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PAPER

A stereoselective, Sm(II)-mediated approach to decorated *cis*-hydrindanes: synthetic studies on faurinone and pleuromutilin†‡

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The *cis*-hydrindane motif is found in a number of natural products that display important biological activity. A flexible, stereoselective approach to the framework has been developed that features highly diastereoselective, SmI_2-mediated cyclisations. The strategy has been exploited in the first synthesis of the proposed structure of faurinone and an approach to the skeleton of the antibacterial natural product, pleuromutilin.

Introduction

Since its introduction to the synthetic community by Kagan, the one-electron reducing agent samarium(II) iodide (SmI_2) has found widespread use in organic synthesis.[1] The reagent has been used to mediate processes ranging from functional group interconversions to complex carbon-carbon bond-forming sequences in which molecular complexity is increased dramatically in a single operation.[1] Cyclisation reactions are among the most useful transformations mediated by SmI_2 and these have proved to be valuable tools for natural product synthesis.[1b,d] The intramolecular addition of radicals, generated from aldehydes and halides, to alkenes, is an important class of cyclisation mediated by the reagent.[1]

The hydrindane skeleton is found in many biologically active natural products. We wished to develop a stereoselective approach to the *cis*-hydrindane skeleton **1** that would allow stereocontrolled installation of substituents around the bicyclic structure.[2] A flexible approach to **1** would facilitate approaches to a number of natural products, many of which display important biological activity (Fig. 1). The sesquiterpene glycosides, dendronobilosides A and B, display immunomodulatory activity,[3] and are closely related to faurinone **2**.[4] Pleuromutilin **3** has an inhibitory effect against the bacteria *Staphylococcus aureous* and is known to prevent bacterial protein synthesis.[5] Bakkenolides, such as **4**, display a variety of biological activities including selective cytotoxicity.[6]

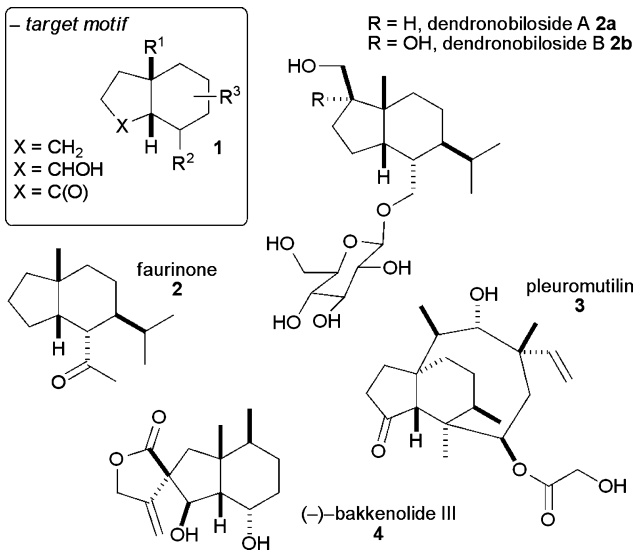

Fig. 1 Selected natural products containing a substituted *cis*-hydrindane core.

Here we describe in full a flexible approach to the substituted *cis*-hydrindane skeleton that exploits highly diastereoselective SmI_2-mediated cyclisations of aldehyde and halide substrates.[7] We have applied the approach in the first synthesis of the proposed structure of *rac*-faurinone and in an approach to the skeleton of the antibacterial natural product pleuromutilin.

Results and discussion

We envisaged constructing the quaternary stereocentre in **1** by conjugate addition to substituted β-alkyl cyclohexenones. Prior to our work, little was known about the efficacy and diastereoselectivity of such additions.[8] Aldehydes or halides **5** would therefore be accessible from enones **7** *via* protected intermediates **6**. We believed

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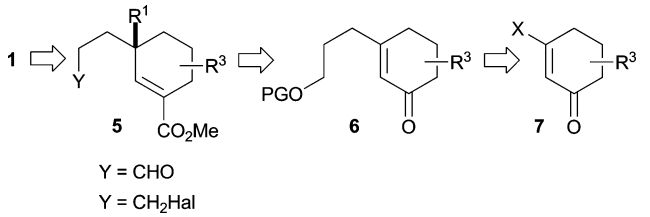
† Dedicated to Professor Athel Beckwith for his pioneering work on organic free radicals

‡ Electronic supplementary information (ESI) available: NMR spectra and X-ray structure of **59** CCDC reference number 802039. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c0ob01086c

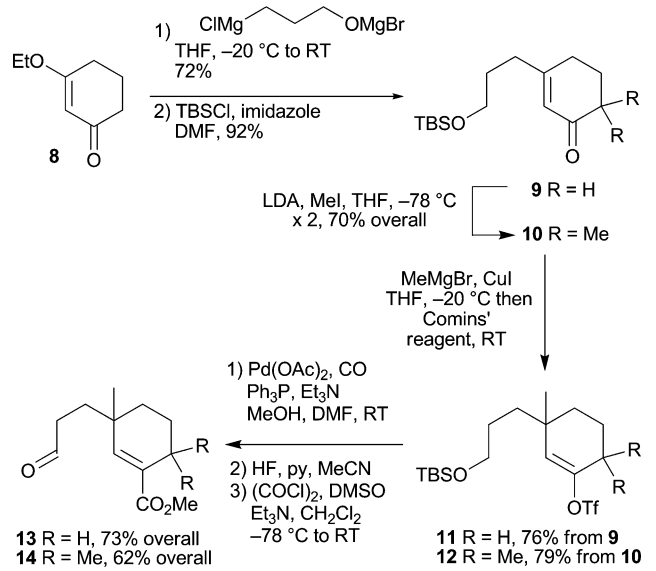
that substrates **5** would undergo highly stereoselective 5-*exo*-trig cyclisations on treatment with SmI_2 (Scheme 1).



Scheme 1 A proposed approach to the *cis*-hydrindane skeleton (PG = protecting group, X = H or OEt).

Aldehydes **13** and **14** were prepared to investigate the diastereoselectivity of the proposed SmI_2-mediated construction of the *cis*-hydrindane system. Addition of the Grignard reagent derived from 3-chloropropan-1-ol to **8**[9] according to the procedure of Tietze,[10] and protection of the primary hydroxyl gave **9** (Scheme 2). Subsequent dimethylation of enone **9** gave **10**. Treatment of enones **9** and **10** with dimethylcuprate and trapping of the resultant enolates with Comins' reagent[11] gave enol triflates **11** and **12**. Palladium-catalyzed methoxycarbonylation, deprotection, and oxidation then gave **13** and **14** in good overall yield (Scheme 2).

The route can be readily adapted to access a range of decorated cyclisation substrates (Scheme 3). For example, methylation of enone **9** and conjugate addition using a range of alkylmetals, followed by enolate trapping gave enol triflates **15–18** in good yield and with moderate diastereoselectivity, thus illustrating the utility of the conjugate addition for the stereocontrolled construction of the quaternary stereocentre. The stereochemistry of the major diastereoisomer from the addition of methylcuprate was assigned by NOE studies on the deprotected ketone adduct, isolated when Comins' reagent was omitted. Enol triflate **23** was prepared by

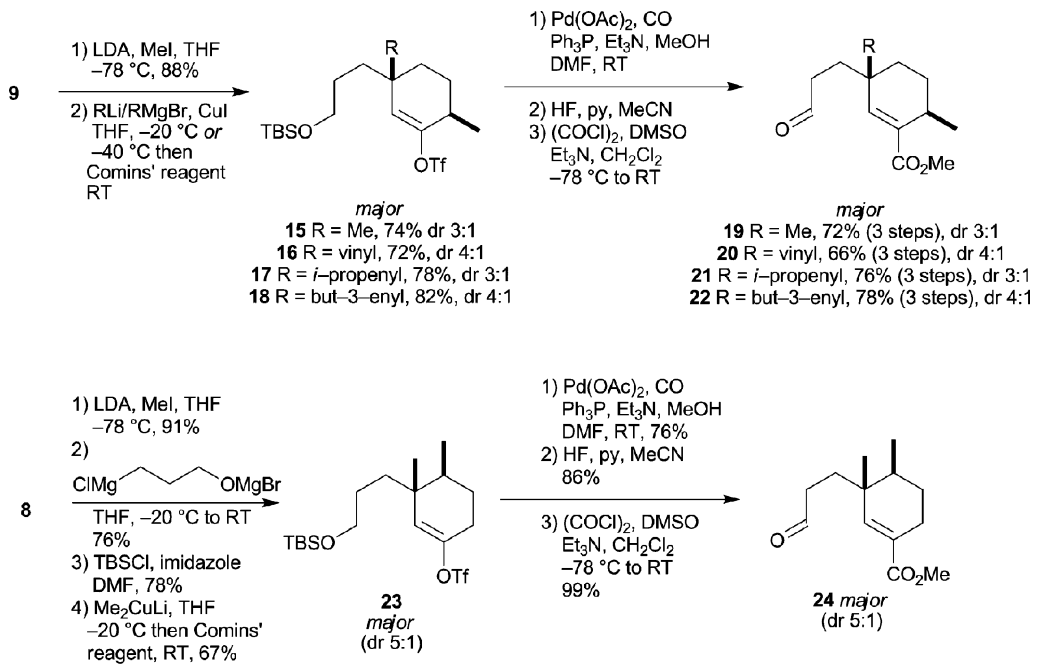


Scheme 2 General route to unsaturated aldehyde cyclisation substrates (Comins' reagent = *N*-(5-chloro-2-pyridyl)triflimide).

methylation of enol ether **8**, Grignard addition, protection, and methylcuprate addition-enolate trapping. Enol triflates **15–18** and **23** were then converted to cyclisation substrates **19–22** and **24** using the straightforward sequence outlined in Scheme 2.

Upon treatment with SmI_2 in THF and *t*-BuOH, the unsaturated aldehyde substrates, **13**, **14**, **19–22** and **24**, underwent cyclisation in high yield and with high diastereoselectivity (>10 : 1 dr by ^{1}H NMR, α- to the ester) observed in the construction of three stereocentres (Fig. 2).

The stereochemistry of **26** and **27** was confirmed by treatment with 1-naphthyl isocyanate to give carbamates **32** and **33**,



Scheme 3 Synthesis of unsaturated aldehyde cyclisation substrates (Comins' reagent = *N*-(5-chloro-2-pyridyl)triflimide).

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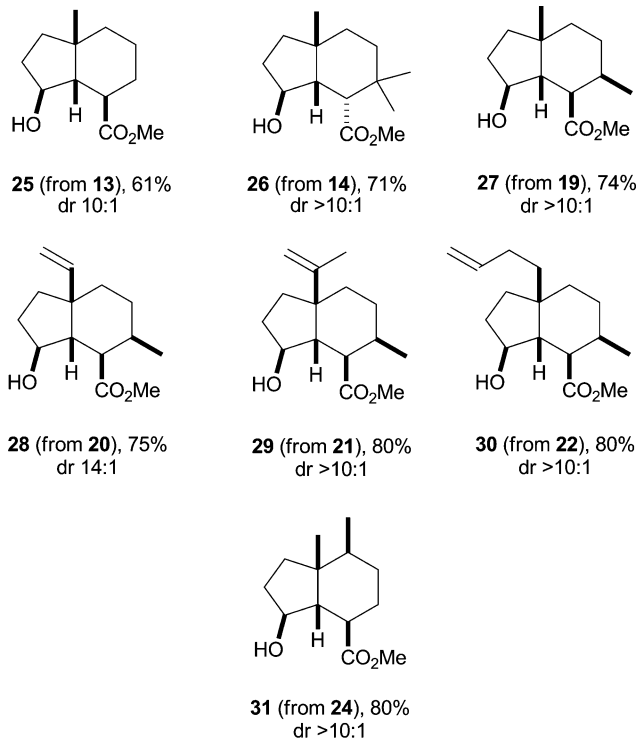
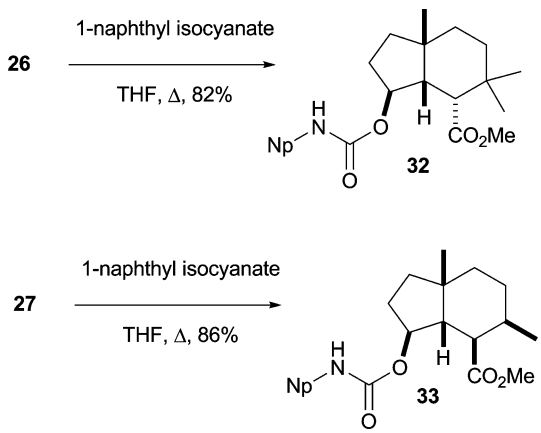


Fig. 2 *cis*-Hydrindane products from stereoselective SmI_2-mediated cyclisations of aldehydes.

respectively, followed by X-ray crystallographic analysis (Scheme 4).[12] The stereochemistry of **25**, **28–30** was inferred from the stereochemistry of **27**. (The stereochemistry of **28** was also confirmed by NOE studies). The stereochemistry of **31** was assigned on the basis of NOE studies.



Scheme 4 Determination of stereochemistry in **26** and **27**.

All substrates gave the *syn*,*syn*-diastereoisomeric products with the exception of **14** which underwent cyclisation to give **26** as the *syn*,*anti*-diastereoisomer. The SmI_2-mediated cyclisations proceed by reduction of the aldehyde and addition of the resulting ketyl-radical anion to the alkene through *anti*-intermediate **34** to give samarium(III)-enolates.[13] Cyclisation of **13** gives samarium(III)-enolate **35** that undergoes protonation selectively from the open α-face. In contrast, cyclisation of **14** gives samarium(III)-enolate **36**, possessing the alternative chair conformation. Protonation then occurs selectively from the open β-face (Fig. 3). Indirect, support for this explanation comes from the X-ray crystal structures of **32** and **33** that clearly show different conformations.

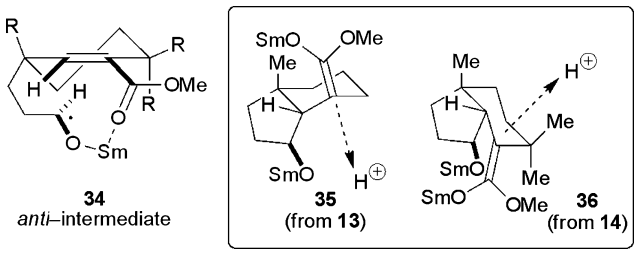


Fig. 3 Origin of diastereoselectivity in the protonation of samarium(III)-enolate intermediates.

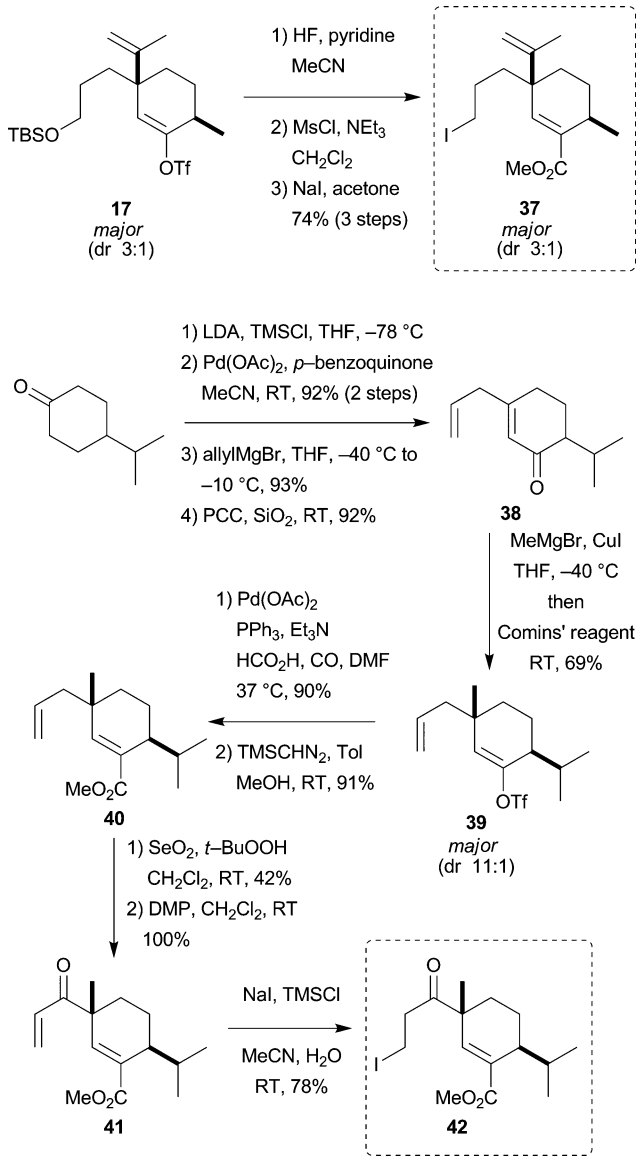
Alkyl iodide cyclisation substrates have also prepared: alkyl iodide **37** was prepared from **17** in three steps and β-keto iodide **42** was prepared in 10 steps from 4-isopropylcyclohexanone. In the synthesis of **42**, Grignard addition to 4-isopropylcyclohex-2-enone and oxidative rearrangement gave **38**. Conjugate addition followed by enolate trapping gave enol triflate **39** (dr 11 : 1) and Pd-catalyzed carbonylation and esterification of the resultant acid then gave **40** as a single diastereoisomer. The use of formic acid in the Pd-catalysed carbonylation, rather than MeOH, proved crucial to avoid side reactions. Finally, allylic oxidation, to give an inconsequential 4 : 1 mixture of allylic alcohol diastereoisomers, and oxidation gave enone **41** that was smoothly converted to β-keto iodide **42** using TMSI generated *in situ* (Scheme 5).[14]

Iodide **37** and β-keto iodide **42** underwent highly diastereoselective cyclisations on treatment with SmI_2-HMPA (Scheme 6).[15] In the case of **42**, cyclization gave a mixture of ketone **45** and over-reduction product, secondary alcohol **44** (obtained as a single diastereoisomer), in 75% yield. Alcohol **44** could be oxidized to ketone **45** in 74% yield using the Dess–Martin periodinane (Scheme 6). The stereochemistry of **44** and **45** was assigned on the basis of NOE studies. SmI_2-mediated halide-alkene cyclisations provide a convenient alternative for the synthesis of less-oxygenated targets.

Cyclisation products **27–30** possess the substitution pattern found in the *cis*-hydrindane core of pleuromutilin **3**, while products **31** and **45** display the *cis*-hydrindane cores of bakkenolide III **4** and the dendronobilosides **2a**/**2b**, respectively (see Fig. 1).

We have exploited the approach in a concise synthesis of the proposed structure of faurinone **2**, a sesquiterpene ketone isolated from *valeriana officinalis* (Fig. 1).[4] Grignard addition to 4-i-propylcyclohexenone and oxidative rearrangement of the resultant tertiary alcohol with PCC gave enone **46**.[16] Highly diastereoselective organocopper addition, enolate trapping, carbonylation and acetal deprotection then gave aldehyde cyclisation substrate **47** (dr > 20 : 1). Alkyl iodide substrate **48** was prepared from **47** in two steps (Scheme 7).

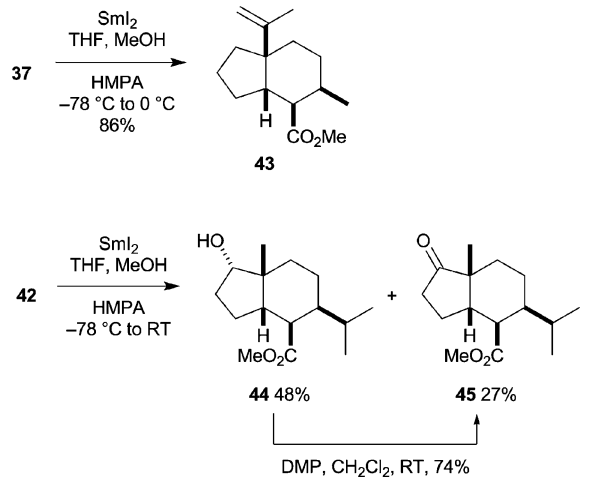
As expected, cyclisation of aldehyde **47** with SmI_2 proceeded with excellent stereocontrol to give **49** as a single diastereoisomer by ^{1}H NMR. The stereochemical outcome of the cyclisation was confirmed by conversion of **49** to the 1-naphthyl carbamate **51** and X-ray crystallographic analysis.[12] Iodide **48** also underwent smooth cyclisation on treatment with SmI_2-HMPA[15] to give **50** as a single diastereoisomer by ^{1}H NMR (Scheme 8).



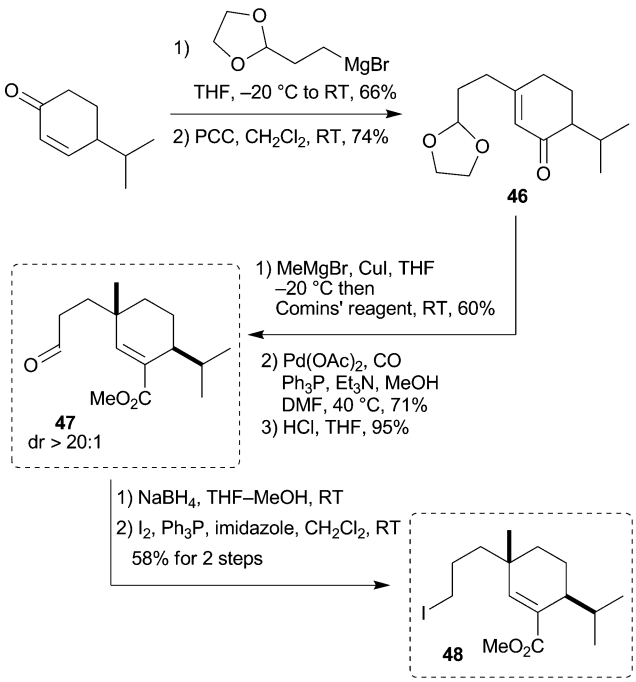
Scheme 5 Diastereoselective synthesis of unsaturated iodide cyclisation substrates.

Our approach to faurinone continued with the epimerisation of **49** and formation of the *bis*-lactone **52**. The structure of **52** was confirmed by X-ray crystallography.[12] Reaction of **52** with methyllithium gave **53** in good yield. We believe the stability of the cyclic, *bis*-hemi-ketal accounts for the smooth mono-addition of methyllithium to each carbonyl group. Conversion of **53** to the corresponding thioimidazolide and radical deoxygenation completes the first synthesis of the proposed structure of faurinone **2** (Scheme 9). While only partial spectroscopic data is available for the natural product, NMR data for synthetic **2** prepared during our studies does not match the partial, data for the natural product reported by Bos.[4] We have also prepared ***epi*-2** from **50** ($TMSCH_2Li$, THF, 0 °C, 77%). ***Epi*-2** also does not match the partial literature data for the natural product.[4]

We have also utilised our approach to *cis*-hydrindanes in a synthesis of the tricyclic skeleton of pleuromutilin.[17,18] Cyclisation products **29** and **30** were converted to aldehydes **54** and **55**, respectively, by a protection, reduction and oxidation sequence.



Scheme 6 SmI_2-mediated cyclisations of alkyliodides for the stereoselective construction of the *cis*-hydrindane skeleton.



Scheme 7 Preparation of cyclisation substrates in an approach to the proposed structure of faurinone.

Aldehyde **54** was then converted to diene **56** by the addition of but-3-enyl magnesium bromide and aldehyde **55** was converted to diene **57** by the addition of vinylmagnesium bromide (Scheme 10). Dienes **56** and **57** were obtained as mixtures of diastereoisomers.

