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Graphical Abstract

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Synthesis of a putative advanced intermediate en route to Elisabethin A

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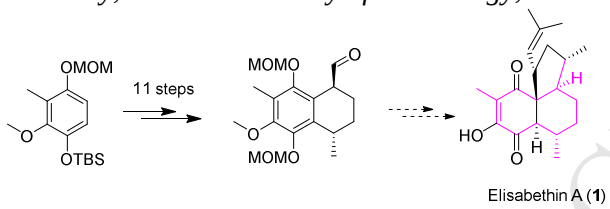

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ABSTRACT

The first generation synthesis of an advanced intermediate en route to elisabethin A is described.
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1. Introduction

Due to their rich functionalization and diverse biological activities marine terpenoids from gorgonian corals of the genus *Pseudopterogorgia* have received enormous attention over the past decade.

In 1998 Rodriguez and coworkers reported the isolation of small quantities (0.0089% dry weight) of the marine diterpenoid elisabethin A (**1**) from West Indian sea whip *Pseudopterogorgia elisabethae*.[1] Subsequent chemical investigations of this gorgonian specimen revealed the presence of structurally related compounds elisapterosin B (**2**)[2] and colombiasin A (**3**)[3] (Fig.1).

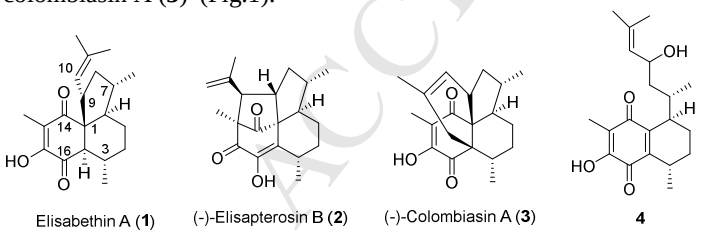

Fig.1.

The constitution of the carbon framework and the relative configuration of elisabethin A were assigned on the basis of exhaustive spectroscopic studies and X-ray diffraction which did not allow establishing the absolute configuration of the natural compound. The complex tricyclic *cis,trans*-fused 5,6,6 ring system of elisabethin A together with a fully substituted enedione functionality and six contiguous stereogenic centers present a considerable challenge for total synthesis.

Although the syntheses of compounds **2** and **3** were reported by several groups,[4] so far only three attempts towards the total synthesis of elisabethin A have been published by Mulzer's[5] and Rawal's[6] groups. Both groups used an intramolecular Diels-Alder reaction (IMDA) to construct the tricyclic core of the molecule but unfortunately, this approach gave two different diastereomers of elisabetine A and it was not possible to convert them to the target molecule.[7] Challenged by this situation, we decided to develop an alternative approach based on the proposed biosynthesis from serrulatane precursor **4**.[1]

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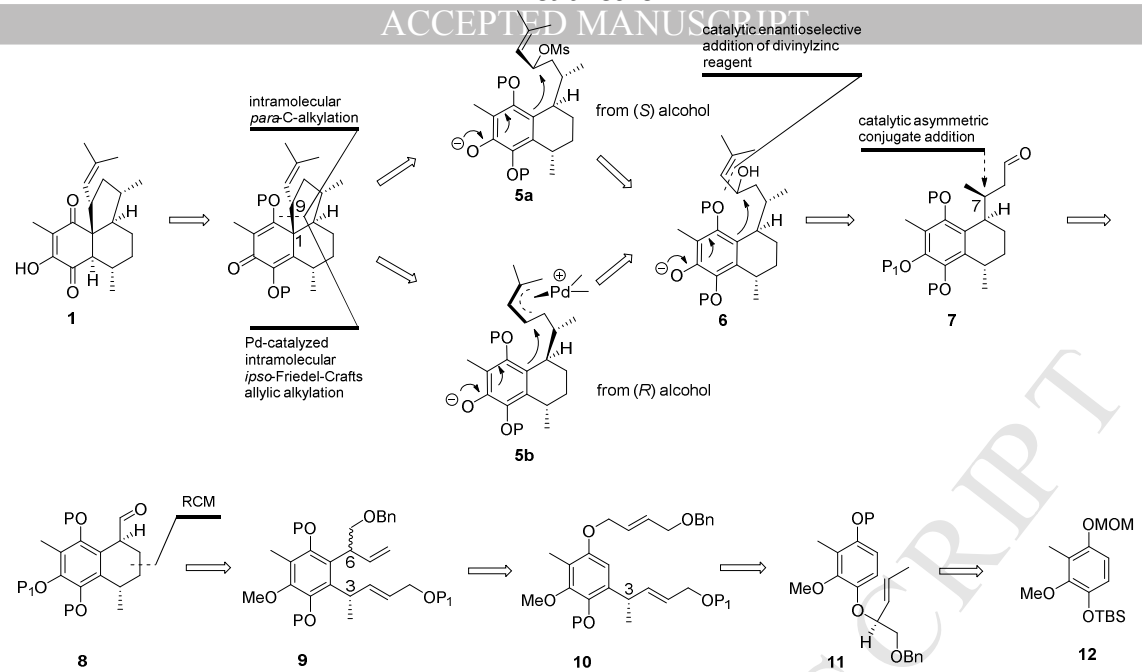


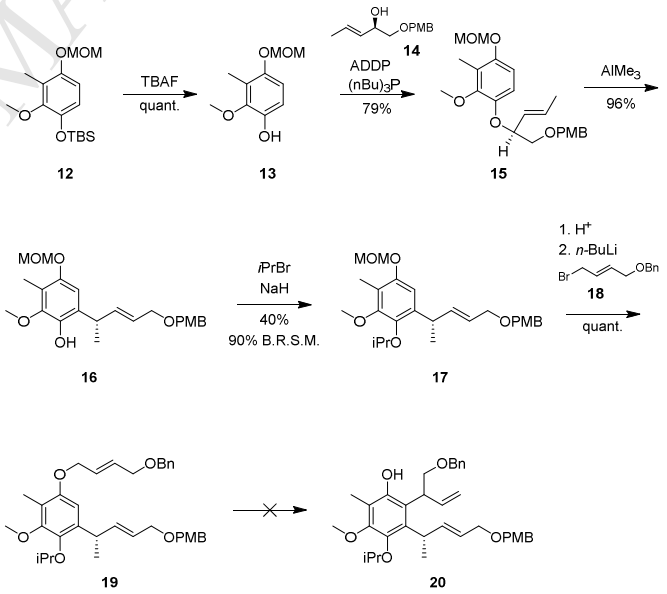
Scheme 1. Retrosynthetic analysis.

