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# Studies toward norzoanthamine: Ireland–Claisen rearrangements of α,β-unsaturated esters in a stereocontrolled synthesis of *trans*-fused 2-cyclohexen-1-ones

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**Dedication:** Dedicated to Professor Dale Boger in celebration of the 2020 Tetrahedron Prize for Creativity in the Chemical Sciences and his many contributions for the advancement of organic chemistry.

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Olefin metathesis

ABSTRACT

The enantiocontrolled preparation of the *trans*-fused ABC ring system of norzoanthamine is described. The synthesis strategy has incorporated studies of Ireland–Claisen rearrangements of esters derived from 3,3-dimethylacrylic acid. Stereocontrol results from competing chair- and boat-like transition states. Introduction of a nitroalkene by application of a modified Henry reaction facilitates an intramolecular Diels–Alder cycloaddition for an effective and simple transformation to the desired conjugated decalone. A fully functionalized AB ring system leads to the cyclization of the *trans*-fused cyclohexenone to complete the ABC system via ring-closing metathesis.



## 1. Introduction

*Zoanthus* alkaloids represent a bioactive family of marine natural products which feature fused cyclic structures characterized by the incorporation of a novel hemiaminal moiety. Examples include zoanthamine (**1**), norzoanthamine (**2**), and zoanthenol (**3**) (Fig. 1) [1]. Several studies have identified additional compounds of this family [2]. Norzoanthamine (**2**) has gained particular attention because of its potent antiosteoporotic effects which suppress the loss of bone weight and bone strength in ovariectomized mice [3]. However, nearly all of the metabolites of this class show varying levels of cytotoxicity, inhibition of human platelet aggregation, and anti-inflammatory activities [4]. The complexity of these structures has stimulated a number of synthesis studies. Notably Miyashita and coworkers completed the first total synthesis of norzoanthamine in 2004 [5], and this laboratory has also described conversions to obtain zoanthamine (**1**) and zoanthenol (**3**) [6]. Kobayashi and coworkers have also achieved a successful synthesis of norzoanthamine [7]. The unique architecture of these natural products has inspired a number of focused studies pertaining to the challenging issues of stereochemistry, functionalization, and cyclization methodology [8]. We are among these practitioners who have repeatedly found interesting, and occasionally valuable, results in our efforts [9].

In this account, we have described studies culminating in the enantiocontrolled synthesis strategy toward substituted, highly functionalized *trans*-decalin systems. Important aspects of these investigations include [3,3]-Claisen rearrangements derived from γ-deprotonation of esters of 3,3-dimethylacrylic acid. This approach provides the enantiocontrolled installation of a key chiral quaternary carbon. Our application directly facilitates an *endo*-selective, intramolecular Diels–Alder reaction of an (*E*)-nitroalkene as a general and effective methodology toward the preparation of highly substituted, conjugated cyclohexenones. This effort has

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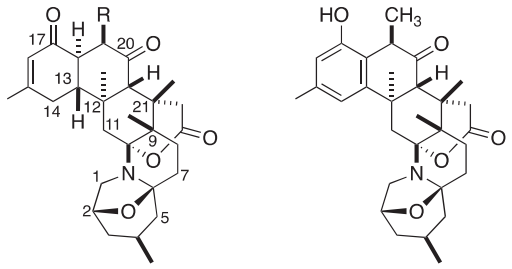


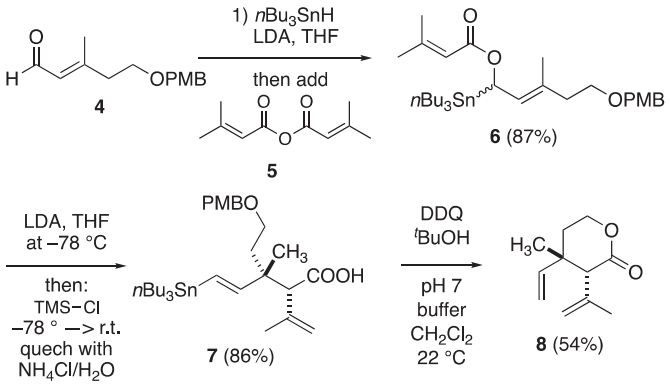

**Fig. 1.** Examples of *Zoanthus* alkaloids.

culminated in the enantiocontrolled synthesis of the *trans*-fused ABC tricycle of norzoanthamine.

## 2. Results and discussion

The impetus for this study began with the observation of the Ireland–Claisen rearrangement of Scheme 1 [10]. The alkoxide derived from the reaction of *n*-$Bu_3SnLi$ and aldehyde **4** was quenched with the 3-methyl-2-butenoic anhydride **5** to yield ester **6**. An Ireland–Claisen rearrangement of **6** afforded an intermediate silyl enol ether following the γ-deprotonation which, upon warming, led to carboxylic acid **7** as a single diastereoisomer (86% yield). The exclusive formation of the *E*-alkenylstannane in **7** provided a valuable extension of Claisen methodology for direct linkage with Stille cross-coupling processes. DDQ deprotection of **7** was accompanied by destannylation and produced the desired six-membered lactone **8**. NMR analysis of this lactone using NOESY correlations supported the assignment of the relative stereochemistry.

More than a decade after this initial study, we enlisted the use of the Ireland–Claisen rearrangement of esters of 3-methyl-2-butenoic acid to specifically address the chirality and substitution of the *trans*-decalone of norzoanthamine (**2**). As summarized in Scheme 2, the chiral, nonracemic allyl alcohol **11** was prepared in standard fashion by application of a symmetric Evans aldol reaction of aldehyde **4** with the *Z*(O)-boron enolate generated from **9** [11]. The *syn*-product **10** was obtained as a single diastereomer and reductive cleavage of the auxiliary using $LiBH_4$ was followed by selective *tert*-butyldiphenylsilyl protection of the intermediate diol to give **11**. The stereochemistry of the secondary alcohol of **11** was verified by an advanced Mosher ester analysis [12]. Esterification of this allylic alcohol with 3-methyl-2-butenoic acid using EDCI in

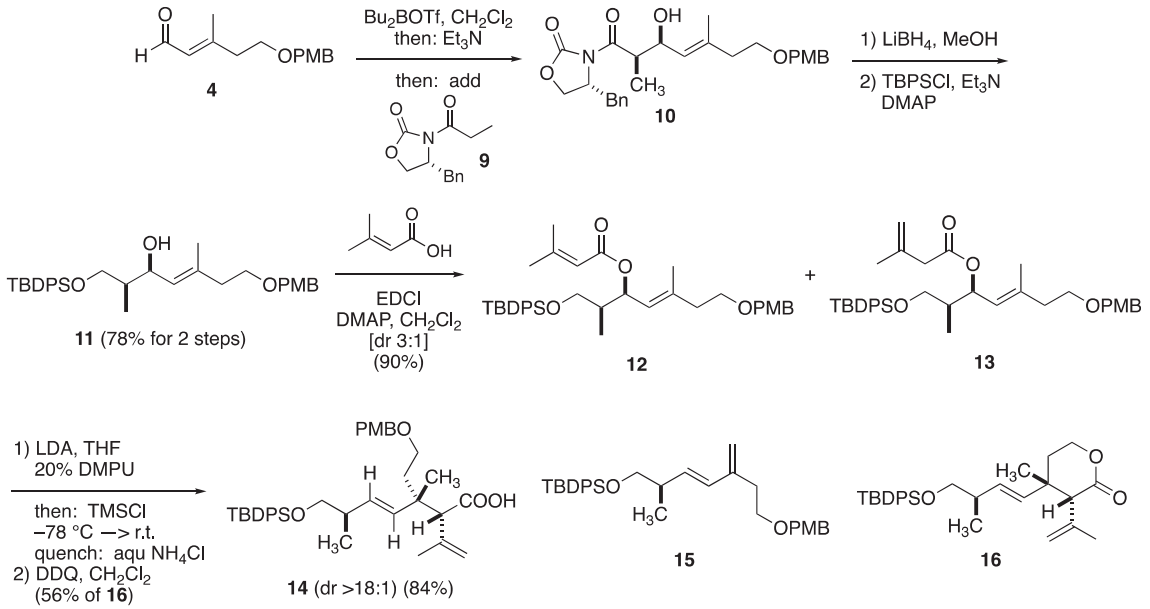



**Scheme 1.** Claisen rearrangement of stannane **6**.

$CH_2Cl_2$ in the presence of a slight excess of DMAP (1.4 equiv) yielded an inseparable mixture of the conjugated and nonconjugated esters **12** and **13** in a 3:1 ratio (90% yield) [13]. Treatment of the mixture of esters with LDA (1.1 equiv) in THF at −78 °C was followed by the addition of freshly distilled TMSCl. After warming to 25 °C, the desired acid **14** was isolated as the major product (dr 6:1). Diastereoselectivity was substantially increased and afforded **14** as a single diastereomer by the use of 45% DMPU in THF as the solvent for this reaction. However, these conditions led to a diminished yield of the desired carboxylic acid as well as the appearance of the elimination product **15**. Optimization of this Ireland–Claisen rearrangement utilized 20% DMPU in THF as the solvent to give an 18:1 ratio of isomers favoring **14** (84% yield) while minimizing production (<5%) of diene **15**. After purification of **14**, deprotection with DDQ provided lactone **16** as a single diastereomer. NMR analysis of **16** identified key NOESY correlations as shown in Fig. 2, that supported the assigned stereochemistry of the Claisen rearrangement product **14** arising from the nonracemic alcohol **11**.

Our studies also examined the Ireland–Claisen rearrangement from nonracemic **17** as shown in Scheme 3. This sample was prepared, beginning with the alcohol **17**, which was obtained in the manner as described for **11**, using the antipodal **9**. Esterification with 3-methyl-3-butenoic acid (EDCI, DMAP, $CH_2Cl_2$) also resulted in the thermodynamic 3:1 ratio of inseparable α,β- and β,γ-unsaturated products **18** and **19**. As in the prior example, this ratio was determined by the integration of vinylic hydrogen signals in the $^1H$ NMR spectrum of the mixture. Ireland–Claisen rearrangement of this mixture in the absence of DMPU gave the carboxylic acid **20** as the major diastereomer (dr 6:1) in 84% yield. Deprotection of the purified **20** afforded lactone **21** which was utilized to support the assignment of stereochemistry via NOESY techniques. The key NOESY correlations are shown in Fig. 3.

Generally four factors control the stereochemical outcome of the [3,3]-Claisen rearrangement: (a) the configuration of the C=C alkene, (b) the chirality of starting allylic alcohol, (c) the geometry of the enolate (silyl enol ether), and (d) steric factors [14]. Since our starting esters were inseparable mixtures of conjugated and nonconjugated isomers, the expectation of diastereoselectivity was in doubt because we had little reason to anticipate the production of identical ratios of *E*/*Z*-enolates from each contributing ester. The kinetic deprotonation of alkyl esters with LDA in THF is known to substantially favor formation of the *E*(O) enolate [15]. This fact has been confirmed by trapping enolates with $^tBuMe_2SiCl$ to characterize stable silylketene acetals. We have also recorded the production of the *E*-trimethylsilyl ketene acetal (*E*/*Z* ratio 10:1) from kinetic deprotonation of a closely-related ester in the course of our australifungin studies [16]. On the other hand, Ireland's original studies demonstrated kinetic enolate formation in a solvent mixture of 23% HMPA in THF leading to *Z*(O)-enolate and the corresponding (*Z*)-TBS silylketene acetal [15b]. Weiler and coworkers [17] have shown that ester derivatives of 3-methyl-2-butenoic acids undergo selective γ-deprotonation via lithium coordination of the carbonyl oxygen to yield *Z*(O)-enolates, and several literature reports support this observation in examples of stereoselective Claisen rearrangements which are consistent with *Z*(O)-enolate formation [18]. The results of our studies sound a cautionary note regarding these assumptions and the expectation of reactions proceeding via chair-like transition states. In fact, the carboxylic acid **14** (Scheme 2) is envisioned from the chair-like transition state **22** which arises from the *Z*(O)-enolate via the TMS silylketene acetal. The ratio of products (6:1 dr) indicates a modest enrichment in the formation of *Z*(O)-enolate from the mixture of esters featuring kinetic γ- and α-deprotonations of **12** and **13**, respectively. The inclusion of 20% DMPU has a dramatic effect on the course of deprotonation and substantially favors production of the




**Scheme 2.** Preparation of unsaturated esters and studies of Ireland–Claisen stereocontrol.

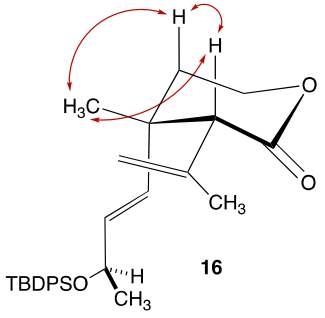



**Fig. 2.** Featured 2D NOESY correlations in lactone **16**.

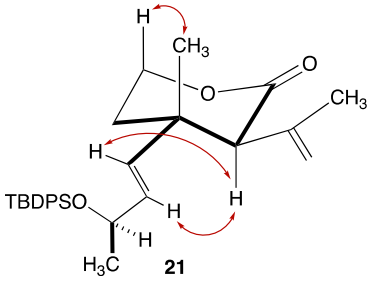
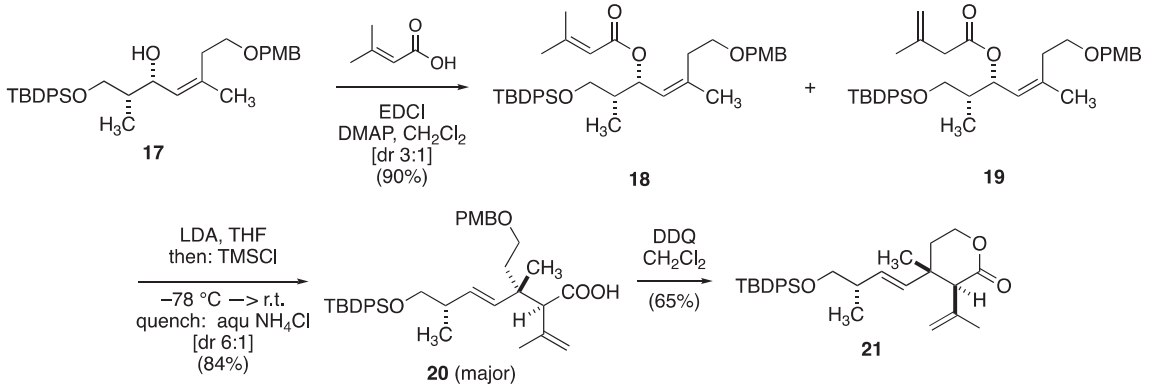



**Fig. 3.** Featured 2D NOESY correlations in **21**.

*Z*(O)-enolate leading to **14** (>18:1 dr). We had theorized that DMPU would produce similar results as observed in the use of HMPA for kinetic α-deprotections. In fact, kinetic γ-deprotonation must also demonstrate highly selective *Z*(O)-enolate formation under these conditions. On the other hand, product **20** (Scheme 3) can be rationalized from the chair arrangement of **23** which must incorporate the TMS enol ether of the *E*(O)-enolate. This hypothesis seems unlikely since we utilized identical conditions and mixtures of conjugated and nonconjugated esters in each case. It is feasible that the pseudoaxial substituents in **23** are destabilizing and the observed product **20** is produced from the boat transition state **24** via the predominant formation of the *Z*(O)-enolate. While boat-like transition states have been identified in Claisen processes [19], we had not anticipated a change from chair to boat TS preferences because of the apparent structural similarities of the esters of Schemes 2 and 3 [20]. In fact, products resulting from boat-like transition states have usually been observed for esters derived




**Scheme 3.** Studies of Ireland–Claisen rearrangements of **18** and **19**.

from substituted, cyclic allylic alcohols [19a,b,c,f]. Recent studies have detailed Ireland–Claisen rearrangements of α-hetero-substituted esters via boat-like transition states [19d]. However, acyclic esters are thought to predominantly give products via chair-like arrangements. Indeed, we have concluded that this is not the case for the rearrangement resulting in the major product **20**. In either case, the kinetic production of *Z*(O)- vs *E*(O)-enolates does not reflect the composition of the starting conjugated and nonconjugated esters under conditions of kinetic deprotonation. Hence, it was important to effect the chemical transformation to the six-membered lactones to establish the stereochemical outcome of these sigmatropic processes (see Fig. 4).

