# Relay ring-closing metathesis strategies towards the synthesis of the ABC tricycle of Taxol

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ABSTRACT

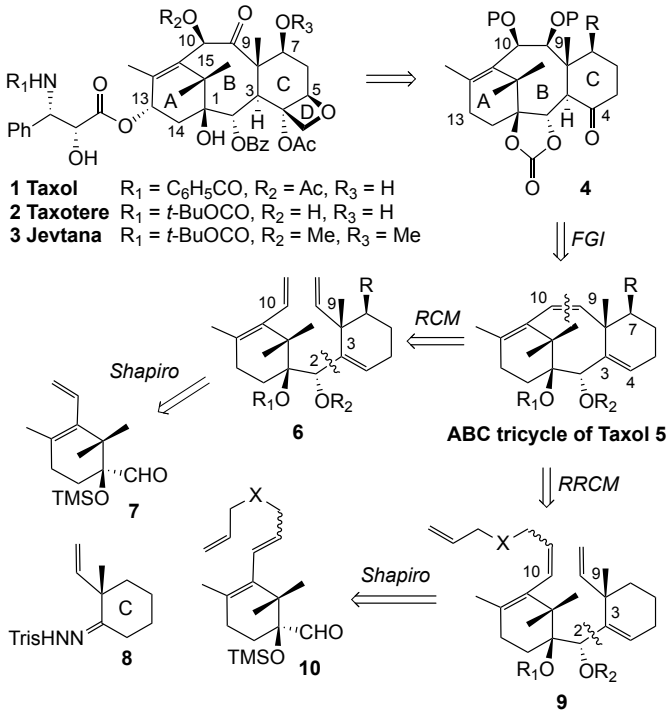
Two synthetic routes towards the ABC tricycle of Taxol are presented. They both involve a relay ring-closing metathesis reaction to make the central B ring in a convergent fashion. In the first approach, the extender arm is positioned on the A ring, and the C ring bears the relay tether in the second route. Metathesis precursors with diverse extender arms were efficiently synthesised; unfortunately, the crucial metathesis reactions failed to deliver the target compounds in all cases.

## 1. Introduction

Taxol® (paclitaxel) is one of the most affordable and best-selling anticancer drugs. It was approved by the FDA in 1992 and is prescribed nowadays in generic form or as the albumin-bound Abraxane®, which generated more than 1 billion USD in sales in the year 2020 alone.[1] Taxol® and its derivatives Taxotere® (docetaxel) and Jevtana® (cabazitaxel) are widely used for the treatment of a broad range of malignancies.[2] These three compounds have very similar structures, only differing by the functionalisation of the amine on the side chain and the hydroxyl groups at C10 and C7 (Scheme 1). While Taxol is currently being manufactured through plant cell fermentation by Phyton Biotech, LLC, a DFB Pharmaceuticals Company for Bristol-Myers Squibb, Taxotere and Jevtana are produced by semisynthesis from 10-deacetylbaccatin III by Sanofi, which still requires an expensive extraction process of natural resources. Eight total syntheses of Taxol have been reported by the groups of Holton,[3] Nicolaou,[4] Danishefsky,[5] Wender,[6] Mukaiyama,[7] Kuwajima[8] and recently Baran[9] and Li,[10] as well as three formal syntheses by the groups of Takahashi,[11] Nakada[12] as well as Sato and Chida.[13] An efficient synthesis of the tricyclic core of Taxol where all the functional groups required for activity are present or in a latent form, would allow access to a range of novel compounds with potential anticancer activity. Earlier attempts in our hands to use diene ring-closing metathesis to close the B ring resulted in the synthesis of BC bicycles,[14] and we successfully employed an ene-yne-ene metathesis cascade to construct the ABC tricycle in one step from the A ring.[15] However, we wanted to explore a convergent approach that would involve a diene ring-closing metathesis reaction to close the B ring, and our effort towards this goal are presented herein.

## 2. Results and discussion

The convergent retrosynthesis we envisaged for Taxol is outlined in Scheme 1. Compound **4** appears to be a good precursor for the target molecule. Indeed, Nicolaou *et al.* have shown that a diol moiety at C9-C10 could be easily converted to the required acetoxy ketone;[4] in their synthesis of Taxol, the Holton group started from a ketone at C4 to elaborate the oxetane ring and converted the carbonate at C1-C2 to the corresponding benzoate by addition of phenyllithium;[3] finally, the hydroxyl group at C13 bearing the side chain could be introduced by an allylic oxidation/diastereoselective reduction sequence.[16,9] This precursor of Taxol could be accessed in a few functional group interconversions (FGI) from the ABC tricycle core of Taxol **5**. In our previous work[17] a direct convergent approach was explored, and the B ring was disconnected at the C9-C10 olefin, revealing the ring-closing metathesis (RCM) substrate **6**. Model compounds **6** (R = H) were synthesised from aldehyde **7** and hydrazone **8**, utilising a Shapiro coupling to




**Scheme 1.** Convergent retrosynthesis of Taxol.

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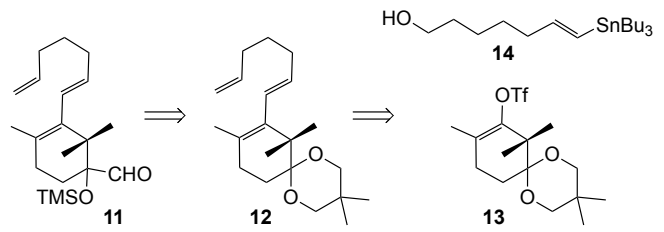
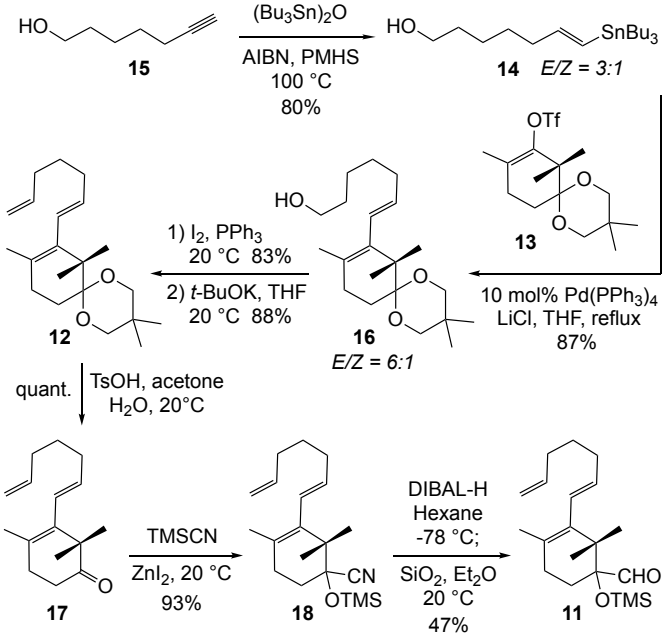
form the C2-C3 bond. Unfortunately, all metathesis attempts on dienes **6** with diverse cyclic and acyclic protecting groups for the C1-C2 diol only resulted in full recovery of the starting material.[18] This result implies that the two olefins at C9 and C10 are not reacting with the metathesis catalysts. To circumvent this lack of reactivity, a relay ring-closing metathesis (RRCM) approach was envisioned, and the disconnection of the B ring led to the trienes **9** encompassing the relay handle on the A ring (X = $CH_2$ or O). These compounds would be prepared by a Shapiro reaction between the previously reported hydrazone **8**[18] and aldehydes **10**.

We first embarked on the synthesis of the racemic aldehyde **11** containing an all-carbon extender arm. This compound could be obtained from acetal **12**, which in turn would result from a Stille coupling between triflate **13** and stannane **14** (Scheme 2).




**Scheme 2.** Retrosynthesis of aldehyde **11**.

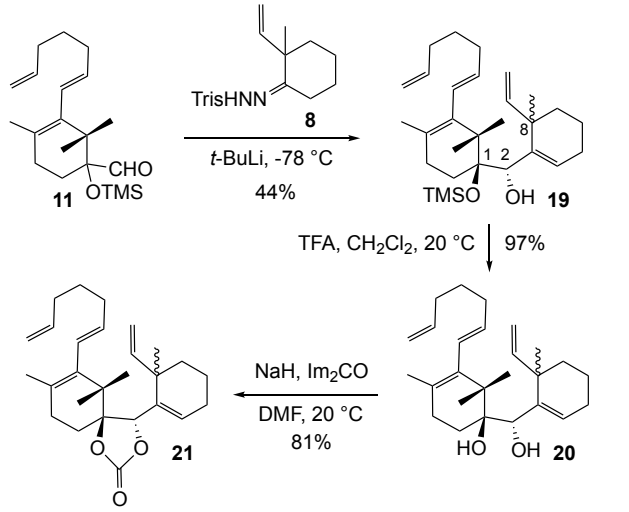
Stannane **14** was obtained by radical hydrostannylation of the known alcohol **15**[19] and as a 3:1 mixture of *E* and *Z* isomers (Scheme 3). Stille coupling of this stannane with triflate **13**,[20] an intermediate in the synthesis of aldehyde **7**, delivered diene **16** in 87% yield, which was converted to acetal **12** in two steps *via* the corresponding iodide. Following the route previously reported for the synthesis of aldehyde **7**,[20] the acetal was hydrolysed under acidic conditions to give ketone **17**, which was homologated in two steps into aldehyde **11** by formation of cyanohydrin **18** and subsequent DIBAL-H reduction. The last reaction was problematic, contrary to the reduction leading to aldehyde **7**. No conversion was observed when the reaction was performed in ether or dichloromethane, even when the temperature was raised to 0 °C. As cyanohydrin **18** is very nonpolar, we selected less




**Scheme 3.** Synthesis of aldehyde **11**.

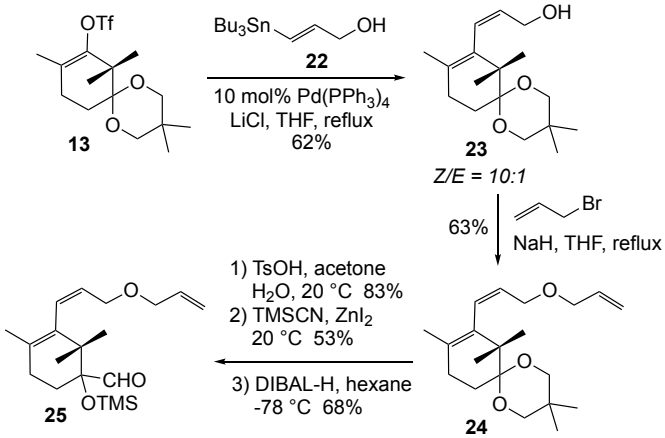
polar solvents for this reduction: a yield of 35% was obtained in toluene at -78 °C, but the best result was a yield of 47% in hexane.

Shapiro coupling between the racemic hydrazone **8** and aldehyde **11** gave the desired product **19** in 44% unoptimised yield (Scheme 4). As previously observed for the formation of compounds **6**,[21] the reaction is highly diastereoselective, giving only the *trans* diol derivatives[22] at C1-C2. Since the two partners are racemic, compound **19** was obtained as a 1:1 mixture of diastereomers at C8, which could not be separated. Cleavage of the TMS ether under acidic conditions followed by carbonate formation from the diol **20** led to the metathesis precursor **21** in good yield.



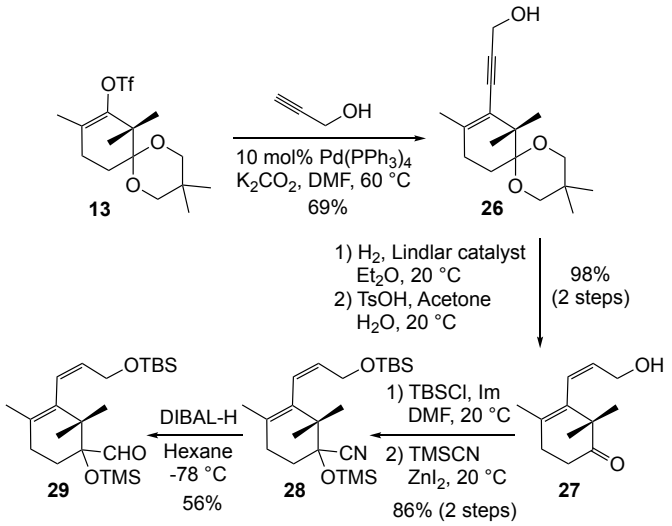

**Scheme 4.** Synthesis of metathesis precursor **21**.

We then turned to the synthesis of metathesis precursors with a tether bearing an oxygen atom. Triflate **13** was engaged in a Stille coupling with the known stannane **22**[23] (Scheme 5). This coupling occurred with isomerisation of the olefin, giving diene **23** as a 10:1 mixture of *Z*/*E* isomers. Such isomerisation reactions have been observed before, but the mechanism has not been determined.[24] Allylation of the primary alcohol in **23** led to **24**, which was transformed to the corresponding aldehyde **25** following the route described for the preparation of the aldehyde **11**. This time, the cyanohydrin formation was low yielding, because the allylic ether might be degraded by zinc diiodide, but the DIBAL-H reduction of the cyanohydrin was uneventful. A Shapiro coupling of hydrazone **8** and aldehyde **25** was attempted, but only decomposition was observed. This is probably due to the metalation of the allylic ether by *tert*-BuLi, which can occur even at low temperature.[25]



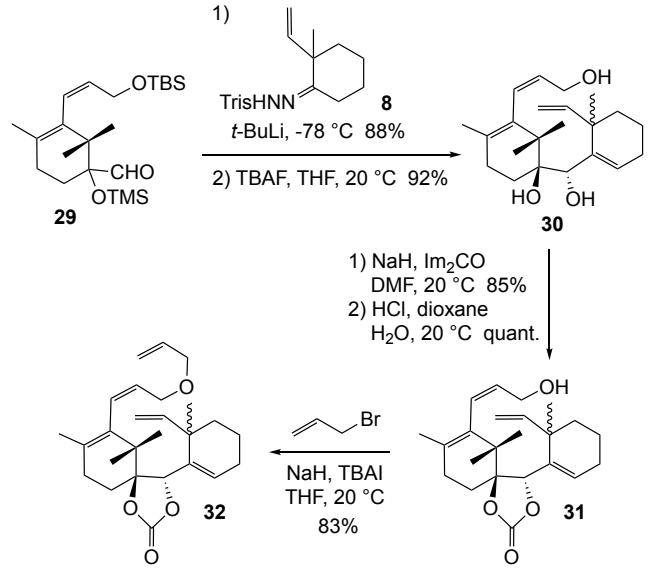

**Scheme 5.** Synthesis of aldehyde **25**.

At this point, it was evident that the allylic ether had to be installed after the Shapiro coupling. We also decided to form the diene moiety by a Sonogashira coupling, to avoid the use of toxic stannyl derivatives, and triflate **13** reacted with propargyl alcohol to give enyne **26** in good yield (Scheme 6). Lindlar hydrogenation furnished diene **23** as a single isomer, and subsequent hydrolysis of the acetal afforded ketone **27** in excellent yield for the two steps. The primary alcohol was protected as a TBS ether and the ketone converted to the corresponding cyanohydrin. Gratifyingly, the latest step occurred in 91% yield. Aldehyde **29** was then obtained by DIBAL-H reduction of cyanohydrin **28**.



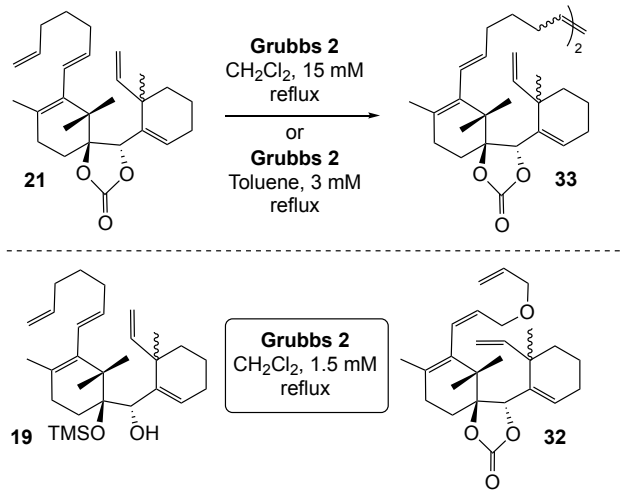

**Scheme 6.** Synthesis of aldehyde **29**.

Shapiro reaction between hydrazone **8** and aldehyde **29** proceeded in excellent yield, and both silyl ethers were cleaved with TBAF to give triol **30** (Scheme 7). Treatment of this triol with carbonyldiimidazole in the presence of sodium hydride in DMF resulted in the formation of C1-C2 carbonate and the primary alcohol was converted to the carbamate, which was subsequently hydrolysed under acidic conditions. The resulting primary alcohol **31** was then allylated to furnish the metathesis precursor **32** in good yield.




**Scheme 7.** Synthesis of metathesis precursor **32**.

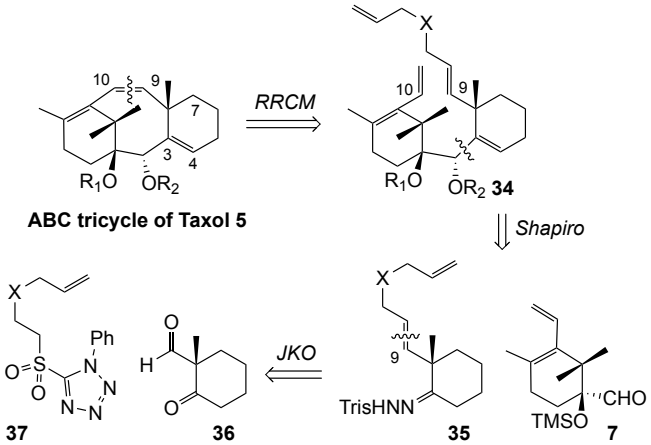
The key RRCM reaction was first tested on compound **21**. In the presence of Grubbs second-generation catalyst in dichloromethane at reflux, only the dimer **33** was observed, even at a concentration of 15 mM (Scheme 8). The reaction was then performed at lower concentration in toluene at reflux in order to favour the relay pathway, but with no success. During our previous work on RCM to construct the BC ring system of Taxol, we had observed that the nature of the protecting group of the diol at C1-C2, cyclic or acyclic, had a dramatic influence on the outcome of the metathesis reactions.[14] The metathesis reaction was then attempted on compound **19** at very low concentration (1.5 mM) in dichloromethane at reflux, but unfortunately only a complex mixture of products was observed. The same conditions were applied to compound **32** with an oxygenated tether; none of the desired tricyclic product could be observed in the mixture of obtained products. Efforts were made to synthesise a derivative of compound **32** encompassing an acyclic protecting group for the diol at C1-C2. Treatment of **32** with phenyllithium to form the corresponding benzoate or with sodium hydroxide to hydrolyse the carbonate only led to decomposition. Compound **31** was protected as a TBS ether but unfortunately the carbonate moiety in the resulting product could not be converted to the benzoate; even with a




**Scheme 8.** RRCM attempts.

large excess (30 equiv) of phenyllithium, no reaction occurred.