2. Results and discussion

Our retrosynthetic plan is shown in Scheme 1. Guided by the suggested biosynthetic pathway we intended to construct the five membered ring of elisabethin A via an intramolecular *para*-C-alkylation[8] or via a Pd or Ir catalyzed intramolecular *ipso*-Friedel-Crafts alkylation[9,10a,b,] of serrulatane intermediates **5a** and **5b**, respectively. Both intermediates could be obtained from corresponding (*R*)- or (*S*)- alcohol **6** which in turn could be synthesized from aldehyde **7**. Further disconnection gives the key intermediate **8**[11] which was planned to be formed by ring-closing metathesis (RCM) of diene **9**. The latter could be assembled by two successive Claisen rearrangement of **10** and **11**, respectively which can be easily obtained from the known compound **12**.[12] This highly biomimethic approach necessitates efficient syntheses of bicyclic compound **8** and here we present our first results towards elaboration of compound **12** to aldehyde **8**.

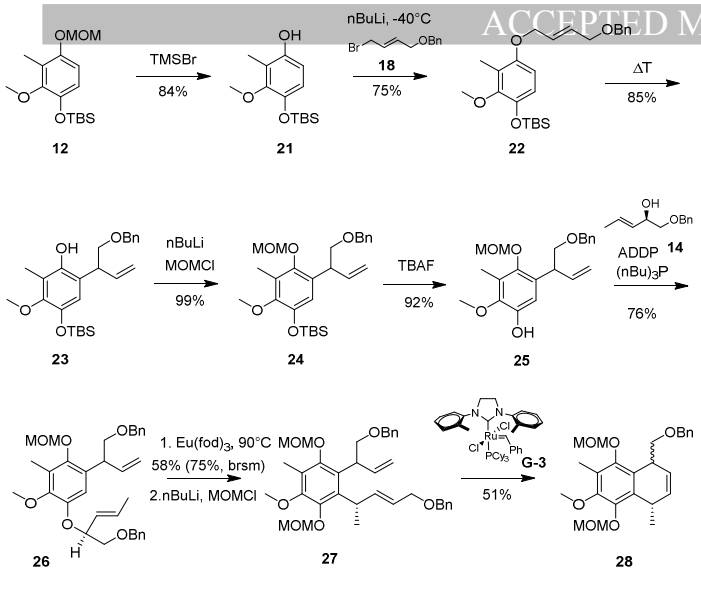
Starting from **12** would allow us to install and rearrange the "northern" and the "southern" allyl ethers independently. Since the "northern" allylether in **10** is prochiral, we were interested to see whether there would be influence of C3 chiral centre (from the first rearrangement) on the stereochemical outcome of the second Claisen rearrangement.

Our synthesis commenced with TBS[13] deprotection of **12** (TBAF/THF) followed by coupling of the obtained phenol **13** with alcohol **14**[14] under modified Mitsunobu conditions[15] to give allyl ether **15** in 79% yield. Treatment of **15** with trimethylaluminium in *n*-hexane at room temperature resulted in clean and virtually quantitative rearrangement to compound **16**. Protection of phenol **16** as isopropyl ether, cleavage of MOM group and subsequent installation of the allyl ether functionality set the scene for the second Claisen rearrangement. Unfortunately all our attempts to perform the rearrangement failed. Heating in DMF or *N*,*N*-dimethylaniline only produced a complex mixture, while the Lewis acids (trimethylaluminium, BF_3 and $Eu(fod)_3$) (*vide supra*) failed to produce any conversion at all. Therefore this approach was abandoned and we turned our attention to the inverted sequence of rearrangements (Scheme 3). Although this way would give a 1:1 mixture of diastereomers we hoped that after RCM we can equilibrate the undesired *cis* isomer to the *trans* product.



Scheme 2."Southern" approach.

To remove the MOM group, compound **12** was treated with TMSBr and the obtained phenol was coupled with allyl bromide **18**[16] to give allylether **22** in 75% yield together with a small amount of S_N2' product (Scheme 3). The first Claisen rearrangement of **22** was achieved by heating at 210° C in

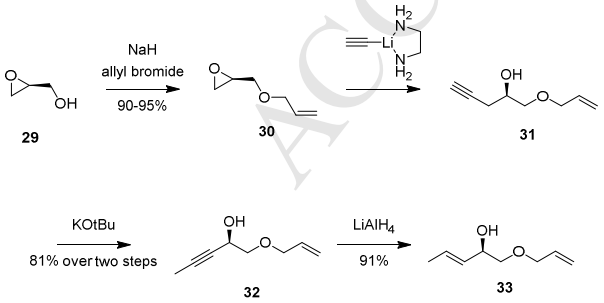


Scheme 3. "Northern" approach – synthesis of **28**.

N,*N*-dimethylaniline to give **23** in high yield. Protection of **23** (BuLi/MOMCl) followed by TBS cleavage and subsequent reaction with alcohol **14** afforded allylether **26** in a 76% yield.

Next, we turned our attention to the second rearrangement which proved to be much more challenging than we expected. Initial attempts to perform the reaction in the presence of trimethylaluminium failed and only starting material were recovered. Thermal rearrangement similar to the first Claisen rearrangement with both conventional and microwave heating also failed. Finally, treatment with $Eu(fod)_3$[17] in toluene at elevated temperatures led to a 1:1 mixture of the desired product and phenol **25**. The rearrangement product was protected (BuLi/MOMCl), setting the stage for the following ring closing metathesis. In view of the steric hindrance of the diene **27** we expected some problems for the RCM. In fact, attempts to perform the reaction in presence of 2nd generation Grubbs or Grubbs-Hoveyda catalyst in different solvents and at different temperatures failed. Finally, using catalyst **G-3**[18] the desired product **28** was obtained although in a moderate yield and with high catalyst loading (17 mol %).

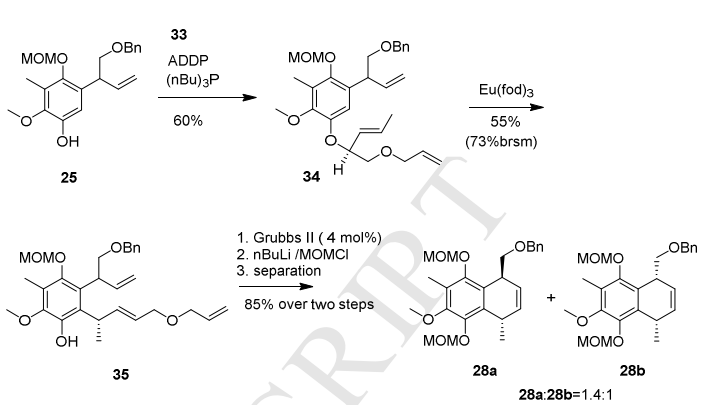
To circumvent this reactivity issue we decided to step back and to try the ring formation via relay ring closing metathesis (RRCM).[19]



Scheme 4. Preparation of **33**.