We next investigated the formation of the 8-membered ring of the pleuromutilin skeleton using ring-closing metathesis (RCM).[19–21] Diene **56** was subjected to the Grubbs II catalyst in CH_2Cl_2 at temperatures between room temperature and reflux but no cyclisation was observed. The corresponding acetate also failed to undergo cyclisation. Repeating the reactions in refluxing dichloroethane gave complex mixtures. It appeared that the i-propenyl group was too hindered for RCM to occur. By moving the reaction site away from the quaternary centre of the hydrindane skeleton we hoped to successfully achieve cyclisation. It is also

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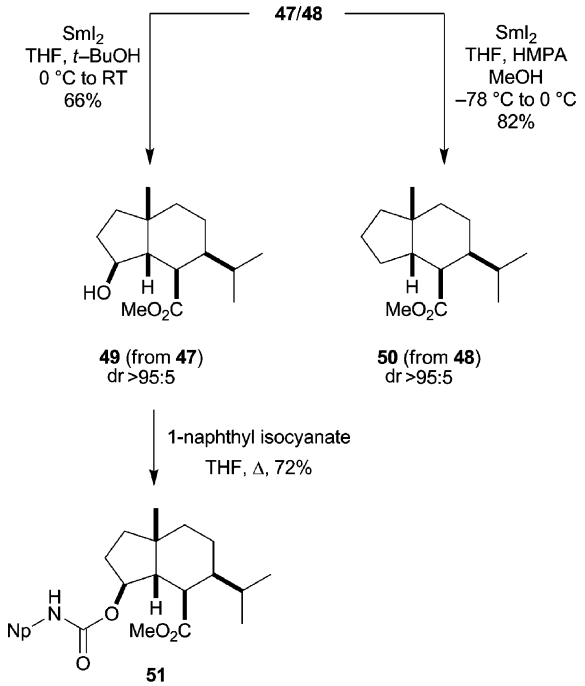
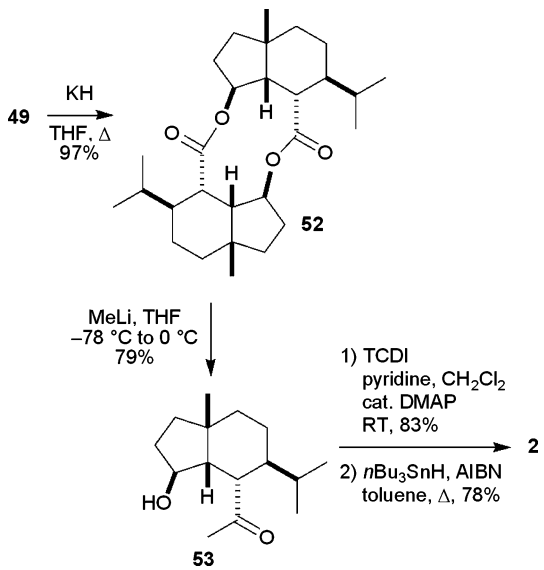
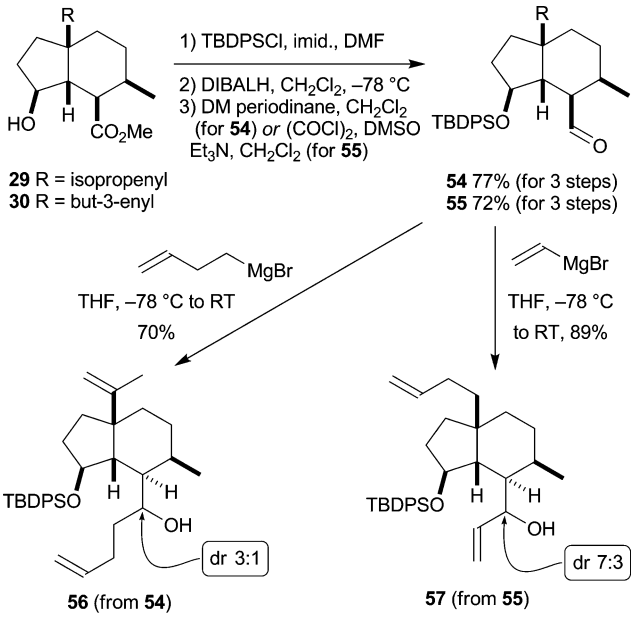


Scheme 8 Diastereoselective samarium(II)-mediated cyclisations in an approach to the proposed structure of faurinone.

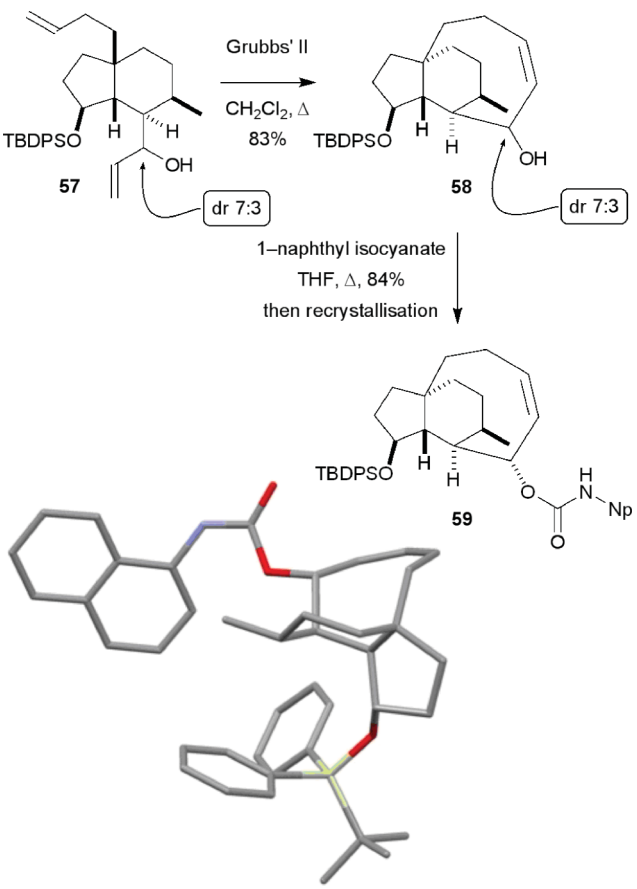


Scheme 9 Completing an approach to the proposed structure of faurinone.

known that the presence of allylic hydroxyl groups in diene substrates can accelerate the rate of carbene-exchange between the proximal alkene and ruthenium alkylidenes.[22] Pleasingly, slow addition of diene **57** (2 : 1 dr) in CH_2Cl_2 to Grubbs' II catalyst in CH_2Cl_2 at 40 °C resulted in complete cyclisation after 6 h and **58** was isolated as a 2 : 1 mixture of diastereoisomers in 83% yield. Tricycle **58** was converted to the corresponding naphthyl carbamate **59** in 84% and recrystallisation gave a single diastereoisomer that was subjected to X-ray crystallographic analysis (Scheme 11).[12]



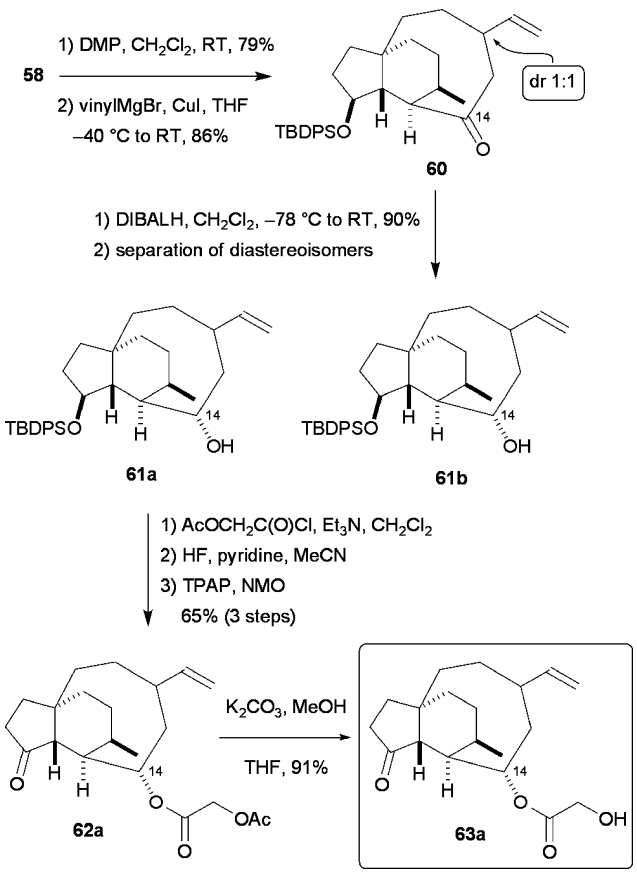
Scheme 10 Synthesis of RCM substrates in an approach to the tricyclic core of pleuromutilin.



Scheme 11 Synthesis of the tricyclic core of pleuromutilin.

Preliminary studies have been carried out to show the feasibility of preparing simplified analogues of pleuromutilin using our approach. Tricycle alcohol **58** was oxidised to the corresponding enone and vinylcuprate addition gave **60** as a 1 : 1 mixture of

diastereoisomers. Selective reduction with DIBALH gave **61** as a separable mixture of diastereoisomers in 90% yield. Unfortunately, NOE studies have not allowed unambiguous assignment of the relative stereochemistry in the two diastereoisomers. We tentatively assign the relative stereochemistry at C14 on the basis of work by Gibbons[17c] and Boeckman[23] who independently found that DIBALH reduction of C14 ketones proceeds from the β-face (Scheme 12).



Scheme 12 Synthesis of a simplified analogue of pleuromutilin.

Acylation of the C14 hydroxyl in **61a**, silyl ether deprotection and oxidation, gave **62a** in good overall yield. Finally, acetate hydrolysis gave simplified pleuromutilin analogue **63a**.

In summary, we have developed a flexible, stereoselective approach to the *cis*-hydrindane motif found in a number of biologically active natural products that utilises highly diastereoselective SmI_2-mediated cyclisations of aldehyde and halide substrates. The strategy has been exploited in the first synthesis of the proposed structure of faurinone, a sesquiterpene ketone isolated from *valeriana officinalis*, and in a preliminary approach to analogues of the antibacterial natural product, pleuromutilin.

Experimental

1 General Procedures

All reactions were carried out under an inert nitrogen atmosphere unless otherwise stated. Glassware for inert atmosphere reactions was oven-dried and cooled under a flow of nitrogen. Tetrahydrofuran (THF) was distilled over sodium wire and benzophenone, dichloromethane, toluene and triethylamine were distilled over calcium hydride and dimethyl formamide (DMF) was dried over activated molecular sieves. All other solvents and reagents were purchased from commercial sources and used as supplied. ^{1}H NMR spectra were recorded on a 300, 400 or 500 MHz spectrometer; ^{13}C NMR spectra were recorded at 75, 100 or 125 MHz. All chemical shift values are reported in ppm, with coupling constants in Hz. The notation of signals is: δ_H *chemical shift in ppm* (*number of protons*, *multiplicity*, *J value*(*s*), *proton assignment*). δ_C *chemical shift in ppm* (*carbon assignment*). If assignment is ambiguous, for example in the case of overlapping aromatic signals, a range of shifts is reported. Routine TLC analysis was carried out on aluminium sheets coated with silica gel 60 F254, 0.2 mm thickness using petroleum ether 40–60/ethyl acetate mixtures as solvent systems. Plates were viewed with a 254 nm ultraviolet lamp and dipped in aqueous potassium permanganate, *p*-anisaldehyde or DNP. Flash column chromatography was carried out on 40–63 μ, 60A silica gel. Low-resolution mass and high resolution mass spectra were obtained using electron impact ionisation (EI) and chemical ionisation (CI) techniques, or positive and/or negative electrospray ionisation (ES). Melting points were measured on a variable heater apparatus and are uncorrected. IR spectra were recorded on a FTIR spectrometer as evaporated films (from dichloromethane) or neat, using sodium chloride windows.

Full experimental detail, characterisation and spectra for compounds **2**, **8–14**, **17**, **18**, **21**, **23–26**, **29**, **31–33**, **37**, **43** and **46–53** have been previously reported.[7,18]

2.1 General procedure 1. Formation of vinyl triflates

To a stirred suspension of copper(I) iodide in THF at –45 °C or –20 °C was added a solution of the Grignard reagent or organolithium over 30 min. After stirring for a further 30 min, a solution of the α,β-unsaturated ketone in THF was added dropwise. The reaction was stirred at –45 °C or –20 °C until the disappearance of the α,β-unsaturated ketone was observed by TLC analysis of the reaction mixture. This generally occurred after approximately 1 h. A solution of Comins' reagent in THF was added and the reaction was allowed to warm to room temperature and stirred until completion as judged by TLC analysis. The reaction was quenched by the addition of aqueous saturated NH_4Cl and the aqueous phase was extracted with Et_2O (× 3). The combined organic fractions were dried (Na_2SO_4) and concentrated *in vacuo*. The crude vinyl triflate was purified by chromatography on silica gel.

2.2 General procedure 2. Carbonylative coupling of vinyl triflates with MeOH or formic acid

Carbon monoxide gas was bubbled through a suspension of the vinyl triflate (1 equiv), palladium acetate (0.1 or 0.2 equiv), triphenylphosphine (0.2 or 0.4 equiv), MeOH or formic acid and triethylamine (2 equiv) in DMF for 30 min. The reaction was then heated at 40 °C under an atmosphere of carbon monoxide until the disappearance of the vinyl triflate was observed by TLC analysis. Upon cooling, the reaction was quenched with water and extracted with Et_2O (× 3). The combined organic extracts were dried (Na_2SO_4) and concentrated *in vacuo*. The crude products were purified by chromatography on silica gel.

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2.3 General procedure 3. HF-pyridine mediated TBS ether cleavage

To a solution of the TBS ether (1 equiv) in a 2 : 1 mixture of acetonitrile and pyridine at 0 °C was added dropwise aqueous HF (10–25 equiv). The reaction was then stirred at room temperature until the starting alcohol had been consumed (TLC analysis). The reaction was quenched by dropwise addition of aqueous saturated $NaHCO_3$. Once effervescence had subsided, the mixture was extracted with Et_2O (× 3). The combined organic extracts were washed with aqueous saturated $CuSO_4$ (× 2), brine (× 2) and then dried (Na_2SO_4). Concentration *in vacuo* gave the alcohols which in some cases required purification by chromatography on silica gel.

2.4 General Procedure 4. Swern oxidation

DMSO (2 equiv.) was added to a stirred solution of oxalyl chloride (1.2 equiv.) in CH_2Cl_2 at −78 °C and the resulting solution was stirred for 15 min. A solution of the alcohol in CH_2Cl_2 was added and the solution was stirred for 1 h at −78 °C before triethylamine (5 equiv.) was added. Upon warming to room temperature the reaction was stirred for 2 h before being quenched by the addition of aqueous saturated $NaHCO_3$. The mixture was extracted with Et_2O (× 3), the combined organic fractions were dried (Na_2SO_4) and concentrated *in vacuo*. The crude aldehyde was purified by chromatography on silica gel.

2.5 General procedure 5. SmI_2-mediated cyclisations

SmI_2 in THF (0.1 M, 2.5 equiv) was added to degassed *t*-BuOH and the resulting solution was stirred under a nitrogen atmosphere for 20 min before being cooled to 0 °C (ice bath). After cooling, the aldehyde (1 equiv) was added dropwise as a solution in THF and the reaction was stirred at 0 °C or 20 °C until complete consumption of the aldehyde was observed by TLC analysis of the reaction mixture. Upon completion, the excess SmI_2 was quenched by allowing air to reach the reaction and an aqueous saturated solution of $NaHCO_3$ was added. The crude reaction mixture was then extracted with Et_2O (× 3). The combined organic fractions were washed with water and brine, dried (Na_2SO_4) and concentrated *in vacuo*. The crude products were purified by chromatography on silica gel.

3 Formation of aldehyde cyclisation substrates

3.1 Preparation of aldehyde 19

3.1.1 *Rac*-(3*S*,6*R*)-3-(3-((*tert*-butyldimethylsilyl)oxy)propyl)-3,6-dimethylcyclohex-1-en-1-yl trifluoromethanesulfonate 15. General procedure 1, at −20 °C using MeLi (1.6 M in Et_2O, 33.73 mL, 5.96 mmol)), copper(I) iodide (567 mg, 2.98 mmol) in THF (15 mL), **9** (400 mg, 1.49 mmol) in THF (10 mL) and Comins' reagent (1.05 g, 2.68 mmol) in THF (10 mL) after 24 h gave **15** (475 mg, 1.10 mmol, 74%; dr ~ 3 : 1) as a pale yellow oil. For the mixture: ^{1}H NMR (500 MHz, $CDCl_3$) δ_H 5.48 (1H, s, C═C*H*), 3.63–3.58 (2H, m, CH_2OTBDMS), 2.53–2.50 (1H, m, C*H*CH_3), 1.98–1.90 (1H, m, 1H from C$H_2$$CHCH_3$), 1.53–1.44 (4H, m, 2H C$H_2$$CH_2$$CH_2$OTBDMS and 1H from CH_3CHCH_2 and 1H from C$H_2$$CH_2$OTBDMS), 1.43–1.34 (3H, m, 1H from C$H_2$$CH_2$OTBDMS and C$H_2$$CH_2$$CHCH_3$), 1.14 (3H, d, J = 7.0 Hz, CH_3CH), 1.05 (3H, s, CH_3C), 0.90 (9H, s, SiC(CH_3)$_3$), 0.06 (6H, s, Si(CH_3)$_2$); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 152.4 (OTf*C*═C), 127.0 (H*C*═COTf), 117.1 (SO_2CF_3, q, J = 128 Hz), 63.5 (*C*H_2OTBDMS), 38.4 (*C*$H_2$$CH_2$$CHCH_3$), 36.1 ($CH_3$*C*), 32.6 (*C*$HCH_3$), 32.0 (*C*$H_2$$CH_2$$CH_2$OTBDMS), 28.7 (*C*$H_2$$CHCH_3$), 27.5 (*C*$H_2$$CH_2$OTBDMS), 26.7 (*C*$H_3$C), 25.9 (SiC(*C*$H_3$)$_3$), 18.3, (Si*C*(CH$_3$)$_3$), 17.7 (*C*$H_3$CH), −5.3 (Si(*C*$H_3$)$_2$); ν_{max} (liquid film)/cm^{-1} 1404 m (O═S═O), 1140 m; MS (ES$^+$) m/z (%) 453 (100 [M + Na]$^+$); Calcd for $C_{18}H_{33}O_4F_3Ssi$ + Na^+: 453.1713, found: m/z 453.1705.

3.1.2 *Rac*-(3*S*,6*R*)-methyl 3-(3-((*tert*-butyldimethylsilyl)oxy)-propyl)-3,6-dimethylcyclohex-1-enecarboxylate. General procedure 2 using **15** (75 mg, 0.174 mmol; dr ~ 3 : 1), palladium acetate (4 mg, 17.4 μmol), triphenylphosphine (9 mg, 34.8 μmol), MeOH (0.282 mL, 6.97 mmol) and triethylamine (49 μL, 0.348 mmol) in DMF (1.1 mL) after 24 h gave *rac*-(3*S*,6*R*)-methyl 3-(3-((*tert*-butyldimethylsilyl)oxy)propyl)-3,6-dimethylcyclohex-1-enecarboxylate (45 mg, 0.132 mmol, 77%; dr ~ 3 : 1) as a colourless oil. For the mixture: ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 6.63 (1H, s, C═C*H*), 3.73 (3H, s, CO_2CH_3), 3.56 (2H, t, J = 6.7 Hz, CH_2OTBDMS), 2.68–2.58 (1H, m, CH_3C*H*), 1.81–1.71 (1H, m, 1H from CH_2CH), 1.53–1.43 (3H, m, 1H from CH_2CH and 2H from C$H_2$$CH_2$OTBDMS), 1.41–1.25 (4H, m, 2H from C$H_2$$CCH_3$ and 2H from C$H_2$$CH_2$$CH_2$OTBDMS), 1.06 (3H, d, J = 5.8 Hz, CH_3CH), 1.02 (3H, s, CH_3C), 0.89 (9H, s, OSiC(CH_3)$_3$), 0.04 (6H, s, OSi(CH_3)$_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 168.5 (*C*O_2Me), 148.0 (*C*H═C), 133.9 (*C*CO_2Me), 64.0 (*C*H_2OTBDMS), 51.7 (CO_2CH_3), 37.9 (*C*$H_2$$CH_2$$CH_2$OTBDMS), 35.8 (*C*$CH_3$), 35.3 (*C*$H_2$CH), 30.6 (*C*$H_2$$CH_2$OTBDMS), 29.1 (*C*$H_3$CH), 28.5 (*C*$HCH_3$), 27.1 (C$H_2$$CCH_3$), 26.2 (OSiC(*C*$H_3$)$_3$, 20.4 (*C*$H_3$C), 18.6 ((OSi*C*(CH$_3$)$_3$), −5.0 (OSi(*C*$H_3$)$_2$); ν_{max} (liquid film)/cm^{-1} 2961 m, 2361 m, 2040 m, 1720 m (C═O), 1260 m, 1058 s; MS (ES$^+$) m/z (%) 358 (100 [M + NH_4]$^+$); Calcd for $C_{19}H_{36}O_3Si$ + NH_4^+: 358.2772, found: m/z 358.2775.

3.1.3 *Rac*-(3*S*,6*R*)-methyl 3-(3-hydroxypropyl)-3,6-dimethylcyclohex-1-enecarboxylate. General procedure 3 using *rac*-(3*S*,6*R*)-methyl 3-(3-((*tert*-butyldimethylsilyl)oxy)propyl)-3,6-dimethylcyclohex-1-enecarboxylate (280 mg, 0.822 mmol; dr ~ 3 : 1), aqueous 40% HF (0.308 mL, 6.16 mmol), pyridine (6.13 mL) and MeCN (12.3 mL), after 2.5 h, gave *rac*-(3*S*,6*R*)-methyl 3-(3-hydroxypropyl)-3,6-dimethylcyclohex-1-enecarboxylate (182 mg, 0.804 mmol, 98%; dr ~ 3 : 1) as a colourless oil. For the mixture: ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 6.62 (1H, s, C═C*H*), 3.72 (3H, s, CO_2CH_3), 3.60 (2H, t, J = 6.6 Hz, CH_2OH), 2.68–2.57 (1H, m, CH_3C*H*), 1.81–1.64 (2H, m, CH_2CH), 1.58–1.50 (2H, m, C$H_2$$CH_2$OH), 1.48–1.36 (4H, m, 2H from CH_2 and 2H from C$H_2$$CH_2$$CH_2$OH), 1.05 (3H, d, J = 6.9 Hz, CH_3CH), 1.03 (3H, s, CH_3C); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 168.5 (*C*O_2CH_3), 168.3 (*C*O_2CH_3 (minor diastereoisomer)), 147.7 (*C*H═C (minor diastereoisomer)), 147.6 (*C*H═C), 134.1 (*C*CO_2Me), 63.7 (*C*H_2OH), 51.7 (CO_2CH_3), 38.7 (*C*$H_2$$CH_2$$CH_2$OH (minor diastereoisomer)), 37.5 (*C*$H_2$$CH_2$$CH_2$OH), 35.8 (*C*$CH_3$ (minor diastereoisomer)), 35.3 (*C*CH_3), 30.7 (*C*$H_2$$CH_2$OH), 28.9 (*C*$HCH_3$), 28.5 (*C*$H_2$CH), 28.1 (*C*$H_3$CH), 27.8 (*C*$H_3$CH (minor diastereoisomer)), 27.3 (*C*$H_2$$CH_2$$CHCH_3$), 27.2 (*C*$H_2$$CH_2$$CHCH_3$ (minor diastereoisomer)), 20.4 (*C*H_3C), 20.2 (*C*H_3C (minor diastereoisomer)); ν_{max} (liquid film)/cm^{-1} 3403 m (OH), 1705 s

(C═O); MS (ES$^+$) *m/z* (%) 227 (100 [M + H]$^+$); Calcd for $C_{13}H_{22}O_3$ + H$^+$: 227.1642, found *m/z* 227.1650.

