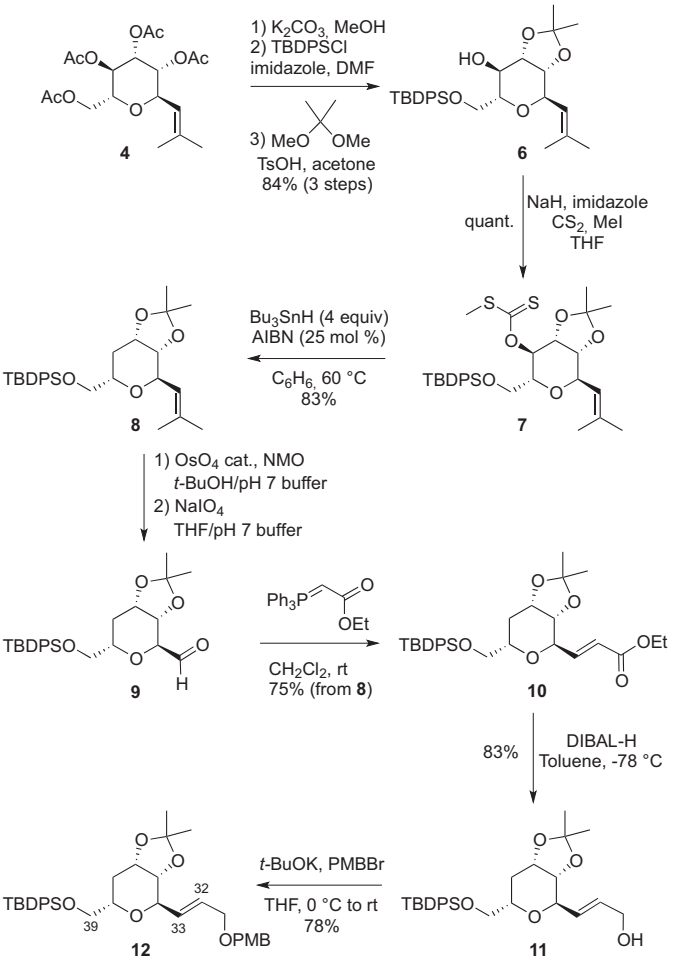
Entry	Substrate	Grignard	Conditions	Product (yield)
1	 **1**	 (2 equiv)	TMEDA (1.9 equiv) Addition rate 2.5 mmol h^{-1} 0 °C to rt	—
2	**1**	 (4 equiv)	TMEDA (3.8 equiv) Addition rate 200 mmol h^{-1} rt, 2.5 mmol scale	 **4** (40–65%)
3	**1**	 (2 equiv)	TMEDA (1.9 equiv) Addition rate 200 mmol h^{-1} rt, 50 mmol scale	**4** (72%)
4	**1**	 (2 equiv)	TMEDA (1.9 equiv) Addition rate 200 mmol h^{-1} rt	—
5	**1**	 (2 equiv)	TMEDA (1.9 equiv) Addition rate 200 mmol h^{-1} rt	—
6	 **2**	 (2 equiv)	TMEDA (1.9 equiv) Addition rate 200 mmol h^{-1} rt	 **5** (43%)
7	 **3**	 (2 equiv)	TMEDA (1.9 equiv) Addition rate 200 mmol h^{-1} rt	—

THF at 0 °C, was treated with a THF solution containing 2-methyl-1-propenylmagnesium bromide (2 equiv) and 1.9 equiv of TMEDA with an addition rate of 2.5 mmol h^{-1},[14] no cross-coupling was observed (Table 1, entry 1). When *C*-bromo mannopyranoside **1** in the presence of $FeCl_3$ (10 mol%) in THF at room temperature was treated with 2-methyl-propenylmagnesium bromide (4 equiv) and 3.8 equiv of TMEDA with an addition rate of 200 mmol h^{-1}, a full conversion of bromide **1** was observed and the desired cross-coupling product **4** was isolated in variable yields (40–65%) depending on the quality of the starting *C*-bromo mannopyranoside (Table 1, entry 2). Gratifyingly, on a larger scale (50 mmol of freshly prepared *C*-bromo mannopyranoside **1**), the cross-coupling was efficient with only 2 equiv of 2-methyl-propenylmagnesium bromide (addition rate of 200 mmol h^{-1}) and 1.9 equiv of TMEDA as it allows the isolation of the cross-coupling product **4** in 72% yield (Table 1, entry 3). This cross-coupling is chemoselective as it tolerates acetate groups on the substrate, and diastereoselective as only the *trans*-tetrahydropyran **4** was obtained (dr>9:1, the *trans*-relationship was confirmed by NOE studies).[17] At this stage, we were interested to know if vinylmagnesium bromide (Table 1, entry 4) or a functionalized Grignard reagent (Table 1, entry 5) could be involved in this cross-coupling. Unfortunately, the cross-coupling of **1** with these Grignard reagents produced mixture of compounds with no traces of the desired products (Table 1, entries 4 and 5). Different protecting groups of the *C*-bromo mannopyranoside were investigated (Table 1, entries 6 and 7). When the benzoyl protected *C*-bromo mannopyranoside **2** was involved in the cross-coupling with 2-methyl-1-propenylmagnesium bromide, the expected *trans*-tetrahydropyran **5** was diastereoselectively obtained (dr>9:1) and isolated in 43% yield (Table 1, entry 6), whereas the acetonide protected *C*-bromo mannopyranoside **3** was unable to deliver the corresponding cross-coupling product as only decomposition of the starting material was observed (Table 1, entry 7).

Considering the observed α-diastereoselectivity of the cross-coupling, leading to the *trans*-tetrahydropyran, one can suppose that an anomeric radical intermediate is formed during the oxidative addition of the low-valent iron species on the C–Br bond of the electrophile.[14,18] These results are in agreement with our recently reported diastereoselective cobalt-catalyzed cross-coupling of *C*-bromo glycosides with aryl and vinyl Grignard reagents processing with an α-selectivity due to the formation of an anomeric radical intermediate.[19]

2.2. Synthetic approach toward the C31–C52 fragment (*ent*-A)

Having obtained **4**, featuring four of the six stereocenters in *ent*-**F**, the C37 position had to be deoxygenated. Methanolysis of the acetate groups in **4**, followed by selective protection of the primary alcohol at C39 as a TBDPS ether delivered a triol, which was directly treated with 2,2-dimethoxypropane in acetone to provide the secondary alcohol **6**. The resulting tetrahydropyran **6** was deoxygenated under the Barton–McCombie conditions.[20] The secondary alcohol in **6** was first transformed to a xanthate (NaH, imidazole, CS_2, MeI) leading quantitatively to **7**, which was treated with Bu_3SnH (4 equiv) in the presence of AIBN (0.25 mol %) in benzene at 60 °C, providing the deoxygenated product **8** in 83% yield. At this stage, the C32–C33 double bond had to be transformed to generate the C32 and C33 stereogenic carbinols. As olefin **8** appeared to be unreactive with ethyl acrylate under cross-metathesis conditions (Hoveyda–Grubbs II cat., CH_2Cl_2, reflux), the double bond was oxidatively cleaved in two steps (OsO_4, NMO, then $NaIO_4$) providing aldehyde **9**, which was directly treated with (carbethoxymethylene)triphenylphosphorane to yield the α,β-unsaturated ester **10** in 75% yield (from **8**, three steps). Reduction of ester **10** with DIBAL-H delivered allylic alcohol **11** (83% yield), which was then protected as a PMB ether (*t*-BuOK, PMBBr, THF, 0 °C to rt) providing **12** in 78% yield (Scheme 3).

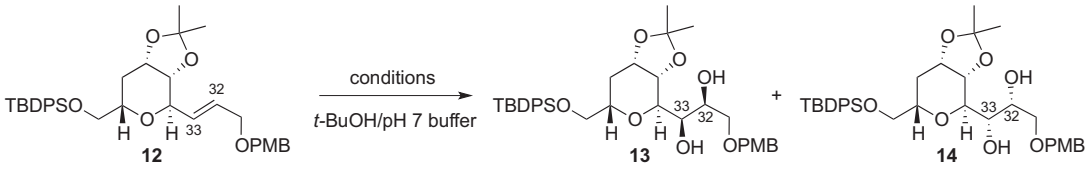


Scheme 3.

In order to install the C32 and C33 stereogenic centers, a Sharpless asymmetric cis-dihydroxylation of the C32–C33 double bond in **12** was envisaged.[21] Because of diastereoselectivity issues, the dihydroxylation was realized with OsO_4/NMO, AD-mix-β, and AD-mix-α. The latter reagent should theoretically give the expected stereoisomer through the dihydroxylation of the α-face of the olefin. The results are highlighted in Table 2. The dihydroxylation of **12** with OsO_4/NMO provided a 1:1 mixture of the two diastereoisomers **13** and **14** with a global yield of 71%, without any diastereoselectivity in the absence of any chiral ligand (Table 2, entry 1). When the asymmetric dihydroxylation was achieved using AD-mix-β, in the presence of methanesulfonamide, with reinforced conditions in ligand $(DHQD)_2PHAL$ and osmium reagent ($K_2OsO_4 \cdot 2H_2O$), a 1:9 mixture of **13** and **14** was obtained in favor of the undesired diastereomer **14** with a 75% global yield (Table 2, entry 2) whereas AD-mix-α, in the presence of methanesulfonamide, with reinforced conditions in ligand $(DHQ)_2PHAL$ and osmium reagent ($K_2OsO_4 \cdot 2H_2O$), afforded a 9:1 mixture of the two diastereoisomers **13** and **14** in favor of the desired isomer **13** (71% yield) (Table 2, entry 3).[22b,c] With these results in hand, we can conclude that no match/mismatch effect is existing in the Sharpless dihydroxylation of **12**.

