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Synthetic approaches to the daucane sesquiterpene derivatives employing the intramolecular Buchner cyclisation of α-diazoketones

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ABSTRACT

The use of the intramolecular Buchner cyclisation of an α-diazoketone as an approach to the synthesis of daucane sesquiterpenes is described; in particular the synthesis of the *cis*-fused analogue of dihydro CAF-603. The key step in the synthesis is the intramolecular Buchner cyclisation, which provides the bicyclo [5.3.0]decane framework with the required stereochemistry at the quaternary centre generated in the cyclisation. A synthetic route enabling access to an asymmetric synthesis is also outlined.

1. Introduction

CAF-603 **1** (Fig. 1), a carotane or daucane sesquiterpenoid, was first isolated from the culture broth of a strain of *Trichoderma virens* (*Gliocladium virens* IFO 9166), by Watanabe and co-workers in 1990.[1] The structure was elucidated by spectroscopic methods. It was also discovered separately by researchers at Merck in 1995.[2] On this occasion it was isolated from a fungal source, *Arthrinium phaeospermum*, and was found to have almost identical spectroscopic data to a compound discovered some five years earlier. The structure was further verified by X-ray crystallography.

As part of this work, it was revealed that CAF-603 **1** possessed antifungal activity against *Candida albicans* strains. The biological activity of this sesquiterpenoid was further exhibited by the later study, where the compound was reported as a potent modulator of the large conductance, calcium-activated potassium (Maxi-K) channel, a member of a large group of proteins present in neuronal and smooth muscle tissue.[3] These channels play an important role in controlling a number of cellular processes, such as neurotransmitter release, neuroendocrine secretion and smooth muscle contraction. As a result of this, agonists of Maxi-K may be useful in the treatment of neurological disorders and airway smooth muscle disorders, such as asthma. Compounds **2** and **3**, derivatised from 14-hydroxy CAF-603 **4**,[4] and L-735,334 **5** (Fig. 1), which has been isolated from natural sources, displayed distinct biological activity on the Maxi-K channels.[5,6] To date, no total synthesis of CAF-603 or its derivatives has been published.

Over the last four decades, a number of synthetic methodologies towards the formation of the bicyclo[5.3.0]decane skeleton have been described, including ring closing metathesis, solvolysis, cycloaddition and transition metal catalysed chemistry.[7–9] The use of α-diazocarbonyl chemistry in total synthesis has also been well documented.[10–12] The intramolecular Buchner aromatic addition reaction of α-diazoketones is one such method that has been exploited in the area of bicyclic sesquiterpenoid natural product synthesis, namely the synthesis of the pseudoguaianolide (+)-confertin.[13,14] The intramolecular Buchner reaction, one of the mildest methods for transforming aromatic compounds to more reactive systems, has been studied for many years in our team.[15–20] Areas that have been investigated include the stereo-, regio- and enantiocontrol of this chemical transformation. A large number of azulenones have been synthesised using this methodology, some of which include products bearing the core skeleton of the daucane (carotane) group of sesquiterpene natural products. We describe here the extension of this methodology to the synthesis of the *cis*-fused derivative of dihydro CAF-603 **6**.

2. Results and discussion

The synthetic strategy devised to generate the required bicyclo [5.3.0]decane skeleton possessed by CAF-603 **1** and its analogues, emanated from the intramolecular Buchner cyclisation of α-diazoketone **7** to generate the azulenone **8**, as outlined in Scheme 1. This transformation provides the required carbon skeleton, while also controlling the stereochemistry at the key quaternary bridgehead centre. This compound was generated in three steps from the commercially available *para*-methylcinnamic acid **9**, via 1,4-addition of the isopropyl Grignard reagent, followed by conversion to the α-diazoketone employing the Arndt–Eistert

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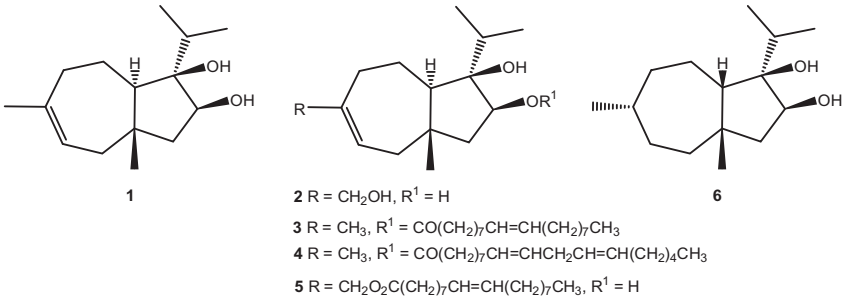
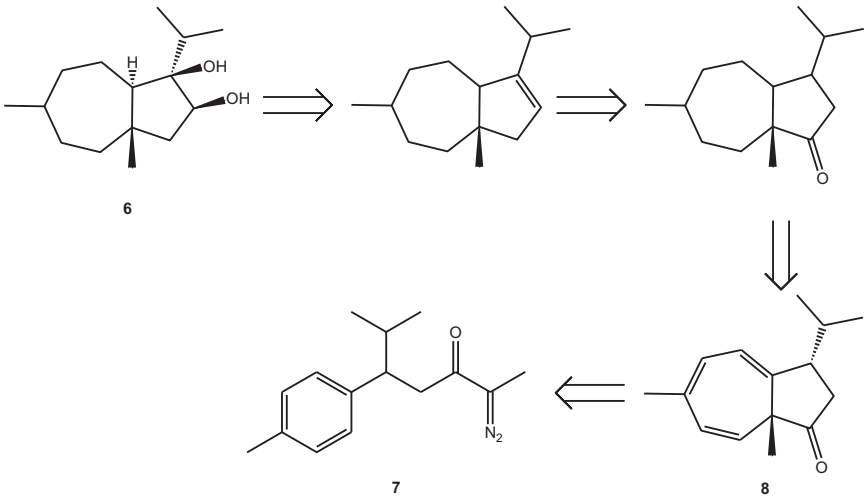


Fig. 1. CAF-603 and analogues.

diazoketone synthesis.[21,22] Manipulation of the azulene framework would facilitate introduction of the alkene bond into the five-membered ring, whereby dihydroxylation would result in the completion of the synthesis.

ratios of >98:2 reported for analogous substrates.[15–17,26] A ^{1}H NMR spectrum of the crude product was obtained to determine the efficiency (94%, the remainder consisted of aromatic side products described in previous publications[27]), which was in agreement



Scheme 1. Retrosynthetic analysis.

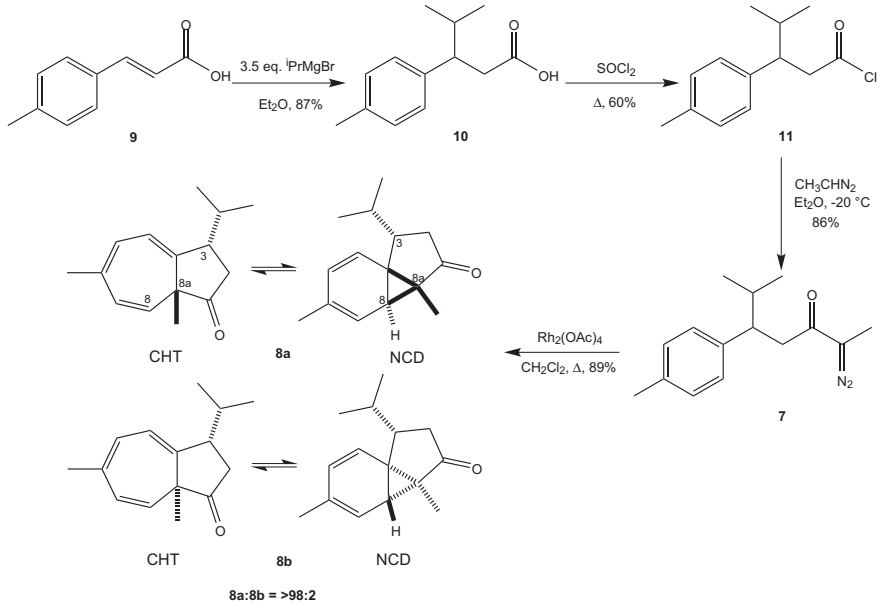
The 1,4-addition of isopropyl magnesium bromide was an efficient way of transforming the conjugated carboxylic acid **9** to its corresponding isopropyl substituted analogue **10**. The procedure used was modified from that described by Wotiz[23] and used 3.5 equiv of freshly prepared isopropyl magnesium bromide, to which the cinnamic acid **9** was added, giving the β-substituted carboxylic acid **10** in 87% yield. Due to poor recovery of material following chromatography or recrystallisation, the acid **10** was carried forward to the next step without purification. The crude carboxylic acid **10** was then treated with 10 equiv of thionyl chloride, which was heated under reflux for 3 h, and following purification by vacuum distillation, the pure acid chloride **11** was obtained in 60% yield. The final transformation in the synthesis of the α-diazoketone **7**, was achieved by treating the acid chloride **11** with an excess (7 equiv) of diazoethane, which was freshly prepared from *N*-ethyl-*N*-nitrosourea, via literature procedures[21,24] (Scheme 2).

The pivotal transformation in the synthesis was the intramolecular Buchner cyclisation of α-diazoketone **7** to furnish azulenone **8a** in 89% yield. The azulenone product exists as an equilibrating mixture of cycloheptatriene (CHT) and norcaradiene (NCD) tautomers, which results in time averaged signal being observed on the NMR timescale.[25] The diastereoselectivity of this reaction has been well established, with *trans*:*cis* diastereomeric with the observed mass yield. This also aided in the determination of the *trans*:*cis* ratio[‡] of azulenone products, *trans*-**8a** and *cis*-**8b**, which was found to be >98:2. The crude azulenone **8a** was purified by column chromatography on silica gel, and no change in the *trans*:*cis* ratio of >98:2 was noted between the crude and pure products, i.e., the *cis*-isomer[§] **8b** was never observed when $Rh_2(OAc)_4$ was used.[28] This transformation not only provided access to the required bicyclo[5.3.0]decane structure, but the inherent diastereoselectivity of the transformation provided the required stereocontrol at the key quaternary bridgehead centre, based on the influence of the single stereogenic centre present in the α-diazoketone precursor.

The formation of the azulenone **8a** provided access to the bicyclo[5.3.0]decane ring core of the carotane sesquiterpenoid, with the stereochemistry of the quaternary centre established, albeit as an equilibrating system with the tricyclic isomer (NCD). Saturation of the ring system was seen as a route to removing

[‡] The *trans*:*cis* ratio was calculated by the integration of the signal for the H-8 proton of the major **8a** and minor **8b** isomers.

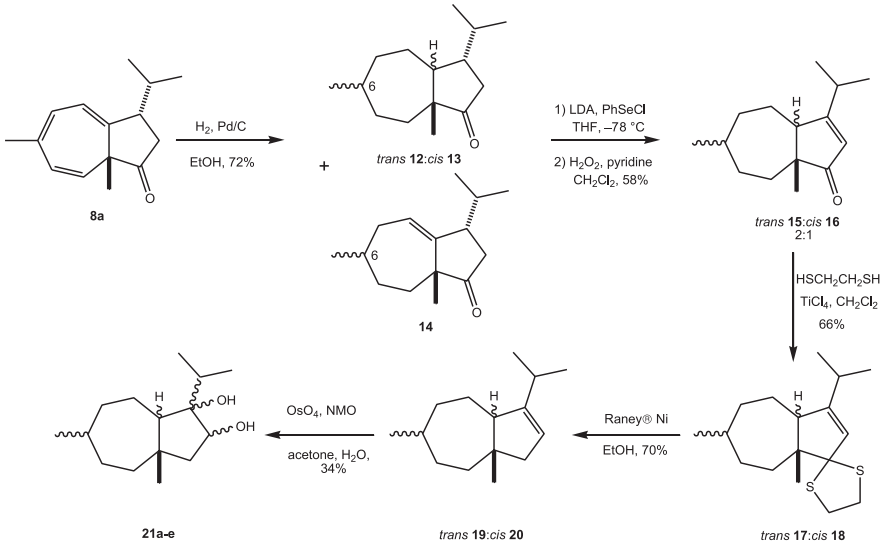
[§] The terms *trans* and *cis* labels in azulenones refer to the stereochemical relationship between the methyl group at C-8a and the substituent at C-3 in the azulenone system.



Scheme 2.

access to this tautomeric form, which resulted from an electrocyclic ring opening/ring closing process. An initial investigation into the hydrogenation of the azulenone **8a** revealed that a number of saturated products resulted from the hydrogenation process. A sample of the *trans*-azulenone **8a** was hydrogenated using palladium on carbon (5%) as catalyst, under 50 psi of hydrogen for 12 h. This gave a mixture of perhydroazulenones products **12** and **13** (*trans*- and *cis*-fused), and the mono-alkene **14** in a ratio of 54:23:23, with a combined yield of 85% (Scheme 3). In a separate experiment ratio is tentatively assigned due to the complexity of the ^{1}H and ^{13}C NMR spectra, as separation of the product mixture could not be achieved.

The complex mixture of compounds **12**, **13** and **14** (54:23:23) was then converted to the corresponding α,β-enones, via α-selenylation and oxidative elimination, again resulting in a mixture of products. Two compounds were detected in the ^{1}H NMR spectrum following chromatography, an inseparable mixture of α,β-unsaturated hydroazulenones **15** and **16**, formed in a ratio of 2:1. In



Scheme 3.

employing palladium on carbon (10%) the ratio of perhydroazulenones was found to be 70:30 (**12**:**13**), with the product mixture containing a minor amount of **14** (5%). Each of the perhydroazulenones **12** and **13** consisted of 1:1 ratio of α and β C-6 methyl isomers, indicating very poor diastereoselectivity in the hydrogenation of the azulenone **8a**. The assignment of the *trans*:*cis* this case individual signals for the C-6 isomers were not observed from the NMR spectra, indicating the possibility of solely *cis*- and *trans*-fused isomers, although multiple diastereomers could not be ruled out, as the structural difference between the two isomers at C-6 may not have been sufficiently significant to alter the NMR signals. From the *trans*-**12** to *cis*-fused **13** ratio in the starting

material, it is assumed that the *trans*-fused isomer predominates in the product mixture.

With the double bond of the enones **15** and **16** in the required position for dihydroxylation, the deoxygenation of the carbonyl group at C-1 was carried out. This was achieved by the initial dithioketalisation, followed by desulfurisation with Raney® nickel. The ratio of thioketal isomers **17** and **18** was 70:30, while the proportion of *trans*- **19** to *cis*-fused alkene **20** diastereomers was 3:1. Dihydroxylation of the olefins **19** and **20** with osmium tetroxide and 4-methylmorpholine-*N*-oxide (NMO), furnished a number of diastereomeric diols **21a** to **21e**.