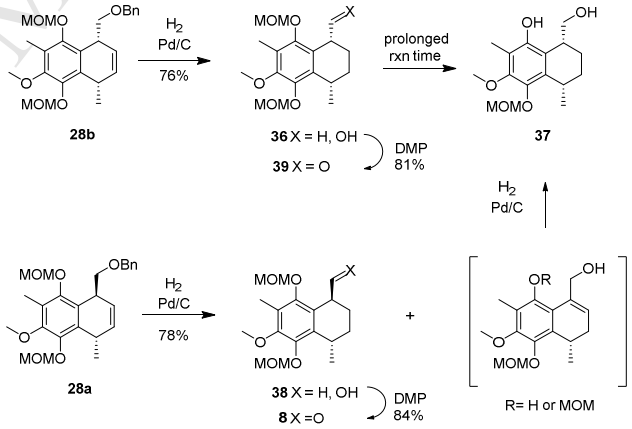
Hence, the required allyl ether **33** was synthesized in a four step sequence as it is shown in Scheme 4 and reacted with phenol **25** to give ether **34** in a good yield (Scheme 5). Compound **34** was subjected to Claisen rearrangement in presence of $Eu(fod)_3$ to yield triene **35** in 55% yield (73% brsm).

To our delight, treatment of **35** with Grubbs 2nd generation catalyst (4 mol %) yielded bicyclic compound in 88 % yield. Subsequent MOM protection of OH group enabled us to separate the two diastereomers chromatographically. The stereochemistry of both diastereomers was proven by NOESY experiments.



Scheme 5. Synthesis of **28** via relay ring closing metathesis.

With compounds **28** in hand we turned our attention to the next step - reduction of the double bond and simultaneous cleavage of Bn group (Scheme 6). Thus, exposure of *cis* diastereomer **28b** to hydrogen (4 bars) in presence of Pd/C gave after 30 min alcohol **36** in 76% yield. To our surprise, prolonged reaction times led to partial, yet selective cleavage of the "northern" MOM group (as confirmed by NOESY) to give **37**.



Scheme 6. Synthesis of **8** and **39**.

Under the same conditions hydrogenation of *trans* diastereomer **28a**, took much longer (3 h) to give **38** in 78 % yield.[20] It also underwent MOM cleavage to a certain extent dependent on the overall reaction time. Interestingly, when the reaction time was extended to 5 hours, we detected a small quantity of undesired *cis* diastereomer **37**. Most probably, the observed epimerization occurs via double bond migration and subsequent hydrogenation from the sterically less hindered face resulted in a formation of cis diastereomer **37**.

Finally, both alcohols **36** and **38** were oxidized (DMP/CH_2Cl_2) to give aldehyde **8** and **39** in 84% and 81% yield respectively (Scheme 6). The *cis* isomer **39** was treated with tBuOK in tBuOH to give after 30 min a 1:1 mixture of both isomers in a 76% yield thus increasing the yield of desired *trans* aldehyde.

3. Conclusion

We have synthesized the desired *trans* aldehyde **8** in 11 steps and 10 % overall yield. The main features of our synthesis include two sequential Lewis acid mediated Claisen rearrangements for introducing of two branched allylic chains followed by relay ring closing metathesis (RRCM) to create the B ring of elisabethin A. Although this first generation synthesis of the key intermediate **8** suffers from lack of selectivity in the first Claisen rearrangement (and as a consequence significantly reduces the overall yield) the information obtained in this approach provides valuable insight into the reactivity of the compounds in this sequence. The knowledge gained from this work helped us to develop a second generation enantio and diastereoselective synthesis of **8** which will be presented soon.

4. Experimental section

4.1. General experimental procedures

The following general procedures were used in all reactions unless otherwise noted. Glassware was oven-dried at 115°C and assembled while still hot. Schlenk flasks were flame-dried. Oxygen and moisture sensitive reactions were carried out under a slight argon overpressure using Schlenk techniques and in dry solvents. Sensitive liquids and solutions were transferred via double tipped cannula or syringes through rubber septa. All reactions were stirred magnetically unless otherwise stated.

The solvents used were purified and dried according to common procedures as follows. Dry methylene chloride and diethyl ether were retrieved from an Innovative Technologies PureSolv system. Dry tetrahydrofurane was pre-dried using an Innovative Technologies PureSolv system, refluxed over sodium/benzophenone ketyl and freshly distilled. Dry toluene and hexane were p.a. and HPLC grade, respectively, refluxed over sodium and freshly distilled. Dry DMF and DMSO were used as purchased. Ethyl acetate, petroleum ether and diethyl ether (technical grade) were distilled prior to use. Methylene chloride (technical grade) was distilled from potassium carbonate prior to use. All other solvents used were p.a. or HPLC grade. All reagents were used as received, except diisopropylethylamine (Hünig's base) and N,N-dimethylaniline, which were freshly distilled from CaH_2, and chloromethyl methyl ether[42] (MOMCl) as well as Dess-Martin periodinane which were prepared according to literature procedures.

^{1}H and ^{13}C NMR spectra were recorded on a Bruker AC 200 at 200 and 50 MHz or on a Bruker AC 400 at 400 and 100 MHz, using the solvent signal as reference. ^{13}C NMR spectra were run in proton-decoupled mode and multiplicities from APT were referred to as s (singlet), d (doublet), t (triplet), q (quartet). Multiplicities of ^{1}H signals were referred to as s (singlet), d (doublet), t (triplet), q (quartet), quin (quintet), sext (sextet), sept (septet) and m (multiplet).

IR spectra were recorded on a Perkin Elmer Spectrum 65 FT IR Spectrometer equipped with a specac MK II Golden Gate Single Reflection ATR unit.

TLC-analysis was done with precoated aluminium-backed plates (Silica gel 60 F254, Merck). Compounds were visualized by submerging in an acidic phosphomolybdic acid / cerium sulphate solution and heating. Column chromatography was carried out with silica gel Merck 60. Specific rotations were measured on an Anton Parr MCP 500 polarimeter in at 20°C and 589nm.

HR/MS: Measured at Vienna University of Technology, Institute of Chemical Technology and Analytics by Prof. Erwin Rosenberg. Samples were dissolved in CH_3CN and measured with a LC-IT-TOF-MS, EI, APCI in positive- and negative-ion-mode.