Carboxylic acid **14** incorporated the desired C-12 and C-21 chirality of norzoanthamine and was transformed into the diene **33** to serve as a fully functionalized component for a subsequent cycloaddition (Scheme 4). Upon deprotection of **26**, derived from the methyl ester **25**, an efficient conversion to the *o*-nitrophenylselenide **27** proceeded smoothly, and led to the conjugated diene of **28** via facile oxidative *syn*-elimination [21]. This procedure avoided the α-epimerization seen under $E_2$ elimination conditions to afford diene **26** via the alcohol **24** by conversions to standard leaving groups. The aldehyde **30** was obtained in two additional steps using a high yielding DIBAL reduction and Dess–Martin oxidation sequence. The introduction of the desired C-20 stereochemistry of **32** could not be achieved with a Felkin–Anh preference via nucleophilic addition to the carbonyl of **30** because of the steric interactions imposed by the alkyl substituents of α-and β-substitution. For example, a number of asymmetric acetate aldol methods were attempted in conjunction with aldehyde **30**. The Nagao tin enolate methodology [22] and the titanium enolate described by Villarasa [23] failed to form detectable quantities of aldol adducts, and decomposition of **30** was observed upon warming. The Braun methodology [24] gave 75% yield of aldol adducts with low (3:2 dr) selectivity, whereas the lithium enolate of methylacetate quantitively reacted with **30** in an unselective manner (1:1 dr). As an alternative, we also explored the Brown asymmetric allylation [25] of aldehyde **30**. Reactions with either (+)-$Ipc_2$ or (−)-$Ipc_2$ allyl species resulted in 35%–50% yields of homoallylic alcohols with low (3:2 dr) selectivity. Attempted asymmetric allylations using nonracemic B-allyl-1,3-bis[(4-methylphenyl)sulfonyl]-4,5-diphenyl-1,3,2-diazaborolidines [26] led to the recovery of starting **30**. After an examination of these methods, the adoption of the Duthaler procedure [27] using titanium enolate **31** afforded alcohol **32** as a single diastereomer (dr > 19:1) in 70% yield over two steps from **29**. While a detailed analysis of asymmetric induction in this reaction is difficult, our modeling has suggested that access to boat-like transition states may be essential for high stereoselectivity in α,β,β′-branched aldehydes [16]. Exposure of **32** to an excess of methyl chloromethyl ether (MOMCl) in the presence of DMAP furnished the desired acetal without evidence of β-elimination, and immediate reduction with $LiAlH_4$ at 0 °C cleanly gave the primary alcohol for IBX oxidation to the aldehyde of **33** (95%).

The introduction of a nitroalkene as a reactive dienophile utilized a modified Henry reaction of aldehyde **33** (Scheme 5) with nitromethane at room temperature in the presence of potassium fluoride [28]. A mixture of diastereomeric alcohols **34** (dr 2:1) was isolated in 84% yield, and elimination readily produced **35** upon treatment with methanesulfonyl chloride and $Et_3N$ at 0 °C. Triene **35** was not stable at 22 °C. We found that traces of acid in chloroform solutions of this material slowly produced the Diels–Alder products as well as other unidentified substances. Based on this observation, crude triene **35** was directly refluxed in benzene under argon in the presence of butylated hydroxytoluene (BHT) to yield decalins **37** and **38** as a 10:1 mixture of diastereomers (56%). Separation by flash chromatography, and 1-D as well as 2-D NMR analyses of each cycloaddition product led to the determination of relative stereochemistry via extensive NOESY correlations.

For the *trans*-fused **37**, the NOESY correlations of axial hydrogens at C-13, C-17, C-19 and C-21 (norzoanthamine numbering) are observed (Fig. 5), whereas the bottom face of **37** indicates crosspeaks for C-18, C-20, and the methyl substituent located at C-22. Support for the minor isomer **38** is summarized by the observed NOESY correlations (Fig. 5) that indicate crosspeaks for axial hydrogens at C-18, C-20, and the methyl substituent at C-22. Other NOESY correlations indicate the *cis*-fused ring system such as the NOESY crosspeak for vinylic hydrogen at C-14 with the axial hydrogen at C-21. As expected, the major isomer **37** is the result of the favored *endo*-transition state **36** in which the B-ring substituents are pseudoequatorial in a chair-like conformation of this facile intramolecular process. The alternative *exo*-transition state accounts for the formation of *cis*-fused **38** [16,29].

The Nef reaction was then explored for conversion of the *trans*-fused decalin **37** to directly produce the conjugated enone of **39** (Scheme 6). We have previously described the use of dimethyldioxirane (DMDO) for a similar transformation [30]. However, the application of these conditions in the case of **37** led to low yields and extensive decomposition. Ultimately, *trans*-2-(phenylsulfonyl)-3-phenyloxaziridene [31] was found to be a very effective oxidant for treatment of the potassium nitronate of **37**, and warming to 0 °C prior to quenching, also resulted in the C=C isomerization to exclusively afford the enone (83%). In tandem with the high *endo* selectivity of the [4π+2π] reaction of nitroalkenes, this two-step process provided an effective and general strategy for the synthesis of substituted *trans*-fused enones. This pathway was advanced to complete the *trans*-fused ABC ring system of norzoanthamine as documented in Scheme 6. Luche reduction [32] of **39** proceeded to yield a single diastereomer. The equatorial alcohol was assigned by

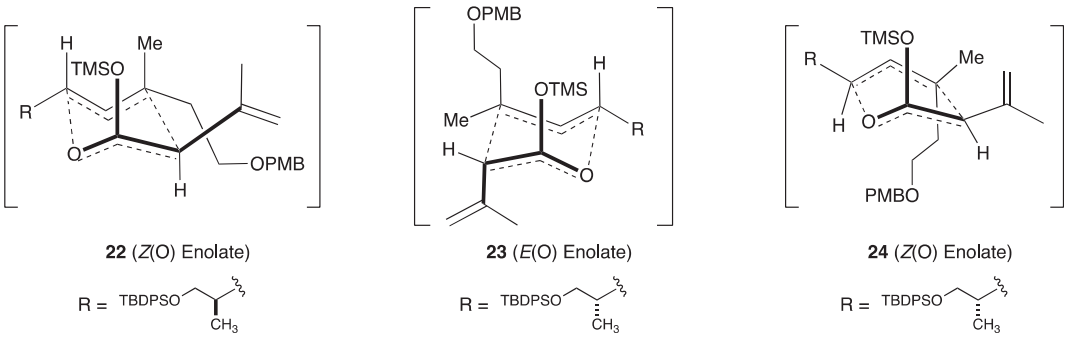
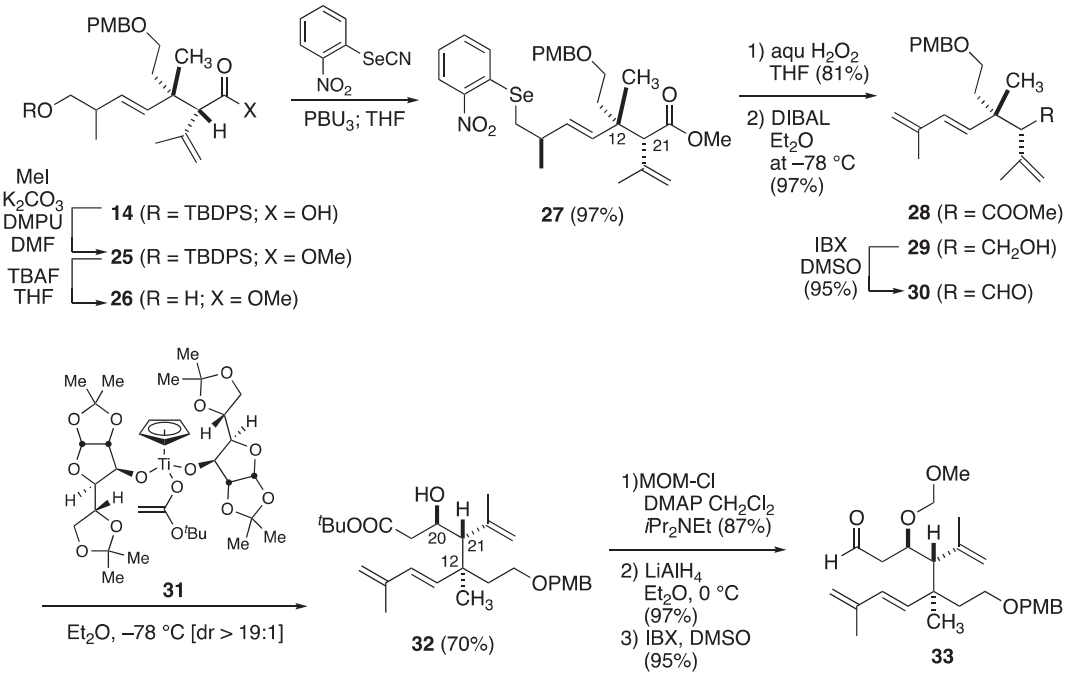
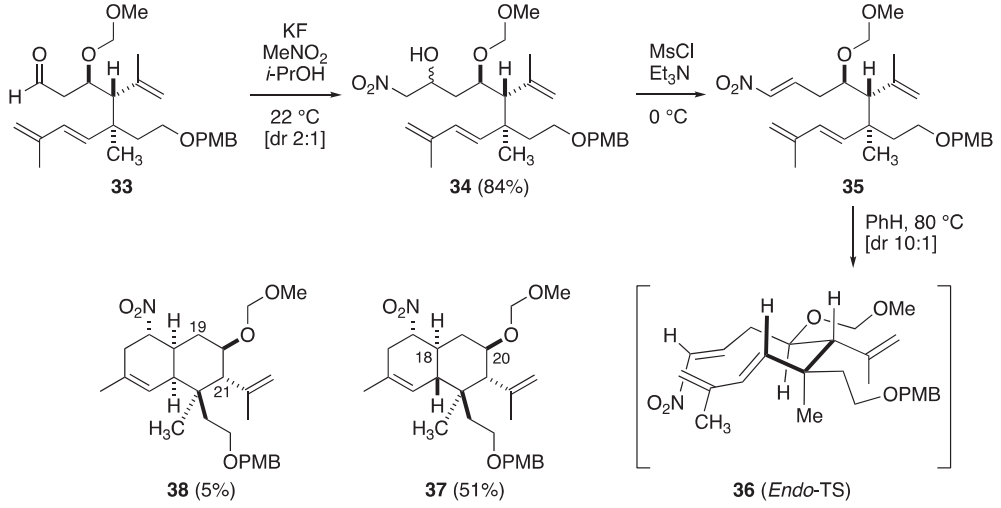



**Fig. 4.** Transition state analyses of Ireland–Claisen processes.




**Scheme 4.** Preparation of diene **33**.




**Scheme 5.** Formation of IMDA products.

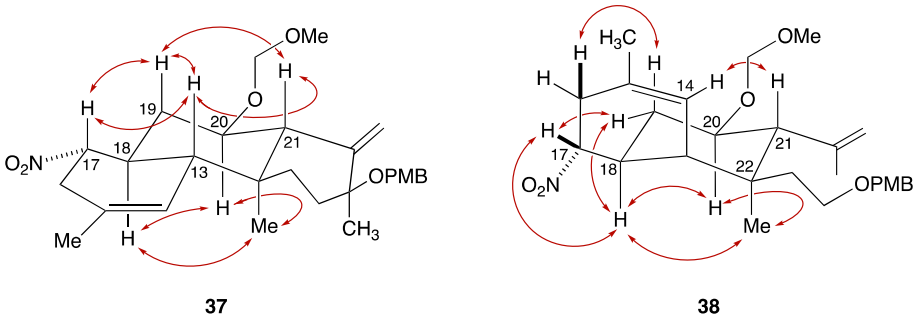
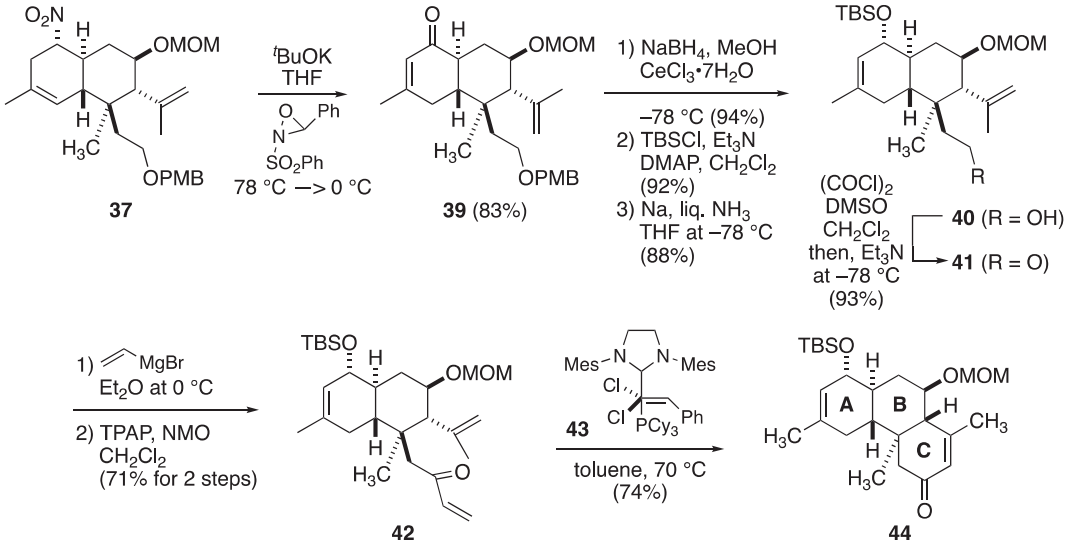



**Fig. 5.** Key NOESY correlations for structures **37** and **38**.




**Scheme 6.** Synthesis of the ABC tricycle **42** of norzoanthamine.

the large ($J$ = 9.1 Hz) vicinal coupling of the axial hydrogen appearing at $\delta$ 3.54, and was protected as its TBS silyl ether prior to exposure to Birch reduction conditions yielding the primary alcohol **40** (88%). Upon Swern oxidation, the resulting aldehyde **41** was treated with vinylmagnesium bromide followed by a Ley oxidation (TPAP, NMO) [33] to yield the enone of **42** (71% over 2 steps), and the synthesis of the *trans*-fused ABC tricycle **44** was finalized by a ring-closing metathesis (RCM) using the Grubbs II catalyst (**43**) under standard conditions [34].

## 3. Conclusion

In conclusion, an enantiocontrolled synthesis of the *trans*-fused ABC ring system of zoanthamine has been described. Our study has explored the diastereoselectivity for Ireland–Claisen [3,3]-rearrangements of mixtures of α,β- and β,γ-unsaturated esters derived from 3-methyl-2-butenoic acid. Substituent effects play a significant role in determining chair versus boat-like transition states, and the inclusion of DMPU improves the stereoselectivity of the reaction. The [3,3]-transposition has established critical vicinal stereochemistry, including asymmetry of a quaternary carbon. The transformations to afford the nitroalkene, designed for an intramolecular Diels–Alder cycloaddition, have featured the asymmetric Duthaler condensation as the preferred method to install C-20 stereochemistry. Subsequently the [4π+2π] reaction has proven to be an endo-selective event, and our modification of the Nef reaction has provided an effective preparation of *trans*-fused 2-cyclohexen-1-ones. Overall, this synthetic sequence has introduced five contiguous chiral carbon centers within the cyclohexane ring, and ring-closing metathesis has led to the *trans*-fused tricycic ABC system of norzoanthamine.

## 4. Experimental section

### 4.1. General information

Unless otherwise noted, all reactions were performed in flame-dried or oven-dried glassware under argon atmosphere. All non-volatile samples were pumped to constant weight at ambient temperature (0.2–0.1 mmHg) following removal of solvents by rotary evaporation. Non-aqueous reagents were transferred using syringe techniques under argon atmosphere. Bulk grade hexanes and ethyl acetate for chromatography were distilled prior to use. Tetrahydrofuran (THF), dimethylformamide (DMF), toluene, acetonitrile (AcCN), diethyl ether ($Et_2O$) and dichloromethane (DCM) were obtained anhydrous by degassing with argon and then passing through activated alumina columns to remove water. Triethylamine ($Et_3N$), 1,3-dimethyl-3,4,5,6-tetrahydro-2-pyrimidinone (DMPU), and diisopropylethylamine (DIPEA) were distilled from $CaH_2$ under dry argon immediately before use. Commercial reagents were used as obtained unless otherwise specified. Air-sensitive reagents were handled inside a glovebox. Reactions were monitored by standard thin-layer chromatography (tlc) techniques using EMD silica gel 60 F254 pre-coated plates (0.25 mm thickness). Following the run, tlc plates were visualized under UV light and/or by appropriate stains (*p*-anisaldehyde or ceric ammonium nitrate or potassium permanganate). Flash column chromatography was performed with Silica-P Flash Silica Gel (ultra-pure 40–63 μm) from Silicycle Chemical Division (Quebec QC, Canada).