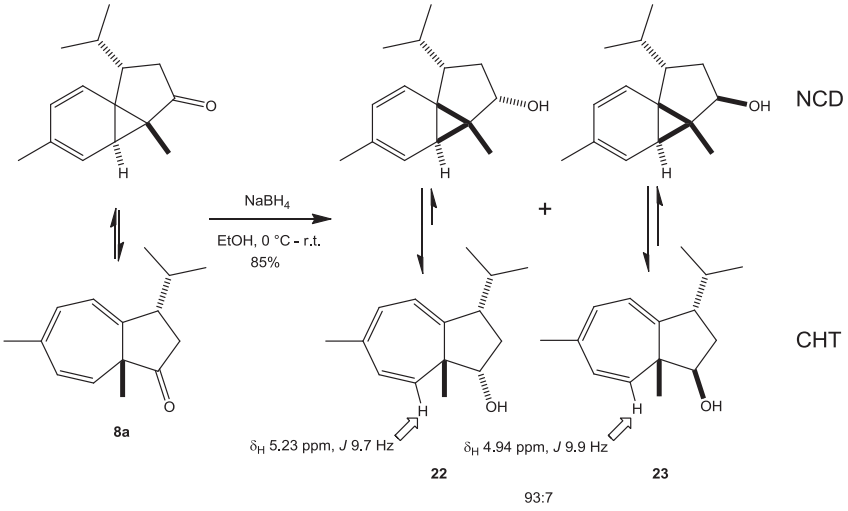
The initial investigations into the hydrogenation of the azulenone **8a**, demonstrated the viability of the synthesis of the natural product analogue **6** via the construction of the carbon framework employing the intramolecular Buchner cyclisation. However, the formation of multiple isomers, as a result of poor diastereoselectivity in the hydrogenation of **8a** needed to be addressed and hence the synthesis was revisited. In an attempt to control the number of diastereomers resulting from the hydrogenation step, the azulenone **8a** was reduced to the azulenol **22** using sodium borohydride.[13,14]

The azulenol **22** was isolated as the major product, but a minor isomer was observed in the ^{1}H and ^{13}C NMR spectra, present in 7%. This isomer was presumed to be the isomer **23** epimeric at C-1, as the azulenone precursor **8a** was diastereomerically pure. This would rule out the possibility of the minor compound having *cis* relative stereochemistry between the isopropyl and angular methyl group. The diastereomeric ratio of azulenols observed would appear to suggest that the transformation is very selective. The presence of the isopropyl group on the α-face clearly hinders the approach of the borohydride, thereby resulting in selective reduction from the β-face, to produce the azulenol **22** as the major product (Scheme 4).

a combination of saturated products. One of these, employed Raney® nickel catalyst, which was shaken with an ethanolic solution of the azulenols under hydrogen at high pressure (40–50 psi) for 48 h. Significantly, after chromatography the sole product **24** was isolated as a single diastereomer in 77% yield; the presence of any other isomer derived from hydrogenation of the minor azulenol **23** or otherwise, could not be detected in the ^{1}H or ^{13}C NMR spectra. While additional signals were present in the ^{1}H NMR spectrum of the crude product, they could not be definitively assigned to a diastereomeric alcohol. The product now existed as solely the bicyclo [5.3.0]decane carbocyclic structure **24**. Saturation of the C(5)–C(6) and C(7)–C(8) bonds had removed access to the equilibrium that was present in the parent azulenone **8a** and azulenol **22**. The stereochemistry of the methyl at C-6 was assigned as being on the α-face on the basis of the X-ray crystal structure obtained of the final *cis*-fused dihydro CAF-603 **6** obtained (see later, Fig. 3). The stereofacial selectivity of the Raney® nickel hydrogenation of **22** may be attributed to the conformation attained during the transformation. Hydrogenation occurs from the *exo*-face, due to the molecule adopting a V-shape, whereby the β- or upper face is less hindered than the lower or α-face. This results in the 6-methyl being *syn* to the isopropyl and hydroxyl groups.

Total saturation of the hydroazulene system was not observed under these conditions, although in a few batches synthesised, the diene **25** (Scheme 5) was also observed as part of a mixture with **24**, in the ^{1}H NMR spectrum, presumably due to differing activity of the Raney® nickel catalyst. Re-exposure of the crude product mixture containing **25** resulted in complete conversion to the required product **24** The presence of compound **25** indicates that it is the disubstituted C(7)–C(8) double bond that is the first to undergo saturation.

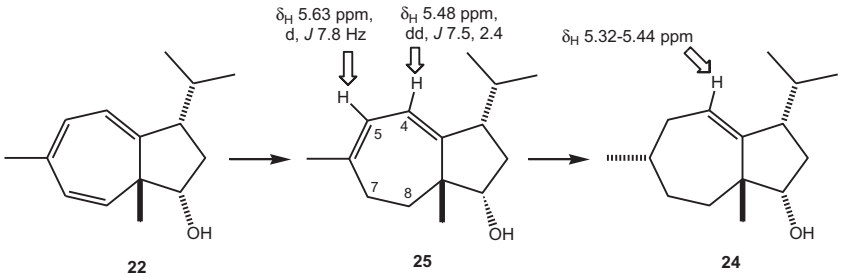
During attempts to fully hydrogenate the ring system, it was discovered the tetra-substituted alkene **26** was isolated from



Scheme 4.

While it has been common practice in the literature to depict azulenols solely as the CHT tautomeric form,[13,14,27] these compounds also exist in dynamic equilibrium with their NCD tautomer, although the CHT form predominates to a very large extent. The time averaged chemical shift for the H-8 proton for each diastereomer indicates that the equilibrium lies further towards the CHT tautomer for **22** than **23**.[25]

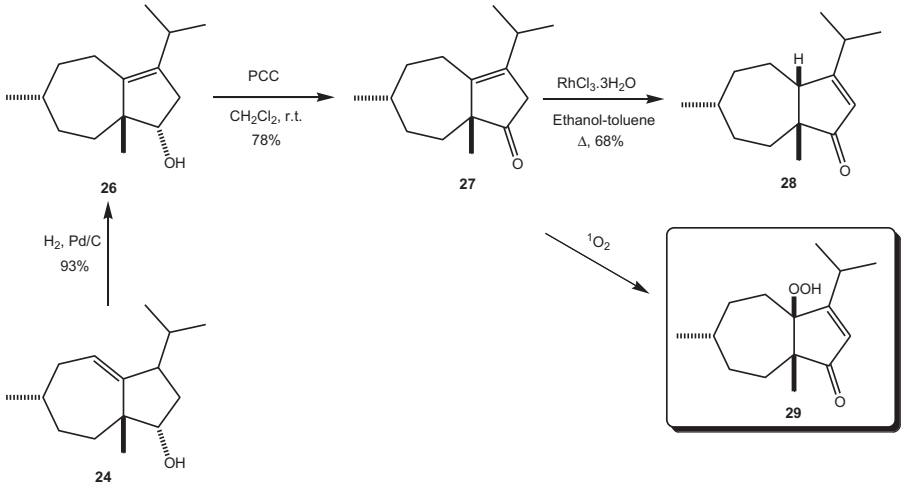
The mixture of azulenols **22** and **23** were then subjected to a number of hydrogenation conditions, many of which led to a mixture of saturated products, following palladium on carbon hydrogenation of the azulenols **22** and **23**. This compound was of particular interest as the double bond had migrated from the seven-membered ring to the five-membered one. The advantage to this was that manipulation of the five-membered ring could allow for the movement of this double bond into the required position for dihydroxylation, thus removing the need to incorporate this alkene by alternative synthetic means. This isomerisation was optimised by exposing the mono-alkene **24** to hydrogenation conditions (viz.



Scheme 5.

palladium on carbon and hydrogen at 50 psi), producing the isomerised product **26** as a single diastereomer in multi-gram quantities and in 93% yield following column chromatography (Scheme 6). All attempts to achieve total saturation of **24** via hydrogenation over palladium on carbon failed.

alkene **24** is examined (Fig. 2), (not all protons are shown for clarity), it may be clearly seen that the α-face of the molecule is more sterically crowded than the β-face. This is due to the conformation adopted and the presence of the bulky isopropyl group, which blocks interaction with the catalyst on that side. Approach of the



Scheme 6.

While the reaction conditions are those designed for hydrogenation, saturation of the hydroazulenol skeleton was not the outcome of the transformation. Instead the product formed **26** was one in which the alkene bond migrated into the five-membered ring. The driving force for the generation of **26** is presumably due to the formation of the stable tetrasubstituted alkene. Since saturation of the double bond in the C(3a)–C(4) position proved futile, presumably the conformation adopted by **24** hinders hydrogenation, with the isopropyl group blocking approach from below and the quaternary bridgehead methyl obstructing approach from above. One interesting feature of this migration is that while it could be classified as an oxidative addition–reductive elimination process, when the same experiment was conducted in the absence of hydrogen, no migration was observed, and only starting material **24** was recovered. This shows that the presence of hydrogen is required for the migration process to occur. This type of transformation has been reported previously for the hydrogen–palladium induced migration of olefinic bonds.[29] In this publication the stereochemical requirements for preferential migration over hydrogenation are outlined. According to the authors, normal hydrogenation of double bonds may be superseded by migration if the olefinic bond is tri- or tetrasubstituted and in a very hindered position. Also the allylic proton to be removed has to be accessible to the catalyst. When the 3-D diagram of the mono-

catalyst surface on the upper face meets the criteria for alkene migration to occur, i.e., *cis* removal and addition of the hydrogen attached to C-3 is possible, thus furnishing the isomerised product **26**. The new double bond that is formed is tetrasubstituted, and therefore resistant to further hydrogenation. There was no evidence for the formation of the perhydroazulenol product by saturation of **26**, although the possibility that this may occur under more forcing conditions was not explored.

Oxidation of the secondary alcohol functional group of **26** was sought, with the ultimate goal to migrate the tetrasubstituted olefinic bond into conjugation with the resultant carbonyl group. While the Swern oxidation conducted at −78 °C proved successful as a method of oxidation, the same transformation was achieved with pyridinium chlorochromate (PCC), which could be conducted at room temperature in only 2 h, compared to the much slower Swern. This procedure resulted in the isolation of β,γ-unsaturated ketone **27** (Scheme 6) from the reaction mixture in 78% yield, without the need for further purification.

It was noted that upon storage near at room temperature formation of **28** resulted, which increased to a maximum yield of 33% after 6–10 days, but this was accompanied by the formation of a second compound, the hydroperoxide **29**. Although these two compounds could be separated by column chromatography, the ratio in which they were formed fluctuated from 2:1 to 5:1 of **29**:**28**.

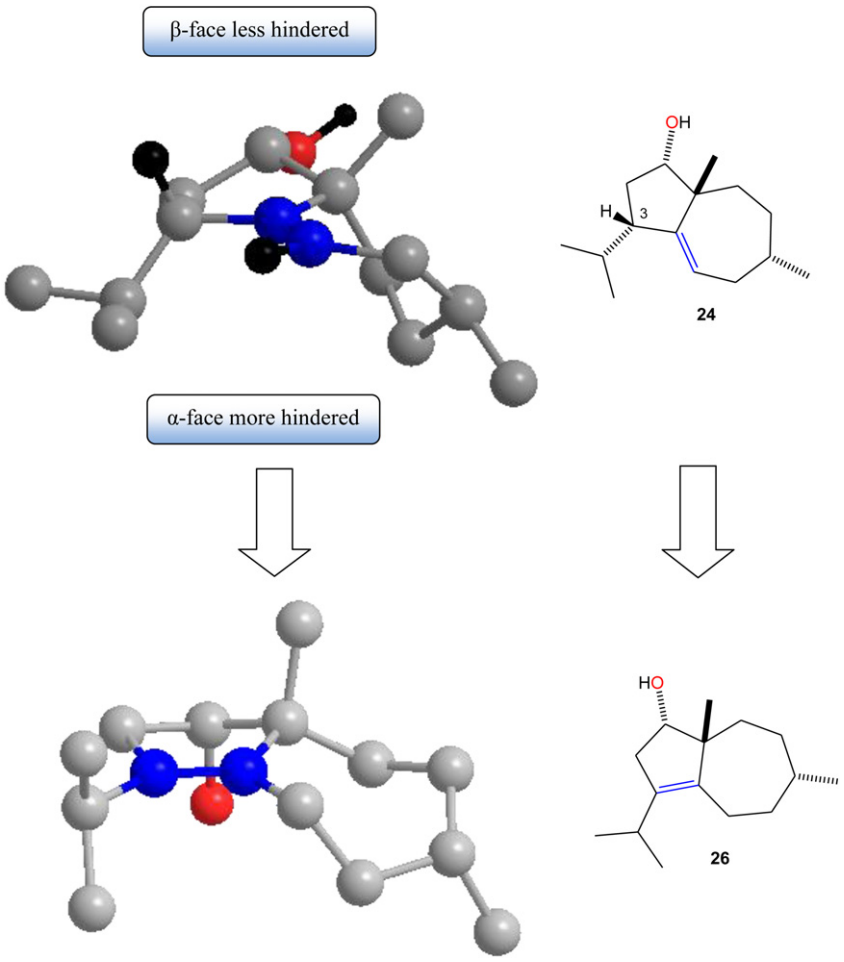


Fig. 2. 3-D representation of mono-alkenes **24** and **26** (MM2 minimisation energy calculation).

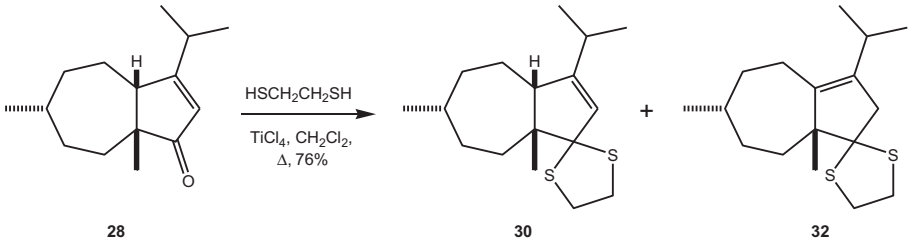
This discovery showed promise, as spontaneous migration of the alkene into the conjugated position appeared to be a favourable process. The source and structure of the hydroperoxide **29** was attributed to reaction of **27** with singlet oxygen, and this was confirmed by generating a sample of **29** by the irradiation of 5,10,15,20-tetraphenyl-21*H*,23*H*-porphine (TPP) in carbon tetrachloride with a sodium lamp (λ 589 nm) under an atmosphere of oxygen.

Having shown that the hydroperoxide **29** was generated as a result of the reaction of the β,γ-unsaturated ketone **27** with singlet oxygen, the issue of the alkene migration to form the α,β-unsaturated ketone **28**, avoiding the formation of this unwanted side-product was explored. From the migration that transpired on storage of **27**, it appeared that the increased stability of the alkene in conjugation with the carbonyl group provided the driving force for this transformation. Storage of this compound under nitrogen and in the dark prevented migration. A number of attempts were made to realise this transformation by chemical means, the most useful of which was rhodium trichloride trihydrate, which has been used in the literature as a way of migrating double bonds to produce conjugated products.[30,31] This procedure facilitated the production of multi-gram quantities of the *cis*-fused α,β-unsaturated ketone **28**. The spectral data was in agreement with the compound formed on storage, as described earlier. Significantly, the migration occurred to produce the *cis*-fused α,β-unsaturated ketone **28** as a single diastereomer. The relative stereochemistry was established by transformation of **28** to the *cis*-diol **6**, whereby an X-ray crystal structure was obtained determining the stereochemistry.

The mechanistic details behind the isomerisation of **27** to **28** are thought to be related to the oxidative addition, reductive elimination process attributed to many transition metal mediated migrations.[32–35] The process is believed to proceed via a metal hydride, whereby addition of the hydride takes place on the same side of the alkene as the metal.[36] Addition of the hydrogen then creates a vacant site at the metal, and this then facilitates *syn* β-elimination, furnishing the alkene in conjugation with the carbonyl group. The stereofacial selectivity of the transformation, producing only the *cis*-fused isomer, arises due to the conformation of the β,γ-unsaturated ketone **27**, where the α-face is significantly more sterically hindered than the β-face. This directs the metal hydride species to the less hindered *exo*-face or β-face.

With access to sufficient quantities of the α,β-unsaturated ketone **28** as a single isomer now available, the remaining steps in the synthesis of *cis*-fused dihydro CAF-603 **6** could be completed. The deoxygenation of **28** was conducted by the initial formation of the thioketal **30**, followed by the subsequent reduction of the dithiolane intermediate to provide the bicyclic alkene **31**. Similar methodology has also been applied in the total synthesis of the marine sesquiterpenes dactylol and africanol by Paquette[37].