4.2. Experimental procedures

(*R*)-2-((Allyloxy)methyl)oxirane (**30**)

Sodium hydride (3.0 g; 60% dispersion in mineral oil; 75.0 mmol; 1.1 equiv.) was suspended in 250 mL of dry DMF. Allyl bromide (6.4 mL; 74.2 mmol; 1.1 equiv.) was added and the mixture was placed in an ice bath. (*S*)-(-)-Glycidol (5.1 g; 68.8 mmol) was added slowly, the ice bath was removed and the mixture was stirred overnight. After TLC confirmed completion the reaction was quenched with 20 mL of saturated ammonium chloride solution and the resulting mixture was poured onto 250 mL of diethyl ether and 250 mL of n-pentane. After stirring for 20 minutes the layers were separated, the organic layer was washed twice with water and once with brine, respectively, and dried over sodium sulphate. The solution was carefully concentrated at 40°C and ambient pressure, yielding 30 (12.7 g) as clear colourless oil.[*] NMR analysis of the crude mixture confirmed 90-95% yield.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 5.87-5.99 (1H, m); 5.31 (1H, d, *J* = 17.2 Hz); 5.22 (1H, d, *J* = 10.5 Hz); 4.00-4.13 (2H, m); 3.75 (1H, dd, *J* = 11.0, 3.4 Hz); 3.43 (1H, dd, *J* = 11.4, 5.8 Hz); 3.15-3.22 (1H, m); 2.80-2.86 (1H, m) 2.64 (1H, dd, *J* = 5.0, 2.6 Hz).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 134.4 (d); 117.4 (t); 72.8 (t); 70.8 (t); 50.8 (d); 44.4 (t).

(*R*)-1-(Allyloxy)pent-3-yn-2-ol (**32**)

To a cooled (10°C) suspension of lithium acetylide ethylenediamine complex (2.6 g; 28 mmol; 1.2 equiv.) in DMSO (50 mL) and THF (70 mL) a solution of epoxide **30** (2.7 g; 24 mmol) in of THF (10 mL) was added slowly. The mixture was stirred for 2 hours. When TLC confirmed completion aqueous HCl (5%) was added slowly until a pH of 4 was reached. Diethyl ether (180 mL) was added and the layers were separated. The aqueous layer was extracted four times with 50 mL of diethyl ether. The combined organic layers were washed six times with 20 mL of water, once with saturated sodium bicarbonate and once with brine, respectively, and dried over sodium sulphate. The solvent was removed at 200 mbar and room temperature, yielding **31** (93% according to NMR).

The crude product was dissolved in 50 mL dry DMSO. Potassium tert-butoxide (2.4 g, 21 mmol, 1 equiv.) was dissolved in dry DMSO (15 mL) and added slowly and the mixture was stirred at room temperature. After two hours[†] diethyl ether (200 mL) and solid ammonium chloride (1 g) were added and the mixture was washed with five portions of water and one portion

[*] Compound **30** is highly hygroscopic and was used in the next step without further purification. For spectral characterization it was distilled under reduced pressure to give colorless liquid.

[†] Longer reaction time or excess of potassium tert-butoxide significantly reduce the yield due to the isomerization to the corresponding vinyl ether.

of brine. After drying over sodium sulphate removal of the solvent in *vacuo* gave **32** (2.6 g, 81%) as colorless oil that could be used without further purification.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 5.83-5.95 (1H, m); 5.16-5.31 (2H, m); 4.46-4.52 (1H, m); 4.05 (2H, d, *J* = 5.6 Hz); 3.56 (1H, dd, *J* = 9.8, 3.4 Hz); 3.44-3.50 (1H, m); 2.52 (1H, broad s); 1.82 (3H, d, *J* = 2.0 Hz).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 134.2 (d); 117.6 (t); 82.0 (s); 76.9 (s); 73.9 (t); 72.3 (t); 61.7 (d); 3.6 (q).

IR: ν = 3398, 2921, 2857, 2241, 1647, 1421, 1317, 1261, 1143, 1106, 1071, 1013, 926, 890, 802, 551, 538, 515 cm^{-1}.

$[\alpha]^{20}_D$ = -13.6 (c = 0.98, CH_2Cl_2)

(*R*,*E*)-1-(Allyloxy)pent-3-en-2-ol (**33**).

To a suspension of $LiAlH_4$ (1.8 g; 48 mmol; 2 equiv.) in dry THF (20 mL) was added slowly a solution of **32** (3.4 g; 24 mmol) in THF (20 mL) and the mixture was heated to 65°C for 2 hours. After cooling to room temperature the completion was confirmed by NMR.

The mixture was cooled on ice and slowly hydrolyzed with ice-cold water. Diethyl ether (100 mL) and saturated solution of Rochelle salt (25 mL) were added and the slurry was stirred overnight. The layers were then separated and the aqueous layer was extracted with diethyl ether five times. The combined organic layers were washed with water, saturated ammonium chloride and brine, respectively, and dried over sodium sulphate.

The solution was carefully concentrated in vacuo, and the crude product was purified via column chromatography yielding **33** (3.1 g, 91%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 5.94-5.81 (m, 1H); 5.80-5.68 (m, 1H); 5.42 (ddd, 1H, *J* = 15.38, 6.67, 1.50 Hz); 5.24 (dd, 1H, *J* = 17.23, 1.38 Hz); 5.16 (dd, 1H, *J* = 10.30, 0.86 Hz); 4.27-4.18 (m, 1H); 3.99 (d, 2H, *J* = 5.64 Hz); 3.42 (dd, 1H, *J* = 9.68, 3.32 Hz); 3.28 (dd, 1H, *J* = 9.42, 8.42 Hz); 1.66 (d, 3H, *J* = 6.56 Hz).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 134.5 (d); 129.5 (d); 128.6 (d); 117.4 (t); 74.3 (t); 72.2 (t); 71.3 (d); 17.9 (q).

IR: ν = 3419, 2857, 1647, 1450, 1421, 1378, 1349, 1248, 1092, 1063, 1001, 965, 922, 558, cm^{-1}.

$[\alpha]^{20}_D$ = -19.2 (c 0.98, CH_2Cl_2)

4-((tert-Butyl(ethyl)(methyl)silyl)oxy)-3-methoxy-2-methylphenol (**21**)

A Schlenk flask was charged with **12** (4.7 g; 14.5 mmol) in dry methylene chloride and cooled to -20°C in a liquid nitrogen / acetone bath. Bromotrimethylsilane (4.8 mL; 36.3 mmol; 2.5 equiv.) was added slowly causing the mixture to turn to a dark orange. The reaction was held at about 4°C for six hours (TLC control) and subsequently quenched with 50 mL of saturated sodium bicarbonate. The layers were separated, the aqueous layer was extracted with dichloromethane and the combined organic layers were washed with brine and dried over sodium sulphate. The solvent was removed in vacuo and the resulting crude reddish brown oil was purified via column chromatography to give **21** (3.4 g 84%). Spectroscopic data are identical to those reported in the literature.[12]

(*E*)-(4-((4-(Benzyloxy)but-2-en-1-yl)oxy)-2-methoxy-3-methyl-phenoxy)(tert-butyl)(ethyl)(methyl)silane (**22**).