Proton nuclear magnetic resonance ($^1$H NMR) spectra were recorded on Varian VXR 400 (400 MHz), Varian INOVA 400 (400 MHz) or Varian 500 (500 MHz) instruments. Carbon nuclear magnetic resonance ($^{13}$C NMR) spectra were measured using Varian VXR 400 (101 MHz), Varian INOVA 400 (101 MHz) or Varian 500 (125 MHz) instruments. NMR coupling constants and signal patterns are reported as $J$ values in Hz and d values in parts per million (ppm). $^1$H and $^{13}$C NMR spectra are internally referenced to residual solvent signals ($CDCl_3$ referenced to d 7.26 and 77.16 ppm respectively). The following abbreviations were used to indicate the multiplicities: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet. High resolution mass measurements (HRMS) were obtained on Thermo Electron Corporation MAT 95XP (EI/CI) or Agilent 1200 HPLC-6130 MSD (ESI). Optical rotation data were obtained on Perkin Elmer Model S-3 343 polarimeter and are reported in terms of degree of rotation of plane-polarized light. IR spectra were recorded on a FTIR spectrometer and are reported in terms of frequency of absorption ($cm^{-1}$).

Common commercial reagents that are described with lettered abbreviations include 4-dimethylaminopyridine (DMAP), dimethylformamide (DMF), *t*-butyldimethylsilyl chloride (TBSCl), *t*-butyldiphenylsilyl chloride (TBDPSCl), trimethylsilyl chloride (TMSCl), *tert*-butylammonium fluoride (TBAF), methoxymethyl chloride (MOMCl), pyridinium chlorochromate (PCC), butylated

hydroxytoluene (BHT), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDCI), and 2-iodoxybenzoic acid (IBX).

#### 4.1.1. Preparation of allylstannane (**6**)

$^{n}Bu_3SnH$ (1.27 mL, 4.70 mmol) was dissolved in THF (11.0 mL), cooled to 0 °C and then freshly prepared LDA (1.0 M in THF, 4.70 mL, 4.70 mmol) was added to it. The light yellow solution was stirred for 30 min at 0 °C, cooled to −78 °C and aldehyde **4** (1.00 g, 4.27 mmol) was added as a precooled (−78 °C) solution in THF (3.0 mL) via cannula. The mixture was stirred for 1 h and then a precooled (−78 °C) solution of 3-methyl-prop-2-enoic acid anhydride **5** (700 mg, 3.84 mmol) in THF (3.0 mL) was added via cannula. After stirring for 1 h, analysis by tlc revealed the consumption of the anhydride. The reaction was quenched with saturated aq. $NH_4Cl$ (10 mL), warmed to room temperature, diluted with water (20 mL) and then extracted with $Et_2O$ (2 × 50 mL). The combined $Et_2O$ extracts were dried ($MgSO_4$), filtered, concentrated, and purified via flash silica gel chromatography (gradient elution of 1.5–2.5% EtOAc/hexanes) to yield 2.03 g (87%) of **6** as a clear oil which was characterized as follows: $R_f = 0.70$ (25% EtOAc/hexanes); IR (neat) 2955, 2925, 2853, 1692, 1641, 1513, 1248, 1233, 1034 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.24 (d, $J = 8.4$ Hz, 2H), 6.87 (d, $J = 8.4$ Hz, 2H), 5.66 (s, 1H), 5.57 (A of AB, $J_{AB} = 10.4$ Hz, 1H), 5.55 (B of AB, $J_{AB} = 10.4$ Hz, 1H), 4.43 (s, 2H), 3.80 (s, 3H), 3.51 (t, $J = 7.4$ Hz, 2H), 2.33, (m, 2H), 2.15 (s, 3H), 1.88 (s, 3H), 1.64 (s, 3H), 1.56–1.40 (m, 6H), 1.28 (sext, $J = 7.2$ Hz, 6H), 0.88 (m, 15H); $^{13}C$ NMR (101 MHz, $CDCl_3$) $\delta$ 166.6, 149.1, 155.3, 130.6, 129.2, 128.0, 126.3, 116.2, 113.7, 72.5, 69.1, 55.2, 39.6, 30.6, 29.7, 29.0, 27.4, 20.1, 17.0, 13.7, 10.0; HRMS *m/z* calcd for $C_{31}H_{52}O_4Sn$ $(M)^+$ 608.2888, found 608.2885.

#### 4.1.2. Carboxylic acid (**7**)

Stannyl ester **6** (509 mg, 0.838 mmol) was dissolved in THF (4.00 mL), cooled to −78 °C and LDA (0.5 M in THF, 3.35 mL, 1.68 mL) was added dropwise. After stirring for 10 min TMSCl (214 μL, 1.68 mmol) was added and the reaction was allowed to warm to room temperature gradually. It was quenched with aq. pH 7 phosphate buffer (10.0 mL) and then the mixture was extracted with $Et_2O$ (2 × 25 mL). The ethereal layers were combined, dried ($MgSO_4$), filtered and concentrated. The crude material was purified by flash silica gel chromatography (gradient elution 5–30% EtOAc/hexanes to provide 435 mg (86%) of acid **7** as a colorless oil which was characterized as follows: $R_f = 0.46$ (25% EtOAc/hexanes); IR (neat) 3400, 3072, 2957, 1705 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 8.65 (br s, 1H), 7.24 (d, $J = 8.5$ Hz, 2H), 6.87 (d, $J = 8.5$ Hz, 2H), 6.18 (d, $J = 19.4$, 1H), 5.93 (d, $J = 19.4$, 1H), 5.00 (br s, 1H), 4.95 (br s, 1H), 4.41 (A of AB, $J_{AB} = 11.6$ Hz, 1H), 4.38 (B of AB, $J_{AB} = 11.6$ Hz, 1H), 3.80 (s, 3H), 3.50–3.36 (m, 2H), 3.09 (S, 1H), 2.00–1.88 (m, 1H), 1.86–1.70 (m, 4H), 1.54–1.42 (m, 6H), 1.36–1.20 (m, 6H), 1.12 (s, 3H), 0.98–0.76 (m, 15H); $^{13}C$ NMR (101 MHz, $CDCl_3$) $\delta$ 172.4, 149.1, 153.4, 139.9, 130.6, 129.2, 126.3, 117.0, 113.7, 72.7, 67.2, 62.1, 55.2, 51.2, 43.9, 38.5, 29.1, 27.3, 23.9, 19.8, 13.7, 9.4; HRMS *m/z* calcd for $C_{27}H_{43}O_4Sn$ $(M - C_4H_9)^+$ 551.2178, found 551.2184.

#### 4.1.3. (3R,4S)-4-methyl-3-(prop-1-en-2-yl)-4-vinyltetrahydro-2H-pyran-2-one (**8**)

To carboxylic acid **7** (25 mg, 41 μmol) in $CH_2Cl_2$ (2.0 mL) was added *tert*-butanol (0.20 mL), aq. phosphate pH 7 buffer (1.0 mL) and 2,3-dichloro-5,6-dicyanoquinone (37 mg, 0.17 mmol) in that order. The red reaction mixture was stirred for 10 h and then quenched with saturated aq. $NaHCO_3$ (2.0 mL). The mixture was extracted with $Et_2O$ (2 × 10 mL), the ethereal layers were combined, dried ($MgSO_4$), filtered, and concentrated. Purification by flash silica gel chromatography (gradient elution of 5–10% EtOAc in hexanes) provided 4.0 mg (54%) of **8** as a white solid which was characterized as followed: $R_f = 0.30$ (10% EtOAc/hexanes; IR (neat) 2920, 1719, 1641, 1202, 1080 $cm^{-1}$; $^1H$ NMR (400 MHz $CDCl_3$) $\delta$ 5.98 (dd, $J = 17.6$, 10.8 Hz, 1H), 5.17–5.07 (m, 2H), 5.04 (s, 1H), 4.84 (s, 1H), 4.52–4.38 (m, 2H), 3.04 (s, 1H), 2.02 (ddd, $J = 13.2$, 6.6, 6.6 Hz, 1H), 1.82–1.74 (m, 4H), 1.22 (s 3H); $^{13}C$ NMR (101 MHz, $CDCl_3$) $\delta$ 171.3, 142.1, 140.5, 117.7, 113.9, 66.1, 60.2, 38.9, 34.0, 25.1, 22.8; HRMS *m/z* calcd for $C_{11}H_{16}O_2$ $(M)^+$ 180.1145, found 180.1142.

#### 4.1.4. (R)-4-benzyl-3-((2R,3S,E)-3-hydroxy-7-((4-methoxybenzyl)oxy)-2,5-dimethylhept-4- enoyl)oxazolidin-2-one (**10**)

To a 0 °C solution of oxazolidinone **9** (0.625 g, 2.68 mmol) [11] was added di-*n*-butylboron triflate (1 M solution in $CH_2Cl_2$, 2.93 mL, 2.93 mmol) dropwise followed by a slow addition of $Et_3N$ (0.44 mL, 3.17 mmol). The reaction was stirred at 0 °C for 30 min and cooled to −78 °C. A solution of aldehyde **4** (0.540 g, 2.44 mmol) in $CH_2Cl_2$ (6 mL) was added slowly over 10 min. The reaction was stirred at −78 °C for 3 h, warmed to 0 °C and quenched by sequential dropwise addition of a 2:1 mixture of MeOH/pH 7.1 M aqueous phosphate buffer (5 mL) and a 2:1 mixture of MeOH/30% aqueous $H_2O_2$ (5 mL). The mixture was stirred at 0 °C for 30 min. The layers were separated and the aqueous layer was extracted with $Et_2O$ (3 × 10 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated. Purification by flash chromatography (gradient elution of 10–50% EtOAc/hexanes) gave 0.94 g (82%) of alcohol **10** as a viscous, colorless oil: $R_f$ 0.12 (3:1 hexanes/EtOAc); $[\alpha]_D^{21}$ −26.5 (c 0.75, $CHCl_3$); IR (neat) 3499, 2967, 2918, 1780, 1698, 1613, 1512, 1254, 1383, 1246, 1211, 1094, 1034, 912, 824, 756, 704 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.35–7.17 (m, 7H), 6.86 (d, $J = 8.2$ Hz), 5.32 (d, $J = 7.8$ Hz, 1H), 4.71–4.36 (m, 2H), 4.43 (s, 2H), 4.19–4.13 (m, 2H), 3.90–3.87 (m, 1H), 3.79 (s, 3H), 3.53 (t, $J = 7.1$, 2H), 3.23 (dd, $J = 13.6$, 3.5 Hz, 1H), 2.78 (dd, $J = 13.3$, 9.4 Hz, 1H), 2.51 (br s, 1H), 2.33 (apparent t, $J = 5.5$, 2H), 1.71 (s, 3H), 1.29 (d, $J = 7.1$, 3H); $^{13}C$ NMR (100 MHz, 69.1, 68.4, 66.1, 55.2, 55.1, 43.0, 39.6, 37.8, 17.1, 11.9; HRMS *m/z* calcd for $C_{27}H_{33}NO_6$ $(M + Na)^+$ 490.2206, found 490.2226.

#### 4.1.5. (2S,3S,E)-7.4((4-methoxybenzyl)oxy)-2,5-dimethylhept-4-ene-1,3-diol

To a solution of **10** (9.1 g, 19.5 mmol) and $Et_2O$ (160 mL) was added MeOH (3.9 mL, 97.3 mmol). The solution was cooled to 0 °C and stirred for 30 min $LiBH_4$ (2.12 g, 97.3 mmol) was added in one portion. The reaction was slowly allowed to warm to room temperature and stirred for 2 h. The reaction was quenched by a careful addition of saturated $NH_4Cl$ (50 mL). The reaction mixture was stirred at room temperature for 1 h. The layers were separated and the aqueous layer was extracted with $Et_2O$ (3 × 75 mL). Combined organic extracts were dried over $Na_2SO_4$, filtered and concentrated to yield the crude diol for conversion to **11**. The crude material was used in the next reaction without additional purification. A small amount of this diol was purified for characterization: $R_f$ 0.15 (1:1 hexanes/EtOAc); $[\alpha]_D^{21}$ +3.2 (c 0.57, $CHCl_3$); IR (neat) 3386, 2933, 1613, 1514, 1463, 1362, 1302, 1248, 1175, 1090, 1034, 821, 704 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.22 (d, $J = 8.6$ Hz, 2H), 6.85 (d, $J = 8.6$ Hz, 2H), 5.36 (d, 8.9 Hz, 1H), 4.46 (m, 1H), 4.41 (s, 2H), 3.78 (s, 3H), 3.66–3.60 (m, 1H), 3.57–3.49 (m, 3H), 2.45 (br s, 1H), 2.37–2.24 (m, 2H), 1.97 (br s, 1H), 1.93–1.87 (m, 1H), 1.67 (s, 3H), 0.87 (d, $J = 6.7$ Hz, 3H); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 159.2, 136.4, 130.3, 129.3, 126.8, 113.8, 72.5, 71.9, 68.0, 66.2, 55.3, 40.9, 39.7, 16.8, 12.2; HRMS *m/z* calcd for $C_{33}H_{44}O_4Si$ $(M + Na)^+$ 317.1729, found 317.1739.

#### 4.1.6. (2S,3S,E)-1-((tert-butyldiphenylsilyl)oxy)-7-((4-methoxybenzyl)oxy)-2,5-dimethylhept-4-en-3-ol (**11**)

To a solution of DMAP (0.542 g, 4.44 mmol), $Et_3N$ (12.4 mL, 88.76 mmol) and the crude diol (13 g, 44.4 mmol) from **10** in $CH_2Cl_2$ (220 mL) was added TBDPSCl (12.7 mL, 48.8 mmol). The reaction

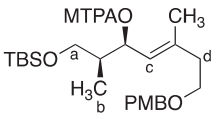
was stirred at room temperature for 48 h. Saturated aqueous $NH_4Cl$ (200 mL) was added, the layers were separated and aqueous layer was extracted with $Et_2O$ (3 × 150 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated. Flash chromatography gave the desired, pure silyl ether **11** (14.22 g, 78% over 2 steps based on recovered diol) and starting diol (2.33 g, 18%): Characterization of **11**: $R_f$ 0.51 (4:1 Hexanes/EtOAc); $[\alpha]_D^{21}$ +4.4 (c 0.86, $CHCl_3$); IR (neat) 3445, 3071, 3048, 2958, 2931, 2857, 1613, 1588, 1531, 1463, 1389, 1361, 1302, 1248, 1173, 1112, 1036, 1007, 823, 741, 703, 613 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.69–7.65 (m, 4H), 7.46–7.37 (m, 6H), 7.24 (d, $J$ = 8.6 Hz, 2H), 6.86 (d, $J$ = 8.6 Hz, 2H), 5.33 (d, $J$ = 9.0 Hz, 1H), 4.58–4.53 (m, 1H), 4.42 (s, 2H), 3.79 (s, 3H), 3.66–3.64 (m, 2H), 3.52 (t, $J$ = 7.1 Hz, 2H), 2.63 (br s, 1H), 2.38–2.28 (m, 2H), 1.93–1.87 (m, 1H), 1.68 (s, 3H), 1.06 (s, 9H), 0.87 (d, $J$ = 7.0 Hz, 3H); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 159.1, 135.63, 135.55, 135.5, 133.2, 130.5, 129.8, 129.7, 129.2, 127.7, 127.2, 113.7, 72.5, 70.7, 68.8, 67.3, 55.2, 40.8, 39.7, 26.9, 19.1, 17.0, 11.5; HRMS *m/z* calcd for $C_{33}H_{44}O_4Si$ $(M + Na)^+$ 555.2906, found 555.2906.

#### 4.1.7. General procedure for the formation of C14 Mosher esters of alcohol **11**

To a room temperature solution of alcohol **11** (0.0054, 0.0132 mmol) in $CH_2Cl_2$ was added EDCI (0.0094 g, 0.0489 mmol), DMAP (0.0045 g, 0.0367 mmol) and (*S*)-(−)-α-methoxy-α-trifluoromethylphenylacetic acid (*S*-MTPA) (0.0086 g, 0.0367 mmol). The mixture was stirred overnight and diluted with water. The layers were separated and the aqueous layer was extracted with $CH_2Cl_2$ (3 × 1 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated. The crude oil was purified by flash chromatography (2 mL silica gel, 5% EtOAc/hexanes) to yield the (*S*)-MTPA of **11** (0.0075 g, 91%). In a separate flask the same procedure was employed utilizing (*R*)-(−)-α-methoxy-α-trifluoromethylphenylacetic acid to yield the (*R*)-MTPA of **11** (0.0051 g, 83%). The analysis [12b] is described using selected proton shifts as listed below.