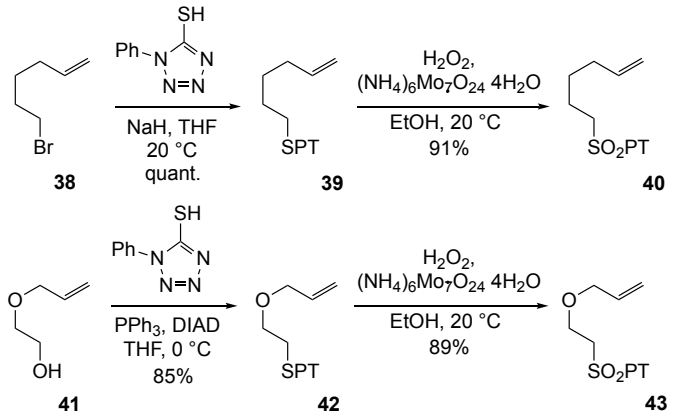
In view of the results outlined above, we envisioned an alternative route towards the construction of the B ring of Taxol. The new retrosynthetic analysis is illustrated in Scheme 9 and focused on the installation of the tether on the C ring instead of the A ring. The metathesis precursors **34** would be obtained by a Shapiro coupling between hydrazones **35** and aldehyde **7**. The synthesis of hydrazones **35** would




**Scheme 9.** Retrosynthesis using an alternative RRCM strategy.

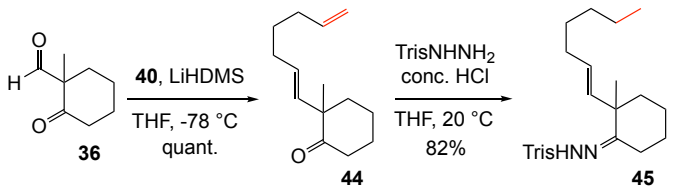
involve a Julia-Kocienski olefination (JKO) between ketoaldehyde **36** and phenyltetrazolyl sulfones **37**.

The synthesis of the phenyltetrazolyl (PT) sulfone **40** with an all-carbon substituent started with the substitution of bromide **38** by 1-phenyl-1*H*-tetrazole-5-thiol to furnish sulfide **39** in quantitative yield (Scheme 10). The corresponding oxygenated sulfide **42** was prepared in 85% yield by a Mitsunobu reaction between the commercially available alcohol **41** and 1-phenyl-1*H*-tetrazole-5-thiol. Subsequent oxidation of sulfides **39** and **42** afforded sulfones **40** and **43**, respectively, in excellent yields.



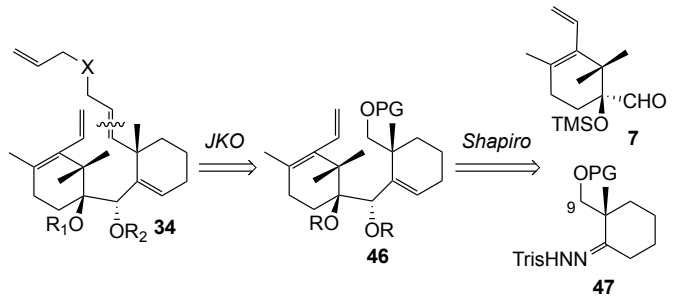

**Scheme 10.** Synthesis of sulfones **40** and **43**.

The racemic ketoaldehyde **36**, obtained by IBX oxidation of the corresponding known primary alcohol **48**[26] (see Scheme 13 for structure), was submitted to a JKO reaction to give the desired diene **44** in quantitative yield (Scheme 11). Unfortunately, hydrazine condensation was accompanied by reduction of the terminal double bond and alkene **45** was obtained in 82% yield. A precedent in the literature was found for the reduction of non-hindered olefins by *o*-nitrobenzenesulfonylhydrazide.[27]



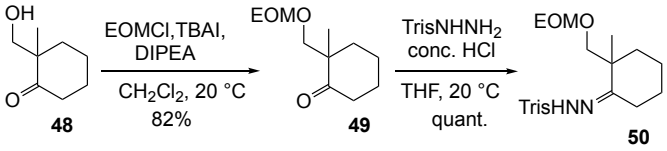

**Scheme 11.** Attempted synthesis of hydrazone **35** (X = $CH_2$).

A revised synthesis plan was then envisaged. As shown in Scheme 12, the extending arm would be installed on compound **46**, obtained by Shapiro reaction of aldehyde **7** and hydrazone **47**, which bears a protected alcohol at C9. This approach is less convergent but allows for diversification at a later stage in the synthesis.



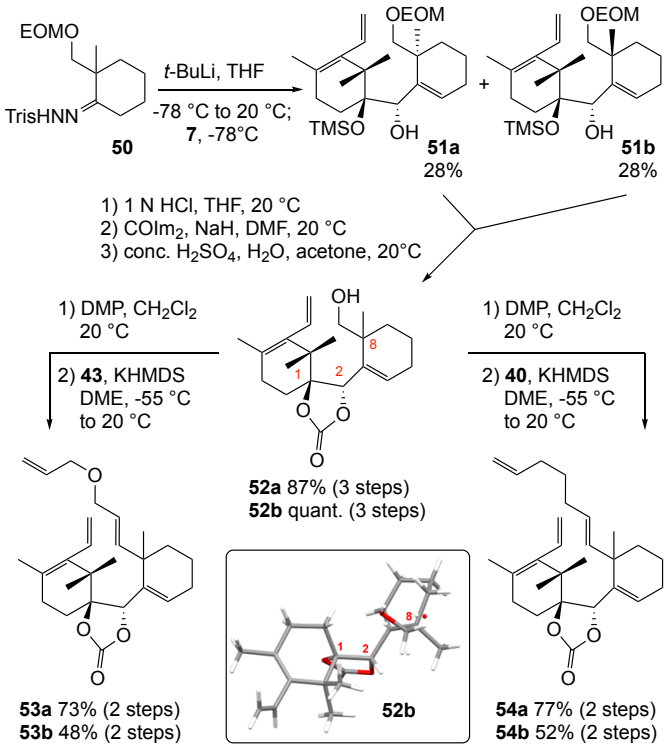

**Scheme 12.** Revised retrosynthesis.

The racemic hydrazone **50** was obtained in 82% yield over 2 steps when the previously prepared alcohol **48**[21] was protected as the corresponding ethoxymethyl (EOM) ether (Scheme 13).




**Scheme 13.** Synthesis of hydrazone **50**.

The racemic aldehyde **7**,[28] synthesised during our previous work,[20] was engaged in a Shapiro reaction with hydrazone **50** to afford a 1:1 mixture of the two diastereomers **51a** and **51b** in 56% yield (Scheme 14). Once again, this coupling is very diastereoselective, affording only the *trans* diols at C1-C2. These diastereomers could be separated at this stage and the synthesis of

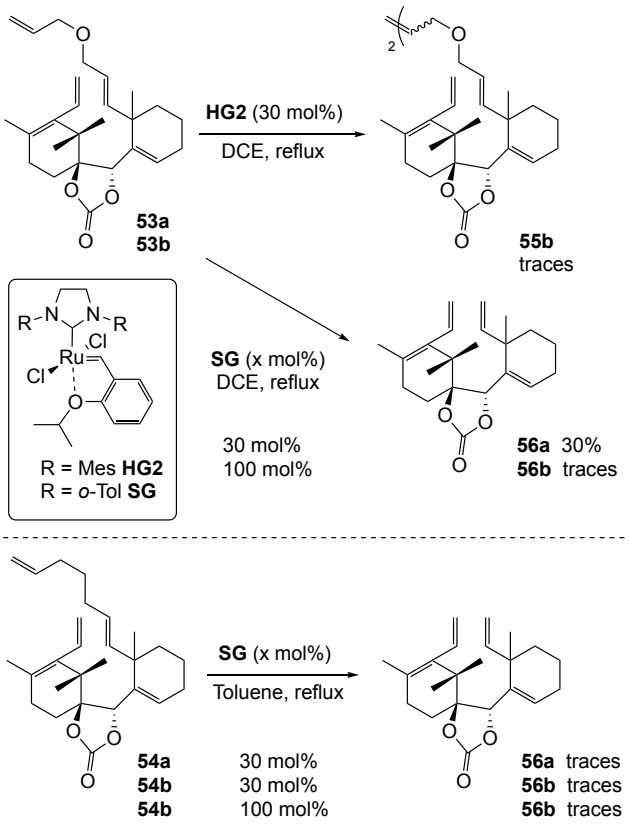



**Scheme 14.** Synthesis of RRCM precursors.

the metathesis precursors **53** and **54** was conducted on both diastereomers separately. The TMS ether in **51a-b** was hydrolysed in the presence of aqueous HCl and subsequent treatment of the diols with NaH and $COIm_2$ afforded the desired carbonates, which were exposed to sulfuric acid to furnish the primary alcohols **52a-b** in excellent yield for the three steps. To our delight, compound **52b** was isolated as a crystalline solid, and its X-ray diffraction analysis confirmed that it possessed the require relative configuration at C1, C2 and C8 for Taxol.[29] Finally, alcohols **52a-b** were oxidised to the corresponding unstable aldehydes, which were treated without purification with KHMDS in the presence of either sulfone **43** or **40**, resulting in the formation of the RRCM precursors **53a-b** and **54a-b**, respectively.

With **53a-b** and **54a-b** in hand, different conditions for the RRCM reaction were explored. The oxygenated versions **53a-b** were added dropwise to a refluxed solution of the second generation Hoveyda-Grubbs catalyst **HG2** in toluene ("infinite dilution" conditions), but only a small amount of the starting material was recovered in each case, along with the product resulting from cleavage of the allyl ether in **53a-b** (Scheme 15). We thus employed milder conditions with these substrates. Traces of the dimer **55b** were observed when **53b** was used as the starting materials and DCE as solvent, as evidenced by mass spectrometry. Interestingly, the combination of the Stewart-Grubbs catalyst (**SG**) and DCE afforded the truncated product **56a** in 30% yield when

30 mol% of the catalyst were employed with the Taxol un-like metathesis precursor **53a**. However, only recovery of the SM and traces on the truncated product **56b** were recovered when using **53b** under the same conditions. It seems that the first step of the RRCM process can take place on **53a**, but the newly formed carbene at C9 is not reactive enough under the reaction conditions to form the desired B ring. We decided to test the non-oxygenated metathesis precursors **54a-b**. Unfortunately, only traces of the truncated products **56a-b** were detected by $^1$H NMR spectroscopy and HRMS. Finally, it was decided to explore whether an increase of the catalyst loading could form the desired tricyclic core with




**Scheme 15.** RRCM results.

the desired Taxol-like configuration. Disappointingly, 50-60% of the starting material **54b** was recovered when a full equivalent of **SG** was employed. A comparison of the results obtained suggested that the Taxol-like configuration is less reactive towards the relay reaction than the Taxol-unlike one. We also synthesised a RRCM precursor with an acyclic protecting group for the C1-C2 diol. Compound **53b** was treated with an excess of phenyllithium to furnish the corresponding benzoate, which was subjected to the **SG** catalyst in refluxing DCE; unfortunately, only a mixture of the metathesis precursor and the truncated product was isolated.

## 3. Conclusion

Diverse metathesis precursors with extender arms on either the A or C ring have been efficiently prepared. When the relay tether was positioned on the A ring, only dimeric products were observed. When metathesis precursors bearing an oxygenated extender arm on the C ring were exposed to metathesis catalysts, the truncated product was obtained for one of the diastereomeric precursors. It seems that the first step of the relay metathesis occurred in the latter case, but that the desired tricycle is too strained to be formed.

## 4. Experimental section

Air or moisture sensitive reactions were carried out in pre-dried glassware; either overnight in an oven (125 °C) or by flame drying under vacuum. Argon was used to create an inert atmosphere. Degassing solvent was done using freeze and thaw method. Reactions were collected from an in-house solvent purification system (THF, $CH_2Cl_2$, $Et_2O$, $CH_3CN$, and toluene). Chromatography solvents were HPLC grade solvents, stored in Winchester bottles. All reagents were used directly from supplier, unless prior purification is explicitly stated. Flash chromatography was executed under forced flow conditions, using the indicated solvent system and the EMD Geduran silica gel 60 as solid support. Thin layer chromatography (TLC) was carried out on Merck silica gel 60 covered aluminium sheets, and monitored by UV-light or by staining with a solution of anisaldehyde or $KMnO_4$ mixture. NMR spectra were recorded using a Bruker DPX-400 spectrometer ($^1$H NMR: 400 MHz, $^{13}$C NMR: 101 MHz) and a Bruker DPX-500 spectrometer ($^1$H NMR: 500 MHz, $^{13}$C NMR: 126 MHz). Deuterated chloroform ($CDCl_3$) was used as the solvent for both $^1$H and $^{13}$C NMR, with residual solvent peak δ 7.26 being used for calibration of $^1$H NMR and $CDCl_3$ peak at δ 77.16 for $^{13}$C. Signal splitting patterns are described as: singlet (s), doublet (d), triplet (t), quartet (q), quintet (quint), sextet (sext), octet (oct), nonet (non), multiplet (m), broad singlet, or any combination of the above. Two dimensional experiments (COSY, HSQC, HMBC, and HMQC) were recorded, where necessary, for assignment. Sn-H and Sn-C couplings were averaged over 117/119Sn. IR spectra were recorded using a Golden Gate™ attachment, utilizing a type IIa diamond as a single reflection element, allowing for the direct reading of powder and oil samples. High resolution mass spectra were recorded under FAB, ESI and CI conditions by the University of Glasgow analytical service.

### *4.1. 7-(Tributylstannyl)hept-6-en-1-ol (**14**) diazoacetate (7**b**)*

*bis*-(Tributyltin) oxide (3.2 mL, 6 mmol, 0.7 equiv) and polymethylhydrogensiloxane (0.8 g) were heated at 100°C for 30 min. Compound **15** (1.0 g, 8.9 mmol) and a few milligrams of AIBN were then added. The mixture was stirred at 100°C for 6h. Occasionally, a few milligrams of AIBN were added during the process. The resulting mixture was then directly purified by flash chromatography on silica gel ($Et_2O$/petroleum ether 30:70) to afford **14** (2.4 g, 66%, *E*/*Z* = 3:1) as a colourless oil.**$^1$H NMR (400 MHz, $CDCl_3$)** δ ppm: 6.52 (m, 0.25H), 5.92 (m, 1.75H), 3.65 (m, 2H), 2.17 (m, 1.5 H), 2.04 (m, 0.5H), 1.25-1.65 (m, 18H), 0.89 (m, 15H).**$^{13}$C NMR (100 MHz, $CDCl_3$)** δ ppm: 149.5, 149.0, 128.1, 127.5, 63.2, 63.1, 37.9, 37.2, 32.9, 32.8, 29.3, 29.2, 27.5, 27.4, 27.4, 25.7, 25.3, 13.8, 10.3, 10.2, 10.0, 9.5.**IR ($CH_2Cl_2$):** 3280, 2958, 2927, 2872, 2857, 2336, 1720, 1651, 1591, 1518, 1464, 1417, 1368, 1348, 1256, 1178, 1149, 1077, 1042, 947 cm$^{-1}$.

### *4.2. (E)-7-(3,3,7,7,9-Pentamethyl-1,5-dioxaspiro[5.5]undec-8-en-8-yl)hept-6-en-1-ol (**16**)*

To a slurry of LiCl (170 mg, 3.9 mmol, 3.0 equiv) and $Pd(PPh_3)_4$ (160 mg, 0.13 mmol, 0.1 equiv) in THF (20 mL) was added the vinyltriflate **13** (498 mg, 1.3 mmol) and the stannane **14** (2.1 g, 5.3 mmol, 4.0 equiv). The resulting mixture was heated to reflux under argon for 4 days, with extra addition of *ca.* 0.1 equiv of $Pd(PPh_3)_4$ every day. The resulting solution was washed with water, with a 5% aqueous ammonium hydroxide solution, and with brine, filtered and concentrated *in vacuo*. The crude mixture was then purified by flash chromatography on silica gel ($Et_2O$/petroleum ether 20:80 to 30:70) to afford **16** (380 mg, 87%, *E*/*Z* = 6:1) as a sticky yellow oil. **$^1$H NMR (400 MHz, $CDCl_3$)** δ ppm: 5.80 (dd, *J* = 15.8, 0.9 Hz, 1H), 5.38 (dt, *J* = 15.7, 6.9 Hz), 3.71 (d, *J* = 11.2 Hz, 2H), 3.65 (d, *J* = 11.2 Hz, 2H), 3.38 (d, *J* =

11.5 Hz, 2H), 2.11 (m, 4H), 2.02 (d, *J* = 6.2 Hz, 2H), 1.68 (s, 3H), 1.57 (m, 2H), 1.43 (m, 4H), 1.20 (s, 3H), 1.09 (s, 6H), 0.74 (s, 3H). **$^{13}$C NMR (100 MHz, $CDCl_3$)** δ ppm: 136.6, 135.1, 127.6, 126.0, 100.4, 70.3, 63.2, 43.6, 33.1, 32.8, 30.0, 29.9, 29.5, 25.4, 23.3, 22.7, 22.4, 21.1, 18.6. **IR ($CDCl_3$):** 3622, 2931, 2866, 1467, 1385, 1210, 1115, 1065, 1039, 991 cm$^{-1}$. **HRMS (EI):** Calcd for $C_{21}H_{36}O_3^+$ $[M]^+$, 336.2265; found, 336.2264.

*4.3. (E)-8-(7-Iodohept-1-enyl)-3,3,7,7,9-pentamethyl-1,5-dioxaspiro[5.5]undec-8-ene (**S1**)*

To a solution of **16** (1.3 g, 3.8 mmol) in THF (25 mL) was added imidazole (0.51 g, 7.6 mmol, 2.0 equiv), triphenylphosphine (1.8 g, 6.8 mmol, 1.8 equiv) and iodine (1.8 g, 7.2 mmol, 1.9 equiv). The resulting mixture was stirred at rt for 1h. The solution was diluted with $Et_2O$, washed with water and brine, filtered and concentrated *in vacuo*. The crude mixture was then purified by flash chromatography on silica gel ($Et_2O$/petroleum ether 5:95) to afford **210** (1.4 g, 83%) as a pale yellow oil. **$^1$H NMR (400 MHz, $CDCl_3$)** δ ppm: 5.80 (dd, *J* = 15.8, 0.9 Hz, 1H), 5.36 (dt, *J* = 15.7, 6.9 Hz, 1H), 3.71 (d, *J* = 11.2 Hz, 2H), 3.38 (d, *J* = 11.5 Hz, 2H), 3.19 (t, *J* = 7.1 Hz, 2H), 2.07 (m, 6H), 1.85 (m, 2H), 1.68 (s, 3H), 1.44 (m, 4H), 1.20 (s, 3H), 1.09 (s, 6H), 0.74 (s, 3H). **$^{13}$C NMR (100 MHz, $CDCl_3$)** δ ppm: 136.5, 134.9, 127.8, 126.1, 100.4, 70.3, 43.6, 33.6, 33.0, 30.2, 30.0, 29.9, 28.6, 23.3, 22.8, 22.5, 21.2, 18.5, 7.2. **IR ($CDCl_3$):** 2954, 2933, 2867, 1722, 1463, 1380, 1286, 1166, 1124, 1043 cm$^{-1}$. **HRMS (EI):** Calcd for $C_{21}H_{35}IO_2^+$ $[M]^+$, 446.4059; found, 446.4064.

