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Gram scale synthesis of the C(1)–C(9) fragment of amphidinolide C

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ABSTRACT

An allylic *cis*-epoxide prepared by Sharpless asymmetric epoxidation was transformed in nine steps and 41% overall yield to the cyclization precursor **4** via a key one carbon homologation. Cobalt-catalyzed aerobic oxidative cyclization of **4** gave the *trans*-THF in 94% yield at gram scale. Subsequent manipulations, including a Still–Gennari olefination, Sharpless asymmetric dihydroxylation, Corey–Fuchs alkynylation, and Kazmaier hydrostannylation provided the fully functionalized C(1)–C(9) fragment **2** suitable for cross-coupling. The sequence is readily scalable and provides gram quantities of **2**.

1. Introduction

The amphidinolides are a structurally diverse family of biologically active macrolides and linear polyketides isolated from the symbiotic marine dinoflagellate *Amphidinium* sp. by Kobayashi and co-workers.[1] Amphidinolide C (**1**, Fig. 1) is one of the most complex members featuring a 25-membered macrocycle, 2 *trans*-THF rings, and 12 stereocenters, and it displays potent bioactivities of 5.8 and 4.6 ng/mL against murine lymphoma and human epidermoid carcinoma cells, respectively.[2] The synthesis of amphidinolide C has been approached by many groups, resulting in the completion of several fragments, but no total synthesis has been reported to date.[3] The total synthesis of amphidinolide F, which contains the same macrocyclic core but a simpler side chain, has been reported by the groups of Carter and Fürstner.[4] In particular, the C(1)–C(9) fragment has attracted

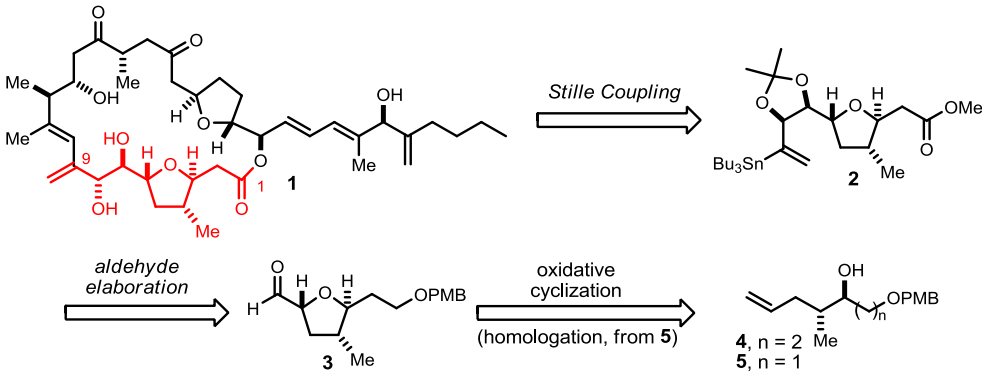

Fig. 1. Retrosynthesis of the C(1)–C(9) fragment.

considerable synthetic attention due to its significant stereochemical complexity. It contains a methyl-substituted *trans*-THF ring, an *anti*-diol, and an exocyclic olefin that is part of an unusual diene system. An efficient and scalable synthesis of the

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C(1)–C(9) fragment will be central for the total synthesis of amphidinolide C.

Our initial retrosynthetic disconnection of amphidinolide C involved a macrolactonization and C(9)–C(10) Stille cross-coupling to form the unique diene system (Fig. 1).[5] This disconnection would lead to a difunctionalized C(1)–C(9) intermediate (**2**) that would allow for straightforward late stage fragment coupling. To access the vinyl stannane, we envisioned functionalization of the THF aldehyde **3**, which could be easily achieved via a cobalt-catalyzed Mukaiyama oxidative cyclization of **4** employing our second generation catalyst, $Co(nmp)_2$.[6] We have previously reported the cyclization precursor, pentenol **4** that was made in four steps from 2,3-dihydrofuran.[7] Alternatively, we considered oxidation of **5** followed by a subsequent homologation. In this paper we describe an alternative and more practical procedure to prepare **4** via the 1-carbon homologation of **5** and the elaboration of **4** to **2**.

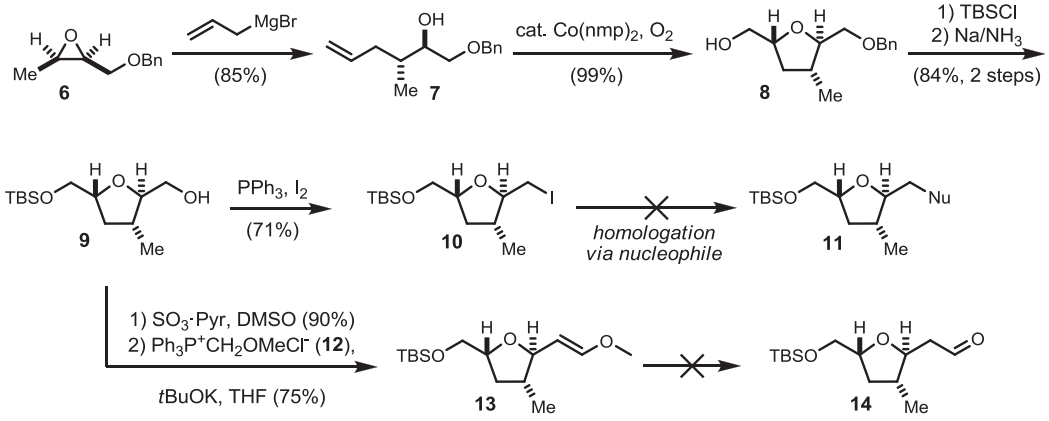
2. Results and discussion

Our synthetic route began with a strategy to homologate subsequent to the oxidative cyclization. The benzyl-protected epoxide **6**, which was easily accessed in three steps from 2-butynol and Sharpless epoxidation (Scheme 1), was converted to pentenol **7** by opening with allyl magnesium bromide. The aerobic oxidative cyclization with $Co(nmp)_2$ furnished THF alcohol **8** in quantitative yield.[6b] It is worth noting that the yield was considerably lower when employing the first generation catalysts, $Co(modp)_2$ and $Co(piper)_2$.[8]

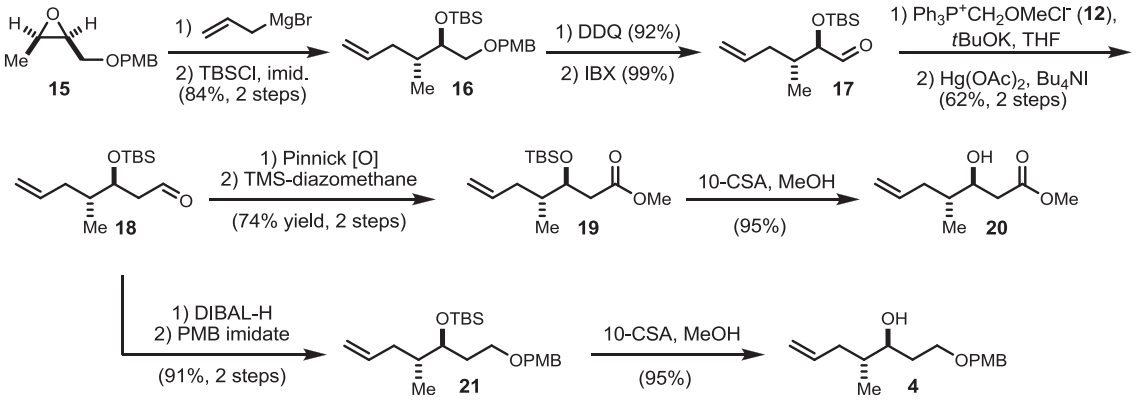
The newly formed primary alcohol was protected as a silyl ether, and the benzyl group was removed using reductive conditions to expose alcohol **9** destined for one carbon homologation. Initially, we had envisioned an umpolong nucleophilic homologation approach; thus the alcohol **9** was converted to the iodide **10**. However, the iodide failed to alkylate successfully using a variety of nucleophiles (2-Li-furan, NaCN, 2-Li-1,3-dithiane) and conditions (THF, ether, HMPA), presumably due to steric hindrance around the primary iodide.

Given the failure of homologation via nucleophilic substitution, attempts were made to lengthen the molecule by hydrolysis of an enol ether prepared by a Wittig–Schlosser olefination. Thus, alcohol **9** was oxidized to the corresponding aldehyde under Parikh–Doering conditions, followed by reaction with the ylide prepared in situ from **12** to form enol ether **13**. Presumably, a simple acid-mediated hydrolysis of the enol ether would lead to the homologated aldehyde **14**, which could serve as a key intermediate toward the C(1)–C(9) fragment. Unfortunately, despite a rigorous screen of reagents and conditions (including mercury salts), successful hydrolysis of the enol ether was not achieved. ^{1}H NMR analysis of the complex reaction mixtures suggested that cleavage of the THF was a competitive decomposition pathway. To avoid the problematic homologation with the THF intact, it was decided to address the 1-carbon homologation prior to the formation of the THF ring.

To this end, we began by opening the known Sharpless epoxide **15** (having been protected as the PMB ether) using allyl magnesium bromide followed by conversion of the resulting alcohol into the silyl ether (Scheme 2). Treatment of **16** with DDQ revealed the



Scheme 1. Failed homologation via nucleophilic substitution and enol ether hydrolysis.



Scheme 2. Successful homologation prior to THF ring formation.

primary alcohol, which was promptly oxidized to the corresponding aldehyde (**17**) using IBX. This aldehyde was converted to the enol ether using the previously optimized Wittig–Schlosser conditions, and, as anticipated, hydrolysis to the homologated aldehyde **18** proceeded smoothly using $Hg(OAc)_2$ and Bu_4NI.[9]

Aldehyde **18** could be easily converted into the methyl ester derivative **19**, which is the oxidation state found in the natural product, by Pinnick oxidation and methylation, followed by acidic TBS removal to give pentenol **20**. To converge with a previously reported route,[7] aldehyde **18** was reduced using DIBAL-H and the corresponding alcohol was protected as the PMB ether (**21**). Treatment of **21** with acidic methanol removed the TBS group in 95% yield, giving the known PMB protected pentenol **4**.[7] Compared with our previously reported route,[7] this process is longer (nine vs four steps) and lower yielding (41% vs 52%). However, it benefits from the use of inexpensive reagents, is easily scalable and successfully provides the multi-gram quantities of **20** and **4** that were required.

With a cost effective and scalable route to pentenols **20** and **4** secured, attention was given to the oxidative cyclization to form the *trans*-THF ring **25** and **26** (Table 1). Initial cyclizations using the methyl ester pentenol **20** and $Co(modp)_2$ (**23**) were unsuccessful (entry 1), and reactions using $Co(nmp)_2$ resulted in complex reaction mixtures (entry 2). Pre-activation of the catalyst (entry 3), as well as lowering both the reaction temperature and catalyst loading led to improved yields (entries 4–6), with the optimal conditions of 10% catalyst loading at 30 °C resulting in an 88% yield of **25**.

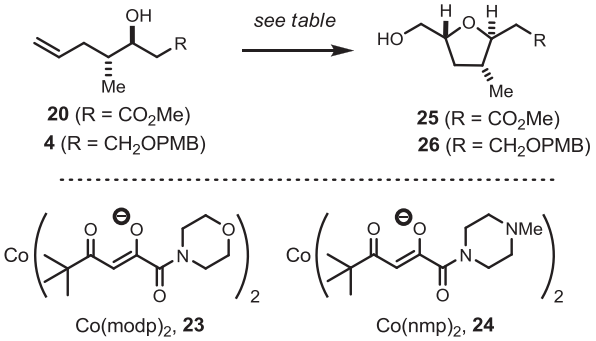
variable upon scale-up. The inconsistency rested in the cyclization being complete within an hour (which we had not observed before). After some optimization, a 94% yield of **26** on multi-gram scale was obtained using 10% catalyst loading, and a simple filtration as the only method of purification (entries 12 and 13).

To achieve the desired THF aldehyde intermediate envisioned in our retrosynthesis (**3**), both **25** and **26** were oxidized to the corresponding aldehydes (**27** and **3**) in good yield using the Parikh–Doering procedure, thus setting the stage for the final functionalization of the C(1)–C(9) fragment (Scheme 3).

We had initially envisioned the use of Williams 1-alkoxyallene (**28**) for a stereocontrolled allylation, which as reported was successfully deployed with a variety of aldehydes including a TBS-protected derivative of **3**.[10] Unfortunately, when we attempted to apply the allylation reaction on **3**, a 40:60 mixture diastereomers was obtained along with significant destannylated product. The initial report speculated that destannylation occurred via acid-mediated protonolysis that could be avoided by ensuring basic reaction conditions and work-up. In this regard, to simplify characterization the reaction mixture was treated with a 1 N HCl/THF solution for prolonged reaction times (1–4 h), but the tin moiety persisted while the MOM group was removed, which suggests that the destannylation mechanism is not due to a rapid protodestannylation.