The synthesis of vinyl tetrahydropyran **18**, which is a synthetic equivalent of *ent*-**F**, was then completed in four steps from **13**

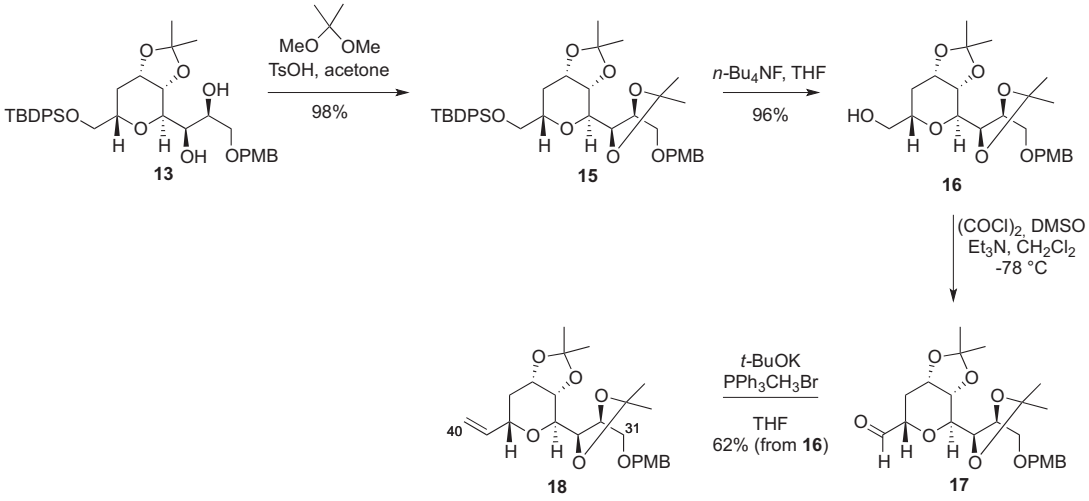
Table 2
Stereoselective dihydroxylation of olefin **12**



Entry	Conditions	Yield (%)	**13**/**14**
1	OsO_4 cat., NMO	71	1:1
2	AD-mix-β, $MeSO_2NH_2$ $(DHQD)_2PHAL$, $K_2OsO_4\cdot 2H_2O$	75	1:9
3	AD-mix-α, $MeSO_2NH_2$ $(DHQ)_2PHAL$, $K_2OsO_4\cdot 2H_2O$	71	9:1

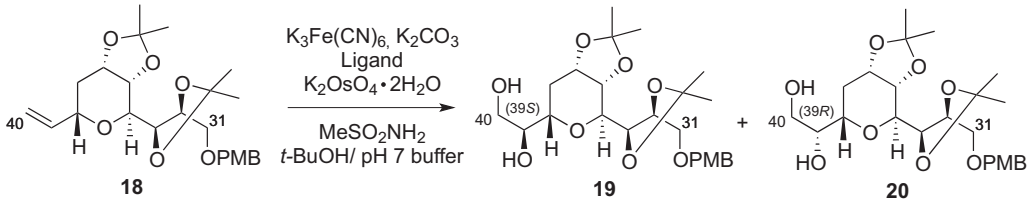
(Scheme 4). Diol **13** was protected as an acetonide (2,2-dimethoxypropane, TsOH, acetone, 98%) delivering **15**; the TBDPS ether was cleaved using *n*-Bu_4NF and the obtained primary alcohol **16** (96%) was oxidized to aldehyde **17** (Swern oxidation) and, after methylenation with methylenetriphenylphosphorane, **18** was isolated in 62% yield (for the two steps). To summarize, the common fragment **18**, required to access the two tetrahydropyran moieties of *ent*-**A**, was obtained in 18 steps from D-mannose with an overall yield of 10%.

Starting from **18**, the synthesis of the mirror image of the C31–C42 fragment of AM3 (*ent*-**C**), requires the introduction of the C39 oxygenated stereocenter. To achieve the challenging asymmetric Sharpless dihydroxylation of the terminal olefin in **18**, a systematic study was realized varying the ligand required for the Sharpless dihydroxylation. The results are reported in Table 3. When $(DHQ)_2PHAL$ (AD-mix-α) (Table 3, entry 1) and $(DHQD)_2PHAL$ (AD-mix-β) (Table 3, entry 2) were used, the same undesired epimer **20**, possessing the (*R*)-configuration at C39, was obtained with a **19**/**20** ratio of 20:80 and 30:70, respectively. When $(DHQD)_2AQN$ was used as the ligand (Table 3, entry 3), the same diastereoselectivity was observed with a 30:70 ratio of **19**/**20**. We were pleased to observe that the use of $(DHQD)_2PYR$ (Table 3, entry



Scheme 4.

Table 3
Asymmetric dihydroxylation of terminal olefin **18**



Entry	Ligand	Yield	**19**/**20**
1	$(DHQ)_2PHAL$	—	20:80
2	$(DHQD)_2PHAL$	—	30:70
3	$(DHQD)_2AQN$	—	30:70
4	$(DHQD)_2PYR$	Quant.	65:35

Table 4
^{1}H NMR analysis (400 MHz, $CDCl_3$) of the two methoxyphenyl esters **26** and **27**

	δ^R of **26**	δ^S of **27**	$\Delta\delta^{RS}=\delta^R-\delta^S$
H_{36}	4.30	4.22	0.08
H_{37}	1.98	1.90	0.08
$H_{37'}$	1.65	1.59	0.06
H_{38}	4.17	4.09	0.08
H_{40}	3.69	3.86	−0.17
$H_{(t\text{-Bu})}$	0.96	1.04	−0.08

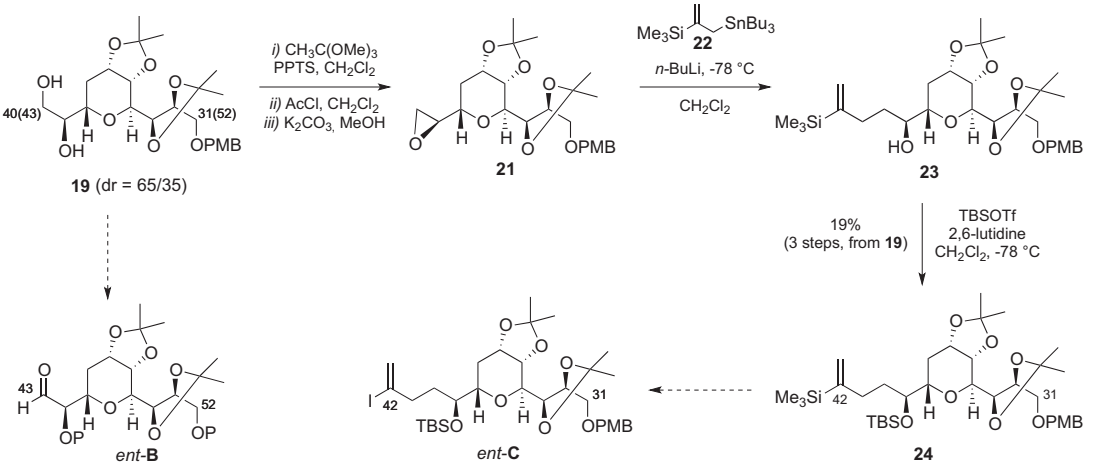
4) led to the opposite diastereoselectivity as **19**, possessing the (*S*)-configuration at C39, was obtained as the major product however with a diastereomeric ratio **19**/**20** of 65:35. Unfortunately, these epimers could not be separated by chromatography. It is worth pointing out that the (*S*)- and (*R*)-configurations at C39 in **19** and **20** were, respectively, determined by synthesizing the corresponding methoxyphenylacetic esters and by analyzing their ^{1}H NMR spectra (Table 4).[22,23]

The 65:35 mixture of **19** and **20** was then transformed to the corresponding epoxides in a one-pot three-step procedure ($CH_3C(OMe)_3$, PPTS; then AcCl; then K_2CO_3, MeOH) and epoxide **21** was separated from its epimer at C39 by silica gel chromatography (Scheme 5). The ring-opening of epoxide **21** was realized with the lithiated anion of allylstannane **22**, leading to vinylsilane **23** that was finally protected as a TBS ether (TBSOTf, 2,6-lutidine, 19% from **19**). Vinylsilane **24**, the enantiomer of the C31–C42 fragment of AM3, and the precursor of vinyl iodide *ent*-**C**, was finally synthesized in six steps from **18** in 15% yield. We have to point out that compound **19** should also be the precursor of the mirror image of the C43–C52 fragment of AM3, and should be transformed in four steps in *ent*-**B**.

3. Experimental

3.1. General remarks

Infrared (IR) spectra were recorded on a Bruker TENSOR TM 27 (IRFT), wave numbers are indicated in cm^{-1}. NMR spectra were recorded on a Bruker AVANCE 400. ^{1}H NMR spectra were recorded at 400 MHz and data are reported as follows: chemical shift in parts per million (ppm) from tetramethylsilane as an internal standard with the residual solvent peak as an internal indicator ($CDCl_3$ δ: 7.26 ppm), multiplicity (s=singlet, d=doublet, t=triplet, q=quartet, sept=septuplet, m=multiplet or overlap of non-equivalent resonances, br=broad), integration. ^{13}C NMR spectra were recorded at 100 MHz and the data are reported as follows: chemical shift in parts per million from tetramethylsilane as an internal standard with the residual solvent peak as an internal indicator ($CDCl_3$ δ: 77.1), multiplicity (s=C, d=CH, t=CH_2, q=CH_3). THF was dried over Na/benzophenone prior to distillation or using a MBraun MB SPS-800 solvent, purification system. TMEDA was dried over CaH_2 prior to distillation. All commercially obtained chemicals were used as received without further purification. TLC was performed on silica gel plates visualized either with a UV lamp (254 nm), or using solution of *p*-anisaldehyde–sulfuric acid–acetic acid in EtOH followed by heating. Purification was performed on silica gel (Merck-Kieselgel 60, 230–400 mesh). Chromatography solvents used were ethyl acetate (EtOAc), and low-boiling petroleum ether (PE) (40–60 °C). Mass spectra with electronic impact (MS-EI) were recorded on a GC/MS (70 eV). HRMS were performed at the Laboratoire de Spectrométrie de Masse SM3E de l'Université Pierre et Marie Curie de Paris.



Scheme 5.

2.3. Conclusion

We have developed a chemoselective and diastereoselective iron-catalyzed cross-coupling between *C*-bromo mannopyranoside derivatives and a vinyl Grignard reagent, providing *trans*-tetrahydropyrans. Using this method, a common precursor to both tetrahydropyrans embedded in AM3 was obtained starting from D-mannose and used in the synthesis of the mirror image of the C31–C42 and C43–C52 fragments of amphidinol 3. These two tetrahydropyrans incorporate 14 of the 15 stereocenters present in the C31–C52 fragments of AM3.