*4.4. (E)-8-(Hepta-1,6-dienyl)-3,3,7,7,9-pentamethyl-1,5-dioxaspiro[5.5]undec-8-ene (**12**)*

To a solution of **S1** (1.4 g, 3.1 mmol) in THF (25 mL) was added potassium *tert*-butoxide (0.53 g, 4.7 mmol, 1.5 equiv). The resulting mixture was stirred at rt for 30 min. The reaction was quenched with water. The aqueous layer was extracted with $Et_2O$, and the combined organic extracts were washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The crude mixture was then purified by flash chromatography on silica gel ($Et_2O$/petroleum ether 2:98) to afford **12** (0.87 g, 88%) as a colourless oil. **$^1$H NMR (400 MHz, $CDCl_3$)** δ ppm: 5.82 (m, 2H), 5.38 (dt, *J* = 15.7, 6.9 Hz, 1H), 5.02 (dd, *J* = 17.1, 1.5 Hz, 1H), 4.96 (dd, *J* = 10.2, 1.1 Hz, 1H), 3.71 (d, *J* = 11.3 Hz, 2H), 3.38 (d, *J* = 11.5 Hz, 2H), 2.08 (m, 8H), 1.68 (s, 3H), 1.51 (m, 2H), 1.20 (s, 3H), 1.09 (s, 6H), 0.74 (s, 3H). **$^{13}$C NMR (100 MHz, $CDCl_3$)** δ ppm: 139.0, 136.6, 135.0, 127.8, 126.0, 114.6, 100.4, 70.4, 43.6, 33.4, 32.6, 30.0, 29.9, 23.3, 22.8, 22.5, 21.2, 18.5. **IR ($CH_2Cl_2$):** 2957, 2932, 2868, 2336, 1717, 1465, 1380, 1261, 1115, 1036 cm$^{-1}$. **HRMS (EI):** Calcd for $C_{21}H_{34}O_2^+$ $[M]^+$, 318.2559; found, 318.2563.

*4.5. (E)-3-(Hepta-1,6-dienyl)-2,2,4-trimethyl-1-(trimethylsilyl oxy)cyclohex-3-enecarbonitrile (**18**)*

To a solution of **12** (850 mg, 2.7 mmol) in acetone (20 mL) and water (2 mL) was added a catalytic amount of *para*-toluenesulfonic acid. The resulting mixture was stirred overnight at rt. The mixture was then partitioned with diethyl ether and a saturated aqueous $NaHCO_3$ solution. The aqueous layer was extracted with $Et_2O$, and the combined organic extracts were washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The crude mixture was then purified by flash chromatography on silica gel ($Et_2O$/petroleum ether 5:95) to afford **17** (620 mg, 99%) as a colourless oil. $^1$H NMR (400 MHz, $CDCl_3$) δ ppm: 5.82 (m, 2H), 5.49 (dt, *J* = 15.8, 6.9 Hz, 1H), 5.03 (ddd, *J* = 17.1, 3.5, 1.6 Hz, 1H), 4.98 (dtd, *J* = 10.1, 2.2, 1.2 Hz, 1H), 2.56 (t, *J* = 7.0 Hz, 2H), 2.39 (t, *J* = 7.0 Hz, 2H), 2.13 (m, 4H), 1.77 (s, 3H), 1.54 (m, 2H), 1.16 (s, 6H). IR ($CH_2Cl_2$): 2973, 2931, 2868, 2336, 1716, 1459, 1377, 1263, 1102, 1041 cm$^{-1}$. HRMS (EI): Calcd for $C_{16}H_{24}O^+$ $[M]^+$, 232.1827; found, 232.1830. To a solution of **17** (55 mg, 0.24 mmol) in $CH_2Cl_2$ (2 mL) was added a catalytic amount of zinc iodide and trimethylsilylcyanide (50 µl, 0.32 mmol, 1.3 equiv). The mixture was stirred at rt for 2h, and the solvent was removed *in vacuo* to give a yellow oil that was purified by flash chromatography on silica gel ($Et_2O$/petroleum ether 1:99) to afford **18** (73 mg, 93%) as a colourless oil.**$^1$H NMR (400 MHz, $CDCl_3$)** δ ppm: 5.81 (m, 2H), 5.39 (dt, *J* = 15.8, 6.9 Hz, 1H), 5.03 (ddd, *J* = 17.1, 3.3, 1.6 Hz, 1H), 4.97 (dd, *J* = 10.1, 0.9 Hz, 1H), 2.34 (m, 2H), 2.13 (m, 6H), 1.67 (s, 3H), 1.52 (m, 2H), 1.19 (s, 3H), 1.01 (s, 3H), 0.26 (s, 9H). **$^{13}$C NMR (100 MHz, $CDCl_3$)** δ ppm: 138.9, 135.8, 135.2, 127.0, 126.4, 121.6, 114.7, 76.4, 42.7, 33.4, 32.6, 31.0, 29.6, 28.9, 23.8, 22.5, 21.1, 1.4. **IR ($CH_2Cl_2$):** 2973, 2927, 2360, 1641, 1444, 1255, 1123, 1088, 1034, 972 cm$^{-1}$. **HRMS (EI):** Calcd for $C_{17}H_{24}ON^+$ $[M\text{-}TMS]^+$, 258.1858; found, 258.1845.

*4.6. (E)-3-(hepta-1,6-dienyl)-2,2,4-trimethyl-1-(trimethylsilyloxy) cyclohex-3-enecarbaldehyde (**11**)*

To a solution of **18** (0.86 g, 2.6 mmol) in hexane (50 mL) at -78°C was added DIBAL-H (5.0 mL, 1 M in hexane, 5.0 mmol, 1.9 equiv). The mixture was stirred at this temperature for 7 h. $Et_2O$ and $SiO_2$ were then added, and the mixture was allowed to warm up to rt overnight. Silica was filtered off, and the solvent was removed *in vacuo* to give a yellow oil that was purified by flash chromatography on silica gel ($Et_2O$/petroleum ether 1:99) to afford **11** (0.41 g, 47%) as a colourless oil. **$^1$H NMR (400 MHz, $CDCl_3$)** δ ppm: 9.79 (s, 1H), 5.81 (m, 2H), 5.39 (dt, *J* = 15.7, 6.9 Hz, 1H), 5.02 (ddd, *J* = 17.1, 3.5, 1.6 Hz, 1H), 4.97 (ddd, *J* = 10.1, 2.2, 1.2 Hz, 1H), 2.13 (m, 6H), 1.90 (ddd, *J* = 8.1, 7.2, 3.9 Hz, 2H), 1.69 (s, 3H), 1.53 (m, 2H), 1.03 (s, 3H), 0.95 (s, 3H), 0.14 (s, 9H). **$^{13}$C NMR (100 MHz, $CDCl_3$)** δ ppm: 205.3, 138.9, 136.4, 135.6, 127.2, 126.7, 114.7, 83.3, 41.0, 33.4, 32.6, 29.8, 28.9, 28.1, 24.1, 22.5, 21.1, 2.6. **IR ($CH_2Cl_2$):** 2966, 2930, 1728, 1640, 1603, 1446, 1381, 1252, 1175, 1133, 1097, 1038, 972, 956 cm$^{-1}$. **HRMS (EI):** Calcd for $C_{20}H_{34}O_2Si^+$ $[M]^+$, 334.2328; found, 334.2331.

*4.7. (R*)-3-((E)-Hepta-1,6-dienyl)-2,2,4-trimethyl-1-((R*)-((6R*S*)-methyl-6-vinylcyclohex-1-enyl)(trimethylsilyloxy) methyl)cyclohex-3-enol (**19**)*

To a solution of hydrazine **8** (0.84 g, 2.0 mmol, 2.0 equiv) in THF (6 mL) at -78°C was added dropwise *t*BuLi (3.1 mL, 1.6 M in pentane, 5.0 mmol, 5.0 equiv). The solution turned orange and nitrogen bubbles appeared. The solution was stirred at this temperature for 30 min, warmed for a few minutes to room temperature, and cooled down to -78°C. A solution of aldehyde **11** (0.35 g, 1.0 mmol) in THF (1 mL) was then added *via* cannula. The resulting mixture became yellow and was stirred at -78°C for 30 min. The reaction was quenched with saturated aqueous $NaHCO_3$. The aqueous layer was extracted with $Et_2O$, and the combined organic extracts were washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The crude mixture was then purified by flash chromatography on silica gel ($Et_2O$/petroleum ether 1:99) to afford **19** (0.20 g, 44%, 1:1 mixture of diastereomers) as a colourless oil.**$^1$H NMR (400 MHz, $CDCl_3$)** δ ppm: 6.00 (m, 2H), 5.82 (m, 2H), 5.31 (m, 1H), 4.95-5.14 (m, 4H), 4.43 (s, 0.5H), 4.41 (s, 0.5H), 3.92 (s, 0.5H), 3.72 (s, 0.5H), 1.82-2.39 (m, 8H), 1.68 (s, 1.5H), 1.67 (s, 1.5H), 1.49–1.68 (m, 8H), 1.28, 1.16, 1.10, 1.04, 1.02, 0.98 (6s, 9H), 0.14 (s, 4.5H), 0.12 (s, 4.5H). **$^{13}$C NMR (100 MHz, $CDCl_3$)** δ ppm: 147.5, 141.4, 139.0, 136.7, 134.7, 129.6, 128.8, 127.5, 127.4, 114.5, 112.7, 76.1, 44.1, 44.0, 40.6, 40.3, 38.8, 38.4, 32.6, 32.6, 29.6, 29.5, 28.4, 28.1, 26.3, 25.9, 25.5, 25.0, 24.5, 24.4, 21.8, 21.5, 21.5, 18.6, 18.3, 1.4, 1.3. **IR ($CH_2Cl_2$):** 3524, 3082, 2930, 1712, 1640, 1558, 1454, 1413, 1374, 1301, 1251, 1095, 1061, 997 cm$^{-1}$. **HRMS (EI):** Calcd for $C_{29}H_{48}O_2Si^+$ $[M]^+$, 456.3424; found, 456.3413.

*4.8. (R*)-3-((E)-hepta-1,6-dienyl)-1-((R*)-hydroxy((6R*S*)-methyl-6-vinylcyclohex-1-enyl)methyl)-2,2,4-trimethylcyclohex-3-enol (**20**)*

To a solution of **19** (37 mg, 0.080 mmol) in $CH_2Cl_2$ (5 mL) were added 3 drops of TFA. The resulting solution was stirred at rt for 5 min, and then concentrated *in vacuo*. The resulting crude product was then purified by flash chromatography on silica gel ($Et_2O$/petroleum ether 10:90) to afford **20** (30 mg, 97%, 1:1 mixture of diastereomers) as a colourless oil. **$^1$H NMR (400 MHz, $CDCl_3$)** δ ppm: 6.32 (t, *J* = 4.1 Hz, 0.5H), 6.30 (t, *J* = 4.1 Hz, 0.5H), 5.72–5.95 (m, 3H), 5.30 (ddd, *J* = 15.6, 12.0, 6.8 Hz, 1H), 4.95–5.13 (m, 4H), 4.18 (s, 0.5H), 4.16 (s, 0.5H), 2.82 (s, 0.5H), 2.73 (s, 0.5H), 2.02-2.28 (m, 8H), 1.94 (m, 2H), 1.78 (m, 1H), 1.68 (s, 1.5H), 1.66 (s, 1.5H), 1.50–1.60 (m, 6H), 1.27, 1.17, 1.10, 1.05, 1.00 (5s, 9H). **$^{13}$C NMR (100 MHz, $CDCl_3$)** δ ppm: 146.9, 146.8, 145.9, 145.5, 139.0, 136.9, 136.9, 135.0, 134.9, 128.3, 128.2, 127.5, 127.3, 127.2, 114.6, 114.4, 112.8, 112.5, 76.5, 76.4, 71.0, 70.7, 44.2, 44.1, 41.3, 41.2, 37.9, 37.6, 33.4, 32.6, 29.0, 28.8, 28.7, 28.0, 28.0, 25.9, 25.8, 25.7, 24.5, 24.0, 23.0, 22.7, 21.5, 18.6, 18.5. **IR ($CCl_4$):** 3614, 3558, 3082, 2974, 2930, 1640, 1455, 1373, 1315, 1249, 1219, 1192, 1118, 1087, 1022, 1004, 971 cm$^{-1}$. **HRMS (EI):** Calcd for $C_{26}H_{40}O_2^+$ [M]$^+$, 384.3028; found, 384.3027.

*4.9. (4R*,5R*)-7-((E)-hepta-1,6-dienyl)-6,6,8-trimethyl-4-((6R*S*)-methyl-6-vinylcyclohex-1-enyl)-1,3-dioxaspiro[4.5]dec-7-en-2-one (**21**)*

To a solution of **20** (30 mg, 0.080 mmol) in DMF (0.5 mL) were added NaH (60% in mineral oil, 7.5 mg, 0.18 mmol, 2.2 equiv) and 1,2-diimidazocarbonyle (65 mg, 0.40 mmol, 5 equiv). The resulting solution was stirred at rt for 1.5 h, and then diluted with $Et_2O$, washed with saturated aqueous $NH_4Cl$ and brine, filtered and concentrated *in vacuo*. The crude mixture was then purified by flash chromatography on silica gel ($Et_2O$/petroleum ether 5:95) to afford **21** (26 mg, 81%, 1:1 mixture of diastereomers) as a pale yellow oil. **$^1$H NMR (400 MHz, $CDCl_3$)** δ ppm: 5.93 (t, *J* = 4.0 Hz, 0.5H), 5.90 (t, *J* = 4.0 Hz, 0.5H), 5.63–5.86 (m, 3H), 5.36 (dtd, *J* = 15.7, 6.9, 4.4 Hz, 1H), 4.95-5.19 (m, 4H), 4.92 (s, 0.5H), 4.86 (s, 0.5H), 2.12 (m, 10H), 1.65 (s, 1.5H), 1.64 (s, 1.5H), 1.60 (m, 2H), 1.51 (m, 4H), 1.27, 1.08, 1.07, 1.07, 1.02 (5s, 9H). **$^{13}$C NMR (100 MHz, $CDCl_3$)** δ ppm: 155.6, 155.6, 145.6, 145.2, 138.8, 138.4, 137.5, 136.1, 135.9, 134.7, 134.4, 132.4, 131.3, 127.6, 127.4, 127.2, 127.1, 114.7, 113.8, 90.1, 79.0, 78.2, 43.5, 43.3, 41.0, 40.5, 38.0, 37.6, 33.4, 32.5, 29.2, 29.2, 28.9, 25.8, 25.5, 25.4, 25.2, 25.1, 24.6, 23.4, 21.4, 21.2, 21.1, 20.8, 18.1. **IR ($CH_2Cl_2$):** 3083, 2980, 2931, 1802, 1640, 1455, 1372, 1344, 1264, 1223, 1175, 1142, 1127, 1070, 1052, 1014, 973 cm$^{-1}$. **HRMS (EI):** Calcd for $C_{27}H_{38}O_3^+$ [M]$^+$, 410.2821; found, 428.2810.

*4.10. (4R*,5R*)-7-((E)-hepta-1,6-dienyl)-6,6,8-trimethyl-4-((6R*S*)-methyl-6-vinylcyclohex-1-enyl)-1,3-dioxaspiro[4.5]dec-7-en-2-one (**21**)*

To a solution of **20** (30 mg, 0.080 mmol) in DMF (0.5 mL) were added NaH (60% in mineral oil, 7.5 mg, 0.18 mmol, 2.2 equiv) and 1,2-diimidazocarbonyle (65 mg, 0.40 mmol, 5 equiv). The resulting solution was stirred at rt for 1.5 h, and then diluted with $Et_2O$, washed with saturated aqueous $NH_4Cl$ and brine, filtered and concentrated *in vacuo*. The crude mixture was then purified by flash chromatography on silica gel ($Et_2O$/petroleum ether 5:95) to afford **21** (26 mg, 81%, 1:1 mixture of diastereomers) as a pale yellow oil. **$^1$H NMR (400 MHz, $CDCl_3$)** δ ppm: 5.93 (t, *J* = 4.0 Hz, 0.5H), 5.90 (t, *J* = 4.0 Hz, 0.5H), 5.63–5.86 (m, 3H), 5.36 (dtd, *J* = 15.7, 6.9, 4.4 Hz, 1H), 4.95-5.19 (m, 4H), 4.92 (s, 0.5H), 4.86 (s, 0.5H), 2.12 (m, 10H), 1.65 (s, 1.5H), 1.64 (s, 1.5H), 1.60 (m, 2H), 1.51 (m, 4H), 1.27, 1.08, 1.07, 1.07, 1.02 (5s, 9H). **$^{13}$C NMR (100 MHz, $CDCl_3$)** δ ppm: 155.6, 155.6, 145.6, 145.2, 138.8, 138.4, 137.5, 136.1, 135.9, 134.7, 134.4, 132.4, 131.3, 127.6, 127.4, 127.2, 127.1, 114.7, 113.8, 90.1, 79.0, 78.2, 43.5, 43.3, 41.0, 40.5, 38.0, 37.6, 33.4, 32.5, 29.2, 29.2, 28.9, 25.8, 25.5, 25.4, 25.2, 25.1, 24.6, 23.4, 21.4, 21.2, 21.1, 20.8, 18.1. **IR ($CH_2Cl_2$):** 3083, 2980, 2931, 1802, 1640, 1455, 1372, 1344, 1264, 1223, 1175, 1142, 1127, 1070, 1052, 1014, 973 cm$^{-1}$. **HRMS (EI):** Calcd for $C_{27}H_{38}O_3^+$ [M]$^+$, 410.2821; found, 428.2810.

*4.11. (Z)-3-(3,3,7,7,9-Pentamethyl-1,5-dioxaspiro[5.5]undec-8-en-8-yl)prop-2-en-1-ol (**23**)*

To a slurry of LiCl (330 mg, 8 mmol, 6 equiv) and $Pd(PPh_3)_4$ (150 mg, 0.13 mmol, 0.10 equiv) in THF (20 mL) was added vinyltriflate **13** (469 mg, 1.3 mmol) and stannane **22** (1.3 g, 3.7 mmol, 2.8 equiv). The resulting mixture was heated to reflux under argon for 2 days, with extra addition of *ca.* 0.1 equiv of $d(PPh_3)_4$ after one day. The resulting solution was washed with water, with a 5% aqueous ammonium hydroxide solution, and with brine, filtered and concentrated *in vacuo*. The crude mixture was then purified by flash chromatography on silica gel ($Et_2O$/petroleum ether 30:70) to afford **23** (218 mg, 62%, *E*/*Z* = 1:10) as a colourless oil.**$^1$H NMR (400 MHz, $CDCl_3$)** δ ppm: 5.96 (dd, *J* = 11.3, 1.1 Hz, 1H), 5.74 (dt, *J* = 11.4, 6.3 Hz, 1H), 4.02 (d, *J* = 6.0 Hz, 2H), 3.69 (d, *J* = 11.2 Hz, 2H), 3.36 (d, *J* = 11.5 Hz, 2H), 2.06 (m, 4H), 1.52 (s, 3H), 1.18 (s, 3H), 1.07 (s, 6H), 0.72 (s, 3H). **$^{13}$C NMR (100 MHz, $CDCl_3$)** δ ppm: 133.7, 131.2, 129.0, 127.6, 100.1, 70.3, 60.6, 43.5, 30.0, 29.4, 23.3, 22.3, 20.8, 18.4. **HRMS (EI):** Calcd for $C_{17}H_{28}O_3^+$ [M]$^+$, 280.2039; found, 280.2035.