It was suggested that the *E*/*Z* ratio of 1-alkoxyallene **28** controls the *syn*/*anti* selectivity of the alkylation;[10] however it has been

Table 1
Oxidative cyclization of **20** and **4** using $Co(modp)_2$ and $Co(nmp)_2$

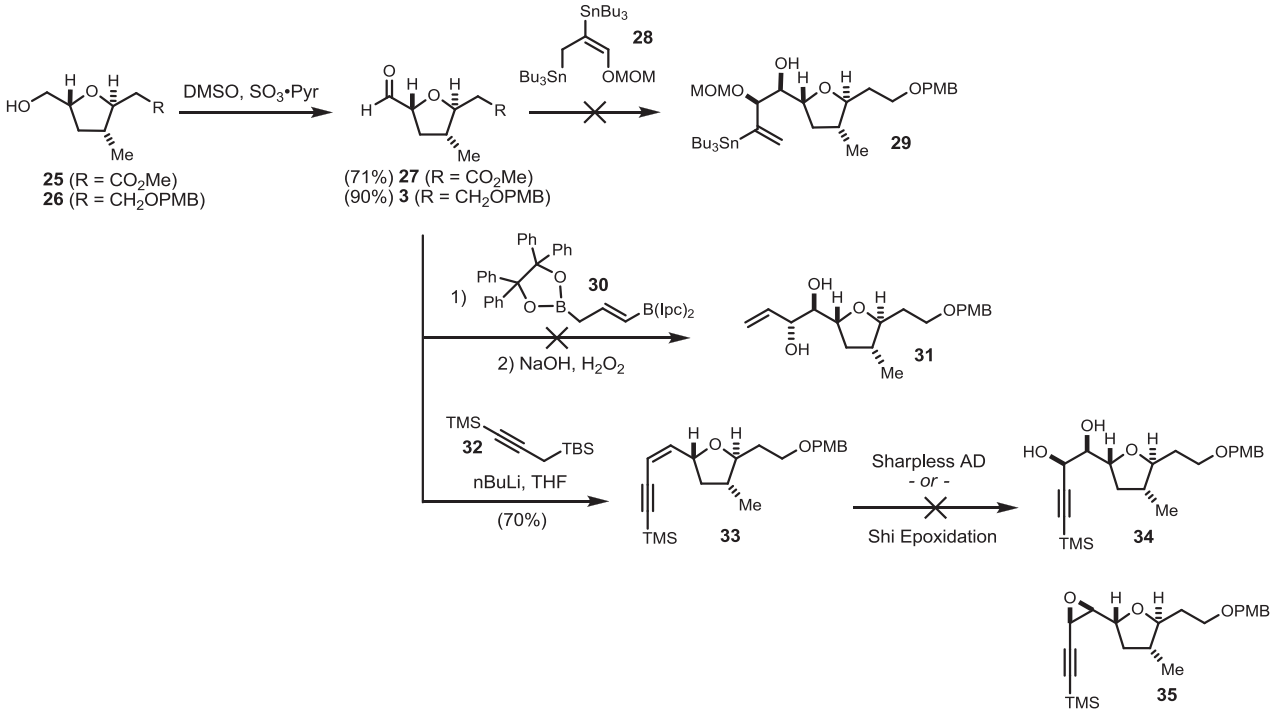


Entry	Starting material	Catalyst	Loading (mol %)	Temp (°C)	Time (h)	Product	Yield (%)
1	**20**	$Co(modp)_2$ (**23**)	15	55	16	**25**	0
2	**20**	$Co(nmp)_2$ (**24**)	15	55	16	**25**	30
3	**20**	$Co(nmp)_2$ (**24**)	15[b]	55	16	**25**	74
4	**20**	$Co(nmp)_2$ (**24**)	12[b]	40	16	**25**	80
5	**20**	$Co(nmp)_2$ (**24**)	10[b]	30	16	**25**	88
6	**20**	$Co(nmp)_2$ (**24**)	10[b]	22	24	**25**	33 (90[a])
7	**4**	$Co(modp)_2$ (**23**)	15	55	16	**26**	0
8	**4**	$Co(nmp)_2$ (**24**)	15	55	16	**26**	10
9	**4**	$Co(nmp)_2$ (**24**)	15	45	16	**26**	55
10	**4**	$Co(nmp)_2$ (**24**)	15[b]	35	16	**26**	81
11	**4**	$Co(nmp)_2$ (**24**)	15[b]	22	16	**26**	67 (85[a])
12	**4**	$Co(nmp)_2$ (**24**)	15[b]	55	1	**26**	91
13	**4**	$Co(nmp)_2$ (**24**)	10[b]	55	1	**26**	9274[c]

[a] Yields based on recovered starting material.
[b] Catalyst was pre-activated.
[c] Reaction performed on a 15 mmol scale.

As shown previously, the first generation catalyst $Co(modp)_2$ (**23**) was incompatible with the PMB protecting group,[6b] and its use gave a complex mixture of products (entry 7). The use of pre-activated $Co(nmp)_2$, lowering both the reaction temperature and catalyst loading improved the reaction yield (entries 8–11), but the yields were found to be uncharacteristically

reported in the pioneering work of Mitchell that 1-alkoxyallene (**28**) isomerizes under the $BF_3{\cdot}OEt_2$ reaction conditions employed by Williams.[11] Moreover, it was found that using either pure *trans*-**28** or a 60:40 trans/cis mixture gave identical results (a 60:40 mixture of products) using a variety of aldehydes, including hexanal.

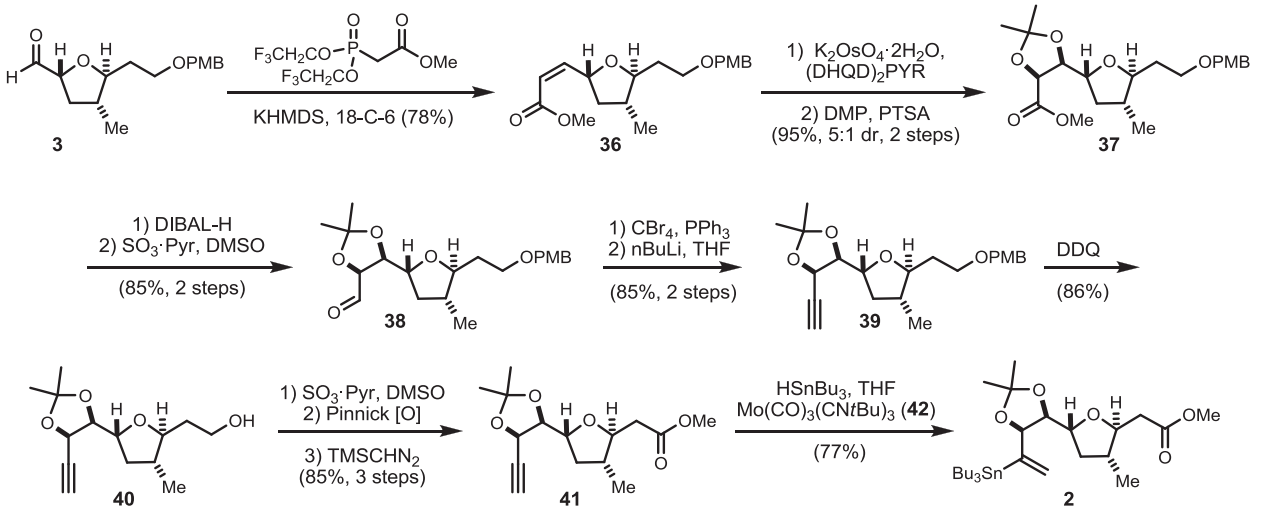


Scheme 3. Three unsuccessful approaches to functionalize the THF aldehydes **3** and **27**.

While work on the Williams allylation procedure was ongoing, the allylation/hydroboration procedure using **30** reported by Roush was explored as an alternative.[12] Unfortunately, initial attempts at reproducing the allylation conditions using **27** or **30** were unsuccessful, resulting in complex reaction mixtures. Met with early complications, this route was quickly abandoned, mostly due to the product not containing the desired vinyl-stannane moiety required for Stille cross-coupling.

A third attempt at functionalizing THF aldehyde **3** for coupling started with a Peterson–Yamamoto olefination using **32** to give **33** in a 70% yield as an 11:1 ratio of the desired cis to trans diastereomer.[13] It was speculated that the diol could be installed by either dihydroxylation or an epoxidation, ring opening, and inversion sequence. Unfortunately, when the ene–yne **33** was subjected to either Sharpless asymmetric dihydroxylation (**34**) or Shi epoxidation (**35**) conditions only starting material was recovered in all cases.

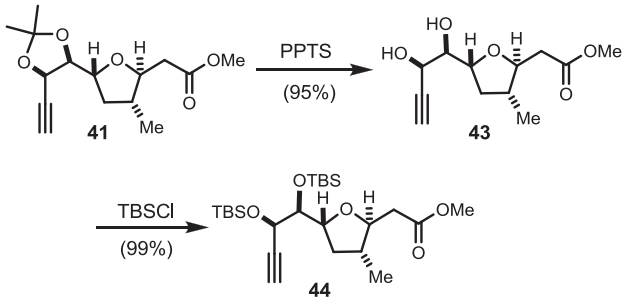
Ene–yne **33** appeared to be an ideal substrate for accessing the target **2** due to the potential conversion of the alkyne to the desired stannyl-alkene. However, with the failure of **3** to undergo dihydroxylation or epoxidation a more activated *cis* olefin was explored. Thus, *cis* α,β-unsaturated ester **36** was prepared with 14:1 cis/trans selectivity by treatment of aldehyde **3** with the Still–Gennari phosphonate (Scheme 4). The activated olefin was successfully dihydroxylated via Sharpless asymmetric dihydroxylation to give a diol as a 5:1 ratio of diastereomers, which was protected as the acetonide. Note that **37** contains the entire carbon framework and stereocenters of the C(1)–C(9) portion of amphidinolide C.



Scheme 4. Completion of the C(1)–C(9) fragment of amphidinolide C.

To fully functionalize **37** for fragment coupling, the ester was converted to the terminal alkyne (**39**) in a four-step procedure. Reduction of the ester using DIBAL-H, followed by oxidation to aldehyde **38** in 85% yield over two steps, and Corey–Fuchs reaction furnished alkyne **39** in 85% yield. The PMB protecting group was cleaved with DDQ **39** to reveal alcohol **40** in 86% yield, which was oxidized to the acid and quantitatively methylated to give methyl ester **41**. A related compound has been previously shown[3c] to undergo regioselective Kazmaier[14] hydro-stannylation with Coville's catalyst (**42**),[15] and indeed we found that the procedure proceeded smoothly to furnish the C(1)–C(9) fragment **2** in 77%.

To ensure the correct stereochemistry at the C(7)–C(8) diol, a small amount of acetonide **41** was converted to the known bis-silylated species (**44**, Scheme 5). To that end, **41** was subjected to PPTS to remove the acetonide, followed by treatment of diol **43** with 2 equiv of TBSCl to form **44** in 94% yield over two steps. The spectral data of **44** matched the reported spectra exactly, confirming the structural assignment.[3c]



Scheme 5. Conversion of **41** to **44** for stereochemical confirmation.

3. Conclusions

In summary, we have reported an inexpensive and scalable procedure to form pentenol **4** (nine steps, 41% yield) to complement our previously reported method (four steps, 52% yield). This compound was elaborated into methyl ester derivative **25**, and the versatility of the second generation $Co(nmp)_2$ has been demonstrated in the cyclization of both substrates (**4** and **20**) in excellent yield. The THF alcohol **26** was then elaborated to the fully functionalized C(1)–C(9) fragment **2** using a Still–Gennari modified HWE reaction, Sharpless asymmetric dihydroxylation, Corey–Fuchs alkynylation, and Kazmaier regioselective hydrostannylation. Further deployment of **2** for progress toward amphidinolide C is underway and will be reported in due time.

4. General details

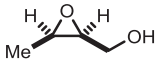
All reactions were run under an argon atmosphere unless otherwise indicated. Reaction mixtures were stirred with a magnetic stir bar. Flasks were oven dried and cooled in a desiccator or flame dried under high vacuum (1 mmHg) prior to use unless water was used in the reaction. Solvents and reagents were purified by standard methods.[16] Dichloromethane, diethyl ether, and tetrahydrofuran (THF) were purified by passing the solvents through activated alumina columns and further dried over 4 Å molecular sieves. *i*-Propanol (99.5%, 0.2% H_2O) was used as received from Caledon Laboratory Chemicals. All other chemicals were of reagent quality and used as obtained from commercial sources unless otherwise noted. The progress of reactions was monitored by thin layer chromatography (TLC) performed on F254 silica gel plates. The plates were visualized by staining with ceric ammonium molybdate (CAM)[17] or *p*-anisaldehyde. Column chromatography was performed with Silica Flash P60 60 Å silica gel from Silicycle according to the Still method.[18] Centrifugations were conducted with an International Clinical Centrifuge model CL at approximately 8000 rpm for 10 min (International Equipment Company, USA).