A three-necked round bottomed flask with septum, dropping funnel and argon inlet was charged with phenol **21** (7.3 g; 25.9 mmol) in 300 mL of dry THF and cooled to -40°C in a liquid nitrogen / acetone bath. n-Butyllithium solution (16.2 mL; 1.6 M in hexanes; 25.9 mmol; 1 equiv.) was added slowly through the septum, causing the solution to turn brightly yellow. The temperature was held at -40°C for one hour. Then allyl bromide **18** (6.3 g; 25.9 mmol; 1 equiv.) in dry DMF (100 mL) was added slowly via the dropping funnel. The solution turned greenish and then orange. After the addition was complete the cooling bath was removed and the mixture was stirred overnight. After TLC confirmed completion the reaction was quenched with 10 mL of saturated ammonium chloride solution and one spatula of solid ammonium chloride. The mixture was concentrated to about 100 mL and partitioned between 100 mL of water and 180 mL of diethyl ether. The layers were separated and the aqueous layer was extracted with 180 mL of diethyl ether two more times. The combined organic layers were washed with brine and dried over sodium sulphate. The solvent was removed in *vacuo* and the resulting crude yellow oil was purified via column chromatography, yielding **22** (yellow oil, 8.6 g (75%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.40-7.27 (m, 5H); 6.64 (d, 1H, *J* = 8.76 Hz); 6.47 (d, 1H, *J* = 8.76 Hz); 6.05-5.93 (m, 2H); 4.54 (s, 2H); 4.52-4.46 (m, 2H); 4.12-4.06 (m, 2H); 3.76 (s, 3H); 2.18 (s, 3H); 1.42-1.14 (m, 2H); 1.03 (s, 9H); 0.94-0.65 (m, 3H); 0.18 (s, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 151.7 (s); 150.1 (s); 143.2 (s); 138.3 (s); 129.3 (d); 128.8 (d); 128.5 (d, 2C); 127.9 (d, 2C); 127.8 (d); 121.6 (s); 117.3 (d); 107.3 (d); 72.4 (t); 70.2 (t); 68.7 (t); 60.1 (q); 26.4 (q, 3C); 18.9 (s); 9.4 (q); 7.6 (q); 4.9 (t); -6.5 (q).

IR: ν = 2955, 2930, 2857, 1483, 1417, 1252, 1100, 1031, 1004, 967, 882, 834, 781, 735, 697 cm^{-1}.

HRMS for $C_{26}H_{38}O_4Si$: $[M+H]^+$ calcd. 443.2612, found: 443.2618

6-(1-(Benzyloxy)but-3-en-2-yl)-4-((tert-butyl (ethyl) (methyl) silyl) oxy)-3-methoxy-2-methylphenol (**23**)

A glass pressure tube with magnetic stirring bar was charged with allyl ether **22** (2.5 g; 5.7 mmol) in of N,N-dimethylaniline (10 mL), purged with argon and screwed shut. The solution was heated to 220°C in an oil bath for 3.5 hours. After TLC confirmed completion the mixture was transferred to a separating funnel with 80 mL of diethyl ether and washed with 60 mL of 1N HCl (0.9 equivalents in respect to the dimethylaniline) in several small portions. The organic layer was then washed with saturated sodium bicarbonate and brine, respectively, and dried over sodium sulphate. The solvent was removed in *vacuo* and the resulting crude brown oil was purified via column chromatography, yielding **23** (2.1 g, yellow oil, 85%)

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.40-7.26 (m, 5H); 6.49 (s, 1H); 6.14-6.01 (m, 1H); 5.23 (d, 1H, *J* = 10.56 Hz); 5.11 (d, 1H, *J* = 17.45 Hz); 4.61 (dd, 2H, *J* = 20.59 Hz, *J* = 12.06 Hz); 3.93 (dd, 1H, *J* = 12.64, 7.92 Hz); 3.79 (s, 3H); 3.76-3.70 (m, 2H); 2.21 (s, 3H); 1.04 (s, 9H); 1.02-0.85 (m, 3H); 0.85-0.65 (m, 2H); 0.18 (s, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 148.8 (s); 147.7 (s); 142.0 (s); 137.1 (s); 136.9 (d); 128.6 (d, 2C); 128.1 (d); 127.9 (d, 2C); 123.5 (s); 120.7 (s); 118.2 (d); 116.2 (t); 74.9 (t); 73.8 (t); 60.1 (q); 45.2 (d); 26.4 (q, 3C); 18.8 (s); 9.7 (q); 7.6 (q); 4.9 (t); -6.5 (q).

IR: ν = 3316, 2955, 2929, 2858, 1639, 1604, 1481, 1455, 1421, 1361, 1341, 1296, 1251, 1208, 1093, 1062, 1004, 959, 916, 879, 827, 783, 736, 697, 662 cm^{-1}.

HRMS for $C_{26}H_{38}O_4Si$: $[M+H]^+$ calcd. 443.2612, found: 443.2622.

(5-(1-(Benzyloxy)but-3-en-2-yl)-2-methoxy-4-(methoxymethoxy) -3-methylphenoxy) (tert-butyl) (ethyl) (methyl)silane (**24**).

A Schlenk flask was charged with phenol **23** (0.5 g; 1.2 mmol) in dry THF (8 mL) and cooled to -40°C in a liquid nitrogen / acetone bath. n-Butyllithium solution (800 µL; 1.6 M in hexanes; 1.3 mmol; 1.1 equiv.) was added slowly and the mixture was stirred for 30 minutes. Then N,N-dimethylformamide (2.5 mL) and chloromethyl methyl ether (135 µL, 1.7 mmol, 1.5 equiv.) were added. The cooling bath was removed and the solution was slowly warmed to room temperature. After one hour TLC (toluene : EA 12:1) confirmed completion. The reaction was quenched with 1 mL of trimethylamine and 1 mL of saturated sodium bicarbonate. After stirring for 5 minutes the mixture was transferred to a separating funnel and extracted twice with 40 mL of toluene. The combined organic layers were washed with brine and dried over sodium sulphate. Removal of the solvent in *vacuo* yielded **24** (0.56 g, 99%) as a colourless oil which could be used without further purification.

5-(1-(Benzyloxy)but-3-en-2-yl)-2-methoxy-4-(methoxymethoxy)-3-methylphenol (**25**).