3.1.4 *Rac*-(3*S*,6*R*)-methyl 3,6-dimethyl-3-(3-oxopropyl)-cyclohex-1-enecarboxylate 19. General procedure 4 using DMSO (95 μL, 1.34 mmol) and oxalyl chloride (65 μL, 0.74 mmol) in CH_2Cl_2 (2 mL), with *rac*-(3*S*,6*R*)-methyl 3-(3-hydroxypropyl)-3,6-dimethylcyclohex-1-enecarboxylate (134 mg, 0.592 mmol; dr ~ 3 : 1) in CH_2Cl_2 (11 mL) and triethylamine (0.62 mL, 4.43 mmol) gave **19** (125 mg, 0.557 mmol, 94%; dr ~ 3 : 1) as a colourless oil. For the mixture: ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 9.79 (1H, t, *J* = 1.5 Hz, C*H*O), 6.58 (1H, s, C*H*═C), 3.74 (3H, s, CO_2CH_3), 2.68–2.60 (1H, m, C*H*CH_3), 2.48–2.42 (2H, m, CH_2CHO), 1.80–1.58 (4H, m, CH_2CH_2CHO and CH_2CHCH_3), 1.57–1.39 (2H, m, CH_2CH_2CHCH_3), 1.07 (3H, d, *J* = 7.0 Hz, CH_3CH), 1.04 (3H, s, CCH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 202.4 (*C*HO), 168.2 (*C*O_2CH_3), 146.1 (C═*C*H), 135.0 (*C*CO_2CH_3), 51.8 (O*C*H_3), 39.5 (*C*H_2CHO), 34.9 (*C*H_2CHCH_3), 33.0 (*C*H_2CH_2CHO), 30.7 (*C*H_2CH_2CHCH_3), 28.5 (*C*HCH_3), 27.1 (C*C*H_3), 26.6 (*C*CH_2), 20.3 (CH*C*H_3); ν_{max} (liquid film)/cm^{-1} 2722 m (CHO), 1712 m (CHO), 1621 m (C═O); MS (CI$^+$) *m/z* (%) 225 (100 [M + H]$^+$); Calcd for $C_{13}H_{20}O_3$ + NH_4 (ES$^+$): 242.1751, found *m/z* 242.1757.

3.2 Preparation of aldehyde 20

3.2.1 *Rac*-(3*S*,6*R*)-3-(3-((*tert*-butyldimethylsilyl)oxy)propyl)-6-methyl-3-vinylcyclohex-1-en-1-yl trifluoromethanesulfonate 16. General procedure 1, at –45 °C using vinyl magnesium bromide (1.0 M in THF, 7.04 mL, 7.04 mmol), copper(I) iodide (674 mg, 3.54 mmol) in THF (20 mL), **9** (500 mg, 1.77 mmol) in THF (12 mL) and Comins' reagent (1.25 g, 3.19 mmol) in THF (12 mL) after 24 h gave **16** (564 mg, 1.27 mmol, 72%; dr 4 : 1) as a pale yellow oil. For the mixture: ^{1}H NMR (500 MHz, $CDCl_3$) δ_H 5.67 (1H, dd, *J* = 17.5, 10.5 Hz, *H*C═CH_2), 5.65 (dd, *J* = 17.5, 10.5 Hz, *H*C═CH_2 (minor diastereoisomer)), 5.55 (s, *H*C═C (minor diastereoisomer)), 5.54 (1H, d, *J* = 0.5 Hz, *H*C═C), 5.13 (1H, dd, *J* = 10.5, 1.1 Hz, *cis* HC═C*H*H), 5.11 (dd, *J* = 10.5, 1.1 Hz, *cis* HC═C*H*H (minor diastereoisomer)), 4.97 (dd, *J* = 17.5, 1.1 Hz, *trans* HC═CH*H* (minor diastereoisomer)), 4.91 (1H, dd, *J* = 17.5, 1.1 Hz, *trans* HC═CH*H*), 3.63–3.57 (2H, m, CH_2OTBDMS), 2.55–2.46 (1H, m, C*H*CH_3), 1.86–1.80 (1H, m, 1H from CH_2CHCH_3), 1.53–1.38 (7H, m, 1H from CH_2CHCH_3, CH_2CH_2CHCH_3, C$H_2CH_2CH_2$OTBDMS and CH_2CH_2OTBDMS), 1.15 (d, *J* = 6.5 Hz, CH_3CH (minor diastereoisomer)), 1.13 (3H, d, *J* = 6.5 Hz, CH_3CH), 0.90 (s, SiC(CH_3)$_3$ (minor diastereoisomer)), 0.89 (9H, s, SiC(CH_3)$_3$), 0.05 (6H, s, (CH_3)$_2$Si); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 153.7 (*C*OTf), 144.0 (*C*H═CH_2), 122.9 (*C*HCOTf), 118.5 (SO_2CF_3, q, *J* = 319.5), 115.2 (*C*H_2═CH), 63.3 (*C*H_2OTBDMS), 43.4 (*C*CHCOTf), 37.4 (*C*$H_2CH_2CH_2$OTBDMS), 33.0 (*C*HCH_3), 31.9 (*C*H_2CH_2OTBDMS), 28.3 (*C*H_2CHCH_3), 27.4 (*C*H_2CH_2CHCH_3), 25.9 (SiC(*C*H_3)$_3$), 18.3 (Si*C*(CH_3)$_3$), 17.6 (*C*H_3CH), –5.3 (Si(*C*H_3)$_2$); ν_{max} (liquid film)/cm^{-1} 1417 m (O═S═O), 1100 m (Si–O); MS (CI$^+$) *m/z* (%) 443 (100 [M + H]$^+$); Calcd for $C_{19}H_{33}O_4F_3SSi$ + H$^+$ (ES$^+$): 443.1894, found *m/z* 443.1887.

3.2.2 *Rac*-(3*S*,6*R*)-methyl 3-(3-((*tert*-butyldimethylsilyl)oxy)-propyl)-6-methyl-3-vinylcyclohex-1-enecarboxylate. General procedure 2 using **16** (405 mg, 0.915 mmol; dr 4 : 1), palladium acetate (21 mg, 91.5 μmol), triphenylphosphine (48 mg, 0.183 mmol), MeOH (1.86 mL, 36.8 mmol) and triethylamine (0.255 mL, 1.83 mmol) in DMF (3 mL) after 24 h gave *rac*-(3*S*,6*R*)-methyl 3-(3-((*tert*-butyldimethylsilyl)oxy)propyl)-6-methyl-3-vinylcyclohex-1-enecarboxylate (250 mg, 0.709 mmol, 77%; dr 4 : 1) as a colourless oil. For the mixture: ^{1}H NMR (500 MHz, $CDCl_3$) δ_H 6.68 (1H, s, C*H*═C), 5.74 (1H, dd, *J* = 17.5, 10.5 Hz, *H*C═CH_2), 5.66 (dd, *J* = 17.5, 10.5 Hz, *H*C═CH_2 (minor diastereoisomer)), 5.07 (1H, dd, *J* = 10.5, 0.9 Hz, *cis* HC═C*H*H) 5.05 (dd, *J* = 10.5, 0.9 Hz, *cis* HC═C*H*H (minor diastereoisomer)), 4.92 (1H, dd, *J* = 17.5, 1.0 Hz, *trans* HC═CH*H*), 4.81 (dd, *J* = 17.7, 1.0 Hz, *trans* HC═CH*H* (minor diastereoisomer)), 3.74 (3H, s, CO_2CH_3), 3.63–3.55 (2H, m, CH_2OTBDMS), 2.64–2.58 (1H, m, C*H*CH_3), 1.81–1.75 (1H, m, 1H from CH_2CHCH_3), 1.61–1.56 (2H, m, CH_2CH_2CHCH_3), 1.53–1.36 (5H, m, 1H from CH_2CHCH_3 and C$H_2CH_2CH_2$OTBDMS and CH_2CH_2OTBDMS), 1.06 (3H, d, *J* = 6.9 Hz, C*H*CH_3), 0.90 (9H, s, SiC(CH_3)$_3$), 0.05 (6H, s, Si(CH_3)$_2$); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 168.1 (*C*═O), 144.6 (*C*H═CH_2), 143.5 (C═*C*H), 135.5 (*C*CO_2CH_3), 113.9 (*C*H_2═CH), 63.5 (*C*H_2OTBDMS), 51.5 (CO_2CH_3), 43.4 (*C*CH═CH_2), 36.4 (*C*$H_2CH_2CH_2$OTBDMS), 29.7 (*C*H_2CH_2OTBDMS), 28.9 (*C*HCH_3), 27.4 (*C*H_2CHCH_3), 27.0 (*C*H_2CH_2CHCH_3), 25.9 (SiC(*C*H_3)$_3$), 20.0 (*C*HCH_3), 18.4 (Si*C*(CH_3)$_3$), –5.3 (Si(*C*H_3)$_2$); ν_{max} (liquid film)/cm^{-1} 1418 m (O═S═O), 1100 m (Si–O); MS (ES$^+$) *m/z* (%) 375 (100 [M + Na]$^+$); Calcd for $C_{20}H_{36}O_3Si$ + Na$^+$: 375.2326, found *m/z* 375.2325.

3.2.3 *Rac*-(3*S*,6*R*)-methyl 3-(3-hydroxypropyl)-6-methyl-3-vinylcyclohex-1-enecarboxylate. General procedure 3 using *rac*-(3*S*,6*R*)-methyl 3-(3-((*tert*-butyldimethylsilyl)oxy)propyl)-6-methyl-3-vinylcyclohex-1-enecarboxylate (250 mg, 0.709 mmol; dr 4 : 1), aqueous 40% HF (0.70 mL, 14.2 mmol), pyridine (5.5 mL) and MeCN (11 mL), after 2.5 h, gave *rac*-(3*S*,6*R*)-methyl 3-(3-hydroxypropyl)-6-methyl-3-vinylcyclohex-1-enecarboxylate (152 mg, 0.638 mmol, 90%; dr 4 : 1) as a colourless oil. For the mixture: ^{1}H NMR (500 MHz, $CDCl_3$) δ_H 6.69 (1H, s, C*H*═C), 5.74 (1H, dd, *J* = 17.7, 10.5 Hz, *H*C═CH_2), 5.65 (1H, dd, *J* = 17.7, 10.5 Hz, *H*C═CH_2 (minor diastereoisomer)), 5.08 (1H, dd, *J* = 10.5, 1.0 Hz, *cis* HC═C*H*H) 5.06 (1H, dd, *J* = 10.5, 1.0 Hz, *cis* HC═C*H*H (minor diastereoisomer)), 4.92 (1H, dd, *J* = 17.7, 1.0 Hz, *trans* HC═CH*H*), 4.81 (1H, dd, *J* = 17.7, 1.0 Hz, *trans* HC═CH*H* (minor diastereoisomer)), 3.74 (3H, s, CO_2CH_3), 3.64–3.60 (2H, m, CH_2OH), 2.64–2.58 (1H, m, C*H*CH_3), 1.82–1.76 (1H, m, 1H from CH_2CHCH_3), 1.64–1.55 (2H, m, CH_2CH_2CHCH_3), 1.55–1.37 (5H, m, 1H from CH_2CHCH_3 and C$H_2CH_2CH_2$OH and CH_2CH_2OH), 1.07 (3H, d, *J* = 7.1 Hz, CH_3CH (minor diastereoisomer)), 1.06 (3H, d, *J* = 7.1 Hz, CH_3CH); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 168.1 (*C*═O), 144.5 (*C*H═CH_2), 143.1 (C═*C*H), 135.6 (*C*CO_2CH_3), 114.1 (*C*H_2═CH), 63.3 (*C*H_2OH), 51.5 (CO_2CH_3), 42.2 (*C*CH═CH_2), 36.5 (*C*$H_2CH_2CH_2$OH), 29.9 (*C*H_2CH_2OH), 29.0 (*C*HCH_3), 27.9 (*C*H_2CH_2CHCH_3), 27.4 (*C*H_2CHCH_3), 20.1 (*C*HCH_3); ν_{max} (liquid film)/cm^{-1} 3375 m (O–H), 1655 m (C═O); MS (ES$^+$) *m/z* (%) 261 (100 [M + Na]$^+$); Calcd for $C_{14}H_{22}O_3$ + Na$^+$: 261.1461, found *m/z* 261.1466.

3.2.4 *Rac*-(3*S*,6*R*)-methyl 6-methyl-3-(3-oxopropyl)-3-vinylcyclohex-1-enecarboxylate 20. General procedure 4 using DMSO (86 μL, 1.21 mmol) and oxalyl chloride (59 μL,

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0.656 mmol) in CH_2Cl_2 (4 mL), with *rac*-(3*S*,6*R*)-methyl 3-(3-hydroxypropyl)-6-methyl-3-vinylcyclohex-1-enecarboxylate (125 mg, 0.525 mmol; dr 4 : 1) in CH_2Cl_2 (8 mL) and triethylamine (0.42 mL, 2.99 mmol) gave **20** (115 mg, 0.487 mmol, 93%; dr 4 : 1) as a colourless oil. For the mixture ^{1}H NMR (500 MHz, $CDCl_3$) δ_H 9.76 (1H, s, C*H*O), 6.61 (1H, s, C*H*═C), 5.67 (1H, dd, *J* = 17.7, 10.5 Hz, *H*C═CH_2), 5.59 (dd, *J* = 17.7, 10.5 Hz, *H*C═CH_2 (minor diastereoisomer)), 5.10 (1H, dd, *J* = 10.5, 1.0 Hz, *cis* HC═C*H*H) 5.08 (dd, *J* = 10.5, 1.0 Hz, *cis* HC═C*H*H (minor diastereoisomer)), 4.93 (1H, dd, *J* = 17.7, 1.0 Hz, *trans* HC═CH*H*), 4.83 (dd, *J* = 17.7, 1.0 Hz, *trans* HC═CH*H* (minor diastereoisomer)), 3.72 (3H, s, CO_2CH_3), 2.62–2.56 (1H, m, C*H*CH_3), 2.48–2.39 (2H, m, CH_2CHO), 1.79–1.70 (3H, m, 1H from CH_2CHCH_3 and CH_2CH_2CHO), 1.62–1.56 (1H, m, CH_2CH_2CHCH_3), 1.45–1.35 (2H, m, 1H from CH_2CHCH_3 and 1H from CH_2CH_2CHCH_3), 1.05 (d, *J* = 7.0 Hz, CH_3CH (minor diastereoisomer)), 1.03 (3H, d, *J* = 7.0 Hz, C*H*CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 201.9 (*C*HO), 167.8 (*C*═O), 143.7 (*C*H═CH_2), 141.7 (C═*C*H), 136.4 (*C*CO_2CH_3), 115.0 (*C*H_2═CH), 51.6 (CO_2CH_3), 42.1 (*C*CH═CH_2), 39.0 (*C*H_2CHO), 31.7 (*C*H_2CHCH_3), 29.8 (*C*H_2CH_2CHO), 28.9 (*C*HCH_3), 26.9 (*C*H_2CH_2CHCH_3), 20.0 (CH*C*H_3); ν_{max} (liquid film)/cm^{-1} 2043 m (CHO), 1657 m (C═O); MS (ES$^+$) *m*/*z* (%) 259 (100 [M + Na]$^+$); Calcd for $C_{14}H_{20}O_3$ + Na^+: 259.1305, found *m*/*z* 259.1312.

3.3 Preparation of aldehyde 22

3.3.1 *Rac*-(3*S*,6*R*)-methyl 3-(but-3-en-1-yl)-3-(3-((*tert*-butyldimethylsilyl)oxy)propyl)-6-methylcyclohex-1-enecarboxylate. General procedure 2 using **18** (2.80 mg, 5.95 mmol; dr 3 : 1), palladium acetate (262 mg, 1.19 mmol), triphenylphosphine (390 mg, 1.49 mmol), MeOH (28 mL, 691 mmol) and triethylamine (1.67 mL, 11.9 mmol) in DMF (20 mL) after 24 h gave *rac*-(3*S*,6*R*)-methyl 3-(but-3-en-1-yl)-3-(3-((*tert*-butyldimethylsilyl)-oxy)propyl)-6-methylcyclohex-1-enecarboxylate (1.81 mg, 4.76 mmol, 80%; dr ~ 4 : 1) as a colourless oil. For the mixture: ^{1}H NMR (500 MHz, $CDCl_3$) δ_H 6.66 (1H, s, C*H*CCO_2CH_3), 5.85–5.75 (1H, m, C*H*═CH_2), 5.02 (1H, dd, *J* = 17.0, 1.5 Hz, *trans* CH_2═CH), 5.00 (dd, *J* = 17.0, 1.5 Hz, *trans* CH_2═CH (minor diastereoisomer)), 4.97 (1H, d, *J* = 10.0 Hz, *cis* CH_2═CH), 4.93 (dd, *J* = 10.0, 1.0 Hz, *cis* CH_2═CH (minor diastereoisomer)), 3.74 (3H, s, CO_2CH_3), 3.60–3.54 (2H, m, CH_2OTBDMS), 2.69–2.64 (1H, m, C*H*CH_3), 2.09–2.02 (1H, m, 1H from CH_2CH═CH_2), 2.00–1.91 (1H, m, 1H from CH_2CH═CH_2), 1.80–1.73 (1H, m, 1H from CH_2CHCH_3), 1.62–1.56 (1H, m, 1H from CH_2CH_2CHCH_3), 1.52–1.31 (8H, m, CH_2CH_2OTBDMS, CH_2CH_2CH_2OTBDMS, CCH_2CH_2CH═CH_2, 1H from CH_2CHCH_3, 1H from CH_2CH_2CHCH_3), 1.07 (3H, d, *J* = 7.0 Hz, CH_3CH), 0.90 (s, OSiC(CH_3)$_3$ (minor diastereoisomer)), 0.89 (9H, s, OSiC(CH_3)$_3$), 0.06 (s, OSi(CH_3)$_3$ (minor diastereoisomer)), 0.05 (6H, s, OSi(CH_3)$_2$); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 168.0 (*C*═O), 146.6 (*C*H═CCO_2CH_3), 139.0 (*C*H═CH_2), 134.4 (═*C*CO_2CH_3), 114.3 (*C*H_2═CH), 63.6 (*C*H_2OTBDMS), 51.5 (CO_2CH_3), 38.5 (C*C*H_2CH_2CH═CH_2), 37.9 (*C*CHCCO_2CH_3), 35.1 (*C*H_2CH_2CH_2OTBDMS), 28.4 (*C*H_2CH═CH_2), 27.9 (*C*HCH_3), 27.3 (*C*H_2CH_2OTBDMS), 27.0 (*C*H_2CH_2CHCH_3), 26.5 (*C*H_2CHCH_3), 25.9 (SiC(*C*H_3)$_3$), 20.1 (*C*H_3CH), 18.3 (Si*C*(CH$_3$)$_3$), −5.3 (Si(*C*H$_3$)$_2$); ν_{max}/(liquid film) cm^{-1} 2929 s (CH_2s), 1718 s (C═O), 1435 m (Si–C), 1099 m (Si–O), 836 w (C═C); MS (ES$^+$) *m*/*z* (%) 403 (100 [M + Na]$^+$); Calcd for $C_{22}H_{40}O_3Si$ + NH_4^+: 398.3085, found *m*/*z* 398.3091.

3.3.2 *Rac*-(3*S*,6*R*)-methyl 3-(but-3-en-1-yl)-3-(3-hydroxypropyl)-6-methylcyclohex-1-enecarboxylate. General procedure 3 using *rac*-(3*S*,6*R*)-methyl 3-(but-3-en-1-yl)-3-(3-((*tert*-butyldimethylsilyl)oxy)propyl)-6-methylcyclohex-1-enecarboxylate (1.41 g, 3.70 mmol; dr 3 : 1), aqueous 60% HF (1.23 mL, 37.0 mmol), pyridine (7.5 mL) and MeCN (15 mL), after 2.5 h, gave *rac*-(3*S*,6*R*)-methyl 3-(but-3-en-1-yl)-3-(3-hydroxypropyl)-6-methylcyclohex-1-enecarboxylate (955 mg, 3.59 mmol, 97%; dr ~ 4 : 1) as a colourless oil. For the mixture: ^{1}H NMR (500 MHz, $CDCl_3$) δ_H 6.65 (1H, s, C*H*CCO_2CH_3), 5.84–5.73 (1H, m, C*H*═CH_2), 5.02 (1H, d, *J* = 17.0 Hz, *trans* CH_2═CH), 5.01 (dd, *J* = 16.0, 1.0 Hz, *trans* CH_2═CH (minor diastereoisomer)), 4.97 (1H, d, *J* = 10.0 Hz, *cis* CH_2═CH), 4.93 (dd, *J* = 10.0, 1.0 Hz, *cis* CH_2═CH, minor diastereoisomer)), 3.73 (3H, s, CO_2CH_3), 3.68–3.58 (2H, m, CH_2OH), 2.68–2.65 (1H, m, C*H*CH_3), 2.09–2.00 (1H, m, 1H from CH_2CH═CH_2), 1.98–1.91 (1H, m, 1H from CH_2CH═CH_2), 1.80–1.73 (1H, m, 1H from CH_2CHCH_3), 1.64–1.52 (3H, m, 1H from CH_2CH$_2$OH, 1H from CH_2CH_2CHCH_3, 1H from CH_2CH_2CH_2OH), 1.48–1.43 (4H, m, 1H from CH_2CHCH_3, 1H from CH_2CH_2CHCH_3, CCH_2CH_2CH═CH_2) 1.42–1.35 (3H, m, 1H from CH_2CH$_2$OH, 1H from CH_2CH_2CH_2OH, CH$_2$O*H*), 1.06 (3H, d, *J* = 7.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 167.9 (*C*═O), 146.3 (*C*H═CCO_2CH_3), 138.9 (*C*H═CH_2), 134.7 (═*C*CO_2CH_3), 114.4 (*C*H_2═CH), 63.5 (*C*H_2OH), 51.5 (CO_2CH_3), 38.4 (C*C*H_2CH_2CH═CH_2), 37.9 (*C*CHCCO_2CH_3), 35.2 (*C*H_2CH_2CH_2OH), 28.3 (*C*H_2CH═CH_2), 27.8 (*C*HCH_3), 27.3 (*C*H_2CH_2OH), 27.0 (*C*H_2CH_2CHCH_3), 26.5 (*C*H_2CHCH_3), 20.1 (*C*H_3CH); ν_{max}/(liquid film) cm^{-1} 3403 s (O–H), 1720 s (C═O), 1252 s (Si–C), 1059 w (Si–O), 769 w (C═C); MS (ES$^+$) *m*/*z* (%) 289 (100 [M + Na]$^+$); Calcd for $C_{16}H_{26}O_3$ + NH_4^+: 284.2220, found *m*/*z* 282.2230.