Production of the thioketal **30** was realised by the addition of 7 equiv of 1,2-ethanedithiol to a solution of α,β-unsaturated ketone **28** and 3 equiv of titanium tetrachloride at 0 °C.[38] The mixture was then stirred for a further 30 min at room temperature. Conducting the addition at 0 °C was optimum for the process, as addition at room temperature resulted in reduced yields. Also, when the mixture was heated to reflux without first stirring at room



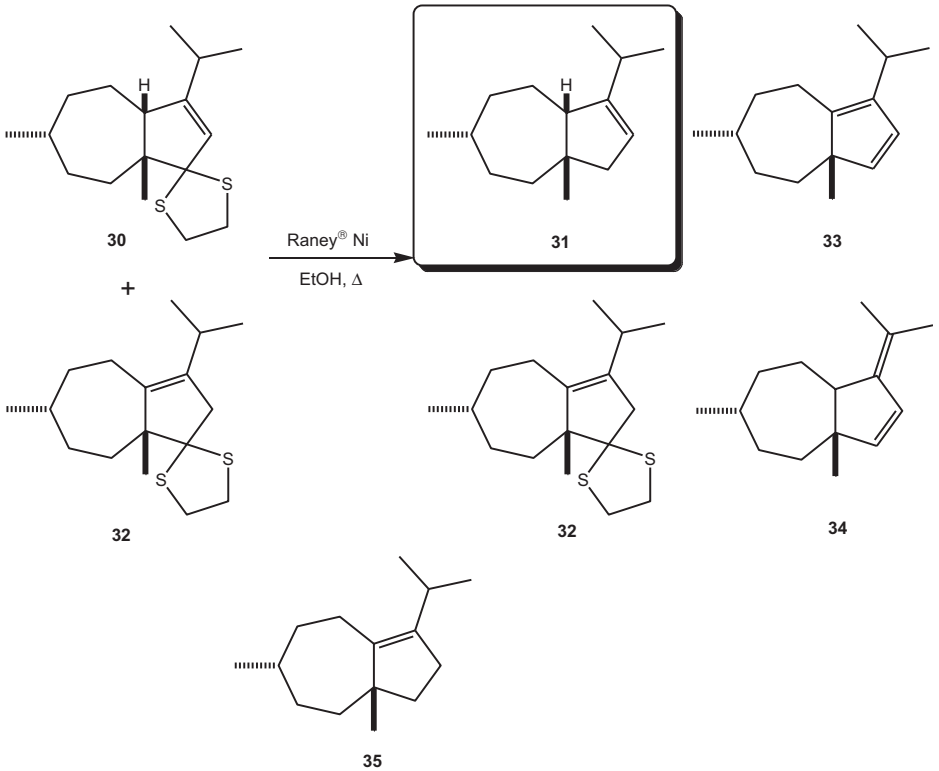
28 30 32

Scheme 7.

temperature, a drop in yield was noticed. The crude product was obtained following work-up and was isolated by chromatography on silica gel and was found to contain a mixture of two isomeric products **30** and **32** in an overall yield of 76%. The major compound in the inseparable mixture was the required product **30**, while 25–30% was found to be the tetrasubstituted isomer **32** (Scheme 7).

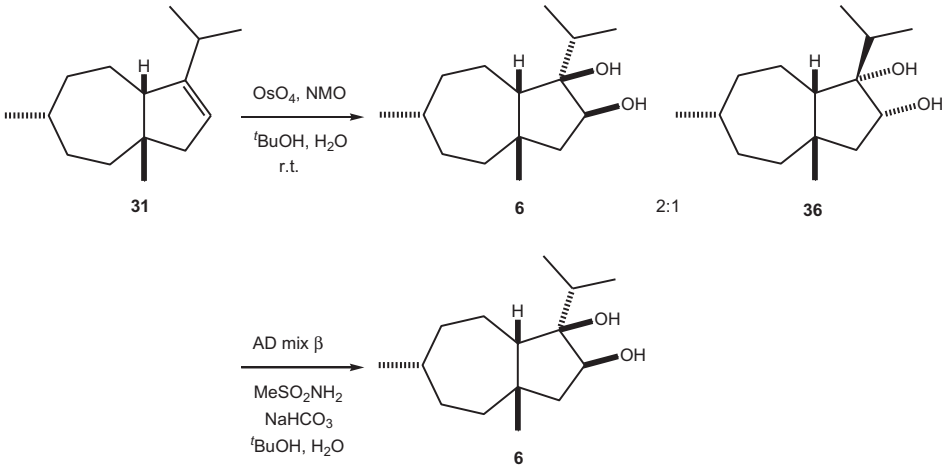
The second part of this two step deoxygenation process entailed the Raney® nickel cleavage of the thioketal moiety, to reveal the methylene carbon at that position.[39–41] The mixture of thioketals **30** and **32** was dissolved in ethanol and was heated to reflux in the presence of Raney® nickel catalyst, while stirring under an atmosphere of nitrogen. A mixture of the alkene **31**, unreacted **32** and two diene side-products **33** and **34** in a ratio of 1:0.20:0.55:0.37 was detected in the ^{1}H NMR spectrum of the colourless oil obtained. The carbocyclic alkene **31** was isolated in 42% yield as a single compound following purification. There was no evidence for the migration of **31** to the tetrasubstituted alkene **35**, even after prolonged storage. Also the tetrasubstituted alkene thioketal **32** appeared to be particularly resistant to cleavage under these conditions, and was consistently isolated following chromatography, with no evidence at any point for desulfurisation to the tetrasubstituted alkene **35** (Scheme 8). The reason for this compound withstanding the reductive process is unclear, but its isolation from this reaction (following chromatographic separation), proved useful in its characterisation and hence its determination as a side-product of the thioketalisation step, as was discussed previously.

Initial work on the dihydroxylation of a diastereomeric mixture of alkenes (Scheme 3) demonstrated the ability of conducting dihydroxylation of the olefinic bond employing osmium tetroxide. With a pure sample of the alkene **31** isolated, it was dissolved in a *tert*-butanol/water mixture containing 4-methylmorpholine *N*-oxide (NMO), to which a solution of osmium tetroxide (0.05 mol %) in water was added and the reaction mixture stirred at room temperature for two weeks. Following careful work-up, a ^{1}H NMR spectrum of this revealed that the mixture consisted of 50% unreacted alkene precursor, as well as evidence for the formation of a mixture of diol products. This residue was purified by column chromatography to give the diols **6** and **36** as a white solid, in a ratio of 2:1. The products were isolated in a combined yield of 13%, but when the fact that only half of the starting material was consumed, then this figure can be revised upwards to 26% (Scheme 9).



30 31 33 32 32 34 35

Scheme 8.



Scheme 9.

^{1}H NMR analysis of this solid revealed that compound isolated was a mixture of two diastereomers **6** and **36**. The presence of this mixture was verified by obtaining a ^{13}C NMR spectrum, where the two sets of signals could be clearly identified, corresponding to the two diastereomers of *cis*-fused dihydro CAF-603 **6** and **36**. The two diastereomers had identical R_f values on TLC, and therefore could not be separated from each other chromatographically.

In order to provide increased diastereoselection in the transformation, the AD mixes were used. The use of AD mix α resulted in another complex mixture, from which no individual compound could be isolated. However, employing AD mix β proved more successful, with the diol **6** isolated as a single diastereomer in 41% yield, following recrystallisation, with identical spectral characteristics to the major compound formed previously using osmium tetraoxide and NMO. This was then used to obtain an X-ray crystal structure (Fig. 3), which enabled the retrospective determination of the relative stereochemistry of the final product **6**. This established the *cis* relative stereochemistry of the bridgehead proton and the quaternary methyl group, as well as that of the methyl group at C-6. The stereochemistry identified in the final product was used to assign the relative stereochemistry of those compounds from which it was synthesised. While kinetic resolution in the oxidation of the racemic alkene can be envisaged, this was not explored in detail in this work.

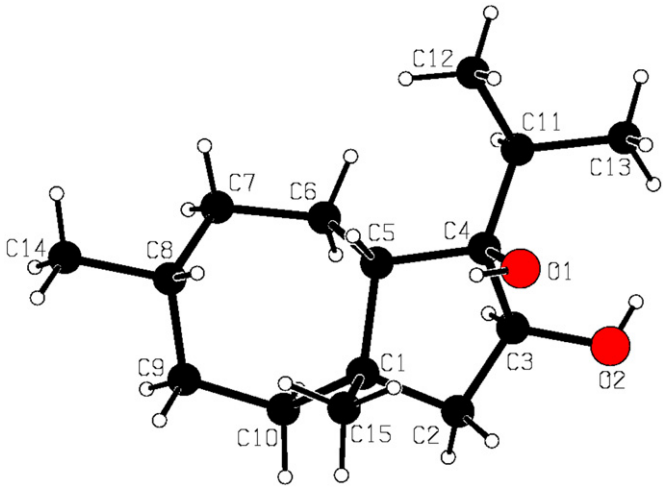


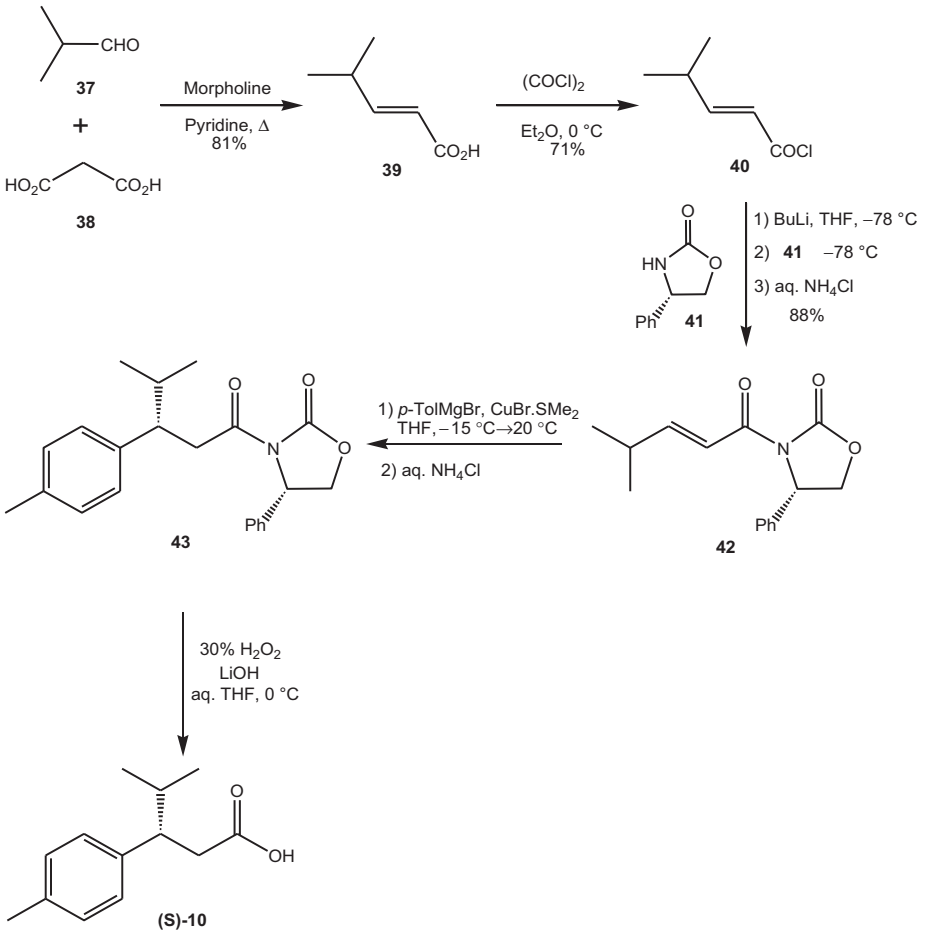
Fig. 3. X-ray crystal structure of *cis*-fused derivative of CAF-603 **6**.

The *cis* ring-fusion which was established in the alkene migration of **27** to **28** was not that possessed by the natural product CAF-603 **1**, however, the synthesis of the *cis*-fused derivative of dihydro CAF-603 **6** was achieved, which demonstrated that the intramolecular Buchner cyclisation provides a viable route to daucane sesquiterpenes.

Having completed the racemic synthesis of the *cis*-fused derivative of dihydro CAF-603 **6**, the enantioselective synthesis of the key azulenone intermediate **8a** was sought. The synthesis of enantioenriched samples of the isopropyl substituted carboxylic acid **10** was achieved following procedures first outlined by Hruby in the synthesis of novel amino acids.[42–45] The synthetic route is outlined in Scheme 10. The first step involved the Knoevenagel condensation of isobutyraldehyde **37** and malonic acid **38**, which produced **39** in 81% yield. The acid **39** was then converted to the acid chloride **40** by treatment with 1.5 equiv of oxalyl chloride. The product was purified by distillation at atmospheric pressure, but as the acid chloride **40** was found to hydrolyse extremely easily, the distillation apparatus was attached to a nitrogen line, in order to prevent this. The acid chloride **40** was always used in the next step within a week of its isolation, due to its lability.

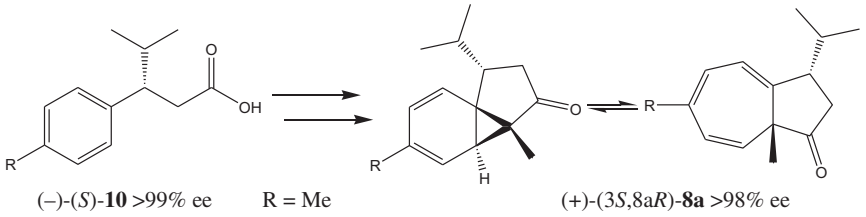
Coupling of the commercially available oxazolidinone **41** with the acid chloride **40**, was conducted by the initial deprotonation of the oxazolidinone with butyllithium at −78 °C. The acid chloride **40** was then added to generate **42** in 88% yield. The next step in the synthetic route to the enantiopure compound **10** was organocuprate addition to the acyl oxazolidinone **42**. The procedure involved generation of the Grignard reagent from *para*-bromotoluene, to which the acyl oxazolidinone **42** was added. The product **43** was isolated in 34% yield. This sample contained 10% of an unidentified minor compound, which was initially thought to be the diastereomer with the aryl group on the opposite face to that of **43**. However, this possibility is unlikely as exposure of the mixture of compounds to lithium hydroxide and hydrogen peroxide in aqueous THF, resulted in the cleavage of the oxazolidinone group to give the enantioenriched acid (*S*)-**10** in enantiomeric excess of >99%. This HPLC analysis of the carboxylic acid **10**, would appear to rule out the minor product of the organocuprate coupling being a diastereomer of the major component.

The enantioenriched acid (*S*)-**10** was subsequently converted to the corresponding α-diazoketone (*S*)-**7**, before rhodium(II) catalysed cyclisation, furnishing the azulenone **8** in 98% ee. The enantiomeric purity of the aromatic addition products was determined by ^{1}H NMR spectroscopy, using the chiral shift reagent tris-[3-heptafluoropropylhydroxymethylene-(+)-camphorato]europium



Scheme 10.

(III) derivative [Eu(hfc)$_3$]. This research established that the stereochemistry at C-3 could be ultimately transferred from the acid (−)-(*S*)-**10**, to the quaternary bridgehead centre of the azulenone (+)-(3*S*,8a*R*)-**8a** (Scheme 11).



Scheme 11.

3. Conclusion

The racemic synthesis of the *cis*-derivative of dihydro CAF-603 **6** was achieved in 13 synthetic steps from commercially available starting material. The bicyclic skeleton was established in excellent yield in only four steps, using the rhodium catalysed intramolecular Buchner cyclisation. This was the key step in the synthesis, providing access to the bicyclo[5.3.0]decane framework of the daucane sesquiterpenes and establishing the stereochemistry at the quaternary bridgehead centre. This transformation utilised the single stereogenic centre at C-3 in the acyclic precursor **7** to selectively induce the stereochemistry at the quaternary bridgehead centre in azulenone **8a**, which would otherwise be challenging to establish. Thus, the mild transition metal catalysed transformation furnished the bicyclo[5.3.0]decane ring system characteristic of daucane sesquiterpenes in excellent yield. The synthesis of this key azulenone intermediate **8a** in enantiopure form was also realised, enabling the asymmetric synthesis. The manipulation of the five,seven-membered fused ring system was also described, encompassing a number of transition metal catalysed alkene migrations culminating in the Sharpless dihydroxylation to complete the synthesis of **6**.