(*R*)-MTPA ester of **11**: $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 5.27 (d, $J$ = 9.8 Hz, 1H, H(c)), 3.39 (d, $J$ = 5.5 Hz, 2H, H(a)), 2.34 (d, $J$ = 6.8 Hz, 2H, H(d)), 0.88 (d, $J$ = 6.3 Hz, 3H, H(b)).

(*S*)-MTPA ester of **11**: $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 5.11 (d, $J$ = 9.4 Hz, 1H, H(c)), 3.46 (d, $J$ = 5.9, Hz, 2H, H(a)), 2.32 (t, $J$ = 6.8 Hz, 2H, H(d)), 0.94 (d, $J$ = 6.6 Hz, 3H, H(b)).




| Proton | $\delta_S$ (ppm) | $\delta_R$ (ppm) | $\delta_S - \delta_R$ (ppm) |
|---|---|---|---|
| a | 3.46 | 3.39 | +0.07 |
| b | 0.94 | 0.88 | +0.06 |
| c | 5.11 | 5.27 | −0.16 |
| d | 2.32 | 2.34 | −0.02 |

#### 4.1.8. (2S,3S,E)-1-((tert-butyldiphenylsilyl)oxy)-7-((4-methoxybenzyl)oxy)-2,5-dimethylhept-4-en-3-yl3-methylbut-2-enoate (12) and (2S,3S,E)-1-((tert-butyldiphenylsilyl)oxy)-7-((4-methoxybenzyl)oxy)-2,5-dimethylhept-4-en-3-yl 3-methylbut-3-enoate (13)

DMAP (6.10 g, 49.89 mmol), EDCI (7.66 g, 39.91 mmol) and 3,3-dimethylacrylic acid (3.66 g, 36.58 mmol) were dissolved in $CH_2Cl_2$ (18 mL) and stirred at room temperature for 15 min. A solution of alcohol 11 (17.72 g, 33.26 mmol) in $CH_2Cl_2$ (17 mL) was added and stirred overnight. The reaction mixture was poured into $H_2O$ (50 mL), the layers were separated and the aqueous layer was extracted with $CH_2Cl_2$ (3 × 10 mL). The combined organic layers were dried over $MgSO_4$ and concentrated. The crude product was purified by flash chromatography (gradient elution of 5–30% EtOAc in Hexanes) to yield 18.20 g (89%) of an inseparable 3:1 mixture of olefin isomers 12 and 13: $R_f$ 0.73 (3:1 Hexanes/EtOAc); IR (neat) 3071, 3048, 2933, 2857, 1716, 1651, 1613, 1513, 1463, 1428, 1380, 1360, 1302, 1247, 1172, 1148, 1109, 1036, 1008, 999, 924, 850, 823, 741, 704, 691, 614 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.67–7.63 (m, 4H), 7.44–7.32 (m, 6H), 7.24 (d, $J$ = 8.6 Hz, 2H), 6.88–6.85 (m, 2H), 5.70 (dd, $J$ = 9.0, 5.8 Hz), 5.64 (s, 0.75H), 5.19–5.15 (m, 1H), 4.87 (s, 0.25H), 4.81 (s, 0.25H), 4.40 (s, 2H), 3.80 (s, 3H), 3.62–3.45 (m, 4H), 2.96 (s, 0.5H), 2.30 (app t, $J$ = 5.1 Hz), 2.14 (s, 2.25H), 1.89 (s, 3H), 1.77 (s, 3H), 1.06 (s, 9H), 0.97 (d, $J$ = 6.6 Hz); $^{13}C$ NMR (125 MHz, $CDCl_3$) $\delta$ 170.5, 165.9, 159.1, 155.7, 138.8, 137.8, 137.0, 135.6, 135.5, 133.82, 133.76, 133.62, 133.58, 130.6, 130.5, 129.6, 129.52, 129.48, 129.1, 127.6, 127.5, 124.2, 123.6, 116.6, 114.4, 113.7, 72.5, 72.1, 70.8, 68.65, 68.58, 65.2, 65.1, 55.2, 43.7, 40.6, 40.5, 39.7, 27.3, 27.0, 26.8, 22.4, 20.2, 19.2, 17.2, 17.1, 12.2, 12.1; HRMS *m/z* calcd for $C_{33}H_{44}O_4Si$ $(M + Na)^+$ 637.3325, found 637.3326.

#### 4.1.9. (2R,3S,6R,E)-7-((tert-butyldiphenylsilyl)oxy)-3-(2-((4-methoxybenzyl)oxy)ethyl)-3,6-dimethyl-2-(prop-1-en-2-yl)hept-4-enoic acid (**14**)

To a 0 °C solution of diisopropylamine (1.57 mL, 11.22 mmol) in THF (11 mL) was added *n*-BuLi (3.0 mL, 2.5 M in hexanes). The mixture was stirred for 10 min at 0 °C and cooled to −78 °C. DMPU (5.5 mL) was added and the mixture was stirred for 10 min. To this mixture was added a solution of esters **12** and **13** (2.3 g, 3.74 mmol) in THF (7 mL). The reaction was stirred for 5 min and freshly distilled TMSCl (1.42 mL, 11.22 mmol) was added. The cooled bath was removed and the mixture was allowed to stir at room temperature overnight. Saturated aqueous $NH_4Cl$ (30 mL) was added, the layers were separated and the aqueous layer was extracted 3x with EtOAc (15 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated. The crude acid **14** was used in the next step without further purification. A small amount of **14** was purified for characterization: $R_f$ 0.19 (3:1 hexanes/EtOAc); $[\alpha]_D^{21}$ +12.9 (c. 0.94, $CHCl_3$); IR (neat) 3340, 3070, 2931, 2857, 1705, 1613, 1513, 1463, 1383, 1362, 1302, 1248, 1173, 1112, 1037, 823, 741, 703, 614 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.69–7.66 (m, 4H), 7.44–7.36 (m, 6H), 7.20 (d, $J$ = 8.6 Hz, 2H), 6.84 (d, $J$ = 8.6 Hz, 2H), 5.73 (d, $J$ = 16 Hz, 1H), 5.32 (dd, $J$ = 16.0, 7.8 Hz, 1H), 5.00 (s, 1H), 4.95 (s, 1H), 4.30 (ABq, $J_{AB}$ = 11.3 Hz, $\Delta\nu_{AB}$ = 11.3 Hz, 2H), 3.78 (s, 3H), 3.56–3.35 (m, 4H), 3.04 (s, 1H), 2.45–2.38 (m, 1H), 1.94–1.86 (m, 1H), 1.82 (s, 3H), 1.79–1.70 (m, 1H), 1.10 (s, 3H), 1.07 (s, 9H), 1.00 (d, $J$ = 7.0 Hz, 3H); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 172.7, 159.1, 139.6, 135.6, 134.8, 133.9, 132.2, 130.4, 129.5, 129.3, 127.6, 117.4, 113.7, 72.6, 68.9, 67.0, 62.3, 55.2, 40.6, 39.7, 39.0, 26.9, 23.8, 20.8, 19.3, 16.9; HRMS *m/z* calcd for $C_{38}H_{50}O_5Si$ $(M + Na)^+$ 637.3325, found 637.3354.

#### 4.1.10. (3R,4R)-4-((R,E)-4-((tert-butyldiphenylsilyl)oxy)-3-methylbut-1-en-1-yl)-4-methyl-3-(prop-1-en-2-yl)tetrahydro-2H-pyran-2-one (**16**)

To a room temperature solution of acid **14** (0.034 g, 0.055 mmol) in $CH_2Cl_2$ (2 mL) was added DDQ (0.063 g, 0.276 mmol) in one portion. The mixture was stirred overnight and saturated $NH_4Cl$ (2 mL) was added. The layers were separated and the organic layer was extracted with $Et_2O$ (3 × 2 mL). The combined organic layers were dried over $Na_2SO_4$, filtered and concentrated. The crude oil was purified by flash chromatography (1 mL basic alumina, 5% EtOAc/Hexanes) to yield lactone **16** (0.014 g, 56%) as a colorless oil: $R_f$ 0.39 (3:1 hexanes/EtOAc); IR (neat) 3017, 2955, 2860, 1733,

1613 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.66–7.63 (m, 4H), 7.45–7.35 (m, 6H), 5.58 (d, $J = 8.6$ Hz, 1H), 5.45 (dd, $J = 16.0$, 7.4 Hz, 1H), 5.00 (t, $J = 1.6$ Hz, 1H), 4.80 (s, 1H), 4.43–4.34 (m, 2H), 3.50 (d, $J = 6.6$ Hz, 2H), 2.99 (s, 1H), 2.43–2.35 (m, 1H), 1.95–1.86 (m, 1H), 1.79–1.74 (m, 1H), 1.73 (s, 3H), 1.18 (s, 3H), 1.04 (s, 9H), 0.99 (d, $J = 6.7$ Hz, 3H); HRMS *m/z* calcd for $C_{30}H_{40}O_3Si$ $(M + Na)^+$ 499.2644, found 499.2631.

#### 4.1.11. (2R,3R,Z)-1-((tert-butyldiphenylsilyl)oxy)-7-((4-methoxybenzyl)oxy)-2,5-dimethylhept-4-en-3-ol (**17**)

The preparation of the mixture of nonracemic esters **18** and **19** followed the same sequence of reactions as described for **12** and **13**. Details and full characterizations of the starting alcohol **17** is included here.

To a 0 °C solution of (*S*)-4-benzyl-3-propionyloxazolidin-2-one[11] (2.4 g, 10.2 mmol) in $CH_2Cl_2$ (33 mL) was added di-*n*-butylboron triflate (1 M solution in $CH_2Cl_2$, 12.0 mL, 12.0 mmol) dropwise followed by a slow addition of $Et_3N$ (2.4 mL, 17.1 mmol). The reaction was stirred at 0 °C for 30 min and cooled to −78 °C. A solution of (*Z*)-5-((4-methoxybenzyl)oxy)-3-methylpent-2-enal (2.00 g, 8.54 mmol in $CH_2Cl_2$ (17 mL) was added slowly over 10 min. The reaction was stirred at −78 °C for 2 h, warmed to 0 °C and quenched by sequential addition of 2:1 MeOH/pH 7.1 M aqueous phosphate buffer (15 mL) and 2:1 MeOH/30% aqueous $H_2O_2$ (15 mL). The mixture was stirred at 0 °C for 30 min. The layers were separated and the aqueous layer was extracted with $Et_2O$ (3 × 30 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated. Purification by flash chromatography (10–50% EtOAc/hexanes) gave 3.91 g (98%) of the desired aldol adduct as a viscous, colorless oil: $R_f$ 0.16 (3:1 Hexanes/EtOAc); IR (neat) 3449, 2967, 2918, 2864, 1780, 1698, 1613, 1512, 1454, 1383, 1246, 1211, 1094, 1034, 912, 824, 756, 704 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.45–7.18 (m, 7H), 6.90 (d, $J = 8.6$ Hz, 2H), 5.54 (d, $J = 8.2$ Hz, 1H), 4.77–4.59 (m, 2H), 4.49–4.30 (ABq, $J_{AB} = 11.9$ Hz, $\Delta\nu_{AB} = 7.7$ Hz, 2H), 4.26–4.13 (m, 2H), 3.98 (m, 1H), 3.83 (s, 3H), 3.65–3.42 (m, 2H), 3.37–3.17 (m, 2H), 2.81 (dd, $J = 9.6$, 13.5 Hz, 1H), 2.73–2.62 (m, 1H), 2.22 (td, $J = 4.9$, 13.7 Hz, 1H), 1.76 (s, 3H), 1.35 (d, $J = 6.6$ Hz, 3H); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 176.0, 159.1, 153.0, 137.3, 135.2, 129.8, 129.4, 129.2, 128.8, 127.5, 127.2, 113.7, 72.6, 68.1, 66.9, 65.9, 55.2, 55.1, 42.7, 37.7, 32.7, 23.4, 12.4; HRMS *m/z* calcd for $C_{27}H_{34}NO_6$ $(M^+)$ 468.2386, found 468.2389.

To a solution of the aldol adduct (4.0 g, 8.56 mmol) in $Et_2O$ (70 mL) was added MeOH (1.0 mL, 25.7 mmol). The solution was cooled to 0 °C and stirred for 30 min $LiBH_4$ (0.056 g, 25.7 mmol) was added in one portion. The reaction was slowly allowed to warm to room temperature with stirring overnight. The reaction was quenched by addition of saturated $NH_4Cl$ (50 mL), and the mixture was stirred at room temperature for 1 h. The layers were separated and the aqueous layer was extracted with $Et_2O$ (3 × 50 mL), and combined organic extracts were dried over $Na_2SO_4$, filtered and concentrated. The crude material was diluted in $CH_2Cl_2$ (43 mL) and $Et_3N$ (2.4 mL, 17.1 mmol), DMAP (0.10 g, 0.856 mmol) and TBDPSCl (2.89 mL, 11.1 mmol) was added. The mixture was stirred at room temperature for 24 h and saturated $NH_4Cl$ (40 mL) was added. The layers were separated and the aqueous layer was extracted with $CH_2Cl_2$ (3 × 40 mL). The combined organic layers were dried over $Na_2SO_4$, filtered and concentrated. The crude oil was purified by flash chromatography to yield the desired secondary alcohol **17** as a pure diastereomer (2.99 g, 65% for 2 steps): $R_f$ 0.54 (4:1 Hexanes/EtOAc); IR (neat) 3480, 2959, 2861, 1613, 1514, 1468, 1248, 1109, 1036, 824, 704, $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.5–7.84 (m, 4H), 7.32–7.53 (m, 6H), 7.24 (d, $J = 8.6$ Hz, 2H), 6.86 (d, $J = 8.6$ Hz, 2H), 5.46 (d, $J = 8.6$ Hz, 1H), 4.45 (s, 2H), 4.44–4.42 (m, 1H), 3.79 (s, 3H), 3.58–3.71 (m, 2H), 3.39–3.54 (m, 2H), 3.08 (d, $J = 2.0$ Hz, 1H), 2.66 (ddd, $J = 13.7$, 8.6, 6.2 Hz, 1H), 2.14 (dt, $J = 13.6$, 4.9 Hz, 1H), 1.86–1.80 (m, 1H), 1.72 (s, 3H), 1.07 (s, 9H), 1.01 (d, $J = 7.0$ Hz, 3H); $^{13}C$ NMR (125 MHz, $CDCl_3$) $\delta$ 159.3, 136.1, 135.8, 135.7, 133.7, 133.6, 130.1, 129.8, 129.7, 129.5, 129.5, 127.8, 127.8, 113.9, 72.8, 69.1, 67.3, 66.9, 55.4, 41.0, 32.9, 27.0, 24.8, 23.7, 19.4, 12.3; HRMS *m/z* calcd for $C_{33}H_{43}O_3Si$ $(M^+ - OH)$ 515.2983, found 515.2979.