3.3.3 *Rac*-(3*S*,6*R*)-methyl 3-(but-3-en-1-yl)-6-methyl-3-(3-oxopropyl)cyclohex-1-enecarboxylate. General procedure 4 using DMSO (0.85 mL, 11.9 mmol) and oxalyl chloride (0.56 mL, 6.22 mmol) in CH_2Cl_2 (50 mL), with *rac*-(3*S*,6*R*)-methyl 3-(but-3-en-1-yl)-3-(3-hydroxypropyl)-6-methylcyclohex-1-enecarboxylate (1.38 mg, 5.18 mmol; dr 3 : 1) in CH_2Cl_2 (50 mL) and triethylamine (4.13 mL, 29.5 mmol) gave **22** (1.36 g, 5.18 mmol, quant.; dr ~ 4 : 1) as a colourless oil. For the mixture: ^{1}H NMR (500 MHz, $CDCl_3$) δ_H 9.80 (s, C*H*O (minor diastereoisomer)), 9.77 (1H, s, C*H*O), 6.59 (1H, s, C*H*CCO_2CH_3), 5.83–5.72 (1H, m, C*H*═CH_2), 5.03 (1H, dd, *J* = 15.4, 1.6 Hz, *trans* CH_2═CH), 5.02 (dd, *J* = 15.4, 1.6 Hz, *trans* CH_2═CH (minor diastereoisomer)), 4.96 (1H, d, *J* = 10.1 Hz, *cis* CH_2═CH), 4.95 (d, *J* = 10.1 Hz, *cis* CH_2═CH (minor diastereoisomer)), 3.74 (3H, s, CO_2CH_3), 2.69–2.66 (1H, m, C*H*CH_3), 2.46–2.42 (2H, m, CH_2CHO), 2.09–2.01 (1H, m, 1H from CH_2CH═CH_2), 1.98–1.91 (1H, m, 1H from CH_2CH═CH_2), 1.80–1.62 (5H, m, 1H from CH_2CHCH_3, CH_2CH_2CHO, CH_2CH_2CHCH_3), 1.49–1.39 (3H, m, 1H from CH_2CHCH_3, CCH_2CH_2CH═CH_2), 1.07 (3H, d, *J* = 6.9 Hz, CH_3CH); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 202.0 (*C*HO), 167.7 (*C*O_2CH_3), 144.9 (*C*HCCO_2CH_3), 138.5 (*C*H═CH_2), 135.6 (*C*CO_2CH_3), 114.7 (*C*H_2═CH), 51.6 (*C*H_3O_2C), 39.3 (*C*H_2CHO (minor diastereoisomer)), 39.0 (*C*H_2CHO), 38.6

($CCH_2CH_2CH_2CH{=}CH_2$ (minor diastereoisomer)), 38.4 ($CCH_2CH_2CH_2CH{=}CH_2$), 37.6 ($CCHCO_2CH_3$), 30.9 (CH_2CH_2CHO), 28.3 ($CH_2CH{=}CH_2$), 27.8 ($CHCH_3$), 26.9 ($CH_2CH_2CCH_3$), 26.5 (CH_2CHCH_3), 20.0 (CH_3CH); ν_{max}/(liquid film) cm^{-1} 2928 m (CH_2s), 1717 m (C=O), 1110 m (Si–O), 823 w (C=C); MS (ES^+) *m/z* (%) 287 (90 [M + Na]$^+$); Calcd for $C_{16}H_{24}O_3 + NH_4^+$: 282.2064, found *m/z* 282.2051.

4 SmI_2-mediated Cyclisation of aldehydes 19, 20 and 22

4.1 *Rac*-(3*S*,3a*S*,4*R*,5*R*,7a*S*)-methyl 3-hydroxy-5,7a-dimethyl-octahydro-1*H*-indene-4-carboxylate 27

General procedure 5 using **19** (52 mg, 0.23 mmol; dr ~ 3 : 1) in THF (2.4 mL), SmI_2 (0.1 M in THF, 4.6 mL, 0.46 mmol) and *t*-BuOH (1.7 mL) gave **27** (38 mg, 0.17 mmol, 74%, dr >10 : 1) as a colourless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ_H 3.97–3.93 (1H, m, C*H*OH), 3.69 (3H, s, CO_2CH_3), 2.37 (1H, dd, *J* = 9.4, 4.7 Hz, C*H*CO_2CH_3), 2.16–2.07 (2H, m, C*H*CH_3 and 1H from C*H*$_2$CHOH), 1.85 (1H, dd, *J* = 9.4, 3.7 Hz, C*H*CHOH), 1.71–1.62 (2H, m, 1H from C*H*$_2$CHOH and 1H from C*H*$_2CH_2$CHOH), 1.61–1.50 (2H, m, C*H*$_2CHCH_3$), 1.47–1.41 (2H, m, 1H from C*H*$_2CH_2$CHOH and 1H from C*H*$_2CH_2CHCH_3$), 1.37–1.32 (1H, m, C*H*$_2CH_2CHCH_3$), 1.14 (3H, s, C*H*$_3$C), 0.89 (3H, d, *J* = 6.9 Hz, C*H*$_3$CH); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 175.8 (*C*=O), 79.6 (*C*HOH), 52.5 (*C*HCHOH), 51.5 (CO_2CH_3), 46.7 (H*C*CO_2CH_3), 39.7 (*C*CH_3), 36.6 (*C*H_2CH_2CHOH), 31.9 (*C*H_2CHOH), 31.5 (*C*$H_2CH_2CHCH_3$), 29.9 (*C*HCH_3), 28.9 (*C*H_3C), 27.2 (*C*H_2CHCH_3), 15.5 (*C*H_3CH); ν_{max}/(liquid film) cm^{-1} 3410 s (O–H), 1730 s (C=O); MS (EI^+) *m/z* (%) 227 (100 [M + H]$^+$); Calcd for $C_{13}H_{22}O_3 + NH_4^+$ (ES^+): 244.1907, found *m/z* 244.1907.

4.2 *Rac*-(3*S*,3a*S*,4*R*,5*R*,7a*S*)-methyl 3-hydroxy-5-methyl-7a-vinyloctahydro-1*H*-indene-4-carboxylate 28

General procedure 5 using **20** (100 mg, 0.423 mmol; dr 4 : 1) in THF (4.28 mL), SmI_2 (0.1 M in THF, 8.47 mL, 0.847 mmol) and *t*-BuOH (3.18 mL) gave **28** (75 mg, 0.317 mmol, 75%, dr 14 : 1) as a colourless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 5.96 (1H, dd, *J* = 17.7, 10.7 Hz, C*H*=CH_2), 5.12 (1H, d, *J* = 17.7 Hz, *trans* CH=C*H*$_2$), 5.04 (1H, d, *J* = 10.7 Hz, *cis* CH=C*H*$_2$), 3.92 (1H, quint (app), *J* = 4.1 Hz, C*H*OH), 3.68 (3H, s, CO_2CH_3), 2.41 (1H, dd, *J* = 10.1, 4.9 Hz, C*H*CO_2CH_3), 2.18 (1H, dd, *J* = 10.1, 3.5 Hz, C*H*CHOH), 2.15–2.07 (2H, m, C*H*CH_3 and 1H from C*H*$_2$CHOH), 1.77–1.69 (1H, m, 1H from C*H*$_2CHCH_3$), 1.66–1.58 (4H, m, 1H from C*H*$_2CHCH_3$, 1H from C*H*$_2CH_2$CHOH and 1H from C*H*$_2CH_2CHCH_3$ 1H from C*H*$_2$CHOH), 1.54–1.47 (1H, m, 1H from C*H*$_2CH_2$CHOH), 1.35–1.30 (1H, m, 1H from C*H*$_2CH_2CHCH_3$), 0.89 (3H, d, *J* = 7.0 Hz, C*H*$_3$CH); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 175.4 (*C*=O), 148.0 (H*C*=CH_2), 111.4 (HC=*C*H$_2$), 79.4 (H*C*OH), 51.6 (H*C*CH_3), 51.5 (H*C*CHOH), 50.5 (CO_2CH_3), 46.5 (*C*HCO_2CH_3), 46.2 (*C*CH=CH_2), 33.8 (*C*H_2CHCH_3), 32.0 (*C*$H_2CH_2CHCH_3$), 29.7 (*C*H_2CHOH), 27.2 (*C*H_2CH_2CHOH), 15.4 (*C*H_3CH); ν_{max}/(liquid film) cm^{-1} 3400 s (O–H), 2949 s (CH_2s),1732 s (C=O), 837 w (C=C); MS (ES^+) *m/z* (%) 261.2 (100 [M + Na]$^+$); Calcd for $C_{14}H_{22}O_3 + NH_4^+$: 256.1907, found *m/z* 256.1913.

4.3 *Rac*-(3*S*,3a*S*,4*R*,5*R*,7a*S*)-methyl 7a-(but-3-en-1-yl)-3-hydroxy-5-methyloctahydro-1*H*-indene-4-carboxylate 30

General procedure 5 using **22** (690 mg, 2.62 mmol; dr ~ 4 : 1) in THF (22.5 mL), SmI_2 (0.1 M in THF, 52.4 mL, 5.24 mmol) and *t*-BuOH (18.8 mL) gave **30** (558 mg, 2.10 mmol, 80%, dr >10 : 1) as a colourless oil. For the mixture: ^{1}H NMR (500 MHz, $CDCl_3$) δ_H 5.82 (1H, ddt, *J* = 17.0, 10.1, 6.6 Hz, C*H*=CH_2), 5.01 (1H, d, *J* = 17.0 Hz, *trans* C*H*$_2$=CH), 4.92 (1H, d, *J* = 10.1 Hz, *cis* C*H*$_2$=CH), 3.97 (1H, dt, *J* = 8.0, 4.2 Hz, C*H*OH), 3.71 (s, CO_2CH_3 minor diastereoisomer), 3.68 (3H, s, CO_2CH_3), 2.41 (1H, dd, *J* = 8.5, 4.7 Hz, C*H*CO_2CH_3), 2.32 (dd, *J* = 11.7, 4.1 Hz, C*H*C*H*CO_2CH_3 (minor diastereoisomer)), 2.20 (1H, s broad, CHO*H*), 2.11–2.02 (3H, m, 1H from C*H*$_2$CHOH, 1H from C*H*$_2$CH=CH_2, C*H*CH_3), 2.00 (1H, m, 1H from C*H*$_2$CH=CH_2), 1.92 (1H, dd, *J* = 8.7, 3.6 Hz, C*H*CHCO_2CH_3), 1.65–1.46 (6H, m, 1H from C*H*$_2$CHOH, 1H from C*H*$_2CH_2$CHOH, C*H*$_2CH_2$CH=CH_2, C*H*$_2CHCH_3$), 1.33–1.25 (1H, m, 1H from C*H*$_2CH_2$CHOH), 0.89 (3H, d, *J* = 7.3 Hz, CHC*H*$_3$), 0.86 (d, *J* = 6.3 Hz CHC*H*$_3$ (minor diastereoisomer); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 175.7 (*C*=O), 139.5 (*C*H=CH_2), 139.1 (*C*H=CH_2 (minor diastereoisomer)), 115.21 ((*C*H_2=CH) (minor diastereoisomer)), 114.0 (*C*H_2=CH), 79.1 (*C*HOH), 78.7 ((*C*HOH) (minor diastereoisomer)), 51.6 (minor diastereoisomer), 51.1 (minor diastereoisomer), 51.5 (*C*HCHCO_2CH_3), 51.3 (CO_2CH_3), 47.4 (minor diastereoisomer), 46.5 (*C*HCO_2CH_3), 42.5 (*C*CH_2CH_2CH=CH_2), 38.7 (*C*H_2CH_2CH=CH_2), 33.5 (*C*H_2CHCH_3), 33.4 (minor diastereoisomer), 31.2 (*C*H_2CHOH), 31.1 (minor diastereoisomer), 30.4 (minor diastereoisomer), 30.0 (minor diastereoisomer), 29.8 (*C*HCH_3), 29.0 (*C*H_2CH_2CHOH), 28.6 (minor diastereoisomer), 28.5 (*C*H_2CH=CH_2), 28.4 (minor diastereoisomer), 27.0 (*C*$H_2CH_2CHCH_3$), 15.6 (*C*H_3CH); ν_{max}/(liquid film) cm^{-1} 3400 s (O–H), 2949 s, 1732 s (C=O), 837 w (C=C); MS (ES^+) *m/z* (%) 289 (100 [M + Na]$^+$); Calcd for $C_{16}H_{26}O_3 + NH_4^+$: 284.2220, found *m/z* 284.2210.

5 The formation and SmI_2-mediated cyclisation of alkyl iodide 42

5.1 1-Allyl-4-isopropylcyclohex-2-enol

Allyl magnesium bromide (1.0 M in THF, 58.0 mL, 58.0 mmol) was added dropwise to a solution of 4-isopropylcyclohex-2-enone[7] (4.00 g, 29 mmol) in THF (80 mL) at –40 °C. The reaction was allowed to warm to 10 °C over 20 h before being quenched with aqueous saturated NH_4Cl (50 mL). The mixture was extracted with EtOAc (3 × 50 mL), the combined organic fractions were washed with water and brine, dried (Na_2SO_4) and concentrated *in vacuo* to give 1-allyl-4-isopropylcyclohex-2-enol (4.87 g, 27 mmol, 93%) as a pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 5.95–5.84 (1H, m, C*H*=CH_2), 5.68 (1H, ddd, *J* = 10.3, 2.8, 1.0 Hz, CH=C*H*), 5.59 (1H, ddd, *J* = 10.2, 2.4, 1.3 Hz, mm C*H*=CH), 5.19–5.10 (2H, m, CH=C*H*$_2$), 2.38–2.24 (2H, m, C*H*$_2$CH=CH_2), 2.00–1.87 (2H, m, 1H from C*H*$_2CH_2CHCH(CH_3)_2$ and C*H*$CH(CH_3)_2$), 1.76–1.66 (1H, m, 1H from C*H*$_2CHCH(CH_3)_2$), 1.64–1.55 (2H, m, 1H from C*H*$_2CH_2CHCH(CH_3)_2$ and C*H*$(CH_3)_2$), 1.47–1.37 (1H, m, 1H from C*H*$_2CHCH(CH_3)_2$), 0.91 (3H, d, *J* = 6.8 Hz, CH(C*H*$_3$)$_2$), 0.88 (3H, d, *J* = 6.8 Hz, CH(C*H*$_3$)$_2$); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 133.7 (*C*H=CH_2), 133.2 (CH=*C*H), 132.3 (C*H*=CH), 118.7 (CH=*C*H$_2$), 70.5 (*C*(OH)), 45.7 (*C*H_2CH=CH_2), 41.5

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($CHCH(CH_3)_2$), 35.1 ($CH_2CH_2CHCH(CH_3)_2$), 31.7 ($CH(CH_3)_2$), 22.8 ($CH_2CHCH(CH_3)_2$), 19.8 ($CH(CH_3)_2$), 19.5 ($CH(CH_3)_2$); ν_{max} (liquid film)/cm^{-1} 2956 s, 2871 s, 1638 m, 1465 m, 1384 m, 1367 m, 1332w, 1196w, 1136w, 1030m; MS (CI$^+$) *m/z* (%) 139 (100 [M-C_3H_5]; Calcd for $C_9H_{15}O$ [M-C_3H_5]: 139.1117, found: *m/z* 139.1120.

5.2 3-Allyl-6-isopropylcyclohex-2-enone 38

A solution of 1-allyl-4-isopropylcyclohex-2-enol (3.00 g, 16.7 mmol) in CH_2Cl_2 (15 mL) was added to a suspension of pyridinium chlorochromate (5.39 g, 25.0 mmol) and SiO_2 (5.39 g) in CH_2Cl_2 (135 mL) at 20 °C and the reaction was stirred at the same temperature for 18 h. The mixture was filtered through a plug of silica gel and washed through with Et_2O (300 mL). The combined washings were concentrated *in vacuo* to yield **38** (2.77 g, 15.3 mmol, 92%) as a pale yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ_H 5.84 (1H, s, C=C*H*), 5.83–5.74 (1H, m, C*H*=CH_2), 5.16–5.09 (2H, m, CH=CH_2), 2.92 (2H, d, *J* = 6.7 Hz, CH_2CH=CH_2), 2.41–2.31 (2H, m, 1H from $(CH_3)_2CHCHCH_2CH_2$ and $CH(CH_3)_2$), 2.23–2.31 (1H, m, 1H from $(CH_3)_2CHCHCH_2CH_2$), 2.05 (1H, dt, *J* = 10.7, 4.7 Hz, C*H*$CH(CH_2)_3$), 1.98–1.95 (1H, m, 1H from $(CH_3)_2CHCHCH_2$), 1.85–1.75 (1H, m, 1H from $(CH_3)_2CHCHCH_2$), 0.94 (3H, d, *J* = 6.9 Hz, $CH(CH_3)_2$), 0.85 (3H, d, *J* = 6.9 Hz, $CH(CH_3)_2$); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 201.3 (*C*=O), 162.5 (*C*=CHC=O), 133.4 (*C*H=CH_2), 126.4 (C=*C*HC=O), 118.1 (CH=*C*H_2), 51.9 (*C*$HCH(CH_3)_2$), 41.9 (CH_2CH=CH_2), 28.8 ($(CH_3)CHCHCH_2CH_2$), 25.8 ($CH(CH_3)_2$), 23.0 ($(CH_3)CHCHCH_2$), 20.6 ($CH(CH_3)_2$), 18.5 ($CH(CH_3)_2$); ν_{max} (liquid film)/cm^{-1} 2958 m, 2871 w, 1669 s (C=O), 1465 w, 1427 w, 1367 w, 1206 w; MS (ES$^+$) *m/z* (%) 380 (45), 368 (43), 233 (50), 201 (100 [M + Na]$^+$); Calcd for $C_{12}H_{18}ONa$: 201.1250, found: *m/z* 201.1247.

5.3 *Rac*-(3*S*,6*S*)-3-allyl-6-isopropyl-3-methylcyclohex-1-en-1-yl trifluoromethanesulfonate 39

General procedure 1, at –45 °C using MeMgBr in Et_2O (3.0 M in THF, 4.70 mL, 14.1 mmol), copper(I) iodide (2.68 mg, 14.1 mmol) in THF (55 mL), **38** (1.67 g, 9.37 mmol) in THF (15 mL) and Comins' reagent (5.52 g, 14.1 mmol) in THF (10 mL) after 72 h gave **39** (2.11 g, 6.47 mmol, 69%; dr 11 : 1) as a pale yellow oil. For the mixture: ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 5.81–5.70 (1H, m C*H*=CH_2), 5.61 (1H, s, C=C*H*), 5.58 (s, C=C*H* (minor diastereoisomer)) 5.14–5.01 (2H, m CH=CH_2), 2.48–2.40 (1H, m, C*H*$CH(CH_3)_2$), 2.21–2.10 (2H, m, 1H from CH_2CH=CH_2 and $CH(CH_3)_2$), 2.10–2.02 (1H, m, 1H from CH_2CH=CH_2), 1.78–1.70 (1H, m, 1H from $(CH_3)_2CHCHCH_2$), 1.65–1.54 (1H, m, 1H from $(CH_3)_2CHCHCH_2$), 1.53–1.39 (2H, m, $(CH_3)_2CHCHCH_2CH_2$), 1.04 (3H, s, C=CHCCH_3), 0.99 (d, *J* = 7.1 Hz, $CH(CH_3)_2$ (minor diastereoisomer)), 0.98 (3H, d, *J* = 7.1 Hz, $CH(CH_3)_2$), 0.87 (d, *J* = 6.9 Hz, $CH(CH_3)_2$ (minor diastereoisomer)), 0.85 (3H, d, *J* = 6.9 Hz, $CH(CH_3)_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 151.4 (CH=*C*OTf), 133.7 (*C*H=CH_2), 128.1 (*C*H=COTf), 118.3 (CH=*C*H_2), 47.3 (CH_2CH=CH_2), 43.1 (*C*$HCH(CH_3)_2$), 36.2 (C=CH*C*CH_3), 32.8 ($(CH_3)_2CHCHCH_2CH_2$), 27.3 ($CH(CH_3)_2$), 25.9 (C=CHCCH_3), 20.0 ($CH(CH_3)_2$), 19.5 ($(CH_3)_2CHCH_2$), 16.5 ($CH(CH_3)_2$); ν_{max} (liquid film)/cm^{-1} 2965 m, 1592 w, 1418 s (O=S=O), 1247 w, 1209 s, 1143 s; Mass ion not detected.

5.4 *Rac*-(3*S*,6*S*)-3-allyl-6-isopropyl-3-methylcyclohex-1-enecarboxylic acid

General procedure 2 using **39** (200 mg, 0.613 mmol; dr 11 : 1), palladium acetate (42 mg, 0.184 mmol), triphenylphosphine (97 mg, 0.368 mmol), formic acid (1.4 mL, 36.8 mmol) and triethylamine (0.17 mL, 1.23 mmol) in DMF (10 mL) after 40 h gave *rac*-(3*S*,6*S*)-3-allyl-6-isopropyl-3-methylcyclohex-1-enecarboxylic acid (122 mg, 0.550 mmol, 90%; dr 12 : 1) as a colourless oil. For the mixture: ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 6.80 (1H, s, C*H*=CCO_2H), 6.78 (s, C*H*=CCO_2H (minor diastereoisomer)), 5.83–5.72 (1H, m, C*H*=CH_2), 5.37–5.25 (m, CH=CH_2 (minor diastereoisomer)), 5.10–5.01 (2H, m, CH=CH_2), 2.49–2.44 (1H, m, C*H*$CH(CH_3)_2$), 2.15–2.05 (3H, m, C$H(CH_3)_2$ and CH_2CH=CH_2, 1.67–1.58 (2H, m, $(CH_3)_2CHCHCH_2$), 1.47–1.42 (2H, m, $(CH_3)_2CHCHCH_2CH_2$), 1.04 (3H, s, C=CHCCH_3), 1.01 (s, C=CHCCH_3 (minor diastereoisomer), 0.95 (3H, d, *J* = 7.1 Hz, $CH(CH_3)_2$), 0.81 (3H, d, *J* = 7.0 Hz, $CH(CH_3)_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 173.9 (*C*O_2H), 149.7 (*C*H=CCO_2H), 134.2 (*C*H=CH_2), 132.7 (CH=*C*CO_2H), 117.9 (CH=*C*H_2), 46.4 (CH_2CH=CH_2), 38.7 (*C*$HCH(CH_3)_2$), 35.5 (C=CH*C*CH_3), 31.6 ($(CH_3)_2CHCHCH_2CH_2$), 29.6 ($CH(CH_3)_2$), 25.9 (C=CHCCH_3), 20.9 ($CH(CH_3)_2$), 19.5 ($(CH_3)_2CHCH_2$), 18.3 ($CH(CH_3)_2$); ν_{max}/(liquid film) cm^{-1} 3436 s, 2101 w, 1769 w, 1640 s (C=O), 1459 w, 1170 w, 1127 w; MS (ES$^+$) *m/z* (%) 465 (12), 443 (8), 221 (100 [M – H]$^+$); Calcd for $C_{14}H_{21}O_2$ [M – H]: 221.1536, found: *m/z* 221.1541.

5.5 *Rac*-(3*S*,6*S*)-methyl 3-allyl-6-isopropyl-3-methylcyclohex-1-enecarboxylate 40

$TMSCHN_2$ (2.0 M in hexane, 5.91 mL, 11.8 mmol) was added to a solution of *rac*-(3*S*,6*S*)-3-allyl-6-isopropyl-3-methylcyclohex-1-enecarboxylic acid (1.19 g, 5.37 mmol; dr 12 : 1) in toluene (40 mL) and MeOH (10 mL) and the reaction was stirred at 20 °C for 19 h. Concentration of the reaction mixture *in vacuo* and chromatography on silica gel gave **40** (1.15 g, 4.87 mmol, 91%) as a colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 6.57 (1H, s, C*H*=C), 5.82–5.70 (1H, m, C*H*=CH_2), 5.08–4.99 (2H, m, CH=CH_2), 3.73 (3H, s, CO_2CH_3), 2.50–2.44 (1H, m, C*H*$CH(CH_3)_2$), 2.05 (2H, dd, *J* = 7.4, 1.1 Hz, CH_2CH=CH_2), 2.03–1.95 (1H, m, C$H(CH_3)_2$), 1.62–1.56 (2H, m, $(CH_3)_2CHCHCH_2$), 1.45–1.40 (2H, m, $(CH_3)_2CHCHCH_2CH_2$), 1.02 (3H, s, CH_3), 0.91 (3H, d, *J* = 7.1 Hz, $CH(CH_3)_2$), 0.77 (3H, d, *J* = 6.9 Hz, $CH(CH_3)_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 169.2 (*C*O_2CH_3), 146.9 (*C*H=CCO_2CH_3), 134.4 (*C*H=CH_2), 133.5 (CH=*C*CO_2CH_3), 117.7 (CH=*C*H_2), 51.5 (CO_2CH_3), 46.5 (CH_2CH=CH_2), 39.1 (*C*$HCH(CH_3)_2$), 35.3 (C=CH*C*CH_3), 31.7 ($(CH_3)_2CHCHCH_2CH_2$), 29.6 ($CH(CH_3)_2$), 26.0 (C=CHCCH_3), 20.3 ($CH(CH_3)_2$), 19.5 ($(CH_3)_2CHCH_2$), 18.3 ($CH(CH_3)_2$); ν_{max}/(liquid film) cm^{-1} 3400 s, 2958 m, 2092 w, 1716 s (C=O), 1644 s, 1456 w, 1247 s, 1075 w; MS (ES$^+$) *m/z* (%) 495 (58), 291 (61), 259 (100 [M + Na]$^+$); Calcd for $C_{15}H_{24}O_2$: 236.1771, found: *m/z* 236.1766.