*4.12. (Z)-3-(3-(Allyloxy)prop-1-enyl)-2,2,4-trimethylcyclohex-3-enone (**S2**)*

To a solution of **23** (218 mg, 0.80 mmol) in THF (5 mL) was added sodium hydride, 60% in mineral oil, (65 mg, 1.6 mmol, 2.0 equiv) at 0°C. The mixture was stirred at 0°C for 30 min, and allyl bromide (90 µl, 1.0 mmol, 1.3 equiv) was added dropwise. The mixture was stirred at reflux overnight. The reaction was quenched with water and extracted with $Et_2O$. The combined organic layers were washed with water and with brine, and dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* to give a yellow oil that was purified by flash chromatography on silica gel ($Et_2O$/petroleum ether 5:95) to afford **24** (156 mg, 63%) as a colourless oil. $^1$H NMR (400 MHz, $CDCl_3$) δ ppm: 6.0 (d, *J* = 11.5 Hz, 1H), 5.92 (ddt, *J* = 17.2, 10.5, 5.6 Hz), 5.75 (dt, *J* = 11.5, 6.2 Hz, 1H), 5.27 (ddd, *J* = 17.3, 3.3, 1.6 Hz, 1H), 5.17 (ddd, *J* = 10.4, 2.9, 1.3 Hz, 1H), 3.96 (dt, *J* = 5.6, 2.3 Hz, 2H), 3.87 (dd, *J* = 6.2, 1.5 Hz, 2H), 3.71 (d, *J* = 11.3 Hz, 2H), 3.38 (d, *J* = 11.5 Hz, 2H), 2.03–2.22 (m, 4H), 1.51 (s, 3H), 1.20 (s, 3H), 1.09 (s, 6H), 0.74 (s, 3H). To a solution of **24** (140 mg, 0.44 mmol) in a 10:1 mixture of acetone/water (11 mL) was added a catalytic amount of *p*-toluenesulfonic acid monohydrate. The mixture was stirred at 20°C for 2 h, concentrated, diluted in a saturated aqueous $NaHCO_3$ solution, and extracted with $Et_2O$. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* to give a yellow oil that was purified by flash chromatography on silica gel ($Et_2O$/petroleum ether 10:90) to afford **S2** (85 mg, 83%) as a pale yellow oil. **$^1$H NMR (400 MHz, $CDCl_3$)** δ ppm: 5.96 (d, *J* = 12.5 Hz), 5.85 (m, 2H), 5.24 (dd, *J* = 17.2, 1.6 Hz, 1H), 5.15 (dd, *J* = 10.4, 1.2 Hz, 1H), 3.94 (d, *J* = 5.6 Hz, 2H), 3.87 (dd, *J* = 6.2, 1.5 Hz, 2H), 2.55 (t, *J* = 7.0 Hz, 2H), 2.39 (t, *J* = 6.7 Hz, 2H), 1.60 (s, 3H), 1.13 (s, 6H). **$^{13}$C NMR (100 MHz, $CDCl_3$)** δ ppm: 214.8, 134.8, 134.3, 130.7, 129.6, 128.0, 117.0, 71.6, 67.6, 47.0, 35.9, 31.4, 24.6, 21.0. **IR ($CH_2Cl_2$):** 3401, 2975, 2927, 2853, 2733, 1856, 1709, 1453, 1359, 1260, 1081, 1004 cm$^{-1}$. **HRMS (EI):** Calcd for $C_{15}H_{22}O_2^+$ [M]$^+$, 234.1620; found, 234.1620.

*4.13. (Z)-3-(3-(Allyloxy)prop-1-enyl)-2,2,4-trimethyl-1-(trimethyl silyloxy)cyclohex-3-enecarbonitrile (**S3**)*

To a solution of **S2** (42 mg, 0.18 mmol) in $CH_2Cl_2$ (2 mL) was added a catalytic amount of zinc iodide and trimethylsilylcyanide (40 µl, 0.30 mmol, 1.5 equiv). The mixture was stirred at 20°C for 2 h, and the solvent was removed *in vacuo* to give a yellow oil that was purified by flash chromatography on silica gel ($Et_2O$/petroleum ether 2:98) to afford **S3** (41 mg, 68%) as a pale yellow oil. **$^1$H NMR (400 MHz, $CDCl_3$)** δ ppm: 5.93 (m, 2H), 5.79 (dt, *J* = 11.4, 6.3 Hz, 1H), 5.27 (ddd, *J* = 17.2, 3.2, 1.6 Hz, 1H), 5.17 (ddd, *J* = 10.4, 2.8, 1.2 Hz, 1H), 3.96 (d, *J* = 5.6 Hz, 2H), 3.85 (d, *J* = 6.1 Hz, 2H), 2.34 (m, 1H), 2.19 (m, 1H), 2.05 (dd, *J* = 8.4, 5.5 Hz, 2H), 1.53 (s, 3H), 1.20 (s, 3H), 1.02 (s, 3H), 0.26 (s, 9H). **$^{13}$C NMR (100 MHz, $CDCl_3$)** δ ppm: 134.9, 132.4, 130.4, 128.7, 128.0, 121.4, 117.1, 76.1, 71.8, 68.0, 42.7, 30.9, 29.8, 29.1, 22.4, 20.9, 1.4. **HRMS (EI):** Calcd for $C_{19}H_{31}NO_2Si^+$ $[M]^+$, 333.2124; found, 333.2139.

*4.14. (Z)-3-(3-(allyloxy)prop-1-enyl)-2,2,4-trimethyl-1-(trimethylsilyloxy)cyclohex-3-enecarbaldehyde (**25**)*

To a solution of **S3** (160 mg, 0.48 mmol) in hexane (10 mL) at -78°C was added DIBAL-H (1 M in hexane, 0.9 mL, 1.9 equiv). The solution was stirred at -78°C for 7h. $SiO_2$ (2 g) was then added and the resulting mixture was stirred at rt overnight. $MgSO_4$ was then added, and the solution was filtered and concentrated *in vacuo* to give a yellow oil that was purified by flash chromatography on silica gel ($Et_2O$/petroleum ether 2:98) to afford **25** (109 mg, 68%) as a colourless oil. **$^1$H NMR (400 MHz, $CDCl_3$)** δ ppm: 9.79 (s, 1H), 5.98 (d, *J* = 11.6 Hz,1H), 5.89 (ddd, *J* = 16.1, 10.9, 5.8 Hz, 1H), 5.76 (td, *J* = 11.4, 6.5 Hz, 1H), 5.25 (dd, *J* = 17.2, 1.4 Hz, 1H), 5.16 (dd, *J* = 10.4, 1.1 Hz, 1H), 3.94 (d, *J* = 5.5 Hz, 2H), 3.84 (d, *J* = 5.9 Hz, 2H), 2.16 (bs, 2H), 1.90 (m, 2H), 1.52 (m, 2H), 1.02 (s, 3H), 0.96 (s, 3H), 0.13 (s, 9H). **$^{13}$C NMR (100 MHz, $CDCl_3$)** δ ppm: 204.8, 134.9, 133.4, 129.9, 128.9, 128.1, 117.0, 83.1, 71.6, 67.7, 41.2, 29.1, 27.5, 23.7, 20.9, 2.5. **IR ($CH_2Cl_2$):** 2959, 2730, 1729, 1647, 1448, 1384, 1329, 1251, 1084 $cm^{-1}$. **HRMS (EI):** Calcd for $C_{19}H_{32}O_3Si^+$ $[M]^+$, 336.2121; found, 336.2123.

*4.15. 3-(3,3,7,7,9-Pentamethyl-1,5-dioxaspiro[5.5]undec-8-en-8-yl)prop-2-yn-1-ol (**26**)*

To a solution of **13** (200 mg, 0.54 mmol), potassium carbonate (220 mg, 1.6 mmol, 3.0 equiv) and $Pd(PPh_3)_4$ (125 mg, 0.10 mmol, 0.20 equiv) in DMF (6 mL) was added propargyl alcohol (100 µL, 1.6 mmol, 3.0 equiv). The resulting mixture was stirred at 60°C overnight. The reaction was quenched with water and extracted with $Et_2O$. The combined organic layers were washed with water and with brine, and dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* to give a yellow oil that was purified by flash chromatography on silica gel ($Et_2O$/petroleum ether 3:7) to afford **26** (103 mg, 69%) as a colourless oil.**$^1$H NMR (400 MHz, $CDCl_3$)** δ ppm: 4.41 (s, 2H), 3.66 (d, *J* = 11.2 Hz, 2H), 3.36 (d, *J* = 11.5 Hz, 2H), 2.06 (s, 4H), 1.98 (bs, 1H), 1.86 (s, 3H), 1.19 (s, 6H), 1.18 (s, 3H), 0.72 (s, 3H). **$^{13}$C NMR (100 MHz, $CDCl_3$)** δ ppm: 139.8, 122.6, 99.6, 90.5, 84.1, 70.3, 51.7, 43.1, 29.9, 29.6, 23.2, 22.3, 22.2, 18.3. **IR ($CH_2Cl_2$):** 3668, 3608, 2958, 2863, 2211, 1712, 1675, 1603, 1469, 1380, 1215, 1187, 1111, 1065, 1010 $cm^{-1}$. **HRMS (EI):** Calcd for $C_{17}H_{26}O_3^+$ $[M]^+$, 278.1882; found, 278.1881.

*4.16. (Z)-3-(3-Hydroxyprop-1-enyl)-2,2,4-trimethylcyclohex-3-enone (**27**)*

A thoroughly degassed solution of **26** (428 mg, 1.50 mmol) and Lindlar catalyst (100 mg) in $Et_2O$ was stirred under $H_2$ atmosphere for 2 h. The resulting mixture was then filtrated through Celite and concentrated *in vacuo* to give a sticky colourless oil that was diluted in a 10:1 mixture of acetone/water (17 mL). To this solution was added a catalytic amount of *p*-toluenesulfonic acid monohydrate. The mixture was stirred overnight at 20°C, concentrated, diluted in a saturated aqueous $NaHCO_3$ solution, and extracted with $Et_2O$. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* to give a yellow oil that was purified by flash chromatography on silica gel ($Et_2O$/petroleum ether 10:90) to afford **27** (432 mg, 99%) as a colourless oil.**$^1$H NMR (400 MHz, $CDCl_3$)** δ ppm: 5.95 (d, *J* = 11.4 Hz, 1H), 5.85 (dt, *J* = 11.3, 5.8 Hz, 1H), 4.07 (d, *J* = 6.3 Hz, 2H), 2.58 (t, *J* = 7.0 Hz, 2H), 2.42 (t, *J* = 6.7 Hz, 2H), 1.64 (s, 3H), 1.16 (s, 6H). **$^{13}$C NMR (100 MHz, $CDCl_3$)** δ ppm: 214.7, 134.4, 132.6, 129.7, 127.6, 60.5, 46.9, 36.0, 31.4, 24.6, 21.1. **IR ($CH_2Cl_2$):** 3683, 3610, 3525, 3064, 3048, 2973, 2932, 1710, 1606, 1464, 1376, 1267, 1090, 1014 $cm^{-1}$. **HRMS (EI):** Calcd for $C_{12}H_{18}O_2^+$ $[M]^+$, 194.1307; found, 194.1307.

*4.17. (Z)-3-(3-(tert-Butyldimethylsilyloxy)prop-1-enyl)-2,2,4-trimethylcyclohex-3-enone (**S4**)*

To a solution of **27** (0.43 g, 2.2 mmol) and imidazole (0.25 g, 3.7 mmol, 1.7 equiv) in DMF (15 mL) was added TBSCl (0.50 g, 3.3 mmol, 1.5 equiv) at 0°C. The resulting mixture was stirred overnight at rt. The reaction was quenched with saturated aqueous $NH_4Cl$, and the aqueous phase was extracted with $Et_2O$. The combined organic layers were washed with water and with brine, and dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* to give a yellow oil that was purified by flash chromatography on silica gel ($Et_2O$/petroleum ether 5:95) to afford **S4** (0.63 mg, 94%) as a colourless oil. **$^1$H NMR (400 MHz, $CDCl_3$)** δ ppm: 5.87 (dd, *J* = 11.5, 1.1 Hz, 1H), 5.78 (dt, *J* = 11.6, 5.9 Hz, 1H), 4.05 (dd, *J* = 5.6, 1.4 Hz, 2H), 2.57 (t, *J* = 7.0 Hz, 2H), 2.41 (t, *J* = 7.0 Hz, 2H), 1.63 (s, 3H), 1.16 (s, 6H), 0.90 (s, 9H), 0.06 (s, 6H). **$^{13}$C NMR (100 MHz, $CDCl_3$)** δ ppm: 215.0, 134.6, 133.7, 129.4, 126.0, 60.9, 47.2, 36.1, 31.4, 26.0, 24.7, 21.1, 18.4, -5.0. **IR ($CH_2Cl_2$):** 3048, 2955, 2931, 2857, 1714, 1464, 1384, 1168, 1075 $cm^{-1}$. **HRMS (EI):** Calcd for $C_{18}H_{32}O_2Si^+$ $[M]^+$, 308.2172; found, 308.2169.

*4.18. (Z)-3-(3-(tert-Butyldimethylsilyloxy)prop-1-enyl)-2,2,4-trimethyl-1-(trimethylsilyloxy) cyclohex-3-enecarbonitrile (**28**)*

To a solution of **S4** (210 mg, 0.68 mmol) in $CH_2Cl_2$ (10 mL) was added a catalytic amount of zinc iodide and trimethylsilylcyanide (150 µl, 1.0 mmol, 1.5 equiv). The mixture was stirred at 20°C for 2 h, and the solvent was removed *in vacuo* to give a yellow oil that was purified by flash chromatography on silica gel ($Et_2O$/petroleum ether 2:98) to afford **28** (250 mg, 91%) as a pale yellow oil. **$^1$H NMR (400 MHz, $CDCl_3$)** δ ppm: 5.83 (d, *J* = 11.5 Hz, 1H), 5.72 (td, *J* = 11.4, 5.9 Hz, 1H), 4.02 (dd, *J* = 6.0, 1.3 Hz, 2H), 2.33 (m, 1H), 2.17 (m, 1H), 2.05 (dd, *J* = 8.3, 5.6 Hz, 2H), 1.54 (s, 3H), 1.20 (s, 3H), 1.02 (s, 3H), 0.90 (s, 9H), 0.26 (s, 9H), 0.06 (s, 6H). **$^{13}$C NMR (100 MHz, $CDCl_3$)** δ ppm: 133.4, 132.5, 127.7, 126.5, 121.3, 76.6, 60.8, 42.8, 31.0, 29.1, 26.1, 22.4, 20.9, 18.4, 1.4, -5.0, -5.1. **IR ($CH_2Cl_2$):** 2960, 2857, 2230, 1940, 1718, 1648, 1471, 1406, 1386, 1361, 1258, 1090 $cm^{-1}$. **HRMS (EI):** Calcd for $C_{22}H_{41}O_2NSi_2^+$ $[M]^+$, 407.2676; found, 407.2677.

*4.19. (Z)-3-(3-(tert-Butyldimethylsilyloxy)prop-1-enyl)-2,2,4-trimethyl-1-(trimethylsilyloxy)cyclohex-3-enecarbaldehyde (**29**)*

To a solution of **28** (0.45 g, 1.1 mmol) in hexane (22 mL) at -78°C was slowly added DIBAL-H (2.2 mL, 1 M in hexane, 2.2 mmol, 2 equiv). The mixture was stirred at this temperature for 5h, and $SiO_2$ (1 g) was added. The mixture was then allowed to warm to rt overnight. Anhydrous $MgSO_4$ was added and the mixture was stirred for 1h. The solids were filtered off, and the solvent was removed *in vacuo* to give an oil that was purified by flash

chromatography on silica gel ($Et_2O$/petroleum ether 1:99) to afford **29** (0.25 g, 56%) as a colourless oil. **$^1$H NMR (400 MHz, $CDCl_3$)** δ ppm: 9.81 (s, 1H), 5.86 (dd, *J* = 11.4, 1.0 Hz, 1H), 5.72 (dt, *J* = 11.4, 6.0 Hz, 1H), 4.01 (m, 2H), 2.17 (m, 2H), 1.98–1.84 (m, 2H), 1.54 (s, 3H), 1.03 (s, 3H), 0.97 (s, 3H), 0.90 (s, 9H), 0.15 (s, 9H), 0.06 (s, 6H). **$^{13}$C NMR (100 MHz, $CDCl_3$)** δ ppm: 204.9, 133.6, 133.0, 128.0, 126.8, 83.2, 60.9, 41.3, 29.1, 27.6, 26.1, 23.8, 21.0, 18.5, 2.5, -5.0. **IR ($CH_2Cl_2$):** 2957, 2931, 2857, 1729, 1471, 1463, 1384, 1361, 1252, 1174, 1086 cm$^{-1}$. **HRMS (EI):** Calcd for $C_{21}H_{39}O_2NSi_2^+$ $[M\text{-}CH_3]^+$, 395.2438; found, 395.2463.

*4.20. (R*)-3-((Z)-3-(tert-Butyldimethylsilyloxy)prop-1-enyl)-2,2,4-trimethyl-1-((R*)-((6R*S*)-methyl-6-vinylcyclohex-1-enyl)(trimethylsilyloxy)methyl)cyclohex-3-enol (**S5**)*

To a solution of hydrazine **13** (0.78 g, 1.9 mmol, 2 equiv) in THF (7 mL) at -78°C was added dropwise *t*BuLi (2.6 mL, 1.6 M in pentane, 4.2 mmol, 4.5 equiv). The solution turned orange and nitrogen bubbles appeared. The solution was stirred at this temperature for 30 min, warmed for a few minutes to room temperature, and cooled down to -78°C. A solution of aldehyde **29** (0.38 g, 0.93 mmol) in THF (1 mL) was then added *via* canula. The resulting mixture became yellow and was stirred at -78°C for 30 min. The reaction was quenched with saturated aqueous $NaHCO_3$. The aqueous layer was extracted with $Et_2O$, and the combined organic extracts were washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The crude mixture was then purified by flash chromatography on silica gel ($Et_2O$/petroleum ether 1:99) to afford **S5** (0.43 g, 88%, 1:1 mixture of diastereomers) as a colourless oil. **$^1$H NMR (400 MHz, $CDCl_3$)** δ ppm: 6.02 (m, 1.5H), 5.88 (d, *J* = 10.4 Hz, 1.5H), 5.65 (td, *J* = 11.4, 5.8 Hz, 1H), 5.04 (m, 2H), 4.42 (s, 0.5H), 4.41 (s, 0.5H), 4.01 (t, *J* = 4.8 Hz, 2H), 3.88 (s, 0.5H), 3.69 (s, 0.5H), 2.35–1.99 (m, 3H), 1.92–1.83 (m, 1H), 1.70–1.44 (m, 6H), 1.52 (s, 1.5H), 1.50 (s, 1.5H), 1.28, 1.10, 1.05, 1.04, 1.00, 0.96 (6s, 9H), 0.96 (s, 9H), 0.14 (s, 4.5H), 0.12 (s, 4.5H), 0.04 (s, 6H). **$^{13}$C NMR (100 MHz, $CDCl_3$)** δ ppm: 147.3, 141.9, 141.4, 133.9, 133.8, 132.1, 132.0, 129.7, 128.9, 128.6, 112.6, 111.8, 76.3, 76.3, 75.9, 60.9, 44.3, 44.3, 40.6, 40.3, 38.8, 38.1, 29.2, 29.0, 28.3, 28.1, 26.3, 26.1, 25.9, 25.5, 24.5, 24.5, 21.2, 18.6, 18.4, 18.3, 1.4, 1.3, -5.0, -5.1. **IR ($CDCl_3$):** 3482, 2958, 2857, 1934, 1840, 1706, 1651, 1633, 1471, 1376, 1361, 1302, 1252, 1080 cm$^{-1}$. **HRMS (EI):** Calcd for $C_{31}H_{56}O_3Si_2^+$ $[M]^+$, 532.3768; found, 532.3762.