#### 4.1.12. (2R,3R,Z)-1-((tert-butyldiphenylsilyl)oxy)-7-((4-methoxybenzyl)oxy)-2,5-dimethylhept-4-en-3-yl-3-methylbut-2-enoate (**18**) and (2R,3R,Z)-1-((tert-butyldiphenylsilyl)oxy)-7-((4-methoxybenzyl)oxy)-2,5-dimethylhept-4-en-3-yl-3-methylbut-3-enoate (**19**)

To a solution of DMAP (1.03 g, 8.42 mmol), and EDCI (1.29 g, 6.73 mmol) in $CH_2Cl_2$ (3 mL) was added 3,3-dimethylacrylic acid (0.62 g, 6.17 mmol) and the mixture was stirred at room temperature for 15 min. A solution of the previously prepared secondary alcohol **17** (2.99 g, 5.61 mmol) in $CH_2Cl_2$ (2 mL) was added, and the mixture was stirred overnight. The reaction mixture was poured into $H_2O$ (20 mL), the layers were separated and the aqueous layer was extracted with $CH_2Cl_2$ (3 × 20 mL)). The combined organic layers were dried over $MgSO_4$ and concentrated. The crude product was purified by flash chromatography (gradient elution of 5–30% EtOAc in Hexanes) to yield an inseparable mixture of **18** and **19** (3.17 g, 92%) as a colorless oil: $R_f$ 0.78 (3:1 Hexanes/EtOAc); IR (neat) 3070, 3049, 2932, 2857, 1715, 1651, 1613, 1588, 1513, 1463, 1588, 1513, 1463, 1428, 1378, 1361, 1302, 1248, 1228, 1172, 1149, 1112, 1037, 1008, 981, 849, 823, 741, 703, 612 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.74–7.64 (m, 4H), 7.44–7.33 (m, 6H), 7.25–7.22 (m, 2H), 6.85 (d, $J = 8.6$ Hz, 2H), 5.74–5.70 (m, 1H), 5.63 (br s, 0.75H), 5.26–5.23 (m, 1H), 4.87 (s, 0.25H), 4.81 (s, 0.25H), 4.41–4.40 (m, 2H), 3.80 (s, 3H), 3.64–3.47 (m, 4H), 2.96 (s, 0.5H), 2.63–2.53 (m, 1H), 2.50–2.44 (m, 1H), 2.15 (s, 2.25H), 1.89 (s, 3H), 1.75 (s, 3H), 1.06 (s, 9H), 0.91–0.90 (m, 3H); $^{13}C$ NMR (125 MHz, $CDCl_3$) $\delta$ 170.4, 165.8, 159.0, 155.5, 138.7, 138.2 137.6, 135.6, 135.54, 135.51, 134.8, 133.8, 133.6, 130.7, 129.6, 129.51, 129.46, 129.1, 127.64, 127.56, 127.52, 124.5, 123.9, 116.6, 114.4, 113.6, 72.30, 72.27, 70.3, 68.62, 68.57, 65.3, 55.2, 43.7, 40.78, 40.74, 32.71, 32.68, 27.3, 26.8, 26.5, 24.11, 24.09, 22.45, 20.2, 19.3, 12.0, 11.8; HRMS *m/z* calcd for $C_{38}H_{50}O_5Si$ $(M^+)$ 613.3344, found 613.3349.

#### 4.1.13. (2S,3S,6S,E)-7-((tert-butyldiphenylsilyl)oxy)-3-(2-((4-methoxybenzyl)oxy)ethyl)-3,6-dimethyl-2-(prop-1-en-2-yl)hept-4-enoic acid (**20**)

To a −78 °C solution of diisopropylamine (1.64 mL) in THF (12 mL) was added *n*-BuLi (2.5 M in hexanes, 3.1 mL). The mixture was warmed to 0 °C for 30 min and cooled to −78 °C. A 3:1 mixture of esters **18** and **19** (2.4 g, 3.90 mmol) was slowly added as a solution in THF (8 mL) at stirred at −78 °C for 1 h. Freshly distilled TMSCl was added and the mixture was stirred for 1 h at −78 °C. The cooling bath was removed and the mixture was allowed to warm to room temperature and then refluxed overnight. The mixture was cooled to room temperature and saturated $NH_4Cl$ was added. The layers were separated and the organic layer was extracted with $Et_2O$ (3 × 20 mL). The combined organic layers were dried over $Na_2SO_4$, filtered and concentrated. The crude oil was purified by flash chromatography (300 mL silica gel, 2–30% EtOAc/Hexanes) to yield acid **20** (2.01 g, 84%) from a 6:1 mixture of diastereomers. For full characterization of **20**: $R_f$ 0.22 (3:1 hexanes/EtOAc); $[\alpha]_D^{21}$ −8.1 (c. 1.34, $CHCl_3$); IR (neat) 3400, 3071, 2957, 2931, 2858, 1706, 1613, 1514, 1463, 1428, 1385, 1363, 1302, 1248, 1208, 1173, 1112, 1037, 824, 741, 703, 614 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.68–7.65 (m, 4H), 7.44–7.36 (m, 6H), 7.22 (d, $J = 8.5$ Hz, 2H), 6.85 (d, $J = 8.6$ Hz, 2H), 5.46 (d, $J = 16.0$ Hz, 1H), 5.32 (dd, $J = 16.0$, 7.0 Hz, 1H), 4.95 (s, 1H), 4.93 (s, 1H), 4.36 (s, 2H), 3.79 (s, 3H), 3.54 (dd, $J = 9.8$, 5.9 Hz, 1H), 3.47–3.41 (m, 3H), 3.02 (s, 1H), 2.43–2.33 (m, 1H), 1.94–1.77 (m, 2H), 1.76 (s, 3H), 1.15 (s, 3H), 1.06 (s, 9H), 1.00 (d, $J = 7.0$ Hz, 3H); $^{13}C$

NMR (100 MHz, $CDCl_3$) $\delta$ 177.0, 159.1, 139.6, 135.6, 135.1, 133.9, 131.6, 130.4, 129.5, 129.3, 127.6, 117.0, 113.8, 72.6, 68.8, 66.9, 61.4, 55.2, 40.6, 39.5, 38.3, 26.9, 24.5, 20.6, 19.3, 16.9; HRMS *m/z* calcd for $C_{38}H_{50}O_5Si$ $(M + Na)^+$ 637.3325, found 637.3315.

#### 4.1.14. (3S,4S)-4-((S,E)-4-((tert-butyldiphenylsilyl)oxy)-3-methylbut-1-en-1-yl)-4-methyl-3-(prop-1-en-2-yl)tetrahydro-2H-pyran-2-one (21)

To a room temperature solution of carboxylic acid 20 (0.136 g, 0.221 mmol) in $CH_2Cl_2$ (2 mL) was added DDQ (0.075 g, 0.332 mmol) in one portion. The mixture was stirred overnight and saturated $NH_4Cl$ (2 mL) was added. The layers were separated and the organic layer was extracted with $Et_2O$ (3 × 2 mL). The combined organic layers were dried over $Na_2SO_4$, filtered and concentrated. The crude oil was filtered through a plug of silica gel to yield lactone 21 (0.067 g, 65%) as a colorless oil: $R_f$ 0.39 (3:1 hexanes/EtOAc); IR (neat) 3068, 2961, 2858, 1735, 1615 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.66–7.44 (m, 4H), 7.44–7.35 (m, 6H), 5.57 (d, $J$ = 16 Hz, 1H), 5.48 (dd, $J$ = 15.6, 7.0 Hz, 1H), 4.99 (t, $J$ = 1.2 Hz, 1H), 4.80 (s, 1H), 4.48–4.34 (m, 2H), 3.55–3.46 (m, 2H), 2.99 (s, 1H), 2.42–2.36 (m, 1H), 1.99–1.84 (m, 1H), 1.77–1.71 (m, 1H), 1.71 (s, 3H), 1.18 (s, 3H), 1.05 (s, 9H), 1.02 (d, $J$ = 6.7 Hz, 3H); HRMS *m/z* calcd for $C_{30}H_{40}O_3Si$ $(M + Na)^+$ 499.2644, found 499.2624.

#### 4.1.15. (2R,3S,6R,E)-methyl 7-((tert-butyldiphenylsilyl)oxy)-3-(2-((4-methoxybenzyl)oxy)ethyl)- 3,6-dimethyl-2-(prop-1-en-2-yl) hept-4-enoate (25)

To 0 °C solution of crude acid **14** (9.75 mmol) in DMF (5 mL) and traces of residual DMPU (10 mL) was added $K_2CO_3$ (4.05 g, 29.3 mmol) followed by a dropwise addition of MeI (1.82 mL, 29.3 mmol). The reaction was allowed to slowly warm to room temperature over 2 h, stirred overnight and quenched with saturated aqueous $NaHCO_3$ (100 mL). The layers were separated and the aqueous layer was extracted 3x with $Et_2O$. The combined organic layers were dried over $MgSO_4$, filtered and concentrated. The crude product was purified via flash chromatography (5% EtOAc/Hexanes) providing ester **25** (4.91 g, 82%) as a colorless oil: $R_f$ 0.78 (3:1 Hexanes/EtOAc); $[\alpha]_D^{21}$ +17.2 (c. 0.68, $CHCl_3$); IR (neat) 3019, 2956, 2857, 1737, 1613, 1513, 1460, 1361, 1301, 1248, 1151, 1112, 1036, 823, 741, 703 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.70–7.68 (m, 4H), 7.45 (m, 6H), 7.20 (d, $J$ = 8.6 Hz, 2H), 6.85 (d, $J$ = 8.6 Hz, 2H), 5.73 (d, $J$ = 15.7 Hz, 1H), 5.32 (dd, $J$ = 16, 7.4 Hz, 1H), 4.99 (s, 1H), 4.94 (s, 1H), 4.30 (ABq, $J_{AB}$ = 11.3 Hz, $\Delta\nu_{AB}$ = 11.3 Hz, 2H), 3.79 (s, 3H), 3.57 (s, 3H), 3.56–3.53 (m, 1H), 3.48–3.35 (m, 3H), 3.03 (s, 1H), 2.48–2.38 (m, 1H), 1.89–1.78 (m, 1H), 1.80 (s, 3H), 1.72–1.65 (m, 1H), 1.11 (s, 3H), 1.08 (s, 9H), 1.03 (d, $J$ = 6.6 Hz, 3H); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 177.3, 159.1, 139.6, 135.6, 134.8, 134.0, 132.2, 130.4, 129.5, 129.3, 127.6, 117.5, 113.7, 72.6, 68.9, 67.0, 62.3, 55.2, 40.7, 39.8, 39.0, 26.9, 23.9, 20.8, 19.3, 16.9; HRMS *m/z* calcd for $C_{39}H_{52}O_5Si$ $(M + Na)^+$ 651.3481, found 651.3461.

#### 4.1.16. (2R,3S,6R,E)-methyl-7-hydroxy-3-(2-((4-methoxybenzyl) oxy)ethyl)-3,6-dimethyl-2-(prop-1-en-2-yl)hept-4-enoate (26)

To a room temperature solution of silyl ether **25** (0.174 g, 0.277 mmol) in THF (3 mL) was added TBAF (0.55 mL, 1 M in THF) and the mixture was stirred for 30 h. Saturated aqueous $NH_4Cl$ (3 mL) was added, the layers were separated and the aqueous layer was extracted (3 × 5 mL) with $Et_2O$. The combined organic layers were dried over $MgSO_4$, filtered and concentrated. The crude product was purified via flash chromatography (15% EtOAc/Hex) to yield alcohol **26** (0.107 g, 99%) as a colorless oil: $R_f$ 0.18 (3:1 Hexanes/EtOAc); $[\alpha]_D^{21}$ + 38.9 (c. 0.82, $CHCl_3$); IR (neat) 3445, 2952, 2860, 1734, 1613, 1514, 1456, 1248, 1171, 1092, 1034; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.22 (d, $J$ = 8.6 Hz, 2H), 6.85 (d, $J$ = 8.6 Hz, 2H), 5.73 (d, $J$ = 16 Hz, 1H), 5.11 (dd, $J$ = 15.6, 8.2 Hz, 1H), 5.00 (s, 1H), 4.93 (s, 1H), 4.37 (s, 2H), 3.78 (s, 3H), 3.58 (s, 3H), 3.50–3.40 (m, 3H), 3.32–3.27 (m, 1H), 3.02 (s, 1H), 2.34–2.29 (m, 2H), 1.80 (s, 3H), 1.78–1.71 (m, 2H), 1.08 (s, 3H), 0.93 (d, $J$ = 6.6 Hz, 3H); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 172.6, 159.1, 139.5, 137.0, 131.2, 130.3, 129.3, 117.3, 113.7, 72.5, 67.3, 66.4, 62.0, 55.2, 51.3, 40.8, 40.2, 38.8, 24.0, 21.1, 16.3; HRMS *m/z* calcd for $C_{23}H_{34}O_5$ $(M + Na)^+$ 413.2304, found 413.2308.

#### 4.1.17. (2R,3S,6R,E)-methyl 3-(2-((4-methoxybenzyl)oxy)ethyl)-3,6-dimethyl-7-((2-nitrophenyl)selenyl)-2-(prop-1-en-2-yl)hept-4-enoate (27)

To a 0 °C solution of alcohol **26** (0.209 g, 0.536 mmol) and *o*-nitrophenyl selenocyanate (0.158 g, 0.697 mmol) in THF (5 mL) was added tributylphosphine (0.201 mL, 0.805 mmol). The cooling bath was removed and the mixture was stirred at room temperature for 4 h. The reaction was quenched with 5% $Na_2CO_3$ (5 mL). The layers were separated and the aqueous layer was extracted with ether (3 × 5 mL). The combined organic layers were dried over $Na_2SO_4$, filtered and concentrated. The crude oil was purified via column chromatography (30 mL silica gel, 2–10% EtOAc/Hexanes) to yield selenide **27** (0.298 g, 97%): $R_f$ 0.30 (3:1 Hexanes/EtOAc); $[\alpha]_D^{21}$ +42.0 (c. 1.17, $CDCl_3$); IR (neat); 3105, 2918, 2850, 1733, 1588, 1566, 1513, 1452, 1303, 1331, 1247, 1151, 1095, 1037 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 8.27 (d, $J$ = 8.2 Hz, 1H), 7.52–7.47 (m, 2H), 7.30 (ddd, $J$ = 8.4, 5.5, 3.1 Hz, 1H), 7.25 (d, $J$ = 8.2 Hz, 2H), 6.84 (d, $J$ = 8.6 Hz, 2H), 5.82 (d, $J$ = 16.0 Hz, 1H), 5.25 (dd, $J$ = 15.6, 8.2 Hz, 1H), 5.00 (s, 1H), 4.93 (s, 1H), 4.41 (ABq, $J_{AB}$ = 11.7 Hz, $\Delta\nu_{AB}$ = 15.6 Hz, 2H), 3.77 (s, 3H), 3.60 (s, 3H), 3.46 (t, 7.3 Hz, 2H), 3.02 (s, 1H), 2.89–2.84 (m, 2H), 2.64–2.54 (m, 1H), 1.87–1.82 (m, 1H), 1.81 (s, 3H), 1.76–1.68 (m, 1H), 1.17 (d, $J$ = 6.6 Hz, 1.11 (s, 3H); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 172.5, 159.1, 146.9, 139.7, 135.8, 134.0, 133.5, 133.1, 130.7, 129.3, 129.2, 126.4, 125.2, 117.3, 113.7, 72.3, 67.0, 62.3, 55.2, 51.3, 41.0, 39.4, 36.8, 33.8, 23.9, 21.6, 20.5.; HRMS *m/z* calcd for $C_{29}H_{37}O_6NSeNa$ $(M + Na)^+$ 598.1786, found 598.1779.

#### 4.1.18. (2R,3S,E)-methyl 3-(2-((4-methoxybenzyl)oxy)ethyl)-3,6-dimethyl-2-(prop-1-en-2-yl)hepta-4,6-dienoate (28)

To a 0 °C solution of **27** (0.021 g, 0.0366 mmol) in THF (0.4 mL) was added $H_2O_2$ (30% in $H_2O$, 0.1 mL, 1.1 mmol). The cooling bath was removed and the mixture was stirred at room temperature for 18 h. The mixture was diluted with $Et_2O$ (2 mL) and saturated sodium thiosulfate (2 mL) was added. The layers were separated and the aqueous layer was extracted with $Et_2O$ (3 × 2 mL). The combined organic layer was dried over $Na_2SO_4$, filtered and concentrated. The crude oil was purified via flash chromatography to yield diene **28** (0.011 g, 81%) as a single diastereomer: $R_f$ 0.46 (3:1 Hexanes/EtOAc); IR (neat) 3100, 2960, 2855, 1734, 1613, 1467 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.24 (d, $J$ = 8.6 Hz, 2H), 6.86 (d, $J$ = 8.2 Hz, 2H), 6.00 (ABq, $J_{AB}$ = 16.4 Hz, $\Delta\nu_{AB}$ = 13.9 Hz, 2H), 4.99 (s, 1H), 4.93 (s, 1H), 4.91 (s, 1H), 4.90 (s, 1H), (ABq, $J_{AB}$ = 12.5 Hz, $\Delta\nu_{AB}$ = 0 Hz, 2H), 3.80 (s, 3H), 3.60 (s, 3H), 4.48–3.34 (m, 2H), 3.07 (s, 1H), 1.93–1.72 (m, 2H), 1.84 (s, 3H), 1.78 (s, 3H), 1.15 (s, 3H); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 172.5, 159.1, 142.2, 139.7, 135.5, 131.4, 130.6, 129.2, 117.3, 115.0, 113.7; HRMS *m/z* calcd for $C_{23}H_{32}O_4Na$ $(M + Na)^+$ 395.2309, found 395.2300.