5.6 *Rac*-(3*R*,6*S*)-methyl 3-(1-hydroxyallyl)-6-isopropyl-3-methylcyclohex-1-enecarboxylate

A solution of **40** (615 mg, 2.61 mmol) in CH_2Cl_2 (8 mL) was added to a suspension of SeO_2 (1.16 g, 10.4 mmol) and *t*-BuOOH (3.79 mL, 20.8 mmol) in CH_2Cl_2 (17 mL) and the reaction was stirred at 20 °C for 68 h. At this time, filtration of the reaction mixture followed by washing of the solids with CH_2Cl_2 (30 mL), concentration of the filtrate *in vacuo* and purification of the crude products by chromatography on silica gel gave *rac*-(3*R*,6*S*)-methyl 3-(1-hydroxyallyl)-6-isopropyl-3-methylcyclohex-1-enecarboxylate (277 mg, 1.10 mmol, 42%; dr 4 : 1) as a pale yellow oil. For the mixture: ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 6.75 (s, C*H*=C (minor diasterisomer)), 6.65 (1H, s, C*H*=C), 5.94 (ddd, *J* = 17.2, 10.6, 6.3 Hz, C*H*=CH_2 (minor diastereoisomer)), 5.87 (1H, ddd, *J* = 17.2, 10.3, 7.1 Hz, C*H*=CH_2), 5.31–5.21 (2H, m, CH=CH_2), 3.88 (1H, d, *J* = 7.1 Hz, C*H*OH), 3.74 (3H, s, CO_2CH_3), 2.52 (1H, m, C*H*CH$(CH_3)_2$), 2.14–2.02 (1H, m, C*H*$(CH_3)_2$), 1.71–1.50 (3H, m, $(CH_3)_2$CHCHCH_2 and 1H from $(CH_3)_2$CHCHCH$_2$CH_2) 1.44–1.38 (1H from $(CH_3)_2$CHCHCH$_2$CH_2), 1.06 (s, CH_3 (minor diastereoisomer)) 1.04 (3H, s, CH_3), 0.93 (3H, d, *J* = 6.8 Hz, CH(CH_3)$_2$), 0.76 (3H, d, *J* = 6.8 Hz, CH(CH_3)$_2$), 0.75 (d, *J* = 6.8 Hz, CH(CH_3)$_2$ (minor diastereoisomer)); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 168.9 (*C*O_2CH_3), 143.8 (*C*H=CCO_2CH_3), 143.4 (*C*H=CCO_2CH_3 (minor diastereoisomer)), 137.2 (*C*H=CH_2 (minor diastereoisomer)), 136.9 (*C*H=CH_2), 135.8 (CH=*C*CO_2CH_3), 135.2 (CH=*C*CO_2CH_3 (minor diastereoisomer)), 117.9 (CH=*C*H_2), 79.8 (*C*HOH), 51.5 (CO_2*C*H_3), 39.8 (C=CH*C*CH_3), 39.6 (C=CH*C*CH_3 (minor diastereoisomer)), 39.4 (*C*HCH$(CH_3)_2$ (minor diastereoisomer)), 39.3 (*C*HCH$(CH_3)_2$), 29.2 (*C*H$(CH_3)_2$), 28.0 ($(CH_3)_2$CHCHCH$_2$*C*H_2), 22.7 (C=CHC*C*H_3), 20.8 ($(CH(CH_3)_2$), 19.0 ($(CH_3)_2$CHCH*C*H_2), 17.7 ($(CH(CH_3)_2$); ν_{max}/(liquid film) cm^{-1} 3434 s, 2098 w, 1644 s, 1456 w, 1258 w; MS (ES$^+$) *m*/*z* (%) 527 (18), 276 (12), 275 (100 [M + Na]$^+$), 270 (100 [M + NH_4]$^+$), 235 (13); Calcd for $C_{15}H_{28}O_3N$: 270.2064, found: *m*/*z* 270.2073.

5.7 *Rac*-(3*R*,6*S*)-methyl 3-acryloyl-6-isopropyl-3-methylcyclohex-1-enecarboxylate 41

Dess–Martin periodinane (25 mg, 59 μmol) was added to a solution of *rac*-(3*R*,6*S*)-methyl 3-(1-hydroxyallyl)-6-isopropyl-3-methylcyclohex-1-enecarboxylate (10 mg, 40 μmol; dr 4 : 1) in CH_2Cl_2 (2 mL) at 20 °C. The reaction was stirred for 45 min before being quenched with aqueous NaOH (1.0 M, 2 mL) and extracted with Et_2O (3 × 5 mL). The combined organic fractions were dried (Na_2SO_4) and concentrated *in vacuo* to yield **41** (10 mg, 40 μmol, quant.) as a colourless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 6.81 (1H, d, *J* = 1.7 Hz, C*H*=C), 6.72 (1H, dd, *J* = 16.9, 10.3 Hz, C*H*=CH_2), 6.36 (1H, dd, *J* = 6.9, 2.0 Hz, 1H from CH=CH_2), 5.69 (1H, dd, *J* = 10.4, 1.9 Hz, 1H from CH=*C*H_2), 3.75 (3H, s, CO_2CH_3), 2.52 (1H, ddd, *J* = 11.3, 5.6, 1.5 Hz, C*H*CH$(CH_3)_2$), 2.08–1.90 (2H, m, C*H*$(CH_3)_2$) and CH_2), 1.74–1.47 (3H, m, CH_2), 1.27 (3H, s, CH_3), 0.93 (3H, d, *J* = 7.0 Hz, CH(CH_3)$_2$), 0.80 (3H, d, *J* = 6.8 Hz, CH(CH_3)$_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 200.3 (*C*=O), 168.5 (*C*O_2CH_3), 139.8 (*C*H=CCO_2CH_3), 136.5 (CH=*C*CO_2CH_3), 131.2 (*C*H=CH_2), 129.4 (CH=*C*H_2), 51.7 (CO_2*C*H_3), 48.3 (C=CH*C*CH_3), 38.7 (*C*HCH$(CH_3)_2$), 29.7 (*C*H$(CH_3)_2$), 28.9 (*C*H_2), 23.5 (C=CHC*C*H_3), 20.9 (CH(*C*H_3)$_2$), 19.8 (*C*H_2), 18.5 (CH(*C*H_3)$_2$); ν_{max}/(liquid film) cm^{-1} 2956 s, 2364 m, 1781w, 1718 s (C=O), 1653 s (C=O), 1457 w, 1387 w, 1259 m, 1098 m; MS (ES$^+$) *m*/*z* (%) 523 (30), 289 (21), 273 (100 [M + Na]$^+$); Calcd for $C_{15}H_{26}O_3N$: 268.1907, found: *m*/*z* 268.1906.

5.8 *Rac*-(3*R*,6*S*)-methyl 3-(3-iodopropanoyl)-6-isopropyl-3-methylcyclohex-1-enecarboxylate 42

A stirred solution of NaI (294 mg, 1.96 mmol) in MeCN (13 mL) was treated with TMSCl (0.250 mL, 1.96 mmol) and H_2O (30 μL, 1.63 mmol) at 20 °C before a solution of **41** (408 mg, 1.63 mL) in MeCN (7 mL) was added. After 36 h, the reaction was quenched by the addition of H_2O (20 mL) and extracted with Et_2O (3 × 25 mL). The combined organic layers were washed with saturated aqueous $Na_2S_2O_3$ (80 mL), dried (Na_2SO_4) and concentrated *in vacuo* to give **42** (481 mg, 1.27 mmol, 78%) as a yellow oil that was used without further purification. ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 6.80 (1H, s, C*H*=C), 3.76 (3H, s, CO_2CH_3), 3.32–3.27 (2H, m, CH_2I), 3.18–3.09 (2H, m, CH_2CH$_2$I), 2.55–2.46 (1H, m, C*H*CH$(CH_3)_2$), 2.05–1.90 (2H, m, C*H*$(CH_3)_2$ and 1H from $(CH_3)_2$CHCHCH$_2$CH_2), 1.75–1.61 (1H, m, 1H from $(CH_3)_2$CHCHCH_2), 1.59–1.45 (2H, m, 1H from $(CH_3)_2$CHCHCH_2 and 1H from $(CH_3)_2$CHCHCH$_2$CH_2), 1.25 (3H, s, CH_3), 0.93 (3H, d, *J* = 7.0 Hz, CH(CH_3)$_2$), 0.81 (3H, d, *J* = 7.7 Hz, CH(CH_3)$_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 209.2 (*C*=O), 168.4 (*C*O_2CH_3), 139.5 (*C*H=CCO_2CH_3), 136.7 (CH=*C*CO_2CH_3), 51.8 (CO_2*C*H_3), 49.2 (C=CH*C*CH_3), 42.3 (*C*H$_2$CH$_2$I), 38.6 (*C*HCH$(CH_3)_2$), 29.9 (*C*H$(CH_3)_2$), 28.9 ($(CH_3)_2$CHCHCH$_2$*C*H_2), 24.1 (C=CHC*C*H_3), 20.9 (CH(*C*H_3)$_2$), 20.2 ($(CH_3)_2$CHCH*C*H_2), 18.8 (CH(*C*H_3)$_2$), –4.02 (*C*H_2I); ν_{max}/(liquid film) cm^{-1} 1718 s (C=O), 1653 s (C=O), 1437 w, 1259 m, 1083 m; MS (ES$^+$) *m*/*z* (%) 396 (100 [M + NH_4]$^+$), 199 (35), 173 (33); Calcd for $C_{15}H_{27}O_3NI$: 396.1030, found: *m*/*z* 396.1041.

5.9 SmI_2-mediated cyclisation of iodide 42: *rac*-(1*S*,3a*S*,4*R*,5*S*,7a*R*)-methyl 1-hydroxy-5-isopropyl-7a-methyloctahydro-1*H*-indene-4-carboxylate 44 and *rac*-(3a*S*,4*R*,5*S*,7a*R*)-methyl 5-isopropyl-7a-methyl-1-oxooctahydro-1*H*-indene-4-carboxylate 45

To a solution of **42** (50 mg, 0.132 mmol) and MeOH (54 μL, 1.32 mmol) in degassed THF (1.5 mL) was added a solution of SmI_2-HMPA in THF (made from HMPA (0.46 mL, 2.64 mmol) dissolved in SmI_2 (0.1 M in THF, 5.29 mL, 0.529 mmol)) at –78 °C. The reaction was warmed to 20 °C over 5 h, additional SmI_2 (0.1 M in THF, 1.98 mL, 0.198 mmol) was added and the reaction stirred for further 1 h before being quenched with saturated aqueous Na/K tartrate (2 mL). The mixture was extracted with Et_2O (5 × 2 mL), the combined organic fractions washed with brine (10 mL) and dried (Na_2SO_4). Concentration *in vacuo*, followed by chromatography on silica gel gave **44** (16 mg, 63.4 μmol; 48%) as a pale yellow oil and **45** (9 mg, 35.4 μmol; 27%) as a pale yellow oil. For **44**: ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 3. 73 (1H, t, *J* = 8.9 Hz, C*H*OH), 3.64 (3H, s, CO_2CH_3), 2.62 (1H, d, *J* = 4.5 Hz, C*H*CO_2CH_3), 2.08–1.97 (2H, m, C*H*CHCO_2CH_3 and 1H from CH_2CHOH), 1.88–1.72 (3H, m, C*H*$(CH_3)_2$, 1H from $(CH_3)_2$CHCHCH_2 and 1H from CH_2CH$_2$CHOH), 1.71–1.61 (1H, m, CH_2), 1.61–1.48 (2H, m, 1H from CH_2CHOH and CH_2), 1.38–1.22 (2H, m, CH_2), 1.21–1.12 (1H, m, C*H*CH$(CH_3)_2$),

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1.00 (3H, s, CH_3), 0.95 (3H, d, J = 6.6 Hz, CH(CH_3)$_2$), 0.80 (3H, d, J = 6.8 Hz, CH(CH_3)$_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 175.2 (*C*O$_2$CH$_3$), 82.9 (*C*HOH), 51.1 (CO$_2$*C*H$_3$), 44.9 (*C*HCCH$_3$), 43.2 (*C*HCO$_2$CH$_3$), 41.3 (CH*C*CH$_3$), 41.2 (*C*HCH(CH$_3$)$_2$), 29.3 (*C*H$_2$CHOH), 29.2 (*C*H(CH$_3$)$_2$), 26.6 (*C*H$_2$), 25.3 (*C*H$_2$), 22.8 (CHC*C*H$_3$), 21.8 (CH(*C*H$_3$)$_2$), 21.3 (*C*H$_2$), 21.0 (CH(*C*H$_3$)$_2$); ν_{max}/(liquid film) cm^{-1} 2943 s, 2353 m, 1728 s (C═O), 1458 m, 1150 m, 1021w; MS (EI$^+$) m/z (%) 254 (16 [M]$^+$), 222 (100), 179 (46), 151 (36), 133 (42), 95 (54); Calcd for $C_{15}H_{26}O_3$: 254.1876, found: m/z 254.1886. For **45**: ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 3.67 (3H, s, CO$_2$CH_3), 2.71 (1H, apparent t, J = 3.8 Hz, C*H*CO$_2$CH$_3$), 2.44 (1H, ddd, J = 19.2, 8.8, 2.8 Hz, 1H from CH_2C═O), 2.36 (1H, ddd, J = 10.5, 7.3, 2.9 Hz, C*H*CCH$_3$), 2.21 (1H, dt, J = 19.2, 9.5 Hz, 1H from CH_2C═O), 2.05–1.96 (1H, m, 1H from CH_2CH$_2$C═O), 1.95–1.84 (2H, m, 1H from CH_2CH$_2$C═O and CH_2), 1.83–1.74 (1H, m, C*H*(CH$_3$)$_2$), 1.62–1.53 (1H, m, CH_2), 1.46–1.37 (1H, m,CH_2), 1.35–1.21 (2H, m, C*H*CH(CH$_3$)$_2$ and CH_2), 1.10 (3H, s, CH_3), 0.94 (3H, d, J = 6.6 Hz, CH(CH_3)$_2$), 0.85 (3H, d, J = 6.6 Hz, CH(CH_3)$_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 222.0 (*C*═O), 174.9 (*C*O$_2$CH$_3$), 51.3 (CO$_2$CH_3), 47.1 (CH*C*CH$_3$), 45.1 (*C*HCCH$_3$), 43.6 (*C*HCO$_2$CH$_3$), 41.4 (*C*HCH(CH$_3$)$_2$), 35.4 (*C*H$_2$C═O), 28.9 (*C*H$_2$), 28.8 (*C*H(CH$_3$)$_2$), 24.1 (*C*H$_2$CH$_2$C═O), 21.9 (*C*H$_2$), 21.6 (CH(*C*H$_3$)$_2$), 21.1 (CH(*C*H$_3$)$_2$), 20.4 (CHC*C*H$_3$); ν_{max}/(liquid film) cm^{-1} 2955 m, 2360 w, 1737 s (C═O), 1463 w, 1196 w, 1153 m; MS (ES$^+$) m/z (%) 307 (82), 275 (100 [M + Na]$^+$); Calcd for $C_{15}H_{24}O_3$: 252.1720, found: m/z 252.1726.

5.10 Oxidation of 44 to 45

Dess–Martin periodinane (38 mg, 89 μmol) was added to a solution of **44** (15 mg, 59 μmol) in CH_2Cl_2 (1.5 mL) at 20 °C. The reaction was stirred for 1 h before being quenched with aqueous NaOH (1.0 M, 2 mL) and extracted with Et_2O (3 × 3 mL). The combined organic fractions were dried (Na_2SO_4) and concentrated *in vacuo* to yield **45** (11 mg, 44 μmol, 74%) as a colourless oil.

6 An approach to the tricyclic core of pleuromutilin

6.1 Formation of ring closing metathesis substrate 56

6.1.1 *Rac*-(3*S*,3a*S*,4*R*,5*R*,7a*R*)-methyl 3-((*tert*-butyldiphenylsilyl)oxy)-5-methyl-7a-(prop-1-en-2-yl)octahydro-1*H*-indene-4-carboxylate. Imidazole (469 mg, 6.89 mmol) was added to a stirred solution of **29** (965 mg, 3.83 mmol) in DMF (10 mL) at room temperature followed by TBDPSCl (1.1 mL, 4.21 mmol). The reaction mixture was then stirred at room temperature for 12 h, quenched with aqueous saturated $NaHCO_3$ (50 mL) and extracted with Et_2O (3 × 50 mL). The organic extracts were washed with H_2O (3 × 50 mL), dried (Na_2SO_4) and concentrated *in vacuo*. The crude material was then purified by silica gel chromatography (5% EtOAc in petroleum ether) to yield *rac*-(3*S*,3a*S*,4*R*,5*R*,7a*R*)-methyl 3-((*tert*-butyldiphenylsilyl)oxy)-5-methyl-7a-(prop-1-en-2-yl)octahydro-1*H*-indene-4-carboxylate (1.46 g, 2.98 mmol, 78%) as a pale yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ_H 7.62 (2H, dd, J = 8.0, 1.4 Hz, 2 × C*H* Ar), 7.56 (2H, dd, J = 8.0, 1.4 Hz, 2 × C*H* Ar), 7.36–7.26 (6H, m, 6 × C*H* Ar), 4.74 (2H, s, C═CH_2), 4.03 (1H, q, J = 6.6 Hz, C*H*OTBDPS), 3.47 (3H, s, CO$_2$CH_3), 2.54 (1H, t, J = 5.7 Hz, C*H*CHOTBDPS), 2.31 (1H, t, J = 4.9 Hz, C*H*CO$_2$CH$_3$), 1.77–1.69 (3H, m, 1H from CH_2CHOTBDPS, 1H from CH_2CH$_2$CHCH$_3$, 1H from CH_2CHCH$_3$), 1.70 (3H, s, CH_3C═CH$_2$), 1.58–1.52 (2H, m, 1H from CH_2CHOTBDPS, 1H from CH_2CH$_2$CHOTBDPS), 1.32–1.23 (2H, m, 1H from CH_2CHCH$_3$, C*H*CH$_3$), 1.20–1.13 (1H, m, 1H from CH_2CH$_2$CHOTBDPS), 1.03–0.95 (1H, m, 1H from CH_2CH$_2$CHCH$_3$), 1.00 (9H, s, SiC(CH_3)$_3$), 0.71 (3H, d, J = 6.9 Hz, CH_3CH); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 174.5 (*C*O$_2$CH$_3$), 149.5 (H$_3$C*C*CH$_2$), 136.0 (4 × *C*H Ar), 134.6 (*C* Ar), 134.0 (*C* Ar), 129.5 (2 × *C*H Ar), 127.5 (4 × *C*H Ar), 109.2 (C═*C*H$_2$), 77.7 (*C*HOTBDPS), 50.8 (CO$_2$*C*H$_3$), 49.7 (*C*HCHOTBDPS), 47.0 (*C*CCH$_2$CH$_3$), 44.3 (*C*HCO$_2$CH$_3$), 35.5 (*C*H$_2$CHCH$_3$), 32.1 (*C*H$_2$CHOTBDPS), 31.3 (*C*H$_2$CH$_2$CHCH$_3$), 29.3 (*C*HCH$_3$), 27.0 (SiC(*C*H$_3$)$_3$), 27.0 (*C*H$_2$CH$_2$CHOTBDPS), 20.2 (*C*H$_3$CCH$_2$), 19.2 (Si*C*(CH$_3$)$_3$), 17.3 (*C*H$_3$CH); ν_{max}/(liquid film) cm^{-1} 1640 s (C═O), 1264 m (Si–C), 1104 w (Si–O), 741 (C═C); MS (ES$^+$) m/z (%) 513 (100 [M + Na]$^+$); Calcd for $C_{31}H_{42}O_3Si$ + Na$^+$: 513.2795, found m/z 513.2802.

6.1.2 *Rac*-((3*S*,3a*S*,4*R*,5*R*,7a*R*)-3-((*tert*-butyldiphenylsilyl)-oxy)-5-methyl-7a-(prop-1-en-2-yl)octahydro-1*H*-inden-4-yl)methanol. DIBAL-H (1.0 M in toluene, 5.54 mL, 5.54 mmol) was added to a stirred solution of *rac*-(3*S*,3a*S*,4*R*,5*R*,7a*R*)-methyl 3-((*tert*-butyldiphenylsilyl)oxy)-5-methyl-7a-(prop-1-en-2-yl)octahydro-1*H*-indene-4-carboxylate (1.36 g, 2.77 mmol) in CH_2Cl_2 (28 mL) at −78 °C and the reaction mixture stirred at room temperature. After 3 h, the reaction mixture was quenched with aqueous saturated Na/K tartrate (10 mL) and stirred for 30 min before extraction with EtOAc (3 × 20 mL). The combined organic layers were dried (Na_2SO_4) and concentrated *in vacuo* to afford *rac*-((3*S*,3a*S*,4*R*,5*R*,7a*R*)-3-((*tert*-butyldiphenylsilyl)oxy)-5-methyl-7a-(prop-1-en-2-yl)octahydro-1*H*-inden-4-yl)methanol (1.28 mg, 2.77 mmol, 100%) as a colourless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ_H 7.70–7.66 (4H, m, 4 × C*H* Ar), 7.45–7.36 (6H, m, 6 × C*H* Ar), 4.87 (1H, s, 1 H from CH_2═C), 4.83 (1H, s, 1 H from CH_2═C), 4.27 (1H, q, J = 7.4 Hz, C*H*OTBDPS), 3.53–3.50 (1H, m, 1 H from CH_2OH), 3.44–3.39 (1H, m, 1 H from CH_2OH), 2.40 (1H, dd, J = 7.6, 2.8 Hz, C*H*CHOTBDPS), 1.95–1.88 (1H, m, 1H from CH_2CHOTBDPS), 1.88 (3H, s, CH_3), 1.85–1.79 (2H, m, 1H from CH_2CHCH$_3$, 1H from CH_2CH$_2$CHCH$_3$), 1.73–1.65 (1H, m, 1H from CH_2CHOTBDPS), 1.54–1.50 (1H, m, C*H*CH$_2$OH), 1.34–1.28 (1H, m, C*H*CH$_3$), 1.27–1.20 (1H, m, 1H from CH_2CHCH$_3$), 1.18–1.14 (2H, m, CH_2CH$_2$CHOTBDPS), 1.10–1.07 (1H, m, 1H from CH_2CH$_2$CHCH$_3$), 1.08 (9H, s, SiCCH_3)$_3$), 0.89 (1H, s brd, O*H*), 0.70, (3H, d, J = 6.9 Hz, CH_3CH); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 150.7 (*C*═CH$_2$), 136.0 (4 × *C*H Ar), 134.5 (2 × *C* Ar), 129.5 (2 × *C*H Ar), 127.5 (4 × *C*H Ar), 109.4 (C═*C*H$_2$), 77.1 (*C*HOTBDPS), 62.0 (*C*H$_2$OH), 49.9 (*C*HCHOTBDPS), 46.4 (*C*CCH$_2$CH$_3$), 41.4 (*C*HCH$_2$OH), 36.5 (*C*H$_2$CHCH$_3$), 32.9 (*C*H$_2$CHOTBDPS), 32.3 (*C*H$_2$CH$_2$CHCH$_3$), 29.1 (*C*HCH$_3$), 27.7 (*C*H$_2$CH$_2$CHOTBDPS), 27.1 (SiC(*C*H$_3$)$_3$), 20.0 (*C*H$_3$CCH$_2$), 19.2 (Si*C*(CH$_3$)$_3$), 18.3 (*C*H$_3$CH); ν_{max}/(liquid film) cm^{-1} 3431 s (O–H), 1265 s (Si–C), 1099 w (Si–O); MS (ES$^+$) m/z (%) 480 (100 [M + NH$_4$]$^+$); Calcd for $C_{30}H_{42}O_2Si$ + NH$_4^+$: 480.3292, found m/z 480.3292.