*4.21. (R*)-1-((R*)-Hydroxy((6R*S*)-methyl-6-vinylcyclohex-1-enyl)methyl)-3-((Z)-3-hydroxyprop-1-enyl)-2,2,4-trimethylcyclohex-3-enol (**30**)*

To a solution of **S5** (312 mg, 0.58 mmol) in THF (10 mL) was added tetrabutylammonium fluoride (1.8 mL, 1 M in THF, 1.8 mmol, 3 equiv). The mixture was stirred overnight at rt. The reaction was quenched with saturated aqueous $NH_4Cl$. The aqueous layer was extracted with $Et_2O$, and the combined organic extracts were washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The crude mixture was then purified by flash chromatography on silica gel (EtOAc/petroleum ether 4:6) to afford **30** (193 mg, 96%) as a white solid. **$^1$H NMR (400 MHz, $CDCl_3$)** δ ppm: 6.33 (m, 1H), 5.88–6.01 (m, 1.5H), 5.73-5.80 (m, 1.5H), 5.02–5.14 (m, 2H), 4.19 (s, 0.5H), 4.18 (s, 0.5H), 4.05 (s, 2H), 2.97 (s, 0.5H), 2.90 (s, 0.5H), 1.75–2.26 (m, 6H), 1.51–1.64 (m, 6H), 1.56 (s, 1.5H), 1.54 (s, 1.5H), 1.27, 1.19, 1.16, 1.11, 1.05, 1.00 (6s, 9H). **$^{13}$C NMR (100 MHz, $CDCl_3$)** δ ppm: 146.8, 146.7, 146.0, 145.5, 131.0, 130.9, 129.9, 128.9, 128.8, 128.5, 127.8, 112.9, 112.6, 76.4, 76.3, 71.0, 60.7, 44.1, 41.4, 41.2, 38.0, 37.6, 28.4, 28.0, 25.9, 25.9, 25.8, 24.6, 24.0, 21.1, 20.9, 18.5, 18.5, 14.2. **IR ($CDCl_3$):** 3614, 2966, 2934, 1709, 1633, 1453, 1374, 1314, 1249, 1194, 1086, 1007 cm$^{-1}$. **HRMS (EI):** Calcd for $C_{22}H_{34}O_3^+$ $[M]^+$, 346.2510; found, 346.2508.

*4.22. (Z)-3-((4R*,5R*)-6,6,8-Trimethyl-4-((6R*S*)-methyl-6-vinylcyclohex-1-enyl)-2-oxo-1,3-dioxaspiro[4.5]dec-7-en-7-yl)allyl 1H-imidazole-1-carboxylate (**S6**)*

To a solution of **30** (50 mg, 0.14 mmol) in DMF (2 mL) was added sodium hydride (20 mg, 60% in mineral oil, 0.5 mmol, 3.5 equiv) and carbonyl diimidazole (120 mg, 0.7 mmol, 5.0 equiv). The mixture was stirred at rt for 3h. The reaction was quenched with saturated aqueous $NH_4Cl$. The aqueous layer was extracted with $Et_2O$, and the combined organic extracts were washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The crude mixture was then purified by flash chromatography on silica gel (EtOAc/petroleum ether 2:8 to 4:6) to afford **S6** (55 mg, 85%) as a sticky colourless oil. **$^1$H NMR (400 MHz, $CDCl_3$)** δ ppm: 8.10 (s, 1H), 7.40 (s, 1H), 7.05 (s, 1H), 6.15 (t, *J* = 8.9 Hz, 1H), 5.87 (m, 2H), 5.68 (m, 1H), 5.08 (m, 2H), 4.93 (s, 0.5H), 4.87 (s, 0.5H), 4.77 (m, 2H), 2.30 (m, 1H), 2.17 (m, 3H), 1.56 (s, 1.5H), 1.55 (s, 1.5H), 1.47–1.70 (m, 6H), 1.25, 1.23, 1.21, 1.09, 1.06 (5s, 9H). **$^{13}$C NMR (100 MHz, $CDCl_3$)** δ ppm: 155.2, 148.7, 145.5, 145.2, 138.2, 137.3, 137.2, 132.6, 131.5, 130.7, 125.5, 125.4, 117.2, 114.8, 114.1, 89.6, 78.8, 77.9, 65.3, 65.3, 43.5, 41.0, 40.5, 38.0, 37.6, 28.9, 25.7, 25.5, 24.8, 23.3, 20.8, 18.0, 18.0, 14.2. **IR ($CDCl_3$):** 3669, 3536, 3166, 3140, 3086, 2939, 2250, 1797, 1653, 1634, 1529, 1472, 1388, 1348, 1318, 1236, 1178, 1128, 1096, 1051, 999 cm$^{-1}$. **HRMS (EI):** Calcd for $C_{27}H_{34}N_2O_5^+$ $[M]^+$, 466.2468; found, 466.2468.

*4.23. (4R*,5R*)-7-((Z)-3-Hydroxyprop-1-enyl)-6,6,8-trimethyl-4-((6R*S*)-methyl-6-vinylcyclohex-1-enyl)-1,3-dioxaspiro[4.5]dec-7-en-2-one (**31**)*

To a solution of **S6** (0.20 g, 0.43 mmol) in dioxane (12 mL) and water (12 mL) was added concentrated hydrochloric acid (0.4 mL). The mixture was stirred overnight at rt. The reaction was quenched with saturated aqueous $NaHCO_3$. The aqueous layer was extracted with $Et_2O$, and the combined organic extracts were washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* to afford **31** (160 mg, quant.) as a white solid. **$^1$H NMR (400 MHz, $CDCl_3$)** δ ppm: 5.60–5.91 (m, 5H), 5.07 (m, 2H), 4.91 (s, 0.5H), 4.86 (s, 0.5H), 3.90 (d, *J* = 6.11 Hz), 2.05–2.38 (m, 4H), 1.55–1.72 (m, 6H), 1.50 (s, 1.5H), 1.49 (s, 1.5H), 1.24, 1.23, 1.17, 1.12, 1.06, 1.05 (6s, 9H). **$^{13}$C NMR (100 MHz, $CDCl_3$)** δ ppm: 155.5, 154.2, 145.5, 145.1, 138.3, 137.3, 132.6, 132.5, 132.4, 132.3, 131.3, 129.0, 128.9, 127.8, 114.6, 114.0, 89.9, 88.2, 78.9, 78.0, 60.1, 60.1, 43.4, 40.9, 40.9, 40.5, 40.4, 37.9, 37.6, 30.1, 29.2, 29.1, 28.8, 27.4, 25.9, 25.7, 25.5, 24.6, 23.8, 23.6, 23.3, 20.9, 20.8, 20.7, 18.0, 14.2. **IR ($CDCl_3$):** 3610, 3094, 3045, 2982, 2935, 1788, 1466, 1423, 1347, 1227, 1177, 1048, 1011 cm$^{-1}$. **HRMS (EI):** Calcd for $C_{23}H_{32}O_4^+$ $[M]^+$, 372.2301; found, 372.2304.

*4.24. (4R*,5R*)-7-((Z)-3-(Allyloxy)prop-1-enyl)-6,6,8-trimethyl-4-((6R*S*)-methyl-6-vinylcyclohex-1-enyl)-1,3-dioxaspiro[4.5]dec-7-en-2-one (**32**)*

To a solution of **31** (0.12 g, 0.33 mmol) in THF (10 mL) was added sodium hydride, 60% in mineral oil, (16 mg, 0.4 mmol, 1.2 equiv) and a catalytic amount of tetrabutylammonium iodide. The mixture was stirred for 30 min, and allyl bromide (50 µl, 0.6 mmol, 1.7 equiv) was added dropwise. The mixture was stirred at reflux overnight. The reaction was quenched with water and extracted with $Et_2O$. The combined organic layers were washed with water and with brine, and dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* to give a yellow oil that was purified by flash chromatography on silica gel ($Et_2O$/petroleum ether 5:95) to afford **32** (0.11 mg, 83%) as a colourless oil. **$^1$H NMR (400 MHz, $CDCl_3$)** δ ppm: 5.63-5.99 (m, 5H), 5.00-5.29 (m, 4H), 4.93 (s, 0.5H), 4.88 (s, 0.5H), 3.95 (d, *J* = 5.4 Hz, 2H), 3.85 (m, 2H), 2.30 (m, 1H), 1.95–2.22 (m, 3H), 1.52 (s, 1.5H), 1.51 (s, 1.5H), 1.49–

1.70 (m, 6H), 1.26 (s, 3H), 1.09 (s, 6H). **$^{13}$C NMR (100 MHz, $CDCl_3$)** δ ppm: 155.4, 145.5, 145.2, 138.4, 137.5, 134.9, 134.9, 132.4, 131.4, 130.5, 130.4, 129.0, 117.0, 114.7, 114.0, 89.9, 88.3, 78.9, 78.0, 71.8, 71.8, 67.6, 43.6, 41.0, 40.5, 38.1, 37.7, 32.0, 29.8, 29.7, 29.4, 29.3, 28.9, 25.8, 25.6, 24.7, 23.4, 22.7, 20.8, 20.8, 18.1, 18.1, 14.2. **IR ($CDCl_3$):** 2936, 2870, 1784, 1649, 1635, 1466, 1371, 1348, 1275, 1228, 1178, 1127, 1068, 1051, 1014 cm$^{-1}$. **HRMS (EI):** Calcd for $C_{26}H_{36}O_4^+$ $[M]^+$, 412.2614; found, 412.2614.

*4.25. 2,2-Dimethylcyclohexane-1,3-dione (**S8**)*[30]

To a stirred solution of diketone **S7** (25.0 g, 198 mmol) in acetone (30 mL) was added $K_2CO_3$ (54.8 g, 396 mmol, 2.0 equiv) and MeI (31 mL, 490 mmol, 2.5 equiv). The reaction mixture was refluxed for 20h. The resulting mixture was filtered, and the filter cake was washed with $Et_2O$. Brine was added to the filtrate and the aqueous layer was extracted with $Et_2O$. The combined organic extracts were washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The crude mixture was then purified by flash chromatography on silica gel (EtOAc/petroleum ether 2:8) to afford the diketone **S8** as a white solid (27.8 g, quant.). **$^1$H NMR (400 MHz, $CDCl_3$)** δ ppm: 2.72–2.62 (m, 4H), 1.99–1.87 (m, 2H), 1.29 (s, 6H). **$^{13}$C NMR (100 MHz, $CDCl_3$)** δ ppm: 210.3, 61.6, 37.2, 22.1, 17.9. **IR (thin film):** 1695, 910 cm$^{-1}$. **HRMS (EI):** Calcd for $C_8H_{12}O_2^+$ $[M]^+$, 140.0837; found, 140.0843.

*4.26. 3,3,7,7-Tetramethyl-1,5-dioxaspiro[5.5]undecan-8-one (**S9**)*[31]

To a stirred solution of diketone **S8** (8.80 g, 62.8 mmol) in $CH_2Cl_2$ (130 mL) was added 2,2-dimethylpropane-1,3-diol (19.9 g, 191 mmol, 3.04 equiv) and *p*-toluenesulfonic acid (200 mg, 1.05 mmol, 0.016 equiv). The reaction mixture refluxed for 4h. The solvent was removed under reduced pressure and the resulting mixture was diluted with hexane and washed with brine. The organic layer was dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure to afford the acetal **S9** as a white crystalline solid (12.7 g, 90%). **$^1$H NMR (400 MHz, $CDCl_3$)** δ ppm: 3.62 (d, $J$ = 11.1 Hz, 2H), 3.32 (dd, $J$ = 10.3, 1.3 Hz, 2H), 2.40 (t, $J$ = 7.0 Hz, 2H), 2.24–2.15 (m, 2H), 1.72–1.61 (m, 2H), 1.19 (s, 6H), 1.15 (s, 3H), 0.71 (s, 3H). **$^{13}$C NMR (100 MHz, $CDCl_3$)** δ ppm: 213.3, 101.9, 70.2, 55.4, 36.4, 29.8, 23.2, 22.3, 20.7, 19.4, 18.7. **IR (thin film):** 1674, 1112, 910 cm$^{-1}$. **HRMS (ESI):** Calcd for $C_{13}H_{22}NaO_3^+$ $[M+Na]^+$, 249.1461; found, 249.1464. **MP:** 67°C.

*4.27. 3,3,7,7,9-Pentamethyl-1,5-dioxaspiro[5.5]undecan-8-one (**S10**)*[20]

To a stirred solution of freshly distilled DIPA (2.45 mL, 17.5 mmol, 1.23 equiv) in THF (33 mL) at -78°C was slowly added *n*-BuLi (12.5 mL, 1.41 M in hexane, 17.6 mmol, 1.23 equiv). The resulting solution was stirred at -78°C for 30 min and then treated with a solution of ketone **S9** (3.23 g, 14.2 mmol) in THF (10 mL). The reaction mixture was allowed to warm up to room temperature and stirred for 40 min. The resulting yellow solution was cooled down to -78°C and MeI (1.40 mL, 22.5 mmol, 1.60 equiv) was added to the reaction mixture. The reaction mixture was allowed to warm to room temperature and was then stirred for 1h. A saturated aqueous solution of $NaHCl_4$ was added and the aqueous layer was extracted with $Et_2O$. The combined organic extracts were washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The crude mixture was then purified by flash chromatography on silica gel ($Et_2O$/petroleum ether 1:9) to afford the ketone **S10** as a white crystalline solid (3.83 g, 91%). **$^1$H NMR (400 MHz, $CDCl_3$)** δ ppm: 3.71 (d, $J$ = 11.3 Hz, 1H), 3.50 (d, $J$ = 11.3 Hz, 1H), 3.37–3.25 (m, 2H), 2.74–2.66 (m, 1H), 2.64–2.53 (m, 1H), 1.87–1.80 (m, 1H), 1.77–1.73 (m, 1H), 1.29–1.22 (m, 1H), 1.20 (s, 3H), 1.18 (s, 3H), 1.14 (s, 3H), 1.01 (d, $J$ = 6.5 Hz, 3H), 0.70 (s, 3H). **$^{13}$C NMR (100 MHz, $CDCl_3$)** δ ppm: 214.0, 102.2, 70.5, 69.7, 55.0, 39.2, 29.8, 27.8, 23.2, 22.3, 21.1, 16.3, 14.9. **IR (thin film):** 2954, 1708, 1128, 1112, 1087, 1029 cm$^{-1}$. **HRMS (ESI):** Calcd for $C_{14}H_{24}NaO_3^+$ $[M+Na]^+$, 263.1618; found, 263.1616. **MP:** 78°C-80°C° (lit.[32] 79.5°C-81.5°C).

*4.28. 3,3,7,7,9-Pentamethyl-1,5-dioxaspiro[5.5]undec-8-en-8-yl trifluoromethanesulfonate (**13**)*[31]

To a stirred solution of freshly distilled DIPA (6.4 mL, 45 mmol, 2.2 equiv) in THF (116 mL) at -78°C was slowly added *n*-BuLi (18.7 mL, 2.40 M in hexane, 44.8 mmol, 2.2 equiv). The resulting solution was stirred at -78°C for 30 min and then treated with a solution of ketone **S10** (4.91 g, 20.4 mmol) in THF (45 mL) and HMPA (9.3 mL, 53 mmol, 2.6 equiv). The yellow reaction mixture was stirred at 0°C for 30 min. A solution of $PhNTf_2$ (11.6 g, 32.6 mmol, 1.6 equiv) in THF (23 mL) was added and the resulting solution was stirred at room temperature for 16h. Water was added, and the aqueous layer was extracted with $Et_2O$. The combined organic extracts were washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The crude mixture was then purified by flash chromatography on silica gel ($Et_2O$/petroleum ether 2.5:100) to afford the triflate **13** as a white crystalline solid (7.60 g, quant.). **$^1$H NMR (400 MHz, $CDCl_3$)** δ ppm: 3.64 (d, $J$ = 11.3 Hz, 2H), 3.38 (dd, $J$ = 10.3, 1.3 Hz, 2H), 2.07 (bs, 4H), 1.75 (s, 3H), 1.21 (s, 6H), 1.18 (s, 3H), 0.73 (s, 3H). **$^{13}$C NMR (100 MHz, $CDCl_3$)** δ ppm: 147.0, 124.4, 118.7 (q, $J$ = 250 Hz), 99.9, 70.5, 45.3, 29.8, 27.7, 23.0, 22.1, 20.5, 18.1, 17.3. **IR (thin film):** 2967, 2880, 1689, 1400, 1242, 1209, 1141, 1020 cm$^{-1}$. **HRMS (ESI):** Calcd for $C_{15}H_{23}F_3NaO_5S^+$ $[M+Na]^+$, 35.1111; found, 395.1105. **MP:** 78°C.

*4.29. 3,3,7,7,9-Pentamethyl-8-vinyl-1,5-dioxaspiro[5.5]undec-8-ene (**S11**)*[20]

To a stirred slurry of LiCl (5.99 g, 141 mmol, 3.0 equiv) and $Pd(PPh_3)_4$ (5.44 g, 4.71 mmol, 0.10 equiv) in THF (300 mL) was added vinyl triflate **13** (17.5 g, 47.0 mmol) and triethyl(vinyl)stannane (21 mL, 72 mmol, 1.5 equiv). The reaction mixture was refluxed for 3 days and the resulting solution was allowed to cool down to room temperature. $Et_2O$ was added to dilute the reaction mixture and the organic layer was washed with water, a 5% aqueous solution of $NH_4OH$ and brine, dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The crude mixture was then purified by flash chromatography on silica gel (petroleum ether/$Et_2O$ 97:3) to afford the diene **S11** as a pale yellow oil (10.7 g, 91%). **$^1$H NMR (400 MHz, $CDCl_3$)** δ ppm: 6.16 (ddd, $J$ = 17.6, 11.2, 1.0 Hz, 1H), 5.25 (dd, $J$ = 11.2, 2.7 Hz, 1H), 4.97 (dd, $J$ = 17.6, 2.7 Hz, 1H), 3.70 (d, $J$ = 11.1 Hz, 2H), 3.37 (dd, $J$ = 10.3, 1.3 Hz, 2H), 2.12–1.93 (m, 4H), 1.68 (s, 3H), 1.18 (s, 3H), 1.09 (s, 6H), 0.72 (s, 3H). **$^{13}$C NMR (100 MHz, $CDCl_3$)** δ ppm: 137.1, 135.3, 126.5, 118.9, 100.2, 70.2, 43.2, 29.9, 29.8, 23.2, 22.5, 22.3, 21.0, 18.4. **IR (thin film):** 2102, 2050, 1500, 1066, 1103, 1066 cm$^{-1}$. **HRMS (ESI):** Calcd for $C_{16}H_{26}NaO_2^+$ $[M+Na]^+$, 273.1825; found, 273.1819.