#### 4.1.19. (2R,3S,E)-3-(2-((4-methoxybenzyl)oxy)ethyl)-3,6-dimethyl-2-(prop-1-en-2-yl)hepta-4,6-dien-1-ol (29)

To a solution of ester **28** (0.220 g, 0.56 mmol) in $Et_2O$ (10 mL) at −78 °C was added via syringe DIBAL (5.7 mL, 1 M in hexanes 5.7 mmol). The reaction was stirred at −78 °C for 2 h and allowed to warm to −30 °C followed by careful addition of a saturated aqueous solution of Rochelle salt. The mixture was allowed to warm to room temperature with vigorous stirring overnight. After filtration to remove solids, the phases were separated, and the organic phase

was extracted with $Et_2O$ (3 × 15 mL). The combined organic extracts were dried over anhydrous $MgSO_4$, filtered, and concentrated to yield crude product which was purified by flash chromatography (10% EtOAc/hexanes) to give alcohol **29** (0.208 mg, 97%). $R_f$ 0.17 (3:1 Hexanes/EtOAc) $[\alpha]_D^{21}$ −4.4 (c. 0.70, $CDCl_3$); IR (neat) 3435, 3075, 2917, 1640, 1612, 1586, 1514, 1464, 1363, 1302, 1248, 1174, 1093, 1035, 976, 891, 821; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.23 (d, $J$ = 8.6 Hz, 2H), 6.86 (d, $J$ = 8.6 Hz, 2H), 6.03 (d, $J$ = 16 Hz, 1H), 5.56 (d, $J$ = 16.4 Hz, 1H), 5.06 (s, 1H), 4.92−4.91 (m, 2H), 4.83 (s, 1H), 4.37 (s, 2H), 3.80 (s, 3H), 3.73 (dd, $J$ = 10.9, 4.7 Hz, 1H), 3.61 (t, $J$ = 10.6 Hz, 1H), 3.46−3.34 (m, 2H), 2.26 (dd, $J$ = 10.4, 4.3 Hz, 1H), 1.82 (s, 3H), 1.78−1.74 (m, 5H), 1.05 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 159.1, 143.9, 141.8, 137.0, 131.2, 130.5, 129.2, 116.0, 115.3, 113.8, 72.7, 66.9, 61.5, 59.0, 55.3, 40.2, 39.7, 23.4, 20.2, 18.8; HRMS *m/z* calcd for $C_{22}H_{32}O_3$ $(M + Na)^+$ 367.2249, found 367.2253.

#### 4.1.20. (2R,3S,E)-3-(2-((4-methoxybenzyl)oxy)ethyl)-3,6-dimethyl-2-(prop-1-en-2-yl)hepta-4,6-dienal (**30**)

To a room temperature solution of alcohol **29** (1.39 g, 4.03 mmol) in DMSO (45 mL) was added IBX (2.26 g, 8.06 mmol). The mixture was stirred for 1 h and water (50 mL) and $Et_2O$ (50 mL) were added. The layers were separated and the aqueous layer was extracted with $Et_2O$ (1 × 50 mL). The combined organic layers were washed with brine (2 × 50 mL), dried over $Na_2SO_4$, filtered and concentrated. Crude aldehyde **30** was used in the next step without further purification: $R_f$ 0.78 (3:1 Hexanes/EtOAc); $[\alpha]_D^{21}$ −12.3 (c. 0.42, $CDCl_3$); IR (neat); 3079, 2917, 2850, 2726, 1721, 1612, 1558, 1513, 1248, 1096, 977, 899, 821 cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 9.63 (d, $J$ = 3.9 Hz, 1H), 7.21 (d, $J$ = 8.2 Hz, 2H), 6.85 (d, $J$ = 8.6 Hz, 2H), 6.08 (d, $J$ = 16.0 Hz, 1H), 5.74 (d, $J$ = 16.4 Hz, 1H), 5.12 (s, 1H), 4.94 (s, 1H), 4.92 (s, 1H), 4.83 (s, 1H), 4.36 (s, 2H), 3.78 (s, 3H), 3.48−3.34 (m, 2H), 2.85, (d, $J$ = 3.5 Hz, 1H), 1.88−1.84 (m, 2H), 1.81 (s, 3H), 1.78 (s, 3H), 1.17 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 201.1, 159.0, 141.6, 138.9, 135.1, 132.0, 130.3, 129.1, 117.7, 115.8, 113.7, 72.6, 68.0, 66.5, 55.1, 41.3, 39.1, 25.1, 21.4, 18.7; HRMS *m/z* calcd for $C_{22}H_{30}O_3$ $(M + Na)^+$ 356.0593, found 365.2083.

#### 4.1.21. (3R,4R,5S,E)-tert-butyl-3-hydroxy-5-(2-((4-methoxybenzyl)oxy)ethyl)-5,8-dimethyl-4-(prop-1-en-2-yl)nona-6,8-dienoate (**32**)

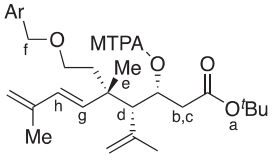
To a 0 °C solution of diisopropylamine (3.15 mL, 22.5 mmol) in $Et_2O$ (75 mL) was added *n*BuLi (7.88 mL, 2.5 M in hexanes, 19.7 mmol). The mixture was stirred at 0 °C for 10 min and cooled to −78 °C. To this solution $^t$BuOAc (2.26 mL, 16.9 mmol) was added dropwise. After 30 min, CpTi(diacetoneglucose)$_2$Cl [27]. (180 mL, 0.09 M in $Et_2O$) was added slowly. After stirring at −78 °C for 30 min the mixture was allowed to slowly warm to −30 °C, stirred at that temperature for 30 min and cooled to −78 °C. Crude aldehyde **30** (3.0 g, 9 mmol) was slowly added as a solution in $Et_2O$ and stirred for 1.5 h at −78 °C. The reaction mixture was quenched by slow addition of aqueous THF (10 mL, 5 M $H_2O$), allowed to warm to room temperature and filtered through a pad of celite. The filtrate was poured into $H_2O$ (200 mL), the layers were separated and the aqueous layer was extracted (3 × 15 mL) with $Et_2O$. The combined organic layers were dried over $MgSO_4$, filtered through a pad of celite and concentrated. The crude product was purified via flash chromatography (gradient elution of 10−20% EtOAc in Hexanes) to yield 2.89 g of alcohol **32** (70% for 2 steps): $R_f$ 0.79 (3:1 Hexanes/EtOAc); $[\alpha]_D^{21}$ + 5.6 (c. 1.90, $CHCl_3$); IR (neat) 3516, 3075, 2971, 2933, 1724, 1632, 1612, 1586, 1514, 1456, 1367, 1302, 1248, 1153, 1093, 1038, 976, 953, 888, 845, 821, 756 cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.23 (d, $J$ = 8.6 Hz, 2H), 6.86 (d, $J$ = 8.6 Hz, 2H), 6.06 (d, $J$ = 16.4 Hz, 1H), 5.86 (d, $J$ = 16.0 Hz, 1H), 5.01 (s, 1H), 4.90 (m, 2H), 4.83 (s, 1H), 4.43−4.39 (m, 1H), 4.37 (s, 2H), 3.79 (s, 1.81 (m, 2H), 1.84 (s, 3H), 1.83 (s, 3H), 1.44 (s, 9H), 1.17 (s, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 172.4, 159.1, 143.0, 142.2, 138.3, 130.7, 130.6, 129.2, 116.9, 114.7, 113.7, 81.0, 72.6, 67.4, 67.2, 60.6, 55.2, 42.3, 41.6, 39.7, 28.1, 22.6, 20.8, 18.9; HRMS *m/z* calcd for $C_{28}H_{42}O_5$ $(M + Na)^+$ 481.2930, found 481.2930.

#### 4.1.22. General procedure for the formation of C20 Mosher esters of 32

To a room temperature solution of (*S*)-(−)-α-methoxy-α-trifluoromethylphenylacetic acid (MTPA) (0.014 g, 0.0595 mmol) and DMF (0.9 μL, 1.2 μmol) in hexanes (2 mL) was added oxalyl chloride (24 μL, 0.283 mmol). The mixture was stirred for 1 h, filtered through glass wool and concentrated. A solution of alcohol **32** (0.0058 g, 0.0126 mmol), DMAP (single crystal) and $Et_3N$ (25 μL, 0.1785 mmol) in $CH_2Cl_2$ (2 mL) was added to the residue. The mixture was stirred overnight and saturated $NaHCO_3$ (1 mL) was added. The layers were separated and the aqueous layer was extracted with $CH_2Cl_2$ (3 × 1 mL). The combined organic layers were dried over $Na_2SO_4$, filtered and concentrated. The crude oil was purified by flash chromatography (2 mL silica gel, 5% EtOAc/hexanes) to yield (*S*)-MTPA-**32** (0.0079 g, 93%). In a separate flask the same procedure was employed utilizing (*R*)-(−)-α-methoxy-α-trifluoromethylphenylacetic acid to yield (*R*)-MTPA-**32** (0.0072 g, 90%). Mosher ester analysis [12b] of selected proton shifts are listed below.

(*R*)-MTPA ester of **32**: $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 5.99 (d, $J$ = 16.4 Hz, 1H, H(h)), 5.59 (d, $J$ = 16.0 Hz, 1H, H(g)), 4.34 (s, 2H, H(f)), 2.56 (dd, $J$ = 15.8, 4.9 Hz, 1H, H(b)), 2.46 (dd, $J$ = 16.1, 8.3 Hz, 1H, H(c)), 2.38 (d, $J$ = 3.2 Hz, 1H, H(d)), 1.42 (s, 9H, H(a)), 0.98 (s, 3H, H(e)).

(*S*)-MTPA ester of **32**: $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 5.83 (d, $J$ = 16.0 Hz, 1H, H(h)), 5.45 (d, $J$ = 16.0 Hz, 1H, H(g)), 4.29 (s, 2H, H(f)), 2.66 (dd, $J$ = 15.7, 4.7 Hz, 1H, H(b)), 2.54 (dd, $J$ = 15.7, 8.6 Hz, 1H, H(c)), 2.30 (d, $J$ = 2.8 Hz, 1H, H(d)), 1.44 (s, 9H, H(a)), 0.65 (s, 3H, H(e)).




| Proton | $\delta_S$ (ppm) | $\delta_R$ (ppm) | $\delta_S - \delta_R$ (ppm) |
|---|---|---|---|
| a | 1.435 | 1.420 | +0.015 |
| b | 2.662 | 2.559 | +0.103 |
| c | 2.539 | 2.464 | +0.075 |
| d | 2.303 | 2.376 | −0.074 |
| e | 0.653 | 0.982 | −0.329 |
| f | 4.291 | 4.337 | −0.046 |
| g | 5.445 | 5.589 | −0.144 |
| h | 5.831 | 5.988 | −0.157 |

#### 4.1.23. (3R,4R,5S,E)-tert-butyl 5-(2-((4-methoxybenzyl)oxy)ethyl)-3-(methoxymethoxy)-5,8- dimethyl-4-(prop-1-en-2-yl)nona-6,8-dienoate

To a 0 °C solution of alcohol **32** (0.205 g, 0.447 mmol) in $CH_2Cl_2$ was added $iPr_2NEt$ (3.11 mL, 17.88 mmol), DMAP (0.055 g, 0.447 mmol) and MOMCl (0.72 mL, 8.94 mmol) sequentially and allowed to warm to room temperature. After 24 h the solution was cooled to 0 °C and MOMCl (0.18 mL, 2.23 mmol) was added and the solution was allowed to warm to room temperature and stirred for 24 h. The solution was cooled to 0 °C, diluted with $CH_2Cl_2$ and quenched with aqueous $NaHCO_3$. The layers were separated and

the aqueous layer was extracted with equal portions of $CH_2Cl_2$ (3 × 10 mL) The combined organic layers were dried over $MgSO_4$ and concentrated. The crude residue was purified by flash chromatography (gradient elution of 5–10% EtOAc in Hexanes) to yield the desired MOM-protected ester of **32** (0.196 g, 87%): $R_f$ 0.85 (3:1 Hexanes/EtOAc); $[\alpha]_D^{21}$ +36.7 (c. 0.15, $CHCl_3$); IR (neat) 2918, 2849, 1726, 1612, 1580, 1537, 1468, 1377, 1302, 1248, 1154, 1100, 1036 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.23 (d, $J$ = 8.6 Hz, 2H), 6.85 (d, $J$ = 8.6 Hz, 2H), 6.03 (d, $J$ = 16.0 Hz, 1H), 5.76 (d, $J$ = 16.4 Hz, 1H), 5.02 (s, 1H), 4.89 (m, 2H), 4.83 (s, 1H), 4.60 (s, 2H), 4.37 (s, 2H), 4.25 (ddd, $J$ = 7.8, 4.7, 2.3 Hz), 3.79 (s, 3H), 3.49–3.33 (m, 2H), 3.31 (s, 3H), 2.65 (dd, $J$ = 16.0, 5.1 Hz, 1H), 2.43 (dd, $J$ = 16.0, 8.6 Hz, 1H), 2.06 (d, $J$ = 2.0 Hz, 1H), 1.93–1.84 (m, 7H), 1.77–1.68 (m, 1H), 1.43 (s, 9H), 1.16 (s, 3H); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 170.8, 159.0, 142.4, 142.2, 138.4, 130.7, 130.5, 129.2, 118.2, 114.5, 113.7, 97.5, 80.2, 72.6, 67.2, 59.6, 55.7, 55.2, 41.6, 40.7, 40.2, 28.1, 22.6, 20.6, 18.9; HRMS *m/z* calcd for $C_{30}H_{46}O_6$ $(M + Na)^+$ 525.3192, found 525.3201.

#### 4.1.24. (3R,4R,5S,E)-5-(2-((4-methoxybenzyl)oxy)ethyl)-3-(methoxymethoxy)-5,8-dimethyl-4-(prop-1-en-2-yl)nona-6,8-dien-1-ol

To a 0 °C solution of MOM-protected ester of **32** (from the previous experiment) (0.200 g, 0.398 mmol) in $Et_2O$ (4 mL) was added $LiAlH_4$ (0.075 g, 1.99 mmol). The mixture was stirred at 0 °C for 15 min and $Na_2SO_4$•$10H_2O$ (0.5 g) was added. The white suspension was stirred at 0 °C for 30 min and at room temperature for an additional hour, filtered, washed with brine (2 × 10 mL), dried over $Na_2SO_4$, filtered and concentrated to yield the expected alcohol (0.161 g, 94%) as a colorless oil: $R_f$ 0.08 (3:1 Hexanes/EtOAc); $[\alpha]_D^{21}$ +20.4 (c. 0.3, $CHCl_3$); IR (neat) 3456, 3073, 2923, 2851, 1632, 1612, 1514, 1464, 1374, 1302, 1149, 1036, 894, 820, 757 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.23 (d, $J$ = 8.2 Hz, 2H), 6.86 (d, $J$ = 8.6 Hz, 2H), 6.02 (d, $J$ = 16.0 Hz, 1H), 5.74 (d, $J$ = 16.0 Hz, 1H), 5.00 (s, 1H), 4.89 (m, 2H), 4.82 (s, 1H), 4.62 (ABq, $J_{AB}$ = 6.7 Hz, $\Delta\nu_{AB}$ = 7.1 Hz, 2H), 4.36 (ABq, $J_{AB}$ = 11.5 Hz, $\Delta\nu_{AB}$ = 8.3, Hz, 2H), 3.99 (td, $J$ = 6.2, 2.7 Hz, 1H), 3.79 (s, 3H), 3.67 (dt, $J$ = 11.2, 5.9 Hz), 3.56 (dt, $J$ = 10.5, 5.3 Hz, 1H), 3.45–3.33 (m, 2H), 3.36 (s, 3H), 2.20 (br s, 1), 2.01 (d, $J$ = 2.3 Hz, 1H), 1.92–1.66 (m, 4H), 1.85 (s, 3H), 1.82 (s, 3H), 1.14 (s, 3H); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 159.1, 143.2, 142.0, 138.5, 130.6, 130.4, 129.3, 117.6, 114.7, 113.7, 97.9, 77.8, 72.7, 67.1, 60.1, 59.7, 56.0, 55.2, 41.4, 40.1, 37.4, 25.3, 20.6, 18.9; HRMS *m/z* calcd for $C_{26}H_{40}O_5$ $(M + Na)^+$ 455.2773, found 455.2795.