6.1.3 *Rac*-(3*S*,3a*S*,4*R*,5*R*,7a*R*)-3-((*tert*-butyldiphenylsilyl)-oxy)-5-methyl-7a-(prop-1-en-2-yl)octahydro-1*H*-indene-4-carbaldehyde 54. Dess–Martin periodinane (2.35 g, 5.54 mmol) was

added to a stirred solution of *rac*-((3*S*,3a*S*,4*R*,5*R*,7a*R*)-3-((*tert*-butyldiphenylsilyl)oxy)-5-methyl-7a-(prop-1-en-2-yl)octahydro-1*H*-inden-4-yl)methanol (1.25 mg, 2.71 mmol) in CH_2Cl_2 (28 mL) and the reaction mixture stirred for 3 h. The reaction mixture was quenched with 0.5 M NaOH (10 mL) and extracted with EtOAc (3 × 20 mL). The combined organic layers were dried (Na_2SO_4) and concentrated *in vacuo* to afford **54** (1.26 g, 2.73 mmol, 99%) as a colourless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ_H 9.68 (1H, d, *J* = 3.5 Hz, C*H*O), 7.70–7.64 (4H, m, 4 × C*H* Ar), 7.45–7.36 (6H, m, 6 × C*H* Ar), 4.84 (1H, s, 1H from C=CH_2), 4.81 (1H, s, 1H from C=CH_2), 4.26 (1H, q, *J* = 7.8 Hz, C*H*OTBDPS), 2.46 (1H, d, *J* = 8.5 Hz, C*H*CHOTBDPS), 2.20 (1H, d, *J* = 3.5 Hz, C*H*CHO), 1.99–1.92 (1H, m, 1H from CH_2CHOTBDPS), 1.89 (1H, d brd, *J* = 4.5 Hz, 1H from CH_2CH$_2$CHCH$_3$), 1.84–1.78 (1H, m, 1H from CH_2CHCH$_3$), 1.75–1.68 (1H, m, 1H from CH_2CHOTBDPS), 1.72 (3H, s, CH_3), 1.51 (1H, qd, *J* = 12.9, 3.0 Hz, 1H from CH_2CH$_2$CHOTBDPS), 1.33–1.26 (1H, m, 1H from CH_2CH$_2$CHOTBDPS), 1.26–1.20 (1H, m, 1H from CH_2CHCH$_3$), 1.13–1.05 (1H, m 1H from CH_2CH$_2$CHCH$_3$), 1.09 (9H, s, SiC(CH_3)$_3$), 0.77 (3H, d, *J* = 7.3 Hz, CH_3CH); ^{13}C NMR 125 MHz, $CDCl_3$) δ_C 205.9 (*C*HO), 148.4 (*C*=CH$_2$), 136.0 (4 × *C*H Ar), 134.4 (*C* Ar), 134.0 (*C* Ar), 129.7 (2 × *C*H Ar), 127.6 (4 × *C*H Ar), 111.3 (C=*C*H$_2$), 75.9 (*C*HOTBDPS), 51.3 (*C*HCHO), 51.0 (*C*HCHOTBDPS), 46.0 (*C*C=CH$_2$), 36.4 (*C*H$_2$CHCH$_3$), 32.7 (*C*H$_2$CHOTBDPS), 32.3 (*C*H$_2$CH$_2$CHCH$_3$), 28.4 (*C*HCH$_3$), 27.8 (*C*H$_2$CH$_2$CHOTBDPS), 27.1 (SiC(*C*H$_3$)$_3$), 19.8 (*C*H$_3$CCH$_2$), 19.2 (Si*C*(CH$_3$)$_3$), 18.7 (*C*H$_3$CH); ν_{max}/(liquid film) cm^{-1} 1700 m (C=O), 1260 m (Si–C), 1041 m (Si–O); MS (ES$^+$) *m*/*z* (%) 483 (100 [M + Na]$^+$); Calcd for $C_{30}H_{40}O_2Si + NH_4^+$: 478.3131, found *m*/*z* 478.3136.

6.1.4 *Rac*-1-((3*S*,3a*S*,4*R*,5*R*,7a*R*)-3-((*tert*-butyldiphenylsilyl)-oxy)-5-methyl-7a-(prop-1-en-2-yl)octahydro-1*H*-inden-4-yl)pent-4-en-1-ol 56. Butenyl magnesium bromide (0.5 M in THF, 3.64 mL, 1.82 mmol) was added dropwise to **54** (700 mg, 1.52 mmol) in THF (15 mL) at −78 °C. After 4 h, the reaction mixture was quenched with aqueous saturated NH_4Cl (10 mL) and extracted with EtOAc (5 × 10 mL). The combined organic layers were dried (Na_2SO_4) and concentrated *in vacuo*. The crude material was purified by silica gel chromatography (10% EtOAc in petroleum ether) to yield **56** (550 mg, 1.07 mmol, 70%; dr 3 : 1) as a pale yellow oil. For the mixture: ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 7.72–7.66 (4H, m, 4 × C*H* Ar), 7.45–7.37 (6H, m, 6 × C*H* Ar), 5.88–5.73 (1H, m, C*H*=CH$_2$), 5.05 (1H, s, 1H from CH_2=CCH$_3$), 5.06–4.92 (2H, m, CH_2=CH), 4.96 (1H, s, 1H from CH_2=CCH$_3$), 4.32 (q, *J* = 7.9 Hz, C*H*OTBDPS (minor diastereoisomer)), 4.14 (1H, td, *J* = 6.3, 3.8 Hz, C*H*OTBDPS), 3.72–3.67 (m, C*H*OH (minor diastereoisomer)), 3.56–3.51 (1H, m, C*H*OH), 2.42 (1H, dd, *J* = 9.5, 3.5 Hz, C*H*CHOTBDPS), 2.33 (d, *J* = 8.8 Hz, C*H*CHOTBDPS (minor diastereoisomer)), 2.25–1.95 (1H, m), 1.92 (3H, s, CH_3C=CH$_2$), 1.87 (s, CH_3C=CH$_2$ (minor diastereoisomer)), 1.86–1.50 (7H, m), 1.47–1.40 (2H, m), 1.39–1.26 (3H, m), 1.23–1.13 (2H, m) 1.07 (s, SiC(CH_3)$_3$ (minor diastereoisomer)), 1.05 (9H, s, SiC(CH_3)$_3$), 0.93 (3H, d, *J* = 6.9 Hz, CH_3CH), 0.81 (d, *J* = 6.9 Hz, CH_3CH (minor diastereoisomer)); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 151.7 (CH$_3$*C*=CH$_2$), 151.4 (CH$_3$*C*=CH$_2$ (minor diastereoisomer)), 139.0 (*C*H=CH$_2$ (minor diastereoisomer)), 138.8 (*C*H=CH$_2$), 136.0 (4 × *C*H Ar) 135.9 (4 × *C*H Ar (minor diastereoisomer)), 134.5 (*C* Ar), 134.3 (*C* Ar), 129.7 (2 × *C*H Ar), 129.6 (2 × *C*H Ar (minor diastereoisomer)), 127.6 (4 × *C*H Ar (minor diastereoisomer)), 127.5 (4 × *C*H Ar), 114.5 (*C*H$_2$=CH), 112.9 (*C*H$_2$=CH (minor diastereoisomer)), 110.0 (*C*H$_2$=C), 79.0 (*C*HOTBDPS), 77.5 (*C*HOTBDPS (minor diastereoisomer)), 72.8 (*C*HOH), 71.1 (*C*HOH (minor diastereoisomer)), 49.6 (*C*HCHOTBDPS), 48.7 (*C*HCHOTBDPS (minor diastereoisomer)), 46.1 (*C*H), 43.4 (*C*H), 37.7 (*C*H$_2$), 36.1 (*C*H$_2$), 35.3 (*C*H$_2$), 34.8 (*C*H$_2$), 34.0 (*C*H$_2$), 33.4 (*C*H$_2$), 32.8 (*C*H$_2$), 31.3 (*C*H$_2$), 30.9 (*C*H$_2$), 30.3 (*C*HCH$_3$), 29.9 (*C*H$_2$), 29.4 (*C*H$_2$), 27.1 (SiC(*C*H$_3$)$_3$ (minor diastereoisomer)), 27.0 (SiC(*C*H$_3$)$_3$), 20.5 (*C*H$_3$C=CH$_2$), 20.3 (*C*H$_3$C=CH$_2$ (minor diastereoisomer)), 19.1 (Si*C*(CH$_3$)$_3$), 18.8 (*C*H$_3$CH (minor diastereoisomer)) 17.2 (*C*H$_3$CH); ν_{max}/(liquid film) cm^{-1} 3420 s (O–H), 2928 m (CH$_2$s), 1265 w (Si–C), 1110 m (Si–O), 821 w (C=C); MS (ES$^+$) *m*/*z* (%) 539 (100 [M + Na]$^+$); Calcd for $C_{34}H_{48}O_2Si + H^+$: 517.3496, found *m*/*z* 517.3498.

6.2 Formation of ring closing metathesis substrate 57

6.2.1 *Rac*-(3*S*,3a*S*,4*R*,5*R*,7a*S*)-methyl 7a-(but-3-en-1-yl)-3-((*tert*-butyldiphenylsilyl)oxy)-5-methyloctahydro-1*H*-indene-4-carboxylate. Imidazole (213 mg, 3.14 mmol) was added to a stirred solution of **30** (556 mg, 2.09 mmol, dr >10 : 1) in DMF (10 mL) at room temperature followed by TBDPSCl (0.37 mL, 2.09 mmol). The reaction mixture was then stirred at room temperature for 12 h. The reaction mixture was quenched with aqueous saturated $NaHCO_3$ (50 mL) and extracted with Et_2O (3 × 50 mL). The organic extracts were washed with H_2O (3 × 50 mL), dried (Na_2SO_4) and concentrated *in vacuo*. The crude material was then purified by silica gel chromatography (5% EtOAc in petroleum ether) to yield *rac*- (3*S*,3a*S*,4*R*,5*R*,7a*S*)-methyl 7a-(but-3-en-1-yl)-3-((*tert*-butyldiphenylsilyl)oxy)-5-methyloctahydro-1*H*-indene-4-carboxylate (650 g, 1.29 mmol, 74%; dr 20 : 1) as a pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.72 (2H, d, *J* = 9.4 Hz, 2 × C*H* Ar), 7.66 (2H, d, *J* = 9.4 Hz, 2 × C*H* Ar), 7.45–7.35 (6H, m, 6 × C*H* Ar), 5.89–5.79 (1H, ddt, *J* = 17.0, 10.0, 6.5 Hz, C*H*=CH$_2$), 5.02 (1H, dd, *J* = 17.0, 1.5 Hz, *trans* CH_2=CH), 4.93 (1H, dd, *J* = 10.0, 1.5 Hz, *cis* CH_2=CH), 4.11–4.06 (1H, m, C*H*OTBDPS), 3.57 (3H, s, CO$_2$CH_3), 3.56 (s, CO$_2$CH_3 (minor diastereoisomer)), 2.35 (1H, t, *J* = 4.9 Hz, C*H*CO$_2$CH$_3$), 2.17 (1H, t, *J* = 5.8 Hz, C*H*CHCO$_2$CH$_3$), 2.13–2.04 (1H, m, 1H from CH_2CH=CH$_2$), 1.99–1.88 (1H, m, 1H from CH_2CH=CH$_2$), 1.88–1.78 (1H, m, 1H from CH_2CHOTBDPS), 1.71–1.60 (4H, m, 1H from CH_2CHOTBDPS, 1H from CCH_2CH$_2$CH=CH$_2$, 1H from CH_2CHCH$_3$, 1H from CH_2CH$_2$CHCH$_3$), 1.54–1.43 (2H, 1H from CCH_2CH$_2$CH=CH$_2$, 1H from CH_2CH$_2$CHOTBDPS), 1.39–1.21 (3H, m, 1H from CH_2CHCH$_3$, 1H from CH_2CH$_2$CHCH$_3$, C*H*CH$_3$), 1.14–1.02 (1H, m, 1H from CH_2CH$_2$CHOTBDPS), 1.10 (9H, s, SiC(CH_3)$_3$), 0.80 (3H, d, *J* = 7.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 175.2 (*C*=O), 139.6 (*C*H=CH$_2$), 136.1 (*C*H Ar), 136.0 (*C*H Ar), 135.8 (*C*H Ar), 134.6 (*C* Ar), 134.1(*C* Ar), 129.9 (*C*H Ar), 129.6 (*C*H Ar), 129.5 (*C*H Ar), 127.5 (4 × *C*H Ar), 113.9 (*C*H$_2$=CH), 78.1 (*C*HOTBDPS), 52.1 (*C*HCHCO$_2$CH$_3$), 51.0 (CO$_2$*C*H$_3$), 44.3 (*C*HCO$_2$CH$_3$), 41.5 (*C*CH$_2$CH$_2$CH=CH$_2$), 37.8 (*C*H$_2$CH$_2$CH=CH$_2$), 34.8 (*C*H$_2$CHCH$_3$), 31.9 (*C*H$_2$CHOTBDPS), 31.3 (*C*H$_2$CH$_2$CHOTBDPS), 29.3 (*C*HCH$_3$), 28.8 (*C*H$_2$CH=CH$_2$), 27.1 (SiC(*C*H$_3$)$_3$), 26.6 (*C*H$_2$CH$_2$CHCH$_3$), 19.2 (Si*C*(CH$_3$)$_3$), 17.2 (*C*H$_3$CH); ν_{max}/(liquid film) cm^{-1} 2929

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m (CH_2s), 1744 s (C═O), 1192 m (Si–C), 1100 (Si–O), 821 w (C═C); MS (ES^+) *m/z* (%) 527 (100 [M + Na]$^+$); Calcd for $C_{32}H_{44}O_3Si + NH_4^+$: 522.3398, found *m/z* 522.3401.

6.2.2 *Rac*-((3*S*,3a*S*,4*R*,5*R*,7a*S*)-7a-(but-3-en-1-yl)-3-((*tert*-butyldiphenylsilyl)oxy)-5-methyloctahydro-1*H*-inden-4-yl)methanol. DIBAL-H (1.0 M in toluene, 3.86 mL, 3.86 mmol) was added to a stirred solution of *rac*- (3*S*,3a*S*,4*R*,5*R*,7a*S*)-methyl 7a-(but-3-en-1-yl)-3-((*tert*-butyldiphenylsilyl)oxy)-5-methyloctahydro-1*H*-indene-4-carboxylate (650 mg, 1.29 mmol, dr 20 : 1) in CH_2Cl_2 (10 mL) at −78 °C and the reaction mixture stirred at room temperature. After 3 h, the reaction mixture was quenched with aqueous saturated sodium/potassium tartrate (10 mL) and extracted with EtOAc (3 × 20 mL). The combined organic layers were dried (Na_2SO_4) and concentrated *in vacuo* to afford *rac*-((3*S*,3a*S*,4*R*,5*R*,7a*S*)-7a-(but-3-en-1-yl)-3-((*tert*-butyldiphenylsilyl)oxy)-5-methyloctahydro-1*H*-inden-4-yl)methanol (610 mg, 1.28 mmol, 99%) as a colourless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ_H 7.70–7.66 (4H, m, 4 × C*H* Ar), 7.45–7.37 (6H, m, 6 × C*H* Ar), 5.89–5.81 (1H, ddt, *J* = 17.0, 10.1, 6.5 Hz, C*H*═CH_2), 5.03 (1H, d, *J* = 17.0 Hz, *trans* CH_2═CH), 4.94 (1H, d, *J* = 10.1 Hz, *cis* CH_2═CH), 4.19 (1H, dt, *J* = 7.9, 5.0 Hz, C*H*OTBDPS), 3.43–3.32 (2H, m, CH_2OH), 2.11–2.00 (2H, m, CH_2CH═CH_2), 1.94–1.86 (1H, m, 1H from CH_2CHOTBDPS), 1.73–1.67 (2H, m, 1H from CH_2CHOTBDPS, C*H*CHOTBDPS), 1.66–1.57 (2H, m, 1H from CH_2CH$_2$CH═CH_2, 1H from CH_2CHCH$_3$), 1.57–1.52 (1H, m, CH_2CH$_2$CHOTBDPS), 1.50–1.42 (2H, m, 1H from CH_2CH$_2$CH═CH_2, C*H*CH$_3$), 1.34–1.29 (2H, m, 1H from CH_2CH$_2$CHOTBDPS, C*H*CH$_2$OH), 1.20–1.12 (3H, m, 1H from CH_2CHCH$_3$, CH_2CH$_2$CHCH$_3$), 1.08 (9H, m, SiC(CH_3)$_3$), 0.83 (1H, s, CH$_2$O*H*), 0.72 (3H, d, *J* = 6.9 Hz, CH_3CH); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 139.7 (*C*H═CH_2), 136.0 (4 × *C*H Ar), 134.6 (*C* Ar), 134.4 (*C* Ar), 129.6 (2 × *C*H Ar), 127.5 (4 × *C*H Ar), 113.8 (*C*H$_2$═CH), 78.4 (*C*HOTBDPS), 63.2 (*C*H$_2$OH), 52.1 (*C*HCHCH$_2$OH), 42.2 (*C*CH$_2$CH$_2$CH═CH_2), 41.6 (*C*HCH$_2$OH), 39.1 (*C*H$_2$CH$_2$CH═CH_2), 34.7 (*C*H$_2$CHCH$_3$), 32.7 (*C*H$_2$CHOTBDPS), 30.3 (*C*H$_2$CH$_2$CHOTBDPS), 28.8 (*C*H$_2$CH═CH_2), 28.4 (*C*HCH$_3$), 27.1 (SiC(*C*H$_3$)$_3$), 27.0 (*C*H$_2$CH$_2$CHCH$_3$), 19.2 (Si*C*(CH$_3$)$_3$), 16.3 (*C*H$_3$CH); ν_{max}/(liquid film) cm^{-1} 3510 s (O–H), 1264 w (Si–C), 1110 m (Si–O), 822 w (C═C); MS (ES^+) *m/z* (%) 499 (100 [M + Na]$^+$); Calcd for $C_{31}H_{44}O_2Si + H^+$: 477.3183, found *m/z* 477.3181.

6.2.3 *Rac*-(3*S*,3a*S*,4*R*,5*R*,7a*S*)-7a-(but-3-en-1-yl)-3-((*tert*-butyldiphenylsilyl)oxy)-5-methyloctahydro-1*H*-indene-4-carbaldehyde 55. General procedure 4 using DMSO (0.21 mL, 2.94 mmol) and oxalyl chloride (0.14 mL, 1.54 mmol) in CH_2Cl_2 (10 mL), with *rac*-((3*S*,3a*S*,4*R*,5*R*,7a*S*)-7a-(but-3-en-1-yl)-3-((*tert*-butyldiphenylsilyl)oxy)-5-methyloctahydro-1*H*-inden-4-yl)-methanol (610 mg, 1.28 mmol) in CH_2Cl_2 (20 mL) and triethylamine (1.02 mL, 7.30 mmol) gave **55** (600 mg, 1.27 mmol, 99%) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 9.64 (1H, s, C*H*O), 7.69–7.63 (4H, m, 4 × C*H* Ar), 7.44–7.38 (6H, m, 6 × C*H* Ar), 5.83–5.74 (1H, ddt, *J* = 17.0, 10.1, 6.6 Hz, C*H*═CH_2), 4.98 (1H, dq, *J* = 17.0, 1.7 Hz, *trans* CH_2═CH), 4.90 (1H, ddt, *J* = 10.1, 2.1, 1.1 Hz, *cis* CH_2═CH), 4.16 (1H, td, *J* = 7.5, 5.4 Hz, C*H*OTBDPS), 2.13–2.08 (2H, m, C*H*CHO, C*H*CHOTBDPS), 2.05–1.88 (3H, CH_2CH═CH_2, 1H from CH_2CHOTBDPS), 1.75–1.63 (2H, m, 1H from CH_2CHOTBDPS, 1H from CH_2CHCH$_3$), 1.51–1.35 (3H, m, 1H from CH_2CH$_2$CHOTBDPS, 1H from CH_2CH$_2$CH═CH_2, 1H from CH_2CH$_2$CHCH$_3$), 1.33–1.22 (4H, C*H*CH$_3$, 1H from CH_2CH$_2$CHCH$_3$, 1H from CH_2CH$_2$CHOTBDPS, 1H from CH_2CHCH$_3$), 1.08 (9H, s, SiC(CH_3)$_3$), 1.04–1.02 (1H, m, 1H from CH_2CH$_2$CH═CH_2), 0.85 (3H, d, *J* = 7.0 Hz, CH_3CH); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 205.2 (*C*HO), 139.2 (*C*H═CH_2), 136.0 (4 × *C*H Ar), 134.3 (2 × *C* Ar), 129.6 (2 × *C*H Ar), 127.6 (4 × *C*H Ar), 114.1 (*C*H$_2$═CH), 76.8 (*C*HOTBDPS), 52.3 (*C*HCHOTBDPS), 51.2 (*C*HCHO), 41.3 (*C*CH$_2$), 37.7 (*C*H$_2$CH$_2$CHOTBDPS), 34.9 (*C*H$_2$CHCH$_3$), 32.2 (*C*H$_2$CHOTBDPS), 31.6 (*C*H$_2$CH$_2$CH═CH_2), 28.8 (*C*HCH$_3$), 28.7 (*C*H$_2$CH═CH_2), 27.2 (*C*H$_2$CH$_2$CHCH$_3$), 27.1 (SiC(*C*H$_3$)$_3$), 19.2 (Si*C*(CH$_3$)$_3$), 18.0 (*C*H$_3$CH); ν_{max}/(liquid film) cm^{-1} 2928 m (CH_2s), 1717 m (C═O), 1110 m (Si–O); MS (ES^+) *m/z* (%) 497 (100 [M + Na]$^+$); Calcd for $C_{31}H_{42}O_2Si + NH_4^+$: 492.3292, found *m/z* 492.3297.