The ^1H and ^{13}C NMR spectra were obtained on 400 or 600 MHz spectrometers. All spectra were obtained in deuterated chloroform and were referenced to residual chloroform at δ 7.25 ppm for ^1H spectra and the center peak of the triplet at δ 77.0 (t) for ^{13}C spectra. When peak multiplicities are given, the following abbreviations are used: s, singlet; d, doublet; dd, doublet of doublets; ddd, doublet of doublet of doublets; t, triplet; q, quartet; m, multiplet; br, broad; a, apparent. EI mass spectra were obtained on a Finnigan MAT 8200.

5. Experimental section

5.1. General

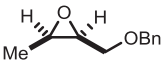
*5.1.1. ((2S,3R)-3-Methyloxiran-2-yl)methanol (**6a**).*



6a

To a 500 mL round bottom flask containing 200 g of activated 4 Å molecular sieves was added CH_2Cl_2 (250 mL), and the flask was placed in a −20 °C cooling bath. (+)-Diethyl tartrate (1.73 g, 8.4 mmol, 0.06 equiv) was added, followed by $Ti(OiPr)_4$ (2.05 mL, 7 mmol, 0.05 equiv), and *cis*-butenol (10 g, 140 mmol, 1 equiv). After 1 h, *t*BuOOH (5.33 M, 52.5 mL, 280 mmol, 2 equiv) was added portion wise over 30 min. After 24 h the septum was removed and dimethylsulfide (20.7 mL, 280 mmol, 2 equiv) was added. The reaction mixture was stirred open to atmosphere for another 24 h before being filtered through a thin pad of packed Celite, and washed with CH_2Cl_2 (500 mL). Solvent was removed under reduced pressure and the crude oil purified by flash chromatography (100% hexanes, 1 L, followed by 70% EtOAc/Hex) to give pure epoxide (**6a**) (9.47 g, 107.8 mmol, 77% yield) as a yellow oil. Spectral data match literature values, $[\alpha]_D^{20}$ −4.28 (*c* 1.0, $CHCl_3$); literature $[\alpha]_D^{20}$ −4.26 (*c* 1.0, $CHCl_3$).[19]

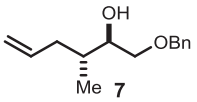
*5.1.2. (2S,3R)-2-(Benzyloxymethyl)-3-methyloxirane (**6**).*



6

To a suspension of NaH (24 mg, 10 mmol, 1.0 equiv) in DMF (10 mL) at 0 °C was added BnBr (1.71 g, 10 mmol, 1.0 equiv), followed by epoxide (880 mg, 10 mmol, 1.0 equiv). The ice bath was removed and after ca. 16 h the reaction mixture was poured into a half-saturated solution NH_4Cl (50 mL) in water ice (50 mL) and stirred for 5 min, after which the aqueous layer was extracted with EtOAc (50 mL×3). The combined organic layers were washed with brine, dried over $MgSO_4$, and filtered through a thin pad of packed Celite. Solvent was removed under reduced pressure and the crude oil was purified by flash chromatography (30% EtOAc/Hex) to yield the benzyl ether (**6**) as a colorless oil (1.61 g, 9.07 mmol, 90.7%). R_f 0.15 (10% EtOAc/Hex); ^1H NMR (400 MHz, $CDCl_3$) δ 7.36–7.27 (m, 5H), 4.63 (d, *J*=11.7, 1H), 4.53 (d, *J*=11.7 Hz, 1H), 3.70–3.66 (m, 1H), 3.58–3.54 (m, 1H), 3.19–3.15 (m, 1H), 3.12–3.07 (m, 1H), 1.26 (d, *J*=5.7 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.9, 128.4, 127.8, 73.3, 68.1, 55.1, 51.8, 13.3. HRMS *m*/*z* 178.0999 (calcd for $C_{11}H_{14}O_2$, 178.2270).

*5.1.3. (2R,3R)-1-(Benzyloxy)-3-methylhex-5-en-2-ol (**7**).*

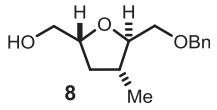


7

To a freshly prepared solution of allyl magnesium bromide (1.0 M in ether, 9 mL, 9 mmol, 1.5 equiv) was added to a flask

charged with CuI (112 mg, 0.58 mmol, 0.1 equiv) cooled to −78 °C. The cuperate was stirred for 30 min at −78 °C before epoxide **6** (1.04 g, 5.89 mmol, 1.0 equiv) was added neat. The cooling bath was packed with dry ice and the reaction mixture was allowed to warm to rt overnight (ca. 16 h). The reaction mixture was carefully poured into a half-saturated solution NH_4Cl (20 mL) in water ice (40 mL) and stirred for 30 min, after which time the aqueous layer was extracted with EtOAc (30 mL×3). The combined organic layers were washed with brine, dried over $MgSO_4$, and filtered through a thin pad of packed Celite. Solvent was removed under reduced pressure and the crude oil was purified by flash chromatography (20% EtOAc/Hex) to yield the major diastereomer **7** (827 mg, 3.76 mmol, 64%) as a yellow oil and the minor diastereomer (194 mg, 0.88 mmol, 15%) as a yellow oil. R_f 0.61 (40% EtOAc/Hex); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38–7.26 (m, 5H), 5.84–5.73 (m, 1H), 5.05–4.98 (m, 1H), 4.55 (s, 2H), 3.63–3.56 (m, 2H), 3.40 (t, J=9.0 Hz, 1H), 2.42 (s, 1H), 2.38–2.31 (m, 1H), 1.99–1.91 (m, 1H), 1.73–1.64 (m, 1H), 0.85 (d, J=7.0 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.0, 137.0, 128.4, 127.8, 127.7, 116.2, 73.8, 72.5, 37.0, 35.8, 15.2. HRMS m/z 220.1459 (calcd for $C_{14}H_{20}O_2$, 220.31).

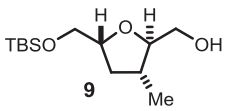
*5.1.4. ((2R,4R,5R)-5-(Benzyloxymethyl)-4-methyltetrahydrofuran-2-yl)methanol (**8**).*



8

The cyclization precursor **7** (200 mg, 0.91 mmol, 1.0 equiv) was added as a solution in 10 mL *i*PrOH to a flask charged with Co(nmp)$_2$ (**24**) (85 mg, 0.15 mmol, 0.15 equiv) under 1 atm of O_2 (via balloon). At room temperature, *tert*-butyl hydrogen peroxide (5.33 M in isooctane, 0.2 mL, 1.0 mmol, 1.1 equiv) was added in one portion, and the resulting solution was heated at 55 °C for 16 h. The flask was then cooled to room temperature, purged with argon, and methyl iodide (0.62 mL, 1.0 mmol, 1.1 equiv) was added to the reaction mixture at room temperature and stirred for 24 h. The solution was concentrated under reduced pressure (0.1 mmHg) to remove all traces of *i*PrOH, and the residue was dissolved in water (10 mL) and CH_2Cl_2 (20 mL). The heterogeneous mixture was separated and the aqueous layer was extracted with CH_2Cl_2 (4×10 mL). The combined organic layers were washed with brine, dried ($MgSO_4$), filtered through a thin pad of silica on top of a thin pad of Celite and concentrated under reduced pressure to yield **8** as a yellow oil (145 mg, 0.61 mmol, 67%), which was used without further purification. R_f 0.23 (70% EtOAc/Hex); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35–7.25 (m, 5H), 4.58 (s, 2H), 4.13–4.05 (m, 1H), 3.70–3.65 (m, 2H), 3.56 (dd, J=7.3, 3.0 Hz, 1H), 23.52–3.46 (m, 2H), 2.10–2.03 (m, 2H), 1.46–1.40 (m, 1H), 1.03 (d, J=7.0 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.2, 128.3, 127.6, 127.6, 84.7, 79.2, 73.4, 71.7, 64.8, 36.5, 36.3, 16.8. HRMS m/z 236.1411 (calcd for $C_{14}H_{20}O_3$, 236.31).

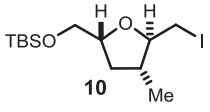
*5.1.5. ((2R,3R,5R)-5-((tert-Butyldimethylsilyloxy)methyl)-3-methyltetrahydrofuran-2-yl)methanol (**9**).*



9

To a solution of alcohol (**8**) (1.56 mg, 6.6 mmol, 1 equiv) in CH_2Cl_2 (100 mL) was added imidazole (830 mg, 12.3 mmol, 2 equiv), followed by TBSCl (994 mg, 6.6 mmol, 1 equiv) and DMAP (5 mg, catalytic). The reaction mixture was stirred overnight (ca. 16 h) before being poured into a half-saturated solution of NH_4Cl (200 mL), and the aqueous layer was extracted with CH_2Cl_2 (3×200 mL) and the combined organic layers were washed with brine (200 mL) and dried over $MgSO_4$. Solvent was removed under reduced pressure to give the TBS alcohol, which was used without further purification. An empty 250 mL round bottom flask equipped with a septa with a syringe in it, and a needle attached to a tank of gaseous ammonia was cooled to −78 °C. The ammonia tank was opened to allow a slow but steady stream of ammonia until approximately 50 mL had condensed in the flask. To the flask containing the liquid ammonia was slowly added THF (50 mL) and a large chunk of sodium. The reaction mixture was stirred at −78 °C for 40 min, by which time the sodium dissolved and the solution turned blue. The TBS alcohol in THF (20 mL) was added dropwise over 10 min, and the reaction mixture was stirred for an additional 30 min. The cooling bath was removed, the flask was allowed to warm to room temperature, and stirred for 30 min to allow evaporation of the ammonia. The reaction mixture was then poured into a solution of half-saturated NH_4Cl (200 mL) and the aqueous layer was extracted with EtOAc (3×100 mL). The combined organic layers are dried over $MgSO_4$, filtered through a pad of Celite and concentrated to dryness under vacuum. The crude material was purified by column chromatography to give the product alcohol (**9**) as a yellow oil (1.20 g, 4.62 mmol, 70% yield over two steps). R_f 0.42 (50% EtOAc/Hex); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.06–4.02 (m, 1H), 3.74 (dd, J=11.3, 2.3 Hz, 1H), 3.62 (d, J=4.7 Hz, 2H), 3.54–3.49 (m, 2H), 2.15–2.09 (m, 2H), 1.46–1.41 (m, 1H), 1.02 (d, J=6.4 Hz, 3H), 0.89 (s, 9H), 0.05 (6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 85.9, 79.3, 66.0, 62.9, 37.4, 34.8, 25.9, 18.4, 16.4, −5.3. HRMS m/z 261.1877 (calcd for $C_{13}H_{28}O_2Si$, 260.45).

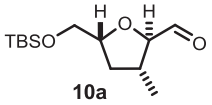
*5.1.6. tert-Butyl(((2R,4R,5R)-5-(iodomethyl)-4-methyltetrahydrofuran-2-yl)methoxy) dimethylsilane (**10**).*



10

To a flask charged with alcohol **9** (250 mg, 0.96 mmol, 1.0 equiv), triethylamine (0.3 mL, 1.92 mmol, 2.0 equiv), diluted with CH_2Cl_2 (10 mL) and cooled to 0 °C was added methanesulfonyl chloride (0.081 mL, 1.05 mmol, 1.1 equiv) dropwise. The reaction mixture was allowed to stir at rt for 30 min before being poured into a half-saturated solution of ammonium chloride (10 mL) and diluted with CH_2Cl_2 (50 mL). The aqueous layer was extracted with CH_2Cl_2 (3×50 mL) and the combined organic layers were washed with brine, dried with $MgSO_4$, and filtered through a thin pad of Celite. Solvent was removed under reduced pressure to afford the mesylate as a yellow oil (325 mg, 0.96 mmol, 100%), which was used without further purification. To a flask charged with the mesylate (325 mg, 0.96 mmol, 1 equiv) in wet acetone (10 mL) equipped with a reflux condenser was added NaI (720 mg, 4.8 mmol, 5.0 equiv). The reaction mixture was heated to vigorous reflux and allowed to stir overnight (ca. 16 h) before being cooled to 0 °C and filtered through a thin pad of silica over Celite. Solvent was removed under reduced pressure to afford a yellow oil, which was purified by column chromatography (10% EtOAc/Hex) to afford **10** (287 mg, 0.78 mmol, 81%) as a yellow oil. R_f 0.47 (10% EtOAc/Hex); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.12–4.08 (m, 1H), 3.66–3.62 (m, 2H), 3.39 (dd, J=11.3, 2.3 Hz, 1H), 3.34 (dt, J=10.3, 2.5 Hz, 1H), 3.22 (dd, J=6.4, 4.5 Hz, 1H), 2.20–2.16 (m, 1H), 2.06–2.00 (m, 1H), 1.61–1.55 (m, 1H), 1.05 (d, J=7.0 Hz, 3H), 0.89 (s, 9H), 0.06 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 84.0, 79.0, 65.7, 40.4, 37.3, 26.0, 18.4, 17.0, 10.1, −5.2.