#### 4.1.25. (3R,4R,5S,E)-5-(2-((4-methoxybenzyl)oxy)ethyl)-3-(methoxymethoxy)-5,8-dimethyl-4-(prop-1-en-2-yl)nona-6,8-dienal (**33**)

To a room temperature solution of the alcohol described above (1.67 g, 3.87 mmol) in DMSO (40 mL) was added IBX (2.17 g, 7.73 mmol). The solution was stirred at room temperature for 1.5 h, diluted with cold water (200 mL) and extracted with $Et_2O$ (3 × 200 mL). The combined organic layers were washed with brine (3 × 200 mL), dried with $MgSO_4$ and filtered through a plug of silica gel to provide aldehyde **33** (1.60 g, 96%) without the need for additional purification: $R_f$ 0.71 (2:1 Hexanes/EtOAc $[\alpha]_D^{21}$ +29.3 (c. 0.63, $CHCl_3$); IR (neat) 2937, 2728, 1722, 1632, 1612, 1586, 1454, 1372, 1302, 1248, 1209, 1150, 1093, 1036, 978, 916, 822 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 9.66 (s, 1H), 7.22 (d, $J$ = 8.3 Hz, 2H), 6.85 (d, $J$ = 8.6 Hz, 2H), 6.03 (d, $J$ = 16.1 Hz, 1H), 5.76 (d, $J$ = 16.1 Hz, 1H), 5.01 (s, 1H), 4.90 (s, 2H), 4.81 (s, 1H), 4.60 (s, 2H), 4.43–4.30 (m, 3H), 3.78 (s, 3H), 3.47–3.33 (m, 2H), 3.28 (s, 3H), 2.75 (ddd, $J$ = 17.3, 5.2, 2.3 Hz, 1H), 2.61 (dd, $J$ = 17.3, 7.0 Hz, 1H), 2.00 (d, $J$ = 2.8 Hz, 1H), 1.95–1.86 (m, 1H), 1.84 (s, 3H), 1.83 (s, 3H), 1.75–1.68 (m, 1H), 1.15 (s, 3H); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 200.6, 159.3, 142.7, 142.2, 138.3, 130.9, 130.8, 128.3, 118.5, 114.7, 113.9, 97.7, 75.4, 72.7, 67.2, 60.7, 55.7, 55.3, 49.3, 41.8, 40.3, 25.1, 21.0, 18.9; HRMS *m/z* calcd for $C_{26}H_{38}O_5$ $(M + Na)^+$ 453.2617, found 453.2624.

#### 4.1.26. (4R,5R,6S,E)-6-(2-((4-methoxybenzyl)oxy)ethyl)-4-(methoxymethoxy)-6,9-dimethyl-1-nitro-5-(prop-1-en-2-yl)deca-7,9-dien-2-ol (**34**)

To a room temperature solution of aldehyde **33** (1.60 g, 3.71 mmol) in *i*-PrOH (40 mL) was added KF (0.22 g, 3.87 mmol) followed by $MeNO_2$ (3.04 mL, 58.1 mmol). The solution was stirred for 20 h, concentrated and purified by flash chromatography (10% EtOAc/hexanes) to yield a 2:1 mixture of diastereomeric alcohols **34** (1.60 g, 84%). For characterization of isomer **34a**: $R_f$ 0.39 (3:1 Hexanes/EtOAc); $[\alpha]_D^{21}$ +39.6 (c. 0.09, $CHCl_3$); IR (neat) 3424, 2937, 1612, 1555, 1513, 1453, 1373, 1302, 1248, 1148, 1094, 1035, 901 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.23 (d, $J$ = 8.6 Hz, 2H), 6.86 (d, $J$ = 8.6 Hz, 2H), 6.03 (d, $J$ = 16.0 Hz, 1H), 5.66 (d, $J$ = 16.4 Hz, 1H), 5.03 (s, 1H), 4.92 (s, 1H), 4.91 (s, 1H), 4.86 (s, 1H), 4.66 (d, $J$ = 6.7, 1H), 4.56 (d, $J$ = 7.0 Hz, 1H), 4.57–4.46 (m, 1H), 4.39–4.25 (m, 4H), 4.07–4.05 (m, 1H), 3.80 (s, 3H), 3.72 (d, $J$ = 4.7 Hz, 1H), 3.42–3.31 (m, 2H), 3.40 (s, 3H), 2.00 (d, $J$ = 2.7 Hz, 1H), 1.91–1.80 (m, 1H), 1.84 (s, 3H), 1.82 (s, 3H), 1.70–1.64 (m, 2H), 1.46–1.39 (m, 1H), 1.12 (s, 3H); $^{13}C$ NMR (125 MHz, $CDCl_3$) $\delta$ 159.3, 143.2, 141.9, 138.2, 131.0, 130.6, 129.5, 117.7, 115.4, 113.9, 99.2, 80.7, 78.2, 72.9, 67.1, 65.6, 61.2, 56.4, 55.4, 51.6, 40.4, 39.5, 25.9, 20.4, 19.0; HRMS *m/z* calcd for $C_{27}H_{41}NO_7$ $(M + Na)^+$ 514.2781, found 514.2806. For characterization of isomer **34b**: $R_f$ 0.37 (3:1 Hexanes/EtOAc); $[\alpha]_D^{21}$ +37.0 (c. 0.10, $CHCl_3$); IR (neat) 3407, 2936, 1612, 1554, 1514, 1441, 1377, 1302, 1248, 1148, 1093, 1035, 893 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.24 (d, $J$ = 8.6 Hz, 2H), 6.87 (d, $J$ = 8.6 Hz, 2H), 6.02 (d, $J$ = 16.0 Hz, 1H), 5.83 (d, $J$ = 16.0 Hz, 1H), 5.00 (s, 1H), 4.90 (m, 2H), 4.79 (s, 1H), 4.62 (s, 2H), 4.41–4.26 (m, 5H), 4.12–4.08 (m, 1H), 3.80 (s, 3H), 3.51–3.35 (m, 3H), 3.34 (s, 3H), 2.18 (br s, 1H), 2.00–1.93 (m, 1H), 1.88–1.79 (m, 1H), 1.84 (s, 3H), 1.82 (s, 3H), 1.67–1.64 (m, 2H), 1.12 (s, 3H); $^{13}C$ NMR (125 MHz, $CDCl_3$) $\delta$ 159.6, 143.3, 142.3, 138.6, 130.6, 130.4, 129.6, 118.4, 114.9, 114.1, 98.1, 81.0, 77.6, 73.0, 67.2, 67.0, 59.2, 56.0, 55.5, 51.6, 40.1, 38.6, 24.9, 21.7, 19.0; HRMS *m/z* calcd for $C_{27}H_{41}NO_7$ $(M + Na)^+$ 514.2781, found 514.2775.

#### 4.1.27. (1S,2R,3R,4aS,5S,8aR)-1-(2-((4-methoxybenzyl)oxy)ethyl)-3-(methoxymethoxy)-1,7-dimethyl-5-nitro-2-(prop-1-en-2-yl)-1,2,3,4,4a,5,6,8a-octahydronaphthalene (37)

To a 0 °C solution of alcohol 34 (1.60 g, 3.25 mmol) in $CH_2Cl_2$ (32 mL) was added $Et_3N$ (1.36 mL, 9.76 mmol) followed by MsCl (0.38 mL, 4.88 mmol). The mixture was stirred at 0 °C for 15 min, saturated aqueous $NaHCO_3$ (0.5 mL) was added and stirred at room temperature for 15 min. The layers were separated and the aqueous layer was extracted with $CH_2Cl_2$ (3 × 1 mL), dried over $Na_2SO_4$, filtered and concentrated. The crude residue was immediately dissolved in benzene (65 mL) and BHT (single crystal) was added. The solution was placed under argon atmosphere and was refluxed for 16 h, cooled to room temperature and concentrated. The crude oil was purified by flash chromatography (gradient elution of 5–10% EtOAc/hexanes) to yield decalin 37 (0.783 g, 51% for 2 steps) and 38 (80 mg, 5% for two steps) as colorless oils. For characterization of pure 37: $R_f$ 0.51 (3:1 Hexanes/EtOAc); $[\alpha]_D^{21}$ −24.1 (c. 0.13, $CHCl_3$); IR (neat) 2934, 1640, 1549, 1441, 1380, 1248, 1096, 1036, 916, 820 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.23 (d, $J$ = 8.6 Hz, 2H), 6.86 (d, $J$ = 8.6 Hz, 2H), 5.40 (s, 1H), 5.02 (s, 1H), 4.73 (s, 1H), 4.66–4.58 (m, 1H), 4.52–4.36 (m, 4H), 3.81 (s, 3H), 3.82–3.70 (m, 1H), 3.55–3.49 (m, 1H), 3.46–3.40 (m, 1H), 3.28 (s, 3H), 2.68–2.61 (m, 1H), 2.45 (dd, $J$ = 16.2, 5.7 Hz, 1H), 2.04–1.95 (m, 2H), 1.82–1.67 (m, 3H), 1.76 (s, 3H), 1.73 (s, 3H), 1.09 (q, $J$ = 12.1 Hz, 1H), 0.80 (s, 3H); $^{13}C$ NMR (125 MHz, $CDCl_3$) $\delta$ 159.6, 144.0, 132.0, 130.9, 129.3, 121.6, 114.1, 96.0, 89.1, 74.8, 72.9, 65.3, 56.3, 55.7, 55.5, 45.8, 40.3, 36.8, 36.4, 35.8, 35.3, 23.1, 19.3; HRMS *m/z* calcd for $C_{27}H_{39}NO_6$ $(M + Na)^+$ 496.2675, found 496.2681.

For full characterization of (1*S*,2*R*,3*R*,4a*S*,5*S*,8a*S*)-1-(2-((4-methoxybenzyl)oxy)ethyl)-3-(methoxymethoxy)-1,7-dimethyl-5-nitro-2-(prop-1-en-2-yl)-1,2,3,4,4a,5,6,8a-octahydronaphthalene (38): $R_f$ 0.39 (3:1 Hexanes/EtOAc); $[\alpha]_D^{21}$ −6.6 (c. 0.76, $CHCl_3$); IR (neat) 2938, 2890, 1613, 1544, 1513, 1443, 1363, 1248, 1097, 1038 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) $\delta$ 7.20 (d, $J = 8.5$ Hz, 2H), 6.85 (d, $J = 8.3$ Hz, 2H), 5.44 (s, 1H), 4.95 (s, 1H), 4.74 (s, 1H), 4.61 (br s, 1H), 4.54 (d, $J = 6.8$ Hz, 1H), 4.47 (dd, $J = 6.1$, 3.1 Hz, 1H), 4.36 (ABq, $J_{AB} = 11.5$ Hz $\Delta\nu_{AB} = 11.1$ Hz, 2H), 3.80 (br s, 1H), 3.77 (s, 3H), 3.42 (t, $J = 7.5$ Hz, 2H), 3.30 (s, 3H), 2.77 (dd, $J = 13.8$, 4.0 Hz, 1H), 2.69 (d, $J = 19.5$ Hz, 1H), 2.24 (d, $J = 19.6$ Hz, 1H), 1.99−1.90 (m, 2H), 1.87−1.81 (m, 2H), 1.75 (s, 3H), 1.73 (s, 3H), 1.60 (d, $J = 14.4$, 7.4 Hz, 1H), 1.29 (q, $J = 12.2$ Hz, 1H), 1.03 (s, 1H); $^{13}C$ NMR (125 MHz, $CDCl_3$) $\delta$ 159.3, 130.69, 130.71, 129.1, 119.6, 113.9, 96.3, 84.8, 77.4, 728, 65.8, 55.6, 55.2, 38.9, 38.2, 33.2, 32.6, 28.9, 23.2, 21.0. HRMS *m/z* calcd for $C_{27}H_{39}NO_6$ $(M + Na)^+$ 496.2675, found 496.2668.

### 4.1.28. (4aR,5S,6R,7R,8aS)-5-(2-((4-methoxybenzyl)oxy)ethyl)-7-(methoxymethoxy)-3,5-dimethyl-6-(prop-1-en-2-yl)-4a,5,6,7,8,8a-hexahydronaphthalen-1(4H)-one (**39**)

To a room temperature solution of **37** (0.485 g, 1.02 mmol) in THF (10 mL) was added $^t$BuOK (276 mg, 2.46 mmol). The mixture was stirred for 5 min, cooled to −78 °C and *trans*-2- (phenylsulfonyl)-3-phenyloxaziridine [31] (533 mg, 2.04 mmol) was added as a solution in THF (10 mL) dropwise down the side of the flask. The reaction was stirred for 1 h at −78 °C then warmed to 0 °C and stirred for 30 min. The reaction was quenched with saturated aqueous $NH_4Cl$ (20 mL) and diluted with $CH_2Cl_2$ (30 mL). The layers were separated and the aqueous layer was extracted with $CH_2Cl_2$ (3 × 20 mL). The combined organic layers were dried with $MgSO_4$, filtered and concentrated. Purification by silica gel chromatography (gradient elution of 15%−25% EtOAc/hexanes) provided enone **39** (375 mg, 83%): $R_f$ 0.18 (hexanes/EtOAc (2:1)); $[\alpha]_D^{20}$ −21.6 (c 0.73, $CHCl_3$); IR (film) 2930, 1663, 1613, 1514, 1441, 1380, 1248, 1096, 1037, 821 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) $\delta$ 7.19 (d, $J = 8.6$ Hz, 2H), 6.48 (d, $J = 8.6$ Hz, 2H), 5.84 (s, 1H), 5.04 (s, 1H), 4.74−4.72 (m, 2H), 4.56 (d, $J = 6.9$ Hz, 1H), 4.37 (s, 2H), 3.83−3.77 (m, 1H), 3.79 (s, 3H), 3.56−3.44 (m, 2H), 3.35 (s, 3H), 2.79 (dt, $J = 13.4$, 4.5 Hz, 1H), 2.35 (dd, 17.9, 4.4 Hz, 1H), 2.20−2.04 (m, 3H), 1.83 (s, 3H), 1.79 (s, 3H), 1.77−1.62 (m, 3H), 1.09 (q, $J = 12.2$ Hz, 1H), 0.92 (s, 3H); $^{13}C$ NMR (100 MHz, $CDCl_3$) $\delta$ 200.3, 161.7, 159.6, 143.9, 130.7, 129.5, 125.7, 114.1, 95.8, 74.9, 73.1, 65.5, 56.5, 55.9, 55.5, 44.6, 43.2, 40.7, 36.9, 33.3, 31.7, 24.4, 18.5; HRMS *m/z* calcd for $C_{27}H_{38}O_5$ $(M + Na)^+$ 465.2617, found 465.2610.

### 4.1.29. (1R,4aR,5S,6R,7R,8aS)-5-(2-((4-methoxybenzyl)oxy)ethyl)-7-(methoxymethoxy)-3,5-dimethyl-6-(prop-1-en-2-yl)-1,4,4a,5,6,7,8,8a-octahydronaphthalen-1-ol

To a room temperature solution of **39** (375 mg, 849 mmol) in MeOH (14.5 mL) was added $CeCl_3 \bullet 7H_2O$ (0.54 g, 1.45 mmol). The reaction was stirred for 5 min at room temperature, cooled to −78 °C and $NaBH_4$ (82 mg, 2.17 mmol) was added. After 1 h at −78 °C the reaction was quenched with acetone (1 mL) warmed to room temperature and concentrated. The resulting crude mixture was partitioned between EtOAc and a 1:1 mixture of saturated aqueous $NaHCO_3$ and brine. The layers were separated and the aqueous layer was extracted with EtOAc (4 × 5 mL). The combined organic layers were dried with $MgSO_4$, filtered through a plug of silica gel and concentrated to provide the desired allylic alcohol of **39** (0.356 mg, 94%) as a single diastereomer: $R_f$ 0.22 (1:1 Hexanes/EtOAc); $[\alpha]\ ^{21}_D$ +3.1 (c. 0.14, $CHCl_3$); IR (neat) 3426, 2925, 1640, 1613, 1513, 1453, 1376, 1302, 1248, 1154, 1096, 1037, 920, 820 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) $\delta$ 7.22 (d, $J = 8.8$ Hz, 2H), 6.86 (d, $J = 8.8$ Hz, 2H), 5.34 (s, 1H), 5.02 (s, 1H), 4.74 (s, 1H), 4.70 (d, $J = 6.9$ Hz, 1H), 4.57 (d, $J = 6.9$ Hz, 1H), 4.40 (ABq, $J_{AB} = 11.7$ Hz, $\Delta\nu_{AB} = 11.8$ Hz, 2H), 3.80 (s, 3H), 3.80−3.75 (m, 2H), 3.54 (td, $J = 9.1$, 5.2 Hz, 1H), 3.48−3.44 (m, 1H), 3.34 (s, 3H), 2.72 (dt, 12.5, 4.3 Hz, 1H), 2.09 (d, $J = 10.9$ Hz, 1H), 1.95−1.82 (m, 2H), 1.80 (s, 3H), 1.65−1.56 (m, 2H), 1.66 (s, 3H), 1.40−1.30 (m, 3H), 0.98 (q, $J = 11.6$ Hz, 1H), 0.88 (s, 3H); $^{13}C$ NMR (125 MHz, $CDCl_3$) $\delta$ 159.5, 144.2, 136.3, 130.9, 129.3, 124.5, 114.1, 96.0, 75.3, 729, 65.5, 57.2, 55.8, 55.5, 41.6, 40.3, 40.1, 38.0, 37.1, 30.1, 23.3, 17.8; HRMS *m/z* calcd for $C_{27}H_{40}O_5$ $(M + Na)^+$ 467.2773, found 467.2757.