6.2.4 *Rac*-1-((3*S*,3a*S*,4*R*,5*R*,7a*S*)-7a-(but-3-en-1-yl)-3-((*tert*-butyldiphenylsilyl)oxy)-5-methyloctahydro-1*H*-inden-4-yl)prop-2-en-1-ol 57. Vinyl magnesium bromide (0.94 M in THF, 1.08 mL, 1.01 mmol) was added dropwise to **55** (320 mg, 0.675 mmol) in THF (10 mL) −78 °C and the solution allowed to warm to room temperature. After 4 h, the reaction mixture was quenched with aqueous saturated NH_4Cl (10 mL) and extracted with EtOAc (5 × 10 mL). The combined organic layers were dried (Na_2SO_4) and concentrated *in vacuo*. The crude material was purified by silica gel chromatography (10% EtOAc in petroleum ether) to yield **57** as a (305 mg, 0.607 mmol, 89%; dr 7 : 3). For the mixture: ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.74–7.66 (4H, m, 4 × C*H* Ar), 7.46–7.35 (6H, m, 6 × C*H* Ar), 5.94–5.74 (2H, m, 2 × C*H*═CH_2), 5.14–4.91 (4H, m, 2 × CH_2═CH), 4.41–4.36 (m, C*H*OTBDPS (minor diastereoisomer)), 4.21 (1H, dt, *J* = 7.3, 3.9 Hz, C*H*OTBDPS), 4.08 (q, *J* = 5.0 Hz, C*H*OH (minor diastereoisomer)), 3.97 (1H, q, *J* = 5.0 Hz, C*H*OH), 2.20–2.10 (1H, m, 1H from CH_2), 2.09–2.00 (1H, m, 1H from CH_2), 2.00 (1H, dd, *J* = 9.1, 3.3 Hz, C*H*CHOTBDPS), 1.95–1.92 (m, C*H*CHOTBDPS (minor diastereoisomer)), 1.90–1.66 (4H, m, C*H*CH$_3$, 1H from CH_2, 1H from CH_2, 1H from CH_2), 1.66–1.56 (2H, m, 1H from CH_2, 1H from CH_2), 1.56–1.44 (m, C*H*CH$_3$ (minor diastereoisomer), CH_2), 1.44–1.21 (3H, m, CH_2, 1H from CH_2), 1.18–1.12 (1H, m, C*H*CHOH), 1.07 (9H, s, SiC(CH_3)$_3$), 1.06 (s, SiC(CH_3)$_3$ (minor diastereoisomer)), 0.87 (3H, d, *J* = 7.3 Hz, CH_3CH), 0.78 (d, *J* = 6.3 Hz, CH_3CH (minor diastereoisomer)); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 142.3 (*C*H═CH_2 (minor diastereoisomer)), 140.9 (*C*H═CH_2), 140.1 (*C*H═CH_2 (minor diastereoisomer)), 139.9 (*C*H═CH_2), 136.0 (4 × *C*H Ar), 134.7 (*C* Ar), 134.6 (*C* Ar), 134.6 (*C* Ar), 134.4 (*C* Ar), 129.7 (*C*H Ar), 129.6 (*C*H Ar), 129.5 (*C*H Ar), 127.6 (*C*H Ar), 127.5 (*C*H Ar), 127.4 (*C*H Ar), 114.2 (*C*H═CH_2), 114.0 (*C*H═CH_2 (minor diastereoemer)), 113.7 (*C*H═CH_2), 113.6 (*C*H═CH_2 (minor diastereoisomer)), 79.1 (*C*HOTBDPS), 78.9 (*C*HOTBDPS (minor diastereoisomer)), 74.0 (*C*HOH), 73.1 (*C*HOH (minor diastereoisomer)), 51.2 (*C*HCHOTBDPS), 50.5 (*C*HCHOTBDPS (minor diastereoisomer)), 44.5 (*C*HCHOH), 43.1 (*C*HCHOH (minor diastereoisomer)), 41.4 (*C*CH$_2$CH$_2$CH═CH_2), 39.9 (*C*H$_2$), 38.8 (*C*H$_2$ (minor diastereoisomer)), 35.1 (*C*H$_2$ (minor diastereoisomer)), 34.1 (*C*H$_2$), 33.1 (*C*H$_2$), 32.4 (*C*H$_2$ (minor diastereoisomer)), 30.0 (*C*HCH$_3$), 29.0 (*C*H$_2$), 28.8 (*C*HCH$_3$ (minor diastereoisomer)), 28.7 (*C*H$_2$), 28.6 (*C*H$_2$), 28.3 (*C*H$_2$), 27.1 (SiC(*C*H$_3$)$_3$), 19.2

(Si*C*$(CH_3)_3$ (minor diastereoisomer)), 19.1 (Si*C*$(CH_3)_3$), 17.3 (*C*H_3CH (minor diastereoisomer)), 16.9 (*C*H_3CH); ν_{max}/(liquid film) cm^{-1} 3435 m (O–H), 1240 w (Si–C), 1110 m (Si–O); MS (ES^+) *m/z* (%) 525 (100 [M + Na]$^+$); Calcd for $C_{33}H_{46}O_2Si$ + H^+: 503.3340, found *m/z* 503.3336.

6.3 Ring closing metathesis of 57 to form 58

A solution of **57** (300 mg, 0.597 mmol; dr 7 : 3) in CH_2Cl_2 (20 mL) was added dropwise to a stirred solution of Grubbs' II catalyst (25 mg, 0.003 mmol) in CH_2Cl_2 (80 mL) at room temperature and the reaction mixture was heated under reflux. After 6 h the reaction mixture was cooled and concentrated *in vacuo*. The crude material was purified by silica gel chromatography (10% EtOAc in petroleum ether) to afford **58** (235 mg, 0.467 mmol, 83%; dr 7 : 3) as a yellow oil. For the mixture ^{1}H NMR (500 MHz, $CDCl_3$) δ_H 7.66 (4H, ddd, *J* = 9.9, 8.1, 1.3 Hz, 4 × C*H* Ar), 7.44–7.36 (6H, m, 6 × C*H* Ar), 5.65–5.61 (1H, m, CH_2CH═CH), 5.32–5.27 (1H, m, CH═C*H*CHOH), 4.84 (1H, s, C*H*OH), 4.35 (1H, td, *J* = 8.8, 6.0 Hz, C*H*OTBDPS), 2.27 (1H, d, *J* = 9.2 Hz, C*H*CHOTBDPS), 2.24–2.22 (1H, m, 1H from CH_2CH═CH), 2.00–1.92 (1H, m, 1H from CH_2CHOTBDPS), 1.83–1.75 (2H, m, 1H from CH_2CH_2CH═CH, 1H from $CH_2CH_2CHCH_3$), 1.67–1.56 (1H, m, CH_2CHOTBDPS), 1.39–1.36 (1H, m, C*H*CHOH), 1.34–1.11 (6H, m, CH_2CHCH_3, 1H from $CH_2CH_2CHCH_3$, 1H from CH_2CH═CH, 1H from CH_2CHCHOTBDPS, C*H*CH_3), 1.11–1.08 (1H, m, CH_2CH_2CH═CH), 1.06 (9H, s, SiC(CH_3)$_3$), 0.98–0.84 (1H, m, CH_2CH_2CHOTBDPS), 0.78 (3H, d, *J* = 6.9 Hz, CH_3CH); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 136.0 (4 × *C*H Ar), 134.7 (*C* Ar), 134.6 (*C* Ar), 133.4 (HC═*C*HCHOH), 130.4 (CH_2*C*H═CH), 129.5 (2 × *C*H Ar), 127.5 (4 × *C*H Ar), 75.9 (*C*HOTBDPS), 69.2 (*C*HOH), 51.8 (*C*HCHOTBPDS), 43.9 (*C*HCHOH), 41.4 (CCH_2), 34.6 (CH_2CH_2CHOTBDPS), 34.2 ($CH_2CH_2CHCH_3$), 32.1 (CH_2CHOTBDPS), 31.9 (CH_2CH_2CH═CH), 29.0 (*C*HCH_3), 27.1 (SiC(CH_3)$_3$), 27.1 (CH_2CHCH_3), 26.6 (CH_2CH═CH), 21.1 (*C*H_3CH), 19.2 (Si*C*$(CH_3)_3$); ν_{max}/(liquid film) cm^{-1} 3470 s (O–H), 1635 m (C═CCOH), 1110 w (Si–O); MS (ES^+) *m/z* (%) 497 (100 [M + Na]$^+$); Calcd for $C_{31}H_{42}O_2Si$ + NH_4^+: 492.3292, found *m/z* 492.3293.

6.4 Naphthyl carbamate 59

To a solution of **58** (30 mg, 0.060 mmol; dr 7 : 3) in THF (3 mL) was added 1-naphthyl-isocyanate (17 μl, 0.179 mmol) at room temperature and the reaction mixture was heated at reflux for 24 h before being cooled to room temperature and concentrated *in vacuo* to give an off white solid. The residue was then suspended in CH_2Cl_2 (10 mL), the suspension filtered, and the filtrate concentrated *in vacuo*. The product was purified by silica gel chromatography (5% EtOAc in petroleum ether) to yield **59** (32 mg, 0.050 mmol, 84%) as a sticky oil. Subsequent crystallisation from hexane gave white needles. Mpt 148 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.90 (3H, d, *J* = 8.1 Hz, 3 × C*H* Ar), 7.68–7.67 (5H, m, 5 × C*H* Ar), 7.60–7.51 (3H, m, 3 × *C*H Ar), 7.48–7.32 (7H, m, 7 × C*H* Ar), 6.89 (1H, s broad, N*H*), 5.95 (1H, s broad, C*H*OCO), 5.75 (1H, dd, *J* = 12.6, 2.0, CH═C*H*CH_2), 5.29 (1H, dt, *J* = 12.6, 2.1, CH═C*H*CHOCO), 4.38 (1H, s broad, C*H*OTBDPS), 2.36–2.21 (3H, m, C*H*CHOTBDPS, CH_2CH═CH), 2.02–1.92 (2H, m, 1H from CH_2CHOTBDPS, 1H from CH_2CH_2CH═CH_2), 1.84–1.77 (2H, m, C*H*CHOCO, 1H from CH_2CH_2CHOTBDPS), 1.69–1.60 (1H, m, 1H from CH_2CHOTBDPS), 1.51–1.35 (1H, m, 1H from $CH_2CH_2CHCH_3$), 1.30–1.22 (1H, m, C*H*CH_3), 1.20–0.95 (5H, m, CH_2CHCH_3, 1H from CH_2CH_2CH═CH, 1H from $CH_2CH_2CHCH_3$, 1H from CH_2CH_2CHOTBDPS), 1.11 (9H, s, SiC(CH_3)$_3$), 0.80–0.59 (3H, m, CH_3CH); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 164.8 (N*C*═O), 136.0 (4 × *C*H Ar), 134.5 (*C* Ar), 134.0 (2 × *C* Ar), 132.6 (2 × *C* Ar), 131.9 (*C*H═CH), 129.5 (*C*H Ar), 129.4 (*C*H Ar), 129.3 (CH═*C*H), 128.7 (2 × *C*H Ar), 127.5 (5 × *C*H Ar), 126.2 (2 × *C*H Ar), 125.9 (*C*H Ar), 125.8 (*C*H Ar), 76.7 (*C*HOC(O)N), 73.5 (*C*HOTBDPS), 50.9 (*C*HCHOTBDPS), 41.1 (CCH_2), 39.2 (*C*HCHOCO), 34.4 (CH_2CHCH_3), 33.9 (CH_2CH_2CHOTBPDS), 31.9 (CH_2CHOTBDPS), 31.6 (CH_2CH_2CH═CH), 29.7 (*C*HCH_3), 27.1 (SiC(CH_3)$_3$), 27.0 (CH_2CH═CH), 26.3 ($CH_2CH_2CHCH_3$), 19.9 (*C*H_3CH), 19.3 (Si*C*$(CH_3)_3$); ν_{max}/(liquid film) cm^{-1} 2340 m (O═C–N), 1733 m (C═O), 1206 w (Si–C), 1110 m (Si–O); MS (ES^+) *m/z* (%) 661 (100 [M + NH_4]$^+$); Calcd for $C_{42}H_{49}O_3Nsi$ + NH_4^+: 661.3820, found *m/z* 661.3834.

6.5 *rac*-(3*S*,3a*S*,4*R*,9a*S*,12*R*,*Z*)-3-((*tert*-butyldiphenylsilyl)oxy)-12-methyl-2,3,3a,4,8,9-hexahydro-4,9a-propanocyclopenta[8]annulen-5(1*H*)-one

Dess–Martin periodinane (442 mg, 1.04 mmol) was added to a stirred solution of **58** (350 mg, 0.738 mmol) in CH_2Cl_2 (12 mL) and the reaction mixture stirred for 3 h. The reaction was quenched with 0.5 M NaOH (10 mL) and extracted with EtOAc (3 × 20 mL). The combined organic layers were dried (Na_2SO_4) and concentrated *in vacuo* to give a colourless oil. The crude product was purified by silica gel chromatography (10% EtOAc in petroleum ether) to afford *rac*-(3*S*,3a*S*,4*R*,9a*S*,12*R*,*Z*)-3-((*tert*-butyldiphenylsilyl)oxy)-12-methyl-2,3,3a,4,8,9-hexahydro-4,9a-propanocyclopenta[8]annulen-5(1*H*)-one (275 mg, 0.583 mmol, 79%) ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.65–7.63 (4H, m, 4 × C*H* Ar), 7.46–7.35 (6H, m, 6 × C*H* Ar), 6.01 (1H, dt, *J* = 13.1, 3.9 Hz, C*H*═CH), 5.64 (1H, dt, *J* = 13.1, 2.1 Hz, C*H*═CH), 4.41 (1H, td, *J* = 8.7, 5.8 Hz, C*H*OTBDPS), 2.72 (1H, d, *J* = 8.8 Hz, C*H*CHOTBDPS), 2.30–2.26 (2H, m, CH_2CH═CH_2), 2.13 (1H, s, C*H*CO), 2.06–1.97 (1H, m, 1H from CH_2CHOTBDPS), 1.85–1.77 (1H, m, 1H from CH_2CH_2CHOTBDPS), 1.74–1.67 (2H, m, 1H from CH_2CHOTBDPS, 1H from CH_2CH_2CH═CH_2), 1.59–1.50 (2H, m, CH_2CHCH_3), 1.22–1.10 (4H, m, C*H*CH_3, $CH_2CH_2CHCH_3$, 1H from CH_2CH_2CH═CH), 1.09–1.02 (1H, m, CH_2CH_2CHOTBDPS), 1.06 (9H, s, SiC(CH_3)$_3$), 1.02 (3H, d, *J* = 7.0 Hz, CH_3CH); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 211.8 (*C*═O), 137.0 (*C*H═CH), 135.8 (4 × *C*H Ar), 134.3 (2 × *C* Ar), 129.7 (2 × *C*H Ar), 127.6 (4 × *C* Ar), 127.3 (*C*H═CH), 75.4 (*C*HOTBDPS), 51.2 (*C*HCHOTBDPS), 49.9 (*C*HCO), 41.6 (CCH_2), 35.2 ($CH_2CH_2CHCH_3$), 33.7 (CH_2CH_2CHOTBPDS), 31.9 (CH_2CHOTBDPS), 31.0 (CH_2CH_2CH═CH_2), 29.1 (*C*HCH_3), 27.2 (CH_2CH═CH), 27.0 (SiC(CH_3)$_3$), 25.9 (CH_2CHCH_3), 20.4 (*C*H_3CH), 19.2 (Si*C*$(CH_3)_3$); ν_{max}/(liquid film) cm^{-1} 2929 s (CH_2s), 1700 m (C═O), 1280 w (Si–C), 1110 s (Si–O), 946 w (C═O); MS (ES^+) *m/z* (%) 495 (100 [M + Na]$^+$); Calcd for $C_{31}H_{40}O_2$ Si + NH_4^+: 490.3136, found *m/z* 490.3143.

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6.6 *Rac*-(3*S*,3a*S*,4*R*,9a*R*,12*R*)-3-((*tert*-butyldiphenylsilyl)oxy)-12-methyl-7-vinyloctahydro-4,9a-propanocyclopenta[8]annulen-5(1*H*)-one 60

Vinyl magnesium bromide in THF (0.94 M in THF, 2.03 mL, 1.91 mmol) was added dropwise to a stirred suspension of CuI (182 mg, 0.953 mmol) in THF (5 mL) at −40 °C. The resulting dark brown solution was stirred for 20 min and treated dropwise with *rac*-(3*S*,3a*S*,4*R*,9a*S*,12*R*,*Z*)-3-((*tert*-butyldiphenylsilyl)oxy)-12-methyl-2,3,3a,4,8,9-hexahydro-4,9a-propanocyclopenta[8]annulen-5(1*H*)-one (150 mg, 0.318 mmol) in THF (4 mL). The reaction mixture was then stirred at room temperature. After 1 h, reaction mixture was quenched with aqueous saturated NH_4Cl (10 mL) and extracted with Et_2O (5 × 10 mL). The combined organic layers were dried (Na_2SO_4) and concentrated *in vacuo*. The crude material was purified by silica gel chromatography (1% EtOAc in petroleum ether) to yield **60** (137 mg, 0.273 mmol, 86%; dr 1 : 1). For the mixture: ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 7.69–7.65 (8H, m, 4 × C*H* Ar both diastereoisomers), 7.46–7.36 (12H, m, 6 × C*H* Ar both diastereoisomers), 6.15 (1H, ddd, *J* = 17.2, 10.5, 6.6 Hz, C*H*═CH_2), 5.88 (1H, ddd, *J* = 17.2, 10.5, 6.6 Hz, C*H*═CH_2), 5.08–4.97 (4H, m, CH_2═CH both diastereoisomers), 4.45 (2H, tt, *J* = 8.6, 4.4 Hz, C*H*OTBDPS both diastereoisomers), 3.02 (1H, dd, *J* = 11.4, 5.0 Hz, 1H from CH_2C═O), 2.82–2.77 (1H, m, C*H*C═O), 2.77–2.71 (1H, m, 1H from CH_2C═O), 2.57 (2H, t, *J* = 8.6 Hz, C*H*CHCO), 2.58–2.48 (1H, m, C*H*CH═CH_2), 2.15–2.06 (2H, m, C*H*CHCO, 1H from CH_2C═O), 2.05–1.93 (4H, m, 1H from CH_2C═O, 1H from CH_2CHOTBDPS both diastereoisomers), 1.79–1.73 (2H, m, 1H from CCH_2CH_2CHCH═CH_2 both diastereoisomers), 1.73–1.63 (4H, m, 1H from CH_2CHOTBDPS both diastereoisomers, 1H from CH_2 both diastereoisomers), 1.63–1.51 (2H, m, 1H from CH_2 both diastereoisomers), 1.42–1.24 (3H, m, C*H*CH_3, CH_2CH_2CHOTBDPS both diastereoisomers), 1.15–1.05 (13H, m, SiC(CH_3)$_3$ both diastereoisomers, CH_2 both diastereoisomers, 1H from CCH_2CH_2CHCH═CH_2 both diastereoisomers, 1H from CH_2 both diastereoisomers), 0.93 (3H, d, *J* = 6.8 Hz, CH_3CH), 0.92 (3H, d, *J* = 6.8 Hz, C*H*CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 214.7 (*C*═O), 213.8 (*C*═O), 143.4 (*C*H═CH_2), 141.6 (*C*H═CH_2), 136.0 (4 × *C*H Ar), 135.8 (4 × *C*H Ar), 134.2 (2 × *C* Ar), 129.7 (*C*H Ar), 127.6 (*C*H Ar), 113.5 (CH_2═CH), 112.5 (CH_2═CH), 75.5 (*C*HOTBDPS), 50.6 (*C*HCHCO), 50.1 (*C*HCHCO), 46.2 (*C*HCH═CH_2), 45.2 (CH_2C═O), 44.2 (CH_2C═O), 42.1 (*C*HC═O), 41.5 (CCH_2), 41.4 (CCH_2), 35.3 (CH_2), 35.0 (CH_2), 34.9 (CH_2), 34.6 (CH_2), 32.5 (CH_2), 31.7 (*C*H_2CHOTBDPS), 31.4, (*C*H_2CHOTBDPS), 28.5 (*C*HCH_3), 28.3 (CH_2), 27.1 (SiC(*C*H_3)$_3$), 26.0 (CH_2), 25.5 (CH_2), 25.3 (CH_2), 19.8 (*C*H_3CH), 19.7 (*C*H_3CH), 19.2 (Si*C*(CH_3)$_3$); ν_{max}/(liquid film) cm^{-1} 2930 s (CH_2s), 1699 s (C═O), 1260 m (Si–C), 1076 m (Si–O); MS (ES$^+$) *m*/*z* (%) 523 (100 [M + Na]$^+$); Calcd for $C_{33}H_{44}O_2Si$ + NH_4^+: 518.3449, found *m*/*z* 518.3449.

6.7 DIBAL-H reduction of 60 to give 61a and 61b

DIBAL-H (1.0 M in toluene, 0.24 mL, 0.240 mmol) was added dropwise to a stirred solution of **60** (60 mg, 0.120 mmol, dr 1 : 1) in CH_2Cl_2 (2.5 mL) at −78 °C and the reaction mixture stirred at room temperature. After 3 h, the reaction mixture was quenched with aqueous saturated Na/K tartrate solution (10 mL) and stirred for 30 min before extraction with Et_2O (5 × 20 mL). The combined organic layers were washed with brine (10 mL), dried (Na_2SO_4) and concentrated *in vacuo*. The crude material was purified by silica gel chromatography (1% EtOAc in petroleum ether) to afford diastereoisomer **61a** (26 mg, 0.052 mmol) and diastereoisomer **61b** (28 mg, 0.056 mmol) in an overall yield of 90%. For **61a** ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 7.68–7.65 (4H, m, 4 × C*H* Ar), 7.45–7.37 (6H, m, 6 × C*H* Ar), 5.94 (1H, ddd, *J* = 17.3, 10.4, 6.9 Hz, C*H*═CH_2), 5.05–4.80 (2H, m, CH_2═CH), 4.40–4.35 (2H, m, C*H*OH, C*H*OTBDPS), 2.53–2.28 (1H, m, C*H*CH═CH_2), 2.08–1.83 (4H, m, C*H*CHOTBDPS, 1H from CH_2CHOTBDPS, 1H from CH_2, 1H from CH_2), 1.70–1.61 (5H, m, 1H from CH_2CHOTBDPS, 1H from CH_2, 1H from CH_2, 1H from CH_2, 1H from CH_2), 1.52–1.50 (1H, m, C*H*CHOH), 1.35–1.20 (4H, from C*H*CH_3, 1H from CH_2, 1H from CH_2, 1H from CH_2), 1.12–1.04 (3H, m, 1H from CH_2, 1H from CH_2, 1H from CH_2), 1.08 (9H, s, SiC(*C*H_3)$_3$), 0.85 (3H, d, *J* = 6.9 Hz, *C*H_3CH); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 146.3 (*C*H═CH_2), 136.0 (4 × *C*H Ar), 134.7 (2 × *C* Ar), 129.5 (2 × *C*H Ar), 127.5 (4 × C*H* Ar), 111.4 (*C*H_2═CH), 76.6 (*C*HOTBDPS), 70.2 (*C*HOH), 49.3 (*C*HCHOTBDPS), 39.0 (*C*CH_2), 39.0 (*C*HCH═CH_2), 37.1 (*C*H_2CHOTBDPS), 35.8 (*C*H_2), 34.1 (*C*H_2), 32.0 (*C*H_2), 31.3 (*C*HCHOH), 29.7 (*C*HCH_3), 29.7 (*C*H_2), 28.9 (*C*H_2), 28.2 (*C*H_2), 27.2 (SiC(*C*H_3)$_3$), 19.3 (*C*H_3CH), 14.2 (Si*C*(CH_3)$_3$). For **61b** ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 7.72 (2H, dd, *J* = 7.9, 1.3 Hz, 2 × C*H* Ar), 7.66 (2H, dd, *J* = 7.9, 1.3 Hz, 2 × C*H* Ar), 7.47–7.38 (6H, m, C*H* Ar), 5.82 (1H, ddd, *J* = 17.2, 10.1, 6.8 Hz, C*H*═CH_2), 4.92 (1H, d, *J* = 17.2 Hz, *trans* CH_2═CH), 4.86 (1H, d, *J* = 10.1 Hz, *cis* CH_2═CH), 4.24 (1H, s brd, C*H*OTBDPS), 3.62 (1H, d, *J* = 9.5 Hz, C*H*OH), 2.45–2.05 (1H, m, C*H*CH═CH_2), 2.05–1.90 (2H, m, C*H*CHOTBDPS, C*H*CHOH), 1.68–1.57 (9H, m, CH_2C*H*CH_3, 1H from CH_2CHOTBDPS, 1H from CH_2CHOH, 1H from CH_2, CH_2, CH_2), 1.27–1.28 (3H, m, 1H from CH_2CHOTBDPS, 1H from CH_2CHOH, 1H from CH_2), 1.18–1.09 (3H, m, C*H*CH_3, CH_2CH_2CHOTBDPS), 1.09 (9H, s, SiC(*C*H_3)$_3$), 0.85 (3H, d, *J* = 7.3 Hz, *C*H_3CH), 0.81 (1H, s brd, O*H*); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 145.8 (*C*H═CH_2), 136.0 (4 × *C*H Ar), 135.1 (*C* Ar), 134.4 (*C* Ar), 129.7 (2 × *C*H Ar), 127.6 (4 × C*H* Ar), 110.9 (*C*H_2═CH), 80.5 (*C*HOH), 77.1 (*C*HOTBDPS), 42.3 (*C*HCHOTBDPS), 39.5 (*C*CH_2), 33.9 (*C*H_2CHOTBDPS), 32.0 (*C*H_2), 31.0 (*C*H_2), 29.7 (*C*H_2), 29.4 (*C*H_2), 29.4 (*C*H), 28.4 (*C*HCH_3), 27.1 (SiC(*C*H)$_3$), 22.7 (*C*H_2), 20.3 (*C*H_3CH), 19.3 (Si*C*(CH_3)$_3$); ν_{max}/(liquid film) cm^{-1} 3450 s (O–H), 2928 s (CH_2s), 1265 m (Si–C), 1105 m (Si–O); MS (ES$^+$) *m*/*z* (%) 525 (100 [M + Na]$^+$); Calcd for $C_{33}H_{46}O_2Si$ + NH_4^+: 520.3605, found *m*/*z* 520.3597.