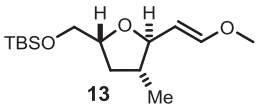
*5.1.7. (2R,3R,5R)-5-((tert-Butyldimethylsilyloxy)methyl)-3-methyltetrahydrofuran-2-carbaldehyde (**10a**).*



10a

A 50 mL round bottom flask containing oxalyl chloride (0.20 mL, 2.4 mmol, 1.2 equiv) in 15 mL of CH_2Cl_2 was cooled to −78 °C and DMSO (0.34 mL, 4.8 mmol, 2.4 equiv) in 5 mL CH_2Cl_2 was added slowly portion wise over 20 min. After stirring for 45 min, alcohol **10** (285 mg, 1.09 mmol, 1 equiv) was added in 5 mL CH_2Cl_2 over 5 min slowly dropwise. After stirring for 1.5 h at −78 °C, triethylamine (1 mL, 10 mmol, 5 equiv) was added portion wise over 5 min. After stirring for 15 min the dry ice/acetone bath was replaced with a water ice/ice bath and the reaction mixture was allowed to warm to 0 °C, and stirred for 15 min. The reaction mixture was poured into 10% HCl (50 mL), extracted with CH_2Cl_2 (3×50 mL), and the combined organic layers were washed with saturated sodium bicarbonate (50 mL), brine (50 mL), and dried over $MgSO_4$. Excess solvent was removed under reduced pressure, giving **10a** (282 mg, 1.09 mmol, 99% yield), which was used without further purification. R_f 0.69 (50% EtOAc/Hex); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.62 (s, 1H), 4.18 (td, J=9.9, 4.1 Hz, 1H), 3.75 (dd, J=9.3, 2.9 Hz, 1H), 3.72 (dd, J=11.3, 4.1 Hz, 1H), 3.65 (dd, J=11.3, 4.1 Hz, 1H), 2.31–2.24 (m, 1H), 2.18–2.14 (m, 1H), 1.57–1.52 (m, 1H) 1.14 (d, J=7.0 Hz, 3H), 0.89 (s, 9H), 0.06 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.4, 138.0, 88.9, 81.3, 65.3, 36.9, 36.5, 25.9, 16.3, −5.4.

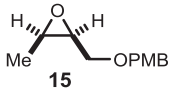
*5.1.8. tert-Butyl(((2R,4R,5R)-5-((E)-2-methoxyvinyl)-4-methyltetrahydrofuran-2-yl)methoxy)dimethylsilane (**13**).*



13

To a solution of *t*BuOK (134 mg, 1.2 mmol, 1.3 equiv) in THF (3 mL) was added Ph_3PCH_2OMeCl (479 mg, 1.4 mmol, 1.5 equiv) in one portion, and the red solution was stirred at rt for 1 h. To the red solution was added crude aldehyde (**10a**) (235 mg, 0.9 mmol, 1 equiv) in a minimal amount of THF (ca. 2 mL). After 1 h the crude reaction mixture was poured into a rapidly stirring solution of half-saturated NH_4Cl (30 mL), and the aqueous layer was extracted with CH_2Cl_2 (3×20 mL) and the combined organic layers were washed with brine, dried over $MgSO_4$ and filtered through a thin pad of packed Celite/silica. Solvent was removed under reduced pressure to give the crude enol ether (**13**) (192 mg, 0.67 mmol, 75%) used in the next reaction without further purification. R_f 0.28 (10% EtOAc/Hex); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 6.52 (d, J=12.9 Hz, 0.5H), 6.06 (d, J=5.5 Hz, 0.5H), 4.69 (dd, J=12.7, 8.8 Hz, 0.5H), 4.40–4.33 (m, 1.5H), 4.10–4.04 (m, 1H), 3.73–3.56 (m, 6H), 2.20–2.13 (m, 1H), 1.89–1.83 (m, 1H), 1.55–1.43 (m, 2H), 1.00 (d, J=7.0 Hz, 1.5H), 0.98 (d, J=7.0 Hz, 1.5H), 0.91 (s, 9H), 0.06 (s, 6H). HRMS m/z 286.1973 (calcd for $C_{15}H_{30}O_3Si$, 286.48).

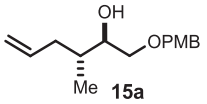
*5.1.9. (2S,3R)-2-((4-Methoxybenzyloxy)methyl)-3-methyloxirane (**15**).*



15

To a solution of NaH (2.3 g, 95.7 mmol, 1.1 equiv) in DMF (200 mL) cooled to 0 °C was added 4-methoxybenzyl bromide (20.3 g, 101 mmol, 1.16 equiv), followed by dropwise addition of epoxide **6a** (7.7 g, 87 mmol, 1 equiv). The reaction mixture was warmed to rt and after 30 min it was judged to be complete by TLC analysis. The reaction mixture was poured into a solution of saturated NH_4Cl (200 mL) in water ice (500 mL) and stirred for 10 min, after which the aqueous layer was extracted with EtOAc (300 mL×3). The combined organic layers were washed with brine, dried over $MgSO_4$, and filtered through a thin pad of packed Celite. Solvent was removed under reduced pressure and the crude oil was purified by flash chromatography (20% EtOAc/Hex) to yield **15** (15.6 g, 74.8 mmol, 86%) as a yellow oil. R_f 0.40 (30% EtOAc/Hex); ^{1}H NMR ($CDCl_3$, 600 MHz): δ 7.27 (d, J=8.7 Hz, 2H), 6.87 (d, J=8.7 Hz, 2H), 4.51 (ABd, J=11.7 Hz, 2H), 3.79 (s, 3H), 3.63 (dd, J=10.5, 4.7 Hz, 1H), 3.53 (dd, J=11.3, 6.4 Hz, 1H), 3.14 (dt, J=6.2, 4.2 Hz, 1H), 3.08 (pent, J=5.1 Hz, 1H), 1.25 (d, J=5.9 Hz, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 159.2, 129.9, 129.4, 113.9, 72.9, 67.7, 55.2, 55.0, 51.7, 13.3. HRMS m/z 208.1099 (calcd for $C_{12}H_{16}O_3$, 208.1099).

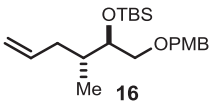
*5.1.10. (2R,3R)-1-(4-Methoxybenzyloxy)-3-methylhex-5-en-2-ol (**15a**).*



15a

To a freshly prepared solution of allyl magnesium bromide (1.0 M in ether, 90 mL, 90 mmol, 1.5 equiv) was added to a flask charged with CuI (1.12 g, 5.88 mmol, 0.1 equiv) cooled to −78 °C. The cuperate was stirred for 30 min at −78 °C before epoxide **15** (12.26 g, 58.9 mmol, 1 equiv) was added neat. The cooling bath was packed with dry ice and the reaction mixture was allowed to warm to rt overnight (ca. 16 h). The reaction mixture was carefully poured into a half-saturated solution NH_4Cl (200 mL) in water ice (400 mL) and stirred for 30 min, after which the aqueous layer was extracted with EtOAc (300 mL×3). The combined organic layers were washed with brine, dried over $MgSO_4$, and filtered through a thin pad of packed Celite. Solvent was removed under reduced pressure and the crude oil was purified by flash chromatography (20% EtOAc/Hex) to yield the major diastereomer **15a** (12.06 g, 48.2 mmol, 85%) as a yellow oil and the minor diastereomer (1.34 g, 5.36 mmol, 9%) as a yellow oil. R_f 0.28 (20% EtOAc/Hex); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 (d, J=9.0 Hz, 2H), 6.88 (d, J=9.0 Hz, 2H), 5.77 (dddd, J=16.9, 10.2, 7.8, 6.4 Hz, 1H), 5.03–4.99 (m, 2H), 4.48 (d, J=1.6 Hz, 2H), 3.79 (s, 3H), 3.56–3.53 (m, 1H), 3.39–3.35 (m, 1H), 2.42 (br s, 1H), 2.37–2.31 (m, 1H), 1.98–1.89 (m, 1H), 1.73–1.63 (m, 1H), 0.85 (d, J=6.6 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.2, 137.0, 130.0, 129.2, 116.0, 113.7, 73.6, 72.9, 72.1, 55.1, 36.9, 35.7, 15.1. HRMS m/z 250.1572 (calcd for $C_{15}H_{22}O_3$, 250.1569).

*5.1.11. tert-Butyl((2R,3R)-1-(4-methoxybenzyloxy)-3-methylhex-5-en-2-yloxy)dimethylsilane (**16**).*

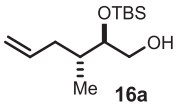


16

To a solution of alcohol (**15a**) (10.7 g, 42.6 mmol, 1 equiv) in DMF (300 mL) was added imidazole (5.8 g, 85.2 mmol, 2 equiv), followed by TBSCl (6.6 g, 42.6 mmol, 1 equiv) and DMAP (50 mg, catalytic). The reaction mixture was stirred overnight (ca. 16 h) before being poured into a half-saturated solution of NH_4Cl, and the aqueous layer was extracted with CH_2Cl_2 (5×200 mL) and the combined organic layers were washed with brine and dried over $MgSO_4$. Solvent was removed under reduced pressure to give the TBS alcohol, which was purified by flash chromatography (5% EtOAc/Hex) to give the pure alcohol (**16**) as a yellow oil (15.3 g, 42.2 mmol, 99% yield). R_f 0.53 (10% EtOAc/Hex); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.25 (d, J=8.8 Hz, 2H), 6.88 (d, J=8.8 Hz, 2H), 5.80–5.75 (m, 1H), 5.01–4.97 (m, 2H), 4.44 (q, J=9.4 Hz, 2H), 3.80 (s, 3H), 3.71 (q, J=4.8 Hz, 1H), 3.46 (dd, J=9.7, 5.0 Hz, 1H), 3.37 (dd, J=9.7, 6.2 Hz, 1H), 2.25–2.21

(m, 1H), 1.87–1.82 (m, 1H), 1.79–1.72 (m, 1H), 0.89 (s, 3H), 0.89 (s, 9H), 0.06 (s, 6H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 159.0, 138.0, 130.5, 129.2, 115.5, 113.6, 75.1, 72.9, 72.5, 55.2, 36.5, 36.0, 25.9, 18.2, 15.9, −4.2, −4.9. HRMS *m/z* 363.2341 (calcd for $C_{21}H_{36}O_3Si$, 364.2434). $[\alpha]_D^{20}$ +4.11 (*c* 1.0, $CHCl_3$).

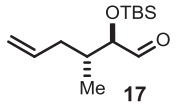
*5.1.12. (2R,3R)-2-(tert-Butyldimethylsilyloxy)-3-methylhex-5-en-1-ol (**16a**).*



16a

PMB alcohol (**16**) (6.89 g, 18.9 mmol, 1 equiv) was dissolved in CH_2Cl_2 (140 mL), water (35 mL), and saturated sodium bicarbonate (10 mL). DDQ (8.58 g, 37.8 mmol, 2 equiv) was added in one portion and the reaction mixture was rigorously stirred for 1.5 h at which point the reaction was judged to be complete by TLC analysis. The reaction mixture was poured into a rapidly stirring solution of half-saturated sodium bicarbonate (100 mL) and half-saturated sodium thiosulfate (200 mL), and the aqueous layer was extracted with CH_2Cl_2 (5×200 mL) and the combined organic layers were washed with brine and dried over $MgSO_4$. Solvent was removed under reduced pressure to give the crude alcohol, which was purified by flash chromatography (10% EtOAc/Hex) to give the pure alcohol **16a** as a yellow oil (4.24 g, 17.4 mmol, 92% yield). R_f 0.51 (20% EtOAc/Hex); ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.74 (ddd, *J*=17.0, 10.1, 7.0 Hz, 1H), 5.03–4.98 (m, 2H), 3.59–3.55 (m, 3H), 2.25–2.21 (m, 1H) 1.84–1.77 (m, 3H), 0.90 (s, 9H), 0.87 (s, *J*=7.0 Hz, 3H), 0.06 (s, 6H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 137.3, 115.9, 76.2, 63.5, 37.2, 36.3, 25.8, 18.1, 14.9, −4.4, −4.5. HRMS *m/z* 245.1942 (calcd for $C_{13}H_{28}O_2Si$, 244.1859). $[\alpha]_D^{20}$ −4.36 (*c* 1.0, $CHCl_3$).