3.2. Synthesis of vinylsilane 24

3.2.1. 1,2,3,4,6-Penta-O-acetyl-α-D-mannopyranose.[16a] To a solution of D-mannose (21.6 g, 120.0 mmol, 1.0 equiv) in acetic anhydride (62.3 mL, 660.0 mmol, 5.5 equiv) at 0 °C were added DMAP (1.46 g, 12.0 mmol, 10 mol %) and pyridine (240 mL) and the mixture was allowed to warm to room temperature. The solution was stirred for 3 h and the reaction was quenched by addition of a 10% aqueous solution of $CuSO_4$ (250 mL) and Et_2O (250 mL). The two phases were separated and the organic layer was washed with a 10% aqueous solution of $CuSO_4$ (5×150 mL) in order to remove pyridine.

The organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure to afford 1,2,3,4,6-penta-*O*-acetyl-α-D-mannopyranose (46.5 g, quant.) as a white waxy solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.07 (d, *J*=1.8 Hz, 1H), 5.34–5.32 (m, 2H), 5.25–5.24 (m, 1H), 4.27 (dd, *J*=12.4, 4.9 Hz, 1H), 4.08 (dd, *J*=12.4, 2.5 Hz), 4.06–4.00 (m, 1H), 2.16 (s, 3H) 2.16 (s, 3H), 2.08 (s, 3H), 2.04 (s, 3H), 1.99 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.8 (s), 170.1 (s), 169.9 (s), 169.6 (s), 168.2 (s), 90.7 (d), 70.7 (d), 68.8 (d), 68.4 (d), 65.6 (d), 62.2 (t), 21.0 (q), 209.0 (q), 20.8 (3q).

*3.2.2. 2,3,4,6-Tetra-O-acetyl-α-D-mannopyranosyl bromide (**1**).*[16b] To a solution of 1,2,3,4,6-penta-*O*-acetyl-α-D-mannopyranose (9.98 g, 25.6 mmol, 1.0 equiv) in CH_2Cl_2 (120 mL) at 0 °C was added slowly a solution of HBr (150 mL, 33 wt % in acetic acid) and the solution was allowed to warm up to room temperature. The solution was then stirred for 3 h and diluted with water (100 mL). The two phases were separated and the aqueous layer was extracted with CH_2Cl_2 (3×75 mL). The combined organic layers were washed with a saturated aqueous solution of $NaHCO_3$ (with care, very exothermic) until neutral pH, and then with brine (50 mL). The organic layer was then dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel (PE/EtOAc: 6:4) to afford the brominated compound **1** (10.50 g, quant.) as a yellow waxy solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.28 (d, *J*=1.6 Hz, 1H), 5.70 (dd, *J*=10.2, 3.4 Hz, 1H), 5.43 (dd, *J*=3.4, 1.6 Hz, 1H), 5.35 (t, *J*=10.2 Hz, 1H), 4.31 (dd, *J*=12.6, 5.0 Hz, 1H), 4.21 (ddd, *J*=10.2, 5.0, 2.3 Hz, 1H), 4.12 (dd, *J*=12.6, 2.3 Hz, 1H), 2.16 (s, 3H), 2.09 (s, 3H), 2.06 (s, 3H), 1.99 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.6 (s), 169.8 (s), 169.7 (2s), 83.2 (d), 72.9 (d), 72.2 (d), 68.0 (d), 65.4 (d), 61.6 (t), 20.9 (q), 20.8 (2q), 20.7 (q).

*3.2.3. (2R,3R,4R,5R,6R)-2-(Acetoxymethyl)-6-(2-methylprop-1-en-1-yl)tetrahydro-2H-pyran-3,4,5-triyl triacetate (**4**).* A freshly prepared solution of $FeCl_3$ (0.1 M in THF, 25.0 mL, 2.50 mmol, 0.1 equiv) was mixed with **1** (10.275 g, 25.0 mmol, 1.0 equiv). To this solution was added dropwise via a syringe pump (200 mmol h^{-1}; 400 mL h^{-1}) at room temperature, a mixture of commercially available 2-methyl-1-propenylmagnesium bromide (0.5 M in THF, 100.0 mL, 50.0 mmol, 2.0 equiv) and TMEDA (7.11 mL, 47.5 mmol, 1.9 equiv). The mixture was then stirred at room temperature for 1 h and quenched by the addition of a saturated aqueous solution of NH_4Cl (100 mL) and a 0.5 M aqueous solution of HCl (10 mL) in order to dissolve the magnesium salts. The mixture was filtered on Celite®, the two phases were separated and the aqueous layer was extracted with CH_2Cl_2 (2×50 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel (PE/EtOAc: 7:3–6:4) to afford the coupling product **2** (6.96 g, 72%) as a colorless oil. $[\alpha]_D^{20}$ +25.5 (*c* 1.00, $CHCl_3$); IR (neat): 2973, 2944, 1741, 1668, 1437, 1368, 1218, 1116, 1045 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.35 (dsept, *J*=7.0, 1.4 Hz, 1H), 5.31–5.22 (m, 2H), 5.18–5.16 (m, 1H), 4.67 (br d, *J*=7.0 Hz, 1H), 4.27 (dd, *J*=12.3, 5.5 Hz, 1H), 4.04 (dd, *J*=12.3, 2.6 Hz, 1H), 3.89 (ddd, *J*=9.4, 5.5, 2.6 Hz, 1H), 2.14 (s, 3H), 2.08 (s, 3H), 2.02 (s, 3H), 2.00 (s, 3H), 1.79 (s, 3H), 1.73 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.9 (s), 170.6 (s), 170.3 (s), 169.8 (s), 143.1 (s), 116.8 (d), 73.1 (d), 71.7 (d), 70.3 (d), 69.5 (d), 67.0 (d), 63.0 (t), 26.2 (q), 21.2 (q), 20.9 (3q), 18.8 (q); MS (EI) *m*/*z*: 284 (1), 206 (17), 193 (45), 164 (21), 151 (100), 139 (29), 111 (14), 98 (20), 97 (28), 85 (46), 83 (19), 81 (22), 69 (20), 55 (13); HRMS (ESI): *m*/*z* calcd for $C_{18}H_{26}NaO_9$ $[M+Na]^+$ 409.1469, found 409.1464.

*3.2.4. (3aR,4R,6R,7R,7aS)-6-((tert-Butyldiphenylsilyloxy)methyl)-2,2-dimethyl-4-(2-methyl-prop-1-en-1-yl)tetrahydro-3aH-[1,3]dioxolo[4,5-c]pyran-7-ol (**6**).* To a solution of **4** (386 mg, 1.0 mmol, 1.0 equiv) in MeOH (8.5 mL) was added K_2CO_3 (35 mg, 0.25 mmol, 0.25 equiv) and the solution was stirred overnight at room temperature. The solvent was then removed under reduced pressure, the crude product was diluted with acetonitrile, and the solvents were co-evaporated again; this procedure was repeated thrice to remove all traces of methanol. The obtained tetraol ((2*R*,3*S*,4*R*,5*S*,6*R*)-2-(hydroxymethyl)-6-(2-methylprop-1-en-1-yl) tetrahydro-2*H*-pyran-3,4,5-triol) was directly engaged in the next step without further purification.

To a solution of this tetraol (1.0 mmol, 1.0 equiv) in DMF (5 mL) at 0 °C were added imidazole (143 mg, 2.1 mmol, 2.1 equiv) and, dropwise, TBDPSCl (272 μL, 1.05 mmol, 1.05 equiv). The solution was warmed to room temperature, stirred for 5 h, and a saturated aqueous solution of $NaHCO_3$ (5 mL) was added. The two phases were separated and the aqueous layer was extracted with EtOAc (3×10 mL). The combined organic layers were washed with water (2×5 mL) and brine (2×5 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude triol ((2*R*,3*S*,4*R*,5*S*,6*R*)-2-(2-methylprop-1-en-1-yl)-6-((*tert*-butyldiphenylsilyloxy)methyl)tetrahydro-2*H*-pyran-3,4,5-triol) was directly engaged in the next step without any further purification.

To a solution of the obtained triol (1.0 mmol, 1.0 equiv) in acetone (10 mL) at 0 °C, were added 2,2-dimethoxypropane (370 μL, 3.0 mmol, 3.0 equiv) and TsOH (35 mg, 0.2 mmol, 0.2 equiv). The mixture was allowed to warm to room temperature over 1 h and then stirred for 3 h at room temperature. Et_3N (100 μL) was added, and the solvent was removed under reduced pressure. The mixture was diluted with water (10 mL) and the solution was extracted with EtOAc (3×10 mL). The combined organic layers were washed with brine (10 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure to afford alcohol **6** (418 mg, 84% over three steps) as a colorless oil. $[\alpha]_D^{20}$ +7.9 (*c* 1.55, $CHCl_3$); IR (neat) 3448, 2931, 2857, 2361, 1668, 1589, 1472, 1428, 1380, 1243, 1217, 1111, 1067 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71–7.65 (m, 4H, H_{ar}), 7.46–7.34 (m, 6H, H_{ar}), 5.21 (dsept, *J*=8.0, 1.4 Hz, 1H), 4.53 (dd, *J*=8.0, 5.8 Hz, 1H), 4.17 (dd, *J*=7.8, 6.9 Hz, 1H), 4.12–4.07 (m, 2H), 3.89 (dd, *J*=10.6, 4.3 Hz, 1H), 3.85 (dd, *J*=10.6, 5.3 Hz, 1H), 3.53 (ddd, *J*=9.5, 5.3, 4.3 Hz, 1H), 2.79 (d, *J*=2.8 Hz, 1H, OH), 1.77 (d, *J*=1.4 Hz, 3H), 1.67 (d, *J*=1.4 Hz, 3H), 1.53 (s, 3H), 1.37 (s, 3H), 1.07 (s, 9H, Si–C(CH_3)$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.4 (s), 135.8 (2d), 135.7 (2d), 133.0 (s), 132.9 (s), 130.1 (d), 130.0 (d), 128.0 (2d), 127.9 (2d), 121.9 (d), 109.7 (s), 78.4 (d), 77.4 (d), 72.7 (d), 71.6 (d), 70.4 (d), 65.6 (t), 27.8 (q), 27.0 (3q, Si–C(CH_3)$_3$), 26.2 (q), 25.6 (q), 19.3 (s, Si–*C*(CH_3)$_3$), 18.8 (q); MS (EI) *m*/*z* 381 (2), 303 (12), 241 ($[M-OTBDPS]^+$, 15), 199 (34), 181 (17), 163 (31), 139 (41), 135 (30), 123 (15), 121 (14), 111 (28), 105 (13), 97 (37), 95 (19), 93 (14), 91 (20), 85 (31), 83 (21), 81 (23), 79 (26), 77 ($[Ph]^+$, 21), 69 (100), 67 (12), 59 (34), 57 ($[t\text{-}Bu]^+$, 29), 55 (31), 53 (15); HRMS (ESI): *m*/*z* calcd for $C_{29}H_{40}NaO_5Si$ $[M+Na]^+$ 519.2537, found: 519.2532.