6.8 *Rac*-(3*S*,3a*S*,4*R*,5*S*,7*S* or 7*R*,9a*R*,12*R*)-3-((*tert*-butyldiphenylsilyl)oxy)-12-methyl-7-vinyldecahydro-4,9a-propanocyclopenta[8]annulen-5-yl 2-acetoxyacetate

Et_3N (67.2 μL, 0.477 mmol), acetoxyacetyl chloride (25.6 μL, 0.240 mmol) and DMAP (2 mg, 0.016 mmol) were added to a stirred solution of **61a** (40 mg, 0.080 mmol) in CH_2Cl_2 (2 mL) at room temperature. After 28 h, the reaction mixture was quenched with aqueous saturated $NaHCO_3$ (10 mL) and extracted with Et_2O (3 × 10 mL). The combined organic layers were dried (Na_2SO_4) and concentrated *in vacuo* to give a brown oil. The crude material was purified by silica gel chromatography (2.5%

EtOAc in petroleum ether) to afford *rac*-(3*S*,3a*S*,4*R*,5*S*,7*S* or 7*R*,9a*R*,12*R*)-3-((*tert*-butyldiphenylsilyl)oxy)-12-methyl-7-vinyldecahydro-4,9a-propanocyclopenta[8]annulen-5-yl 2-acetoxyacetate (35 mg, 0.058 mmol, 73%). ^{1}H NMR (500 MHz, $CDCl_3$) δ_H 7.66–7.62 (4H, m, 4 × C*H* Ar), 7.44–7.36 (6H, m, 6 × C*H* Ar), 5.84 (1H, ddd, *J* = 17.2, 10.1, 6.6 Hz, C*H*═CH_2), 5.35 (1H, t, *J* = 7.1 Hz, C*H*OCO), 5.02 (1H, d, *J* = 17.2, *trans* CH_2═CH), 4.93 (1H, d, *J* = 10.1 Hz, *cis* CH_2═CH), 4.62 (2H, s, CH_2OAc), 4.34 (1H, d, *J* = 4.1 Hz, C*H*OTBDPS), 2.25–2.16 (1H, m, 1H from CH_2CHOCO), 2.16 (3H, s, CH_3CO), 2.09–1.92 (3H, m, C*H*CHOTBDPS, C*H*CH═CH_2, 1H from CH_2CHOTBDPS), 1.86 (1H, dd, *J* = 13.2, 10.6 Hz, CH_2), 1.71–1.54 (6H, C*H*CHOCO, 1H from CH_2CHOCO, 1H from CH_2CHCH$_3$, 1H from CH_2CHOTBDPS, CH_2), 1.40–1.32 (1H, m, 1H from CH_2), 1.33–1.21 (2H, m, C*H*CH$_3$, 1H from CH_2), 1.19–1.13 (1H, m, 1H from CH_2), 1.09–1.03 (3H, m, 1H from CH_2CHCH$_3$, CH_2), 1.07 (9H, s, SiC(CH_3)$_3$), 0.56 (3H, d, *J* = 6.3 Hz, CH_3CH); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 170.2 (*C*═O), 167.0 (*C*═O), 144.8 (*C*H═CH_2), 135.9 (4 × *C*H Ar), 134.5 (2 × *C* Ar), 129.6 (2 × *C*H Ar), 127.6 (4 × *C*H Ar), 112.2 (*C*H_2═CH), 76.2 (*C*HOTBDPS), 75.2 (*C*HOCO), 60.9 (*C*H_2OAc), 49.0 (*C*HCHOTBDPS), 39.6 (*C*HCH═CH_2), 39.0 (*C*CH_2), 37.4 (*C*HCHOCO), 35.9 (*C*H_2CHCH$_3$), 33.8 (*C*H_2), 33.3 (*C*H_2CHOCO), 31.8 (*C*H_2CHOTBDPS), 31.2 (*C*H_2), 29.7 (*C*H_2), 28.2 (*C*HCH$_3$), 27.7 (*C*H_2), 27.1 (SiC(*C*H$_3$)$_3$), 20.6 (*C*H$_3$CO), 19.2 (Si*C*(CH$_3$)$_3$), 18.2 (*C*H$_3$CH); ν_{max}/(liquid film) cm^{-1} 1700 m (C═O), 1684 m (C═O), 1265 m (Si–C), 895 w (C═C); MS (ES$^+$) *m*/*z* (%) 625 (100 [M + Na]$^+$); Calcd for $C_{37}H_{50}O_5Si$ + Na^+: 625.3320, found *m*/*z* 625.3306.

6.9 *Rac*-(3*S*,3a*S*,4*R*,5*S*,7*S* or 7*R*,9a*R*,12*R*)-3-hydroxy-12-methyl-7-vinyldecahydro-4,9a-propanocyclopenta[8]annulen-5-yl 2-acetoxyacetate

HF (60% aqueous solution, 74 μl, 2.32 mmol) was added dropwise to a solution of *rac*-(3*S*,3a*S*,4*R*,5*S*,7*S* or 7*R*,9a*R*,12*R*)-3-((*tert*-butyldiphenylsilyl)oxy)-12-methyl-7-vinyldecahydro-4,9a-propanocyclopenta[8]annulen-5-yl 2-acetoxyacetate (28 g, 0.046 mmol) in pyridine (1 mL) at 0 °C. The resulting cloudy solution was allowed to warm to room temperature and stirred for 12 h. The reaction was then quenched with aqueous saturated $NaHCO_3$ (20 mL) and extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with aqueous saturated $CuSO_4$ (3 × 5 mL), dried (Na_2SO_4) and concentrated *in vacuo* to give a colourless oil. The crude material was purified by silica gel chromatography (5% EtOAc in petroleum ether then 30% EtOAc in petroleum ether) to afford *rac*-(3*S*,3a*S*,4*R*,5*S*,7*S* or 7*R*,9a*R*,12*R*)-3-hydroxy-12-methyl-7-vinyldecahydro-4,9a-propanocyclopenta[8]annulen-5-yl 2-acetoxyacetate (15 mg, 0.041 mmol, 89%) as a colourless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 5.79 (1H, dt, *J* = 17.2, 10.1 Hz, C*H*═CH_2), 5.60–5.50 (1H, m, C*H*OCO), 4.98 (1H, d, *J* = 17.2, *trans* CH_2═CH), 4.89 (1H, d, *J* = 10.1 Hz, *cis* CH_2═CH), 4.67 (2H, s, CH_2OAc), 4.45–4.35 (1H, m, C*H*OH), 2.31–2.11 (2H, m, 1H from CH_2, 1H from CH_2CHOH), 2.17 (3H, s, CH_3CO), 2.09–1.83 (6H, m, C*H*CHOH, C*H*CHOCO, C*H*CH$_3$, 1H from CH_2CHCH$_3$, CH_2), 1.80–1.57 (3H, m, 1H from CH_2CHOH, 1H from CH_2CHOCO, 1H from CH_2), 1.55–1.41 (1H, m, 1H from CH_2), 1.40–1.23 (6H, m, C*H*CH═CH_2, 1H from CH_2CHCH$_3$, 1H from CH_2, 1H from CH_2, CH_2), 1.23–1.16 (2H, m, 1H from CH_2CHOCO, 1H from CH_2), 0.94 (3H, d, *J* = 4.0 Hz, CH_3CH); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 170.2 (*C*═O), 166.9 (*C*═O), 144.5 (*C*H═CH_2), 112.3 (*C*H_2═CH), 75.4 (*C*HOH), 75.1 (*C*HOCO), 61.0 (*C*H_2OAc), 49.1 (*C*HCHOH), 39.7 (*C*CH_2), 38.3 (*C*HCHOCO), 35.8 *C*H_2CHOCO), 33.8 (*C*H_2), 33.2 (*C*H_2CHOH), 31.7 (*C*H_2), 31.1 (*C*H_2CHCH$_3$), 29.7 (*C*HCH═CH_2), 28.6 (*C*HCH$_3$), 28.2 (*C*H_2), 27.9 (*C*H_2), 20.5 (*C*H$_3$CO), 18.3 (*C*H$_3$CH); ν_{max}/(liquid film) cm^{-1} 3400 s (O–H), 1700 m (C═O), 1638 m (C═O); MS (ES$^+$) *m*/*z* (%) 387 (100 [M + Na]$^+$); Calcd for $C_{21}H_{32}O_5$ + Na^+: 387.2142, found *m*/*z* 387.2130.

6.10 *Rac*-(3a*S*,4*R*,5*S*,7*R* or 7*S*,9a*R*,12*R*)-12-methyl-3-oxo-7-vinyldecahydro-4,9a-propanocyclopenta[8]annulen-5-yl 2-acetoxyacetate 62a

TPAP (0.6 mg, 0.002 mmol) and NMO (19 mg, 0.165 mmol) were added to a stirred solution of *rac*-(3*S*,3a*S*,4*R*,5*S*,7*S* or 7*R*,9a*R*,12*R*)-3-hydroxy-12-methyl-7-vinyldecahydro-4,9a-propanocyclopenta[8]annulen-5-yl 2-acetoxyacetate (20 mg, 0.055 mmol) in CH_2Cl_2 (1 mL) with crushed molecular sieves at room temperature. After 2 h, the resulting black solution was filtered through a silica gel pad (30% EtOAc in petroleum ether) and concentrated *in vacuo* to afford **62a** (19.5 mg, 0.054 mmol, 98%). ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 5.75 (1H, dt, *J* = 17.2, 10.1 Hz, C*H*═CH_2), 5.56 (1H, broad s, C*H*OCO), 4.99 (1H, d, *J* = 17.2 Hz, *trans* CH_2═CH), 4.91 (1H, d, *J* = 10.1 Hz, *cis* CH_2═CH), 4.67 (2H, s, CH_2OAc), 2.36–2.25 (4H, m, C*H*C═O, C*H*CHOCO, CH_2C═O), 2.18 (3H, s, CH_3CO), 2.15–2.02 (2H, m, C*H*CH═CH_2, 1H from CH_2), 1.89–1.72 (3H, m, 1H from CH_2, 1H from CH_2, 1H from CH_2), 1.66–1.42 (5H, C*H*CH$_3$, CH_2, 1H from *C*H$_2$, 1H from *C*H$_2$), 1.42–1.23 (4H, m, CH_2, 1H from *C*H$_2$, 1H from *C*H$_2$), 0.92 (3H, d, *J* = 5.3 Hz, CH_3CH); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C (*C*═O) not observed <220, 170.2 (*C*═O), 166.8 (*C*═O), 144.1 (*C*H═CH_2), 112.6 (*C*H_2═CH), 74.0 (*C*HOCO), 60.9 (*C*H_2OAc), 53.4 (*C*HC═O), 39.2 (*C*HCH═CH_2), 38.9 (*C*CH_2), 37.0 (*C*HCHOCO), 34.6 (*C*H_2C═O), 33.8 (*C*H_2), 32.8 (*C*H_2), 31.4 (*C*H_2), 30.6 (*C*HCH$_3$), 29.7 (*C*H_2), 28.6 (*C*H_2), 27.0 (*C*H_2), 20.5 (*C*H$_3$CO), 18.2 (*C*H$_3$CH); ν_{max}/(liquid film) cm^{-1} 1700 m (C═O), 1653 m (C═O); MS (ES$^+$) *m*/*z* (%) 385 (100 [M + Na]$^+$); Calcd for $C_{21}H_{30}O_5$ + NH_4^+: 380.2431, found *m*/*z* 380.2429.

6.11 *Rac*-(3a*S*,4*R*,5*S*,7*R* or 7*S*,9a*R*,12*R*)-12-methyl-3-oxo-7-vinyldecahydro-4,9a-propanocyclopenta[8]annulen-5-yl 2-hydroxyacetate 63a

Aqueous K_2CO_3 (0.17 M, 1.0 mL, 0.170 mmol) was added to a stirred solution of **62a** (30 mg, 0.083 mmol) in THF (1 mL) and MeOH (2 mL) at room temperature. After 1.5 h, the reaction mixture was quenched with aqueous saturated NH_4Cl (5 mL) and extracted with EtOAc (3 × 5 mL). The combined organic layers were dried (Na_2SO_4) and concentrated *in vacuo*. The crude material was purified by silica gel chromatography (20% EtOAc in petroleum ether) to afford **63a** (24 mg, 0.075 mmol, 91%). ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 5.77 (1H, broad s, C*H*═CH_2), 5.60 (1H, broad s, C*H*OCO), 4.96 (1H, d, *J* = 17.7 Hz, *trans* CH_2═CH), 4.94–4.91 (1H, m, *cis* CH_2═CH), 4.23 (2H, s brd, CH_2OH), 2.52 (1H, s brd, O*H*), 2.36–2.27 (5H,

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m, C*H*C═O, C*H*CH═CH_2, CH_2C═O, 1H from CH_2CHOCO), 2.03 (1H, d, J = 8.3 Hz, C*H*CHOCO), 1.80–1.71 (3H, m, 1H from CH_2C*H*CH_3, 1H from CH_2, 1H from CH_2), 1.54–1.44 (4H, C*H*CH_3, 1H from CH_2, CH_2), 1.39–1.24 (5H, m, 1H from CH_2CHOCO, 1H from CH_2C*H*CH_3, 1H from CH_2, CH_2), 0.89 (3H, d, J = 4.8 Hz, CH_3CH); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 219.5 (*C*═O), 172.2 (O*C*═O), 144.0 (*C*H═CH_2), 112.6 (*C*H_2═CH), 74.1 (*C*HOCO), 60.8 (*C*H_2OH), 53.4 (*C*HC═O), 39.4 (*C*HCHOCO), 38.9 (*C*CH_2), 37.0 (*C*HCH═CH_2), 34.6 (*C*H_2C═O), 33.9 (*C*H_2CHCH═CH_2), 32.6 (*C*H_2), 31.4 (*C*H_2), 30.6 (*C*HCH_3), 29.7 (*C*H_2), 28.5 (*C*H_2), 27.1 (*C*H_2CHCH_3), 18.3 (*C*H_3CH); ν_{max}/(liquid film) cm^{-1} 3400 s (O–H), 1700 m (C═O), 1653 m (C═O); MS (ES$^+$) m/z (%) 343 (100 [M + Na]$^+$); Calcd for $C_{19}H_{28}O_4$ + NH_4^+: 338.2326, found m/z 338.2322; Anal. Calcd for $C_{19}H_{28}O_4$: C, 70.56; H, 8.55. Found: C, 70.83; H, 9.12.

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Notes and references

1 For a review of metal-mediated radical reactions: (*a*) A. Gansauer and H. Bluhm, *Chem. Rev.*, 2000, **100**, 2771; (*b*) For recent reviews on the use of samarium(II) iodide: D. J. Procter, R. A. Flowers II and T. Skrydstrup, *Organic Synthesis using Samarium Diiodide: A Practical Guide*, RSC Publishing, Cambridge, 2010; (*c*) K. C. Nicolaou, S. P. Ellery and J. S. Chen, *Angew. Chem., Int. Ed.*, 2009, **48**, 7140; (*d*) K. Gopalaiah and H. B. Kagan, *New J. Chem.*, 2008, **32**, 607; (*e*) R. A. Flowers, *Synlett*, 2008, 1427; (*f*) D. J. Edmonds, D. Johnston and D. J. Procter, *Chem. Rev.*, 2004, **104**, 3371; (*g*) A. Dahlén and G. Hilmersson, *Eur. J. Inorg. Chem.*, 2004, 3393; (*h*) H. B. Kagan, *Tetrahedron*, 2003, **59**, 10351; (*i*) P. G. Steel, *J. Chem. Soc., Perkin Trans. 1*, 2001, 2727; (*j*) H. B. Kagan and J. L. Namy, In *Lanthanides: Chemistry and Use in Organic Synthesis*, S. Kobayashi, Ed.; Springer, Berlin, 1999; p 155; (*k*) G. A. Molander and C. R. Harris, *Tetrahedron*, 1998, **54**, 3321.

2 For selected, recent approaches to the hydrindane skeleton, see: (*a*) T. Kusakabe, K. Kato, S. Takaishi, S. Yamamura, T. Mochida, H. Akita, T. A. Peganova, N. V. Vologdin and O. V. Gusev, *Tetrahedron*, 2008, **64**, 319; (*b*) A-S. Chapelon, C. Ollivier and M. Santelli, *Tetrahedron Lett.*, 2006, **47**, 2747; (*c*) G. Pandey and S. B. Raikar, *Tetrahedron Lett.*, 2006, **47**, 2029; (*d*) R. Rodriguez, C. Ollivier and M. Santelli, *Synlett*, 2006, 312; (*e*) Y. Nakai and Y. Uozumi, *Org. Lett.*, 2005, **7**, 291; (*f*) H. Araki, M. Inoue and T. Katoh, *Synlett*, 2003, 2401; (*g*) I. Prowotorow, W. Stepanenko and J. Wicha, *Eur. J. Org. Chem.*, 2002, 2727; (*h*) G. Mehta and K. Islam, *Angew. Chem., Int. Ed.*, 2002, **41**, 2396; (*i*) D. N. Jones, M. W. J. Maybury, S. Swallow, N. C. O. Tomkinson and W. W. Wood, *Tetrahedron Lett.*, 2001, **42**, 2193.

3 W. Zhao, Q. Ye, X. Tan, H. Jiang, X. Li, K. Chen and A. D. Kinghorn, *J. Nat. Prod.*, 2001, **64**, 1196.

4 (*a*) H. Hikino, Y. Hikino, K. Agatsuma and T. Takemoto, *Chem. Pharm. Bull.*, 1968, **16**, 1779; (*b*) R. Bos, H. Hendriks, J. Kloosterman and G. Sipma, *Phytochemistry*, 1983, **22**, 1505.

5 (*a*) F. Kavanagh, A. Hervey and W. J. Robbins, *Proc. Natl. Acad. Sci. U. S. A.*, 1951, **37**, 570; (*b*) B. Vester, S. M. Poulsen, M. Karlsson and L. B. Johansson, *Mol. Microbiol.*, 2001, **41**(5), 1091; (*c*) F. Schlünzen, E. Pyetan, P. Fucini, A. Yonath and J. M. Harms, *Mol. Microbiol.*, 2004, **54**(5), 1287.

6 (*a*) N. Abe, R. Onoda, K. Shirahata, T. Kato, M. C. Woods, Y. Kitahara, K. Ro and T. Kurihara, *Tetrahedron Lett.*, 1968, **9**, 1993; (*b*) T. J. Brocksom, F. Coelho, J-P. Deprés, A. E. Greene, M. E. Freire de Lima, O. Hamelin, B. Hartmann, A. M. Kanazawa and Y. Wang, *J. Am. Chem. Soc.*, 2002, **124**, 15313.

7 T. J. K. Findley, D. Sucunza, L. C. Miller, D. T. Davies and D. J. Procter, *Chem.–Eur. J.*, 2008, **14**, 6862.

8 (*a*) A. Solladié-Cavallo, L. Jierry, L. Bouérat and P. Taillasson, *Tetrahedron: Asymmetry*, 2001, **12**, 883; (*b*) L. M. Urbaneja, A. Alexakis and N. Krause, *Tetrahedron Lett.*, 2002, **43**, 7887.

9 W. F. Gannon and H. O. House, *Organic Synth*, 1973, **Coll. Vol. 5**, 539.

10 L. F. Tietze, H. Schirok and M. Wöhrmann, *Chem.–Eur. J.*, 2000, **6**, 510.

11 D. L. Comins and A. Dehghani, *Tetrahedron Lett.*, 1992, **33**, 6299.

12 See ref. 7 and the ESI for CCDC numbers.

13 For a review on Sm-enolates, see: I. M. Rudkin, L. C. Miller and D. J. Procter, *Organomet. Chem.*, 2008, **34**, 19.

14 S. Irifune, T. Kibayashi, Y. Ishii and M. Ogawa, *Synthesis*, 1988, 366.

15 (*a*) S. M. Bennett, R. K. Biboutou, Z. Zhou and R. Pion, *Tetrahedron*, 1998, **54**, 4761; (*b*) For fundamental studies on the rate and mechanism of reduction of alkyl halides by SmI_2-HMPA, see: D. P. Curran, T. L. Fevig, C. P. Jasperse and M. J. Totleben, *Synlett*, 1992, 943; (*c*) E. Hasegawa and D. P. Curran, *Tetrahedron Lett.*, 1993, **34**, 1717; (*d*) M. Shabangi and R. A. Flowers II, *Tetrahedron Lett.*, 1997, **38**, 1137.

16 Access to enantiomerically-enriched 4-alkylcyclohexenones allows the asymmetric synthesis of *cis*-hydrindanes using our approach. For example, see: K. Aoki, M. Nakajima, K. Tomioka and K. Koga, *Chem. Pharm. Bull.*, 1993, **41**, 994.

17 For previous synthetic studies on pleuromutilin, see: (*a*) E. G. Gibbons, *J. Org. Chem.*, 1980, **45**, 1540; (*b*) M. Kahn, *Tetrahedron Lett.*, 1980, **21**, 4547; (*c*) E. G. Gibbons, *J. Am. Chem. Soc.*, 1982, **104**, 1767; (*d*) L. A. Paquette, P. C. Bulman-Page, P. D. Pansegrau and P. E. Wiedeman, *J. Org. Chem.*, 1988, **53**, 1450; (*e*) L. A. Paquette, P. D. Pansegrau, P. E. Wiedeman and J. P. Springer, *J. Org. Chem.*, 1988, **58**, 1461; (*f*) L. A. Paquette, P. E. Wiedeman and P. C. Bulman-Page, *J. Org. Chem.*, 1988, **53**, 1441; (*g*) R. K. J. Boeckman, D. M. Springer and T. R. Alessi, *J. Am. Chem. Soc.*, 1989, **111**, 8284; (*h*) E. Bacqué, F. Pautrat and S. Z. Zard, *Org. Lett.*, 2003, **5**, 325; (*i*) M. D. Helm, M. Da Silva, D. Sucunza, T. J. K. Findley and D. J. Procter, *Angew. Chem., Int. Ed.*, 2009, **48**, 9315; (*j*) J. Liu, S. D. Lotesta and E. J. Sorensen, *Chem. Commun.*, 2011, **47**, 1500.

18 We have reported a SmI_2-mediated cascade approach to the tricyclic core of pleuromutilin, see ref. 17i. For preliminary studies on the SmI_2-mediated cascade approach, see: (*a*) M. D. Helm, D. Sucunza, M. Da Silva, M. Helliwell and D. J. Procter, *Tetrahedron Lett.*, 2009, **50**, 3224; (*b*) M. D. Helm, M. Da Silva, D. Sucunza, M. Helliwell and D. J. Procter, *Tetrahedron*, 2009, **65**, 10816.

19 For a review on RCM, see: T. M. Trnka and R. H. Grubbs, *Acc. Chem. Res.*, 2001, **34**, 18.

20 For a review of the use of RCM in natural product synthesis, see: K. C. Nicolaou, P. G. Bulger and D. Sarlah, *Angew. Chem., Int. Ed.*, 2005, **44**, 4490.

21 Sorenson has recently reported an RCM approach to the 8-membered ring of pleuromutilin, see ref. 17j.

22 T. R. Hoye and H. Zhao, *Org. Lett.*, 1999, **1**, 1123.

23 R. K. J. Boeckman, Ed. *Strategies and tactics in organic synthesis*, 1st edition; Academic Press, Inc., 1991; Vol. 3.