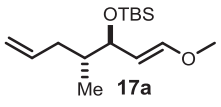
*5.1.13. (2R,3R)-2-(tert-Butyldimethylsilyloxy)-3-methylhex-5-enal (**17**).*



17

Alcohol **16a** (4.02 g, 16.4 mmol, 1 equiv) was dissolved in wet EtOAc (120 mL), and IBX (9.2 g, 32.9 mmol, 2 equiv) was added. The suspension was stirred at 80 °C for 5 h, at which point the reaction was judged complete by TLC analysis. The flask was removed from the heat and allowed to cool to rt before the solution was filtered through a thin pad of silica over a pad of packed Celite, and the filter cake was washed with 400 mL EtOAc. Solvent was removed under reduced pressure to give the pure aldehyde **17** (3.97 g, 16.3 mmol, 99% yield), which was used in the next step without further purification. R_f 0.72 (20% EtOAc/Hex); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.61 (d, *J*=2.0 Hz, 1H), 5.69 (ddd, *J*=17.0, 10.0, 7.2 Hz, 1H), 5.05–4.99 (m, 2H), 3.79 (dd, *J*=4.3, 2.0 Hz, 1H), 2.26–2.20 (m, 1H) 2.05–1.89 (m, 2H), 0.95 (s, 9H), 0.92 (d, *J*=6.6 Hz, 3H), 0.06 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 205.0, 136.9, 116.8, 81.2, 37.3, 35.8, 25.7, 18.2, 16.1, −4.5, −4.6.

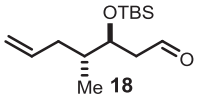
*5.1.14. tert-Butyl((3R,4R,E)-1-methoxy-4-methylhepta-1,6-dien-3-yloxy)dimethylsilane (**17a**).*



17a

To a solution of *t*BuOK (3.90 g, 34.8 mmol, 2.0 equiv) in THF (200 mL) was added Ph_3PCH_2OMeCl (13.1 g, 38.3 mmol, 2.2 equiv) in one portion, and the red solution was stirred at rt for 1 h. To the red solution was added crude aldehyde (**17**) (3.97 g, 16.4 mmol, 1 equiv) in a minimal amount of THF (ca. 20 mL). After 16 h the crude reaction mixture was poured into a rapidly stirring solution of half-saturated NH_4Cl (300 mL), and the aqueous layer was extracted with CH_2Cl_2 (3×200 mL) and the combined organic layers were washed with brine, dried over $MgSO_4$, and filtered through a thin pad of packed Celite/silica. Solvent was removed under reduced pressure to give the crude enol ether (**17a**), which was contaminated with some Wittig byproducts, and the crude mixture was used in the next reaction without further purification.

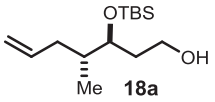
*5.1.15. (3S,4R)-3-(tert-Butyldimethylsilyloxy)-4-methylhept-6-enal (**18**).*



18

The crude mixture of enol ether (**17a**) and Wittig byproducts was dissolved in wet THF (300 mL) and water (30 mL), and $Hg(OAc)_2$ (7.84 g, 24.6 mmol, 1.5 equiv) was added in one portion. The solution was stirred at rt for 1.5 h at which point disappearance of the enol ether was confirmed by TLC analysis. Tetrabutylammonium iodide (18.1 g, 49.2 mmol, 3 equiv) was added in one portion, and the reaction mixture was stirred for 1 h at rt before being poured into a rapidly stirring solution of half-saturated KI (100 mL) and half-saturated sodium thiosulfate (200 mL), and the aqueous layer was extracted with CH_2Cl_2 (4×200 mL) and the combined organic layers were washed with brine dried over $MgSO_4$ and filtered through a thin pad of packed Celite. Solvent was removed under reduced pressure to give the crude aldehyde, which was purified by flash chromatography (20% EtOAc/Hex) to give the pure aldehyde **18** (2.60 g, 10.2 mmol, 62% yield over two steps). R_f 0.50 (10% EtOAc/Hex); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.79 (s, 1H), 5.78–5.71 (m, 1H), 5.02–5.00 (m, 2H), 4.14 (dt, *J*=8.2, 4.1 Hz, 1H), 2.54–2.49 (m, 1H), 2.42–2.26 (m, 1H), 2.11–2.07 (m, 1H), 1.85 (dt, *J*=14.3, 7.5 Hz, 1H), 1.74 (dt, *J*=12.9, 6.4 Hz, 1H), 0.88 (d, *J*=7.0 Hz, 3H), 0.86 (s, 9H), 0.04 (d, *J*=17.5 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.5, 136.8, 116.2, 71.0, 46.5, 39.1, 37.4, 25.7, 18.0, 14.0, −4.5, −4.6.

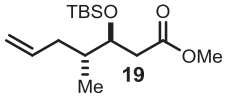
*5.1.16. (3S,4R)-3-(tert-Butyldimethylsilyloxy)-4-methylhept-6-en-1-ol (**18a**).*



18a

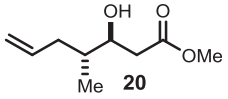
To a round bottom flask cooled to 0 °C and charged with DIBAL-H (1.0 M, 82 mL, 82 mmol, 2.0 equiv) in CH_2Cl_2 (200 mL) was added aldehyde (**18**) (10.5 g, 41 mmol, 1 equiv) portion wise over 10 min. The reaction mixture was stirred at rt until completion by TLC analysis (ca. 0.5 h). The reaction mixture was poured into half-saturated solution of NH_4Cl (200 mL) and a solution of Rochelle's salt (25 g in 100 mL water), and CH_2Cl_2 was added. The solution was stirred vigorously until it became homogenous (ca. 16 h), after which the aqueous layer was extracted with CH_2Cl_2 (3×100 mL) and the combined organic layers were washed with brine and dried with $MgSO_4$. Solvent was removed under reduced pressure to afford the crude product, which was purified by flash chromatography (10% EtOAc/Hex) to give alcohol (**18a**) as a yellow oil (9.85 g, 38.1 mmol, 93% yield). R_f 0.46 (20% EtOAc/Hex); ^{1}H NMR (600 MHz, $CDCl_3$) δ 5.74 (ddt, *J*=17.3, 10.0, 7.1 Hz, 1H), 5.01–4.97 (m, 2H), 3.79–3.71 (m, 3H), 2.21 (br t, *J*=4.9 Hz, 1H), 2.13–2.06 (m, 1H), 1.85–1.75 (m, 1H), 1.74–1.68 (m, 1H), 1.68–1.61 (m, 2H), 0.88 (s, 9H), 0.85 (d, *J*=6.6 Hz, 3H), 0.06 (d, *J*=3.9 Hz, 6H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 137.3, 115.8, 74.4, 60.7, 38.4, 37.8, 33.3, 25.8, 18.0, 13.8, −4.4, −4.6. HRMS *m/z* 259.2085 (calcd for $C_{14}H_{30}O_2Si$, 258.2015).

*5.1.17. (3S,4R)-Methyl 3-(tert-butyldimethylsilyloxy)-4-methylhept-6-enoate (**19**).*



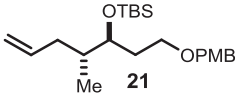
To the crude aldehyde **18** (100 mg, 0.4 mmol, 1.0 equiv) and 2-methyl-2-butene (0.17 mL, 1.6 mmol, 4 equiv) in *t*BuOH (3 mL) and pH 7 buffer (0.67 M, 2 mL) was added $NaClO_2$ (113 mg, 1 mmol, 2.5 equiv) in water (1 mL). The reaction mixture was monitored by TLC until completion (ca. 30 min) at which point it was poured into a half-saturated solution of sodium sulfate (30 mL) and acidified with HCl (2 M solution, 3 mL). The aqueous layer was extracted with CH_2Cl_2 (5×20 mL) and the combined organic layers were washed with brine and dried over $MgSO_4$. Solvent was removed under reduced pressure, and the crude oil was dissolved in MeOH (10 mL) and CH_2Cl_2 (10 mL) and a stir bar was added. To the solution was added TMS–diazomethane (1.0 M solution) dropwise until the yellow color persists (ca. 0.1 mL). The reaction mixture was stirred an additional 5 min before excess acetic acid (1 mL) was added in one portion and the color dissipates. Volatiles were removed under reduced pressure and the oil was purified by flash chromatography (20% EtOAc/Hex) to give pure methyl ester **19** (81 mg, 0.297 mmol, 74%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.76 (ddt, J=16.9, 10.0, 7.0 Hz, 1H), 5.01 (d, J=7.0 Hz, 1H), 4.97 (s, 1H), 4.12 (dt, J=8.0, 4.2 Hz, 1H), 3.64 (s, 3H), 2.42–2.21 (m, 2H), 2.11–2.05 (m, 1H), 1.85–1.77 (m, 1H), 1.75–1.66 (m, 1H), 0.87 (t, J=7.0 Hz, 3H), 0.86 (s, 9H), 0.03 (d, J=17.2 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.5, 136.7, 116.0, 71.2, 51.5, 37.9, 36.6, 14.8.

*5.1.18. (3S,4R)-Methyl 3-hydroxy-4-methylhept-6-enoate (**20**).*



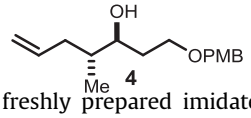
To a solution of methyl ester (**19**) (836.4 mg, 2.92 mmol, 1 equiv) in MeOH (20 mL) was added 10-CSA (677 mg, 2.92 mmol, 1 equiv). The reaction mixture was stirred at rt until completion by TLC analysis (ca. 1 h). The reaction mixture was poured into half-saturated solution of sodium bicarbonate (50 mL) and diluted with EtOAc (50 mL), the aqueous layer was extracted with EtOAc (4×30 mL) and the combined organic layers were washed with brine and dried with $MgSO_4$. Solvent was removed under reduced pressure to afford **20** as a yellow oil, which was used without further purification (481 mg, 2.80 mmol, 96% yield). R_f 0.25 (40% EtOAc/Hex); R_f=0.44 (40% EA/Hex); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.81–5.75 (m, 1H), 5.07–4.99 (m, 1H), 3.88–3.82 (m, 1H), 3.71 (s, 3H), 2.91 (d, J=3.5 Hz, 1H), 2.54–2.51 (m, 1H), 2.44–2.39 (m, 1H), 2.32–2.26 (m, 1H), 1.97–1.92 (m, 1H), 1.70–1.65 (m, 1H), 0.88 (d, J=7.0, 3H).

*5.1.19. tert-Butyl((3S,4R)-1-(4-methoxybenzyloxy)-4-methylhept-6-en-3-yloxy)dimethylsilane (**21**).*



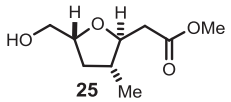
To a solution of freshly prepared PMB-imidate (9.0 g, 31.9 mmol, 1.5 equiv) in toluene (150 mL) was added alcohol **18a** (5.50 g, 21.3 mmol, 1 equiv) followed by $Yb(OTf)_3$ (20 mg, catalytic). The reaction mixture was stirred at rt until completion by TLC analysis (ca. 0.5 h). Solvent was removed under reduced pressure to afford the crude product, which was purified by flash chromatography (2% EtOAc/Hex) to yield **21** as a yellow oil (7.89 g, 20.8 mmol, 98% yield). R_f 0.71 (20% EtOAc/Hex); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24 (d, J=8.6 Hz, 2H), 6.86 (d, J=8.6 Hz, 2H), 5.75 (ddt, J=17.0, 10.0, 7.2 Hz, 1H), 5.01–4.95 (m, 2H), 4.40 (ABd, J=11.7 Hz, 2H), 3.80 (s, 3H), 3.72 (dt, J=8.1, 4.0 Hz, 1H), 3.50 (sex, J=7.4 Hz, 2H), 2.13–2.07 (m, 1H), 1.85–1.78 (m, 1H), 1.71–1.63 (m, 2H), 0.86 (s, 9H), 0.83 (d, J=6.6 Hz, 3H), 0.00 (d, J=3.9 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.1, 137.7, 130.7, 129.2, 115.5, 113.7, 72.5, 72.4, 67.3, 55.2, 38.7, 37.3, 32.1, 25.9, 18.1, 14.1, −4.4, −4.6. HRMS m/z 377.2524 (calcd for $C_{22}H_{38}O_3Si$, 378.2590).