4. Experimental

4.1. General

All solvents were distilled prior to use by the following methods: dichloromethane was distilled from phosphorus

pentoxide and when used for diazoketone decompositions was further distilled from calcium hydride, ethyl acetate was distilled from potassium carbonate or phosphorous pentoxide, acetone was distilled from potassium permanganate followed by potassium carbonate, toluene was distilled from sodium benzophenone ketyl, hexane was distilled prior to use, ethanol and methanol were distilled from the corresponding magnesium alkoxide and stored over 3 Å molecular sieves, diethyl ether was distilled from lithium aluminium hydride or from sodium benzophenone ketyl, tetrahydrofuran (THF) was distilled from sodium benzophenone ketyl,[1] dimethylsulfoxide (DMSO) was stored for 24 h over calcium hydride then distilled under reduced pressure and stored over 4 Å molecular sieves, pyridine was distilled from potassium hydroxide. Molecular sieves were dried by heating at >100 °C under vacuum overnight. Organic phases were dried using anhydrous magnesium sulfate. All commercial reagents were used without further purification. All reactions were carried out under an inert nitrogen atmosphere unless otherwise indicated. Infra red spectra were recorded as thin films on sodium chloride plates for oils or as potassium bromide (KBr) discs for solids or as solution spectra in deuterated chloroform on a Perkin Elmer Paragon 1000 FT-IR spectrometer. ^{1}H (300 MHz) and ^{13}C (75.5 MHz) NMR spectra were recorded on a Bruker Avance 300 NMR spectrometer. All spectra were recorded at 20 °C in deuterated chloroform ($CDCl_3$) using tetramethylsilane (TMS) as an internal standard unless otherwise stated. Chemical shifts (δ_H and δ_C) are reported in parts per million (ppm) relative to TMS and coupling constants are expressed in Hertz (Hz). Splitting patterns in ^{1}H NMR spectra are designated as s (singlet), br s (broad singlet), br d (broad doublet), br t (broad triplet), d (doublet), t (triplet), q (quartet), dd (doublet of doublets), dt (doublet of triplets), ddd (doublet of doublet of doublets), ddt (doublet of doublet of triplets), ABq (AB quartet) and (m) multiplet. ^{13}C spectra were calibrated using the solvent signals, i.e., $CDCl_3$: δ_C 77.0 ppm. All spectroscopic details for compounds previously made were in agreement with those previously reported, unless otherwise stated. Diastereomeric ratios (d.r.) were determined by ^{1}H NMR spectroscopy. When only one diastereomer could be detected, the d.r. is quoted as >98:2. Melting points were measured on a Uni-Melt Thomas Hoover capillary melting point apparatus and are uncorrected. Wet flash column chromatography was carried out using Kieselgel 60, 0.040–0.063 mm (Merck). Thin layer chromatography (TLC) was carried out on precoated silica gel plates (Merck 60 PF_{254}). Visualisation was achieved by UV light detection (254 nm), vanillin staining, ceric sulfate staining and potassium permanganate staining. Bulb to bulb distillations were carried out on a Buchi GKR-50 Kugelrohr apparatus and the oven temperature is given as the boiling point of the substrate. The Microanalysis Laboratory, National University of Ireland, Cork, performed elemental analysis using a Perkin–Elmer 240 and Exeter Analytical CE440 elemental analysers. Low resolution mass spectra were recorded on a Waters Quattro Micro triple quadrupole instrument in electrospray ionisation (ESI) mode using 50% acetonitrile–water containing 0.1% formic acid as eluent; samples were made up in acetonitrile. High resolution precise mass spectra (HRMS) were recorded on a Waters LCT Premier ToF LC–MS instrument in electrospray ionisation (ESI) mode, using 50% acetonitrile–water containing 0.1% formic acid as eluent; samples were made up in acetonitrile.

4.1.1. 3-(4′-Methylphenyl)-4-methylpentanoic acid ***10***.[23,46–48] All glassware was flame dried before use. 2-Bromopropane (35 mL, 373 mmol) in diethyl ether (anhydrous, 150 mL) was added dropwise to a suspension of magnesium turnings (9.07 g, 373 mmol) in diethyl ether (anhydrous, 400 mL), containing 2–3 crystals of iodine, while stirring under nitrogen. Following the addition of 8–9 mL of the 2-bromopropane solution, the mixture was heated until a colour change from brown, to cloudy grey was observed. The remaining solution was then added dropwise to the self refluxing mixture. Once the addition was complete, the reaction mixture was stirred for a further 20 min at room temperature. The freshly prepared solution of isopropyl magnesium bromide was then cooled to 0 °C and *para*-methylcinnamic acid **9** (20.2 g, 124 mmol) was added portion-wise. The solution was then stirred at room temperature for 16 h. After this time the reaction mixture was quenched by pouring onto ice and adding concentrated hydrochloric acid, until acidified. The phases were separated and the aqueous layer was washed with diethyl ether (150 mL). The organic phases were combined and washed with water (300 mL), brine (200 mL), dried and concentrated under reduced pressure, to give the crude acid **10** (22.2 g, 87%) as an orange solid, which was used without further purification. A sample was prepared for analysis, by purification by flash chromatography on silica gel, eluted with ethyl acetate/hexane (40:60), giving a white solid: mp 70–72 °C (lit.,[48] 74–76 °C); (found: C, 75.67; H, 8.67. $C_{13}H_{18}O_2$ requires C, 75.69; H, 8.80%); ν_{max}/cm^{-1} (KBr) 3403, 2959, 1702; δ_H (300 MHz, $CDCl_3$) 0.74 [3H, d, *J* 6.6, one of CH(CH_3)$_2$], 0.91 [3H, d, *J* 6.6, one of CH(CH_3)$_2$], 1.75–1.90 [1H, m, C(4)H], 2.30 [3H, s, C(4′)CH_3], 2.58 [1H, dd, A of ABX, J_{AB} 15.3, J_{Ax} 9.6, one of C(2)H_2], 2.70–2.90 [2H, m, B and X of ABX, one of C(2)H_2, C(3)H], 6.96–7.11 (4H, m, ArH); δ_C (75.5 MHz, $CDCl_3$) 20.1, 20.5,21.0 (3× CH_3), 33.1 [CH, C(4)H], 38.1[CH_2, C(2)H_2], 48.0 [CH, C(3)H], 128.1, 128.8 (2× CH, aromatic CH), 135.8, 139.4 (2× C, quaternary aromatic C), 179.0 (C, C=O); *m*/*z* (ES$^+$) 189 [M+H−H_2O]$^+$ (12), 179 (10), 142 (29), 105 (98), 84 (28), 83 (100%).

4.1.2. 3-(4′-Methylphenyl)-4-methylpentanoyl chloride ***11***.[46,47] 3-(4′-Methylphenyl)-4-methylpentanoic acid **10** (24.5 g, 119 mmol) in thionyl chloride (87 mL, 1.19 mol) was heated under reflux for 2 h, while stirring under nitrogen. The reaction mixture was then allowed to cool to room temperature and the excess thionyl chloride was removed under reduced pressure to give the crude acid chloride **11**, as a brown oil. Purification by vacuum distillation gave the acid chloride **11** (16.1 g, 60%) as a yellow oil: bp 90 °C at 0.03 mmHg (lit.,[46] 113 at 1 mmHg); ν_{max}/cm^{-1} (film) 2962, 1802, 1514; δ_H (300 MHz, $CDCl_3$) 0.77 [3H, d, *J* 6.7, one of CH(CH_3)$_2$], 0.96 [3H, d, *J* 6.7, one of CH(CH_3)$_2$], 1.82–1.98 [1H, m, C(4)H], 2.32 [3H, s, C(4′)CH_3], 2.83–3.00 [1H, m, X of ABX, C(3)H], 3.16 [1H, dd, A of ABX, J_{AB} 16.2, J_{Ax} 9.5, one of C(2)H_2], 3.32 [1H, dd, B of ABX, J_{AB} 16.2, J_{BX} 5.3, one of C(2)H_2], 6.96–7.16 (4H, m, ArH).

4.1.3. N-Ethyl-N-nitrosourea ***24***. Aqueous ethylamine (70%, 193 g) and water (230 mL) were stirred in a 3 L round bottom flask and cooled to 0 °C. Concentrated hydrochloric acid (37%, 310 mL) was added slowly until the solution was strongly acidified. Water (204 mL) was then added. Urea (600 g) was added portion-wise over 30 min, after which the solution was heated under reflux, gently for 2.5 h and then vigorously for 30 min. The solution was then cooled to room temperature and sodium nitrite (210 g) was added. Once the sodium nitrite had dissolved, the solution was cooled to 0 °C. The solution was then added slowly over 2 h to a mechanically stirred mixture of concentrated sulfuric acid (200 g) and ice (1.20 kg), cooled to −20 °C using a salt-ice bath. *N*-Ethyl-*N*-nitrosourea formed as a foamy crystalline precipitate, which was collected by suction filtration and washed with ice-cooled water (3×40 mL), to give a pale peach powder (~200 g) that was used without further purification and was stored in the freezer.

4.1.4. Diazoethane ***24***. *N*-Ethyl-*N*-nitrosourea (12.3 g, 105 mmol) was added portion-wise over 30 min to a mixture of diethyl ether (78 mL) and aqueous potassium hydroxide (50% w/w, 33.5 mL) while stirring at −20 °C. Once the addition was complete, the reaction mixture was stirred for a further 30 min at −20 °C. The ethereal solution of diazoethane was then decanted into a 250 mL conical

flask containing 5–10 potassium hydroxide pellets, which was also cooled at −20 °C using a salt-ice bath. The solution was then dried over two further portions of potassium hydroxide pellets, to give a solution of diazoethane in diethyl ether, which was used without further purification and freshly prepared each time before use.

CAUTION! Diazoethane is both toxic and explosive. All operations should be carried out in a well ventilated fume-hood, with adequate shielding. The glassware used for the generation of diazoethane should have clear-glass joints to minimise the risk of explosion. Any items, which come into contact with diazoethane solution should be washed with aqueous acetic acid before being removed from the fume-hood.

4.1.5. 2-Diazo-5-(4′-methylphenyl)-6-methylheptan-3-one ***7***. 3-(4′-Methylphenyl)-4-methylpentanoyl chloride **11** (6.32 g, 28.1 mmol) was dissolved in diethyl ether (100 mL) and added dropwise over 1 h to an ethereal solution of diazoethane [freshly prepared from *N*-ethyl-*N*-nitrosourea (23.0 g, 197 mmol)], while stirring at −20 °C under nitrogen. The solution was then allowed to slowly return to room temperature over 3 h, with the inert atmosphere removed for the last 0.5 h. The ether and residual diazoethane were evaporated under reduced pressure at ca. 15 °C, using a rotary evaporator fitted with an acetic acid trap. Purification by flash chromatography on silica gel, eluted with ethyl acetate/hexane (10:90) gave the pure α-diazoketone **7** (5.87 g, 86%) as a yellow oil: ν_{max}/cm^{-1} (film) 2959, 2071, 1636, 1514, 1369, 1288; δ_H (300 MHz, $CDCl_3$) 0.74 [3H, d, *J* 6.6, one of CH(CH_3)$_2$], 0.96 [3H, d, *J* 6.6, one of CH(CH_3)$_2$], 1.66–1.96 {4H, m, containing 1.77 [3H, br s, C(1)H_3], C(6)H}, 2.30 [3H, s, C(4′)CH_3], 2.63–2.83 [2H, m, C(4)H_2], 2.84–3.04 [1H, m, C(5)H], 6.95–7.13 (4H, m, ArH); δ_C ($CDCl_3$, 75.5 MHz) 8.0 [CH_3, br, C(1)H_3], 20.3, 20.8 [2× CH_3, CH(CH_3)$_2$], 20.9 [CH_3, C(4′)CH_3], 32.9 [CH, C(6)H], 41.5 [CH_2, C(4)H_2], 48.7 [CH, C(5)H], 62.8 [C, br, C(2)], 127.9, 128.7 (CH, 4× aromatic CH), 135.6, 139.7 (C, 2× quaternary aromatic C), 193.9 (C, C=O).

4.1.6. trans-(3S,8aR*)-3-Isopropyl-6,8a-dimethyl-2,3-dihydroazulen-1(8aH)-one* ***8a***.[49] A three necked round-bottomed flask with a condenser and pressure equalising addition funnel were flame dried. Doubly distilled dichloromethane (450 mL) was subsequently added to the flask and heated under reflux under an atmosphere of nitrogen for 2 h. Rhodium(II) acetate (1.00 mg) was then added and heated under reflux for a further 15 min. 2-Diazo-5-(4′-methylphenyl)-6-methylheptan-3-one **7** (7.43 g, 30.4 mmol) in doubly distilled dichloromethane (150 mL) was then added dropwise over 2 h to the solution. The progress of the reaction was monitored by TLC and was found to be complete once all of the α-diazoketone had been added. The reaction mixture was concentrated under reduced pressure to give the crude azulenone **8** as a yellow oil. A ^{1}H NMR spectrum of the crude reaction mixture estimated the efficiency of the reaction as 94%* and the diastereomeric ratio of *trans*-**8a**:*cis*-**8b** as >98:2. Purification by flash chromatography on silica gel, eluted with ethyl acetate/hexane (5:95) gave the pure azulenone **8** (5.87 g, 89%) as a pale yellow oil. The diastereomeric ratio of the purified product was *trans*-**8a**:*cis*-**8b**, >98:2. Spectral characteristics for the *trans*-isomer **8a**: ν_{max}/cm^{-1} (film) 3014–2872, 1745, 1713, 1640; δ_H (300 MHz, $CDCl_3$) 0.67 [3H, s, C(8a)CH_3], 0.80 [3H, d, *J* 6.9, one of CH(CH_3)$_2$], 0.89 [3H, d, *J* 6.9, one of CH(CH_3)$_2$], 1.54–1.70 [1H, sym m, C*H*(CH_3)$_2$], 1.86–2.04 {4H, m, containing 1.93 [3H, s, C(6)CH_3], one of C(2)H_2}, 2.32–2.60 [2H, m, C(3)H, one of C(2)H_2], 3.35 [1H, d, *J* 6.6, C(8)H], 5.78 [1H, d, *J* 6.9, C(7)H], 5.90–6.10 [2H, m, C(4)H, C(5)H].