*3.2.5. O-((3aR,4R,6R,7R,7aR)-6-((tert-Butyldiphenylsilyloxy)methyl)-2,2-dimethyl-4-(2-methylprop-1-en-1-yl)tetrahydro-3aH-[1,3]dioxolo[4,5-c]pyran-7-yl)-S-methyl carbonodithioate (**7**).* To a solution of alcohol **6** (824 mg, 1.66 mmol, 1.0 equiv) in THF (30 mL) at 0 °C were added NaH (60% in oil, 332 mg, 8.31 mmol, 5.0 equiv) and imidazole (45 mg, 0.66 mmol, 0.4 equiv). The mixture was warmed to room temperature and after 15 min, CS_2 (971 μL, 16.61 mmol, 10.0 equiv) was added. The solution was stirred at room temperature for 30 min and then iodomethane (310 μL, 4.98 mmol, 3.0 equiv) was added. After 10 min, a saturated aqueous solution of NaCl (20 mL) was added, the two phases were separated and the aqueous layer was extracted with Et_2O (3×20 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel (PE/Et_2O: 9:1–7:3) to afford xanthate **7** (946 mg, 97%)

as a yellow oil. $[\alpha]_D^{20}$ +13.6 (*c* 0.65, $CHCl_3$); IR (neat) 3424, 2955, 2927, 2856, 1718, 1463, 1428, 1362, 1253, 1211, 1158, 1114, 1062, 1104, 1006 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.71–7.64 (m, 4H, H_{ar}), 7.43–7.32 (m, 6H, H_{ar}), 6.19 (dd, *J*=7.2, 6.1 Hz, 1H), 5.28 (dsept, *J*=8.0, 1.4 Hz, 1H), 4.62 (dd, *J*=8.0, 4.9 Hz, 1H), 4.37 (t_{app}, *J*=5.9 Hz, 1H), 4.10 (dd, *J*=5.8, 4.9 Hz, 1H), 3.89–3.73 (m, 3H), 2.55 (s, 3H), 1.78 (d, *J*=1.4 Hz, 3H), 1.69 (d, *J*=1.4 Hz, 3H), 1.52 (s, 3H), 1.36 (s, 3H), 1.03 (s, 9H, Si–C(CH_3)$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 215.4 (s), 140.8 (s), 135.9 (2d), 135.8 (2d), 133.5 (s), 133.4 (s), 129.7 (2d), 127.8 (2d), 127.7 (2d), 121.5 (d), 109.9 (s), 78.0 (d), 77.1 (d), 75.4 (d), 73.0 (d), 69.7 (d), 62.8 (t), 27.8 (q), 26.9 (3q, Si–C(CH_3)$_3$), 26.3 (q), 26.1 (q), 19.5 (q), 19.4 (s, Si–*C*(CH_3)$_3$), 18.9 (q); MS (EI) *m*/*z* 371 (1), 289 (10), 200 (19), 199 (100), 157 (12), 147 (51), 133 (15), 131 (45), 89 (11), 79 (12), 78 (16), 77 ($[Ph]^+$, 31), 75 (23), 73 (82), 59 (14), 57 ($[t\text{-}Bu]^+$, 18); HRMS (ESI) *m*/*z* calcd for $C_{31}H_{42}NaO_5S_2Si$ $[M+Na]^+$ 609.2159, found 609.2165.

*3.2.6. tert-Butyl(((3aS,4R,6S,7aS)-2,2-dimethyl-4-(2-methylprop-1-en-1-yl)tetrahydro-3aH-[1,3]dioxolo[4,5-c]pyran-6-yl)methoxy)diphenylsilane (**8**).* To a solution of xanthate **7** (120 mg, 0.20 mmol, 1.0 equiv) in benzene (1 mL) at 60 °C were added AIBN (8.5 mg, 0.05 mmol, 0.25 equiv) and Bu_3SnH (220 μL, 0.82 mmol, 4 equiv). The solution was stirred at reflux for 2.5 h and was then cooled to room temperature. The solvent was removed under reduced pressure and the crude oil was purified by flash chromatography on silica gel (PE/Et_2O: 9:1) to afford **8** (80 mg, 83%) as a colorless oil. $[\alpha]_D^{20}$ +18.9 (*c* 0.70, $CHCl_3$); IR (neat) 2961, 2931, 1589, 1462, 1428, 1379, 1240, 1210, 1160, 1111, 1052 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.69–7.64 (m, 4H, H_{ar}), 7.44–7.34 (m, 6H, H_{ar}), 5.19 (dsept, *J*=8.1, 1.4 Hz, 1H), 4.43 (t_{app}, *J*=7.8 Hz, 1H), 4.39 (dt, *J*=9.4, 6.6 Hz, 1H), 3.93 (dd, *J*=7.5, 6.6 Hz), 3.82–3.67 (m, 3H), 2.13 (ddd, *J*=13.6, 6.4, 3.9 Hz, 1H), 1.95 (ddd, *J*=13.6, 10.5, 9.4 Hz, 1H), 1.77 (d, *J*=1.4 Hz, 3H), 1.68 (d, *J*=1.4 Hz, 3H), 1.47 (s, 3H), 1.35 (s, 3H), 1.05 (s, 9H, Si–C(CH_3)$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.6 (s), 135.8 (4d), 133.6 (2s), 129.8 (2d), 127.8 (4d), 122.8 (d), 108.7 (s), 76.8 (d), 71.9 (d), 70.6 (d), 69.4 (d), 66.5 (t), 29.6 (t), 27.8 (q), 27.0 (3q, Si–C(CH_3)$_3$), 26.3 (q), 25.4 (q), 19.4 (s, Si–*C*(CH_3)$_3$), 18.9 (q); MS (EI) *m*/*z* 465 ($[M-Me]^+$, 1), 365 (21), 287 (12), 241 ($[M-TBDPS]^+$, 35), 225 ($[M-OTBDPS]^+$, 16), 199 (24), 197 (11), 183 (18), 181 (12), 163 (24), 140 (11), 139 (100), 135 (40), 123 (22), 121 (23), 111 (23), 105 (16), 97 (52), 95 (16), 93 (12), 91 (11), 83 (12), 81 (23), 79 (22), 77 ($[Ph]^+$, 10), 69 (39), 55 (14); HRMS (ESI) *m*/*z* calcd for $C_{29}H_{40}NaO_4Si$ $[M+Na]^+$ 503.2588, found 503.2579.

*3.2.7. (E)-Ethyl 3-((3aS,4R,6S,7aS)-6-((tert-butyldiphenylsilyloxy) methyl)-2,2-dimethyl-tetrahydro-3aH-[1,3]dioxolo[4,5-c]pyran-4-yl) acrylate (**10**).* To a solution of olefin **8** (360 mg, 0.75 mmol, 1.0 equiv) and NMO (175 mg, 1.50 mmol, 2.0 equiv) in a mixture *t*-BuOH/buffer pH 7 (1:1, 10 mL) was added a solution of OsO_4 in *t*-BuOH (2.5 wt%, 376 μL, 30 μmol, 0.04 equiv). The solution was stirred overnight at room temperature, and then a saturated aqueous solution of $Na_2S_2O_3$ (10 mL) was added. The mixture was stirred with Celite® for 30 min and filtered through a pad of Celite®. The two phases were separated and the aqueous layer was extracted with EtOAc (3×10 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure to afford a diol, which was engaged in the next step without further purification.

To a solution of the obtained diol in a mixture THF/buffer pH 7 (1:1, 10 mL) was added $NaIO_4$ (482 mg, 2.25 mmol, 3.0 equiv). The solution was stirred at room temperature for 4 h and then filtered through a pad of Celite®. The two phases were separated and the aqueous layer was extracted with EtOAc (3×10 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure to afford aldehyde **9**, which was engaged in the next step without further purification.

To a solution of (carbethoxymethylene)triphenylphosphorane (522 mg, 1.50 mmol, 2.0 equiv) in CH_2Cl_2 (7.5 mL) was added dropwise a solution of aldehyde **9** in CH_2Cl_2 (7.5 mL) and the mixture was stirred at room temperature for 1 h and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel (PE/EtOAc: 9:1) to afford **10** (293 mg, 75%) as a colorless oil. $[\alpha]_D^{20}$ +14.9 (*c* 1.30, $CHCl_3$); IR (neat) 2933, 2858, 1720, 1660, 1589, 1472, 1428, 1371, 1301, 1265, 1284, 1210, 1163, 1111, 1048 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.69–7.64 (m, 4H, H_{ar}), 7.44–7.34 (m, 6H, H_{ar}), 7.00 (dd, *J*=15.8, 4.0 Hz, 1H), 6.16 (dd, *J*=15.8, 1.8 Hz, 1H), 4.37 (dt_{app}, *J*=9.2, 6.5 Hz, 1H), 4.33 (ddd, *J*=8.0, 4.0, 1.8 Hz, 1H), 4.21 (q, *J*=7.2 Hz, 2H), 3.93 (dd, *J*=8.0, 6.5 Hz, 1H), 3.88 (dt_{app}, *J*=10.2, 4.6 Hz, 1H), 3.76 (dd, *J*=10.7, 5.0 Hz, 1H), 3.70 (dd, *J*=10.7, 5.0 Hz, 1H), 2.10 (ddd, *J*=13.9, 6.2, 4.6 Hz, 1H), 1.96 (ddd, *J*=13.9, 10.2, 9.2 Hz, 1H), 1.43 (s, 3H), 1.34 (s, 3H), 1.30 (t, *J*=7.2 Hz, 3H), 1.05 (s, 9H, Si–C(CH_3)$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.5 (s), 145.3 (d), 135.8 (4d), 133.4 (2s), 129.9 (d), 129.8 (d), 127.9 (4d), 122.0 (d), 109.3 (s), 75.4 (d), 71.9 (d), 71.7 (d), 71.4 (d), 66.1 (t), 60.6 (t), 29.0 (t), 27.7 (q), 26.9 (3q, Si–C(CH_3)$_3$), 25.4 (q), 19.4 (s, Si–*C*(CH_3)$_3$), 14.4 (q); MS (EI) *m*/*z* 468 ($[M-t\text{-}Bu]^+$, 1), 241 (31), 225 (14), 199 (19), 197 (10), 184 (13), 183 (100), 163 (24), 139 (12), 137 (18), 135 (37), 113 (18), 105 (12), 97 (18), 91 (12), 85 (28), 77 ($[Ph]^+$, 11), 69 (11), 55 (12); HRMS (ESI) *m*/*z* calcd for $C_{30}H_{40}NaO_6Si$ $[M+Na]^+$ 547.2486, found: 547.2477.