To a solution of silyl ether **24** (1.8 g; 3.8 mmol) in dry THF (20 mL) was added TBAF solution (4.2 mL; 1 M in THF; 4.2 mmol; 1.1 equiv.) and the mixture was stirred for 15 minutes at ambient temperature. After TLC confirmed completion the reaction was quenched with saturated ammonium chloride solution (20 mL). The mixture was extracted two times with 50 mL of diethyl ether, the combined organic layers were washed with 20 mL of water and brine, respectively, and dried over sodium sulphate. The solvent was removed in *vacuo* and the resulting crude brown oil was purified via column chromatography to give **25** (1.2 g, 92%) as a pale yellow oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.38-7.23 (m, 5H); 6.67 (s, 1H); 6.02 (ddd, 1H, *J* = 17.18 Hz, *J* = 10.37 Hz, *J* = 6.81 Hz); 5.72 (s, OH); 5.18-5.02 (m, 2H); 4.93 (dd, 2H, *J* = 8.04 Hz, *J* = 5.80 Hz); 4.54 (s, 2H); 4.17-4.07 (m, 1H); 3.75 (s, 3H); 3.71-3.57 (m, 2H); 3.61 (s, 3H); 2.28 (s, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 147.5 (s); 145.6 (s); 144.3 (s); 139.0 (d); 138.4 (s); 130.9 (s); 128.3 (d, 2C); 127.7 (d, 2C); 127.5 (d); 124.9 (s); 116.0 (t); 112.0 (d); 100.2 (t); 73.4 (t); 73.0 (t); 60.7 (q); 57.5 (q); 42.1 (d); 10.8 (q).

IR: ν = 3397, 2940, 2863, 2249, 1637, 1594, 1482, 1454, 1431, 1401, 1361, 1302, 1272, 1189, 1158, 1098, 1050, 972, 907, 727, 698, 648 cm^{-1}.

HRMS for $C_{21}H_{26}O_5$: $[M+Na]^+$ calcd. 381.1672, found: 381.1670.

1-(((*S*,*E*)-1-(Allyloxy)pent-3-en-2-yl)oxy)-5-(1-(benzyloxy)but-3-en-2-yl)-2-methoxy-4-(methoxymethoxy)-3-methylbenzene (**34**).

A Schlenk flask was charged with phenol **25** (0.60 g, 1.69 mmol) and allyl alcohol **33** (0.31 g, 2.19 mmol, 1.3 equiv.) in dry benzene (10 mL) and cooled to about 4°C in a water bath. Tri-n-butylphosphine (630 µL, 2.53 mmol, 1.5 equiv.) and 1,1′-(azodicarbonyl)dipiperidine (0.64 g, 2.53 mmol, 1.5 equiv.) were added in this order under vigorous stirring and the cooling bath was removed. Then the reaction was stirred overnight. After TLC confirmed completion the mixture was diluted with n-hexane (20 mL) and the tributylphosphine oxide precipitate was filtered off. The solvent was removed in *vacuo* and the resulting crude yellow oil was purified via column chromatography, yielding **34** (0.44 g, 54%) as an inseparable mixture of diastereomers.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.36-7.21 (m, 5H); 6.68-6.61 (m, 1H); 6.08-5.84 (m, 2H); 5.76-5.64 (m, 1H); 5.53-5.41 (m, 1H); 5.33-5.01 (m, 4H); 4.93-4.85 (m, 2H); 4.67 (quin, 1H, *J* = 5.92 Hz); 4.57-4.46 (m, 2H); 4.16-4.08 (m, 1H); 4.08-4.03 (m, 2H); 3.82 (s, 3H); 3.72-3.56 (m, 4H); 3.58 (s, 3H); 2.22 (s, 3H); 1.68-1.61 (m, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 148.4 (s); 148.3 (s); 147.7 (s); 147.6 (s); 147.6 (s); 147.5 (s); 139.2 (d); 139.2 (d); 138.4 (s); 134.8 (d); 134.7 (d); 130.3 (d); 130.1 (d); 129.1 (s); 129.1 (s); 128.3 (d, 2C); 128.0 (d); 127.8 (d); 127.6 (d, 2C); 127.5 (d, 2C); 127.5 (d); 127.5 (d); 125.6 (s); 125.5 (s); 116.9 (t); 115.7 (t); 115.6 (t); 114.6 (d); 114.2 (d); 100.0 (t); 79.4 (d); 79.2 (d); 73.5 (t); 73.0 (t); 72.9 (t); 72.3 (t); 60.3 (q); 60.2 (q); 57.5 (q); 41.9 (d); 41.9 (d); 17.8 (q); 10.5 (q).

IR: ν = 2857, 2248, 1637, 1588, 1482, 1453, 1434, 1399, 1336, 1236, 1204, 1158, 1058, 966, 909, 729, 698, 648, 609, 562, 549, 538, 522, 502 cm^{-1}.

HRMS for $C_{29}H_{38}O_6$: $[M+Na]^+$ calcd. 505.2561, found: 505.2603.

2-((*S*,*E*)-5-(Allyloxy)pent-3-en-2-yl)-3-(1-(benzyloxy)but-3-en-2-yl)-6-methoxy-4-(methoxymethoxy)-5-methylphenol (**35**).

A Schlenk flask was charged with allyl ether **34** (0.33 g, 676 µmol) and $Eu(fod)_3$ (0.11 g, 101 µmol, 0.15 equiv.) in degassed dry toluene (25 mL) and heated to 100°C for 8 hours. Afterwards the mixture was filtered over a plug of silica and the solvent was removed in vacuo. Purification via column chromatography gave **35** (0.17 g, 52%) as an inseparable mixture of diastereomers and **25** (0.15 g, 44%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.36-7.23 (m, 5H); 6.32-6.18 (m, 1H); 6.18-6.06 (m, 1H); 5.98-5.84 (m, 1H); 5.68-5.62 (m, 1H); 5.60-5.38 (m, 1H); 5.31-5.08 (m, 3H); 5.05-4.94 (m, 1H); 4.91-4.79 (m, 2H); 4.60-4.44 (m, 3H); 4.00-3.88 (m, 5H); 3.80-3.53 (m, 8H); 2.24 (s, 3H); 1.35 (dd, 3H, *J* = 6.50 Hz, *J* = 4.46 Hz).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 147.9 (s); 145.0 (s); 139.6 (d); 138.6 (s); 138.5 (s); 137.9 (d); 137.5 (d); 135.1 (d); 129.4 (s); 129.2 (s); 128.4 (d, 2C); 128.4 (d, 2C); 128.3 (s); 128.0 (s); 127.8 (d, 2C); 127.6 (d); 127.6 (d); 125.6 (d); 125.3 (d); 122.4 (s); 122.3 (s); 117.0 (t); 115.4 (s); 115.0 (s); 100.1 (t); 73.4 (t); 73.3 (t); 73.0 (t); 71.0 (t); 71.0 (t); 70.8 (t); 70.7 (t); 60.8 (q); 60.8 (q); 57.6 (q); 18.9 (q); 10.9 (q).