*The efficiency of the reaction describes the % conversion to azulenone product, the remainder consist of aromatic by-products.[27]

4.1.7. (3S,3aR*,8aR*)-Octahydro-3-isopropyl-6,8a-dimethylazulen-1(2H)-one* ***12***, *(3S*,3aS*,8aR*)-octahydro-3-isopropyl-6,8a-dimethylazulen-1(2H)-one* ***13***, *(3S*,8aR*)-3,6,8,8a-hexahydro-3-isopropyl-6,8a-dimethylazulen-1(2H)-one* ***14***

4.1.7.1. Method (a). A mixture of *trans*-(3*S**,8a*R**)-3-isopropyl-6,8a-dimethyl-2,3-dihydroazulen-1(8a*H*)-one **8a** (700 mg, 3.47 mmol) and palladium on carbon (10%, 70.0 mg) in ethanol (50 mL), was shaken under hydrogen at 34 psi, for 8 h at room temperature. The crude reaction mixture was filtered through a column of silica gel using ethyl acetate as eluant, to remove the hydrogenation catalyst. Purification by chromatography on silica gel using ethyl acetate–hexane (5:95) as eluant gave a colourless oil, (554 mg, 72%), which contained a mixture of products, which could not be separated chromatographically. The mixture contained a diastereomeric mixture of the perhydroazulenones **12** and **13** (70:30) and the monoalkene **14** (ca. 5%), assignment of the *trans*- and *cis*-fused perhydroazulenones was difficult as each of the diastereomers was further split into an equimolar ratio of the compounds resulting from α and β hydrogenation of the C-5, C-6 double bond. ν_{max}/cm^{-1} (film) 1736, 1466, 1408; (3*S**,3a*R**,8a*R**)-octahydro-3-isopropyl-6,8a-dimethylazulen-1(2*H*)-one **12** δ_H ($CDCl_3$) 0.78–0.89 [2× d, 2× CH(CH_3)$_2$], 0.90–0.94 [2× d, 2× C(6)CH_3], 0.95–0.96 [2× s, 2× C(8a)CH_3], 0.98–1.00 [2× d, 2× one of CH(CH_3)$_2$], 1.15–2.55 (10× CH_2,6× C*H*). The two diastereomers of (3*S**,3a*S**,8a*R**)-octahydro-3-isopropyl-6,8a-dimethylazulen-1(2*H*)-one **13** could be detected in the ^{1}H NMR spectrum of the product mixture following chromatography at δ_H 1.08 [s, C(8a)CH_3] and δ_H 1.17 [s, C(8a)CH_3], diastereomeric ratio 50:50. Found (HRMS, EI): *m*/*z* 222.19704. $C_{15}H_{26}O$ requires M^+ 222.19837; 222 (13), 177 (100), 135 (32%). Repeated chromatography allowed some resolution and eventually a sample was obtained, which was predominantly (ca. 90–95%) the monoalkene **14**; ν_{max}/cm^{-1} (film) 1736, 1465, 1373; δ_H ($CDCl_3$) 0.76–0.78 [3H, d, *J* 6.9, one of CH(CH_3)$_2$], 0.81–0.83 [3H, d, *J* 6.9, one of CH(CH_3)$_2$], 0.86–0.89 [3H, d, *J* 7.0, C(6)HCH_3], 1.15 [3H, s, C(8a)CH_3], 1.25–2.81 (11H, m, 4× CH_2,3× CH), 5.51–5.52 [1H, m, C(4)H]; δ_C ($CDCl_3$) 15.8, 18.9, 19.3, 20.7 (4× CH_3), 28.5 [CH,CH(CH_3)$_2$], 29.1, 31.1, 32.2 (3× CH_2), 33.4 (CH), 38.5 (CH_2), 44.8 (CH), 53.8 (C), 120.6 [C(4)H], 148.7 [C(3a)]; HRMS (EI): exact mass calculated for $C_{15}H_{24}O$ $[M]^+$, 220.18272. Found 220.18261. *m*/*z* (EI): 220 $[M]^+$(42), 205 (51), 177 (48), 151 (52), 135 (40%).

4.1.7.2. Method (b). A mixture of *trans*-(3*S**,8a*R**)-3-isopropyl-6,8a-dimethyl-2,3-dihydroazulen-1(8a*H*)-one **8a** (2.56 g, 11.9 mmol) and palladium on carbon (5%, 100 mg) in ethanol (150 mL), was shaken under hydrogen at 50 psi for 12 h. The crude reaction mixture was then filtered through a short column of silica gel using ethyl acetate (5:95) as eluant, to remove the hydrogenation catalyst and the solvent was evaporated under reduced pressure. Purification by column chromatography, using gradient ethyl acetate–hexane as eluant, gave a colourless oil (2.25 g, 85%), which contained a mixture of products, which could not be separated chromatographically. The mixture contained a diastereomeric mixture, of the perhydroazulenones **12**, **13** and the mono-alkene **14** (54:23:23).

4.1.8. Benzeneselenenyl bromide. This was freshly prepared in situ in solution in THF before each reaction by the following method. A solution of bromine (67.5 mg, 0.422 mmol) in THF (5 mL) was added slowly via syringe to a solution of diphenyl diselenide (132 mg, 0.423 mmol) in THF (5 mL). The dark brown/orange solution was briefly agitated by shaking the addition funnel to dissolve any $PhSeBr_3$ formed.

4.1.9. (3aS,8aR*)-4,5,6,7,8,8a-Hexahydro-3-isopropyl-6,8a-dimethylazulen-1(3aH)-one* ***15***, *(3aR*,8aR*)-4,5,6,7,8,8a-hexahydro-3-isopropyl-6,8a-dimethylazulen-1(3aH)-one* ***16***. *n*-Butyllithium (6.20 mL, 1.60 M in hexanes, 9.92 mmol) was added dropwise to a solution of diisopropylamine (1.39 mL, 9.86 mmol) in THF (20 mL), while stirring under nitrogen at −78 °C. A solution of the perhydroazulenones

12, **13** and the monoalkene **14** (54:23:23), (2.00 g, 9.01 mmol) in THF (10 mL) was then added dropwise over 2 min, and the solution stirred for 30 min. A solution of benzeneselenenyl bromide (9.00 mmol) in THF (50 mL) [freshly prepared from diphenyl diselenide (1.41 g, 4.52 mmol) and bromine (0.72 g, 4.51 mmol)] was added quickly to the enolate solution and an immediate decolourisation was noted. The reaction mixture was stirred for 3 min and the cold solution poured into ether–hexane-10% HCl (50:50:100 mL) and the mixture stirred for 5 min. The layers were separated and the organic layer washed with water (40 mL) and saturated sodium hydrogen carbonate solution (40 mL). Evaporation of the solvent at reduced pressure gave the crude selenide as an orange solid. Hydrogen peroxide (15% in H_2O, 5 mL) was added dropwise to a stirring solution of the crude selenide in dichloromethane (25 mL) and pyridine (0.1 mL) at 0 °C. The ice-bath was removed and stirring was continued for 30 min at room temperature, the reaction mixture was then diluted with dichloromethane (30 mL) and sodium hydrogen carbonate solution (10%, 30 mL). The layers were separated and the aqueous layer was washed with dichloromethane (2×20 mL). The combined organic layers were washed with dilute hydrochloric acid (10%, 10 mL) and brine (40 mL). Purification by chromatography on silica gel, using gradient ethyl acetate–hexane as eluant, gave a diastereomeric mixture of the hydroazulenones **15** and **16** (1.15 g, 58%), as a colourless oil. The ratio of the two compounds was 2:1: ν_{max}/cm^{-1} (film) 1703, 1604; δ_H ($CDCl_3$) 0.90–1.02 [2× d, *J* 6.9, one of $CH(CH_3)_2$ (major), one of $CH(CH_3)_2$ (minor)], 1.05 [3H, s, C(8a)CH_3 (minor)], 1.09–1.17 [m, containing s at 1.13, one of $CH(CH_3)_2$ (major), C(8a)CH_3 (major), C(6)HCH_3 (major and minor), one of $CH(CH_3)_2$ (minor)], 1.17–2.10 [m, C(4)H_2, C(5)H_2, C(6)H, C(7)H_2, C(8)H_2 (both major and minor)], 2.51–2.68 [1H, m, $CH(CH_3)_2$], 2.83–2.97 [1H, m, A of ABX, C(3a)H], 5.73 [1H, br s, C(2)H (major)], 5.81 [1H, br s, C(2)H (minor)]; δ_C ($CDCl_3$) Those signals, which are identifiable as those of the major or minor isomers are identified by (maj) and (min), respectively; 18.8 [C(8a)CH_3], 21.0, 21.5, 21.6 (3× CH_3), 22.9, (CH_2), 24.7, 25.4, 26.5 (3× CH_3), 29.0 (min), 29.1 (maj) (2× CH), 31.7 (CH_2), 32.4 (min), 33.9 (maj) (2× CH), 34.0 (min), 34.7 (maj), 35.0 (3× CH_2), 35.6 (C), 38.5 (CH_2), 50.1 (maj), 50.1 (min) (2× CH), 122.7 (maj), 123.3 (min) (2× CH), 186.0 (maj), 186.7 (min) (2× C, C-3), 213.1 (min), 214.4 (maj) (2× C=O). (EI) 220 $[M]^+$(33), 205 $[M-CH_3]^+$ (100), 177 (74), 163 (57), 150 (52), 135 (53%).

This sample is not analytically pure, impurities are seen at δ_H 5.90, 6.12 (ca. 10%) and δ_C 52.7 (C), 140.5 (CH).

*4.1.10. Dithioketalisation of **15** and **16** to give **17** and **18**.* Titanium tetrachloride (5.00 mL, 1 M solution in dichloromethane, 5.00 mmol) was added cautiously to a stirring solution of the two hydroazulenones **15** and **16** (ca. 2:1) (573 mg, 2.60 mmol) and 1,2-ethanedithiol (0.50 mL, 5.96 mmol) in dichloromethane (5 mL). The cloudy brown reaction mixture was heated to reflux for 2 h and was then cooled to room temperature and washed with potassium hydroxide (1 M, 3×20 mL), water (20 mL) and brine (30 mL), dried and the solvent removed under reduced pressure to give the crude thioketals **17** and **18**, which were purified by column chromatography, using ethyl acetate–hexane (1:99) as eluant, to give the purified thioketals **17** and **18** (70:30) (0.51 g, 66%) as a colourless oil with a pungent sulfur odour; ν_{max}/cm^{-1} (film) 1693, 1455; Signals due to the major product **17**; δ_H ($CDCl_3$) 0.91, 0.98, 1.08 [3× 3H, 3× d, *J* 6.9, C(6)CH_3, $CH(CH_3)_2$], 1.17 [3H, s, C(8a)CH_3], 1.19–2.60 (10H, complex m), 2.8–3.4 (5H, m, containing SCH_2CH_2S), 5.36 [1H, br s, C(2)H]; δ_C ($CDCl_3$) 21.0, 21.8, 23.2 (3× CH_3), 27.6 (CH), 28.3 (CH_3), 28.9, 32.3, 32.5 (3× CH_3), 38.4 (CH), 39.3, 40.4, 40.6 (3× CH_2), 52.4 (C, C-8a), 59.1 (CH, C-3a), 84.1 (C, C-1), 127.7 (CH, C-2), 153.0 (C, C-3).

Signals due to the minor product **18**; δ_C ($CDCl_3$) 0.99 (3H, d, *J* 6.9, CH_3), 1.18 [3H, s, C(8a)CH_3]; the other signals are obscured by those of the major isomer; δ_C ($CDCl_3$) 19.9 (CH_3), 25.0, 27.6, 30.1 (3× CH_2), 30.5 (CH), 48.6 (CH_2), 58.0 (CH, C-3a), 84.6 (C, C-1), 127.8 (CH, C-2), 152.8 (C, C-3).

HRMS, (EI): exact mass calculated for$C_{17}H_{28}S_2$ $[M]^+$ 296.1633. Found 296.1638 *m*/*z* (EI): 296 $[M]^+$(85), 268 (100), 253 (27), 235 (36), 203 (34), 105 (50%).

This sample also has other minor signals in the ^{13}C NMR, which may be due to other minor regio- or stereoisomers.

4.1.11. (8aS)-3-Isopropyl-6,8a-dimethyl-1,3a,4,5,6,7,8,8a-octahydroazulenes **19** and **20**.* Raney® nickel (2.00 g) was added to a solution of the thioketals **17** and **18** (70:30) (200 mg, 0.676 mmol) in ethanol (20 mL). The resulting suspension was refluxed for 2 h and then cooled to room temperature and the nickel removed by filtration through Celite® and rinsed with ethanol (10 mL). The combined filtrates were diluted with dichloromethane (100 mL) and washed with water (3×60 mL) and brine (150 mL), dried and the solvent removed under reduced pressure to give the crude product. Purification by column chromatography, using hexane as eluant, gave a mixture of alkenes **19** and **20** (3:1) (97.0 mg, 70%), which also contains minor unidentified products (<10%); ν_{max}/cm^{-1} (film) 1705 (w), 1458, 1378; Spectral details of the major isomer **19**; δ_H ($CDCl_3$, 500 MHz) 0.81 [3H, d, *J* 8.0, C(6)CH_3], 0.80–1.60 {17H, complex m, containing 0.89 [3H, d, *J* 7.0, one of $CH(CH_3)_2$], 0.92 [3H, s, C(8a)CH_3], 1.00 [3H, d, *J* 7.0, one of $CH(CH_3)_2$], C(4)H_2, C(6)H}, 1.74–1.92 [3H, m, containing dd, *J* 16.2, 2.0 at 1.85 for one of C(1)H_2, one of C(8)H_2, C(3a)H], 2.04–2.17 {2H, m, containing 2.08 [1H, brdd, *J* 16.2, 1.2, one of C(1)H_2], $CH(CH_3)_2$}, 5.06 [1H, d, *J* 2.0 C(2)H]; δ_C ($CDCl_3$) 21.7, 22.5[2× CH_3, $CH(CH_3)_2$], 24.3 [CH_3, C(6)CH_3], 27.5 [CH, $CH(CH_3)_2$], 28.4 (CH_2, one of C-4, C-7), 29.8 [CH_3, C(8a)CH_3], 33.6 (CH_3, one of C-4, C-5, C-7), 38.2 (CH, C-6), 39.5 (CH_2, one of C-4, C-5, C-7), 40.5 (CH_2, C-8), 45.0 (C, C-8a), 48.3 (CH_2, C-1), 59.1 (CH, C-3a), 118.3 (CH, C-2), 154.4 (C, C-3).

Signals due to the minor isomer 20; δ_H ($CDCl_3$, 500 MHz) 0.77 [3H, d, *J* 7.0, C(6)CH_3], 0.88 [3H, d, *J* 7.0, one of $CH(CH_3)_2$], 0.93 [3H, s, C(8a)CH_3], 1.02 [3H, d, *J* 7.0, one of $CH(CH_3)_2$], 5.15 [1H, br s C(2)H]; the other signals due to this isomer are obscured by the signals of 19; δ_C ($CDCl_3$) 21.5, 22.4 [2× CH_3, $CH(CH_3)_2$], 26.2 [CH, $CH(CH_3)_2$], 32.7, 34.2, 42.9, 46.0 (4× CH_2, C-4, C-5, C-7, C-8), 57.0 (CH, C-3a), 119.4 (CH, C-2); Signals due to C-1, C-8a, C(8a)CH_3, C-6, C(6)CH_3 are not seen, these signals are either coincident with the equivalent signals of the major diastereomer or the intensity of the signals is not sufficient to distinguish them from the impurity signals. HRMS (EI): exact mass calculated for $C_{15}H_{25}$ $[M-1]^+$ 205.1956. Found 205.1961. *m*/*z* (EI) 205 $[M-1]^+$ (100), 175 (7), 163 (10), 147 (19%).

*4.1.12. Diastereomeric mixture of diols **21a–e**.* The mixture of alkenes **19** and **20** (3:1) (201 mg, 0.976 mmol), *N*-methylmorpholine *N*-oxide monohydrate (NMO) (220 mg, 1.63 mmol), osmium tetroxide (0.5 mL, 5 mol % solution in H_2O, 0.250 mmol) were stirred in acetone (4 mL) and water (1 mL). The reaction was monitored by TLC. After 18 and 42 h the starting material was still evident along with some products (visualisation using $KMnO_4$ stain). At this time the reaction mixture was diluted with dichloromethane (50 mL) and the resulting solution was washed with 5 M HCl and then shaken vigorously for several minutes with aqueous sodium metabisulfite (3 mL). The mixture was separated, dried, and the solvent removed under reduced pressure. Purification by column chromatography using gradient ethyl acetate–hexane as eluant, gave five compounds. An inseparable mixture of compounds **21a** and **21b** (15.0 mg, 6%) were isolated as a precipitate from toluene when the reaction mixture was being applied to the column. The other four were isolated from the column itself. The least polar fraction contained starting material **19** and **20** (63.0 mg, 32%) (3:1) and the other three **21c** (15.0 mg, 6%), **21d** (17.0 mg, 7%), **21e** (32.0 mg, 14%).