*3.2.8. (E)-3-((3aS,4R,6S,7aS)-6-((tert-Butyldiphenylsilyloxy)methyl)-2,2-dimethyltetrahydro-3aH-[1,3]dioxolo[4,5-c]pyran-4-yl)prop-2-en-1-ol (**11**).* To a solution of ester **10** (1.26 g, 2.40 mmol, 1.0 equiv) in toluene (20 mL) at −78 °C was added dropwise a solution of DIBAL-H (1.0 M in hexanes, 6.00 mL, 6.00 mmol, 2.5 equiv). The reaction medium was allowed to warm to 0 °C and after 1 h at 0 °C, the reaction was quenched by addition of a saturated aqueous solution of Rochelle salt (20 mL) and the mixture was stirred for 3 h. The two phases were separated and the aqueous layer was extracted with EtOAc (3×20 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel (PE/EtOAc: 65:35) to afford alcohol **11** (962 mg, 83%) as a colorless oil. $[\alpha]_D^{20}$ +25.7 (*c* 1.05, $CHCl_3$); IR (neat) 3424, 2932, 2858, 1738, 1589, 1461, 1428, 1373, 1239, 1211, 1162, 1111, 1048 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.70–7.64 (m, 4H, H_{ar}), 7.44–7.34 (m, 6H, H_{ar}), 5.97 (dtd, *J*=15.6, 5.2, 1.4 Hz, 1H), 5.77 (ddt_{app}, *J*=15.6, 5.5, 1.5 Hz, 1H), 4.37 (dt_{app}, *J*=9.3, 6.4 Hz, 1H), 4.24–4.16 (m, 3H), 3.95 (dd, *J*=7.7, 6.7 Hz, 1H), 3.85 (dq_{app}, *J*=10.5, 4.8 Hz, 1H), 3.76 (dd, *J*=10.5, 4.8 Hz, 1H), 3.70 (dd, *J*=10.5, 4.8 Hz, 1H), 2.12 (ddd, *J*=13.8, 6.4, 4.4 Hz, 1H), 1.94 (ddd, *J*=13.8, 10.5, 9.3 Hz, 1H), 1.45 (s, 3H), 1.35 (s, 3H), 1.05 (s, 9H, Si–C(CH_3)$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.8 (4d), 133.6 (s), 133.5 (s), 132.4 (d), 129.8 (2d), 129.1 (d), 127.8 (4d), 109.0 (s), 76.1 (d), 72.4 (d), 71.9 (d), 71.1 (d), 66.3 (t), 63.3 (t), 29.3 (t), 27.7 (q), 27.0 (3q, Si–C(CH_3)$_3$), 25.4 (q), 19.4 (s, Si–*C*(CH_3)$_3$); MS (EI) *m*/*z* 349 (1), 241 (27), 199 (47), 197 (18), 183 (22), 181 (22), 163 (36), 141 (100), 139 (36), 135 (54), 123 (17), 121 (15), 117 (19), 111 (17), 105 (35), 95 (27), 91 (31), 85 (18), 83 (21), 81 (30), 79 (19), 77 ($[Ph]^+$, 28), 71 (22), 69 (49), 67 (21), 59 (62), 57 ($[t\text{-}Bu]^+$, 65), 55 (61), 53 (18); HRMS (ESI) *m*/*z* calcd for $C_{28}H_{38}NaO_5Si$ $[M+Na]^+$ 505.2381, found: 505.2380.

*3.2.9. tert-Butyl(((3aS,4R,6S,7aS)-4-((E)-3-(4-methoxybenzyloxy) prop-1-en-1-yl)-2,2-dimethyltetrahydro-3aH-[1,3]dioxolo[4,5-c]pyran-6-yl)methoxy)diphenylsilane (**12**).* To a solution of alcohol **11** (651 mg, 1.35 mmol, 1.0 equiv) in THF (30 mL) at 0 °C were added *t*-BuOK (302 mg, 2.70 mmol, 2.0 equiv) and, dropwise, PMBBr (326 mg, 1.62 mmol, 1.2 equiv). The solution was allowed to warm to room temperature and after 3 h, the reaction was quenched with a saturated aqueous solution of NH_4Cl (25 mL). The two phases

were separated and the aqueous layer was extracted with Et_2O (3×25 mL). The combined organic layers were washed with brine (25 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel (PE/EtOAc: 7:3) to afford PMB ether **12** (633 mg, 78%) as a yellow oil. $[\alpha]_D^{20}$ +8.4 (*c* 0.95, $CHCl_3$); IR (neat) 2932, 2857, 1736, 1612, 1512, 1462, 1428, 1371, 1302, 1247, 1212, 1163, 1111, 1047 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.70–7.65 (m, 4H, H_{ar}), 7.43–7.34 (m, 6H, H_{ar}), 7.26 (d, *J*=8.5 Hz, 2H), 6.87 (d, *J*=8.5 Hz, 2H), 5.94 (dtm, *J*=15.7, 5.6 Hz, 1H), 5.80 (ddm, *J*=15.7, 5.1 Hz, 1H), 4.45 (s, 2H), 4.36 (dt_{app}, *J*=9.3, 6.3 Hz, 1H), 4.26 (t_{app}, *J*=6.1 Hz, 1H), 4.04 (d, *J*=5.6 Hz, 2H), 3.97 (t_{app}, *J*=6.9 Hz, 1H), 3.88–3.81 (m, 1H), 3.80 (s, 3H), 3.76 (dd, *J*=10.5, 4.8 Hz, 1H), 3.70 (dd, *J*=10.5, 5.3 Hz, 1H), 2.09 (ddd, *J*=13.5, 6.1, 4.3 Hz, 1H), 1.91 (dt_{app}, *J*=13.5, 10.0 Hz, 1H), 1.45 (s, 3H), 1.35 (s, 3H), 1.06 (s, 9H, Si–C(CH_3)$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.3 (s), 135.8 (4d), 133.5 (2s), 130.5 (d), 130.5 (s), 129.8 (2d), 129.5 (d), 129.5 (d), 127.8 (4d), 113.9 (2d), 108.9 (s), 76.0 (d), 72.5 (d), 72.0 (t), 71.9 (d), 70.9 (d), 70.0 (t), 66.3 (t), 55.4 (q), 29.4 (t), 27.8 (q), 26.9 (3q, Si–C(CH_3)$_3$), 25.5 (q, C_b), 19.4 (s, Si–*C*(CH_3)$_3$); MS (EI) *m*/*z* 424 (3), 423 (10), 241 (22), 225 (15), 199 (22), 197 (10), 183 (15), 181 (11), 163 (24), 140 (10), 139 (100), 135 (39), 125 (27), 123 (10), 121 ($[PMB]^+$, 10), 117 (15), 105 (14), 91 (14), 81 (19), 77 ($[Ph]^+$, 11), 69 (27), 59 (11), 55 (13), 53 (12); HRMS (ESI) *m*/*z* calcd for $C_{36}H_{46}NaO_6Si$ $[M+Na]^+$ 625.2956, found 625.2958.

*3.2.10. (1R,2S)-1-((3aS,4R,6S,7aS)-6-((tert-Butyldiphenylsilyloxy) methyl)-2,2-dimethyltetrahydro-3aH-[1,3]dioxolo[4,5-c]pyran-4-yl)-3-((4-methoxybenzyl)oxy)propane-1,2-diol (**13**).* To a solution of olefin **12** (545 mg, 0.91 mmol, 1.0 equiv) in a mixture *t*-BuOH/buffer pH 7 (1:1, 25 mL) at 5 °C were successively added $(DHQ)_2PHAL$ (106 mg, 0.136 mmol, 0.15 equiv), AD-mix-α (1.27 g, 1.4 g/mmol),[21b] $K_2OsO_4 \cdot 2H_2O$ (6.7 mg, 0.018 mmol, 0.02 equiv), and $CH_3SO_2NH_2$ (90 mg, 0.951 mmol, 1.05 equiv).[21c] The mixture was stirred at 5 °C for 40 h, and diluted with a saturated aqueous solution of $Na_2S_2O_3$ (20 mL). EtOAc (20 mL) and Celite® were added and the mixture was stirred for 30 min and then filtered through a pad of Celite®. The two phases were separated and the aqueous layer was extracted with EtOAc (3×20 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel (PE/EtOAc: 6:4) to afford diol **13** (410 mg, 71%; dr=9:1). $[\alpha]_D^{20}$ +6.6 (*c* 0.90, $CHCl_3$); IR (neat) 3416, 3071, 2931, 2858, 1699, 1612, 1513, 1463, 1428, 1363, 1303, 1248, 1111, 1036 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.68–7.64 (m, 4H, H_{ar}), 7.43–7.34 (m, 6H, H_{ar}), 7.24 (d, *J*=8.8 Hz, 2H), 6.85 (d, *J*=8.8 Hz, 2H), 4.51–4.45 (m, 2H), 4.37 (dt_{app}, *J*=9.0, 6.2 Hz, 1H), 4.29 (dd, *J*=8.0, 6.8 Hz, 1H), 4.03–3.96 (m, 1H), 3.90–3.80 (m, 1H), 3.85–3.77 (m, 1H), 3.79 (s, 3H), 3.77–3.69 (m, 2H), 3.65 (dd, *J*=10.7, 4.9 Hz, 1H), 3.62–3.55 (m, 2H), 3.23 (d, *J*=4.5 Hz, 1H, OH), 2.91 (d, *J*=5.5 Hz, 1H, OH), 2.06 (dt_{app}, *J*=13.8, 5.3 Hz, 1H), 1.84 (dt_{app}, *J*=13.8, 9.7 Hz, 1H), 1.42 (s, 3H), 1.34 (s, 3H), 1.04 (s, 9H, Si–C(CH_3)$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.4 (s), 135.7 (4d), 133.4 (2s), 130.1 (s), 129.9 (2d), 129.6 (2d), 127.9 (4d), 113.9 (2d), 109.3 (s), 73.4 (d), 73.4 (t), 72.6 (d), 72.3 (d), 72.0 (d), 71.8 (t), 71.7 (d), 69.3 (d), 65.9 (t), 55.4 (q), 28.8 (t), 27.6 (q), 26.9 (3q, Si–C(CH_3)$_3$), 25.4 (q), 19.3 (s, Si–*C*(CH_3)$_3$); HRMS (ESI) *m*/*z* calcd for $C_{36}H_{48}NaO_8Si$ $[M+Na]^+$ 659.3011, found 659.3005.