### 4.1.30. Tert-butyl(((1R,4aR,5S,6R,7R,8aS)-5-(2-((4-methoxybenzyl)oxy)ethyl)-7-(methoxymethoxy)-3,5-dimethyl-6-(prop-1-en-2-yl)-1,4,4a,5,6,7,8,8a-octahydronaphthalen-1-yl)oxy)dimethylsilane

To a room temperature solution of the previously prepared allylic alcohol of **39** (preceding experiment) (100 mg, 0.225 mmol) in $CH_2Cl_2$ (0.75 mL) was added $Et_3N$ (0.25 mL, 1.8 mmol), DMAP (1 crystal) and TBSCl (170 mg, 1.12 mmol). The mixture was stirred at room temperature for 40 h and quenched with saturated aqueous $NaHCO_3$. The layers were separated and the aqueous layer was extracted with $CH_2Cl_2$ (2 × 2 mL). The combined organic layers were dried with $MgSO_4$, filtered and concentrated. Purification by silica gel chromatography (1%−3% EtOAc/hexanes) provided the desired TBS silyl ether (100 mg, 92% brsm) characterized as follows: $R_f$ 0.82 (3:1 Hexanes/EtOAc); $[\alpha]_D^{21}$ +25.6 (c. 1.04, $CHCl_3$); IR (neat) 2928, 2856, 1640, 1613, 1513, 1463, 1362, 1301, 1249, 1150, 1071, 1040, 920, 892, 836, 774 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) $\delta$ 7.22 (d, $J = 8.2$ Hz, 2H), 6.85 (d, $J = 8.3$ Hz, 2H), 5.27 (s, 1H), 5.01 (s, 1H), 4.73 (s, 1H), 4.65 (d, $J = 6.9$ Hz, 1H), 4.59 (d, $J = 6.9$ Hz, 1H), 4.41 (ABq, $J_{AB} = 11.7$ Hz, $\Delta\nu_{AB} = 15.0$ Hz, 2H), 3.83 (d, $J = 7.3$ Hz, 1H), 3.79 (s, 3H), 3.75 (td, $J = 11.1$, 5.1 Hz, 1H), 3.54 (td, $J = 9.1$, 5.3 Hz, 1H), 3.49−3.41 (m, 1H), 3.33 (s, 3H), 2.69 (dt, $J = 12.8$, 4.5 Hz, 1H), 2.06 (d, $J = 10.9$ Hz, 1H), 1.91−1.84 (m, 2H), 1.79 (s, 3H), 1.64 (s, 3H), 1.61−1.55 (m, 2H), 1.48−1.29 (m, 2H), 0.93 (s, 9H), 0.87 (s, 3H), 0.10 (s, 3H), 0.09 (s, 3H); $^{13}C$ NMR (125 MHz, $CDCl_3$) $\delta$ 159.4, 144.3, 134.7, 130.9, 129.3, 125.5, 114.0, 96.3, 76.0, 75.4, 72.8, 65.5, 57.3, 55.7, 55.4, 41.5, 50.3, 39.4, 38.6, 37.0, 30.0, 26.1, 23.4, 18.3, 17.7, −3.8, −4.3; HRMS *m/z* calcd for $C_{33}H_{54}O_5Si$ $(M + Na)^+$ 581.3638, found 581.3638.

### 4.1.31. 2-((1S,2R,3R,4aS,5R,8aR)-5-((tert-butyldimethylsilyl)oxy)-3-(methoxymethoxy)-1,7-dimethyl-2-(prop-1-en-2-yl)-1,2,3,4,4a,5,8,8a-octahydronaphthalen-1-yl)ethanol (40)

To a two-neck flask, charged with a stir bar and cooled by a −78 °C bath, $NH_{3(l)}$ (10 mL) was condensed, and Na° (40 mg 1.7 mmol) was added in small pieces directly into the flask to provide an inky blue solution. After 10 min, the previously prepared TBS silyl ether (100 mg, 0.179 mmol) was added as a solution in THF (1 mL, with 1 mL rinse). The reaction was stirred at −78 °C for 10 min, then $^i$PrOH (3 mL) was added dropwise until the blue color dissipated to provide a clear colorless solution. Saturated aqueous $NH_4Cl$ (3 mL) was added and the cooling bath was removed and replaced with a warm water bath. Stirring for 30 min allowed for the evaporation of $NH_{3(l)}$, and the remaining liquid was concentrated under reduced pressure to an aqueous slurry. The slurry was extracted with $CH_2Cl_2$ (3 × 5 mL), dried with $MgSO_4$, filtered and concentrated. Purification by silica gel chromatography (gradient elution of 5−40% EtOAc/hexanes) provided 40 (69.1 mg, 88%) as a colorless oil: $R_f$ 0.29 (hexanes/EtOAc (2:1)); $[\alpha]_D^{21}$ +15.4 (c 0.88, $CHCl_3$); IR (film) 3268, 2930, 2857, 1472, 1369, 1255, 1104, 1073, 1040, 836, 771 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) $\delta$ 5.27 (s, 1H), 5.04 (s, 1H), 4.80 (s, 1H), 4.65 (d, $J = 6.9$ Hz, 1H), 4.58 (s, $J = 6.9$ Hz, 1H), 3.84 (d, $J = 7.3$ Hz, 1H), 3.79−3.73 (m, 2H), 3.65 (td, $J = 9.8$, 6.7 Hz, 1H), 3.33 (s, 3H), 2.69 (dt, $J = 12.7$, 4.5 Hz, 1H), 2.10 (d, $J = 10.9$ Hz, 1H), 1.89−1.86 (m, 2H), 1.83 (s, 3H), 1.66 (s, 3H), 1.59−1.52 (m, 2H), 1.44 (tdd, $J = 12.0$, 8.1, 4.2 Hz, 1H), 1.36 (ddd, 12.2, 9.9, 6.4 Hz, 1H), 0.91 (s, 9H), 0.88 (s, 3H), 0.09 (s, 3H), 0.07 (s, 3H); $^{13}C$ NMR

(125 MHz, $CDCl_3$) $\delta$ 144.4, 134, 5, 125.7, 114.9, 96.3, 75.9, 75.2, 58.4, 57.5, 55.7, 41.7, 40.4, 40.3, 39.4, 38.5, 30.0, 26.1, 23.4, 18.3, 17.7, −3.8, −4.4; HRMS *m/z* calcd for $C_{25}H_{46}O_4Si$ $(M + Na)^+$ 461.3063, found 461.3075.

*4.1.32. 2-((1S,2R,3R,4aS,5R,8aR)-5-((tert-butyldimethylsilyl)oxy)-3-(methoxymethoxy)-1,7-dimethyl-2-(prop-1-en-2-yl)-1,2,3,4,4a,5,8,8a-octahydronaphthalen-1-yl)acetaldehyde (**41**)*

To a −78 °C solution of $(COCl)_2$ (0.39 μL, 0.46 mmol) in $CH_2Cl_2$ (0.5 mL) was added dry DMSO (0.05 mL, 0.68 mmol). The mixture was stirred for 10 min and **40** (21.7 mg, 0.0495 mmol) was added as a solution in $CH_2Cl_2$ (0.2 mL, with 0.2 mL rinse). After stirring at −78 °C for 20 min, $Et_3N$ (0.54 mL, 3.86 mmol) was added, the cooling bath was removed, and the reaction was allowed to warm to room temperature. The solution was diluted with water (1 mL). The layers were separated and the aqueous layer was extracted with $CH_2Cl_2$ (3 × 2 mL). The combined organic layers were dried with $MgSO_4$, filtered and concentrated. Purification by silica gel chromatography (10% EtOAc/hexanes) provided aldehyde **41** (20.2 mg, 93%) as a colorless oil: $R_f$ 0.68 (hexanes/EtOAc (2:1)); $[\alpha]_D^{20}$ +37.8 (c 0.21, $CHCl_3$); IR (film) 2954, 2928, 2856, 1716, 1471, 1362, 1250, 1152, 1105, 1072, 1041, 836, 774 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) $\delta$ 9.87 (dd, $J$ = 3.3, 1.6 Hz, 1H), 5.28 (s, 1H), 5.08 (s, 1H), 4.84 (s, 1H), 4.68 (d, $J$ = 6.9 Hz, 1H), 4.61 (d, $J$ = 6.9 Hz, 1H), 3.87 (d, $J$ = 7.8 Hz, 1H), 3.80 (td, $J$ = 10.9, 4.9 Hz, 1H), 3.34 (s, 3H), 2.74 (dt, $J$ = 12.7, 4.6 Hz, 1H), 2.49−2.41 (m, 2H), 2.26 (dd, $J$ = 16.4, 3.3 Hz, 1H), 1.90−1.70 (m, 3H), 1.83 (s, 3H), 1.66 (s, 3H), 1.47 (tdd, $J$ = 12.8, 8.3, 4.3 Hz, 1H), 0.97 (s, 3H), 0.92 (s, 9H), 0.10 (s, 3H), 0.09 (s, 3H); $^{13}C$ NMR (125 MHz, $CDCl_3$) $\delta$ 202.1, 144.4, 134.0, 125.9, 96.3, 75.7, 74.8, 58.5, 55.8, 51.1, 42.7, 51.9, 39.4, 38.4, 30.1, 26.1, 23.3, 18.3, 16.7, −3.8, −4.3; HRMS *m/z* calcd for $C_{25}H_{44}O_4Si$ $(M + Na)^+$ 459.2906, found 459.2914.

*4.1.33. 1-((1S,2R,3R,4aS,5R,8aR)-5-((tert-butyldimethylsilyl)oxy)-3-(methoxymethoxy)-1,7- dimethyl-2-(prop-1-en-2-yl)-1,2,3,4,4a,5,8,8a-octahydronaphthalen-1-yl)but-3-en-2-one (42)*

To a −78 °C solution of aldehyde 41 (25 mg, 0.058 mmol) in THF (1.2 mL) was added vinylmagnesium bromide (0.29 mL, 0.29 mmol, 1 M in THF). The mixture was stirred at 0 °C for 15 min, quenched with saturated aqueous $NH_4Cl$, diluted with $CH_2Cl_2$ and allowed to warm to room temperature. The layers were separated and the aqueous layer was extracted with $CH_2Cl_2$ (3 × 4 mL). The combined organic layers were dried with $MgSO_4$, filtered and concentrated to provide the corresponding allylic alcohol as a 3:2 mixture of diastereomers which were utilized without additional purification. The crude oil was dissolved in $CH_2Cl_2$ (1.2 mL) and TPAP [33] (2 mg, 0.0058 mmol) followed by *N*-methyl-morpholine-*N*-oxide (NMO) (20 mg, 0.17 mmol) was added. The black mixture was stirred at room temperature for 30 min, diluted with 20% EtOAc in hexanes, filtered through a plug of silica gel using 20% EtOAc in hexanes and concentrated to provide 42 (19 mg, 71% for two steps) as a colorless oil: $R_f$ 0.72 (3:1 Hexanes/EtOAc); $[\alpha]_D^{21}$ +48.9 (c. 0.32, $CHCl_3$); IR (neat) 2955, 2928, 2856, 1708, 1685, 1639, 1611, 1471, 1400, 1250, 1152, 1070, 1041, 836, 774 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) $\delta$ 6.28 (dd, $J$ = 17.6, 10.5 Hz, 1H), 6.15 (d, $J$ = 17.6 Hz, 1H), 5.76 (d, $J$ = 10.6 Hz, 1H), 5.27 (s, 1H), 4.97 (s, 1H), 4.72 (s, 1H), 4.69 (d, $J$ = 6.8 Hz,1H), 4.61 (d, $J$ = 6.8 Hz, 1H), 3.90 (d, $J$ = 7.3 Hz, 1H), 3.80 (td, $J$ = 11.0, 4.9 Hz, 1H), 3.36 (s, 3H), 2.87 (d, $J$ = 10.7 Hz, 1H), 2.72 (dt, $J$ = 12.8, 4.6 Hz, 1H), 2.58 (d, $J$ = 18.6 Hz, 1H), 2.50 (d, $J$ = 18.4 Hz, 1H), 2.34 (td, $J$ = 11.6, 6.1 Hz, 1H), 1.85−1.79 (m, 1H), 1.75 (s, 3H), 1.67−1.56 (m, 1H), 1.62 (s, 3H), 1.44 (dddd, $J$ = 15.4, 11.4, 7.7, 3.6 Hz, 1H), 1.07 (q, $J$ = 12.0 Hz, 1H), 0.93 (s, 9H), 0.90 (s, 3H), 0.10 (s, 6H); $^{13}C$ NMR (125 MHz, $CDCl_3$) $\delta$ 199.2, 137.6, 134.1, 126.8, 126.1, 96.2, 75.9, 55.7, 46.2, 41.3, 39.8, 39.4, 38.2, 30.3, 29.8, 26.2, 23.4, 18.3, 17.5, −3.8, −4.3; HRMS *m/z* calcd for $C_{27}H_{46}O_4Si$ $(M + Na)^+$ 485.3063, found 485.3079.

*4.1.34. (4aS,4bR,8R,8aS,10R,10aR)-8-((tert-butyldimethylsilyl)oxy)-10-(methoxymethoxy)-1,4a,6-trimethyl-4,4a,4b,5,8a,9,10,10a-octahydrophenanthren-3(8H)-one (**44**)*

To a room temperature solution of **42** (19 mg, 0.045 mmol) in toluene (1.8 ml) was added Grubbs II catalyst [34] (**43**) (3.8 mg, 0.0045 mmol) as a solution in toluene (0.5 mL). The reaction was heated in a 70 °C bath. After 30 min, the mixture was concentrated and purified by silica gel chromatography (5−15% EtOAc/hexanes) to provide the ABC tricycle **44** (14.4 mg, 74%) characterized as follows: $R_f$ 0.32 (3:1 Hexanes/EtOAc); $[\alpha]_D^{21}$ +34.1 (c. 0.18, $CHCl_3$); IR (neat) 2955, 2928, 2855, 1668, 1471, 1442, 1377, 1257, 1148, 1102, 1070, 1040, 835, 775 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) $\delta$ 5.91 (s, 1H), 5.29 (s, 1H), 4.76 (ABq, $J_{AB}$ = 8.3 Hz, $\Delta\nu_{AB}$ = 6.9 Hz, 2H), 3.87 (br s, 1H), 3.65 (td, $J$ = 10.7, 5.1 Hz, 1H), 3.40 (s, 3H), 2.89 (ddd, $J$ = 13.3, 5.1, 3.3 Hz, 1H), 2.48 (d, $J$ = 16.6 Hz, 1H), 2.41 (d, $J$ = 10.3 Hz, 1H), 2.11 (d, $J$ = 16.6 Hz, 1H), 2.11 (s, 3H), 1.84−1.79 (m, 2H), 1.66 (s, 3H), 1.49−1.45 (m, 2H), 1.11−1.04 (m, 1H), 0.93 (s, 9H), 0.87 (s, 3H), 0.11 (s, 3H), 0.10 (s, 3H); $^{13}C$ NMR (125 MHz, $CDCl_3$) $\delta$ 198.3, 163.9, 134.4, 128.3, 125.6, 97.1, 75.8, 75.3, 56.5, 53.2, 51.6, 45.5, 42.3, 39.3, 38.6, 29.5, 26.1, 25.5, 23.4, 18.3, 14.0, −3.9, −4.4; HRMS *m/z* calcd for $C_{25}H_{42}O_4Si$ $(M + H)^+$ 436.2959, found 436.3014.

## Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: David R Williams reports financial support was provided by National Science Foundation.

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