*5.1.20. (3S,4R)-1-(4-Methoxybenzyloxy)-4-methylhept-6-en-3-ol (**4**).*



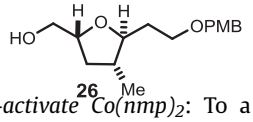
To a solution of freshly prepared imidate (9.0 g, 31.9 mmol, 1.5 equiv) in toluene (150 mL) was added alcohol (**18a**) (5.50 g, 21.3 mmol, 1 equiv) followed by $Yb(OTf)_3$ (20 mg, catalytic). The reaction mixture was stirred at rt until completion by TLC analysis (ca. 0.5 h). Solvent was removed under reduced pressure to afford the crude product, which was purified by flash chromatography (2% EtOAc/Hex) to yield (**4**) as a yellow oil (7.89 g, 20.8 mmol, 98% yield). R_f 0.71 (20% EtOAc/Hex); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.24 (d, J=8.7 Hz, 2H), 6.86 (d, J=8.7 Hz, 2H), 5.79 (ddt, J=17.3, 10.0, 7.1 Hz, 1H), 5.04–4.97 (m, 2H), 4.45 (m, 2H), 4.45 (s, 2H), 3.79 (s, 3H), 3.71 (dt, J=9.5, 4.9 Hz, 1H), 3.61 (q, J=6.4 Hz, 2H), 3.00 (d, J=2.3 Hz, 1H), 2.30–2.26 (m, 1H), 1.90 (dt, J=13.9, 8.3 Hz, 1H), 1.73–1.70 (m, 2H), 1.64–1.59 (m, 1H), 0.86 (d, J=6.4 Hz, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 159.3, 137.6, 130.0, 129.3, 115.8, 113.8, 75.2, 73.0, 69.4, 55.3, 38.6, 36.9, 32.8, 15.1. HRMS m/z 264.1725 (calcd for $C_{16}H_{24}O_3$, 264.1725). $[\alpha]_D^{20}$ +1.73 (c 1.0, $CHCl_3$). The ee was determined to be 85% by (*R*)-Mosher's analysis.

*5.1.21. Methyl 2-((2S,3R,5R)-5-(hydroxymethyl)-3-methyltetrahydrofuran-2-yl)acetate (**25**).*



The pre-activated $Co(nmp)_2$ (**24**) (prepared above, 0.1 mmol, 0.1 equiv) was diluted with 10 mL *i*PrOH, and alcohol (**20**) was added (172 mg, 1.0 mmol, 1 equiv). The reaction mixture was heated to 30 °C under an oxygen atmosphere for 16 h. Solvent was removed under reduced pressure, followed by high vacuum (0.1 mmHg) to remove all traces of *i*PrOH. The crude mixture was diluted with EtOAc (10 mL) and filtered through a thin pad of silica (<1 cm) over packed Celite to remove the catalyst. The pad was washed with EtOAc (100 mL) and the filtrate was concentrated under reduced pressure to give THF alcohol (**25**) (177 mg, 0.94 mmol, 94%) as a yellow oil, which was used without further purification. ^{1}H NMR (600 MHz, $CDCl_3$) δ 4.12–4.08 (m, 1H), 3.85 (td, J=8.5, 4.1 Hz, 1H), 3.69 (s, 3H), 3.65 (dd, J=11.7, 2.9 Hz, 1H), 3.48 (dd, J=11.7, 5.9 Hz, 1H), 2.56–2.53 (m, 1H), 2.49–2.45 (m, 1H), 2.08 (dd, J=12.4, 6.4 Hz, 1H), 2.02–1.95 (m, 2H), 1.43 (ddd, J=12.1, 10.7, 9.4 Hz, 1H), 1.03 (d, J=7.0 Hz, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 171.9, 81.6, 78.8, 64.8, 51.7, 39.9, 39.1, 36.2, 16.2. HRMS m/z 189.1119 (calcd for $C_9H_{16}O_4$, 188.2).

*5.1.22. ((2R,4R,5S)-5-(2-(4-Methoxybenzyloxy)ethyl)-4-methyltetrahydrofuran-2-yl)methanol (**26**).*

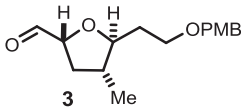


Procedure to pre-activate Co(nmp)$_2$: To a flask charged with $Co(nmp)_2$ (**24**) (452 mg, 0.8 mmol, 0.1 equiv) and *i*PrOH (100 mL)

was added *t*BuOOH (5.33 M, 0.2 mL, 1.08 mmol, 0.14 equiv). The reaction mixture was heated to 55 °C under an oxygen atmosphere for 1 h, and solvent was removed under reduced pressure. The activated $Co(nmp)_2$ was dried under high vacuum (0.1 mmHg) for 5 min to ensure that any remaining peroxide was removed.

Cyclization: The pre-activated $Co(nmp)_2$ (**24**) (prepared above, 0.8 mmol, 0.1 equiv) was diluted with 100 mL *i*PrOH, and alcohol (**4**) was added (2.06 g, 7.8 mmol, 1 equiv). The reaction mixture was heated to 55 °C under an oxygen atmosphere for exactly 1 h, and allowed to cool to rt. Solvent was removed under reduced pressure, followed by high vacuum (0.1 mmHg) to remove all traces of *i*PrOH. The crude mixture was diluted with EtOAc (40 mL) and filtered through a thin pad of silica (<1 cm) over packed Celite to remove the catalyst. The pad was washed with EtOAc (400 mL) and the filtrate was concentrated under reduced pressure to give THF alcohol (**26**) (2.05 g, 7.34 mmol, 94%) as a yellow oil, which was used without further purification. The product rapidly decomposes, and the decomposition product characteristically results in broad peaks at 3.65 and 3.45 ppm. The presence of the decomposition product leads to the loss of fine splitting and peaks are reported as multiplets. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.25 (d, J=8.6 Hz, 2H), 6.87 (d, J=8.6 Hz, 2H), 4.43 (d, J=2.0 Hz, 2H), 4.06 (ddt, J=9.4, 6.2, 3.1 Hz, 1H), 3.79 (s, 3H), 3.62–3.48 (m, 4H), 2.09–2.03 (m, 1H), 1.94–1.85 (m, 2H), 1.73–1.65 (m, 1H), 1.37–1.29 (m, 1H), 1.01 (d, J=6.6 Hz, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 159.1, 130.6, 129.2, 113.7, 82.4, 78.3, 72.6, 67.4, 65.2, 55.3, 40.1, 36.6, 34.3, 16.4. HRMS *m*/*z* 280.1667 (calcd for $C_{16}H_{24}O_4$, 280.1675).

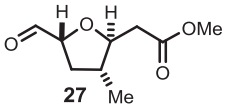
*5.1.23. (2R,4R,5S)-5-(2-(4-Methoxybenzyloxy)ethyl)-4-methyltetrahydrofuran-2-carbaldehyde (**3**).*



3

A flask charged with freshly prepared alcohol **26** (2.24 g, 8 mmol, 1 equiv), and DMSO (3.12 g, 40 mmol, 5 equiv) in CH_2Cl_2 (120 mL) was cooled to 0 °C and Hünig's base (9.6 mL, 56 mmol, 7 equiv) was added. The reaction mixture was stirred for 5 min before sulfurtrioxide–pyridine complex (3.82 g, 24 mmol, 3 equiv) was added in one portion. The reaction mixture was stirred at 0 °C for 2 h before being poured into half-saturated solution of sodium bicarbonate (150 mL) and diluted with CH_2Cl_2 (100 mL), the aqueous layer was extracted with CH_2Cl_2 (3×50 mL) and the combined organic layers were washed with brine, and dried with $MgSO_4$. Solvent was removed under reduced pressure to afford the crude product, which was purified by flash chromatography (40% EtOAc/Hex) to yield aldehyde **3** (2.0 g, 7.4 mmol, 90% yield) as a yellow oil. R_f 0.62 (70% EtOAc/Hex); ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.63 (s, 1H), 7.25 (d, J=8.6 Hz, 2H), 6.87 (d, J=8.6 Hz, 2H), 4.44 (s, 2H), 4.26–4.23 (m, 1H), 3.79 (s, 3H), 3.63–3.56 (m, 3H), 2.33 (dt, J=12.9, 7.6 Hz, 1H), 1.95–1.89 (m, 2H), 1.73 (dt, J=14.3, 5.9 Hz, 1H), 1.58–1.53 (m, 1H), 1.00 (d, J=7.0 Hz, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 203.0, 159.1, 130.5, 129.2, 113.7, 84.2, 81.6, 72.7, 67.1, 55.2, 39.3, 36.0, 34.0, 16.2. HRMS *m*/*z* 278.1510 (calcd for $C_{16}H_{22}O_4$, 278.1518).

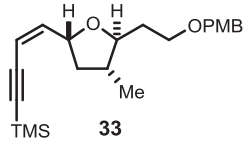
5.1.24. Methyl 2-((2S,3R,5R)-5-formyl-3-methyltetrahydrofuran-2-yl)acetate.



27

A 25 mL round bottom flask was charged with alcohol **25** (90 mg, 0.48 mmol, 1 equiv), diluted with CH_2Cl_2 (5 mL) and cooled to 0 °C. DMSO (186 mg, 2.39 mmol, 5 equiv) was added, followed by Hünig's base (430 mg, 3.34 mmol, 7 equiv). The reaction mixture was allowed to stir for 10 min before SO_3·Pyr (227 mg, 1.43 mmol, 3 equiv) was added portion wise over 5 min. The reaction was monitored by TLC until completion (ca. 2 h) before being slowly poured into a half-saturated solution of sodium bicarbonate (10 mL), and diluted with CH_2Cl_2 (10 mL). The aqueous layer was extracted with CH_2Cl_2 (3×20 mL) and the combined organic layers were washed with brine, and dried with $MgSO_4$. Solvent was removed under reduced pressure, and the crude residue was dissolved in EtOAc (10 mL) and water (30 mL). The aqueous layer was extracted with EtOAc (3×20 mL) and the combined organic layers were washed with brine, and dried with $MgSO_4$. Solvent was removed under reduced pressure, to afford **27** as a yellow oil (42 g, 0.226 mmol, 47% yield), which was used without further purification. The second extraction using EtOAc removes oxidation byproducts from the reaction mixture without using column chromatography, which was shown to decompose the aldehyde. ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.65 (d, J=1.7 Hz, 1H), 4.29 (td, J=8.2, 2.3 Hz, 1H), 3.94 (td, J=8.2, 4.1 Hz, 1H), 3.69 (s, 3H), 2.59–2.56 (m, 1H), 2.53–2.49 (m, 1H), 2.34 (dt, J=12.4, 7.5 Hz, 1H), 2.05–1.97 (m, 1H), 1.59 (dt, J=12.3, 9.1 Hz, 1H), 1.02 (d, J=6.4 Hz, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 202.6, 171.4, 83.1, 81.9, 51.8, 39.0, 38.7, 35.8, 16.1. HRMS *m*/*z* 187.0974 (calcd for $C_{13}H_{28}O_2Si$, 186.2).

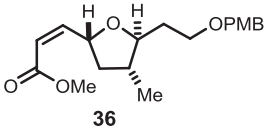
*5.1.25. ((Z)-4-((2R,4R,5S)-5-(2-(4-Methoxybenzyloxy)ethyl)-4-methyltetrahydrofuran-2-yl)but-3-en-1-ynyl)trimethylsilane (**33**).*



33

To a 50 mL round bottomed flask charged with *tert*-butyldimethyl(3-(trimethylsilyl)prop-2-ynyl)silane (240 mg, 1.06 mmol, 2.0 equiv) in THF (5 mL) cooled to −78 °C was added *n*BuLi (2.28 M, 0.47 mL, 1.06 mmol, 2.0 equiv). The reaction mixture was warmed to −20 °C and stirred for 1 h before being re-cooled to −78 °C before $Ti(OiPr)_4$ (301 mg, 1.06 mmol, 2.0 equiv) was added. The reaction mixture was stirred for 10 min before aldehyde (**27**) (120 mg, 0.53 mmol, 1.0 equiv) was added. The reaction mixture was stirred at −78 °C for 1 h, warmed to −20 °C, and monitored by TLC until complete (1 h). The reaction mixture was then poured into a solution of half-saturated NH_4Cl (100 mL) and the aqueous layer was extracted with EtOAc (3×500 mL). The combined organic layers are dried over $MgSO_4$, filtered through a pad of Celite, and concentrated to dryness under vacuum. The crude material was purified by column chromatography to give the product ene–yne (**33**) as a yellow oil as a 14:1 cis/trans mixture (128 mg, 0.34 mmol, 65% yield). R_f 0.48 (20% EtOAc/Hex); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 (d, J=8.7 Hz, 2H), 6.86 (d, J=8.7 Hz, 2H), 5.96 (dd, J=11.4, 8.0 Hz, 1H), 5.51 (d, J=10.9 Hz, 1H), 4.94–4.88 (m, 1H), 4.44 (s, 2H), 3.79 (s, 3H), 3.65–3.55 (m, 3H), 2.34 (dt, J=12.4, 6.5 Hz, 1H), 1.94–1.85 (m, 2H), 1.72–1.69 (m, 1H), 1.32–1.25 (m, 2H), 1.02 (d, J=6.6 Hz, 3H), 0.17 (s, 9H).