*3.2.11. tert-Butyl(((3aS,4S,6S,7aS)-4-((4R,5S)-5-((4-methoxybenzyloxy)methyl)-2,2-dimethyl-1,3-dioxolan-4-yl)-2,2-dimethyltetrahydro-3aH-[1,3]dioxolo[4,5-c]pyran-6-yl)methoxy)-diphenylsilane (**15**).* To a solution of diol **13** (350 mg, 0.55 mmol, 1.0 equiv) in acetone (15 mL) at 0 °C, were added 2,2-dimethoxypropane (338 μL, 2.75 mmol, 5.0 equiv) and TsOH (38 mg, 0.22 mmol, 0.4 equiv). The mixture was allowed to warm to room temperature over 1 h and after 3 h at room temperature, triethylamine (100 μL) was added, and the solvent was removed under reduced pressure. The mixture was then diluted with water (15 mL) and the solution was extracted with EtOAc (3×20 mL). The combined organic layers were washed with brine (15 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel (PE/EtOAc: 8:2) to afford alcohol **15** (363 mg, 98%) as a colorless oil. $[\alpha]_D^{20}$ −1.4 (*c* 1.15, $CHCl_3$); IR (neat) 2932, 2858, 1719, 1612, 1588, 1513, 1461, 1428, 1370, 1302, 1247, 1215, 1169, 1105, 1052 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.69–7.63 (m, 4H, H_{ar}), 7.44–7.33 (m, 6H, H_{ar}), 7.21 (d, *J*=8.5 Hz, 2H), 6.82 (d, *J*=8.5 Hz, 2H), 4.48 (d, *J*=11.8 Hz, 1H), 4.44 (d, *J*=11.8 Hz, 1H), 4.36–4.26 (m, 3H), 4.05 (dd, *J*=8.5, 3.2 Hz, 1H), 3.88–3.80 (m, 2H), 3.77 (s, 3H), 3.73 (dd, *J*=10.7, 4.9 Hz, 1H), 3.67 (dd, *J*=10.7, 5.1 Hz, 1H), 3.52 (d, *J*=4.5 Hz, 2H), 2.01 (ddd, *J*=13.6, 5.2, 4.7 Hz, 1H), 1.83 (dt_{app}, *J*=13.6, 9.8 Hz, 1H), 1.43 (s, 9H), 1.34 (s, 3H), 1.03 (s, 9H, Si–C(CH_3)$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.3 (s), 135.7 (4d), 133.5 (2s), 130.2 (s), 129.8 (2d), 129.4 (2d), 127.8 (4d), 113.8 (2d), 109.9 (s), 108.8 (s), 79.0 (d), 76.8 (d), 73.2 (t), 72.8 (d), 72.1 (d), 71.5 (d), 71.4 (d), 70.3 (t), 66.2 (t), 55.4 (q), 29.3 (t), 28.0 (q), 27.4 (q), 27.0 (q), 26.9 (3q, Si–C(CH_3)$_3$), 25.7 (q), 19.4 (s, Si–*C*(CH_3)$_3$); HRMS (ESI) *m*/*z* calcd for $C_{39}H_{52}NaO_8Si$ $[M+Na]^+$ 699.3324, found 699.3323.

*3.2.12. ((3aS,4S,6S,7aS)-4-((4R,5S)-5-((4-Methoxybenzyloxy) methyl)-2,2-dimethyl-1,3-dioxo-lan-4-yl)-2,2-dimethyltetrahydro-3aH-[1,3]dioxolo[4,5-c]pyran-6-yl)methanol (**16**).* To a solution of **15** (970 mg, 1.43 mmol, 1.0 equiv) in THF (3 mL) at 0 °C was added dropwise a solution of TBAF (1 M in THF, 2.9 mL, 2.87 mmol, 2.0 equiv). The solution was allowed to warm to room temperature over 2 h and after an additional 2 h at room temperature, the reaction was quenched by addition of a saturated aqueous solution of $NaHCO_3$ (10 mL). The two phases were separated and the aqueous layer was extracted with EtOAc (3×10 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel (PE/EtOAc: 5:5) to afford primary alcohol **16** (602 mg, 96%) as a colorless oil. $[\alpha]_D^{20}$ +3.5 (*c* 0.88, $CHCl_3$); IR (neat) 3474, 2985, 2934, 1737, 1613, 1586, 1513, 1457, 1370, 1302, 1244, 1215, 1168, 1033 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.26 (d, *J*=8.8 Hz, 2H), 6.87 (d, *J*=8.8 Hz, 2H), 4.52 (s, 2H), 4.34 (dt, *J*=8.6, 6.0 Hz, 1H), 4.26–4.20 (m, 2H), 4.08 (dd, *J*=8.3, 3.5 Hz, 1H), 3.92 (dd, *J*=5.5, 3.5 Hz, 1H), 3.87–3.80 (m, 1H), 3.80 (s, 3H), 3.66–3.57 (m, 3H), 3.55–3.48 (m, 1H), 2.12–2.07 (m, 1H, OH), 1.92 (ddd, *J*=13.8, 6.0, 4.3 Hz, 1H), 1.63 (ddd, *J*=13.8, 9.6, 8.8 Hz, 1H), 1.46 (s, 3H), 1.42 (s, 3H), 1.42 (s, 3H), 1.33 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.4 (s), 130.0 (s), 129.6 (2d), 113.9 (2d), 110.0 (s), 108.8 (s), 79.4 (d), 76.9 (d), 73.3 (t), 72.5 (d), 71.5 (d), 71.3 (d), 71.2 (d), 70.3 (t), 64.8 (t), 55.4 (q), 29.1 (t), 28.1 (q), 27.3 (q), 27.0 (q), 25.9 (q); MS (EI) *m*/*z* 439 ($[M]^{+\bullet}$, 1), 137 (7), 136 (5), 122 (10), 121 (100), 99 (6), 83 (6), 71 (6), 69 (8), 59 (10); HRMS (ESI) *m*/*z* calcd for $C_{23}H_{34}NaO_8$ $[M+Na]^+$ 461.2146, found 461.2138.

*3.2.13. (3aS,4S,6S,7aS)-4-((4R,5S)-5-((4-Methoxybenzyloxy)methyl)-2,2-dimethyl-1,3-dioxolan-4-yl)-2,2-dimethyl-6-vinyltetrahydro-3aH-[1,3]dioxolo[4,5-c]pyran (**18**).* To a solution of oxalyl chloride (81 μL, 0.94 mmol, 1.1 equiv) in CH_2Cl_2 (0.5 mL) at −60 °C was added dropwise DMSO (122 μL, 1.72 mmol, 2.0 equiv) and after 20 min, a solution of alcohol **16** (376 mg, dr=9:1, 0.86 mmol, 1.0 equiv) in CH_2Cl_2 (2.0 mL) was added dropwise. After an additional 20 min at −60 °C, triethylamine (478 μL, 3.43 mmol, 4.0 equiv) was added and the mixture was stirred for 10 min at −60 °C, and then warmed up to room temperature and stirred for an additional 2 h. The reaction was then stopped by the addition of a saturated aqueous solution of NaCl (5 mL), the two phases were separated, and the aqueous layer was extracted with CH_2Cl_2

(2×5 mL) and petroleum ether (5 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was quickly filtered through a pad of silica gel (PE/EtOAc: 7:3–6:4) to afford aldehyde **17** (291 mg, 78%) as a colorless oil. This aldehyde was not stable and was directly engaged in the next step.

To a solution of PPh_3CH_3Br (480 mg, 1.34 mmol, 2.1 equiv), previously dried at 60 °C under vacuum, in THF (1.2 mL) at −10 °C was added dropwise a solution of *t*-BuOK (143 mg, 1.28 mmol, 2.0 equiv) in THF (1.2 mL). The mixture was allowed to warm up to room temperature, stirred for 10 min at this temperature, and then cooled to −10 °C. A solution of aldehyde **17** (279 mg, 0.64 mmol, 1.0 equiv) in THF (0.6 mL) was then added and the solution was allowed to warm up to room temperature and stirred for 1 h. The solvent was removed under reduced pressure and the crude product was purified by flash chromatography on silica gel (PE/EtOAc: 9:1) to afford olefin **18** (219 mg, 79%, dr ~ 9:1) as a colorless oil. $[\alpha]_D^{20}$ +8.9 (*c* 0.95, $CHCl_3$); IR (neat) 2985, 2935, 1737, 1612, 1586, 1513, 1457, 1370, 1302, 1245, 1216, 1168, 1056 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.25 (d, *J*=8.5 Hz, 2H), 6.86 (d, *J*=8.5 Hz, 2H), 5.88 (ddd, *J*=17.2, 10.6, 5.3 Hz, 1H), 5.24 (dt, *J*=17.2, 1.5 Hz, 1H), 5.13 (dt, *J*=10.6, 1.5 Hz, 1H), 4.52 (br s, 2H), 4.34 (dt_{app}, *J*=8.4, 6.0 Hz, 1H), 4.30–4.25 (m, 2H), 4.25–4.18 (m, 1H), 4.09 (dd, *J*=8.5, 3.5 Hz, 1H), 3.88 (dd, *J*=6.1, 3.5 Hz, 1H), 3.80 (s, 3H), 3.59 (d, *J*=4.5 Hz, 2H), 2.10–2.01 (m, 1H), 1.73 (dt_{app}, *J*=13.7, 8.7 Hz, 1H), 1.44 (s, 6H), 1.43 (s, 3H), 1.34 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.3 (s), 137.8 (d), 130.2 (s), 129.5 (2d), 115.9 (t), 113.9 (2d), 109.9 (s), 108.8 (s), 79.2 (d), 76.9 (d), 73.3 (t), 72.1 (d), 71.8 (d), 71.4 (d), 71.2 (d), 70.3 (t), 55.4 (q), 32.6 (t), 28.1 (q), 27.3 (s), 27.0 (q), 26.0 (q); MS (EI) *m*/*z* 434 ($[M]^{+\bullet}$, 1), 221 (6), 137 (5), 136 (5), 125 (5), 122 (9), 121 (100), 95 (8), 85 (6), 71 (5), 67 (10), 59 (9), 55 (7); HRMS (ESI) *m*/*z* calcd for $C_{24}H_{34}NaO_7$ $[M+Na]^+$ 457.2197, found: 457.2193.