IR: ν = 3407, 2961, 2920, 2851, 1633, 1603, 1455, 1422, 1401, 1362, 1263, 1208, 1157, 968, 922, 803, 737, 698 cm^{-1}.

HRMS for $C_{29}H_{38}O_6$: $[M+Na]^+$ calcd. 505.2561, found: 505.2562.

(*1S*,*4S*)-1-((Benzyloxy)methyl)-6-methoxy-5,8-bis(methoxy-methoxy)-4,7-dimethyl-1,4-dihydronaphthalene (**28a**) and (*1R*, *4S*)-1-((benzyloxy)methyl)-6-methoxy-5,8-bis (methoxy methoxy)-4,7-dimethyl-1,4-dihydronaphthalene (**28b**).

A three-necked round bottomed flask with argon inlet was charged with **35** (0.16 g, 341 µmol) in 150 mL of dry dichloromethane. The mixture was degassed by freeze-pump-

thaw cycling three times. Then Grubbs catalyst 2nd generation (14.3 mg, 17 µmol, 2 mol%) was added and the solution was heated to 35°C for one hour. TLC showed incomplete conversion, therefore additional Grubbs catalyst (9.0 mg, 11 µmol, 2 mol%) was added and the mixture was stirred overnight. After TLC confirmed completion the reaction was quenched by bubbling air through the solution for 10 minutes. The resulting mixture was concentrated to about 10 mL and filtered over a plug of silica. After removal of the solvent in vacuo purification via column chromatography yielded 0.14 g (88%) of product as an inseparable mixture of diastereomers which was used directly for the next step.

A Schlenk flask was charged with crude product (55.3 mg, 144 µmol, mixture of diastereomers) in 15 mL of dry THF and cooled to -40°C in a liquid nitrogen / acetone bath. n-Butyllithium solution (90 µL; 1.6 M in hexanes; 144 µmol; 1 equiv.) was added and the mixture was stirred for one hour. Then DMF (1 mL) and chloromethyl methyl ether (16 µL, 216 µmol, 1.5 equiv.) were added subsequently, the cooling bath was removed and the mixture stirred overnight. After TLC confirmed completion the reaction was quenched with 0.5 mL of trimethylamine and 1 mL of saturated sodium bicarbonate solution. The resulting mixture was extracted two times with diethyl ether and the combined organic layers were subsequently washed with water and brine, dried over sodium sulphate and concentrated in vacuo. Column chromatography of the crude product yielded **28a** (35.2 mg, 57%) and **28b** (25 mg, 40%).

28a

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.38-7.23 (m, 5H); 6.07 (dd, 1H, *J* = 10.28 Hz, *J* = 2.20 Hz); 5.84 (dd, 1H, *J* = 10.28 Hz, *J* = 2.32 Hz); 5.14 (d, H, *J* = 6.0 Hz); 5.03 (d, H, *J* = 6.0 Hz); 4.97 (d, 1H, *J* = 6.0 Hz); 4.89 (d, 1H, *J* = 6.0 Hz); 4.53 (d, 1H, *J* = 12.0 Hz); 4.43 (d, 1H, *J* = 12.0 Hz); 4.0 (dd, 1H, *J* = 8.4, 3.5 Hz); 3.80 (s, 4H); 3.67-3.56 (m, 1H); 3.61 (s, 3H); 3.59 (s, 3H); 3.29 (t, 1H, *J* = 8.48 Hz); 2.20 (s, 3H); 1.34 (d, 3H, *J* = 7.00 Hz).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 151.0 (s); 150.3 (s); 145.4 (s); 139.0 (s); 133.2 (s); 130.3 (d); 128.4 (d, 2C); 127.6 (d, 2C); 127.4 (d); 124.7 (d); 123.8 (s); 123.7 (s); 99.9 (t); 99.5 (t); 75.8 (t); 73.1 (t); 60.2 (q); 57.6 (q); 57.6 (q); 36.4 (d); 30.7 (d); 24.0 (q); 10.2 (q).

$[\alpha]^{20}_D$ = +165.1 (c 0.78, CH_2Cl_2)

28b

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.38-7.24 (m, 5H); 6.17 (dd, 1H, *J* = 9.84 Hz, *J* = 4.44 Hz); 6.05 (dd, 1H, *J* = 9.86 Hz, *J* = 4.94 Hz); 5.06 (d, H, *J* = 6.0 Hz); 4.96 (d, H, *J* = 6.0 Hz); 4.86 (d, 1H, *J* = 6.0 Hz); 4.75 (d, 1H, *J* = 6.0 Hz); 4.53 (d, 1H, *J* = 12.0 Hz); 4.43 (d, 1H, *J* = 12.0 Hz); 3.99-3.90 (m, 2H); 3.80 (s, 3H); 3.70 (quin, 1H, *J* = 6.21 Hz); 3.60 (s, 6H); 3.33 (t, 1H, *J* = 10.04 Hz); 2.20 (s, 3H); 1.31 (d, 3H, *J* = 6.96 Hz).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 150.6 (s); 150.1 (s); 144.6 (s); 138.8 (s); 133.7 (s); 131.9 (d); 128.4 (d, 2C); 127.7 (d, 2C); 127.5 (d); 127.1 (d); 125.0 (s); 123.2 (s); 99.7 (t); 99.3 (t); 76.5 (t); 73.1 (t); 60.0 (q); 57.6 (q); 57.5 (q); 36.6 (d); 30.9 (d); 23.8 (q); 10.5 (q).

$[\alpha]^{20}_D$ = -84.9 (c 0.43, CH_2Cl_2)

IR: ν = 3031, 2927, 1597, 1455, 1434, 1422, 1398, 1328, 1246, 1207, 1158, 1072, 1035, 968, 928, 821, 799 cm^{-1}.

((1*S*,4*S*)-6-methoxy-5,8-bis(methoxymethoxy)-4,7-dimethyl-1,2,3,4-tetrahydronaphthalen-1-yl)methanol (**38**).