Spectral details of **21a**; δ_H ($CDCl_3$, 270 MHz) 0.87, 0.91, 0.99 [3× 3H, 3× d, *J* 6.9, $CH(CH_3)_2$, C(6)CH_3], 1.06–1.29 (1H, m), 1.33 [3H, s,

C(3a)CH_3], 1.38–2.00 (11H, m, containing br s at 1.55 due to H_2O), 4.00 [1H, t, *J* 6.9, C(2)H]; A minor diastereomer **21b** (30%) was detected in the ^{1}H NMR spectrum with characteristic signals; δ_H ($CDCl_3$, 270 MHz) 0.88, 0.93, 1.00 (3× 3H, 3× d, *J* 7.0, CH(CH_3)$_2$, C(6)CH_3)], 1.30 [3H, s, C(3a)CH_3], other signals for the minor diastereomer were obscured by those for the major diastereomer.

Spectral details of **21c**; δ_H ($CDCl_3$, 270 MHz) 1.05 (3H, d, *J* 7.0), 1.12 (3H, d, *J* 7.0), 1.26 (6H, d, *J* 7.0), 1.38 (2H, t, *J* 7.0), 1.45–2.42 (m), 2.87–3.19 (m).

Spectral details of **21d**; δ_H ($CDCl_3$, 270 MHz) 0.75–2.15 (m, multiple ^{i}Pr), 2.94 (q, *J* 7.0), 3.96–4.08 (m).

Spectral details of **21e**; δ_H ($CDCl_3$, 270 MHz) 0.80–2.62 (m, multiple ^{i}Pr), 3.25–3.32 (m), 3.40–3.53 (m), 5.16, 5.25 (2× br d, *J* 11.2).

The signals for **21a** and **21d** at ca. 4.00 ppm are in close agreement with the corresponding signals for the natural product CAF-603 **1**. The signals due to the methyl resonances are also in close agreement.

4.1.13. (1S,3S*,8aR*)-3-Isopropyl-6,8a-dimethyl-1,2,3,8a-tetrahydroazulen-1-ol **22**.* *trans*-(3S*,8aR*)-3-Isopropyl-6,8a-dimethyl-2,3-dihydroazulen-1(8a*H*)-one **8** (5.38 g, 24.9 mmol) in ethanol (40 mL) was added dropwise over 10 min to a suspension of sodium borohydride (4.70 g, 124 mmol) in ethanol (60 mL), while stirring at 0 °C under an atmosphere of nitrogen. The reaction mixture was stirred for 2 h while slowly returning to room temperature. The solution was quenched by the dropwise addition of water (40 mL) at 0 °C. The volatiles were removed under reduced pressure and the resulting aqueous solution was extracted with ether (3×40 mL). The combined organic extracts were washed with brine (40 mL), dried and the solvent removed under reduced pressure to give the azulenol **22** (4.64 g, 85%) as a colourless oil: ν_{max}/cm^{-1} (film) 3351, 2957, 1454; δ_H (300 MHz, $CDCl_3$) 0.53 [3H, d, *J* 6.8, one of CH(CH_3)$_2$], 0.62 [3H, s, C(8a)CH_3], 0.94 [3H, d, *J* 6.8, one of CH(CH_3)$_2$], 1.10–1.30 [1H, m, one of C(2)H_2], 1.85–2.08 {6H, m, containing 2.05 [3H, s, C(6)CH_3], C*H*(CH_3)$_2$, one of C(2)H_2, C(1)OH}, 2.57–2.68 [1H, br m, C(3)H], 4.11 [1H, dd, *J* 10.6, 5.8, C(1)H], 5.23 [1H, d, *J* 9.7, C(8)H], 5.89–6.04 {2H, m, containing 5.99 [1H, d, *J* 9.6, C(7)H], one of C(4)H or C(5)H}, 6.30 [1H, d, *J* 6.8, one of C(4)H or C(5)H]; δ_C (75.5 MHz, $CDCl_3$) 16.2 [CH_3, one of CH(*C*H_3)$_2$], 16.8 [CH_3, C(8a)*C*H_3], 21.9 [CH_3, one of CH(*C*H_3)$_2$], 24.0 [CH_3, C(6)*C*H_3], 28.1 [CH, *C*H(CH_3)$_2$], 32.9 [CH_2, C(2)H_2], 44.7[C, C(8a)], 46.0 [CH, C(3)H], 80.5 [CH, C(1)H], 111.6 [CH, C(8)H], 117.8 (CH), 125.9 (CH), 126.5[CH, C(7)H], 133.2, 135.6 [2× C, C(3a), C(6)]; HRMS (ES^+): exact mass calculated for $C_{15}H_{23}O$ $[M+H]^+$, 219.1749. Found 219.1738.

A minor isomer **23** (7%) was detected in both the ^{1}H NMR and ^{13}C NMR spectra. This is due to the presence of a diastereomer, epimeric at C(1)*: δ_H (300 MHz, $CDCl_3$) 0.63 [3H, s, C(8a)CH_3], 0.93 [3H, d, *J* 6.6, one of CH(*C*H_3)$_2$], 4.94 [1H, d, *J* 9.9, C(8)H]; δ_C (75.5 MHz, $CDCl_3$) 17.2 (CH_3), 21.7 (CH_3), 24.3 (CH_3), 30.0 (CH), 34.3 [CH_2, C(2)H_2], 47.6 [CH, C(3)H], 80.7 [CH, C(1)H], 118.0, 125.4, 126.2, 127.4 (4× CH).

*Some signals not observed in the ^{1}H NMR spectrum due to overlap with signals for the major isomer **22**.

4.1.14. (1S,3S*,6S*,8aR*)-3-Isopropyl-6,8a-dimethyl-1,2,3,5,6,7,8,8a-octahydroazulen-1-ol **24**.* (1S*,3S*,8aR*)-3-Isopropyl-6,8a-dimethyl-1,2,3,8a-tetrahydroazulen-1-ol **22** (1.19 g, 5.45 mmol) was dissolved in ethanol (20 mL) and added to a suspension of Raney® nickel (1.00 g, weighed as a slurry in water) in ethanol (10 mL). The mixture was shaken under hydrogen at 50 psi for 48 h at room temperature. The reaction mixture was then filtered through a plug of Celite® to remove the catalyst and washed several times with ethanol. The organic washes were combined and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel, eluted with ethyl acetate/hexane (5:95), to give the pure octahydroazulenol **24** (0.93 g, 77%) as a colourless oil: ν_{max}/cm^{-1} (film) 3394, 2955, 1459; δ_H (300 MHz, $CDCl_3$) 0.80 [3H, d, *J* 6.8, one of CH(*C*H_3)$_2$], 0.93, 0.94 [6H, 2× d, *J* 6.4, 6.8, C(6)CH_3, one of CH(*C*H_3)$_2$], 1.09 [3H, s, C(8a)CH_3], 1.25 [1H, br s, C(1)OH], 1.32–1.50 [3H, m, containing C(2)H_2], 1.74–2.24 (7H, m), 2.46–2.58 [1H, br m, C(3)H], 3.64 [1H, br s, C(1)H], 5.32–5.44 [1H, m, C(4)H]; δ_C (75.5 MHz, $CDCl_3$) 16.5 [CH_3, one of CH(*C*H_3)$_2$], 21.4, 22.4 [2× CH_3, one of CH(*C*H_3)$_2$, C(6)*C*H_3], 23.0 [CH_3, C(8a)*C*H_3], 27.3 (CH), 28.0 (CH_2), 32.0 (CH), 32.0, 32.1, 33.5 (3× CH_2), 46.5 [CH, C(3)H], 50.2 [C, C(8a)], 82.3 [CH, C(1)H], 120.3 [CH, C(4)H], 151.0 [C, C(3a)]; HRMS (ES^+): exact mass calculated for $C_{15}H_{25}$ $[M+H-H_2O]^+$, 205.1951. Found 205.1952 *m*/*z* (ES^+): 205 $[M+H-H_2O]^+$ (100), 179 (8), 146 (4), 105 (12), 42 (5%).

In one experiment, the diene **25** was isolated for characterisation as a colourless oil: δ_H (300 MHz, $CDCl_3$) 0.80 [3H, d, *J* 6.9, one of CH(*C*H_3)$_2$], 0.95 [3H, d, *J* 6.6, one of CH(*C*H_3)$_2$], 0.98 [3H, s, C(8a)CH_3], 1.24 (1H, d, *J* 6.6), 1.38–1.54 (1H, m), 1.60–2.08 {6H, m containing 1.82 [3H, s, C(6)CH_3]}, 2.11–2.49 (3H, m), 2.70 [1H, br s, C(1)OH], 3.73–3.86 [1H, m, C(1)H], 5.48 [1H, dd, *J* 7.5, 2.4, C(4)H], 5.63 [1H, d, *J* 7.8, C(5)H]; δ_C (75.5 MHz, $CDCl_3$) 16.9, 22.1, 23.0, 27.1 (4× CH_3), 28.3 (CH), 28.9, 31.5, 32.8 (3× CH_2), 47.4 (CH), 50.0 [C, C(8a)], 81.9 [CH, C(1)H], 116.0, 120.0 [2× CH, C(4)H, C(5)H], 139.7, 153.6 [2× C, C(3a), C(6)]. These samples were re-exposed to hydrogenation conditions to effect complete hydrogenation to the mono-alkene **24**.

4.1.15. (1S,6R*,8aR*)-3-Isopropyl-6,8a-dimethyl-1,2,4,5,6,7,8,8a-octahydroazulen-1-ol **26**.* (1S*,3S*,6S*,8aR*)-3-Isopropyl-6,8a-dimethyl-1,2,3,5,6,7,8,8a-octahydroazulen-1-ol **24** (5.65 g, 25.4 mmol) was dissolved in ethanol (80 mL) and added to a suspension of palladium on carbon (5% by weight, 0.500 g) in ethanol (20 mL). The mixture was shaken under hydrogen at 50 psi for 120 h. The reaction mixture was then filtered through a plug of Celite® to remove the catalyst and washed several times with ethanol. The organic washes were combined and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel, eluted with ethyl acetate/hexane (20:80), to give the isomerised octahydroazulenol **26** (5.26 g, 93%) as a colourless oil: ν_{max}/cm^{-1} (film) 3419, 2854, 2924, 1456; δ_H (300 MHz, $CDCl_3$) 0.75–0.96 {10H, m, containing 0.82 [3H, s, C(8a)CH_3], 0.87 [3H, d, *J* 6.6, C(6)CH_3], 0.92 [3H, d, *J* 6.8, one of CH(*C*H_3)$_2$]}, 1.04 [3H, d, *J* 6.8, one of CH(*C*H_3)$_2$], 1.08–1.87 {7H, complex m, containing 1.35 [1H, br s, C(1)OH], 1.69 (1H, tt, *J* 13.2, 2.1), 1.77–1.87 (1H, m)}, 2.01–2.14 [2H, m, A of ABX, one of C(2)H_2], 2.47 (1H, ddd, *J* 13.6, 2.5, 2.3), 2.56–2.78 {2H, m, containing 2.61 [1H, ddd, B of ABX, *J* 16.7, 5.5, 2.1, one of C(2)H_2], 2.70 [1H, septet, *J* 6.8, C*H*(CH_3)$_2$]}, 3.79 [1H, d, X of ABX, *J* 5.1, C(1)H]; δ_C (75.5 MHz, $CDCl_3$) 21.1, 21.8 [2× CH_3, CH(*C*H_3)$_2$], 24.0 [CH_3,C(6)*C*H_3], 24.3 (CH_2), 25.6 [CH_3, C(8a)*C*H_3], 26.5 [CH, *C*H(CH_3)$_2$], 35.1, 35.8 (2× CH_2), 38.2 [CH_2, C(2)H_2], 38.7 [CH, C(6)H], 39.4 (CH_2), 54.0 [C, C(8a)], 80.5 [CH, C(1)H], 137.0, 139.8 [2× C, C(3), C(3a)]; HRMS (ES^+): exact mass calculated for $C_{15}H_{25}$ $[M+H-H_2O]^+$, 205.1951. Found 205.1949.

4.1.16. (6R,8aR*)-3-Isopropyl-6,8a-dimethyl-4,5,6,7,8,8a-hexahydroazulene-1(2H)-one **27**.* (1S*,6R*,8aR*)-3-Isopropyl-6,8a-dimethyl-1,2,4,5,6,7,8, 8a-octahydroazulen-1-ol **26** (1.06 g, 4.77 mmol) was dissolved in dichloromethane (30 mL) and pyridinium chlorochromate (3.08 g, 14.3 mmol) was added to the solution. The reaction mixture was stirred under nitrogen for 2 h at room temperature. The mixture was then filtered through a short plug of silica gel. This was washed several times with dichloromethane to elute the product, giving the crude β,γ-unsaturated ketone **27** as an orange oil. Purification by flash chromatography on silica gel, eluted with ethyl acetate/hexane (10:90), gave the pure β,γ-unsaturated ketone **27** (0.81 g, 78%)as a clear oil: ν_{max}/cm^{-1} (film) 2958, 2924, 1749, 1457; δ_H (300 MHz, $CDCl_3$) 0.61–1.09 {14H, m, containing 0.86 [3H, d, *J* 6.6, C(6)H_3], 1.01 [3H, d, *J* 6.8, one of CH(*C*H_3)$_2$], 1.01 [3H, s,

C(8a)CH_3], 1.04 [3H, d, *J* 6.8, one of CH(CH_3)$_2$]}, 1.14–1.28 (1H, m), 1.32–1.47 (2H, m), 1.72–1.91 (2H, m), 2.25 (1H, dd, *J* 14.7, 7.7), 2.52–3.02 {4H, m, containing, 2.57 (br d), 2.66 [1H, d, A of ABq, *J* 22.2, one of C(2)H_2], 2.91 [1H, septet, *J* 7.0, C*H*(CH$_3$)$_2$], 2.96 [1H, d, B of ABq, *J* 22.2, one of C(2)H_2]}; δ_C (75.5 MHz, $CDCl_3$) 21.2 (2× CH_3), 23.9 (CH_2), 24.0, 24.5 (2× CH_3), 26.2 (CH), 33.6, 34.6 (2× CH_2), 38.4 (CH), 38.9, 39.1 (2× CH_2), 56.9 [C, C(8a)], 136.1, 140.7 [2× C, C(3), C(3a)], 221.4 (C, C=O); HRMS (ES^+): exact mass calculated for $C_{15}H_{25}O$ $[M+H-H_2O]^+$, 221.1900. Found 221.1900.