5.1.26. (Z)-Methyl 3-((2R,4R,5S)-5-(2-(4-methoxybenzyloxy)ethyl)-4-methyltetrahydrofuran-2-yl)acrylate.

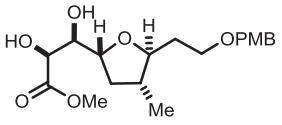


36

To a solution of the Still–Gennari phosphonate (5.10 g, 16.0 mmol, 1.5 equiv) in THF (60 mL) and 18-crown-6 ether (11.3 g, 42.8 mmol, 4.0 equiv) cooled to −78 °C was added KHMDS (0.91 M,

17.6 mL, 16.0 mmol, 1.5 equiv) dropwise over 5 min. The reaction mixture was stirred at −78 °C for 20 min before a solution of aldehyde **3** (2.98 g, 10.7 mmol, 1.0 equiv) in THF (20 mL) was added dropwise over 10 min. The reaction mixture was stirred at rt for 3 h at −78 °C, warmed to rt, and stirred for an additional 10 min before being poured into a half-saturated solution NH_4Cl (150 mL). The aqueous layer was extracted with EtOAc (50 mL×3), and the combined organic layers were washed with brine, dried over $MgSO_4$, and filtered through a thin pad of packed Celite. Solvent was removed under reduced pressure and the crude oil was purified by flash chromatography (20% EtOAc/Hex) to yield **36** (2.79 g, 8.35 mmol, 78%) as a yellow oil. R_f 0.68 (50% EtOAc/Hex); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27 (d, J=8.6 Hz, 2H), 6.86 (d, J=8.6 Hz, 2H), 6.29 (dd, J=11.5, 7.2 Hz, 1H), 5.73 (dd, J=11.5, 1.5 Hz, 1H), 5.38 (ddd, J=13.8, 9.8, 1.5 Hz, 1H), 4.43 (s, 2H), 3.79 (s, 3H), 3.68 (s, 3H), 3.63–3.52 (m, 3H), 2.49 (dt, J=12.7, 6.5 Hz, 1H), 1.98–1.85 (m, 2H), 1.76 (m, 2H), 1.31–1.23 (m, 1H), 1.00 (d, J=6.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.3, 159.1, 152.4, 130.7, 129.2, 118.2, 113.7, 82.9, 74.8, 72.6, 67.4, 55.2, 51.2, 41.2, 40.0, 34.3, 16.4. HRMS m/z 334.1773 (calcd for $C_{19}H_{26}O_5$, 334.1780).

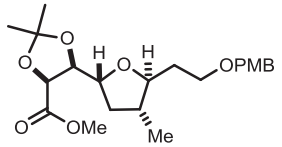
*5.1.27. (2S,3R)-Methyl 2,3-dihydroxy-3-((2R,4R,5S)-5-(2-(4-methoxybenzyloxy)ethyl)-4-methyltetrahydrofuran-2-yl)propanoate (**36a**).*



36a

To a solution of alkene **36** (1.32 g, 4.0 mmol, 1 equiv) in *t*BuOH (15 mL) and distilled water (15 mL) cooled to 0 °C were added AD-mix (5.6 g), K_2OsO_4 (140 mg, 0.12 mmol, 0.06 equiv), and $(DHQD)_2PYR$ (104 mg, 0.06 mmol, 0.03 equiv). The reaction mixture was stirred at 0 °C and monitored by TLC analysis until complete (ca. 3 days). Upon completion, the contents were poured into a solution consisting of half-saturated NH_4Cl (50 mL), half-saturated sodium thiosulfate (50 mL), and water (50 mL). The reaction mixture was stirred rigorously for 10 min, diluted with CH_2Cl_2 (100 mL), and the aqueous layer was extracted with CH_2Cl_2 (50 mL×4), and the combined organic layers were washed with brine, dried over $MgSO_4$, and filtered through a thin pad of packed Celite. Solvent was removed under reduced pressure and the crude oil (**36a**) was used in the next reaction without further purification. R_f 0.73 (75% EtOAc/Hex); ^{1}H NMR (400 MHz, $CDCl_3$, major diastereomer) δ 7.22 (d, J=8.7 Hz, 2H), 6.85 (d, J=8.7 Hz, 2H), 4.40 (s, 2H), 4.25 (dd, J=8.2, 4.1 Hz, 1H), 4.01 (ddd, J=9.7, 6.2, 2.9 Hz, 1H), 3.77 (s, 3H), 3.74 (s, 3H), 3.75–3.68 (m, 1H), 3.56–3.48 (m, 3H), 3.41 (d, J=9.4 Hz, 1H), 2.70 (d, J=7.6 Hz, 1H), 2.04 (dt, J=12.4, 6.4 Hz, 1H), 1.89–1.82 (m, 2H), 1.65–1.57 (m, 2H), 1.00 (d, J=6.4, 3H).

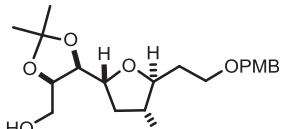
*5.1.28. (4S,5S)-Methyl 5-((2R,4R,5S)-5-(2-(4-methoxybenzyloxy) ethyl)-4-methyltetrahydrofuran-2-yl)-2,2-dimethyl-1,3-dioxolane-4-carboxylate (**37**).*



37

The crude diol **36a** was dissolved in 2,2-dimethoxy propane (50 mL), and *p*-toluene sulfonic acid (50 mg, catalytic) was added in one portion. The reaction mixture was stirred at rt overnight (ca. 16 h) before being poured into a half-saturated solution $NaHCO_3$ (100 mL). The aqueous layer was extracted with EtOAc (50 mL×3), and the combined organic layers were washed with brine, dried over $MgSO_4$, and filtered through a thin pad of packed Celite. Solvent was removed under reduced pressure and the crude oil was purified by flash chromatography (50% EtOAc/Hex) to yield **37** as an inseparable mixture of diastereomers (1.55 g, 3.80 mmol, 95%) as a yellow oil. R_f 0.73 (75% EtOAc/Hex); ^{1}H NMR (400 MHz, $CDCl_3$, major diastereomer) δ 7.25 (d, J=8.8 Hz, 2H), 6.86 (d, J=8.8 Hz, 2H), 4.55 (d, J=7.0 Hz, 1H), 4.42 (ABd, J=11.1 Hz, 2H), 4.26 (dd, J=7.0, 4.7 Hz, 1H), 4.05 (ddd, J=8.8, 6.7, 5.0 Hz, 1H), 3.79 (s, 3H), 3.68 (s, 3H), 3.60–3.48 (m, 3H), 2.17 (dt, J=12.1, 7.1 Hz, 1H), 1.86–1.83 (m, 2H), 1.68–1.61 (m, 1H), 1.59 (s, 3H), 1.56 (d, J=13.5 Hz, 1H), 1.52–1.46 (m, 1H), 1.41 (s, 1H), 1.38 (s, 3H) 1.01 (d, J=6.4 Hz, 3H); HRMS m/z 408.2152 (calcd for $C_{22}H_{32}O_7$, 408.2148).

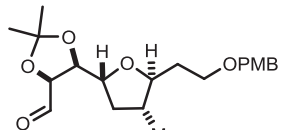
5.1.29. ((4R,5S)-5-((2R,4R,5S)-5-(2-(4-Methoxybenzyloxy)ethyl)-4-methyltetrahydrofuran-2-yl)-2,2-dimethyl-1,3-dioxolan-4-yl) methanol.



37a

To a solution of DIBAL-H (1.0 M, 7.60 mL, 7.60 mmol, 2.0 equiv) in CH_2Cl_2 (20 mL) cooled to 0 °C was added the mixture of diastereomeric esters **37** (1.55 g, 3.80 mmol, 1 equiv) in CH_2Cl_2 (10 mL) portion wise over 10 min. The reaction mixture was stirred at rt until completed by TLC analysis (ca. 3 h). The reaction mixture was poured into half-saturated solution of NH_4Cl (100 mL) and a solution of Rochelle's salt (10 g in 50 mL water), and CH_2Cl_2 (100 mL) was added. The solution was stirred vigorously until it became homogenous (ca. 16 h), after which the aqueous layer was extracted with CH_2Cl_2 (3×50 mL) and the combined organic layers were washed with brine, and dried with $MgSO_4$. Solvent was removed under reduced pressure to afford the crude product, which was purified by flash chromatography (50% EtOAc/Hex) to give alcohol **37a** as a yellow oil (1.14 g, 3.01 mmol, 79% yield) and the diastereomer (285 mg, 0.75 mmol, 19%). R_f 0.22 (50% EtOAc/Hex); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 (d, J=8.2 Hz, 2H), 6.85 (d, J=8.2 Hz, 2H), 4.42 (ABd, J=11.1 Hz, 2H), 4.17–4.12 (m, 2H), 4.07–4.05 (dd, J=6.4, 3.5 Hz, 1H), 3.79 (s, 3H), 3.72–3.64 (m, 3H), 3.61–3.57 (m, 1H), 3.57–3.51 (m, 1H), 3.21 (dd, J=8.8, 4.7 Hz, 1H), 2.15 (dt, J=12.3, 6.7 Hz, 1H), 1.92–1.87 (m, 2H), 1.71–1.63 (m, 2H), 1.49 (s, 3H), 1.36 (s, 3H), 1.02 (d, J=7.0 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.1, 130.6, 129.3, 113.7, 108.4, 83.5, 78.9, 77.5, 75.0, 72.7, 67.4, 61.5, 55.2, 39.6, 27.9, 34.0, 27.4, 25.6, 15.8. HRMS m/z 380.2198 (calcd for $C_{21}H_{32}O_6$, 380.2199).

*5.1.30. (4S,5S)-5-((2R,4R,5S)-5-(2-(4-Methoxybenzyloxy)ethyl)-4-methyltetrahydrofuran-2-yl)-2,2-dimethyl-1,3-dioxolane-4-carbaldehyde (**38**).*

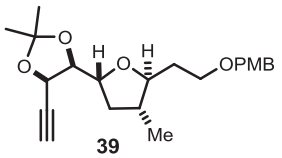


38

Alcohol **37a** was oxidized to the corresponding aldehyde using a procedure analogous to that used for **27**, on a 5.93 mmol scale resulting in aldehyde **38** (1.64 g, 5.93 mmol, 100%), which was used without further purification. R_f 0.19 (20% EtOAc/Hex); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.59 (d, J=2.3 Hz, 1H), 7.24 (d, J=8.8 Hz, 2H), 6.85 (d, J=8.8 Hz, 2H), 4.41 (s, 2H), 4.32 (dd, J=4.1, 2.3 Hz, 2H), 4.05 (ddd, J=9.0, 6.7, 2.9 Hz, 1H), 3.78 (s, 3H), 3.59 (td, J=9.2, 2.6 Hz, 1H), 3.55 (ddd, J=9.2, 7.2, 4.7 Hz, 1H), 3.52–3.48 (m, 1H), 2.10 (dt, J=12.0,

7.5 Hz, 1H), 1.87–1.80 (m, 2H), 1.63–1.58 (m, 2H), 1.55 (s, 3H), 1.38 (s, 3H), 0.99 (d, J=6.4 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.6, 159.1, 130.7, 129.2, 113.7, 111.0, 83.3, 81.7, 81.2, 74.4, 72.7, 67.5, 55.2, 40.3, 36.5, 33.9, 26.9, 25.2, 15.8.