A Parr reaction vessel was charged with compound **28a** (150.0 mg; 350.0 µmol) and palladium (10% on charcoal; 20mg) in 8 mL of ethyl acetate. The mixture was shaken under 4 bars of hydrogen for two hours. After TLC confirmed completion, the mixture was filtered over celite and the solvent was removed in vacuo. Purification via column chromatography yielded 90.3 mg (78%) of clear, yellow oil,

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 5.05 (d, 1H, *J* = 6.0 Hz); 4.97 (d, 1H, *J* = 6.0 Hz); 4.91(d, 1H, *J* = 6.3 Hz); 4.86 (d, 1H, *J* = *J* = 6.3 Hz); 3.68 (s, 3H); 3.51 (s, 3H); 3.46 (dd, 1H, *J* = 10.3, 8.4 Hz); 3.14 (m, 1H,); 2.09 (s, 3H); 1.83 (m, 2H); 1.54 (m, 2H); 1.15 (d, 3H, *J* = 7.0 Hz).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 151.0 (s); 149.6 (s); 145.3 (s); 135.0 (s); 126.1 (s); 122.9 (s); 99.6 (t); 99.2 (t); 66.1 (t); 59.0 (q); 57.5 (q); 57.4 (q); 35.8 (d); 27.4 (d); 24.6 (t); 23.0 (t); 22.2 q); 18.8 (t); (10.2 (q).

$[\alpha]^{20}_D$ = +39.4 (c 1.1, CH_2Cl_2)

((*1R,4S*)-6-Methoxy-5,8-bis(methoxymethoxy)-4,7-dimethyl-1,2,3,4-tetrahydronaphthalen-1-yl)methanol (**36**).

A Parr reaction vessel was charged with compound **28b** (200.8 mg; 480.5 µmol) and palladium (10% on charcoal; 29.8 mg) in 10 mL of ethyl acetate. The mixture was shaken under 4 bar of hydrogen for 30 minutes. After TLC confirmed completion, the mixture was filtered over celite and the solvent was removed in vacuo. Purification via column chromatography yielded **36** (120.6 mg, 76%) as clear, yellow oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 5.07 (d, H, *J* = 5.64 Hz); 4.95 (d, H, *J* = 5.68 Hz); 4.87 (d, 1H, *J* = 6.9 Hz), 4.78 (d, 1H, *J* = 6.9 Hz), 3.83 (dd, 1H, *J* = 10.24 Hz, *J* = 5.92 Hz); 3.76 (s, 3H); 3.59 (s, 3H); 3.57 (s, 3H); 3.30 (m, 1H,); 3.22 (m, 1H,); 2.16 (s, 3H); 1.88-1.73 (m, 2H); 1.64-1.52 (m, 2H); 1.28 (d, 3H, *J* = 7.04 Hz).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 151.1 (s); 149.8 (s); 145.6 (s); 136.1 (s); 127.0 (s); 122.7 (s); 99.7 (t); 99.3 (t); 67.7 (t); 60.0 (q); 57.8 (q); 57.6 (q); 36.2 (d); 28.2 (d); 28.1 (t); 23.0 (t); 21.9 (q); 10.5 (q).

IR: ν = 3434, 2931, 2870, 1593, 1459, 1431, 1420, 1393, 1324, 1248, 1207, 1157, 1107, 1049, 1018, 969, 939, 797, cm^{-1}.

$[\alpha]^{20}_D$ = -19.8 (c 1.04, CH_2Cl_2)

(*1S,4S*)-6-Methoxy-5,8-bis(methoxymethoxy)-4,7-dimethyl-1,2,3,4-tetrahydronaphthalene-1-carbaldehyde (**8**).

A round bottomed flask was charged with alcohol **38** (400 mg; 1 mmol) in dichloromethane (15 mL). Pyridine (1 mL) was added, followed by Dess-Martin periodinane (790 mg; 1.6 equiv.) and the resulting yellowish solution was stirred for 10 minutes. After TLC confirmed completion the mixture was filtered over silica with a mixture of petroleum ether and ethyl acetate (4:1). Removal of the solvent in vacuo yielded **8** (300 mg, (84%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 9.63 (s, 1H); 5.08 (d, 1H, *J* = 5.51 Hz); 4.99 (d, 1H, *J* = 5.51 Hz); 4.87 (d, 1H, *J* = 5.82 Hz); 4.82 (d, 1H, *J* = 5.81 Hz) 3.78 (brd, 1H, *J*= 6.2 Hz); 3. 70 (s, 3H); 3.51 (s, 3H); 3.46 (s, 3H); 3.17 (m, 1H); 3.58 (s, 3H); 3.52 (s, 3H); 3.31-3.22 (m, 1H); 2.14 (m, 1H); 2.11 (s, 3H); 1.89 (m, 1H); 1.60-150 (m, 2H); 1.18 (d, 3H, *J* = 7.00 Hz).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 203.1 (d); 151.3 (s); 150.6 (s); 145.4 (s); 135.5 (s); 122.9 (s); 121.3 (s); 99.5 (t); 99.2 (t); 60.0 (q); 57.4 (q); 57.3 (q); 46.5 (d); 27.2 (t); 26.6 (d); 21.3 (q); 17.9 (t); 10.2 (q).

$[\alpha]^{20}_D$ = +47.2 (c 1.0, CH_2Cl_2)

(*1R,4S*)-6-Methoxy-5,8-bis(methoxymethoxy)-4,7-dimethyl-1,2,3,4-tetrahydronaphthalene-1-carbaldehyde (**39**).

A round bottomed flask was charged with in of dichloromethane (4 mL). Three drops of pyridine were added causing the periodinane to fully dissolve. Then alcohol was transferred into the mixture with three portions of dichloromethane (0.5 mL each) and the resulting yellowish solution was stirred for 10 minutes. After TLC confirmed completion the mixture was filtered over silica with a mixture of petroleum ether and ethyl acetate (4:1). Removal of the solvent in vacuo yielded **39** (180.5 mg, 81%).

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 9.43 (d, 1H, *J* = 4.20 Hz); 5.06 (d, 1H, *J* = 5.72 Hz); 4.99 (d, 1H, *J* = 5.72 Hz); 4.74 (d, 1H, *J* = 6.02 Hz); 4.72 (d, 1H, *J* = 6.00 Hz); 3.78 (s, 3H); 3.62-3.55 (m, 1H); 3.58 (s, 3H); 3.52 (s, 3H); 3.31-3.22 (m, 1H); 2.17 (s, 3H); 1.87-1.71 (m, 4H); 1.26 (d, 3H, *J* = 7.00 Hz).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 201.8 (d); 151.4 (s); 150.8 (s); 145.6 (s); 135.5 (s); 123.2 (s); 121.9 (s); 99.4 (t); 99.3 (t); 60.1 (q); 58.0 (q); 57.6 (q); 48.7 (d); 28.3 (t); 27.5 (d); 21.3 (q); 19.1 (t); 10.4 (q).

$[\alpha]^{20}_D$ = -37.6 (c 0.91, CH_2Cl_2)

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21. Compounds **36** and **38** were used to determinate the enantiopurity of our products. Accordingly, both alcohols were transformed to the corresponding Mosher's esters and based on HPLC and ^{19}F NMR analysis, the enantiomeric excess was proven to be 96%.