*4.30. 2,2,4-Trimethyl-3-vinylcyclohex-3-en-1-one (**S12**)*[20]

To a stirred solution of acetal **S11** (10.7 g, 42.8 mmol) in acetone (360 mL) was added a catalytic amount of *p*-toluenesulfonic acid. The reaction mixture was stirred at room temperature for 2h and the solvent was then removed under reduced pressure. A saturated aqueous solution of $NaHCO_3$ was added to the resulting mixture and the aqueous layer was extracted with $Et_2O$. The combined organic extracts were washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The crude mixture was then purified by flash

chromatography on silica gel ($Et_2O$/petroleum 5:95) to afford the ketone **S12** as a pale yellow oil (7.03 g, quant.). **$^1$H NMR (400 MHz, $CDCl_3$)** δ ppm: 6.21–6.05 (m, 1H), 5.34 (dd, *J* = 11.2, 2.4 Hz, 1H), 5.07 (dd, *J* = 17.6, 2.3 Hz, 1H), 2.54 (t, *J* = 7.0 Hz, 2H), 2.39 (t, *J* = 6.9 Hz, 2H), 1.78 (s, 3H), 1.16 (s, 6H). **$^{13}$C NMR (100 MHz, $CDCl_3$)** δ ppm: 215.1, 137.4, 133.9, 128.7, 119.8, 46.7, 35.9, 31.8, 24.8, 21.1. **IR (thin film):** 2943, 1708, 910 $cm^{-1}$. **HRMS (ESI):** Calcd for $C_{11}H_{16}NaO$, 187.1093$^+$ $[M+Na]^+$; found, 187.1089.

*4.31. 2,2,4-Trimethyl-1-((trimethylsilyl)oxy)-3-vinylcyclohex-3-ene-1-carbonitrile (**S13**) and (**(-)–S13**)*

***Method A*** To a stirred solution of ketone **S12** (1.82 g, 11.1 mmol) in $CH_2Cl_2$ (55 mL) was added $ZnI_2$ (709 mg, 2.22 mmol, 0.20 equiv) and TMSCN (2.90 mL, 22.2 mmol, 2.0 equiv). The reaction mixture was refluxed for 16 h and then allowed to cool down to room temperature. The volatiles were removed under reduced pressure with a trap of aqueous NaOCl/NaOH set up to quench the excess of TMSCN. The crude mixture was then purified by flash chromatography on silica gel ($Et_2O$/petroleum ether 5:100) to afford the cyanohydrin **S13** as a colourless oil (2.47 g, 84%). ***Method B***[33] To a stirred solution of ketone **S12** (246 mg, 1.50 mmol) in $CH_2Cl_2$ (1.50 mL) at -40°C was added (salen)AlCl (*R,R*) (91 mg, 0.15 mmol, 0.10 equiv), (*tert*-butoxycarbonylmethylene) triphenylphosphorane (58 mg, 0.15 mmol, 0.10 equiv) and $Ph_3PO$ (210 mg, 0.75 mmol, 0.50 equiv). The resulting solution was stirred at -40°C for 30 min before TMSCN (400 µL, 3.0 mmol, 2.0 equiv) was added dropwise. The reaction mixture was stirred for 4 days at -40°C and then allowed to warm to room temperature. The volatiles were removed under reduced pressure with a trap of aqueous NaOCl/NaOH set up to quench the excess of TMSCN. The crude mixture was then purified by flash chromatography on silica gel ($Et_2O$/petroleum ether 5:100) to afford the cyanohydrin **(-)–S13** as a colourless oil (396 mg, quant.). **$^1$H NMR (400 MHz, $CDCl_3$)** δ ppm: 6.19–6.02 (m, 1H), 5.29 (dd, *J* = 11.2, 2.5 Hz, 1H), 4.98 (dd, *J* = 17.6, 2.5 Hz, 1H), 2.44–2.26 (m, 1H), 2.38–2.29 (m, 1H), 2.06–1.97 (m, 2H), 1.68 (s, 3H), 1.19 (s, 3H), 1.01 (s, 3H), 0.24 (s, 9H). **$^{13}$C NMR (100 MHz, $CDCl_3$)** δ ppm: 135.6, 134.6, 126.9, 121.3, 119.6, 76.2, 42.3, 30.9, 29.5, 23.5, 22.3, 20.9, 1.3. **IR (thin film):** 1253, 1147, 1126, 910 $cm^{-1}$. **HRMS (ESI):** Calcd for $C_{15}H_{25}NNaOSi^+$ $[M+Na]^+$, 286.1598; found, 286.1588. **$[\alpha]_D$**: -72.8 (*c* 1.0, $CHCl_3$).

*4.32. (S)-1-(Hydroxymethyl)-2,2,4-trimethyl-3-vinylcyclohex-3-en-1-ol (7) and (**(-)–7**)*

To a stirred solution of cyanohydrin **S13** (2.47 g, 9.38 mmol) in freshly distilled hexane (90 mL) at -78°C was added DIBALH (14 mL, 1 M in hexane, 14 mmol, 1.5 equiv). The reaction mixture was allowed to warm to 0°C and was stirred at this temperature for 30 min. The mixture was then cooled down to -78°C, and EtOAc was added dropwise. The resulting mixture was stirred at this temperature for 20 min and then $SiO_2$ (30 g) was added. The reaction mixture was then allowed to warm to room temperature and stirred for 2 h. The resulting suspension was filtered and the silica was washed thoroughly with EtOAc. The solvent was removed under reduced pressure to afford the aldehyde **7** as a pale yellow oil (2.50 g, quant.). The procedure is the same for the obtention of the enantioenriched aldehyde **(-)–7**. **$^1$H NMR (400 MHz, $CDCl_3$)** δ ppm: 9.78 (s, 1H), 6.13 (dd, *J* = 17.6, 11.1 Hz, 1H), 5.29 (dd, *J* = 11.2, 2.5 Hz, 1H), 4.98 (dd, *J* = 17.6, 2.5 Hz, 1H), 2.17 (t, *J* = 6.8 Hz, 2H), 1.90 (t, *J* = 6.8 Hz, 2H), 1.69 (s, 3H), 1.04 (s, 3H), 0.96 (s, 3H), 0.13 (s, 9H). **$^{13}$C NMR (100 MHz, $CDCl_3$)** δ ppm: 205.0, 136.9, 134.8, 127.1, 119.3, 83.0, 40.7, 29.7, 27.8, 24.0, 22.4, 20.9, 2.4. **IR (thin film):** 1728, 1251, 910 $cm^{-1}$. **HRMS (ESI):** Calcd for $C_{15}H_{26}NaO_2Si^+$ $[M+Na]^+$, 289.1594; found, 289.1580.

*4.33. (S)-1-(Hydroxymethyl)-2,2,4-trimethyl-3-vinylcyclohex-3-en-1-ol (**(-)–S14**)*

To a stirred suspension of $LiAlH_4$ (57 mg, 1.5 mmol, 1.5 equiv) in THF (3.5 mL) was added a solution of the aldehyde **(-)–7** (270 mg, 1.00 mmol) in THF (3.5 mL). The reaction mixture was stirred at room temperature for 2 h. An aqueous solution of Rochelle salt (10% wt) was added to quench the reaction and the resulting mixture was stirred at room temperature for 16h. The aqueous layer was extracted with $Et_2O$, and the combined organic extracts were washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure to afford the diol **(-)–S14** as a white solid (153 mg, 78%). **$^1$H NMR (400 MHz, $CDCl_3$)** δ ppm: 6.11 (dd, *J* = 17.1, 11.6 Hz, 1H), 5.28 (d, *J* = 11.1 Hz, 1H), 4.94 (d, *J* = 17.6 Hz, 1H), 3.72 (d, *J* = 11.0 Hz, 1H), 3.47 (d, *J* = 10.9 Hz, 1H), 2.11–2.02 (m, 4H), 1.87–1.68 (m, 2H), 1.68 (s, 3H), 1.06 (s, 3H), 0.93 (s, 3H). **$^{13}$C NMR (100 MHz, $CDCl_3$)** δ ppm: 137.0, 135.0, 127.5, 119.3, 74.9, 65.0, 40.4, 29.1, 26.3, 22.8, 22.7, 21.2. **IR (thin film):** 3379, 2974, 1618, 1458, 915 $cm^{-1}$. **HRMS (ESI):** Calcd for $C_{12}H_{20}NaO_2^+$ $[M+Na]^+$, 219.1356; found, 219.1358.

*4.34. (S)-(1-Hydroxy-2,2,4-trimethyl-3-vinylcyclohex-3-en-1-yl)methyl 4-nitrobenzoate (**(-)–S15**)*

To a stirred solution of diol **(-)–S14** (37 mg, 0.19 mmol) in $CH_2Cl_2$ (4.1 mL) was added triethylamine (66 µL, 0.47 mmol, 2.5 equiv), DMAP (23 mg, 0.19 mmol, 1.0 equiv) and *p*-nitrobenzoyl chloride (71 mg, 0.38 mmol, 2.0 equiv). The reaction mixture was stirred at room temperature for 16 h. A saturated aqueous solution of $NaHCO_3$ was added to quench the reaction. The aqueous layer was extracted with $Et_2O$, and the combined organic extracts were washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The crude mixture was then purified by flash chromatography on silica gel ($Et_2O$/petroleum ether 1:1) to afford the alcohol **(-)–S15** as a white solid (57 mg, 87%) and with 74% *ee* determined by chiral HPLC when using an AD-H column with an injection volume of 20 µL and using 5% *i*PrOH in hexanes as eluent. **$^1$H NMR (400 MHz, $CDCl_3$)** δ ppm: 8.29–8.17 (m, 4H), 6.13 (dd, *J* = 17.6, 11.0 Hz, 1H), 5.32 (dd, *J* = 11.1, 2.4 Hz, 1H), 4.99 (dd, *J* = 17.6, 2.4 Hz, 1H), 4.54 (d, *J* = 11.6 Hz, 1H), 4.44–4.39 (m, 1H), 2.23–2.02 (m, 2H), 1.94–1.87 (m, 2H), 1.70 (s, 3H), 1.14 (s, 3H), 1.07 (s, 3H). **$^{13}$C NMR (100 MHz, $CDCl_3$)** δ ppm: 165.1, 136.9, 135.5, 134.7, 130.7, 130.6, 127.4, 123.5, 119.6, 74.3, 68.9, 40.9, 29.4, 27.2, 23.1, 22.3, 21.0. **HRMS (ESI):** Calcd for $C_{19}H_{23}NaO_5^+$ $[M+Na]^+$, 368.1468; found, 368.1456. **MP:** 121°C. **$[\alpha]_D$**: -29.8 (*c* 1.0, $CHCl_3$), 74% ee.

*4.35. 5-(Hex-5-en-1-ylthio)-1-phenyl-1H-tetrazole (**39**)*

To a stirred suspension of NaH (360 mg, 9.00 mmol, 1.20 equiv) in THF (14 mxL) at 0°C was slowly added 1-phenyl-1H-tetrazole-5-thiol (1.47 g, 8.25 mmol, 1.10 equiv). The reaction mixture was stirred at this temperature for 30 min followed by slow addition of alkene **38** (1.0 mL, 7.5 mmol). The resulting mixture was stirred at room temperature for 3 days and water was then added to quench the reaction. The aqueous layer was extracted with $Et_2O$, and the combined organic extracts were washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure to afford the sulfide **39** as a colourless oil (1.98 g, quant.).**$^1$H NMR (400 MHz, $CDCl_3$)** δ ppm: 7.71–7.42 (m, 5H), 5.77 (m, 1H), 5.09–4.87 (m, 2H), 3.40 (m, 2H), 2.09 (m, 2H), 1.83 (m, 2H), 1.54 (m, 2H). **$^{13}$C NMR (100 MHz, $CDCl_3$)** δ ppm: 154.4, 138.0, 133.7, 130.1, 129.8, 123.8, 115.1, 33.2, 33.1, 28.5, 27.8. **IR (thin film):** 2924, 2856, 1597, 1500, 1413, 910 $cm^{-1}$. **HRMS (ESI):** Calcd for $C_{13}H_{16}N_4NaS^+$ $[M+Na]^+$, 283.0988; found, 283.0978.

*4.36. 5-(Hex-5-en-1-ylsulfonyl)-1-phenyl-1H-tetrazole (**40**)*

To a stirred solution of sulfide **39** (2.16 g, 8.30 mmol) in ethanol (110 mL) at 0°C was added $(NH_4)_6Mo_7O_{24}\cdot H_2O$ (1.64 mg, 1.33 mmol, 0.160 equiv) and 30% $H_2O_2$ (5.40 mL, 47.3 mmol, 5.7 equiv). The resulting mixture was stirred at room temperature for 3 days. Brine was added to quench the reaction and the aqueous layer was extracted with $Et_2O$. The combined organic extracts were washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The crude mixture was then purified by flash chromatography on silica gel (EtOAc/petroleum ether 2:8) to afford the sulfone **40** as a colourless oil (2.09 g, 91%). **$^1$H NMR (400 MHz, $CDCl_3$)** δ ppm: 7.77–7.51 (m, 5H), 5.76 (m, 1H), 5.10–4.95 (m, 2H), 3.74 (m, 2H), 2.12 (m, 2H), 2.03–1.89 (m, 2H), 1.69–1.52 (m, 2H). **$^{13}$C NMR (100 MHz, $CDCl_3$)** δ ppm: 153.4, 137.2, 133.0, 131.4, 129.7, 125.0, 115.7, 55.8, 32.9, 27.3, 21.4. **IR (thin film):** 3306, 2941, 2831, 1448, 1028, 734 cm$^{-1}$. **HRMS (ESI):** Calcd for $C_{13}H_{16}N_4NaO_2S^+$ $[M+Na]^+$, 315.0886; found, 315.0879.

*4.37. 5-((2-(Allyloxy)ethyl)thio)-1-phenyl-1H-tetrazole (**42**)*

To a stirred solution of alcohol **41** (210 µL, 2.00 mmol) and 1-phenyl-1H-tetrazole-5-thiol (463 mg, 2.59 mmol, 1.30 equiv) in THF (7.32 mL) at 0°C was added DIAD (512 µL, 2.60 mmol, 1.30 equiv) and $PPh_3$ (577 mg, 2.20 mmol, 1.10 equiv). The reaction mixture was stirred at this temperature for 1h and then a saturated aqueous solution of $NaHCO_3$ was added to quench the reaction. The aqueous layer was extracted with $Et_2O$, and the combined organic extracts were washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The crude mixture was then purified by flash chromatography on silica gel ($Et_2O$/petroleum ether 2:8 to 4:6) to afford the sulfide **42** as colourless oil (447 mg, 85%). **$^1$H NMR (400 MHz, $CDCl_3$)** δ ppm: 7.72–7.38 (m, 5H), 5.87 (m, 1H), 5.22 (m, 2H), 4.02 (m, 2H), 3.83 (t, *J* = 5.9 Hz, 2H), 3.61 (t, *J* = 5.9 Hz, 2H). **$^{13}$C NMR (100 MHz, $CDCl_3$)** δ ppm: 154.2, 134.1, 133.6, 130.1, 129.8, 123.8, 117.6, 72.0, 67.8, 33.3. **IR (thin film):** 2175, 2162, 1596, 1499, 1384, 1089, 1012 cm$^{-1}$. **HRMS (ESI):** Calcd for $C_{12}H_{14}N_4NaOS^+$ $[M+Na]^+$, 285.0781; found, 285.0771.

*4.38. 5-((2-(Allyloxy)ethyl)sulfonyl)-1-phenyl-1H-tetrazole (**43**)*

To a stirred solution of sulfide **42** (3.90 g, 14.9 mmol) in ethanol (200 mL) at 0°C was added $(NH_4)_6Mo_7O_{24}\cdot H_2O$ (2.94 g, 2.38 mmol, 0.160 equiv) and 30% $H_2O_2$ (9.60 mL, 84.9 mmol, 5.70 equiv). The resulting mixture was stirred at room temperature for 3 days. Brine was added to quench the reaction and the aqueous layer was extracted with $Et_2O$. The combined organic extracts were washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The crude mixture was then purified by flash chromatography on silica gel ($Et_2O$/petroleum ether 3:7 to 1:1) to afford the sulfone **43** as a white solid (3.89 g, 89%). **$^1$H NMR (400 MHz, $CDCl_3$)** δ ppm: 7.81–7.45 (m, 5H), 5.69 (m, 1H), 5.27–5.02 (m, 2H), 3.89–3.77 (m, 6H). **$^{13}$C NMR (100 MHz, $CDCl_3$)** δ ppm: 154.0, 133.2, 133.1, 131.5, 129.6, 125.7, 118.3, 72.2, 62.8, 56.3. **IR (thin film):** 2160, 2011, 2004, 1350, 1151, 906 cm$^{-1}$. **HRMS (ESI):** Calcd for $C_{12}H_{14}N_4NaO_3S^+$ $[M+Na]^+$, 317.0679; found, 301.0677. **MP:** 51°C.

*4.39. (1-Methyl-2-oxocyclohexyl)methyl 2,2,2-trifluoroacetate (**S17**)*[26]

To a stirred solution of **S16** (10.0 mL, 82.5 mmol) in TFA (mL) was added *p*-formaldehyde (8.0 mL, 37% in $H_2O$, 99 mmol, 1.2 equiv) and the reaction mixture was stirred at 25°C for 24h. $Et_2O$ was added to dilute the resulting mixture and the organic layer was washed several times with an aqueous saturated solution of $NaHCO_3$, dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The crude mixture was then purified by flash chromatography on silica gel ($Et_2O$/petroleum ether 5:95 to 2:8) to afford the trifluoroacetate **S17** as a colourless oil (8.96 g, 46%). **$^1$H NMR (400 MHz, $CDCl_3$)** δ ppm: 4.45 (d, *J* = 11.0 Hz, 1H), 4.29 (d, *J* = 11.0 Hz, 1H), 2.51 (m, 1H), 2.34 (m, 1H), 2.07–1.96 (m, 1H), 1.84–1.65 (m, 5H), 1.22 (s, 3H). **$^{13}$C NMR (100 MHz, $CDCl_3$)** δ ppm: 212.0, 157.3 (q, *J* = 40 Hz), 114.5 (q, *J* = 290 Hz) 71.9, 48.3, 38.4, 35.5, 26.9, 20.7, 20.1. **IR (thin film):** 1782, 1697, 1209, 1161 cm$^{-1}$.

*4.40. 2-(Hydroxymethyl)-2-methylcyclohexan-1-one (**S18**)*[26]

To a stirred solution of trifluoroacetate **S17** (24.5 g, 103 mmol) in a 1:1 mixture of MeOH:$H_2O$ (114 mL) at 0°C was added NaOH (5.80 g, 145 mmol, 1.41 equiv). The reaction mixture was stirred at this temperature for 2.5h and a saturated aqueous solution of $NH_4Cl$ was then added to quench the reaction. The aqueous layer was extracted with $Et_2O$, and the combined organic extracts were washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure to afford the alcohol **S18** as a pale yellow oil (14.6 g, quant.). **$^1$H NMR (400 MHz, $CDCl_3$)** δ ppm: 3.48 (d, *J* = 1.3 Hz, 2H), 2.71 (bs, 1H), 2.55–2.42 (m, 1H), 2.26 (m, 1H), 2.01 (m, 1H), 1.89–1.46 (m, 5H), 1.17 (s, 3H). **$^{13}$C NMR (100 MHz, $CDCl_3$)** δ ppm: 218.4, 69.0, 50.1, 38.9, 35.5, 27.3, 20.7, 20.2. **IR (thin film):** 3454, 2938, 1691, 1450, 1265, 1037 cm$^{-1}$. **HRMS (ESI):** Calcd for $C_8H_{14}NaO_2^+$ $[M+Na]^+$, 165.0886; found, 165.0881.