*3.2.14. (S)-1-((3aS,4S,6S,7aS)-4-((4R,5S)-5-((4-Methoxybenzyloxy) methyl)-2,2-dimethyl-1,3-dioxolan-4-yl)-2,2-dimethyltetrahydro-3aH-[1,3]dioxolo[4,5-c]pyran-6-yl)ethane-1,2-diol (**19**).* To a solution of **18** (204 mg, 0.47 mmol, 1.0 equiv) in a mixture *t*-BuOH/buffer pH 7 (1:1, 15 mL) at 5 °C were successively added $(DHQD)_2PYR$ (66 mg, 0.075 mmol, 0.16 equiv), $K_3Fe(CN)_6$ (461 mg, 0.98 g/mmol), K_2CO_3 (178 mg, 0.41 g/mmol), $K_2OsO_4 \cdot 2H_2O$ (4 mg, 0.010 mmol, 0.022 equiv), and $CH_3SO_2NH_2$ (47 mg, 0.49 mmol, 1.05 equiv). The mixture was stirred at 5 °C for 24 h, and a saturated aqueous solution of $Na_2S_2O_3$ (10 mL) was added. EtOAc (10 mL) and Celite® were added and the mixture was stirred for 30 min and filtered on Celite®. The two phases were separated and the aqueous layer was extracted with EtOAc (3×10 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude diol was purified by flash chromatography on silica gel (PE/EtOAc: 3:7) to afford diol **19** as a mixture of two diastereoisomers (220 mg, quant., dr=65:35). IR (neat) 3402, 2930, 2858, 1788, 1723, 1612, 1586, 1514, 1463, 1370, 1302, 1249, 1174, 1083, 1035 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.26 (dm, *J*=8.8 Hz, 2H), 6.88 (dm, *J*=8.8 Hz, 2H), 4.54 (d, *J*=11.7 Hz, 1H), 4.50 (d, *J*=11.7 Hz, 1H), 4.38–4.30 (m, 1H), 4.27–4.17 (m, 2H), 4.06 (ddd, *J*=8.0, 7.3, 3.4 Hz, 1H), 3.93 (dt_{app}, *J*=6.2, 3.4 Hz, 1H), 3.85–3.76 (m, 1H, H_{38}), 3.81 (s, 3H, H_h), 3.74–3.53 (m, 5H, H_{31}, $H_{31'}$, H_{39}, H_{40}, $H_{40'}$), 2.00 (ddd, *J*=13.9, 6.1, 4.7 Hz, 1H, H_{37}), 1.81 (dt_{app}, *J*=13.9, 9.3 Hz, 1H, $H_{37'}$), 1.46 (s, 3H, H_b), 1.41 (s, 6H, H_b), 1.32 (s, 3H, H_b); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.5 (s), 129.9 (s), 129.0 (2d), 114.0 (2d), 109.0 (2s), 79.7 (d), 76.4 (d), 73.3 (t), 72.9 (d), 72.6 (d), 71.8 (d), 71.6 (d), 71.3 (d), 70.5 (t), 63.5 (t), 55.4 (q), 29.0 (t), 27.9 (q), 27.3 (q), 27.0 (q), 25.7 (q); HRMS (ESI) *m*/*z* calcd for $C_{24}H_{36}NaO_9$ $[M+Na]^+$ 491.2252, found 491.2259.

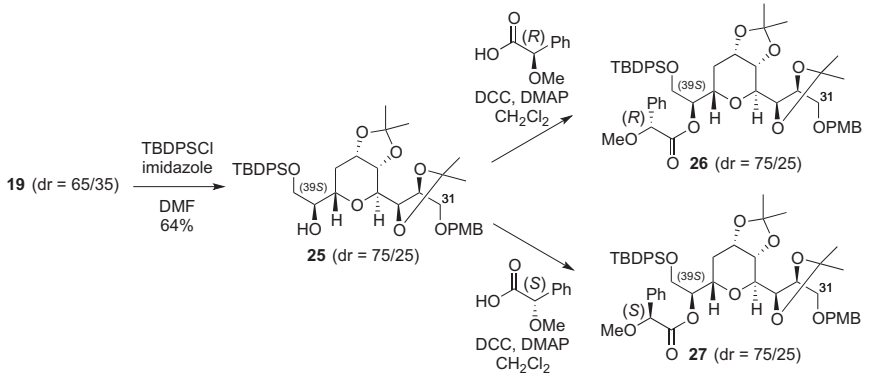
*3.2.15. tert-Butyl(((S)-1-((3aS,4S,6S,7aS)-4-((4R,5S)-5-((4-methoxybenzyloxy)methyl)-2,2-dimethyl-1,3-dioxolan-4-yl)-2,2-dimethyltetrahydro-3aH-[1,3]dioxolo[4,5-c]pyran-6-yl)-4-(trimethylsilyl)pent-4-en-1-yl)oxy)dimethylsilane (**24**).* To a solution of **19** (122 mg, 0.26 mmol, 1.0 equiv, 65:35 epimeric mixture) in CH_2Cl_2 (1.3 mL) were added PPTS (5.2 mg, 0.021 mmol, 0.05 equiv) and trimethyl orthoacetate (69 μL, 0.55 mmol, 2.1 equiv). After 2 h at room temperature, the solvent and excess trimethyl orthoacetate were removed under reduced pressure and the product was diluted in CH_2Cl_2 (1.3 mL). Acetyl chloride (39 μL, 0.55 mmol, 2.1 equiv) was added, the mixture was stirred for 5 h at room temperature and the solvents were removed under reduced pressure. The mixture was diluted with MeOH (2.2 mL) and potassium carbonate (79 mg, 0.57 mmol, 2.2 equiv) was added. After one night at room temperature, the reaction was stopped by the addition of a saturated aqueous solution of NH_4Cl (2.5 mL). The two phases were separated and the aqueous layer was extracted with CH_2Cl_2 (3×5 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was filtered through silica gel (EP/EtOAc: 7:3) to afford epoxide **21** (64 mg, 55%), which was directly engaged in the next step.

To a solution of **22** (25 mg, 0.063 mmol, 1.35 equiv) in THF (150 μL) at −78 °C was added dropwise *n*-BuLi (2.2 M in hexanes, 29 μL, 0.063 mmol, 1.35 equiv) and the (3-lithioprop-1-en-2-yl) trimethylsilane solution was stirred for 20 min at this temperature.

To a solution of **21** (21 mg, 0.047 mmol, 1.0 equiv) in THF (150 μL) at −78 °C was added dropwise the freshly prepared solution of (3-lithioprop-1-en-2-yl)trimethylsilane and the reaction was stirred for 1 h at this temperature. The reaction was then stopped by the addition of water (1 mL) and the mixture was allowed to warm up to room temperature. The two phases were separated and the aqueous layer was extracted with Et_2O (3×5 mL). The combined organic layers were washed with brine (5 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was filtered through silica gel (PE/EtOAc: 8:2) to afford vinylsilane **23** (14 mg, 53%), which was directly engaged in the next step.

To a solution of **23** (14 mg, 0.025 mmol, 1.0 equiv) in CH_2Cl_2 (200 μL) at −78 °C were added dropwise 2,6-lutidine (11.5 μL, 0.099 mmol, 4.0 equiv) and TBSOTf (11.4 μL, 0.050 mmol, 2.0 equiv). The mixture was then allowed to warm up to room temperature overnight and the reaction was stopped by the addition of a saturated aqueous solution of $NaHCO_3$ (1 mL). The two phases were separated and the aqueous layer was extracted with CH_2Cl_2 (3×2.5 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel (PE/EtOAc: 9:1) to afford silyl ether **24** (11 mg, 65%, dr>95:5, 19% from **19**) as a colorless oil. $[\alpha]_D^{20}$ +6.7 (*c* 0.50, $CHCl_3$); IR (neat) 2953, 2933, 2857, 1613, 1586, 1514, 1461, 1370, 1302, 1247, 1215, 1170, 1064 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.25 (dm, *J*=8.8 Hz, 2H), 6.86 (dm, *J*=8.8 Hz, 2H), 5.54 (dm, *J*=2.8 Hz, 1H), 5.30 (dm, *J*=2.8 Hz, 1H), 4.54 (d, *J*=11.5 Hz, 1H), 4.52 (d, *J*=11.5 Hz, 1H), 4.36–4.27 (m, 2H), 4.25 (ddd, *J*=8.7, 5.1, 4.2 Hz, 1H), 4.06 (dd, *J*=8.7, 2.7 Hz, 1H), 3.93 (dd, *J*=5.7, 2.7 Hz, 1H), 3.80 (s, 3H), 3.72 (dt, *J*=12.3, 3.8 Hz, 1H), 3.60 (ddd, *J*=7.6, 4.9, 3.8 Hz, 1H), 3.58–3.54 (m, 2H), 2.26–2.15 (m, 1H), 2.11–2.01 (m, 1H), 1.88 (ddd, *J*=13.2, 5.8, 3.8 Hz, 1H), 1.80–1.69 (m, 2H), 1.54–1.44 (m, 1H), 1.46 (s, 3H), 1.42 (s, 3H), 1.42 (s, 3H), 1.33 (s, 3H), 0.87 (s, 9H, Si–C(CH_3)$_3$), 0.07 (s, 9H, Si–(CH_3)$_3$), 0.05 (s, 3H, Si–(CH_3)$_2$), 0.03 (s, 3H, Si–(CH_3)$_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.3 (s), 152.3 (s), 130.2 (s), 129.4 (2d), 123.7 (t), 113.9 (2d), 110.1 (s), 108.7 (s), 79.8 (d), 76.7 (d), 74.5 (d), 73.6 (d), 73.2 (t), 72.9 (d), 72.8 (d), 71.7 (d), 70.5 (t), 55.4 (q), 32.0 (t), 31.8 (t), 28.4 (t), 27.8 (q), 27.3 (q), 27.0 (q), 26.0 (3q, Si–C(CH_3)$_3$), 25.6 (q), 18.2 (s, Si–*C*(CH_3)$_3$), −1.3 (3q, Si–(CH_3)$_3$), −4.2 (q, Si–(CH_3)$_2$), −4.3 (q, Si–(CH_3)$_2$); HRMS (ESI) *m*/*z* calcd for $C_{36}H_{62}NaO_8Si_2$ $[M+Na]^+$ 701.3875, found 701.3867.