*4.1.17. (3a*R**,6*R**,8a*R**)-3-Isopropyl-6,8a-dimethyl-4,5,6,7,8,8a-hexahydroazulen-1(3aH)-one* ***28****.* (6*R**,8a*R**)-3-Isopropyl-6,8a-dimethyl-4,5,6,7,8,8a-hexahydroazulene-1(2*H*)-one **27** (1.50 g, 6.81 mmol) was dissolved in an ethanol/toluene (20:80) mixture (80 mL) and rhodium trichloride trihydrate (3.00 mg, 0.2 mol %) was added. The reaction mixture was heated under reflux, while stirring under an atmosphere of nitrogen for 24 h. Evaporation of the solvent mixture, followed by purification of the residue by flash chromatography on silica gel, eluting with ethyl acetate/hexane (5:95) gave the pure α,β-unsaturated ketone **28** (1.02 g, 68%) as a colourless oil: ν_{max}/cm^{-1} (film) 2960, 2871, 1701, 1611, 1457; δ_H (300 MHz, $CDCl_3$) 0.60–0.95 {5H, m, containing 0.79 [3H, d, *J* 6.6, C(6)CH_3]}, 1.04 [3H, s, C(8a)CH_3], 1.12 [3H, d, *J* 7.0, one of CH(CH_3)$_2$], 1.23 [3H, d, *J* 6.6, one of CH(CH_3)$_2$], 1.30–1.59 [4H, m, C(6)H], 1.80 [1H, ddd, *J* 14.9, 11.2, 3.6, one of C(4)H_2], 1.89–2.06 [2H, m, one of C(4)H_2], 2.55 [1H, d septets, *J* 6.9, 0.9, C*H*(CH$_3$)$_2$], 2.77 [1H, overlapping ddd, *J* 5.2, 3.5, 1.7, C(3a)H], 6.02 [1H, s, C(2)H]; δ_C (75.5 MHz, $CDCl_3$) 20.3 [CH_3, one of CH(CH_3)$_2$], 21.4 [CH_3, one of CH(CH_3)$_2$], 23.1 [CH_3, C(6)CH_3], 26.2 [CH_2, C(4)H_2], 28.0 [CH_3, C(8a)CH_3], 29.0 [CH, C*H*(CH$_3$)$_2$], 33.3, 34.3, 34.9 [3× CH_2, C(5)H_2, C(6)H_2, C(7)H_2], 37.0 [CH, br, C(6)H], 51.8 [C, C(8a)], 54.1 [CH, C(3a)H], 127.1 [CH, C(2)H], 190.1[C, C(3)], 215.7 (C, C=O); HRMS (ES^+): exact mass calculated for $C_{15}H_{25}O$ $[M+H]^+$, 221.1905. Found 221.1904.

4.1.18. (6R,8aR*)-3-Isopropyl-6,8a-dimethyl-4,5,6,7,8,8a-hexahydro-3aH-spiro[azulene-1,2′-[1,3]dithiolane* ***30*** *and (6R*,8aR*)-3-isopropyl-6,8a-dimethyl-4,5,6,7,8,8a-hexahydro-2H-spiro[azulene-1,2′-[1,3]dithiolane]* ***32****.* 1,2-Ethanedithiol (3.48 mL, 41.4 mmol) was added to a solution of (3a*R**,6*R**,8a*R**)-3-isopropyl-6,8a-dimethyl-4,5,6,7,8,8a-hexahydroazulen-1(3a*H*)-one **28** (1.30 g, 5.91 mmol) in dichloromethane (80 mL), while stirring at 0 °C under an atmosphere of nitrogen. Titanium tetrachloride (17.8 mL, 1 M in dichloromethane, 17.7 mmol), was then added slowly, and the reaction mixture was allowed to warm to room temperature over 30 min. The solution was heated under reflux for 6 h and was then cooled to room temperature, and washed with potassium hydroxide (1 M, 3×80 mL), water (80 mL) brine (80 mL), dried and concentrated under reduced pressure to give the crude thioketal **30** as a pink oil. Purification by flash chromatography on silica gel eluted with ethyl acetate/hexane (20:80), gave the thioketal **30** (1.34 g, 76%), containing 25–30% of a minor compound **32** as a colourless oil with a pungent sulfur odour: ν_{max}/cm^{-1} (film) 2958, 2922, 1455, 1380; δ_H (300 MHz, $CDCl_3$) 0.98, 1.00 [6H, 2× d, *J* 6.8, 6.8, one of CH(CH_3)$_2$, C(6)CH_3], 1.09 [3H, d, *J* 6.7, one of CH(CH_3)$_2$], 1.18 [3H, s, C(8a)CH_3], 1.24–1.71 (7H, m), 1.93–2.08 [1H, m, C(6)H], 2.10–2.29 [2H, m, containing 2.14 (1H, d, *J* 10.5), 2.21 (1H, septet, *J* 6.9, C*H*(CH$_3$)$_2$), 2.44–2.59 (1H, m), 2.89–2.91 (1H, m, one of SCH_2CH_2S), 3.08–3.33 (3H, m, SCH_2CH_2S), 5.37 [1H, s, C(2)H]; δ_C (75.5 MHz, $CDCl_3$) 19.7, 20.8 [2× CH_3, one of CH(CH_3)$_2$, C(6)CH_3], 21.7 [CH_3, one of CH(CH_3)$_2$], 24.8 (CH_2), 26.7 (CH_2), 27.0 (CH), 27.5 [CH_3, C(8a)CH_3], 29.8 (CH_2), 30.3 [CH, C(6)H], 36.0 (CH_2), 37.8 (C), 39.4, 40.1 [2× CH_2, C(4′)H_2, C(5′)H_2], 57.9 [CH, C*H*(CH$_3$)$_2$], 84.3 [C, C(1)], 127.4 [CH, C(2)H], 152.8 [C, C(3)]; HRMS (ES^+): exact mass calculated for $C_{17}H_{29}S_2$ $[M+H]^+$, 297.1705. Found 297.1705.

This sample also contained a small amount (25–30%) of a minor compound, which was identified as **32**: δ_H (300 MHz, $CDCl_3$) 0.89, 0.90 [6H, 2× d, *J* 7.0, 6.0, one of CH(CH_3)$_2$, C(6)CH_3], 1.00 [3H, d, *J* 7.0, one of CH(CH_3)$_2$], 1.07 [3H, s, C(3a)CH_3], 1.15–1.29 (1H, m), 1.33–1.86 [6H, m, containing 1.69 (1H, br t, *J* 13.4, one of CH_2)], 2.07–2.18 (1H, m), 2.51 (1H, ddd, *J* 13.7, 5.8, 2.3, one of CH_2), 2.69 [1H, septet, *J* 7.0, C*H*(CH$_3$)$_2$], 2.76–2.92 [2H, m, C(2)H_2], 3.11–3.37 (4H, m, SCH_2CH_2S); δ_C (75.5 MHz, $CDCl_3$) 20.8, 21.4 [2× CH_3, one of CH(CH_3)$_2$, C(6)CH_3], 23.9 [CH_3, one of CH(CH_3)$_2$], 24.7 (CH_2), 26.0 [CH_3, C(8a)CH_3], 26.3 [CH, C*H*(CH$_3$)$_2$], 36.0, 36.0, 37.7, 37.8 (4× CH_2), 38.3 [CH, C(6)H], 38.7 (CH_2), 50.7 [CH_2, C(2)H_2], 56.0 [C, C(8a)], 80.9 [C, C(1)], 139.6, 141.9 (2× C); HRMS (ES^+): exact mass calculated for $C_{17}H_{29}S_2$ $[M+H]^+$, 297.1705. Found 297.1702.

In another experiment a pure sample of **32** was isolated and characterised, which aided the spectral assignments.

4.1.19. (3aS,6R*,8aS*)-3-Isopropyl-6,8a-dimethyl-1,3a,4,5,6,7,8,8a-octahydroazulene* ***31****.* A mixture of (6*R**,8a*R**)-3-isopropyl-6,8a-dimethyl-4,5,6,7,8,8a-hexahydro-3a*H*-spiro[azulene-1,2′-[1,3]dithiolane **30** and (6*R**,8a*R**)-3-isopropyl-6,8a-dimethyl-4,5,6,7,8,8a-hexahydro-2*H*-spiro[azulene-1,2′-[1,3]dithiolane]**32** (3:1) (0.90 g, 3.04 mmol) were dissolved in ethanol (15 mL) and Raney® nickel (10.5 g, weighed as a slurry in water) was added. The suspension was then heated under reflux for 15 min. The reaction mixture was filtered through a plug of Celite® to remove the catalyst and washed several times with ethanol. The filtrate was then concentrated under reduced pressure to give the crude product as a colourless oil. A ^{1}H NMR spectrum of the crude reaction mixture showed the presence of a number of products, with the alkene **31** as the major component of the mixture, along with dienes **33** and **34** in a ratio of 1:0.55:0.37. Purification by flash chromatography on silica gel eluted with hexane gave the pure alkene **31** (0.26 g, 42%) as a colourless oil: ν_{max}/cm^{-1} (film) 2956, 2914, 2869, 1458, 1379; δ_H (300 MHz, $CDCl_3$) 0.78–1.25 {14H, m, containing 0.85 [3H, d, *J* 6.6, C(6)CH_3], 0.95 [3H, d, *J* 6.9, one of CH(CH_3)$_2$], 1.01 [3H, s, C(8a)CH_3], 1.09 [3H, d, *J* 6.9, one of CH(CH_3)$_2$]}, 1.27–1.75 (7H, m), 1.83–2.01 [1H, m, one of C(1)H_2], 2.03–2.22 [1H, m, C*H*(CH$_3$)$_2$], 2.24–2.43 [2H, m, one of C(1)H_2, C(3a)H], 5.23 [1H, d, *J* 2.1, C(2)H]; δ_C (75.5 MHz, $CDCl_3$)21.1, 22.0 [2× CH_3, CH(CH_3)$_2$], 22.6 [CH_3, br, C(6)CH_3], 25.8 (CH_2), 27.2 [CH, C*H*(CH$_3$)$_2$], 32.6 [CH_3, C(8a)CH_3], 32.9, 33.8 (2× CH_2), 35.2 [CH, br, C(6)H], 37.4 (CH_2), 43.6 [C, C(8a)], 45.5 [CH_2, C(1)H_2], 56.5 [CH, C(3a)H], 119.0 [CH, C(2)H], 152.5 [C, C(3)].

The dienes **33** and **34** were isolated as a mixture following chromatography as a clear oil (0.20 g, 33%) in a ratio of 0.55:0.45. The *endo*-diene **33** displayed characteristic signals in the ^{1}H NMR spectrum δ_H (300 MHz, $CDCl_3$) 2.72 [1H, septet, *J* 6.8, C*H*(CH$_3$)$_2$], 6.02 [1H, d, *J* 5.3, one of C(1)H or C(2)H], 6.26 [1H, d, *J* 5.3, one of C(1)H or C(2)H].

The *exo*-diene **34** displayed characteristic signals in the ^{1}H NMR spectrum δ_H (300 MHz, $CDCl_3$) 1.77, 1.70 [2× 3H, 2× s, CH(CH_3)$_2$], 5.60 [1H, d, *J* 5.8, one of C(1)H or C(2)H], 6.26 [1H, d, *J* 5.3, one of C(1)H or C(2)H].

4.1.20. (1R,2S*,3aS*,6R*,8aS*)-1-Isopropyl-3a,6-dimethyldecahydroazulene-1,2-diol* ***6*** *and (1S*,2R*,3aS*,6R*,8aS*)-1-isopropyl-3a,6-dimethyldecahydroazulene-1,2-diol* ***36***

4.1.20.1. Method (a). Osmium tetroxide (0.150 mL, 4% solution in water, 0.024 mmol) was added to a solution of the alkene **31** (100 mg, 0.485 mmol) and NMO (74.0 mg, 0.631 mmol) in acetone (10 mL) and water (2 mL). The reaction mixture was stirred at room temperature for 3 h. The progress of the reaction was monitored by TLC and the presence of more polar products was observed. The reaction mixture was worked up at this stage, following the procedure described below, and a sample taken for ^{1}H NMR analysis, which only showed starting material. The alkene was re-exposed to osmium tetroxide (0.150 mL, 4% solution in water, 0.024 mmol) and NMO (74 mg, 0.631 mmol) in acetone (10 mL) and water (2 mL). The reaction mixture was stirred at room temperature for two weeks.

Dichloromethane (30 mL) and hydrochloric acid (5 M, 20 mL) were added and the dichloromethane layer was washed with a saturated solution of sodium metabisulfite (20 mL). The organic phase was then washed with water (25 mL), brine (20 mL), dried and concentrated under reduced pressure to give the crude diol as a brown oil. A ^{1}H NMR spectrum showed the presence of unreacted starting material **31** (50%). Purification by flash chromatography on silica gel eluted with ethyl acetate/hexane (10:90), gave the pure diols **6** and **36** (15 mg, 13% by weight, 26%* actual yield) in a ratio of 2:1, as a white solid: mp 101–105 °C; ν_{max}/cm^{-1} (KBr) 3430, 2957, 2919, 1632, 1457; δ_H (300 MHz, $CDCl_3$) 0.87 [3H, d, *J* 6.6, CH(C*H*$_3$)$_2$], 0.92 [3H, d, *J* 6.6, CH(C*H*$_3$)$_2$], 1.00 [3H, d, *J* 6.9, C(6)CH$_3$], 1.09–2.22 {18H, cm, containing 1.29 [3H, s, C(3a)CH$_3$], 1.84 [1H, septet, *J* 6.6, C*H*(CH$_3$)$_2$], 1.97 (1H, dd, *J* 13.4,4.7), 2.12 (1H, br s, OH)}, 4.04 [1H, dd, appears as br t, *J* 8.7, C(2)H]; δ_C (75.5 MHz, $CDCl_3$)17.3, 18.0, 21.7 [3× CH$_3$, CH(*C*H$_3$)$_2$, C(6)*C*H$_3$], 23.6 (CH$_2$), 31.1 (CH), 32.5 (CH), 32.7 (CH$_2$), 32.9 [CH$_3$, C(3a)*C*H$_3$], 35.1 (CH$_2$), 37.8 (CH$_2$), 40.5 [C, C(3a)], 49.5 (CH$_2$), 57.2 (CH), 76.9 [CH, C(2)H], 85.2 [C, C(1)]; HRMS (ES$^+$): exact mass calculated for $C_{15}H_{25}$ [M+H–(2× H_2O)]$^+$, 205.1956. Found 205.1958 *m*/*z* (ES$^+$) 205 [M+H–(2× H_2O)]$^+$ (60), 146 (8), 101 (16), 64 (4%).

This sample also contained a minor isomer **36** with distinguishable signals: δ_H (300 MHz, $CDCl_3$) 0.93 [3H, d, *J* 6.6, CH(C*H*$_3$)$_2$], 2.00 (1H, br s, OH), 4.02–4.12 [1H, m, C(2)H, signal partially obscured by signal for major], remaining signals obscured by major isomer; δ_C (75.5 MHz, $CDCl_3$)17.5 (CH$_3$), 17.6 (CH$_3$), 20.1 (CH$_3$), 21.8 (CH$_2$), 29.7 (CH$_3$), 30.0 (CH), 30.7 (CH$_2$), 34.2 (CH$_2$), 34.5 (CH$_2$), 36.7 (CH), 39.6 [C, C(3a)], 48.6 (CH$_2$), 54.1 (CH), 73.7 [CH, C(2)H], 83.2 [C, C(1)].

*Yield calculated when unreacted starting material was taken into account.

4.1.20.2. Method (b). The deoxygenated alkene **31** (85.0 mg, 0.410 mmol) in *tert*-butanol (0.40 mL) was added to a stirring mixture of AD mix β (which had been fortified to 1 mol % $K_2OsO_2(OH)_4$) [140 mg, consisting AD mix β 139 mg and $K_2OsO_2(OH)_4$ 1.10 mg], methane sulfonamide (9.00 mg, 1 mol %) and sodium hydrogen carbonate (23.0 mg, 3 equiv) in a mixture of *tert*-butanol (0.7 mL) and water (0.7 mL) at 0 °C. The temperature was maintained at 0 °C for 42 h at which stage water (1 mL) was added. The mixture was washed with dichloromethane (2×20 mL). The combined organic phases were washed with KOH (15%, 30 mL) and brine (35 mL), dried and the solvent removed under reduced pressure. The crude product mixture was purified by column chromatography using gradient ethyl acetate–hexane as eluant, giving the product as a white solid (40.8 mg, 41%). The sample isolated following chromatography appeared to contain two diastereomers in the ratio ~3:1. Following recrystallisation only the major diastereomer **6** was isolated, which showed identical spectral characteristics as those described above. Attempts to recover the other diastereomer from the mother liquor were unsuccessful. This diastereomerically pure sample was used to grow the crystal from toluene/dichloromethane, which was subjected to X-ray crystallographic analysis. Crystal data: orthorhombic, $P2_12_12$, $C_{15}H_{28}O_2$, *M*=548.44, *a*=13.445(2) Å, *b*=18.456(3) Å, *c*=5.8042(10) Å, *U*=1440.3(4) Å^3, *F*(000)=536, μ(Mo-Kα)=0.071 mm^{-1}, $R(F_o)$=0.050, for 1124 observed reflections with $I>2\sigma(I)$, $wR_2(F^2)$=0.143 for all 1582 unique reflections. Data were collected and analysed as previously described,[50] using SHELXL-97[51] and PLATON.[52] The data has been deposited with the Cambridge Crystallographic Data Centre. CCDC reference number is 862531.