*4.41. 1-Methyl-2-oxocyclohexane-1-carbaldehyde (**36**)*

To a stirred solution of alcohol **S18** (1.42 g, 10.0 mmol) in DMSO (30 mL) was added IBX (7.92 g, 30.0 mmol, 3.0 equiv). The reaction mixture was stirred at room temperature for 3h. The resulting mixture was then filtered and the filter cake was washed with $Et_2O$. Water was added to the filtrate and the aqueous layer was extracted with $Et_2O$. The combined organic extracts were washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure to afford the aldehyde **36** as a pale yellow oil (1.40 g, quant.). **$^1$H NMR (400 MHz, $CDCl_3$)** δ ppm: 9.50 (s, 1H), 2.54–2.24 (m, 3H), 2.01–1.91 (m, 1H), 1.82–1.55 (m, 4H), 1.24 (s, 3H). **$^{13}$C NMR (100 MHz, $CDCl_3$)** δ ppm: 209.7, 201.0, 61.3, 40.6, 34.7, 26.7, 21.7, 17.9. **HRMS (CI/Isobutane):** Calcd for $C_8H_{13}O_2^+$ $[M+H]^+$, 141.0916; found, 141.0910.

*4.42. (E)-2-(Hepta-1,6-dien-1-yl)-2-methylcyclohexan-1-one (**44**)*

To a stirred solution of sulfone **40** (135 mg, 0.460 mmol) in THF (2.1 mL) at -78°C was added LiHMDS (0.92 mL, 1M in THF, 0.92 mmol, 2.0 equiv). The reaction mixture was stirred at this temperature for 15 min before a solution of aldehyde **36** (132 mg, 0.94 mmol, 2.0 equiv) in THF (1.2 mL) was added. The resulting solution was stirred at -78°C for 2h and a saturated aqueous solution of $NH_4Cl$ was then added to quench the reaction. The aqueous layer was extracted with $Et_2O$, and the combined organic extracts were washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The crude mixture was then purified by flash chromatography on silica gel ($CH_2Cl_2$/petroleum ether 2:8) to afford the diene **44** as a colourless oil (95 mg, quant.). **$^1$H NMR (400 MHz, $CDCl_3$)** δ ppm: 5.88–5.70 (m, 1H), 5.56 (d, *J* = 15.9 Hz, 1H), 5.33 (dt, *J* = 15.8, 6.8 Hz, 1H), 5.07–4.86 (m, 2H), 2.53 (m, 1H), 2.27 (m, 1H), 1.98 (m, 6H), 1.80–1.38 (m, 6H), 1.12 (s, 3H). **$^{13}$C NMR (100 MHz, $CDCl_3$)** δ ppm: 213.8, 138.6, 134.8, 130.7, 114.6, 51.3, 40.4, 39.2, 33.1, 32.2, 28.4, 27.7, 24.6, 21.8. **IR (thin film):** 2916, 2858, 1708, 1448, 972 cm$^{-1}$. **HRMS (ESI):** Calcd for $C_{14}H_{22}NaO^+$ $[M+Na]^+$, 229.1563; found, 229.1555.

*4.43. (Z)-1-(2-((E)-Hept-1-en-1-yl)-2-methylcyclohexylidene)-2-(2,4,6-triisopropylphenyl)hydrazine (**45**)*

To a stirred solution of ketone **44** (888 mg, 4.30 mmol) in THF (25 mL) at 0°C was added TrisNHNH$_2$ (1.44 g, 4.84 mmol, 1.10 equiv) and 2 drops of concentrated HCl. The reaction mixture was stirred at room temperature for 2 h. A saturated aqueous solution of $NaHCO_3$ was added to quench the reaction. The aqueous layer was extracted with $Et_2O$, and the combined organic extracts were washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The crude mixture was then purified by flash chromatography on silica gel ($CH_2Cl_2$/petroleum ether 3:7 to 7:3) to afford the hydrazone **45** as a white solid (1.73 g, 82%). **$^1$H NMR (400 MHz, CDCl$_3$)** δ ppm: 7.98 (bs, 1H), 7.08 (s, 2H), 5.18 (d, *J* = 15.8 Hz, 1H), 4.93–4.74 (m, 1H), 4.18 (m, 2H), 2.88–2.76 (m, 1H), 2.49 (d, *J* = 14.6 Hz, 1H), 1.88–1.79 (m, 1H), 1.77–1.61 (m, 4H), 1.45 (d, *J* = 12.7 Hz, 3H), 1.33–1.03 (m, 25H), 0.90 (s, 3H), 0.80–0.73 (m, 3H). **$^{13}$C NMR (100 MHz, CDCl$_3$)** δ ppm: 161.3, 152.8, 151.2, 136.8, 131.7, 130.1, 123.4, 44.7, 40.1, 34.1, 32.6, 31.3, 29.7, 28.9, 25.9, 24.9, 24.9, 23.7, 23.6, 23.5, 22.4, 22.0, 14.0. **IR (thin film):** 1448, 2928, 1705, 1600, 1448, 1334, 1192, 1126 cm$^{-1}$. **HRMS (ESI):** Calcd for $C_{29}H_{48}N_2NaO_2S^+$ [M+Na]$^+$, 511.3329; found, 511.3344. **MP:** 59°C.

*4.44. 2-((Ethoxymethoxy)methyl)-2-methylcyclohexan-1-one (**49**)*

To a stirred solution of alcohol **48** (2.13 g, 14.9 mmol) in $CH_2Cl_2$ (30 mL) was added TBAI (1.05 g, 2.84 mmol, 0.20 equiv), DIPEA (5.2 mL, 29.9 mmol, 2.0 equiv) and EOMCl (2.3 mL, 29.8 mmol, 2.0 equiv). The reaction mixture was stirred at room temperature for 24h and a saturated aqueous solution of $NaHCO_3$ was then added to quench the reaction. The aqueous layer was extracted with $CH_2Cl_2$, and the combined organic extracts were washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The crude mixture was then purified by flash chromatography on silica gel ($Et_2O$/petroleum ether 2:8) to afford the protected alcohol **49** as a colourless oil (2.45 g, 82%). **$^1$H NMR (400 MHz, CDCl$_3$)** δ ppm: 4.68–4.62 (m, 2H), 3.57 (m, 4H), 2.44–2.36 (m, 2H), 1.94–1.59 (m, 6H), 1.21 (t, *J* = 7.1 Hz, 3H), 1.12 (s, 3H). **$^{13}$C NMR (100 MHz, CDCl$_3$)** δ ppm: 214.1, 95.4, 73.0, 63.3, 49.5, 39.0, 36.3, 27.1, 21.1, 21.0, 15.1. **IR (thin film):** 2932, 2870, 1705, 1450,1115, 1099 cm$^{-1}$. **HRMS (ESI):** Calcd for $C_{11}H_{20}NaO_3^+$ [M+Na]$^+$, 223.1305; found, 223.1297.

*4.45. (Z)-N'-(2-((Ethoxymethoxy)methyl)-2-methyl cyclohexylidene)-2,4,6-triisopropylbenzenesulfonohydrazide (**50**)*

To a stirred solution of ketone **49** (4.31 g, 21.5 mmol) in THF (125 mL) at 0°C was added TrisNHNH$_2$ (7.00 g, 23.6 mmol, 1.10 equiv) and 3 drops of concentrated HCl. The reaction mixture was stirred at room temperature for 2 h. A saturated aqueous solution of $NaHCO_3$ was added to quench the reaction. The aqueous layer was extracted with $Et_2O$, and the combined organic extracts were washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The crude mixture was then purified by flash chromatography on silica gel ($Et_2O$/petroleum ether 2:8 to 1:1) to afford the hydrazone **50** as a white solid (10.3 g, quant.). **$^1$H NMR (400 MHz, CDCl$_3$)** δ ppm: 7.14 (s, 2H), 4.42 (dd, *J* = 15.9, 6.6 Hz, 2H), 4.16 (dt, *J* = 13.5, 6.7 Hz, 2H), 3.48–3.31 (m, 4H), 2.89 (dd, *J* = 13.8, 6.9 Hz, 1H), 2.20 (t, *J* = 5.9 Hz, 2H), 1.65–1.49 (m, 6H), 1.24 (m, 18H), 1.13 (t, *J* = 7.1 Hz, 3H), 0.98 (s, 3H). **$^{13}$C NMR (100 MHz, CDCl$_3$)** δ ppm: 161.1, 152.8,151.0, 131.3, 123.3, 95.1, 73.9, 62.8, 42.6, 35.5, 34.0, 29.6, 25.2, 24.7, 24.6, 23.4, 23.2, 22.5, 20.8, 14.9. **IR (thin film):** 1598, 1163, 1114, 1035, 1014 cm$^{-1}$. **HRMS (ESI):** Calcd for $C_{26}H_{44}NaN_2O_4S^+$ [M+Na]$^+$, 503.2914; found, 503.2917. **MP:** 87°C.

*4.46. (6-((Ethoxymethoxy)methyl)-6-methylcyclohex-1-en-1-yl)(2,2,4-trimethyl-1-((trimethylsilyl)oxy)-3-vinylcyclohex-3-en-1-yl)methanol (**51a-b**)*

To a stirred solution of hydrazone **50** (4.80 g, 10.0 mmol, 1.20 equiv) in THF (12 mL) at -78°C was added dropwise *t*-BuLi (12.4 mL, 1.60 M in hexane, 19.8 mmol, 2.40 equiv). The solution turned dark red. The resulting solution was stirred at this temperature for 30 min and warmed for a few min to room temperature and intense nitrogen bubbling occurred. The red reaction mixture was then cooled down to -78°C and a solution of aldehyde **7** (2.21 g, 8.30 mmol) in THF (6.0 mL) was added. The resulting mixture was stirred at -78°C for 4 h and became yellow. A saturated aqueous solution of $NaHCO_3$ was added to quench the reaction. The aqueous layer was extracted with $Et_2O$, and the combined organic extracts were washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The crude mixture was then purified by flash chromatography (petroleum ether/$Et_2O$ 10:0.25) to afford the title alcohols **51a** (1.05 g, 28%) and **51b** (1.05 g, 28%) as highly viscous yellow oils. **51a $^1$H NMR (400 MHz, CDCl$_3$)** δ ppm: 6.16 (dd, *J* = 17.2, 11.6 Hz, 1H), 5.99 (bs, 1H), 5.24 (dd, *J* = 11.1, 2.6 Hz, 1H), 4.91 (dd, *J* = 17.6, 2.6 Hz, 1H), 4.65 (s, 2H), 4.61 (s, 1H), 3.78 (bs, 1H), 3.63–3.45 (m, 4H), 2.30 (dd, *J* = 17.3, 8.2 Hz, 1H), 2.17–2.01 (m, 2H), 1.87 (dd, *J* = 17.6, 5.1 Hz, 1H), 1.76–1.71 (m, 1H), 1.68 (s, 3H), 1.63–1.53 (m, 4H, CH2-6), 1.34 (dd, *J* = 13.4, 6.9 Hz, 1H), 1.20 (t, *J* = 7.1 Hz, 3H), 1.13–1.01 (m, 9H), 0.12 (s, 9H). **$^{13}$C NMR (100 MHz, CDCl$_3$)** δ ppm: 141.3, 137.3, 136.4, 130.6, 127.8, 118.7, 95.2, 76.2, 74.0, 70.9, 63.1, 43.7, 38.1, 33.9, 29.4, 28.1, 26.0, 25.4, 23.6, 21.8, 21.4, 18.1, 15.1, 1.1. **IR (thin film):** 2931, 1375, 1251, 1097, 1047 cm$^{-1}$. **HRMS (ESI):** Calcd for $C_{26}H_{46}NaO_4Si^+$ [M+Na]$^+$, 473.3058; found, 473.3040. **51b $^1$H NMR (400 MHz, CDCl$_3$)** δ ppm: 6.17 (dd, *J* = 17.4, 11.0 Hz, 1H), 6.02 (bs, 1H), 5.25 (dd, *J* = 11.0, 2.8 Hz, 1H), 4.91 (dd, *J* = 17.6, 2.8 Hz, 1H), 4.66 (s, 1H), 4.63 (s, 2H), 3.84 (bs, 1H), 3.59–3.31 (m, 4H), 2.37–2.24 (m, 1H), 2.17–1.99 (m, 2H), 1.87 (dd, *J* = 17.7, 5.8 Hz, 1H), 1.78–1.72 (m, 1H), 1.68 (s, 3H), 1.62–1.53 (m, 4H), 1.47–1.39 (m, 1H), 1.26–1.14 (m, 6H), 1.10–1.02 (m, 6H), 0.13 (s, 9H). **$^{13}$C NMR (100 MHz, CDCl$_3$)** δ ppm: 141.3, 137.3, 136.5, 131.2, 127.7, 118.7, 95.2, 76.1, 74.2, 70.4, 63.1, 43.7, 38.1, 34.1, 29.3, 27.8, 25.9, 24.0, 23.7, 21.3, 18.3, 15.1, 1.3. **IR (thin film):** 2931, 2357, 1465, 1251, 1097, 910 cm$^{-1}$. **HRMS (ESI):** Calcd for $C_{26}H_{46}NaO_4Si^+$ [M+Na]$^+$, 473.3058; found, 473.3052.

*4.47. (R*)-1-((R*)-((R*)-6-((Ethoxymethoxy)methyl)-6-methylcyclohex-1-en-1-yl)(hydroxy)methyl)-2,2,4-trimethyl-3-vinylcyclohex-3-en-1-ol (**S19a**)*

To a stirred solution of alcohol **51a** (342 mg, 0.758 mmol) in THF (2.7 mL) was added a 1N aqueous solution of HCl (2.7 mL) and the resulting mixture was stirred at room temperature overnight. A saturated aqueous solution of $NaHCO_3$ was added to quench the reaction. The aqueous layer was extracted with EtOAc, and the combined organic extracts were washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The crude mixture was then purified by flash chromatography (petroleum ether/$Et_2O$ 8:2 to 1:1) to afford the alcohol **S19a** as a colourless oil (268 mg, 94%). **$^1$H NMR (400 MHz, CDCl$_3$)** δ ppm: 6.56–6.45 (m, 1H), 6.17 (dd, *J* = 17.3, 11.3 Hz, 1H), 5.25 (dd, *J* = 11.0, 2.7 Hz, 1H), 4.91 (dd, *J* = 17.6, 2.6 Hz, 1H), 4.69–4.64 (m, 2H), 4.23 (s, 1H), 3.65–3.57 (m, 3H), 3.39 (s, 1H), 3.26 (d, *J* = 9.6 Hz, 1H), 3.08 (d, *J* = 1.4 Hz, 1H), 2.07 (dd, *J* = 9.0, 5.6 Hz, 4H), 1.96–1.80 (m, 3H), 1.66 (s, 3H), 1.63–1.57 (m, 2H), 1.41–1.32 (m, 1H), 1.25–1.15 (m, 6H), 1.06 (s, 3H), 0.91 (s, 3H). **$^{13}$C NMR (100 MHz, CDCl$_3$)** δ ppm: 142.1, 138.1, 136.2,

130.7, 127.3, 118.6, 95.5, 75.7, 75.4, 69.0, 63.7, 43.9, 38.5, 34.7, 28.7, 27.4, 25.9, 24.7, 23.6, 23.5, 21.1, 18.7, 15.1. **IR (thin film):** 3426, 2910, 1463, 1384, 1112 $cm^{-1}$. **HRMS (ESI):** Calcd for $C_{23}H_{38}NaO_4^+$ $[M+Na]^+$, 401.2662; found, 401.2653.

*4.48. (R*)-1-((R*)-((S*)-6-((Ethoxymethoxy)methyl)-6-methylcyclohex-1-en-1-yl)(hydroxy)methyl)-2,2,4-trimethyl-3-vinylcyclohex-3-en-1-ol (**S19b**)*

The same experimental procedure was applied to alcohol **51b** (417mg, 0.92 mmol) to afford the alcohol **S19b** as a colourless oil (348 mg, quant.). **$^1$H NMR (400 MHz, $CDCl_3$)** δ ppm: 6.25–6.08 (m, 2H), 5.26 (dd, *J* = 11.1, 2.7 Hz, 1H), 4.92 (dd, *J* = 17.6, 2.7 Hz, 1H), 4.64 (s, 2H), 4.35 (d, *J* = 4.2 Hz, 1H), 3.57 (q, *J* = 7.1 Hz, 2H), 3.39–3.30 (m, 2H), 3.00 (s, 1H), 2.62 (bs, 1H), 2.23–2.02 (m, 3H), 1.98–1.85 (m, 1H), 1.80–1.72 (m, 2H), 1.68 (s, 3H), 1.62–1.56 (m, 2H), 1.54–1.47 (m, 1H), 1.42–1.35 (m, 1H), 1.22–1.16 (m, 9H), 1.07 (s, 3H). **$^{13}$C NMR (100 MHz, $CDCl_3$)** δ ppm: 144.8, 137.6, 136.1, 129.7, 127.6, 118.7, 95.2, 76.0, 75.2, 72.4, 63.3, 43.7, 38.2, 34.8, 28.7, 27.7, 25.6, 25.1, 23.9, 22.9, 21.2, 18.3, 15.1. **IR (thin film):** 3423, 2927, 1446, 1383, 1109, 1041 $cm^{-1}$. **HRMS (ESI):** Calcd for $C_{23}H_{38}NaO_4^+$ $[M+Na]^+$ 401.2662; found, 401.2645.

*4.49. (4R*,5R*)-4-((R*)-6-((Ethoxymethoxy)methyl)-6-methylcyclohex-1-en-1-yl)-6,6,8-trimethyl-7-vinyl-1,3-dioxaspiro[4.5]dec-7-en-2-one (**S20a**)*

To a stirred solution of diol **S19a** (253 mg, 0.670 mmol) in DMF (9.3 mL) was added NaH (60 %) (79 mg, 2.0 mmol, 3.0 equiv) and *N,N*-carbonyl diimidazole (541 mg, 3.34 mmol, 5.0 equiv). The reaction mixture was stirred at room temperature for 30 min. A saturated aqueous solution of $NH_4Cl$ was added to quench the reaction. The aqueous layer was extracted with $Et_2O$, and the combined organic extracts were washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The crude mixture was then purified by flash chromatography on silica gel ($Et_2O$/petroleum ether 2:8) to afford the carbonate **S20a** as a pale yellow oil (271 mg, quant.). **$^1$H NMR (400 MHz, $CDCl_3$)** δ ppm: 6.05 (dd, *J* = 17.4, 11.2 Hz, 1H), 5.84 (t, *J* = 3.9 Hz, 1H), 5.26 (dd, *J* = 11.1, 2.4 Hz, 1H), 5.03 (s, 1H), 4.93 (dd, *J* = 17.6, 2.4 Hz, 1H), 4.53 (s, 2H), 3.55–3.43 (m, 2H), 3.29–3.18 (m, 2H), 2.28–1.95 (m, 5H), 1.85–1.78 (m, 1H), 1.72–1.65 (m, 1H), 1.61 (s, 3H), 1.60–1.52 (m, 2H), 1.32 (dd, *J* = 9.3, 5.0 Hz, 1H), 1.13 (t, *J* = 7.1 Hz, 3H), 1.09 (s, 3H), 1.06 (s, 6H). **$^{13}$C NMR (100 MHz, $CDCl_3$)** δ ppm: 155.2, 137.5, 134.7, 134.6, 133.2, 127.9, 119.8, 94.9, 89.8, 77.6, 72.9, 63.1, 42.8, 38.0, 33.6, 28.9, 25.6, 25.1, 24.4, 23.2, 20.8, 20.7, 17.9, 14.9. **IR (thin film):** 2974, 1797, 1458, 1386, 1178, 1043 $cm^{-1}$. **HRMS (ESI):** Calcd for $C_{24}H_{36}NaO_5^+$ $[M+Na]^+$, 427.2455; found, 427.2448.