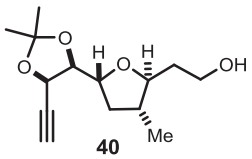
*5.1.31. (4R,5S)-4-Ethynyl-5-((2R,4R,5S)-5-(2-(4-methoxybenzyloxy) ethyl)-4-methyltetrahydrofuran-2-yl)-2,2-dimethyl-1,3-dioxolane (**39**).*



39

A 250 mL flask was charged with triphenylphosphine (7.0 g, 26.6 mmol, 5.0 equiv) and CH_2Cl_2 (70 mL) and was cooled to 0 °C. The septum was temporarily removed to add carbon tetrabromide (4.36 g, 13.3 mmol, 2.5 equiv) in one portion. The ice bath was removed and the reaction mixture was stirred at room temperature for 30 min, after which it was re-cooled to 0 °C. The above crude aldehyde **38** (2.01 g, 5.33 mmol, 1 equiv) was added in one portion and the reaction mixture was stirred for 30 min, at which point it was judged complete by TLC. Hexanes (250 mL) was added, and the reaction mixture was allowed to warm to rt, at which point it was filtered through Celite, and concentrated to dryness. To the crude oil was added more hexanes (500 mL), filtered, and concentrated. This procedure was repeated for a total of three filtrations at which point the crude oil was purified by column chromatography (20% EtOAc/Hex) to afford the dibromide as a yellow oil (2.56 g, 4.80 mmol, 90% yield). A 250 mL flask was charged with dibromide (2.56 g, 4.80 mmol, 1 equiv), diluted with THF (150 mL), and cooled to −78 °C. *n*BuLi (2.50 M, 4.80 mL, 12.0 mmol, 2.5 equiv) was added slowly dropwise over 15 min. The reaction mixture was stirred at −78 °C for 1 h at which point it was judged complete by TLC. The reaction mixture was slowly poured into a half-saturated solution of NH_4Cl (150 mL), the aqueous layer was extracted with CH_2Cl_2 (3×150 mL), and the combined organic layers were washed with brine, and dried with $MgSO_4$. Solvent was removed under reduced pressure, and the crude product was purified by column chromatography (2% EtOAc/Hex) to afford alkyne **39** as a yellow oil (1.61 g, 4.32 mmol, 95% yield). R_f 0.57 (50% EtOAc/Hex); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 (d, J=8.6 Hz, 2H), 6.86 (d, J=8.6 Hz, 2H), 4.66 (dd, J=5.5, 2.3 Hz, 1H), 4.42 (s, 2H), 4.23 (td, J=8.8, 6.2 Hz, 1H), 3.97 (dd, J=8.4, 5.7 Hz, 1H), 3.79 (s, 3H), 3.67–3.55 (m, 3H), 2.47 (d, J=1.9 Hz, 1H), 2.33 (dt, J=12.4, 6.5 Hz, 1H), 2.02–1.93 (m, 1H), 1.89 (ddd, J=14.3, 7.2, 3.1 Hz, 1H), 1.84–1.77 (m, 1H), 1.57 (s, 3H), 1.38 (s, 3H), 1.24–1.13 (m, 2H), 1.02 (d, J=6.6 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.1, 130.7, 129.2, 113.7, 111.5, 83.1, 81.4, 80.1, 77.8, 75.4, 72.6, 67.3, 66.7, 55.2, 39.3, 37.7, 33.8, 29.7, 27.8, 26.3, 16.5.

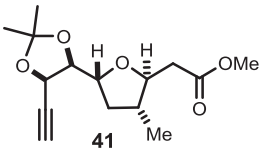
*5.1.32. 2-((2S,3R,5R)-5-((4S,5R)-5-Ethynyl-2,2-dimethyl-1,3-dioxolan-4-yl)-3-methyltetrahydrofuran-2-yl)ethanol (**40**).*



40

The PMB ether (**39**) (1.58 g, 4.22 mmol, 1 equiv) was dissolved in CH_2Cl_2 (150 mL), water (20 mL), and saturated sodium bicarbonate (20 mL). DDQ (1.91 g, 8.44 mmol, 2 equiv) was added in one portion and the reaction mixture was rigorously stirred for 1.5 h at which point the reaction was judged to be complete by TLC analysis. The reaction mixture was poured into a rapidly stirring solution of half-saturated sodium bicarbonate (300 mL) and half-saturated sodium thiosulfate (300 mL), and the aqueous layer was extracted with CH_2Cl_2 (5×300 mL) and the combined organic layers were washed with brine and dried over $MgSO_4$. Solvent was removed under reduced pressure to give the crude alcohol, which was purified by flash chromatography (50% EtOAc/Hex) to give the pure alcohol **40** as a yellow oil (922 mg, 3.63 mmol, 86% yield). R_f 0.22 (50% EtOAc/Hex); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.69 (dd, J=5.8, 2.3 Hz, 1H), 4.26 (dt, J=9.1, 6.9 Hz, 1H), 3.98 (dd, J=7.6, 5.9 Hz, 1H), 3.82–3.75 (m, 2H), 3.63 (td, J=8.6, 3.2 Hz, 1H), 2.79 (br s, 1H), 2.50 (d, J=2.3 Hz, 1H), 2.31 (dt, J=5.9, 5.9 Hz, 1H), 2.00–1.95 (m, 1H), 1.90–1.85 (m, 1H), 1.72–1.66 (m, 1H), 1.53 (s, 3H), 1.35 (s, 3H), 1.27–1.22 (m, 1H), 1.01 (d, J=6.4 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 111.1, 85.2, 80.8, 79.8, 77.7, 75.6, 66.7, 60.9, 39.4, 37.2, 35.3, 29.6, 27.5, 26.0, 16.0.

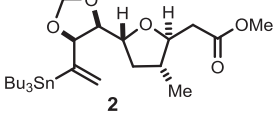
*5.1.33. Methyl 2-((2S,3R,5R)-5-((4S,5R)-5-ethynyl-2,2-dimethyl-1,3-dioxolan-4-yl)-3-methyltetrahydrofuran-2-yl)acetate (**41**).*



41

Alcohol **40** was oxidized to the corresponding aldehyde using a procedure analogous to that used for **27**, on a 4.29 mmol scale resulting in the aldehyde (1.10 g, 4.29 mmol, 83%), which was used without further purification. To the crude aldehyde (1.10 g, 4.29 mmol, 1.0 equiv) and 2-methyl-2-butene (1.20 g, 17.2 mmol, 4 equiv) in *t*BuOH (50 mL) and pH 7 buffer (0.67 M, 20 mL) was added $NaClO_2$ (1.21 g, 10.7 mmol, 2.5 equiv) in water (20 mL). The reaction was monitored by TLC until completion (ca. 30 min) at which point it was poured into a half-saturated solution of sodium sulfate (75 mL) and acidified with HCl (2 M solution, 10 mL). The aqueous layer was extracted with CH_2Cl_2 (5×75 mL) and the combined organic layers were washed with brine and dried over $MgSO_4$. Solvent was removed under reduced pressure, and the crude oil was dissolved in MeOH (50 mL) and CH_2Cl_2 (50 mL) and a stir bar was added. To the solution was added TMS–diazomethane (1.0 M solution) dropwise until the yellow color persists (ca. 3 mL). The reaction mixture was stirred an additional 5 min before excess acetic acid (5 mL) was added in one portion and the color dissipates. Volatiles were removed under reduced pressure and the oil was purified by flash chromatography (20% EtOAc/Hex) to give methyl ester **41** (786 mg, 2.79 mmol, 65%). R_f 0.32 (50% EtOAc/Hex); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.66 (dd, J=5.6, 2.0 Hz, 1H), 4.26 (dd, J=15.2, 8.8 Hz, 1H), 3.99 (dd, J=8.2, 5.9 Hz, 1H), 3.93 (dt, J=8.5, 6.0 Hz, 1H), 3.66 (s, 3H), 2.66 (dd, J=15.5, 6.1 Hz, 1H), 2.51 (dd, J=15.5, 6.1 Hz, 1H), 2.48 (d, J=2.3 Hz, 1H), 2.36 (dt, J=12.4, 6.4 Hz, 1H), 2.10–2.04 (m, 1H), 1.55 (s, 3H), 1.36 (s, 3H), 1.25–1.19 (m, 1H), 1.02 (d, J=7.0 Hz, 3H). The product was of insufficient purity to obtain a ^{13}C NMR and was used without further purification.

*5.1.34. Methyl 2-((2S,3R,5R)-5-((4S,5S)-2,2-dimethyl-5-(1-(tributylstannyl)vinyl)-1,3-dioxolan-4-yl)-3-methyltetrahydrofuran-2-yl)acetate (**2**).*

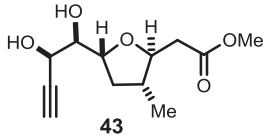


2

To a flask containing BHT (5 mg, catalytic) and $Mo(CO)_3(NCtBu)_3$ (119 mg, 0.28 mmol, 0.1 equiv) was added alkyne **41** (786 mg, 2.79 mmol, 1.0 equiv) in THF (60 mL). To the solution was added tributyltinhydride (2.44 g, 8.37 mmol, 3.0 equiv) and the reaction mixture was heated to 55 °C and monitored by TLC until complete

(24 h). Upon completion, the reaction mixture was loaded onto a silica gel column buffered with 1% triethylamine and eluted with 3–5% EtOAc/hexanes to give **2** as a yellow oil (1.09 g, 1.89 mmol, 68%). R_f 0.57 (20% EtOAc/Hex); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.90 (s, 2H), 5.41 (s, 1H), 4.82 (d, J=5.4 Hz, 1H), 4.05 (t, J=6.7 Hz, 1H), 3.92–3.88 (m, 1H), 3.67 (s, 3H), 2.62 (dd, J=15.0, 6.2 Hz, 1H), 2.46 (dd, J=14.7, 6.4 Hz, 1H), 2.10 (dt, J=12.5, 6.4 Hz, 1H), 1.96–1.91 (m, 1H), 1.52–1.48 (m, 6H), 1.36–1.30 (m, 6H), 1.02 (d, J=6.4 Hz, 3H), 0.97–0.93 (m, 3H), 0.90 (t, J=7.0 Hz, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.5, 115.3, 111.5, 81.8, 81.7, 81.2, 81.1, 79.9, 78.0, 75.6, 75.5, 66.7, 66.6, 51.6, 51.5, 39.5, 38.9, 38.8, 38.8, 37.4, 27.6, 26.2, 26.2, 16.6.

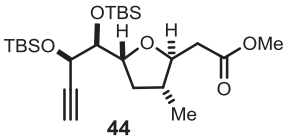
5.1.35. Methyl 2-((2S,3R,5R)-5-((1R,2R)-1,2-dihydroxybut-3-ynyl)-3-methyltetrahydrofuran-2-yl)acetate.



43

To 5 mL round bottom flask charged with acetonide **41** (24.5 mg, 0.087 mmol, 1 equiv) was added wet methanol (2 mL) and a catalytic amount of PPTS was added in one portion. The reaction was monitored by TLC until complete (ca. 6 h), at which point it was diluted with water (30 mL) and EtOAc (30 mL). The aqueous layer was extracted with EtOAc (3×20 mL) and the combined organic layers were washed with brine, and dried with $MgSO_4$. Solvent was removed under reduced pressure, and the crude product was purified by column chromatography (50% EtOAc/Hex) to afford alcohol **43** as a yellow oil (17.7 mg, 0.073 mmol, 84.3% yield). R_f 0.73 (60% EtOAc/Hex); ^{1}H NMR (600 MHz, $CDCl_3$) δ 4.51–4.43 (m, 2H), 3.87 (td, J=8.9, 3.7 Hz, 1H), 3.68 (s, 3H), 3.56–3.54 (m, 1H), 3.49 (br d, J=9.8 Hz, 1H), 2.82 (br d, J=8.2 Hz, 1H), 2.59–2.52 (m, 2H), 2.48–2.42 (m, 1H), 2.12 (dt, J=14.0, 6.1 Hz, 1H), 2.01–1.89 (m, 1H), 1.80–1.72 (m, 1H), 1.05 (d, J=6.6 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.5, 115.3, 111.5, 81.8, 81.7, 81.2, 81.1, 79.9, 78.0, 75.6, 75.5, 66.7, 66.6, 51.6, 51.5, 39.5, 38.9, 38.8, 38.8, 37.4, 27.6, 26.2, 26.2, 16.6.

*5.1.36. Methyl 2-((2S,3R,5R)-5-((5S,6R)-6-ethynyl-2,2,3,3,8,8,9,9-octamethyl-4,7-dioxa-3,8-disiladecan-5-yl)-3-methyltetrahydrofuran-2-yl)acetate (**44**).*



44

To a solution of alcohol **43** (17.7 mg, 0.073 mmol, 1 equiv) in DMF (2 mL) was added imidazole (25 mg, 0.365 mmol, 5.0 equiv), followed by TBSCl (28.4 mg, 0.182 mmol, 2.5 equiv) and DMAP (5 mg, catalytic). The reaction mixture was heated to 60 °C allowed to stir overnight (ca. 16 h) before being cooled to rt and poured into a half-saturated solution of NH_4Cl (20 mL), and the aqueous layer was extracted with CH_2Cl_2 (3×30 mL) and the combined organic layers were washed with brine and dried over $MgSO_4$. Solvent was removed under reduced pressure to give the TBS alcohol **44**, which was purified by column chromatography (5% EtOAc/Hex) to give the pure alcohol as a yellow oil (33.4 mg, 0.071 mmol, 97% yield). Spectral data were identical to the reported literature.[3c]

Acknowledgements

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Supplementary data

^{1}H, ^{13}C NMR spectra of all new compounds. Supplementary data associated with this article can be found in the online version, at http://dx.doi.org/10.1016/j.tet.2013.07.026.

References and notes

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