3.3. Methoxyphenylacetic esters 26 and 27



*3.3.1. (S)-2-(tert-Butyldiphenylsilyloxy)-1-((3aS,4S,6S,7aS)-4-((4R,5S)-5-((4-methoxybenzyloxy)methyl)-2,2-dimethyl-1,3-dioxolan-4-yl)-2,2-dimethyltetrahydro-3aH-[1,3]dioxolo[4,5-c]pyran-6-yl)ethanol (**25**).* To a solution of diol **19** (dr=65:35, 54 mg, 0.124 mmol, 1.0 equiv) in DMF (150 μL) at 0 °C were added imidazole (18 mg, 0.260 mmol, 2.1 equiv) and, TBDPSCl dropwise (35 μL, 0.136 mmol, 1.05 equiv). The solution was warmed to room temperature, and after 4 h, and a saturated aqueous solution of $NaHCO_3$ (3 mL) was added. The two phases were separated and the aqueous layer was extracted with EtOAc (3×5 mL). The combined organic layers were washed with water (2×5 mL) and brine (2×5 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel (PE/EtOAc: 8:2–7:3) to afford product **25** (54 mg, 64%) as a colorless oil and with a dr of 75:25. IR (neat) 3502, 3071, 2985, 2931, 2858, 2249, 1737, 1612, 1588, 1513, 1462, 1428, 1371, 1302, 1245, 1217, 1165, 1110, 1047 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.70–7.62 (m, 4H), 7.44–7.34 (m, 6H), 7.27–7.18 (m, 2H), 6.88–6.80 (m, 2H), 4.53–4.43 (m, 2H), 4.34 (dt_{app}, J=8.7, 6.0 Hz, 1H), 4.27–417 (m, 2H), 4.06 (dd, J=8.5, 2.8 Hz, 1H), 3.99–3.89 (m, 2H), 3.86–3.64 (m, 3H), 3.78 (s, 3H), 3.57 (m, 1H), 3.54–3.48 (m, 1H), 2.02–1.92 (m, 1H), 1.83–1.72 (m, 1H), 1.44 (s, 3H), 1.41 (s, 3H), 1.40 (s, 3H), 1.32 (s, 3H), 1.05 (s, 9H, Si–C(CH_3)$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.4 (s), 135.7 (4d), 133.4 (s), 133.2 (s), 130.1 (s), 130.0 (d), 129.9 (d), 129.5 (2d), 127.9 (4d), 113.9 (2d), 110.0 (s), 108.8 (s), 79.9 (d), 76.5 (d), 73.5 (d), 73.3 (t), 72.6 (d), 71.9 (d), 71.2 (d), 71.0 (d), 70.5 (t), 64.6 (t), 55.4 (q), 29.2 (t), 28.0 (q), 27.3 (q), 27.0 (4q), 25.8 (q), 19.4 (s, Si–C(CH_3)$_3$); HRMS (ESI) m/z calcd for $C_{40}H_{54}NaO_9Si$ $[M+Na]^+$ 729.3429, found 729.3427.

3.3.2. General procedure for the esterification. To a solution of an alcohol (1.0 equiv) in CH_2Cl_2 (30 mL/mmol) were added DCC (1.2 equiv), DMAP (0.2 equiv), and (*R*)- or (*S*)-methoxyphenylacetic acid (1.5 equiv). The mixture was stirred overnight at room temperature and the cloudy solution was filtered on cotton. The solution was then washed with water, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel (PE/Et_2O: 100:0–7:3) to afford the corresponding ester.

*3.3.3. (R)-(S)-2-(tert-Butyldiphenylsilyloxy)-1-((3aS,4S,6S,7aS)-4-((4R,5S)-5-((4-methoxybenzyloxy)methyl)-2,2-dimethyl-1,3-dioxolan-4-yl)-2,2-dimethyltetrahydro-3aH-[1,3]dioxolo-[4,5-c]pyran-6-yl)ethyl 2-methoxy-2-phenylacetate (**26**).* Compound **26** (dr=75:25, 22 mg, 70%) was prepared from **25** (dr=75:25, 26 mg, 36.8 μmol) and (*R*)-methoxyphenylacetic acid (9.2 mg, 55.2 μmol) according to the general procedure for esterification. IR (neat) 2933, 2858, 2250, 1749, 1612, 1513, 1456, 1428, 1371, 1302, 1247, 1214, 1171, 1105 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.71–7.15 (m, 17H, H_{ar}), 6.91–6.78 (m, 2H, H_{ar}), 5.34–5.26 (m, 1H, H_{39}), 4.79 (s, 1H), 4.54 (d, J=11.8 Hz, 1H), 4.50 (d, J=11.8 Hz, 1H), 4.34–4.25 (m, 3H, H_{32}, H_{35}, H_{36}), 4.20–4.14 (m, 1H, H_{38}), 3.94–3.64 (m, 4H, H_{33}, H_{34}, H_{40}, H_{40}'), 3.78 (s, 3H), 3.58–3.53 (m, 1H); 3.50–3.43 (m, 1H), 3.39 (s, 3H), 2.03–1.94 (m, 1H, H_{37}), 1.71–1.60 (m, 1H, H_{37}'), 1.42 (s, 3H), 1.41 (s, 3H), 1.41 (s, 3H), 1.35 (s, 3H), 0.98 (s, 9H, Si–C(CH_3)$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.6 (s), 159.3 (s), 135.8 (2d), 135.6 (2d), 135.5 (2d), 133.3 (s), 133.1 (s), 133.0 (s), 130.4 (s), 129.9 (3d), 129.5 (2d), 128.8 (d), 128.7 (d), 127.9 (2d), 127.8 (d), 127.4 (d), 113.8 (2d), 109.9 (s), 109.2 (s), 83.0 (d), 79.1 (d), 76.3 (d), 71.6 (d), 73.2 (t), 71.8 (d), 71.3 (d), 70.7 (d), 70.4 (t), 70.0 (d), 63.0 (t), 57.7 (q), 55.4 (q), 28.3 (t), 27.9 (q), 27.0 (q), 26.9 (q), 26.8 (3q, Si–C(CH_3)$_3$), 25.8 (q), 19.3 (s, Si–C(CH_3)$_3$); HRMS (ESI) m/z calculated for $C_{49}H_{62}NaO_{11}Si$ $[M+Na]^+$ 877.3954, found 877.3945.

*3.3.4. (S)-(S)-2-(tert-Butyldiphenylsilyloxy)-1-((3aS,4S,6S,7aS)-4-((4R,5S)-5-((4-methoxybenzyloxy)methyl)-2,2-dimethyl-1,3-dioxolan-4-yl)-2,2-dimethyltetrahydro-3aH-[1,3]dioxolo-[4,5-c]pyran-6-yl)ethyl 2-methoxy-2-phenylacetate (**27**).* Compound **27** (dr=75:25, 24 mg, 90%) was prepared from **25** (dr=75:25, 22 mg, 31.2 μmol) and (*S*)-methoxyphenylacetic acid (7.8 mg, 46.7 μmol) according to the general procedure for esterification. IR (neat) 2931, 2857, 1751, 1706, 1670, 1612, 1588, 1513, 1454, 1428, 1370, 1302, 1247, 1212, 1172, 1105 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.71–7.18 (m, 17H, H_{ar}), 6.88–6.80 (m, 2H, H_{ar}), 5.33–5.27 (m, 1H, H_{39}), 4.68 (s, 1H), 4.53–4.46 (m, 2H), 4.25–4.15 (m, 3H, H_{32}, H_{35}, H_{36}), 4.13–4.04 (m, 1H, H_{38}), 3.89–3.83 (m, 1H, H_{40}), 3.81–3.75 (m, 1H, H_{40}'), 3.78 (s, 3H), 3.55–3.32 (m, 4H, H_{31}, H_{31}', H_{33}, H_{34}), 3.37 (s, 3H), 1.97–1.85 (m, 1H, H_{37}), 1.68–1.52 (m, 1H, H_{37}'), 1.44–1.25 (4s, 12H), 1.04 (s, 9H, Si–C(CH_3)$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.5 (s), 159.4 (s), 135.8 (2d), 135.7 (d), 135.6 (3d), 133.3 (2s), 133.2 (s), 130.4 (s), 130.0 (2d), 129.5 (2d), 129.4 (d), 128.8 (d), 128.7 (d), 127.9 (2d), 127.8 (d), 127.5 (d), 113.9 (2d), 109.8 (s), 109.0 (s), 82.6 (d), 79.1 (d), 76.2 (d), 74.4 (d), 73.2 (t), 71.7 (d), 71.1 (d), 70.6 (d), 70.5 (t), 69.8 (d), 63.3 (t), 57.5 (q), 55.4 (q), 28.3 (t), 27.8 (q), 27.4 (q), 26.9 (q), 26.8 (3q, Si–C(CH_3)$_3$), 25.8 (q), 19.4 (s, Si–C(CH_3)$_3$); HRMS (ESI) m/z calcd for $C_{49}H_{62}NaO_{11}Si$ $[M+Na]^+$ 877.3954, found 877.3937.

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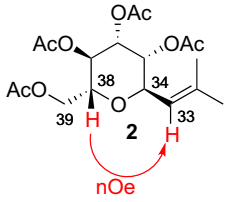

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23. See Experimental part and Table 4.