*4.50. (4R*,5R*)-4-((S*)-6-((Ethoxymethoxy)methyl)-6-methyl cyclohex-1-en-1-yl)-6,6,8-trimethyl-7-vinyl-1,3-dioxaspiro[4.5] dec-7-en-2-one (**S20b**)*

The same experimental procedure was applied to alcohol **S19b** (262 mg, 0.690 mmol) to afford the carbonate **S20b** as a colourless oil (279 mg, quant.). **$^1$H NMR (400 MHz, $CDCl_3$)** δ ppm: 6.10 (dd, *J* = 17.4, 11.1 Hz, 1H), 5.87 (t, *J* = 3.9 Hz, 1H), 5.35 (s, 1H), 5.31 (dd, *J* = 11.1, 2.5 Hz, 1H), 4.97 (dd, *J* = 17.6, 2.5 Hz, 1H), 4.66 (s, 2H), 3.61–3.49 (qd, 2H), 3.49–3.41 (m, 2H), 2.32–2.29 (m, 1H), 2.19–2.13 (m, 2H), 2.10–1.95 (m, 2H), 1.76–1.58 (m, 4H), 1.65 (s, 3H), 1.40–1.35 (m, 1H), 1.20 (t, *J* = 7.1 Hz, 3H), 1.13 (s, 3H), 1.10 (s, 3H), 0.98 (s, 3H). **$^{13}$C NMR (100 MHz, $CDCl_3$)** δ ppm: 155.5, 138.1, 135.0, 134.8, 132.4, 128.0, 119.9, 95.5, 89.9, 77.8, 75.6, 63.4, 43.0, 37.7, 34.9, 29.1, 25.6, 25.2, 24.8, 23.4, 20.9, 20.7, 18.1, 15.1. **IR (thin film):** 1789, 1463, 1386, 1346, 1178, 1047 $cm^{-1}$. **HRMS (ESI**): Calcd for $C_{24}H_{36}NaO_5^+$ $[M+Na]^+$, 427.2455; found, 427.2440.

*4.51. (4R*,5R*)-4-((R*)-6-(Hydroxymethyl)-6-methylcyclohex-1-en-1-yl)-6,6,8-trimethyl-7-vinyl-1,3-dioxaspiro[4.5]dec-7-en-2-one (**52a**)*

To a stirred solution of protected alcohol **S20a** (278 mg, 0.680 mmol) in acetone (11 mL) and water (6 mL) was slowly added concentrated $H_2SO_4$ (1.5 mL). The reaction mixture was stirred at room temperature for 16 h. A saturated aqueous solution of $NaHCO_3$ was added to quench the reaction and the aqueous layer was then extracted with $Et_2O$. The combined organic extracts were washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The crude mixture was then purified by flash chromatography on silica gel ($Et_2O$/petroleum ether 4:6) to afford the alcohol **52a** as a white solid (220 mg, 93%). **$^1$H NMR (400 MHz, $CDCl_3$)** δ ppm: 6.09 (dd, *J* = 17.5, 11.2 Hz, 1H), 6.01 (t, *J* = 4.0 Hz, 1H), 5.30 (dd, *J* = 11.1, 2.5 Hz, 1H), 5.19 (s, 1H), 4.96 (dd, *J* = 17.6, 2.5 Hz, 1H), 3.60 (d, *J* = 11.2 Hz, 1H), 3.45 (d, *J* = 11.2 Hz, 1H), 2.30–2.20 (m, 1H), 2.18–2.12 (m, 3H), 2.02–1.94 (m, 1H), 1.81–1.68 (m, 4H), 1.64 (s, 3H), 1.69–1-49 (m, 1H), 1.41–1.35 (m, 1H), 1.10 (s, 6H), 0.92 (s, 3H). **$^{13}$C NMR (100 MHz, $CDCl_3$)** δ ppm: 155.3, 137.3, 135.2, 134.6, 134.2, 128.2, 119.9, 89.8, 77.3, 69.9, 43.1, 39.1, 34.1, 29.0, 25.7, 25.0, 24.1, 22.7, 21.4, 20.9, 18.2. **IR (thin film):** 3493, 2914, 1786, 1346, 1039 $cm^{-1}$. **HRMS (ESI):** Calcd for $C_{21}H_{30}NaO_4^+$ $[M+Na]^+$, 369.2036; found, 369.2024. **MP:** 159°C.

*4.52. (4R*,5R*)-4-((S*)-6-(Hydroxymethyl)-6-methylcyclohex-1-en-1-yl)-6,6,8-trimethyl-7-vinyl-1,3-dioxaspiro[4.5]dec-7-en-2-one (**52b**)*

To a stirred solution of protected alcohol **S20b** (340 mg, 0.840 mmol) in acetone (14 mL) and water (7 mL) was slowly added concentrated $H_2SO_4$ (1.8 mL). The reaction mixture was stirred at room temperature for 16 h. A saturated aqueous solution of $NaHCO_3$ was added to quench the reaction and the aqueous layer was then extracted with $Et_2O$. The combined organic extracts were washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The crude mixture was then purified by flash chromatography on silica gel ($Et_2O$/petroleum ether 4:6) to afford the alcohol **52b** as a white solid (292 mg, quant.). **$^1$H NMR (400 MHz, $CDCl_3$)** δ ppm: 6.11 (dd, *J* = 17.6, 11.1 Hz, 1H), 5.91 (t, *J* = 4.0 Hz, 1H), 5.32 (dd, *J* = 11.1, 2.5 Hz, 1H), 5.09 (s, 1H), 4.98 (dd, *J* = 17.6, 2.5 Hz, 1H), 3.51 (dd, *J* = 10.8, 5.0 Hz, 1H), 3.33 (dd, *J* = 10.7, 4.9 Hz, 1H), 2.30–1.98 (m, 5H), 1.85 (dd, *J* = 8.5, 3.8 Hz, 2H), 1.73–1.59 (m, 5H), 1.43–1.30 (m, 2H), 1.15–1.07 (m, 9H). **$^{13}$C NMR (100 MHz, $CDCl_3$)** δ ppm: 155.4, 137.5, 134.9, 134.8, 133.6, 128.1, 119.9, 90.1, 78.2, 68.8, 42.9, 39.3, 33.5, 29.0, 25.7, 25.2, 24.3, 22.8, 20.9, 20.8, 18.1. **IR (thin film):** 3477, 1795,73, 1390, 1176 $cm^{-1}$. **HRMS (ESI):** Calcd for $C_{21}H_{30}NaO_4^+$ $[M+Na]^+$, 369.2036; found, 369.2023. **MP:** 155°C.

*4.53. (4R*,5R*)-4-((S*)-6-((E)-3-(Allyloxy)prop-1-en-1-yl)-6-methylcyclohex-1-en-1-yl)-6,6,8-trimethyl-7-vinyl-1,3-dioxaspiro[4.5]dec-7-en-2-one (**53a**)*

To a stirred solution of alcohol **52a** (76 mg, 0.22 mmol) in $H_2O$-saturated $CH_2Cl_2$ (5.6 mL) was added DMP (187 mg, 0.44 mmol, 2.0 equiv). The resulting cloudy solution stirred at room temperature for 2h. The reaction mixture was diluted with $Et_2O$ and then concentrated under reduced pressure. $Et_2O$ was then added and the organic phase was washed with a saturated aqueous solution of $Na_2S_2O_3$ and a saturated aqueous solution of $NaHCO_3$. The aqueous layers were back-extracted with $Et_2O$ and the combined organic extracts were washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. To a stirred solution of this crude mixture and sulfone **43** (194 mg, 0.66 mmol, 3.0 equiv) in DME (7.5 mL) at -55°C was

slowly added KHMDS (0.97 mL, 0.9 M in THF, 0.88 mmol, 4.0 equiv). The reaction mixture stirred at this temperature for 1h and the resulting solution was then warmed up to room temperature and stirred for 1h. Brine was added to quench the reaction and the aqueous layer was extracted with $Et_2O$. The combined organic extracts were washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The crude mixture was then purified by flash chromatography on silica gel ($Et_2O$/petroleum ether 2:8) to afford the *E*-alkene **53a** as a highly viscous colourless oil (66 mg, 73% for two steps). **$^1$H NMR (400 MHz, $CDCl_3$)** δ ppm: 6.08 (dd, *J* = 17.5, 11.2 Hz, 1H), 5.96–5.83 (m, 2H), 5.65–5.55 (m, 2H), 5.34–5.22 (m, 2H), 5.17 (dd, *J* = 10.4, 1.5 Hz, 1H), 4.95 (dd, *J* = 17.6, 2.4 Hz, 1H), 4.90 (s, 1H), 4.04–3.93 (m, 4H), 2.27 (dd, *J* = 17.5, 9.0 Hz, 1H), 2.21–2.12 (m, 2H), 2.06 (d, *J* = 6.2 Hz, 2H), 1.75–1.67 (m, 1H), 1.65 (s, 3H), 1.60–1.47 (m, 4H), 1.13–1.00 (m, 9H). **$^{13}$C NMR (100 MHz, $CDCl_3$)** δ ppm: 155.4, 140.3, 137.5, 134.9, 134.7, 134.6, 132.2, 127.9, 126.6, 119.9, 117.0, 89.9, 78.9, 70.9, 70.5, 43.0, 40.1, 38.0, 29.1, 25.6, 25.4, 25.0, 20.9, 20.6, 18.0. **IR (thin film):** 2927, 2850, 1797, 1446, 1344, 1176 1041 cm$^{-1}$. **HRMS (ESI):** Calcd for $C_{26}H_{36}NaO_4^+$ $[M+Na]^+$, 435.2506; found, 435.2500.

*4.54. (4R*,5R*)-4-((R*)-6-((E)-3-(Allyloxy)prop-1-en-1-yl)-6-methylcyclohex-1-en-1-yl)-6,6,8-trimethyl-7-vinyl-1,3-dioxaspiro[4.5]dec-7-en-2-oneb (**53b**)*

The same experimental procedure was applied to alcohol **52b** (100 mg, 0.29 mmol) to afford the *E*-alkene **53b** as a highly viscous colourless oil (46 mg, 48% for two steps). **$^1$H NMR (400 MHz, $CDCl_3$)** δ ppm: 6.08 (dd, *J* = 17.6, 11.1 Hz, 1H), 5.95–5.79 (m, 2H), 5.60–5.49 (m, 2H), 5.34–5.11 (m, 3H), 4.95 (dd, *J* = 17.6, 2.5 Hz, 1H), 4.87 (s, 1H), 4.08–3.78 (m, 4H), 2.27 (d, *J* = 8.5 Hz, 1H), 2.21–2.13 (m, 2H), 2.13–1.95 (m, 2H), 1.72–1.55 (m, 7H), 1.53–1.47 (m, 1H), 1.25 (d, *J* = 12.3 Hz, 3H), 1.07 (d, *J* = 9.3 Hz, 3H), 0.99 (s, 3H). **$^{13}$C NMR (100 MHz, $CDCl_3$)** δ ppm: 155.4, 139.6, 138.3, 135.0, 134.9, 134.6, 131.2, 127.6, 125.5, 119.8, 117.0, 90.0, 78.0, 71.4, 70.6, 42.9, 39.6, 37.7, 29.2, 25.5, 25.4, 25.2, 23.9, 20.9, 20.5, 18.0. **IR (thin film):** 3340, 2947, 1795, 1068, 1033, 862 cm$^{-1}$. **HRMS (ESI):** Calcd for $C_{26}H_{36}NaO_4^+$ $[M+Na]^+$, 435.2506; found, 435.2500.

*4.55. (4R*,5R*)-4-((S*)-6-((E)-Hepta-1,6-dien-1-yl)-6-methyl cyclohex-1-en-1-yl)-6,6,8-trimethyl-7-vinyl-1,3-dioxaspiro[4.5]dec-7-en-2-one (**54a**)*

To a stirred solution of alcohol **52a** (23 mg, 0.066 mmol) in $H_2O$-saturated $CH_2Cl_2$ (1.7 mL) was added DMP (57 mg, 0.13 mmol, 2.0 equiv). The resulting cloudy solution stirred at room temperature for 2h. The reaction mixture was diluted with $Et_2O$ and then concentrated under reduced pressure. $Et_2O$ was then added and the organic phase was washed with a saturated aqueous solution of $Na_2S_2O_3$ and a saturated aqueous solution of $NaHCO_3$. The aqueous layers were back-extracted with $Et_2O$ and the combined organic extracts were washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. To a stirred solution of this crude mixture and sulfone **40** (58 mg, 0.20 mmol, 3.0 equiv) in DME (2.3 mL) at -55°C was slowly added KHMDS (0.30 mL, 0.9 M in THF, 0.27 mmol, 4.0 equiv). The reaction mixture stirred at this temperature for 1h and the resulting solution was then warmed up to room temperature and stirred for 1h. Brine was added to quench the reaction and the aqueous layer was extracted with $Et_2O$. The combined organic extracts were washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The crude mixture was then purified by flash chromatography on silica gel ($CH_2Cl_2$/petroleum ether 4:6) to afford the *E*-alkene **54a** as a highly viscous colourless oil (19 mg, 70% for two steps). **$^1$H NMR (400 MHz, $CDCl_3$)** δ ppm: 6.09 (dd, *J* = 17.3, 11.6 Hz, 1H), 5.88 (s, 1H), 5.78 (dt, *J* = 16.7, 8.4 Hz, 1H), 5.46–5.40 (m, 1H), 5.35–5.27 (m, 2H), 5.06–4.90 (m, 4H), 2.28 (d, *J* = 13.4 Hz, 1H), 2.17–2.10 (m, 2H), 2.10–2.02 (m, 5H), 1.79–1.68 (m, 2H), 1.66 (s, 3H), 1.58–1.53 (m, 3H), 1.51–1.44 (m, 4H), 1.17–1.11 (m, 2H), 1.07 (s, 6H). **$^{13}$C NMR (100 MHz, $CDCl_3$)** δ ppm: 155.5, 138.6, 138.0, 137.8, 134.9, 134.8, 131.9, 130.3, 128.0, 119.9, 114.6, 89.9, 79.0, 43.0, 40.0, 38.4, 33.2, 32.1, 29.1, 28.8, 25.7, 25.4, 25.2, 25.1, 21.0, 20.5, 18.1. **IR (thin film):** 2954, 2922, 2852, 1805, 1456, 1174 cm$^{-1}$. **HRMS (ESI):** Calcd for $C_{27}H_{38}NaO_3^+$ $[M+Na]^+$, 433.2713; found, 433.2710.

*4.56. (4R*,5R*)-4-((R*)-6-((E)-Hepta-1,6-dien-1-yl)-6-methylcyclohex-1-en-1-yl)-6,6,8-trimethyl-7-vinyl-1,3-dioxaspiro[4.5]dec-7-en-2-one (**54b**)*

The same experimental procedure was applied to alcohol **52b** (120 mg, 0.36 mmol) to afford the *E*-alkene **54b** as a highly viscous colourless oil (75 mg, 52% for two steps). **$^1$H NMR (400 MHz, $CDCl_3$)** δ ppm: 6.09 (dd, *J* = 17.9, 11.0 Hz, 1H), 5.83 (bs, 1H), 5.81–5.71 (m, 1H), 5.48–5.37 (m, 1H), 5.28–5.21 (m, 2H), 5.06–4.92 (m, 3H), 4.88 (s, 1H), 2.35–2.23 (m, 1H), 2.21–2.07 (m, 3H), 2.07–1.84 (m, 5H), 1.71–1.65 (m, 4H), 1.63–1.36 (m, 6H), 1.24 (s, 3H), 1.07 (s, 3H), 1.00 (s, 3H). **$^{13}$C NMR (100 MHz, $CDCl_3$)** δ ppm: 155.5, 138.9, 138.5, 137.5, 135.0, 134.8, 130.8, 129.0, 127.6, 119.8, 114.6, 89.9, 78.0, 42.9, 39.6, 38.1, 33.2, 32.3, 29.2, 28.4, 25.5, 25.4, 25.3, 24.0, 21.0, 20.5, 18.1. **IR (thin film):** 2927, 1789, 1452, 1344, 1265, 1176, 1039 cm$^{-1}$. **HRMS (ESI):** Calcd for $C_{27}H_{38}NaO_3^+$ $[M+Na]^+$, 433.2713; found, 433.2706.

*4.57. (4R*,5R*)-6,6,8-Trimethyl-4-((S*)-6-methyl-6-vinylcyclohex-1-en-1-yl)-7-vinyl-1,3-dioxaspiro[4.5]dec-7-en-2-one (**56a**)*

To a stirred solution of the Stewart-Grubbs catalyst (9.0 mg, 0.015 mmol, 0.30 equiv) in dry and degassed DCE (23 mL) at 50°C was slowly added a solution of carbonate **53a** (20 mg, 0.048 mmol) in DCE (1.0 mL). The reaction mixture was warmed to reflux and stirred for 2 days. The resulting mixture was cooled down to room temperature and diluted with a small amount of $CH_2Cl_2$. The crude mixture was dry loaded and purified by flash chromatography on silica gel ($Et_2O$/petroleum ether 1:9) to afford the truncated product **56a** as a pale yellow oil (5.0 mg, 30%). **$^1$H NMR (400 MHz, $CDCl_3$)** δ ppm: 6.09 (dd, *J* = 17.6, 11.0 Hz, 1H), 5.92 (t, *J* = 4.0 Hz, 1H), 5.73 (dd, *J* = 17.5, 10.6 Hz, 1H), 5.31 (dd, *J* = 11.1, 2.5 Hz, 1H), 5.16 (dd, *J* = 10.6, 1.0 Hz, 1H), 5.06 (dd, *J* = 17.5, 1.0 Hz, 1H), 4.96 (dd, *J* = 17.6, 2.5 Hz, 1H), 4.92 (s, 1H), 2.32–2.26 (m, 1H), 2.18–2.12 (m, 2H), 2.10–2.04 (m, 2H), 1.75–1.70 (m, 1H), 1.66 (s, 3H), 1.52–1.56 (m, 3H), 1.27–1.22 (m, 1H), 1.07 (s, 6H), 1.07 (s, 3H). **$^{13}$C NMR (100 MHz, $CDCl_3$)** δ ppm: 155.5, 145.5, 137.4, 134.9, 134.8, 132.4, 128.0, 120.0, 114.6, 89.9, 78.9, 43.0, 40.9, 38.0, 29.1, 25.7, 25.4, 25.1, 24.5, 21.0, 20.5, 18.0. **IR (thin film):** 2941, 2904, 1788, 1178, 1043, 910 cm$^{-1}$. **HRMS (ESI):** Calcd for $C_{22}H_{30}NaO_3^+$ $[M+Na]^+$, 365.2087; found, 365.2071.

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