4.1.21. (E)-4-Methylpent-2-enoic acid ***39****.*[53,54] Isobutyraldehyde (5.48 g, 76.1 mmol), malonic acid (5.00 g, 48.0 mmol), pyridine (15 mL) and morpholine (75.0 μL) were mixed together and stirred at room temperature under an atmosphere of nitrogen for 24 h. The reaction mixture was then heated under reflux for a further 17 h. The reaction mixture was then poured into a sulfuric acid solution (1 M, 80 mL) and extracted with ether (2×50 mL), and the solvent evaporated under reduced pressure. The residue was re-dissolved in sodium hydroxide solution (1 M, 50 mL) and extracted with ether (2×50 mL). The aqueous phase was acidified with concentrated hydrochloric acid and again extracted with ether (2×50 mL). The organic phase was washed with brine, dried and the solvent removed under reduced pressure to give the acid **39** (4.44 g, 81%) as a colourless oil: δ_H (300 MHz, $CDCl_3$) 1.08 [6H, d, *J* 6.9, CH(C*H*$_3$)$_2$], 2.38–2.61 [1H, sym m, C*H*(CH$_3$)$_2$], 5.75 [1H, dd, *J* 15.9, 1.4, C(2)H], 7.70 [1H, dd, *J* 15.9, 6.6, C(3)H].

4.1.22. (E)-4-Methylpent-2-enoyl chloride ***40****.*[53,54] Oxalyl chloride (6.09 g, 48.0 mmol) was added dropwise to a solution of (*E*)-4-methylpent-2-enoic acid **39** (3.66 g, 32.0 mmol) in diethyl ether (37 mL), while stirring under an atmosphere of nitrogen at 0 °C. The temperature was allowed to warm to room temperature and the reaction mixture was stirred for 24 h. The solvent and excess oxalyl chloride were removed under reduced pressure. Distillation at atmospheric pressure under nitrogen at 132 °C (lit.,[54] 61–62 °C at 25 mmHg) gave the acid chloride **40** (3.02 g, 71%) as a colourless oil. No analysis of this compound was obtained, as it was found to hydrolyse very easily.

4.1.23. (4S,2E)-3-(4′-Methylpent-2′-enoyl)-4-phenyloxazolidin-2-one ***42****.*[43,44] Butyllithium (1.60 M in hexanes, 8.24 mL, 20.6 mmol) was added slowly via syringe to a stirring solution of (4*S*)-4-phenyl-2-oxazolidinone **41** (3.37 g, 20.6 mmol) in THF (30 mL) under an atmosphere of nitrogen at −78 °C. The resulting solution was stirred for 20 min at −78 °C. A solution of (*E*)-4-methylpent-2-enoylchloride **40** (3.01 g, 22.8 mmol) in THF (17 mL) was added slowly by syringe. The temperature was maintained at −78 °C for 30 min at which stage it was raised to 0 °C and the reaction mixture stirred at this temperature for 1.5 h. The reaction mixture was then quenched by the addition of saturated aqueous ammonium chloride (30 mL) and the volatiles were removed under reduced pressure. Ethyl acetate (65 mL) was added, the organic phase separated and washed with saturated aqueous sodium bicarbonate (2×30 mL), brine (30 mL), dried and the solvent removed under reduced pressure to give the crude oxazolidinone **42**. Purification by flash chromatography on silica gel eluting with ethyl acetate/hexane (20:80) gave the pure oxazolidinone **42** (4.71 g, 88%) as a white solid: mp 100–102 °C (lit.,[43] 103–104 °C); $[\alpha]_D^{20}$ +105.8 (*c* 1.0, $CHCl_3$) {lit.,[43] $[\alpha]_D^{20}$ +103.1 (*c* 1.0, $CHCl_3$)}; ν_{max}/cm^{-1} (KBr) 2966, 1778, 1685, 1639; δ_H (300 MHz, $CDCl_3$) 1.06, 1.07 [6H, 2× d, 2× *J* 6.9, CH(C*H*$_3$)$_2$], 2.42–2.63 [1H, sym m, C*H*(CH$_3$)$_2$], 4.27 [1H, dd, A of ABX, *J* 8.7, 3.9, one of C(5)H$_2$], 4.69 [1H, dd appears as t, B of ABX, *J* 8.7, one of C(5)H$_2$], 5.49 [1H, dd, X of ABX, *J* 8.7, 3.9, C(4)H], 7.05 [1H, dd, *J* 15.3, 6.6, C(3′)H], 7.16–7.46 {6H, m, containing 7.22 [1H, dd, *J* 15.3, 1.2, C(2′)H], ArH}; δ_C (75.5 MHz, $CDCl_3$) 21.1, 21.2 [2× CH$_3$, CH(*C*H$_3$)$_2$], 31.4 [CH, *C*H(CH$_3$)$_2$], 57.7 [CH, C(4)H], 69.9 [CH$_2$, C(5)H$_2$], 117.6 [CH, C(2′)H], 125.9, 128.6, 129.1 (3× CH, aromatic CH), 139.1 (C, quaternary aromatic C), 153.7 (C, C=O), 158.1 [CH, C(3′)H], 164.9 (C, C=O).

4.1.24. (3′S,4S)-3-[3′-(4″-Methylphenyl)-4′-methylpentanoyl]-4-phenyloxazolidin-2-one ***43****. para*-Bromotoluene (400 mg, 2.32 mmol), magnesium (56.0 mg, 2.32 mmol) and iodine (one crystal) in THF (15 mL) were heated under reflux for 1 h while stirring under an atmosphere of nitrogen. The solution was then cooled to 0 °C and copper(I) bromide dimethyl sulfide complex (480 mg, 2.32 mmol) was added and the suspension stirred for 30 min. The temperature of the reaction mixture was then reduced to −15 °C and (4*S*,2*E*)-3-(4′-methylpent-2′-enoyl)-4-phenyloxazolidin-2-one **42**

(300 mg, 1.16 mmol) was added and stirring was continued for 1.5 h, and then allowed to warm to room temperature over 1 h. The reaction mixture was quenched by the addition of saturated aqueous ammonium chloride (20 mL), washed with ether (3×20 mL) and the combined organic phases were washed with water (2×20 mL), brine (20 mL), dried and the solvent removed under reduced pressure to give the crude substituted acyl oxazolidinone **43**. Purification by flash chromatography on silica gel eluting with ethyl acetate/hexane (20:80) gave the pure substituted acyl oxazolidinone **43** (140 mg, 34%) as a white solid: mp 87–89 °C; ν_{max}/cm^{-1} (KBr) 2962, 1775, 1708; δ_H (300 MHz, $CDCl_3$) 0.73 [3H, d, *J* 6.6, one of CH(CH_3)$_2$], 0.95 [3H, d, *J* 6.6, one of CH(CH_3)$_2$], 1.74–1.94 [1H, sym m, C*H*(CH_3)$_2$], 2.33 [3H, s, C(4″)CH_3], 2.79–2.97 [1H, m, X of ABX, C(3′)H], 3.11 [1H, dd, A of ABX, *J* 15.6, 5.1, one of C(2′)H_2], 3.71 [1H, dd, B of ABX, *J* 15.6, 10.2, one of C(2′)H_2], 4.09 [1H, dd, A of ABX, *J* 8.7, 4.2, one of C(5)H_2], 4.58 [1H, dd appears as t, B of ABX, *J* 8.7, one of C(5)H_2], 5.31 [1H, dd, X of ABX, *J* 8.7, 4.2, C(4)H], 6.80 (2H, d, *J* 6.6, ArH), 6.94–7.45 (7H, m, ArH); δ_C (75.5 MHz, $CDCl_3$) 20.2, 20.8, 21.1 [3× CH_3, CH(CH_3)$_2$, C(4″)CH_3], 33.3 [CH, *C*H(CH_3)$_2$], 38.2 [CH_2, C(2′)H_2], 48.4 [CH, C(3′)H], 57.5 [CH, C(4)H], 69.7 [CH_2, C(5)H_2], 125.2, 128.1, 128.4, 128.7, 128.9 (5× CH, aromatic CH), 135.5, 138.5, 139.4 (3× C, quaternary aromatic C), 153.7 (C, C=O), 172.2 (C, C=O); HRMS (ES^+): exact mass calculated for $C_{22}H_{26}NO_3$ $[M+H]^+$, 352.1913. Found 352.1909 *m*/*z* (ES^+): 352 $[M+H]^+$ (100), 309 (2), 286 (2), 281 (4%).

A second set of signals for a minor compound (10%) could be observed in the ^1H NMR spectrum, with distinguishable signals: δ_H (300 MHz, $CDCl_3$) 0.77 [3H, d, *J* 6.9, one of CH(CH_3)$_2$], 0.83 [3H, d, *J* 6.9, one of CH(CH_3)$_2$], 3.33 (1H, dd, *J* 11.1, 4.5), 4.31 (1H, dd, *J* 9.0, 4.8), 4.77 (1H, dd appears as t, *J* 9.0), 5.49 (1H, dd, *J* 9.0, 4.8), 6.30 (1H, d, *J* 11.1).

*4.1.25. (+)-(3S)-3-(4′-Methylphenyl)-4-methylpentanoic acid (−)-(S)-**10**.* (3′*S*,4*S*)-3-[3′-(4″-Methylphenyl)-4′-methylpentanoyl]-4-phenyloxazolidin-2-one **43** (1.70 g, 4.84 mmol) was dissolved in THF (100 mL) and water (20 mL). The mixture was cooled to −10 °C and hydrogen peroxide (30% in H_2O, 6.20 mL, 54.7 mmol) was added via syringe over 5 min. A solution of lithium hydroxide monohydrate (0.62 g, 14.8 mmol) in water (7 mL) was added dropwise. The reaction mixture was stirred at 0 °C for 2 h and then warmed to room temperature, before the addition of sodium sulfite solution (1.6 M, 50 mL). The solution was stirred at room temperature for 30 min, and the volatiles were then removed under reduced pressure. The resulting aqueous suspension was extracted with dichloromethane (3×40 mL), to remove the chiral auxiliary. The remaining aqueous was cooled to 0 °C and acidified to pH 1 using 10% hydrochloric acid solution, and extracted with dichloromethane (4×40 mL). The combined organic extracts were then dried and the solvent removed under reduced pressure to give the acid (+)-(*S*)-**10** (0.99 g, 99%) as a white solid; mp 75–77 °C [lit.[48] 74–76 °C (racemic sample)]; $[\alpha]_D^{20}$ +33.0 (*c* 1, $CHCl_3$), with identical spectral characteristics to those described previously for the racemic compound **10**. Chiral HPLC carried out on a Chiralpak AS column, using hexane/*iso*-propylalcohol/trifluoroacetic acid (95:5:0.4) as eluant, indicated an enantiomeric excess of >99%. Detection was at λ 252 nm. In the racemic sample of 3-(4′-methylphenyl)-4-methylpentanoic acid **10** two peaks were detected at 5.06 min and 5.61 min. The latter signal was found to be the signal due to (3*S*)-3-(4′-methylphenyl)-4-methylpentanoic acid (+)-(*S*)-**10**.

*4.1.26. (+)-(5S)-2-Diazo-5-(4′-methylphenyl)-6-methylheptan-3-one (+)-(S)-**7**.* Oxalyl chloride (1.00 mL, 11.5 mmol) was added dropwise over 5 min to (−)-(3*S*)-3-(4′-methylphenyl)-4-methylpentanoic acid (−)-(*S*)-**10** (900 mg, 4.37 mmol) in dry ether (50 mL), while stirring at 0 °C under nitrogen. The solution was allowed to slowly return to room temperature while stirring for 18 h. The solvent and residual reagent were removed under reduced pressure to give the acyl chloride, which was used without further purification. An etheral diazoethane solution was prepared from *N*-ethyl-*N*-nitrosourea (11.0 g, 93.9 mmol) and cooled to −20 °C using a salt-ice bath. The crude acyl chloride in dry ether (20 mL) was added dropwise over 20 min to the stirring diazoethane solution under nitrogen. The solution was then allowed to return to room temperature while stirring for 4 h. The ether and residual diazoethane were evaporated under reduced pressure on a rotary evaporator fitted with an acetic acid trap. Purification by chromatography on silica gel, using ethyl acetate–hexane (5:95) as eluant, gave the α-diazoketone (+)-(*S*)-**7** (600 mg, 56%) as a yellow oil; $[\alpha]_D^{20}$ +41.0 (*c* 1.5 $CHCl_3$). This compound was found to have the same spectral characteristics as the racemic α-diazoketone **7**.

4.1.27. (+)-trans-(3S,8aR*)-3-Isopropyl-6,8a-dimethyl-2,3-dihydroazulen-1(8aH)-one (+)-(3S,8aR)-**8a**.* This was prepared following the procedure described for the racemic azulenone **7**, from (5*S*)-2-diazo-5-(4′-methylphenyl)-4-methylheptan-3-one (+)-(*S*)-**7** (100 mg, 0.410 mmol) in dichloromethane (100 mL) and using rhodium(II) acetate (0.50 mg) as catalyst, in dichloromethane (100 mL). A ^1H NMR spectrum of the crude product was recorded to determine the efficiency of the cyclisation (81%) and the diastereomeric ratio of the azulenones formed: diastereomeric ratio, (+)-(3*S*,8a*R*)-**8a**:(3*S*,8a*S*)-**8b**, >98:2. Only one enantiomer of the azulenone was detected in the chiral shift ^1H NMR studies. The rotation of the crude compound was measured $[\alpha]_D^{20}$ +14.33 (*c* 1, $CHCl_3$). Purification by column chromatography on silica gel, using gradient ethyl acetate–hexane as eluant, gave a single diastereomer of the azulenone (+)-(3*S*,8a*R*)-**8a** (66.0 mg, 75%) as a colourless oil; $[\alpha]_D^{20}$ +21.0 (*c* 1, $CHCl_3$). This compound was found to have the same spectral characteristics as the racemic azulenone **8a**. Only one enantiomer of the azulenone was detected in the chiral shift ^1H NMR studies of both the crude and purified product. The enantiomer detected was that at higher field.

Chiral shift data for racemic azulenone **8a** at 14.5 mol % Eu(hfc)$_3$; 0.89 [3H, appears as dd actually two d overlapping, *J* 7.0, both enantiomers of one of CH(CH_3)$_2$], 1.01 [3H, appears as dd actually two d overlapping, *J* 7.0, both enantiomers of one of CH(CH_3)$_2$], 1.34, 1.37 [3H, 2× s, two enantiomers of C(8a)CH_3], 1.71–1.95 [1H, m, C*H*(CH_3)$_2$], 2.06 [3H, s, no splitting of this signal, C(6)CH_3], 2.75–3.00 [2H, m, C(2)H_2], 3.12–3.43 [1H, m, C(3)H], 3.80–3.92 [1H, m, splitting of d into two overlapping d, C(8)H], 6.03 [1H, br d, *J* 6.1, C(7)H], 6.16–6.22 [2H, m, C(4)H, C(5)H].

Enantiomeric excess was estimated by integration of the two singlets due to C(8a)CH_3 for the two enantiomers.

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Supplementary data

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